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The Effect of Aqueous Extract of Mentha Longifolia on the Clinical and Paraclinical Status of Patients with COVID-19

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ABSTRACT

Background and Objective: Following the outbreak of the COVID-19 pandemic, numerous industrial and traditional medicines have been proposed and used to treat this disease. Given the lack of standard treatment and effective medicine for COVID-19 and the effectiveness of Mentha longifolia on pulmonary diseases, this study was designed and conducted to determine the effect of aqueous extract of Mentha longifolia on the clinical and paraclinical status of patients with COVID-19.

Methods: This clinical trial was conducted on 60 patients with COVID-19 hospitalized at Razi Hospital in Ghaemshahr (Mazandaran) in 2021. Patients were selected through purposive sampling. 30 people were randomly assigned into control group with standard treatment, and 30 people in the intervention group who received Mentha longifolia extract in the form of a nasal spray 2 puffs every 12 hours in addition to standard treatment. The main clinical variables included fever, cough, chest pain, shortness of breath, fatigue, and chills. Chest radiography was interpreted by a radiologist. The clinical definition of complete recovery included the absence of fever for two days, respiratory rate less than or equal to 15-20 breaths per minute, oxygen saturation greater than 95%, no cough or mild dry cough, and the clinical definition of partial recovery included body temperature less than or equal to 37.9 ºC orally or 37.2 ºC axillary, respiratory rate 20-24 breaths per minute, oxygen saturation between 93-95%, no cough or mild dry cough.

Findings: The two groups did not differ significantly in terms of gender, age, BMI, and underlying disease. The mean length of stay in the intervention group was 2.5 days shorter than in the control group (12.1±6.8 days in the control group and 9.6±7.1 days in the intervention group) (p=0.171). The number of deaths was not statistically significant but was clinically significant (6.7% in the intervention group and 16.7% in the control group). 26.7% of the control group and 50% of the intervention group had a complete recovery within the first 7 days after discharge. 30% of the control group still did not feel better 15 days after discharge, while this rate was zero in the intervention group.

Conclusion: The results of the study showed that aqueous extract of Mentha longifolia reduced the length of hospital stay and improved symptoms in patients with COVID-19.

Keywords: *Coronavirus, COVID-19, Mentha Longifolia, Persian Medicine.*

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Introduction

Since December 2019, a novel coronavirus (COVID-19) has caused an outbreak of pneumonia (1), leading to the declaration of a global health emergency by the World Health Organization. This strain of coronavirus belongs to the family of coronaviruses that is responsible for Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), and its most common symptoms include fever, fatigue, anorexia, dry cough, and shortness of breath (2). Less common symptoms include diarrhea, nausea, vomiting, runny nose, chest pain, feeling of fullness in the veins and body, muscle pain, headache, and sore throat (3). According to the priorities announced by the World Health Organization, it is very important to identify the clinical and paraclinical patterns of this disease and to study the characteristics related to the severity of the disease in order to control it (4).

One of the important features of COVID-19 was the absence of a clear mechanism of action and due to the pandemic, the produced drugs could not pass the safety and toxicity tests in a short period of time, which further limited the global response to the COVID-19 challenge. One of the strategies proposed for the treatment of this disease is the use of herbal medicines, which some countries such as China, India, Iran, Macau, the United States and South Korea have resorted to in accordance with their traditional medicine (5). Plants such as Satureja hortensis, Hypericum perforatum and Foeniculum vulgare can be mentioned as important medicinal plants in Persian medicine (6).

The Persian medical school has considerable clinical experience in using effective and appropriate herbal medicines based on patients' symptoms in the prevention and treatment of microbial infections and respiratory diseases. Natural products, their derivatives and preparations have potential functions in the treatment of viral infections (7). According to authoritative sources of Persian medicine such as The Canon of Medicine, Kamil as-sina a attibbiyyah, Zakhireye Khwarazmshahi and Exir-e Azam, Mentha longifolia is one of the medicinal plants that has been used either alone or in combination with other medicinal plants in the treatment of various lung diseases that are accompanied by thick and viscous secretions such as pneumonia, asthma, shortness of breath, cough and pleurisy. This plant is very strong in expelling mucus and thick viscous phlegm from the chest and cleanses the lungs from these substances. Various studies have shown the therapeutic and pharmacological effects of Mentha longifolia as a medicinal plant (7).

Recent studies have shown that Mentha longifolia has pharmacological effects including antimicrobial, antiviral, antibacterial, antifungal, analgesic, anti-inflammatory, antioxidant, and spasmolytic activities. The main beneficial compounds of the plant are pulegone, menthone, and menthol. The anti-inflammatory and antiviral effects of Mentha longifolia, which are due to the phenolic compounds in it, may be important in the effectiveness of Mentha longifolia on pneumonia. From a pathophysiological perspective, since the secretion of inflammatory cells, including macrophages, can worsen the condition of pneumonia patients, Mentha longifolia, with its anti-inflammatory properties, can be effective in controlling inflammation by reducing the secretion of NO (nitric oxide) in macrophages and reducing the release of TNFα (8).

Considering the very high prevalence and mortality of COVID-19, the lack of standard and effective drug treatment for this disease, and the effectiveness of Mentha longifolia on pulmonary diseases, this study was designed and implemented to determine the effect of aqueous extract of Mentha longifolia on the clinical and paraclinical status of patients with COVID-19.

Methods

After approval by the Ethics Committee of Mazandaran University of Medical Sciences with the code IR.MAZUMS.REC.1400.680 and registration in the Iranian Clinical Trial System with the code IRCT20200809048337N1, this randomized controlled clinical trial was conducted on 60 patients with COVID-19 (in two groups of 30) aged 18 to 75 years who referred to Razi Hospital, Ghaemshahr, Mazandaran Province in 2021. Based on searches conducted by the research team, no previous study whose results could be used to estimate the sample size was found. Therefore, it was considered as a pilot study. With this approach, 60 samples were considered (30 people in each group). The infection of these patients was confirmed based on the clinical diagnosis of an infectious disease specialist and changes in lung CT scan or standard COVID test (PCR) and they were subjected to routine drug treatment. Thirty people in the control group received only standard treatment, and 30 people in the intervention group were given Mentha longifolia extract as a nasal spray, 2 puffs in each nostril twice a day, in addition to standard treatment, during their hospitalization.

The product used in this trial was prepared in the form of nasal spray at the Faculty of Pharmacy of Shahid Beheshti University. The parts of the plant used in the product in question were the aerial parts including leaves and branches, and the purchased plant was identified and confirmed by the Botany Center of the Faculty of Pharmacy of Shahid Beheshti University of Medical Sciences under the Herbarium No.: SBMU-1078. To prepare the spray, first, the aqueous extract of Mentha longifolia was prepared and then concentrated to the point where it became a dry extract. Given that the concentration of aromatic products should not exceed 2%, the desired product was made using carbopol at a concentration of 1.5% as a dilute gel and with a pH of 6 to prevent mucosal damage. The natural pH of the nose was 6.3 and the pH of Mentha longifolia liquid was 6. The active ingredient in the aqueous extract prepared from Mentha longifolia was phenolic compounds (flavonoids), which were quantified by the TLC scanner method. Before use, the drug was examined from a microbial perspective. The drug substance was sterilized during the manufacturing process, and on the other hand, the prepared spray was examined for sterility in the microbial laboratory of Shahid Beheshti Faculty of Pharmacy.

For intervention, after explaining the project to eligible hospitalized patients at Razi Hospital in Ghaemshahr (from July to October 2021) and obtaining written consent from them, 60 hospitalized patients were selected. These patients had positive RT-PCR or pneumonia confirmed by chest imaging or blood oxygen saturation less than 93% (in room air). Patients were randomly assigned to intervention and control groups. The randomization program was designed and presented by a third party using a computer program using randomized block method. A random sample number was created and each patient was identified with a number. Thirty patients (control group) received common drug recommendations such as azithromycin, hydroxychloroquine, and Kaletra (lopinavir/ritonavir) according to the Ministry of Health guidelines, and another 30 patients (intervention group) received herbal products (nasal spray 2 puffs in each nostril in the morning and evening) in addition to common drugs from the first group during the hospitalization period. Patients were examined on the first, third, seventh, and tenth days by the researcher (a doctoral student in Persian medicine) and were determined and graded based on a checklist. The checklist included 25 questions for clinical symptoms with a rating from zero to five, which had been previously used in other similar trials (9). After data collection, 60 patients who had completed the study program were included in the statistical analysis.

Patients aged 18-75 years of both sexes who had one or more of the following symptoms were included in the study: acute respiratory disease, respiratory rate greater than 30 breaths per minute, oxygen saturation less than 93%, pulmonary infiltration on chest radiography, no intubation, and no concurrent serious heart, brain, lung, or metabolic disease. Patients were excluded from the study if they were pregnant,

breastfeeding, had a history of allergy to herbal products, were unable to take medication, had any condition that prevented the continuation of drug intervention (based on the physician's opinion and decision), had nausea and vomiting, had resistant hypoxemia, had low level of consciousness, and had hemodynamic instability, hypercapnia, and respiratory fatigue (Figure 1).

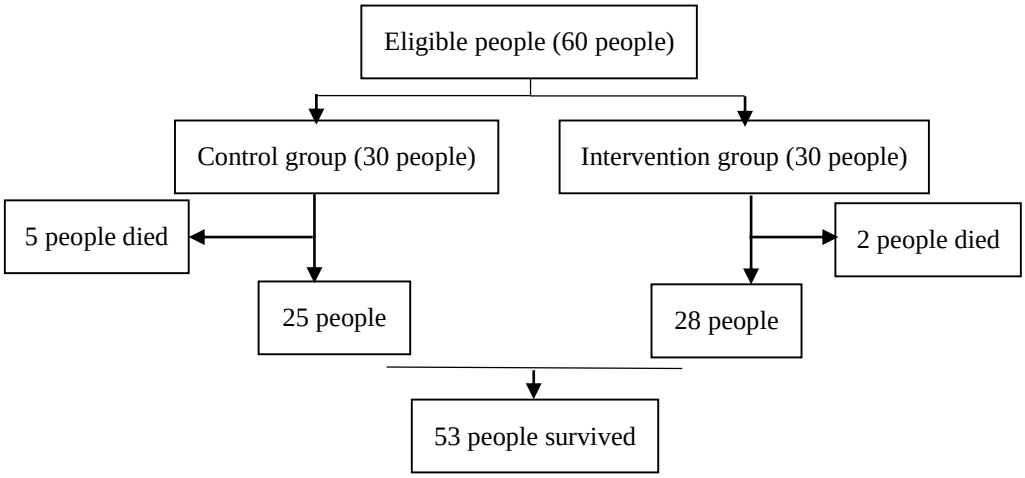

Figure 1. Consort Flow Diagram

The primary clinical issue was the length of hospital stay (from the start of treatment to discharge). To be discharged from hospital, patients must have had fever for at least 24–48 hours without the use of antipyretics, respiratory symptoms such as cough should be improving (sustained cessation of cough), no shortness of breath, and a $SpO_2 \leq 93\%$ without a ventilator, or if it is low, oxygen saturation levels should be stable at an acceptable level ($SpO_2 \geq 90\%$) for two to three consecutive days and do not decline and other discharge criteria must be met (1).

Secondary outcomes included reduction in chest pain, dry cough, fatigue, muscle pain, nausea, cramps, chills, diarrhea, anorexia, shortness of breath, cough with phlegm, and dizziness. These symptoms were determined and evaluated based on a checklist. After data collection, 53 people whose study program had been completed entered statistical analysis. Data were analyzed using SPSS version 21. Variable descriptions were presented as percentages, means, and standard deviations. Quantitative variables were compared between the two groups using independent t-test or its nonparametric equivalent, and qualitative variables were compared between the two groups using the chi-square test or Fisher's exact test.

Results

According to the results, there was no significant difference between the two groups in terms of gender (p=0.602), age (p=0.640), BMI (p=0.882), and underlying disease (p=0.180). The mean length of stay in the intervention group was 2.5 days less than the control group (12.1±6.8 days in the control group and 9.6±7.1 days in the intervention group) (p=0.171). The number of cases admitted to the ICU was 6.7% in the intervention group and 13.3% in the control group. Underlying diseases were 53.3% in the control group and 73.3% in the intervention group. The number of cases of death was not statistically significant but was clinically significant (6.7% in the intervention group and 16.7% in the control group). In the follow-up,

26.7% of the control group and 50% of the intervention group had a complete recovery during the first 7 days after discharge. 30% of the control group still did not feel any improvement after 15 days after discharge, which was zero in the intervention group. At the end of the study, in terms of general condition, 83.3% of the control group and 93.3% of the intervention group had a complete recovery (Table 1). An examination of the improvement of clinical symptoms in discharged patients showed that symptoms of fever, fatigue, chest pain, and cough in the intervention group and symptoms of fever, chest pain, and cough in the control group were completely (100%) resolved at the time of discharge (Table 2).

Table 1. Comparison of epidemiological and clinical characteristics of the study population between the two groups

Variable	Total	Intervention Number(%)	Control Number(%)	p-value Chi-square or) (Fisher's exact test
Gender				
Male	26	12(40)	14(46.7)	0.602
Female	34	18(60)	16(43.3)	
Age group				
<29	3	1(3.3)	2(6.7)	
30-44	9	3(10)	6(20)	0.640
45-59	27	14(46.7)	13(43.3)	
≥60	21	12(40)	9(30)	
BMI				
<25	10	4(13.3)	6(20)	
25-29.9	19	10(33.3)	9(30)	0.882
≥30	31	16(53.3)	15(50)	
Comorbidity				
Yes	36	22(73.3)	14(46.7)	0.180
No	24	8(26.7)	16(53.3)	
ICU admission				
No	54	28(93.3)	26(86.7)	0.036
Yes	6	2(6.7)	4(13.3)	
Discharge status				
Complete recovery	8	7(23.3)	1(3.3)	
Relative recovery	45	21(70)	24(80)	0.044
Death	7	2(6.7)	5(16.7)	
Follow-up				
Complete recovery at discharge	8	7(23.3)	1(3.3)	
Recovery within 7 days after discharge	23	15(50)	8(26.7)	
Recovery 8-15 days after discharge	13	6(20)	7(23.3)	0.100
Recovery 16-29 days after discharge	8	0(0)	8(26.7)	
Having symptoms more than 30 days after discharge	1	0(0)	1(3.3)	
Death	7	2(6.7)	5(16.7)	

Table 2. Rate of improvement in clinical symptoms in discharged patients

Symptoms / Group	No fever		No shortness of breath		No fatigue	
	On the first day Number(%)	On the last day Number(%)	On the first day Number(%)	On the last day Number(%)	On the first day Number(%)	On the last day Number(%)
Control	6(20)	30(100)	2(6)	24(80)	14(47)	29(97)
Intervention	2(7)	30(100)	7(23)	28(93)	14(47)	30(100)
Symptoms / Group	**No chest pain**		**No hypoxia**		**No cough**	
	On the first day Number(%)	On the last day Number(%)	On the first day Number(%)	On the last day Number(%)	On the first day Number(%)	On the last day Number(%)
Control	28(93)	30(100)	5(17)	18(60)	7(23)	30(100)
Intervention	24(80)	30(100)	5(17)	25(83)	8(27)	30(100)

The study of underlying diseases showed that in the intervention group, high blood pressure had the highest frequency (9 people). Similarly, no significant difference was observed between the frequency of diabetes, high blood pressure, cardiovascular disease, thyroid, asthma, mental illness, and digestive problems in the intervention and control groups.

The results of the PCR test were positive in 22 people in the intervention group and 23 people in the control group, and no significant difference was observed between the two groups. The level of Cr. was reported to be normal in most people in the intervention group (24 people) and control (28 people), and no significant difference was observed. The level of BUN was also normal in most people in the intervention group (25 people) and control (23 people), and no significant difference was observed between these two groups. The level of ALT was increased in most people in the intervention group (19 people) and control (19 people), and no significant difference was observed. The level of AST was increased in 16 people in the intervention group and 15 people in the control group. Lymph was decreased in 18 people in the intervention group and 17 people in the control group, and no significant difference was observed between the two groups. WBC was normal in 13 people in the intervention group and 12 people in the control group, and no significant difference was observed between the two groups.

The CT scan results showed that only 3 patients were in a normal state (1 patient from the intervention group and 2 controls). Patients with 25% to 49.9% lung involvement were the most frequent (5 patients from the intervention group and 8 controls). Comparison of the CT scan results in the study population did not show any significant difference between the two groups (Table 3).

Table 3. Comparison of CT scans of the study population between the two groups

Chest CT scan score	Total	Intervention Number(%)	Control Number(%)	p-value Chi-square or) (Fisher's exact test
Normal	3	1(3.3)	2(6.7)	0.106
<25	12	8(26.7)	4(13.3)	0.106
25-49.9	13	5(16.7)	8(26.7)	0.106
50-75	12	9(30)	3(10)	0.106
>75	7	1(3.3)	6(20)	0.106
No CT scan	13	6(20)	7(23.3)	0.106

Discussion

In this study, the mean length of stay in the intervention group was 2.5 days shorter than the control group. Although this was not statistically significant between the two groups, the reduction in length of stay could be clinically significant. In terms of overall condition, 93.3% of the intervention group achieved complete recovery, while 83.3% of the control group achieved complete recovery.

In line with the present study, some studies have reported the use of Mentha longifolia extract in the treatment of clinical manifestations of patients with COVID-19. Silveira et al. described the benefits of Mentha longifolia herbal medicine in the treatment of patients with COVID-19 to be promising (10). In another study, Akbulut mentioned various Mentha longifolia species as one of the preferred herbal medicines for the treatment of COVID-19 symptoms in Central and Eastern Anatolia (11); they only discussed the effectiveness of Mentha longifolia on the clinical manifestations of COVID-19 and did not mention the reduction in the length of hospitalization. In the study by Liu et al., who evaluated the effectiveness of herbal therapy in COVID-19 patients in China, they stated that herbal therapy was reported to relieve some mild clinical symptoms and shorten the length of stay in COVID-19 patients (5).

In the present study, which was conducted as a randomized controlled clinical trial, the highest number of hospitalizations was in the age group of above 45 years. In comparison, the study by Mesgarian et al. showed that the highest number of hospitalizations was in people aged 75 years or older (12). Chen et al. reported the mean age of patients as 55 years (13). The study by Ghavami et al. (14) and the study by Telle et al. (15) showed that age is directly related to hospitalization of patients with COVID-19.

In the present study, the two groups did not differ significantly in terms of BMI, but the highest hospitalization rate was in patients with a BMI greater than 30. In support of this result, the study of Ghavami et al. can be cited. They conducted a review article on factors associated with hospitalization of patients with COVID-19 and found that body mass index was directly related to hospitalization of patients (14). However, Bhasin et al. found no association between body mass index and hospitalization of patients with COVID-19 (16).

In this study, the number of ICU admissions and the number of deaths were higher in the control group and the number of patients discharged with complete recovery was higher in the intervention group. Although this difference was not statistically significant, it is clinically important.

Severe hypoxemia resulted in death in 3 cases in the control group and 0 in the intervention group. This finding of the present study is supported by the study by Maleki et al. They found that the highest mortality rate in patients with COVID-19 was due to severe hypoxia (4).

In this study, life-threatening hypoxemia occurred in seven cases in the control group and zero in the intervention group. The number of patients requiring continuous supplemental oxygen during hospitalization was higher in the control group than in the intervention group. There was no significant difference between the two groups in terms of laboratory findings and prescribed medications. There were more underlying diseases in the intervention group than in the control group. In the follow-up, 26.7% of the control group and 50% of the intervention group had a complete recovery within the first 7 days after discharge. All patients in the intervention group had complete recovery 15 days after discharge. The most common clinical symptoms included fever, shortness of breath, fatigue, cough, chest pain, and hypoxia. An examination of the changes in clinical symptoms after using Mentha longifolia spray showed that in the intervention group, the frequency of people with a fever above 39 degrees centigrade had a decreasing trend. Chen et al. also reported similar clinical manifestations in their study. Fever was the most frequent among the clinical manifestations. Among the patients studied, 11% of them developed acute conditions and became critically ill within a short period of time and eventually died (13). In the present study, the mortality rate due to shortness of breath showed that on the tenth day of follow-up, 1 person in the intervention group

and 3 people in the control group died. The trend of changes in shortness of breath over the 10 days was a decreasing trend. In their study, Babamahmoodi et al. found that the duration of treatment and clinical symptoms, including shortness of breath, were significantly reduced by the use of the herbal medicines Thymus vulgaris, fennel, and Hypericum perforatum (6).

Fatigue assessment in the subjects of this study showed that most of them in the intervention and control groups had mild fatigue that could be relieved with rest. The highest severity of cough and chest pain in the follow-ups was moderate, which showed a decreasing trend. Hypoxia assessment showed that the highest need for intermittent oxygen in patients with oxygen saturation less than 93% was 9 people on the third day, and it was not life-threatening is any of cases and emergency action was not necessary. Previous studies reported similar clinical symptoms in SARS and MERS viral infections (12).

The study of comorbidities showed that hypertension was the most common comorbidity in the intervention group. Heydari et al. reported that comorbidities were common in major hospital admissions. They reported a higher prevalence of headache in patients with stable clinical status than in patients with severe or critical conditions (17). The study of Maleki et al. showed that most patients with COVID-19 who died had an underlying medical condition. High blood pressure, diabetes, and heart problems accounted for the highest percentage of reported comorbidities (4).

According to CT scan results, 73.7% of the patients in the present study had lung involvement. Only 3 patients had normal CT scans (1 in the intervention group and 2 in the control group) and 13 patients had 25% to 49.9% lung involvement (5 in the intervention group and 8 in the control group). Comparison of CT scans of the study population did not show any significant difference between the two groups. In assessment of CT scans of patients with COVID-19 by Godazandeh et al., 39.9% of patients had lung involvement at the time of CT scan (18), compared to 87.5% in the study by Ai et al. (19). Moreover, in a study of CT scan findings of patients with COVID-19 by Shadkam et al., lung involvement was definitely confirmed in 26% of patients, and among confirmed cases of the disease with positive CT, the prevalence of a solitary nodule was determined to be 0.6% in all initially suspected cases and 2.4% for all individuals with a definite diagnosis of the disease with a positive CT scan (20). This difference in statistics can be attributed to the accuracy of the measuring devices, human operator error, and the time of CT scan compared to the time of onset of clinical manifestations.

The present study demonstrated that the use of aqueous extract of Mentha longifolia, along with standard treatment, reduces the length of hospital stay and accelerates the improvement of clinical symptoms in COVID-19 patients. Considering the pharmacological effects of Mentha longifolia, including antiviral, antibacterial, antifungal, analgesic, anti-inflammatory, antioxidant, and spasmolytic activities, as well as the effect of nitric oxide secretion reduction in macrophages and TNFα release reduction, which can be effective in controlling inflammation, it can be recommended as a herbal product for COVID-19 patients. Although conducting this study at the Hospital accepting COVID-19 patients was an advantage due to easy access to patients, the special conditions of the pandemic and the priority of treatment considerations inevitably led to restrictions on entering the wards and cooperation of the medical staff. Repetition of the clinical trial on a larger scale is recommended.

Conflict of Interest: The authors declare that they have no conflict of interest.

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