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Efficacy of herbal tea preparation including mallow flower, chicory seeds, sweet violet, *Melilotus officinalis*, and bindii for improving respiratory symptoms in patients with COVID-19; a randomized controlled clinical trial

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) as a viral disease has now become a public health emergency of international concern and has not yet received an approved treatment protocol. The potential of a phytotherapy approach in the management of this disease and also numerous claims regarding its effect on the recovery of COVID-19 patients has received remarkable attention especially in developing countries.
Objectives: The present study aimed at investigating the efficacy of the combination of bindii, *Melilotus officinalis*, sweet violet, chicory seeds and mallow flower used as an herbal tea for improving respiratory symptoms in patients with COVID-19.
Patients and Methods: The present randomized controlled clinical trial was conducted on 80 patients with COVID-19 that were divided into one control group and one case group. Patients in the control group received only the routine treatment while the case group, in addition to receiving the routine treatment, also received the herbal medicine combination prepared in this study. Then, patients' cough severity and also respiratory symptoms such as the shortness of breath, the percentage of the saturation of peripheral oxygen (SpO2) and the number of breaths were evaluated and recorded daily and then compared between the two groups.
Results: The results of this study revealed that 75% of patients in the case group had no cough at all on the fifth day of the intervention while the cough of only 35% of patients in the control group was completely eliminated ($P<0.001$). In addition, the patients' cough severity, SpO2 and shortness of breath followed up from the intervention onset up to the fifth day after the intervention had a significant improvement in the case group as compared to the control group ($P<0.05$).
Conclusion: According to the results of the present study, the mentioned herbal tea used in this study had a significant effect on improving respiratory symptoms and cough severity in COVID-19 patients. Therefore, it can be stated that the use of herbal compounds, especially the herbal tea introduced in this study, as a complementary treatment can play a significant role in improving the patients' condition.
Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trial (# IRCT20200806048318N1; https://en.irct.ir/trial/50227, ethical code; IR.MUI.MED.REC.1399.359).

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Introduction

Cases of novel coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China on 31 December 2019. Genomic analysis revealed that this novel virus has a high sequence similarity to severe acute respiratory syndrome (SARS) virus and the Middle East respiratory syndrome (MERS) virus discovered in 2003 and 2012, respectively (1). The majority of the 2019 novel coronavirus-(2019-nCoV-) infected cases have symptoms like dry cough, sore throat and fever; however, most of these patients recover spontaneously. In addition, the virus can cause shortness of breath and pneumonia. In the next stage, with the immune system involvement and its exit from the state of equilibrium mediated by the cell membrane receptor, lung damage is seen in the epidermal growth factor receptor (EGFR) and heparin-binding EGF-like growth factor (HB-EGF) in some cases, which lead to the fibrosis and impaired arterial blood gas exchange (2,3). Given the various fatal complications of COVID-19 including organ

Key point

In this study, 80 patients with COVID-19 were divided into two groups. Patients in the control group received only the routine treatment while the case group, in addition to receiving the routine treatment, also received the herbal medicine. The results of this study revealed that the mentioned herbal tea used in this study had a significant effect on improving respiratory symptoms and cough in COVID-19 patients.

failure, septic shock, pulmonary edema, severe pneumonia and acute respiratory distress syndrome (ARDS) and also the economic consequences of the COVID-19 worldwide, many studies have been carried out to offer the appropriate anti-viral medication (4). The vaccines and anti-viral drugs are effective for both the treatment and prevention of the viral infections; however, currently there is no approved treatment or effective vaccine against COVID-19. Development of such therapies to cure or control the disease may take months or even years. It seems that herbs can serve as a potentially valuable source for this purpose. Numerous studies have investigated the efficacy of herbal medicines in treating COVID-19 infection. For example, Zhang et al, in a study on 125 Chinese herbs, reported that these compounds might directly inhibit 2019-nCoV (4-6). One of these herbs is *Viola odorata* L., which is commonly known as sweet violet and is used for treating fever, cough and sleep disorders. This herb has substances such as flavonoids, saponins, mucilage, and vitamin C and has significant anti-oxidant and anti-inflammation effects and also is effectively used in the treatment of tumors. The study of Bigdeli et al revealed the effectiveness of *Viola odorata* L. in treating gastrointestinal and genitourinary tumors by influencing EGFR (7). *Cichorium intybus* L. commonly known as chicory has anti-oxidant and anti-inflammatory properties and also protective effects on liver diseases. The mentioned plant is proven to have anti-proliferative and anti-fibrotic effects by reducing the EGFR activity (8). In addition to affecting EGFR, *Malva sylvestris* L. (Malvaceae) has anti-inflammatory, anti-oxidant and anti-viral effects (9, 10). Similarly, *Melilotus officinalis* has strengthening and anti-inflammatory effects. The study by Aggarwal et al indicated that this plant has anti-proliferative, anti-inflammatory and anti-cancer effects by reducing the activation of human epidermal growth factor receptor 2 (HER2), EGFR and tumor necrosis factor (TNF) (8). *Tribulus terrestris* L. (Bindii) has long been used for reducing inflammation of mouth reduces the temperature of body and helps stop bleeding. The chemical composition of this plant contains alkaloids, a small amount of volatile essential oil, some fixed oils, resins and nitrates. This plant has a variety of anti-cell growth, anti-bacterial and anti-viral effects that contribute to reducing the growth of solid tumor cells (11). In Iran, several studies have been conducted on plants such as thyme, pomegranate, chamomile, jujube, mint, licorice, turmeric, rosa canina extract, chicory, nettles, broadleaf plantain and purslanes; however, no results have been reported yet.

Objectives

Therefore, the very aim of the present study was to investigate the efficacy of herbal tea preparation including chicory seeds, *melilotus officinalis*, sweet violet, bindii and mallow flower in improving respiratory symptoms in patients with COVID-19.

Patients and Methods

Study design

The present randomized controlled clinical trial was conducted on all patients with COVID-19 that referred to Shafa specialized hospital (Kalishad and Sudarjan) Baharestan, Kalishad, Isfahan, Iran, during 2020. Around 80 ones were randomly selected to participate in the pilot study. The inclusion criteria were as follows: (*i*) having the positive result of polymerase chain reaction (PCR) test or moderate COVID-19 diagnosis confirmed by computed tomography (CT) scan according to international standards with moderate COVID-19 who received herbal tea via oral gavage, (*ii*) age range of 15 to 60 years and (*iii*) providing the written informed consent to participate in the study. Moreover, patients with the blood pressure of less than 90/40 mm Hg, a heart rate (HR) of equal or more than 30/min, the resting blood oxygen saturation level of 93% or less, the PaO2-to-FiO2 ratio of less than or equal to 300 mm Hg, more than 50% of exudative lesions demonstrated in lung images within 24-48 hours, pregnant patients and patients with diseases such as Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), neuromuscular disorders and myasthenia gravis were excluded from the study. In addition, the patients were excluded from the study in case of their unwillingness to continue their participation in the study and worsening of their condition based on physician's diagnosis; however, no case was excluded from the present study. After obtaining written consent from eligible patients, they were randomly divided into one case group and one control group, each consisting of 40 patients (Figure 1). The patients' demographic information including gender, age, body mass index (BMI), cigarette smoking status, comorbidities such as diabetes, hypertension, cardiovascular disease, kidney diseases, lung diseases, cancer and neurological diseases and also the duration of their symptoms before the first medical visit were recorded. Furthermore, the patients' clinical information including early symptoms and clinical manifestations such as body temperature, shortness of breath, HR and saturation of peripheral oxygen (SpO2) were reordered. Patients were requested to grade their cough severity based on the following scale; 0; no cough; 1; a tickling sensation in the throat; 2; mild cough that did not interfere with daily activities; 3; moderate cough that was tolerable but severe enough to interrupt activities for some time; and 4; severe cough that persisted, interfered with daily activities and disturbed

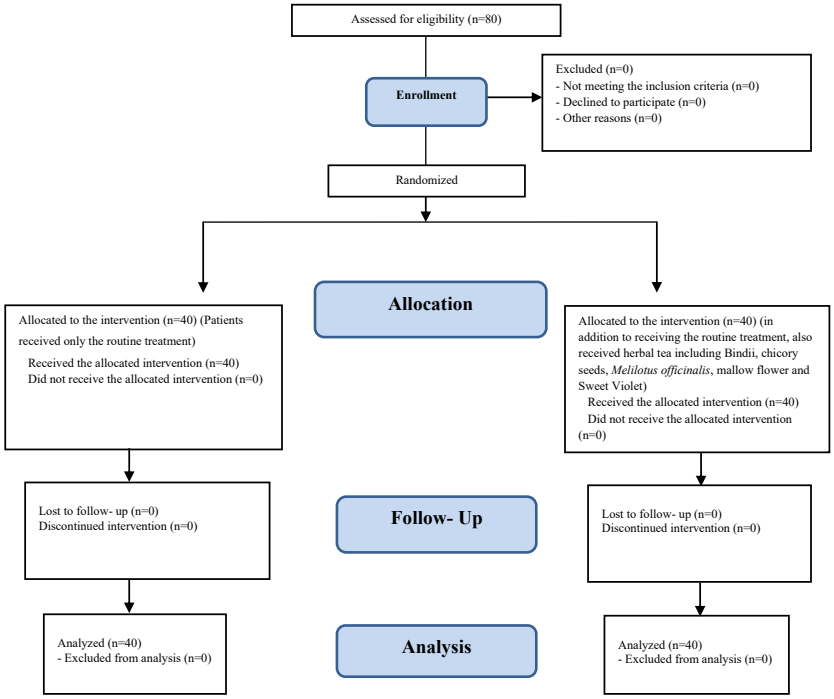

Figure 1. Consort flowchart of patients.

sleep at night. In addition to scoring the cough severity, the cough frequency score (0-10) was measured using the following visual analog scale; 0=I never cough; 10=I cough throughout the day. The control group received only the routine treatment while the case group, in addition to receiving the routine treatment, also received herbal tea including bindii, chicory seeds, *Melilotus officinalis*, mallow flower and sweet violet. To prepare the herbal tea, a jam spoon (equivalent to 5 g of the prepared herbal composition powder) with a cup of boiling water (equivalent to 150 cc) was brewed for 25-30 minutes. The prepared tea was given to the patient for five days half an hour after lunch. The patients' body temperature on a daily basis, cough severity, shortness of breath, SpO2 and number of breaths per day were reordered by the treatment team during the intervention. In addition, the length of stay in hospital and patient outcomes including recovery, deterioration or death were recorded after the intervention. The patient outcomes were assessed by the nursing team under the supervision of a head nurse that was not aware of the type of the therapeutic intervention used in this study; however, the researcher was aware of the type of therapeutic intervention because of different treatment methods. It should be noted that the prepared herbal tea in this study has not been used in any previous clinical trials, while the most frequently-reported side effect in this respect was allergic skin reactions according to physicians' desk reference (PDR) for herbal medicines. Moreover, there is no specific study addressing the interactions between the components in the herbal tea and other drugs. Furthermore, the risk of QT interval prolongation on electrocardiogram (ECG) and other specific changes in ECG components were not reported following the use of the components of the prepared herbal tea.

Statistical analysis

Statistical analysis was conducted by Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, Illinois, USA). Data were presented as means ± standard deviation (SD) and percentage (%). Chi-square test, independent samples *t* test and the repeated measures analysis of variance (ANOVA) were employed to analyze the data. *P* value less than 0.05 (typically ≤ 0.05) was considered to be statistically significant.

Results

In the present study, there were 15 males (37.5 %) and 25 females (62.5 %) with the mean age of 48.95 ± 11.73 years in the case group. The control group included nine males (22.5%) and 31 females (77.5%) with the mean age of 50.27 ± 9.63 years ($P > 0.05$; Table 1).

Regarding the severity of cough, 15% of patients in both the control and case groups had no cough at all before the intervention. Moreover, on the fifth day of the intervention, 35% and 75% of patients had no cough in the control and case groups, respectively. Both groups indicated significant improvements; however, the severity of cough significantly decreased in the case group as compared to the control group ($P < 0.001$; Figure 2).

Moreover, there were no significant differences between the two groups with respect to the mean body temperature,

Table 1. Basic and clinical characteristics of patients in two groups

Variables	Control group	Case group	*P* value
Gender			
Male	9 (22.5%)	15 (37.5%)	0.143
Female	31 (77.5%)	25 (62.5%)	
Age(year)	50.27±9.63	48.95±11.73	0.584
Comorbidities			
Kidney disease	0 (0.0%)	1 (2.5%)	0.314
Thyroid disease	0 (0.0%)	2 (5.0%)	0.241
Diabetes	14 (35.0%)	12 (30%)	0.812
Hypertension	8 (20.0%)	9 (22.5%)	0.785
Heart disease	4 (10.0%)	5 (12.5%)	0.732
Lung disease	0 (0.0%)	1 (2.5%)	0.314
Asthma disease	2 (5.0%)	4 (10.0%)	0.675
Nervous disease	1 (2.5%)	0 (0.0%)	0.314
Mastectomy/breast cancer	1 (2.5%)	0 (0.0%)	0.314
Smoking	1 (2.5%)	4 (10%)	0.346
Height(cm)	163.12±5.76	166.05±9.38	0.098
Weight(kg)	74.72±10.91	78.08±12.18	0.201
BMI(kg/m^2)	28.29±4.39	28.33±4.21	0.976
Interval between the onset of symptoms and the first medical visit (day)	8.80±3.13	9.40±2.11	0.318

cough severity, SpO2, respiratory rate (RR), and shortness of breath before the intervention ($P>0.05$). On the fifth day of the intervention, no significant difference was observed between the two groups in terms of the mean body temperature ($P>0.05$). However, the severity of cough, SpO2, RR, and shortness of breath significantly improved in the case group as compared to the control group on the fifth day of intervention ($P<0.05$). In addition, the shortness of breath in the case group was significantly lower than that of the control group on the third day of the intervention ($P<0.001$; Table 2).

Additionally, no significant differences were figured out between the two groups with respect to the length of hospital stay and patient outcomes ($P>0.050$). Furthermore, none of the patients had complications after the intervention (Table 3).

Discussion

Natural products and herbal medicine have long been taken into account in the treatment of respiratory infection. Majority of the mentioned products are approved as non-prescribed drugs and nutritional or food additives. Generally, these products are satisfactory and safety. For a long-term use, they are ideal prophylactic candidates due to their minimal toxicity. Recently, an *in silico* experiment has figured out that a category of natural products is so effective in the blockage of the enzyme function and the receptors existing on the membrane of the human coronavirus (12).

The COVID-19 is an enveloped positive-strand RNA virus. Recent investigations have revealed its phylogenetic relation with the SARS coronaviruses (13). Previously, many plant extracts were examined and the most

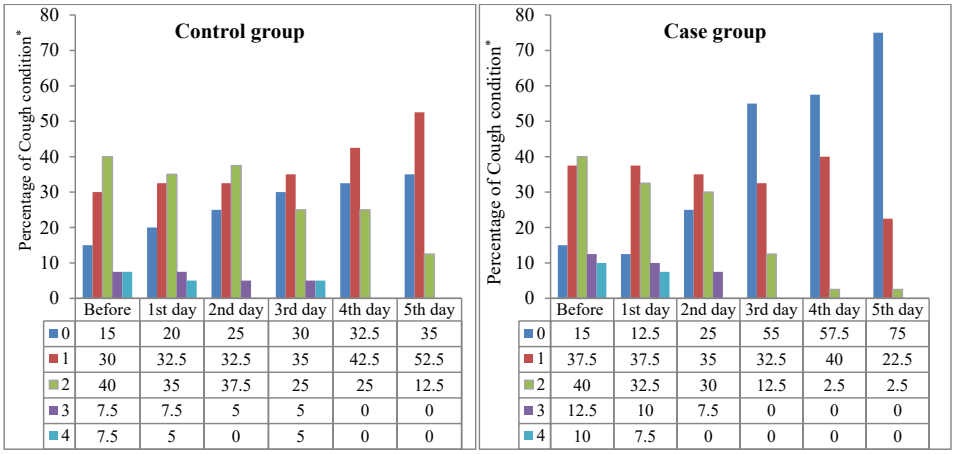

Figure 2. Percentage of cough condition in patients at the time of study between the two groups. * Severity of cough was defined as: 0: no cough; 1: a tickling sensation in the throat; 2: mild cough that did not interfere with daily activities; 3: moderate cough that was tolerable but severe enough to interrupt activities for some time; and 4: severe cough that persisted, interfered with daily activities, and disturbed sleep at night.

Table 2. Comparison of clinical symptoms and hemodynamic parameters of patients at different times between the two groups

Variables	Control group	Case group	P_1
Body temperature °C			
Before intervention	36.68±0.40	36.65±0.45	0.753
First day	36.65±0.44	36.63±0.48	0.923
Second day	36.56±0.46	36.57±0.43	0.901
Third day	36.53±0.37	36.49±0.47	0.755
Fourth day	36.57±0.41	36.45±0.28	0.166
Fifth day	36.45±0.27	36.44±0.37	0.931
P_2	0.115	0.164	
Intensity of cough (score)			
Before intervention	5.07±3.01	6.09±2.68	0.851
First day	4.72±2.48	5.95±2.41	0.024
Second day	4.11±2.04	3.09±2.41	0.044
Third day	3.85±2.12	2.92±1.75	0.033
Fourth day	3.38±1.94	2.10±1.09	<0.001
Fifth day	2.69±1.47	2.00±1.47	0.039
P_2	<0.001	<0.001	
SpO2 (%)			
Before intervention	85.00±4.16	82.99±5.17	0.061
First day	86.60±3.46	83.67±4.72	0.001
Second day	86.35±4.32	89.23±3.14	0.003
Third day	87.23±3.59	91.05±2.38	<0.001
Fourth day	87.85±3.48	92.49±2.19	<0.001
Fifth day	89.45±2.33	93.87±1.99	<0.001
P_2	0.011	<0.001	
Reparatory Rate (bpm)			
Before intervention	27.99±4.61	28.11±4.02	0.901
First day	26.08±4.90	28.38±4.82	0.030
Second day	26.10±4.95	23.97±3.78	0.025
Third day	26.08±3.90	28.38±4.82	<0.001
Fourth day	25.68±3.60	21.44±2.92	<0.001
Fifth day	24.05±3.71	19.85±2.09	<0.001
P_2	<0.001	<0.001	
Shortness of breath			
Before intervention	38(95%)	40(100%)	0.658
First day	37(92.5%)	40(100%)	0.241
Second day	37(92.5%)	35(87.5%)	0.456
Third day	38(95.0%)	15(37.5%)	<0.001
Fourth day	32(80.0%)	6(15.0%)	<0.001
Fifth day	27(67.5%)	2(5%)	<0.001
P_2	<0.001	<0.001	

* Severity of cough was defined as: 0: no cough; 1: a tickling sensation in the throat; 2: mild cough that did not interfere with daily activities; 3: moderate cough that was tolerable but severe enough to interrupt activities for some time; and 4: severe cough that persisted, interfered with daily activities, and disturbed sleep at night.

Table 3. Comparison of the frequency distribution of patient outcome and hospitalization between the two groups

Variables	Control group	Case group	*P* value
Outcome			
Recovery	38 (95.0%)	39 (97.5%)	
Worsening of the disease	2 (5.0%)	1 (2.5%)	0.143
Death	0 (0%)	0 (0%)	
Hospitalization(day)	9.30±3.82	9.20±4.23	0.912

remarkable effect on the ACE inhibition was principally observed up to 100% in relation to Alef., *Rubia tinctorum* L., Moench, *Alcea digitata* (Boiss.), and *Cerasus avium* L., *Berberis integerrima* Bge., *Peganum harmala* L., *Allium sativum* L., and *Citrus aurantium* L. were also found to have a similar effect up to 70% or more in this regard (6). Therefore, after conducting the necessary in-vitro and in-vivo evaluations, it could be suggested that the mentioned herbal products or the ones with similar mechanisms might be considered for fighting against the COVID-19 outbreak. Furthermore, it is worth noting that ACE inhibitors may result in the up-regulation of the receptor and increase the COVID-19 infection susceptibility in the long run.

The use of moderate doses of such bioactive compounds can prevent or at least decrease the infection process of SARS-CoV-2. Additionally, as the progression of COVID-19 is associated with an uncontrolled inflammation leading to cytokine release syndrome, the use of anti-inflammatory herbs can be an effective choice to suppress such a deadly symptom (14).

The current study was performed on 80 COVID-19 patients and investigated the efficacy of herbal tea preparation (including bindii, *Melilotus officinalis*, sweet violet, chicory seeds, and mallow flower) in improving target patients' respiratory symptoms. It has been approved that the Iranian herbal medicine has substances such as flavonoids, saponins, mucilage, and vitamin C with the significant anti-oxidant and anti-inflammatory effects.

At present, herbal medicines play a key role in preventing and treating many diseases such as the novel coronavirus. Through the recent SARS-COV outbreak, the traditional Chinese medicine (TCM) has been widely applied in China. Lonicerae Japonicae Flos, Atractylodis Macrocephalae Rhizoma (Bai Zhu), Saposhnikoviae Radix (Fangfeng), Astragali Radix (Huangqi), and Glycyrrhizae Radix et Rhizoma (Gancio) were the five most famous applied herbal plants (15,16).

The significant effects of herbal medicine in combination with Western medicine have been evaluated in a meta-analysis that showed the impact of the combined therapy on the total effective rate, the disappearance rate (cough and sputum production), the TCM syndrome score (cough, fatigue, dry and sore throat, and fever), and the complete blood count (C-reactive protein, white blood cell and lymphocyte counts, procalcitonin level, and lymphocyte percentage). The findings of the mentioned study were in line with the results of the present study (5).

Two studies evaluated the disappearance rate of the respiratory symptoms between the two groups of patients. One study reported significant improvements in the disappearance rate of cough and sputum production after the intervention. Improvements in the disappearance rate of fever, fatigue, cough, sputum production, and diarrhea were also significantly observed after the intervention in another study. In a meta-analysis, the significant effect of

the combined herbal therapy on the disappearance rate of cough and sputum production was reported (17-19).

The symptom score measured using the TCM syndrome score was addressed in a review study and assessed in four studies (19,20). Regarding the total syndrome score, one study reported promising results with respect to the use of the combined therapy of herbal medicine with Western medicine (5). A similar finding was reported in the other three studies; however, they only reported the syndrome score for various clinical symptoms.

The current study supports the strong evidence regarding the herbal medicine as a potentially-effective anti-viral agent to prevent COVID-19. The results of this study revealed significant improvements of the symptoms in both groups; however, the use of herbal tea significantly reduced the severity of cough in the case group as compared to the control group. Moreover, the severity of cough, SpO2, RR and shortness of breath were improved on the fifth day of the intervention. In addition, the shortness of breath in the case group was significantly lower than the control group on the third day of the intervention. The presented results showed that the Iranian herbal medicine can also be as effective as TCM. Therefore, different geographical areas and the availability and also the acceptability of the used plants should be attended to in pertinent studies.

There are a wide variety of foods and herbs that are characterized by their anti-viral and immunomodulatory properties. For instance, *Angelica gigas* (Korean angelica), *Astragalus membranaceus* (Mongolian milkvetch), *Aloe vera, Panax ginseng* (ginseng), *Scutellaria baicalensis* (Chinese skullcap) and *Ganoderma lucidum* (lingzhi mushroom) have been reported to show immunomodulatory activities (21). They act based on the selective stimulation of cytokines, the activation of lymphocytes, the increase of natural killer cell counts and the strengthening of the macrophage actions. Some other herbs such as wheat bran, *Echinacea purpurea* (Eastern purple coneflower), *Rice bran, Lawsonia alba* (hina), *Cissampelos pareira* Linn (velvetleaf), and *Plumbago zeylanica* (Ceylon leadwort) are also recognized to have immunomodulatory properties by stimulating phagocytosis. Improving the innate cell-mediated immune response is reported following the use of eucalyptus essential oil that may be applied as an immunomodulatory agent for treating infectious diseases (15,16). The use of these immunomodulatory foods and herbs collectively could improve the immune system and help the body to fight against COVID-19. However, it is essential to conduct more scientific or clinical studies to verify these observations (22).

Recent academic viewpoints discuss that the potential of herbal medicine as an appropriate therapy for COVID-19 is questionable as the medicinal mechanism of these plants is undecided and challenging to be fully investigated (23). Several recent clinical studies have demonstrated that herbal medicines abundant in flavonoid compounds have an anti-viral function in some human lung cell lines (24). Thus, further studies should be conducted to examine the underlying mechanisms and identify active ingredients for obtaining a more effective and preventive application of medicinal plants.

An herbal formulation suggested by the National Health Commission (NHC) of the People's Republic of China was evaluated in a clinical case in March 2020 and was found to be effective in reducing ARDS in a mild COVID-19 patient (25). It was for the first time to show the potential benefits of herbs in the treatment of COVID-19. The frequent use of herbal medicines in China during the COVID-19 pandemic has been more recently summarized in several systemic reviews and meta-analysis to illustrate its therapeutic outcome (4). Xiong et al concluded that bitter apricot seed (*Prunus armeniaca* L., Pinellia Rhizome [*Pinellia ternata* (Thunb.)], Makino Liquorice Root (*Glycyrrhiza glabra* L), forsythia fruit [*Forsythia suspensa* (Thunb.) Vahl], and Baical skullcap root (*Scutellaria baicalensis* Georgi) are the most frequently prescribed herbs among the widely distributed herbal medicines. The mentioned meta-analysis suggested that herbal medicines are effective in the prevention of the disease progression from mild to critical, the reduction of hospitalization rate, the decrease of the length of hospital stay and the ease of COVID-19-associated symptoms such as fever, cough, fatigue and inflammation (26).

Although herbal medicines might be useful agents for treating COVID-19 patients according to the conducted studies, no significant differences were observed between the two groups with respect to the length of stay in hospital and patient outcomes since no complications were reported after the intervention in our study. Considering the obtained findings, it is still not recommended to take supplements containing one of these compounds to prevent or cure the COVID-19 disease without consulting with a specialist or being under a physician's direct supervision. Clinicians are suggested to cautiously administer these herbal medicines due to various inconsistent findings regarding these agents. Therefore, it is possible that the proposed herbal-based treatment may be associated with some harmful effects. Since, preclinical and clinical trials addressing the effect of herbal medicines on COVID-19 have not been widely conducted, further studies are warranted in this regard.

Conclusion

The results of the present study demonstrated that although both groups had a significant improvement, respiratory symptoms were significantly improved in the case group as compared to the control group. Moreover, the severity of cough was significantly decreased in the case group as compared to the control group. Therefore, administration of herbal tea, especially as it was prepared in this study is recommended. This medicine can be used as a complementary therapy in addition to the current treatment protocols used for patients with COVID-19.

Limitations of the study

One of the limitations of the current study was the evaluation of the patients' cough severity during the intervention. It was suggested that future studies evaluate the effectiveness of this herbal tea in the long-term and after discharge from the hospital.

Authors' contribution

MM, MB and ME were the principal researchers of the study. ME participated in preparing the concept and design of the study. ZV and ZV revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the study.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical issues

The research was conducted based on the tenets of the Declaration of Helsinki. The ethics committee of Isfahan University of Medical Sciences approved this study (IR.MUI.MED.REC.1399.359). Accordingly, written informed consent was obtained from all participants before the intervention. The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20200806048318N1; https://irct.ir/trial/50227). Additionally, ethical issues including plagiarism, data fabrication, and double publication have been completely observed by the authors.

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