Research Article

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The effects of combination of *Zingiber officinale* and Echinacea on alleviation of clinical symptoms and hospitalization rate of suspected COVID-19 outpatients: a randomized controlled trial

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Abstract

Objectives: Herbal medicines, as a treatment method, have received a great deal of attention. The effects of two herbal medicines namely *Zingiber officinale* and Echinacea on alleviation of clinical symptoms and hospitalization rate of suspected COVID-19 outpatients were examined.

Methods: A clinical trial with 100 suspected COVID-19 outpatients as participants was conducted. The participants were allocated randomly to two groups of 50 members. The intervention group received concurrent *Zingiber officinale* (Tablet Vomigone 500 mg II tds) and Echinacea (Tablet Rucoldup I tds) for seven days in addition to the standard treatment. The control group only received the standard treatment (Hydroxychloroquine). After seven days, alleviation of clinical symptoms and hospitalization rate were examined. In addition, 14 days after treatment, the hospitalization was assessed again by telephone follow up.

Results: The two groups were identical in terms of basic characteristics. Improvement level as to coughing, dyspnea, and muscle pain was higher in the intervention group (p value <0.05). There was no significant difference between the two groups in terms of the other symptoms. In addition, the hospitalization rate in the intervention and control groups were 2 and 6% respectively, which are not significantly different (p value >0.05).

Conclusions: Taking into account the efficiency and trivial side-effects of *Zingiber officinale* and Echinacea, using them for alleviation and control of the clinical symptoms in COVID-19 outpatients is recommended.

Keywords: clinical symptoms; COVID-19; Echinacea; hospitalization rate; outpatients; *Zingiber officinale*.

Introduction

The pneumonia caused by COVID-19 has become a global highly infectious disease so that the virus is a serious threat to public health [1]. The World Health Organization declared the wide spread of the disease as a public health emergency. The virus responsible for the 2019–2020 pandemic is highly similar to severe acute respiratory syndrome (SARS). This contagious disease spreads through respiratory droplets and the common clinical symptoms are fever, dry cough, and tightness of breath that may lead to pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and multiple organ failure. Aged individuals with background conditions (e.g. asthma, diabetes, and heart failure) and weak immunity system are at more risk of infection by the virus [2–4].

Fighting the virus as an international emergency is seriously pursued in all countries. There is a bitter fight between the virus and human intelligence and brain power and winning this fight, along with taking protective and personal hygiene measures, entails taking proper control and timely therapeutic measures [5].

Most COVID-19 cases present influenza-like symptoms, and are hence eligible for outpatient or primary care management in first instance. However, most studies to date have focused on inpatient COVID-19 cases [6].

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There is no specific anti-virus medicine for coronavirus and preservative cares including preserving vital signs, oxygen and blood pressure regulation, and alleviating the symptoms are the major approaches to treat the disease [7].

Herbal medicines, today, are considered as a way for treatment and preservation of health. Easy access and low prices of these medicines have added to the popularity of these medicines mostly in the developing countries. According to the National Administration of Traditional Chinese Medicine (NATCM), 90% of COVID-19 patients who received Qing Fei Pai Du Tang herbal medicine (a mixture of ginger, belamcanda, dioscoreae, glycyrrhiza glabra, etc.) showed positive responses to the treatment [8].

Among herbal medicines, Echinacea has been used for centuries for common cold, cough, bronchitis, upper respiratory system infection, and other inflammations. Studies have shown that Echinacea and its active compounds affect phagocyte immune system. Still, they do not affect special immune system. The medicine is used for viral, bacteria, radiation, and fungous infections. In addition, it is used as an anti-inflammatory [9]. Echinacea affects the immunity system from several aspects including increasing the count of white blood cells in the blood circulation system. Echinacea also improves phagocyte, improves lymphocytes activities, stimulates cytokine generation, and alleviates apoptosis. It stimulates macrophage activity and release of tumor necrosis factor (TNF), interleukin-1, interleukin-6, and interferon *in vitro* [10].

However, contradictory results have been published regarding the effect of Echinacea on increasing cytokines. In one study Echinacea increase significantly TNFa [11], whereas no effect on TNFa was for Echinacea in another study [12]. Also, in another study results support the Echinacea preparations are capable of neutralizing the virus-induced elevation in secreted chemokines and other cytokines and reversed the viral stimulation, thus providing a basis for the anti-inflammatory properties attributed to Echinacea [13].Contradictory results were obtained in cytokine, possibly due to different preparation used production[14].

There are also reports of antivirus activity against influenza, herpes simplex virus, and poliovirus. Phenol compound in Echinacea also demonstrates antioxidant activities [15].

Ginger is a key spice and a herbal medicine that is widely used. Suppressing synthesis of some of Proinflammatory cytokines such as interleukin-1, interleukin-8, and tumor necrosis factor alpha (TNF-alpha) are some of the effects of ginger. It also suppresses responses derived from T-helper1 activity [16].

A study showed that a mixture containing *Zingiber officinale* and *Althaea officinalis* extracts alleviated coughing, and the acute tracheitis-induced chest pain in patients [17]. Moreover, studies have shown that *Zingiber officinale* has anti-inflammatory effects and it is used for the treatment of arthritis rheumatoid and osteoarthritis [18, 19]. It was shown in [20] that *Zingiber officinale* was effective in alleviating asthma symptoms, although, it did not change the disease stage or spirometric indices.

Taking into account the potential effects of *Zingiber officinale* and Echinacea on alleviation of clinical symptoms in respiratory diseases, the study tries to examine the therapeutic effects of these two herbal medicines on hospitalization rate and the symptoms in suspected COVID-19 outpatients.

Methodology

Study design

The study was carried out as a randomized, controlled clinical trial with two parallel arms. The study site was an urban community health center in Saveh, Iran.

Study participants

Study population comprised all individuals with suspicious COVID-19 who needed outpatient treatment. Suspicious COVID-19 outpatients identified base on positive chest CT scan/X-ray and clinical symptom for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It should be noted that during the early phase of the COVID-19 epidemic in Iran, outpatients with good general appearance were identified and treated based on clinical symptoms and radiologic findings. However, RT-PCR testing is currently performed in all suspected patients. The inclusion criteria were suspicious COVID-19 outpatients based on COVID-19 diagnosis and treatment flowchart by the ministry of health of Iran, age range 18–65, and signing an informed consent form. The exclusion criteria were pregnancy, breastfeeding, history of pharmaceutical allergy, complicated cases of bacterial infections, background disease (heart disease, hypertension, diabetes, renal failure, liver failure, cardiovascular cerebrovascular diseases, chronic pulmonary disease, malignancy, endocrine and metabolic diseases, thyroid disorders, any immune system problem, encephalopathy, and neuropathy).

Sample size estimation

The sample size was determined based on a pilot study and the formula for comparing two proportions. Accordingly, with a confidence level of 95% and a power of 80%, a sample of 45 patients per group was identified. Yet, considering an attrition rate of 10%, the sample size was expanded to 50 per group or one hundred in total.

n = sample size required in each group,
p1 = proportion of subject cured in treatment group = 0.9
p2 = proportion of subject cured in control group = 0.7
d = clinically significant difference = 0.23
Zα/2: on level of significance for 5% = 1.96
Zβ: power for 80% = 0.84

$$N = \frac{(1.96 + 0.84)2 \times \{(0.9 \times 0.1) + (0.7 \times 0.3)\}}{(0.23)^2} = 45$$

Randomization

Fifty participants were selected for each group so that 100 suspicious COVID-19 patients under the diagnosis and treatment protocol of the ministry of health for COVID-19 entered the study. The participants were allocated to two groups through block randomization method with a block size of six (n=10) and four (n=10) using a computer program. We used the Sequentially Numbered Opaque Sealed Envelope method (SNOSE) method for allocation concealment.

Intervention

In the intervention group, the patients received oral *Zingiber officinale* and Echinacea herbal medicines for seven days along with the standard treatment. In the control group, the 50 patients only received the standard treatment (Hydroxychloroquine). The patients and attending physician knew about the intervention group, while the author in charge of analyzing the data was blind to the groups. The two herbal medicines were prescribed for free as follows: *Zingiber officinale* (Tablet Vomigone 500 mg II tds, Dineh Iran Pharmaceutical Company, Iran Registration Code (IRC): 9406633051781240) and Echinacea (Tablet Rucoldup I tds, Ghaem Darou Pharmaceutical Company, IRC: 6563916081842893). The tool used in this study was a two-section questionnaire including demographical information and clinical information (fever, sore throat, coughing, and the like) and hospitalization rate. Monitoring the patient's clinical condition and daily taking of medicines was assessed by telephone follow up.

Outcome measures

The main outcome in this study was alleviation of clinical symptoms and the secondary was hospitalization rate. After seven days of intervention, the clinical symptoms (fever, coughing, muscle pain, difficulty breathing, and sore throat) and hospitalization rate were checked through telephone call or visiting the patients if necessary. In addition, 14 days after the start of treatment, the hospitalization was assessed again by telephone follow up.

Statistical analysis

The collected data was analyzed using SPSS 19 (SPSS, Inc., Chicago, IL, USA). After testing the normality of data with Kolmogorov–Smirnov test, independent samples t-test and Chi-square for baseline characteristics and analysis of variance tests for outcomes variables were used in the statistical analysis. p-value < 0.05 was considered significant.

Ethical considerations

The study was approved by the Institutional Review Board and the Ethics Committee of Saveh University of Medical Sciences, Saveh, Iran (approval code: IR.SAVEHUMS.REC.1399.004) and registered in the Iranian Registry of Clinical Trials (Registration code: IRCT20200415047089N1). All participants were informed about the study objectives, their freedom to participate in or withdraw from the investigation at any time, and the confidential management of their data and participants were given an opportunity to ask questions for clarification. Then, written informed consent was obtained from the patients prior to the beginning of the study.

Results

A total of 139 patients were screened for eligibility from April 2020 to June 2020. The whole trial was proceeded according to the Flow Chart (Figure 1).

The rate of adherence to drug treatment by patients participating in the study was complete. No specific side effects were reported during the study.

At baseline there were no statistically significant differences between the two groups in terms of the demographic characteristics (Table 1).

Baseline clinical symptoms for the 100 participants were evaluated (Table 2).

As shown in Table 2, all clinical symptoms of the two groups except cough were not significantly different at the beginning of the study. Because in data analysis, the rate of symptom improvement is compared in two groups, the difference in the frequency of cough in the two groups has no effect on the results.

Comparison of alleviation of clinical symptoms in control and treatment groups are presented in Table 3. In general, the results showed that the level of alleviation of coughing, muscular pain, and shortness of breath in the intervention group was better than that in the control group. There was no significant difference between the two groups in terms of other variables.

As shown in Table 3, 97.6% of patients in the intervention groups and 78.8% of the patients in the control groups had alleviated coughing problems after one week of the treatment. Chi squared test showed that this difference was significant (p value = 0.009) so that the rate of improvement of coughing problem in the intervention group was higher. The alleviation rate of muscle pain was 96%in

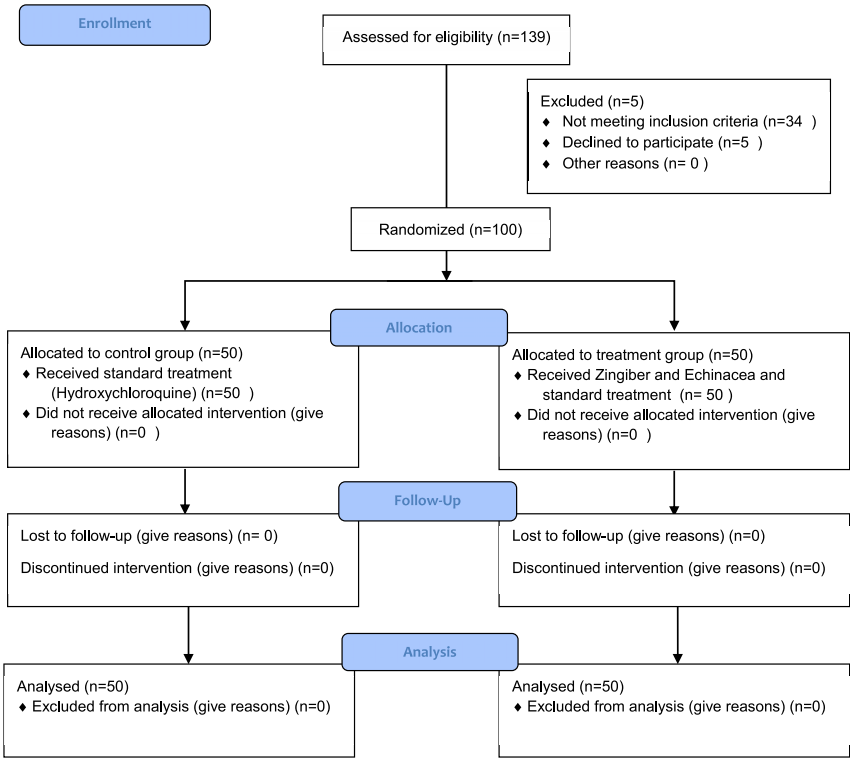

Figure 1: Flow-chart of study randomization, allocation, follow-up, and analysis.

Table 1: Distribution of baseline demographic of patients by group.

Groups characteristics	Control		Treatment		p-Value
	n	%	n	%	
Gender					
Female	21	42	19	38	>0.05
Male	29	58	31	62	
Age					
Mean ± SD		45.46 ± 13.46		47.1 ± 15.53	>0.05
Weight					
Mean ± SD		77.34 ± 11.2		78.57 ± 10.11	>0.05
<B>BMI</B>					
Mean ± SD		24.98 ± 3.02		25.11 ± 2.97	>0.05
Days spent from beginning illness					
Mean ± SD		1.14 ± 0.75		1.28 ± 0.65	>0.05

the intervention group and 76.47% in the control group, which was also statistically significant (p value = 0.009). Also, 91.17% of patients in the intervention groups and 69.23% of the patients in the control groups had alleviated shortness of breath problems after one week of the treatment, which was statistically significant (p value = 0.02).

Table 4 lists the hospitalization rate in the two groups 14 days after the start of treatment.

As the results showed, hospitalization rate in the control and intervention groups was 6 and 2% respectively. Although, this rate was lower in the intervention groups, Chi squared test did not support a significant difference (Chi squared = 1.04, p value = 0.3).

Discussion

To the best of authors' knowledge, this study is the first of its kind to survey the effects of Echinacea and *Zingiber officinale* in suspected COVID-19 outpatients. The results

Table 2: Frequency of clinical symptoms in control and treatment groups in the baseline.

	Control group		Treatment group		p-Value
	n	%	n	%	
Fever	8	16	15	30	0.09
Coughing	33	66	42	84	0.03
Muscle pain	34	68	25	50	0.06
Shortness of breath	39	78	34	68	0.26
Sore throat	12	24	16	32	0.37

Table 3: Comparison of alleviation of clinical symptoms in control and treatment groups.

	Control group		Treatment group		Chi^2	p-Value
	n	%	n	%		
Fever	7	87.5	14	93.33	0.22	0.63
Coughing	26	78.78	41	97.61	6.87	0.009
Muscle pain	26	76.47	24	96	4.25	0.03
Shortness of breath	27	69.23	31	91.17	5.39	0.02
Sore throat	10	83.33	15	93.75	0.37	0.77

Table 4: Hospitalization rate in in control and treatment groups.

Hospitalization						
	Yes		No		Total	
	n	%	n	%	n	%
Control	3	6	47	94	50	100
Treatment	1	2	49	98	50	100

showed that adding the Echinacea and *Z. officinale* to the standard treatment protocol attenuated some of the clinical symptoms (coughing, shortness of breath, and muscle pain) in the subjects. Still, the hospitalization rate was not significantly changed.

In previous studies, researchers used Echinacea and ginger to treat respiratory diseases, separately. Echinacea shows *in vitro* antivirus activity against influenza virus and traditionally it is used to treat common cold and influenza [21, 22]. For instance, a study reported that Echinacea was as effective as oseltamivir in shortening the treatment duration of influenza. In addition, this medicine has a fewer side effects [21]. Another study reported that Echinacea significantly lowered the symptoms of common cold [23]. A study on the effects of Echinacea on prevention of acute respiratory infection in children at age range 1–5 years showed that there was a fewer incidence cases of upper air ways infections and sinusitis in the intervention group [24]. On the other hand, a clinical trial on patients inflicted by rhinovirus reported that in comparison with placebo, Echinacea did not alleviate the symptoms [25]. A metanalysis study showed that Echinacea decreased the incidence and duration of common cold [26]. Potentially, Echinacea decreases the risk of respiratory infections and the pertinent side-effects. Immunity adjustment, antivirus, and anti-inflammatory effects of Echinacea might help alleviation of clinical symptoms in respiratory patients [27]. Given the differences in methodologies and type of diseases under study, the findings by other studies are not perfectly comparable with the present study.

Ginger in traditional medicine is used for a wide range of diseases like asthma, arthritis rheumatoid, neural disease, diabetes, constipation, common cold, and influenza [28, 29]. A study on the effects of a mixture of *Althaea officinalis* and *Zingiber officinale* on bronchitis coughing showed the positive effects of the mixture in the form of less coughing attacks and chest pain caused by tracheitis (through alleviation of inflammation) [17]. Another study showed that ginger in asthma patients decreased the symptoms, while it did not change the stage of disease or spirometric results [20]. In [16], powdered ginger rhizome capsule as an add on inhalant corticosteroid and long-acting β2 agonist is effective in the improvement of forced expiratory volume at 1 s (FEV1), secondary efficacy variables were the peak expiratory flow (PEF), and the asthma control test (ACT) scores of the patients of a moderate type of persistent asthma uncontrolled on standard treatment.

In present study, hospitalization rate in the control and intervention groups was 6 and 2% respectively. In the study of Prieto-Alhambra et al. [6] the rate of hospitalization of COVID-19 outpatients was reported to be 15%. Of course, this study was a cohort study with prospectively collected data from the information system for research in primary care [6].

By prescribing Echinacea and *Zingiber officinale* herbal medicine simultaneously, the authors tried to improve synergistic effects of the medicines on strengthening the immune system and anti-inflammatory effects, which resulted in improving some of clinical symptoms of COVID-19 suspicious outpatients. Given the results, using the herbal medicines as a supplementary treatment for the patients is recommended. Alleviation of the symptoms like coughing, shortness of breath, and muscle pain

in COVID-19 patients is highly important and needs low risk treatments that patients find them acceptable.

Limitations

To facilitate matching between the two groups, patients with background diseases were excluded. To improve generalizability of the findings to other patients, future works can cover other groups of patients. Despite, we adjusted for likely confounders, including age, gender and excluded patients with underlying diseases, it is still possible that some amount of unmeasured confounding remains. Finally, the single-center design may limit the generalizability of these results.

Conclusion

Taking into account the efficiency and minimal side-effects of Echinacea and *Zingiber officinale*, they are recommended for coronavirus outpatients. The authors hope that until the introduction of vaccine and specific drug for COVID-19, herbal medicine (Echinacea and *Zingiber officinale*) could help COVID-19 suspicious outpatients.

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Competing interests: The authors have declared no conflict of interest.
Ethical approval: The study was approved by the Institutional Review Board and the Ethics Committee of Saveh University of Medical Sciences, Saveh, Iran (approval code: IR.SAVEHUMS.REC.1399.004) and registered in the Iranian Registry of Clinical Trials (Registration code: IRCT20200415047089N1).

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