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Original Article

Efficacy of a Persian herbal medicine compound on coronavirus disease 2019 (COVID-19): A randomized clinical trial

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ABSTRACT

Background: The global attention to the capacities of traditional medicine for alleviating the clinical manifestations of COVID-19 has been growing. The present trial aimed to evaluate the efficacy and safety of a Persian herbal medicine formula among patients with COVID-19.

Methods: The present trial was conducted in Afzalipour hospital, Kerman, Iran, from June to September 2020. Hospitalized COVID-19 patients were randomly divided into intervention (Persian herbal medicine formula + routine treatment) or control (only routine treatment) groups. The intervention group received both capsule number 1 and 2 every 8 hours for 7 days. Capsule number 1 contained extract of the *Glycyrrhiza glabra, Punica granatum*, and *Rheum palmatum*, and the second capsule was filled by *Nigella sativa* powder. Participants were followed up to 7 days. The primary outcome was the number of hospitalization days, while cough, fever, and respiratory rate, days on oxygen (O_2) therapy, and mortality rate were considered as the secondary outcomes.

Results: Eighty-two patients were enrolled to the study, while 79 cases completed the trial and their data were analyzed (mean age: 59.1 ± 17.1 years). Based on the results, the Persian medicine formula decreased the mean hospitalization days, so that the mean difference of length of hospitalization as primary outcome was 2.95 ± 0.43 days. A significant clinical improvement was observed regarding dyspnea, need for O_2) therapy, and respiratory rate in the intervention group. No adverse effects were reported.

Conclusion: The present study supported the use of the Persian medicine formula as an adjuvant therapy for hospitalized COVID-19 patients. Study registration: Iranian Registry of Clinical Trials (www.irct.ir): IRCT20200330046899N1.

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1. Introduction

Throughout history, viruses have repeatedly caused diseases among humans and animals, and imposed great costs on human societies in some cases.[1] Over the past twenty years, the world has experienced three outbreaks of coronaviruses. Each of the outbreaks, especially the recent pandemic by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has aroused great concerns in global health.[2] Worldometer, a reference website of live world statistics (www.worldometers.info/coronavirus/), has reported above 289 million confirmed cases and about 5.5 million deaths from coronavirus disease 2019 (COVID-19) as of December 30, 2021.

Coronaviruses are morphologically enveloped, which have positive-sense, single-stranded RNA genomes ((+)ssRNA).[3] The common symptoms of COVID-19 include respiratory symptoms,

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fever, and cough, as well as shortness of breath. In more severe cases, the infection can lead to pneumonia, severe acute respiratory syndrome, and even death. The symptoms may appear 2-14 days after exposing to the virus.[4] In addition, extra-pulmonary manifestations such as nausea, vomiting, coagulopathy, and smell and taste disturbances have been found in many patients.[5] Further, a larger mortality rate has been observed among high risk groups such as patients with metabolic syndrome or cardiovascular diseases.[6]

So far, no definitive or standard treatment has been presented for this disease and most therapies are supportive. Over the past year, many researchers have tried to find a solution for this problem. Furthermore, many studies are ongoing or have been conducted on conventional treatments or complementary and alternative medicine such as Unani, Persian, and traditional Chinese medicine.[7–11] Today, traditional and complementary medicines are considered as a new source of access to natural remedies. The positive therapeutic effects of herbs on controlling infectious diseases were reported during the outbreak of severe acute respiratory syndrome (SARS) in 2003. Additionally, the results of the recent studies have confirmed that the integration of traditional Chinese and conventional medicine for COVID-19 can improve the disappearance of many clinical manifestations and reduce the adverse effects of the drugs applied for managing the disease[12].

Persian medicine is one of the most important traditional medical systems in the world with a history of more than 7000 years.[13,14] The search throughout the manuscripts of Persian medicine represented that many medicinal plants have been introduced for preventing or treating respiratory disorders, the relevant pharmacological properties of a significant number of which have been proven in the recent studies. The remedies are potentially valuable options to be evaluated as the natural-based drugs against COVID-19 [15–17].

According to the main Persian medicine textbooks such as the Comprehensive Book on Medicine by Rhazes (865-925 AD)[18] and Canon of Medicine by Avicenna's (980-1037 AD),[19] *Glycyrrhiza glabra* L., *Punica granatum* L., *Rheum palmatum* L., and *Nigella sativa* L. are the herbs recommended for treating respiratory disorders and infections. Recently, several studies have approved the relevant pharmacological properties of the herbs, which are hoped to be helpful in the better management of COVID-19.

N. sativa (*Shoniz* in Persian) contains several bioactive ingredients such as phenolic compounds (i.e., thymoquinone, dithymoquinone, thymohydroquinone, and thymol), alkaloids (i.e., nigellidine and nigellicine), saponin, flavonoids, nutrients (i.e., carbohydrates, fatty acids, and essential amino acids), and some minerals.[20] Based on the results of the recent studies, the herb exhibit antiviral, antimicrobial, anti-inflammatory, immunomodulatory, and antitussive effects.[21–24]

The next herb, *G. glabra* (*Shirinbayan* in Persian), is native to Iran. The most important phytochemical component of the root includes triterpenoid saponin, called as glycyrrhizic acid or glycyrrhizin, with a sweetness of 30-50 times that of sucrose.[25] This substance is widely used in pharmaceutical and food industries. *G. glabra* as a potent natural antiviral agent is effective against viruses such as Epstein-Barr, SARS-CoV, hepatitis C, and human immunodeficiency viruse-1 (HIV-1).[26–29] Further, it effectively decreases inflammation by inhibiting glucocorticoid accumulation followed by preventing reactive oxygen species (ROS) production by neutrophils.[25] Several studies approved the antibacterial, antioxidant, and immune enhancement of the medicinal plant.[30,31]

P. granatum, known as *Anar* in Persian, contains polyphenolic compounds, sugars, fatty acids, aromatic substances, amino acids, tocopherols, sterols, terpenoids, alkaloids, anthocyanins, alginic acid, and the like.[32] Ellagic acid, the epigallocatechin gallate of this herb has anti-inflammatory activity[33] by preventing prostaglandin or leukotriene production through inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) enzymes.[32,34] This medicinal plant is considered as an efficient antiviral agent against the various types of viruses.[35,36]

Another study evaluated the efficacy of the extract of *R. palmatum* (*Rivande-Chini* in Persian) against coronavirus and reported its antiviral activity by inhibiting 3C-like protease.[37] The results of the recent research demonstrated that emodin, an active ingredient of this herb, blocks SARS-CoV spike protein and angiotensin-converting enzyme 2 in a dose and time-dependent manner.[38] Based on the results of an animal study on asthmatic mice, emodin efficiently reduces airway inflammation and activated macrophages.[39]

The ancient data related to Persian medicine supported by the results of the recent studies confirm that the combination of the four herbs is worth trying against this viral infection. Therefore, the present trial mainly aimed to determine the efficacy and safety of a Persian medicine formula among admitted confirmed COVID-19 patients.

2. Methods

2.1. Study design

This randomized open-labeled clinical trial was conducted in the Afzalipour hospital affiliated with the Kerman University of Medical Sciences, from June to September 2020.

2.2. Ethical consideration

The Local Medical Ethics Committee of Kerman University of Medical Sciences approved the protocol of this trial (code: IR.KMU.REC.1399.055, webpage of ethical approval code: yun.ir/12qol1). In addition, the protocol was registered at the Iranian Registry of Clinical Trials website (code: IRCT20200330046899N1). This trial was performed in accordance with the Declaration of Helsinki guidelines. The procedure was explained to the patients meeting the inclusion criteria, the participants signed informed consent, and they were free to withdraw from the trial at any time.

2.3. Preparation and standardization of the Persian herbal medicine product

The intended herbal product was prepared and standardized in Department of Traditional Pharmacy, School of Persian Medicine at Tehran University of Medical Sciences. In this regard, the required medicinal plants including the rhizome of *G. glabra*, the fruit peels of *P. granatum*, the root of *R. palmatum*, and the seed of *N. sativa* were purchased from an herbal shop in Tehran. Then, their genus and species (scientific name) were identified and registered in the Herbarium Center of the School of Pharmacy, Tehran University of Medical Sciences. The assigned voucher codes for *G. glabra, P. granatum, R. palmatum*, and *N. sativa* were PMP-1227, PMP-1747, PMP-1226, and PMP-1744, respectively.

In order to prepare capsules, the herbs were carefully cleaned and powdered.

For preparing capsule no.1, the root of *G. glabra*, rhizome of *R. palmatum*, and peel of *P. granatum* were mixed in a ratio of 0.5:1:1, the 70% ethanolic hydroalcoholic extract of which was obtained through using percolation method (3 days). After filtering the extract, it was concentrated by using a rotary evaporator, placed in a vacuum oven for 3 hours, and kept in the freezer at -70°C for 1 day, followed by preparing lyophilized powder by a freeze-dryer. Then, the dry extract of the mixture of the three herbs was mixed

with starch (Merck, Germany) as filler and packed in 500 mg capsules. Each capsule contained the extract of the raw materials of *G. glabra* (0.5 g), *R. palmatum* (1 g), and *P. granatum* (1 g).

In order to prepare capsule no. 2, the black seed was powdered distinctly. For preparing powder, the seeds were ground for 2 minutes and passed through a #40 mesh sieve. Then, filled in a 500 mg capsule separately.

The preparations were standardized based on the total phenolic (mg of gallic acid equivalent (GAE) per g of product) and total flavonoid content (mg of quercetin equivalent (QE) per g of product) by measuring absorbance at 765 and 415 nm on a spectrophotometer, respectively.[40,41]

2.4. Sample size

Due to the lack of previous similar study, 80 subjects were considered as the primary sample size (40 patients in each arm).

2.5. Randomization and allocation concealment

In the study, block randomization method was used. The treatment assignment was in a 1:1 ratio, and there were 2 groups, then, the block size was chosen 4. In addition, possible balanced combinations (meaning that there is a balance in sample size across groups) were calculated with 2 subjects in both control and intervention groups (6 possibilities). In all four block size, 2 patients were assigned to each of the intervention and control groups. Further, the blocks were randomly selected to allocate all subjects in the 2 groups. It should be noted that Random Allocation Software version 1.0 was used to generate random sequence numbers. In order to avoiding selection bias, a hospital nurse who had been instructed to apply a randomized list, randomly allocated the participants to intervention or control groups.

2.6. Inclusion and exclusion criteria

COVID-19 patients having hospital admission indication[5] and no history of serious concomitant underlying diseases such as hypertension, cardiovascular, pulmonary, cerebral, and endocrine diseases, aging 18-75 years old, and with capability and desire to participate in the study and fill out the personal consent form were included in the study.

The exclusion criteria included pregnancy or lactation and incapability to consume oral drug, as well as the history of allergy to any of the components of the intended drug and existence of any condition for discontinuing the therapeutic intervention based on the physician's judgment.

2.7. Intervention

The eligible patients were randomly divided into intervention (Persian medicine products) group or control group. The patients in the control group were treated routinely based on the Protocol for Diagnosis and Treatment of Novel Coronavirus Pneumonia. However, those in the intervention group received Persian medicine capsules (both capsule no.1 and capsule no.2, every 8 hours for 7 days) along with routine treatment. Then, all participants were followed up daily up to 7 days after starting the intervention.

2.8. Outcome measures

The primary outcome was the number of hospitalization days.

Additionally, the secondary outcomes were obtained as follows.

- Fever severity was assessed in the 1st, 4th, and 7th days after the intervention.
  1. No fever: under 37.2°C (orally).
  2. Mild: 37.2 – 37.8°C.
  3. Moderate: 37.9 – 39.4°C.
  4. Severe: 39.5 – 40.5°C.
  5. Very intense: above 40.5°C.
- Respiratory rate was daily measured in the days 1-7 after the intervention onset.
- Severity of cough was examined at the 1st and 7th days following the intervention.
  1. No cough.
  2. Occasional cough which does not last long.
  3. Frequent coughing which interferes briefly with daily activities.
  4. Annoying cough which greatly interferes with daily activities.
- Dyspnea severity was determined in the 1st, 4th, and 7th days after starting the intervention.
  1. No dyspnea.
  2. Dyspnea with moderate respiratory effort which restricts individual's excessive activities.
  3. Resting dyspnea limiting the daily personal activities of individual.
  4. Dyspnea with the life-threatening complications which requires emergency measures.
- Number of days requiring adjuvant oxygen therapy.
- Number of the patients having disease progression or died ones.
- Oxygen saturation percentage was evaluated at the days 1-7 after the intervention onset.

2.9. Statistical analysis

The mean length of hospitalization, as the primary outcome, as well as days on oxygen therapy between the 2 groups were compared using independent sample t-test. The mean difference between the 2 groups and its 95% confidence interval (CI) were reported. In addition, repeated-measures ANOVA was used to test the change of continuous variables during the follow-up period. Intervention status and time-point were respectively considered as between- and within-subject factor. The normality of continuous variables was checked using Kolmogorov–Smirnov test. For ordinal outcomes such as level of fever and severity of cough, ordinal logistic regression analysis was performed to obtain the odds ratio (OR) and its 95% CI. For binary outcomes including death, binary logistic regression analysis was used to obtain OR and its 95% CI. Wald Chi-Square test was used. Furthermore, the results were reported as mean ± standard deviation and frequency (%) for quantitative and categorical variables, respectively. The data were analyzed based on the per-protocol method and all analyses were performed by using IBM SPSS Statistics 22.0 program software.

3. Results

3.1. Preparation and standardization of capsules

In the study, 2 types of capsules (no. 1 and 2) were prepared, the total phenolic contents of which were determined 15.44 ± 0.34 and 4.52 ± 0.14 mg GAE/g, respectively. In addition, the total flavonoid contents of capsules no. 1 and 2 were 7.81 ± 0.81 and 3. 65 ± 0.18 mg QE/g, respectively.

3.2. Study flow

Based on the inclusion criteria, 82 eligible COVID-19 patients were included in the study and randomly divided into intervention

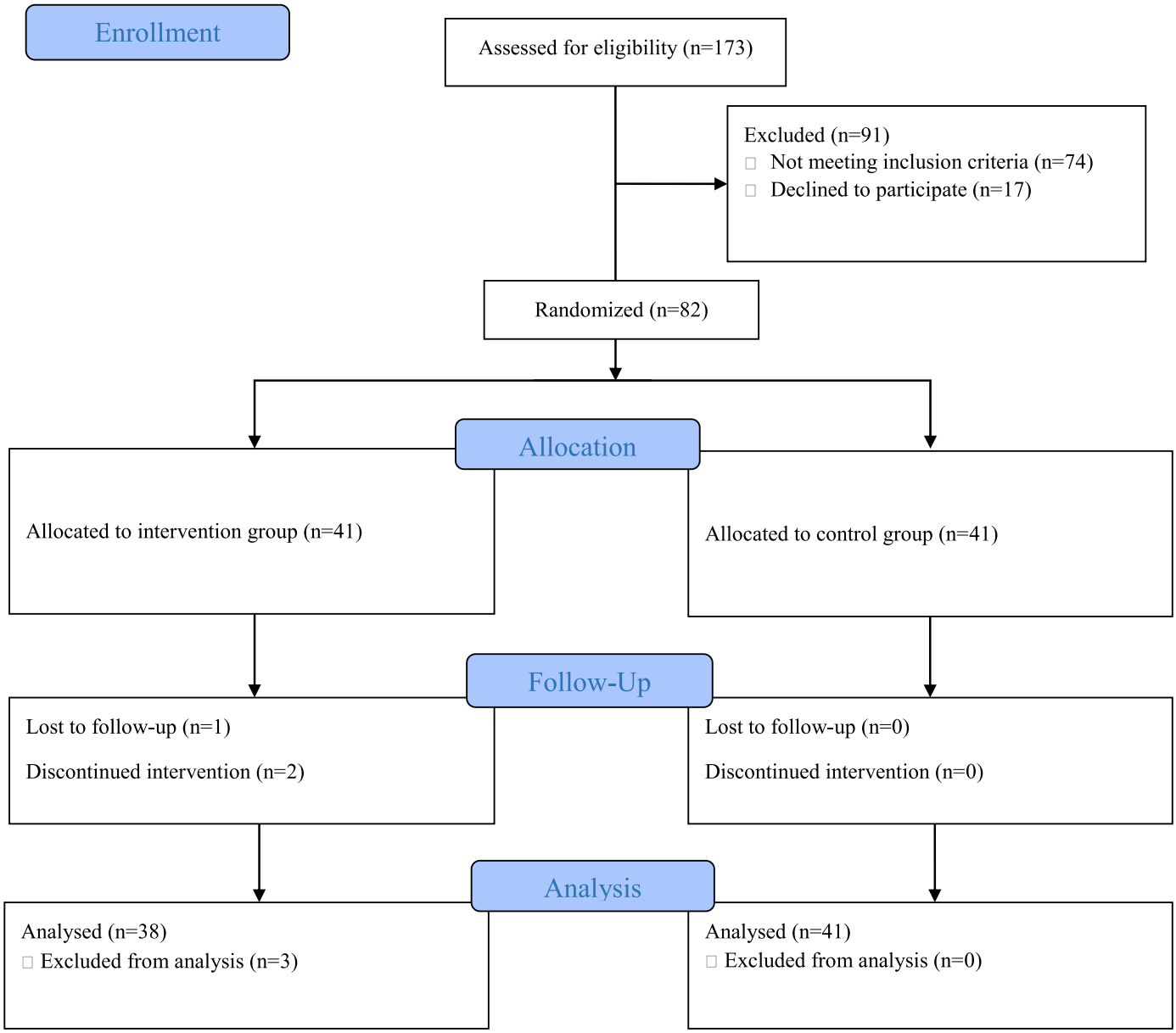

Fig. 1. CONSORT flow diagram of the study.

and control groups (41 participants in each group). However, 3 participants were excluded from the intervention group due to failure in following up (1 participant) and discontinuation of the herbal treatment (2 participants). Finally, 79 patients completed the trial. Fig. 1 displays the trial flow.

3.3. Baseline and demographic characteristics

Among the 38 participants in the intervention group and 41 participants in the control group, there were slightly more males in both groups (53.7% in the control vs. 55.3% in the intervention group, *p*-value: 0.88). Based on the results, no significant difference was observed regarding the mean age of patients in the groups (59.2 ± 17.2 in the control vs. 59.1 ± 17.1 in the intervention). At baseline, fever level, cough severity, dyspnea, respiratory rate, and oxygen (O_2) saturation were not significantly different between the 2 groups. Table 1 summarizes the baseline data.

Table 1
Demographic and baseline clinical characteristics of patients in the 2 groups of the study.

Variables		Intervention	Control
Demographic information			
Sex, No. (%)	Male	21 (55.3)	22 (53.7)
	Female	17 (44.7)	19 (46.3)
Age (years)		59.1 ± 17.1	59.2 ± 17.2
Baseline clinical characteristics			
Fever, No. (%)	None	15 (39.5)	14 (34.1)
	Mild	12 (31.6)	13 (31.7)
	Moderate	11 (28.9)	14 (34.1)
Dyspnea, No. (%)	None	2 (5.3)	3 (7.3)
	Mild	26 (68.4)	31 (75.6)
	Moderate	10 (26.3)	7 (8.9)
Cough, No. (%)	None	25 (65.8)	29 (70.7)
	Sometimes	10 (26.3)	12 (29.3)
	Frequently	3 (7.9)	0 (0.0)
Respiratory rate (breaths/min)		19.4 ± 3.0	18.8 ± 3.1
Oxygen (O_2) saturation (%)		83.4 ± 11.0	84.8 ± 11.6

Table 2
Comparison of clinical outcomes of patients infected with COVID-19 between intervention (n=38) and control (n=41) groups.

Variables			Intervention	Control	Effect size		p-value
			Frequency (%)		Odds ratio	95% confidence interval	
Fever†	Baseline	None	15 (39.5)	14 (34.1)	0.79	0.35-1.78	0.79
		Mild	12 (31.6)	13 (31.7)			
		Moderate	11 (28.9)	14 (34.1)			
	Day 4	None	29 (78.4)	28 (68.3)	0.68	0.25-1.89	0.46
		Mild	3 (8.1)	10 (24.4)			
		Moderate	5 (13.5)	3 (7.3)			
	Day 7	None	11 (84.6)	17 (94.4)	2.79	0.22-34.47	0.42
		Mild	1 (7.7)	0 (0.0)			
		Moderate	1 (7.7)	0 (0.0)			
		High	0 (0.0)	1 (5.6)			
Dyspnea†	Baseline	None	2 (5.3)	3 (7.3)	1.66	0.61-4.46	0.31
		Mild	26 (68.4)	31 (75.6)			
		Moderate	10 (26.3)	7 (8.9)			
	Day 4	None	28 (75.7)	21 (51.2)	0.34	0.13-0.90	0.03
		Mild	8 (21.6)	18 (43.9)			
		Moderate	1 (2.7)	2 (4.9)			
	Day 7	None	12 (100)	10 (50)	0.5	0.32-0.77	0.001
		Mild	0 (0.0)	10 (50)			
Cough†	Baseline	None	25 (65.8)	29 (70.7)	1.39	0.54-3.57	0.49
		Sometimes	10 (26.3)	12 (29.3)			
		Frequently	3 (7.9)	0 (0.0)			
	Day 7	None	36 (94.7)	33 (80.5)	0.24	0.04-1.21	0.08
		Sometimes	1 (2.6)	8 (19.5)			
		Frequently	1 (2.6)	0(0.0)			
Death▼		Yes	1 (2.6)	1(2.4)	1.08	0.06-17.91	0.95
		No	37 (97.4)	40 (97.6)			
Mean (standard deviation)					**Mean difference**	**95% confidence interval**	**P-value**
Hospitalization days*			5.7 (1.9)	8.0 (1.8)	2.29	1.42-3.16	<0.001
Days on O_2 therapy*			3.0 (1.6)	4.1 (1.9)	1.12	0.32-1.92	0.007

† ordinal logistic regression analysis was used for statistical analysis of this variable.
▼ binary logistic regression analysis was used for statistical analysis of this variable.
* independent sample t-test was used for statistical analysis of this variable.

3.4. Clinical outcomes

The patients in each arm of trial were followed for 7 days following intervention onset. Considering length of hospitalization as primary outcome, the intervention group was averagely hospitalized significantly less than the control (8.05 ± 1.8 vs. 5.1 ± 1.9, $p<0.001$).The mean difference (CI 95%) was 2.95 (1.42-3.16) days. Furthermore, at the end of follow-up, a significant difference was obtained between the 2 groups regarding dyspnea, need to O_2 therapy, and respiratory rate. However, fever severity, cough severity, and death percentage were not statistically significant difference between groups (Table 2 & Fig. 2). Additionally, the percentage of subjects without dyspnea increased from 5.3 to 100% in the intervention group and 7.3 to 50% in the control ($p=0.001$).The odds of being in a higher category of dyspnea in intervention group significantly decreased by a factor of 0.34 and 0.5 at the days of 4 and 7 respectively. Furthermore, a significant lower mean days on oxygen therapy was observed among the intervention group (3.0 ± 1.6 vs. 4.1 ± 1.9, $p=0.007$) (Table 2). The mean respiratory rate decreased significantly in both groups ($F=53.3$, $p<0.001$), the difference of which was significant between the 2 groups ($F=4.5$; $p=0.04$) (Fig. 2). despite the lack of interaction between intervention and time. Finally, a significant enhancement was obtained in the O_2 saturation of both groups ($F=25.1$, $p<0.001$), while the difference between the 2 groups was insignificant ($F=0.45$, $p=0.50$). In this trial, no adverse events were reported during the intervention period.

4. Discussion

The present study assessed the efficacy and safety of Persian herbal medicine formula on hospitalized COVID-19 patients. Based on the results, the compound herbal remedies decreased dyspnea significantly at the 4th ($p=0.03$) and 7th days ($p=0.001$) after intervention. In addition, the hospitalization days and days on O_2 therapy of the intervention group were significantly less than those of the control group ($p<0.001$ and $p=0.007$, respectively). The intervention group had lower respiratory rate at the 2nd day after starting intervention, which continued until the end of the day 7. Also, a greater O_2 saturation level was observed in the intervention group in the 1st, 3th, 4th, 5th, 6th, and 7th days after starting the intervention. The 2 groups were not significantly different in terms of fever, cough severity and mortality rate.

The effectiveness of the Persian medicine formula on improving dyspnea, and respiratory rate, as well as reducing hospitalization days and days on O_2 therapy was obtained as the significant outcome of the present trial. Based on the results of the studies on the pathophysiology of COVID-19 as well as the guidelines proposed for managing this disease, antiviral and anti-inflammatory agents seem to be the wings for controlling the disease. Accordingly, the widespread effects of the intended herbal formula can be justified by the potent anti-inflammatory and antiviral properties of its components. *G. glabra* induces anti-inflammatory activity through various pathways. It inhibits prostaglandin E2 (PGE2), COX, and LOX significantly[42] and modulates nuclear factor kappa B/mitogen-activated protein kinases (NF-kB/MAPK) pathway.[43] Additionally,

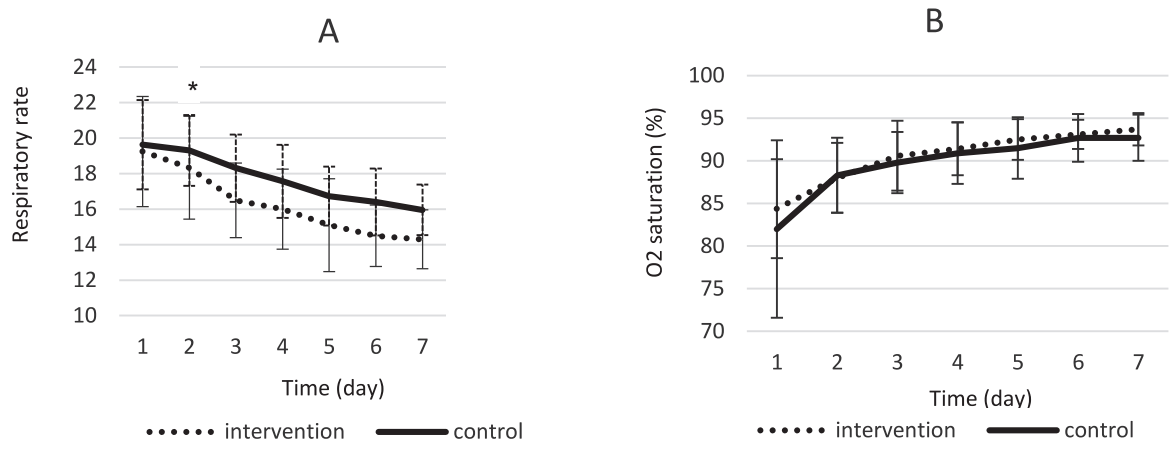

Fig. 2. (A) Change in respiratory rate, and (B) O_2 saturation over the study period between the intervention and the control groups. *The point of starting significant difference (Day 2).

the herb inhibits lipopolysaccharide-interferon-γ (LPS-IFN-γ) inflammation via regulating the expression of nitric oxide (NO) synthesis.[44] Some constituents of *G. glabra* prevent LPS-induced NO, interleukin-6 (IL-6), and interleukin-1 beta (IL-1 beta).[45] The next herb, *R. palmatum*, can regulate the NF-κB signaling pathway. It may decrease the content of liver enzyme and inflammatory factors in the serum though the pathway[46] and inhibit IL-6 production.[47] Ellagic acid, gallic acid, and punicalagin A&B, as the phytochemical components of *P. granatum*, prevent LPS-induced IL-6, NO, and PGE-2 production.[48] A systematic review and meta-analysis of randomized clinical trials about the effects of *N. sativa* on oxidative stress and circulating inflammatory markers reported that this medicinal plant significantly reduced malondialdehyde (MDA) and C-reactive protein (CRP) concentrations. Further, *N. sativa* enhanced total antioxidant capacity levels.[49] The results of a study among patients with Hashimoto thyroiditis indicated that this herb can statistically decrease interleukin 23 (IL-23) level.[50] Furthermore, some phytochemical constituents of *N. sativa* exhibit significant inhibitory activity against COX.[51] Each component of the Persian medicine formula has antiviral effect against different viral species, the possible anti-coronavirus activity of some of which has been suggested in the recent studies. For example, Glycyrrhizin, an active ingredient of *G. glabra*, represents antiviral effect against SARS-CoV. It prevents the virus absorption and penetration, along with inhibiting its replication in vero cells.[27] *R. palmatum*, another component of the Persian medicine formula, exhibits inhibitory effect against SARS-CoV 3CL protease and has been proposed as a potential therapeutic agent for SARS-CoV.[38] The results of a mini review of in silico studies demonstrated that some components of *N. sativa* have moderate to high affinity with the proteins and enzymes of SARS-CoV-2. Therefore, they may potentially prevent SARS-CoV-2 attachment to the receptors of host cell, as well as their replication.[52] Based on the Persian medicine manuscripts, *G. glabra* is effective for asthma, cough, excessive phlegm, respiratory infections, and dyspnea relief, while *P. granatum* is recommended for cough due to warm temperament and as a liver tonic. In addition, *R. palmatum* is suggested for chronic cough, asthma, and dyspnea, and as a liver tonic, and *N. sativa* is helpful for fever, cough, orthopnea, headache, and rhinorrhea. The pharmacological effects of herbal components reported in the scientific databases and supported by the properties mentioned in the Persian medicine textbooks can justify the appropriate therapeutic response of the Persian medicine formula on COVID-19.[53]

The results of the present trial are approximately consistent with those of Liu et al.[12] on the efficacy of integrated traditional Chinese and conventional medicine for COVID-19. Their meta-analysis systematic review involved eleven relevant studies (randomized controlled trials and case control studies) with the sample size ranged between 42 to 200 subjects (total 982), which were published since December 1, 2019 to March 24, 2020. In the studies, the traditional Chinese medicine including Chinese patent medicine and Chinese medicine compound drugs was considered as intervention. Based on the results of the review study, overall response, cure, and severity illness rate, and hospitalization day were significantly better in the intervention group compared to the control. Further, integrated traditional Chinese and conventional medicine could accelerate the disappearance rate of cough, fever, chest tightness, fatigue, and anorexia, and reduce the duration of fever and fatigue.[12] The results of the review regarding fever and cough severity are not in line with those of the present study. Furthermore, some items such as fatigue and chest tightness were not measured in the present study, which can be considered as the study limitations. The other limitation was evaluating the efficacy of the Persian medicine formula on the extra pulmonary clinical manifestation of COVID-19 such as taste/smell disorder, nausea, vomiting, and diarrhea. Furthermore, due to lack of number of patients and limited duration of follow-up, the study findings should be interpreted with caution.

In conclusion, the present study supported the use of intended Persian medicine formulas as a supportive treatment for the hospitalized COVID-19 patients in order to improve their sign and symptoms, accelerate treatment, and shorten their hospitalization day during the disease period. It is recommended to conduct more clinical studies with bigger sample size for better evaluation.

Conflict of interest

There was no conflict of interest in this study.

CRediT authorship contribution statement

Mohammad Setayesh: Investigation, Writing – review & editing, Supervision. **Mehrdad Karimi:** Conceptualization, Methodology, Writing – review & editing. **Arman Zargaran:** Investigation, Writing – review & editing. **Hamid Abousaidi:** Resources. **Armita Shahesmaeili:** Formal analysis, Writing – review & editing. **Fatemeh Amiri:** Resources. **Fatemeh Sadat Hasheminasab:** Writing – original draft, Writing – review & editing.

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Ethical statement

This research was reviewed and approved by the Local Medical Ethics Committee of Kerman University of Medical Sciences (code: IR.KMU.REC.1399.055, webpage of ethical approval code: yun.ir/12qol1). Informed consent was obtained from all participants.

Data availability

All data analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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