Original Article

Dose Kelofan Syrup Effective for Clinical Symptoms and Biochemical Factorsin COVID-19 Patients? A double-Blind Clinical Trials

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Abstract

Introduction: COVID-19 is one of the most severe, intestinal, respiratory, and systemic infections in animals and humans. The purpose of this experiment was to evaluate the effect of kelofan syrup on biochemical factors and clinical signs of patients with COVID-19. **Materials and Methods:** This randomized clinical trial was performed on 60 hospitalized patients with moderate or severe COVID-19. The intervention group received 7.5 cc of kelofan syrup(a traditional Persian medicine product) every 12 hours for one week and the placebo group received 7.5 cc of placebo syrup. Serum levels of white blood cells (WBCs), C - reactive protein (CRP), lactate dehydrogenase (LDH), creatinine, lymphocyte, and clinical outcomes were measured before the beginning of the intervention and on day 7. **Results:** Kelofan syrup enhanced the white blood cell and reduced creatinine and LDH in the syrup group. However, serum levels of WBC, lymphocyte, CRP, LDH, and creatinine($P > 0.05$) in the kelofan group at the end of the study did not significantly change than in the placebo group. Also, clinical outcomes such as fever, respiratory rate, saturated oxygen, cough, dyspnea, myalgia, duration of hospitalization, and fatigue did not change significantly from in the placebo group. **Conclusion:** our findings indicate that kelofan syrup for seven days could not alter biochemical and clinical outcomes than in the placebo group in patients with COVID-19. However, in some clinical symptoms such as cough, dyspnea, weakness, and biochemical factors like WBC, Cr, and LDH, a significant change was observed at the end of hospitalization in the intervention group.

Keywords: *Clinical trial, COVID-19, kelofan, persian medicine*

Introduction

COVID-19 is one of the most severe, respiratory, intestinal, and systemic infections in both animals and humans.CoVs, from the family Coronaviridae and the subfamily Orthocoronavirinae, include alpha, beta, gamma, and delta CoVs.[1–3] At the end of 2019, the COVID-19 was recognized in Wuhan, the influenza-like COVID-19. Evidence suggests that the COVID-19 is transmitted from human to human through close contact namely breathing, eyes, and mouth.[4,5] The organization declared a pandemic of the disease on March 11, 2020. By June 2021, approximately 179 million people globally have been infected with the COVID-19, of whom over3.5 million died.[6] Acute respiratory distress syndrome (ARDS) is one of the chief reasons for death in patients with COVID-19, which consequently leads to sepsis, septic shock, and multiple organ failure.[7] The elderly and people with major chronic diseases such as diabetes, cardiovascular diseases, high blood pressure, and cancer are at the highest risk for COVID-19.[8] The key reason for the elevated conduction rate of COVID-19 is that genetic recombination occurs in the S protein in the receptor-binding domain (RBD) of the virus. RNA SARS-CoV-2 sequence has approximately 30,000 bases in duration.[9,10] Studies show many similarities between the SARS-CoV and SARS-CoV-2 genome sequences in the binding domain (RBD).[11] RBD has a strong affinity for angiotensin-converting enzyme (ACE2) receptors in humans, which are mainly expressed in numerous cells of the brain, kidneys, lungs, and gastrointestinal tract.[12] ACE2 might regulate the renin-angiotensin system (RAS) via mitigating angiotensin II expression and might play a protective role in the progression of acute lung failure.[13] SARS-CoV-2 appears to infect host cells via ACE2. It is suggested that reduced ACE2 activity in host cell membranes might attenuate the potency of

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SARS-CoV-2 in enteringcells.[14] According to the studies, the virus enters the cells and increases inflammatory activity, which leads to earnest damage to opposite parts of the body, particularly the respiratory system.[15–17] The virus also upsets the balance of various biochemical factors namely BUN, Urea, and LDH in the body.[18] Although many treatments, including antimicrobials, anti-inflammatory drugs, immune suppressants, and dietary supplements, have been prescribed to treat COVID-19, no standard treatment has yet been proposed for the complete cure of COVID-19.[19] Therefore, the use of some herbal medicines due to their anti-inflammatory, anti-microbial, and anti-oxidative stress properties, along with the medications administered in COVID-19, can be effective ways to reduce the complications caused by this disease.[20] One of these plant compounds is kelofan, which consists of *Ziziphus jujuba* (containing flavonoid compounds, polysaccharides, and triterpene acid),[21] *Nigella sativa* (containing alkaloid compounds, saponin, flavonoids, and thymoquinone),[22] *Glycyrrhiza glabra* (containing triterpene compounds, saponins, Flavonoids, hydroxy coumarin, and steroids),[23] *Adiantum capillus-veneris* (containing compounds such as flavonoids, hydroxy-cinnamic acid esters and proanthocyanidins),[24] *Hyssopus officinalis* (containing compounds such as tannins, hesperidin, flavonoids, fenobide and fennel Triterpene acid),[25] *Viola odorata* (containing saponins, alkaloids),[26] *Malva sylvestris* (containing flavonoids, tannins, polysaccharides, and anthocyanins).,[27] *and Foeniculum vulgare*)Fennel(seeds (contain phenolic compounds such as anethole and terpenoid compounds such as fencon, and flavonoids, especially quercetin).[28,29] Therefore, given the antioxidant, antimicrobial and anti-inflammatory impactsof these compounds and their synergistic effects together, it seems that kelofan syrup could improve the symptoms and complications of COVID-19. Therefore, this double-blind clinical trial study was conducted to investigate the therapeutic effects of this Persian medicine compound on pulmonary manifestations, clinical and laboratory parameters in patients with moderate and severe COVID-19.

Materials and Methods

Participants and study design

This randomized, double-blind placebo-controlled clinical trial was conducted in the COVID-19 ward of Imam Khomeini hospital of Ardabil University of Medical Sciences from January 2020 to February 2021. After receiving the Medical Research Ethics Committee and Iranian Registry of Clinical Trials (IRCT) codes (IRCT20200405046960N2) and before entering the study, all patients, as well as the patient's companions, received informed consent. The inclusion criteria of the study were as followings: [1] Patients with COVID-19; [2] Positive PCR test; [3] Pulmonary involvement confirmed by CT-Scan; [4] Age upper than 18; [5] Signing an informed consent form; [6] The severity of the disease is moderate and severe; [7] No connection to the ventilator. Exclusion criteria included: [1] Lactating and pregnant women; [2] Un-control cardiovascular disease; [3] Un-control blood pressure; [4] History of allergies to herbs; [5] Uncontrolled diabetes; [6] Liver and kidney failure; [7] Alcohol consumption; [8] Transplant patients. The current study was approved by the Medical Research Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1399.009). After the ratification of the Medical Ethics Committee, 60 patients (30 patients in the kelofan group and 30 patients in the placebo group) were included. All patients were aware of the study protocols and signed the written informed consent.

Sample size

For this study, the sample size was considered 60, based on the serum levels of CRP determined according to the study by Tay, Poh[17] with the power of 80% and confidence interval of 95% in bilateral testing through sample size software and power analysis (PASS; NCSS, LLC, USA)

Randomization and intervention

Based on age and gender and using random allocation software (RAS), the patients were randomly divided into placebo or kelofan groups in a 1-to-1 proportion. Also, for concealing the allocation, an individual outside of the research team encoded the syrups (A and B), placed them in the closed and opaque packet according to the randomization list, and numbered them consecutively. The patients and investigators were blind to the study allocation. In the intervention group, 30 patients received 7.5 cc of kelofan syrup every 12 hours for seven days with routine treatment. In the control group, 30 patients received routine medications plus placebo syrup every 12 hours, which was similar in appearance, color, and size to the intervention.

Preparation, extraction, and standardization of kelofan syrup

In this study, total aqueous extracts of *Ziziphus jujube* (fruits), *Nigella sativa* (seeds), *Glycyrrhiza glabra* (roots), *Adiantum capillus-veneris* (leaves), *Hyssopus officinalis* (leaves), *Viola odorata* (flowers), *Malva sylvestris* (leaves), and *Foeniculum vulgare* (seeds) were used to prepare kelofan syrup. Considering the medicinal formulations reported in the books of Persian medicine and pharmacy in the treatment of pulmonary disease, the mentioned plants were used in the ratio of 1: 1: 1: 2: 3: 1: 1: 1 to prepare kelofan syrup, respectively. First, all the plants were bought from a local market in Ardabil Bazar in northwestern Iran hence identified and approved by the relevant pharmacognosy professors. Then the plants were cleaned and placed in washing tanks. The plants were then transferred to other tanks filled with water solvent. Also, for the aqueous extraction of plants, the water temperature was raised to 60°C with indirect heat. After 20 minutes, the aqueous extract of the plants was extracted by the maceration method and then natural sweeteners were added to it. After

homogenization of the compounds, the extract was filtered several times to obtain a smooth and well-mixed solution. In the next step, the solution was pasteurized at a temperature of 70°C and transferred to a covered tank at a temperature of 55°C. Finally, patients received kelofan syrup (120cc) in dark bottles. The dose of all plants was determined and standardized based on their aqueous extract. After preparing the syrup, microbial examinations were done to assure their safety for clinical use at Ardabil University of Medical Sciences. Then, standardization of kelofan syrup based on total phenolic compounds (as Gallic acid equivalents) according to to the Folin-ciocalteu method was performed in the laboratory of the Islamic Azad University of Isfahan (total amounts of phenol of kelofan syrup were 6.08 mg gallic acid equivalent (GAE)/g). Sweetener, non-absorbable stevia drops, and permitted food colors were used to prepare placebo syrup. Etemad Tabiat Peyk Shafa Company prepared the syrup and placebo syrup.

Blood sampling and laboratory analysis

At the first and end of hospitalization, blood samples were drawn from patients. Then, the serums were afterward centrifuged at 1000 r.p.m for ten minutes (Hettich, Germany) and stored at 70°C until the assay. Biochemical factors such as WBC, LYM, BUN, CR, and LDH were measured by spectrophotometric methods with commercial kits (Pars Azmoun Co, Tehran, Iran) in an automated analysis (Abbott model Alcyone 300; Abbott Park, USA). Clinical results such as Pao_2, respiration rate, and temperature were measured by a checklist every day at 12 P.M.

Statistical analysis methods

We used SPSS 24 software (SPSS, Chicago, IL, USA) for statistical analysis. The normality of data distribution was assessed with the Kolmogorov–Smirnov test. Normal or non-normal data distribution is reported as the median. Comparisons of changes (endpoint minus baseline) between groups were assessed by chi-square and Mann–Whitney U test. Statistical significance of differences between baseline and after the intervention was tested using Wilcoxon paired rank test (pre-and post-intervention changes in each group). To evaluate the differences and control confounders between groups post-intervention, an analysis of covariance (ANCOVA) test was applied. *P*-values less than 0.05 were regarded as statistically significant.

Results

Study population characteristics

An assembled of 60 patients were included in this examination. Three patients in the placebo group and three in the intervention group were deprived of the study due to refusing to use kelofan syrup for the complete length of treatment and transfer to the intensive care unit. Also, one patient due to death in the placebo group was excluded from the study. Therefore,27 patients in the intervention group and 26 patients in the control group completed the study [Figure 1]. It should be noted that based on the tests performed, the supplement did not contain any microbial pollution. of patients are included in [Table 1].

Specifications and symptoms of the disease at the time of admission

All patients in both groups had a positive chest CT-Scan. Twenty-five patients (% 92.6) in the kelofan group and 26 (% 100) had positive PCR tests, which was not remarkably different between the two groups. There was no significant difference in fever, chill, cough, dyspnea, weakness, myalgia, or gastrointestinal symptoms between the kelofan group and the control group at the beginning of the study [Table 2].

Clinical outcomes

Clinical results obtained from patients are presented in [Table 3]. There was no major difference between the two groups in Pao_2, respiratory rate, and body temperature. (90.78 (5.30) vs. 91.85 (7.48), $P = 0.546$), 19.33 (1.52) vs. 18.70 (5.30) $P = 0.170$, 37.02 (5.30) vs. 37.01 (0.09) $P = 0.660$, respectively).

Symptoms of the disease during the study

Symptoms of the disease obtained from patients are shown in [Table 4]. Although clinical signs such as cough, dyspnea, ague, myalgia, weakness, and gastrointestinal problems improved in the kelofan group, no considerable difference in these symptoms were observed between the two groups. (P>0.05).

Biochemistry indices

The effect of kelofan syrup on biochemical parameters in patients with COVID-19 is given in [Table 5]. Although in the kelofan syrup group, there was a significant change level of some factors such as WBC, Cr, LDH at the end of hospitalization but serum levels of WBC, LYM, CRP, BUN, CR, LDH at the end of hospitalization did not change significantly compared to the placebo group, (WBC($P = 0.522$), CRP ($P = 0.660$), LYM($P = 0.202$), BUN ($P = 0.051$), CR ($P = 0.291$), LDH ($P = 0.962$)).

Discussion

Little clinical study has been done on the effects of mixed herbal kelofan syrup on COVID-19 disease and its complications. Traditional Persian medicine recommends different medicinal plants to treat many diseases such as asthma, influenza, and COPD.[30–32] This study is the first RCT to assess the effects of kelofan intervention on symptoms of disease and biochemical parameters in patients with moderate and severe COVID-19. A study by Koshak, Wei.[33] showed that daily consumption of *black cumin* seed oil capsules in 40 asthmatic patients for four weeks improved forced expiratory volume (FEV1), decreased eosinophils, and ultimately improved lung function in asthmatic patients. *Nigella sativa* has been shown to regulate leukocytes and

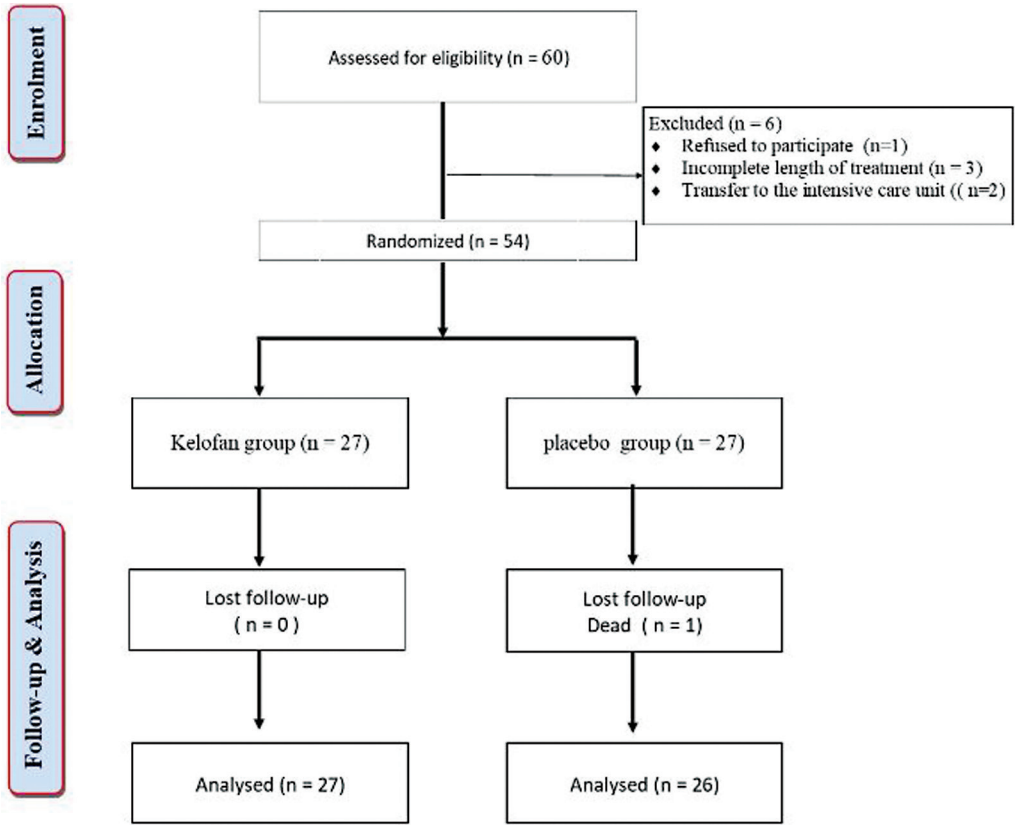

Figure 1: Flowchart of the study design

Table 1: Demographic and baseline characteristics

Variables		kelofan group (n = 27)	Placebo group (n = 26)	*P*
Age, y		55.56 ± 7.3	49.03 ± 6.7	0.127[¥]
Sex, n (%)	Male	12(%44.44)	12(%46.15)	0.951[†]
	Female	15 (%55.55)	14 (%53.84)	
Marital status, n (%)	Single	2 (%7.40)	3 (%11.53)	0.854[†]
	Married	25 (%92.6)	23 (%88.46)	
Educational level, n (%)	Illiterate	10(%37.03)	5 (%19.26)	0.296[†]
	High school diploma or below	10(%37.03)	16 (%61.53)	
	University graduate	7(%25.92)	5 (%19.23)	
Habituation, n (%)	Urban	22 (%81.48)	25 (%96.1)	0.426[†]
	Rural	5 (%18.52)	1 (%3.8)	
Travel history, n (%)	Yes	7 (%25.9)	7 (%26.9)	1.00[†]
	No	20 (%74.1)	19 (%73.1)	
Chronic Diseases	Yes	15 (%55.5)	9 (%34.61)	0.313[†]
	No	12 (%44.44)	17 (%65.38)	
History of using Persian medicines	Yes	11 (%40.74)	7 (%26.9)	0.212[†]
	No	16 (%59.26)	19 (%73.1)	

Data are expressed as means ± SD; p-value < 0.05 is significant
[¥] Based on independent sample *t*-test.
[†] Based on Pearson chi-squared test

lymphocytes in septic rats. In opposition to our findings animal study showed that pretreatment with 100, 200, and 400 mg/kg *Nigella sativa* modulates WBC, lymphocyte, neutrophils, eosinophils, and monocytes counts.[34] In addition, in a study conceded by Ahmad Abadi *et al*.[35] examining the effect of liquorice on SARS-CoV-2, liquorice significantly inhibited SARS-CoV-2 replication *in vitro*. Contrary to the results of our study, Wang, and Zhao[32] showed that Glycyrrhizin improved pulmonary, metabolic status, and oxygen exchange.Also, it stabilized systemic hemodynamics. Glycyrrhizin modulates white blood cells and lymphocytes and reduces organ damage. Lee, Kang[35] considered the effects of *Foeniculum vulgare* on sepsis-induced acute-lung injury in mice. The authors reported that

Table 2: Baseline medical characteristics of patients

Variables	kelofan group (n = 27)	Placebo group (n = 26)	*P*
PCR+	25 (% 92.6)	26 (% 100)	0.725†
Lung CT+	27 (% 100)	26 (% 100)	0.830†
Fever	16 (% 59.25)	16 (% 61.53)	1.00†
Chill	13 (% 48.14)	13 (% 48.14)	1.00†
Cough	21 (% 77.8)	21 (% 80.76)	1.00†
Dyspenea	16 (% 59.25)	18 (% 69.23)	0.694†
Weakness	10 (% 37)	15 (% 57.69)	0.301†
Myalgia	9 (% 33.3)	11 (% 42.30)	0.563†
Gastrointestinal symptoms	17 (% 62.9)	13 (% 50)	0.521†
parosmia	4 (% 14.8)	4 (% 15.38)	1.00†

P-value < 0.05 is significant
† Based on Pearson chi-squared test

treatment with *Foeniculum vulgare* significantly decreased the LDH activity, and cytokine production. *Foeniculum vulgare* reduces inflammatory and tissue damage by inhibiting NF-κB and MAPK expression as well as reducing extracellular signal-regulated kinase (ERK)-induced lipopolysaccharides (LPS) phosphorylation. Also, another study carried out by Ezzeldin, Zikri[36] in 2015, studied the effect of herbal products containing *Foeniculum vulgare, Glycyrrhiza glabra, Pimpinella anisum* on asthmatic patients. Consumption of these herbal compounds for four weeks in 10 patients with asthma reduces the use of corticosteroids and improves lung function without serious side effects. Moreover, in experimentally induced colitis rats, *Adiantum capillus-veneris* supplementation significantly reduced myeloperoxidase (MPO) and inflammation factors.[37] In conformity with our findings, recent RCT experimental results by Javid,

Table 3: Intergroup comparison of primary outcomes before and after intervention in the studied population

Variables		kelofan group (n = 27)	Placebo group (n = 26)	*P*v
O2 Saturation %	Before	87.89 (3.83)	89.37 (3.83)	0.170¥
	After	90.78 (5.30)	91.85 (7.48)	0.546 ¥
	P†	0.055	0.033	
Respiratory rate	Before	19.19 (1.18)	18.85 (0.86)	0.241¥
	After	19.33 (1.52)	18.70 (5.30)	0.170¥
	P†	0.637	0.685	
Temperature	Before	36.94 (0.86)	37.01 (0.50)	0.664¥
	After	37.02 (5.30)	37.01 (0.09)	0.660 ¥
	P†	0.363	0.799	

p-value <0.05 is significant
† Based on Mann-Whitney U
¥ Based on independent Wilcoxon

Table 4: Intergroup comparison of secondary outcomes before and after intervention in the studied population

Variables		kelofan group (n = 27)	Placebo group (n = 26)	*P*v
Cough	Before	2.59 (1.22)	2.33 (1.33)	0.494¥
	After	0.61 (0.94)	0.58 (0.90)	0.917¥
	P†	<0.001	<0.001	
Dyspenea	Before	2.59 (1.42)	1.63 (1.55)	0.018¥
	After	0.64 (1.19)	0.54 (0.95)	0.845¥
	P†	<0.001	<0.001	
Ague	Before	2.11 (1.40)	1.89 (1.48)	0.567¥
	After	3 (0)	3(0)	1.000¥
	P†	0.002	0.005	
Myalgia	Before	1.00 (1.52)	1.33 (1.54)	0.530¥
	After	0.15 (0.05)	0.12 (0.04)	0.219¥
	P†	0.007	0.018	
Weakness (%)	Before	20 (74.1)	16 (59.3)	0699¥
	After	5 (7.2)	3 (5.5)	0.212¥
	P†	< 0.0001	< 0.0001	
Gastro-intestinal symptoms, n (%)	Before	10 (37)	9 (33.3)	0.711¥
	After	4 (5.4)	0 (0)	0.110¥
	P†	0.109	0.004	

p-value < 0.05 is significant
¥Based on Mann-Whitney U
†Based on Wilcoxon

Table 5: Biochemical factors in the study of patients at baseline and after intervention

Variables		kelofan group (n = 27)	Placebo group (n = 26)	*P*v	*P*v
WBC	Before	6852 (2964.81)	6092 (3278.40)	0.187¥	0.427£
	After	9004 (4958.32)	8365 (5278.74)	0.522 ¥	
	P†	0.005	0.049		
LYM	Before	22.62 (11.53)	18.96 (6.54)	0.190¥	0.265£
	After	21.11 (11.71)	16.96 (7.34)	0.202 ¥	
	P†	0.571	0.312		
CRP	Before	10.79 (21.81)	5.65 (6.54)	0.664¥	0.174£
	After	6.80 (11.71)	18.15 (39.46)	0.660 ¥	
	P†	0.567	0.048		
BUN	Before	35.56 (0.86)	28.75 (0.50)	0.358¥	0.236£
	After	39.35 (5.30)	30.73 (0.09)	0.051 ¥	
	P†	0.271	0.745		
Cr	Before	0.98 (0.36)	0.91 (0.15)	0.358¥	0.413£
	After	0.88 (0.22)	0.83 (0.16)	0.291 ¥	
	P†	0.049	0.001		
LDH	Before	643.45 (188.62)	650.71 (181.19)	0.898¥	0.456£
	After	536.76 (136.01)	539.21 (217.87)	0.962 ¥	
	P†	0.019	0.016		

p-value < 0.05 is significant
† Based on Mann-Whitney U
¥ Based on independent Wilcoxon
£ Based on ANCOVA after logarithmically converting; adjusted for baseline values

Motevalli Haghi,[25] investigated the effect of the traditional herbal mixture (comprised of *Matricaria chamomilla*, *Althaea Officinalis*, *Malva sylvestris*, *Hyssopus officinalis*, *Adiantum capillus-veneris, Glycyrrhiza glabra,* and *Ziziphus jujube*) for 14 days on cold asthma symptoms in children. They have shown that there were no remarkable differences in respiratory distress, PEF rate, wheezing, tachypnea, outpatient visits, absence from school, asthma exacerbation, and oral prednisolone or β-agonist usage using herbal mixture supplementation. Also, the hospitalization did not significantly differ between the herbal mixture and placebo groups. A study carried out by Hong, Song[38] on human lung, A549 cancer cells and C57BL / 6 mice showed that betulinic acid isolated from Jujube without any cytotoxic effects had anti-influenza properties. A study by Abdolahinia, Naseri[39] in 2018 on 78 patients with mild to moderate COPD showed that daily consumption of 10 cc of hyssop syrup with routine treatments could significantly improve FEV1, FEV1 / FVC. According to the results of these clinical trials, the anti-inflammation possessions of this plant may have improved patients' symptoms. According to a 2015 study by Wang, and Li,[40] hyssop syrup improves lung function in mice with airway stenosis by reducing eosinophils and neutrophils. It should be noted that the different nature and design of this study may produce conflicting results. Some studies have examined the mechanism of action of these plants, called kelofan in this study, in the pathogenesis of coronavirus and other diseases such as sepsis, asthma, and COPD.[25,41,42] A body of scientific evidence suggests that *nigella sativa* regulates immune responses by downregulation of toll-like receptor-4 (TLR-4) expression and modulation of natural killer (NK) cell lytic activity macrophages activity, neutrophil chemotaxis, and lymphocyte proliferation, and exerts favorable effects against viral diseases.[43,44] In addition, *Nigella sativa* inhibits the production of inflammatory cytokines such as of monocyte chemoattractant protein 1 (MCP-1), IL-6, tumor necrosis factor-α (TNF-α), IL-1β,and cyclooxygenase-2 by inhibiting KB (NF-kB).[43,45,46] Glycyrrhizinin licorice has been a potent inhibitor of replication of viruses including SARS.[47] *Glycyrrhiza glabra*inhibits SARS virus replication by inducing NO synthesis. Glycyrrhizin also affects cellular signaling pathways, including protein activator 1, casein kinase 2, protein kinase c, and NF-kB.[48,49] Also, focusing on clinical symptoms, the last studies have been related to laboratory data, such as lymphocyte count, WBC, elevated LDH, and C-reactive protein (CRP). Studies have shown that certain admitted patients with COVID-19 may have acute kidney injury, heart injury, and liver function impairment. Abnormally in laboratory parameters, especially blood biochemical parameters might be related to the intensity of multiple organ dysfunction. Kelofan, which is composed of various plants as a strong phytochemical, affects hematological indicators in diseases such as colds, asthma, etc. by increasing erythropoiesis and leukocytosis and regulating the activity of the immune system.[25,32,39] Although kelofan syrup has no significant effect on clinical symptoms and blood and inflammatory markers in COVID-19 patients, it may be more effective in other diseases such as asthma, COPD, and influenza in which the duration of intervention can be longer. Our investigation has many powerful points, among that having been carried out for the first time stands out in COVID-19. Also the increase in CRP factor in placebo group might be due to an increase in inflammatory storm that occurs in some stages of COVID-19. Likewise, proper

tolerance to kelofan and no side effects were other benefits of this study. The study also used stratified permuted block randomization and a double-blind design that strengthened the validity of our findings. One of the limitations of the study includesthe lack of follow-up of patients after discharge from the hospital. Also, lack of performing tests of patients at the end of hospitalization is another limitation. In addition, due to ethical principles, we were not able to discontinue the routine treatment to prevent the possible effects of different drugs from on the findings of the study. Moreover, syrup in greater dosages and over a longer period may contribute to greater efficacy.

Conclusion

According to the results of this study, after 7 days of kelofan consumption, there was no significant change in clinical symptoms and biochemical factors such as LYM, BUN, and CRP levels in COVID-19 patients compared to the placebo group. However, in some clinical symptoms such as cough, dyspnea, weakness, and biochemical factors like WBC, Cr, and LDH, a significant change was observed at the end of hospitalization in the intervention group. It is suggested that future studies are needed to be performed in larger sample size, longer duration, and control of other confounding factors to make the results more conclusive.

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

Consent for publication

Not applicable.

Authors' contributions

Arezoo Moini Jazani: Writing - original draft, Conceptualization, Methodology, Software. Shahram Habibzadeh, Hamidreza Nasimi Doost Azgomi, Alireza Nasimi Doost Azgomi, Moharram Aghabalaii; Investigation, Writing - original draft, Writing - review and editing. Ramin Nasimi Doost Azgomi: Supervision, Project administration, Formal analysis, Writing - original draft,.

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Competing interests

All the authors except Alireza and Hamidreza Nasimi Doost Azgomi are academic professors in Ardabil University of Medical Sciences. Alireza and Hamidreza Nasimi Doost Azgomi are medical students in Ardabil University of Medical Sciences. All the authors except Alireza and Hamidreza Nasimi Doost Azgomi are employees of Ardabil University of Medical Sciences. Alireza and Hamidreza Nasimi Doost Azgomi are medical students in Ardabil University of Medical Sciences. They are Ramin 's sons. They contributed to the study design, data collection and manuscript writing. Arezoo is MD-Ph.D of traditional Persian medicine. She is Ramin 's wife. She contributed to the design and implementation of the research, data collection, aiding in interpreting the results and to the writing of the manuscript. No stocks or shares in companies. No patent. Alireza and Hamidreza Nasimi Doost Azgomi are not members of any governmental or non-governmental organization.

Ethical approval

Ethical number: IR.ARUMS.REC.1399.009.

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