Immunopathologia Persa
http www.immunopathol.com
DOI:10.34172/ipp.2022.31355

The combined effect of Algomed and a quadruple herbal brew of Iranian traditional medicine on the severity and outcome of COVID-19; a randomized controlled clinical trial recruiting inpatients

Rahimeh Eskandarian[1], Bahador Bagheri[2], Mehrdad Zahmatkesh[1], Farhad Malek[1], Mahboubeh Darban[1], Mohammad Memarian[1], Ali Gohari[1], Mohammad Amir Sarabi[1], Majid Mirmohammadkhani[3*]

[1]Clinical Research Development Unit, Kowsar Educational, Research and Therapeutic Hospital, Semnan University of Medical Sciences, Semnan, Iran
[2]Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran
[3]Social Determinants of Health Research Center, Department of Epidemiology and Biostatistics, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

***Correspondence to**
Majid Mirmohammadkhani
Email: majidmirmohammadkhani@yahoo.com, Majidmir@semums.ac.ir

Received 2 Jan. 2021
Accepted 26 Feb. 2021
Published online 7 Mar. 2021

Keywords: COVID-19, Complementary medicine, Iranian traditional medicine

Citation: Eskandarian R, Bagheri B, Zahmatkesh Z, Malek F, Darban M, Memarian M, Gohari A, Sarabi MA, Mirmohammadkhani M. The combined effect of Algomed and a quadruple herbal brew of Iranian traditional medicine on the severity and outcome of COVID-19; a randomized controlled clinical trial recruiting inpatients. Immunopathol Persa. 2023;9(2):e31355. DOI:10.34172/ipp.2022.31355.

Abstract

Introduction: Given the importance of coronavirus disease 2019 (COVID-19) as a worldwide issue and its health, psychological and social effects and some serious complications and consequences, it needs to find appropriate treatment for this emerging disease.
Objectives: To evaluate the effectiveness of combination of Algomed and *Mentha longifolia, Matricaria recutita, Althaea rosea* and *Malva sylvestris* on the severity and outcomes of COVID-19.
Patients and Methods: In a randomized clinical trial we included 68 participants with confirmed COVID-19 through PCR tests and/or CT scan, who were admitted to non-ICU wards. The intervention group received four 300-mg Algomed tablets daily, and the quadruple herbal brew three times a day additionally while the control group received routine treatments. The brew was prepared using a large teabag containing 6 g of the four herbs (2 g of *Mentha longifolia*, 2 g of *M. recutita*, 1.4 g of *Malva sylvestris* and 0.6 g of *A. rosea*). The patients were compared daily from their admission to the end of the third day in terms of clinical and para-clinical symptoms, and outcomes.
Results: The two groups were not significantly different in terms of age ($P=0.657$) and gender ($P=0.798$). The median and inter-quartile range of length of stay were respectively 3 and 2-4 days in the intervention group and 5 and 3-9 days in the controls, significantly higher in the control group ($P<0.001$). Comparing the two groups in terms of the difference between the third and the first day values showed a significant difference in white blood cells count, a reduction of 432.9 in the intervention group vs. an increase of 65.5 in the controls ($P=0.049$). Except for diarrhea, which happened more in the control group ($P=0.020$), the two groups were not significantly different in terms of other variations.
Conclusion: The present study results indicated the effects of a combination of Algomed and the brew of *M. longifolia, M. recutita, A. rosea* and *Malva sylvestris* on reducing the length of stay. It is suggested that the findings of this research should be confirmed by more detailed study with bigger sample size. It is also recommended that same or similar research should be conducted in different geographic locations of the world to confirm the outcome of this research. The main limitation of this study is that it was performed only on hospitalized patients who had a milder form of the disease in terms of disease severity. Therefore, the benefits of the interventions cannot be generalized to all patients.
Trial Registration: Registration of trial protocol has been approved by Iranian Registry of Clinical Trials (#IRCT20151228025732N51, https://en.irct.ir/trial/46828, ethical code#IR.SEMUMS.REC.1398.325).

Introduction

Coronavirus is one of the main pathogens among viruses that primarily targets the respiratory system in humans. Previous coronavirus epidemics included severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), both of which were recognized as a public health-threatening factor (1,2). The novel coronavirus causing the so-called COVID-19 as a pandemic has so far resulted in a multitude of infections and high mortality (3-5). Mortality from COVID-19 mainly

Key point

In a Randomized clinical trial, we included 68 participants with confirmed COVID-19. Our results showed the combination of Algomed and the brew of Mentha longifolia, *Matricaria recutita, Althaea rosea* and *Malva sylvestris* may reduce the length of stay of COVID-19 patients.

caused by severe respiratory involvement is reported in 2%-3% of the cases and often in the eighth decade of life (6).

According to the available scientific evidence, the symptoms of COVID-19 infection emerge after an incubation period of 5-6 days, and the interval between the onset of symptoms and death or recovery is 6-41 days with a mean length of 14 days. This interval depends on age and the immune system status and is longer at over 70 years of age compared to the younger ages (6,7). The most prevalent symptoms of this disease include fever, cough and fatigue and the other symptoms include headache, runny nose, sneeze, sore throat and mucus secretion from the airways (5,6,8). Although targeting the airways constitutes the main feature of this virus, gastrointestinal symptoms, including dyspepsia and diarrhea, and symptoms relating to the nervous system involvement such as loss of consciousness and seizure have been reported in many of the patients. This disease was also found to be associated with increased risk of depression, anxiety and sleep disorders (9-11). In contrast, similar atypical symptoms have been rarely reported in MERS-CoV or SARS-CoV. Severe COVID-19 symptoms have been associated with an increased mortality across the world (12,13). The in-vitro symptoms of COVID-19 include lymphocytosis, lymphopenia and high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels. In addition, increased levels of inflammatory cytokines, eosinophilia and positive D-dimer results reported have been associated with poor prognosis in some of the patients (14).

In addition to the lack of an appropriate and effective vaccine, therapeutic strategies for this disease are still in the exploratory stage. Given the current unavailability of effective antiviral drugs in COVID-19 in humans, supportive therapies, including oxygen therapy and respiratory support, coupled with a wide range of antiviral drug are considered the main treatment options before a definitive treatment is found (14). Given the type of medications used, the risk of adverse drug reactions (ADRs) increases owing to simultaneously administering several medicines in one patient. ADRs were reported mainly as gastrointestinal complications and liver diseases in 8.37% of COVID-19 patients (15). In infection with COVID-19, the role of inflammatory and immune mediators has been confirmed in exacerbating the disease and its symptoms. Increasing immunity while reducing the inflammatory process constitutes a treatment goal in infection with COVID-19 (6).

According to the World Health Organization and international assemblies, fighting with this disease requires a comprehensive and trans-sectoral approach. Complementary medicine has always held a special and acceptable position in treating or reducing the severity of many diseases. Using and evaluating the effect of potentially-effective and low-complication complementary medicine methods such as herbal medicines and traditional medicine in conjunction with other known supportive and medicinal methods can significantly help reduce the symptoms and complications of diseases or shorten the recovery period (16, 17).

Given the history of traditional medicine in China as the country where the epidemic started, using traditional medicine was considered by researchers and physicians in the country from the onset of this disease (16). In recent years, taking a scientific approach to Iranian traditional medicine in addition to its long and glorious history has increasingly attracted public attention. Herbal brews commonly used in this medicine have been welcomed by the public and the medical community owing to their cost effectiveness, simplicity and negligible side-effects (18). Despite the potentially-negligible effects of individual herbal medicines on treating diseases such as COVID-19, the likelihood of the synergetic effectiveness of several therapeutic methods as an option raises a question on the minds of researchers and therapists if combining a number of known and acceptable herbal medicines can yield better treatment or supportive outcomes in COVID-19 patients.

Objectives

To answer this question and based on Iranian traditional medicine, the present exploratory randomized controlled clinical trial assessed the combined effect of Algomed as a well-known nutritional-medicinal supplement and the quadruple herbal brew of *Mentha longifolia, Matricaria recutita, Althaea rosea and Malva sylvestris* on the severity and outcomes of COVID-19 in patients admitted to a teaching hospital in Iran.

Patients and Methods

Study design

The present clinical trial included 68 patients with confirmed COVID-19 through PCR tests and/or CT scan, who were admitted to non-ICU wards and were willing to participate in the study. The exclusion criteria comprised meeting nothing by mouth (NPO) conditions, an age of below 18 years, pregnancy, a history of malignancies or cardiothoracic surgeries or underlying pulmonary diseases such as asthma and chronic obstructive pulmonary disease and hospitalization in the ICU upon admission owing to severity of their disease, loss of consciousness or the need for mechanical ventilation. The inclusion criteria consisted of hospitalization due to the disease for the first time and the time elapsed since the onset of symptoms being below 72 hours. The patients who were discharged or died within 24

hours of their hospitalization were excluded. The patients were briefed on the study objectives and process, asked to sign written informed consent forms and then interviewed by a physician, who recorded their details, including age, gender and history of diabetes, hypertension and heart disease. The patients were assigned into the two groups, an intervention or a control group using permuted block randomization. The control group received only routine antibiotic and antiviral drugs, whereas the intervention group received both the routine treatment and four 300-mg supplementary *Chlorella vulgaris* (Algomed) tablets (Bio-product Company, Steinberg, Germany) daily, two with breakfast, one with lunch and one with dinner. In addition to this supplement, the intervention group received the quadruple herbal brew containing *M. longifolia, Matricaria recutita, Althaea rosea* and *Malva sylvestris,* three times a day. The brew was prepared using a large teabag containing 6 g of the four herbs (2 g of *M. longifolia*, 2 g of *M. recutita*, 1.4 g of *Malva sylvestris* and 0.6 g of *Althaea rosea*). After purchasing standard basic ingredients, each teabag was made in a standard condition under the supervision of the research group through milling, weighing, and packaging by experts in herbal brews. The brew was prepared by holding a teabag in a glass of boiling water for 15 minutes. The patient drank half of this glass of brew half an hour before each meal under the supervision of the ward nurses. The patients used the brew for a minimum of two days (at least six times), and the intervention continued until the end of hospitalization with the patients' consent. In case of nausea, vomiting or gastrointestinal intolerance, the patients were allowed to postpone drinking the brew or miss a maximum of one brew on condition that they have taken at least six brews and tablets totally.

The patients were evaluated daily from their admission to the end of the third day in terms of clinical symptoms, i.e., temperature, respiratory rate, heart rate, blood pressure, coughs, diarrhea, myalgia and intensity of dyspnea, and para-clinical symptoms, i.e. complete blood count (CBC), serum creatinine levels, ESR and CRP. The intensity of dyspnea was measured on a visual analogue scale. The assessment results were recorded in a checklist. At the end of hospitalization, the two groups were compared in terms of the recorded disease outcomes (length of stay, transfer to the ICU, and need for mechanical ventilation) and the patient's ultimate status (deceased or discharged).

Statistical analysis

The minimum sample size for this initial exploratory study was calculated as 30 per group using G*Power taking the number of days of hospitalization as an initial outcome with an effect size of 0.8, a 95% confidence interval and a power of 80% for comparing two independent samples. To obtain the minimum sample size required, 80 hospitalized COVID-19 patients who consented to use the herbal medicine were assessed in terms of other criteria. Ten of these patients were excluded for not satisfying the inclusion criteria. Two excluded patients out of the remaining 70, who were randomly divided into two groups, included one in the intervention group due to the intolerance of the herbal medicine taste and one in the controls due to early discharge. The data of 68 patients in two groups of 34 were ultimately analyzed as per Figure 1.

The two groups were compared in terms of age, gender and underlying diseases using the chi-square test. To evaluate the potential effects of the intervention on the clinical variables (vital signs) and laboratory variables, the two groups were compared in terms of the difference in the variables between the third and first days using the Mann-Whitney U test. In each group, the changes in the qualitative variables (coughs, diarrhea and myalgia) between the third and first days were compared using the McNemar's test and the ratios between the two groups were compared using the Z-test. The data collected were analyzed by SPSS version 23.

Results

The present study recruited 68 COVID-19 patients, including 45 (66.2%) males (23 in the intervention and 22 in the control group), hospitalized in Kowsar hospital, Semnan, Iran. The mean age of the patients was 54.66 ± 19.1 years (the intervention group: 52.91 ± 20.7 years and the control group: 56.41 ± 17.5 years). The two groups were not significantly different in terms of age distribution ($P = 0.657$), gender distribution ($P = 0.798$) and frequency distribution of the underlying diseases such as diabetes, hypertension, angina, cardiac failure and chronic renal failure ($P = 0.476$; Table 1).

During the hospitalization, no need for transfer to the ICU, respiratory intubation or mechanical ventilation and no deaths were reported in either group. All the participants were discharged with a good general health status. The median and inter-quartile range of length of stay were respectively 3 and 3-6 days in all the patients, 3 and 2-4 days in the intervention group and 5 and 3-9 days in the controls. The length of stay was also significantly higher in the control group ($P < 0.001$). Table 2 presents the mean values of vital signs and laboratory symptoms in the patients in the first three days of hospitalization. Comparing the two groups in terms of the difference between the third and the first day values showed a significant difference in WBC in a way that a reduction of 432.9 was observed in the intervention group and an increase of 65.5 in the controls over the three days ($P = 0.049$). Except for WBC, the two groups were not significantly different in terms of variations in any of the cited variables.

Table 3 shows the process of recovery in the two groups based on three measurements of the cough, diarrhea and myalgia in the first three days of hospitalization in two groups. Except for diarrhea, which happened more in the control group ($P = 0.020$), the two groups were not significantly different in terms of other variations.

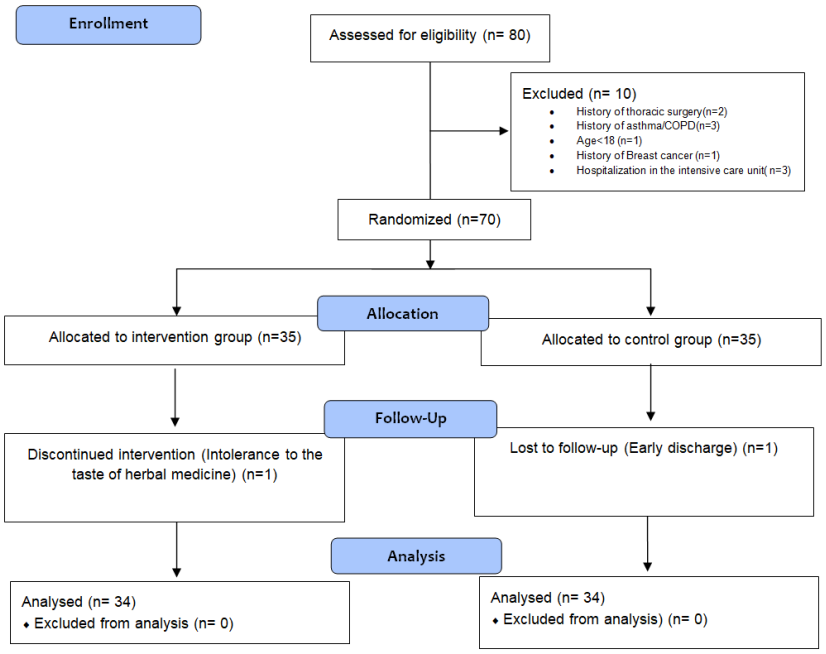

Figure 1. Flow diagram of enrollment and random assignment of study participants.

Discussion

Scientifically known as *Chlorella vulgaris*, Algomed is a commercial name for a medication prepared from a single-cell alga. Algomed is in fact a nutritional-medicinal supplement rich in beneficial fibers-minerals that contains many essential vitamins and amino acids. Owing to its anti-oxidant, antiseptic, immune-boosting and inflammation inhibiting properties, this medicine has been used in many diseases, including the prevention and treatment of influenza (19,20). Investigated the effects of Algomed on pulmonary symptoms and function in patients with silicosis, Tavana et al reported reduced coughs, sputum and dyspnea and improved lung function at the end of an eight-week treatment (21). Investigating the effect of Chlorella vulgaris on antioxidant status in e smokers, Lee et al reported a significant increase in plasma vitamin C (44.4%), alpha-tocopherol (15.7%), and erythrocyte catalase and superoxide dismutase (SOD) activities at the end of a six-week treatment. The *C. vulgaris* extract was also found to significantly decrease in lymphocyte DNA damage, as measured by comet assay, placebo supplementation also decreased the measured amount of lymphocyte DNA damage in chronic smokers (22). Examining the effect of the C. *vulgaris* extract on the antioxidant status showed to reduce SOD activity in senescent human diploid fibroblasts (HDFs). *C. vulgaris* has the potential as anti-ageing entities which compensated the role of antioxidant enzymes in cellular ageing of HDFs (23). Cultivation of green microalgal species Chlorella vulgaris resulted in a significant production of extracellular polysaccharide (EPS) and showed that caused significant bronchodilatory, anti-inflammatory and antitussive effects in test animals.

Table 1. Characteristic of participants by two groups

Characteristics		Count (%)		Total	*P* value
		Intervention	Control		
Age group (year)	<40	10 (29.4)	7 (20.6)	17 (25.0)	0.657
	40-60	11 (32.4)	11 (32.4)	22 (32.4)	
	>60	13 (38.2)	16 (47.1)	29 (42.6)	
Gender	Male	23 (67.6)	22 (64.7)	45 (66.2)	0.798
	Female	11 (32.4)	12 (35.3)	23 (33.8)	
Underlying disease	No	18 (52.9)	15 (44.1)	33 (48.5)	0.467
	Yes	16 (47.1)	19 (55.9)	35 (51.5)	
	Diabetes Mellitus	5	5	10	
	Hypertension	8	9	17	
	Cardiac angina	1	3	4	
	Heart failure	1	1	2	
	Chronic renal failure	2	0	2	
Total		34 (50)	34 (50)	68 (100)	

Table 2. Mean and standard deviation of patients' vital and laboratory symptoms in the first three days of hospitalization in the two groups

Sign/ Index	Group	First day		Second day		Third day		*P* value*
		Mean	SD	Mean	SD	Mean	SD	
DS (scale)	Intervention	4.1	2.3	3.6	1.9	3.5	2.0	0.516
	Control	5.5	1.5	5.5	2.1	4.7	1.5	
SBP (mm Hg)	Intervention	117.8	11.9	114.7	8.6	114.7	7.7	0.472
	Control	126.7	17.1	119.3	11.4	121.3	11.8	
DBP (mm Hg)	Int	74.5	7.3	72.5	5.6	72.0	4.9	0.515
	Control	78.7	7.4	74.2	7.7	75.8	6.3	
PR (pulse/min)	Intervention	88.6	11.0	84.9	10.4	82.8	8.5	0.931
	Control	88.5	11.0	84.2	12.2	83.3	8.8	
RR (breath/min)	Intervention	19.7	2.6	18.7	1.9	18.6	2.0	0.950
	Control	19.5	2.1	18.3	1.4	18.6	1.9	
T (ºC)	Intervention	36.8	0.5	36.7	0.2	36.6	0.2	0.995
	Control	37.1	0.8	37.0	0.6	36.9	0.5	
Cr (mg/dL)	Intervention	1.0	0.3	1.0	0.3	1.0	0.3	0.564
	Control	1.5	1.7	1.5	1.7	1.5	1.7	
CRP (qualitative)	Intervention	2.0	0.5	1.9	0.5	1.7	0.5	0.630
	Control	3.2	0.4	3.1	0.4	3.2	0.4	
ESR (mm/h)	Intervention	34.9	23.1	34.1	21.4	34.1	21.4	0.180
	Control	43.7	27.3	43.7	27.3	43.7	27.3	
WBC (/µL)	Intervention	7599.1	2227.1	7166.1	1821.2	7166.1	1821.2	0.049
	Control	7622.3	2824.1	7687.9	2755.7	7687.9	2755.7	
Lymph (%)	Intervention	32.5	9.7	30.7	10.4	30.7	10.4	0.988
	Control	25.8	12.0	22.7	10.2	22.7	10.2	

DS: Dyspnea severity, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pals rate, RR: Respiratory rate, T: Temperature, Cr: Creatinine, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood-cell count, Lymph: Lymphocyte cell count, SD: Standard deviation, SE: Standard error, ES: Estimated average based on repeated measurements ANOVA model.

**P* value of U Mann-Whitney test to compare the two groups in terms of the difference between the first day and the third day

Table 3. Number and percentage of patients' symptoms (cough, diarrhea and myalgia) in the first three days of hospitalization in two groups

Sign		First day		Second day		Third day		Change% (i-j)	*P**	*P***
		No	Yes (i)	No	Yes	No	Yes (j)			
Cough	Intervention	13 (38.2)	21 (61.8)	18 (52.9)	16 (47.1)	25 (73.5)	9 (26.5)	35.3	<0.001	0.804
	Cnl	12 (35.3)	22 (64.7)	16 (47.1)	18 (52.9)	25 (73.5)	9 (26.5)	38.2	0.004	
Diarrhea	Intervention	32 (94.1)	2 (5.9)	33 (97.1)	1 (2.9)	32 (94.1)	2 (5.9)	0	>0.999	0.020
	Control	33 (97.1)	1 (2.9)	30 (88.2)	4 (11.8)	28 (82.4)	6 (17.6)	-14.7	0.063	
Myalgia	Intervention	15 (44.1)	19 (55.9)	22 (64.7)	12 (35.3)	29 (85.3)	5 (14.7)	41.2	0.001	0.616
	Control	16 (47.1)	18 (52.9)	27 (79.4)	7 (20.6)	28 (82.4)	6 (17.6)	35.3	0.002	

*McNemar Test comparing first and third days, **Two-sample z-test of proportion.

Chlorella EPS appears to be a promising agent for the prevention of chronic airway inflammation, which is the basic pathogenic mechanism of many respiratory diseases, including bronchial asthma (24).

The four main herbal medicines in Iranian traditional medicine include *M. longifolia, M. recutita, A. rosea* and *M. sylvestris*, which have been long used as a brew to treat many diseases, especially cold and respiratory diseases (25, 26). In addition to its antioxidant and antimicrobial properties, the potent anti-inflammatory effects of the chamomile extract have been shown in in-vitro studies. This plant contains active compounds such as terpenoids and flavonoids, and the relationship of terpenoids with anti-inflammatory effects has been demonstrated (27, 28). The *M. longifolia* extract has antioxidant and antimicrobial properties and its antimicrobial properties are attributed to the presence of pulegone, menthone and neo-menthone groups (26, 29). *M. sylvestris* has also been recommended in Iranian traditional medicine for the treatment of respiratory problems. *M. sylvestris* is a Mediterranean plant with a reported origin in the Middle East. Its scientific name "Althaea" in Greek refers to repairing and healing. This plant was used by ancient Egyptians traditional medicine to treat coughs (26). Furthermore, *A. rosea* is used to treat infectious and respiratory diseases due to its triple properties, i.e. antimicrobial and immune system moderating properties and dilution of respiratory tract secretions (30, 31). The present study showed that adding the Algomed supplement and a brew of *M. longifolia, M. recutita, A. rosea* and *M. sylvestris* to common COVID-19

treatments reduces the length of stay of the patients. Research suggests the anti-inflammatory effects of each of the four herbs. Algomed also has anti-inflammatory and immune system moderating properties. An overactive immune system and overproduction of inflammatory cytokines are observed in the pathogenesis of COVID-19, especially in its severe and critical cases. Therefore, prescribing medications with anti-inflammatory mechanisms of effect appears beneficial. The present study found reductions in inflammatory indicators, even though the difference between the two groups was insignificant, which can be explained by small sample; nevertheless, this reduction is clinically significant. An important point about medications with significant effects on the immune system is the administration timing and dose. At what stage of infectious diseases such as COVID-19 these medications should be administered is clinically controversial. Increasing the dose of these compounds or prolong the treatment might improve the clinical status of the patients and reduce their immune and inflammatory functions. It is recommended that further studies be conducted to determine other factors that potentially affect the reduction in length of stay in patients receiving this medication regimen. The two groups were different in terms of the prevalence of diarrhea in a way that diarrhea was less prevalent in the intervention group. Many studies have demonstrated the positive effects of Algomed and chamomile on the gastrointestinal tract, especially in dyspepsia. The effects of these compounds on the treatment of diarrhea and prevention of stomach involvement are mediated by reducing bowl movements.

Conclusion

The present study results indicated the effects of a combination of Algomed and the brew of *M. longifolia*, *M. recutita*, *A. rosea* and *M. sylvestris* on reducing the length of stay of COVID-19 patients. More detailed studies with bigger sample size should be conducted for confirming findings of this research. It is also recommended that same or similar research should be carried out in different geographic locations of the world to confirm the outcome of this research.

Limitation of the study

The main limitation of this study is that it was performed only on hospitalized patients who had a milder form of the disease in terms of disease severity. Therefore, the benefits of the interventions cannot be generalized to all patients.

Disclaimer

Lepidus stadium was removed from the intervention in order to reduce the volume of the brew and increase patient collaboration when the study began. Actually, it was supposed to be in the composition at first, but it was removed due to its similarity in effects with other elements. Since no new drug was added to the registered protocol and only a fraction of the herbal brew was reduced, the authors do not believe that there was a serious deviation in the protocol. However, the necessary correspondence will be done with the Iranian website of IRCT for correction. Regarding the issue of random allocation, since the intervention and data collection process was to be done during the epidemic peak and high stress on hospital medical staff, the researchers were not sure that could easily and carefully perform random assignment. But in practice it was done correctly and therefore it was mentioned in the article. Because the action taken is superior to what was written in the protocol in terms of accuracy and internal validity, in the opinion of the authors, there is no adverse or serious deviation from it.

Acknowledgments

We would like to appreciate the Centre for Clinical Research Development Unit of Kowsar Hospital the Vice Chancellor for Research and Technology of the Semnan University of Medical Sciences for approval of this work. Also, the authors thank all patients for helping and participating in the study.

Authors' contribution

Conceptualization: RE, MZ, MaM.
Methodology: MaM, MZ.
Validation: MaM, RE.
Formal analysis: RE, MZ, MaM.
Investigation: MaM, RE.
Resources: RE, MZ, MaM.
Data curation: MaM, RE.
Writing–original draft: MaM, RE.
Writing–review and editing: FM, MaD, MM, AG, MAS.
Visualization: MaM, RE.
Supervision: BB.
Project administration: MaM.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study is a randomized controlled trial registered in the Iranian Registry of Clinical Trials (identifier: IRCT20151228025732N51, https://en.irct.ir/trial/46828). The research followed the tenets of the Declaration of Helsinki. The study was reviewed and approved by the committee of Semnan University of Medical Sciences (ethical code#IR.SEMUMS.REC.1398.325). Additionally, written informed consent was taken from all participants before the study. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by research deputy of Semnan University of Medical Sciences (Grant# A-28-10-229).

References

1. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. J Travel Med. 2020;27:1-3. doi: 10.1093/jtm/taaa008.
2. Hattam C, Evans L, Morrissey K, Hooper T, Young K, Khalid F, et al. Building resilience in practice to support coral communities in the Western Indian Ocean. Environ Sci Policy. 2020;106:182-90. doi: 10.1016/j.envsci.2020.02.006.
3. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Int J Infect Dis. 2020;92:214-7. doi: 10.1016/j.ijid.2020.01.050.
4. Du Toit A. Outbreak of a novel coronavirus. Nat Rev Microbiol. 2020;18:123-. doi: 10.1038/s41579-020-0332-0.

5. Ren L-L, Wang Y-M, Wu Z-Q, Xiang Z-C, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020;133:1015-24. doi: 10.1097/cm9.0000000000000722.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395:497-506. doi: 10.1016/S0140-6736(20)30183-5.
7. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020;35:e79. doi: 10.3346/jkms.2020.35.e79.
8. Carlos WG, Cruz CSD, Cao B, Pasnick S, Jamil S. Novel Wuhan (2019-nCoV) Coronavirus. Am J Respir Crit Care Med. 2020;201:P7-P8. doi: 10.1164/rccm.2014P7.
9. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res. 2020;288:112954. doi: 10.1016/j.psychres.2020.112954.
10. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17:1729. doi: 10.3390/ijerph17051729.
11. Pfefferbaum B, North CS. Mental Health and the Covid-19 Pandemic. N Engl J Med 2020;383:510-12. doi: 10.1056/NEJMp2008017.
12. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. 2013;13:752-61. doi: 10.1016/S1473-3099(13)70204-4.
13. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020:2000524. doi: 10.1183/13993003.00524-2020.
14. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269-71. doi: 10.1038/s41422-020-0282-0.
15. Sun J, Deng X, Chen X, Huang J, Huang S, Li Y, et al. Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System. Clinical pharmacology and therapeutics. 2020;18:1-7. doi: 10.1002/cpt.1866.
16. Luo H, Tang Q-L, Shang Y-X, Liang S-B, Yang M, Robinson N, et al. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. Chin J Integr Med. 2020;26:243-50. doi: 10.1007/s11655-020-3192-6.
17. Hao Y XT, Hu H, Wang P, Bai Y Prediction and analysis of Corona Virus Disease 2019. PLoS One. 2020;15:e0239960. doi: 10.1371/journal.pone.0239960.
18. Nontokozo Z. Msomi, Simelane MBC. Herbal Medicine: IntechOpen; 2018 [November 5th 2018]. Available from: https://www.intechopen.com/books/herbal-medicine/herbal-medicine.
19. Smith TJ, George DR, Sparagano OA, Seal C, Shiel RS, Guy JH. A pilot study into the chemical and sensorial effect of thyme and pennyroyal essential oil on hens eggs. Int J Food Sci Technol. 2009;44:1836-42. doi: 10.1111/j.1365-2621.2009.02008.x.
20. Hage-Sleiman R, Mroueh M, Daher CF. Pharmacological evaluation of aqueous extract of *Althaea officinalis* flower grown in Lebanon. Pharmaceutical biology. 2011;49:327-33. doi: 10.3109/13880209.2010.516754.
21. Tavana S, Kamelian T, Javadi A, Nooraei N, Hashemian SM. Positive effect of *Chlorella vulgaris* complementary therapy on the symptoms and pulmonary function in patients with silicosis. Arch Crit Care Med. 2015;1:e3400. doi: 10.17795/accm-3400.
22. Lee SH, Kang HJ, Lee H-J, Kang M-H, Park YK. Six-week supplementation with *Chlorella* has favorable impact on antioxidant status in Korean male smokers. Nutrition. 2010;26:175-83. doi: 10.1016/j.nut.2009.03.010.
23. Makpol S, Yeoh TW, Ruslam FA, Arifin KT, Yusof YA. Comparative effect of *Piper betle, Chlorella vulgaris* and tocotrienol-rich fraction on antioxidant enzymes activity in cellular ageing of human diploid fibroblasts. BMC Complement Altern Med. 2013;13:210. doi: 10.1186/1472-6882-13-210.
24. Barboríková J, Šutovská M, Kazimierová I, Jošková M, Fraňová S, Kopecký J, et al. Extracellular polysaccharide produced by *Chlorella vulgaris* - Chemical characterization and anti-asthmatic profile. Int J Biol Macromol. 2019;135:1-11. doi: 10.1016/j.ijbiomac.2019.05.104.
25. Setorki M, Moshfegh A, Raoufi N. Effect of hydroalcoholic extract of *Matricaria chamomilla* on passive avoidance memory and pain induced by global cerebral ischemia in Wistar rat. J Shahrekord Univ Med Sci. 2016;17:76-86.
26. Teixeira B, Marques A, Ramos C, Batista I, Serrano C, Matos O, et al. European pennyroyal (*Mentha pulegium*) from Portugal: Chemical composition of essential oil and antioxidant and antimicrobial properties of extracts and essential oil. Ind Crops Prod. 2012;36:81-7.
27. Borowitzka M. Vitamins and fine chemicals from micro-algae. Cambridge University Press; 1988.
28. Tomada M, Shimada K, Shimizu N. Plant Mucilages. XXXII. A Representative Mucilage," Althaea-Mucilage R," from the Roots of *Althaea rosea*. Chem Pharm Bull. 1983;31:2677-84.
29. Schubert L. The use of spirulina and *Chlorella* as food resource for animals and humans. In: Round FE, ed. Progressing Physiological Research. Bristol, UK: Biopress Ltd; 1988.
30. Ayrle H, Mevissen M, Kaske M, Nathues H, Gruetzner N, Melzig M, et al. Medicinal plants--prophylactic and therapeutic options for gastrointestinal and respiratory diseases in calves and piglets? A systematic review. BMC Vet Res. 2016;12:89. doi: 10.1186/s12917-016-0714-8.
31. Alamgeer, Younis W, Asif H, Sharif A, Riaz H, Bukhari IA, et al. Traditional medicinal plants used for respiratory disorders in Pakistan: a review of the ethno-medicinal and pharmacological evidence. Chin Med. 2018;13:48. doi: 10.1186/s13020-018-0204-y.