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Clinical trial

Effect of a diet based on Iranian traditional medicine on inflammatory markers and clinical outcomes in COVID-19 patients: A double-blind, randomized, controlled trial

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ABSTRACT

Introduction: SARS-CoV-2 causes severe acute respiratory syndrome prompting worldwide demand for new antiviral treatments and supportive care for organ failure caused by this life-threatening virus. This study aimed to help develop a new Traditional Persian Medicine (TPM) -based drug and assess its efficacy and safety in COVID-19 patients with major symptoms.

Methods: In February 2022, a randomized clinical trial was conducted among 160 patients with a confirmed diagnosis of COVID-19 admitted to Emam Reza (AJA) Hospital in Tehran, Iran. During their hospitalization, the intervention group received a treatment protocol approved by Iran's Ministry of Health and Medical Education (MOHME), consisting of an Iranian regimen, Ficus carica; Vitis vinifera, Safflower, Cicer arietinum, Descurainiasophia seeds, Ziziphus jujuba, chicken soup, barley soup, rose water, saffron, and cinnamon spices. All patients were compared in terms of demographics, clinical, and laboratory variables.

Results: One hundred and sixty COVID-19 patients were divided into two groups: intervention and control. In baseline characteristics, there was no significant difference between the intervention and control groups ($p>0.05$). Using SPSS software version 22, statistical analysis revealed a significant difference in four symptoms: myalgia, weakness, headache, and cough ($p<0.05$). During the 5-day treatment period, the control group had significantly lower C-reactive protein ($p<0.05$).

Conclusion: While more research with a larger sample size is needed, the proposed combination appears to be effective in the treatment of symptoms as well as inflammatory biomarkers such as C-reactive protein in COVID-19 patients.

Iranian registry of clinical trials (IRCT) IRCT20220227054140N1.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; Cr, creatinine; FAS, Fatigue Assessment Scale; HB, hemoglobin; ICU, Intensive care unit; LDH, lactate dehydrogenase; MOHME, Ministry of Health and Medical Education; PCR, Polymerase chain reaction; RBC, red blood cells; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOD, Superoxide dismutase; TPM, Traditional Persian Medicine; VAS, Visual analog scale; WBC, white blood cells.

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1. Introduction

Severe acute respiratory syndrome (SARS-CoV-2) is a new member of the Coronaviridae family which has recently caused a global outbreak of a disease called Coronavirus disease 2019 (COVID-19). Although various antiviral agents are currently used for the management of hospitalized patients such as remdesivir, ritonavir, lopinavir, and ribavirin, still a growing number of deaths occur all around the world, which has made scientists seek more effective therapeutic agents [1].

Despite its long history, traditional medicine is still of interest to its believers, especially in Asia and Africa, to cure various human diseases. The main reasons for this preference are low cost, cultural acceptability, and high efficacy to cure diseases. Consequently, new interventions have been performed to incorporate traditional medicine in promoting health in societies with traditional beliefs [2]. In recent years, the use of complementary therapies in the control of inflammation and oxidative stress as well as clinical outcomes in critically ill patients has increased and it has been shown that it can be effective [3–5]. In the previous studies, it has been shown that the use of evidence-based traditional and complementary medicine can be effective in improving the clinical outcomes of patients with COVID-19 [6, 7].

Traditional Persian Medicine (TPM), one of the most ancient medical doctrines, is mostly known through manuscripts by Persian scientists such as *The Great Continens* by *Rhazes* and *The Canon of Medicine* by Avicenna [8]. Valuable manuscripts regarding anatomy and physiology, surgery instruments, disease diagnosis, and single and compound natural medicines have been published based on TPM [9] Moreover, TPM has various recommendations for the management of organ damage due to infections [10]. One of the most important approaches in both primary and secondary treatments of diseases in TPM is protecting the four body humors (phlegm, blood, bile, and melancholy) from infection [11]. Several types of infections with various clinical manifestations, described in TPM textbooks and manuscripts, have similar features to that of SARS-CoV-2. A pathological condition explained in TPM for the humors is “humor excitation”, equivalent to the activation of inflammatory pathways [12]. The antiviral potential of components of this TPM based regimen has been previously investigated in vivo and in vitro. In a recent study Ali et al. reported the identification of potential SARS-CoV-2 main protease inhibitors from *Ficus carica* latex. These phytochemicals had noticeable pharmacokinetics, physicochemical, and drug-likeness properties and did not possess any significant detrimental effects hence could be considered as potential drug candidates against SARS-CoV-2 [13]. The present randomized controlled trial was performed to determine the effect of a diet based on the principles of the TPM on inflammatory pathways and clinical outcomes in patients with COVID-19.

2. Methods

2.1. Study design

The current study is a 5 days RCT that was conducted in February 2022 to April 2022 from patients who were admitted with a diagnosis of COVID-19 in Emam Reza (AJA) Hospital Tehran, Iran.

2.2. Ethical considerations

The research method was explained to the patients before they were enrolled in the trial, and they gave their informed consent. Researchers followed the principles of the *Declaration of Helsinki (DoH)* and kept patient information secret throughout the trial. The researchers paid for the entire project, and the patients didn’t have to pay anything extra. This study was approved by the ethics committee of AJA University of Medical Sciences under the ethical code IR.AJAUMS.REC.1400.307 and was registered in the Iranian registry of clinical trials (IRCT) under the number IRCT20220227054140N1.

2.3. Sampling

The study population was patients admitted with a definitive diagnosis of COVID-19 in the wards of *Emam Reza (AJA) Hospital* in Tehran. We used G*Power software to calculate study sample size; Assuming α=0.05, study power=80% and effect size=0.4, total sample size was calculated 196 individuals, and finally 80 patients were included in each of the intervention and control groups. The samples were then randomly assigned using block randomization with a fixed block size of 4 (to ensure that everyone had an equal chance of being in the two groups) to control or L-intervention group assigned to the study groups. In two groups, after 24-hour of admission in the wards and when hemodynamic resuscitation and stabilization were carried out, nutrition was initiated to provide 80 to 100% of the energy requirements of each patient.

2.4. Inclusion criteria

Subjects admitted with a definitive diagnosis of PCR test for COVID-19, aged over 18 years, positive clinical symptoms including fever greater than 38°, hot flush with at least one of the symptoms of dry cough; 24 $\leq$ respiratory rate (per minute); headache or body aches; weakness and lethargy; anosmia or anorexia nervosa. The patients were also expected to be hospitalized for at least 5 days and had no need to be admitted to the intensive care unit (ICU). Patients with respiratory distress, any allergies or uncontrolled complications, or who have been discharged, were not included in the study. These criteria were overseen by an infectious disease specialist.

2.5. Exclusion criteria

Dissatisfaction with continued Iranian regimen supplementation, dissatisfaction with study participation, history of uncontrolled diabetes, severe cardiovascular disease, severe shortness of breath, severe liver or kidney disease, or any uncontrolled systemic disease, history of current anti-psychosis, drug abuse, and being lactating or pregnant.

2.6. Intervention

After receiving a written agreement and outlining the study conditions, all patients who met the inclusion criteria at the time of the study were invited to participate. By tossing coins, patients in the current trial were separated into control and intervention groups. Patients’ ages were taken into account. The following was the treatment procedure for the control and intervention groups during the period of hospitalization. The treatment plan for the intervention group was approved by the Ministry of Health of Iran. The traditional Persian supplement was obtained from the combination of *Ficus carica;* Vitis vinifera; Cicer arietinum; *Descurainiasophia* seeds, Safflower, Ziziphus jujuba, chicken soup; barley soup, rose water, and saffron and cinnamon spices, seven times a day. The control group in this investigation only were given the approved treatment protocol. Optimal doses along with the lowest risk of side effects were chosen based on literature studies. For the first meal, a tablespoon of *Descurainiasophia* seeds dissolved in boiling water was given, when the person was fasting. One soft-boiled egg with 5 gs of butter and one teaspoon of honey was considered breakfast each day. For the third meal, 5 *Ficus carica* in a glass of boiling water with a tablespoon of honey was used. One hour later, a teaspoon of Vitis vinifera was received by the patients. A combination of 50 gs Cicer arietinum, 10 gs rice, and 30 gs lamb meat, 15 gs Safflower with saffron and cinnamon spices was employed once per day as lunch. In the evening and as a high-tea meal, 5 Ziziphus jujuba in half a glass of boiling water along with rose water was given to the subjects once per day. In addition, chicken soup and barley soup were approved for dinner.

2.7. Control group

During the hospitalization, the control group was to be given a normal hospital diet approved by the Iran's Ministry of Health and Medical Education. Energy requirement was calculated to provide 25–30 kgcalories of energy per kilogram of the body weight of each patient. The standard protocol diet was designed by a dietician for the control group of patients, and in this diet, based on the patient's requirements and the hospital's food plan, the macronutrients included in the standard protocol diet consist of 55% of carbohydrates, 30% of fat, and 15% of protein.

2.8. Data collection

In terms of demographics, vital signs, laboratory, and clinical characteristics of all patients were compared. Gender, age, smoking history, BMI, height, and weight were among the demographic factors studied. Heart rate, respiration rate temperature, arterial blood oxygen saturation, and diastolic and systolic blood pressure, were all monitored and recorded daily in both groups. Pulse rate, blood pressure, respiration rate, blood oxygen saturation, and temperature, were all monitored three times a day. Clinical features, such as dyspnea, cough, headache, fatigue, myalgia, rhinorrhea, and sputum discharge were examined daily using two specially devised questionnaires, the Visual analog scale (VAS) [14] and the Fatigue Assessment Scale (FAS) [15]. The patient makes a mark on a 10 cm line that corresponds to the severity of pain when using the VAS to assess pain. The score is calculated by measuring the distance from the "no pain" end of the line to the mark. The items are assessed on a 7-point scale, with 1 indicating severe disagreement and 7 indicating strong agreement, when using FAS to detect fatigue. The lowest possible score is 9 and the highest possible score is 63 [16]. The higher the score, the more severe the weariness. Another method of scoring is to take the average of all the scores, with the lowest score being 1 and the highest being. The severity of the disease was assessed using the American Thoracic Society guidelines for community-acquired pneumonia. The first to fifth days of hospitalization were used to perform laboratory tests. Laboratory markers included blood urea nitrogen (BUN), aspartate aminotransferase (AST), Albumin, Superoxide dismutase (SOD), C-reactive protein (CRP), hemoglobin (HB), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), creatinine (Cr), platelet, white blood cells (WBCs), red blood cells (RBCs), neutrophil, and lymphocyte counts. Major symptoms of patients in both control and the intervention groups were assessed daily during treatment, employing a modified WHO CRF for COVID-19 outpatients.

2.9. Data analysis

The descriptive statistic indicators were used to analyze the data such as percentage, confidence interval, frequency, mean and standard deviation, and also inferential statistical tests (Wilcoxon-Mann-Whitney, Chi-square, Fisher exact, Q-Q plot, ANOVA, and skewness) using SPSS software version 22. In this study, the one-sided p-value compares the probability distribution of COVID-19 symptoms or inflammatory biomarkers on the 5th day to the 1st day of treatment in each group. The significance level was considered $P<0.05$.

3. Results

In the current randomized clinical trial study, 160 patients with confirmed COVID-19 diagnosis by nasopharyngeal swab testing employing radiological lesions found in a computed tomographic scan and reverse transcriptase-polymerase chain reaction were screened for eligibility from February to April 2022. Patients were divided into control ($n = 80$) and intervention ($n = 80$) groups. There were 52 (65%) males and 28 (35%) females in the control group and 55 (68.8%) male and 25 (31.3%) female subjects in the intervention group (Table 1).

Table 1
Baseline Characteristics of intervention and control groups.

	Variable	Control($n = 80$)		Intervention($n = 80$)		P-value
		Frequency	Percent	Frequency	Percent	
Age	<30	8	10	6	7.5	
	30–39	22	27.5	21	26.3	0.682
	40–49	15	18.8	11	13.8	
	50–59	16	20	24	30	
	60–69	16	20	16	20	
	≥70	3	3.8	2	2.5	
Gender	Male	52	65	55	68.8	0.614
	Female	28	35	25	31.3	

None of the patients were discharged during the study. Table 2 shows the baseline severity of some symptoms between two groups and table 3 shows baseline quantitative characteristics of the patients in two groups of intervention and control. The outcomes of statistical analysis indicated that the control and intervention groups were not significantly different in terms of gender, age, sputum, Gastrointestinal disorders, temperature, SPO2, ESR, WBC, neutrophil, lymphocyte, hemoglobin, platelet, AST, ALT, creatinine, LDH, and Albumin ($P>0.05$) (Table 2,3.). Symptom disappearance was evaluated for the major symptoms. The statistical analysis results showed a statistical difference in the 4 symptoms; mean difference for weakness 0.8 (95% CI: −0.14–1.74; $p = 0.031$), and cough 0.44 (95% CI: 0.09–0.78; $p = 0.043$), and frequency for myalgia ($p = 0.021$), and headache ($p = 0.035$) (Table 4 and Table 5). The trend of C-reactive protein in the group who were receiving herbal supplements was decreasing from the first to the 5th day at 2.26 (95% CI: 0.46–4.07; $p = 0.045$) (Table 4). The average number of days spent in the hospital was not significantly lower in the herbal supplement group than in the control group 0.4 (95% CI: 0.09–0.79; $p = 0.097$) (Table4.). ICU admission only occurred in 5 (6.3%) patients of the intervention and 9 (11.3%) of the control group (table 6).

4. Discussion

The current RCT showed that a diet based on TPM alongside standard supportive care was associated with significant improvement of the symptoms (including headache, myalgia, cough, and weakness) and C-reactive protein (CRP) levels in the patients with COVID-19.

The improvement of the clinical symptoms was also mentioned in another RCT that investigated the effect of Persian medicine herbal formulations on patients with COVID-19 [17]. Patients in the mentioned study also reported significant improvement in fatigue, cough, myalgia, headache as well as fever, GI symptoms, vertigo, and chest pain as well as significantly shortened average length of hospital stay. The main feature of the intervention in Karimi et al.'s study was anti-inflammatory, antioxidant, antiviral, mucolytic, a bronchodilator, antitussive, and immunomodulatory effects of their traditional remedy.

Elevated serum levels of CRP, as a marker of systemic inflammation, are known to be associated with severe diseases in viral infections. An elevated level of C-reactive protein may be an early marker to predict the risk for severity of COVID-19 [18]. In this study, a TPM-based diet reduced levels of CRP levels showing its anti-inflammatory potential, which has also been mentioned in previous studies [19].

Zannella et al. investigated the antiviral activity of *Vitis vinefra* leaf extract. Accordingly, leaf extract was able to inhibit SARS-CoV-2 replication in the early stages of infection by directly blocking the proteins enriched on the viral surface [20]. Moreover, the anti-inflammatory effect of *Cicer arietinum* and *Descurainiasophia* [21, 22], and also antitussive effects of Ziziphus jujuba have been evidenced before [23]. In TPM, *Ziziphus jujuba* is mainly regarded as a modulator humor quality, mostly by preventing the adverse effects of excess heat. Moreover, *Z. Jujuba* has been reported to have a soothing effect on the shortness of breath and pulmonary inflammations [19]. Besides the nutritive value,

Table 2
Comparison of baseline severity symptoms between intervention and control groups.

Variable	Control($n = 80$) Frequency(Percent)						Intervention($n = 80$) Frequency(Percent)						P-value
	None	Very Mild	Mild	Moderate	Severe	Very Severe	None	Very Mild	Mild	Moderate	Severe	Very Severe	
Sputum	26 (32.5)	33 (41.3)	15 (18.8)	6 (7.5)	0 (0)	0 (0)	28 (35)	35 (43.8)	13 (16.3)	4 (5)	0 (0)	0 (0)	0.903
Headache	32 (40)	20 (25)	20 (25)	4 (5)	4 (5)	0 (0)	32 (40)	12 (15)	16 (20)	12 (15)	4 (5)	4 (5)	0.062
Myalgia	4 (5)	8 (10)	8 (10)	24 (30)	20 (25)	16 (20)	4 (5)	4 (5)	8 (10)	24 (30)	24 (30)	16 (20)	0.889c
Gastrointestinal disorders	52 (65)	5 (6.3)	15 (18.8)	8 (10)	0 (0)	0 (0)	48 (60)	11 (13.8)	14 (17.5)	7 (8.8)	0 (0)	0 (0)	0.497

C = Pearson Chi-Square test.

Table 3
Baseline quantitative characteristics between intervention and control groups.

Variable	Control($n = 80$) Mean (SD)	Intervention($n = 80$) Mean (SD)	P-value
Weakness	40.8 (4.1)	40.78 (4.13)	0.945
Temperature	38.06 (0.48)	38.06 (0.47)	0.978
SPO2	90.25 (2.93)	89.65 (2.55)	0.060
CRP	55.1 (36.31)	56.36 (37.01)	0.564
ESR	53.03 (12.5)	52.48 (13.22)	0.757
WBC	7650 (1663.15)	7532.5 (1888.32)	0.924
Neutrophil	61.41 (4.6)	62.19 (4.9)	0.481
Lymphocyte	32 (7.6)	32.1 (7.54)	0.897
Hemoglobin	15.15 (0.62)	15.17 (0.61)	0.926
Platelet	202,500 (44,975.4)	207,375 (53,674.9)	0.929
AST	30.24 (11.09)	30.35 (12.04)	0.943
ALT	30.13 (9.79)	30.03 (9.59)	0.963
Creatinine	1.17 (0.46)	1.19 (0.51)	0.643
LDH	481 (336.56)	492.5 (347.29)	0.601
Albumin	4.64 (0.45)	4.63 (0.44)	0.852
Cough	6.7 (2.57)	7 (2.42)	0.459

jujube is widely known as a rich source of bioactive secondary metabolites like polysaccharides, polyphenols, and terpenoids [24]. A triterpene jujube fruit constituent, betulinic acid, has demonstrated antiviral function against the influenza A virus in vivo and in vitro. Betulinic acid at a concentration of 50 μM, inhibited the virus cytopathic effects by 98%; meanwhile, it exerted no toxicity to the host cells. Despite the fact that the symptoms in the infected animals disappeared, no marked changes were seen in viral replication as well as pro-inflammatory cytokines except IFNγ. Therefore, further investigations on the underlying mechanisms are required to prove the antiviral potential of this compound [25]. Acidic polysaccharides are also among the active components of *Z. jujuba* with immunostimulatory activities. The potential was evident from the heightened indices of main lymphatic organs, such as the thymus and spleen in vivo, demonstrating an elevated immune cell proliferation. Moreover, these polysaccharides may harbor metal ions which may exert roles in biological activities [26]. *Jujuboside A*, a triterpenoid, has shown in vitro cardio-protection through regulation of the PI3K/AKT/mTOR autophagic pathway [27].

In TPM, saffron has been known as a tonic for the kidneys and lungs for a long time. It is valued not only as a cardiotonic medication but also as an enhancer of other medicinal ingredients delivered to the heart. Thus, saffron is among the most commonly used components of multi-component TPM-based preparations for heart diseases [28]. Crocin and picrocrocin as well as the aqueous extract of saffron, have been previously investigated regarding in vitro antiviral potential against HIV-1. These carotenoids showed antiviral activities with a relatively low IC50 of 5 and 8 μM and high SI of more than 187 and 600, demonstrating potential as effective antiviral agents. However, the aqueous extract demonstrated no marked antiviral function, which implies that the antiviral potential of this herb is mainly attributed to its lipophilic compounds including carotenoids [29]. Saffron and cinnamon have also been well studied for their anti-COVID-19 potential [30–32]. Damask

Table. 4
Comparison of inflammatory biomarkers and clinical symptoms between intervention and control groups (Post Intervention).

Variable	Control Mean ± SD	Intervention Mean ± SD	Mean Difference	CI	P-value
Weakness final	32.45 ± 3.28	31.65 ± 2.68	0.8	−0.14 to 1.74	0.031*
Hospitalization	6.95 ± 1.33	6.55 ± 1.17	0.4	0.09 to 0.79	0.097
Temperature	37.32 ± 0.11	37.29 ± 0.12	0.03	−0.006 to 0.068	0.128
Length of cough	6.31 ± 1.97	6.19 ± 1.31	0.125	−0.4 to 0.65	0.118
Length of Sputum	2.2 ± 2.35	1.88 ± 2.13	0.33	−0.37 to 1.02	0.445
Length of Headache	2.35 ± 2.72	1.55 ± 2.07	0.8	0.04 to 1.56	0.190
Length of Myalgia	6.75 ± 1.44	6.23 ± 1.26	0.52	0.1 to 0.95	0.086
Length of GI	2 ± 3.17	1.15 ± 1.97	0.85	0.025 to 1.67	0.461
SPO2	96.65 ± 1.43	96.26 ± 1.26	0.39	−0.03 to 0.81	0.142
CRP	14.38 ± 6.68	12.11 ± 4.7	2.26	0.46 to 4.07	0.045*
ESR	22.38 ± 4.58	22.16 ± 4.44	0.21	−1.19 to 1.62	0.823
WBC	5291.25 ± 813.7	5255 ± 826.1	36.25	−219.81 to 292.31	0.706
Neutrophil	61.43 ± 3.49	62.13 ± 3.63	−0.7	−1.81 to 0.41	0.298
Lymphocyte	30.43 ± 4.36	30 ± 4.17	0.42	−0.91 to1.76	0.459
Hemoglobin	15.19 ± 0.69	15.25 ± 0.7	−0.05	−0.27 to 0.16	0.682
Platelet	229,250 ± 47,978.8	237,750 ± 50,277.1	−8500	−23,846.33 to 6846.33	0.286
AST	27.34 ± 9.76	26.96 ± 9.9	0.37	−2.69 to 3.44	0.775
ALT	27.18 ± 9.61	27.28 ± 9.56	−0.1	−3.09 to 2.89	0.922
Creatinine	1.068 ± 0.237	1.071 ± 0.242	−0.004	−0.08 to 0.07	0.805
LDH	163 ± 33.74	167.19 ± 33.99	−4.19	−14.76 to 6.39	0.308
Albumin	4.68 ± 0.45	4.67 ± 0.44	0.01	−0.13 to 0.15	0.868
Cough	1.94 ± 1.28	1.5 ± 0.9	0.44	0.09 to 0.78	0.043*

* = P-value < 0.05.

Table 5
Comparison of severity of symptoms between intervention and control groups (Post Intervention).

Variable	Control($n = 80$) Frequency(Percent)						Intervention($n = 80$) Frequency(Percent)						P-value
	None	Very Mild	Mild	Moderate	Severe	Very Severe	None	Very Mild	Mild	Moderate	Severe	Very Severe	
Sputum	70 (87.5)	10 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	73 (91.3)	7 (8.8)	0 (0)	0 (0)	0 (0)	0 (0)	0.609
Headache	54 (67.5)	17 (21.3)	9 (11.3)	0 (0)	0 (0)	0 (0)	67 (83.8)	9 (11.3)	3 (3.8)	1 (1.3)	0 (0)	0 (0)	0.035*
Myalgia	14 (17.5)	20 (25)	18 (22.5)	28 (35)	0 (0)	0 (0)	19 (23.8)	10 (12.5)	32 (40)	19 (23.8)	0 (0)	0 (0)	0.021*
Gastro intestinal disorders	65 (81.3)	15 (18.8)	0 (0)	0 (0)	0 (0)	0 (0)	59 (73.8)	21 (26.3)	0 (0)	0 (0)	0 (0)	0 (0)	0.344

* = P-value < 0.05.

Table 6
Comparison of patients admitted to intensive care (Post Intervention).

	Frequency	Control	Intervention	Relative Risk	95% CI	P-value
ICU admission	Count	9	5	0.556	0.195 to 1.585	0.272
	Percent	11.3	6.3			

Rose another component of the TPM also used in this study has been evidenced to help the body to excrete the harmful watery phlegm humor highly susceptible to infection and therefore is a tonic of the lungs [10]. Moreover, the components of this regimen are sources of various types of vitamins and minerals, with proven potency as immunity boosters in the fight against COVID-19 [33]. These data support the findings of our study.

Our study has some limitations. First, although in this study, all patients in the control group used the standard hospital diet and their diet was the same, it would be better if we measured the dietary intake of all participants. The second limitation was the short duration of the intervention (5-day). We suggest that larger and longer intervention studies are required to document the effects of TPM on inflammatory indices and clinical outcomes in COVID-19 patients.

5. Conclusion

This RCT showed that a diet based on TPM may benefit COVID-19 patients in terms of improving some clinical symptoms as well as inflammatory biomarkers. TPM has great potential and thus could be recommended for the treatment of COVID-19, while more research with larger sample size is required to investigate the safety and efficacy of other components of TPM on SARS-CoV-2 infection.

CRediT authorship contribution statement

Ramtin Hajibeygi: Conceptualization, Investigation, Writing – original draft, Funding acquisition, Formal analysis. **Sayid Mahdi Mirghazanfari:** Conceptualization, Investigation, Writing – original draft, Funding acquisition, Formal analysis. **Naseh Pahlavani:** Conceptualization, Investigation, Writing – original draft, Funding acquisition, Formal analysis. **Abduladheem Turki Jalil:** . **Shadia Hamoud Alshahrani:** . **Jasur Alimdjanovich Rizaev:** . **Saeid Hadi:** Conceptualization, Investigation, Writing – original draft, Funding acquisition, Formal analysis. **Vahid Hadi:** Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Nafiseh Hosseini Yekta:** Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

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Data availability

The data that support the findings of this study are available from department of Health, school of Medicine, AJA University of Medical Sciences, but restrictions apply to the availability of this data, which were used under license for the current study, and are not publicly available. Data are however available from the authors upon reasonable request and with permission of department of Health, school of Medicine, AJA University of Medical Sciences.

References

[1] M. Hossain, et al., Clinical efficacy and safety of antiviral drugs in the extended use against COVID-19: what we know so far, Biologics 1 (2) (2021) 252–284.
[2] M.J. Ehsani, et al., Effect of diet based on the principles of Iranian traditional medicine on cirrhosis (a clinical trial), Complement Ther. Med. 29 (2016) 35–41.
[3] A. Molfino, et al., Omega-3 polyunsaturated fatty acids in critical illness: anti-inflammatory, proresolving, or both? Oxid. Med. Cell Longev. 2017 (2017).
[4] K. Zhang, et al., The combined therapy of a traditional Chinese medicine formula and Western medicine for a critically ill case infected with COVID-19, Complement Ther. Med. 52 (2020), 102473.
[5] K. Richards, et al., Use of complementary and alternative therapies to promote sleep in critically ill patients, Critical. Care Nurs. Clinics 15 (3) (2003) 329–340.
[6] D. Wang, et al., The significance of natural product derivatives and traditional medicine for COVID-19, Processes 8 (8) (2020) 937.
[7] Y. Xiong, et al., International policies and challenges on the legalization of traditional medicine/herbal medicines in the fight against COVID-19, Pharmacol. Res. 166 (2021), 105472.
[8] A. Hamedi, et al., Herbal medicinal oils in traditional Persian medicine, Pharm. Biol 51 (9) (2013) 1208–1218.
[9] R. Moeini, N. Gorji, Persian medicine in the world of research; review of articles on iranian traditional medicine, Iran. J. Med. Sci. 41 (3) (2016) S7. Suppl.
[10] R. Bahramsoltani, R. Rahimi, An evaluation of traditional Persian medicine for the management of SARS-CoV-2, Front Pharmacol. 11 (2020), 571434.
[11] R. Kopaei, A. Khajegir, S. Kiani, The Association between dystemperament and prevention of diseases: a systematic review, J. Clin. Diagn. Res. 10 (9) (2016) YE01.
[12] M.H. Aghili Khorasani, Makhzan-al-Adviah, 1st ed, Tehran University of Medical Sciences, Tehran, 1771 (Rewritten by Shams Ardakani MR, Rahimi R, Farjadmand F.
[13] M.C. Ali, et al., Identification of potential sars-cov-2 main protease inhibitors from ficus carica latex: an in-silico approach, J. Adv. Biotechnol. Experim. Therapeutics 3 (Special Issue 4) (2020) 57–67.

[14] G.A. Hawker, et al., Measures of adult pain: visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap), Arthritis Care Res. (Hoboken) 63 (S11) (2011) S240–S252.
[15] J. De Vries, et al., Measuring fatigue in sarcoidosis: the fatigue assessment scale (FAS), Br. J. Health Psychol. 9 (3) (2004) 279–291.
[16] A. Shahid, et al., Fatigue Assessment Scale (FAS), in STOP, THAT and One Hundred Other Sleep Scales, Springer, 2011, pp. 161–162.
[17] M. Karimi, et al., Efficacy of Persian medicine herbal formulations (capsules and decoction) compared to standard care in patients with COVID-19, a multicenter open-labeled, randomized, controlled clinical trial, Phytoth. Res. 35 (11) (2021) 6295–6309.
[18] N. Ali, Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19, J. Med. Virol. 92 (11) (2020) 2409–2411.
[19] R. Bahramsoltani, R. Rahimi, An evaluation of traditional persian medicine for the management of SARS-CoV-2, Front Pharmacol. 11 (2020).
[20] C. Zannella, et al., Antiviral activity of vitis vinifera leaf extract against SARS-CoV-2 and HSV-1, Viruses 13 (7) (2021) 1263.
[21] Y.J. Lee, et al., Cytotoxic and anti-inflammatory constituents from the seeds of Descurainia sophia, Arch. Pharm. Res. 36 (5) (2013) 536–541.
[22] S. Shafeen, Anti-inflammatory activity of Cicer arietinum seed extracts, Asian J. Pharm. Clin. Res. 5 (1) (2012) 64–68.
[23] H. Mohammadi Kenari, et al., Herbal recommendations for treatment of COVID-19 symptoms according to Persian medicine, J. Medic. Plants 20 (77) (2021) 1–14.
[24] M. Wang, et al., The jujube (Ziziphus jujuba Mill.) fruit: a review of current knowledge of fruit composition and health benefits, Chinese Dates (2016) 53–82.
[25] E.-.H. Hong, et al., Anti-influenza activity of betulinic acid from Zizyphus jujuba on influenza A/PR/8 virus, Biomol. Ther. (Seoul) 23 (4) (2015) 345.
[26] M. Zou, et al., Immunomodulatory acidic polysaccharides from Zizyphus jujuba cv. Huizao: insights into their chemical characteristics and modes of action, Food Chem 258 (2018) 35–42.
[27] D. Han, et al., Jujuboside a protects H9C2 cells from isoproterenol-induced injury via activating PI3K/Akt/mTOR signaling pathway, Evidence-Based Complemen. Alternat. Med. 2016 (2016).
[28] S.N. Sadati, et al., Review of scientific evidence of medicinal convoy plants in traditional Persian medicine, Pharmacogn. Rev. 10 (19) (2016) 33.
[29] S. Soleymani, et al., Antiviral effects of saffron and its major ingredients, Curr. Drug Deliv. 15 (5) (2018) 698–704.
[30] A.M. Husaini, K.N. Jan, G.A. Wani, Saffron: a potential drug-supplement for severe acute respiratory syndrome coronavirus (COVID) management, Heliyon 7 (5) (2021) e07068.
[31] M. Yakhchali, et al., Cinnamon and its possible impact on COVID-19: the viewpoint of traditional and conventional medicine, Biomed. Pharmacoth. 143 (2021), 112221.
[32] Pahlavani, N. and J. Navashenaq, Current nutritional support in critical Ill Covid-19 patients: a brief review. 2021. 8: p. 1–5.
[33] P. Kumar, et al., Role of vitamins and minerals as immunity boosters in COVID-19, Inflammopharmacology 29 (4) (2021) 1001–1016.