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Original Research

Evaluation of a Persian Natural Topical Medicine Based on Sesame Oil on Mild-to-Moderate Outpatient Coronavirus Disease-19 Patients: A Randomized Triple-Blind Placebo-Controlled Clinical Trial

Reza Ahmadi[1], Hossein Mohammadzadeh-Moghadam[2]*, Reza Esmaeili[2], Abdoljavad Khajavi[3], Maryam Ghahramany[4,5], Davoud Salarbashi[6,7], Mahdieh Bahramizadeh[8], Sepideh Elyasi[8]*

[1]Department of Family, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Public Health, School of Health, Social Development and Health Promotion Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
[3]Department of Community Medicine, School of Medicine, Gonabad University of Medical Sciences, Gonabad, Iran
[4]Department of Health Education and Promotion, school of Health, Mashhad University of Medical Sciences, Iran
[5]Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[6]Department of Food Science, Nutrition and Clinical Biochemistry, School of Medicine, Gonabad University of Medical Sciences, Gonabad, Iran
[7]Research Center for Food Hygiene and Safety, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[8]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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Abstract

Sesame oil (SO) or so-called Tahini has been traditionally used for management of various conditions including burns and wounds and relief of pain, fever, and inflammation n Persian Medicine. It poses anti-inflammatory, antioxidant, and anti-carcinogenic activities; then it could be used in various inflammatory conditions. A triple-blind randomized placebo-controlled clinical trial was carried out to examine the efficacy of a Persian natural topical medicine based on sesame oil in outpatients suffering mild and moderate coronavirus disease-19 (COVID-19). The participants were 101 COVID-19 patients who met the inclusion criteria. The participants were allocated randomly to treatment (n = 51) group who received topical Sesame oil formulation five times daily on the chest and back skin for 1 week or the placebo (n = 50) group. The symptoms were examined at admittance and over a follow-up course and the results were compared in the two groups after 3 and 7 days. After three days, fever (7.84 vs. 20.41%, P=0.05), chills (3.92 vs. 16.33%, P=0.03), cough (severe 0 vs. 8.6, intermediate 50.98 vs. 65.31%, P=0.007) and headache (mild 7.84 vs. 30.61, moderate 5.88 vs. 0, P=0.004) had a significant lower prevalence in the treatment group. However, after 7 days, all symptoms had insignificant difference between two groups (P>0.05). No significant adverse reaction reported in both groups. As the results indicated, topical formulation consisting of sesame oil and cow butter, rubbing on the chest and back of the mild-to-moderate COVID-19 patients five times daily could significantly improve cough, fever, chills and headache, in 3 days. But it could not be effective on final outcome of the patients. More works covering a larger sample size are needed.

Keywords: Coronavirus Disease of 2019 (COVID-19); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); Sesame oil; Tahini; Cow butter; Clinical response

Introduction

Corona virus disease (COVID-19) as a global epidemic, imposes a great deal on health systems all around the world, in terms of disability, mortality, and socioeconomic effects [1]. The wide range of symptoms such as fever, loss of taste, headache, diarrhea, dry

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*Corresponding Authors: Sepideh Elyasi
Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
Email: elyasis@mums.ac.ir

Hossein Mohammadzadeh-Moghadam
Department of Public Health, School of Health, Social Development and Health Promotion Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
Email: Homm1349@gmail.com

cough, dyspnea, fatigue, acute respiratory distress, and even hypoxia necessitating supplemental oxygen therapy and mechanical ventilation can happen during the disease course. Severe acute respiratory syndrome–related coronavirus (SARS-CoV-2) can cause adaptive and innate immune reactions. However, failing to control inflammatory innate responses and compromised adaptive immune responses can cause various local and systemic tissue damages [2]. Most of mild-to-moderate COVID-19 patients are recommended to receive treatment in outpatient setting with symptomatic therapy and COVID-19 specific therapies including nirmatrelvir-ritonavir, remdesivir, bebtelovimab and high-titer convalescent plasma are just indicated in patients with an increased risk for progression to severe disease (e.g., elderly, immunecompromised patients, and some comorbidities). However, these treatments are not easily available for patients all over the world.

Tahini or tahina is a Middle Eastern condiment obtained from toasted ground hulled sesame. Sesame (Sesamum indicum L.) is initially used for producing oil. It can be used orally and 50-60% of it is constituted of a variety of bioactive elements such as phytosterols, tocopherol homologues, polyunsaturated fatty acids, along with lignans [3]. The bioactive components have several vital activities such as regulating lipid profile and blood pressure [4]. Sesame oil (SO) is effective in relief of pain, fever, and inflammation and also as a diuretic and for healing burns and wounds [5]. Moreover, it poses antioxidant, anti-inflammatory and anti-carcinogenic activities which claims for liver and heart protection. It also exhibits antitumor property and could be used in various inflammatory conditions like rheumatic inflammatory diseases [6].

It is normally used for massage work in Ayurvedic medicine, and surprisingly, it is known as a sacred oil [5]. Folk medicine stated that intranasal use of sesame oil can stop the spread of COVID-19, considering its warm and wet nature. It also can show considerable effects on cough and dyspnea. This ability proposed to be resulted from the physicochemical characteristics of sesame oil, like high boiling point, immiscible with water, low surface tension, and viscosity, and antivirus activity [7].

Moreover, the Indian government recommended that using two drops of sesame oil in each nostril every day can inhibit the SARS-CoV-2 [8].

Some Persian medicine resources, like *Makhzan- Al' Advieh* [9] and *Tohfato Al'-Momenin* [10], suggest that rubbing cow butter on the body may result in maturation of the chest discharges and their excretion and could be useful for pneumonia.

So, the present study assesses the efficacy of a topical Persian Medicine product containing sesame oil and cow butter for managing mild-to-moderate COVID-19 patients.

Methods

Study design

The study conducted as a randomized triple-blind placebo-controlled clinical trial between May 2020 and August 2020 at Quaem Hospital outpatient clinic and Seyyedi clinic affiliated to Mashhad University of Medical Sciences, Mashhad, Iran.

Study population

The participants who met the inclusion criteria were recruited: age higher than 15 years old, diagnosis of COVID-19 by infectious disease specialist using a (a) a positive real-time polymerase chain reaction (RT-PCR) of the respiratory tract samples, (b) clinical symptoms/ signs at least three items such as chills, dyspnea, cough, hoarseness, fever, sore throat, myalgia, and weakness), (c) image showing very suspicious COVID-19 like ground-class pattern in chest X ray, with mild-to-moderate disease according to the latest national diagnosis and treatment standard who received treatment as outpatient without respiratory rate below 30/min, harsh dyspnea, SaO2 above 93% at ambient condition and patients who expressed their written consent. The patients who had their case diagnosed more than seven days ago, pregnant women, breastfeeding women, or individuals with a history of hypersensitivity to sesame oil or cow butter, individuals with concomitant complication like severe renal failure (estimated glomerular filtration rate (eGFR)<30 mL/min), heart failure (ejection fraction (EF)<40%), hepatic failure (Child-Pugh Score B/C), active malignancy, chronic lung disease, immune system impairment (e.g., HIV), and auto-immune disease. Patients were excluded if their condition exacerbated required admission to hospital.

Ethics

The Ethics Board of Gonabad University of Medical Sciences approved the project (Code: IR.GMU.REC.1399.014), registered at the Iranian Registry of Clinical Trials (IRCT20140407017169N2). The subjects were briefed and informed about the protocol of study and expressed their consent in a written form.

Study protocol

One hundred patients were allocated to the treatment (n=51) or placebo (n=49) group randomly. The herbal medicine in this trial was topical formulation of sesame oil and cow butter which was mixed in equal proportions and the placebo was paraffin. For making placebo, yellow color was solved in about 500 mL water, then was added to 500 g eucerin and thereafter was mixed with 800 g liquid paraffin. Saman Sesa-

me Oil (Saman Sesame Oil Co, Iran, with health code No. 10264/13) extracted from Iranian white sesame seeds was used. Gas chromatographic (GC) analysis was performed on the oil. As shown by GC results, linoleic acid (39.11%), oleic acid (44.01%), stearic acid (5.55%), palmitic acid (9.23%), gamma-linolenic acid (0.15%), and alpha-linolenic acid (0.33%) were the main constituents of the oil. Two grams of these formulations (one tablespoon) were applied on the patients' chest and back five times daily, every 4 hours. As this study was the first clinical trial on sesame oil use in COVID-19, the recommended dose was defined by the Persian medicine specialist. As topical sesame oil produced by Barij Esssence® Company, standardized based on 39 to 59% linoleic acid is recommended to be used 2-3 times daily as skin moisturizing agent and anti-inflammation in burns, we asked patients to use sesame oil five times daily for better efficacy in COVID-19 pneumonia. Both treatment and placebo formulations were filled in boxes with identical appearance. The treatment and placebo formulations were developed in pharmaceutics lab of School of Pharmacy, Mashhad, Iran. The participants underwent standard treatment according to the national treatment guideline (version, April 2, 2020), including hydroxychloroquine, naproxen and azithromycin. In addition, all the subjects had the same nutritional instruction. The subjects were asked to avoid using other medications without prior consultation. In the case of exacerbated infection, the patients would be excluded and received other available treatments.

Outcome

The demographics of the participants along with past medication and drug history were checked and logged. In addition, the patients were examined by infectious disease specialists given the different symptoms and signs of COVID-19 infection (e.g., chills, fever, cough, sore throat, headache, taste disturbance, anosmia, weakness, myalgia, gastrointestinal and dermatologic complications, and dyspnea) before initiation of the study and after 3 days and 1 week by phone call. The patients were asked to score the symptoms between 0-10. The symptoms are considered mild if she/he scored it 0-3, moderate with score of 4-6 and severe if it scored 7-10.

In the course of study, we checked adherence to treatment and the unwanted side-effects. The patients were considered adherent to the protocol when they used more than 80% of their administered medicine/placebo [11].

Sample size

As far as the authors know, this study is the first clinical study in this field. The study can be considered as a pilot work and the group size was 50 in each group. According to Whitehead et al. [12], with a power of 90% and two-sided 5% significant, pilot trial sample size for each treatment arm was 75, 25, 15, 10 is adequate for standardized effect sizes that are extra small (<=0.1), small (0.2), medium (0.5), or large (0.8) respectively. Considering this topical formulation effect small or extra small regarding the proposed mechanism of action, 50 participants in each group was adequate.

Randomization and blinding

The random allocation sequence was formed through a computer-generated randomized list (www.graphpad.com site). Then, opaque sealed envelopes (SNOSE) and sequentially numbered method were employed for randomization. A number of envelopes were prepared and each number is recorded on a card according to the prepared list and the cards were placed inside the envelopes. In order to maintain a random sequence, envelopes were numbered in the same manner on the outer surface. Finally, the envelopes were closed and placed inside the box. At the beginning of the study, based on the order of entry of eligible participants, one envelope was opened and the assigned group of the patient was revealed. Patients received the box contained treatment/placebo formulation which was adequate for 14 days course of treatment. Patients were assessed in the course of treatment using phone call. Data gathering and analysis were carried out by researchers who were blind to the grouping.

Statistical methods

Data analysis was done in SPSS (V.25) and the findings were reported as median (range) or mean ± SD for non-normally and normally distributed data respectively. In addition, nominal parameters were reported as percentages and numbers. Kolmogorov–Smirnov test was employed to examine normality of the data.

Mann–Whitney U-test and independent sample t-test were utilized to compare non-normally and normally distributed variables in the two groups respectively. To compare proportions Fisher's exact test was used; $p < 0.05$ was considered as significant. It is worth to mention that intention-to-treat analysis was carried out.

Results

Baseline characteristics

In total, 101 patients were selected out of 107 evaluated patients based on the inclusion criteria (50 patients in the placebo group and 51 patients in the treatment group). Throughout the study, 51 patients in treatment and 49 patients in placebo group completed the trial (Figure 1).

The mean age of the participants was 46.25±16.12 years, and 59% of the participants were men.

Table 1 lists the rest of key characteristics of the patients. There was not any significant difference regarding these characteristics between two groups. All patients reported some degree of cough, fatigue and myalgia. The incidence of various symptoms was comparable between two groups.

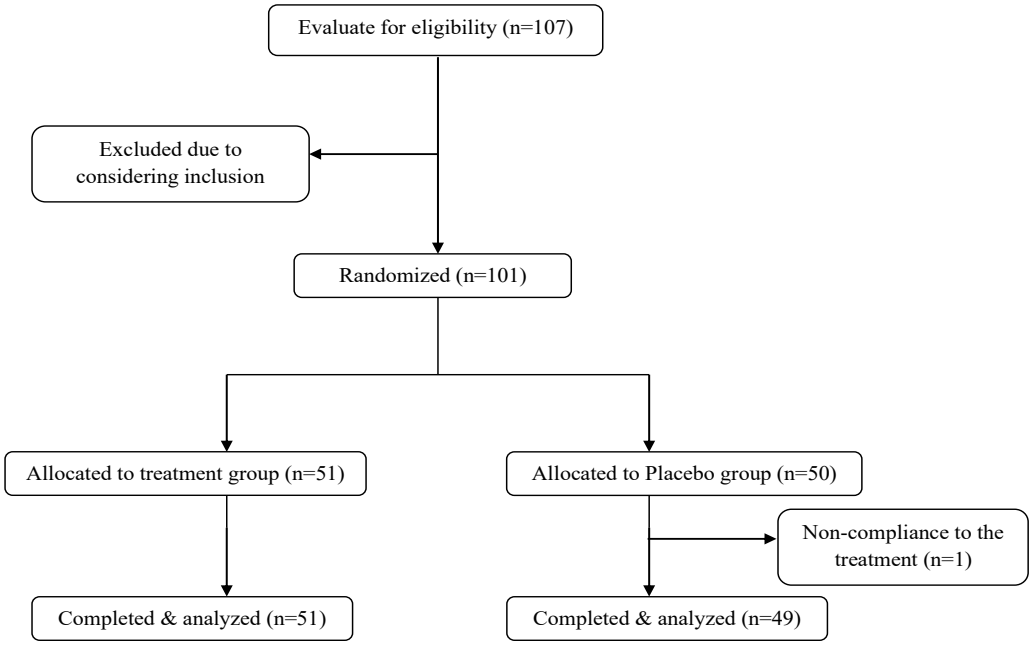

Figure 1. Flow diagram of the study design

Table 1. Patients' characteristics

		Treatment (n=51)	Placebo (n=49)	P value
Gender (male/ female ratio)		31/20	28/21	0.76[b]
Age (year)		49±15.5	43.5±16.5	0.23[a]
Comorbidity (%)		80.39	91.84	0.19[b]
Fever (%)		5.88	6.12	0.96[b]
Cough (%)	Severe	37.25	36.73	0.95[a]
	Intermediate	62.74	63.26	
Headache (%)	Mild	33.33	26.53	0.89[a]
	Moderate	45.1	51.02	
Chills (%)		3.92	6.12	0.61[a]
Myalgia (%)	Mild	1.96	0	0.59[a]
	Moderate	43.14	46.94	
	Severe	54.9	53.06	
Fatigue (%)	Mild	1.96	0	0.54[a]
	Moderate	43.14	48.98	
	Severe	54.9	51.02	
Dyspnea (%)	Moderate	62.75	71.43	0.63[a]
	Severe	35.29	26.53	
Olfactory disturbances (%)		52.94	59.18	0.53[a]
Taste disturbances (%)		56.86	59.18	0.81[a]

[a] Fisher's exact test
[b] independent sample t-test

Efficacy of treatment

After three days, fever (7.84 vs. 20.41%, P=0.05), chills (3.92 vs. 16.33%, P=0.03), cough (severe 0 vs. 8.6, intermediate 50.98 vs. 65.31%, P=0.007) and headache (mild 7.84 vs. 30.61, moderate 5.88 vs. 0, P=0.004) had a significant lower prevalence in the treatment group, but the other symptoms still were comparable between two groups (P>0.05). After 7 days, all symptoms had insignificant difference between two groups (Table 2).

Table 2. Comparison of patients' symptoms between two groups

symptoms		Three days			One week		
		Treatment (n=51)	Placebo (n=49)	P value	Treatment (n=51)	Placebo (n=49)	P value
Fever (%)		7.84	20.41	0.05[a*]	0	0	1[a]
Cough (%)	Severe	0	8.16	0.007[a*]	0	0	0.73[a]
	Intermediate	50.98	65.31		7.84	10.2	
Headache (%)	Mild	7.84	30.61	0.004[a*]	0	6.12	0.11[a]
	Moderate	5.88	0		0	2.04	
Chills (%)		3.92	16.33	0.03[a*]	0	0	1[a]
Myalgia (%)	Mild	49.02	32.65	0.51[a]	23.53	16.33	0.53[a]
	Moderate	17.65	22.45		0	2.04	
	Severe	5.88	8.16		0	0	
Fatigue (%)	Mild	21.57	26.53	0.45[a]	11.76	6.12	0.39[a]
	Moderate	37.25	24.49		0	2.04	
	Severe	1.96	6.12		0	0	
Dyspnea (%)		43.14	48.98	0.54[a]	1.96	8.16	0.19[a]
Olfactory disturbances (%)		19.61	18.37	0.95[a]	1.96	4.08	0.6[a]
Taste disturbances (%)		13.72	16.33	0.65[a]	0	4.08	0.22[a]

[a] Fisher's exact test
[b] independent sample t-test

Safety of treatment

No adverse reaction related to topical medicine was reported in the placebo and treatment groups.

Discussion

COVID-19 pandemic is happened by novel corona virus with substantial death all over the world. At the moment, limited numbers of treatments are available for management of COVID-19 infection [13]. We evaluated a topical Persian Medicine product containing sesame oil and cow butter efficacy as a supplemental treatment beside standard measures in COVID-19 patients as the first human study. Based on our findings, application of topical formulation containing sesame oil and cow butter on the patients' chest and back, 5 times daily significantly effective in management of cough, fever, chills and headache in patients with COVID-19 after three days of use. But after one week, no significant different was found.

Some traditional Persian medicine resources like *Makhzan- Al' Advieh* [9] and *Tohfato Al'-Momenin* [10] rubbing cow butter on the body, may result in maturation of the chest discharges and their excretion and could be useful for pneumonia. Also, sesame oil, which is attained from the grinding and crushing of sesame, has a warmer nature and is effective in shortness of breath and dry cough, and has been introduced as stronger than sesame itself. In recent studies, the anti-inflammatory properties of sesame oil are known and it is used in the treatment of trauma [14] and rheumatoid arthritis. It also poses antioxidant and anti-inflammatory properties, could be absorbed through the

skin and shows its efficacy in topical formulation in osteoarthritis and trauma [15-17]. The antioxidant property of sesame oil and the constituents were applied by decrease of superoxide, lipid peroxidation, and nitric oxide production and also rise of antioxidant enzyme (catalase, reduced glutathione, and superoxide dismutase) level, which strongly correlate with the anti-inflammatory activity. The anti-inflammatory property of SO and the ingredients can be resulted by downregulation of prostaglandin-E2 and cyclooxygenase and also inhibition of proinflammatory cytokines. Sesamin, sesamol, sesamolin, and sesaminol are the key active ingredients of SO which have responsibility for above-mentioned activities [18].

As far as the authors know, there is no other clinical or pre-clinical study on this topical formulation in COVID-19 management. Allam et al. conducted an in silico study and found that a lignan isolated by the total methanolic extract of S. indicum seeds (sesame); hydroxymatairesinol, has a high affinity for three vital COVID-19 protein targets, namely, papain-like protease (PLpro), main protease (Mpro), and RNA-dependent RNA polymerase (RdRp). These proteins are essential for proliferation and replication of the virus in the human cell. This extract works particularly against the SARS-CoV-2 Mpro that is more potent than the presently used SARS-CoV-2 Mpro inhibitor darunavir and also, displaying a comparable binding energy at SARS CoV-2 PLpro compared to the co-crystallized ligand. The action also covered the RdRp as it showed a similar docking score with remdesivir. Inferiorly, two others isolated lignans, sesamin and sesamolin also exhibited comparable triple inhibitory effect on three crucial proteins; while spicatolignan showed a dual inhibitory role towards PLPro and RdRp. The compounds were examined in terms of Absorption, Distribution, Metabolism, and Excretion (ADME) and drug similarity characteristics, which presented satisfactory ADME properties and following five parameters rule of Lipinski. It could be determined that the extracted compounds from sesame lignans can be a substitute source for the production of novel natural subjects towards SARS-CoV-2 [19]. It is also proposed that nasal use of sesame oil make enormous extent of defensive coating to prevent viral binding for a long period of time because of the boiling point (about 21°C). Sesame oil could simply deceive infections in breathing and diminish direct viral contamination risk at the entry point. AYUSH guidelines for the SARS-CoV-2 likewise suggest the application of sesame oil for kavala or oil pulling followed by warm water rinse to reduce risk of infection [20].

So, available data mostly suggested sesame oil in the nostrils for preventing COVID-19 spread; however, in present study based on accessible formula we used it as a topical formulation on skin, which has acceptable absorption based on previous studies. However, further studies on nasal use are also recommended. Based on our findings, use of this formulation on first days of infection can accelerate patients' improvement rate. But it may not be effective on final outcome of the patients.

As the key limitation of this research, lots of patients involved in this research did not have PCR confirmed COVID-19, according to the available national guideline, the PCR test was not necessary for the outpatient setting. Given that the COVID-19 symptoms and CXR/lung CT view are not specific enough, inclusion of patients in study just based on presumptive symptoms and signs and/or CXR/lung CT could be as one important limitation of this work. Moreover, assessment of COVID-19 symptoms improvement was based on patients' scoring and reports which makes the evaluation inaccurate. No inflammatory marker like C-reactive protein, erythrocyte sedimentation rate, and white blood cells count were assessed in these patients. The sample size also could be larger in future studies.

Conclusion

A topical Persian Medicine formulation consisting of sesame oil and cow butter, rubbing on chest and back of the COVID-19 patients five time daily could significantly improve some major symptoms of patients including cough, fever, chills and headache, in three days. But it could not be effective on final outcome of the patients. Similar studies with more participants with positive COVID-19 PCR are recommended.

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Data availability

Data can be obtained from the author on request.

Conflict of Interests

None to declare. The study followed the Declaration of Helsinki, US, and/or European Medicines Agency Guidelines for human subjects.

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