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TANAFFOS

Effect of Herbal Medicine Formulation (Compound Honey Syrup) on Quality of Life in Patients With COPD: A Randomized Clinical Trial

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Background: Chronic obstructive pulmonary disease (COPD) as one of the health-threatening problems imposes many economic costs on health systems. Today, there is a greater tendency to use complementary and alternative therapies in the treatment of diseases. This study aimed to evaluate the efficacy of a Persian herbal formulation in patients with COPD.

Materials and Methods: This randomized clinical trial was conducted on 76 patients with mild-severe COPD assigned to 2 groups (in each group n=38) for 8 weeks. The interventional group received Compound Honey Syrup (CHS), consisting of combination of honey and extracts of five medicinal plants (i.e., ginger, cinnamon, saffron, cardamom, and galangal) and the control group received a placebo. The COPD Assessment Test (CAT), St George's Respiratory Questionnaire (SGRQ), and lung function test were used before and after.

Results: Seventy-six patients, 88.6% male and 55.7% under 60 years of age, completed the course of treatment. At the end of the study, the overall score of the CAT questionnaire was significantly different between the first and fourth week (P=0.029). Meanwhile the findings of SGRQ questionnaire were significantly different between the interventional and control groups at other times (P=0.001). FEV1 and FEV1/FVC were found to be significantly different between two groups in weeks 4 and 8 (P <0.05). At the end of the study, no side effects of CHS were reported.

Conclusion: Based on the data presented herein, CHS could be effective as a complementary and safe drug in increasing the quality of life of with COPD.

Key words: COPD; Honey; Persian Medicine; COPD Assessment Test (CAT); Clinical trial

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic and persistent inflammatory disease of the airways. Inflammation, chronic obstruction, increased secretions, and increased airway irritability are considered to be the most important physiopathology of COPD. In COPD, the airways and air sacs sometimes lose their elastic quality. The wall between many air sacs sometimes collapses. The airway walls may become thick and inflamed, or the airways may become thicker and/or may be blocked (1). The general mechanism including protease and anti-protease imbalance, oxidative stress, changes in the expression and balance of some mediators, genetics along microbial and viral infections are involved in the pathogenesis of COPD (2). Most patients with COPD suffer from both emphysema and chronic bronchitis.

Symptoms can include shortness of breath, coughing, wheezing, chest pain, dizziness, nausea and vomiting. Risk factors for COPD include high blood pressure, diabetes, high cholesterol, obesity, smoking and alcohol consumption with respiratory infections (3). COPD is prevalent in about 5% of the general population, reaching as high as 10% in patients over 65 years of age, with more than 24% of men and 16% of women. It was reported as the fourth leading cause of death worldwide (5.1%) in 2004 and is projected to occupy the third position (8.6%) in 2030 (4). In different countries such as Brazil, Greece, China, Vietnam, and Singapore, the prevalence of COPD has been estimated to be 10.2, 15.2, 8.4, 6.5, 6.7 and 3.5%, respectively (5); while the prevalence of COPD in Iran has been estimated as 4.9%, according to the Global Initiative for Chronic Obstructive Lung Disease criteria (6).

The ultimate goal of COPD treatment is to prevent the patient from developing symptoms, psychological and functional complications. One of the most common treatments in this group of patients are bronchodilators such as sympathomimetics, muscarinic antagonists, methylxanthines, and leukotriene inhibitors (7,8). Different drugs from phosphodiesterase-4 inhibitors such as Roflumilast and Cilomilast as an anti-inflammatory to Infliximab (an immune system suppressor) are studied in COPD (9). The treatment costs for a COPD patient are very high. Costs attributable to having COPD were $32.1 billion in 2010 with a projected increase to $49.0 billion by 2020 (10). Regarding the high economic and social burden of COPD, the wrong belief, the lack of proper treatments, and the side effects of administered drugs, many types of research are conducted to find treatments with better efficiencies and fewer side effects (11,12).

Nowadays, most of the population utilizes traditional medicines in developed countries. Each culture possesses specific traditional and indigenous medicine including the use of plants, animals, and minerals (13). Persian Medicine (PM) is assumed as the alternative or complementary treatment (14) for treating diseases by making advices for a better lifestyle along with the utilization of selected food and herbal medicines with about ten thousand years of history (15). In the texts of PM, consumption of honey added to a herbal formulation is common to improve lung disease, depending on the type of disease and the different temperaments. The extracts of various plants such as ginger, cinnamon, galangal, mastic, saffron, clove, pepper, rose and cardamom are combined with honey for preparing a new formula (16,17).

Compound Honey Syrup (CHS) is a mixture of honey (18-21) and the extracts of five herbal medicine consisting of ginger (22-25), cinnamon (26-28), saffron (29-31), cardamom (32) and galangal (33,34) that each of which plays anti-inflammatory, antibacterial, and antitussive, bronchodilator and anticholinergic roles in treating lung diseases. To the best of our knowledge, no clinical trial has examined the efficacy of CHS on the clinical manifestations of COPD.

In this double-blind randomized clinical trial study, a traditional herbal formulation was added to classical treatment in the management of COPD with the aim to evaluate the efficacy and safety of CHS as compared with placebo.

MATERIALS AND METHODS

Patients

This randomized double-blind clinical trial was performed on 82 subjects with a diagnosis of mild to severe COPD, referring to the division of pulmonary medicine of Baqiyatallah Hospital, Tehran, Iran from December 2018 to September 2019. All patients signed an informed consent form before inclusion. Table 1 shows the inclusion and exclusion criteria of the study in detail.

Table 1. Inclusion and exclusion criteria of the patients for the study

Inclusion Criteria	Exclusion Criteria
• Signed inform consent • Positive COPD diagnosis • Mild to severe COPD • Medically stable • Aged between 18 and 75 years • No allergic to any components of intervention drug • Lack of recent participation in other clinical trials	• Very severe disease • Recent exacerbation • Severe comorbid disease • Pregnancy or breast-feeding • Serious hepatic and renal diseases • Administration of drugs such as aspirin, beta-blockers, and NSAIDs

Sample Size

According to the previous studies and experimental design, based on the statistical calculations, sample size of 76 patients (38 patients each in the intervention and the control group) was considered with a 25% possibility of withdrawal.

Drug Preparation

In this study, Compound Honey Syrup (CHS) was formulated according to documented pharmaceutical Persian Medicine texts with slight modifications (15-17,35). This PM product has a license from the Iranian Food and Drug Administration (IFDA) affiliated to The Ministry of Health of Iran (license number: S-94-0425). Plants used in CHS were prepared and controlled using standard methods at quality control laboratory, Niak Company. CHS with the batch number of 96133, 22.10.2018 was given to each patient. Each 100 ml of CHS consisted of honey (40 gr.), and the extracts of ingredients of plants (7 gr.), (Table 2). The placebo was prepared in a similar appearance with water and sugar.

Ethical Issue

The study was approved by Ethics Committee of the Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1396.399). The study is registered in the Iranian Clinical Trial Registry (IRCT20190217042737N2). The study protocol followed the ethical guidelines of the Declaration of Helsinki.

Study Design

Intervention

Initially, patients were randomly divided by a third-party pharmacologist into intervention and control groups based on chains and quadruple blocks (Intervention Group [CHS]), Oral Syrup, 10 ml in 100 ml of warm water, three times a day) and control group (placebo, Oral Syrup, 10 ml in 100 ml of warm water, three times a day). Before the study, patients were asked to complete the COPD Assessment Test (CAT) and St. George's Respiratory (SGRQ) questionnaires and spirometry was performed during the study visit (36, 37). In the intervention group, patients received CHS in addition to the standard treatments, which included Seretide spray (fluticasone and salmeterol) and NAC, while patients received placebo besides the standard treatments in the control group. Patients in both groups were followed up at the end of weeks 4 and 8 and also visited by a pulmonologist for clinical examinations and completion of the CAT, and SGRQ questionnaires. Furthermore, spirometry was performed and interpreted according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) joint guidelines to determine the status of the disease. This statement was defined a 'positive' bronchodilator response (BDR) as an absolute 0.2 L and a 12% increase from baseline in either forced expiratory volume in 1s (FEV_1) or in forced vital capacity (FVC); BDR was classified as 'negative' if neither criterion was met. Besides, the patient-reported side effect questionnaire was also obtained at each visit.

Data collection tools

Demographic characteristics of the subjects [e.g., gender, age, body mass index (BMI)], education, and smoking status were obtained using a data-gathering questionnaire. The CAT is a valuable instrument for measuring response to treatment in patients with COPD. Components of the CAT test are eight questions regarding cough, phlegm, chest tightness, breathlessness during activities, activity limitations at home, confidence in leaving home, sleep and energy. The scoring range of each item is between 0 and 5, with a maximum score of 40 and patients with CAT scores >10 revealed test positivity (36).

The SGRQ questionnaire, which included the symptoms, activity and impact, were completed for all patients. The scores of the SGRQs were calculated using an Excel-based scoring calculator (37). It should be noted that we utilized the validated Persian version of the CAT and the SGRQ in this study (36, 38).

Standard spirometry tests (multifunctional spirometer HI-801; Chest MI, Inc., Tokyo, Japan) were performed in all patients. The FEV1, FVC and FEV1/FVC were measured and expressed as a percentage of the predicted values. The best of three consecutive spirometry recordings was used. The severity of the airway obstruction was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (39).

Table 2. Specifications of honey add-on plants used in Compound Honey Syrup, *Weight in grams per 100 ml of water-honey

Botanical name	Family	Common name	Part used	Weight (gr.) *
Zingiber officinale Roscoe	Zingiberaceae	Ginger	Root	1
Cinnamomum verum J Presl	Lauraceae	Cinnamon	Bark	2
Crocus sativus L.	Iridaceae	Saffron	Stigma	1
Elettaria cardamomum (L) Maton	Zingiberaceae	Cardamom	Fruit	2
Alpinia galanga (L) Willd	Zingiberaceae	Galangal	Root	1

Statistical Analysis

Data analysis was performed by using SPSS V. 21 (IBM Corporation). The distribution of all variables was tested for normality using the Kolmogorov–Smirnov test. Therefore, it was decided to use robust non-parametric methods for descriptive and inference statistics. Differences between three COPD stages were assessed utilizing the Kruskal–Wallis test. Moreover, subsequent pairwise comparisons were carried out with the Mann–Whitney U test. A P-value less than 0.05 was considered to be statistically significant. Pearson Chi-Square Test and Fisher Exact Test were used to determine the relationship between qualitative variables. The Wilcoxon Signed Ranks Test was used to compare quantitatively measured variables at two different times.

RESULTS

Out of 83 cases included in the study, one patient was excluded due to failure to refer for the second spirometry. The consort graph demonstrates the flowchart of the study. Of the 82 enrolled subjects, 76 (38 in the intervention, 38 in the control groups) completed the study (Figure 1). All patients were informed about the possible adverse effects of the medication, but two patients were excluded due to failure to refer for the third spirometry in the intervention group and two patients were excluded in the placebo group because of dyspepsia and vomiting. All included patients were clinically stable and did not show any signs of exacerbation.

Table 3 demonstrates demographic variables of the included patients before randomization and therapy. No statistically significant relationship was found between variables and intervention/control groups. These results verify the randomization process in the study.

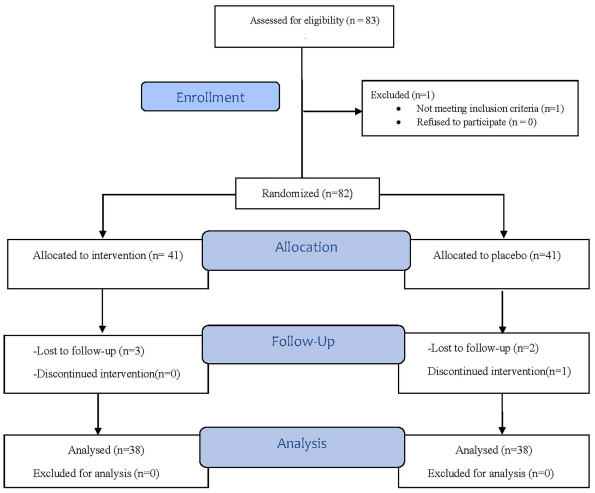

Figure 1. CONSORT flowchart of participants

According to Mann-Whitney U test, detailed CAT scores are demonstrated in Table 4. It is clear that no significant improvement was found in total CAT score in 4th week and 8th week in two groups, but absolute value of difference between baseline and 4th-week was observed to be significant in intervention and control groups. Also, coughing and phlegm production were found to be significantly reduced in 4th week when compared with the first checkup. Confident leaving home scores were significantly improved during 8th week checkup between intervention and control groups. No significant improvement was observed between groups in terms of chest tightness, dyspnea, limitation of the activities and having energy. However, sleeping disorders were found to be significantly reduced in 8th week compared with the first checkup.

Table 1. Baseline characteristics of all included patients

Number	A(n=38)	B(n=38)	P value
Age (<60 / 60<)	24/14	18/20	0.166*
Gender (♀ / ♂)	29/9	33/5	0.237**
BMI	26.61±4.9	27.65±4.76	0.266***
Comorbidity Disease (Yes/No)	12/26	18/20	0.159*
Smoking (Ne. /Fo. /Cm.)	8/14/16	3/21/14	0.149*
Mean Pack Year	13.33±13.71	16.91±14.9	0.205***
COPD Stage (Mi. /Mo. /Se.)	13/19/6	13/19/6	0.998*

Categorical variables were tested using * Pearson Chi-Square Test and ** Fisher Exact Test Continuous variables were tested using *** Mann-Whitney U Test
Ne: Never been smoker, Fo: Former smoker, Cm: Currently smoker, Mi: Mild, Mo: Moderate, Se: Severe

Table 2. Total and items CAT scores between between inteventional and control groups

Subscales of CAT Scores		Visiting Times				
		Baseline	4th Week	8th Week	Difference of baseline to 4th	Difference of baseline to 8th
Cough	A	3.34±1.34	2.34±1.36	2.11±1.27	-1±0.74	-1.24±1.02
	B	3.61±1.20	3±1.16	2.61±1.33	-0.61±0.72	-1±1.01
	p-value*	0.434	**0.039**	0.098	0.008	0.312
Phlegm	A	3.24±1.38	2.39±1.22	2.18±1.31	-0.84±0.86	-1.05±0.87
	B	3.55±1.39	3.08±1.26	2.71±1.31	-0.47±0.69	-0.84±0.86
	p-value*	0.274	**0.021**	0.073	0.042	0.254
Chest Tightness	A	3.26±1.22	2.24±1.28	2.03±1.39	-1.03±0.85	-1.24±0.97
	B	3.42±1.13	2.66±1.02	2.47±.1.11	-0.76±0.71	-0.95±1.09
	p-value*	0.626	0.114	0.112	0.245	0.335
Dyspnea	A	3.74±1.16	2.76±1.22	2.63±1.17	-0.97±0.85	-1.11±0.83
	B	3.79±1.17	3.08±1.15	2.95±1.27	-0.71±0.69	-0.84±1
	p-value*	0.748	0.253	0.283	0.154	0.200
Activity Limitation	A	3.08±1.28	2.29±1.49	2.03±1.35	-0.79±0.78	-1.05±0.84
	B	3.24±1.24	2.37±1.13	2.24±1.08	-0.87±0.62	-1±0.7
	p-value*	0.604	0.957	0.414	0.448	0.774
Leaving Home	A	2.0.5±1.48	1.89±1.45	1.61±1.37	-0.61±75	-0.89±1.01
	B	3.18±1.31	2.45±1.20	2.21±1.19	-0.74±0.60	-0.97±0.79
	p-value*	0.045	0.091	0.041	0.284	0.399
Sleeping Disorder	A	3.55±1.29	3.08±1.24	2.92±1.28	-0.47±0.76	-0.63±0.63
	B	3.42±1.33	3.18±1.27	3.13±1.28	-0.24±0.49	-0.29±0.57
	p-value*	0.653	0.756	0.362	0.130	0.027
Having Energy	A	3.39±1.18	2.32±1.23	2.08±1.15	-1.08±0.78	-1.32±0.9
	B	3.42±1.08	2.61±1	2.32±0.99	-0.82±0.61	-1.11±0.95
	p-value*	0.957	0.168	0.215	0.114	0.211
Total CAT score	A	26.11±7.08	19.32±7.90	17.85±7.86	-6.79±3.43	-8.52±3.3.78
	B	27.63±6.26	22.42±5.36	20.63±5.60	-5.21±3.39	-7.00±4.96
	p-value*	0.325	0.066	0.068	0.029	0.163

*p-value were tested with * Mann-Whitney U Test

Table 5 illustrates the total and item scores of SGRQ. The total SGRQ between intervention and control groups were found to be significantly improved in 4th and 8th weeks checkups. Also, symptom, activity and impact scores improved significantly among all checkup timings as revealed by Mann-Whitney U test.

Table 6 shows changes in total and item scores of the SGRQ test among mild, moderate, and severe categories of COPD patients according to GOLD standard criteria. There was no significant difference between all stages of the disease between intervention and control groups in the various times of study. Results of the spirometry test in detail are presented in Table 7. Absolute value of difference of FEV_1(L) between baseline and the 4th week (1.88, 2.39) showed a statistically significant difference (p=0.044) in two groups, whereas there were no

statistically significant alterations between the 4th and 8th weeks (2.39, 2.38), respectively. In addition, FEV_1/FVC ratios showed meaningful changes from the second medical checkup, but also improvement was revealed by comparing the baseline with the second (p=0.011) and third visits (p=0.019).

Table 5. SGRQ total and items scores between inteventional and control groups

SGRQ scores		Visiting Times				
		Baseline	**4th Week**	**8th Week**	**Diff. between of baseline to 4th**	**Diff. between of baseline to 4th**
	A	71.20±18.71	52.11±22.34	46.78±18.10	-19.09±12.28	-24.33±9.76
Symptom score (%)	B	76.19±18.78	67.46±18.70	60.18±19.81	-8.73±6.45	-16.01±13.05
	p-value	0.182	**0.002**	**0.003**	**0.001**	**0.002**
	A	58.92±26.39	38.93±20.62	36.25±19.04	-19.99±12.53	-22.67±13.43
Activity score (%)	B	66.89±24.49	56.19±24.72	53.21±25.25	-10.70±9.93	-13.68±12.15
	p-value	0.235	**0.003**	**0.003**	**0.001**	**0.002**
	A	45.93±2085	29.69±18.85	27.07±17.78	-16.24±11.93	-18.85±12.05
Impact score (%)	B	48.89±20.94	40.14±19.97	39.49±21.21	-8.75±10.33	-9.40±13.32
	p-value	0.470	**0.007**	**0.002**	**0.001**	**0.001**
	A	50.06±19.99	36.21±17.93	33.14±16.45	-17.85±9.10	20.92±9.47
SGRQ score (%)	B	58.88±19.02	49.54±18.60	47.08±19.77	-9.34±8.04	-11.79±11.00
	p-value	0.209	0.001	0.001	**0.001**	0.001

*p-value was tested with * Mann-Whitney U Test

Table 6. SGRQ total and item scores between inteventional and control groups

	Diff. Between of Times	Mild (No=26)		Moderate (No=38)		Severe (No=12)		P Value*
		Mean	S.D.	Mean	S.D.	Mean	S.D.	
Total SGRQ	**Baseline** - 4th	-12.15	8.44	-15.21	10.27	-11.59	9.27	0.396
	Baseline - 8th	-13.7	7.43	-18.42	13.26	-15.58	10.20	0.340
Symptom	**Baseline** - 4th	-16.58	13.72	-13.07	9.68	-10.79	7.75	0.466
	Baseline - 8th	-20.07	12.19	-20.95	13.15	-17.93	9.26	0.878
Activity	**Baseline** - 4th	-11.99	10.23	-16.41	12.26	-19.25	14.77	0.346
	Baseline - 8th	-13.80	10.74	-10.10	14.05	-21.58	15.67	0.144
Impact	**Baseline** - 4th	-10.86	9.64	-15.19	13.27	-7.47	8.46	0.153
	Baseline - 8th	-11.65	7.82	-16.68	16.93	-11.42	9.56	0.461

p-values were tested with Kruskal-Wallis H Test

Table 7. Spirometry items of the patients during the study between inteventional and control groups

		Visiting times				
		Baseline	**4th Week**	**8th Week**	**Difference of 1st to 4th**	**Difference of 1st to 8th**
	A	64.97±20.45	73.95±19.28	74.63±18.28	8.97±10.30	9.66±10.42
FEV1 (%)	B	66±18.05	70.42±18.28	71±17.97	4.42±5.44	5±7.06
	p-value	0.578	0.394	0.304	**0.011**	**0.009**
	A	1.98±0.75	2.33±0.83	2.38±0.77	0.34±0.54	0.39±0.53
FEV_1 (L)	B	2.06±0.75	2.18±0.75	2.20±0.71	0.12±0.3	0.14±0.36
	p-value	0.575	0.448	0.337	**0.044**	**0.028**
	A	45.45±22.08	59.39±28.69	61.92±27.90	13.95±19.23	16.47±20.66
MEF (%)	B	47.29±22.66	54.72±27.45	58.16±29.52	7.42±18.51	10.87±18.62
	p-value	0.659	0.519	0.499	0.067	0.232
	A	1.68±0.96	2.12±1.12	2.18±1.08	0.43±0.65	0.5±0.71
MEF (L)	B	1.63±84	1.83±1.06	1.95±1.08	0.2±0.63	0.32±0.62
	p-value	0.913	0.285	0.321	0.097	0.209
	A	64.87±8.26	72.71±8.96	73.42±9.58	7.84±8.68	8.55±8.75
FEV_1/FVC	B	64.92±7.57	67.11±8.57	68.11±9.12	2.18±8.67	3.18±8.78
	p-value	0.978	**0.011**	**0.019**	**0.001**	**0.003**

*p-value was tested with * Mann-Whitney U Test

DISCUSSION

In this randomized controlled trial, we assessed the effects of a polyherbal product on the quality of life in patients with COPD and reported it based on the CONSORT (Consolidated Standards of Reporting Trials) checklist. The subjects had consumption of conventional COPD medicine during the study period. It was tried to minimize the possible effects of placebo and confounding factors. Our results showed no significant improvement trend in total CAT score in intervention and control groups ($p>0.05$), but a significant difference was found between two groups in 4th visit when compared with 1st visit ($p=0.029$); whereas, no difference was observed in 8th visit compared with 1st visit ($p=0.163$). Most detailed CAT scores did not show any significant differences in any stages. Then, the unaltered status of dyspnea, activity limitations, and chest tightness, as well as coughing along with phlegm production were found to be significantly reduced in the 4th week compared with the baseline, while sleeping disorders showed significant changes in the 8th week compared with the 1st visit,

Also, total SGRQ score showed significant changes in 4th and 8th weeks compared with baseline. On the other hand, detailed SGRQ scores, which demonstrated improvements in impact, symptoms, and activities, had significant changes in 4th and 8th weeks compared with baseline in intervention and control groups. Besides, none of the patients showed statistically significant improvement based on the classification of the disease (mild, moderate, severe) in detailed SGRQ scores. In present study, improvement in forced expiratory volume in first second over than 0.2 L was observed in the intervention group compared with control group after 4 weeks.

Nevertheless, these changes in FEV1quantities were no found to be continued enough until the 8th week. But FEV_1/FVC ratio showed significant changes from the 4th week until the end of the study ($P=0.011$, 0.019, respectively) between two groups. This ratio is the most practical element in clinical studies, capable of determining the changes in lung capabilities along with ease of breathing.

Regarding the debilitating consequences, complications, and economic burden of COPD, the need for a study to achieve safe treatments is of great importance (40). There is currently no known ultimate cure for COPD, but slowing the progression of disease and improving mortality are important goals of therapy. Pharmacotherapy has not definitely been confirmed to affect these outcomes and it can only delay the progression and exacerbation of the disease relatively, while none has reported drastic change in the quality of life of patients (41). Thus, adding short-term use of corticosteroids, and supplemental oxygen along with specific exercises apparently may be capable of improving health-related quality of life compared to routine care systems (42). Nevertheless, there is an extensive history of utilizing herbal medicines for the treatment of COPD patients, particularly in Asian countries. Also, several studies have assessed the effectiveness of herbal medicines for the treatment of COPD for many years (43).

For instance, in a study conducted by Abdolahinia et al. revealed that Nepeta bracteate could be capable of reducing symptoms in patients with mild to moderate COPD and improving the CAT score by about 56% in the intervention group, whereas this improvement was 20% in the placebo after four weeks (44). These results are similar to our study in improvement of SGRQ score by about 31 and 16% in the intervention group and the control group, respectively. Although, our findings revealed that the CAT score has not improved significantly by about 26 and 21% in the intervention and control groups after four weeks, respectively.

Likewise, in China, Hong et al. (2018), Liu et al. (2016), and Liu et al. (2014) studied the effects of variuos kinds of Chinese herbal medicine on the quality of life of COPD patients according to SGRQ and CAT scores (45-47). Also, Mukaida et al. in Japan performed a pilot study showing that the multiherb Kampo medicine as bakumondoto could be effective in improving the symptoms of COPD patients

(48). In our research, a herbal formulation (CHS) was combined with routine treatments for the treatment of COPD patients. It showed similar outcomes on the quality of life along with SGRQ, a significant improvement in total CAT score from 4th week and the improvement of pulmonary function test FEV1 (L) by 0.26 L. Sadr et al. also confirmed that the prescription of CHS significantly improved clinical manifestations of pediatric asthma and increased FEV1% in lung function test (17). The main base of CHS was honey that when combined with five plant components, could easily be available at low costs and widely administered. Due to the therapeutic properties and low side effects of honey, it seems to be helpful in the treatment of COPD and could be coped with casual treatments including dextromethorphan and diphenhydramine (49).

Moreover, the major cause of the symptoms was associated with decreased pulmonary function in chronic respiratory diseases, as COPD is inflammation and airway remodeling changes. These modifications include changes in the composition and organization of cellular and molecular constituents of the normal airway wall structure (50). On the other hand, the symptoms of COPD are caused by an inflammatory process in the airways, followed by bronchospasm due to cholinergic stimulations (51). Amongst all herbal plants used in the formula of CHS, ginger and its active components including 6-gingerol, 8-gingerol, and 6-shogoal induce bronchodilation by modulating intracellular calcium in airway smooth muscle, with beta-2 agonist properties, anti-inflammatory and anticholinergic effects; also, it was capable of reducing interleukin-8 production in human bronchial epithelial cells (24, 52). In addition, cinnamon as an influencing element of the formula in our study, contains alkaloids, essential oil and type II ribosome-inactivating proteins (cinnamomin and camphorin) that inhibits the production of nitrogen oxide (NO), IL2, and TNF-α and also possess anti-inflammatory effects (53, 54).

Stress-related exacerbation of COPD in bronchial epithelial cells is induced by a combination of different cytokines that results in an increase in nitric oxide production (NO), as well as induces nitric oxide synthase (iNOS) levels, peroxynitrite ion generation, and cytochrome c release. Saffron treatment was capable of reducing induced nitric oxide synthase (iNOS) levels in epithelial cells (55). Treatment with saffron and its constituents, safranal and crocin, was also able to reduce oxidative stress in bronchial epithelial cells through iNOS reduction and prevention of apoptosis in these cells (31). Saffron have recently been proved to possess anti-inflammatory, antioxidant, and anti-cholinergic properties (29).

On the other hand, in the current study, *Alpinia officinarum* as another ingredient of the formula not only showed inhibition of Th2 cytokines expression including IL4 and IL13 and Th1 cytokines (such as IL12α and interferon-gamma), but also decreased IgE production, resulting in bronchodilation conditions (56). In an in vivo study conducted by Su et al. Alpinetin use was found to be associated with decreased levels of the inflammatory factors and biochemical markers due to reduction of TGF-β1, α-SMA, and TNF-α expression levels ($p < 0.05$), and declined Caspase-3 and Caspase-9 ($p < 0.01$), resulting in suppression of the alveolar cells injury. Moreover, protective effect of Alpinetin was capable of downregulating the IL-6 and upregulating the IL-10 ($p <0 .01$). Additionally, protective effect of Alpinetin inhibited the apoptosis, inflammation, and fibrosis of alveolar cells in rat models and significantly increased FEV1/FVC ratio (57).

Likewise, Cardamom, an ingredient of CHS, was capable of producing anti-inflammatory and bronchodilator effects. Cardamom also inhibited muscarinic receptors on airway smooth muscle with 1,8-cineole compound, and provided precise interest in the treatment of COPD (32).

In the present study, CHS could relieve bronchial stenosis and improve symptoms. This study demonstrated a significant improvement in the quality of life of COPD patients by providing a formulation of honey adds on the

medicinal plants, which is less studied in the world for their therapeutic effects on lung disorders including COPD. The limitation of the study was the short-term prescription of the mentioned drug. Another limitation was the use of CHS with classical therapy in COPD patients, and the effect of conventional therapy that may affect the study results.

CONCLUSION

In conclusion, this study is the original study that scientifically discusses the impacts of a traditional combination honey based on herbal formulation on COPD patients. The results of this study demonstrated that this traditional formula could be a safe and effective complementary medicine for the treatment and enhancement of the quality of life of COPD patients. It was suggested that further controlled experiments over longer periods with larger sample sizes are needed to assess other parameters involved in the drug efficacy. Furthermore, further studies without conventional therapy should validate the effect of this herbal formulation on quality of life of COPD.

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Conflict of Interest

The authors have no other conflict of interest to declare.

Ethical statement

This research has been approved by Baqiyatallah University of Medical Sciences, Tehran, Iran. (Approval Number: IR.BMSU.REC.1396.399). Informed consent was obtained from all participants.

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