Evaluation of the Effect of "Honey Zufa" Herbal Syrup on Cough in Hospitalized Patients With COVID-19: A Double Blind Randomized Clinical Trial

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Abstract- Cough is one of the most prevalent symptoms of COVID-19, affecting over 60% of patients. This symptom significantly diminishes quality of life, causing fatigue, insomnia, dysphonia, musculoskeletal pain, and urinary incontinence. Honey Zufa herbal syrup is a well-known antitussive remedy in the Iranian market and was evaluated for its potential to alleviate this symptom. This study aimed to assess the efficacy and safety of Honey Zufa herbal syrup in treating acute cough resulting from mild to moderate COVID-19. A randomized controlled trial was conducted with 200 patients assigned to either the treatment group, receiving Honey Zufa herbal syrup, or the placebo group, receiving a placebo. Both groups also received standard cough control medications. Cough severity was measured using three different scoring systems. The impact of Honey Zufa on cough severity, the influence of other medications, and changes in laboratory parameters were monitored over a 14-day period. Honey Zufa herbal syrup significantly reduced cough severity compared to the placebo across all scoring systems. The treatment group experienced a greater reduction in cough severity than the placebo group. However, there was no significant difference between the groups in terms of antitussive medication regimens. Laboratory parameters remained stable, and no significant side effects were observed. Honey Zufa herbal syrup effectively reduces cough severity in patients with mild to moderate COVID-19, suggesting it could serve as a useful complementary and alternative treatment option for COVID-19-induced cough.

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Introduction

The novel coronavirus (2019-nCoV) has had a significant global impact, with over 600 million confirmed cases and 6.5 million deaths reported worldwide (1). The pandemic has led to an increased need for patient and healthcare (2,3), as well as negative effects on mental and physical health (4-6). Cough is one of the most common symptoms of COVID-19 (1), with over 60% of patients affected (1,2,4). This symptom can lead to a decreased quality of life, including fatigue, insomnia, dysphonia, musculoskeletal pain, and urinary incontinence (5,6). The prolongation and severity of coughing attacks can also greatly affect a patient's ability

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to stop coughing (7). Recording the intensity, frequency, and duration of accompanying symptoms is a crucial goal in the treatment of COVID-19. Furthermore, controlling cough can help to prevent transmission to others and eliminate the stigma associated with the symptom (1).

Various drugs, such as diphenhydramine, codeine, dextromethorphan, and guaifenesin are widely used as treatments for cough (8,9). Expectorants can also be used to decrease inflammation and improve bronchitis symptoms (10). The use of corticosteroids for cough should be carefully considered due to potential adverse effects (11). Treatment options for coughs caused by viral infections such as colds and flu are usually over the counter (OTC) medications. Although there are many drugs in the market to treat cough, there is limited data proving their effectiveness in treating cough related to respiratory infections (1). According to evaluations, dextromethorphan and diphenhydramine and the second generation of antihistamines have been found to have no efficacy more than placebo (12-14). The use of combination antitussive products is concerning due to the lack of data on their efficacy, while increasing the possibility of adverse effects (10).

Although there is limited understanding of the mechanisms that cause cough in COVID-19, viral invasion of vagal sensory neurons or neuroinflammatory responses or both may cause peripheral or central sensitization of cough pathways (1). The best treatment for cough caused by COVID-19 is not yet clear (1).

Therefore, there is no doubt that finding new remedies for solving cough problem of COVID-19 patients is welcome. Natural products are one of the options that their popularity is increasing worldwide. Herbal medication in cough as an expectorant has been proved in clinical conditions (5). In recent twenty years, the scientific and general population even in a developed country have been interested in traditional or alternative medicine (10,15). Traditional medicine and its remedies contribute to a major role in the current health care systems of several countries (16).

Cough is the first 14th respiratory disorder that can be cured by herbal medicine (17). These plants improve cough with different mechanisms including inducing secretion and containing mucilage (18). Some of these plants after immunity and efficacy approvement are used in today's medicine (5). So lower cost and more efficiency with the less side effects are the valuable benefits of some of these herbal medicines (19).

Iran, as a country with thousands of years history and civilization in the Middle East, has a traditional system of medicine rooted in the history, called Persian medicine. Also, there are a wide range of plants species (more than 8000 species), in particular medicinal plants and ethnopharmacological knowledge all around the country (20,21). In Iranian market there are many herbal medicines which are claimed to treat cough.

Honey Zufa herbal syrup is one of these products as a combination of different ingredients mentioned in Persian medicine sources, that have been proven effective in both animal and human studies to treat cough (22). This herbal syrup contains Marsh Mallow (*Althaea officinalis* L.), Zufa (*Hyssopus officinalis*), Fig fruit (*Ficus carica* L.), Jujube (*Zizyphus jujuba* Mill.), Violet (*Viola odorata*), Maidenhair (*Adiantum capillus-veneris* L.), Thyme (*Thymus vulgaris)*, Common mallow (*Malva sylvestris* L.), Pomegranate extract (*Punica granatum* L.) and Honey. After *T. vulgaris*, Zufa is the most commonly used herbal medicine to treat cough (23,24). There are some studies which evaluated polyherbal syrup containing Zufa as treatment of some respiratory diseases. According to these studies which have not reported any specific adverse effect and promising result of these studies and meta-analysis of herbal medicine encouraged us to design a study to assess the effect of Honey Zufa herbal syrup on cough COVID-19 (25-31).

Materials and Methods

Study design and participants

This randomized, double blinded, placebo-controlled clinical trial employed a two-arm parallel design, with an allocation ratio of 1:1 for the control and intervention groups. Hospitalized Patients with mild to moderate symptoms from February 2021 to June 2021 for 5 months were included in study. Mild severity was defined by "mild symptoms without dyspnea" while clinical or radiographic evidence of lower respiratory tract infection without need to ICU admission and absence of severe symptoms based on physician examination and patient self-declaration considered as moderate severity (32).

Preparation of materials

There are some commercial natural products under the name of Zufa herbal Syrup (produced according to the Persian Medicine sources) in the Iranian market. We supplied Honey Zufa herbal syrup that was manufactured by Razak Pharmaceutical Company (Tehran, Iran). It was chosen because of our pre-study evaluation about the content of total flavonoid of all Zufa Syrups in the Iranian market via spectrophotometry method and this product has the most content of total flavonoids equivalent to Quercetin/ mL of product. This product has Iranian Food

and Drug Administration approval to be produced (IRC Code: 4699872348044316). The product is standardized based on a minimum of 0.440 mg/5ml of Thymol.

The placebo was also prepared by mixing 5% (V/V) Honey Zufa herbal syrup (Razak Co.) with simple syrup BP (33) in the same bottle with the same color and odor with Honey Zufa herbal syrup.

Inclusion criteria

Inclusion criteria of study include the following:

- Mild to moderate COVID-19: mild severity was defined by "mild symptoms without dyspnea" while clinical or radiographic evidence of lower respiratory tract infection without need to ICU admission and absence of severe symptoms based on physician examination and patient self-declaration considered as moderate severity (32).
- informed consent from patients.
- Age 18 to 75 years (according to the studies conducted on medicinal plants in the adult population and the lack of information in the population under 18 years and over 75 years old).
- Respiratory infection confirmed through physical examination, radiological or laboratory data and by a physician (supervisor/ thesis professor)
- Cough caused by COVID-19.

Exclusion criteria

Exclusion criteria of study include the following:

- Renal failure (GFR[1] <30 mL/min/1.73m^2) based on Cockroft-Galt formula
- Liver failure (AST or ALT >3x ULN)
- Psychiatric diseases that affect the adherence to medication and the correct implementation of the study protocol
- Participating in another study
- History of heart disease
- Hemoptysis (possibility of other serious diseases) (14)
- Need for urgent or chronic treatment: If the clinical evaluation of the patient shows that the cough control in the patient needs quick intervention and the continuation of the cough may threaten the patient's life, we will treat the patient, and it is not ethical for them to enter the study. If the cough is caused by an underlying disease such as asthma or COPD that requires long-term treatment, they will be excluded from the study because the need for drug treatment is more than symptom treatment and participation in the study.
- Rhinitis and allergy (due to the presence of allergens in some coughs) (34)
- Forgetting more than three doses of honey hyssop syrup (for more than three doses, we cannot be sure that the improvement is caused by the drug).
- Type 1 and 2 diabetes mellitus (honey: hyperglycemia, mallows (35), and maidenhair (36): hypoglycemic)
- Seizures (hyssop): Hyssop has been shown to lower the seizure threshold in studies (37)
- Taking venlafaxine (combined with jujube causes serotonin syndrome), phenytoin and phenobarbital (jujube increases the effect of these drugs in animal studies) (38), gentamicin (Mallow extract in combination with aminoglycosides increases nephrotoxicity) (35).
- Gastrointestinal reflux disorder (some coughs are caused by digestive disorders that are cured by antiacid treatment) (17). Gastro esophageal reflux disease is a condition that develops when the physiologic reflux episodes are long-lived, occur during sleep and cause troublesome symptoms and/or complications (39).
- Smoking or any environmental factors (working in mine, polluted weather, or with special materials like asbestos) damaging the lungs that may cause cough or an underlying disease
- History of allergy to any of the medicinal plants in honey hyssop syrup.
- Pregnancy and breastfeeding (almost all plants, there is no study due to their safety)
- Taking medications that may cause cough such as ACEI (17).
- Use of other herbal medicines which are used in our products and any plants may be useful in relieving cough like ginger, liquorice, turmeric and peppermint (40). Herbal medicine is defined as any type of medicine or raw herbal materials that use roots, stems, leaves, flowers or seeds of plants to improve health, prevent disease, and treat illness (41).

It should be noted that Some patient's received N acetyl cysteine as expectorant to relieve cough and is not considered as an exclusion criterion.

Intervention

Standard treatment

All the patients at both groups received standard treatment which was administered in the hospital. COVID-19 treatment was Dexamethasone and other

glucocorticoids, IL-6 pathway inhibitors like tocilizumab, Remdesivir, hydroxychloroquine, lopinavir-ritonavir and sofosbuvir. Cough treatment used in patients included antihistamine, cough suppressant like dextromethorphan and expectorant.

Placebo and test drug

Drug and Placebo were prescribed to be used by patients for two weeks. Patients had to use 10cc of Honey Zufa herbal syrup / placebo three times a day.

Outcome measures

"Visual Analogue Scale" (VASS), "Cough Symptom Score" (CSS) and "Simplified Cough Score" (SCC) was used as the primary outcome measure. Data collection was done on the first day, 48 hours, one and two weeks after the intervention.

Patients are followed up through the phone and virtual space for two weeks, and communication is made about the patient's clinical condition, the occurrence of possible complications and the emphasis on drug consumption. In case of possible complications, Naranjo scale was evaluated and recorded (39).

Randomization and blinding

Randomization was done based on quadruple block, which was generated by Excel software. This blocking was done in a way that when the patient entered the hospital, 4 cards A, B, C, D were presented to the patient and the patient had the right to choose one card. Then, based on the block of 4 numbers, the patients were randomly allocated to "Drug" and "Placebo" groups.

All treatment providers (researchers), patients and statisticians were blinded. Also, placebo was produced as mentioned above with similar color and odor with drug and packed in similar containers.

Statistical analysis

The sample size for the study was determined by considering a two-tailed significance level of 0.05 and a power of 0.95. Additionally, accounting for a potential drop-out rate of 20%, the required population size was calculated to be 50 patients in each group. Also, there was the Kolmogorov-Smirnov test performed to assess whether there was a significant difference between the rank numerical and biomass abundances and a long–normal distribution. Since it was not normal distribution, nonparametric version of the tests was done. Demographic and basement clinical data of the enrolled patients were presented in the form of median (Q1-Q3). Statistical analysis was conducted using techniques such as paired and independent t-tests, Mann-Whitney tests, and Fisher exact tests. A *P* of less than 0.05 was considered statistically significant. We also examined intergroup and intragroup changes. All of medication which were prescribing as anticough was compared between two groups. For performing statistical analyses, SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

RCT results and outcomes

A total of 535 cases with mild to moderate COVID-19 symptoms, specifically cough, were assessed, from February 2021 to June 2021. These cases were selected based on specific inclusion criteria. Of these, 387 patients were excluded due to not meeting the inclusion criteria, and an additional 48 patients were excluded due to non-compliance or deterioration in their health status. Ultimately, 100 patients were included in the study, as outlined in Consort Flowchart (Figure 1) of the study process. The patients were divided into two groups, with 50 cases in each group: an intervention group and a control group. There was no significant difference between the baseline characteristics of the two groups (Table 1).

According to Table 2. The effect of Honey Zufa herbal syrup on cough severity, as measured by Visual Analogue Scale (VAS), was found to be significant in comparison to the placebo during a 14-day and night period.

Table 3 presents the results of the evaluation of anti-cough effect of Honey Zufa herbal syrup in comparison with the placebo using CSS at day and night time. There was no significant difference in CSS score between the two groups on the first day (P=0.53) and night (P=0.64), while the score for the Honey Zufa herbal syrup group was significantly reduced compared to the placebo group on the second, seventh, and fourteenth days and nights (P<0.05).

As demonstrated in the table provided below, the Simplified Cough Score (SCS) confirms the findings of previous results. While the SCS score on the first day and night was no significant difference between the two groups (P=0.78, 0.53 respectively), on the second day and night, seventh and fourteenth days and night, the SCS score for the group receiving the Honey Zufa herbal syrup was found to be significantly lower compared to the placebo group (P<0.05; Table 4).

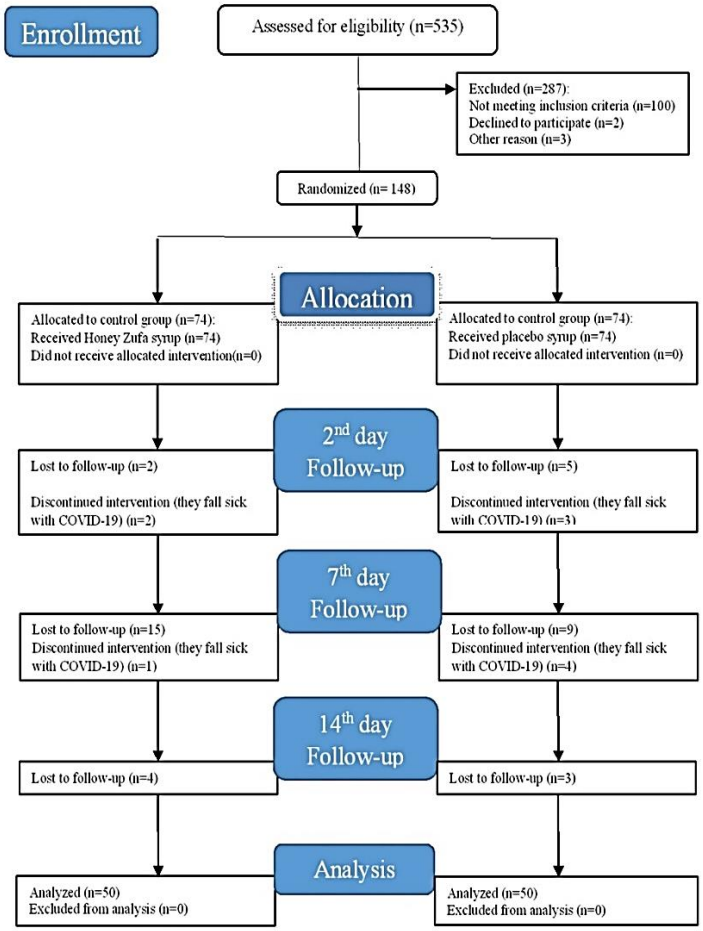

Figure 1. CONSORT Flowchart of a clinical trial investigating the anti-cough effect of Honey Zufa syrup in hospitalized patients with mild to moderate COVID-19

Table 1. Baseline demographic, laboratory and clinical data of hospitalized patients with moderate COVID-19

Demographic data	Zufa syrup (n=50)	Placebo (n=50)	*P**
Age, year, mean±SD	50.10 (±13.16)	52.88 (±14.67)	0.30
Gender, (male) (%)	26 (50.00%)	35 (70.00%)	0.06
Weight (kg), mean±SD	77.36 ±15.66	79.72 ±15.70	0.55
Height (cm), mean±SD	169.06 ±9.70	165.27 ±10.61	0.13
Body mass index (kg/m^2), mean ±SD	28 ±5.79	27.5 ±4.80	0.07
Laboratory data, Median (Q1-Q3)			
ALT, U/L	43.50 (31-59)	41.50 (30-62)	0.06
AST, U/L	52 (39-63)	46.5 (35-58)	0.10
ALP, U/L	136 (117-164)	143 (114-173)	0.08
PLT *10^3/mm^3	215 (170-260)	186 (149-256)	0.11
Hb, (g/dL)	13.6 0 (12.1-15)	14.15 (12.8-15.3)	0.36
WBC (10^3/mm3)	5 (7.15-9.4)	4.80 (6-9.3)	0.08
Cough duration before Zufa initiation (days)	6 (3-7)	5 (3-7)	0.07

Abbreviations: Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), Platelets (PLT), Visual analog scale (VAS)
**P* <0.05 is considered as significant

Table 2. Comparing the anti-cough effect of Honey Zufa herbal syrup with placebo using the VAS1 criterion during 14 days

Intervention	VAS [1]											
	Day 1			Day 2			Day 7			Day 14		
	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3
Zufa, n=50	2	4	6	1	2	4	0	0.5	2	0	0	1
Placebo, n=50	3	4	6	2	3.5	5	2	3	4	0	2	3
P		0.36			0.004			0.001			0.0001	

Q_1: quarter one
Q_3: quarter three
P<0.05 is significant.
**P* after treatment versus baseline.
1- Visual Analog Scale

Table 3. Comparing the anti-cough effect of Honey Zufa herbal syrup with placebo using the CSS1 criterion during 14 days and nights

Intervention	CSS [1]											
	Day 1			Day 2			Day 7			Day 14		
	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3
Zufa, n=50	1	2	4	1	1	2	0	0.5	1	0	0	1
Placebo, n=50	2	3	4	2	2	3	2	2	3	0	1	2
P*		0.53			0.001			0.0001			0.001	
	Night 1			Night 2			Night 7			Night 14		
	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3
Zufa, n=50	1	2	4	0	1	2	0	0	0	0	0	0
Placebo, n=50	1	2.5	3	1	2	3	1	2	2	0	1	2
P*		0.64			0.01			0.001			0.0001	

Q_1:quarter one
Q_3: quarter three
P<0.05 is significant.
**P* after treatment versus baseline.
1-Cough Symptom Score

Table 4. Comparison of the anti-cough effect of Honey Zufa herbal syrup with placebo based on SCS1 criteria within 14 days and nights

Intervention	SCS [1]											
	Day 1			Day 2			Day 7			Day 14		
	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3
Zufa, n=50	2	1	3	1	1	2	0.5	0	1	0	0	1
Placebo, n=50	2	2	3	2	1	2	1	1	2	1	0	2
P		0.78			0.005			0.001			0.0001	
	Night 1			Night 2			Night 7			Night 14		
	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3	Q_1	Median	Q_3
Zufa, n=50	0	2	3	0	0	1	0	0	0	0	0	0
Placebo, n=50	1	2	2	0	1	2	0	1	2	0	0	1
P*		0.53			0.005			0.001			0.0001	

Q_1: quarter one
Q_3: quarter three
P<0.05 is significant.
**P* after treatment versus baseline
1- Simplified Cough Score

In addition to the comparison between the two groups, the results of an evaluation of cough severity have also been investigated within each group individually. As measured by VAS, CSS and CSS in both group of participants who received a Honey Zufa herbal syrup and placebo over a 14-day and night period were significantly reduced (*P*<0.05).

Another investigation was conducted to assess the

effect of other effective drugs on associated cough as monotherapy and combination therapy between two groups. We enumerate the various antitussives that were prescribed to all patients. The *P* reported indicate that there was not any significant difference between the two groups in terms of the regimen of antitussive medication ($P<0.05$).

The results of the investigation conducted to assess the impact of Honey Zufa herbal syrup and placebo on the laboratory parameters (ALT, AST, ALP, WBC, Hb, platelet, FBS) of patients illustrate consuming Honey Zufa herbal syrup and placebo did not result in significant alteration of the laboratory parameters of the patients. During the study, no side effects were observed with Honey Zufa herbal syrup and placebo, and the patients did not report any side effects.

Safety assessment

During follow-up visits, patients in both groups were questioned regarding any observed adverse effects. According to the reports, there were no serious adverse effects during the follow-up period. Using such a natural product which was approved by Iran food and drug organization (FDO) has some advantages as safety, effectiveness, cost-effectiveness, and accessibility.

Discussion

The results of this study demonstrate that Honey Zufa herbal syrup significantly ($P<0.05$) reduced coughs caused by respiratory infections of COVID-19. The results are due to the ingredients of the product listed as below:

Zufa (*H.officinalis)* has been used as an herbal expectorant and antitussive for a long time (40, 41). There is no human study available but in the animal study, anti-inflammatory and antitussive effects of zufa have been approved (42). Airways remodeling decreased with taking Zufa in the animal model. These symptoms were the same as another group who receive dexamethasone. The same research was done on immunity. Asthmatic mouse model that was treated by Zufa extract had a significant decrease in mucus secretion and immunoglobulin E and G that was the same with dexamethasone group (43).

A.officinalis is a medicinal herb that is used for dry cough (36). *In-vitro* and *in-vivo* studies show dose-dependent antitussive effect. The root of this plant contains much amount of mucilage which causes expectorant effect (8). In one clinical study, 90.2 % of patients were satisfied with root products to treat cough (9).

Fig fruit (*F.carica*) is also used traditionally to cure cough and sore throat (44,45). This plant contains a huge amount of Mucilage which explains its.

Jujube (*Z.vulgaris*) is another plant that is used to treat cough. The fruit of this plant is used for fever and chronic bronchitis in traditional medicines (46). Its seeds were used to cure nonproductive cough (47).

Another plant is violet (*V.odorata*) in Persian medicine and another traditional medicines is used to cure cough and cold (28,29). This plant with an expectorant ingredient leads to decrease in pulmonary and mucosal membrane inflammation and improves respiration by its antitussive effect. In one clinical study in asthmatic pediatric, violet syrup improves cough significantly in patients (48).

The most important usage of Maidenhair (*A.capillus-veneris*) is to cure respiratory disorders like cough and dyspnea (49,50). Pomegranate (*P.granatum*) extract has been used in the treatment of cough and sore throat (51).

Periodic studies have demonstrated the effectiveness of honey in reducing the frequency of cough, including night cough in children with respiratory infections (34,52-54). Meta-analyses have also shown that the use of honey after tonsillectomy can lead to reduced pain and improved wound healing, as well as reduced discomfort caused by the wounds. In laboratory and animal models of pain and inflammation, honey has been found to have a pain-relieving effect, particularly in reducing inflammatory pain (34).

Also, there are some other studies on herbal syrups containing Zufa in the literature. It should be noted the ingredients of these Honey Zufa herbal syrup are different based on the Persian medicine sources used to formulate them. In a triple blind study conducted by Broujerdi *et al*., at Shahid Beheshti Clinic in Qom, Iran, 116 outpatients with mild to moderate COVID-19 were prescribed 7.5 milliliters of Zufa herbal syrup every four hours for ten days. Both the Zufa herbal syrup and placebo groups showed improvement in symptoms such as cough, headache, shortness of breath, muscle pain, anorexia, anxiety, and insomnia, but there were no observed significant differences between the two groups (25). In the study conducted by Boroujerdi *et al*., in addition to cough, other symptoms such as shortness of breath, headache, myalgia, anorexia, anxiety, and insomnia were also evaluated. During follow-up, pulse rate and oxygen saturation were also monitored in the study group. However, this study did not utilize a scoring system, and symptoms were simply evaluated for severity on a scale of zero to three. In contrast, the focus of our study was

specifically on cough, which is a common and bothersome symptom of COVID-19, and assessment was performed using three scores: VAS, CSS and SCS.

In a separate clinical evaluation of Zufa Murakkab syrup, 30 patients with chronic bronchitis consumed 20 ml of Zufa syrup twice daily for 45 days. At the beginning of the study, all patients were screened for airway obstruction using a pulmonary function test (FET: Forced Expiratory Time, PEEF: Peak Expiratory Flow Rate) and only those with irreversible airway obstruction were included in the study. After consuming the Zufa Murakkab syrup, a significant improvement was observed in both the symptoms of the disease and the patients' pulmonary function. Some of these ingredients, such as southern maidenhair fern, possess anti-inflammatory properties, while others, such as Zufa and marshmallow, have mucolytic properties (26).

The main difference between the syrup studied in the present research and the syrup evaluated in the previous clinical evaluation is the inclusion of ingredients such as licorice, iris, anise, celery seed, and grapes in the latter. Both syrups contain figs, viola, southern maidenhair fern, and Zufa, but the syrup used in the present study also contains pomegranate extract and Thyme, which are not found in any other Zufa products. One advantage of the syrup used in the present study is that it does not contain licorice, which allows it to be prescribed to patients with high blood pressure, a population that constitutes a large proportion of patients. However, the absence of licorice does not negatively impact the antitussive effect of Honey Zufa syrup (55).

Zufa species are a famous medicine against cough and shortness of breath in Persian medicine (19). Previous studies have proven the antioxidant and antibacterial effect of this plant (27,56). With use of Zufa, it has been observed to control and improve the symptoms of other respiratory diseases (19).

In a study conducted at Mashhad University of Medical Sciences, 46 children with asthma were given syrup containing Zufa for a 5-day period at the onset of symptoms of viral respiratory infection. The results showed that this treatment significantly increased the severity of cough and waking at night compared to placebo. While the use of this short-term treatment did not have a significant effect on reducing wheezing, tachypnea, respiratory distress, Peak Expiratory Flow Rate (PEFR), absenteeism from school, outpatient visits, asthma exacerbation, use of oral prednisolone, beta-agonists and hospitalization. The Zufa syrup contained ingredients such as chamomile, violet, marshmallow, Zufa, southern maidenhair fern, licorice, and jujube (57).

In the present study, the combination treatment group, which included the usual cough control treatment and Honey Zufa syrup, showed a significant reduction in cough as evaluated using all three scores (VAS, SCS and CSS) over a 14-day period in comparison with placebo and baseline scores of the patients. While it is expected that patients taking their main cough control drug would show a therapeutic response, the significant difference observed between the drug and placebo groups suggests that Honey Zufa herbal syrup enhances the anti-cough effect of other cough control medications.

The results of the present study showed that the difference between Honey Zufa herbal syrup and the placebo became statistically significant from the second day of treatment. This suggests that there was no delay phase in the treatment with Honey Zufa herbal syrup, which is an additional advantage of this syrup.

In present study evaluating the effect of other drugs used to control cough on the treatment response of patients, no significant difference was found between the drug and placebo groups after statistical analysis. It is worth noting that, due to the wide range of drugs available, it is not possible to accurately determine the lack of synergistic effect between these drugs and Honey Zufa herbal syrup through comparison.

In the present study, an improvement in the condition of the patients was also observed in the placebo group. The meta-analysis conducted by Luo et al. did not reject the possibility of a placebo effect for cough (30).

Some studies did not include a placebo group in their design while one of the strengths of the present study is that it included a placebo group and the researchers, physician and the patients were blinded to the treatment assignment.

One of the potential concerns with the clinical use of medicinal plants is the possibility of drug interactions that could either induce or inhibit the metabolism of enzymes and alter the serum levels of other drugs, particularly antiviral medications, or increase the likelihood of side effects (22). Because of these potential risks, the possibility of poisoning with these drugs has been investigated in many studies. In the present study, no specific complications related to the use of Honey Zufa herbal syrup were reported. Similarly, the data from the study conducted by Quddus et al. did not report any complications associated with the consumption of 20 ml of Zufa syrup twice daily for up to 45 days (26). In the study by Boroujerdi *et al*., only one case of headache was reported, which was excluded from the study. The ingredients of this syrup are described above (25).

The results of Table 1 indicate that both the drug and

the placebo did not have a significant effect on changes in laboratory parameters, suggesting that Honey Zufa herbal syrup is safe for use in the study population.

The results of this controlled trial demonstrated that the use of Honey Zufa herbal syrup for a period of two weeks led to a statistically significant improvement in cough in hospitalized patients with mild to moderate acute cough caused by COVID-19 ($P<0.05$). Based on its ability to improve symptoms, its safety profile, and reasonable price, Honey Zufa syrup could potentially be used as a complementary treatment in such patients. However, additional future research in this field is needed to confirm these findings.

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