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Original Article

The Clinical Efficacy of *Tiban* Syrup as Adjuvant Treatment in Patients with COVID-19: A Randomized, Double-Blind Clinical Trial

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Abstract

Since the outbreak of the COVID-19 pandemic, we have witnessed extensive morbidity and mortality worldwide. However, an appropriate pharmaceutical treatment has not yet been introduced for this disease, and finding a safe and effective treatment is still ongoing. This study aimed to evaluate the safety and efficacy of *Tiban* (Mocozift) syrup (an herbal product of *Trachyspermum ammi* (L.) Sprague (Ajwain) and *Ziziphus jujuba* Mill. (jujube)) in adult patients with COVID-19. Patients with laboratory-confirmed SARS-CoV-2 infection were enrolled and randomly assigned to receive either placebo or *Tiban* syrup 5 cc, three times a day for 14 days, in addition to standard medications of COVID-19. Improvement in clinical outcomes, including cough, fatigue, dyspnea, appetite, and the occurrence of in-hospital mortality, were recorded.A total of 50 patients completed the study. The mean age of the patients was 56.5 years. There were 21 (42%) male and 29 (58%) female patients. There was a significant reduction in dyspnea after taking medication (p=0.001). Patients' appetite significantly increased in the *Tiban* group (p=0.001). Also, a significant decrease was observed in the severity of fatigue score in the *Tiban* group (p=0.001). Compared to the placebo group, an increase in appetite and a decrease in fatigue occurred earlier in the *Tiban* group.The findings of this study suggest that the combination therapy with *Tiban* syrup and conventional medicine can reduce severity of dyspnea and fatigue, while it can increase appetite in patients with mild to moderate COVID-19.

Keywords: Appetite, COVID-19, Dyspnea, Fatigue, Mocozift, Tiban, Trachyspermum ammi, Ziziphus jujube.

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1. **Introduction**

In late 2019, the first cases of patients with pneumonia caused by a novel coronavirus, initially observed in Wuhan, China, were reported. This virus was initially named 2019-novel coronavirus (2019-nCoV) and is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. It spread worldwide very fast and soon became a pandemic [3]. The World Health Organization (WHO) recognized coronavirus disease 2019 (COVID-19) as a global health emergency requiring an international concern [2-4]. The COVID-19 pandemic was associated with extensive morbidity and mortality worldwide [5, 6]. SARS-CoV-2 belongs to the Coronaviridae family and is closely similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), causing large outbreaks in 2002 and 2012, respectively. However, there are some uncertainties about its exact origin, transmission, and mechanisms of action [3, 5]. According to the current studies, common clinical manifestations of COVID-19 at the onset of the illness are fever, non-productive cough, shortness of breath, myalgia, and fatigue, and less common symptoms include nausea or vomiting, diarrhea, confusion, headache, and sore throat [1-3, 5-7]. Typically, most of the patients experience mild symptoms with self-limiting respiratory tract infections and have a good prognosis; however, elderly patients with underlying diseases are susceptible to developing severe pneumonia and multiple organ failure, resulting in death [1-3, 6]. Among hospitalized patients, the most common co-morbidities were hypertension, diabetes mellitus (DM), cardiovascular diseases (CVD), and malignancies [3, 5, 6]. Although a number of antiviral drugs have been widely evaluated, none of them have been approved as a specific treatment for COVID-19, and current therapeutic methods are based on management of patient's symptoms [8-11]. Accordingly, vaccines, monoclonal antibodies and new investigational therapies are currently in development [12]. Following the pandemic of viral infections in recent years, the investigation of less toxic antiviral phytomolecules has been considered in scientific communities. Several studies have demonstrated that plants and their secondary metabolites provide us with diverse bioactive phytochemicals such as alkaloids, lectins, polysaccharides, terpenes, polyphenols, flavonoids and proteins, which have antiviral properties [13-15]. Moreover, there are a number of medicinal plants with immunosuppressive and anti-inflammatory properties, which have shown beneficial effects on the function of the immune system [16]. *Trachyspermum ammi* (L.) Sprague commonly known as ajwain is a medicinal

plant, which is widely used as a dietary spice due to its aromatic smell and pleasant flavor [17, 18]. It has been administered in traditional medicine for the treatment of a variety of ailments, including febrile conditions, cough, respiratory distress, fatigue, nausea, vomiting, reflux, abdominal cramps, and loss of appetite. Ajwain has carminative, analgesic, and anti-inflammatory properties and is also used for the management of paralysis, tremor, and other neurological disorders such as neuropathic pain as well as chronic pains [18-20]. Current pharmacological studies have shown that this plant has numerous therapeutic properties, including antifungal, antioxidant, antimicrobial, immunomodulatory, antihypertensive, antispasmodic, antitussive, and bronchodilator activities [17-19, 21].

Ziziphus jujuba Mill. (commonly known as jujube) has been used as a popular food for a long time for its nutritional value. Also, it is traditionally wildly prescribed for fever, cough, asthma, anorexia, and fatigue [22, 23]. This plant has numerous pharmacological effects, including anti-inflammatory, antioxidant, antibacterial, antiviral, antiplatelet, antinociceptive, antipyretic, antispasmodic, antitussive, expectorant, and immunostimulant properties [22-25].

The evidence to support the effectiveness of ajwain and jujube in patients with COVID-19 is unknown. Therefore, we designed this study to evaluate the efficacy of *Tiban* (Mocozift) syrup (an herbal product of *Trachyspermum ammi* (L.) Sprague and *Ziziphus jujuba* Mill.) on cough, fatigue, dyspnea, and loss of appetite in hospitalized adult patients with confirmed COVID-19.

2. Materials and Methods

2.1. Standard Protocol Approvals, Registrations, and Patient Consents

This study was a randomized parallel double-blinded placebo-controlled clinical trial performed from April 8 to May 9, 2020, in a tertiary care center. The study protocol was reviewed and approved by the Medical Ethics Committee of Arak University of Medical Sciences [Code: IR. ARAKMU. REC. 1398. 342] and registered in the Iranian Registry of Clinical Trials [registration code. IRCT20180610040049N3]. The objectives and details of the study were clearly explained to all participants and written informed consent was obtained from them at the beginning of the trial.

2.2. Study Participants

Mainly mild to moderate hospitalized adult patients with confirmed COVID-19 were enrolled in the study. According to the inclusion criteria, both male and female patients aged between 20 to 70 years old with a positive laboratory specimen (RT-PCR) of SARS-CoV-2 and/or pneumonia confirmed by positive findings of chest computed tomography (CT) scan were included in the study. The exclusion criteria were known allergy or hypersensitivity to ajwain or jujube, pregnancy or breastfeeding, inability to swallow, complicated cases with bacterial infection, severe and critical illness, and the

physician's clinical decision that participation in the study would be inappropriate for the patient.

2.3. Sample Size

When this clinical trial was designed, there was minimal information available on the clinical outcomes in hospitalized patients with COVID-19. To determine the sample size in the study, type one error was considered equal to 0.05 ($\alpha = 0.05$) and the study power equal to 90%. According to a pilot study at our center (Valiasr Hospital, Arak, Iran), the standard deviation (SD) of the anorexia score among COVID-19 patients was 3. Based on the opinions and assessments of competent experts (infectious disease specialists), it was expected that the herbal syrup used in the study would act as an adjunct to improve the anorexia score by 3 points along with other treatments. Accordingly, the required sample size of 21 patients was estimated by using the following formula, where $z_{1-\frac{\alpha}{2}}$ is 1.96, $Z_{1-\beta}$ is 1.28, σ is 3, and d (the expected difference between the means of anorexia score between two groups) is 3. Ultimately, 25 patients were recruited in each group.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times 2\sigma^2}{d^2} = \frac{(1.96 + 1.28)^2 \times 2(3)^2}{3^2} \cong 21$$

2.4. Randomization and Masking

The patients who met the inclusion criteria were enrolled and randomly divided into the intervention and placebo groups. The permuted block randomization design with block size 4 was used to allocate patients into two groups. For allocation concealment, a unique code was assigned to each individual and attached to the drug packages to help the blinding and concealment process. This study was conducted as a double-blinded trial and participants, care providers (the person administering our intended treatment) also the outcome assessor were blind to the assigned treatment of the groups during the study.

2.5. Interventions

Eligible participants who had the inclusion criteria with written informed consent were randomly divided into two groups. The participants took a drug/placebo for two weeks. The intervention group (n=25) received an oral dose of *Tiban* syrup, 5 cc, three times a day for two weeks. The patients in the control group (n=25) received the placebo based on the same regimen and for the same period of time. All patients continued to receive the same conventional medical treatments for the management of COVID-19 during the study period. Routine standard care for patients, including oxygen therapy, rehydration, nutritional support, antipyretic therapy, antiviral treatment (e.g., hydroxychloroquine) were carried out daily.

Moreover, antibiotic therapy with levofloxacin and vancomycin was initiated in case of bacterial infection. The status of clinical parameters of cough, fatigue, dyspnea, and appetite was measured by the outcome assessor to assess efficacy and safety

outcomes at the beginning of the study and then after the completion of the intervention. CONSORT flow diagram of the study is shown in Fig. 1.

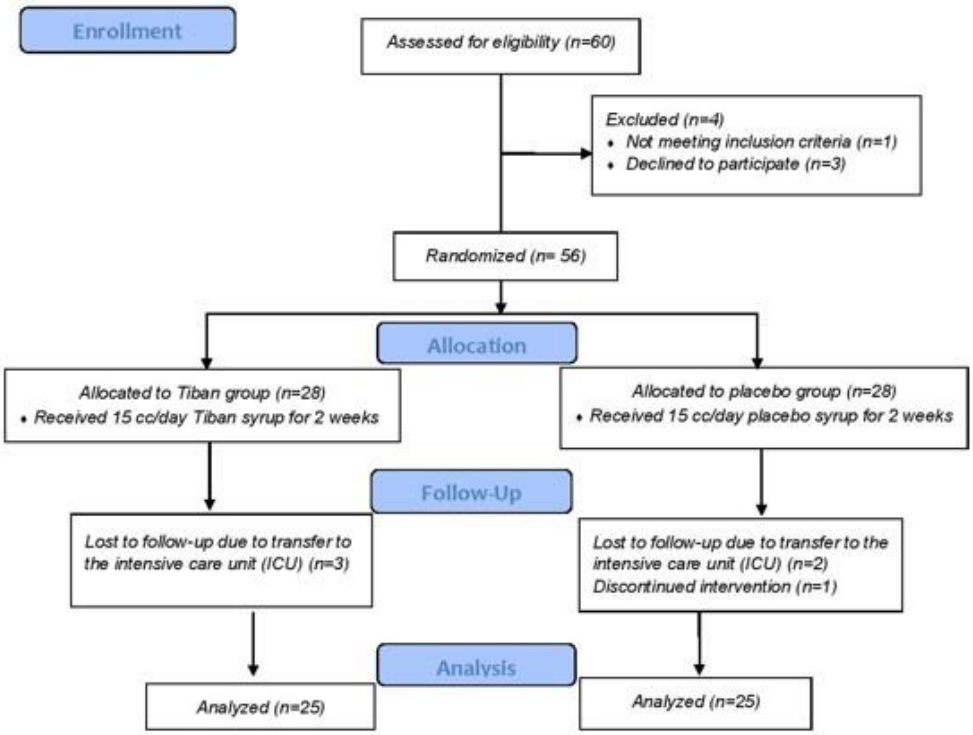

Figure 1. CONSORT flow diagram of enrollment of the participants, allocation, intervention, follow up, and analysis.

2.6. Preparation of Tiban Syrup

The herbal syrup of *Trachyspermum ammi* (L.) Sprague (Synonym: *Trachyspermum copticum* L. and *Carum copticum* L.) fruit and *Ziziphus jujuba* Mill. the fruit was produced under PLANT-BASED SYRUP® (Mocozift) trademark in BEHDANEH BARAN SALEM ABI Co., Tehran, IRAN. The plant materials were identified and authenticated by a botanist in the herbarium center of the pharmacy school, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Voucher number for ajwain: SBMU-8130 and voucher number for jujube: SBMU-8131).

The placebo syrup was produced according to the United States Pharmacopeia 34 (USP 34) with the same dark brown edible color and taste and filled in the same bottle and packaging. Eventually, the liquid fragrance of *Rosa Damascena* Mill (0.005 %) was added to both herbal and placebo syrups to make them more similar. Therefore, the herbal and placebo syrups had the same color, odor, and taste.

2.7. Outcome Measurements

The main outcomes were improvements in patients' clinical manifestations, including cough, fatigue, dyspnea, and appetite. The

measurements included fatigue severity scale (FSS) [26], Simplified Nutritional Appetite Questionnaire (SNAQ) [27], Modified Medical Research Council (mMRC) Dyspnea Scale [28] and cough visual analogue scale (VAS) [29]. Ordinal scales were used as the endpoint measurements compared to the baseline values in hospitalized patients at the end of the study.

2.8. Statistical Analysis

Quantitative variables were reported as mean (± SD), and qualitative variables were presented as the percentage of the frequency. The Shapiro-Wilk test was used to check the normality assumption. T-test, likelihood ratio Chi-square test (LR Chi^2), and two-sample Wilcoxon rank-sum test (Mann-Whitney U test) were used to analyze the data. The change score approach was used to adjust the initial values of the variables, and the amount of change of the variables was calculated and compared between the two groups. All statistical analyses were performed using Stata software version 14, and p-values <0.05 were considered statistically significant.

3. Results and Discussion

3.1. Results

A total of 60 patients with laboratory-confirmed SARS-CoV-2 infection were enrolled in the study (Figure 1). There were 50 patients who completed the study and were included in the analysis (25 patients in the *Tiban* group and 25 patients in the placebo group). The baseline characteristics and clinical information of patients are presented in Table 1. The participants' mean age (± SD) was 56.36 ± 16.8 years. In the present study, 21 (42%) patients were male, and 29 (58%) were female. There was no clinically significant difference between the two groups regarding baseline demographic and clinical characteristics.

Moreover, 22 patients (44%) presented underlying diseases, including hypertension, CVD, and DM. The most common clinical manifestations at the onset of the illness were dyspnea (80%) followed by cough (48%), myalgia (40%), diarrhea (32%), and loss of sense of smell or taste (26%). Among the study participants, 14 patients (28%) reported a history of exposure to a patient with confirmed or probable COVID-19.

The comparison of clinical outcomes between the two groups following the intervention is shown in Table 2. The two groups did not show a statistical difference in cough severity post-intervention (p=0.269). There were significant differences in the severity of dyspnea, fatigue score, and length of hospitalization in the *Tiban* group compared to the placebo group following the intervention. According to the between-group analysis, there was a significant reduction in dyspnea among patients who received herbal treatment (p=0.001). After taking medication, patients' appetite significantly increased in the *Tiban* group (p=0.001). Also, a significant reduction was observed in the severity of fatigue score in the *Tiban* group (p=0.001). The average number of days for anorexia (p=0.001) and the average number of days for

Table 1. The baseline clinical/socio-demographic information of the study participants.

Variables	Tiban group	Placebo group	P-value
Age, years, mean ± SD	53.5±17.3	59.2±16.3	0.244[a]
Gender, n (%)			
Male	9 (36%)	12 (48%)	0.390[b]
Female	16 (64%)	13 (52%)	
A history of exposure to a patient with confirmed or probable COVID-19, n (%)			
Yes	9 (36%)	5 (20%)	0.023[b]
No	10 (40%)	19 (76%)	
Unknown	6 (24%)	1 (4%)	
Symptoms and signs on admission			
Fever, mean ± SD	37.2 (0.68)	37.4 (0.63)	0.262[a]
Myalgia or arthralgia, n (%)	12 (48%)	8 (32%)	0.248[b]
Dyspnea, n (%)	18 (72%)	22 (88%)	0.157[b]
Cough, n (%)	13 (52%)	11 (44%)	0.571[b]
Diarrhea, n (%)	12 (48%)	4 (16%)	0.015[b]
Headache, n (%)	6 (24%)	8 (32%)	0.529[b]
Vertigo, n (%)	2 (8%)	3 (12%)	0.637[b]
Coexisting conditions, n (%)	12 (48%)	10 (40%)	0.569[b]
Measurements, mean ± SD			
Dyspnea	1.44 (1.2)	2 (1.3)	0.127[c]
Anorexia	9.9 (3.2)	8.9 (2.6)	0.233[a]
Cough	2.12 (2.3)	1.92 (2.5)	0.770[c]
Fatigue	43.5 (10.9)	49.0 (11.6)	0.090[a]

Abbreviations: SD, standard deviation; COVID-19, coronavirus disease 2019; n, number;
[a] t-test
[b] Likelihood ratio Chi-square test (LR Chi^2)
[c] Mann-Whitney U test

Table 2. Comparison of clinical outcomes in the two groups following the intervention (at endpoint).

Variables	Tiban group Mean ± SD	Placebo group Mean ± SD	P-value
Cough	0.68 (1.4)	1.2 (1.6)	0.269[a]
Dyspnea	0.28 (0.45)	1.28 (0.97)	0.001[a]
Anorexia	16 (3.3)	10.6 (2.6)	0.001[b]
Days to anorexia	3.1 (1.3)	8.4 (4.3)	0.001[b]
Fatigue	16.3 (5.0)	33.5 (11.1)	0.001[b]
Days to fatigue	4.6 (1.8)	10.1 (5.2)	0.001[b]
Length of hospitalization, days	6.9 (2.9)	11.9 (5.5)	0.001[b]

Abbreviation: SD, standard deviation
[a] Mann-Whitney U test
[b] t-test

fatigue in the *Tiban* group were significantly lower than in the placebo group post-intervention (p=0.001). The results showed that in the *Tiban* group, the patients' appetite began to improve in 3.08 ± 1.35 days post-intervention, whereas an improvement in

appetite was observed in 8.36 ± 4.28 days post-intervention in the placebo group.

Moreover, in the *Tiban* group, the fatigue score decreased by 4.6 ± 1.82 days post-intervention. In the placebo group, fatigue was reduced in 10.12 ± 5.16 days of the study compared to the baseline values. The length of hospitalization in the *Tiban* and placebo groups were 6.92 ± 2.94 and 11.88 ± 5.47 days, respectively. The patients in the *Tiban* group showed a significantly shorter hospitalization length than the placebo group (p=0.001). At the end of the study, among the patients in the *Tiban* group, 24 cases were discharged and one person remained in the hospital. These items in the placebo group were 20 and 4 cases, respectively; however, one patient in the placebo group died.

In order to calculate the change scores, analyses were performed with adjustments for baseline values. The results showed that the increase in the appetite score in the *Tiban* group was significantly higher than in the placebo group (p=0.001). Also, the reduction in the severity of fatigue score in the *Tiban* group was significantly higher than the placebo group (p=0.001).

The mean changes observed in the severity of dyspnea (p=0.056) and the severity of cough (p=0.069) were not statistically significant. During the study, adverse drug effects were infrequent and mild; only two patients reported nausea and itching.

3.2. Discussion

In the present study, we evaluated the efficacy and safety of *Tiban* syrup in hospitalized patients with COVID-19 in a double-blinded placebo-controlled clinical trial. The findings of this trial indicate a significant improvement in some clinical manifestations of patients with COVID-19 in response to *Tiban* syrup. Although the patients in the placebo group were recovered, their recovery speed was slower than the treatment group.

According to our results, the combination therapy with *Tiban* syrup significantly decreased the severity of dyspnea and fatigue and increased appetite compared to the placebo syrup. Moreover, increased appetite and decreased fatigue occurred earlier in the *Tiban* group.

Recent evidence has suggested that cytokine storm plays an important role in the pathogenesis of COVID-19. Elevated levels of inflammatory cytokines, including interleukin-2 (IL-2), IL-6, IL-8, IL-17, IL-1β, and tumor necrosis factor-alpha (TNF-α), are reported among the patients with COVID-19 [30-32]. Phytochemical studies have revealed that thymol is the major component found in ajwain, which has antiseptic, antifungal, antibacterial, and antioxidant and anti-inflammatory activities. It has been shown that thymol can reduce C-reactive protein (CRP), IL-1β, IL-6, TNF-α, TNF-β, and matrix metalloproteinase 9 (MMP9) levels. Carvacrol, found in this plant, is the isomerism of thymol, which has the same anti-inflammatory activities [20]. Moreover, aqueous extract of ajwain showed a significant change in IL-1β and IL-6 gene expression levels in mice models of irritant contact

dermatitis [33, 34]. Although those preclinical studies have suggested anti-inflammatory activities of ajwain by reducing inflammatory cytokines, its potential effects on pro-inflammatory cytokines in patients with COVID-19 was not measured in our study.

The essential oil of ajwain fruit has shown antiviral activities in addition to antibacterial and antifungal activities. It directly inactivates the virion, thereby inhibiting the adsorption of virus particles to host cells [35]. Additionally, a significant inhibitory effect on Hepatitis C virus protease has been observed in an *in vitro* study on the methanolic extract of the herb [19].

The beneficial effects of ajwain on reducing the number of coughs were demonstrated in an animal study. The antitussive activity of two different concentrations of aqueous and macerated extracts of ajwain seeds and carvacrol, codeine, and saline were evaluated. The results of that study revealed a significant reduction in cough number by both concentrations of ajwain seeds [36]. However, the cough-reducing effects of this herbal treatment were not observed in our study, and the comparison of cough severity between the two groups following the intervention showed no significant difference.

Bronchodilator effect of ajwain has also been reported. The anticholinergic and histamine (H1) inhibitory effects of ajwain extract on isolated guinea pig tracheal chains have been described [37]. Ajwain seeds also have anti-asthma and anti-dyspnea effects. Its bronchodilator effects can be due to the presence of carvacrol [38]. According to the results of a clinical study on patients with asthma, ajwain seeds have a relatively bronchodilator effect on asthmatic airways compared to theophylline [39]. Our study also showed shortness of breath after taking herbal medication in patients with mild to moderate symptoms, with no severe multi-organ damages. According to the results of this trial, combination therapy with *Tiban* syrup showed an increase in appetite in patients with mild to moderate COVID-19.

Traditionally, ajwain is used for loss of appetite, gastric disturbances, and a digestive aid [17-19]. This plant is a pungent spice that has stimulating properties. Pungent spices with volatile compounds stimulate the appetite through hormonal and metabolic factors. These spices improve digestion by stimulating saliva secretion as well as gastrointestinal secretions. Moreover, some of them, like ginger, are useful for stimulating appetite and plasma-leptin levels in humans [40, 41].

According to historical medical manuscripts, ajwain was applied by medieval practitioners for treating fatigue and myalgia [18]. Both total alcoholic and aqueous extract of the ajwain seeds showed significant anti-inflammatory potential in a rat model with edema and granuloma [42]. Its aqueous extract increased the antioxidant markers and reduced the inflammatory markers in mice arthritis [43]. Aqueous extract of ajwain showed an anti-inflammatory effect on collagen-induced arthritis (CIA) in rats and reduced paw

thickness, arthritis score, and the expression of the genes involved in the inflammation process [20]. Nitric oxide (NO) has a significant role in inflammatory processes such as chronic fatigue syndrome (CFS). Moreover, anti-inflammatory and antioxidant agents may be beneficial in managing CFS. In an *in vitro* study, ethanolic extract of ajwain had a potent inhibitory effect on scavenging NO [44]. In addition, ajwain has analgesic and antinociceptive activities [19]. A clinical study has confirmed the effectiveness of a traditional formulation with ajwain in the quality of life and fatigue in multiple sclerosis [21]. In the current study, a significant decrease in the severity of fatigue score in the *Tiban* group compared to the placebo group was observed. In addition, a reduction in fatigue was observed more rapidly in patients who consumed the herbal syrup.

Jujube has antioxidant, anti-inflammatory, and anti-complementary effects and has been consumed traditionally for fever, cough, asthma, anorexia, and fatigue [22-24]. Ethanolic extract of jujube and its natural saponin, namely Jujuboside B (JB), has been examined against the inflammation of airways in several laboratory animal models. Accordingly, both ethanolic extracts of jujube and JB have shown significant antihistaminic activities as well as anti-allergic, mast cell stabilizing, anti-inflammatory, and immunomodulatory properties. Moreover, JB has exhibited a protective effect on airway inflammation by reducing the secretion of T-helper type 2 (TH2) cytokines and infiltration of inflammatory cells [23]. Betulinic acid (BeA) of the jujube tree has displayed anti-influenza viral activities via anti-inflammation. BeA significantly attenuated necrosis, frequency of inflammatory cells, and pulmonary edema at a concentration of 50 μM without significant cytotoxicity compared with the oseltamivir-treated mice model [22]. In an animal study, the effect of jujube on appetite has been shown. The body weights in rats treated with jujube increased dose-dependently. Jujube might increase animal appetite by a NO-dependent mechanism, leading to weight gain [25].

3.3. Study limitations

This study has several limitations, which should be taken into consideration. First, the relatively small sample size restricts the power of the study; thus, it is recommended to conduct studies with larger sample sizes with a multi-center clinical approach/trial. Second, when this clinical trial was being designed, there was minimal information available on the clinical outcomes in hospitalized patients with COVID-19. So, all clinical outcomes of this study in the two groups following the intervention were qualitative and based on the symptom-rating scale, and we did not measure quantitative information. Third, and the most important one, chest CT images and pro-inflammatory cytokines were not compared at baseline and endpoint. This trial included patients with mild to moderate symptoms of COVID-19 only, thus the results of this study cannot be generalized to the whole patients

with COVID-19, especially those with severe symptoms and those with co-morbidities.

4. Conclusion

The combination therapy of *Tiban* syrup and conventional medicine of COVID-19 can reduce the severity of dyspnea and fatigue in patients with mild to moderate COVID-19. It can also improve appetite in these patients. Contrary to our assumption, this syrup had no significant effect on the cough number. The findings of the study can contribute to the management of COVID-19 and a better understanding of the potential properties of the *Tiban* syrup. Long-term randomized controlled trials with larger sample sizes and longer follow-up periods are still necessary to confirm the findings of the present study.

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