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Original Research Article

Efficacy of a standardized herbal formulation from *Glycyrrhiza glabra* L. as an adjuvant treatment in hospitalized patients with COVID-19: A Randomized Controlled trial

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Introduction: As no specific pharmacological intervention has been known for COVID-19, medicinal plants may be a suitable candidate for management of this disease. The aim of this study was to investigate the efficacy of a herbal syrup from licorice as an adjuvant treatment in hospitalized patients with COVID-19.

Materials and methods: 213 hospitalized patients diagnosed with COVID-19 were assigned to receive either standardized licorice syrup as an adjuvant treatment plus standard care [Syrup Group (SYRUP), N = 91], or standard care alone [Standard Group (STANDARD), N = 104], for 7 days. The primary endpoint was duration of hospitalization in survivors. The secondary endpoints included 25% increase in oxygen saturation, C-reactive protein (CRP) difference and lymphocyte difference from baseline, number of death and number of patients transferred to ICU.

Results: Mean duration of admission was 5.24 days in SYRUP and 7.14 days in STANDARD ($p < 0.001$). Oxygen saturation increased in 86 of 91 patients (94.5%) in the licorice group, compared to 83 of 104 patients (79.8%) in the control group ($p = 0.002$). There was no significant difference between the two groups in the number of patients died during hospitalization ($p = 0.837$). Five patients in SYRUP and 16 patients in STANDARD were transferred to ICU ($p < 0.026$). Mean reduction in CRP ($p < 0.001$) and mean increase in the number of lymphocytes ($p = 0.008$) in SYRUP were significantly higher than STANDARD.

Discussion: Licorice syrup as an adjuvant treatment demonstrated promising results on duration of hospital admission, O2 saturation as well as inflammatory markers in COVID-19 patients; however, further clinical studies with larger sample size are suggested to achieve more conclusive results.

1. Introduction

COVID-19 is a recent coronavirus outbreak caused by SARS-CoV-2 and which was firstly reported in the Wuhan city of China in December 2019 and then spread worldwide. While the infectivity of SARS-CoV-2 has been fully recognized, its antigenic structure, mechanism of action, and pathogenicity not yet completely understood [1].

Sequence similarity of the SARS-CoV-2 with a bat coronavirus proposes that it has originated in bats; however, it is still unknown whether this virus has transmitted directly from the bats or there are some other intermediate hosts [2].

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The most common clinical symptoms are cough, fever, fatigue, headache and mylagia. Dyspnea, sore throat, diarrhea, anosmia and rhinorrhea, dyspnea and hypoxemia have been recorded as other symptoms with lower prevalence. Some showed dyspnea and hypoxemia, In severe cases, COVID-19 could lead to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes [3].

In spite of many studies conducting on different conventional drugs, no specific pharmacological intervention has been known for treatment of COVID-19 and observing preventive protocols and vaccination are the best available methods for fighting disease [4]. Medicinal plants are considered as a valuable source for new drug discovery, including antiviral drugs. Surprisingly, oseltamivir, one of the most famous antiviral agents against influenza A and B virus has been originated from a plant-derived compound, shikimic acid, which is mainly isolated from star anise (*Illicium verum* Hook.f.) [5]. Many medicinal plants have been examined for their antiviral activities; however, most of studies are experimental and conducting clinical trials for elucidating their efficacy seems to be necessary. Traditional Persian medicine is one of the most ancient medical doctrines which is mostly known with the pioneer physicians such as Avicenna and Rhazes, as well as their tremendous manuscripts, including the Canon of Medicine and the Great Continens [6]. There are several medicinal plants in traditional Persian medicine that claimed to have potential to alleviate cough, fever, chills, pneumonitis and pulmonary disorders besides their potent anti-inflammatory properties and anti-antiviral activity against RNA viruses. So, it seems that they have potential to manage COVID-19 [6]. One of these valuable plants is licorice with scientific name of *Glycyrrhiza glabra* L. which have been used in traditional Persian medicine for fever, cough, pneumonitis and pulmonary disorders. It is also one of the most studied plants regarding its antiviral activity [6]. The aim of this study is to evaluate the efficacy of a herbal medicine containing aqueous extract of licorice as well as four other medicinal plants with antiviral activity as an adjuvant treatment on COVID-19 symptoms in hospitalized patients with COVID-19.

2. Materials and Methods

2.1. Formulation of licorice syrup

Licorice syrup is composed of aqueous extracts of five medicinal plants demonstrated in Table S1. The medicinal plants were purchased from a traditional herbal market. They were identified and approved by botanist at the Herbarium Center of the School of Pharmacy, Tehran University of Medical Sciences.

2.2. Standardization of licorice syrup

2.2.1. Total phenolic content

The total phenolic content was estimated by the Folin-Ciocalteu method and was stated as mg of Gallic acid Equivalents (GAE) [7]. Calibration curve for gallic acid is shown in Fig. S1.

2.2.2. Total flavonoid content

Total flavonoid content was calculated by the aluminium chloride colorimetric test and was expressed as mg of quercetin equivalents (QE) [8]. Calibration curve for quercetin is demonstrated in Fig. S1.

2.2.3. HPLC analysis (high performance liquid chromatography)

HPLC analysis was carried out using an Agilent Technologies 1260 Infinity Π apparatus attached to an Agilent HPLC column Eclipse − XBD-C18, 5 μm column (4.6 mm × 150 mm) for the quantification of glycyrrhizic acid as one of the major compounds of *G. glabra* using an isocratic mobile phase of glacial acetic acid (Merck, Germany), acetonitrile (Merck, Germany), water (6:30:64 V/V/V) at a flow rate of 1.5 ml/min. UV monitoring was carried out at 254 nm [9]. For preparation of test sample, 1 ml of syrup was mixed with 1% w/v of Ammoniac (Merck, Germany) and centrifuged. 1 ml of above content was diluted by 1% w/v of Ammoniac to 10 ml. The solution was filtered through a 0.45 mm filter before injection. Data analysis was performed using Agilent ChemStation software.

2.2.3.1. Calibration curve. The glycyrrhizic acid stock solution (500 μg/ml) was prepared by dissolving 10 mg of glycyrrhizic acid mono-ammonium salt (Sigma Aldrich, India) in 20 ml of hot water. The stock solution was diluted to the range 200 μg/ml to 12.5 μg/ml of glycyrrhizic acid for analysis. Each dilution was injected in triplicates. Calibration curve was drawn for quantification purpose (Fig. S1).

2.3. Study design

This study was a multicenter, randomized, controlled, parallel group, open label clinical trial to evaluate the efficacy of licorice syrup as an adjuvant treatment in hospitalized patients with COVID-19.

2.4. Ethical issues

The trial was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. The protocol was approved by the Research Ethic Committee of AJA University of Medical Sciences (IR.AJAUMS.REC.1398.267). Also, it was registered as IRCT20160316027081N1 at the Iranian Registry of Clinical Trials (IRCT). All participants were aware about protocol of trial and fulfilled the written informed consent.

2.5. Participants and intervention

Hospitalized patients with COVID-19 were diagnosed by nasopharyngeal reverse transcription–polymerase chain reaction (RT-PCR) or lung computed tomography (CT), and had oxygen saturation lower than 93% in the emergency room or respiratory rate more than 24 per minute, were enrolled in the study. The trial was conducted at the medical centers of AJA University of Medical Sciences including Khanevadeh, Be'sat, Golestan, and Imam Reza hospitals from March 19, 2020, through May 2, 2020. After elucidating the study process to patients and taking their informed consent, patients that fulfilled the inclusion criteria were enrolled to the study.

The inclusion criteria were age>18, diagnosis of COVID-19 with moderate severity, including oxygen saturation between 92 and 85% in the emergency room, and respiratory rate more than 24 per minute. The exclusion criteria were pregnancy, lactation, comorbidity diseases (diabetic ketoacidosis, pregnancy, decompensated cirrhosis, non-viral sepsis, active gi bleeding, acute trauma or surgical emergency, unstable angina, chronic renal failure with uremic symptoms), inability to take oral feeding, severe COVID-19 symptoms requiring admission to intensive care unit (ICU) in the first 48 h after hospitalization, including respiratory rate more than 30 per minutes, oxygen saturation lower than 85% in the room, severe pulmonary ground-glass opacity more than 50% in CT, loss of consciousness, alcohol or drug addiction, decompensated cirrhosis, active gastro intestinal bleeding, myocardial infarction, and pulmonary thromboembolism.

Patients were randomly allocated to receive either licorice syrup (10 ml every 8 h, orally) plus standard care [Syrup Group (SYRUP), N = 91], or standard care alone [Standard Group (STANDARD), N = 104], for 7 days. Standard care for not-ICU inpatient treatment consisted of hydroxy chloroquine plus lopinavir/ritonavir, oxygen supplement, and analgesics, according to the fifth edition of diagnosis and treatment of COVID-19 guideline, by Iranian ministry of health.

Randomization was performed by using a permuted block randomization with four size blocks and a random number table. Patients were randomly allocated to receive either licorice syrup (10 ml every 8 h, orally) plus standard care, or standard care alone, for 7 days. Standard care for not-ICU inpatient treatment consisted of hydroxychloroquine plus lopinavir/ritonavir, oxygen supplement, and analgesics, according to the fifth edition of diagnosis and treatment of COVID-19 guideline, by Iranian ministry of health.

2.6. Sample size calculation

The minimum sample size considering 80% efficacy of the standard treatment protocol and 90% in the group receiving licorice, the study power of 90%, and the statistically significant level of 95% was calculated for total 180 patients.

2.7. Outcome measures

The primary endpoint outcome was the duration of hospitalization in survivors. The secondary endpoints included 25% increase in oxygen (O2 saturation), C-reactive protein (CRP) difference and lymphocyte difference between baseline and 3 days after beginning of licorice syrup administration, number of death and number of patients transferred to ICU.

2.8. Statistical analysis

SPSS version 25 was applied for the statistical calculations. Descriptive statistics were used to report frequencies and percentages. Kolmogorov–Smirnov test was used to examine normal distribution of variables. The independent T-test was used for normally-distributed variables. Chi-square test was used to compare the qualitative variables and Fisher's exact test was used if necessary. p Value lower than 0.05 was considered statistically significant.

3. Results

3.1. Total phenol and flavonoid contents of licorice syrup

The total amounts of phenols and flavonoids of syrup were 121.74 ± 0.31 GAE and 62.53 ± 0.68 QE in each ml of the syrup, respectively.

3.2. Glycyrrhizic acid content of licorice syrup

The amount of glycyrrhizic acid in the licorice syrup was quantified as 1.21 ± 0.003 mg/ml.

3.3. Baseline characteristics

Registration of patients is demonstrated in the CONSORT flowchart (Fig. 1). 213 patients with confirmed COVID-19 were enrolled in the trial from March 23, 2020. The baseline characteristics are presented in Table 1. No significant difference was observed between licorice syrup and control group in any of demographic variables.

3.4. Outcomes

Qualitative and quantitative outcomes have been demonstrated in Table 2, respectively. Mean duration of admission was 5.24 days in SYRUP and 7.14 days in STANDARD ($p < 0.001$). 25% increase in O2 saturation occurred in 86 of 91 patients (94.5%) in the licorice group, compared to 83 of 104 patients (79.8%) in the control group ($p = 0.002$). The number of patients died during hospitalization was 3 in SYRUP and 4 in STANDARD without a significant difference between the two groups in this regard ($p = 0.837$). Five patients in SYRUP and 16 patients in STANDARD were transferred to ICU ($p < 0.026$). There were not any significant differences in the rising of creatinine or cardiac complications such as myocardial Infarction or acute coronary ischemia between the two groups. The mean reduction in CRP from baseline in SYRUP was significantly higher than STANDARD ($p < 0.001$). The mean increase in the number of lymphocytes in SYRUP was significantly higher than STANDARD ($p = 0.008$).

Ten patients in the licorice group had to discontinue the syrup, consisted of six patients for taste intolerance and four patients for hyperglycemia. But There were not any other adverse events related to licorice syrup in the patients.

4. Discussion

Since the management of COVID-19 is challenging and there is no definitive treatment for this viral disease, many studies are evaluating different non-pharmacological and pharmacological modalities to discover an optimum treatment strategy for COVID-19. Herbal medicine as a worthwhile source for drug discovery, is taken to the special consideration. In this study, we assessed the efficacy of a herbal preparation formulated based on traditional Persian medicine as an adjuvant treatment in hospitalized patients with COVID-19. This herbal preparation remarkably reduced hospital stay and number of patients transferred to ICU; however, it did not have a significant effect on the number of deaths during hospitalization. Moreover, it considerably improved CRP and number of lymphocytes in comparison with the control group.

There is strong evidence about each of the medicinal plants used in the formulation of this herbal syrup as well as their phytochemicals. Furthermore, the therapeutic activities of these plants according to traditional Persian medicine is described in Table S1. Different licorice species have demonstrated antiviral activity especially against respiratory infections [10–12]. Licorice extract and glycyrrhizin have shown *in vitro* antiviral effects against clinical isolates of SARS [13]. Also, they could ameliorate influenza A H5N1 infection in human airway epithelial cells [14]. In an animal model of lipopolysaccharide (LPS)-induced pulmonary inflammation, licorice and glycyrrhizic acid demonstrated a significant reduction in lung manifestations via modulation of autophagy and reduction of pro-inflammatory cytokines like TNF-α and IL-1β [15,16]. Jujube fruit and its major triterpene, betulinic acid, revealed *in vitro* and *in vivo* antiviral activity against influenza A virus infection. Moreover, they exhibited immunostimulatory effects and increased production of immune cells [17,18]. Antiviral activity of damask rose and its flavonoids have been demonstrated against HIV which is an RNA virus [19]. Additionally, damask rose has cardiotonic properties which would be helpful in preventing cardiac complications of COVID-19 [6]. Saffron and its main compounds showed antiviral activity as well as anti-inflammatory effects in airway inflammation. Crocin and picrocrocin, two carotenoids from saffron, have demonstrated potent antiviral activity against HIV [20]. Safranal, present in saffron essential oil, has shown a considerable anti-inflammatory activity in animal model of airway inflammation which was even more potent than dexamethasone [21]. In animal

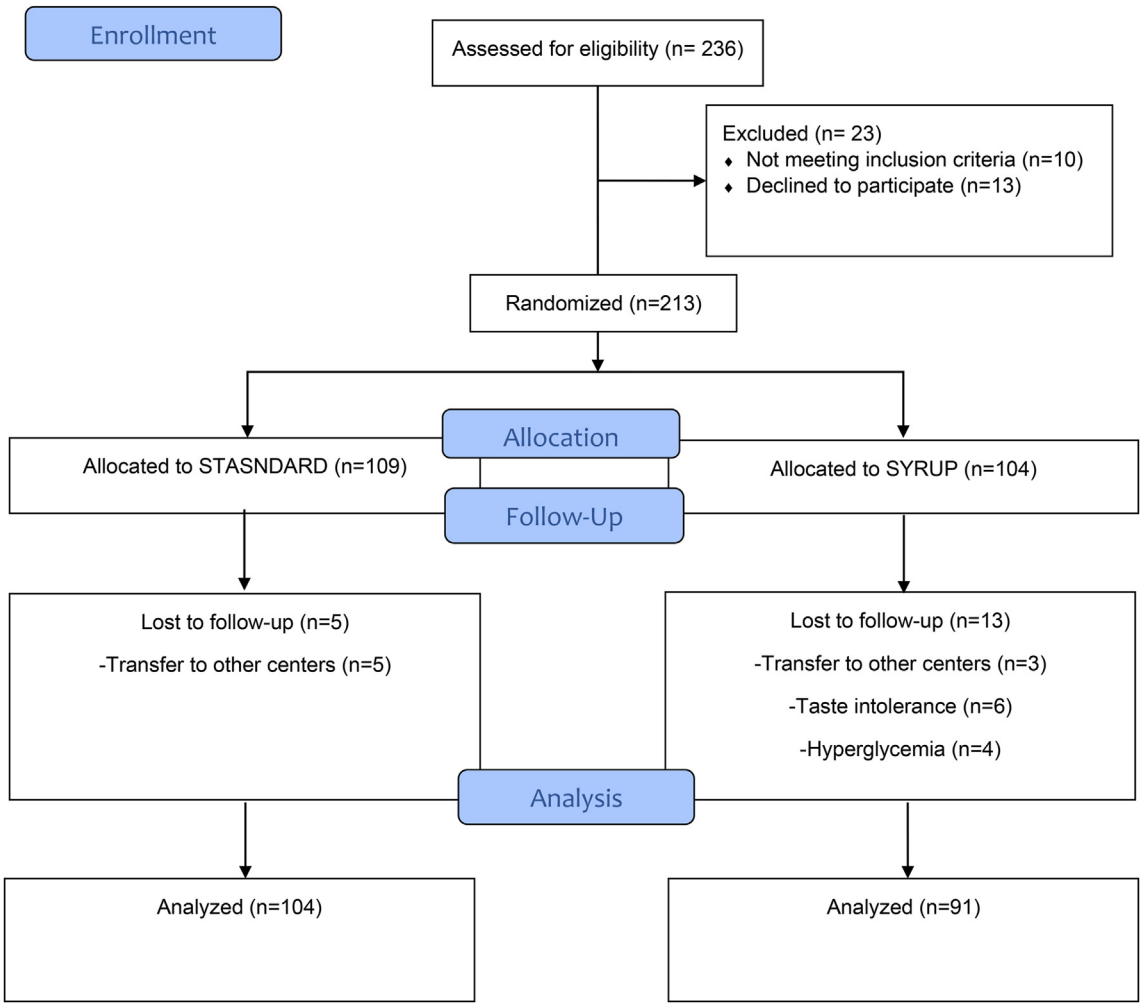

Fig. 1. CONSORT Flow Diagram of randomized controlled clinical for Covid-19 patients.

Table 1
Baseline characteristics of patients included in the study.

Demographic variables		SYRUP (n = 91) (intervention)	STANDARD (n = 104) (control)	P value
Gender (M/F)		66/25	74/30	0.832
Age (mean)		52.7 ± 19.6	54.6 ± 15.2	0.424
BMI (mean)		27.5 ± 2.8	27.1 ± 3.2	0.152
SARS-CoV2 PCR positivity (n)		38	54	0.360
SpO2		90.12 ± 6.80	89.33 ± 9.25	0.810
HTN		37 (40.66%)	52 (50%)	0.191
DM		21 (23.1%)	27 (25.9%)	0.641
IHD		7 (7.7%)	8 (7.7%)	1.000
COPD		2 (2.2%)	2 (1.9%)	1.000
Clinical Symptoms (n)	Fever and Chills	66 (72.5%)	80 (76.9%)	0.511
	Dyspnea	72 (79.1%)	78 (75%)	0.610
	Cough	35 (38.4%)	58 (55.7%)	0.071
	Myalgia	25 (27.4%)	28 (26.9%)	1.000
	Diarrhea	20 (21.9%)	15 (14.4%)	0.193
	Malaise or weakness	34 (37.3%)	38 (36.5%)	1.000
The First Lymphocyte (mean ± SD)		1209 ± 515	1300 ± 644	0.281
The First Qualitative CRP (mean ± SD)		36.89 ± 19.9	32.77 ± 15.01	0.209

BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: Diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease; SpO_2: oxygen saturation.

models of bleomycin-induced pulmonary fibrosis and LPS-induced lung inflammation, crocin could suppress lung damage via reduction of pro-inflammatory cytokines production and inhibition of nuclear factor-κB (NF-κB) pathway [22,23]. Also, saffron was effective to improve spirometry parameters in patients with asthma [24]. Rhubarb and its anthraquinones as its major constituents revealed antiviral activity and reduced pro-inflammatory cytokines [25–27]. Emodin and chrysophanol, two major anthraquinones of rhubarb, have shown *in vivo* antifibrotic and anti-inflammatory properties in animal models of lung manifestations

Table 2
Outcomes investigated in this trial.

Variables	SYRUP (intervention) n = 91	STANDARD (control) n = 104	*P* value
Death (No. of patients)[b]	3	4	0.837
Transfer to ICU (No. of patients)[b]	5	16	0.026[a]
Increasing O2 saturation more than 25% (No. of patients)[b]	86	83	0.002[a]
Myocardial Infarction or Unstable angina (No. of patients)[b]	5	7	0.773
Creatinine rising more than 25% (No. of patients)[b]	3	2	0.665
Days of admission (Mean ± SEM)[c]	5.24 ± 0.22	7.14 ± 0.40	<0.001[a]
CRP[1] difference (Mean ± SEM)[c]	16.65 ± 5.09	8.27 ± 2.02	<0.001[a]
Lymphocyte[2] difference (Mean ± SEM)[c]	397 ± 38.5	225 ± 49.5	0.008[a]

[a] Statistically significant ($p < 0.05$).
[b] Analyzed by Chi-square and Fischer Exact Test.
[c] Analyzed by Independent Sample t-test; 1 the unit of CRP is mg/L; 2 the unit of lymphocyte is cells/μL.

[28,29]. Moreover, in a clinical study in hospitalized patients with ARDS, rhubarb syrup could make a noticeable improvement of the oxygenation, as well as a reduction in pulmonary vascular permeability index [30].

There are some other reports on the beneficial effects of Complementary approaches based on traditional Persian medicine in patients with COVID-19 [31,32]. Also, there are some evidence on the benefits of other traditional medicines such as Kampo (traditional Japanese medicine) and traditional Chinese medicine in COVID-19 patients [33,34].

The study had some limitations including small sample size and study design that was open-label not double-blind placebo trial. So, designation of a randomized double-blind placebo-controlled trial with larger sample size is recommended to achieve more conclusive results.

5. Conclusions

Conclusively, the licorice syrup as an adjuvant treatment demonstrated promising results on duration of hospital admission and oxygen saturation as well as inflammatory markers. Our research implicated that the licorice syrup can be used as adjuvant treatment for mild to moderate Covid-19 concomitant with the standard treatment.

Ethical approval

The local Institutional Review Board deemed the study exempt from review. The protocol was approved by the Research Ethic Committee of AJA University of Medical Sciences (IR.AJAUMS.REC.1398.267).

Research funding

Not applicable.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Informed consent

Informed consent was obtained from all individuals included in this study.

Declaration of competing interest

Authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2022.100670.

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