Original Article

Efficacy of Licorice as Adjunctive Therapy in Critically Ill Patients with COVID-19: A Randomized, Placebo-Controlled, Double-Blind Clinical Trial

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Abstract

Objective: There is no definitive pharmacological strategy for COVID-19; thus, medicinal herbs can be an appropriate option for COVID-19 management. We investigated the efficacy of a D-reglis® tablet (root extract of licorice) as adjuvant therapy in critically ill patients with COVID-19 at intensive care units (ICUs) of Alzahra Teaching Hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. **Methods:** In the present double-blind, randomized, placebo-controlled clinical trial, critically ill cases with COVID-19 (n = 52) received a D-reglis® tablet (760 mg) or a placebo tablet for 5 days. The ICU stay length was the primary outcome. The secondary outcome included the changes in oxygen saturation, duration of mechanical ventilation, mortality rate, and Sequential Organ Failure Assessment (SOFA) Score during the study period. **Findings:** The ICU stay was significantly lower in the licorice group than in the placebo group (P = 0.015). No significant difference was detected between the groups regarding oxygen saturation, SOFA score, duration of mechanical ventilation, and mortality rate. **Conclusion:** The licorice tablet (D-reglis®) as an adjuvant treatment showed promising results regarding the ICU stay length in critically ill COVID-19 patients. However, further clinical trials with larger sample sizes, further duration of intervention, measurement of inflammatory markers, and further study about the molecular mechanism of the effect of licorice on COVID-19 should be done to obtain more conclusive findings.

Keywords: *COVID-19, critical care, Glycyrrhiza glabra extract, Licorice*

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Introduction

Since the first announcement of COVID-19 (December 2019) in China, more than 667 million cases have been detected and 6.74 million deaths reported.[1] Of the total cases, 7.5 million cases and 145k deaths belonged to Iran.[2] The COVID-19 disease manifests as a spectrum from asymptomatic to severe acute respiratory distress syndrome (ARDS) and pneumonia cases. The symptoms are not stable, and the patients may go to the next stage at any time.[3] Following entrance into the alveolar epithelial cells, COVID-19 can replicate rapidly and trigger a strong immune reaction, leading to cytokine storm syndrome and pulmonary tissue damage which lead to severe COVID-19 disease.[4] Cytokine storm causes the immune system to overproduce pro-inflammatory and chemokines, next causing abnormal blood coagulation in patients and thromboembolism, which results in multiple organ damage. A large number of experimental data showed that the plasma numbers of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-γ inducible protein, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-α, and tumor necrosis factor (TNF)-α were higher in patients

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with the intensive care unit (ICU).[5] The available evidence highlights the crucial role of the dysregulation of the innate and adaptive immune response, and the associated maladaptive hyperinflammatory response, in the initiation and exacerbation of COVID-19 disease. Therefore, anti-inflammatory therapy is crucial for the management of patients with severe symptoms of COVID-19.[6]

About 15% of patients with severe symptoms need hospitalization, among them 5% become critical and need intensive care admission.[7] Fever (98%), cough (76%), myalgia or fatigue (46%), sputum production (28%), and headache (9%) are common COVID-19 symptoms.[8] In cases of shortness of breath, hypoxia, decreased level of consciousness, shock, and diffuse lung involvements based on CT scans, patients need hospitalization.[9] Patients with severe cardiovascular diseases, malignancies, chronic renal failure, COPD, obesity, organ transplantation, and type 2 diabetes are at risk of severe disease caused by COVID-19.[10] Severe COVID-19 is characterized by dyspnea, tachypnea, hypoxemia, and bilateral pulmonary infiltrates.

Currently, the WHO therapeutics and COVID-19 living guideline[11] recommend the following agents for nonsevere COVID-19: Nirmatrelvir-ritonavir, remdesivir, molnupiravir, neutralizing monoclonal (casirivimab and imdevimab), and sotrivumab. Convalescent plasma, ivermectin, hydroxychloroquine, and lopinavir/ritonavir are no longer recommended.[11]

In patients with severe and critical COVID-19 following drugs were recommended, aa combination of neutralizing monoclonal antibodies (casirivimab and imdevimab), baricitinib, in combination with corticosteroids. Ruxolitinib and tofacitinib (conditional), IL-6 receptor blockers (tocilizumab or sarilumab), and systemic corticosteroids. All these approved drugs have anti-inflammatory potential. Among them, only corticosteroids and tocilizumab (very restricted) are available in our country (Iran), and along with remdesivir are used for critical patients with severe COVID-19. Due to limited resources in our country, the other approved drugs for severe COVID-19 are not available or accessible, so investigation for finding suitable alternatives from chemical or herbal sources is ongoing.

Coronavirus has four protein components that can be used as targets for drug production, including envelope glycoprotein (E), spike glycoprotein (S), membrane protein (M), and nucleocapsid (N), due to their multiple mechanisms of action, medicinal plants are an invaluable source for new drug discovery, such as antivirals.[12] Many secondary metabolites of plants, such as alkaloids, flavonoids, polyphenols, tannins, lignans, coumarins, and terpenoids, have antiviral properties that have been shown in various studies about COVID-19 virus. Plants are also effective in the reduction of symptoms.[13-15]

Glycyrrhizin or glycyrrhizic acid is a triterpenoid saponin obtained from the *Glycyrrhiza glabra* (licorice) roots and has been applied in traditional Persian medicine for cough, fever, pulmonary disorders, and pneumonitis.[16] Licorice has gastroprotective, hepatoprotective, anti-inflammatory, immunomodulatory, antimicrobial, anticough, anticonvulsant, antioxidant, antidiabetic, antiallergic, and cholesterol-lowering effects.[17]

Licorice has antiviral effects which have been confirmed *in vitro*,[18] *in vivo*,[19] and *in silico*.[20] It inhibits 3C protease, papain-like protease, M protein, and S protein of coronavirus and also prevents its entry into the cells.[21] Licorice also modulates the release of cytokines, such as IL-6, TNF, IL-17, INF-Ɣ, VFGF, and NF-KB, and therefore, has anti-inflammatory and immunomodulatory effects that are important in the management of severe stage COVID-19.[22] We evaluated the effect of licorice root extract, as an adjuvant therapy on critically ill COVID-19 cases. The main objective was the ICU length of stay; however, duration of mechanical ventilation, changes in the sequential organ failure assessment (SOFA) score, the changes in C-reactive protein (CRP), white blood cell (WBC), platelet, and mortality rate were evaluated in this study.

Methods

This double-blind, placebo-controlled, randomized study was done between February 2022 and June 2022 at the ICUs of Alzahra Teaching Hospital affiliated with Isfahan University of Medical Sciences (IUMS), Isfahan, Iran. The Ethics Committee of IUMS approved the protocol, and the trial was registered at IRCT (IRCT20081208001497N10). Informed consent was received from all patients or next of kin. The cases were critically ill COVID-19 patients (dominant variant: Omicron variants).

COVID-19 patients diagnosed by nasopharyngeal reverse transcription-polymerase chain reaction, aged >18 years, and hospitalized at the ICU were included. The trial was done at the ICUs of Alzahra Teaching Hospital affiliated with IUMS.

The exclusion criteria were as follows: (1) hypertension (>140/90), (2) patients with chronic heart failure, (3) patients with severe liver and renal failure and thyroid diseases, (4) simultaneous use of warfarin, SSRI, MAOI, diuretics, and antiarrhythmic drugs, (5) treatment with antiviral or investigational

drugs during a clinical study 1 month before entering this study, (6) allergy to licorice, (7) pregnancy and breastfeeding, (8) lack of consent of the patient or his legal guardian, and (9) having COVID-19 for at least 20 days before entering the study.

Randomization and drug delivery were done by a research coordinator. The participant and collaborating physician were blinded to the intervention. The subjects were randomly allocated 1:1 to the placebo or treatment group based on a considered randomization list with a block size of four. The D-reglis® and placebo were in tablet form and identical in appearance. They were prepacked in bottles and consecutively numbered according to the randomization schedule by the principal investigator. The random allocation sequence remains concealed from those enrolling patients in the study.

The treatment group was treated with 760 mg (two tablets) of D-reglis® (Iran Darouk, Tehran, Iran) orally for 5 days. The control group was treated with the same dose of the placebo (Iran Darouk) for 5 days. The placebo tablets were similar to D-reglis® tablets in color and size. The researcher delivered the placebo or drug in the same packaging containers. The tablet contains 380 mg of standardized dried licorice root extract, whose glycyrrhizin content has been reduced to 3%.

Patients in each group received standard care for ICU patients,[23] with COVID-19 consisting of supportive measures (oxygen supplementation and mechanical ventilation), correction of fluid and electrolyte imbalance, antivirals (e.g., remdesivir), anti-inflammatory (e.g., interferon beta), anticoagulants (heparin and enoxaparin), corticosteroids, and antibiotics.

Basic information about the patients such as age and sex, underlying disease, duration of infection with COVID-19 before hospitalization in the ICU, duration of hospitalization in the ICU, and mortality rate were recorded. Furthermore, the Acute Physiology and Chronic Health Evaluation II score noted on admission and the SOFA Score were determined at baseline and endpoints.

The main endpoint was the ICU stay duration. The secondary outcomes include the disappearance rate of the main symptoms of COVID-19 in critically ill patients, duration of mechanical ventilation, changes in the SOFA score on days 1, 3, and 5 of the study, the changes in CRP, WBC, platelet, and mortality rate.

The improvement in the control and treatment groups was assessed by the following criteria by our clinicians: (1) improving respiratory distress and oxygenation above 60 mmHg and $PaCO_2$ below 50 mmHg, (2) no need for cardiovascular support with MAP higher than 65 mmHg, (3) no need for inotrope and vasopressor support, (4) cessation of fever and stability of vital signs at the end of intervention [day 5], and (5) no need for mechanical ventilation. Furthermore, the achievement of these criteria means the end of the need for ICU care.

Since the results of clinical trial studies that have been conducted directly with licorice in COVID-19 were not available (at the time of study design), to determine the sample size, the results of a study that used a combination of herbal-containing licorice[24] and endpoint as the mortality rate was used. Therefore, considering P1 as the survival rate of the treatment group and P2 (survival rate of the control group) as a 10% drop rate, the sample size was calculated for a total of 60 patients (formula below).

$$N = (z_{\alpha/2} + z_{\beta})^2 \times (P1\,[1 - P1] + P2\,[1 - P2])/(P1 - P2)^2$$

$$Z_{\alpha/2} = 1.96\ Z_{\beta} = 0.84\ P1 = 90\%\ P2 = 70\%$$

Statistical analyses were done following the intention-to-treat approach. The Shapiro–Wilk test assessed the normality of continuous data. Data were expressed as mean ± standard deviation independent-sample *t*-test and repeated-measure ANOVA were applied to respectively compare the normal variables between and within groups. Mann–Whitney *U*-test and Wilcoxon signed-rank test were, respectively, used to assess between-and within-group differences. The categorical variables were reported as frequency and percentage, and the Chi-square test or Fisher's exact test assessed comparisons between groups. $P \leq 0.05$ was considered statistically significant. Data analyses were done by SPSS 24.0 (SPSS Inc.; Chicago, IL, USA).

Results

In this research, of 83 eligible critically ill COVID-19 patients, 70 cases were randomly assigned (35 cases to the placebo group and 35 cases to the licorice group) to the groups with a 1:1 ratio between February 2022 and June 2022. Finally, 29 cases in the treatment group and 22 cases in the placebo group completed the protocol. Figure 1 indicates the reasons for the treatment interruption.

Table 1 indicates the patients' baseline demographic, clinical, and laboratory values. The patients of the two groups were homogeneous regarding baseline values.

The ICU stay as the primary outcome was significantly lower in the licorice group ($P = 0.015$). Licorice was not significantly effective in improving the oxygen saturation, SOFA score, and other laboratory values compared to placebo during the 5 days of the study [Table 2].

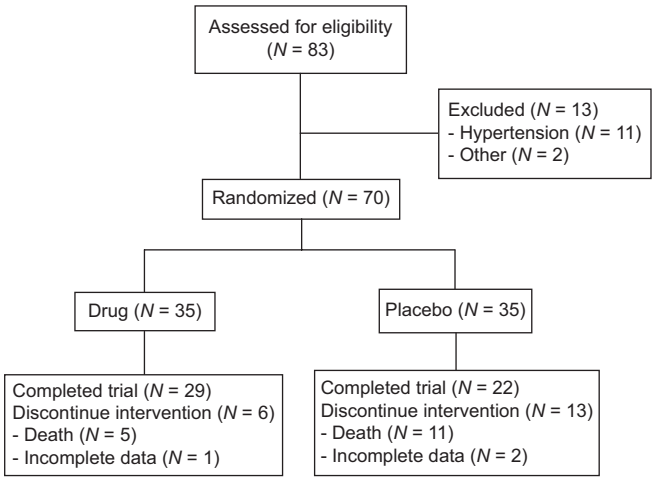

Figure 1: The trial diagram

Table 1: The demographic, clinical, and laboratory values of the patients in the intervention and placebo groups at baseline

Variables	Drug (*n*=29)	Placebo (*n*=22)	*P*
Age (years)	67.6±17.9	61.4±15.9	0.2
Gender (male/female)	16/13	15/7	0.1
APACHE II	19.1±8.1	17.8±5	0.5
Laboratory data			
PO_2 (mmHg)	64.7±26.7	58.9±33.4	0.5
Creatinine (mg/dL)	1.7±0.18	2.1±0.18	0.5
WBC (cell/mm^3)	113,622.1±6377.9	11,180.9±6654.7	0.9
Platelet (cell/mm^3)	237.6±131.7	215.9±81.14	0.5
GCS	10.3±4.4	9.9±4.2	0.75
MAP (mmHg)	95.2±16.1	95.1±16.3	0.9
CRP	64.9±35	63.2±35.8	0.7
Past medical history			
Cardiovascular diseases	5	3	0.16
Renal failure	2	1	
Asthma	4	1	
Alzheimer	2	1	
Parkinson disease	2	1	
Stroke	1	1	
Cancer	1	0	
Rheumatoid arthritis	1	1	

Data are presented as mean±SD, where applicable. SD=Standard deviation, APACHE II=Acute Physiology and Chronic Health Evaluation II, GCS=Glasgow Coma Scale, CRP=C reactive protein, MAP=Mean arterial pressure, WBC=White blood cell

No significant difference was observed in the O_2 saturation and mean respiratory rate between groups during the research. However, in the licorice group, PO_2 increased during the intervention, and it was decreased in the placebo group. Furthermore, leukocytosis decreased but not significantly.

No significant differences were detected in the number of patients receiving mechanical ventilation (P = 0.07) between the groups. Although the hospital stay was shorter in the licorice group compared to the placebo group, the difference was not significant (P = 0.07). The study groups indicated no significant difference in mortality rate (P = 0.16). No significant side effects or drug interactions were observed during the research.

Discussion

We assessed the effectiveness of licorice root extract as a formulation of D-reglis® tablet as an adjuvant therapy in critically ill COVID-19 patients. This product significantly reduced ICU stay as the main outcome of our study. However, it did not have a significant effect on the mortality rate, SOFA score, number of mechanical ventilation, and O_2 saturation.

The treatment of COVID-19 is challenging with no definitive treatment; therefore, several studies are assessing different pharmacological and nonpharmacological modalities to find an optimal treatment method for COVID-19.

Herbal medication as a global source of drug discovery has been widely considered.[14] Soleiman-Meigooni *et al*.[25] investigated the effect of a licorice-based herbal syrup as adjuvant therapy in 213 hospitalized cases with moderate severity of COVID-19 (including O_2 saturation from 92% to 85% in the room and respiratory rate >24/min). There was no placebo group and the control group received just standard care. The syrup was administered for 7 days and significantly decreased hospital length and the number of cases transferred to ICU. Nonetheless, it had no significant effect on the mortality rate. It improved O_2 saturation and reduced CRP level. Although the setting of our study was different, D-reglis® tablets significantly reduced ICU stay without effect on other clinical outcomes. Nearly one-fifth of all patients with COVID-19 progress to the critically ill phase and experience severe symptoms. The virus can invade and enter type 2 alveolar epithelial cells using the host receptor ACE-1 and start replication to generate more viral nucleocapsids. The virus-laden pneumocyte releases several inflammatory markers and cytokines, such as interleukins, INF-Ɣ, TNF-α, and MIP-1. This cytokine storm is responsible for inflammation, diffuse alveolar damage, and eventually acute respiratory syndrome.[26,27] Experimental studies have proposed that licorice and glycyrrhizin reduce the pulmonary accumulation of platelets and suppress proinflammatory cytokine secreted by activated inflammatory cells in the ARDS initial stage.[28-31] Treatment with glycyrrhizin reduced the levels of HMGB1 and IL-33 in the bronchoalveolar fluid and serum and lung tissue of mice with lung injury caused by LPS.[32] IL-33 is likely a major factor in ARDS.[33] Studies have shown that licorice and its

Table 2: Comparison of primary and secondary outcomes between study groups during the intervention

Variables	Drug (*n*=29)	Placebo (*n*=22)	*P**
ICU stay (days)	13.1±9.9	25±4.9	0.015
Hospital stay (days)	23.7±13.4	35.1±29.4	0.07
Mortality (*n*)	14	11	0.16
Mechanical ventilation (*n*)	26	17	0.07
SOFA, day 1	7.3±3.1	6.5±2.8	0.22
SOFA, day 3	7.2±2.9	6.5±3.2	
SOFA, day 5	7.1±3.7	6±2.8	
*P***	0.39		
PO_2, day 1	76.7±33.3	81.1±39.2	0.43
PO_2, day 3	82.2±3.6.7	76.8±27.8	
PO_2, day 5	87.8±42.7	73.8±25.9	
*P***	0.55		
GCS, day 1	10.3±4.4	9.7±4.5	0.35
GCS, day 3	10±4.4	9.2±4.8	
GCS, day 5	10.4±4.3	8.9±4.7	
*P***	0.5		
MAP, day 1	87.9±13.1	91.6±13.3	0.016
MAP, day 3	86.2±10.2	92.5±11.8	
MAP, day 5	87.1±11.5	95.1±15.8	
*P***	0.4		
Creatinine (mg/dL), day1	1.5±0.17	1.5±0.12	1
Creatinine (mg/dL), day3	1.5±0.16	1.5±0.12	
Creatinine (mg/dL), day5	1.4±0.14	1.5±0.14	
*P***	0.9		
WBC (cell/mm^3), day 1	12,214±8093	10,119±4339	0.68
WBC (cell/mm^3), day 3	11,859±9037	10,514±5375	
WBC (cell/mm^3), day 5	10,293±8332	11,281±6395	
*P***	0.05		
Platelet (cell/mm^3), day 1	184,931±99,157	172,476±84,453	0.6
Platelet (cell/mm^3), day 3	167,448±92,255	173,524±87,971	
Platelet (cell/mm^3), day 5	153,345±8911	194,952±165,735	
*P***	0.05		
Recovery rate (days)	1.6±0.27	1.6±0.32	0.9
Respiratory rate (per min)	19.1±2.3	18.1±2.5	0.2

*Within-group analysis, **Between groups analysis.
SOFA=Sequential organ failure assessment, GCS=Glasgow Coma Scale, MAP=Mean arterial pressure, ICU=Intensive care unit, WBC=White blood cell

flavonoids have anti-inflammatory effects, mechanisms related to inhibiting pro-inflammatory cytokines, and inflammatory mediators that participate in the MAPK signaling pathway and promote immune function.[34] Therefore, the effect of licorice on the reduction of ICU stay might be related to the immunomodulatory effects of licorice in critically ill patients. Other studies with licorice on respiratory tract infection and pneumonia have shown shorter hospitalization. Glycyrrhizin not only has antiviral activity but also displays significant anti-inflammatory effects and modulates the immune system by affecting different pathways.

Gomaa and Abdel-Wadood[35] reviewed the effect of licorice extract on combating COVID-19 and related conditions. The licorice extract possesses a high antiviral effect against different viruses, such as COVID-19 by disrupting the virus entrance into host cells (ACE). Furthermore, licorice is effective in the management of COVID-19, secondary bacterial infection, oxidative stress, autoimmune aggressive response, acute lung injury, inflammation, and cardiovascular diseases.[36]

Zhou *et al*.,[37] in a clinical trial on COVID-19 patients used glycyrrhizin diamine enteric-coated capsule (150 mg, 3 times for 2 weeks). The cure rate in the observation group showed a significant increase compared to the control group. The mean level of inflammatory markers (e.g., CRP, IL-6, and TNF-α) was significantly lower compared to the control group. Glycyrrhizin possibly is highly safe and effective in the treatment of patients with COVID-19 by inhibiting the inflammatory response and improving immune function. Although, in our study, we did not find a significant effect of licorice on the clinical outcome, in the licorice group, the PO_2 was increased, which led to a reduction in ICU stay. This reduction is very valuable in resource-limited countries and could be very important in the reduction of total health-related costs and the burden of disease in circumstances like pandemics.

There are many studies on the effectiveness of licorice in COVID-19 patients.[38] Furthermore, there are other traditional medicines, such as rhubarb and Imfluna® (traditional Persian medicine),[39] Kampo® (traditional Japanese medicine),[40] and traditional Chinese medicine effective for COVID-19.[41]

Our research has some limitations such as a small sample size and short duration of intervention and not assessing the biomarkers of inflammation. Further study about the molecular mechanism of the effect of licorice ON COVID-19 is necessary.

In conclusion, the D-reglis® tablet (extract from the root of licorice) as an adjuvant therapy showed promising results on ICU stay length in critically ill patients with COVID-19. This tablet is applicable as an adjuvant therapy for severe COVID-19 along with the standard treatments.

Authors' Contribution

SM drafted the paper, RS, BA, and AY corrected the draft. SM supervised the experimentators and BA and MH performed the experiment. All data generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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