Oral Hydroalcoholic Extract of Licorice for Management of Mild to Moderate Coronavirus Disease-19 Patients: A Double-Blind Randomized Clinical Trial

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Abstract

Background: Licorice is proposed as a treatment option for coronavirus disease-19 (COVID-19) by inhibiting the virus binding, penetration and replication; it also modulates various cellular signaling pathways. In this double-blind randomized-controlled trial, efficacy of Licorice hydroalcoholic extract oral formulation has been evaluated in patients with mild–moderate COVID-19in an outpatient clinic.

Methods: A total of 40 mild to moderate outpatient Covid-19cases were randomly assigned into either Licorice or placebo groups (n=20 in each). Patients in Licorice group were given 700 mg capsules of hydroalcoholic extract of Licorice, trice a day for 2 weeks, while controls were given placebo capsules that were filled with Avicel (microcrystalline cellulose). Blood samples were collected from all participants before starting the medication and on days three, seven, and 14 for laboratory parameters including quantitative C-reactive protein (CRP), WBCs, lymphocytes, and neutrophils counts. The clinical symptoms were also recorded.

Results: Our results showed that Licorice extract significantly decreased the frequency of cough on day seven (P=0.004) and the frequency of dyspnea on day three (P=0.02). No significant differences were found in the frequency of nausea, diarrhea, body pain, sore throat, runny nose, dizziness, lethargy, and loss of taste or smell between the two groups. Patients in Licorice group showed significantly higher oxygen saturations on days three, seven, and 14. Other laboratory parameters did not show any changes between the two groups.

Conclusion: Licorice extract improved some clinical symptoms such as cough and dyspnea while only increased the oxygen saturation. Further studies with larger sample sizes at different stages of Covid-19are suggested.
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Keywords: Licorice; Covid-19; Clinical Trial

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) first happened in late 2019, Wuhan, China. On January 30, 2020, the World Health Organization (WHO) officially declared COVID-19, a new coronavirus (SARS-CoV-2), as an international public health crisis. COVID-19is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a large family of viruses and a subset of Coronaviridae (1, 2). These viruses contain nucleocapsid-positive and single-stranded RNA and their size under electron microscope has been reported as 400-300 nm (3). About 17% of the cases require hospitalization in the intensive care unit (ICU) due to respiratory failure (4), many of them require intubation or mechanical ventilation due to the acute respiratory distress syndrome (ARDS) (4). Covid-19-associated ARDS includes infiltration, severe pulmonary edema, and inflammation leading to impaired alveolar homeostasis and pulmonary fibrosis (5). The SARS-CoV-2 proliferation cycle includes attachment, endocytosis, biosynthesis, maturation, and exocytosis (6). The four structural proteins of the virus are consisted of the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (7). The initial stage in COVID-19infection is the interaction between human airway epithelial cells and the surface spike protein. SARS-

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CoV-2 S protein predominantly binds to the Angiotensin Converting Enzyme (ACE) II receptor expressed in the lungs. After entering the cell, the gene expression and genome encoding of the virus occurs (8). However, the pathogenesis of COVID-19is extremely complicated and various factors are involved. Inflammatory and immune factors such as IL-2, IL-7, macrophage inflammatory protein (MIP)1-α, granulocyte colony–stimulating factor (G-CSF), tumor necrosis factor (TNF)-α, interferon-γ inducible protein 10 (IP-10), and monocyte chemoattractant protein (MCP)-1, may contribute to the multiorgan failure in COVID-19(9-11). So far, there has been no drug for the successful and definitive treatment of Covid-19; however, various drugs have been experimented and reported, including: Chloroquine and Hydroxychloroquine, Lopinavir, Ritonavir, Favipiravir, Umifenovir, Nitazoxanide, Ivermectin, Corticosteroids, Tocilizumab, Ribavirin, Famotidine, Statins, and Aspirin (12-14).

Medicinal plants have been recognized as important sources for new molecules to treat important human diseases (15). Liquorice (UK) or licorice (US) (Glycyrrhiza glabra), a perennial herb, belongs to pea (Fabaceae) family and is renowned for its ethnopharmacological values (16). More than 400 compounds have been extracted from the genus Glycyrrhiza and a systematic database has been created (17). These components can be classified according to their chemical structures as flavonoids, saponins, coumarins, phenolic compounds, essential oils, and other compounds (18). Flavonoids and triterpenoid saponins are abundant in licorice root or rhizomes (19). A compound of the triterpenoid saponins called glycyrrhizin is the most effective constituent of licorice, which can be found naturally in licorice root (15). Pharmacological studies have demonstrated a wide range of biological activities for licorice such as: antiviral (20), antimicrobial (21), anti-inflammatory (22), antitumor (23), antioxidant (24), liver protective (25), cardiovascular protective (26), anti-depressant (27), memory booster (28), anti-diabetic (29), and anti-allergic (30). Studies have shown that three triterpenes and 13 flavonoids were mostly responsible for the anti-inflammatory effect of licorice via different mechanisms, particularly downregulation of mediators such as prostaglandin E2, tumor necrosis factor and matrix metalloproteinases (31). The antiviral activity of licorice is attributed to glycyrrhizin and 18β-glycyrrhetinic acid by inhibiting virus gene expression and replication, prevention of viral attachment, internalization and stimulation of interferon secretion, and reducing high-mobility-group box1(HMGB) binding to DNA (32, 33). Also, they can improve host cell activity by preventing IκB degradation, enhancement of T lymphocyte proliferation, and suppression of host cell apoptosis. Four flavones (licochalcone A, licochalcone E, glabridin, liquiritigenin) and one triterpene (18β-glycyrrhetinic acid) appear to have antimicrobial properties in licorice (34, 35).

In vitro studies have revealed that glycyrrhizin has stronger antiviral activity than ribavirin against SARS-associated coronavirus (SARS-CoV). In addition to prevention of virus replication, glycyrrhizin was able to inhibit the adsorption and penetration of initial steps of the virus replication cycle (36). In an eight-week clinical trial in China, the no-observed-adverse-effect level (NOAEL) for glycyrrhizin in humans was determined as 2 mg/kg (1). This value means that in a person with a body weight of 70kg, daily consumption of 140 mg glycyrrhizic acid for eight weeks did not show any dangerous side effects (1).

There is currently no definitive treatment for covid-19. Antiviral drugs used in severe cases are mainly related to treatment of other known viruses including HIV and influenza. Nearly 80% of Covid-19patients are asymptomatic or mild, and 20% patients show pneumonia development and progression to respiratory failure. Mild cases may not require hospitalization, but there is a possibility of disease progression. Considering the anti-viral and anti-inflammatory effects of licorice extract this double-blinded randomized clinical trial was designed to evaluate the efficacy of oral administration of licorice hydroalcoholic extract on the treatment of Covid-19outpatients.

Methods

This double-blind placebo-controlled clinical trial was conducted on adult outpatients with confirmed SARS-CoV-2 infection at Shahid Hasheminejad Hospital, Mashhad University of Medical Sciences, Mashhad, Iran from June to October 2020. The ethics committee at Mashhad University of Medical Sciences approved the study protocol (IR.MUMS.REC.1399.047). The study was also registered at the Iranian Registry of Clinical Trials (IRCT20200404046933N1). An informed consent was signed by all participants.

Patients with the following criteria were included in the study: confirmed diagnosis of COVID-19based on (a) positive real-time reverse transcription-polymerase chain reaction (RT-PCR) of the respiratory tract samples and (b) clinical signs/symptoms for COVID-19; 18<age<65 years with mild to moderate disease based on national diagnosis and treatment guideline (Mild COVID-19patients have mild symptoms without dyspnea, " but moderate patients have clinical or radiographic evidence of lower respiratory

tract infection with oxygen saturations above 94%)(37, 38); indication of home quarantine and the possibility of taking medicine on an outpatient basis; and signed informed consent. Patients were not included if they had a history of allergy to licorice and its derivatives; were pregnant or lactating women; or had any concomitant diseases including: heart failure (EF<40%), severe renal failure (eGFR<30 ml/min), hepatic failure (Child-Pugh Score B or C), chronic lung disease, transplant patients or immunocompromised patients ,active malignancy, autoimmune disease (RA, SLE, etc.), or were in need for hospitalization according to the clinical and laboratory criteria, consumption of cytotoxic drugs or corticosteroids, history of gastrointestinal diseases, migraine, diabetes, and smoking. Patients were excluded from study if any allergic reaction or any intolerable side effects were caused by the drug (licorice extract).

Licorice powder was extracted in a 20 percent hydro-ethanolic solution; the yelled solution was placed on a rotary for ethanol evaporation. The concentrated solution then was introduced to freeze-dryer instrument to become powder. Glycyrrhizin was assessed by High-Performance Liquid Chromatography (HPLC) method and each gram of powder was contained 120 mg of Glycyrrhizin(1, 39).

All participants were randomly allocated into 2 groups while computerized random numbers procedures were used for consideration patients into case or control groups. The patients in case group were asked to consume 700 mg capsules of licorice hydroalcoholic extract (each containing 84 mg glycyrrhizin as active ingredient), three times a day for two weeks. Patients in control group received placebo capsules containing 600 mg of Avicel (microcrystalline cellulose) with the same rout of consumption. All the capsules were manufactured at the department of Pharmacognosy and Pharmaceutics, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. Treatment assignments were blinded from researchers and all patients to complete a data analytics project. In this double-blind study, capsules (licorice and placebo) were labeled A and B in the laboratory without awareness of research team. Both placebo and licorice hydroalcoholic extract capsules were identical in terms of shape, color, weight, packing, and odor. Patients in both control and treatment groups were not deprived of standard treatment on the basis of national diagnosis and treatment guidelines(40).

At the beginning of the study, the patients' demographic information, medical history, and medications were recorded. The primary outcome of the study was to evaluate duration of clinical symptoms improvement of COVID-19infection such as fever, cough, runny nose, dizziness, lethargy, loss of taste or smell, sore throat, headache, shortness of breath, tiredness, and gastrointestinal symptoms at days one, three, seven, and 14. Secondary outcome was considered as O2 saturation and laboratory parameters including: C-reactive protein and differential complete blood count which were measured on admission and at days three, seven, and 14. Patients where free to report their symptoms and the researchers also checked the patients at days three, seven, and 14 to evaluate their symptom and sings. In every visit the patients were asked about probable adverse effect of drugs.

Statistical analysis

As the current study was the first clinical trial on oral formulations of licorice efficacy for treatment of mild to moderate COVID-19infections, the sample size for a pilot study was determined as 20 patients in each group. The study of Whitehead and his workers recommended for a trial designed with 90% power and two-sided 5% significance, pilot trial sample sizes per treatment arm of 75, 25, 15, and 10 are enough for standardized effect sizes that are extra small (≤0.1), small (0.2),medium (0.5), or large (0.8), respectively (41). So, proposing the licorice extract effect medium regarding the proposed mechanism of action, 20 patients in each arm could be acceptable.

Data analysis was performed using SPSS 19 (Chicago, IL, USA). Values were reported as mean ± standard error (SE). The Kolmogorov–Smirnov test was used to evaluate the normality of distribution of the variables. The independent sample t test was used to compare the variables between the two groups. Also, Chi-square test was used to evaluate the association between the independent variables. A $P<0.05$ was defined as statistically significant.

Results

A total of 59 patients were assessed for the inclusion criteria and 40 patients were qualified for enrollment in the study (Figure1). Half of the patients (n=20) received Licorice capsules, while, the next half (n=20) received placebo capsules. The average ages were 38.6±8 and 41±12 years in case and control groups, respectively (P=0.45), while 75% and 80% of participants in case and control groups, respectively, were male (P=0.7). No significant differences were found between Licorice and placebo groups in the baseline characteristics including O2 saturation (P=0.150) (Figure 2), and levels of platelets (P=0.682, white blood cells (P=0.439) (Figure 4), neutrophils (P=0.49), and lymphocytes (P=0.634) (Figure 5).

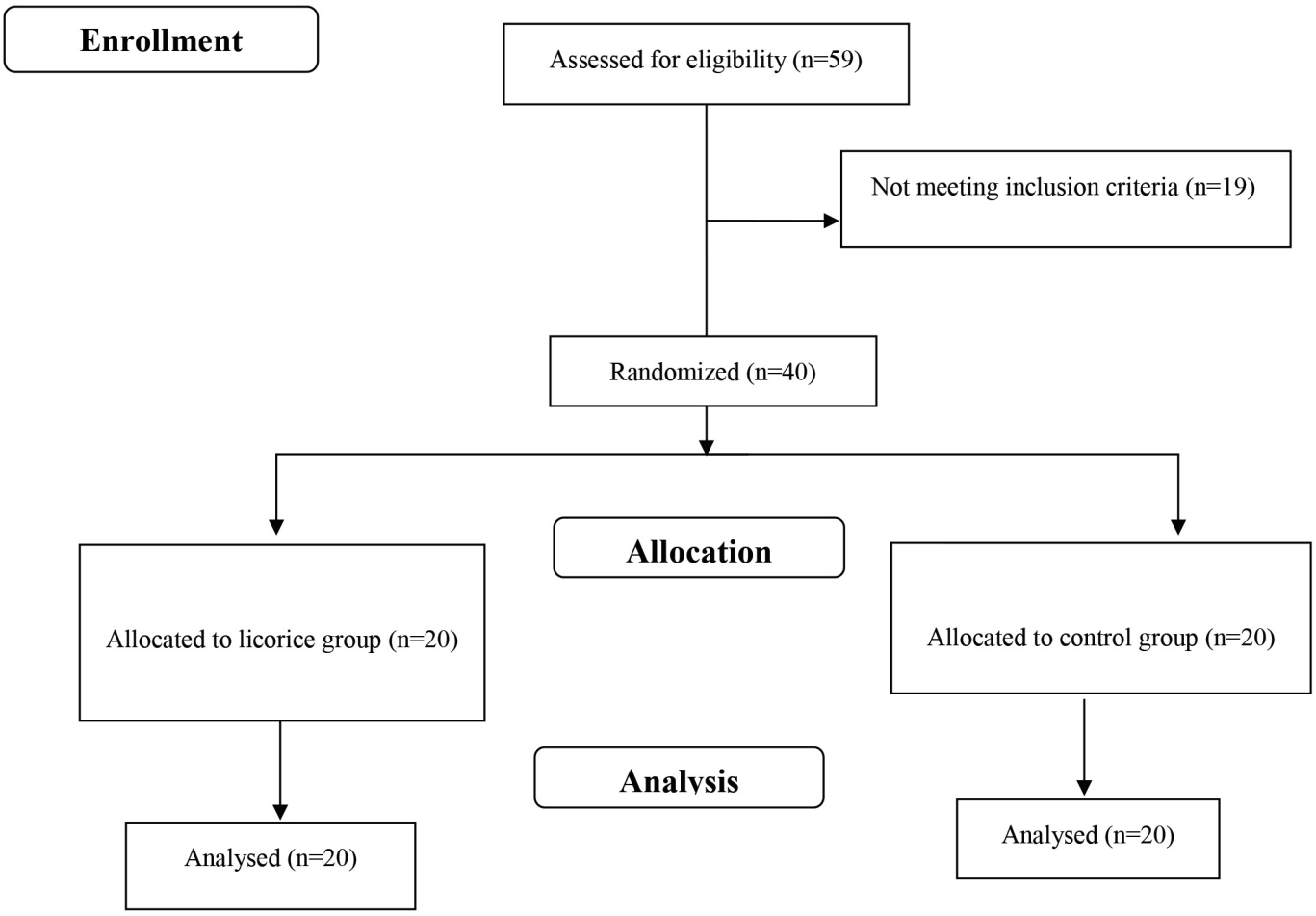

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow chart for study design.

While the rate of cough was lower in patients who received Licorice, the difference between the two groups was significant only on day seven (P=0.004). The frequency of dyspnea was also lower in Licorice group, but the difference was significant only on day three (P=0.02). No significant differences were found in the frequency of nausea, diarrhea, body pain, sore throat, runny nose, dizziness, lethargy, and loss of taste or smell between the two groups. The time of improvement of clinical symptoms in licorice group (10.1±4.16 days) was no significantly lower compared to the placebo group (11.8±3.95 days) (P=0.2).

While the two groups were homogeneous in terms of O2 saturation at the beginning of the study, patients who received Licorice showed significantly higher percentage of oxygen saturation on days three, seven, 14 (Figure 2). Although the patients who received Licorice had lower levels of CRP compared to those in placebo group, the difference was not significant at various time points (Figure 3). Platelet count showed an increasing trend through day zero to day 14; however, the difference between the two groups was not significant.

White blood cell count showed an increasing trend through day zero to day 14; however, the difference between the two groups was not significant (Figure 4). Lymphocyte count showed an increasing trend through day zero to day 14, however, the difference between the two groups was not significant (Figure 5). No significant difference was seen in neutrophil count between the placebo and Licorice groups during the 14-day study.

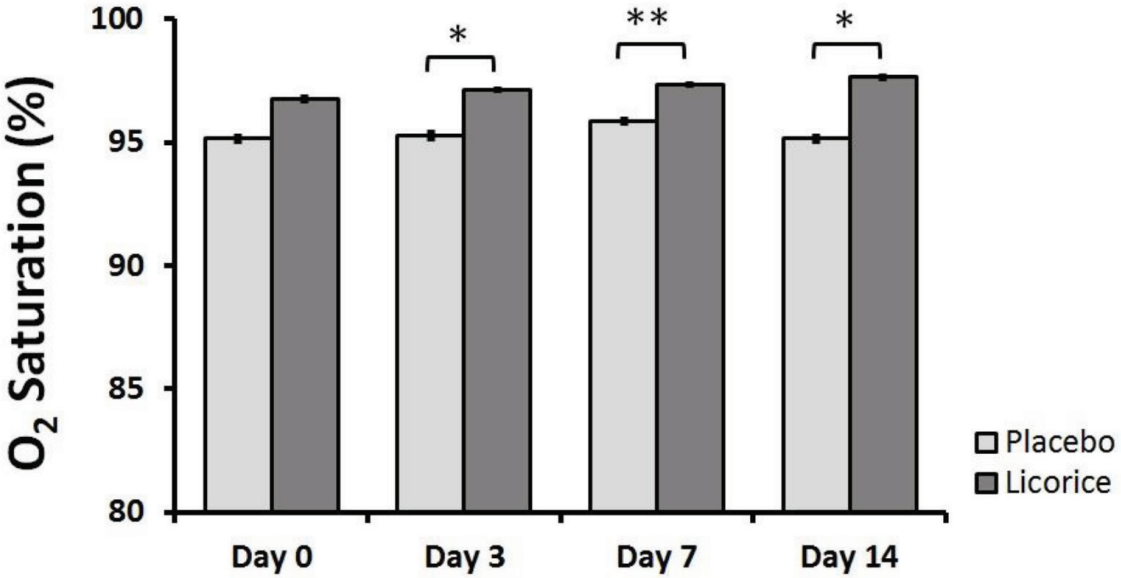

Figure 2. Licorice treatment in mild to moderate Covid-19outpatients significantly increased O2 saturation levels at Day 3, Day 7, and Day 14 compared to the control group. Data was analysed by T-test and expressed by mean±SEM (n=20). *: P<0.05, **: P<0.01

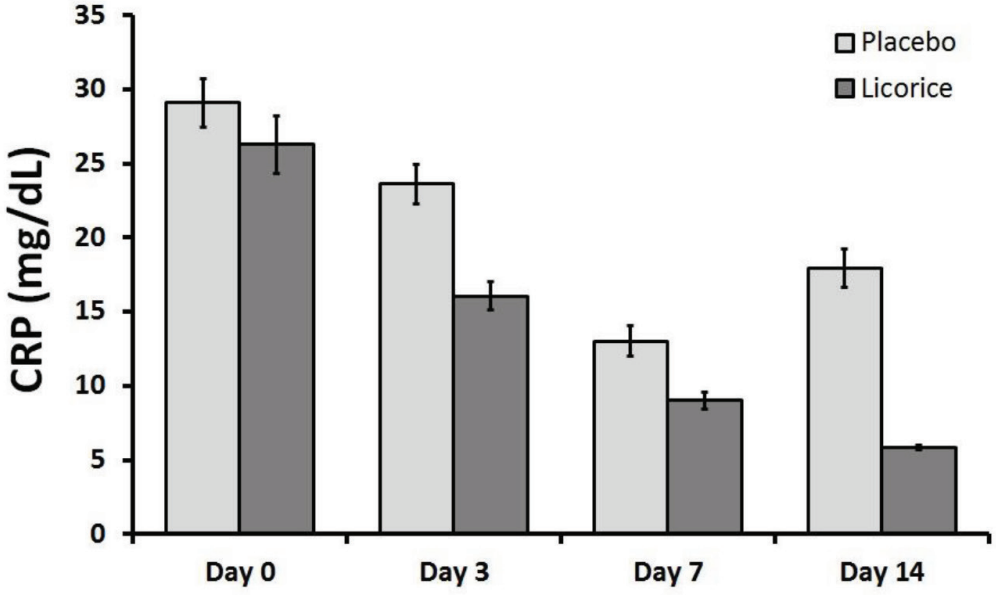

Figure3. Licorice treatment in mild to moderate Covid-19outpatients nonsignificantly decreased CRP levels at Day 3, Day 7, and Day 14 compared to the control group. Data was analyzed by T-test and expressed by mean±SEM (n=20).

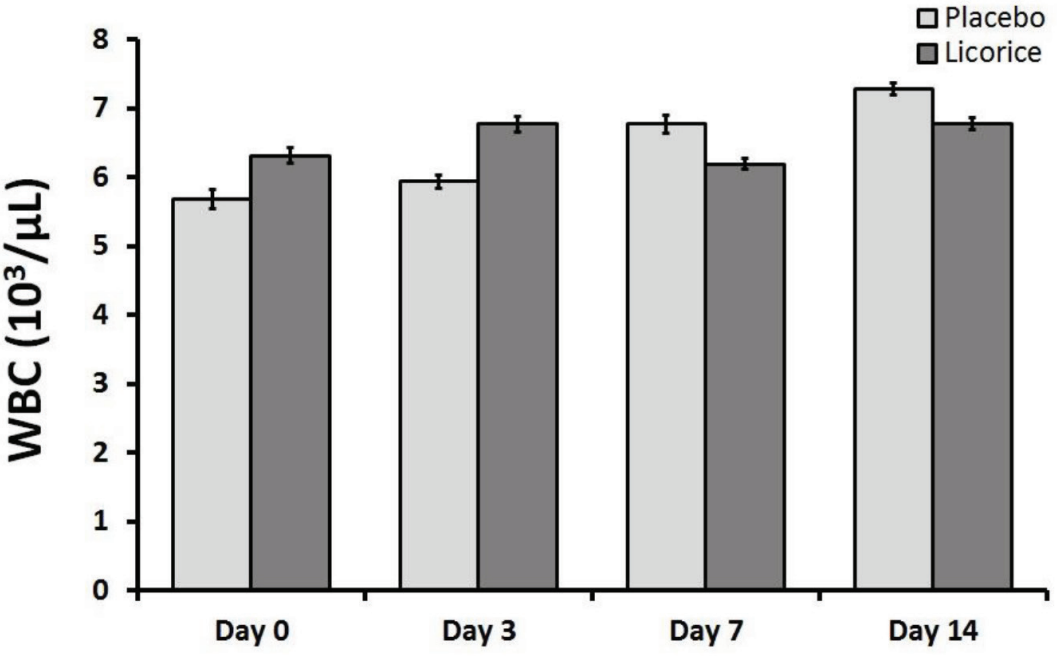

Figure 4. Licorice treatment in mild to moderate Covid-19outpatients did not significantly change the WBC count at Day 3, Day 7, and Day 14 compared to the control group. Data was analyzed by T-test and expressed by mean±SEM (n=20).

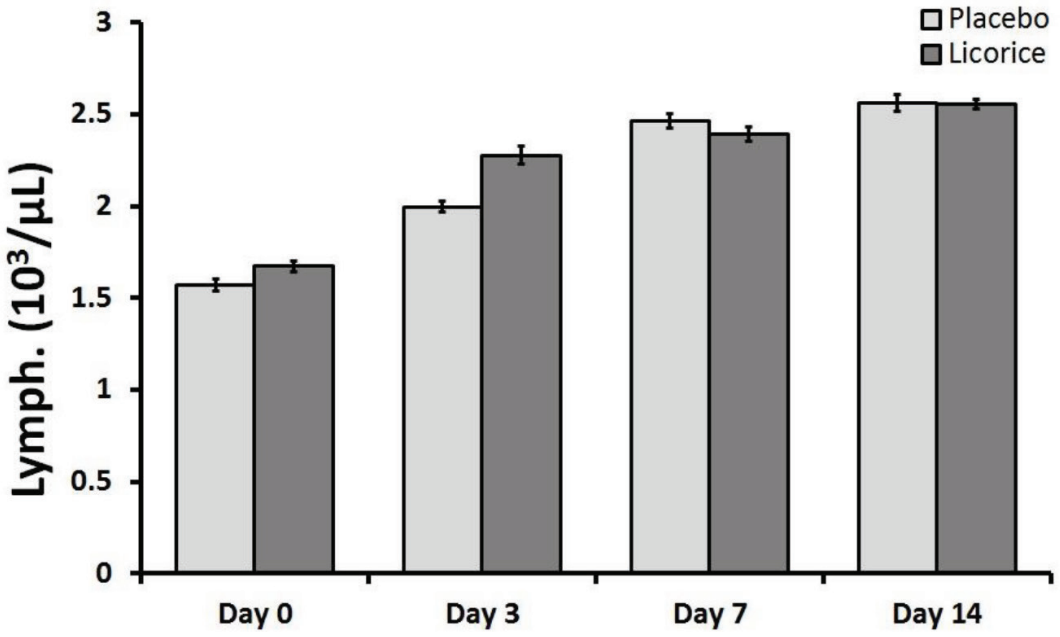

Figure 5. Licorice treatment in mild to moderate Covid-19outpatients did not significantly change the Lymph. count at Day 3, Day 7, and Day 14 compared to the control group. Data was analyzed by T-test and expressed by mean±SEM (n=20).

Discussion

According to the findings of this pilot study, Licorice possesses some clinical and paraclinical effects on Covid-19outpatients; however, considering the relative small sample size, majority of the findings were not statistically significant and hence, non-generalizable at this point. Moreover, uncertainty about patients' complete adherence to the treatment regimen can be assumed another limitation.

Bioinformatics analysis and molecular studies have shown that licorice can significantly improve clinical symptoms such as fever, dry cough and shortness of breath in COVID-19patients with no significant adverse effects. Cao and his worker reported that Glyasperin F a component of licorice may regulate cell growth via inhibition of the activation of MMP1; Phaseol another component of licorice may diminish inflammatory response and inflammatory cell activation by inhibiting the activation of CXCL8 and IL2RA. Glycyrol in licorice with acting on STAT3 may regulate cell proliferation and survival, thus reducing tissue damage and cell death caused by excessive inflammatory response and promoting the growth of new tissues (42). Other studies have confirmed the anti-inflammatory and antioxidant effects of this plant (43-45) .Also, Licorice plant derivatives such as Glycyrrhizin and glycyrrhetinic acid exert antiviral and antibacterial effects via inhibition of the synthesis of inflammatory factors and inflammatory mediators by blocking the binding of ACE 2 to virus spike protein(46, 47). Additionally, Van de Sand et al., recommended consumption of glycyrrhizin-containing products such as licorice root tea of black licorice for treatment of COVID -19 patients; they proposed that glycyrrhizin block the viral replication by inhibiting the viral main protease (48).

Licorice has been used for respiratory disorders as an expectorant and antitussive agent since long time ago (49). Significant improvements in clinical symptoms including dyspnea and dry coughs have already been reported following Licorice use (47). Ding et al., reported clinical improvement in a 62-year-old woman with non-hospital Covid-19using a combination treatment of diammonium glycyrrhizinate (DG) (150 mg orally, trice daily) with Vitamin C (VC) (200 mg orally trice daily) for eight days. This treatment protocol reduced her symptoms such as vomiting, fever, shortness of breath, and dry coughs. Considering the low cost and wide availability of DG and VC, their combination might be a good candidate for alternative medicine against Covid-19(50). In another study, after glycyrrhizin treatment, dyspnea, dry cough, and chest distress ameliorated promptly and the elevated serum level of aminotransferase reduced (51). According to our findings, oral administration of Licorice capsules thrice a day for two weeks can significantly decrease the rate of cough on day seven (P=0.004) as well as the frequency of dyspnea on day three (P=0.02); however, the effects were nonsignificant at other time points.

Activation of proliferation and maturation in the bone marrow erythroid stem and hence, increased RBC, WBC, and platelet count has been reported following consumption of licorice root in murine model (52).

In this study, Licorice consumption caused significantly higher O2 saturations. Considering that Licorice capsules have alleviated respiratory symptoms like cough and dyspnea, this increase in O2 saturation is clinically worthy and considerable. Although O2 saturation may seem a changeable variable, it was measured at different time points in outpatients and the overall mean O2 saturation was found to be higher in patients receiving Licorice.

Considering the fact that this was a pilot study, the sample size was not large enough to yield significant results and therefore this result may not be attributed to all patients affected by Covid-19. Another limitation of this study is that molecular mechanisms were not study. nevertheless, it can be overall concluded that oral administration of hydroalcoholic extract of Licorice can be effective in management of Covid-19 patients. Confirmation of the clinical efficacy of Licorice Covid-19 patients would need larger randomized trials.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

References

1. van Gelderen CE, Bijlsma JA, van Dokkum W, Savelkoul TJ. Glycyrrhizic acid: the assessment of a no effect level. Hum Exp Toxicol. 2000;19(8):434-9.
2. Guo YR, Cao QD, Hong ZS,et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11.
3. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science (New York, NY). 2020;367(6483):1260-3.
4. Pfortmueller CA, Spinetti T, Urman RD, Luedi MM, Schefold JC. COVID-19 associated acute respiratory distress syndrome (CARDS): Current knowledge on pathophysiology and ICU treatment-

A narrative review. Best Pract Res Clin Anaesthesiol. 2021;35(3):351-68.

5. Krynytska I, Marushchak M, Birchenko I, Dovgalyuk A, Tokarskyy O. COVID-19-associated acute respiratory distress syndrome versus classical acute respiratory distress syndrome (a narrative review). Iran J Microbiol. 2021;13(6):737-747.
6. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427-.
7. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-23.
8. Jia HP, Look DC, Shi L, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol. 2005;79(23):14614-21.
9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
10. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30-e1.
11. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. Crit Care Med. 2016;44(2):275-81.
12. Amawi H, Abu Deiab GI, A Aljabali AA, Dua K, Tambuwala MM. COVID-19 pandemic: an overview of epidemiology, pathogenesis, diagnostics and potential vaccines and therapeutics. Ther Deliv. 2020;11(4):245-268.
13. Khan M, Adil SF, Alkhathlan HZ, et al. COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far. Molecules. 2020;26(1):39.
14. Uddin M, Mustafa F, Rizvi TA, et al. SARS-CoV-2/COVID-19: Viral Genomics, Epidemiology, Vaccines, and Therapeutic Interventions. Viruses. 2020;12(5):526.
15. El-Saber Batiha G, Magdy Beshbishy A, El-Mleeh A, Abdel-Daim MM, Prasad Devkota H. Traditional Uses, Bioactive Chemical Constituents, and Pharmacological and Toxicological Activities of Glycyrrhiza glabra L. (Fabaceae). Biomolecules. 2020;10(3):352.
16. Asl MN, Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phytother Res. 2008;22(6):709-24.
17. Xiang C, Qiao X, Ye M, Guo DA. Classification and distribution analysis of components in Glycyrrhiza using licorice compounds database. Yao Xue Xue Bao. 2012;47(8):1023-30. Chinese.
18. Mamedov NA, Egamberdieva D. Phytochemical Constituents and Pharmacological Effects of Licorice: A Review. In: Ozturk M, Hakeem KR, editors. Plant and Human Health, Volume 3: Pharmacology and Therapeutic Uses. Cham: Springer International Publishing; 2019. p. 1-21.
19. Cheng M, Zhang J, Yang L, et al. Recent advances in chemical analysis of licorice (Gan-Cao). Fitoterapia. 2021;149:104803.
20. Fiore C, Eisenhut M, Krausse R, et al. Antiviral effects of Glycyrrhiza species. Phytother Res. 2008;22(2):141-8.
21. Gupta VK, Fatima A, Faridi U, et al. Antimicrobial potential of Glycyrrhiza glabra roots. J Ethnopharmacol. 2008;116(2):377-80.
22. Matsui S, Matsumoto H, Sonoda Y, et al. Glycyrrhizin and related compounds down-regulate production of inflammatory chemokines IL-8 and eotaxin 1 in a human lung fibroblast cell line. Int Immunopharmacol. 2004;4(13):1633-44.
23. Yang R, Wang L-q, Liu Y. Antitumor Activities of Widely-used Chinese Herb-Licorice. Chinese Herbal Medicines. 2014;6(4):274-81.
24. Lateef M, Iqbal L, Fatima N, et al. Evaluation of antioxidant and urease inhibition activities of roots of Glycyrrhiza glabra. Pakistan Journal of Pharmaceutical Sciences. 2012;25(1):99-102.
25. Wan XY, Luo M, Li XD, He P. Hepatoprotective and anti-hepatocarcinogenic effects of glycyrrhizin and matrine. Chem Biol Interact. 2009;181(1):15-9.
26. Ojha S, Golechha M, Kumari S, Bhatia J, Arya DS. Glycyrrhiza glabra protects from myocardial ischemia-reperfusion injury by improving hemodynamic, biochemical, histopathological and ventricular function. Exp Toxicol Pathol. 2013;65(1-2):219-27.
27. Dhingra D, Sharma A. Antidepressant-like activity of Glycyrrhiza glabra L. in mouse models of immobility tests. Prog Neuropsychopharmacol Biol Psychiatry.2006;30(3):449-54.
28. Dhingra D, Parle M, Kulkarni SK. Memory

enhancing activity of Glycyrrhiza glabra in mice. J Ethnopharmacol. 2004;91(2-3):361-5.

29. Kalaiarasi P, Pugalendi KV. Antihyperglycemic effect of 18 beta-glycyrrhetinic acid, aglycone of glycyrrhizin, on streptozotocin-diabetic rats. Eur J Pharmacol. 2009;606(1-3):269-73.
30. Shin YW, Bae EA, Lee B, et al. In vitro and in vivo antiallergic effects of Glycyrrhiza glabra and its components. Planta Medica. 2007;73(3):257-61.
31. Yang R, Yuan BC, Ma YS, Zhou S, Liu Y. The anti-inflammatory activity of licorice, a widely used Chinese herb. Pharm Biol. 2017;55(1):5-18.
32. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharm Sin B. 2015;5(4):310-5.
33. Diomede L, Beeg M, Gamba A, Fumagalli O, Gobbi M, Salmona M. Can Antiviral Activity of Licorice Help Fight COVID-19Infection? Biomolecules. 2021;11(6).
34. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharm Sin B. 2015;5(4):310-5.
35. Wahab S, Annadurai S, Abullais SS, Das G, et al. Glycyrrhiza glabra (Licorice): A comprehensive review on its phytochemistry, biological activities, clinical evidence and toxicology. Plants (Basel). 2021;10(12):2751.
36. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 2003;361(9374):2045-6.
37. World Health O. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. Geneva: World Health Organization, 2020. Report No.: Contract No.: WHO/nCoV/Clinical/2020.3.
38. Blair JE, Gotimukul A, Wang F, et al. Mild to moderate COVID-19illness in adult outpatients: Characteristics, symptoms, and outcomes in the first 4 weeks of illness. Medicine. 2021;100(24):e26371.
39. Tan R, Xiang X, Chen W, et al. Efficacy of diammonium glycyrrhizinate combined with vitamin C for treating hospitalized COVID-19 patients: a retrospective, observational study. QJM. 2022;115(2):77-83.
40. Nicola M, O'Neill N, Sohrabi C, Khan M, Agha M, Agha R. Evidence based management guideline for the COVID-19pandemic - Review article. International Journal of Surgery. 2020;77:206-16.
41. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016;25(3):1057-73.
42. Cao JF, Gong Y, Wu M, et al. Exploring the mechanism of action of licorice in the treatment of COVID-19through bioinformatics analysis and molecular dynamics simulation. Front Pharmacol. 2022;13:1003310.
43. Michaelis M, Geiler J, Naczk P, et al. Glycyrrhizin exerts antioxidative effects in H5N1 influenza A virus-infected cells and inhibits virus replication and pro-inflammatory gene expression. PloS One. 2011;6(5):e19705.
44. Bhattacharjee S, Bhattacharjee A, Majumder S, Majumdar SB, Majumdar S. Glycyrrhizic acid suppresses Cox-2-mediated anti-inflammatory responses during Leishmania donovani infection. J Antimicrob Chemother. 2012;67(8):1905-14.
45. Gao L, Tang H, He H, et al. Glycyrrhizic acid alleviates bleomycin-induced pulmonary fibrosis in rats. Front Pharmacol. 2015;6:215.
46. Li J, Xu D, Wang L, Zhang M. Glycyrrhizic acid inhibits SARS-CoV-2 Infection by blocking spike protein-mediated cell attachment. Molecules. 2021;26(20):6090.
47. Zhang Qh, Huang Hz, Qiu M, et al. Traditional Uses, pharmacological effects, and molecular mechanisms of licorice in potential therapy of COVID-19. Front Pharmacol. 2021;12:719758.
48. van de Sand L, Bormann M. Glycyrrhizin effectively inhibits SARS-CoV-2 Replication by inhibiting the viral main protease. Viruses. 2021;13(4):609.
49. Dastagir G, Rizvi MA. Review - Glycyrrhiza glabra L. (Liquorice). Pak J Pharm Sci. 2016;29(5):1727-1733.
50. Ding H, Deng W, Ding L, Ye X, Yin S, Huang W. Glycyrrhetinic acid and its derivatives as potential alternative medicine to relieve symptoms in nonhospitalized COVID-19 patients. J Med Virol. 2020;92(10):2200-4.
51. LU H, HUO N, WANG G, LI H, NIE L, XU X. Clinical observation of therapeutic effect of compound glycyrrhizin on SARS. China Pharmacy. 2001.

52. Adamyan TI, Gevorkyan ES, Minasyan SM, Oganesyan KR, Kirakosyan KA. Effect of licorice root on peripheral blood indexes upon vibration exposure. Bull Exp Biol Med. 2005;140(2):197-200.

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