Advances in Applied Science Research
ISSN: 0976-8610

Open Access Review Article

# The Relationships between COVID-19 and Licorice 2022

**Shammah AA***

*Department of Clinical Technology, Umm Al-Qura University, Mecca, Saudi Arabia*

## ABSTRACT

**Background:** Recent dramatic consideration of herbal medicine in evidence-based medicine has prompted development of rigorous analytical methods for evaluation of herbal medicines such as *Glycyrrhiza* spp. extracts. Glycyrrhizin and glycyrrhetinic acid have been identified as the compounds responsible for the phytotherapeutic properties of *Glycyrrhiza glabra* (licorice), whose extracts are used for therapeutic virological interventions.

**Objec ives:** This systematic literature review and meta-analysis were conducted to highlight the progress made in research concerning the association of licorice and Covid 19.

**Design:** Systematic literature review and meta-analysis.

**Methods:** This review was reported based on guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Literature searches were carried out on PubMed and Google Scholar. A second search was performed on the reference lists of the studies obtained in the initial search.

**Results:** Sixty-eight abstracts were obtained from the initial search, for which a full-text review to assess eligibility was done, with 24 studies meeting the full inclusion criteria 19 of included studies were experimental and they all used a qualitative research design as they reported on primary data outcomes. The five studies used for meta-analysis included one randomized controlled trial, two retrospective study, one clinical study and one observational study. The meta-analysis shows a pooled association of 82% between therapeutic use of herbal concoctions containing licorice and COVID patient recovery, with the confidence interval ranging from 63% to 92%. From this review, licorice extracts have a high potential for therapeutic use against the SARS-CoV-2 virus that causes COVID. The most promising phytoconstituents found in licorice are glycyrrhizin licochalcone, liquiritin and glycyrrhetinic acid.

**Conclusion:** This study established that licorice extracts have a high potential for therapeutic use against the SARS-CoV-2 virus that causes COVID. The most promising phytoconstituents found in licorice are Glycyrrhizin (GR), licochalcone, liquiritin and Glycyrrhetinic Acid (GA). These flavonoids

| | | | |
|---|---|---|---|
| **Received:** | 04-August-2023 | **Manuscript No:** | AASRFC-23-17333 |
| **Editor assigned:** | 09-August-2023 | **PreQC No:** | AASRFC-23-17333 (PQ) |
| **Reviewed:** | 23-August-2023 | **QC No:** | IAASRFC-23-17333 |
| **Revised:** | 31-August-2023 | **Manuscript No:** | AASRFC-23-17333 (R) |
| **Published:** | 28-September-2023 | **DOI:** | 10.36648/0976-8610.14.3.113 |

**Corresponding author:** Shammah AA, Department of Clinical Technology, Umm Al-Qura University, Mecca, Saudi Arabia; E-mail: ahghamdi2@gmail.com

**Citation:** Shammah AA (2023) The Relationships between COVID-19 and Licorice 2022. Adv Appl Sci Res. 14:113.

have an average docking score of -8.25, which is better than most antivirals available for the management of COVID.

**Keywords:** COVID-19; Licorice; Phytoconstituents; Glycyrrhizin

## INTRODUCTION

The common name of licorice is *Glycyrrhiza glabra*. However, there are other species within the *Glycyrrhiza* genus that are also referred to as licorice, including the American and Chinese licorice (Fabaceae Tribe FABEAE in Flora of China @ Efloras.org, n.d.). The scientific names of the American and Chinese licorice are *Glycyrrhiza lepidota* and *Glycyrrhiza uralensis*. The common licorice is endemic to Western Asia, North Africa, and the European continent and is also referred to as the European licorice. It is a flowering plant belonging to the legume family *Fabaceae* and the genus *Glycyrrhiza*. *Glycyrrhiza* spp. extracts have long been used in traditional medicine and as natural flavoring compounds in candies and tobacco (Licorice Root, n.d.).

The prevalent use of *Glycyrrhiza* spp. in traditional medicine is due to their ease in cultivation; nevertheless, their use was experimental and pseudoscientific. However, in recent decades, herbal medicine has gained traction within evidence-based medicine. Rigorous analytical methods have, for instance, been developed for the evaluation of *Glycyrrhiza* spp. extracts as therapeutic virological interventions. One such development is native mass spectrometry which is being used to identify possible protein inhibitors from herbal extracts and that can be used against SARS-CoV-2 3CLpro. During the COVID pandemic, as treatment options were being researched and evaluated, herbal medicine gained renewed attention and consequently, clinical trials have been conducted to assess the efficacy of traditional medicine in managing SARS coronavirus [1].

Despite the challenges encountered in the determination of chemical constituents within herbal extracts that can be used to treat COVID, there is ample traditional, experimental and scientific evidence to guide clinical research. Vardhan and Sahoo report that protein-ligand interaction analysis illustrated the potential use of phytochemicals extracted from licorice and other herbal medicines against the therapeutic protein targets of SARS-CoV-2. Nevertheless, the novelty of emerging COVID strains introduces uncertainty in the understanding of the pathogenesis and proliferation pathways, thus slowing down the progress made in phytotherapy. The clinical use of licorice, however, should be conducted with caution since it may have amplified the side effects of other drugs, particularly for patients with the mutated HSD11B2 gene.

Glycyrrhizin (GR) and Glycyrrhetinic Acid (GA) have been identified as the compounds responsible for the phytotherapeutic properties of *Glycyrrhiza glabra* (licorice). These compounds have been appropriated in various herbal concoctions for the treatment and management of different viruses. In their study almost two decades ago, determined that glycyrrhizin was effective against coronavirus (SARS). Glycyrrhizin outperformed other antivirals such as mycophenolic acid, 6-aziridine and ribavirin, although the mechanism of its action was not yet established and has been a subject of research ever since.

A systematic review conducted to determine the efficacy of glycyrrhizin preparations on SARS established that glycyrrhizin has a high potential for use in the management of COVID. Nevertheless, further research is required to illustrate the appropriate dosages and usage duration Lee et al. report that Traditional Chinese herbal medicine (TCM) had an efficacy of above 90% when used in the treatment of COVID in the Wuhan district. Underscore that within TCM, licorice has shown exceptional potential for use as a therapeutic intervention for COVID. In silico docking studies have demonstrated that glycyrrhizin and glycyrrhetinic acid may have a limiting effect on the viral internalization and replication function of the Angiotensin-Converting Enzyme 2 (ACE2). Furthermore, *in vitro* studies have shown that glycyrrhizin has an antiviral effect by interacting directly with SARS proteins, although the anti-inflammatory and antioxidant effects should not be ignored determined that GB-1 and theaflavin-3-gallate are potential antivirals against SARS-CoV-2 by inhibiting protein expression of ACE2 [2].

Glycyrrhizin has been predicted to reduce infection severity by reducing cell entry points and by an inflammatory mechanism that does not depend on ACE2. On the other hand, glycyrrhetinic acid has a possible inhibitive action on the cytokine storms resulting from SARS-CoV-2 infection. A systematic review conducted to comprehensively describe the nature of critical trials on therapeutic interventions for COVID reported that from 3018 studies, 23 (10.6%) trials focused on herbal medicines. A comprehensive review of the relationship between licorice and COVID is lacking; as such, this study seeks to highlight the progress made in research concerning the association between licorice and COVID [3].

### Objectives

The main aim was to highlight the progress made in research concerning the association of licorice and COVID. As such, the objective of this research was to assess the therapeutic use of licorice constituents against COVID-19. It sought to provide a comprehensive assessment of current literature on the mechanism of action of licorice therapeutic agents that have been made available within the past five years. To achieve this objective, the extent of this review was delineated as:

- To assess the relationship of licorice extracts in boosting the immunity of COVID-19 patients.

- To determine the phytochemicals agents in licorice responsible for therapeutic action against the coronaviruses.
- To determine the mechanism of action of phytochemicals agents in licorice responsible for therapeutic action against the coronaviruses.
- To determine the safety of licorice extracts for use as treatment alternatives in covid patients.

## LITERATURE REVIEW

### Study Design

This research paper was reported based on guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The review process was informed by JBI (Joanna Briggs Institute) approaches to systematic reviews. Moreover, the reviewers of this study performed a systematic search of the literature to determine its value and contribution to the existing body of knowledge on the therapeutic use of licorice constituents against COVID-19 [4].

The review was carried out to mitigate the lack of a comprehensive review on the relationship between licorice and COVID. As such, the review question asked in the analysis was, "What is the therapeutic relationship of licorice extracts in COVID-19 patients?" This was developed using the PICO framework, as seen in **Table 1**.

**Table 1:** Description of the PICO (P=Population, I=Phenomenon of interest, C=Context, O=Outcome) elements.

| Elements | Description |
|---|---|
| Research question | What are the therapeutic use of licorice constituents against COVID-19? |
| Population | People diagnosed with COVID-19 |
| Phenomenon | Therapeutic use of phytoconstituents extracted from licorice |
| Interest | Mechanism of action of these phytoconstituents |
| Context | Global setting |
| Other considerations | Published articles |

### Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were guided by the PICO framework as described in Table 1. The included articles had to meet the following requirements.

**Inclusion criteria:**

- The article focuses on the therapeutic relationship of licorice extracts in COVID-19 patients.
- The article states that it discusses the mechanism of action of phytoconstituents in licorice against the therapeutic relationship of licorice extracts in COVID-19 patients.
- There is a description of the experimental tools used.
- Primary outcomes are the prevalence and risk factors of depression and anxiety.
- Articles published in English.

**Exclusion criteria:**

- The articles focused on areas other than the therapeutic relationship of licorice extracts in COVID-19 patients.
- Unpublished article.
- Articles whose full text was not accessible.
- Case reports or case series.
- Personal opinion, descriptive paper, letter to the editor or interviews.
- Pilot studies.
- Proof of concept.

### Search Strategy

This review was reported based on guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Literature searches were carried out on PubMed and Google Scholar. A second search was performed on the reference lists of the studies obtained in the initial search. Similar articles recommended by the digital libraries mentioned above were included in the results of the second literature search.

Keywords used were licorice, Glycyrrhizin (GR) and Glycyrrhetinic Acid (GA), *Glycyrrhiza glabra*, *Glycyrrhiza* spp., phytotherapeutic properties, licochalcone, liquiritin, SARS CoV-2 and COVID-19. Boolean operators "AND" and "OR" were used in the advanced search in PubMed to connect the search words, thus generating a search string. The literature search initially resulted in 68 publications. Articles obtained included peer-reviewed, English-language, experimental studies published between 2017 and 2022, as shown in **Figure 1**.

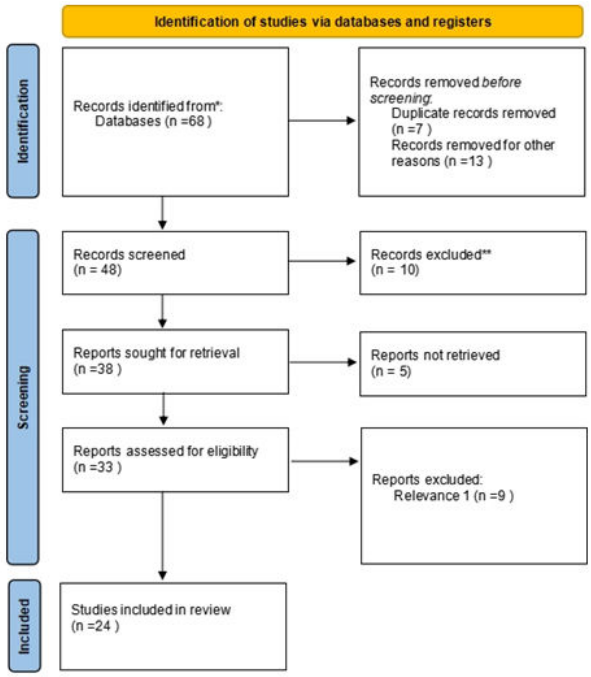


**Figure 1:** PRISMA flow diagram.

## Quality Appraisal

Two reviewers participated in the quality appraisal to guarantee the methodological process was appropriate, bias in reporting was limited and results were applicable to this systematic review. Duplicate studies were also excluded. Articles with individual keywords were excluded as most of them did not contain information relevant to this analysis. The titles of the articles obtained in the initial search were analyzed to determine that they covered the subject of study of this analysis. The abstracts of the remaining articles were then studied to establish the relevance of the given articles to the current study, such that they made an effort to answer the questions posed herein. At this point, the articles that passed the described eligibility criteria were then thoroughly read to determine their utility and significance in achieving the goal of the systematic review. The Johanna Briggs Institution (JBI) critical appraisal checklist for qualitative research was used to determine the methodological validity, the potential for bias, reliability and appropriateness of the research question. The studies had to meet a minimum requirement by responding "yes" to at least 70% of the JBI assessment questions. Quality appraisal was performed on twenty four papers, none of which were omitted. The appraisal process is illustrated [5].

## Data Extraction and Analysis

The data from the studies that passed the exclusion and inclusion criteria were extracted into a pre-defined extraction table. The author's name, study design, the theme of study, experimental tools used, docking score and results were extracted into the table. The extraction table provided a means of assessing the reliability of the included papers according to the parameters described. Thematic analysis was carried out during the literature search stage to arrive at the central theme of this review. The thematic analysis determined that the current literature on the therapeutic use of licorice constituents against COVID-19 focused on the mechanism of action of the phytoconstituents, the efficacy and the safety of clinical use of licorice [6].

## Search Findings

Sixty-eight abstracts were obtained from the initial search, for which a full-text review to assess eligibility was done, with 24 studies meeting the full inclusion criteria (Figure 1).

## Study Characteristics

19 of included studies were experimental, and they all used a qualitative research design as they reported on primary data outcomes. The five studies used for meta-analysis included one randomized controlled trial, two retrospective study, one clinical study and one observational study. All the studies included in this systematic review focused on the therapeutic relationship of licorice extracts in COVID-19 patients [7].

Hejazi et al. report that licochalcone and liquiritin, both phytoconstituents from licorice, have good scores for binding affinity with 3Clpro, which is better than most of the FDA approved repurposed drugs. These phytoconstituents bind with the main protease 6LU7 of SARS CoV-2, thus acting as antiviral drugs. Molecular docking analysis has shown that *Glycyrrhiza* can be enhanced by ephedra by forming the *Ephedra-Glycyrrhiza* pair and binding to therapeutic protein targets of COVID report that according to molecular docking simulation, glycyrrhizin might improve the efficacy of other drugs by increasing their solubility and stability. One particular drug is nifedipine, which dissolves more easily through the lipid layer due to a reduction in the energy barrier. As such, glycyrrhizin can be used as a drug-delivering system. Another study reported that β-boswellic acid and glycyrrhizic acid showed the highest binding energies at -9.1 kcal/mol.

Functionality loss and structural disruptions with 90% were observed by UV-spectra and fluorescent-based analyses. Demonstrated that when rats are fed with a diet containing licorice extracts, the gene expression of ACE2 in the small intestines is greatly reduced. Nevertheless, this effect was absent in non-target tissues such as the brain cortex and heart. However, the reported effect demonstrates the potential therapeutic use of licorice extracts to reduce the entry points of COVID viruses. Nevertheless, this result requires further evaluation through clinical trials. Tsai et al. report that GB-2, a component in licorice extracts, has potential therapeutic use for the prevention and treatment of different SARS-CoV-2 strains due to its effect of impeding binding between ACE2 and RBD with K417N-E484K-N501Y mutations or L452R mutation [8].

Niu et al. determined that the phytoconstituents responsible for the therapeutic effects of licorice are quercetin, glabridin and gallic acid. These phytoconstituents downregulate the ACE2 protein, thus preventing the entrance of COVID. These phytoconstituents were identified from traditional Chinese

medicine through enrichment analysis. *In vitro* analysis shows that glycyrrhizin regulates the replication of SARS-CoV-2. This effect is due to the mechanism of action of glycyrrhizin which blocks viral replication by inhibiting the main protease Mopar. Furthermore, the consumption of foodstuffs containing licorice extracts, such as licorice root tea, may have a therapeutic effect on SARS-CoV-2 patients. Report that licorice-saponin A3 (A3) and Glycyrrhetinic Acid (GA) may effectively inhibit SARS-CoV-2 infection, with EC50 of 75 nM and 3.17 μM, respectively. Furthermore, the A3 primarily targets the nsp7 protein and GA binds to the spike protein RBD of Coronaviruses.

Niu et al. determines that the binding affinity and the antiviral properties of the ligand demonstrated its potential use as COVID prophylaxis. The study also reported that the active site analysis of protein interactions showed that active compounds within licorice extracts could be used for managing COVID-19 infections. Using molecular dynamic simulations, inferred that the COVID pandemic could be alleviated by the use of licorice which has phytoconstituents that dock with the lead molecule in SARS-CoV-2. At the same time, docking studies have shown that GA, L and G make non-covalent bonds with enzymes and amino acids present in the active site of Mopar. These enzymes and amino acids include His41, Gly143, Gln189, Glu 166, Cys 145, Thr25, Asn142, Met49, Cys44, Thr45 and pro168. According to *in silico* ADMET, the phytoconstituents from licorice have good permeation, absorption, and solubility. Nevertheless, glycyrrhizic acid has the highest binding affinity compared to L and G [9].

Sinha et al. report that according to the binding interactions, glyasperin A demonstrated a high affinity for Nsp15 endoribonuclease with uridine specificity. Furthermore, GA was found to be the most suitable for the binding pocket of spike glycoprotein. GA prevented the entry of SARS-CoV-2 into the host cell. Ibrahim et al. reported that from ten flavonoids obtained from licorice root extracts through biologically-guided isolation, the best performing was Liquirtin. Liquirtin had the most effect with an $IC_{50}$ of 5.15 μM. Another study that obtained six compounds from licorice extracts showed that glycyrrhizic acid had the highest affinity for the protein target, despite Liquirtin being present in the extracted flavonoids. The study, nevertheless, reported that liquirtin performed fairly well in terms of affinity towards Mopar [10].

Niu et al. determined that *Glycyrrhizin* (1), licorice saponin G2 (2), and liquiritin/liquiritin apioside were the major phytoconstituents of Gancao, although they had poor intestinal absorption. A study seeking to identify the inhibitory compounds for ACE2 blockade against the RBD part of the S1 protein in the SARS-CoV-2 established that glycyrrhizin was among the top five potential inhibitors of the SARS-CoV-2 binding site of ACE2. A study seeking to investigate the antiviral effect of Glycyrrhetinic Acid (GA) using a pseudotyped lentivirus that has the SARS-CoV-2 S protein on its envelope (Lenti-S) reports that GA particularly targets the virus in favor of the host cells by interacting with the s protein. GA blocked a recombinant s protein from attaching to the host cells, and as such, another potential mechanism of licorice extracts is illustrated. Essentially GA prevents the interaction between the virus and the host cells [11].

### Meta-Analysis

The meta-analysis showed a pooled association of 82% between therapeutic use of herbal concoctions containing licorice and COVID patient recovery, with the confidence interval ranging from 63% to 92%. Moreover, the GLMM and logit-transformed proportions have indeed been used to pool the effects. Finally, we see the estimate of the between-study heterogeneity ($\tau^2$= 0.4540) but no confidence interval around it (**Figure 2**) [12].

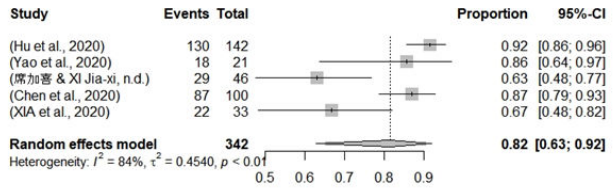


**Figure 2:** Forest plot showing the pooled correlation between therapeutic uses of herbal concoctions including licorice on COVID patient recovery.

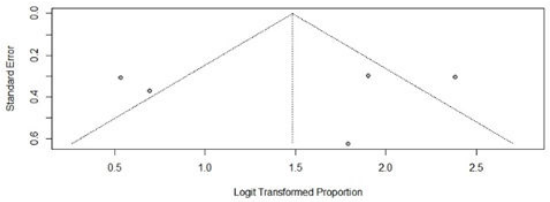


**Figure 3:** Funnel plot showing the pooled correlation between therapeutic uses of herbal concoctions including licorice on COVID patient recovery.

The asymmetric funnel indicates the possibility of either publication bias or a systematic difference between studies of higher and lower precision. The asymmetry maybe is due to the measure of the correlation between licorice and its therapeutic use within the presence of other compounds from other herbal extracts (**Figure 3**) [13].

## DISCUSSION

There are few clinical studies available depicting the efficacy of licorice in managing Covid infections; nevertheless, those available underscore the high therapeutic potential of licorice phytoconstituents. The meta-analysis shows a pooled association of 82% between therapeutic use of herbal concoctions containing licorice and COVID patient recovery, with the confidence interval ranging from 63% to 92%. According to this systematic literature review, licorice extracts have a high potential for therapeutic use against the SARS-CoV-2 virus that causes COVID. The most promising phytoconstituents found in licorice are Glycyrrhizin (GR), licochalcone, liquiritin, and Glycyrrhetinic Acid (GA). These

flavonoids have an average docking score of -8.25, which is better than most antivirals available for the management of COVID. These compounds work by varying mechanisms, but the most reported is molecular interactions with therapeutic protein targets of COVID. Glycyrrhizin has been reported to interfere with the virus replication, and this was substantiated by in silico simulations. The SARS-CoV-2 main protease Mopar also referred to as the 3CL protease, is a key component for processing the viral polyproteins that are translated from SARS-CoV-2 RNA, an important step in viral replication. However, the phytoconstituents in licorice extracts, particularly glycyrrhizin, have a protease inhibitory effect on the main protease Mopar. Nevertheless, these results are obtained from in silico and *in vitro* studies and are yet to be supported by clinical trials [14].

Licorice appears in many herbal formulations that have been used for the management of COVID. An example is traditional Chinese medicine which had reported efficacy of above 91% when it was used in Wuhan during the COVID pandemic. Glycyrrhizin has been shown to effectively inhibit Mopar activity at a concentration of 2000 µM (1.6 mg/mL) and reduce its activity by 70.3% at a concentration of 30 µM (0.024 mg/mL). Nevertheless, the optimal dosage and course of treatment are yet to be decided upon by the conduction of clinical trials using infected patients. The major mechanism of licorice antiviral activity is a consequence of the disruption of viral entry into host cells and affects the interaction between the Receptor-Binding Domain (RBD) of SARS-COV2 and ACE2. The 19 included studies indicate that glycyrrhizin and licorice extracts also have significant antioxidant, anti-inflammatory, and immunomodulatory effects. Molecular modeling and molecular docking have shown their efficacy in accelerating drug discovery and progress; nevertheless, the efficiency of these research tools may be quenched by the progress made in the management of COVID [15].

## CONCLUSION

Although licorice extracts are promising for therapeutic use against the SARS-CoV-2 virus that causes COVID, the results are obtained from in silico and *in vitro* studies and are yet to be supported by clinical trials. Until clinical trials are conducted, the results obtained from this systematic literature review will not be useful to the scientific community. This systematic review, therefore, serves to direct future research on the therapeutic effects of licorice on COVID infections and the mechanisms of action of the licorice phytoconstituents. Nevertheless, the urgency of these clinical trials is pegged on the desire by clinical researchers to obtain cheap and effective interventions against COVID to facilitate mortality rate reduction and spread management. It remains to be seen if further progress will be made in this area of clinical research, considering that 11,324,805,837 vaccine doses have been administered as of Sunday, April 17, 2022 and most nations seem to have the COVID disease under control (World Health Organization, 2022).

## LIMITATIONS

The mechanism of action through molecular docking inhibition of therapeutic agents from licorice extracts has been predicted by *in vitro*, *in silico* studies and verified by animal experiments. Nevertheless, the clinical efficacy in human subjects is yet to be established. The optimal dosage and course of treatment will only be determined once the clinical efficacy and effectiveness of licorice constituents are verified through clinical trials.

## ACKOWLEDGMENT

I am very thankfully appreciating the contribution and the effort of all the people who helped us in this research. Also the author would like to thank the deanship of scientific research at Umm Al-Qura university for supporting this work by grant code: (23UQU4210127DSR05)

## REFERENCES

1. Aishwarya S, Gunasekaran K, Jansi RS, Sangeetha G (2021) From genomes to molecular dynamics-A bottom up approach in extrication of SARS CoV-2 main protease inhibitors. Comput Toxicol. 18:100156.
2. Asili P, Mirahmad M, Tabatabaei-Malazy O, Manayi A, Haghighat E, et al. (2021) Characteristics of published/ registered clinical trials on COVID-19 treatment: A systematic review. Daru. 29(2):449-467.
3. Brendler T, Al-Harrasi A, Bauer R, Gafner S, Hardy ML, et al. (2020) Botanical drugs and supplements affecting the immune response in the time of COVID -19: Implications for research and clinical practice. Phytother Res. 35(6): 3013-3031.
4. Chen J, Lin S, Niu C, Xiao Q (2020) Clinical evaluation of Shufeng Jiedu capsules combined with umifenovir (*Arbidol*) in the treatment of common-type COVID-19: A retrospective study. Expert Rev Respir Med. 15(2): 257-265.
5. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, et al. (2003) Glycyrrhizin, an active component of licorice roots, and replication of SARS-associated coronavirus. Lancet. 361(9):374.
6. Diomede L, Beeg M, Gamba A, Fumagalli O, Gobbi M, et al. (2021) Can antiviral activity of licorice help fight COVID-19 infection? Biomolecules. 11(6):855.
7. Fatima SW, Alam S, Khare SK (2022) Molecular and structural insights of β-boswellic acid and glycyrrhizic acid as potent SARS-CoV-2 envelope protein inhibitors. Phytomed Plus. 2(2):100241.
8. Gomaa AA, Abdel-Wadood YA (2021) The potential of glycyrrhizin and licorice extract in combating COVID-19 and associated conditions. Phytomed Plus. 1(3):100043.
9. Hejazi II, Beg MA, Imam MA, Athar F, Islam A (2021) Glossary of phytoconstituents: Can these be repurposed against SARS CoV-2? A quick *in silico* screening of various phytoconstituents from plant *Glycyrrhiza glabra* with

SARS CoV-2 main protease. Food Chem Toxicol. 150:112057.

10. Hu K, Guan W, Bi Y, Zhang W, Li L, et al. (2020) Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. Phytomedicine. 85:153242.
11. Husain I, Bala K, Khan IA, Khan SI (2021) A review on phytochemicals, pharmacological activities, drug interactions, and associated toxicities of licorice (*Glycyrrhiza* sp.). Food Front. 2(4):449-485.
12. Ibrahim RS, Mahrous RSR, Abu El-Khair RM, Ross SA, Omar AA, et al. (2021) Biologically guided isolation and ADMET profile of new factor Xa inhibitors from *Glycyrrhiza glabra* roots using *in vitro* and *in silico* approaches. RSC Adv. 11(17):9995-10001.
13. Jezova D, Karailiev P, Karailievova L, Puhova A, Murck H (2021) Food Enrichment with *Glycyrrhiza glabra* extract suppresses ACE2 mRNA and protein expression in rats-possible implications for COVID-19. Nutrients. 13(7): 2321.
14. Kim AV, Shelepova EA, Evseenko VI, Dushkin AV, Medvedev NN, et al. (2021) Mechanism of the enhancing effect of glycyrrhizin on nifedipine penetration through a lipid membrane. J Mol Liq. 344:117759.
15. Lan X-F, Olaleye OE, Lu J-L, Yang W, Du F-F, et al. (2021) Pharmacokinetics-based identification of pseudoaldosterogenic compounds originating from *Glycyrrhiza uralensis* roots (Gancao) after dosing the LianhuaQingwen capsule. Acta Pharmacol Sin. 42(12): 2155-2172.