


BMJ Open Clinical efficacy and security of glycyrrhizic acid preparation in the treatment of anti-SARS-CoV-2 drug-induced liver injury: a protocol of systematic review and meta-analysis

Xia Tian ¹, Wenfan Gan,¹ Yisen Nie,¹ Rongtao Ying,¹ Yongji Tan,² Junli Chen,² Mei Chen,³ Chuantao Zhang¹

To cite: Tian X, Gan W, Nie Y, *et al.* Clinical efficacy and security of glycyrrhizic acid preparation in the treatment of anti-SARS-CoV-2 drug-induced liver injury: a protocol of systematic review and meta-analysis. *BMJ Open* 2021;**11**:e051484. doi:10.1136/bmjopen-2021-051484

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-051484>).

XT and WG contributed equally.

XT and WG are joint first authors.

Received 20 March 2021

Accepted 08 June 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Chuantao Zhang;
zhangchuantao@cdutcm.edu.cn

ABSTRACT

Introduction COVID-19 is a highly infectious acute pneumonia. Glycyrrhizic acid preparation (GAP) has been found to have hepatoprotective and antiviral effects, but there is no supporting evidence on its efficacy and security for patients with COVID-19.

Methods and analysis The systematic review methods will be defined by Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This study will start on 1 July 2021 and end on 31 October 2021. A comprehensive electronic search will be conducted with the search of Web of Science, PubMed, Ovid web, China National Knowledge Infrastructure, Chinese Scientific and Journal Database, Wanfang Database and grey literature, and manual search will be conducted to search literature of randomised controlled trials, single-arm trials and retrospective studies about GAP in the treatment of anti-SARS-CoV-2 drug-induced liver injury from 1 December 2019 to 1 July 2021. There is no time limitations of publication and language will be restricted to Chinese and English. Retrieved studies will be independently screened by two researchers and relevant data will be extracted from studies. Interstudy heterogeneity will be assessed using the I^2 statistic and explored through meta-regressions and subgroup analyses. Depending on data availability, we plan to conduct subgroup analyses by study population, geographical region and other selected clinical variables of interest. Quality assessment of the studies will be performed. Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias, and Grading of Recommendations Assessment, Development and Evaluation will be used to access the confidence in cumulative evidence.

Ethics and dissemination Ethical approval will not be required for no primary data of individual patients will be collected. The final report will be shared with the scientific community through publication in a peer-reviewed journal, as well as with key stakeholders, including patients, healthcare professionals and those working on COVID-19 research.

PROSPERO registration number CRD42021234647.

INTRODUCTION

Since the outbreak of COVID-19 reported in Wuhan, China at the end of December

Strengths and limitations of this study

- We adopted strict inclusion and exclusion criteria and applied a recognised tool to evaluate the quality of the included studies. These ensured, to some extent, that our review could serve as an up-to-date and comprehensive summary of the published evidence on the topic of treatment for patients with COVID-19 hepatocellular injury. Given the different measures of outcomes adopted in these studies, it was dimensional and interventional.
- Some of the negative results may not have been published and excluded; as a result, publishing bias is not applicable. Failure to report details of design methodology is also a potential source of increased heterogeneity in the included studies.
- The sample size might not be large enough to estimate the accurate efficacy which there exists, a problem that it is probably impossible to evaluate the therapeutic effect in multiple dimensions.
- Nearly all the studies included focused on short-term outcomes only, and follow-up duration in the long term was reported merely. So further prognosis cannot be determined without adequate information.

2019, the virus has rapidly spread around the world. More than 1 billion (165 772 430) people have been confirmed positive and over 3 million (3 437 545) have died as of 27 May 2021. COVID-19 is a highly infectious acute pneumonia. Although COVID-19 is controlled within China, it has been affecting other countries around the world since 25 February 2021, especially the USA, India and Brazil.¹ The WHO has declared COVID-19 a global pandemic; moreover, Europe and the USA are now at the centre of the pandemic.² Up to now, some countries have developed a variety of vaccines and anti-COVID-19 drugs, and some of them have entered the clinical observation stage. It was found that some

vaccines and anti-COVID-19 drugs are effective against COVID-19 after clinical studies, but the efficacy and safety are still to be improved; so it is urgently demanded to have safe and efficient vaccines and anti-COVID-19 drugs to fight the pandemic.

Antiviral therapy becomes a routine treatment for COVID-19, however, these drugs can damage the liver of patients with COVID-19. In addition, although COVID-19 is highlighted by atypical pneumonia, some patients may present with abnormal liver function, which suggests that the disease can be associated with liver injury.³⁻⁵ Therefore, patients with COVID-19 are often combined with impairment of liver function due to the application of conventional antiviral therapy.

Glycyrrhizic acid preparation (GAP) (eg, monopotassium glycyrrhizinate, monoammonium glycyrrhizinate, compound ammonium glycyrrhizinate, compound glycyrrhizin, etc) has long been found to have hepatoprotective effects and applied in the treatment of liver disease. In Japan, glycyrrhizic acid has been used for more than 40 years as treatment for liver diseases, in particular to treat chronic hepatitis.⁶ It is an efficient hepatoprotective medication in patients with chronic hepatitis C⁷ and more broadly to protect from a variety of hepatic diseases such as chronic viral hepatitis and drug-induced or chemical-induced liver injury.⁸ The drug is considered as medicine with a good safety and economical profile. It is increasingly used clinically. With certain pharmacological activities, glycyrrhetic acid (C₃₀H₄₆O₄, molecular weight=470.7) is the main component in *Glycyrrhizae Radix et Rhizome* (Gan Cao). It can be used against different viruses, including human and animal coronaviruses like SARS, and it has been shown to be an effective immunoactive anti-inflammatory drug.⁹ Glycyrrhizic acid extracts can selectively inhibit the synthesis of single-negative RNA encapsulated viral protein,¹⁰ and some derivatives of glycyrrhizic acid have strong anti-SARS-CoV activity with fewer adverse reactions.^{11 12} Glycyrrhetic acid is a non-haemolytic saponin which displays both cytoplasmic and membrane effects, and an amphiphilic compound like a saponin could interfere with the virus entry into cells, owing to the well-known membrane effects of this class of compounds.⁹ *Glycyrrhizae Radix et Rhizome* appears as one of the highest frequencies in the Pneumonia Treatment Protocol for Novel Coronavirus Infection and in the recommended Chinese herbal compound.¹³ Ding *et al's* study¹⁴ reported glycyrrhetic acid and its derivatives as potential complementary medicine to relieve symptoms in non-hospitalised patients with COVID-19. Diammonium glycyrrhizinate, one of the derivatives of glycyrrhetic acid, can be metabolised into glycyrrhetic acid. With the similar chemical structure to corticosteroid, it functions just like glucocorticoid, helping boost the immune system against cytokine storm and reduce inflammation, although might be less stringent than steroids.¹⁵ It was reported that the active compounds of *Glycyrrhizae Radix et Rhizome* possess antiviral, antimicrobial, anti-inflammatory and

immunoregulatory functions, which can protect nervous, alimentary, respiratory, endocrine and cardiovascular systems.¹⁶ Molecular docking technology has been used to screen ACE2-binding compounds in traditional Chinese medicine, and the results showed that glycyrrhetic acid can bind to ACE2, suggesting that glycyrrhetic acid is a potential anti-SARS-CoV-2 compound.¹⁷ Vardhan and Sahoo found that the GAP is a potential phytochemical agent against COVID-19 by having a good deal of computational work, because glycyrrhizic acid binds at the active site of all the five protein targets of SARS-CoV-2.¹⁸ It was reported that glycyrrhizin and 18 β -glycyrrhetic acid can suppress the activation of proinflammatory cytokine cyclo-oxygenase-2, interleukin (IL)-6, IL-10, transforming growth factor- β and ABCA1.¹⁹⁻²⁶ Additionally, glycyrrhizin, 18 β -glycyrrhetic acid and licochalcone A presented immunoregulatory activity.²⁷⁻³² Glycyrrhizin revealed a fine immune stimulant and antiviral effect against duck hepatitis virus (DHV).²⁹ A combination of glutamyl-tryptophan and glycyrrhizin exerted a protective effect in reducing the death of H3N2 IAV-infected mice.³⁰ Studies have shown that these compounds can protect mice against disseminated candidiasis both in vivo and in clinic,³³ relieve experimental autoimmune encephalomyelitis in mice,³⁴ increase the endpoint serum antibody titres and perform as an immune stimulant against DHV.³² All of these reports affirmed the antiviral effect and immunoregulatory activity of *Glycyrrhizae Radix et Rhizome*.

Therefore, GAP is expected to become a complementary drug for SARS-CoV-2 and improve anti-SARS-CoV-2 drug-induced liver injury. The aim of this study is to provide a systematic review of the clinical efficacy and security of GAP in the treatment of anti-SARS-CoV-2 drug-induced liver injury.

METHODS

The systematic review will be performed in accordance with the guideline of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015.³⁵ The results of the review will be reported according to the recommendation of PRISMA.³⁶ The study has been registered on PROSPERO, and will start on 1 July 2021 and end on 31 October 2021.

Inclusion criteria

Types of studies

We will include randomised controlled trials (RCTs) on GAP for anti-SARS-CoV-2 drug-induced liver injury in the experimental groups. If multiarm RCTs are included, we will select the group which used GAP and another without GAP for analysis. In addition, single-arm trials and retrospective studies will also be included in this systematic review. Studies in English and Chinese language will be included.

Types of participants

Patients suffering from anti-SARS-CoV-2 drug-induced liver injury with COVID-19 will be included. Because the

population is generally susceptible to SARS-CoV-2, there is no restriction on the age of patients with COVID-19. The confirmation of COVID-19 is that the SARS-CoV-2 will be detected by real-time reverse transcription PCR.³⁷ Liver injury will be diagnosed through abnormal liver function tests.³⁸ We defined alanine aminotransaminase (ALT) and/or aspartate aminotransferase (AST) over three times the upper limit unit of normal (ULN); alkaline phosphatase (ALP), gamma-glutamyl transferase, and/or total bilirubin over two times ULN as liver injury. Participants of any sex and ethnicity will be enrolled.

Types of interventions

The experimental group using GAP alone or combined with conventional therapy, and the control group receiving conventional therapy will be included. There will be no restrictions on the types, dosage forms, doses and methods of the use of GAP.

Types of outcome measures

Primary outcome

Liver function will be tested with serum ALT, serum AST and ALP. Length of stay will be evaluated by days of hospitalisation.

Secondary outcome

Mortality rate will be defined as the percentage of deaths to the total number after treatment. Blood test will be evaluated by C reactive protein, procalcitonin and white cell count.

Safety outcome

Incidence of adverse reactions will be observed by kidney function, bilirubin level, gastrointestinal symptoms (eg, nausea, vomiting, abdominal pain, diarrhoea) and rash.

Exclusion criteria

1. GAP was not only in the experimental group but also in the control group.
2. The patients with pre-existing liver disease (eg, cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease, autoimmune liver diseases or liver transplant).
3. Liver injury resulting from toxicity from commonly used drugs.
4. The data cannot be extracted, and the correct data cannot be obtained by contacting authors and data calculation.
5. Repeatedly published studies, literature reviews, meta-analyses, case reports, etc.

Search strategy

Electronic searches

Main information resource databases include: PubMed, Web of Science, Ovid web, China National Knowledge Infrastructure, Chinese Biomedical Database, Chinese Scientific and Journal Database and Wanfang Database. The search time limit is from 1 December 2019 to 1 July 2021. The search terms are 'glycyrrh*', 'COVID-19 combined with liver injury', 'clinical efficacy', etc. The language is limited to Chinese and English. The detailed search strategy from Web of Science is listed in [table 1](#), and the search strategy will be modified according to other different databases.

Other search strategies

Manual search will be performed using conference papers and searched literature references. In addition, preprinted websites including *arXiv* (<http://arxiv.org/>), *BioRxiv* (<https://www.biorxiv.org/>), *F1000* (<https://f1000.com/>) and *PeerJ Preprints* (<https://peerj.com/preprints>) will also be searched to find more unpublished papers.

Data collection and analysis

Literature screening

All search results will be imported into EndNote V.X9 for classification and sorting, and duplicate studies will be excluded. Two researchers (XT and WG) will independently screen the titles and abstracts of the literature, and screen the literature based on the inclusion criteria. For any potentially related research, we will download and read the full text. If there is disagreement during the screening process, a discussion with the third researcher (YN) will be done to make a decision. A research flow chart will be drawn to show the whole process of research selection ([figure 1](#)).

Data extraction

According to the inclusion criteria, the results of the included studies and all valuable information will be correctly extracted. Two researchers (XT and WG) will complete this work independently and review with each other. Data extraction includes five aspects: basic research information (eg, title, journal, research ID number, author, contact information, etc), research method (eg, research design, random unit, random method, etc), observation object (eg, age, gender, sample size, etc), intervention measures (eg, treatment course information, etc), and measurement indicators (eg, measurement

Table 1 Search strategy from Web of Science

# 4	#3 AND #2 AND #1
# 3	TS=(randomised controlled trial OR controlled clinical trial OR randomized OR single-arm trial OR retrospective study OR placebo OR drug therapy OR randomly OR trial OR groups)
# 2	TS=(COVID-19 OR Novel Coronavirus Pneumonia OR 2019-nCoV OR SARS-CoV-2)
# 1	TS=(glycyrrh* OR glycyrrhizic acid OR monopotassium glycyrrhizinate OR monoammonium glycyrrhizinate OR compoundammonium glycyrrhizinate OR compound glycyrrhizin OR compoundmonoammonium glycyrrhizinate OR diammonium glycyrrhizinate OR glycyrrhizic acid preparation OR magnesium isoglycyrrhizinate)

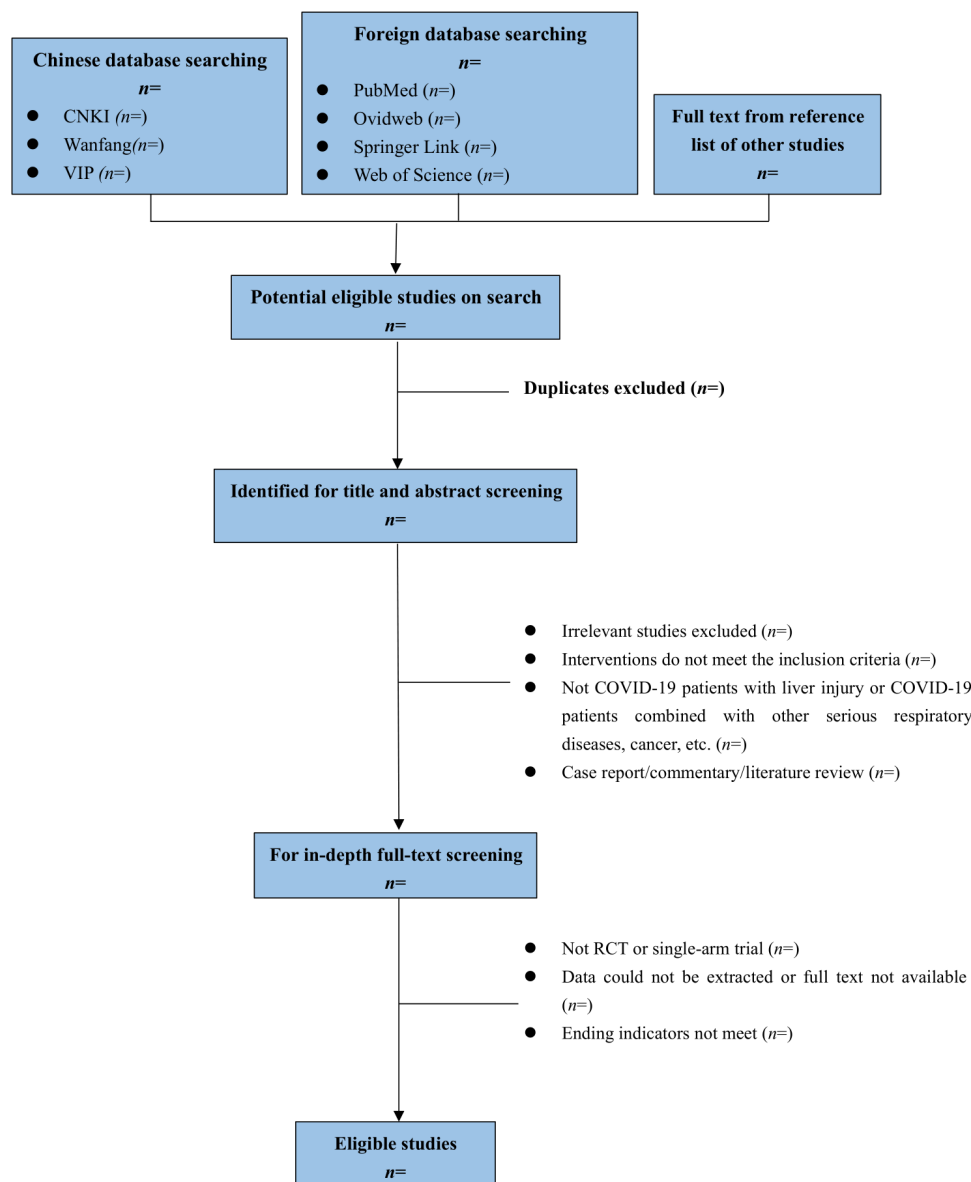


Figure 1 Flow diagram of study selection. CNKI, China National Knowledge Infrastructure; RCT, randomised controlled trial.

indicators and time points for judgement, judgement indicators, measurement units, etc). If the data are missing, we will try to contact the original author. If data are unavailable, we will exclude the study. Similarly, if the data are disputed, it will be resolved by discussing with the third researcher (YN). Once the extraction is completed, the two researchers (XT and WG) will check with each other to ensure the accuracy of the data.

Assessment of risk of bias in included studies

All the included studies will be evaluated based on the guidelines of Cochrane Handbook V.5.2.0 for Systematic Reviews of Interventions.^{39 40} Different risk of bias assessment tools will be used according to different types of studies. There are seven domains, and each item should be judged as ‘low risk’, ‘high risk’ and ‘unclear’ deviations according to the quality classification standards. If there is a difference, it will be decided through collective consultation. The risk of bias of RCTs will be conducted

using version 2 of the Cochrane risk of bias tool. The risk of bias tool in non-randomised studies of interventions will be used to assess the risk of bias of non-RCTs according to Cochrane Handbook.

Assessment of heterogeneity

The heterogeneity of the included studies is measured by Q-test and I^2 statistic. When I^2 is more than or equal to 50%, the heterogeneity will be considered large. For this reason, we will use a random-effects model to analyse the data. If I^2 is less than 50%, it can be considered that the included studies are homogeneous, and the fixed-effects model can be used to analyse the data.

Data synthesis

The meta-analysis will be performed using RevMan V.5.3 software provided by the Cochrane Collaboration Center. Binary variables and continuous variables are included in the results of interest. If the statistical heterogeneity is low

($p > 0.1$ or $I^2 < 50\%$), we will use the fixed-effects model to combine the data; but if the statistical heterogeneity is high ($p < 0.1$ or $I^2 > 50\%$), we will use the random-effects model. However, if the heterogeneity level has much significance, a descriptive analysis will be performed.

Subgroup analysis and investigation of heterogeneity

A subgroup analysis will be performed to explore whether the results of the study are different due to the existence of some factors that may affect the prognosis. These factors include the dosage of conventional therapy, course of treatment, intervention measures, etc. If there are enough data, we will conduct subgroup analysis to explore the source of heterogeneity.

Sensitivity analysis

To determine the stability and reliability of the summary results, a sensitivity analysis will be performed. We will remove some studies with high risk of bias, or check processing method of missing data.

Assessment of reporting bias

If more than 10 studies are included, we will make a funnel chart based on the data of the included studies to assess the deviation. When the funnel chart is asymmetrical, indicating that there may be publication bias, we will discuss the source and explain the possible causes of the bias.

Grading the quality of evidence

In order to rate the quality of evidence, understand the actual situation of the evidence rating and analyse the possible problems, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)⁴¹ will be used to evaluate the evidence quality. According to the recommendations of the GRADE working group, the evaluation of the evidence quality of the key outcome indicators can be divided into four levels: high (++++), moderate (++) , low (++) and very low (+).

Amendments

We will show all the amendments with detailed description and rationale in the amendments of this study.

Ethics and dissemination

A meta-analysis is an analysis of previous research data and uses data that existed in studies published, so this review does not require ethical approval. The results of this review will be published in peer-reviewed journals.

DISCUSSION

COVID-19 is a global pandemic. A vaccine is the key to the prevention and control of this disease. Current clinical studies confirmed that the vaccine is safe and effective with few adverse reactions, but the vaccine can only reduce the risk of SARS-CoV-2 infection. There is insufficient clinical evidence to confirm that anti-SARS-CoV-2 drugs (eg, alpha-interferon, lopinavir/ritonavir, ribavirin and chloroquine phosphate) are effective in suppressing the virus, and also

cause a variety of adverse effects such as diarrhoea, elevated transaminases and skin rash.^{42–44} One study consolidated and reviewed the available clinical and preclinical relevant results, showing mixed results in terms of efficacy within the framework of current clinical protocols.⁴⁵ Therefore, it is necessary to find an effective and safe scheme for the treatment of anti-SARS-CoV-2 drug-induced liver injury.

One study explored the possibilities for the treatment of COVID-19 by systematically reviewing evidence on the efficacy and safety of GAP for SARS and Middle East respiratory syndrome (MERS).⁴⁶ Based on the available evidence related to GAP for the treatment of SARS and MERS, Li *et al* postulated that compound glycyrrhizin could be an optional strategy for the treatment of SARS-CoV-2 infections, especially those with complex liver injury.⁴⁷ Recently, a study found that glycyrrhizic acid showed significant inhibition towards various types of viruses and considered glycyrrhizic acid as a potential drug for the treatment of COVID-19.⁴⁷ Therefore, there is a strong case for conducting this review. In this review, we aim to assess the available evidence on the clinical efficacy and safety of GAP for the treatment of anti-SARS-CoV-2 drug-induced liver injury.

The results of this study may have valuable practical implications for patients, healthcare professionals and those working on COVID-19 research. Our findings will be expected to provide validated clinical decision support for COVID-19. It can also be used to guide healthcare professionals in the treatment of COVID-19.

The results of this review will be published in a peer-reviewed journal, and we believe the results will benefit clinicians, patients and guideline makers.

Author affiliations

¹Department of Respiratory Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China

²College of Clinical Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China

³Department of Respiratory Medicine, Chengdu Fifth People's Hospital, Chengdu, People's Republic of China

Contributors XT and WG contributed equally to this work as co-first authors and initially conceived the study. RY and YT performed the preliminary search. XT designed the study and produced the first draft of the study. XT, WG, YN and JC searched for references. MC and CZ revised the manuscript.

Funding This work is supported by Sichuan Science and Technology Program (2020JDRC0114, 2020YFH0164), "100 Talent Plan" Project of Hospital of Chengdu University of Traditional Chinese Medicine (Hospital office [2020] 42), "Xinglin Scholar" Research Promotion Project of Chengdu University of Traditional Chinese Medicine (XGZX2003), National Training Program for Innovative Backbone Talents of Traditional Chinese Medicine (No. 128 [2019] of the State Office of Traditional Chinese Medicine), Sichuan Provincial Administration of Traditional Chinese Medicine Science and Technology Research Special Project (2021MS093) and Chengdu Science and Technology Bureau (2020-YF05-00139-SN).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID ID

Xia Tian <http://orcid.org/0000-0002-4845-3602>

REFERENCES

- 1 WHO. Coronavirus disease (COVID-19) pandemic, 2020. Available: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
- 2 Ryan J. Who declares coronavirus outbreak a pandemic CNET, USA, 2020. Available: <http://125.221.83.226:18/rwt/SCI/https/P75YPLUDN3TYILUDN7XB/news/who-declares-coronavirus-outbreak-a-pandemic>
- 3 Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- 4 Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9.
- 5 Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- 6 Li J-yuan, Cao H-yan, Liu P, *et al.* Glycyrrhizic acid in the treatment of liver diseases: literature review. *Biomed Res Int* 2014;2014:872139–15.
- 7 Tanaka N, Horiuchi A, Yamaura T, *et al.* Efficacy and safety of addition of minor Bloodletting (petit phlebotomy) in hepatitis C virus-infected patients receiving regular glycyrrhizin injections. *J Gastroenterol* 2009;44:577–82.
- 8 Li X, Sun R, Liu R. Natural products in licorice for the therapy of liver diseases: progress and future opportunities. *Pharmacol Res* 2019;144:210–26.
- 9 Bailly C, Vergoten G. Glycyrrhizin: an alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? *Pharmacol Ther* 2020;214:107618.
- 10 Nomura T, Fukushi M, Oda K, *et al.* Effects of traditional kampo drugs and their constituent crude drugs on influenza virus replication *In Vitro*: suppression of viral protein synthesis by glycyrrhizae radix. *Evid Based Complement Alternat Med* 2019;2019:1–12.
- 11 Hoever G, Baltina L, Michaelis M, *et al.* Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. *J Med Chem* 2005;48:1256–9.
- 12 Pompei R, Laconi S, Ingianni A. Antiviral properties of glycyrrhizic acid and its semisynthetic derivatives. *Mini Rev Med Chem* 2009;9:996–1001.
- 13 Xiu-Wei Y. Antiviral effect of glycyrrhizic acid. *Mod chin Med*;22:533–41.
- 14 Ding H, Deng W, Ding L, *et al.* Glycyrrhetic acid and its derivatives as potential alternative medicine to relieve symptoms in nonhospitalized COVID-19 patients. *J Med Virol* 2020;92:2200–4.
- 15 Redeploying plant defences. *Nat Plants* 2020;6:177.
- 16 Yang R, Wang L-qiang, Yuan B-chuan, *et al.* The pharmacological activities of licorice. *Planta Med* 2015;81:1654–69.
- 17 CHEN HS, DU Q H. Potential natural compounds for preventing 2019-nCoV infection.
- 18 Vardhan S, Sahoo SK. In silico ADMET and molecular docking study on searching potential inhibitors from limonoids and triterpenoids for COVID-19. *Comput Biol Med* 2020;124:103936.
- 19 Luo L, Jin Y, Kim I-D, *et al.* Glycyrrhizin attenuates kainic acid-induced neuronal cell death in the mouse hippocampus. *Exp Neurobiol* 2013;22:107–15.
- 20 Imai K, Takagi Y, Iwazaki A, *et al.* Radical scavenging ability of glycyrrhizin. *Free Radicals and Antioxidants* 2013;3:40–2.
- 21 Fu Y, Zhou E, Wei Z, *et al.* Glycyrrhizin inhibits the inflammatory response in mouse mammary epithelial cells and a mouse mastitis model. *Febs J* 2014;281:2543–57.
- 22 Ni Y-F, Kuai J-K, Lu Z-F, *et al.* Glycyrrhizin treatment is associated with attenuation of lipopolysaccharide-induced acute lung injury by inhibiting cyclooxygenase-2 and inducible nitric oxide synthase expression. *J Surg Res* 2011;165:e29–35.
- 23 Wang C-Y, Kao T-C, Lo W-H, *et al.* Glycyrrhizic acid and 18 β -glycyrrhetic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF- κ B through PI3K p110 δ and p110 γ inhibitions. *J Agric Food Chem* 2011;59:7726–33.
- 24 Bhattacharjee S, Bhattacharjee A, Majumder S, *et al.* Glycyrrhizic acid suppresses COX-2-mediated anti-inflammatory responses during *Leishmania donovani* infection. *J Antimicrob Chemother* 2012;67:1905–14.
- 25 Ishida T, Miki I, Tanahashi T, *et al.* Effect of 18 β -glycyrrhetic acid and hydroxypropyl γ -cyclodextrin complex on indomethacin-induced small intestinal injury in mice. *Eur J Pharmacol* 2013;714:125–31.
- 26 Oztanir MN, Ciftci O, Cetin A, *et al.* The beneficial effects of 18 β -glycyrrhetic acid following oxidative and neuronal damage in brain tissue caused by global cerebral ischemia/reperfusion in a C57BL/6 mouse model. *Neuro Sci* 2014;35:1221–8.
- 27 Kim ME, Kim HK, Kim DH, *et al.* 18 β -Glycyrrhetic acid from licorice root impairs dendritic cells maturation and Th1 immune responses. *Immunopharmacol Immunotoxicol* 2013;35:329–35.
- 28 Ma C, Ma Z, Liao X-lin, *et al.* Immunoregulatory effects of glycyrrhizic acid exerts anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4(+)CD25(+)Foxp3+ regulatory T cells in ovalbumin-sensitized mice. *J Ethnopharmacol* 2013;148:755–62.
- 29 Li J, Tu Y, Tong L, *et al.* Immunosuppressive activity on the murine immune responses of glycyrol from *Glycyrrhiza uralensis* via inhibition of calcineurin activity. *Pharm Biol* 2010;48:1177–84.
- 30 Lee JY, Lee J-H, Park JH, *et al.* Liquiritigenin, a licorice flavonoid, helps mice resist disseminated candidiasis due to *Candida albicans* by Th1 immune response, whereas liquiritin, its glycoside form, does not. *Int Immunopharmacol* 2009;9:632–8.
- 31 Fontes LBA, Dos Santos Dias D, de Carvalho LSA, *et al.* Immunomodulatory effects of licochalcone A on experimental autoimmune encephalomyelitis. *J Pharm Pharmacol* 2014;66:886–94.
- 32 Hendricks JM, Hoffman C, Pascual DW, *et al.* 18 β -glycyrrhetic acid delivered orally induces isolated lymphoid follicle maturation at the intestinal mucosa and attenuates rotavirus shedding. *PLoS One* 2012;7:e49491.
- 33 Soufy H, Yassein S, Ahmed AR, *et al.* Antiviral and immune stimulant activities of glycyrrhizin against duck hepatitis virus. *Afr J Tradit Complement Altern Med* 2012;9:389–95.
- 34 Smirnov VS, Zarubaev VV, Anfimov PM, *et al.* [Effect of a combination of glutamyl-tryptophan and glycyrrhizic acid on the course of acute infection caused by influenza (H3H2) virus in mice]. *Vopr Virusol* 2012;57:23–7.
- 35 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- 36 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- 37 Bai Y, Yao L, Wei T, *et al.* Presumed asymptomatic carrier transmission of COVID-19. *JAMA* 2020;323:1406–7.
- 38 Cai Q, Huang D, Yu H, *et al.* COVID-19: abnormal liver function tests. *J Hepatol* 2020;73:566–74.
- 39 Higgins JPT, Savovic' J, Page MJ. Chapter 8: assessing risk of bias in a randomized trial. Cochrane Handbook for systematic reviews of interventions version 6. 0. London: Cochrane, 2019. www.training.cochrane.org/handbook
- 40 Sterne JAC, Hernán MA, McAleenan A. Chapter 25: assessing risk of bias in a non-randomized study. Cochrane Handbook for systematic reviews of interventions version 6.0 (updated July 2019). London: Cochrane, 2019. www.training.cochrane.org/handbook
- 41 Guyatt G, Oxman AD, Akl EA, *et al.* Grade guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
- 42 ZHAO L, ZHAO P. Efficacy of lopinavir/ritonavir and interferon in treatment of COVID-19. *Infect Dis Info*;34:15–19.
- 43 Fu-jing GE. Glycyrrhizic acid: a potential drug against COVID-19. *Acta Pharmaceutica Sinica*;56:1211–6.
- 44 Airong YU. Clinical efficacy and safety of lopinavir/ritonavir combined with other antiviral in the treatment of coronavirus disease 2019 (COVID-19). *Herald of Medicine* 2020;39:628–32.
- 45 Abbaspour Kasgari H, Moradi S, Shabani AM, *et al.* Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Antimicrob Chemother* 2020;75:3373–8.
- 46 Maciorowski D, Idrissi SZE, Gupta Y, *et al.* A review of the preclinical and clinical efficacy of Remdesivir, hydroxychloroquine, and Lopinavir-Ritonavir treatments against COVID-19. *SLAS Discov* 2020;25:1108–22.
- 47 Li H, Hu Y, Tang H, *et al.* The potential of glycyrrhizinate in the management of COVID-19: a systematic review of the efficacy and safety of glycyrrhizin preparations in the treatment of SARS and MERS. *Am J Chin Med* 2020;48:1539–52.