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,2 Chuantao Zhang1

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 I² 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 2019, the virus has rapidly spread around the world. More than 1 billion (1 657 722 430) 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. 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 glycerrhizin, 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. It is an efficient hepatoprotective medication in patients with chronic hepatitis C and more broadly to protect from a variety of hepatic diseases such as chronic viral hepatitis and drug-induced or chemical-induced liver injury. The drug is considered as medicine with a good safety and economical profile. It is increasingly used clinically. With certain pharmacological activities, glycyrrhetinic 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. Glycyrrhizic acid extracts can selectively inhibit the synthesis of single-negative RNA encapsulated viral protein, and some derivatives of glycyrrhizic acid have strong anti-SARS-CoV activity with fewer adverse reactions. Glycyrrhetinic 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. 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.

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. The results of the review will be reported according to the recommendation of PRISMA. 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. Liver injury will be diagnosed through abnormal liver function tests. 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 VX9 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...
Chinese database searching
- CNKI (n=)
- Wanfang (n=)
- VIP (n=)

Foreign database searching
- PubMed (n=)
- Ovidweb (n=)
- Springer Link (n=)
- Web of Science (n=)

Full text from reference list of other studies
- n=

Potential eligible studies on search
- n=

Duplicates excluded (n=)

Identified for title and abstract screening
- n=

- Irrelevant studies excluded (n=)
- Interventions do not meet the inclusion criteria (n=)
- Not COVID-19 patients with liver injury or COVID-19 patients combined with other serious respiratory diseases, cancer, etc. (n=)
- Case report/commentary/literature review (n=)

For in-depth full-text screening
- n=

- Not RCT or single-arm trial (n=)
- Data could not be extracted or full text not available (n=)
- Ending indicators not meet (n=)

Eligible studies
- n=

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

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. 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 I² statistic. When I² 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 I² 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...
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) 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-19.48 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, 2020HH0164), “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 (XGZK2003), 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/wtv/SCIhttps://P75YPLUDSTYULDN7XB/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;323:1016–20.
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. Glycyrrhizinic acid in the treatment of COVID-19: evidence and future opportunities. Pharmaco Res 2019;141:210–26.
7. 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.
8. Nomura T, Fukushima 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 glycyrrhiza radix. Evid Based Complement Alternat Med 2019;2019:1–12.
9. Hoever G, Batina L, Michaelis M, et al. Antiviral activity of glycyrrhizinic acid derivatives against SARS-coronavirus. J Med Chem 2005;48:1256–9.
10. Pompei R, Lacono S, Ingiani A. Antiviral properties of glycyrrhizin acid and its semisynthetic derivatives. Mini Rev Med Chem 2009;9:996–1001.
11. Xu-Wei Y. Antiviral effect of glycyrrhetic acid. Mod Chin Med 22:533–41.
12. Ding H, Deng W, Ding L, et al. Glycyrrhizin acid and its derivatives as potential alternative medicine to relieve symptoms in nonhospitalized COVID-19 patients. J Med Virol 2020;92:2200–4.
13. Redeploying plant defences. Nat Plants 2020;6:177.
14. Yang R, Wang L-qiang, Yuan B-chuan, et al. The pharmacological activities of licorice. Planta Med 2015;81:1645–69.
15. CHEN HS, DU O H. Potential natural compounds for preventing 2019-ncov infection.
16. 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.
17. Luo L, Jin Y, Kim D, et al. Glycyrrhizin attenuates kaicin acid-induced neuronal cell death in the mouse hippocampus. Exp Neurobiol 2013;22:107–15.
18. Imai K, Takagi Y, Iwazaki A, et al. Radical scavenging ability of glycyrrhizin. Free Radicals and Antioxidants 2013;3:40–2.
19. Fu Y, Zhou F, et al. Glycyrrhizin inhibits the inflammatory response in mouse mammary epithelial cells and a mouse mastitis model. Febs J 2014;281:2543–57.
20. 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 IL-6, TNF-α and inducible nitric oxide synthase expression. J Surg Res 2011;165:e29–35.
21. Wang C-Y, Kao T-C, Lo W-H, et al. Glycyrrhizinic acid and 18β-glycyrrhetinic acid modulate lipopolysaccharide-induced inflammatory response by suppressing NFκB through PI3K p110α and p110β inhibitions. J Agric Food Chem 2011;59:7726–33.
22. Bhattacharjee S, Bhattacharjee A, Majumder S, et al. Glycyrrhizin acid suppresses COX-2-mediated anti-inflammatory responses during Lishmania donovani infection. J Antimicrob Chemother 2012;67:1905–14.
23. Ishida T, Miki I, Tanahashi T, et al. Effect of 18β-glycyrrhetinic acid and hydroxypropyl cyclodextrin complex on indomethacin-induced small intestinal injury in mice. Eur J Pharmacol 2013;714:125–31.
24. Oztanir MN, Ciftci Ö, Cetin A, et al. The beneficial effects of 18β-glycyrrhetinic acid following oxidative and neuronal damage in brain tissue caused by central cerebral ischemia/reperfusion in a C57BL/6j mouse model. Neurol Sci 2014;35:1221–8.
25. Kim ME, Kim KH, Kim DH, et al. 18β-Glycyrrhetinic acid from licorice root impairs dendritic cell maturation and Th1 immune responses. Immunopharmacol Immunotoxicol 2013;35:293–309.
26. Ma C, Ma Z, Liao X-lin, et al. Immunoregulatory effects of glycyrinic acid exerts anti-inflammatory 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.
27. Lee J, Yu T, Tong L, et al. Immunosuppressive activity on the murine immune responses of glycyrrhiza uralensis via inhibition of calcineurin activity. Pharm Biol 2010;48:1177–84.
28. 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.
29. Hendricks JM, Hoffman C, Pascual DW, et al. 18β-glycyrrhetic acid delivered orally induces isolated lymphoid follicle maturation at the intestinal mucosa and attenuates rotavirus shedding. PLoS One 2012;7:e49491.
30. Soufy H, Yassein S, Ahmed AR, et al. Antiviral and immune stimulant activities of glycyrrhizin againstduck hepatitis virus. Afr J Tradit Complement Altern Med 2012;9:389–95.
31. Smirnov VS, ZarubaevVV, Anfimov PM, et al. [Effect of a combination of glucomaly-trypophan and glycyrrhizinic acid on the course of acute hepatitis (H3X2 virus) in mice]. Vopr Virusol 2015;50:273–9.
32. Shamess I, 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.
33. 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.
34. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020;323:1406–7.
35. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol 2020;73:566–7.
36. 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
37. Sterne JAC, Hernán MA, McAleenan A, Chapter 25: assessing risk of bias in a nonrandomized study. Cochrane Handbook for systematic reviews of interventions version 6 0 (updated July 2019). London: Cochrane, 2019. www.training.cochrane.org/handbook
38. 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.
39. Zhao L, Zhao P. Efficacy of lopinavir/ritonavir and interferon in treatment of COVID-19. Infect Dis Info;34:15–19.
40. Fu-jing GE. Glycyrrhizinic acid: a potential drug against COVID-19. Acta Pharmacologica Sinica 56:1211–6.
41. Arioglu YU. Clinical efficacy and safety of lopinavir/ritonavir combined with other antiviral in the treatment of coronavirus disease 2019 (COVID-19). J Infect 2020;90:628–32.
42. Abbasapour S, Kasravi H, Moradi A, 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.
43. Maciorowski D, Irensi SZ, Gupta V, 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.
44. Li H, Ju T, Yuan B, 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.