Clinical Evidence on the Use of Chinese Herbal Medicine for Acute Infectious Diseases: An Overview of Systematic Reviews

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Background: Acute infectious diseases constitute the most prevalent public health emergency (PHE) in China. Chinese herbal medicine (CHM) has long been used in the treatment of acute infections, but the overall evidence of its benefit and harm has not been comprehensively and systematically evaluated.

Methods: We searched CBM, CNKI, Wanfang, PubMed, Cochrane Library, embase and preprint platforms to retrieve systematic reviews (SRs) on CHM for acute infectious. Participants with COVID-19, SARS, H1N1, tuberculosis, bacillary dysentery, mumps, herpangina, hand-foot-and-mouth disease (HFMD), and other acute infectious diseases were included. Intervenational group consisting of patients treated with CHM combined with Western medicine or CHM alone. The AMSTAR 2 tool was used to assess the methodological quality of the retrieved studies. Information on interventions, control measures and outcomes of the included studies was extracted, and meta-analyses were qualitatively synthesized.

Abbreviations: AMSTAR 2, A MeaSurement Tool to Assess systematic Reviews 2; CBM, Chinese Biomedical Literature database; CD4, Cluster of differentiation 4; CHM, Chinese herbal medicine; COS, Core Outcome Set; CNKI, China National Knowledge Infrastructure; COVID-19, Coronavirus disease 2019; CONSORT, Consolidated Standards of Reporting Trials; H1N1, Influenza A H1N1 influenza; HFMD, Hand-foot-and-mouth disease; IL-6 level, Interleukin-6 level; IFN-α, Interferon-alpha; MD, Mean difference; OR, Odds ratio; PHE, Public health emergency; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomised controlled trial; RD, Rate difference, Risk difference; RoB, Risk of Bias; RR, Relative risk; SARS, Severe Acute Respiratory Syndrome; SMD, Standardized mean difference; SR, Systematic review; SUCRA, Surface under the cumulative ranking; TCM, Traditional Chinese Medicine.
INTRODUCTION

Public health emergencies (PHEs) are extraordinary events that are determined to constitute public health risks to other states through the international spread of disease and that potentially require a coordinated international response (World Health Organization, 2005). Acute infectious diseases are among the most common PHEs (World Health Organization, 2017). In China, Chinese herbal medicine (CHM) has a long history of treating acute infections such as smallpox, plague, scarlet fever, cholera, typhoid fever, and malaria (Jiang and Wen, 2021). Given the occurrence and epidemics of infectious diseases across different periods, valuable experience has been accumulated in the use of CHM to fight against infectious diseases, which was often documented in classical literature and monographs (Wang W. et al., 2020). Specifically, Yellow Emperor's Internal Classic, released in approximately 5,000 years ago, was the first publication to find that the occurrence of infectious diseases was closely related to climate change. Treatise on Cold Attack, released in the Eastern Han Dynasty, was written after a large-scale epidemic of acute infectious diseases. Doctor Zhongqing Zhang summarized the development of infectious diseases in the book and recorded many classical formulas such as Xiaochaihu Decoction and Maxing Shigan Decoction, that have been used since then. In late Ming China, with the further deepening of the understanding of infectious diseases in traditional Chinese medicine (TCM), Systematic Differentiation of Warm Pathogen disease authored by Doctor Jutong Wu, systematically expounded the general laws of the occurrence, development, evolution and treatment of infectious diseases, in which, Yinqiao Powder and Sangju Drink, was first documented, and continues to be used for acute upper respiratory disease.

Results: A total of 51 SRs and meta-analyses were eligible for this overview, including 19 for COVID-19, 11 for hand-foot-and-mouth disease, 8 for severe acute respiratory syndrome (SARS), 4 for tuberculosis, 3 for mumps, 2 for bacillary dysentery, 2 for H1N1 influenza and 2 for herpangina. Six systematic reviews were of high quality, all of which were on the use of CHM for COVID-19; 24 were of moderate quality; 10 were of low quality; and 11 were of very low quality. CHM appeared to have potential benefits in improving clinical symptoms and signs for most infections with an acceptable safety profile, and the clinical evidence of the benefits of CHM for acute respiratory infections such as COVID-19, SARS and H1N1 seems more sufficient than that for other acute infections.

Conclusion: Overall, CHM, both decoction and Chinese patent medicine, used alone or in combination with conventional medicine may offer potential benefits to relieving symptoms of people with acute respiratory infections. Full reporting of disease typing, staging, and severity, and intervention details is further required for a better evidence translation to the responses for PHE. Future CHM research should focus mainly on the specific aspects of respiratory infections such as its single use for mild infections, and the adjunct administration for severe infections, and individual CHM prescriptions for well-selected outcomes should be prioritized.

Keywords: Chinese herbal medicine, acute infectious diseases, overview of systematic reviews, COVID-19, public health emergency

The clinical effectiveness of some classical CHM prescription has been investigated in rigorous randomised controlled trials (RCTs). For example, a single RCT published in Ann Intern Med in 2011 suggested that a CHM formula combining Maxin Shigan Decoction and Yinqiao Power, alone and in combination with an anti-virus pharmacotherapy oseltamivir, can reduce the time for a fever to resolve in patients with H1N1 influenza infection (Wang et al., 2011). Another outstanding example is artesminin, which was recorded in A Handbook of Prescriptions for Emergencies (Doctor Hong Ge, Eastern Jin Dynasty) for treating malaria. Later, this CHM formula has been developed to artemisinin, and transferred to clinical practice of malaria, for which Tu Youyou won the Nobel Prize (Tu, 2016).

In modern China, CHM continues to be applied to a wide range of emergent infectious diseases, such as severe acute respiratory syndrome (SARS), H1N1 influenza, and Coronavirus disease 2019 (COVID-19). And there are many clinical trials and systematic reviews of CHM that have been published. However, there has been no comprehensive study describing the status of the treatment of acute infectious diseases with CHM in the manner of critical appraisal. Therefore, we conducted this study to provide an overview of systematic reviews (SRs) of the treatment of infectious diseases with CHM that could serve as a reference for decision-making in this field.

METHODS

We followed the guidance of overviews of reviews published by Hunt et al. (2018). We also reported this overview according to
the PRISMA statement (Moher et al., 2009). We have registered this study with the registration DOI: 10.17605/OSF.IO/VZ4S7.

**Inclusion and Exclusion Criteria**

**Study Types Included in This Overview**

Systematic reviews (SRs) and meta-analyses, language limited to Chinese and English.

**Participants**

Participants with COVID-19, SARS, H1N1, tuberculosis, bacillary dysentery, mumps, herpangina, hand-foot-and-mouth disease (HFMD), and other acute infectious diseases were included, as identified according to the current list of public PHEs in China (Liu et al., 2019).

**Interventions**

Interventional group consisting of patients treated with CHM combined with Western medicine or CHM alone, where CHM interventions included proprietary Chinese medicine and traditional Chinese medicine decoction. There was no requirement for what should be included in the control group.

**Outcomes**

Outcomes including effectiveness related outcomes which evaluated by the investigator or reported by patients, laboratory tests and radiological imaging, and safety related outcomes such as adverse events, adverse reactions, and toxic scale. The primary outcomes included effectiveness, mortality and adverse events, and secondary outcomes included symptom score, length of stay, laboratory tests and radiological imaging, etc.

**Exclusion Criteria**

Studies were excluded from the search when they were conference abstracts, duplicate publications, unpublished data, and those without full details of a SR.

**Literature Search and Screening**

We searched the Chinese Biomedical Literature database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang database, PubMed, Cochrane Library, embase, medRxiv, bioRxiv, China Association of Chinese Medicine, China Association for Acupuncture and Moxibustion, Chinese Medical Journal Network, and Chinese Medicine Journal Network to retrieve relevant systematic reviews/meta-analyses, and the search time was from the date of database creation to 30 October 2020. Before published of this article, we updated the search time to 31 March 2021. For literature screening, two authors read the title and abstract, and after downloading the full text, it was read and used to further screen the articles, and the results were submitted to a third author for confirmation and verification. The search strategy was specified in Supplementary 1.

**Methodological Quality and Level of Evidence Assessment**

The methodological quality of the included studies was evaluated independently by two authors using A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) (Shea et al., 2017), and a third author assisted in the judgement in cases of disagreement. The methodological quality of AMSTAR2 for systematic review is divided into 16 entries, among which item 2, item 4, item 7, item 9, item 10, item 11, item 13 and item 15 are recommended critical items for determine methodological quality. Considering the specificity of TCM research, we made the following adjustments to the key items. Since some systematic reviews were published before the establishment of the registration platform and the registration platform does not have a Chinese registration language, it was difficult to obtain the protocols of these previous Chinese systematic reviews, so we did not include item 2 as a key entry. Chinese medicine research is mainly published in Chinese language, and most Chinese journal submission systems do not support the presentation of a list of excluded studies, so item 7 was not considered a key entry.

The final evaluation results were classified as 1) “high quality” when there was no or one non-critical weakness, 2) “medium quality” when there was more than one non-critical weakness, 3) “low quality” when there was one critical flaw with or without non-critical weaknesses, or 4) “very low quality” when there was more than one critical flaw with or without non-critical weaknesses.

We also evaluated the level of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for primary outcomes.

**Data Extraction and Data-Analysis**

Two authors independently collected the data on publication information, demographic characteristics, details of the interventions and control measures, outcomes, and statistical results, which were finally checked and confirmed by a third authors. For data analysis, a qualitative integration of the study results was performed for SRs evaluated as having moderate-high quality according to AMSTAR 2.

**RESULTS**

**Results of the Searching and Screening**

A total of 46,138 relevant records were obtained from the initial search and 6,468 records were identified from updated search, and after screening, 51 systematic reviews (Liu and Dong, 2021; Liu et al., 2004; Zhang et al., 2004; Zhao et al., 2004; Hao, 2005; Hao et al., 2005; Liu et al., 2005; Chen et al., 2007; Guo et al., 2010; Liu et al., 2012; Ding et al., 2013; Lu et al., 2013; Wang et al., 2013; Xiong et al., 2013; Zhang et al., 2014; Zhang and Wei, 2014; Zhao, 2014; Zhao et al., 2014; Wu et al., 2015; Han, 2016; Li et al., 2016; Liu et al., 2016; Zhang, 2016; Wang et al., 2017; Yan and Gao, 2017; Yue et al., 2017; Jin et al., 2018; Xiong et al., 2019; Ang et al., 2020; Yang et al., 2020a; Yu et al., 2020a; Yang et al., 2020b; Yu et al., 2020b; Fan et al., 2020; Gao et al., 2020; He, 2020; Jin et al., 2020; Li et al., 2020; Liu et al., 2020; Pang et al., 2020; Qi et al., 2020; Wang et al., 2020; Sun et al., 2020; Wu et al., 2020; Xiong et al., 2020; Yan et al., 2020; Zeng et al., 2020; Zhou et al., 2021a; Zhou et al., 2021b;
Luo et al., 2021; Ouyang et al., 2021) were finally included. Among them, 33 (Liu and Dong, 2021; Zhao et al., 2004; Hao, 2005; Hao et al., 2005; Liu et al., 2005; Ding et al., 2013; Lu et al., 2013; Wang et al., 2013; Xiong et al., 2013; Zhang et al., 2014; Zhang and Wei, 2014; Zhao, 2014; Han, 2016; Liu et al., 2016; Zhang, 2016; Wang et al., 2017; Xiong et al., 2019; Yang M. et al., 2020; Yu et al., 2020; Yang Z. et al., 2020; Gao et al., 2020; He, 2020; Qi et al., 2020; Wang S. et al., 2020; Wu et al., 2020; Zhou L. P. et al., 2021; Zhou F. et al., 2021; Luo et al., 2021) were written in Chinese, and 18 (Liu et al., 2004; Zhang et al., 2004; Chen et al., 2007; Liu et al., 2012; Zhao et al., 2014; Wu et al., 2015; Li et al., 2016; Ang et al., 2020; Fan et al., 2020; Jin et al., 2020; Liu et al., 2020; Pang et al., 2020; Sun et al., 2020; Xiong et al., 2020; Yan et al., 2020; Zeng et al., 2020; Zhou L. P. et al., 2021; Luo et al., 2021) were written in English. The literature screening process and results are shown in Figure 1.

The excluded references are stated in Supplementary 2. The ingredients of the formulas are specified in Supplementary 3.

Basic Characteristics of the Included Literature

The disease with the largest proportion in the of systematic reviews was COVID-19, with 19 articles (Liu and Dong, 2021; Ang et al., 2020; Yang M. et al., 2020; Fan et al., 2020; Gao et al., 2020; Jin et al., 2020; Liu et al., 2020; Pang et al., 2020; Qi et al., 2020; Wang S. et al., 2020; Sun et al., 2020; Wu et al., 2020; Xiong et al., 2020; Zeng et al., 2020; Zhou L. P. et al., 2021; Zhou F. et al., 2021; Luo et al., 2021; Ouyang et al., 2021), followed by 11 articles on HFMD (Ding et al., 2013; Wang et al., 2013; Xiong et al., 2013; Zhang et al., 2014; Zhang and Wei, 2014; Xiong et al., 2019; Yu et al., 2020; Yang Z. et al., 2020; Yu et al., 2020b; He, 2020; Yan...
| Study            | Disease type | Disease stage | Disease classification | Number of included studies | Intervention types | Traditional Chinese medicine treatment                                                                 | Outcomes | Frequency of the formulas | Adverse event |
|------------------|--------------|---------------|------------------------|----------------------------|--------------------|----------------------------------------------------------------------------------------------------------------|----------|--------------------------|---------------|
| Fan et al. (2020)| COVID-19     | NS            | NS                     | 7                          | Traditional Chinese + H2: H44 medicine + western medicine conventional treatment VS Western medicine treatment | Qingfei touxiefuzheng decoction, Jinhuaqinggan granule, Qingfeipaidu decoction, Toujie qingwen granule, Jiaxiedayuan granule, Shengfutang decoction, Maxingxuanfeijiedu Decoction | (13) (44) (19) | | NS                        |
| Pang et al. (2020)| COVID-19     | NS            | NS                     | 11                         | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Qingfei touxiefuzheng decoction, Jinhuaqinggan granule, Qingfeipaidu decoction, Maxingxuanfeijiedu Decoction | (21) (29) (44) (31) (56) (19) | | NS                        |
| Jin et al. (2020)| COVID-19     | NS            | NS                     | 5                          | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Qingfei touxiefuzheng decoction, Lianhuaqinggan granule, Lianhuaqingke granule, Xuebijing injection | (13) | | NS                        |
| Luo et al. (2021)| COVID-19     | NS            | NS                     | RCT:6, CCT:13               | Traditional Chinese medicine + western medicine conventional treatment | Lianhuaqingwen granule, Shufengjiu capsule, Toujie qingwen granule, Reyanning mixture, Jinhuaqinggan granule, Jiaxiedayuan decoction | (10) (18) (45) (44) (21) (19) | | NS                        |
| Sun et al. (2022)| COVID-19     | NS            | NS                     | 7                          | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine conventional treatment | Shufengjiu capsule, Toujie qingwen granule, Reyanning mixture, Qingfei touxiefuzheng formula, Feidian No.1 formula, Feidian No.2 formula, Jinhuaqinggan granule | (13) (19) (29) (18) (25) | | NS                        |
| Zeng et al. (2020)| COVID-19     | NS            | NS                     | 2                          | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine conventional treatment | Lianhuaqingwen granule | (6) (10) (11) (12) (13) (14) (15) (16) (17) (18) (22) | | NS                        |
| Wang S. et al. (2020)| COVID-19     | NS            | NS                     | 7                          | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine conventional treatment | Lianhuaqingwen granule | (12) (62) (16) (26) | | NS                        |
| Yang M. et al. (2020)| COVID-19     | Ordinary type | RCT:2, NRCT:1           | Traditional Chinese medicine + western medicine conventional | Lianhuaqingwen granule | (3) (25) (19) (36) (48) | | NS                        |

(Continued on following page)
| Study                          | Disease type | Disease stage | Disease classification | Number of included studies | Intervention types                                                                                   | Traditional Chinese medicine treatment                                                                 | Outcomes                                                                                     | Frequency of the formulas | Adverse event |
|-------------------------------|--------------|---------------|------------------------|----------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------|--------------|
| Ang et al. (2020)             | COVID-19     | NS            | NS                     | 7                          | treatment vs Western medicine conventional treatment                                               | Traditional Chinese medicine + Western medicine treatment                                               | Lianhuaqingwen granule Shufengjiedu capsule Touxiuewen granule Jinhuayinggan granule         | (1) (5) (9) (10) (13) (18) (26) (31) (41) (45) | Lianhua Qingke granules, 1 packet for 3 times daily for 14 days; Shufeng Jiedu capsules, 4 capsules for 3 times daily for 2 weeks; Jinhuas Ginggan granules, 2 packets for 3 times daily for 5 days; Touxiu Wen granules, 1 packet per time for 2 times daily for 10-15 days | Y |
| Xiong et al. (2020)           | COVID-19     | NS            | Minor illnesses, major illnesses | 18                         | Treatment vs Western medicine conventional treatment                                               | Traditional Chinese medicine + Western medicine treatment + Traditional Chinese medicine placebo           | Maxingshi gan decoction/ Chalingpingwei decoction/ Haoaqingyan decoction/ Huoxiangzhi decoction/ Modified Buzhongyiqi decoction/Pneumonia No. 1 formula/Powerful Pneumonia No. 1 formula/Pneumonia No. 2 formula/Qingfei toujue fuzheng decoction/formula/Yiyi yu qian formula/Yiyi yu qian formula/Qiwei decoction/ Touxiu Wen granules/Shufeng Jiedu capsules/Lianhuaqingwen granules and capsule/Xuanfu si rou mixture/Shuanghuanglian oral liquis/Yu ping feng granules/Ganlu xiao zhu decoction/Luoxiangzhi yingyuan liquid/ Reyanning mixture/Jinhuayinggan granules/Kexiajing injection/Tianningjection/Shengmai injection/Shenju injection/Lianhuaqingke granules/Maxingxiangfei decoction | (2) (11) (29) (41) (44) (45) (21) (33) (13) (27) (18) | CHM (1dose/d, 10 days); Qingfei Touxiu Fuzheng decoction (1dose/d, 10 days); Touxiu Wen granules (1dose/d, 10 days); Jinhuas Ginggan granules (10 g, tid, 5 days); Reyanning mixture (10-20 ml, bid-q6 h, 7 days); Shufeng Jiedu capsules (2.08g, tid, 10-14 days); Jinhuas Ginggan granules (1 bag, tid, 14 days); Lianhua Qingwen capsules (1.4 g, tid, 14 days) | Y |
| Liu et al. (2020)             | COVID-19     | NS            | NS                     | RCT:4 NRCT:7                | Traditional Chinese medicine + Western medicine conventional treatment                              | Lianhuaqingwen granule Shufengjiedu capsule Touxiuewen granule Jinhuayinggan granule                  | Lianhuaqingwen granule maxingxiangfei decoction                                          | (12) (19) (62) (54) (16) (64) | Diammonium glycyrrhizinate enteric coated capsules (150 mg, tid); Qingfei toujue fuzhengfang (150 ml, bid); Shufeng Jiedu Capsule (2.08 g, tid); Lianhua Qingwen granules (6 g, tid); Reyanning mixture (10-20 ml, bid); Tongxiquen granule formula (150 ml, bid); Jinhuas Ginggan granules (10 g, tid) | Y |
| Gao et al. (2020)             | COVID-19     | NS            | NS                     | RCT:4 NRCT:8                | Treatment vs Western medicine conventional treatment                                               | Lianhuaqingwen granule Shufengjiedu capsule Touxiuewen granule Jinhuayinggan granule                  | Lianhuaqingwen granule maxingxiangfei decoction                                          | (10) (61) (5) (18) (11) (12) (29) (45) | NS | NS |
| Liu et al. (2020)             | COVID-19     | Medical Observation Period | Minor illness, general type | RCT:1 NRCT:8                | Traditional Chinese medicine + Western medicine conventional treatment                              | Lianhuaqingwen granule Shufengjiedu capsule Touxiuewen granule Jinhuayinggan granule                  | Lianhuaqingwen granule maxingxiangfei decoction                                          | (12) (25) (28) (29) (41) | NS | NS |

(Continued on following page)
| Study            | Disease type | Disease stage | Disease classification                              | Number of included studies | Intervention types                                                                 | Traditional Chinese medicine treatment | Outcomes | Frequency of the formulas | Adverse event |
|------------------|--------------|---------------|---------------------------------------------------|----------------------------|------------------------------------------------------------------------------------|----------------------------------------|----------|---------------------------|---------------|
| Qi et al. (2020) | COVID-19     | NS            | Ordinary type                                     | RCT:2 NRCT:3               | Traditional Chinese medicine + western medicine conventional treatment             | Lianhuaqingwen granule                | (10) (36) (5) (6) (11) (12) (36) (44) (19) | Lianhuaqingwen granule: 1 bag per time (6 g), tid | NS            |
| Wu et al. (2020) | COVID-19     | NS            | Minor/general/severe/critical illnesses           | RCT:1 NRCT:7               | Traditional Chinese medicine + western medicine conventional treatment             | Lianhuaqingwen granule                | (12) (13) (18) (26) (27) (29) (25)         | NS                  | NS            |
| Zhou L.P. et al. (2021) | COVID-19 | NS            | NS                                                | 10                         | Traditional Chinese medicine + western medicine conventional treatment             | Jinhua Qinggan granule               | (5) (12) (13) (18) (19)                   | Jinhua Qinggan granule: 2 times a day, once 10 g; Qingfei Touxie Fuzheng recipe (one dose a day, 2 times a day, in the morning and in the evening); Toujie Quwen granules (2 times a day); Lianhua Qingke granule (once 1 bag, 3 times a day); Fexyanyihao Chinese Medicine granules (one dose a day, 2 times a day); Jinyinhua oral liquid (once 60 ml, 3 times a day); Diammonium glycyrrhizinate entericoated capsule (once 150 mg, 3 times a day); Lianhua Qingwen capsule (once 6 g, 3 times a day); Lianhua Qingwen capsule (4 capsules thrice daily) | Y             |
| Liu et al. (2020) | COVID-19     | Medical Observation Period | Minor illness, general type                        | RCT:1 NRCT:6               | Traditional Chinese medicine + western medicine conventional treatment             | Shufeng jiedu granule                | (5) (6) (10) (11) (12) (18) (44)          | NS                  | Y             |
| Zhou F. et al. (2021) | COVID-19 | NS            | Minor illness, general type                        | 6                          | Traditional Chinese medicine + western medicine conventional treatment             | Xuanfei Baidu decoction               | (5) (10) (11) (13) (18) (19) (21) (27) (62) | CHM: 1 dose of 300 ml/day, 100ml/time; CHM: 1 dose/day, 250 ml/time, bid; CHM: 19.4 g, bid; CHM: 200 ml/bag/time, bid | Y             |
| Ouyang et al. (2021) | COVID-19 | NS            | Minor illness, general type                        | RCT:6 NRCT:4               | Traditional Chinese medicine + western medicine conventional treatment             | Reyanning mixture                    | (5) (6) (10) (11) (12) (18) (19) (24) (29) (64) | NA                  | Y             |
| Study | Disease type | Disease stage | Disease classification | Number of included studies | Intervention types | Traditional Chinese medicine treatment | Outcomes | Frequency of the formulas | Adverse event |
|-------|--------------|---------------|------------------------|----------------------------|-------------------|-----------------------------------------|----------|--------------------------|---------------|
| Chen et al. (2007) | SARS | NS | NS | RCT:15; NRCT:9 | Traditional Chinese medicine + Placebo | NS | (1) (2) (5) (9) (12) | NS | NS |
| Liu et al. (2004) | SARS | NS | NS | RCT:8; NRCT:8 | Traditional Chinese medicine + Western medicine conventional treatment | Feidian No.1/2/3 formula Feidian No.4 formula Guoyao No.2/3 formula Yiayang formula/Bufeiqingsha formula/ Yangyinqingre formula Qiankunning capsule Chuanhuining injection, Shenmai injection, hufeiqingsha decoction/ Jieduxihong capsule/Zhuoysansan capsule | (2) (3) (4) (6) (8) (9) (11) (14) | NS | TCM: decoction, one dosage daily, for treatment of 21 days; Qiankunning: 6 tablets/time, 4 times daily, for 14 days |
| Liu et al. (2012) | SARS | NS | NS | 12 | Traditional Chinese medicine + Western medicine conventional treatment | Feidian No.1/2 formula Feidian No.1 formula Hufeiqingsha decoction Jieduxihong capsule Zhuoysansan capsule Qingkailing sprs Feidian No.2/3/4 formula | (2) (3) (5) (6) (7) (8) (9) (13) (14) (15) | NS | NS |
| Hao et al. (2005) | SARS | NS | NS | RCT:5; CCT:6 | Traditional Chinese medicine + Western medicine conventional treatment | Feidian No.1/2/3/4 formula Guoyao No.2/3/4 formula Chuanhuino injection/Shennai injection/hufeiqingsha decoction Shufengxuanfei formula Xingnaojing injection + Shenmai injection HOUTTUYNIA CORDATA (Chinese pinyin: yuxingcao) injection + Qingkailing injection | (12) (27) (83) | NS | NS |
| Hao et al. (2005) | SARS | NS | NS | RCT:5; CCT:4 | Traditional Chinese medicine + Western medicine conventional treatment | NS | (27) | NS | NS |
| Liu 2005 | SARS | NS | NS | RCT:8; NRCT:8 | Traditional Chinese medicine + Western medicine conventional treatment | Yiayang formula | (27) (12) (18) (20) (19) (63) | NS | Yiayang formula: 1 dose/d, 3 weeks; CHM 1 dose/d, 12 days; (Continued on following page) |
| Study          | Disease type | Disease stage | Disease classification | Number of included studies | Intervention types                                                                 | Traditional Chinese medicine treatment                                                                 | Outcomes               | Frequency of the formulas | Adverse event |
|---------------|--------------|---------------|------------------------|----------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------|--------------------------|--------------|
| Zhao et al. (2004) | SARS         | NS            | NS                     | RCT:5 NRCT:4               | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Chuanyuqing injection/Shenmai injection/Hufeiqingsha decoction/ Jieduzhitong capsule Qiankunning capsule / Guoyao No.2/3/4 formula | NS                     | (27) (4) (12) (18) (5) (23) (19) (63) | NS           |
| Zhao et al. (2004) | H1N1         | NS            | NS                     | 5                         | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Shenma injection/Hufeiqingsha decoction/Neiyezisui capsule/Qinghualing spray Guoyao No.2/3/4 formula | NS                     | (2) (3) (4) (5) (6)                          | NS           |
| Li et al. (2016)  | H1N1         | NS            | NS                     | 30                        | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Fanggan decoction Lianhuaqingwen capsule Yinjiao decoction Maxingshigan decoction RADIX SATIS (Chinese pinyin: Banlangen) granule Qingkailing injection + Tanreqing injection | NS                     | (1) (8) (7)                             | NS           |
| Jin et al. (2018) | Tuberculosis | NS            | NS                     | 45                        | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Traditional Chinese medicine + western medicine conventional treatment | NS                     | (29) (22) (41) (15) (19)                 | NS           |
| Yan and Gao (2017) | Tuberculosis | NS            | NS                     | 16                        | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine conventional treatment | Tuberculous pill | NS                     | (29) (22) (81)                           | NS           |
| Yue et al. (2017) | Tuberculosis | NS            | NS                     | 20                        | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine conventional treatment | Traditional Chinese medicine + western medicine conventional treatment | NS                     | (39) (18) (15) (61) (19)                 | NS           |
| Guo et al. (2013) | Tuberculosis | NS            | NS                     | 6                         | Traditional Chinese medicine + western medicine conventional treatment | Traditional Chinese medicine + western medicine conventional treatment | NS                     | (29) (39) (22)                           | NS           |
TABLE 1 | (Continued) Basic characteristics of included literature.

| Study | Disease type | Disease stage | Disease classification | Number of included studies | Intervention types | Traditional Chinese medicine treatment | Outcomes | Frequency of the formulas | Adverse event |
|-------|--------------|---------------|------------------------|---------------------------|--------------------|----------------------------------------|-----------|-------------------------|--------------|
|       |              |               |                        |                           |                    | Modified Huangqijianzhong decoction     |           |                         |              |
|       |              |               |                        |                           |                    | Baozhen decoction                      |           |                         |              |
|       |              |               |                        |                           |                    | Self-made decoction                    |           |                         |              |
| Wang et al. (2017) | Bacterial dysentery | Acute phase | NS | 12 | Traditional Chinese medicine + Western medicine conventional treatment vs Western medicine conventional treatment  | (10) (12) (40) (19) | NS |                         | Y            |
|       |              |               |                        |                           |                    | Modified Bai touweng decoction         |           |                         |              |
|       |              |               |                        |                           |                    | Shizi decoction                        |           |                         |              |
|       |              |               |                        |                           |                    | Modified Da chai hu decoction          |           |                         |              |
|       |              |               |                        |                           |                    | Modified Shaoyao decoction            |           |                         |              |
|       |              |               |                        |                           |                    | Shizi formula                          |           |                         |              |
|       |              |               |                        |                           |                    | Shao yuan decoction+Bai touweng decoction |           |                         |              |
|       |              |               |                        |                           |                    | Dima mixture                           |           |                         |              |
|       |              |               |                        |                           |                    | Gan cao cao lan porridge               |           |                         |              |
|       |              |               |                        |                           |                    | Self-made decoction                    |           |                         |              |
| Han (2016) | Bacterial dysentery | Acute phase | Minor, General, Major | 28 | Traditional Chinese medicine + Western medicine conventional treatment vs Western medicine conventional treatment | (10) (50) | NS |                         | NS          |
| Wu et al. (2015) | Mumps | NS | NS | 11 | Traditional Chinese medicine + Western medicine conventional treatment vs Western medicine conventional treatment | (4) (12) (10) (9) | Potassium Dehydroandrographolide Succinate Injection: 5–30 mg/(kg.d) | Y            |
|       |              |               |                        |                           |                    | ANDROGRAPHIS PANICULATA (Chinese pinyin: chuanxianlian) injection |           |                         |              |
| Zhang (2016) | Mumps | NS | NS | 7 | Traditional Chinese medicine + Western medicine conventional treatment | (10) | NS |                         | NS          |
| Zhao (2014) | Mumps | NS | NS | 33 | Traditional Chinese medicine + Western medicine conventional treatment | (10) | NS |                         | Y            |

(Continued on following page)
| Study | Disease type | Disease stage | Disease classification | Number of included studies | Intervention types | Traditional Chinese medicine treatment | Outcomes | Frequency of the formulas | Adverse event |
|-------|--------------|---------------|------------------------|---------------------------|-------------------|----------------------------------------|----------|--------------------------|-------------|
| Lu et al. (2013) | Mumps | Acute phase | NS | 12 | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Compound oral mixture of Folium Isatidis (Chinese pinyin: Daqingye) and external application of Cactus Xiangfanghuoming decocion + Zijin Cube with vinegar External application of Zhitongyanyan ointment + Conventional treatment Shuanghuanglian injection Self-made decoction External application of Wanyin ointment External application of Qushailing ointment | Pudilanxiaoyan oral liquid | (10) (19) (44) | NS | Y |
| Liu et al. (2016) | Herpangina | NS | NS | 17 | Traditional Chinese medicine + western medicine conventional treatment VS Western medicine treatment | Modified Yinqiao decoction Qingleyan decoction Modified Xieinduixi decoction Self-made Qingyaoxuehuang decoction Mixture of Yinqiao decoction Self-made Qingyaoxuehuang decoction | (10) (19) (12) | NS | NS |
| Zhang et al. (2014) | Hand foot mouth disease | NS | Ordinary type | 21 | Traditional Chinese medicine + western medicine conventional treatment/Traditional Chinese medicine vs Western medicine treatment | Chaohuang granule Modified Gegenpiaoyan decoction Modified Jiduixi decoction Jieduiqing decoction Jinlian mixture Kangyuixian + Qingyaoxuehuang oral liquid Pudilanxiaoyan oral liquid + Yanhping injection | (13) (12) (90) | NS | NS |

(Continued on following page)
| Study          | Disease type                  | Disease stage | Disease classification       | Number of included studies | Intervention types                                                                 | Traditional Chinese medicine treatment                                                                 | Outcomes | Frequency of the formulas | Adverse event |
|---------------|-------------------------------|---------------|------------------------------|---------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------|--------------------------|----------------|
| Zhang et al. (2014) | Hand foot mouth disease     | Normal type, heavy duty | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | 6                          | Xyayping injection                                                               |                                                                                                  | (10) (14) | NS                       | NS             |
| Xiong et al. (2013)  | Hand foot mouth disease    | NS            | NS                           | 24                        | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Xyayping injection                                                               | (10) (14) (19) (12) | Xyayping injection: 1–10 mg/kg, iv, qd | Y              |
| Wang et al. (2013)   | Hand foot mouth disease     | NS            | NS                           | 11                        | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Xyayping injection                                                               | (12) (14) (19) (23) | NS                       | Y              |
| Ding et al. (2013)   | Hand foot mouth disease     | NS            | NS                           | 17                        | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Reduning injection/Tanreqing injection/Xyayping injection/Yanhuning injection         | (10) (12) (14) (19) (23) | Reduning injection: 0.3–15 ml/kg, qd; Tanreqing injection: 0.3–0.5 ml/kg, qd; Xyayping injection: 0.2–10 ml/kg, qd; Yanhuning injection: 5–10 ml/kg, qd | Y              |
| Yu et al. (2020a)    | Hand foot mouth disease     | NS            | NS                           | 24                        | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Lanqin oral liquid                                                              | (10) (12) (14) (19) (23) | NS                       | Y              |
| Yang Z. et al. (2020) | Hand foot mouth disease     | NS            | NS                           | 5                         | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Jinlianqingre effervescent tablets/Jinzhen oral liquid/Kangbingdu oral liquid/Reduning injection/Xyayping injection | (12) (26) (14) (19) | NS                       | Y              |
| Yan et al. (2020)    | Hand foot mouth disease     | NS            | NS                           | 11                        | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Tanreqing injection/Xyayping injection/Reduning Injection                          | (10) (12) (28) (14) (19) | Tanreqing injection: 0.3–0.5 ml/kg, 5–10 days; Xyayping injection: 5–10 mg/kg, 3–10 days; Reduning Injection: 1–5 years, 0.5 ml/kg; 6–10 years, 10 ml; 11–13 years 15ml, 3–10 d | Y              |
| Xiong et al. (2019)  | Hand foot mouth disease     | NS            | NS                           | 14                        | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Xyayping injection + Chinese patent medicine (Lanjin oral liquid/Kangfu oral liquid/Pudilan oral liquid/Jinhoujian spray/Tanreqing injection) | (10) (12) (14) (19) (37) | NS                       | NS             |
| He (2020)            | Hand foot mouth disease     | NS            | NS                           | 5                         | Traditional Chinese medicine + western medicine conventional treatment vs Western medicine conventional treatment | Xyayping injection + Chinese patent medicine (Lanjin oral liquid/Kangfu oral liquid/Pudilan oral liquid/Jinhoujian spray/Tanreqing injection) | (10) (12) (14) (19) (37) | NS                       | NS             |
### TABLE 1 (Continued) Basic characteristics of included literature.

| Study     | Disease type          | Disease stage | Disease classification | Number of included studies | Intervention types                                                                 | Traditional Chinese medicine treatment | Outcomes                                                                 | Frequency of the formulas | Adverse event |
|-----------|-----------------------|---------------|------------------------|----------------------------|----------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------|---------------------------|----------------|
| Yu et al. (2020b) | Hand foot mouth disease | NS            | NS                     | 26                         | Treatment VS Western medicine treatment                                           | Langin oral liquid                     | (10) (12) (14) (19) (30) (57)                                          | Fuganlin oral liquid: 10 ml, tid; Huangzhihua oral liquid: 10 ml, tid or 5–20 ml, bid; Kangbingdu oral liquid: 10 ml tid; Huangqing oral liquid: 10 ml, tid; Pandian oral liquid: 5–10 ml, tid | Y  |

Outcomes:
1. Anxiety relief
2. C reaction protein levels
3. Chest tightness disappearance rate
4. Complications due to hormone use (secondary bleeding, infection, diabetes, hypertension)
5. Cough improvement (cough symptom score, cough disappearance time, cough disappearance rate, number of cough disappearance cases, difference in points before and after cough, cough relief rate, cough duration)
6. Cough sputum disappearance rate
7. D-di-concentration level
8. Diarrhea improvement (diarrhoea disappearance rate, diarrhea remission rate)
9. Discharge rate
10. Efficiency
11. Fatigue improvement (weak disappearance time, fatigue disappearance rate, fatigue improvement rate, fatigue improvement case count, fatigue duration, fatigue symptom integration)
12. Fever mitigation (number of cases of fever, fever symptom score, fever disappearance rate, fever time, fever control rate)
13. Healing rate
14. Healing time for rashes or mouth ulcers
15. Hollow improvement (shrink rate, close rate)
16. IFN-α
17. IL-6 level
18. Improvement of pulmonary CT (rate of improvement of CT in the lungs, effective rate of improvement in CT in the lungs, absorption rate of pneumonia, improvement rate of imagery of the lungs, lesions absorption)
19. Incidence of adverse reactions (liver damage, diarrhoea, nausea and vomiting...)
20. Incidence of secondary fungal infections following the use of hormones
21. Length of stay
22. Lesions absorption rate
23. Lung immersion absorption (lung immersion absorption time, lung immersion absorption score, number of cases of lung immersion absorption, pulmonary immersion absorption rate)
24. Lymphocyte improvement (number of lymphocytes, lymphocyte toxicity, percentage of lymphocytes)
25. Major symptoms and inflammatory markers integral
26. Mild to severe (severe conversion rate, number of cases of severe illness) (hand, foot and mouth disease)
27. Mortality
28. Nausea disappearance rate
29. Nucleic acid to negative
30. Oral ulcers are cured
31. Oxygenation index
32. Percentage of neutrophils
33. Points for dry throat symptoms
34. Progress rate of hand, foot and mouth disease
35. Quality of life
36. Respiratory Difficulty Disappearance Rate
37. Resume feeding time
38. Secondary infection rate
39. Sputum bacteria turn negative
40. Stop the time
41. TCM Certificate Improvement
42. The duration of the sore throat
43. The duration of the virus shedding

(Continued on following page)
| Study | Disease type | Disease stage | Disease classification | Traditional Chinese medicine treatment | Frequency of the outcomes | Adverse event |
|-------|--------------|---------------|------------------------|----------------------------------------|--------------------------|---------------|
|       |              |               |                        | CHM decoction (11, 21.57%)             |                          |               |
|       |              |               |                        | proprietary CHM drugs (11, 21.57%)    |                          |               |
|       |              |               |                        | Western medicine (Lu et al., 2013; Zhang and Wei, 2014; Yu et al., 2020b) and 6 SRs (11.76%) including studies with CHM alone (Zhao et al., 2014; Liu et al., 2016; Zhang, 2016; Xiong et al., 2019). |                          |               |
|       |              |               |                        | Ding et al., 2013; Yu et al., 2020a; Yang et al., 2020b), with two SRs (3.92%) including studies with CHM alone (Zhao et al., 2014; Yu et al., 2020b) and 6 SRs (11.76%) including studies investigating CHM alone and CHM in combination with Western medicine (Lu et al., 2013; Zhang and Wei, 2014; Zhao, 2014; Lu et al., 2016; Zhang and Wei, 2014; Zhang et al., 2014; Xiong et al., 2013; Wang et al., 2013; Ding et al., 2013; Yu et al., 2020a; Yang et al., 2020b). |                          |               |
|       |              |               |                        | The most frequently studied herbal preparations were proprietary CHM drugs (n = 37, 80.43%), followed by CHM decoction (n = 20.43%). |                          |               |
|       |              |               |                        | In terms of pre-defined outcomes, the most used for all diseases were the rate of improvement of clinical symptoms or signs such as fever and cough (n = 47, 92.16%), followed by overall effectiveness (n = 25, 49.02%), adverse events (n = 16, 31.37%), mortality (n = 11, 21.57%), and the proportion of lung X-ray shadows absorbed (n = 11, 21.57%). |                          |               |
|       |              |               |                        | Detailed data are shown in Table 1. |                          |               |
|       |              |               |                        | Eighteen systematic reviews on COVID-19 that reported on specific drugs showed that the most used proprietary CHM drugs were Lianhua Qingwen Granule/Capsule (n = 14, 77.78%) and Shufeng Jiedu Capsule (n = 10, 55.56%), and the most used CHM decoction were Qingfei Touxi Fuzheng Decoction (n = 7, 38.89%). Six studies that reported specific drugs for SARS showed that the most used prescription was SARS No.2 formula (n = 6, 75.00%), SARS No.1 formula (n = 5, 62.50%), SARS No.3 formula (n = 5, 62.50%) and SARS No.4 formula (n = 5, 62.50%). The two H1N1 SRs used Lianhua Qingwen Capsule (n = 2, 100.00%). The three tuberculosis studies that reported specific drugs showed common use of Astragalus Membranaceus (Chinese pinyin: Huangqi) preparations (n = 2). One SR for bacillary dysentery reported the use of CHM decoctions such as Baiouweng Decoction, Shaoyao Decoction, and Jiawei Dachaihu Decoction. The two SRs for mumps that reported specific drugs used Chuanxinliang injections, externally applied |                          |               |
Fuhuang ointment, and Pajixiaodu Decoction. The two SRs for herpangina reported specific drugs, including Pudilan Xiaoyan Oral Solution and Yinqiao Decoction. Ten SRs that reported on specific drugs for HFMD most used herbal injections, such as Xiyanping Injection ($n = 7, 70.00\%$), Reduning Injection ($n = 3, 30.00\%$) and Tapreqing Injection ($n = 3, 30.00\%$). Twenty-three SRs reported safety issues, among which one SR concluded that there were no adverse reactions to CHM. Twenty-one SRs reported adverse events, the most common of which were abdominal distension, diarrheaea, nausea, and vomiting, and poor appetite. Detailed data are shown in Table 1.

Results of AMSTAR2 Quality Assessment

The results of the AMSTAR2 evaluation showed that of the 51 systematic reviews, three (6.52%) were of high quality (Wang S. et al., 2020; Zeng et al., 2020; Luo et al., 2021), 22 (47.83%) were of moderate quality (Zhang et al., 2004; Zhao et al., 2004; Hao, 2005; Hao et al., 2005; Liu et al., 2005; Zhao, 2014; Zhao et al., 2014; Wu et al., 2015; Wang et al., 2017; Yan and Gao, 2017; Yue et al., 2017; Jin et al., 2018; Xiong et al., 2019; Yang M. et al., 2020; Yu et al., 2020a; Yang Z. et al., 2020; Fan et al., 2020; Gao et al., 2020; Jin et al., 2020; Pang et al., 2020; Sun et al., 2020; Xiong et al., 2020), ten (21.74%) were of low quality (Liu et al., 2004; Chen et al., 2007; Guo et al., 2010; Liu et al., 2012; Han, 2016; Li et al., 2016; Ang et al., 2020; Liu et al., 2020; Qi et al., 2020; Wu et al., 2020), and 11 (23.91%) were of very low quality (Liu and Dong, 2021; Sun et al., 2020; Sun et al., 2020; Wu et al., 2020).

Six of the high-quality SRs were on TCMs against COVID-19 (Wang S. et al., 2020; Zeng et al., 2020; Zhou L. P. et al., 2021; Zhou F. et al., 2021; Fan et al., 2020; Pang et al., 2020; Jin et al., 2020; Sun et al., 2020; Qi et al., 2020; Wu et al., 2020), followed by SARS ($n = 5, 62.50\%$) (Zhang et al., 2004; Zhao et al., 2004; Zhao et al., 2005), HFMD ($n = 4, 36.36\%$) (Xiong et al., 2019; Yu et al., 2020a; Yang Z. et al., 2020; Yu et al., 2020b), tuberculosis ($n = 3, 75.00\%$) (Yan and Gao, 2017; Yue et al., 2017; Jin et al., 2018), mumps ($n = 2, 66.67\%$) (Zhao, 2014; Wu et al., 2015), H1N1 ($n = 1, 50.00\%$) (Zhao et al., 2014) and bacillary dysentery ($n = 1, 50.00\%$) (Wang et al., 2017). Among the lower-quality SRs, COVID-19 was also the most frequent disease ($n = 4, 21.05\%$) (Ang et al., 2020; Liu et al., 2020; Qi et al., 2020; Wu et al., 2020), followed by SARS ($n = 3, 37.50\%$) (Liu et al., 2004; Chen et al., 2007; Liu et al., 2012), H1N1 ($n = 1, 50.00\%$) (Li et al., 2016), tuberculosis ($n = 1, 25.00\%$) (Guo et al., 2010) and bacillary dysentery ($n = 1, 50.00\%$) (Han, 2016). The highest number of very low-grade SRs reported on HFMD ($n = 7, 63.64\%$) (Ding et al., 2013; Wang et al., 2013; Xiong et al., 2013; Zhang et al., 2014; Zhang and Wei, 2014; He, 2020; Yan et al., 2020), followed by herpangina ($n = 2, 100.00\%$) (Lu et al., 2013; Liu et al., 2016), COVID-19 ($n = 1, 5.26\%$) (Liu and Dong, 2021) and mumps ($n = 1, 33.33\%$) (Zhang, 2016). The summary of AMSTAR 2 assessment is shown in Figure 2. The details of each evaluation item are shown in Supplementary 4.

Qualitatively Analysis of Medium-And-High-Quality Systematic Reviews

The only two SRs on herpangina was excluded from the data-synthesis due to very low quality. SRs of medium- and high-quality for COVID-19, SARS, H1N1 type influenza, tuberculosis, bacillary dysentery, mumps, and HFMD were included to qualitative data-synthesis. Detailed data are shown in Table 2.

COVID-19

Six high-quality SRs (Wang S. et al., 2020; Zeng et al., 2020; Zhou L. P. et al., 2021; Zhou F. et al., 2021; Luo et al., 2021; Ouyang et al., 2021) and eight moderate-quality SRs (Liu and Dong, 2021; Fan et al., 2020; Pang et al., 2020; Jin et al., 2020; Sun et al., 2020; Yang M. et al., 2020; Xiong et al., 2020; Gao et al., 2020) evaluated the efficacy and safety of conventional therapy combined with CHM decoction/proprietary CHM drugs and the results all suggested that this combination therapy was better than conventional therapy alone in improving the overall treatment efficiency for COVID-19 patients.

One single high-quality SR including 19 controlled trials (Luo et al., 2021) identified the efficacy and safety of conventional therapy combined with TCM/tonics, the results showed that the combined with TCM/tonics could improve the appearance of pulmonary CT lesions and the nucleic acid conversion rate, improve the alleviation of symptoms such as fever, cough, malaise, reduce hospitalization time and the rate of clinical cases from mild to severe. However, there was no difference in the incidence of adverse events between the treatments.

Specific to Lianhuaqingwen Capsule, a proprietary CHM drug, a moderate quality SR involving seven RCTs (Wang S. et al., 2020) identified the CHM combined with conventional therapy vs. conventional therapy to treat the COVID-19 patients, and the results suggested that the CHM combined with conventional therapy could improve the appearance of pulmonary CT lesions, shorten the fever duration and the time in hospital, and reduce the possibility being worsening. As for safety, no adverse events were reported.

One moderate quality SR including 12 RCTs with mild and ordinary COVID-19 patients (Gao et al., 2020) suggested that the combined with CHM decoction/proprietary CHM drugs could reduce the duration of fever, fatigue, and cough, improve the appearance of pulmonary CT lesions and the nucleic acid conversion rate, and reduce the rate of clinical cases from mild to severe. However, another high-quality systematic review (Ouyang et al., 2021) including six RCTs and four cohort studies identified the efficacy and safety of TCM in the treatment of common or mild COVID-19 patients, showing that TCM was superior to the control group in improving efficiency and reducing the duration of fever, but there was no difference in the relief of related symptoms such as fever and malaise and the incidence of adverse effects between the two groups.

One moderate quality SR involving seven RCTs (Fan et al., 2020) identified the CHM combined with conventional therapy vs. conventional therapy to treat the COVID-19 patients ranging from being mild to severe, and the results suggested that the CHM combined with conventional therapy could improve the
appearance of pulmonary CT lesions and reduce C-reactive protein. As for safety, no adverse events were reported.

One single moderate-quality SR including three RCTs (Yang M. et al., 2020) evaluated the efficacy and safety of Lianhuaqingwen capsule, and the results suggested that in combination with conventional treatment, they could improve the alleviation of symptoms such as fever, cough, fatigue, and chest tightness, dyspnoea, and loss of appetite in ordinary COVID-19 patients better than conventional treatment alone. Regarding safety, there was no difference in the incidence of adverse events between the treatments.

One high-quality network meta-analysis including five RCTs (Jin et al., 2020) evaluated the efficacy of four CHM prescripts, namely, Qingfei Touxie Fuzheng Decoction, Lianhua Qingwen Granule, Lianhua Qingke Granule, and Xuebijing Injections, and the results suggested that the combination of symptomatic and supportive treatment with either one of four prescriptions could better improve the appearance of lungs on pulmonary CT than symptomatic treatment alone. Among them, the combination of symptomatic and supportive care with Lianhua Qingke Granule had the highest surface under the cumulative ranking (SUCRA) value, suggesting it had the highest overall effectiveness.

Two high-quality systematic reviews (Zhou L. P. et al., 2021; Zhou F. et al., 2021) identified the add-on effect of TCM for COVID-19. One included 10 RCTs and the other included 6 RCTs, and both studies suggested that TCM may be an effective auxiliary treatment for COVID-19 patients, which is likely to help improve the main symptoms, such as fever, cough, and fatigue, shorten the hospital stay and reduce disease progression.

SARS

Five moderate-quality SRs (Zhang et al., 2004; Zhao et al., 2004; Hao, 2005; Hao et al., 2005; Liu et al., 2005) evaluated the effectiveness of CHM combined with Western medicine for SARS, and the results all suggested that the combination better improved the clinical progression of SARS patients; however, the benefits to specific outcomes varied across SRs.

One moderate-quality SR including eight controlled trials (Liu et al., 2005) suggested that the additional use of CHM reduced the mortality, the incidence of secondary fungal infections in the lungs, shorten the duration of fever, the persisting clinical symptoms and the time for Chest X-ray to return normal appearance. There were no adverse events for the combination treatments.

Another moderate-quality SR including six RCTs with mild-to-sever patients (Zhang et al., 2004) showed that the improvement of the appearance of abnormal chest X-ray shadows was better in the group treated with CHM decoction and conventional medicine than the conventional treatment alone. However, there was no statistical difference in the reduction of mortality, and dose of corticosteroids, and the alleviation of cough and dyspnoea between two groups.

Two other moderate-quality SR (Hao, 2005; Hao et al., 2005) supported the conclusion the combination of CHM and conventional medicine was better in reducing the duration of fever and mortality among the patients with SARS; however, the use of corticosteroids had not been reduced due to the additional use of CHM.

Another moderate-quality SR (Zhao et al., 2004) did not support the benefits to improving Chest X-ray imaging among the SARs patients when CHM was used alongside conventional medicine; it confirmed the superiority of CHM in reducing the duration of fever, mortality dose of corticosteroids and complications due to overuse of corticosteroids as well as improving clinical symptoms.

H1N1 Influenza

One moderate-quality SR including five RCTs (Zhao et al., 2014) suggested that the use of Lianhua Qingwen Capsule was better at reducing the duration of symptoms such as fever, cough, sore throat, and body pain in H1N1 patients compared with the use of oseltamivir. However, there was no statistical difference of the time to conversion to nucleic acid negativity between two treatments. Regarding safety, no details of adverse events were reported.
TABLE 2 | Medium and high-quality literature details.

| Study | Diagnosis | Comparison (T vs C) | Outcomes | Estimate (95% CI) | Model | I² | No. participants | No. controlled trials | Level of evidence |
|-------|-----------|--------------------|----------|------------------|-------|----|-----------------|-----------------------|-------------------|
| Fan 2020 COVID-19 | Traditional Chinese medicine + western medicine vs Western medicine | Symptom and inflammatory markers scores | SMD = -1.30 (-2.43, -0.16) | Random | 94% | 261 | 3 | Low |
| | | C-reactive protein | MD = -1.19 (-1.92, -0.46) | Random | 97% | 325 | 5 | Low |
| Pang 2020 COVID-19 | Traditional Chinese medicine + western medicine vs Western medicine | Improvement of lung CT | RR = 1.34 (1.19, 1.51) | Random | 0% | 489 | 4 | Moderate |
| | | Number of severe cases transferred | RR = 0.47 (0.32, 0.69) | Random | 0% | 969 | 8 | High |
| | | Mortality | RR = 0.50 (0.08, 3.00) | Random | 0% | 337 | 2 | Moderate |
| | | Cough disappearance rate (%) | MD = -2.07 (1.01, 3.14) | Random | 92% | 255 | 2 | Very Low |
| Luo 2020 COVID-19 | Traditional Chinese medicine + western medicine vs Western medicine | Length of stay | MD = -5.15 (-7.86, -2.44) | Random | 77% | 250 | 2 | Low |
| | | Nutritional acid negative conversion rate (%) | RR = 1.16 (0.94, 1.42) | Fixed | --- | 12 | 1 | Very Low |
| | | Total score of clinical symptoms | MD = 0.62 (2.15, 0.47) | Random | 94% | 255 | 2 | Very Low |
| | | Time of heat removal | MD = -1.02 (-2.03, -0.02) | Random | 69% | 232 | 3 | Low |
| | | Antipyretic rate (%) | RR = 1.37 (1.19, 1.51) | Random | 0% | 264 | 3 | Low |
| | | Cough disappearance time | MD = -0.33 (-0.78, 0.12) | Random | 94% | 255 | 2 | Very Low |
| | | Weakness disappearance rate (%) | RR = 1.37 (1.02, 1.83) | Random | 11% | 147 | 2 | Low |
| | | Shortness of breath disappearance rate (%) | RR = 2.20 (1.11, 4.39) | Random | --- | 35 | 1 | Very Low |
| | | Diaphoresis remission rate (%) | RR = 0.32 (0.01, 19.49) | Random | 87% | 30 | 2 | Very Low |
| | | Physical pain disappearance rate (%) | RR = 1.17 (0.73, 1.87) | Random | --- | 30 | 1 | Very Low |
| Jin 2020 COVID-19 | Qingfei xiefuzheng prescription + symptomatic support treatment vs Symptomatic support treatment | Lianhuaqingwen granule + symptomatic support treatment vs Symptomatic support treatment | OR = 1.38 (0.91, 2.08) | Random | --- | 397 | --- | Low |
| | | Lianhuaqingwen granule + symptomatic support treatment vs Symptomatic support treatment | OR = 1.26 (1.02, 1.56) | Random | --- | 57 | --- | Very Low |
| | Xuebijing injection + symptomatic support treatment vs Symptomatic support treatment | OR = 0.80 (1.09, 1.82) | Random | --- | 44 | --- | Very Low |
| | Lianhuaqingwen granule + symptomatic support treatment vs Qingfei xiefuzheng prescription + symptomatic support treatment | OR = 0.80 (1.25, 1.51) | Random | --- | 249 | --- | Low |
| | Lianhuaqingwen granule + symptomatic support treatment vs Lianhuaqingwen granule + symptomatic support treatment | OR = 0.57 (0.53, 54.48) | Random | --- | 83 | --- | Very Low |
| | Xuebijing injection + symptomatic support treatment vs Lianhuaqingwen granule + symptomatic support treatment | OR = 0.46 (0.42, 0.52) | Random | --- | 73 | --- | Very Low |
| | Lianhuaqingwen granule + symptomatic support treatment vs Lianhuaqingwen granule + symptomatic support treatment | OR = 0.85 (0.06, 79.96) | Random | --- | 230 | --- | Low |
| | Xuebijing injection + symptomatic support treatment vs Lianhuaqingwen granule + symptomatic support treatment | OR = 0.71 (0.76, 66.50) | Random | --- | 220 | --- | Low |
| | Xuebijing injection + symptomatic support treatment vs Lianhuaqingwen granule + symptomatic support treatment | OR = 0.81 (0.04, 17.89) | Random | --- | 54 | --- | Low |
| Luo 2020 COVID-19 | Traditional Chinese medicine + western medicine vs Western medicine | Cure rate (%) | OR = 2.67 (1.83, 3.88) | Random | 0% | 720 | C07:7 RCT:3 | Moderate |
| | | Improvement of lung CT | OR = 2.43 (1.80, 3.29) | Random | 0% | 965 | C07:9 RCT:4 | Moderate |
| | | Conversion rate of severe cases (%) | OR = 0.40 (0.24, 0.67) | Random | 17.1% | 840 | C07:8 RCT:3 | Moderate |
| | | Nucleic acid negative conversion rate (%) | OR = 2.55 (1.06, 6.17) | Random | 56.4% | 311 | C07:5 | Low |
| | | Cough disappearance rate (%) | OR = 2.96 (1.88, 4.63) | Random | 0% | 468 | C07:3 RCT:2 | Moderate |
| | | Weakness disappearance rate (%) | OR = 2.61 (1.56, 4.34) | Random | 0% | 368 | C07:3 RCT:1 | Moderate |
| | | Fever disappearance rate (%) | OR = 3.17 (1.30, 5.15) | Random | 0% | 468 | C07:3 RCT:2 | Moderate |
| | | Length of stay | OR = 0.46 (0.36, 0.58) | Random | 99.5% | 325 | 5 | Low |
| Sun 2020 COVID-19 | Traditional Chinese medicine + western medicine vs Western medicine | Adverse reactions incidence rate (%) | OR = 1.21 (0.48, 3.07) | Random | 43% | 1,233 | C07:10 RCT:5 | Moderate |
| | | Clinical effective rate (%) | OR = 1.17 (0.39, 3.52) | Random | 62% | 273 | 2 | Low |
| | | Adverse event incidence rate | OR = 1.49 (1.13, 1.97) | Random | 0% | 185 | RCT:3 | Low |
| | | Nucleic acid negative conversion rate | OR = 1.27 (1.12, 1.44) | Random | 0% | 415 | RCT:4 | Low |
| | | White blood cell count | MD = 0.92 (0.70, 1.17) | Random | 87% | 339 | RCT:3 | Low |
| | | Lymphocyte count | MD = 0.33 (0.08, 0.57) | Random | 76% | 188 | RCT:3 | Low |
| | | Percentage of lymphocytes | MD = 0.92 (0.20, 0.63) | Random | 0% | 273 | RCT:2 | Low |
| | | C-reactive protein | MD = -12.66 (-24.40, -0.92) | Random | 97% | 288 | RCT:4 | Very Low |

(Continued on following page)
| Study   | Diagnosis                      | Comparison (T vs C) | Outcomes                            | Estimate (95% CI) | Model  | I²     | No. participants | No. controlled trials | Level of evidence |
|---------|--------------------------------|--------------------|-------------------------------------|--------------------|--------|--------|------------------|-----------------------|--------------------|
| Zeng    | COVID-19 Lianhuaqingwen granule + western medicine vs Western medicine | Other symptoms disappearance rate (%) | MD = -8.17 (-22.40, 6.06) | Random 73% | 166 | RCT:2 | Very Low |
|         |                                | Heating time       | OR = 3.44 (2.06, 5.44)              | Random 0%          | 142   | 2      | Low              |
|         |                                | Main symptoms disappearance rate (%) | OR = 2.42 (1.73, 10.26) | Fixed 37.9% | 142 | 2      | Low              |
|         |                                | Fever (Main symptoms disappearance rate (%)) | OR = 2.03 (2.06, 5.44) | Fixed 0%          | 142   | 2      | Low              |
|         |                                | Weakness (Main symptoms disappearance rate (%)) | OR = 2.67 (2.06, 5.44) | Fixed 0%          | 142   | 2      | Low              |
|         |                                | Muscle soreness (Main symptoms/Secondary symptoms disappearance rate (%)) | OR = 7.17 (1.63, 32.12) | Random 0%        | 142   | 2      | Low              |
|         |                                | Sputum (Main symptoms/Secondary symptoms disappearance rate (%)) | OR = 2.02 (2.02, 32.18) | Random 0%        | 142   | 2      | Low              |
|         |                                | Shortness of breath (Main symptoms/Secondary symptoms disappearance rate (%)) | OR = 2.02 (2.02, 32.18) | Random 0%        | 142   | 2      | Low              |
|         |                                | Chest tightness disappearance rate (%) | OR = 1.21 (1.01, 1.97) | Random 0%          | 142   | 2      | Low              |
|         |                                | Dyspnea (Main symptoms/Secondary symptoms disappearance rate (%)) | OR = 1.21 (1.01, 1.97) | Random 0%          | 142   | 2      | Low              |
|         |                                | Loss of appetite (Main symptoms/Secondary symptoms disappearance rate) | OR = 1.21 (1.01, 1.97) | Random 0%          | 142   | 2      | Low              |
| Wang    | COVID-19 Lianhuaqingwen granule + western medicine vs Western medicine | Effective rate of main clinical symptoms | RR = 1.24 (1.12, 1.38) | Fixed 0%          | 576   | 5      | Moderate         |
|         |                                | CT improvement     | RR = 1.14 (1.02, 1.28) | Random 53.9%       | 403   | 5      | Low              |
|         |                                | Clinical conversion to severe | RR = 0.48 (0.31, 0.72) | Fixed 10.8%       | 439   | 4      | Moderate         |
|         |                                | Duration of fever | SMD = -0.07 (-1.22, -0.52) | Fixed 0%          | 186   | 3      | Low              |
|         |                                | Clinical symptoms disappearance time | SMD = -0.19 (-1.56, -0.92) | Fixed 0%          | 151   | 3      | Low              |
|         |                                | Length of stay     | SMD = -0.61 (0.91, -0.30) | Fixed 19.6%       | 416   | 4      | Moderate         |
| Yang    | COVID-19 Lianhuaqingwen granule + western medicine vs Western medicine | Fever disappearance rate (%) | RR = 1.76 (1.05, 2.96) | Random 82.8%       | 197   | 3      | Very Low         |
|         |                                | Cough disappearance rate (%) | RR = 1.96 (1.43, 2.68) | Fixed 24.0%       | 197   | 3      | Low              |
|         |                                | Weakness disappearance rate (%) | RR = 1.77 (1.36, 2.30) | Fixed 49.2%       | 197   | 3      | Low              |
|         |                                | Chest tightness disappearance rate (%) | RR = 2.19 (0.69, 5.40) | Fixed 82.8%       | 197   | 3      | Very Low         |
|         |                                | Dyspnea disappearance rate (%) | RR = 4.60 (2.39, 8.79) | Fixed 35.5%       | 197   | 3      | Low              |
|         |                                | Loss of appetite disappearance rate (%) | RR = 1.36 (1.00, 1.84) | Fixed 1.9%        | 197   | 3      | Low              |
| Xiong   | COVID-19 Traditional Chinese medicine + western medicine vs Western medicine | Lung CT improved | RR = 1.23 (1.15, 1.32) | Fixed 0%          | 1,402 | 13     | High             |
|         |                                | Mortality (%)       | RR = 0.34 (0.05, 2.18) | Fixed 0%          | 463   | 4      | Moderate         |
|         |                                | Cure rate (%)       | RR = 1.18 (1.13, 1.24) | Fixed 24%         | 1,523 | 7      | High             |
|         |                                | The number of severe to mild cases | RR = 1.54 (0.47, 5.85) | Fixed 0%          | 167   | 2      | Low              |
|         |                                | The number of cases from mild to severe | RR = 0.40 (0.09, 0.58) | Fixed 0%          | 1,246 | 11     | High             |
|         |                                | Length of stay (d)  | MD = -1.99 (-3.68, 0.70) | Fixed 0%          | 119   | 2      | Low              |
|         |                                | Total score of clinical symptoms | MD = -1.84 (-3.10, -0.58) | Fixed 0%          | 133   | 2      | Low              |
|         |                                | Antipyretic cases   | RR = 1.28 (0.98, 1.67) | Random 66%       | 388   | 5      | Low              |
|         |                                | Time of heat removal (d) | MD = -1.36 (1.8, -0.93) | Random 58%       | 1,017 | 10     | Low              |
|         |                                | Fever symptom score | MD = -0.6 (-0.99, -0.55) | Random 61%       | 886   | 3      | Low              |
|         |                                | Number of cases with cough disappeared | RR = 1.50 (1.36, 1.78) | Fixed 0%          | 422   | 1      | Low              |
|         |                                | Cough symptom score | MD = -0.78 (-1.32, -0.24) | Random 99%       | 934   | 4      | Low              |
|         |                                | Cough disappearance time | MD = -1.42 (-2.82, -0.01) | Random 90%       | 698   | 6      | Low              |
|         |                                | Weakness Number of improved cases | RR = 1.73 (1.39, 2.16) | Fixed 0%          | 307   | 5      | Moderate         |
|         |                                | Weakness Symptom score | MD = -0.70 (-0.9, -0.42) | Random 97%       | 934   | 4      | Low              |
|         |                                | Weakness disappearance rate (%) | MD = -0.70 (-0.9, -0.42) | Random 97%       | 934   | 4      | Low              |
|         |                                | Improvement of TCM syndromes (%) | MD = 3.67 (4.6, -0.73) | Random 86%       | 225   | 5      | Low              |
|         |                                | Nucleic acid negative conversion rate (%) | RR = 1.18 (1.14, 1.34) | Fixed 41%       | 469   | 4      | Low              |
|         |                                | WBC count (10^9 cell/L) | MD = 0.22 (0.22, 0.78) | Random 96%       | 1,151 | 5      | Low              |
|         |                                | Lymphocytosis | MD = 0.24 (0.04, 0.51) | Random 97%       | 485   | 4      | Low              |
|         |                                | C-reactive protein level (mg/L) | MD = 0.24 (0.04, 0.51) | Random 97%       | 1,150 | 6      | Low              |

(Continued on following page)
| Study  | Diagnosis                                                                 | Comparison                  | Outcomes                                                                 | Estimate (95% CI)              | Model  | I²    | No. participants | No. controlled trials | Level of evidence |
|-------|----------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------|-------------------------------|--------|-------|------------------|----------------------|---------------------|
| Guo 2020 COVID-19 | Traditional Chinese medicine + western medicine vs Western medicine          | Adverse reactions           | MD = 8.91                                                                  | (2.56, 15.27)                | Fixed  | 46%   | 1,069            | RCT:2                 | Very Low            |
|       |                                                                            | Total effective rate (%)    | RR = 1.31 (1.11, 1.56)                                                     | Fixed  | 0%    | 138              | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Difference of total score of symptoms before and after treatment | SMD = 0.62 (0.00, 1.61)                                                    | Fixed  | 84.9% | 240              | Prospective NRCT: 2 RCT:1 | Very Low            |
|       |                                                                            | Difference of total score of symptoms before and after treatment (RCT subgroup) | SMD = 0.20                   | Random  | ---   | 123              | RCT:1                 | Very Low            |
|       |                                                                            | Difference of total score of symptoms before and after treatment (RCT subgroup) | SMD = 1.17 (0.41, 1.93) | Random  | 66.6% | 117              | Prospective NRCT: 2 RCT:1 | Very Low            |
|       |                                                                            | Fever control rate (%)      | RR = 1.30 (1.16, 1.45)                                                    | Fixed  | 42.9% | 536              | Prospective NRCT: 3 RCT:3 | Very Low            |
|       |                                                                            | Fever integral              | SMD = 0.76 (0.57, 2.10)                                                    | Random  | 94.4% | 187              | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Fever score (RCT subgroup)  | SMD = 1.46 (1.08, 1.83)                                                    | Fixed  | 0%    | 138              | RCT:2                 | Very Low            |
|       |                                                                            | Fever score (NRCT subgroup) | SMD = -0.64 (1.21, -0.96)                                                  | Random  | ---   | 49               | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Utration of fever           | MD = -1.58 (1.08, -1.17)                                                   | Fixed  | 9.2%  | 333              | Prospective NRCT: 1 RCT:2 | Moderate            |
| Luo 2020 COVID-19 | Traditional Chinese medicine + western medicine + Chinese medicine + western medicine | Weakness Improvement rate (%) | RR = 1.55 (1.21, 1.99)                                                    | Fixed  | 0%    | 368              | Prospective NRCT: 2 RCT:4 | Moderate            |
|       |                                                                            | Weakness Symptom score      | SMD = 1.49 (0.68, 2.30)                                                    | Random  | 83.3% | 187              | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Weakness symptom score (RCT subgroup) | SMD = 1.43 (0.14, 2.73)                                                       | Random  | 91.3% | 138              | RCT:2                 | Very Low            |
|       |                                                                            | Weakness symptom score (RCT subgroup) | SMD = -0.12 (0.07, -2.27)                                                     | Random  | ---   | 49               | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Weakness duration           | MD = -1.74 (2.01, -1.48)                                                   | Fixed  | 0%    | 172              | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Cough Improvement rate (%)  | RR = 1.65 (1.34, 2.04)                                                    | Fixed  | 42.2% | 468              | Prospective NRCT: 2 RCT:5 | Very Low            |
|       |                                                                            | Cough integral difference before and after | SMD = 1.96 (1.13, 2.77)                                                    | Random  | 81.4% | 187              | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Cough duration              | MD = -1.71 (2.30, -1.12)                                                   | Fixed  | 0%    | 172              | Prospective NRCT: 1 RCT:2 | Very Low            |
|       |                                                                            | Improvement rate of lung CT | RR = 1.28 (1.04, 1.57)                                                    | Random  | 68.30% | 526             | Prospective NRCT: 2 RCT:3 | Very Low            |
|       |                                                                            | Nucleic acid negative conversion rate (%) | RR = 1.43 (0.94, 2.16)                                                      | Fixed  | 0%    | 138              | Prospective NRCT: 2 RCT:4 | Very Low            |
|       |                                                                            | Conversion rate of severe cases (%) | RR = 0.44 (0.26, 0.67)                                                      | Fixed  | 10.30% | 842             | Prospective NRCT: 3 RCT:5 | Very Low            |
| Zhou F. et al. (2021) | Traditional Chinese medicine + western medicine + Chinese medicine + western medicine vs Chinese medicine + western medicine | Adverse reaction           | OR = 0.87 (0.67, 1.14)                                                    | Fixed  | ---   | ---             | ---                   | Low                |
|       |                                                                            | Mortality                  | OR = 0.33 (0.09, 1.34)                                                    | Fixed  | ---   | ---             | ---                   | Low                |
|       |                                                                            | Cure rate                  | OR = 0.15 (0.10, 1.73)                                                    | Random  | 65%   | 976             | 6                      | Low                |
|       |                                                                            | Lowering body temperature  | RR = 1.10 (0.94, 1.29)                                                    | Fixed  | 85%   | ---             | 9                      | Low                |
|       |                                                                            | Relieving cough            | ---                                                                      | ---   | ---   | ---             | 9                      | ---                |
|       |                                                                            | Improvement in chest CT images | ---                                                                  | ---   | ---   | ---             | 5                      | ---                |
|       |                                                                            | Deterioration of condition | RR = 0.98 (0.43, 2.17)                                                    | Fixed  | 0%    | ---             | 6                      | Low                |
|       |                                                                            | Adverse effects            | RR = 0.81 (0.42, 1.57)                                                    | Fixed  | 56%   | ---             | 9                      | Low                |
| Liu 2021 COVID-19 | Traditional Chinese medicine + western medicine + Chinese medicine + western medicine vs Chinese medicine + western medicine | Severe conversion rate     | OR = 0.35 (1.80, 6.68)                                                    | Fixed  | 0%    | 326             | 3                      | High               |
|       |                                                                            | Total effective rate       | OR = 2.50 (1.46, 5.29)                                                    | Fixed  | 0%    | 346             | 3                      | High               |
|       |                                                                            | Pulmonary imaging (CT) improvement rate | OR = 2.27 (1.37, 3.77)                                                       | Fixed  | 33%   | 346             | 3                      | Moderate           |
|       |                                                                            | Heating duration           | SMD = -0.81 (1.25, -1.08)                                                  | Random  | 75%   | 414             | 4                      | Low                |
|       |                                                                            | Fever disappearance rate   | OR = 0.05 (1.85, 5.01)                                                    | Fixed  | 0%    | 343             | 4                      | Moderate           |
|       |                                                                            | Disappearance rate of cough| OR = 3.90 (1.84, 8.89)                                                    | Fixed  | 0%    | 322             | 4                      | Moderate           |
|       |                                                                            | Disappearance rate of fatigue | OR = 2.60 (1.56, 4.33)                                                     | Fixed  | 0%    | 263             | 4                      | Moderate           |
|       |                                                                            | Disappearance rate of expectoration | OR = 1.94 (1.93, 1.95)                                                    | Fixed  | 56%   | 315             | 4                      | Low                |
|       |                                                                            | Healing time of oral ulcer | ---                                                                      | ---   | ---   | 1,33            | 7                      | ---                |
|       |                                                                            | Adverse reaction           | RR = 0.87 (0.67, 1.14)                                                    | Fixed  | ---   | 812             | 5                      | Low                |
|       |                                                                            | Cure rate                  | RR = 1.63 (1.36, 1.93)                                                    | Fixed  | ---   | ---             | ---                   | Low                |
|       |                                                                            | Total effective rate       | RR = 1.25 (1.04, 1.47)                                                    | Fixed  | 0%    | 427             | 4                      | Moderate           |
| Chu et al. (2021) | Traditional Chinese medicine + western medicine + Chinese medicine + western medicine vs Chinese medicine + western medicine | Total effective rate       | OR = 1.40 (1.14, 1.40)                                                    | Fixed  | 0%    | 427             | 4                      | Moderate           |
|       |                                                                            | Heating duration           | WMD = -1.21 (1.71, -0.71)                                                  | Random  | 55%   | 414             | 2                      | Low                |
| Ou 2021 COVID-19 | Traditional Chinese medicine + western medicine + Chinese medicine + western medicine vs Chinese medicine + western medicine | Disappearance rate of novel coronavirus pneumonia related symptoms | RR = 1.25 (0.88, 1.80)                                                    | Random  | ---   | ---             | 5                      | Moderate           |
|       |                                                                            | Placebo = Traditional Chinese medicine vs Western medicine conventional treatment | ---                                                                  | ---   | ---   | ---             | ---                   | ---                |

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### TABLE 2 (Continued) Medium and high-quality literature details.

| Study | Diagnosis | Comparison (T vs C) | Outcomes | Estimate (95% CI) | Model | I² | No. participants | No. controlled trials | Level of evidence |
|-------|-----------|---------------------|----------|-------------------|-------|----|------------------|-----------------------|-------------------|
| **Zhao 2004** | SARS | Combination of Chinese and Western medicine vs Western medicine | Pharynx absorption rate | RR = 1.15 (0.53, 2.43) | Random | 94% | —— | 6 | Low |
| | | GuoYaoNO.2.3.4 formula + western medicine vs Western medicine | Disappearance rate of weakness | RR = 1.36 (0.71, 2.62) | Random | 75% | —— | —— | Low |
| | | GuoYaoNO.2.3.4 formula + western medicine vs Western medicine | Disappearance rate of cough | RR = 1.67 (0.58, 6.08) | Random | 97% | —— | —— | Low |
| | | FeidianNO.1 formula + western medicine vs Western medicine | Virus neutralizing antibody negative rate | RR = 1.47 (1.05, 2.05) | Fixed | 0% | —— | 3 | High |
| | | FeidianNO.1 formula + western medicine vs Western medicine | Leukocyte count | RR = 0.74 (0.26, 2.12) | Random | 75% | —— | 2 | Low |
| | | FeidianNO.1 formula + western medicine vs Western medicine | Lymphocyte count | RR = 0.21 (0.15, 0.27) | Fixed | 0% | —— | 2 | High |
| | | FeidianNO.1 formula + western medicine vs Western medicine | Percentage of lymphocytes | RR = 2.69 (1.32, 4.74) | Fixed | 31% | —— | 2 | High |
| **Hao 2005** | SARS | Traditional Chinese medicine + western medicine vs Western medicine | Mortality (%) | RR = 0.86 (0.22, 3.39) | Random | —— | 139 | 6 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Secondary infection rate | RR = 0.42 (0.11, 1.62) | Fixed | —— | 53 | 6 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Lung infiltration and absorption (%) | RR = 5.45 (1.54, 19.26) | Fixed | —— | 53 | 6 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Lung infiltration and absorption (%) | RR = 6.68 (2.30, 19.24) | Random | —— | 139 | 6 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Lung infiltration and absorption (%) | MD = 0.24 (0.02, 0.46) | Fixed | —— | 40 | 6 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Dyspnea disappearance | RR = 1.50 (0.41, 4.93) | Fixed | —— | 38 | 1 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Cough disappearance | RR = 1.29 (0.30, 5.43) | Fixed | —— | 30 | 1 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Average total dosage of hormone (mg) | MD = -39.65 (-116.84, 37.54) | Random | —— | 98 | 2 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Average dosage of hormone (mg) | SMD = -1.40 | Fixed | 95.30% | 175 | 5 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Mean heating time | RD = -0.65 | Random | 21.10% | 73 | 4 | Very Low |
| **Liu 2005** | SARS | Traditional Chinese medicine + western medicine vs Western medicine | Mortality (%) | RR = 0.34 (0.13, 0.43) | Random | —— | 539 | 9 | High |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Secondary fungal infection incidence rate (%) | RR = 0.35 (0.14, 0.90) | Random | —— | 128 | 2 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Complications caused by hormone use (%) | OR = 0.32 (0.14, 0.71) | Random | 96.9% | 333 | 4 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Time of heat removal (d) | MD = -0.83 (-1.33, -0.35) | Fixed | —— | 182 | 3 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Symptom relief time (d) | MD = -1.23 (-2.3, -0.37) | Fixed | —— | 119 | 2 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Abnormal chest X-ray | MD = 0.29 (0.15, 0.58) | Random | —— | 126 | 2 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Average total dosage of hormone (mg) | RR = -54.13 (-120.63, 12.38) | Random | —— | 126 | 2 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Daily average total dosage of hormone (mg) | SMD = -1.40 | Fixed | 95.30% | 175 | 5 | Very Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Recovery time of chest X-ray (d) | MD = -2.27 | Fixed | —— | 175 | 2 | Low |
| | | | % Recovery time of chest X-ray (d) | MD = -1.56 | Fixed | 95.30% | 175 | 5 | Very Low |
| | | | Secondary fungal infection incidence rate (%) | MD = -0.35 (0.14, 0.90) | Random | —— | 128 | 2 | Low |
| **Zhan 2004** | SARS | Traditional Chinese medicine + western medicine vs Western medicine | Mortality (%) | OR = 0.32 (0.14, 0.71) | Random | 96.9% | 333 | 4 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Complications caused by hormone use (%) | OR = 0.29 (0.13, 0.66) | Random | 96.9% | 333 | 4 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Time of heat removal (d) | MD = -1.17 (-1.83, -0.5) | Fixed | 11.00% | —— | —— | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Absorption time of lung shadow on chest X-ray | MD = -0.63 (-1.33, 2.59) | Fixed | 99.20% | 109 | 2 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Absorption ratio of lung shadow on chest X-ray | MD = 0.24 (0.02, 0.46) | Fixed | 99.20% | 109 | 2 | Low |
| | | Traditional Chinese medicine + western medicine vs Western medicine | Recovery time of chest X-ray (d) | MD = -2.27 | Fixed | —— | 175 | 2 | Low |
| | | | % Recovery time of chest X-ray (d) | MD = -1.56 | Fixed | 95.30% | 175 | 5 | Very Low |
| | | | Secondary fungal infection incidence rate (%) | MD = -0.35 (0.14, 0.90) | Random | —— | 128 | 2 | Low |
| **Pan 2014** | H1N1 | Chinese patient medicine vs Western medicine | Average time of hormone use (d) | MD = -1.67 (-3.3, -0.08) | Fixed | —— | 69.08% | —— | Very Low |
| | | Chinese patient medicine vs Western medicine | Fever duration (d) | MD = -0.65 | Fixed | 71.8% | —— | 5 | Low |
| | | Chinese patient medicine vs Western medicine | Cough duration (d) | MD = -0.79 | Fixed | 11.2% | 320 | 4 | Low |
| | | Chinese patient medicine vs Western medicine | Sore throat duration (d) | MD = -13.01 | Fixed | 87.1% | 321 | 4 | Low |
| | | Chinese patient medicine vs Western medicine | Physical pain time (d) | MD = -16.68 | Fixed | 89.7% | 137 | 3 | Very Low |
| | | Chinese patient medicine vs Western medicine | Nucleic acid negative conversion time [d] | MD = -0.34 | Fixed | 49.6% | —— | 5 | Low |
| **Jin 2018** | Tuberculosis | Traditional Chinese medicine + chemotherapy vs Chemotherapy | Sputum negative conversion rate (%) | RR = 1.30 (1.22, 1.39) | Fixed | 35% | 2,479 | 21 | High |
| | | Traditional Chinese medicine + chemotherapy vs Chemotherapy | Sputum negative conversion rate (%) | RR = 1.41 (1.281.55) | Fixed | 0% | 1,784 | 21 | High |
| | | Traditional Chinese medicine + chemotherapy vs Chemotherapy | Sputum negative conversion rate (%) | RR = 1.30 (1.22, 1.39) | Fixed | 35% | 2,479 | 21 | High |
| | | Traditional Chinese medicine + chemotherapy vs Chemotherapy | Sputum negative conversion rate (%) | RR = 1.35 (1.24, 1.46) | Fixed | 40% | 1,060 | 11 | High |

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# TABLE 2 | (Continued) Medium and high-quality literature details.

| Study | Diagnosis | Comparison | Outcomes | Estimate (95% CI) | Model | I² | No. participants | No. of controlled trials | Level of evidence |
|-------|-----------|------------|----------|------------------|-------|----|------------------|-------------------------|------------------|
| Luo et al. 2017 | Chinese Herbal Medicine for Infections | | Sputum negative conversion rate (%) (after 2 months of treatment) | RR = 1.36 (1.21, 1.50) | Random | 29% | 3,484 | 16 | Moderate |
| | | | | | | | | | |
| Wang 2017 | Bacterial dysentery | Traditional Chinese medicine + Western medicine | Total effective rate (%) (after 9 months of treatment) | OR = 1.20 (1.01, 1.42) | Fixed | 41% | 1,340 | 12 | High |
| | | | | | | | | | |
| Wu 2015 | Mumps | | Total effective rate (%) (no antibiotics) | OR = 1.30 (1.12, 1.50) | Fixed | 23% | 550 | 3 | Moderate |

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TABLE 2 | (Continued) Medium and high-quality literature details.

| Study | Diagnosis | Comparison | Outcomes | Estimate | Model | I2 | No. participants | No. controlled trials | Level of evidence |
|-------|-----------|------------|----------|----------|-------|----|------------------|----------------------|------------------|
| Zhao 2014 | Mumps | Traditional Chinese medicine vs Western medicine | Total effective rate (%) OR = 3.70 (0.60, 2.24) | Fixed | 86 | Very Low | 86 | 204 | Moderate |
| | | Traditional Chinese medicine vs Chinese patent medicine | Time of heat removal (Use of antibiotics) MD = -2.20 (2.72, -1.69) | Random | 60 | 1 | Very Low | 60 | 1 | Very Low |
| | | Traditional Chinese medicine vs Western medicine | Total effective rate (%) OR = 6.17 (2.39, 5.72) | Fixed | 264 | Low | 264 | 19 | Low |
| | | | Time of heat removal (Use of antibiotics) MD = -1.47 (-2.01, -0.93) | Fixed | 264 | Low | 264 | 19 | Low |
| | | | Skin rash regression time (d) MD = -1.99 (-2.80, -1.17) | Fixed | 414 | Low | 414 | 21 | Low |
| | | | Healing time of oral ulcer (d) MD = -3.58 (-6.52, -0.58) | Fixed | -- | Low | -- | -- | Low |
| | | | Adverse reactions incidence rate (%) OR = 1.29 (0.33, 3.81) | Fixed | -- | Low | -- | -- | Low |
| | | | Length of stay (d) MD = 2.53 (-5.14, 0.18) | Fixed | 150 | Low | 150 | 20 | Low |
| | | Ribavirin vs Tanniquing | Total effective rate (%) OR = 2.28 (0.72, 5.43) | Fixed | 86 | Very Low | 86 | 204 | Very Low |
| | | | Time of heat removal (d) MD = -2.21 (-4.40, -0.07) | Fixed | 86 | Very Low | 86 | 204 | Very Low |
| | | | Healing time of oral ulcer (d) MD = -1.57 (-5.80, 2.70) | Fixed | 86 | Very Low | 86 | 204 | Very Low |
| | | | Length of stay (d) MD = 2.60 (0.60, 2.24) | Fixed | 86 | Very Low | 86 | 204 | Very Low |
| Yu 2020 | Hand, foot and mouth disease in children | Ribavirin vs Reduning | Total effective rate (%) OR = 1.90 (0.59, 7.02) | Fixed | 64 | Very Low | 64 | 204 | Very Low |
| | | | Time of heat removal (d) MD = -0.98 (-3.14, 1.12) | Fixed | 64 | Very Low | 64 | 204 | Very Low |
| | | | Skin rash regression time (d) MD = -0.84 (-2.29, 0.45) | Fixed | 64 | Very Low | 64 | 204 | Very Low |

(Continued on following page)
### TABLE 2 (Continued) Medium and high-quality literature details.

| Study | Diagnosis | Comparison (T vs C) | Outcomes | Estimate (95% CI) | Model | I2 | No. participants | No. controlled trials | Level of evidence |
|-------|-----------|---------------------|----------|-------------------|-------|----|-----------------|-----------------|------------------|
| Luo et al. | Chinese herbal medicine for infections | Traditional treatment of western medicine vs Conventional therapy of western medicine | Healing time of oral ulcer (d) | MD = 1.80 (-1.47, 5.17) | Fixed | 76% | 943 | 9 Low | Moderate |
| | | | Length of stay (d) | MD = 3.38 (7.44, 0.06) | Fixed | 95% | 553 | 7 Low | Moderate |
| | | | Adverse reactions incidence rate (%) | OR = 0.15 (0.01, 1.83) | Fixed | 98% | 2,708 | 19 Low | Moderate |
| Tanreqing vs Yanhuning | Total effective rate (%) | OR = 0.96 (0.02, 9.78) | Fixed | 98% | 875 | 5 Low | Moderate |
| | Healing time of oral ulcer (d) | MD = 0.44 (-2.13, 3.15) | Fixed | 98% | 1,029 | 9 Low | Moderate |
| | Length of stay (d) | MD = 3.32 (2.44) | Fixed | 98% | 4,451 | 4 Moderate |
| Xiong et al. (2019) | Hand, foot and mouth disease in children | Tanreqing + conventional therapy vs Traditional treatment of western medicine | Total effective rate (%) | OR = 0.50 (0.01, 1.83) | Fixed | 98% | 338 | 4 Low | Very Low |
| | | Time of heal removal (d) | MD = 0.48 (-1.58, 2.56) | Fixed | 98% | 4,451 | 4 Moderate |
| | | Skin rash regression time (d) | MD = 1.96 (0.10, 2.88) | Fixed | 98% | 1,320 | 10 Moderate |
| | | Healing time of oral ulcer (d) | MD = 1.00 (-0.08, 4.07) | Fixed | 98% | 848 | 4 Very Low |
| | | Length of stay (d) | MD = 1.76 (-1.57, 4.91) | Fixed | 98% | 848 | 4 Very Low |
| | | Adverse reactions incidence rate (%) | OR = 0.50 (0.01, 1.83) | Fixed | 98% | 848 | 4 Very Low |
| Yang 2020 | Hand, foot and mouth disease in children | Chinese patent medicine/Chinese patent medicine + Western medicine vs Western medicine | Total effective rate (%) | OR = 2.88 (1.62, 5.10) | Fixed | 98% | 1,029 | 9 Low | Moderate |
| | | Time of heal removal (d) | MD = 1.20 (-1.44, -0.90) | Fixed | 98% | 848 | 4 Very Low |
| | | Herpes disappearance time (d) | MD = 1.78 (-2.10, -1.46) | Fixed | 98% | 848 | 4 Very Low |
| | | Healing time of oral ulcer (d) | MD = 1.45 (-1.62, -1.27) | Fixed | 98% | 848 | 4 Very Low |
| | | Total duration of disease (d) | OR = 0.25 (0.01, 6.76) | Fixed | 98% | 848 | 4 Very Low |
| | | Adverse reactions incidence rate (%) | OR = 0.15 (0.01, 1.82) | Fixed | 98% | 848 | 4 Very Low |
| | | Time of rash regression (d) | MD = 1.37 (-5.00, 2.52) | Fixed | 98% | 848 | 4 Very Low |

(Continued on following page)
TABLE 2 | (Continued) Medium and high-quality literature details.

| Study | Diagnosis | Comparison | Outcomes | Estimate (95% CI) | Model | I² | No. participants | No. controlled trials | Level of evidence |
|-------|-----------|------------|----------|------------------|-------|----|-----------------|----------------------|------------------|
|       |           | (T vs C)   |          |                  |       |    |                 |                      |                  |
| Xieyanping injection, Reduning injection, Tanreqing injection | Time of heat removal (h) (Subgroup analysis by traditional Chinese medicine injection) | MD = −18.26 (−27.34, −9.17) | Random | 89% | 1,326 | 8 | Low |
| Xieyanping injection, Reduning injection + Traditional treatment of western medicine vs Traditional treatment of western medicine | Time of heat removal (h) (Subgroup analysis according to traditional Chinese medicine injection variety, separate analysis) | MD = −22.00 (−30.39, −13.62) | Random | 81% | 322 | 2 | Low |
| Xieyanping injection, Reduning injection + Traditional treatment of western medicine vs Traditional treatment of western medicine | Time of heat removal (h) (Subgroup analysis by traditional Chinese medicine injection, Xieyanping) | MD = −12.02 (−15.47, −8.56) | Random | 0 | 413 | 4 | Low |
| Xieyanping injection, Reduning injection + Traditional treatment of western medicine vs Traditional treatment of western medicine | Time of heat removal (h) (Subgroup analysis by traditional Chinese medicine injection and Reduning) | MD = −30.48 (−51.96, −9.01) | Random | 91% | 590 | 5 | Low |
| Xieyanping injection, Reduning injection, Reduning injection | Conversion rate of severe cases (%) | OR = 0.83 (0.45, 1.53) | Fixed | 0% | 1,331 | 8 | High |
| Xieyanping injection, Reduning injection + Traditional treatment of western medicine vs Traditional treatment of western medicine | Adverse reactions incidence rate (%) | OR = 2.37 (0.39, 14.40) | Fixed | 0% | 1,815 | 10 | Moderate |
| Yu 2020  Hand, foot and mouth disease | Disappearance rate of other symptoms | OR = 6.54 (3.59, 11.90) | Fixed | 0% | 142 | 2 | Low |

---: Not Reported.

**Tuberculosis**

One moderate-quality SR (Jin et al., 2018) evaluated the efficacy of CHM decoction/proprietary CHM drugs combined with chemotherapy, and the results suggested that the combination better improved the negative conversion rate of sputum bacteria, lesion absorption rate, lung cavity closure rate, clinical symptom improvement rate, and overall effectiveness of patients with multi-drug-resistant tuberculosis over chemotherapy alone. In terms of safety, the incidence of adverse events was more reduced with the combination treatment.

Specifically, a moderate-quality SR including 16 RCTs (Yan and Gao, 2017) suggested that the proprietary CHM drugs *Jiehe* Pills in combination of chemotherapy better improved the rate of sputum conversion and lesion resorption and alleviated clinical symptoms and signs such as cough, haemoptysis, fever, emaciation, fatigue, and night sweats in tuberculosis patients over chemotherapy alone. In terms of safety, the incidence of digestive discomforts was more reduced with the combination treatment. Another moderate-quality SR including 20 RCTs (Yue et al., 2017) evaluated the efficacy of oral proprietary CHM drugs including Astragalus membranaceus in combination with chemotherapy better improved the rate of sputum conversion and lesion resorption, with less adverse events related to digestive discomforts, liver injury and the occurrence of rash.

**Bacillary Dysentery**

One moderate-quality SR (Wang et al., 2017) evaluated the efficacy of the combined use of CHM decoction and Western conventional therapy, and the results suggested that the combination better improved the overall effectiveness and shortened the time to fever and to diarrhoeal alleviation in adults with bacillary dysentery over Western conventional therapy alone; in terms of safety, digestive disorders were observed (intervention: control: 2 cases versus 5 cases).

**Mumps**

One moderate-quality SR including 11 RCTs (Wu et al., 2015) evaluated the effectiveness of the combined use of *Chuanhuning* Injection versus anti-virus pharmacotherapy ribavirin, and the results suggested that the combined use of *Chuanhuning* Injection and routine care better improved the overall effectiveness, shortened the time to fever and cheek swelling reduction, and reduced the occurrence of complications in children with mumps over ribavirin combined with routine care. In terms of safety, no adverse events occurred in the intervention group compared with the control including 4 cases of adverse events.

Another moderate-quality SR (Zhao, 2014) evaluated the effect of treatment with CHM alone, and the results suggested that internal and external treatment with CHM better improved the overall effectiveness, over proprietary CHM drugs alone; the external use of CHM outperformed the oral treatment. For safety, adverse events were observed, but no details were provided for individual groups.

**Hand-Foot-And-Mouth Disease**

A moderate-quality SR (Xiong et al., 2019) evaluated the effectiveness of proprietary CHM injections alone or in...
combination with conventional treatment, and the results suggested the monotherapy or the adjunct use of CHM injections reduced the time to fever and rash resolution, and improved the overall clinical effectiveness in children with HFMD. However, there was no difference in the incidence of adverse events and severe case conversion rate between treatments.

A moderate-quality SR including 24 RCTs (Yang Z. et al., 2020) evaluated the effectiveness of using oral proprietary CHM drug Lanzin Oral Solution in addition to conventional treatment, and the results suggested that the combination treatment better reduced the time to fever and rash reduction and oral ulcer healing and shortened the total duration of illness in children with HFMD. In terms of safety, there was no difference in the incidence of adverse events between treatments.

One moderate-quality SR including 17 RCTs (Yu et al., 2020a) conducted a network meta-analysis of proprietary CHM drugs for HFMD. The results suggested that the Yanhuning Injection, Reduning Injection, Xiyanping injection and Tanreqing injection were significantly better than Ribavirin in improving the total clinical effectiveness; as for oral ulcer healing time and hospitalization time, Xiyanping and Reduning were significantly shorter than ribavirin; in terms of safety, Reduning and Xiyanping were significantly higher than ribavirin.

Another moderate-quality SR (Yu et al., 2020b) conducted a network meta-analysis to identify the effectiveness and safety of Qinqge Jiedu TCM oral liquid in the treatment of HFMD. They concluded that seven TCM oral liquids, including Lanqin oral liquid, Pudilan oral liquid, Yellow Gardenia liquid, Fuganlin oral liquid, Kangbindu oral liquid, Huangqing oral liquid, and Shuanghuanglian oral liquid, had good therapeutic effects in clinical efficacy and recovery time of related symptoms. In the adverse reactions aspect, Pudilan oral liquid had the highest clinical safety.

**Supplementary 5** detailed the amount of each drug in a polyherbal preparation, and the complete species and drug name of the included SRs.

**DISCUSSION**

This study provides a broad review of the efficacy and safety of CHM in the treatment of acute infectious diseases. After a systematic search and screening, we included 46 systematic reviews, and meta-analysis of moderate-to-high-quality showed that CHM alone or in combination with Western medicine was effective in treating acute and emergent respiratory diseases such as COVID-19, H1N1, and SARS in terms of symptom improvement such as fever, cough and dyspnea, without serious adverse events. When combined with Western medicine, CHM shows potential in improving certain outcomes, such as mortality, but the evidence is not yet sufficient. In addition, some studies showed that CHM combined with Western medicine can also improve some intermediate outcomes including white blood cell count, nucleic acid negativity conversion rate, lung CT improvement rate. The adjunct use of CHM may be accounted for treating children with acute infections such as HFMD, bacillary dysentery and mumps; however, safety should be closely monitored before and after the treatment.

In the treatment of COVID-19, several moderate-to-high quality systematic reviews and meta-analyses (Yang M. et al., 2020; Fan et al., 2020; Gao et al., 2020; Jin et al., 2020; Pang et al., 2020; Sun et al., 2020; Xiong et al., 2020; Zeng et al., 2020; Luo et al., 2021) showed that combination therapy had a good overall efficiency and nucleic acid negativity conversion rate and alleviated disease symptoms and that CHM may effectively control cytokine storms by inhibiting the excessive activation of immune cells and reducing inflammatory cytokines in relieving COVID-19 symptoms. According to the current overview, the most common drug in the SRs included in this study was Lianhua Qingwen Capsule, a proprietary CHM drug composed of 13 herbs, namely, the dry fruit of Forsythia suspensa (Thunb.) Vahl, the dry buds or with blooming flowers of Lonicera japonica Thunb., the dry caudex of Ephedra sinica Stapf., Ephedra intermedia Schrenk et C.A.Mey. or Ephedra equisetina Bge., the dry matured seeds of Prunus armeniaca L. var.ansu Maxim., Prunus sibirica L. or Prunus mandshurica (Maxim.) Koehne or Prunus armeniaca L., Gypsum Fibrosum, the dry roots of Isatis indigotica Fort., the dry roots of Dryopteris crassirhiza Nakai., the dry aboveground part of Houttuynia cordata Thunb., the dry aboveground part of Pogostemon cablin (Blanco) Bentho., the dry roots of Rheum palmatum L., the dry roots of Rhodiola crenulata (Hook. f. et Thoms.) H. Obba, the fresh stem of Mentha haplocalyx Briq., and the dry roots and rhizomes of Glycyrrhiza uralensis Fisch., Glycyrrhiza inflata Bat. or Glycyrrhiza glabra L. Its benefits for people infected by H1N1 virus and SARS-CoV-2 has been determined by randomised, large-sample, controlled clinical trials, and explained by its capacity of anti-inflammation and immunoregulation in pharmacological experiments (Duan et al., 2011; Huang et al., 2020; Hu et al., 2021). However, some important CHM interventions, for which no SRs have been published yet, probably due to the urgency of the fight against the epidemic, have been published as original studies, while drugs for which clinical studies have been conducted including Xuebijing Injection, Xuanfeibaidu Decotion, Qinfeipaidu Decotion, and Huashibaidu Decotion (Wang L. et al., 2020; Xiao et al., 2020; Hu et al., 2021). Substantial publications on prospective/retrospective cohort studies for these CHM prescriptions should be included in future updates of SRs on CHM for acute infections.

For other diseases, a moderate-quality systematic review found that CHM combined with Western medicine for epidemic parotitis shortened the time to fever reduction and improved the overall efficiency, with no significant differences in safety. The main modalities of TCM treatment for mumps include both external and internal application, but validation of the efficacy of these regimens is challenging when designing blinded clinical trials. To enhance and promote exploration of this aspect of the study, some objective outcomes can be selected to be measured as much as possible. Additionally, appropriate reporting guidelines can be selected, such as the CONSORT for Non-Pharmacologic Treatment Interventions (Boutron et al., 2017) and the CONSORT for Chinese Herbal Medicine Formulas (Cheng...
et al., 2017), to enhance the convenience and operability in conducting systematic reviews.

In addition, the systematic reviews included in this study showed that CHM injections improved the overall clinical effectiveness and severe conversion rate, reduced the time to fever and rash remission and the time for healing of oral ulcers, and shortened the total duration of illness in patients with HFMD. However, none of these SRs reported the occurrence of adverse reactions. HFMD is most prevalent in children, who are a vulnerable group, and there are challenges in conducting clinical studies for this population. Overall, the safety of CHM injections, particularly regarding the amounts used, continues to be of concern. When using CHM injections, one needs to determine whether they are worth using, and if so, their safety needs to be monitored closely.

To the best of our knowledge, this study is the first overview to analyse and evaluate CHM for acute infectious diseases. We systematically assessed 46 systematic reviews and meta-analyses to describe the status of CHM in the treatment of acute infectious diseases. However, the systematic reviews and meta-analyses of CHM alone or in combination with Western medicine for acute infectious diseases were generally plagued with several problems. First, many clinical trials and systematic reviews on Chinese medicine for acute infectious diseases have been published, but most of them are lacking rigorous design and strict quality control. Though time is pressed for fighting against public health emergencies, complying with relevant regulations and methodological consensuses such as "Best practice in research—overcoming common challenges in phytopharmacological research", is necessary for conducting an ethical and high-quality studies. Theses quality-improving issues should be considered in the future research (Heinrich et al., 2020). Second, we only included studies published in Chinese and English, which may lead to publication bias. Last, we are not able to recommend any specific kind of TCM to be used in public health emergencies as the comparative effectiveness between CHM decoction and Chinese patent medicine is to be determined in future studies.

In general, the clinical applicability of existing SRs on the treatment of acute infectious diseases in CHM is not good, and it is suggested that future studies should focus on the staging and typing of diseases, the type of drugs used, and the singularity of interventions. Second, the reporting of outcomes of these systematic reviews is not standardized, and references can be made to the core set of outcomes in TCM for reporting, such as the COVID-19 core outcome set (COS) (Jin et al., 2020; Qiu et al., 2020). In addition, the low quality of reviews can be addressed by strictly following the standards of PRISMA 2020 (Page et al., 2021) and AMSTAR 2 (Shea et al., 2017) when producing future systematic reviews, thus improving the overall quality in the field. Last but not the least, the precise and appropriate use of botanical scientific nomenclature in CHM SRs is further required to avoid ambiguities and error (Rivera et al., 2014).

Although PHEs are a worldwide issue, China has achieved excellent results by applying CHM and Western medicine. For countries that use traditional medicine, there should be more benefits from applying the wisdom of traditional medicine, especially when there is no drug treatment for new and emergency infectious diseases. Moreover, the richness of traditional medicine may also be a source for developing new drugs for emergency infectious diseases, and it would be worthwhile to conduct in-depth research on drugs with a long history of application and clinical effectiveness. However, due to lack of rigorous regulation, the efficacy, safety and quality of some CHM products need to be proved by more high quality, large sample, unbiased randomized trials.

**CONCLUSION**

Overall, CHM, both decoction and Chinese patent medicine, used alone or in combination with conventional medicine may offer potential benefits to relieving symptoms of people with acute respiratory infections. Full reporting of disease typing, staging, and severity, and intervention details is further required for a better evidence translation to the responses for PHE. Future CHM research should focus mainly on the specific aspects of respiratory infections such as its single use for mild infections, and the adjunct administration for severe infections, and individual CHM prescriptions for well-selected outcomes should be prioritized.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

**AUTHORS CONTRIBUTIONS**

YC and XN conceived the study. XN, XL and YZ drafted the manuscript. XL validated the data and contributed to the methodology. XN designed the study and analyzed the data. YZ, HL, YLL, MR, YWL, YZ, ZK contributed to the literature search, data collection and quality assessment. YC, and XN interpreted the result from the perspective of Chinese medicine practitioner and clinical investigator. XN interpreted the data from the perspective of public health emergency. YC and XL interpreted the result from the perspective of methodology. All authors provided critical review to the manuscript and approved the submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.752978/full#supplementary-material

Hu, K., Guan, W. J., Bi, Y., Zhang, W., Li, L., Zhang, B., et al. (2021). 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. doi:10.1016/j.phymed.2020.153242

Huang, Y. F., Bai, C., He, F., Xie, Y., and Zhou, H. (2020). Review on the Potential Action Mechanisms of Chinese Medicines in Treating Coronavirus Disease 2019 (COVID-19). Pharmacol. Res. 158, 104939. doi:10.1016/j.phrs.2020.104939

Hunt, H., Pollock, A., Campbell, P., Escourt, L., and Bruton, G. (2018). An Introduction to Overviews of Reviews: Planning a Relevant Research Question and Objective for an Overview. Syst. Rev. 7 (1), 39. doi:10.1186/s13643-018-0695-8

Jiang, D., and Wen, X. (2021). Investigation on Origin and Development of Epidemic Disease. J. Liaoning Univ. Traditional Chin. Med. 23 (2), 1–4. doi:10.13194/j.issn.1673-842x.2021.02.001

Jin, L., Xu, Y., and Yuan, H. (2020). Efficacy of Four Types of Integrated Chinese and Western Medicines for the Treatment of COVID-19 in China: a Network Meta-Analysis. Rev. Esp. Med. Bas. 66 (6), 717–777. doi:10.1590/S0005-73212020000700001

Jin, X., Pang, B., Zhang, J., Liu, Q., Yang, Z., Feng, J., et al. (2020). Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (COS-COVID). Engineering (Beijing) 6 (10), 1147–1152. doi:10.1016/j.eng.2020.03.002

Jin, X., Xie, H., Zeng, H., Liu, Y., Zhang, T., Cao, S., et al. (2018). Combined Traditional Chinese and Western Medicine Treatment for Multidrug-Resistant Pulmonary Tuberculosis: A Meta-Analysis of Randomized Controlled Trials. Chin. Med. Guide 24 (1), 84–95. doi:10.13862/j.cnki.cmgci.43-1446/f.2018.01.028

Li, J. H., Wang, R. Q., Guo, W. J., and Li, J. S. (2016). Efficacy and Safety of Traditional Chinese Medicine for the Treatment of Influenza A (H1N1): A Meta-Analysis. J. Chin. Med. Assoc. 79 (5), 281–291. doi:10.1016/j.jcma.2015.10.009

Liu, A., and Dong, J. (2021). Meta-analysis of the Clinical Efficacy of Chinese Patent Medicine Alone or Combined with Western Medicine in the Treatment of COVID-19. Chin. Traditional Patent Med. 43 (3), 836–840. doi:10.3969/j.issn.1001-1528.2021.03.054

Liu, J., Manheimer, E., Shi, Y., and Glied, C. (2004). Chinese Herbal Medicine for Severe Acute Respiratory Syndrome: a Systematic Review and Meta-Analysis. J. Altern. Complement. Med. 10 (6), 1041–1051. doi:10.1089/jac.2004.10.1041

Liu, J. P., Manheimer, E., and Shi, Y. (2005). [Systematic Review and Meta-Analysis on the Integrative Traditional Chinese and Western Medicine in Treating SARS]. Zhongguo Zhong Xi Yi Jie He Za Zhi 25 (12), 1082–1088. doi:10.3321/j.cnki.1003-5370.2005.12.006

Liu, L., Zhang, X., Qu, W., Jing, W., and Wang, Y. (2016). Meta-analysis of Chinese Medicine on Herpangina in Children. Guild J. Tradit Chin. Med. Pharm. 22 (22), 88–94. doi:10.13862/j.cnki.cn63-1446/r.2016.22.031

Liu, M., Gao, Y., Yuan, Y., Yang, K., Shi, S., Zhang, J., et al. (2020). Efficacy and Safety of Integrated Traditional Chinese and Western Medicine for Coronavirus Disease 2019 (COVID-19): a Systematic Review and Meta-Analysis. Pharm. Res. 158, 104896. doi:10.1007/s11095-020-03486-8

Liu, W., Chen, Z., Liu, Y., Li, M., Ma, Y., Lu, J., et al. (2019). Epidemiological Analysis of Public Health Emergencies in Guangzhou from 2004 to 2017. Int. J. Virol. 4, 265–268. doi:10.3760/cma.j.issn.1673-4092.2019.04.014

Liu, X., Zhang, M., He, L., and Li, Y. (2012). Chinese Herbs Combined with Western Medicine for Severe Acute Respiratory Syndrome (SARS). Cochrane Database Syst. Rev. 10 (10), CD004882. doi:10.1002/14651858.CD004882.pub3

Lu, H., Chen, L., Sha, W., Hu, X., and Hu, Z. (2013). Systematic Evaluation on the Safety of Integrated Traditional Chinese and Western Medicine for Severe Acute Respiratory Syndrome (SARS). Zhonghua Er Ke Za Zhi 51 (10), 795–797. doi:10.3760/cma.j.issn.0254-4462.2013.10.031

Luo, X., Ni, X., Lin, J., Zhang, Y., Wu, L., Huang, D., et al. (2021). The Add-On Effect of Chinese Herbal Medicine on COVID-19: A Systematic Review and Meta-Analysis. Phytotherapy 85, 153282. doi:10.1016/j.phymed.2020.153282
Analysis of Randomized, Controlled Trials. *Altern. Ther. Health Med.* 20 (2), 25–30.

Zhou, F., Pu, L., Rong, X., Liu, J., Yang, Y., and Liu, W. (2021). Efficacy and Safety of Chinese Herbal Decoction Combined with Western Medicine in Treatment of COVID-19: A Meta-analysis. *J. Pract. Med.* 37 (5), 564–568. doi:10.3969/j.issn.1006-5725.2021.05.002

Zhou, L. P., Wang, J., Xie, R. H., Pakhale, S., Krewski, D., Cameron, D. W., et al. (2021). The Effects of Traditional Chinese Medicine as an Auxiliary Treatment for COVID-19: A Systematic Review and Meta-Analysis. *J. Altern. Complement. Med.* 27 (3), 225–237. doi:10.1089/acm.2020.0310

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