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Coronavirus Pandemic

Oral traditional Chinese medicine for mild to moderate cases of COVID-19: a network meta-analysis based on RCTs

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Abstract

Introduction: This systemic review examines the effectiveness and safety of combining traditional Chinese medicine with standard therapy in the treatment of mild to moderate cases of coronavirus disease 2019 (COVID-19).

Methodology: We retrieved articles from PubMed, Web of Science, Cochrane, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, Weipi (VIP), and China Biology Medicine disc (CBM). The deadline for retrieval was 20 August 2022, and it was updated on 1 July 2023. Two researchers worked independently on literature screening, data extraction, and evaluation of the quality of the literature.

Results: A total of 21 randomized controlled trials were included in this review; consisting of 9 articles in English and 12 articles in Chinese. According to the fixed-effects model, the results of the traditional meta-analysis indicated a significantly superior efficacy of oral traditional Chinese medicine combined with standard therapy in treating mild to moderate cases of COVID-19, compared to standard treatment (OR = 1.81, 95% CI: 1.59–2.06), with no increased adverse effects (OR = 1.28, 95% CI: 0.95–1.73). The network meta-analysis results revealed Lianhua Qingke, Toujie Quwen, and Jinhua Qinggan granules as the three best Chinese medicines with the most effective treatment outcomes; while Lianhua Qingwen capsule/granules, Reyanning, and Shufeng Jiedu capsules were the top three Chinese medicines with the fewest side effects.

Conclusions The efficacy of oral traditional Chinese medicine combined with standard therapy in treating mild to moderate COVID-19 was significantly superior to standard therapy alone. However, the limited quality of evidence reduces the reliability of the meta-analysis.

Key words: COVID-19; medicine; treatment; meta-analysis; herbs.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic spread worldwide, posing significant challenges to global public health. Vaccines have been developed promptly as a result of the continued efforts of scientists around the world. However, the constant emergence of new variants of the COVID-19 virus indicates that we still have a long way to go in terms of overall prevention and control of COVID-19. As of 7 January 2024, there have been a total of 774,075,242 reported cases of COVID-19, resulting in 7,012,986 deaths [1].

Some COVID-19 patients may exhibit asymptomatic infection, while others may develop pneumonia. Approximately 5% of infected individuals or 20% of hospitalized patients experienced severe symptoms and required intensive care treatment [2]. Mild patients experience symptoms such as fever, fatigue, and a dry cough, while severe cases may have difficulty breathing, acute respiratory distress syndrome, septic shock, uncorrectable metabolic acidosis, and coagulation disorders, among other complications [3]. A considerable amount of research has confirmed that the release of various inflammatory cytokines, including IL-6, IL-12, and tumor necrosis factor-alpha (TNF-α), leading to an inflammatory cytokine storm, is a central pathological process in exacerbating the condition and even causing death in patients with COVID-19. It is also one of the main contributors to poor disease prognosis [4–9]. Therefore, early diagnosis and effective intervention to minimize the occurrence of severe cases are critical steps in the treatment of COVID-19.

Currently, COVID-19 is primarily treated using western medical methods such as immunotherapy, respiratory support, glucocorticoids, blood purification, extracorporeal membrane oxygenation, and others. These methods have somewhat reduced the mortality rate. Traditional Chinese medicine (TCM) uses syndrome differentiation and treatment for COVID-19, tailoring the treatment for each individual. Early intervention with TCM can effectively alleviate

symptoms, shorten the duration of fever and of the disease, and decrease the likelihood of mild and moderate patients developing into severe cases [10]. Various oral Chinese patent medicines, such as Huaqingwen granule, Jinhua Qinggan granule, and Shufeng Jiedu capsule, have been used for treating COVID-19 [11]. Studies suggest that these medicines can impact the coronavirus through multiple components, targets, and pathways. The primary components have a strong binding ability with Mpro and ACE2, and their mechanisms may be associated with broad-spectrum antiviral, antibacterial, antipyretic, antitussive and phlegm-resolving, and immune regulation effects [12,13]. Therefore, the integration of Chinese and western medicine has become a crucial approach to improve the cure rate and reduce mortality rate of COVID-19.

Although several systematic reviews and meta-analyses (SRs/MAs) have already demonstrated the effectiveness and safety of TCM as an additional treatment for COVID-19, there are still some issues that need to be addressed. Firstly, these SRs/MAs have not only included randomized controlled trials (RCTs) but also retrospective studies. By combining and analyzing data from different types of studies, the reliability of the results is somewhat reduced [14–16]. Additionally, published SRs/MAs have examined and analyzed different types of TCMs, but the composition of each TCM varies significantly, making it impossible to determine which drugs are truly effective [16,17]. Furthermore, there are numerous TCM options available as additional treatments for COVID-19, but there is a lack of direct comparative clinical studies evaluating the efficacy of different drugs. Published SRs/MAs have also failed to compare the efficacy of different TCM options [16].

In summary, although there are several TCMs available as an adjunct to western medicine for the treatment of COVID-19, it is essential to rely on reliable evidence to determine the most effective drugs. This will ensure accurate guidance for future clinical treatment. Therefore, the objective of this study was to review a comprehensive range of RCTs on the adjunctive treatment of COVID-19 with TCMs. This study also conducted systematic reviews and network meta-analyses to further investigate the most effective treatments. The ultimate goal was to provide valuable references for future clinical medication.

Methodology

This systematic review and meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The review was registered in advance under the CRD42022362499 identification number in the PROSPERO database.

Inclusion and exclusion criteria

RCTs with patients ≥ 18 years of age who had been diagnosed with COVID-19 based on real time reverse transcriptase polymerase chain reaction (RT-PCR) testing and clinical symptoms were included. Studies that involved oral Chinese patent medicine and conventional therapy (control) were included. Clinical improvement rate was measured as significantly reduced or mostly disappeared signs and symptoms.

Studies indicate that the primary clinical symptoms of COVID-19 are dry cough, fatigue, fever, muscle aches, changes in smell, diarrhea, reduced appetite, nausea, vomiting, and eye symptoms. In order to isolate the impact of the disease itself, we focused solely on evaluating the potential side effects that may arise from drug treatment, effectively excluding the aforementioned symptoms.

The exclusion criteria were (1) patients suspected to have severe or critical illnesses, as well as those with severe underlying conditions such as bronchial asthma, severe pulmonary interstitial lesions, severe immune deficiencies, or congenital heart disease; (2) patients who had received treatment solely with either Chinese herbal medicine or Western medicine, as well as those who had been taking herbal decoctions or injections; (3) studies that did not match the intended type, such as reviews, conference abstracts, letters, and editorials. 4) studies that had not reported the expected outcome measures; (5) studies for which the full text or necessary data could not be obtained.

Data sources and searches

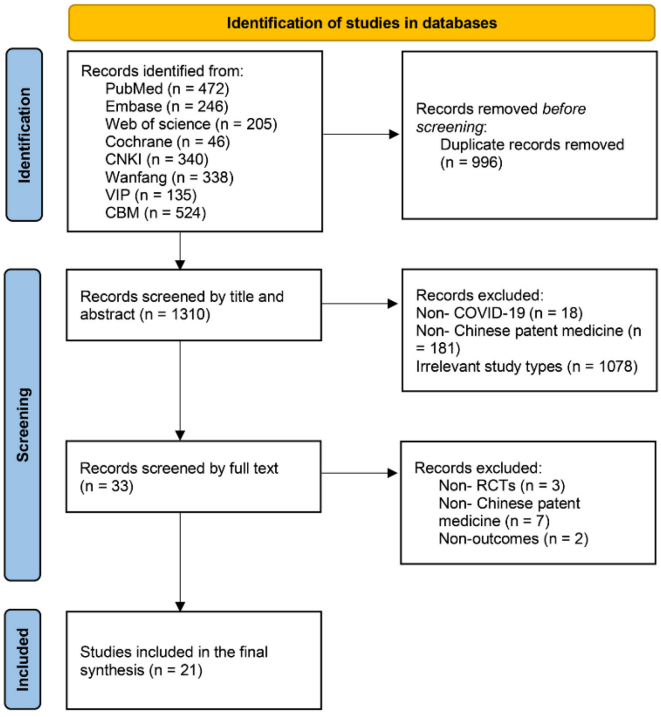
Candidate studies were identified by conducting searches in the following databases: PubMed, Web of Science, Cochrane, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, Weipi (VIP), and China Biology Medicine disc (CBM). The search included articles published from the inception of these databases until 20 August 2022. The retrieval was updated on 1 July 2023. The search strategy utilized the terms (SARS-CoV-2 OR SARS-CoV2 OR 'severe acute respiratory syndrome coronavirus 2' OR 2019-nCoV OR 2019nCoV OR coronavirus OR covid-19 OR COVID19 OR COVID-19) AND (Jinhua Qinggan OR Xuebijing OR Lianhua Qingwen OR Huoxiang Zhengqi OR Toujie Quwen OR Lianhua Qingke OR Chinese patent medicine OR Shuanghuanglian OR

Shufeng Jiedu). More details on the search criteria are listed in Supplementary Table 1. Additionally, the reference lists of the included studies, as well as previously published guidelines and systematic reviews, were also searched.

Literature screening, data extraction, and quality evaluation

Two researchers, with extensive experience in systematic reviews, worked independently to conduct literature screening and cross-checking based on the aforementioned inclusion and exclusion criteria. In cases of disagreement, a third party offered assistance in making judgments. Information was extracted according to a pre-established information extraction table, which included the following: (1) basic information such as author, year, country, number of participants in the experimental and control groups, severity of the condition, age, diagnostic criteria, name, characteristics, and treatment plan of the oral TCM, treatment medication of the control group, and treatment duration; (2) pre-determined outcome measures; and (3) key information for bias risk assessment. Additionally, the quality of evidence from RCTs was assessed using the Cochrane risk of bias assessment tool [19].

Figure 1. PRISMA flow chart with details of literature search.



CBM: China Biology Medicine disc; CNKI: China National Knowledge Infrastructure; VIP: Wanfang: Weipi; COVID-19: coronavirus disease 2019; RCT: randomized control trial.

Statistical analysis

Statistical analysis was performed using STATA 16.0 software [20]. The odds ratio (OR) was used as the effect analysis statistic for binary variables, while the mean difference (MD) was used for continuous variables. All effect sizes were presented with a 95% confidence interval (CI). The network command was utilized for data processing in the network meta-analysis, and network evidence plots were generated to examine various intervention measures. The surface under the cumulative ranking curve (SUCRA) was computed to assess and rank the differences in therapeutic efficacy among different intervention measures. A "correction-comparison" funnel plot was constructed to evaluate publication bias of the included studies. Inconsistency testing was performed when a closed loop was formed.

Results

Literature search results

A total of 2,306 relevant articles were obtained from 8 databases. After removing duplicates and conducting initial screenings by reviewing titles and abstracts, a second screening was carried out by reading the full texts. After the second screening, 21 RCTs were included, with 9 in English [21–29] and 12 in Chinese [30–41] For details on the literature selection outcomes, please refer to Figure 1.

Basic information of included studies

The 21 studies included in this analysis were all RCTs. They involved a total of 5,220 patients, with sample sizes ranging from 48 to 2,800 in each individual study. The patients included in these studies were all over 18 years old, and their average ages varied from 39.65 to 70.05 years across different studies. All COVID-19 patients included in these studies were confirmed through RT-PCR and clinical manifestations. The severity of their condition was categorized as mild, moderate, or common type of COVID-19, with critically ill patients being excluded. The TCM that were orally administered in these studies included Jinhua Qinggan granule (JHQG), Lianhua Qingwen capsule/granules (LHQW), Huoxiang Zhengqi dripping pills (HXZQ), Toujie Quwen granules (TJQW), Lianhua Qingke granules (LHQK), Shuanghuanglian oral liquids (SHL), Shufeng Jiedu capsule (SFJD), Liushen wan (LS), and Reyanning (RYN). These TCMs were available in various forms

such as oral liquids, tablets, granules, pill formulations, and capsules. The frequency of medication for the patients in different studies ranged from 2 to 3 times per day, with a duration of 5 to 14 days. More detailed basic information regarding the included studies is summarized in Supplementary Table 2.

Results of quality evaluation

Out of the 21 studies analyzed, 15 studies employed random number tables or computers to assign participants into groups while the remaining 6 studies did not explicitly state their method of random grouping. Only 4 studies used sealed envelopes to conceal the allocation of participants. Additionally, blinding was implemented for both the subjects and researchers in only 3 studies. Nine studies implemented blinding for outcome evaluators. None of the studies had any patients lost to follow-up, and there were no other potential sources of bias that could influence the study findings. Moreover, a total of 8 studies had their research protocols pre-registered (Figure 2).

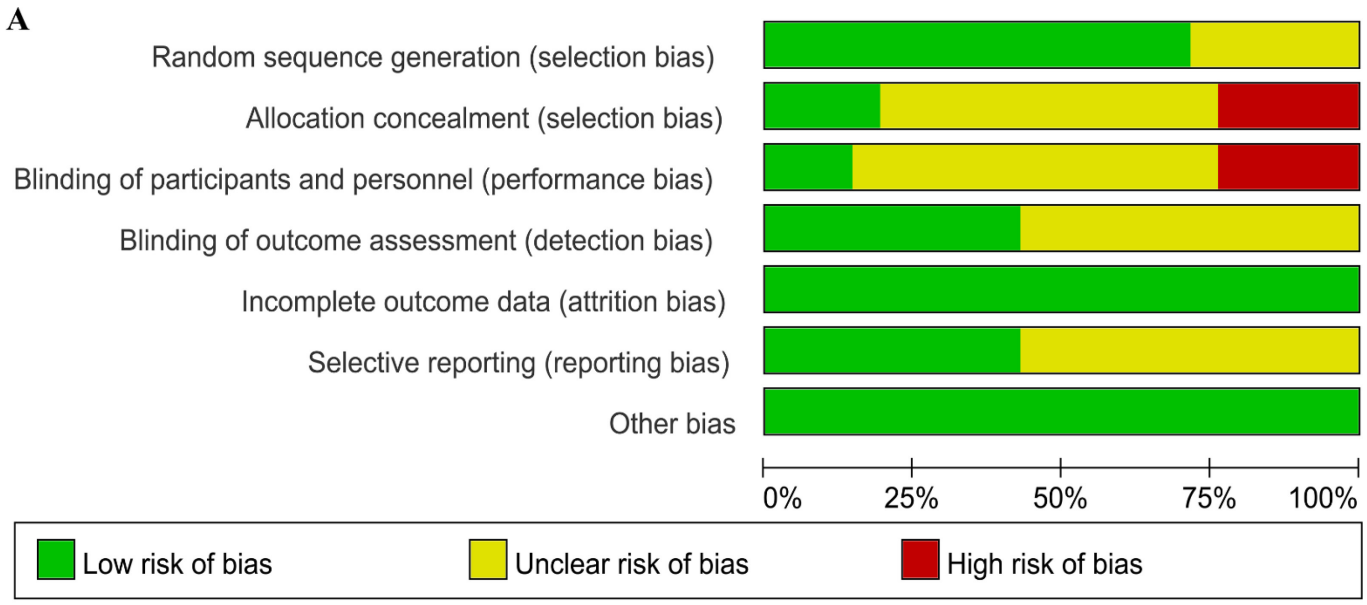
Meta-analysis results

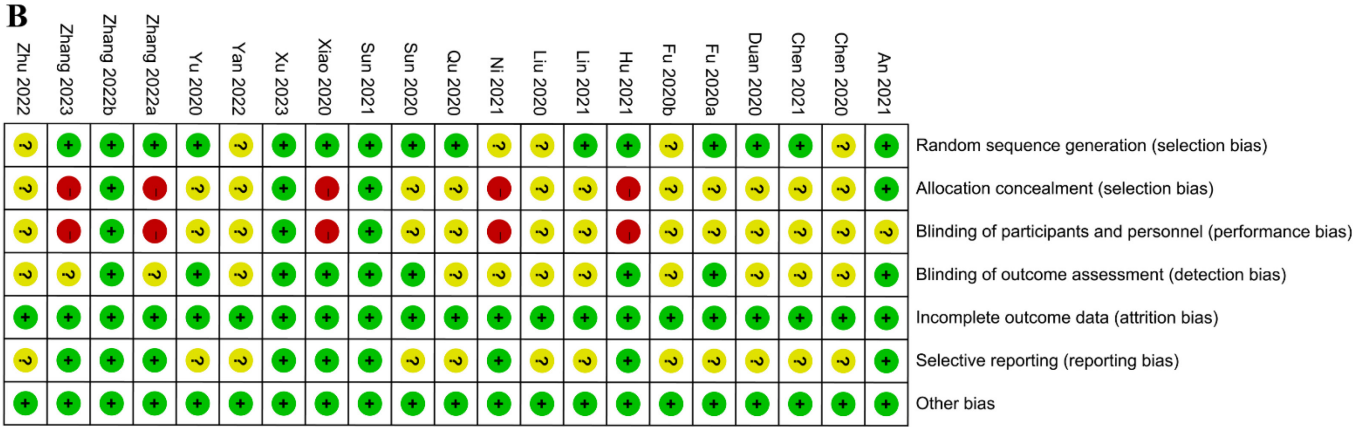
Clinical improvement rate

A total of 19 studies documented the rate of clinical improvement among patients. According to the traditional meta-analysis results, which were based on a fixed-effects model, patients who received oral Chinese patent medicine in addition to standard treatment exhibited a significantly higher clinical improvement rate compared to patients who received standard treatment alone (OR = 1.81, 95% CI: 1.59–2.06; Figure 3).

The network meta-analysis results indicate that the therapeutic effects of the five TCMs, LHQK, JHQG, LHQW, RYN, and TJQW, were significantly superior to conventional therapy (CT). Among the nine TCMs, JHQG, LHQK, LHQW, and TJQW exhibited better

Figure 2. Results of evidence quality assessment. A. Risk of bias graph. B. Risk of bias summary.



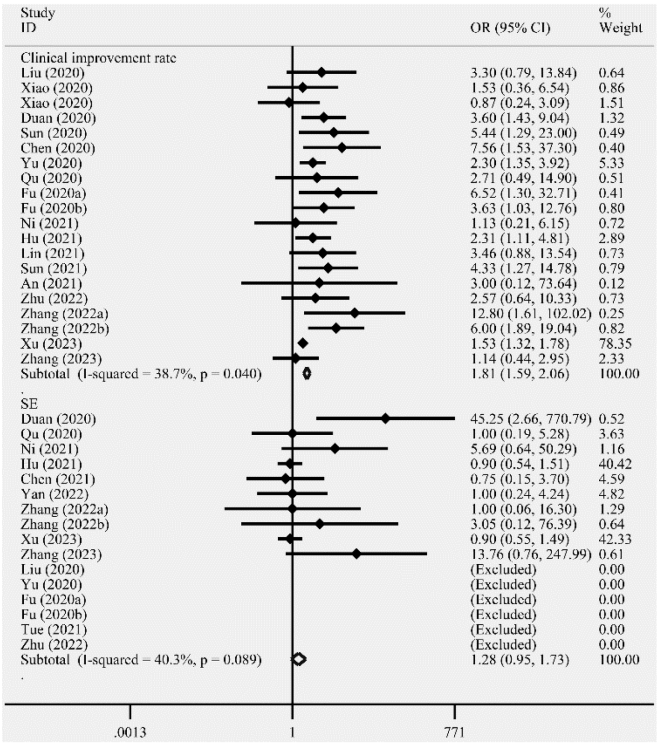


therapeutic effects than RYN, while there was no statistically significant difference in treatment effects between the other TCMs (Figure 4A). The evidence map displayed a total of 19 studies encompassing nine orally administered TCMs, with one study using a combination of HXZQ and LHQW for the treatment of COVID-19 patients (Figure 4B). The SUCRA results revealed that the top three TCMs in terms of treatment effects were LHQK, TJQW, and JHQG (Figure 4C). The comparison-adjusted funnel plot demonstrated a generally symmetrical shape, implying a lower likelihood of publication bias and limited influence from small sample sizes (Figure 4D).

Side effects

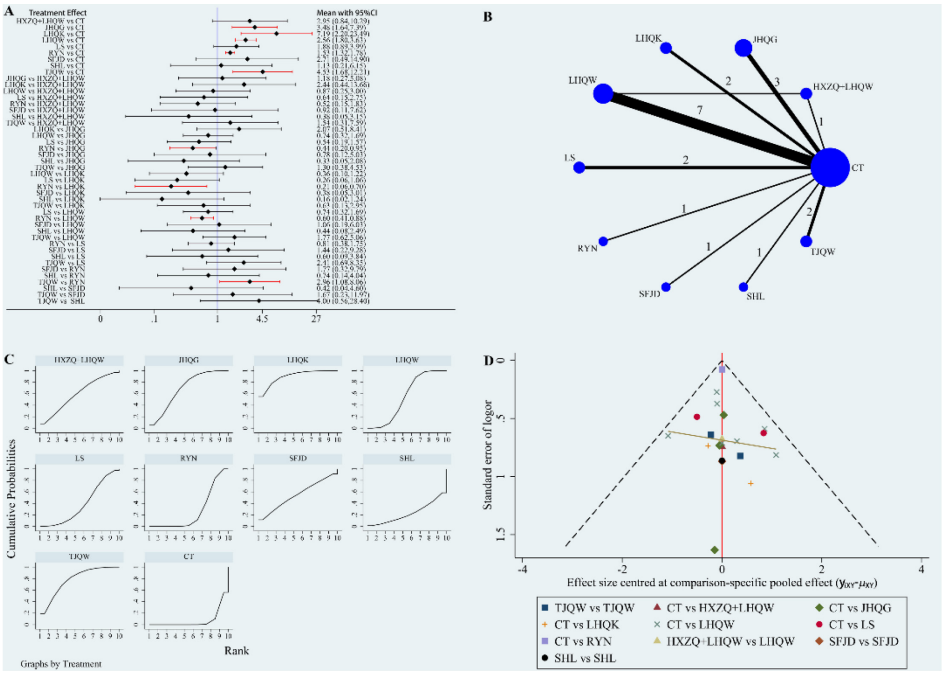
A total of 16 studies documented the side effects of medication in patients. These side effects primarily include drug allergies such as rashes and skin reactions, as well as constipation, urinary tract infections, abnormal liver function, abnormal kidney function, drug-induced diarrhea, myocardial injury, and more. Among these reports, 6 studies stated that no side effects occurred in patients during the treatment period. The results of the traditional meta-analysis, based on a fixed-effects model, showed no statistically significant

Figure 3. Traditional meta-analysis results of clinical improvement rate and side effects.



SE: standard error; OR: odds ratio.

Figure 4. Network meta-analysis results of clinical improvement rate. A. Comparative results between different medications. B. Network plot: the size of the circles represents the total sample size, and the thickness of the lines represents the number of studies. C. Rank probability plot: the larger the area under the curve, the better the therapeutic effect of the medication. D. Comparative adjusted funnel plot.



CT: conventional therapy; HXZQ: Huoxiang Zhengqi dripping pills; JHQG: Jinhua Qinggan granule; LHQK: Lianhua Qingke granules; LHQW: Lianhua Qingwen capsule/granules; LS: Liushen wan; RYN: Reyanning; SFJD: Shufeng Jiedu capsule; SHL: Shuanghuanglian oral liquids; TJQW: Toujie Quwen granules.

difference in the incidence of side effects between patients who received oral Chinese medicine alongside standard treatment, and those who received standard treatment alone (OR = 1.28, 95% CI: 0.95–1.73; Figure 3).

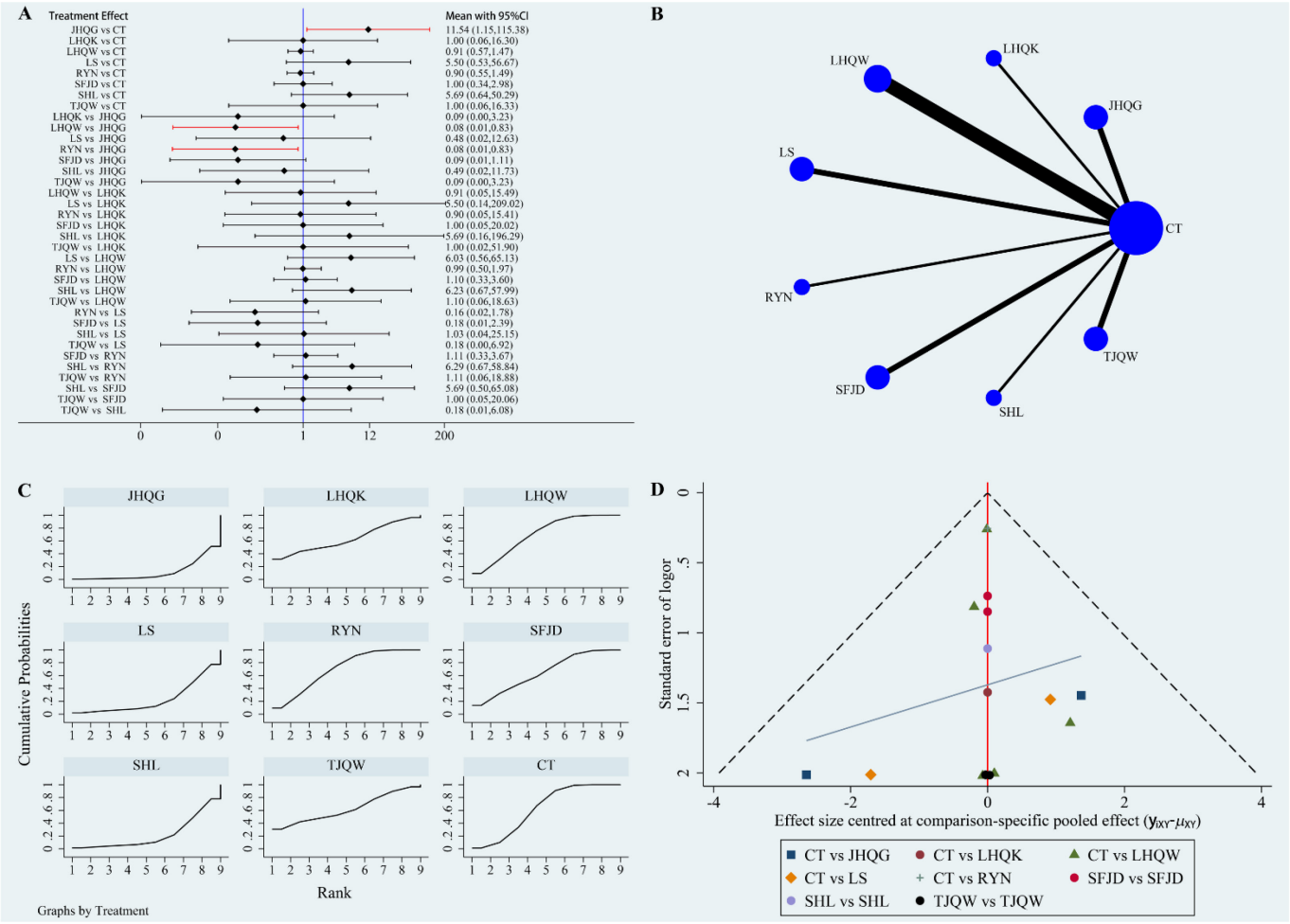
The results of the meta-analysis for the network showed that the incidence rate of adverse effects of JHQG was significantly higher than that of LHQW, CT, and RYN (Figure 5A). However, there were no statistically significant differences in the incidence rates of adverse effects among the other drugs. The evidence map displayed that 16 studies reported adverse effects of 8 TCMs but there was a lack of direct comparison between different TCMs (Figure 5B). The SUCRA results demonstrated that LHQW, RYN, and SFJD had the lowest incidence rates of adverse effects, respectively (Figure 5C). The comparison-adjusted funnel plot exhibited a symmetrical shape, suggesting a relatively low likelihood of publication bias and small sample effects (Figure 5D).

Discussion

Evidence overview

Similar to western medicine, TCM is capable of inhibiting replication of the novel coronavirus by acting on various ribosomal proteins and reducing the release of cytokines from host cells [42]. The combination of Chinese and western medicine can regulate immune and cytokine-related pathways, inhibit and alleviate excessive immune responses, eliminate inflammation, and thus alleviate the clinical symptoms of COVID-19 [43]. In summary, TCM has the advantages of multiple components, multiple pathways, and multiple targets; but this also presents a disadvantage [44]. The

Figure 5. Network meta-analysis results of side effect. A. Comparative results between different medications. B. Network plot: the size of the circles represents the total sample size, and the thickness of the lines represents the number of studies. C. Rank probability plot: the larger the area under the curve, the smaller the side effects of the medication. D. Comparative adjusted funnel plot.



CT: conventional therapy; JHQG: Jinhua Qinggan granule; LHQK: Lianhua Qingke granules; LHQW: Lianhua Qingwen capsule/granules; LS: Liushen wan; RYN: Reyanning; SFJD: Shufeng Jiedu capsule; SHL: Shuanghuanglian oral liquids; TJQW: Toujie Quwen granules.

multitude of pathways and modes of action may cause unexpected side effects of TCM, and there is a lack of strict standards regarding dosage, ingredients, and treatment duration. Therefore, evaluating the effectiveness and safety of TCM through systematic review and exploring the most promising drugs have significant guiding value for future clinical practice. Currently, there are various categories of TCMs available for clinical use, including oral preparations, injections, decoctions, and more. Due to the relatively mature research and commercialization of oral TCM, it is easier for patients to accept. This study specifically analyzed the research on adjuvant treatment of COVID-19 with oral TCM [45]. Moreover, for sudden, emerging, and highly infectious diseases like COVID-19, the guidance from high-quality research evidence obtained through clinical trials is self-evident. Establishing high-quality research evidence based on these clinical trials and assisting healthcare workers in evidence-based decision-making are essential for improving clinical treatment outcomes and serve as the core of evidence-based clinical decisions. Consequently, we only included the results of randomized controlled studies for analysis.

TCM has a positive impact on the prevention and treatment of infectious diseases [46]. Compared to methods used in modern medicine that directly kill or inactivate pathogens, TCM has a broader range of effects on the human body. It can eliminate the novel coronavirus through various mechanisms, including reducing excessive immune response, alleviating inflammation-induced damage, antioxidant activity, and anti-apoptotic effects [47,48]. For instance, the Liushen pill consists of six TCMs: pearl powder, musk, bezoar, realgar, borneol, and toad venom. It possesses heat-clearing, detoxifying, anti-inflammatory, and pain-relieving properties. In vitro experiments have demonstrated its ability to inhibit the proliferation of the novel coronavirus. On the other hand, LHQW comprises more than 10 traditional Chinese medicines, such as forsythia, honeysuckle, fried *Ephedra sinica*, fried bitter apricot, gypsum, and *Isatis* root. It has fever-clearing, detoxifying, and lung-cooling effects. Pharmacological experiments have indicated that high doses of the LHQW can modulate the activity of cyclooxygenase-2 in the arachidonic acid metabolic pathway, reduce the release of cytokines from host cells, and decrease viral replication, significantly improving lung inflammation [49,50]. Based on the results of 21 RCTs, our findings demonstrate that TCM is significantly more effective than western medicine alone as an adjuvant therapy for COVID-19. These findings are consistent with previous research. Liang *et al* summarized the research results of TCM adjuvant treatment for COVID-19 from various study types and discovered that a combination of TCM and conventional western medicine improves the recovery rate of patients, reduces the duration of fever, cough, and fatigue, and increases the negative conversion rate of nucleic acid tests [16]. However, their study did not examine the treatment effects of different TCMs. Therefore, they concluded that the study was exploratory and not directly applicable to clinical practice.

Our network meta-analysis provides additional information. Our results indicate that LHQK, TJQW, and JHQG are the most effective TCMs for adjuvant treatment of COVID-19. These three TCMs consist of various components such as *Forsythia suspensa*, *Lonicera japonica*, and *Isatis indigotica*. According to traditional Chinese medicine theory, honeysuckle and *Isatis indigotica* have anti-inflammatory and antibacterial effects and can enhance the body's immune system [51]. Honeysuckle achieves its therapeutic goals by upregulating IFN-α, reducing IL levels, inhibiting the NF-κB signaling pathway, inhibiting the p38MAPK signaling pathway, regulating non-specific immunity, and inhibiting or blocking viral replication or synthesis [52–54]. Studies have shown that microRNA MIR2911 in honeysuckle extract can bind to multiple sites of the SARS-CoV-2 virus, inhibiting the synthesis of viral proteins. Clinical trials have also demonstrated that taking MIR2911 can accelerate the conversion rate of nucleic acid testing to negative in COVID-19 patients [55]. *Forsythia* is commonly used to clear heat and fire, specifically for treating febrile diseases, acute upper respiratory infections, and coughs. It also has the ability to inhibit various viruses, including influenza A virus, Japanese encephalitis virus, and respiratory syncytial virus [56]. LHQK is also a prominent TCM recommended by the National Health Commission of the People's Republic of China in the " 3 medicines and 3 formulations" [57]. It plays a role in relieving symptoms, reducing the incidence, and reducing mortality rate of critically ill patients with COVID-19 [11,58]. Unfortunately, there is currently no evidence from in vivo studies that fully demonstrate the mechanism of action of the drug components in LHQK. Therefore, more basic experiments and clinical research are needed in the future to further explore the pharmacological mechanisms and efficacy of related TCMs [59]. It is important to note that the patients involved in our study mainly had mild or common symptoms, so the evidence

for the treatment of critically ill patients with TCM is limited.

Although TCM has gained attention from clinical doctors and patients for its effectiveness, its widespread use in clinical practice is limited due to potential side effects. The establishment of accurate standards for toxic substances, safety protocols, specific patient populations, and rational medication in TCM remains inadequate [60]. The clinical application of TCM is complex, and irrational medication practices manifest in various forms, including misuse, abuse, improper solvent usage, pharmacological antagonism, incompatible drug combinations, drug interactions, and inappropriate treatment based on syndrome differentiation. All these factors contribute to an increased likelihood of experiencing side effects. Research has shown that certain TCMs contain nephrotoxins and mutagens, which can increase the risk of hepatic and renal toxicity, arrhythmia, and even shock. These findings have raised concerns about the potential dangers of using TCM [61–63]. Our traditional meta-analysis results suggest that there is no significant statistical difference in the occurrence of adverse effects between TCM and conventional treatment. This indicates that TCM is, to some extent, safe. Additionally, our subsequent network meta-analysis findings reveal that, apart from JHQG, the incidence of adverse effects between other TCMs and standard treatment does not vary significantly. Furthermore, the three safest TCMs, LHQW, RYN, and SFJD, are ranked at the top in terms of safety, whereas standard treatment ranks comparatively lower on the safety scale. Unfortunately, several side effects have been reported as a result of the ongoing research, including drug allergies, constipation, urinary tract infections, abnormal liver and kidney function, drug-induced diarrhea, and myocardial injury. However, due to limitations in both the quantity and quality of the studies conducted, we can only carry out a comprehensive analysis on the side effects caused by TCM treatment in various studies. Rather than investigating the safety of TCM based solely on individual side effects, future research needs to carefully determine whether the symptoms experienced by patients are caused by the novel coronavirus or the drug treatment, and should clearly report these findings in the study. By doing so, we will be able to provide a higher quantity and quality of evidence for clinical practice.

Quality of evidence

Out of the 21 studies analyzed, only 15 provided specific information on how they were randomized, despite all of them being RCTs. Moreover, only 4 studies incorporated both allocation concealment and blinding of participants and researchers, leading to significant biases in participant selection and study performance. To enhance the effectiveness of TCM in treating COVID-19, future studies should focus on carefully designing, executing, and reporting RCTs to minimize biases. While blinding patients in integrated Chinese and western medicine treatments is challenging due to limitations in TCM formulations, it is feasible to blind outcome assessors and analysts. However, only 9 studies successfully blinded outcome assessors. Therefore, future research should prioritize implementing blinding throughout the trial process to reduce biases in study performance and measurement. Additionally, only 8 studies pre-registered their research protocols, leaving 13 studies with uncertain reporting of all research results as planned. Selective reporting of research results can introduce publication bias, potentially compromising the reliability of conclusions. In addition, there were variations in the types of western medications used by different patients while taking traditional Chinese medicine. Furthermore, discrepancies in the frequency of administration (2–3 times/day), duration of treatment (5–14 days), and formulations (including oral liquid, tablets, granules, pills, and capsules) of different traditional Chinese medicines were observed. These differences serve as the primary reasons for the heterogeneity observed among the various studies.

Strengths and limitations of this study

Strengths of this study were: (1) we included only RCTs and conducted comprehensive assessments of the quality of evidence for each study, ensuring the high reliability of our findings; 2) we determined the Chinese patent medicine with the greatest therapeutic potential for COVID-19 by employing a network meta-analysis methodology. This is crucial for informing future clinical practices.

Limitations of this study were: 1) Due to the inclusion of mostly open-label, single-center, and small-sample studies, the testing efficacy of the included studies is limited. In the future, there is a need for more large-sample, high-quality RCTs to investigate the therapeutic effects of orally administered traditional Chinese medicine. 2) Chinese herbal medicines vary greatly in terms of their ingredients and dosage. Furthermore, the limited

number of studies included hinders the possibility of conducting further subgroup analysis. 3) In this study, a combined analysis of different types of side effects was conducted, which may potentially affect the reliability of the meta-analysis results.

Conclusions

The control of the novel coronavirus is challenging, and TCM plays an important role. Combining oral Chinese patent medicine with standard therapy was more effective and safer in treating COVID-19. LHQK, TJQW, and JHQG had the best treatment effect, while LHQW, RYN, and SFJD had the fewest side effects. However, the studies had limitations in randomization, blinding, measurement, and reporting of results. More large-scale trials are needed to investigate the specific role of Chinese patent medicine.

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Authors' contributions

ZZ: project design, manuscript review, and revision; WC: project design, data analysis, and manuscript writing; NH and YL: screening literature and data collection.

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Annex – Supplementary Items

Supplementary Table 1. Chinese and English search strategies.

In order for non-Chinese readers to understand the Chinese search strategy of this article, we have translated the Chinese search terms in the search formula.

1. WOS

(TS=(SARS-CoV-2 OR SARS-CoV2 OR 'severe acute respiratory syndrome coronavirus 2' OR 2019-nCoV OR 2019nCoV OR coronavirus OR covid-19 OR COVID19 OR COVID-19)) AND TS=(Jinhua Qinggan OR Lianhua Qingwen OR Huoxiang Zhengqi OR Toujie Quwen OR Lianhua Qingke OR Chinese patent medicine OR Shuanghuanglian OR Shufeng Jiedu)

2. PubMed

#1: "jinhua qinggan"[Title/Abstract] OR "lianhua qingwen"[Title/Abstract] OR "huoxiang zhengqi"[Title/Abstract] OR "toujie quwen"[Title/Abstract] OR ("Lianhua"[All Fields] AND "Qingke"[Title/Abstract]) OR "chinese patent medicine"[Title/Abstract] OR "Shuanghuanglian"[Title/Abstract] OR "shufeng jiedu"[Title/Abstract]
#2: ((((("jinhua qinggan granules" [Majr]) OR "qingwen baidu" [Supplementary Concept]) OR "Huoxiang-zhengqi" [Supplementary Concept]) OR "shufeng jiedu" [Supplementary Concept]) OR "Medicine, Chinese Traditional"[Mesh]
#3: #1 OR #2
#4: "SARS-CoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "coronavirus"[Title/Abstract] OR "covid 19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "covid 19"[Title/Abstract]
#5: "SARS-CoV-2"[MeSH Terms] OR "Coronavirus"[MeSH Terms] OR "COVID-19"[MeSH Terms]
#6: #4 OR #5
#7: #3 AND #6

3. Cochrane

#1: MeSH descriptor: [Medicine, Chinese Traditional] explode all trees
#2: (Jinhua Qinggan OR Lianhua Qingwen OR Huoxiang Zhengqi OR Toujie Quwen OR Lianhua Qingke OR Chinese patent medicine OR Shuanghuanglian OR Shufeng Jiedu):ti,ab,kw
#3: #1 or #2
#4: (SARS-CoV-2 OR SARS-CoV2 OR 'severe acute respiratory syndrome coronavirus 2' OR 2019nCoV OR coronavirus OR covid-19 OR COVID19 OR COVID-19):ti,ab,kw
#5: MeSH descriptor: [SARS-CoV-2] explode all trees
#6: MeSH descriptor: [COVID-19] explode all trees
#7: MeSH descriptor: [Coronavirus] explode all trees
#8: #4 or #5 or #6 or #7
#9: #3 and #8

4. Embase

#1: ('jinhua qinggan':ab,ti OR 'lianhua qingwen':ab,ti OR 'huoxiang zhengqi':ab,ti OR 'toujie quwen':ab,ti OR 'lianhua qingke':ab,ti OR 'chinese patent medicine':ab,ti OR shuanghuanglian:ab,ti OR 'shufeng jiedu':ab,ti) AND [2019-2022]/py
#2: 'shuanghuanglian'/exp
#3: 'chinese patent medicine'/exp
#4: #1 OR #2 OR #3
#5: ('sars cov 2':ab,ti OR 'sars cov2':ab,ti OR '2019 ncov':ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti OR 2019ncov:ab,ti OR coronavirus:ab,ti OR covid19:ab,ti OR 'covid 19':ab,ti) AND [2019-2022]/py
#6: 'sars cov 2'/exp
#7: 'coronavirus'/exp
#8: 'covid 19'/exp
#9: #6 OR #7 OR #8
#19: #5 AND #10

5. CNKI

主题=(连花清瘟胶囊 OR 疏风解毒胶囊 OR 金花清感颗粒 OR 藿香正气滴丸 OR 透解祛瘟颗粒 OR 连花清咳颗粒 OR 双黄连口服液 OR 中成药) AND (新型冠状病毒肺炎 OR 新冠肺炎 OR 冠状病毒肺炎 OR COVID-19)
Subject: (Jinhua Qinggan OR Lianhua Qingwen OR Huoxiang Zhengqi OR Toujie Quwen OR Lianhua Qingke OR Chinese patent medicine OR Shuanghuanglian OR Shufeng Jiedu) AND COVID-19

6. Wanfang

主题=(连花清瘟胶囊 OR 疏风解毒胶囊 OR 金花清感颗粒 OR 藿香正气滴丸 OR 透解祛瘟颗粒 OR 连花清咳颗粒 OR 双黄连口服液 OR 中成药) AND (新型冠状病毒肺炎 OR 新冠肺炎 OR 冠状病毒肺炎 OR COVID-19)
Subject: (Jinhua Qinggan OR Lianhua Qingwen OR Huoxiang Zhengqi OR Toujie Quwen OR Lianhua Qingke OR Chinese patent medicine OR Shuanghuanglian OR Shufeng Jiedu) AND COVID-19

7. VIP

题名或关键词=(连花清瘟胶囊 OR 疏风解毒胶囊 OR 金花清感颗粒 OR 藿香正气滴丸 OR 透解祛瘟颗粒 OR 连花清咳颗粒 OR 双黄连口服液 OR 中成药) AND (新型冠状病毒肺炎 OR 新冠肺炎 OR 冠状病毒肺炎 OR COVID-19)
Subject: (Jinhua Qinggan OR Lianhua Qingwen OR Huoxiang Zhengqi OR Toujie Quwen OR Lianhua Qingke OR Chinese patent medicine OR Shuanghuanglian OR Shufeng Jiedu) AND COVID-19

8. CBM

#1: ((("连花清瘟胶囊"[不加权:扩展]) OR "疏风解毒"[不加权:扩展]) OR "藿香正气散"[不加权:扩展]) OR "中成药"[不加权:扩展]
#2: "连花清瘟"[常用字段:智能] OR "疏风解毒"[常用字段:智能] OR "金花清感"[常用字段:智能] OR "藿香正气"[常用字段:智能] OR "透解祛瘟"[常用字段:智能] OR "连花清咳"[常用字段:智能] OR "双黄连"[常用字段:智能] OR "中成药"[常用字段:智能]
#3: #1 OR #2
#4: "新型冠状病毒肺炎"[不加权:扩展]
#5: "COVID-19"[常用字段:智能] OR "冠状病毒肺炎"[常用字段:智能] OR "新冠肺炎"[常用字段:智能] OR "新型冠状病毒肺炎"[常用字段:智能]
#6: #4 OR #5
#7: #3 AND #6
#1: ((("Lianhua Qingwen "[unweighted, extended]) OR " Shufeng Jiedu "[unweighted, extended]) OR " Huoxiang Zhengqi "[unweighted, extended]) OR " Chinese patent medicine "[unweighted, extended]
#2: " Lianhua Qingwen "[common field: smart] OR " Shufeng Jiedu "[common field: smart] OR " Jinhua Qinggan "[common field: smart] OR " Huoxiang Zhengqi "[common field: smart] OR " Toujie Quwen "[common field: smart] OR " Lianhua Qingke "[common field: smart] OR " Shuanghuanglian "[common field: smart] OR " Chinese patent medicine "[common field: smart]
#3: #1 OR #2
#4: "COVID-19"[unweighted, extended]
#5: "COVID-19"[common field: smart]
#6: #4 OR #5
#7: #3 AND #6

Supplementary Table 2. Basic information of included studies.

Number [Ref no.]	Author	Year	Country	Number of trial groups	Number of control groups	Severity of disease	Age (years) Mean ± standard deviation	Diagnostic standard	Chinese patent medicine	Characteristics of drugs	Dosage	Control	Therapeutic time
1 [21]	Zhang *et al.*	2022	China	72	72	Mild to moderate	49.56 ± 14.88/52.81 ± 14.83	RT-PCR and clinical manifestations	Lianhua Qingke	Tablet	4 tablets, 3 times/day	Conventional therapy	14 d
2 [22]	Liu *et al.*	2020	China	44	36	Mild to moderate	50.73/51.75	RT-PCR and clinical manifestations	Jinhua Qinggan	Granules	6 g, 2 times/day	Conventional therapy	7 d
3 [23]	Xiao *et al.*	2020	China	119	63	Mild to moderate	56.07 ± 12.10/53.90 ± 13.92	RT-PCR and clinical manifestations	Huoxiang Zhengqi+Lianhua Qingwen/Lianhua Qingwen	Pill/Granules	1 bag, 3 times/day	Conventional therapy	14 d
4 [24]	Ni *et al.*	2021	China	176	59	Mild to moderate	51/54	RT-PCR and clinical manifestations	Shuanghuanglian	Oral liquid	20–60 mL, 3 times/day	Conventional therapy	14 d
5 [25]	Hu *et al.*	2021	China	142	142	Mild to moderate	50.4 ± 15.2/50.4 ± 15.8	RT-PCR and clinical manifestations	Lianhua Qingwen	Capsule	4 grains, 3 times/day	Conventional therapy	14 d
6 [26]	An *et al.*	2021	China	24	8	Mild or normal	50.18 ± 12.25/44.74 ± 11.65	RT-PCR and clinical manifestations	Jinhua Qinggan	Granules	1 bag, 3 times/day	Conventional therapy	14 d
7 [27]	Zhang *et al.*	2022b	China	60	60	Mild or normal	41.07 ± 13.49/44.84 ± 15.41	RT-PCR and clinical manifestations	Lianhua Qingwen	Pill	4 grains, 3 times/day	Conventional therapy	14 d
8 [28]	Xu *et al.*	2023	China	1393	1407	Mild or normal	47 (33–55)/45 (32–56) median with interquartile range	RT-PCR and clinical manifestations	Reyanning	Oral liquid	20 mL, 4 times/day	Conventional therapy	7 d
9 [29]	Zhang *et al.*	2023	China	91	90	Mild or normal	41.09 ± 14.69/40.06 ± 13.52	RT-PCR and clinical manifestations	Liushenwan	Pill	10 pills, 3 times/day	Conventional therapy	7 d
10 [30]	Yu *et al.*	2020	China	147	148	Mild or normal	48. 27 ± 9. 56/47. 25 ± 8. 67	RT-PCR and clinical manifestations	Lianhua Qingwen	Granules	6 g, 3 times/day	Conventional therapy	7 d
11 [31]	Yan *et al.*	2022	China	50	50	Normal	60.26 ± 7.32/5.38 ± 2.03	RT-PCR and clinical manifestations	Shufeng Jiedu	Capsule	4 grains, 3 times/day	Conventional therapy	14 d
12 [32]	Chen *et al.*	2020	China	35	35	Mild to moderate	44.75 ± 4.92/45.21 ± 4.68	RT-PCR and clinical manifestations	Lianhua Qingwen	Granules	1.4 g, 2 times/day	Conventional therapy	15 d
13 [33]	Sun *et al.*	2021	China	40	40	Mild or normal	63. 08 ± 9. 97/60. 28 ± 12. 64	RT-PCR and clinical manifestations	Liushenwan	Pill	10 pills, 3 times/day	Conventional therapy	7 d
14 [34]	Sun *et al.*	2020	China	32	25	Mild to moderate	45.4 ± 14.10/42.0 ± 11.70	RT-PCR and clinical manifestations	Lianhua Qingke	Granules	1 bag, 3 times/day	Conventional therapy	14 d
15 [35]	Qu *et al.*	2020	China	40	40	Normal	39.65 ± 11.20/41.60 ± 10.50	RT-PCR and clinical manifestations	Shufeng Jiedu	Capsule	4 grains, 3 times/day	Conventional therapy	10 d
16 [36]	Lin *et al.*	2021	China	56	55	Normal	68.32 ± 10.16/70.05 ± 9.8	RT-PCR and clinical manifestations	Lianhua Qingwen	Granules	6 g, 3 times/day	Conventional therapy	10 d
17 [37]	Zhu *et al.*	2022	China	26	22	Normal	41.15 ± 14.2/52.18 ± 14.66	RT-PCR and clinical manifestations	Lianhua Qingwen	Granules	1 bag, 3 times/day	Conventional therapy	14 d
18 [38]	Fu *et al.*	2020a	China	32	33	Mild or normal	43.26 ± 7. 15/43. 68 ± 6. 45	RT-PCR and clinical manifestations	Toujie Quwen	Granules	1 bag, 2 times/day	Conventional therapy	10 d
19 [39]	Fu *et al.*	2020b	China	37	36	Normal	45.26 ± 7.25/44.68 ± 7.45	RT-PCR and clinical manifestations	Toujie Quwen	Granules	1 bag, 2 times/day	Conventional therapy	15 d
20 [40]	Duan *et al.*	2020	China	82	41	Mild to moderate	51. 99 ± 13.88/50. 29 ± 13.17	RT-PCR and clinical manifestations	Jinhua Qinggan	Granules	6 g, 3 times/day	Conventional therapy	5 d
21 [41]	Chen *et al.*	2021	China	30	30	Mild to moderate	50.16 ± 5.11/49.52 ± 5.06	RT-PCR and clinical manifestations	Lianhua Qingwen	Capsule	4 grains, 3 times/day	Conventional therapy	10 d