The effects of Chinese herbal injections on patients with COVID-19: a systematic review

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Abstract

Background

COVID-19, caused by SARS-CoV-2, led to a worldwide pandemic of acute respiratory illness resulting in more than 760 million infections and 6.9 million deaths. Recent clinical research has demonstrated the beneficial effects of Chinese herbal injections (CHIs), a novel kind of traditional Chinese medicine preparation, in the treatment of COVID-19. This systematic review aimed to investigate the efficacy and safety of CHIs in treatment of COVID-19 and to evaluate the quality of evidence.

Methods

A systematic search for both human RCTs and non-randomized trials evaluating the efficacy and safety of CHIs in treatment of COVID-19 was performed on PubMed, Cochrane Library, and Ovid, where the language was restricted to English. Quality assessment included the risk of bias (via the Cochrane risk of bias tool) and quality of evidence (via the GRADE system).

Results

Of 3403 articles identified, 6 studies published between 2020 and 2021 with 382 participants met our selection criteria and were included for analysis. The treatment group was defined as the CHI (XBJ, RDN, or XYP injection) combined with routine treatment, to compare with routine treatment alone in the control group. The included studies overall had moderate risk of bias and low quality of evidence, mainly due to being open-label and confounding. The evidence showed that the clinical efficacy of treatment groups was better for the treatment of COVID-19, in terms of clinical symptom resolution, length of hospital stay, time taken for a negative nucleic acid test, and mortality. There was no significant difference in incidence of adverse events between the study groups (P > 0.05).

Conclusions

CHIs can play an effective role in the treatment of COVID-19 and can be safely administered under rational operation. More double-blinded RCTs with larger sample sizes are warranted, and the effects on longer-term symptom resolution or the effects of other different CHIs need to be explored in the future.

Background

The outbreak of Coronavirus disease 2019 (COVID-19) has had a profound impact on global health, presenting significant challenges to healthcare systems worldwide. As of June 2023, the World Health Organisation (WHO) has reported an estimated 691 million cases of COVID-19 and approximately 7 million deaths [1], underscoring the urgent need for alternative treatment approaches. COVID-19 is a highly contagious respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Wuhan, China, in December 2019, and rapidly spreading to become a global pandemic. The virus is primarily transmitted through airborne particles when infected individuals cough, sneeze, talk, or breathe [2].

Patients with COVID-19 can experience a wide range of symptoms, varying from mild manifestations like fever, cough, and exhaustion to severe conditions such as acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS), which can lead to fatalities [3]. The disease's severity is classified into four categories: mild,
moderate, severe, and critical, based on its clinical presentation [4]. Notably, patients initially categorized with mild COVID-19 can rapidly deteriorate and progress to severe cases [5].

Zhang et al. [6] reported that approximately 20% of individuals with COVID-19 may progress to severe status, resulting in an increased risk of mortality [7]. Despite the widespread use of approved vaccines globally, the availability of targeted and effective remedies for COVID-19 remains limited [8]. Extensive research has been conducted on antiviral drugs, including those used to treat human immunodeficiency virus (HIV) and malaria, for their potential in COVID-19 treatment. However, none of these drugs have been licensed due to their high toxicity, lack of therapeutic advantages, and adverse pharmacodynamics [9]. Consequently, further investigation is essential to evaluate alternative potential treatments for COVID-19.

For thousands of years, traditional Chinese medicine (TCM) has been utilized extensively in China to treat various viral respiratory illnesses like SARS, community-acquired pneumonia and influenza [10]. TCM is thought to treat COVID-19 by inhibiting the excessive inflammation [9]. Some TCM remedies have been tested for their effectiveness against COVID-19. For example, the Lianhuaqingwen capsule has been found to prevent the COVID-19 from developing more severe and help patients recover from the disease [11, 12].

Chinese herbal injections (CHIs), a novel kind of TCM preparation, have shown benefits in the treatment of COVID-19, such as shortening the time to achieve negative SARS-CoV-2 RNA tests, improving the symptom resolution rate, and inhibiting the expression of SARS-CoV-2-induced pro-inflammatory cytokines, and are therefore recommended [3, 9, 13]. The valuable and active ingredients from herbs are extracted and purified to produce CHIs using modern scientific techniques and approaches [14]. As an alternative administration form of TCM preparation, CHIs not only have the properties of injection, but also preserves the characteristics of TCMs [15]. However, skepticism exists regarding the efficacy and safety of CHIs due to the lack of standardized quality control and regulatory oversight, raising concerns about the consistency and purity of TCM formulations. Additionally, TCM compounds' complex nature and individual variability in response make it challenging to determine their true effectiveness [16].

The significance of exploring CHIs arises from several reasons. Firstly, the pandemic has placed immense stress on healthcare systems, highlighting the need for readily available therapeutic treatments. Secondly, TCM is widely used in China, playing an important role in the holistic approach to disease management. This approach not only focuses on symptom relief but also considers the significance of individualized imbalances within the body, making it suitable for an integrated treatment strategy. Strengthening our understanding of the mechanisms behind herbal injections will provide further insights into interactions between the immune system and viral replication processes, contributing to the development of targeted therapies and the discovery of novel antiviral agents. Several studies have investigated the effects of Chinese herbal injections on COVID-19 patients, but a systematic review to synthesize the existing evidence is lacking.

In light of these gaps in the literature, this systematic review aimed to evaluate the therapeutic effects of Chinese herbal injections on COVID-19 patients, and to examine the safety profile of CHIs assessing any potential adverse events associated with their use, thereby providing stronger evidence and guidance for the doctors, investigators and policy makers to help combat the global health emergency.

**Methods**

A systematic review was performed to find all human trials that determined the effects of Chinese herbal injections on COVID-19 patients. The review was registered on PROSPERO (CRD42023432074). The methods of review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [17].

**Search strategy**
A systematic search was performed on three databases including PubMed, Cochrane Library, and Ovid. The search keywords used for the databases are as follows: (Coronavirus OR SARSCoV-2 OR COVID-19 OR corona virus disease 2019) AND (Chinese herbal injection OR Traditional Chinese Medicine OR XueBiJing OR XiYanPing OR ReDuNing OR TanReQing OR ShenMai). The language was restricted to English. There was no restriction on publication date.

**Inclusion and exclusion criteria**

The PICOS (Participants, Interventions, Comparisons, Outcomes, and Study designs) criteria are presented in Table 1. The inclusion criteria for this review were as follows: (1) studies that included patients diagnosed with COVID-19; (2) studies that included Chinese herbal injection in the treatment of the patients and evaluated its efficacy; (3) articles in English language.

The exclusion criteria were as follows: (1) duplicate publications; (2) abstracts, books, protocols, conference presentations, literature reviews, or systematic review and meta-analysis; (3) interventions of studies included Chinese herbal injection combined with other drugs; (4) studies included patients under the age of 18; (5) studies included pregnant or lactating women.

<table>
<thead>
<tr>
<th>PICOS criteria</th>
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<tbody>
<tr>
<td>Participants</td>
</tr>
<tr>
<td>Interventions</td>
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<tr>
<td>Comparisons</td>
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<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Study designs</td>
</tr>
</tbody>
</table>

**Screening and selection of studies**

All articles produced by searches were transferred into EndNote 20 software to remove duplicates before screening and the filters were used to exclude Abstract, Books and Documents, and those published in a language other than English. The title and abstract of every article identified were screened for relevance based on the inclusion and exclusion criteria, after which, retrieved, full-text articles were assessed for eligibility. PRISMA 2020 flow diagram was used for screening and selection of studies. The screening was performed by two reviewers independently and consensus was reached through discussion. Any disagreements were resolved by discussion or, if necessary, by the consultation with a third reviewer.

**Data extraction**

The table for data extraction was created based on Cochrane guidelines, and the following study characteristics were extracted from each article: first author, year of publication, study design, study location, total sample size, mean age, clinical status of participants, intervention, control, and main conclusions.

**Quality assessment**

Following the recommendations of Cochrane, the risk of bias in non-randomized trials (including the cohort and case-control study) was assessed using ROBINS-I instrument (Risk Of Bias In Non-randomized Studies - of Interventions) [18], and the risk of bias in randomized trials was assessed using RoB 2, a modified Cochrane risk of bias tool [19]. There are seven and five domains of bias included in ROBINS-I and RoB 2, respectively. The risk-of-bias judgement was made in each domain, with one of three levels: “low risk of bias”, “some concerns”, or “high risk of bias”. According to risk-of-bias judgements within domains, overall risk-of-bias judgement was made.

Additionally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [20] was utilized to assess the quality of evidence in one of four grades (high, moderate, low, and very low). There were five factors for
reducing quality (limitations, inconsistency, indirectness, imprecision, and publication bias) and three factors for increasing quality (large magnitude of effect, effect of plausible residual confounding, and dose-response gradient) to be evaluated, and studies with an overall score < -2, = -2, = -1, or = 0 were considered “very low”, “low”, “moderate”, or “high” quality, respectively.

The quality assessment was conducted by two reviewers independently. Any disagreements were resolved by discussion or, if necessary, by the consultation with a third reviewer.

Results

Study selection

A total of 3403 articles were identified through the initial literature search. After eliminating duplicates and removing Abstracts, Books & Documents, those not open access, and those not in English, 1039 articles remained. Through screening the titles and abstracts, 22 full texts were assessed for eligibility and retrieved for thorough review, excluding 13 literature reviews and 3 systematic reviews and meta-analyses. Finally, 6 studies with 382 participants were included and analyzed in this systematic review, including four randomised controlled trials, one prospective cohort study, and one retrospective case-control study. The whole process of study selection is summarized and presented in Fig. 1.

Characteristics of studies

The characteristics of studies are presented in Table 2. Four of the six included trials published in 2021 used a randomized controlled design, and the other two published in 2020 used a prospective cohort design and a retrospective case-control design respectively. All included trials were conducted in different cities in China. Among the six included studies, the number of participants in each study ranged from 11 to 157 and the mean age ranged from 46 to 60 years old. The dosage of the CHI given varied ranging between 20–200 ml per day. The duration of CHI administration spanned from 7–14 days. Only one study excluded the participants diagnosed with severe or critical COVID-19, limiting their clinical status to mild and moderate, while the clinical status of COVID-19 patients in other studies ranged from mild to critical, and two studies included only patients with severe or critical COVID-19.

Quality assessment

The risk of bias of the RCTs and non-randomized trials is shown in Fig. 2. The risk of bias in three of the RCTs were graded as “some concerns” mainly due to being open-label studies that introduced bias in deviations from intended interventions, and one RCT had an overall low risk of bias. All RCTs demonstrated a low risk of bias regarding the randomization process, missing outcome data, measurement of outcomes, and selection of the reported result. In terms of non-randomized trials, they were judged to be biased in different domains, including confounding bias, participants selection, intervention classification, and deviation from the intended intervention. One study had serious risk of bias due to confounding, but most of the other domains were at low risk, so the overall risk of bias was graded as moderate.

The quality of evidence of the included studies was assessed by the GRADE system and the results are presented in Table 3. One of the six studies was excluded from the GRADE assessment due to the lack of much of the information needed in the assessment. The evidence was of low quality for four studies, and of very low quality for one study. The factors reducing the evidence quality including limitations and imprecision contributed to the low or very low quality of evidence in these studies. There was no factor that can improve the evidence quality identified in any of the five studies.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Design</th>
<th>Location</th>
<th>Total sample size (mean age)</th>
<th>Clinical status of participants</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al. (2021) [9]</td>
<td>A prospective, multicentre, open-label and randomized controlled trial</td>
<td>Jiangxi Province, China</td>
<td>n = 65 (46 years)</td>
<td>Diagnosed (mild and moderate)</td>
<td>XYP injection combined with standard care</td>
<td>Standard symptomatic treatments (supplemental oxygen therapy, antiviral medicines, antibiotic agents and immune modulators)</td>
<td>XYP is safe and effective in improving the recovery of patients with mild to moderate COVID-19.</td>
</tr>
<tr>
<td>Xu et al. (2021) [8]</td>
<td>A randomized, open-labeled, multicenter clinical study</td>
<td>China</td>
<td>n = 157 (50 years)</td>
<td>Diagnosed (mild to severe)</td>
<td>RDN injection combined with routine treatment</td>
<td>Routine treatment (supportive (oxygen), antiviral, and symptomatic treatments)</td>
<td>RDN might be effective and safe in patients with symptomatic COVID-19.</td>
</tr>
<tr>
<td>Luo et al. (2021) [5]</td>
<td>A prospective, single-center, double-blinded, randomized controlled trial</td>
<td>Hubei province, China</td>
<td>n = 57 (60 and 56 years in treatment and control group, respectively)</td>
<td>Diagnosed (severe)</td>
<td>XBJ injection combined with routine medication</td>
<td>Routine medication (nutritional support, oxygen therapy, antiviral therapy) plus saline</td>
<td>XBJ may support possible therapeutic effects although 28-day mortality was not significantly reduced.</td>
</tr>
<tr>
<td>Ma et al. (2021) [13]</td>
<td>A randomized, open-labeled, multicenter, controlled trial</td>
<td>Lianyungang, Nanjing and Yichang, China</td>
<td>n = 50 (51 years)</td>
<td>Diagnosed (mild except for one severe)</td>
<td>RDN injection combined with routine treatment</td>
<td>Routine treatment (supportive (oxygen), antiviral, and symptomatic treatments)</td>
<td>RDN relieves clinical symptoms in patients with COVID-19 and reduces SARS-CoV-2 infection by regulating inflammatory cytokine-related disorders.</td>
</tr>
</tbody>
</table>
Table 2 (continued)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Design</th>
<th>Location</th>
<th>Total sample size (mean age)</th>
<th>Clinical status of participants</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma et al. (2020) [21]</td>
<td>A prospective cohort study</td>
<td>Guangdong Province, China</td>
<td>n = 11 (56 years)</td>
<td>Diagnosed (severe and critical)</td>
<td>XBJ injection</td>
<td>N/A</td>
<td>XBJ may improve lung injury in patients with severe or critical COVID-19. Moreover, XBJ could significantly protect cells from SARS-CoV-2-induced cell death and inhibit the average size and plaque number in vitro.</td>
</tr>
<tr>
<td>Guo et al. (2020) [22]</td>
<td>A retrospective case-control study</td>
<td>Chongqing, China</td>
<td>n = 42 (53 years)</td>
<td>Diagnosed (mild and severe)</td>
<td>XBJ injection combined with routine treatment</td>
<td>Routine treatment (electrolyte balance, blood glucose and blood pressure management, nutritional support, oxygen therapy, and antiviral treatment)</td>
<td>Routine treatment combined with XBJ can better improve the clinical outcomes of COVID-19 patients.</td>
</tr>
</tbody>
</table>


Table 3

The quality of evidence of the included studies assessed by the GRADE system.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al., 2021 [9]</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Xu et al., 2021 [8]</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Very low</td>
</tr>
<tr>
<td>Luo et al., 2021 [5]</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Ma et al., 2021 [13]</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Guo et al., 2020 [22]</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
</tr>
</tbody>
</table>

Very low: overall score < -2; Low: overall score = -2; Moderate: overall score = -1; High: overall score = 0

Efficacy assessment

Mortality
The cases of death were reported in three of the included studies [5, 8, 13]. Xu et al. [8] and Ma et al. [13] both reported that there were three deaths in the control group and none in the RDN group (P > 0.05). During the early stages of the study by Luo et al. [5], one patient in the XBJ group, alongside two patients in the control group, died within a week and was therefore considered drop-out cases; the results also showed the higher 28-day mortality in the control group than in the XBJ group, although the difference was not statistically significant (7 [25%] vs. 1 [3.45%], P = 0.557). There were no deaths in the other included studies.

**Clinical Symptoms**

The clinical symptom resolution rate or time to resolution of the clinical symptoms, including fever, cough, shortness of breath, and fatigue, was reported in five studies [5, 8, 9, 13, 22]. They all showed that the treatment group had a higher symptom resolution rate or a shorter time to resolution of the symptoms than the control group. Zhang et al. [9] found a significantly shorter meantime to complete resolution of both fever and cough in the XYP treatment group than in the control group (8.33 days [SD, 4.87] vs. 11.86 days [SD, 6.93], P = 0.006). For the RDN injection, Xu et al. [8] and Ma et al. (2021) both reported a shorter median time to resolution of the clinical symptoms in the treatment group compared to that in the control group (143 vs. 313.5 h, P < 0.001; 120 vs. 220 h, P < 0.0001), as well as the higher symptom resolution rate at 14 days and 7 days, respectively (84.4% vs. 60.0%, P = 0.0004; 96.30% vs. 39.13%, P < 0.0001). In addition, a shorter duration of primary symptoms in the XBJ treatment group than that in the control group was reported in the study by Luo et al. [5] (P < 0.05), and the number of patients who had a fever after treatment in the XBJ group was significantly lower than that in the control group in the study by Guo et al. (2020) (1 [6.25%] vs. 10 [62.5%], P = 0.002). In the study by Ma et al. [21], the pneumonia severity indexes (PSI) before and after XBJ treatment were reported, and the results showed the significantly better PSI grade and score at day 7 than those at day 1 (P < 0.05), suggesting XBJ injection could be effective in reducing the severity of COVID-19.

In terms of clinical deterioration, Zhang et al. [9] reported that there was no patient who developed severe symptoms during the trial in XYP treatment group, and six patients (9.2%) in the control group showed disease deterioration (P = 0.014). Luo et al. [5] also showed that the percentage of patients in the XBJ group who developed a critical illness during the 14 days was lower than that in the control group (10.3% [3/29] vs. 35.7% [10/28], P = 0.032).

**Length of hospital stay**

The length of hospital stay was reported in four studies [5, 8, 13, 22]. The significantly shorter hospital stay was observed in the RDN group compared with that in the control group in the study by Xu et al. [8] (14.1 vs. 18.1 days, P < 0.001) and the study by Ma et al. [13] (14.8 vs. 18.5 days, P = 0.0002). Additionally, Luo et al. [5] showed that the XBJ group had a significantly shorter intensive care unit (ICU) stay than the control group (8.42 days [SD, 2.26] vs. 10.72 days [SD, 3.64], P = 0.004). On the contrary, Guo et al. [22] found a slightly longer hospital stay in the XBJ group than in the control group (18.4 days [SD, 8.8] vs. 15.1 days [SD, 4.6], P = 0.348).

Although the study by Ma et al. [21] did not report the specific length of hospital stay for each patient, it showed that on day 7 after receiving XBJ treatment, all patients with severe or critical COVID-19 had been healed and discharged from the hospital.

**Time taken for a negative nucleic acid test**

The time taken to achieve a negative nucleic acid test result was reported in four studies [8, 9, 13, 22]. The XYP group had a significantly shorter time of nucleic acid conversion to negative than the control group in the study by Zhang et al. [9] (7.97 days [SD, 4.08] vs. 12.23 days [SD, 5.77], P < 0.001). As for RDN injection, a shorter median time to achieve a negative nucleic acid test was observed in the treatment group compared with the control group in the study by Xu et al. [8] (146.5 vs. 255.5 h, P < 0.001), as well as the study by Ma et al. [13] (215 vs. 310 h, P = 0.0017). Additionally, Guo et al. [22] found a shorter time for a negative nucleic acid test in the XBJ group compared with that in the control group, although not significantly (10.3 days [SD, 4.5] vs. 13.1 days [SD, 4.5], P = 0.183).
Blood and cell experiments

The results of blood and cell experiments were reported in four studies [5, 13, 21, 22]. There was no significant difference in leukocyte count between the treatment group and the control group (P > 0.05) [5, 21, 22]. The XBJ injections significantly improved the lymphocyte count compared with the controls (P < 0.05) [5, 21], while the level of C-reactive protein (CRP) was significantly reduced (XBJ: 6.23 vs. control: 16.73, P < 0.01) [5]. In terms of SARS-CoV-2-induced pro-inflammatory cytokines, including IL-2, IL-6, IL-8, IL-10, TNF-α, TNF-α, MCP-1, MIP-1β, IP-10, CCL-5, IFN-γ, and IFN-α, the levels of them were all significantly reduced by XBJ or RDN injections (P < 0.05) [5, 13, 21, 22].

In addition, the studies [13, 21] conducting the plaque formation assays found that RDN and XBJ injections both significantly reduce the average size and number of plaques in the treatment group compared with the control group in a dose-dependent manner. Furthermore, the cytotoxicity assay and cytopathic effect (CPE) inhibition assay were also performed in the studies [13, 21]. In the cytotoxicity assay, the TC50 value for RDN [13] and XBJ [21] in African green monkey kidney epithelial (Vero E6) cells was 168.2 and 470.7 mg/mL, respectively, and the TC50 value for RDN and XBJ in Human hepatocellular carcinoma cell lines (Huh-7) cells was 30.77 and 78.78 mg/mL, respectively. The CPE inhibition assay showed that the IC50 value of RDN [13] and XBJ [21] was 16.19 and 11.75 mg/mL, respectively, and the selectivity index (SI) of RDN and XBJ was 10.39 and 40.06, respectively.

Adverse events

The adverse events were reported in five studies [5, 8, 9, 13, 21]. In these studies, the incidence of adverse events did not differ significantly between the treatment and control groups (P > 0.05), suggesting that the adverse events were not related to the injections. Zhang et al. [9] showed that the adverse events were observed in 55 patients (84.6%) and 53 patients (81.5%) in the XYP treatment and control group, respectively. The adverse events included 1) abnormal laboratory findings, such as lymphocytopenia, neutrophilia, and increased C-reactive protein level, and 2) other common adverse events, such as chest pain, diarrhea, and nausea, most of which were mild and self-limiting. For the RDN injection, the incidence of adverse events was similar between the two groups in the study by Xu et al. [8] (RDN: 3.9% vs. control: 8.8%, P = 0.383) and study by Ma et al. [13] (RDN: 0.0% vs. control: 5.0%, P = 0.2065), and no allergic reactions or anaphylactic shocks were observed in the both studies. Similarly, there was no significant difference in the occurrence of adverse reactions between the XBJ group and control group (P > 0.05) [5, 21].

Discussion

Our systematic review aimed to investigate the efficacy and safety of Chinese herbal injections (CHIs) in treating COVID-19 while evaluating the quality of the included studies. The results indicate that CHIs, including XYP, RDN, and XBJ injections, exhibited significant therapeutic effects on COVID-19 patients compared to control groups. Most of the included studies reported that the CHI treatment group demonstrated higher rates of symptom resolution, shorter durations of symptoms, hospital stay, and time to negative nucleic acid tests, as well as lower mortality rates than the control group.

Our results are supported by the work of Zhuang and colleagues [23] who in a systematic review and meta analysis (including 53 studies, n = 5,425) evaluated the efficacy and safety of integrated Chinese and Western Medicine (ITCWM) in COVID-19 patients. The statistical analysis of the data revealed that ITCWM demonstrated significantly better outcomes compared to Western medicine alone, showing higher overall clinical effectiveness. These findings are consistent with our own research, demonstrating significant results in terms of overall clinical effectiveness, faster fever resolution, quicker disappearance of cough, and faster time to RT-PCR negativity [23]. The findings from our study coincide with the existing literature on this topic, which is suggestive of a superior effectiveness of Chinese medicine in treating patients with COVID-19, without any apparent safety concerns.
Previous research by Zhang and colleagues [24] also partially supported our findings, in a systematic review and meta-analysis to evaluate the effects of integrated TCM on severe acute respiratory symptoms (SARS) patients. Their analysis included six RCTs involving 366 patients and showed that integrated TCM and Western medicine treatments significantly improved lung infiltrate absorption in two of the six studies but did not find significance in mortality [24].

According to the reports of the included studies [5, 8, 9, 13, 21], there was no significant difference in incidence of adverse events between the treatment and control groups (P > 0.05). The common signs of the adverse events included diarrhoea, rash, nausea, fatigue, skin itching, and chest pain, but they were mild and self-limiting, and were diminished or eliminated after symptomatic therapy or drug discontinuation. No allergic reactions or anaphylactic shock were observed in the patients who received the CHI treatment. Therefore, CHIs can be safely administered to treat COVID-19 patients in general.

**Biological mechanisms**

One of the main pathological characteristics of COVID-19 is a condition known as cytokine storm, which is a highly active immune response that involves the release of interleukins (IL), tumor-necrosis factors (TNF), interferons (IFN), and other pro-inflammatory cytokines [25]. A crucial mediator of the acute inflammatory response is IL-6, which is secreted by endothelial cells when stimulated by hypoxia and inflammatory cytokines [5, 26]. As increased serum IL-6 levels in COVID-19 patients are linked to ARDS, MODS, and sepsis attributed to activation of vascular endothelial cells and coagulation pathway, IL-6 has been suggested to be a good biomarker for earlier identification of COVID-19 progression and an important target for treating COVID-19 [26, 27, 28]. Studies have consistently shown that the XBJ or RDN treatment group had significantly lower levels of IL-6 compared to the control group (P < 0.05) [5, 13, 22]. Network pharmacology analyses further revealed that active ingredients in the XBJ injection, such as rutin, quercetin, luteolin, apigenin, and ursolic acid, could modulate IL-6 and other pro-inflammatory cytokines like TNF, contributing to the anti-inflammatory effects in COVID-19 treatment [29, 30].

In addition to IL-6, two other key targets for COVID-19 treatment are coronavirus 3-chymotrypsin-like protease (3CL\textsuperscript{pro}) and angiotensin-converting enzyme 2 (ACE2) [26]. 3CL\textsuperscript{pro} plays a vital role in the proteolytic maturation of coronaviruses, making it an attractive therapeutic target [26, 31]. ACE2 serves as the receptor for SARS-CoV-2, facilitating its entry into target cells [32]. The RDN injection has been found to effectively regulate 3CL\textsuperscript{pro}, ACE2, and pyridoxal phosphate (PLP), as well as affect cytokine levels to reduce inflammation, thus showing promise in treating COVID-19 [33].

Moreover, RDN and XBJ injections demonstrated inhibitory effects on SARS-CoV-2 proliferation in vitro in a dose-dependent manner, as indicated by reduced average plaque size and number, and protection of cells from SARS-CoV-2-induced cell death [13, 21]. COVID-19 patients often exhibit increased CRP levels and decreased lymphocyte counts, which are correlated with disease severity and organ dysfunction risk [5, 34, 35]. XBJ injections have been shown to effectively increase lymphocyte counts and decrease CRP levels and erythrocyte sedimentation rate (ESR), thus regulating cellular immune function and reducing inflammation [5, 21, 36].

**Strengths**

This study had several strengths. As far as we know, this is the first systematic review in English to comprehensively investigate the effects of CHIs on the treatment of COVID-19. Although several systematic reviews have been conducted to examine the effects of general TCMs, our systematic review focused on more specific aspects (i.e. CHIs), to prevent overgeneralization. Additionally, the open-label design, while a weakness in terms of potential bias, also serves as a strength by reflecting real-world clinical practice and increasing the external validity of the findings. Furthermore, despite the limitation of small sample sizes in some studies, the cumulative data from multiple trials provide valuable insights and corroborate certain outcomes, strengthening the overall evidence base. The systematic review, with its rigorous methodological approach and consideration of diverse Chinese herbal interventions, serves as a valuable resource for clinicians and researchers, informing future studies and potential integration of CHIs into COVID-19 management strategies.

**Limitations**
There were some limitations in this study. Firstly, most of the included studies were conducted in China, raising concerns about the generalizability of the results to wider populations and healthcare systems. Furthermore, the inclusion of open-labeled studies may introduce bias and affect the objectivity of the reported outcomes. The overall quality of evidence was deemed low due to methodological limitations observed across the studies, along with small sample sizes in some of the individual studies, raising questions about the reliability and validity of the findings. Therefore, while the review provides valuable insights into Chinese herbal interventions for COVID-19, it is essential to interpret the results with caution, considering the limitations in drawing conclusive evidence applicable to broader populations and healthcare settings. Future systematic reviews that address these weaknesses and include studies from diverse geographical areas could provide a more comprehensive and reliable understanding of the efficacy of Chinese herbal interventions in COVID-19 management.

Additionally, the relatively small number of clinical trials investigating the effects of CHIs on COVID-19 was identified, partly due to China's relative success in handling the outbreak, which restricted the implementation and progress of trials [37]. Moreover, limiting the language to English resulted in the absence of relevant articles in other languages, such as some COVID-19 studies published only in Chinese. The heterogeneity of efficacy outcome measurements and low quality of results prevented a meta-analysis, and the findings were reported descriptively. Moderate risk of bias and low quality of evidence in the included studies further limited the study's conclusions. Double-blinded RCTs were rare, introducing potential subjective elements and deviations from intended interventions. Covariate adjustments were lacking in most studies, confounding results. Small sample sizes limited the power to identify differences in efficacy outcomes between treatment and control groups, introducing bias. Therefore, future research with larger samples, stratification of COVID-19 severity, and longer-term follow-up is necessary to validate the results. Double-blinded RCTs with standardized criteria and outcomes are essential for reliable meta-analyses. Studies on other CHIs and comparisons between them are warranted to explore optimal therapeutic effects. International collaboration and approval of CHIs in clinical settings can further enhance the treatment options for severe epidemics.

Conclusion

Our research suggests that CHIs have the potential to play an effective role in the treatment of COVID-19, which is mainly reflected in promoting symptom resolution, and shortening the length of hospital stay and time taken for a negative nucleic acid test, although the moderate risk of bias and low quality of evidence of the included studies need to be considered. These improvements are thought to be attributed to the modulation of pro-inflammatory cytokines and immune cells. The lack of significant differences in adverse events between the study groups and the absence of allergic reactions or anaphylactic shocks observed indicate that CHIs can be safely administered under rational operation. More double-blinded RCTs with larger sample sizes and consistent selection criteria and outcome measurements are needed in the future, as well as studies exploring the effects on longer-term symptom resolution or the effects of other different CHIs.

Abbreviations

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
All data used in this systematic review are fully available in the public domain.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
ZS and TR, designed research, undertook study, data extraction, data analysis and wrote the paper. CPC, designed research, undertook data screening and wrote the paper. All authors have read and approved the final version of the manuscript.

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References


Figures
Figure 1

PRISMA flow diagram for study selection.
Figure 2

(a), (b) Risk of bias of included RCTs. (c), (d) Risk of bias of included non-randomized trials.

(a) The summary for risk of bias of included RCTs
(b) The graph for risk of bias of included RCTs
(c) The summary for risk of bias of included non-randomized trials
(d) The graph for risk of bias of included non-randomized trials