Original Article

The efficacy and safety of Wulingsan modified formulas for chronic heart failure patients: a systematic review and meta-analysis

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Contributions: (I) Conception and design: Z Li, J Hu; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Z Li, L Ren; (V) Data analysis and interpretation: Z Li, X Tong, L Ren, R Gu, C Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Chronic heart failure (CHF) is one of the most common cardiovascular diseases, which has caused huge economic burden worldwide. Wulingsan modified formulas have been historically used for CHF in China. However, the efficacy of its treatment for CHF has not been summarized by scholars and lacks of clinical evidence. This study aimed to assess the efficacy and safety of Wulingsan modified formulas for patients with CHF.

Methods: A comprehensive literature search was performed in the PubMed, EMBASE, Cochrane Library, Web of Science, Medline (Ovid), China National Knowledge Infrastructure, WanFang, China Science and Technology Journal Database, and SinoMed databases from the date of their inception up to 1st November, 2021. Only randomized controlled trials evaluating Wulingsan modified formulas in patients with CHF were included. The primary outcome of this study was efficacy of Wulingsan modified formulas in the treatment of CHF, and the secondary outcomes included brain natriuretic peptide, left ventricular ejection fractions, and any other changes in the patients' condition. The risk ratio was applied to evaluate efficiency, and the weighted mean difference (WMD) and 95% confidence interval (CI) were used to merge the continuous variables. The I^2 statistic was used to assess the heterogeneity. Sensitivity analysis was used to evaluate whether the single research affected the whole results. Data were extracted by two independent investigators. The Cochrane Risk of Bias tool (version 2.0) was utilized to evaluate the included studies, STATA (version 15.0) was applied for sensitivity analysis, and RevMan 5.3 software was used to conduct the systematic review and meta-analysis.

Results: Nineteen studies with a total of 1,631 were included in this meta-analysis. The meta-analysis results were as follows: efficiency, the risk ratio =1.21, 95% CI: 1.15, 1.27; brain natriuretic peptide, WMD =–269.14, 95% CI: –349.25, –189.04; and left ventricular ejection fractions, WMD =8.80, 95% CI: 5.93, 11.68. All of these findings were statistically significant. No statistically significant adverse events were reported in the included articles.

Discussion: Wulingsan modified formulas are a reasonable and relatively safe adjuvant therapy for the treatment of CHF.

Keywords: Chronic heart failure; Wulingsan modified formulas; meta-analysis

Submitted Feb 11, 2022. Accepted for publication Apr 20, 2022.
doi: 10.21037/jtd-22-261
View this article at: https://dx.doi.org/10.21037/jtd-22-261

Introduction

Heart failure (HF) is the chronic phase of cardiovascular disease, which has high rates of incidence and mortality. Previous studies have indicated that approximately 64 million people suffer from HF (1,2), and the 5-year mortality rate exceeds 50% (3-5). Chronic heart failure (CHF), a persistent HF state, is an important geriatric syndrome. It also has a high rate of morbidity, mortality, and re-hospitalization (6,7) and results in a considerable economic burden on patients (8). Furthermore, its main symptoms, including fluid retention, dyspnoea, fatigue, and poor exercise tolerance, seriously impact the quality of life of patients (9). Despite the development of medical and cardiac resynchronization therapies, the clinical outcomes of CHF patients remain poor (10), and the costs will further exacerbate the economic burden on patients (8).

Wulingsan originates from "Treatise on Febrile Diseases", which is a traditional Chinese formula composed of polyporus umbellatus, poria cocos, alisma orientalis, atractylodes macrocephala, and cinnamon twig (11,12). It has been reported that Wulingsan exerts protective and fluid balance effects in disorders such as CHF (13), obesity (14), vomiting and diarrhea (15) and dysuria (16). Wulingsan modified formulas (WMF) are made by adding and subtracting herbs from Wulingsan according to the clinical experience, with Wulingsan being the foundation of WMF. Studies have shown that WMF can significantly improve the heart function of patients with CHF and relieve clinical symptoms (17,18).

Due to the high incidence of CHF and its poor therapeutic effect, WMF is expected to become an adjuvant drug for CHF patients. It may relief the huge physical and mental pressure from the chronic illness. However, the efficacy and safety of WMF remain uncertain although some researchers report the positive curative effects (19,20). The clinical application of WMF for CHF is still lacking evidence-based medical analysis. Our study will be the first meta-analysis to assess the efficacy and safety of WMF for CHF patients, in order to provide clinical decision-making recommendations. We present the following article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-261/rc).

Methods

Search strategy

We performed a literature search of the PubMed, EMBASE, Cochrane library, Web of Science, Medline (Ovid), China National Knowledge Infrastructure (CNKI), WanFang, China Science and Technology Journal, and SinoMed databases for articles about the relationship between CHF and the Wulingsan published from the date of inception of the database to the 1st November, 2021.

The specific retrieval strategies applied for PubMed were as follows:

#1 chronic heart failure /exp

#2 ((heart* or cardiac* or myocard*) adj2 (fail* or insuff*)).tw.

#3 (heart* adj2 decomp*).tw.

#4 (chf or hf).tw.

#5 or/1-4

#6 wulingsan /exp

#7 wulingsan*.tw.

#8 or/6-7

#9 #5 and #8

Inclusion criteria

The inclusion criteria were as follows: (I) all patients were diagnosed as CHF; (II) randomized controlled trial (RCT); and (III) studies involving WMF as a main treatment intervention. Articles involving the combination of WMF and other regular treatments compared with those same other regular treatments alone were also included. Regular treatments were included Oxygen inhalation, captopril, furosemide, metoprolol and etc.

Exclusion criteria

The exclusion criteria were as follows: (I) duplicate articles; (II) animal experiments, conference summaries, case reports, and reviews; (III) studies from which no data could be extracted; and (IV) articles lacking sufficient information on baseline or primary/secondary outcome data.

Primary outcome

Efficacy of WMF in the treatment of CHF.

Secondary outcomes

(I) Any brain natriuretic peptide (BNP) changes;
(II) Any left ventricular ejection fractions (LVEF) changes; and
(III) Any changes to the patients' condition.
(IV) Any reports about the adverse events.

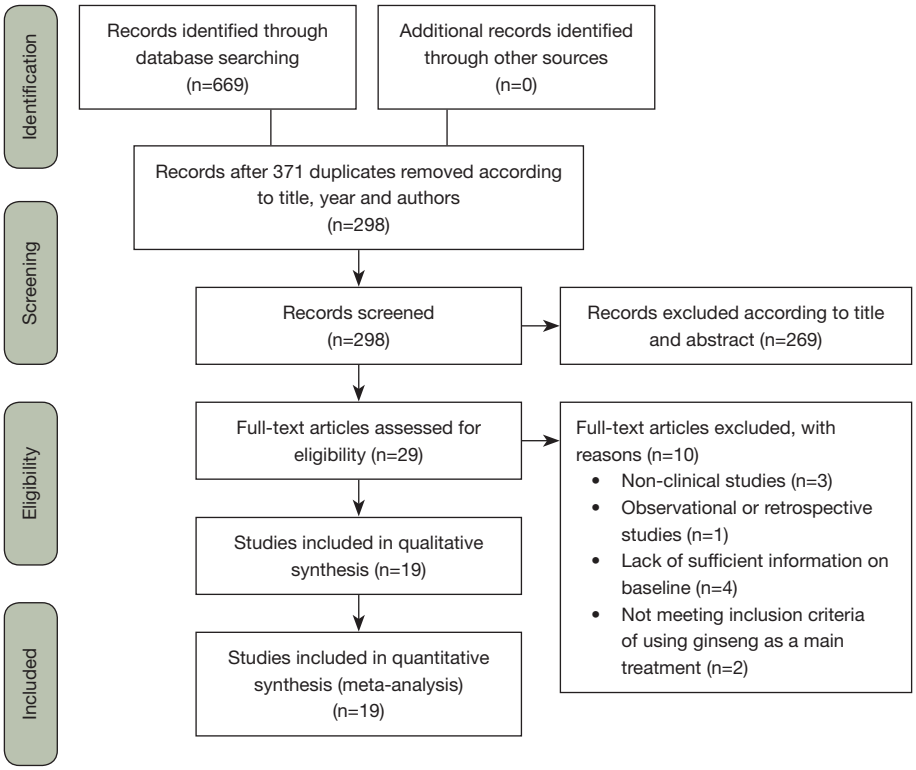

Figure 1 Study selection flow chart.

Data extraction

Two reviewers (ZL and LR) independently evaluated all of the retrieved documents and analyzed the data according to the inclusion/exclusion criteria. In cases of disagreement, the final results were discussed between the two researchers. In addition, the third reviewer (CZ) also helped to resolve any differences. The contents of data extraction included the basic characteristics of the included studies.

Bias risk assessment

Two authors (ZL and LR) independently assessed the risk of bias using the Cochrane Handbook Risk of Bias Assessment Tool (21). Disagreements between the authors were resolved by the third author through consensus.

Statistical analysis

Statistical analyses were conducted using the software RevMan 5.3 (Cochrane Collaboration, Oxford, UK) (22) and STATA version 15.0 (Stata Corp, College Station, TX, USA). The risk ratio (RR) was applied to evaluate efficiency, and the weighted mean difference (WMD) and 95% confidence interval (CI) were used to merge the continuous variables. The I^2 statistic was used to assess the heterogeneity between the included studies; the random effect model was used when I^2>50% (23). Sensitivity analysis was conducted to assess whether a single article result affected the overall conclusion.

Results

Literature search

In total, 669 related studies were retrieved in the initial search. According to the inclusion and exclusion criteria, 29 studies were included for full-text consideration. Finally, 19 studies were included for meta-analysis (*Figure 1*).

Characteristics of the study

Nineteen articles were included in this meta-analysis, and their characteristics are displayed below (*Table 1*).

Table 1 Characteristics of the included studies

Study	Experimental group			Control group			Research designs
	Average age	No.	Treatment method	Average age	No.	Treatment method	
Wang 2010 (19)	62.3±12.58	35	WMF + regular treatment (oxygen inhalation, captopril, furosemide, metoprolol)	63.6±11.37	35	Regular treatment (oxygen inhalation, captopril, furosemide, metoprolol)	RCT
Wang 2011 (20)	N/A	44	WMF + regular treatment (oxygen inhalation, dexamethasone, cedilanid, metoprolol)	N/A	42	Regular treatment (oxygen inhalation, dexamethasone, cedilanid, metoprolol)	RCT
Ning 2012 (24)	61.36±11.65	70	WMF + regular treatment (Isosorbide mononitrate, spironolactone, digoxin)	63.33±7.16	70	Regular treatment (Isosorbide mononitrate, spironolactone, digoxin)	RCT
Huang 2013 (25)	63.51±6.21	48	regular treatment (oxygen inhalation, hydrochlorothiazide, cedilanid or digoxin)	62.83±6.52	48	Regular treatment (oxygen inhalation, hydrochlorothiazide, cedilanid or digoxin)	RCT
Shen 2013 (26)	63±15.2	12	WMF + regular treatment (dobutamine, dobutamine, paracetamol)	62±4.51	12	Regular treatment (dobutamine, dobutamine, paracetamol)	RCT
Zhou 2014 (27)	63.08±5.74	38	WMF + regular treatment	64.83±6.07	38	Regular treatment	RCT
Yang 2014 (28)	62.1+5.9	35	WMF + regular treatment (comprehensive treatment of angiotensin converting enzyme inhibitors and B receptor blockers)	62.7±6.1	35	Regular treatment (comprehensive treatment of angiotensin converting enzyme inhibitors and B receptor blockers)	RCT
Qing 2015 (29)	54.5	41	WMF + regular treatment (digoxin, furosemide)	53.9	37	Regular treatment (digoxin, furosemide)	RCT
Cao 2016 (30)	66.87±9.89	26	WMF + regular treatment (captopril, metoprolol)	67.98±10.32	26	Regular treatment (captopril, metoprolol)	RCT
Liu 2017 (31)	69.2	60	WMF + regular treatment (valsartan hydrochlorothiazide, antiplatelet drugs)	66.2	60	Regular treatment (valsartan hydrochlorothiazide, antiplatelet drugs)	RCT
Yi 2017 (32)	79.2±7.9	46	WMF + regular treatment	75.8±8.5	46	Regular treatment	RCT
Su 2017 (33)	N/A	30	WMF + regular treatment	N/A	30	Regular treatment	RCT
Hong 2018 (34)	68.2±6.6	41	WMF + regular treatment (betaloc, candesartan)	68.1±7.0	41	Regular treatment (betaloc, candesartan)	RCT
Chen 2019 (35)	62.7±0.4	49	WMF + regular treatment (benazepril, spironolactone, furosemide, metoprolol, trimetazidine)	62.5±0.6	49	Regular treatment (benazepril, spironolactone, furosemide, metoprolol, trimetazidine)	RCT
Peng 2019 (36)	62.1±5.8	90	WMF + regular treatment (furosemide)	62.7±6.1	90	Regular treatment (furosemide)	RCT
Tang 2020 (37)	71.5	5l	WMF + regular treatment (valsartan)	70.3	5l	Regular treatment (valsartan)	RCT
Wang 2020 (38)	57.29±4.33	34	WMF + regular treatment (spironolactone, isosorbide mononitrate, digoxin)	57.31±4.11	34	Regular treatment (spironolactone, isosorbide mononitrate, digoxin)	RCT
Hu 2021 (39)	60.27±5.03	46	WMF + regular treatment (trimetazidine, spironolactone, furosemide, irbesartan, isosorbide mononitrate, metoprolol)	60.91±4.82	46	Regular treatment (trimetazidine, spironolactone, furosemide, irbesartan, isosorbide mononitrate, metoprolol)	RCT
Li 2021 (40)	61.71±3.17	44	WMF + regular treatment (Isosorbide mononitrate, spironolactone, digoxin)	61.59±2.86	43	Regular treatment (Isosorbide mononitrate, spironolactone, digoxin)	RCT

WMF, Wulingsan modified formulas; RCT, randomized controlled trial.

J Thorac Dis 2022;14(4):1232-1242 | https://dx.doi.org/10.21037/jtd-22-261

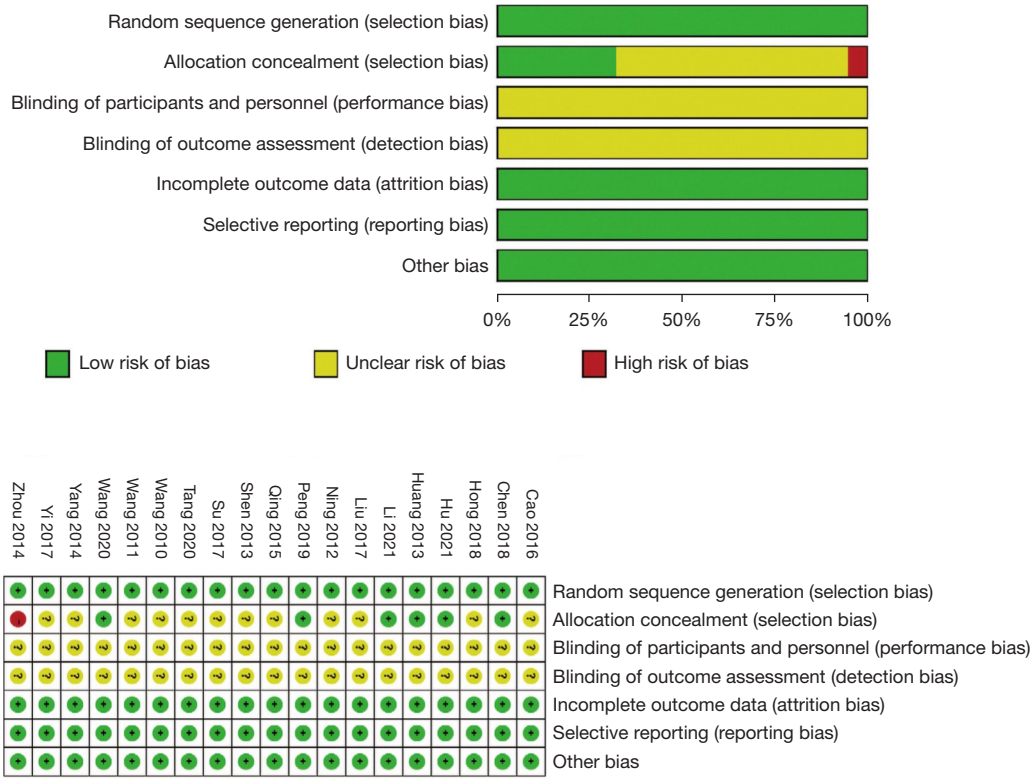

Figure 2 Quality assessment of the included studies.

Risk of bias

The risk of bias assessment of the 19 included studies was summarized in *Figure 2*. All the studies described random sequence generation, attrition bias and reporting bias. None of the studies described performances or detection biases. One study (27) exhibited a high risk of bias allocation concealment.

Efficiency

Eighteen studies reported on the efficiency of WMF in the treatment of CHF. The meta-analysis results showed that WMF was effective in the treatment of CHF (RR =1.21, 95% CI: 1.15, 1.27, P<0.00001) and heterogeneity I^2=3%. The funnel plot displayed bilateral asymmetry, which indicated potential publication bias (*Figure 3A,3B*).

BNP

Seven studies reported on BNP. The meta-analysis results showed that WMF could decrease BNP in CHF patients (WMD =–269.14, 95% CI: –349.25, –189.04, P<0.00001) and heterogeneity I^2=99%. Sensitivity analysis showed that no single article affected the overall analysis results, and all of the included studies were within the acceptable range (see *Figure 4A,4B*).

LVEF

Eight studies reported on the LVEF. The meta-analysis results showed that WMF could increase the LVEF in CHF patients (WMD =8.80, 95% CI: 5.93, 11.68; P<0.00001) and heterogeneity I^2=96%, and the data was statistically significant. Sensitivity analysis showed that no single article affected the overall analysis results, and all of the included studies were within the acceptable range (see *Figure 5A,5B*).

Adverse events

Two studies reported on adverse events. The meta-analysis results showed that (RR =0.57, 95% CI: 0.27, 1.17; P=0.13)

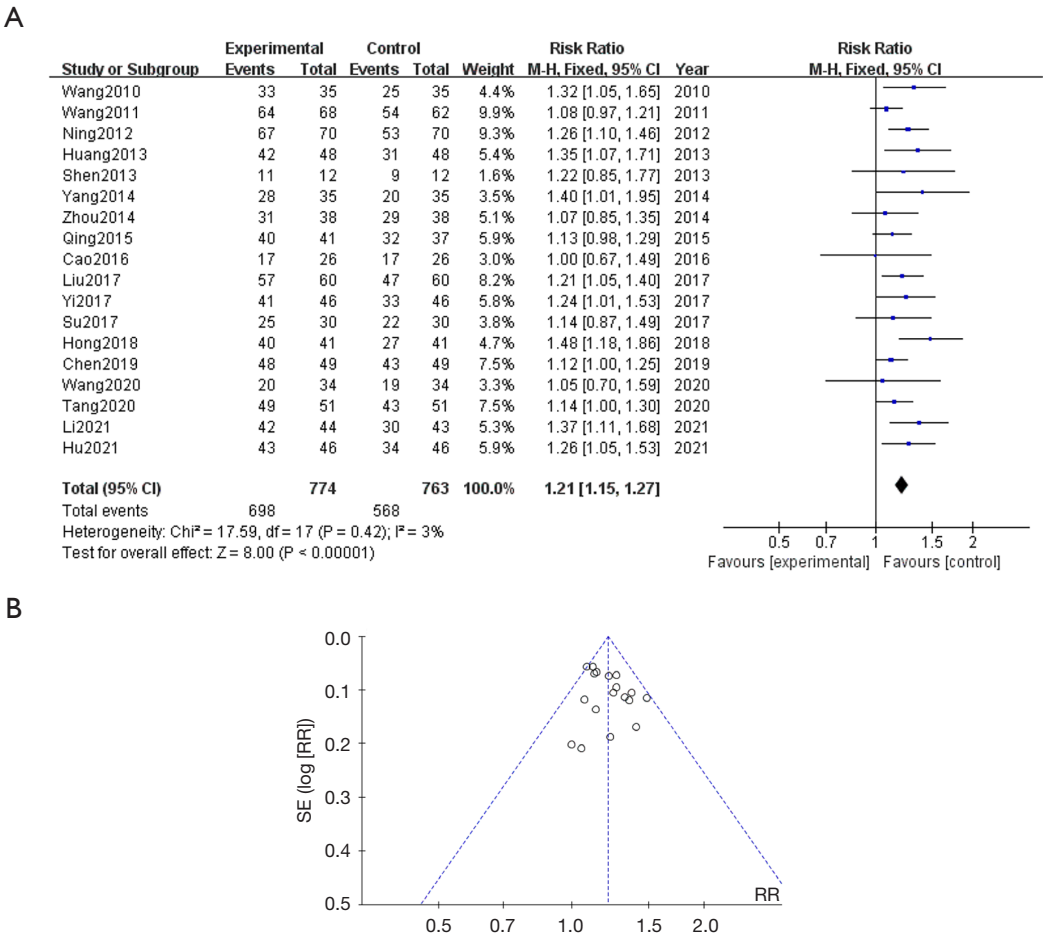

Figure 3 Comparison of efficiency between the experimental and control groups. (A) Forest plot of efficiency; (B) Funnel plot of efficiency. CI, confidence interval; RR, risk ratio; SE, standard error.

and heterogeneity I^2=52%, and the data was not statistically significant. This indicated that there was no difference in the incidence of adverse events between the experimental and control groups, suggesting that WMF was safe for CHF patients (*Figure 6*).

Discussion

Summary of the main findings

In this study, efficacy, BNP, LVEF, and adverse events were included to assess the effectiveness and safety of WMF. The meta-analysis results were as follows: efficiency, RR =1.21, 95% CI: 1.15, 1.27; BNP, WMD =–269.14, 95% CI: –349.25, –189.04; and LVEF, WMD =8.80, 95% CI: 5.93, 11.68. All of these findings were statistically significant. We also found that there was no statistically significant difference in the incidence of adverse events between the experimental and control groups (RR =0.57, 95% CI: 0.27, 1.17; P=0.13). The above results indicate that WMF is a safe and effective treatment for CHF.

Implications for clinical practice and further research

Despite the continuous development of anti-CHF drugs in recent years, the hospitalization and mortality rates of CHF patients remain high. Therefore, there is a pressing need to identify new therapeutic targets, so as to improve the

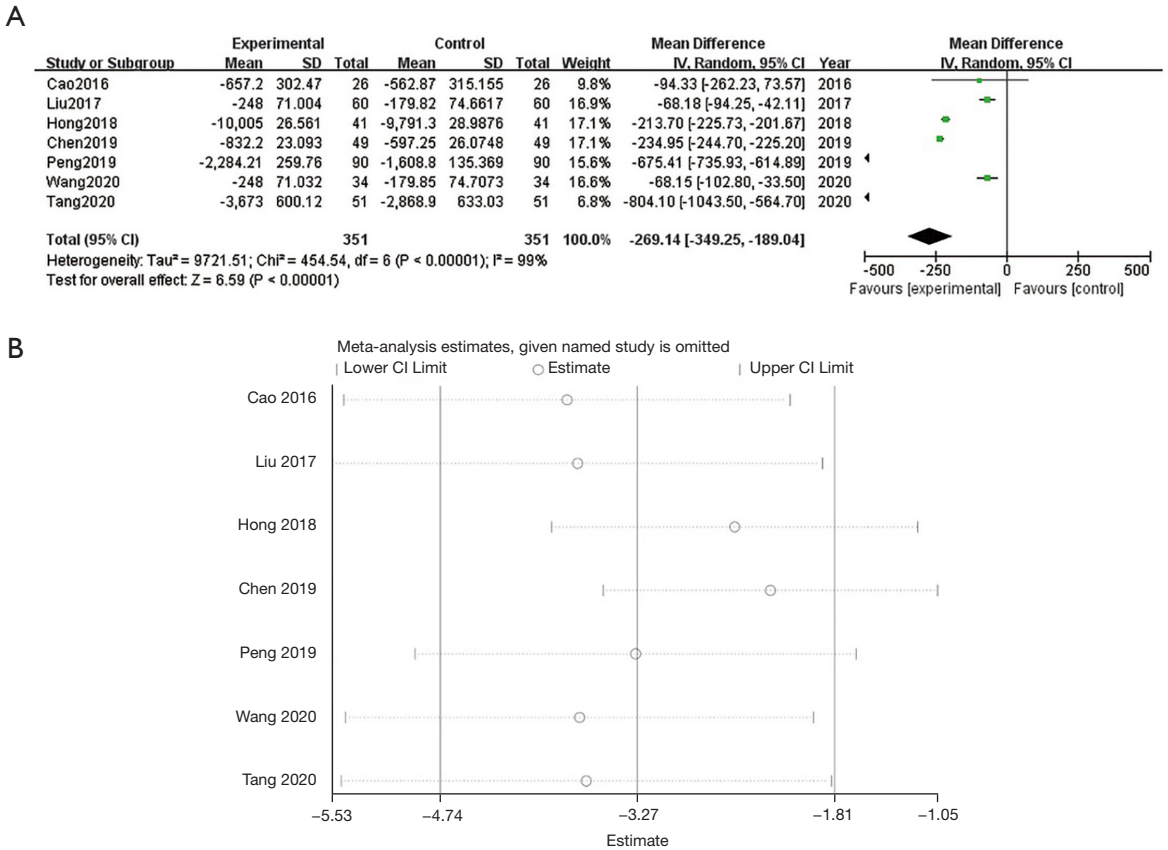

Figure 4 Comparison of BNP between the experimental and control groups. (A) Forest plot of BNP; (B) sensitivity analysis of BNP. SD, standard**;** CI, confidence interval; BNP, brain natriuretic peptide.

prognosis of CHF patients. There is increasing evidence that impaired reduction of BNP levels is associated with a reduced risk of hospitalization due to worsening CHF (41).

Wulingsan, a classic prescription of traditional Chinese medicine, has the effect of warming yang to eliminate wetnessevil and removing dampness. Studies have demonstrated that WMF can protect myocytes and reduce cardiac preload by reducing the level of endothelin and BNP in patients with CHF (42). It can also improve the LVEF and left ventricular end diastolic volume in patients with CHF (43). However, individual studies have not provided sufficient evidence, and the role of WMF for CHF patients remains controversial. This meta-analysis found that WMF was effective for improving heart function, reducing BNP levels, and increasing the LVEF. Our study is the first meta-analysis to assess the effectiveness and safety of WMF in the treatment of CHF, which can provide clinical decision-making recommendations for the application of WMF. In the future, more large-scale and high-quality RCTs need to be conducted to obtain more accurate analysis results.

Limitations

This study had some limitations that should be taken into consideration. Firstly, the strength of evidence in this study was limited due to the risk of bias in the included studies. Secondly, most of the studies included in this review involved WMF instead of Wulingsan, which results in considerable clinical heterogeneity. Third, considering with the risk of bias in this study, clinical implications should be made according to the actual medical conditions. Finally, we conducted subgroup analysis according to age,

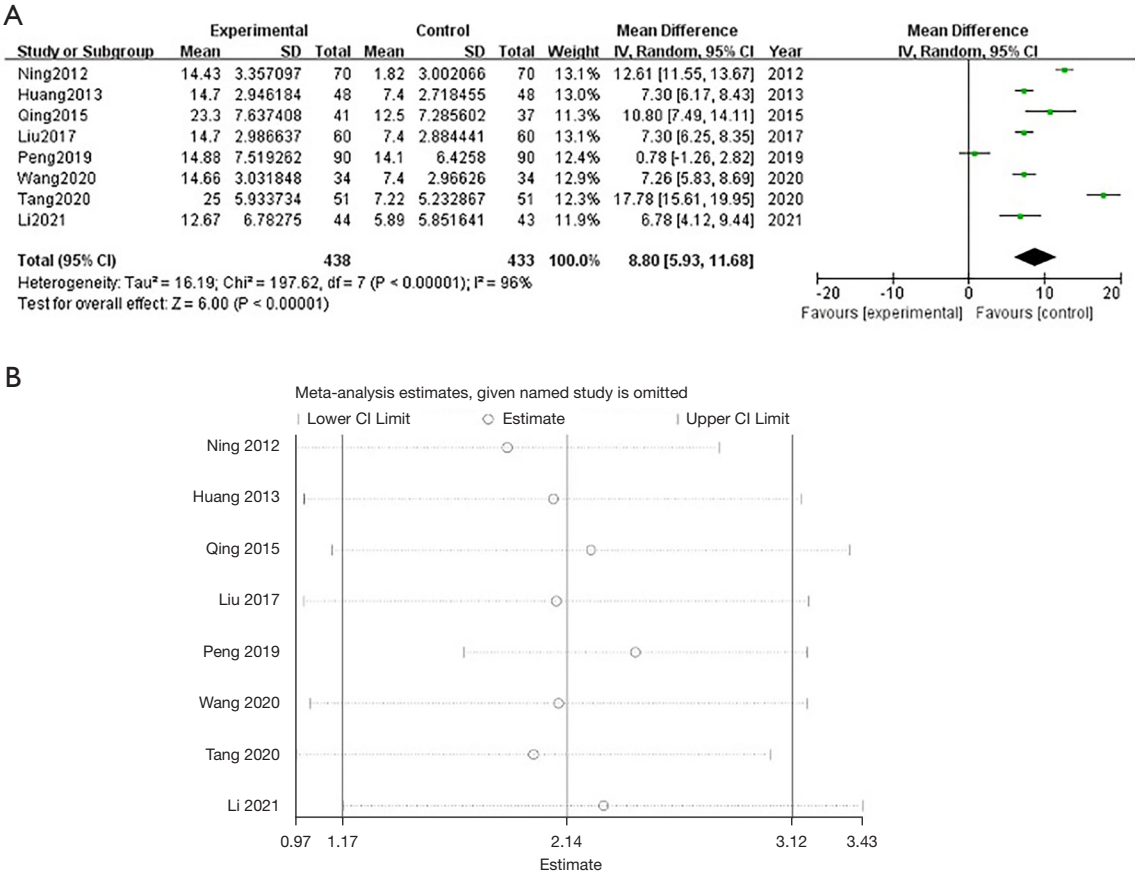

Figure 5 Comparison of left ventricular ejection fractions (LVEF) between the experimental and control groups. (A) Forest plot of LVEF; (B) sensitivity analysis of LVEF. SD, standard; CI, confidence interval.

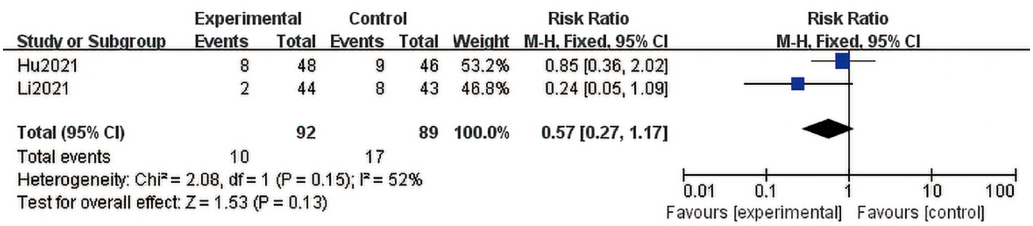

Figure 6 Forest plot of adverse events. CI, confidence interval.

course of disease, etc., which did not resolve the significant heterogeneity between the included studies. Although we adopted the random effects model, the heterogeneity may have still affected the quality of the evidence.

Conclusions

WMF is a reasonable and relatively safe adjuvant therapy for the treatment of CHF. However, more RCTs are needed to evaluate whether WMF is effective in the treatment of CHF.

Acknowledgments

Funding: This project was supported in part by the National Key Research and Development Program of China

(No.2019YFC1708501), the Fundamental Research Funds for the Central Public Welfare Research Institutes (No.YZ-202026), and the Jiangsu College graduate research and innovation projects (No. SJCX21-0753).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-261/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-261/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: A. Kassem)

Cite this article as: Li Z, Ren L, Gu R, Zhou C, Tong X, Hu J. The efficacy and safety of Wulingsan modified formulas for chronic heart failure patients: a systematic review and meta-analysis. J Thorac Dis 2022;14(4):1232-1242. doi: 10.21037/jtd-22-261