Evaluation of the safety and efficacy of Zhenwu decoction as adjuvant therapy for the treatment of heart failure with reduced ejection fraction
A protocol for systematic review and meta-analysis
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Abstract
Introduction: Heart failure with reduced ejection fraction (HFrEF) demonstrates a substantial threat to global public health. Several Chinese studies have been conducted to date evaluating the clinical efficacy of Zhenwu decoction (ZWD) as a treatment for HFrEF. The present systematic review will be conducted to more comprehensively evaluate the impact of ZWD on HFrEF outcomes.
Methods: For this systematic review, all randomized controlled trials (RCTs) reporting on the effectiveness of ZWD as a treatment for HFrEF published as of December 30, 2021 in the Embase, PubMed, Springer, Web of Science, Cochrane Library, China Biomedical Literature Database, China National Knowledge Infrastructure, and the Wan-Fang databases will be identified without any language or publication restrictions. Two researchers will independently choose investigations, extract information, and gauge research quality. Primary outcomes of interest will include all-cause mortality and HF-associated mortality. Secondary outcomes will include the incidence of adverse events, ultrasonic cardiographic indices (including left ventricular ejection fraction and left ventricular mass index), New York Heart Association grade, N-terminal pro-b-type natriuretic peptide, B-type natriuretic peptide, and 6-minute walking distance. RevMan v 5.3 will be used to conduct meta-analyses where possible, with descriptive or subgroup analyses otherwise being conducted. Data will be given as risk ratios for categorical variables and mean difference for continuous variables.
Results: This comprehensive protocol will aid in the systematic and objective evaluation of the efficacy and safety of ZWD as a treatment for HFrEF, providing a scientific basis for the clinical utilization of ZWD.
Abbreviations: CAM = complementary and alternative medicine, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, ZWD = Zhenwu decoction.
Keywords: heart failure with reduced ejection fraction, protocol, systematic review, Zhenwu decoction

1. Introduction
Heart failure with reduced ejection fraction (HFrEF) is a syndrome wherein patients exhibit a reduced ejection fraction, heart failure (HF) symptoms, and aberrant systolic function in the presence or absence of normal diastolic function.[1] Current guidelines define HFrEF as a diagnosis of HF with an EF ≤40%.

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LW is the guarantor of the article. The manuscript was drafted by YH and LH, GZ, XC, and QZ developed the search strategy. MC and MX will independently screen the potential studies and extract data. LM and YH will assess the risk of bias and finish data synthesis. LW will arbitrate any disagreement and ensure that no errors occur during the review. All review authors critically reviewed, revised and approved the subsequent and final version of the protocol.
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As this protocol does not involve animal experiments or patient privacy data and is only intended for ethical review, it does not require ethical approval. The achievements of these analyses will be published through peer-reviewed journals or conference reports.
The authors have no conflicts of interest to disclose.
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist of this protocol is presented in online supplementary.
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
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HF was estimated to affect 5.7 million individuals from 2009 to 2012, rising to 6.5 million individuals from 2011 to 2014, of patients hospitalized for HF for the first time, 53% exhibited HFrEF of whom 70% were black males.[8] Rates of HF vary significantly across Asian countries, affecting an estimated 4.5 million persons in China in 2014.[9] Roughly one in 4 patients hospitalized for HF undergo readmission within 30 days, and this readmission rate is nearly 50% within a 6-month period.[4] HF imposes a substantial burden on global healthcare systems, with a particularly disproportional impact on low- and middle-income nations in South America, Eastern Africa, and Asia-Pacific region where rates of HF are rising rapidly along with other cardiovascular conditions including diabetes mellitus and hypertension.[5] Treatments for HF include the implantation of devices capable of regulating cardiac activity and pharmacological intervention.[6] Even with these interventions, however, HF is incurable and patients generally exhibit high mortality rates and a poor prognosis.[1] There is thus an urgent need to develop novel therapies for affected patients.

Complementary and alternative medicine (CAM) is an area of growing research interest for HFrEF treatment, with several systemic reviews and meta-analyses having been conducted for the exploration of the efficacy of different CAM agents in the treatment of this condition by evaluating results from extant randomized controlled trials (RCTs).[7] Chinese herbal medicines are a form of CAM therapy that have been employed for the treatment of HFrEF-related conditions in China for at least 2500 years. Zhenwu decoction (ZWD) is a traditional herbal preparation employed in traditional Chinese medicine that was formulated by the physician Zhongjing Zhang in Shang Han Lun (Treatise on Febrile and Miscellaneous Diseases) roughly 18 centuries ago. It is composed of Poria (Fu Ling, Scirerottium Poriae Cocos), processed aconite (Fu Zi, Radix Lateralis Praeparata Aconiti Carmichaeli), White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflorae), White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractyloidis Macrocephala), and fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens). In prior pharmacological analyses, ZWD was shown to promote p-ERK5 upregulation within cardiomyocytes while suppressing mitochondrial autophagic gene expression,[9] thereby aiding in HF treatment. Several other studies to date have also explored the clinical potential of ZWD as a treatment for HFrEF among Chinese patients.[9,10] To date, however, there have been no meta-analyses that summarize these results, with several questions remaining regarding the benefits of such treatment. This study will thus be conducted with the following goals:

1. to assess the relative efficacy of ZWD as compared to nontreatment, placebo treatment, or the treatment with anti-HF drugs;
2. to gauge the effectiveness of ZWD along with anti-HF medications relative to anti-HF medications alone; and
3. to establish the safety of ZWD.

2. Methods
This meta-analysis was registered at Open Science Framework registries (OSF, https://osf.io/9fty3) with a registration number of DOI: 10.17605/OSF.IO/9FTY3, and will be executed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement instructions.[11]
2.6. Study selection

Titles and abstracts for identified studies retrieved via the above search will be independently evaluated by 2 investigators who will exclude those investigations not meeting with the criteria of eligibility. The full text will be retrieved for the remaining trials, which will be evaluated for eligibility with the aid of 2 independent reviewers. Trial exclusion rationale at the full-text level will be documented, and through discussion or consensus with a fifth investigator, discrepancies will be resolved. The study selection procedure is outlined in Figure 1.

| Table 1 | Literature-search strategy employed for PubMed repository. |
|---------|-------------------------------------------------------------|
| Number  | Search terms                                  |
| #1      | Heart failure [MeSH]                               |
| #2      | Heart failure [Title/Abstract]                   |
| #3      | Zhenwu Decoction [MeSH]                          |
| #4      | Zhenwu Decoction [Title/Abstract]                |
| #5      | ZWD [Title/Abstract]                             |
| #6      | #4 OR #5 OR #6                                   |
| #7      | Randomized controlled trial [Title/Abstract]     |
| #8      | Clinical study [Title/Abstract]                  |
| #9      | #6 OR #9 OR #10                                  |
| #10     | Controlled study [Title/Abstract]                |
| #11     | #6 AND #7 AND #11                                |
| #12     | #3 AND #4 AND #11                                |

Figure 1. Flow diagram of study selection process.
2.7. Data extraction

A standardized form will be independently used by 2 investigators to extract data including article title, first or corresponding author, country, journal, year of publication, institution, trial setting, sponsor, inclusion/exclusion criteria, trial design specifics (blinding, randomization, allocation concealment), patient characteristics (age, gender, comorbidities, HFrEF severity and course), sample size, intervention and control treatment details (including dosage, ZWD type and composition, duration of treatment, and co-interventions), outcome details (time points, mean values, response/non-response events, and mean difference values), and other factors with the potential to aid in bias detection (termination time, data for analysis, register ID). The division of labor will be identical to that in the section of Study Selection, with a fifth investigator aiding in the resolution of disagreements.

2.8. Risk of bias analyses

The bias risk and methodological quality for included investigations will be evaluated in compliance with the Cochrane Handbook for Systematic Reviews of Interventions, v 6 risk of bias 2.0 (ROB2.0) gadget.[12] These analyses will be independently performed by one investigator and confirmed by another, with a third investigator serving to resolve any discrepancies.

2.9. Data synthesis and analyses

RevMan V 5.3 will be employed to synthesize and scrutinize included information. Continuous data will be assessed based upon mean difference values with 95% CIs, while categorical data will be analyzed using risk ratios with 95% CIs. Potential heterogeneity will be assessed as per the Cochrane Handbook for Systematic Reviews of Interventions based on a visual inspection of forest plots, heterogeneity χ² tests, and Higgins’ I² statistic. Data will be pooled and analyzed using fixed-effects models if I² is < 50% and P > .1, whereas random-effects models will otherwise be employed. Meta-analyses with random-effects models will be implemented to gauge overall treatment efficacy when heterogeneity is observed, but meta-analyses will not be performed when there is considerable heterogeneity among trials, with a qualitative summary instead being provided. Subgroups will be considered for subgroup analyses as appropriate.

2.10. Additional analyses

2.10.1. Subgroup analyses. Subgroup analyses will be performed for available data when factors have the potential to influence outcome results. Potential subgroups of interest will include gender, age, control type (active treatments, sham treatments, or untreated/waiting list participants), follow-up duration (short term [2months or less] vs long term [>2 months]). Causes of identified heterogeneity will be further interpreted in the discussion section.

2.10.2. Sensitivity analyses. Sensitivity analyses will be employed to gauge the reliability and robustness of our results based upon potential methodological weaknesses (such as a lack of adequate allocation concealment or sequence generation), missing data, or sample sizes (more than or less than 30 individuals per group). Risk of bias will be further defined when sensitivity analyses reveal low robustness. Those studies with an unclear or high risk of bias will be excluded from all analyses.

2.11. Publication bias analyses

Funnel plots and Begg test will be conducted using Stata 14 to gauge potential publication bias, with a P > .05 being indicative of a lack of publication bias.

2.12. Quality of evidence analyses

The evidence quality for the obtained results will be assessed based on the Grades of Recommendation, Assessment, Development, and Evaluation[13] method. Analyzed factors will include risk of bias, publication bias, imprecision, and indirectness, with potential assessments including very low, low, moderate, and high.

3. Discussion

Several reports[9,10] have indicated that ZWD treatment can affectively alleviate HFrEF symptoms without inducing significant side effects. No systematic reviews regarding the efficacy of this therapeutic approach, however, have yet been published. There is thus a clear need for such a comprehensive overview, and the analysis proposed herein will consist of 4 key sections: study selection, inclusion, data extraction, and synthesis. Limitations of this protocol include the potential for heterogeneity among studies owing to variations in evaluative criteria and ZWD dosing. The overall goal of this analysis is to provide an evidence-based foundation for clinicians seeking to make more accurate decisions pertaining to HFrEF patient treatment.

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