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Article

Different network pharmacology mechanisms of Danshen-based Fangjis in the treatment of stable angina

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Abstract

Danshen (*Salvia miltiorrhiza*) preparations such as Danhong injection, Danshen injection, Salvianolate injection, compound Danshen injection and Sodium Tanshinone IIA Sulfonate (STS) injection are widely used in China to treat stable angina (angina pectoris) caused by coronary heart disease. In this study we compared the network pharmacological mechanisms of the 5 Danshen preparations. Following a literature search performed in PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI) database, China Biology Medicine (CBM) database, China Conference Paper Database, Wanfang Database, VIP Database and Conference Proceedings Citation Index (through January 2015), 444 randomized controlled trial publications detailing the use of the 5 Danshen-based injections for treating stable angina were identified, and their combined data were analyzed using a network meta-analysis. All of the 5 Danshen-based preparations were effective in treating stable angina with clinical improvement rates of 72.4%–91.6% and electrocardiogram (ECG) improvement rates of 54.5%–71.6%. According to both clinical improvement and ECG improvement, the 5 Danshen-based preparations were ranked as follows: Danhong injection > Salvianolate injection > STS injection > compound Danshen injection > Danshen injection. There were no significant differences among the safety profiles of the 5 Danshen preparations. The meta-analysis results were further examined using a network pharmacology approach and functional enrichment analysis, which revealed that Danshen and Danhong injections affected 4 and 15 signaling pathways, respectively, and that the 4 signaling pathways affected by Danshen were a subset of those influenced by Danhong. Therefore, Danhong injection affected some unique signaling pathways that might regulate lipoprotein metabolism, oxidation, and inflammation, and protect vascular endothelia, reflecting the multi-component and multi-target characteristics of this traditional formula and its strengths in treating complex diseases.

Keywords: stable angina (angina pectoris); coronary heart disease; Danshen preparations; network meta-analysis; network pharmacology; comparative effectiveness; Fangji

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Introduction

Salvia miltiorrhiza root (Danshen) is widely used in Asia because of its cardiovascular benefits and contains both hydrophilic phenolic acids and lipophilic tanshinones, which are believed to be responsible for its therapeutic efficacy[1]. Currently, Danshen (*Salvia miltiorrhiza*) preparations account for a large portion of clinical medications that are used to treat stable angina (angina pectoris) due to coronary heart disease. But physicians often have difficulty in making decisions about the most appropriate drug treatment for individual patients. Comparative effectiveness research aims to enable healthcare practitioners to make optimal decisions when they encounter various treatment options. In the context of "patient-oriented" research, comparative effectiveness studies employ various scientific research methods and data analysis tools to inform clinical decisions. This study used network meta-analysis and network pharmacology approach to review and examine the published results of clinical studies. Our findings may provide useful evidence to support the choice of Danshen-based

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preparations in real-world clinical practice.

Materials and methods

In this study, a network meta-analysis was performed based on the research method recommendations of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[2]. The results were reported according to the guidelines for reporting network meta-analysis issued by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group[3].

Inclusion and exclusion criteria for network meta-analysis

Publications reporting randomized controlled trials (RCTs) that compared the effectiveness of two or more preparations [Danhong, Danshen, Salvianolate, compound Danshen, and sodium tanshinone IIA sulfonate (STS)] for injection to treat stable angina were included in this study (Table 1 and Supplementary Table S1). The inclusion criteria were: cases in the angina onset phase (male or female, age range, 35–85 years); subjects diagnosed with coronary heart disease (CHD) according to the "Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease" developed by the Joint International Society and Federation of Cardiology and World Health Organization (WHO) in 1979, according to the "Chronic Stable Angina Diagnosis and Treatment Guidelines" developed by the Chinese Society of Cardiology (a branch society affiliated with the Chinese Medical Association) in 2007, or as evidenced by the results of coronary angiography. Myocardial ischemia caused by a myocardial infarction was excluded.

Literature sources for network meta-analysis

The search terms were separated into three groups: Danshen preparations, angina, and clinical experimental design. Combining keywords and non-keywords, literature search was performed in PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI) database, China Biology Medicine (CBM) database, China Conference Paper Database, Wanfang Database, VIP Database and Conference Proceedings Citation Index. We also used the following websites: International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), Clinical Trials (https://clinicaltrials.gov/), and Chinese Clinical Trial Register (http://www.chictr.org). Supplementary searches were conducted using Google (http://www.google.com.hk) and Baidu (http://www.baidu.com) to identify the relevant original literature and references included in the publications. All randomized controlled clinical trials conducted prior to January 2015 were reviewed.

Literature screening

Two investigators independently screened the publications. Their initial screening results were compared, and publication data were included in statistical analyses if they were in agreement. A third investigator was involved for further discussion if the results were inconsistent. First, we used literature management software Endnote (Thomson ResearchSoft, Stanford, Connecticut, USA) for literature classification, preparation, and removal of duplicates. Second, we excluded non-relevant studies that did not meet the inclusion criteria after reading the title and abstract of each article. Third, we obtained and read the full text of any potentially related research. Fourth, we analyzed and confirmed duplicate data publications. Fifth, we verified that the publications included in our analysis met the inclusion and exclusion criteria and recorded the detailed reasons for each excluded record. Sixth, for publications containing incomplete data, we contacted the original authors to acquire supplemental information. Lastly, we finalized the list of publications included in this study and extracted the data. See Supplementary Table S2 for the included data items

Table 1. The basic information of five Fangjis including Danshen.

Name	Composition	Main active component	Dosage	Manufacturer
Tanshinone IIA sodium sulfonate injection	Tanshinone IIA sodium sulfonate	Tanshinone IIA sodium sulfonate	40–80 mg/time, added to 250–500 mL of 5% glucose solution or 0.9% saline, once/day	Shanghai First Biochemical Pharmaceutical Co Ltd, *etc*
Compound Danshen injection	Danshen, Jiang xiang	Tanshinones, phenolic acids, Ginsenoside Rb1	8–16 mL added to 100–150 mL of 5% glucose solution, once/day, 2 to 4 weeks for a course of treatment	Shenwei Pharmaceutical Group Co Ltd, *etc*
Danshen injection	Danshen	Tanshinones, phenolic acids	10–20 mL, added to 100–500 mL of 5% glucose solution, once/day	Shandong Huaxin Pharmaceutical Group Co Ltd, *etc*
Salvianolate injection	Salvianolate	Salvianolate	200 mg, added to 250–500 mL of 5% glucose solution, once/day, 2 weeks for a course of treatment	Shanghai Green Valley Pharmaceutical Co Ltd
Danhong injection	Danshen, safflower	Tanshinones, phenolic acids, safflower yellow pigment, safflower glycoside, catechol	Intravenous infusion, 20–40 mL, with 100–500 mL of 5% glucose solution, once or twice per day	Shandong Danhong Pharmaceutical Co Ltd

extracted from the literature.

Quality assessment

The items used for the RCT quality evaluation were established according to the Cochrane Collaboration tool for assessing the risk of bias as described in the Cochrane Handbook Version 5.1.0[4] and included eight aspects: (1) random sequence generation and the correctness of the method used to generate random sequences; (2) allocation concealment and the correctness of the method used to conceal the allocation; (3) blinding of participants and personnel as well as the effectiveness of intentional blinding; (4) blinding of outcome assessment; (5) counts and reasons for loss of follow-up or withdrawal; (6) report of incomplete outcome data; (7) selective reporting; and (8) other sources of bias. See Supplementary Table S3 for the Cochrane quality assessment criteria.

Statistics analysis

The primary statistical software used was RevMan, which was used in combination with GRADEpro to assess the levels of evidence[5]. Network meta-analysis was mainly performed using WinBUGS[6]. GRADEpro was primarily used for the quantitative grading of the evidence and to determine the strength of the recommendations[7].

Construction of the chronic stable angina related network

We used three English terms associated with chronic stable angina (coronary heart disease stable angina pectoris, stable angina pectoris, and stable angina) as search terms to identify disease associated genes in the OMIM database. We then mapped the retrieved genes to the STRING database. Using *Homo sapiens* as the data background, we extracted the first-order approximations to construct the interaction network.

Analysis of the mechanisms of action of Danshen alone and Danshen and safflower combined (Danhong)

We searched for the chemical compositions and genes associated with Danshen and safflower in three separate databases: UniProt (http://www.ebi.ac.uk/uniprot), TCMSP (http://ibts.hkbu.edu.hk/LSP/tcmsp.php), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed). Genes associated with Danshen alone and the Danshen-safflower combination Danhong were mapped to the chronic stable angina network, and the correlation between medication and disease was evaluated.

We performed KEGG pathway functional enrichment analysis on genes associated with Danshen alone and Danhong using the DAVID database (https://david.ncifcrf.gov/). Results with P values <0.05 were retained, and the effectiveness of the use of Danshen alone and in combination with safflower (Danhong) was compared.

Results

Qualified publications included in this study

Using a systematic evaluation strategy, we identified 29 291 publications that potentially met the inclusion and exclusion criteria, of which 1210 were from CNKI, 25 980 from CBM, 1109 from Wanfang, 25 from China Conference Paper Database, and 954 from VIP. We also found 13 additional publications by including the references from the publications or by a manual search. All of the 29 291 potentially qualified publications were verified by software, and a total of 29 175 publications were excluded. We then read the titles and abstracts of the remaining 116 publications, and 27 publications were excluded. Thereafter, we read the full text of the remaining publications, and 45 articles were further excluded, among which 16 were excluded due to disqualified interventions, 19 due to incorrect diseases, 3 due to an unfit study design, and 7 for other reasons. This study ultimately included 44 publications[8-51].

Network meta-analysis

Based on the data FROM the original reports, we performed a network meta-analysis on the clinical improvement rate and electrocardiogram (ECG) improvement rate. We did not perform further network meta-analyses on other indices due to insufficient data in the original studies.

Assumption tests for the network meta-analysis

Because of the low heterogeneity of the original studies included for direct comparison, the assumption of the homogeneity index of the network meta-analysis was sufficiently satisfied. We performed meta-regression analyses on age, gender, and follow-up time and found that these factors were not significant effect modifiers (Supplementary Table S4).

By comparing the residual deviance and deviance information criterion between the consistent and inconsistent network meta-analysis models, we found that different models produced similar indices (Supplementary Table S5). Moreover, the deviations of all included studies in both clinical improvement and ECG improvement rates were comparable under different models (Figure 1), suggesting that the consistency assumptions for these two outcome measures were satisfactorily met.

Clinical improvement

A total of 4458 patients from 43 studies were included in the network meta-analysis of clinical improvement. The results of the direct comparison of this index are presented in Figure 2A and demonstrate that the majority of studies were directly related to a Danhong injection. Direct comparisons between compound Danshen and Salvianolate as well as compound Danshen and STS were lacking. Using other preparations as intermediate nodes, we obtained estimated effects using indirect associations.

The results of the paired-comparisons of the effects of the five Danshen-based preparations on the clinical efficacy are presented in Supplementary Table S6. The network meta-analysis indicated that Danhong injection significantly increased the clinical improvement rate compared with Danshen injection (RR=0.79 [0.65–0.89]), compound Danshen injection (RR=0.87 [0.76–0.94]), and STS injection (RR=0.87 [0.69–0.98]). The clinical improvement rate of Salvianolate

injection was significantly higher than that of Danshen injection (RR=1.23 [1.10–1.43]) and compound Danshen injection (RR=0.90 [0.79–0.98]); however, there were insufficient data to determine the significance of the differences in the clinical efficacy among Salvianolate, compound Danshen, and STS injections.

The absolute effect on clinical improvement and relative ranks of the five Danshen-based preparations are presented in Table 2. Danhong injection was the most effective out of the five preparations, followed by Salvianolate, STS, compound Danshen and Danshen injections. The clinical improvement rate of these injections was ranked from high to low as follows: Danhong injection (91.6%), Salvianolate injection (88.2%), STS injection (79.8%), compound Danshen injection (79.6%), and Danshen injection (72.4%).

Table 2. Network meta-analysis of clinical efficacy, estimated effectiveness, and relative rank.

Danshen preparation injections	Effectiveness [95% CI]	Rank [95% CI]
Danhong	91.6% [85.9%–95.6%]	1.08 [1.00–2.00]
Danshen	72.4% [56.7%–84.7%]	4.83 [4.00–5.00]
Salvianolate	88.2% [77.9%–94.8%]	2.00 [1.00–3.00]
Compound Danshen	79.6% [65.8%–89.5%]	3.58 [3.00–5.00]
STS injection	79.8% [60.9%–91.9%]	3.50 [2.00–5.00]

CI: confidence interval.

ECG improvement

A total of 3049 patients from 32 studies were included in the network meta-analysis of the efficacy of ECG improvement. A diagram illustrating ECG improvement comparisons is presented in Figure 2B. The majority of the included studies were directly related to the Danhong injection. Moreover, there were no direct comparisons between STS and compound Danshen injections. Using other preparations as intermediate nodes, we obtained corresponding indirect estimations.

The results of the paired-comparisons of the effects of the five Danshen-based preparations on ECG improvement are presented in Supplementary Table S7. The network meta-analysis results demonstrated that the Danhong injection was more effective in improving ECG than Danshen injection (RR=0.72 [0.43–0.96]) and compound Danshen injection (RR=0.80 [0.54–0.98]), while he Salvianolate injection was moderately more effective than the compound Danshen injection (RR=0.84 [0.56–1.00]). There was insufficient evidence to determine whether Salvianolate, compound Danshen, and STS injections had significantly different effects on the ECG readings.

The absolute effect on ECG improvement and relative ranks of the five Danshen-based preparations are shown in Table 3. Danhong injection was the most effective out of the five preparations, followed by Salvianolate, STS, compound Danshen, and Danshen injections. ECG improvement rate of these injections was ranked from high to low as follows: Danhong injection (71.6%), Salvianolate injection (68.8%), STS injection (66.2%), compound Danshen injection (59.7%), and Danshen injection (54.5%).

Table 3. Network meta-analysis of ECG improvement, estimated effectiveness, and relative rank.

Danshen preparation injections	Effectiveness [95% CI]	Rank [95% CI]
Danhong	71.6% [22.7%–97.1%]	1.52 [1.00–3.00]
Danshen	54.5% [10.0%–92.9%]	4.86 [4.00–5.00]
Salvianolate	68.8% [19.4%–96.7%]	1.94 [1.00–3.00]
Compound Danshen	59.7% [13.0%–94.5%]	3.72 [3.00–5.00]
STS injection	66.2% [16.0%–96.7%]	2.97 [1.00–5.00]

CI: confidence interval.

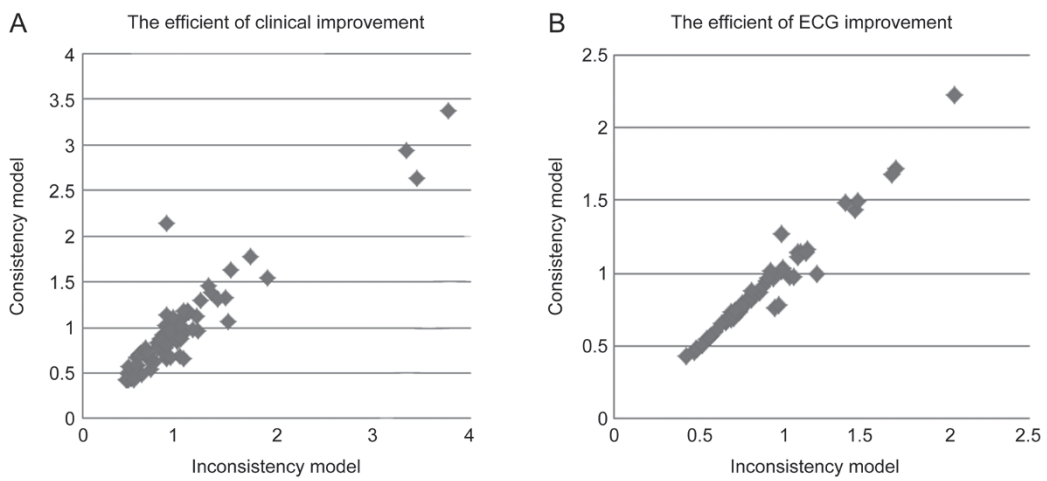

Figure 1. The clinical improvement rate and ECG improvement rate. (A) The clinical improvement rate. (B) The ECG improvement rate.

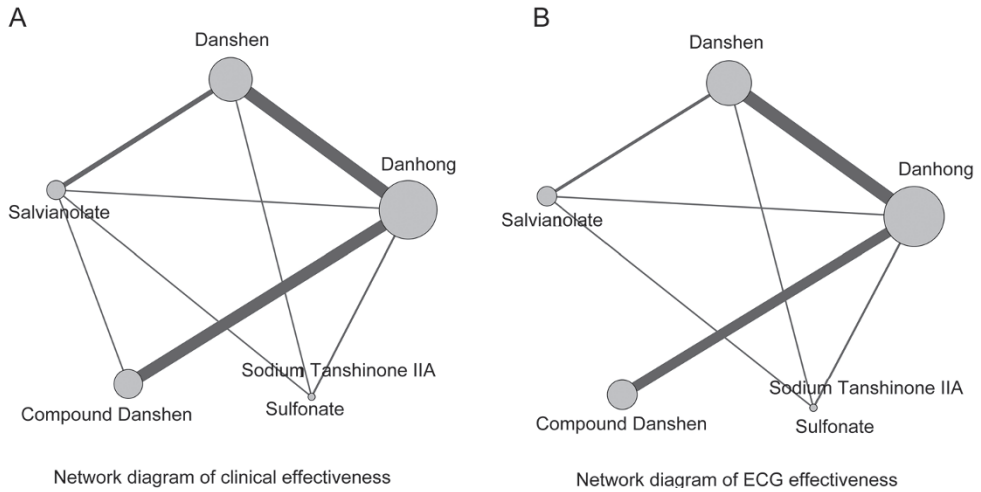

Figure 2. The clinical and ECG effectiveness network of the five Danshen-based preparations based on network meta-analysis. (A) Network diagram of clinical effectiveness. (**B**) Network diagram of ECG effectiveness.

Network construction for chronic stable angina

The search of the OMIM database yielded 19 genes that were associated with chronic stable angina, resulting in a total of 94 corresponding associated genes (Supplementary Table S8). These genes were mapped to the STRING database. Using *Homo sapiens* as the data background, an interaction network was constructed between related genes and their first-order neighbors, and results with an edge weight > 0.7 were retained (234 nodes and 1252 edges) (Figure 3A).

Analysis of the mechanisms of action of Danshen alone and Danhong injections

We searched the chemical compositions and associated genes of Danshen and safflower in UniProt, TCMSP, and PubMed, and identified 31 and 41 genes associated with Danshen and safflower, respectively (Supplementary Table S9). These genes were then mapped to the chronic stable angina network (Figure 3B).

As shown in the Venn diagram in Figure 3C, three overlapping pathways, amyotrophic lateral sclerosis (ALS), arginine and proline metabolism, and calcium signaling pathway, were identified as being affected by both Danshen alone and Danhong (Supplementary Table S10).

Two pathways were unique to safflower: the intestinal immune network for IgA production and NOD-like receptor signaling pathway. Four pathways were unique to Danshen-safflower combination (Danhong): pancreatic cancer, chronic myeloid leukemia, colorectal cancer, and prostate cancer. Only one pathway was shared by Danshen and Danhong: Alzheimer's disease. Seven pathways were shared by safflower and Danhong: complement and coagulation cascades, asthma, neuroactive ligand-receptor interaction, allograft rejection, T cell receptor signaling pathway, bladder cancer, and other forms of cancer.

Functional enrichment analysis was performed, and results with $P<0.05$ were subjected to further analysis (Table 4 and Figure 3C). Four signaling pathways were enriched for Danshen. The addition of safflower resulted in the identification of 15 signaling pathways in total, including the four pathways enriched for Danshen; hence, 11 pathways were enriched due to the addition of safflower.

Discussion

To evaluate comparative clinical effectiveness, two primary research methods are employed: randomized controlled trials and observational studies. Randomized controlled trials provide the most direct evidence; however, for trials to closely reflect reality, a large sample size, long study period, and

Table 4. The signaling pathways of Danshen and Danhong injection.

Name	KEGG pathway	*P* value
Danshen injection	Alzheimer's disease	0.001449576
	Amyotrophic lateral sclerosis (ALS)	0.002621024
	Arginine and proline metabolism	0.002621024
	Calcium signaling pathway	0.013054225
Danhong injection	Complement and coagulation cascades	1.81×10^{-4}
	Calcium signaling pathway	0.002275268
	Pancreatic cancer	0.0022982
	Bladder cancer	0.004186758
	Amyotrophic lateral sclerosis (ALS)	0.008048873
	Arginine and proline metabolism	0.008048873
	Alzheimer's disease	0.008451764
	T cell receptor signaling pathway	0.00977219
	Pathways in cancer	0.012811104
	Neuroactive ligand-receptor interaction	0.013931431
	Chronic myeloid leukemia	0.020602331
	Asthma	0.021425886
	Colorectal cancer	0.027698349
	Allograft rejection	0.032121033
	Prostate cancer	0.032138092

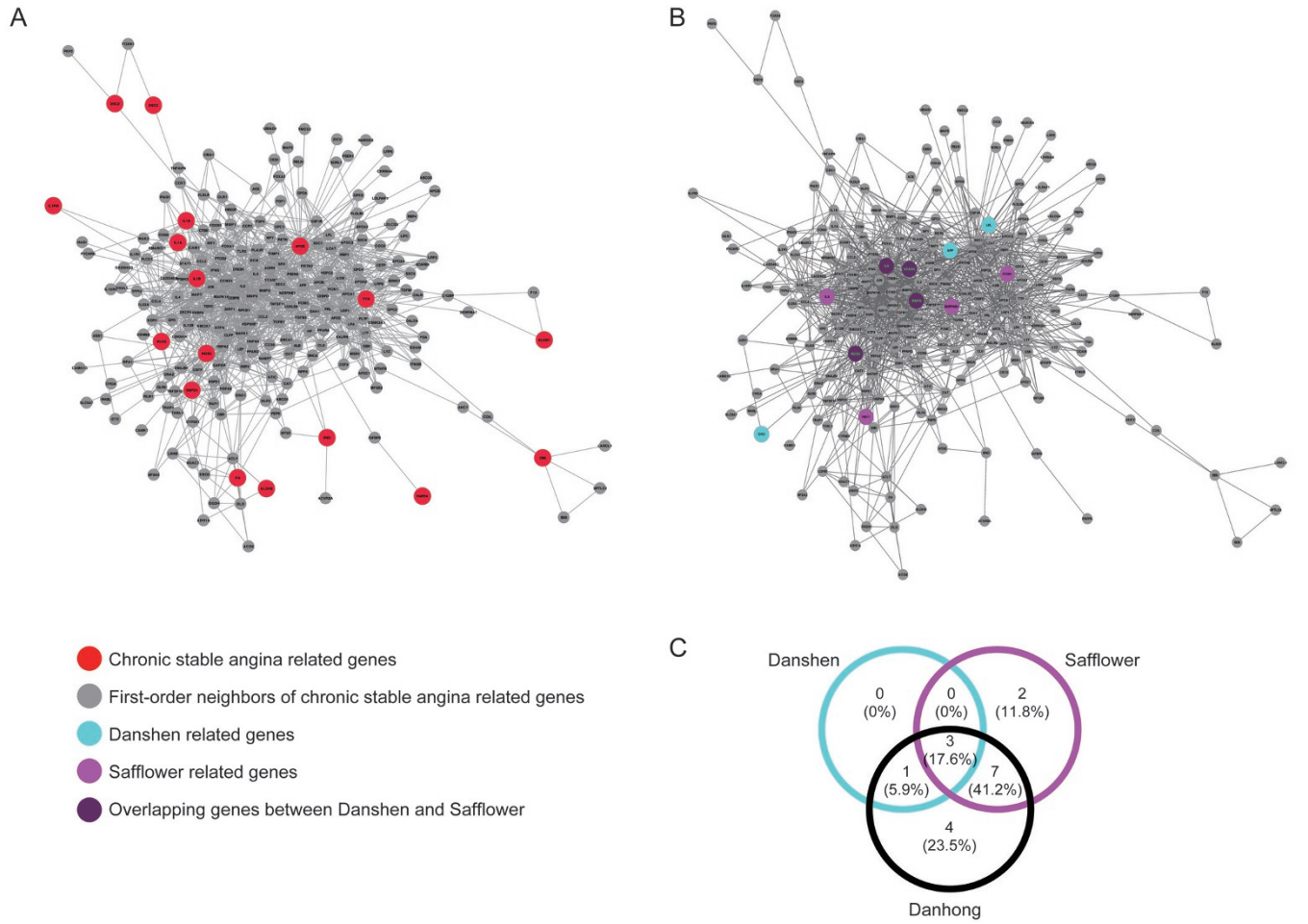

Figure 3. The effect of Danshen, Safflower and Danhong on the network of chronic stable angina. (A) The network of chronic stable angina, the red nodes represent chronic stable angina related genes and the grey nodes represent their first-order neighbors. (B) The related gene of Danshen, Safflower and Danhong mapping to the network of chronic stable angina, the blue, pink and purple nodes represent Danshen, Safflower and Danhong related genes, respectively. (C) The comparison of signaling pathway among the network of Danshen, Safflower and Danhong injection.

numerous personnel to conduct the trial are often required, along with additional resources. The results of observational studies can be universally applied to clinical cases and can be tested on patients to determine their effectiveness. An important method for observational research into comparative clinical effectiveness is network meta-analysis. Network meta-analysis can be used to compare and analyze multiple interventions simultaneously. It can also be used to examine a variety of interventions to identify cost-effective treatment solutions for implementation in clinical practice. Network pharmacology is a new discipline based on systems biology that is used to analyze biological systems networks to select specific signal nodes to enable the design of multi-target molecular drugs. Network pharmacology emphasizes the multi-faceted regulation of signaling pathways to improve the therapeutic effects of drugs and reduce their side effects, thus improving the success rate of clinical trials of new drugs and reducing the cost of drug research and development, and is a more appropriate method when using complex networks to analyze the mechanism of multi-target drugs[52-54]. This approach is comparable to the multi-component and multi-target ideas characterizing traditional Chinese medicine; and in this study, these two methodologies – network meta-analysis and network pharmacology - were combined.

The factors established as affecting the pathogenesis of coronary heart disease include gender, age, hypertension, dyslipidemia, diabetes and impaired glucose tolerance, smoking, obesity, family history, lack of exercise, poor eating habits, excessive alcohol consumption, and psychosocial factors. In recent years, research has uncovered additional risk factors for coronary heart disease, including infections (such as *Chlamydia pneumoniae* and *Helicobacter pylori*), inflammatory responses, autoimmune responses (heat shock protein HSP60), increased insulin resistance, hyperhomocysteinemia, and imbalances of serum-associated components, such as serum protein, blood trace elements, blood vitamins, and blood cell cellulose.

Network meta-analysis of comparative effectiveness

One strength of this study, which used a network meta-analysis based on Bayesian theory, was its ability to rank the effec-

tiveness of the five Danshen-based preparations. We reported three major findings. Firstly, Danhong, Danshen, Salvianolate, compound Danshen, and STS injections were all effective in treating stable angina. The range of clinical improvement rate of the five preparations was 72.4%–91.6% and that of ECG improvement rate was 54.5%–71.6%. Secondly, of these five preparations, Danhong injection was the most effective, followed by Salvianolate, STS, compound Danshen, and Danshen injections. The rankings by both clinical improvement rate and ECG improvement rate were identical. Thirdly, we did not identify any significant differences in the safety profiles of the five preparations, possibly due to insufficient data. With the exception of Danhong injection, the number of published studies for Danshen-based preparations was very limited, and there was even less pieces of data available derived from paired-comparisons of these preparations. Therefore, the results of this study should be considered exploratory. To draw clear and definitive conclusions, more direct paired-comparisons of Danshen-based preparations are required.

Compared to previous meta-analyses, this study employed a more complete systematic search, which included a larger number of publications and cases. Additionally, network meta-analysis was used for the first time in this study, generating a high level of consistency among different outcome indicators and stable results on sensitivity analysis. Moreover, the assumptions of network meta-analysis were highly satisfied; however, this study also has limitations, including the low quality of the original evidence, biased publications, and incomplete data in some original reports.

Similarities and differences in the mechanisms of action of different Danshen-based preparations determined by network pharmacology

The drugs selected in this study were all Danshen-based preparations, of which Salvianolate and STS injections are Danshen extracts. To clarify the mechanism underlying the optimal effectiveness of Danhong injection, we analyzed and compared the pharmacological mechanisms of Danhong and Danshen injections through the construction of two types of Danshen preparation-related gene networks and functional enrichment analysis. Our analysis indicated that the greater effectiveness of Danhong injection might be explained by its additional effect on 11 unique signaling pathways. By searching for existing literature on these 11 signaling pathways, we found that several were linked to coronary heart disease. For example, Wang *et al* reported that coronary heart disease could be treated through modulating adrenergic, angiotensin, calcitonin, and neurotensin receptors of the neuroactive ligand-receptor interaction pathway[55]. In a 3-year, follow-up study, Wang *et al*[56] found that the recurrence rate of coronary heart disease was higher in patients with both coronary heart disease and prostate cancer than that in patients with coronary heart disease alone, suggesting that the incidence of coronary heart disease was closely linked to prostate cancer. Moreover, there is evidence to suggest that factor H and complement C3, of the complement and coagulation cascades pathway, are associated with heart disease[57, 58]. Asthma is associated with the occurrence of coronary heart disease and thus may be a risk factor for this condition[59]. Danshen can help reduce rejection by inducing production of $CD4^+FoxP3^+$ Tregs[60]. Reduced levels of $CD4^+FoxP3^+$ Tregs can interact with other cytokines to aggravate immunopathological damage and inflammatory responses in coronary arteries[61]. T cell-mediated cellular immunity, especially the immune response to antigen-specific oxidized low density lipoproteins (ox-LDLs), plays a significant role in the process of atherosclerosis[62], a chronic inflammatory response to abnormal lipid metabolism and other risk factors. A variety of immune cells and inflammatory molecules are involved in atherosclerosis occurrence and development. In particular, T cells are closely linked to the inflammatory response of atherosclerotic plaques. During the entire process, from the start of coronary heart disease to thrombus formation, the main causes of acute coronary syndrome are the rupture of unstable plaques in the coronary artery and secondary bleeding and thrombosis. In recent years, the mechanism and prevention of coronary atherosclerotic plaque instability has become the focus of increased attention. The levels of inflammatory markers are widely recognized to be major indicators for predicting the risk of acute coronary syndromes and coronary heart disease[63]. The gene encoding p53 (*TP53*) is involved in the process of cardiomyocyte apoptosis[64, 65], and a significant increase in cardiac endothelial cell apoptosis may be associated with increased transcription of *TP53*[66, 67]. Furthermore, one unique pathway of Danhong injection, pancreatic cancer and prostate cancer, is also related with coronary artery disease according to CTD database. Further studies are also required to clarify the potential correlation between each of the 11 signaling pathways and coronary artery disease, which may help us better understand the pharmacological mechanisms of Danhong injection in treating this condition.

In summary, the Danhong injection is more effective for treating coronary heart disease than other Danshen preparations, probably due to its function in regulating additional pathways and its action on more targets. Coronary heart disease related angina is a complex disease with multiple regulatory factors, and its occurrence, development, and prognosis are often associated with a number of signaling pathways, which can also interact with one another. Signaling pathway networks comprise numerous signaling interactions, reflecting the inherent complexity of human biology. Therefore, analyzing and understanding drug efficacy at the level of biological pathways can help greatly in revealing the molecular mechanisms that underlie treatments. In treating diseases, Western medicine follows a simple formula, whereby single drugs are aimed at single targets. By contrast, traditional Chinese medicine attempts to solve problems by addressing the synergy of multiple components, multiple levels, and multiple targets and, as such, may be an alternative and more effective approach for improving symptoms and consequently patient quality of life. Thus, network analysis based on biological signaling pathways may be a more suitable method for analyzing the mechanisms of action of Chinese medicine, which empha-

sizes multiple targets. In conclusion, network meta-analysis combined with network pharmacology may be a promising tool for assessing the comparative effectiveness of several treatments and understanding the pharmacological mechanisms of multi-target treatments.

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Author contribution

Zhong WANG directed the research and revised the manuscript; Guo-xia ZHANG performed the research and wrote the paper; Xiao-xu ZHANG and Ying-ying ZHANG modified the tables and figures and revised the manuscript; Jun LIU, Peng-qian WANG and Qiong LIU revised the manuscript.

Supplementary information

Supplementary information is available at the website of Acta Pharmacologica Sinica.

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