



Status of Clinical Application of Yufeng Ningxin Preparations and the Meta-Analysis of Its Efficacy and Safety in the Treatment of Cardiovascular and Cerebrovascular Diseases

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CMNP 2022;2:e96–e106.

Abstract

Objective The objective of this study was to analyze the status of the clinical application of Yufeng Ningxin (YFNX) preparations and systematically evaluate their efficacy and safety in the treatment of cardiovascular and cerebrovascular diseases.

Methods Through searching databases of China National Knowledge Infrastructure, Wanfang, SinoMed, VIP, PubMed, Embase, and the Cochrane Library, the literature of clinical research on YFNX preparations in treating malignant tumors of cardiovascular and cerebrovascular diseases from the establishment of the databases to February 2021 was collected. The clinical randomized controlled trials and case-control studies of cardiovascular and cerebrovascular diseases treated with these preparations were analyzed. Two reviewers independently screened literature, extracted data, and assessed the risk of bias in the included studies, and meta-analysis was performed by using ReMan 5.3 software to analyze the efficacy and safety of YFNX preparations in the treatment of cardiovascular and cerebrovascular diseases.

Results A total of 29 clinical studies were finally included. The dosage forms were dropping pills, tablets, capsules, and granules. The preparations were used for the treatment of coronary heart disease, hypertension, neuropathic headache, etc. This study systematically evaluated the efficacy and safety of YFNX preparations in the treatment of coronary heart disease, hypertension, and nervous headache. A total of 1,162 cases were included in 13 studies, 582 cases of the YFNX preparation group and 580 cases of the Western medicine group. The results of meta-analysis showed that the clinical efficacy of YFNX preparations combined with the Western medicine group in the treatment of coronary heart disease and hypertension, improving electrocardiogram and reducing the frequency and duration of angina attacks, was

Keywords

- Yufeng Ningxin preparations
- cardiovascular and cerebrovascular diseases
- clinical randomized controlled trials
- case-control study
- meta-analysis

received
January 11, 2022
accepted after revision
March 3, 2022

DOI <https://doi.org/10.1055/s-0042-1750324>.
ISSN 2096-918X.

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

better than that of the simple Western medicine group, and the difference was statistically significant.

Conclusion YFNX preparations are effective for coronary heart disease, hypertension, and neuropathic headache, and the adverse reactions are few.

Introduction

Yufeng Ningxin (YFNX) preparations are pure Chinese medicine preparations, and the main ingredient is Gegen (*Puerariae Lobatae Radix*). Gegen (*Puerariae Lobatae Radix*) was first recorded in *Shennong's Classic of Materia Medica* (*Shen Nong Ben Cao Jing*). It is sweet, pungent in flavor, and cool in nature, with the functions of relieving the exterior, reducing fever, producing body fluid, expelling skin rash, raising yang, and stopping diarrhea. It can be used for headaches due to exogenous fever, stiff neck and back pain, thirst, consumptive thirst, measles, heat dysentery, diarrhea, etc., as mentioned in *Shennong's Classic of Materia Medica* (*Shen Nong Ben Cao Jing*), "It dominates consumptive thirst, high fever of the body, vomiting, various Bi syndromes, lifting yin fluid and eliminating toxicity." Gegen (*Puerariae Lobatae Radix*) contains chemical components of isoflavones, saponins, alkaloids, coumarins, and polysaccharides, among which isoflavones are the most abundant, mainly including daidzin, daidzein, puerarin, etc. The ingredient of the highest content is puerarin.¹ Modern pharmacological studies have shown that puerarin has the functions of protecting blood vessels, resisting oxidative stress, fighting against infection, lowering blood sugar, regulating blood lipids, improving insulin sensitivity index, etc., and has few adverse reactions. It has been clinically applied to the diseases such as cardiovascular and cerebrovascular diseases, cancer, Parkinson's disease, Alzheimer's disease, diabetes, and diabetic complications.²

Cardiovascular and cerebrovascular diseases are characterized by high morbidity, disability rate, mortality rate, and recurrence rate. With the aging of the population in China, the incidence of cardiovascular and cerebrovascular diseases shows a significant upward trend. It is reported that there are 330 million cardiovascular patients in China, including 13 million strokes, 11 million coronary heart disease, 8.9 million heart failure, and 245 million hypertension.³ Cardiovascular and cerebrovascular diseases have been a major public health problem and a prominent social problem. Therefore, it is imperative to give prevention and treatment. YFNX preparations mainly contain puerarin, which has the functions of relieving spasm and pain, enhancing cerebral and coronary blood flow, and has great advantages and potential in the prevention and treatment of cardiovascular and cerebrovascular diseases. However, it lacks a systematical review of the clinical application as well as the evaluations of the efficacy and safety in the prevention and treatment of cardiovascular and cerebrovascular diseases. This study comprehensively retrieved relevant clinical research at home and abroad to systematically analyze the clinical application status of YFNX

preparations and evaluate the clinical efficacy and safety to provide a reference for clinical practice and decision-making.

Current Status of Clinical Application of Yufeng Ningxin Preparation

Materials and Methods

Data Sources

China National Knowledge Infrastructure (CNKI), Wanfang (WF), SinoMed, VIP, PubMed, Embase, and the Cochrane Library databases were searched to collect clinical studies related to YFNX preparations. The retrieval time limit was from the establishment of the databases to February 2021. The Chinese searching term was the English searching terms were YFNX and yu feng ning xin.

Inclusion and Exclusion Criteria of Literature (Self-Made)

The types of literature included in this study were clinical studies, involving YFNX dropping pills as a dosage form, and related preparations, and there were no restrictions on the types of diseases, course of treatment, and evaluation indicators. Theoretical discussions, clinical experience, case reports, animal experiments, and duplicate publications on YFNX preparations were excluded.

Data Extraction and Statistics

Two researchers independently searched and screened the literature and excluded literature that did not meet the inclusion criteria. If there was any disagreement, it was resolved through discussion or consultation with a third researcher. For the included literature, the entry was made, the data were extracted, and the double-entry check was performed according to the design form. This study extracted the literature information from four aspects: (1) the publication year of the literature; (2) the specific intervention measures and syndrome differentiation in each clinical study; (3) the dosage form of YFNX preparations; (4) name of specific clinical disease treated by YFNX preparations.

Results

Literature Publication

By February 2021, a total of 396 related articles were retrieved. NoteExpress document management software was used to check duplicates and excluded 203 duplicate articles. By reading the titles and abstracts, 156 articles which obviously did not meet the inclusion criteria were

Year	number
2020	2
2019	4
2018	1
2017	3
2016	1
2015	1
2014	4
2013	1
2011	2
2010	1
2007	1
2006	1
2004	1
2003	3
2001	1
1999	1
1988	1

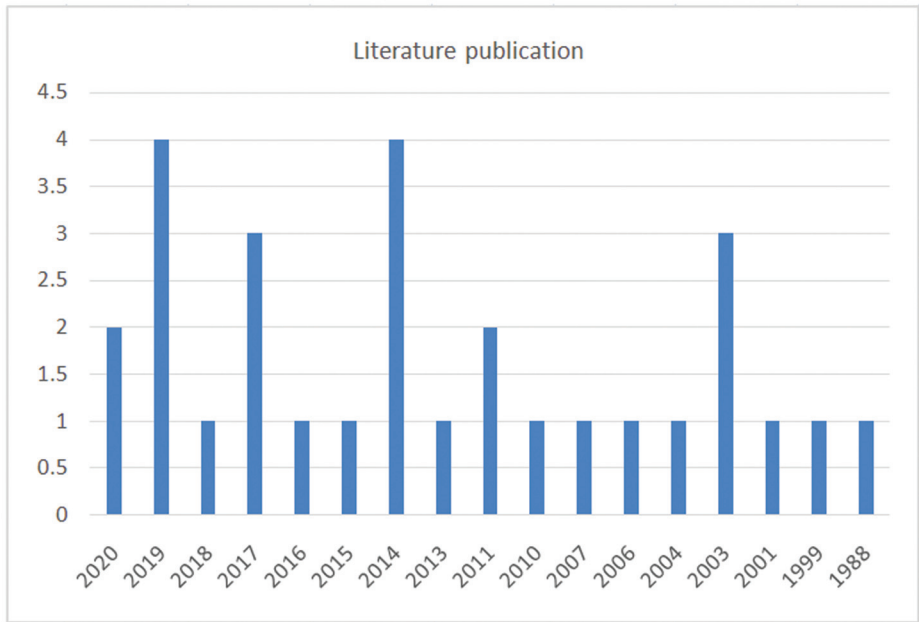


Fig. 1 Publication of clinical literature on YFNX preparations. YFNX, Yufeng Ningxin.

excluded. After reading the full texts, 8 articles that did not meet the inclusion criteria were excluded and 29 articles were finally included.⁴⁻³² The included 29 clinical studies were counted according to the year of publication. The results showed that the earliest clinical study was published in 1988, and the number of studies was increasing year by year. See ▶ **Fig. 1**.

Analysis of Dosage Forms, Clinical Syndromes, Research Types, and Intervention Measures Used in Clinical Research of Yufeng Ningxin Preparations

Among the 29 clinical studies included, YFNX preparations were included in 17 studies in the form of dropping pills, 9 studies in the form of tablets, 2 studies in the form of granules, and 1 study in the form of capsules. The three studies involved TCM syndromes, namely yin deficiency and yang hyperactivity syndrome, heart blood stagnation syndrome, and qi stagnation and blood stasis syndrome. The types of studies involved 15 case-control studies, 11 clinical randomized controlled studies, and 3 before-after self-control studies. The intervention measures involved seven kinds: YFNX preparations versus Chinese medicine, YFNX preparations versus Western medicine group, YFNX preparations + Western medicine group versus Western medicine group, YFNX preparations + Chinese medicine versus Chinese medicine and so on. See ▶ **Table 1**.

Analysis of Yufeng Ningxin Preparations in the Clinical Treatment of Diseases

In the included clinical studies, YFNX preparations were used for the treatment of nine kinds of clinical diseases, namely

coronary heart disease,^{5,7,8,10,11,17,20,21,27,31} neuropathic headache,^{9,12-14,18,22,25,26} hypertension,^{4,6,16} vertebrobasilar insufficiency (vertigo),^{19,23,24} transient cerebrovascular attack,¹⁵ chronic heart rhythm disorders,³² cerebral vasospasm,²⁸ sudden deafness,³⁰ myocardial ischemia.²⁹

Meta-Analysis of the Efficacy and Safety of Yufeng Ningxin Preparations in the Treatment of Cardiovascular and Cerebrovascular Diseases

Materials and Methods

Inclusion Criteria (Self-Made)

(1)The types of studies in the included literature were clinical randomized controlled trials and case-control studies; (2) the subjects of the studies were patients who were clinically diagnosed with cardiovascular and cerebrovascular diseases (coronary heart disease, hypertension, and neuropathic headache), and the age and course of the disease were not limited; (3) the intervention measures were YFNX preparations versus Western medicine group and YFNX preparations + Western medicine group versus Western medicine group (the chemotherapy regimens of the experimental group and the control group in the same study must be consistent); and (4) the main observation indicators involved clinical efficiency, pain scale, and so on.

Exclusion Criteria (Self-Made)

Exclusion criteria were (1) before-after self-control study, cross-sectional study; (2) experiments involving interventions

Table 1 Summary of the clinical research on the intervention measures of YFNX preparations

Included research literature	T	C
Ye and He 2020 ⁴	YFNX dropping pills	YFNX tablets
Yan et al 2020 ⁵	YFNX dropping pills + C	Western medicine routine 1
Cheng 2019 ⁶	YFNX dropping pill + C	general antihypertensive drugs
Yang 2019 ⁷	YFNX dropping pills + C	Western medicine routine 2
Cheng and Jia 2019 ⁸	YFNX tablets + C	Nifedipine sustained release tablets
Sun 2019 ⁹	YFNX dropping pills	Flunarizine hydrochloride capsules
Chen and Wang 2018 ¹⁰	YFNX dropping pills + C	Western medicine routine 3
Zheng and Xiao 2017 ¹¹	YFNX dropping pills + C	Western medicine routine 4
Yan 2017 ¹²	YFNX dropping pills + C	Flunarizine hydrochloride capsules
An 2017 ¹³	YFNX dropping pills	Flunarizine hydrochloride capsules
Dou 2016 ¹⁴	YFNX dropping pills	Flunarizine hydrochloride capsules
Guo et al 2014 ¹⁹	YFNX dropping pills + moxibustion	YFNX dropping pills
He 2014 ¹⁶	YFNX tablets + C	conventional antihypertensive drugs
Liang et al 2014 ¹⁷	YFNX dropping pills + C	Western medicine routine 5
Fu 2014 ¹⁸	YFNX dropping pills	Flunarizine hydrochloride capsules
Xing et al 2013 ²⁰	YFNX tablets + Moricizine tablets	Wenxin granules
Liang et al 2011 ²¹	YFNX dropping pills	—
Shi 2011 ²²	YFNX tablets + Nimodipine	—
Yang et al 2010 ²³	YFNX tablets + Ginkgo Damo injection	Anisodamine + Flunarizine hydrochloride
Feng 2007 ²⁴	Massage	YFNX dropping pills
Zhang et al 2006 ²⁵	YFNX dropping pills	Zhennaoning capsules
Zhu et al 2004 ²⁶	YFNX dropping pills + YFNX tablet simulators	YFNX tablets + YFNX dropping pill simulators
Sun 2003 ²⁷	YFNX tablets	Di'ao Xinxue Kang
Zheng 2003 ²⁸	Tongxinluo capsules	YFNX tablets
Liu et al 2003 ²⁹	YFNX tablets	Danshen tablets
Gu 2001 ³⁰	YFNX granules + Danshen injection	Danshen injection
Wang et al 1999 ³¹	YFNX granules	YFNX tablets
Ling and Li 1988 ³²	YFNX tablets + Amiodarone	Amiodarone
Peng 2015 ¹⁵	YFNX capsules + Compound Danshen injection	—

Abbreviation: “—”, the research does not involve this item; C, medication in the control group; T, medication in the treatment group; YFNX, Yufeng Ningxin.

Notes: Western medicine routine 1: mainly includes antiplatelet aggregation, nitrates, betablockers, etc., and nitroglycerin tablets are taken when angina pectoris occurs; Western medicine routine 2: low molecular weight heparin, statins, aspirin, isosorbide mononitrate; Western medicine routine 3: anticoagulation, nitrates, calcium channel blockers, lipid regulation, antiplatelet, etc.; Western medicine routine 4: antiplatelet aggregation, stabilizing plaque, nourishing myocardium, etc.; Western medicine routine 5: aspirin, clopidogrel, low molecular weight heparin, statins, isosorbide mononitrate, etc., sublingual intake of nitroglycerin during angina attack.

by other Chinese herbs; (3) repeated publications; and (4) the original data that cannot be extracted and cannot be obtained after contacting the author.

Retrieval Strategy

The data source was the same as 2.1.1. In addition, the references and relevant systematic reviews of the included studies were retrospectively reviewed to supplement relevant literature. The Chinese searching term was Yu Feng Ning Xin, and the English searching terms were Yufeng Ningxin, yu feng ning xin.

Literature Screening and Data Extraction

Two researchers independently screened the literature and extracted data and cross-checked them. Disagreements were discussed and resolved, and a third party was consulted to assist in judgment. The data were extracted using a preestablished data extraction form, and the extracted contents included (1) basic information of the included studies, including the first author, title, publication year, etc.; (2) the basic information of the patients, including the number of cases, age, etc.; (3) intervention measures, including the

use of drugs, doses, courses of treatment, etc.; (4) observation indicators and result measurement data; (5) follow-up time; and (6) methodological-related information.

Risk of Bias Assessment of the Included Studies

Clinical randomized controlled studies: According to the modified Jadad scale, the methodological quality of the included studies was evaluated from four aspects: random sequence generation, allocation concealment, blinding, withdrawal, or loss of follow-up (7 points as full score, 4–7 points as high quality, 1–3 points as low quality). **Case-control study:** The Newcastle–Ottawa scale was used to evaluate the quality of the included literature. The scale consisted of three dimensions and eight items, with a total score of 0 to 9. The evaluation included (1) selection of the study population: appropriateness of the cases determination, representativeness of cases, selection of control drugs and determination of control drugs, a total of four items, 4 points; (2) comparability between groups: the comparability of the case drugs and the control drugs, a total of one item, 2 points; and (3) outcome measurement or exposure factor measurement: determination of exposure factors, determination of the case and control exposure factors using the same method, nonresponse rate, a total of three items, 3 points. Total score <4 indicated low-quality research literature, 4 to 6 indicated medium-quality research literature, and >6 indicated high-quality research literature. In the quality evaluation, two researchers independently evaluated, and if there was a dispute, a third researcher was invited to arbitrate.

Statistical Methods

Revman 5.3 software was used for meta-analysis, the relative risk (RR) was used as the effect index for enumeration data, and the mean difference (MD) was used as the effect index for measurement data. Point estimate and 95% confidence interval (CI) were given to each effect size. The heterogeneity among included studies was analyzed by χ^2 test, and the size of heterogeneity was quantitatively judged with I^2 . If the heterogeneity among the results of the studies was not obvious ($I^2 \leq 50\%$), a fixed-effect model was used for meta-analysis. If there was obvious heterogeneity ($I^2 > 50\%$) among the studies, after excluding the obvious clinical heterogeneity, a random effect model was used for meta-analysis. The obvious clinical heterogeneity was progressed by subgroup analysis or sensitivity analysis, etc., or descriptive analysis was performed.

Results

Literature Search Results

According to the above searching strategy, a total of 396 articles were retrieved, including 95 articles from SinoMed database, 97 articles from CNKI database, 121 articles from WF database, and 83 articles from VIP database. NoteExpress was used to automatically check duplicates and obtain 193 articles. The title and abstract were read, 156 articles obviously inconsistent with the study were excluded, and 37

articles from the preliminary screening were obtained. After reading the full texts of the articles, 24 articles including other Chinese medicines or uncontrolled studies in the intervention measures were excluded, and 13 clinical studies were finally included.

Analysis of the Basic Characteristics and Quality

Evaluation of the Included Research Literature

A total of 13 research articles were included, including 6 clinical randomized controlled trials articles^{5–7,10,11,17} and 7 case-control articles.^{8,9,12–14,16,18} One study included YFNX tablets⁸ and the rest included YFNX dropping pills as dosage forms. Included studies were first published in 2014 and latest in 2020. A total of 1,162 patients with cardiovascular and cerebrovascular diseases were included in 13 research papers, including 582 cases of the YFNX preparation group and 580 cases of the Western medicine group. The Western medicine group involved conventional Western medicine intervention for coronary heart disease and angina pectoris, Western medicine of antihypertensive drugs, and flunarizine hydrochloride capsules. Diseases involved angina pectoris, hypertension, and neuropathic headaches. Observation indicators were clinical efficacy, the number of angina pectoris attacks, the duration of angina pectoris, the level of nitric oxide, the level of C-reaction protein, the number of headache attacks, the duration of headache, adverse reactions, etc. See ► **Table 2**.

Clinical Efficacy Analysis of Coronary Heart Disease, Hypertension, and Neuropathic Headache

The clinical efficacy included markedly effective, effective, and ineffective as the clinical judgment criteria. Five studies recorded the clinical efficacy of YFNX preparations + Western medicine group versus Western medicine group in the treatment of coronary heart disease,^{5,7,8,10,11} and the dosage forms were YFNX tablets and YFNX dropping pills, respectively. Two studies observed the clinical efficacy of YFNX preparations + Western medicine group versus Western medicine group in the treatment of hypertension.^{6,16} The dosage forms were YFNX tablets and YFNX dropping pills, respectively.^{6,16} Five studies observed the clinical efficacy of YFNX dropping pills + flunarizine hydrochloride capsules/YFNX dropping pills versus flunarizine hydrochloride capsules in the treatment of neuropathic headache.^{9,12–14,18} The dosage forms were all in the form of YFNX dropping pills. The meta-analysis results of the fixed effect model showed that compared with the pure Western medicine group, the YFNX preparations + Western medicine group/YFNX preparation group could significantly improve the clinical efficacy of coronary heart disease, hypertension, and neuropathic headache, and the difference was statistically significant (RR = 1.25, 95%CI [1.16, 1.35], $p < 0.00001$; RR = 1.21, 95%CI [1.08, 1.36], $p = 0.0008$; RR = 1.29, 95% CI [1.17, 1.41], $p = 0.0008$). See ► **Figs. 2–4**.

Electrocardiogram Analysis of Coronary Heart Disease

Two studies reported the effect of YFNX preparations + Western medicine group versus Western medicine group

Table 2 General characteristics of the included research literature

Included research literature	Types of study	Curing disease	Number of cases (T/C)	Age		Interventions		Course of treatment	Outcome indicator	Jadad score	NOS score
				T	C	T	C				
Yan et al 2020 ⁵	Clinical randomized control	Angina pectoris	42/41	40–75	40–75	YFNX dropping pills + C	Western medicine routine 1	April	①②③④	4 points	—
Cheng and Jia 2019 ⁸	Case-control study	Angina pectoris	46/46	40–68	40–66	YFNX Tablets + C	Nifedipine sustained release tablets	—	①③④⑤⑥	—	5 points
Sun 2019 ⁹	Case-control study	Neuropathic headache	61/61	39.2 ± 2.3	39.2 ± 2.3	YFNX dropping pills	Flunarizine hydrochloride capsules	—	①⑨⑩	—	3 points
Yang 2019 ⁷	Clinical randomized control	Angina pectoris	45/45	67.0 ± 10.1	69.5 ± 10.4	YFNX dropping pills + C	Western medicine routine 2	—	①	2 minutes	—
Cheng 2019 ⁶	Clinical randomized control	Hypertension headache	40/40	53.92 ± 2.75	53.77 ± 2.73	YFNX dropping pills + C	General antihypertensive drugs	—	①	3 points	—
Chen and Wang 2018 ¹⁰	Clinical randomized control	Coronary heart disease	46/46	60.8 ± 5.5	59.9 ± 6.1	YFNX dropping pills + C	Western medicine routine 3	4 wk	①②⑦⑧	3 points	—
Zheng and Xiao 2017 ¹¹	Clinical randomized control	Coronary heart disease	80/80	75.4 ± 1.38	71.13 ± 1.42	YFNX dropping pills + C	Western medicine routine 4	10 d	①	3 points	—
Yan 2017 ¹²	Case-control study	Migraine	29/29	45.1 ± 1.2	45.1 ± 1.2	YFNX dropping pills + C	Flunarizine hydrochloride capsules	9 wk	①⑨⑩	—	3 points
An 2017 ¹³	Case-control study	Neuropathic headache	39/38	37.8 ± 5.6	38.2 ± 5.7	YFNX dropping pills	Flunarizine hydrochloride capsules	—	①	—	3 points
Dou 2016 ¹⁴	Case-control study	Neuropathic headache	30/30	38.27 ± 4.57	39.64 ± 5.36	YFNX dropping pills	Flunarizine hydrochloride capsules	—	①	—	3 points
Liang et al 2014 ¹⁷	Clinical randomized control	Coronary heart disease	64/64	68.5 ± 9.1	68.5 ± 9.1	YFNX dropping pills + C	Western medicine routine 5	15 d	③④	3 points	—
He 2014 ¹⁶	Case-control study	Hypertension	42/42	35–60	35–60	YFNX Tablets + C	Conventional antihypertensive drugs	4 wk	①	—	3 points
Fu 2014 ¹⁸	Case-control study	Neuropathic headache	18/18	32.41 ± 1.03	32.41 ± 1.03	YFNX dropping pills	Flunarizine hydrochloride capsules	—	①	—	3 points

Abbreviation: “—”, This item is not involved in the study; C, medication in the control group; YFNX, Yufeng Ningxin.

Notes: Western medicine routine 1: mainly includes antiplatelet aggregation, nitrates, β -blockers, etc., and nitroglycerin tablets are taken when angina pectoris occurs; Western medicine routine 2: low molecular weight heparin, statins, aspirin, isosorbide mononitrate; Western medicine routine 3: anticoagulation, nitrates, calcium channel blockers, lipid regulation, antiplatelet drugs, etc.; Western medicine routine 4: drugs of anti-platelet aggregation, stabilizing plaque, nourishing myocardium, etc.; Western medicine routine 5: aspirin, clopidogrel, low molecular weight heparin, statins, isosorbide mononitrate, etc., sublingual intake of nitroglycerin during angina attack; (1) clinical efficacy; (2) EKG curative effect; (3) the number of angina attacks; (4) duration of angina pectoris; (5) 6-minute walking test; (6) NO level; (7) CRP level; (8) homocysteine (Hcy) level; (9) the number of headache attacks; (10) fibrinogen level; (12) hemorheology; (13) adverse reactions.

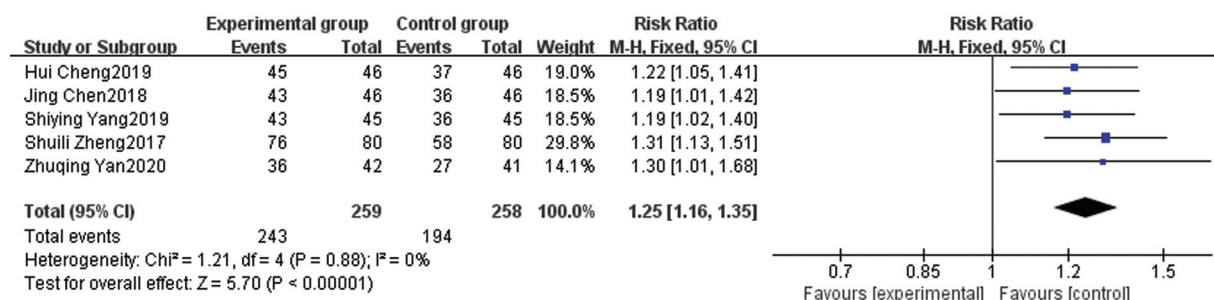


Fig. 2 Meta-analysis forest plot of clinical efficacy of YFNX preparations + Western medicine group versus Western medicine group in the treatment of coronary heart disease.
YFNX, Yufeng Ningxin.

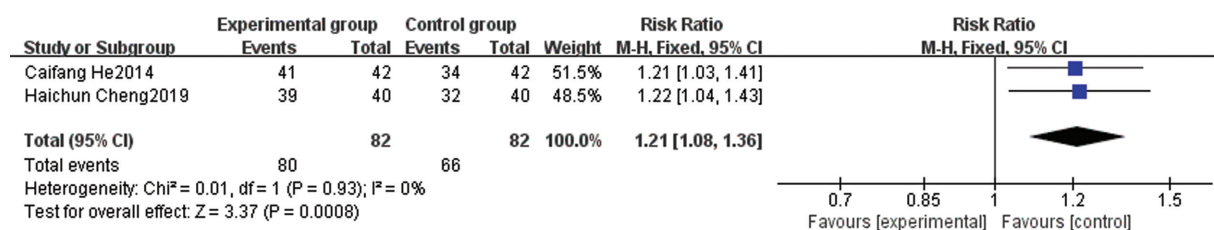


Fig. 3 Meta-analysis forest plot of clinical efficacy of YFNX preparations + Western medicine group versus Western medicine group in the treatment of hypertension.
YFNX, Yufeng Ningxin.

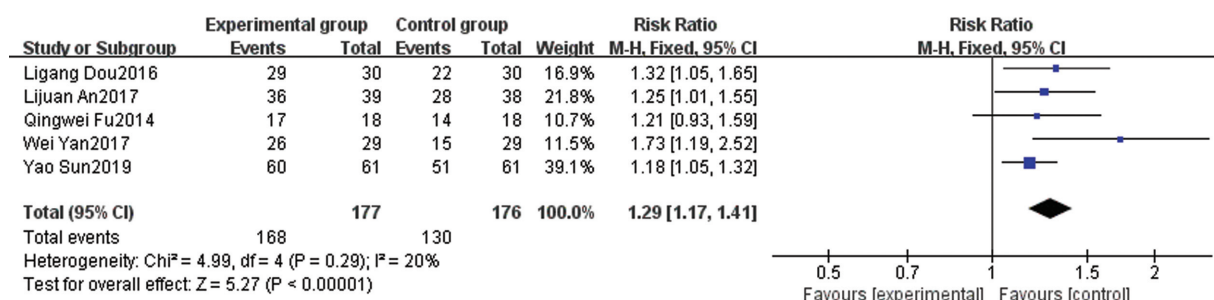


Fig. 4 Meta analysis forest plot of clinical efficacy of YFNX preparations + Western medicine/YFNX preparations VS Western medicine in the treatment of neuropathic headache.

on the electrocardiogram (ECG) of coronary heart disease, and the dosage forms were YFNX dropping pills.^{5,10} The clinical judgment criteria of ECG efficacy included markedly effective, effective, and ineffective. The results of meta-analysis of the fixed-effect model showed that compared with the simple Western medicine group, YFNX dropping pills combined with the Western medicine group could significantly improve the ECG of coronary heart disease,

and the difference was statistically significant (RR = 1.36, 95%CI [1.14, 1.62], $p = 0.0006$). See ►Fig. 5.

Analysis of the Number and Duration of Angina Pectoris Attacks in Coronary Heart Disease

Three studies observed the effect of YFNX preparations + Western medicine group versus Western medicine group on the frequency and duration of angina pectoris attacks in coronary

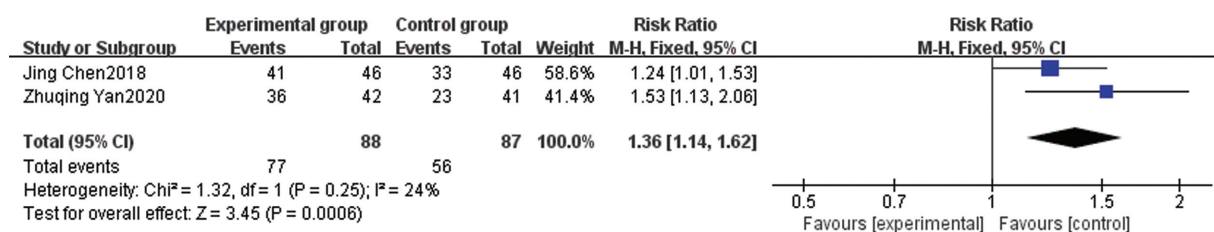


Fig. 5 Meta-analysis forest plot of ECG efficacy of YFNX preparations + Western medicine group versus Western medicine group in the treatment of coronary heart disease.
ECG, electrocardiogram; YFNX, Yufeng Ningxin.

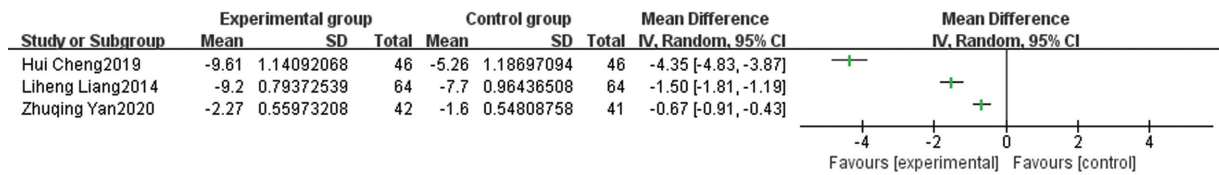


Fig. 6 Meta-analysis forest plot of the number of angina pectoris episodes of coronary heart disease treated by YFNX preparations + Western medicine group versus Western medicine group. YFNX, Yufeng Ningxin.

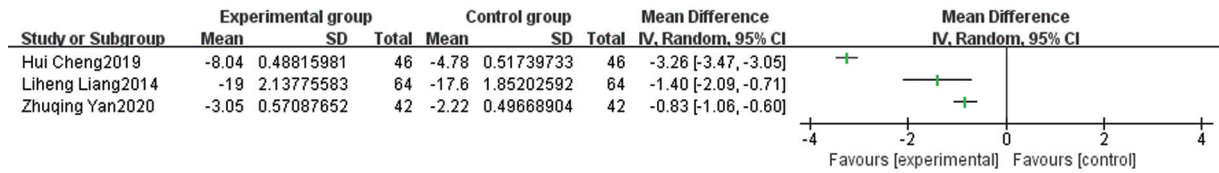


Fig. 7 Meta-analysis forest plot of the angina pectoris duration in coronary heart disease treated by YFNX preparations + Western medicine group versus Western medicine group. YFNX, Yufeng Ningxin.

heart disease.^{5,8,17} The results showed that the data had a high degree of heterogeneity ($p < 0.00001$, $I^2 = 99\%$), and the data consistency was still large after sensitivity analysis, so descriptive analysis was performed. The results showed that compared with the simple Western medicine group, YFNX preparations combined with the Western medicine group could significantly reduce the frequency and duration of angina pectoris attacks of coronary heart disease, and the difference was statistically significant. See ► **Figs. 6 and 7.**

Analysis of Fibrinogen Levels

Two studies reported the effect of YFNX preparations + Western medicine group versus Western medicine group on the level of fibrinogen in coronary heart disease, both of which were in the form of YFNX dropping pills.^{7,17} The meta-analysis of the fixed-effect model showed that YFNX dropping pills combined with the Western medicine group could significantly reduce the level of fibrinogen compared with that treated by the simple Western medicine group, and the difference was statistically significant (MD = -0.64, 95%CI [-0.99, -0.3], $p = 0.0003$). See ► **Fig. 8.**

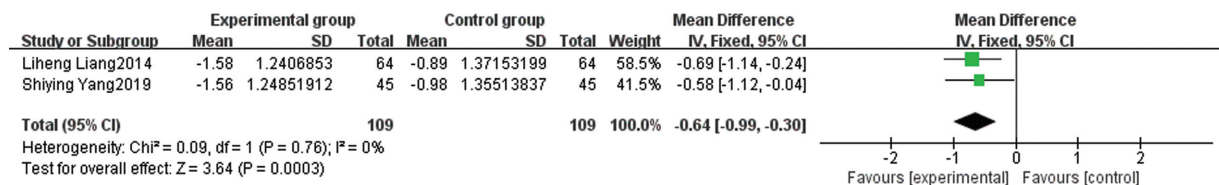


Fig. 8 Meta-analysis forest plot of the effect of YFNX preparations + Western medicine group versus Western medicine group on the level of fibrinogen in coronary heart disease. YFNX, Yufeng Ningxin.

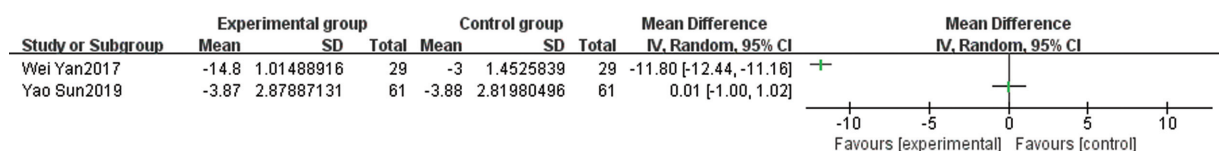


Fig. 9 Meta-analysis forest plot of the number of headache attacks of neuropathic headache treated with YFNX preparations + Western medicine group versus Western medicine group. YFNX, Yufeng Ningxin.

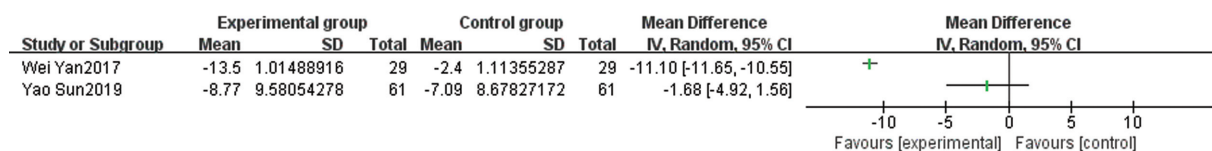


Fig. 10 Meta-analysis forest plot of the duration of neuropathic headache treated with YFNX preparations + Western medicine group versus Western medicine group.
YFNX, Yufeng Ningxin.

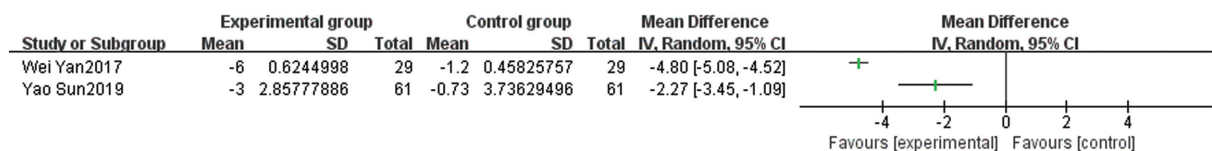


Fig. 11 Meta-analysis forest plot of scores of neuropathic headache treated with YFNX preparations + Western medicine group versus Western medicine group.
YFNX, Yufeng Ningxin.

Adverse Reactions

Three research articles reported the adverse reactions of YFNX dropping pills/tablets in the treatment of coronary heart disease, and one of them reported that there were no adverse reactions in the two groups.^{8,10,11} One research reported one case of headache in the control group, one case of constipation, one case of nausea, and one case of headache in the treatment group, and the incidence of adverse reactions between the two groups was not statistically significant. One research reported one case of abdominal distension, two cases of fatigue, and one case of dizziness, three cases of headache, one case of abdominal distension, seven cases of fatigue, six cases of constipation, eight cases of dry mouth, and three cases of nausea in the control group. The incidence of adverse reactions was 5.00% and 36.25%, respectively.

Publication Bias

Because the number of included studies was small and most of them were different diseases, the combined analysis could not be performed and no funnel plot was drawn.

Discussion

Cardiovascular and cerebrovascular diseases are the general term of cardiovascular and cerebrovascular diseases, generally referring to ischemic or hemorrhagic diseases of the heart, brain, and systemic tissues caused by blood viscosity, hyperlipidemia, and atherosclerosis in Western medicine,³³ which are equivalent to “chest pain and heart pain,” “stroke” “dizziness” and “headache” in TCM. In TCM, it believes that the fundamental pathogenesis of cardiovascular and cerebrovascular diseases lies in “blood stasis,” and blood stasis syndrome is a common syndrome of various cardiovascular and cerebrovascular diseases. Promoting blood circulation and removing blood stasis is a basic therapeutic method in TCM, which promotes a smooth flow of blood by dredging the blood vessels and removing blood stasis, thus having therapeutic and preventive effects on the cardiovascular and

cerebrovascular diseases. Studies have shown that Chinese herbs with the effect of promoting blood circulation and removing blood stasis have the functions of dissipating blood stasis, promoting blood circulation, improving platelet activity, regulating blood lipids, resisting platelet aggregation, and reducing the occurrence of thrombosis. In the clinical treatment of cardiovascular and cerebrovascular diseases, these herbs are often used to increase blood flow velocity, reduce blood viscosity, red blood cell aggregation, blood congestion and capillary permeability, and improve vascular status and vascular oozing.³⁴ Therefore, Chinese herbs with the effect of promoting blood circulation and removing blood stasis have high clinical value in the treatment of cardiovascular and cerebrovascular diseases.

The clinical dosage forms of YFNX preparations include dropping pills, tablets, capsules, and granules, and dropping pills are the main dosage forms currently used in clinical practice. The main component of YFNX dropping pills is puerarin, which has the functions of dilating blood vessels, relieving spasm and pain, and increasing blood flow of heart and cerebral blood and has a significant effect on the prevention and treatment of cardiovascular and cerebrovascular diseases. Studies have shown that the drug can be used for coronary heart disease, neuropathic headache, hypertension, vertebrobasilar insufficiency, transient cerebrovascular attack, chronic arrhythmia, cerebral vasospasm, sudden deafness, myocardial ischemia, etc. Meta-analysis results showed that compared with the simple Western medicine group, YFNX preparations + Western medicine group/YFNX preparation group can significantly improve the clinical efficacy of coronary heart disease, hypertension and neurological headache, improve the ECG of coronary heart disease, reduce the frequency and duration of angina pectoris of coronary heart disease, lower the fibrinogen level and headache score, shorten the duration of headache, and reduce the number of headache attacks, with statistically significant difference. In terms of adverse reactions, only three articles reported adverse reactions in the included studies. The reported adverse reactions included constipation, headache, dizziness, nausea, abdominal distension,

fatigue, etc. The number of adverse reactions was small, and the difference was not statistically significant. Limitations of this study: (1) the quality of the included studies is not high enough. Among the 13 included studies, 6 were clinical randomized controlled studies and 7 were case-control studies. Only one of the randomized controlled clinical trials was of high quality, one of the case-control studies was of moderate quality, and the rest of the articles were of low quality. (2) The included studies were all single-center studies, most of the experiments were small sample, and no study estimated the sample size, which may affect the reliability of the results. (3) The treatment course and dose of each study were different, and the clinical heterogeneity could not be completely eliminated.

To sum up, YFNX preparations are effective for cardiovascular and cerebrovascular diseases such as coronary heart disease, hypertension, neuropathic headache, and no serious adverse reactions have been found. Limited by the quantity and quality of the included studies, the above conclusions need to be verified by more high-quality studies.

Credit Authorship Contribution Statement

Lishuang Zhang: Data curation, visualization, software, formal analysis, and writing—original draft. **Yaxia Ma:** Data curation, formal analysis, and software. **Ying Wang:** Formal analysis, and writing—original draft. **Feng Jiang:** Conceptualization, methodology, funding acquisition, and writing—review & editing.

Funding

This work was supported by Tianjin Municipal Education Commission Scientific Research Program (2021KJ170).

Conflict of Interest

The authors declare no conflict of interest.

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