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Comparative efficacy and safety of ginkgo-based Chinese patent medicines in patients with hypertension

A systematic review and network meta-analysis of randomized clinical trials

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Abstract

Background: The efficacy and safety of different oral ginkgo-based Chinese patent medicines (CPMs) regimens for hypertension patients were analyzed based on the network meta-analysis of the frequency framework.

Methods: We conducted a comprehensive search of PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure, Wanfang, China Science and Technology Journal Database, and Chinese Biomedical Literature Database to gather data on randomized controlled trials (RCTs) evaluating the efficacy of 8 ginkgo biloba oral preparations for the treatment of hypertension. The trials included in the analysis were conducted from the inception of the databases up to September 2023. Methodological quality and risk of bias were assessed using the RoB 2.0 evaluation tool, and a reticulated meta-analysis was conducted using STATA MP 14 software. The RCTs included in this study were published studies and therefore did not require ethics committee review or patient consent.

Results: We ultimately included 46 RCTs covering 8 CPMs including ginkgo biloba tablet (GBT), GB capsule (GBC), ginkgo biloba drop (GBD), ginkgo biloba ketone ester drop, Fufangyinxing capsule, fufangyinxingtongmai oral liquid, Yinxingmihuan oral liquid, Yindanxinanotong softgel capsule (YDXNT). GBD + CT demonstrated the highest effectiveness in reducing systolic blood pressure (surface under the cumulative ranking [SUCRA] = 78.7%) and improving total effective rate (SUCRA = 86.7%). GBC + CT exhibited the greatest efficacy in reducing diastolic blood pressure (SUCRA = 92.6%). GBT + CT was identified as the most effective in lowering total cholesterol (TC) (SUCRA = 100%). Additionally, YDXNT + CT demonstrated notable improvements in triglyceride levels (SUCRA = 92.2%), Nitric oxide (NO) (SUCRA = 93.9%), and ET-1 (SUCRA = 67.5%). In terms of safety, 14 studies reported the occurrence of adverse reactions with a high degree of clinical heterogeneity, which was only qualitatively analyzed in this study.

Conclusion subsections: We found that a combination of 8 ginkgo-based CPMs + CT was effective in hypertension compared with CT. The evidence showed that GBD + CT were the best in improving systolic blood pressure and total effective rate, GBC + CT improved diastolic blood pressure, GBT + CT were the most effective in improving TC, and YDXNT + CT was the most effective in improving TG, NO, and ET-1. Adverse effects were only analyzed qualitatively, and the number of adverse effects of CPMs treatment was relatively low compared to CT. In addition, the quality of the literature included in the study was low, and further validation through RCTs with larger sample sizes, higher quality, and more rigorously designed is needed.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. As this study did not involve clinical data, ethics approval was not applicable.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42023489395.

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Abbreviations: CI = credible intervals, CPMs = Chinese patent medicines, CT = Conventional treatment, ET-1 = endothelin-1, FFYX = fufangyinxing capsule, FFYXTM = fufangyinxingtongmai oral liquid, GBC = ginkgo biloba capsule, GBD = ginkgo biloba drop, GBKED = ginkgo biloba ketone ester drop, GBT = ginkgo biloba tablet, IF = inconsistency factors, MD = mean difference, MeSH = medical subject headings, NMA = Network meta-analysis, NO = nitric oxide, OR = ratio-ratio, RCTs = randomized controlled trials, ROB 2.0 = risk of bias assessment tool 2.0, TC = total cholesterol, TCM = traditional Chinese medical, TG = triglycerides, TNF-α = tumor necrosis factor- α, YDXNT = Yindanxinanotong softgel capsule, YXMH = Yinxingmihuan oral liquid.

Keywords: blood pressure, Chinese patent medicines, ginkgo biloba, hypertension, network meta-analysis.

1. Introduction

Hypertension is a common chronic disease worldwide.[1] Hypertension is a high risk factor for adverse outcomes such as stroke, coronary heart disease, cardiac infarction, heart failure, and renal failure,[2] which seriously affects people's quality of life and life and health, and imposes a huge disease burden on global healthcare.[3] Studies estimate that 31.1% of adults (1.39 billion people) worldwide had hypertension in 2010, with a higher prevalence in low- and middle-income countries (31.5%, 1.04 billion people) compared with 28.5% (349 million people) in high-income countries.[4] Data from the China Hypertension Survey show that the crude prevalence of adult hypertension in 2018 was 27.5%.[5] It is predicted that the number of adults with hypertension will increase to 1.56 billion worldwide by 2025.[6] Awareness and control of hypertension have increased in recent years, mainly in high-income and some middle-income countries, but in low-income countries and most middle-income countries blood pressure control is still suboptimal, and prevalence and health care burden are still increasing.[7]

However, There are limitations to how best to manage hypertension medically. Currently, antihypertensive drug therapy remains the mainstay of hypertension treatment, with 1 mechanism of hypertension corresponding to a corresponding antihypertensive drug. The major guidelines continue to focus on 5 antihypertensive agents: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide diuretics, and beta-blockers.[8] When a patient fails to meet the criteria for lowering blood pressure with a single medication, combination blood pressure lowering becomes a necessity, which also includes the use of compounded agents.[9] There are still some shortcomings in the current treatment of hypertension. Nearly 40% of patients taking antihypertensive medications in developed countries do not reach their blood pressure goals, and the situation is even more bleak in developing countries.[10] Long-term use has unavoidable side effects, such as irritating dry cough, heart rate variability, edema, hyperkalemia, nausea and vomiting.[11] In patients with cardiovascular and cerebrovascular diseases, the combination of medications leads to a relatively complex treatment regimen and reduced adherence. Hypertension, as a major cause of cardiovascular disease and premature death worldwide, how to effectively control blood pressure and reduce the damage of hypertension to the heart, kidney, brain, and other organs still requires our continuous efforts to find more effective drugs and prevention strategies.

The Chinese Expert Consensus on the Clinical Application of Oral Ginkgo Biloba Preparations (2020) states that ginkgo-based Chinese patent medicines (CPMs) are effective not only in the treatment of hypertension, but also in the improvement of symptoms, the protection of target organs and the prevention of complications.[12] Currently, there is a wide variety of oral preparations of ginkgo,[13] with flavonoids, terpenoids, and organic acids as the main active ingredients.[14] Compared with traditional antihypertensive drugs, ginkgo-based CPMs have a variety of biological activities. Basic experiments have found that Ginkgo biloba extract improves blood pressure while improving vascular endothelial function,[15] and protects target organs such as heart, brain and kidney.[16,17] Clinical studies have found that the combination of ginkgo-based CPMs on top of antihypertensive drugs can provide increased efficacy while reducing adverse effects.[18] To date, the evidence base for ginkgo-based CPMs for the treatment of hypertension remains limited. There are many different types of CPMs and fewer studies directly comparing the efficacy of different ginkgo-based CPMs, making it difficult for clinicians to make optimal decisions. Therefore, arriving at the most effective ginkgo-based CPMs will facilitate national guideline writing and clinical decision-making, thus providing more complete evidence for clinical treatment. Reticulated meta can enhance the evidence by combining direct and indirect evidence and comparing different interventions. Therefore, reticulated meta-analysis was used in this study to compare the efficacy and safety of different CPMs in the treatment of hypertension and to provide evidence-based medical support for optimal clinical drug selection.

2. Methods

We performed a systematic review and network meta-analysis (NMA) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[19] In addition, this study has been registered with PROSPERO, under the number CRD42023489395.

2.1. Search strategies

We searched the data in PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database, and Chinese Biomedical Literature Database databases from the database's inception through September 2023 using Medical Subject Headings (MeSH) for "hypertension" and "traditional Chinese medicine" search terms in Appendix 1, Supplemental Digital Content, http://links.lww.com/MD/M253. In order to ensure the comprehensiveness of the study, we conducted additional searches by reviewing the reference lists of previously published systematic reviews that were identified through the Cochrane Database of Systematic Reviews (search terms: hypertension, traditional Chinese medicine; limits: none) and PubMed (search terms: hypertension, traditional Chinese medicine; limits: systematic reviews or meta-analysis). We also searched the Chinese Clinical Trial Registry and Clinicaltrials.gov for some unpublished clinical trials. Using PubMed as an example, the search terms and strategies are as follows.

#1: Hypertension [MeSH Terms]

#2: Blood Pressure, High [Title/Abstract] OR Blood Pressures, High [Title/Abstract] OR High Blood Pressure [Title/Abstract] OR High Blood Pressures [Title/Abstract] OR Abnormal blood pressure [Title/Abstract] OR Vertigo [Title/Abstract] OR Dizziness [Title/Abstract]

#3: #1 OR #2

#4: Ginkgo biloba [MeSH Terms]

#5: Gingko [Title/Abstract] OR Ginko Ginkgophyta [Title/Abstract]

#6: Medicine, Chinese Traditional [MeSH Terms]

#7: Traditional Chinese Medicine [Title/Abstract] OR Zhong Yi Xue [Title/Abstract] OR Chinese Traditional Medicine [Title/Abstract]

#8: Ginkgo Biloba Tablet [Title/Abstract] OR Ginkgo Biloba Capsule [Title/Abstract] OR Ginkgo Biloba Drop [Title/Abstract] OR Ginkgo biloba ketone ester drop [Title/Abstract] OR YinDanXinNaoTong soft capsule [Title/Abstract] OR YinXingMiHuan oral liquid [Title/Abstract] OR FuFangYinXing [Title/Abstract]

#9: #4 OR #5 OR #6 OR #7 OR #8

#10: randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract]

#11: #3 And #9 And #10

2.2. Eligibility criteria

The inclusion criteria were based on the PICOS[19] (participants, interventions, comparators, outcomes, and study design) approach. Inclusion criteria: Participants met a diagnosis of hypertension,[20] Those with systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg measured 3 times on nonsame days without antihypertensive medication, with a previous history of hypertension, and currently on antihypertensive medication. Participants were not limited to age, gender, race, disease duration, or geographic location. The intervention was a combination of ginkgo-based CPMs and antihypertensive medications, and all medications were used in accordance with the diagnostic and treatment protocols. Conventional treatment (CT) is various types of antihypertensive drugs, while underlying diseases are treated symptomatically without the use of traditional Chinese medical (TCM) preparations such as herbal injections, CPMs or soups. Outcomes contain at least one of the outcome indicators specified for this study. The included articles in this study followed a randomized controlled trial design with no language restrictions.

Exclusion criteria: studies that were repeatedly published or from which data could not be extracted. Non-randomized controlled trials (RCTs) studies, such as meta-analyses, reviews, theoretical investigations, clinical experiences, animal experiments, etc Studies without any of the primary outcome indicators or secondary outcome indicators. Studies in which unconventional treatments were included in the interventions, such as other Chinese medicinal preparations for the treatment of hypertension, acupuncture, gua sha, etc Less than 2 pieces of literature related to 1 intervention.

2.3. Outcome indicators

Blood pressure is the standard for hypertension patients' own detection as well as efficacy assessment, so systolic and diastolic blood pressure were selected as the main outcome indicators. Referring to the outcome index of clinical RCTs and the Chinese Guidelines for the Prevention and Treatment of Hypertension,[20] the total effective rate of blood pressure reduction was included as the outcome index. Effective: diastolic blood pressure decreased by ≥10 mm Hg after treatment, or systolic blood pressure decreased by ≥30 mm Hg and reduced to normal range, or diastolic blood pressure decreased by ≥20 mm Hg, effective: diastolic blood pressure decreased by <10 mm Hg but reduced to normal, or diastolic blood pressure decreased by > 10 mm Hg even though it was not reduced to normal, Ineffective: blood pressure did not reach the above criteria. Total effective rate = (number of patients with significant effect + number of patients with effective)/total number of patients × 100%. Hyperlipidemia not only damages the walls of blood vessels and causes them to become less elastic, but also thickens the blood and increases resistance, which affects blood pressure, hence the inclusion of total cholesterol (TC) and triglycerides (TG) as outcome indicators. Nitric oxide (NO) and endothelin-1 (ET-1) are closely related to vasodilatation and constriction, respectively, and are involved in the pathologic process of hypertension onset and progression, and were therefore also included in the study. In order to assess the safety of CPMs, we included adverse reactions in the study.

In summary, primary outcome indicators: systolic blood pressure, diastolic blood pressure. Secondary outcome indicators: total effective rate, TC, TG, NO, ET-1, adverse effects.

2.4. Data collection and quality assessment

Two researchers (YYH and ZGH) searched the literature and exported relevant articles according to the set search form, used Endnote X9 to screen and de-duplicate the imported literature, and then screened the literature independently according to the ranking criteria, and extracted the relevant information from the literature with the help of Excel, including the basic information of the literature, the basic characteristics of the interventions, and the outcome indicators, etc If there was any disagreement during the process, the third researcher (LSM) was consulted. In case of disagreement, the third researcher (LSM) was consulted.

Two investigators (YYH and ZGH) referred to the Cochrane Collaboration's recommendation of the latest Risk of Bias assessment tool 2.0 (ROB 2.0) for risk of bias assessment.[21] ROB 2.0 comprises of 5 modules: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result. the results of each module were assessed using the modular decision pathway diagrams. Ultimately, these results were summarized to determine the overall assessment of bias, which was categorized as "Low risk," "Some concerns," or "High risk" based on the contents of the literature.

2.5. Data synthesis and analysis

Network meta-analysis (NMA) was performed using the network program package of StataMP 14.0, in which ratio-ratio (OR) was used for dichotomous variables, and mean difference was used for continuous variables, both expressed as effect values and their 95% credible intervals (CI). A reticulation of evidence was first plotted, with the size of the points indicating the sample size of the intervention and the thickness of the connecting lines indicating the amount of evidence for 2 direct comparisons. In this study, comparisons were made between different interventions using a two-by-two design. In cases where there was a closed loop, inconsistency tests were performed to assess the consistency between direct and indirect comparisons. The inconsistency factors, 95% CI, and *P* values from Z tests were calculated. If the *P* value was >.05 and the lower limit of the 95% CI of the inconsistency factors value was equal to 0, it was considered as good consistency between the direct and indirect comparisons. On the other hand, if these conditions were not met, the closed loop was considered to have significant inconsistency. However, in this particular case, there was no closed loop detected, so the consistency model was used without further adjustments for inconsistency. The NMA results were produced as a league table and the two-by-two comparisons were judged to be statistically significant or not, based on effect values and confidence intervals. The outcome indicators of each intervention were ranked according to surface under the cumulative ranking (SUCRA) graphs, with a larger area under the curve representing a better intervention. Cluster analysis was performed on the outcome indicators, which led to the result that the 2 outcome indicators of different CPMs did well at the same time. A "comparison-corrected" funnel plot was drawn, and it was observed whether the studies were uniformly distributed on both sides of the median line to determine the small-sample effect.

3. Results

3.1. Literature screening process and basic characteristics

We obtained a total of 1797 articles by searching relevant databases, and 1301 articles were obtained by excluding 496

duplicates. After reading the titles and abstracts of the literature, 1210 articles that clearly did not meet the inclusion criteria were excluded; the remaining 91 articles were further evaluated. In accordance with the inclusion and exclusion criteria, 45 articles were excluded from the literature. Of these, 13 studies did not contain the included outcome metrics, 27 studies had noncompliant interventions, fewer than 2 studies of the same ginkgo-based CPMs were included in the 3 studies, and 2 studies had incomplete data. Finally, 46 studies of RCTs were included, all of which were in Chinese, and the literature screening process is shown in Figure 1.

A total of 46 RCTs involving 8 ginkgo-based proprietary CPMs and 5183 participants were included in this study, including 21 items of ginkgo biloba tablet (GBT),[22–42] 3 items of GB capsule (GBC),[43–45] 6 items of ginkgo biloba drop (GBD),[46–51] 3 items of ginkgo biloba ketone ester drop (GBKED),[18,52,53] 2 items of Fufangyinxing capsule (FFYX),[54,55] 2 items of fufangyinxing-tongmai oral liquid (FFYXTM),[56,57] 2 items of Yinxingmihuan oral liquid (YXMH),[58,59] and 7 items of Yindanxinanotong softgel capsule (YDXNT).[60–66] The basic characteristics of the included literature such as authors, time of publication, subject information (mean age, gender), interventions, duration of treatment, duration of follow-up, and outcome indicators are shown in Table 1.

3.2. Bias risk assessment of involved literature

We assessed the risk of bias in 46 studies[18,22–66] using ROB 2.0. 1 study[53] was grouped according to the order of visit, 13 studies[27,28,35,36,40,47,50,53–56,59,60] used the randomized table of numbers method, 3 studies[31,32,45] used the randomization by lot method, 1 study[49] used a random

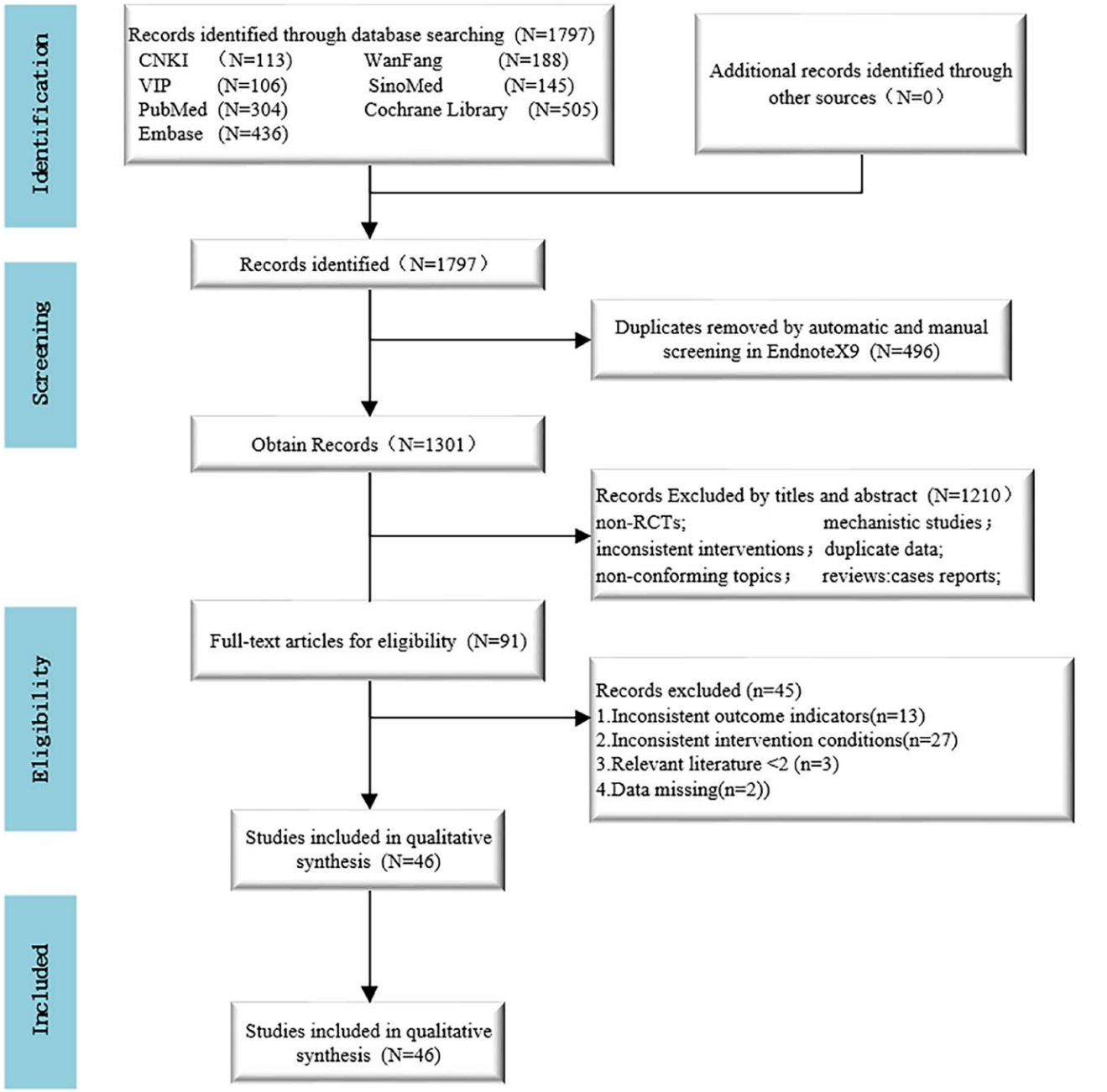

Figure 1. Study selection process.

Table 1

Characteristics of included studies.

Included studies	Sample (E/C)	(Sex (M/F)		Age		Course of disease		Intervention		Disease duration	Outcomes
		E	C	E	C	E	C	E	C		
Wang Qing 2014[22]	39/39	18/21	19/20	71.3 ± 9.4	68.3 ± 8.8	6.2 ± 3.8	6.4 ± 4.0	GBT + CT	CT	NA	Total effective rate
Tu Hao 2007[23]	28/30	18/20	10/20	49.7 ± 3.2	4 8.7 ± 3.0	8.6 ± 2.0	8.4 ± 2.7	GBT + CT	CT	24 wk	Total effective rate TC TG
Tang Xinmei 2009[24]	50/30	50/48		66.3		NA		GBT + CT	CT	60 d	Total effective rate
Sun Lin 2015[25]	35/30	17/18	15/20	67.9 ± 6.5	69.2 ± 7.6	4.8 ± 2.7	5.1 ± 2.5	GBT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure Total effective rate NO ET-1
Qiao Lin 2022[26]	100/100	46/54	45/55	68.34 ± 1.51	68.48 ± 1.14	NA		GBT + CT	CT	30 d	Total effective rate Adverse events
Wang Juli 2014[27]	70/70	NA		NA		NA		GBT + CT	CT	4 mo	Systolic blood pressure Diastolic blood pressure Total effective rate NO ET-1
Li Yaofeng 2018[28]	59/59	38/21	35/24	53.67 ± 5.69	52.19 ± 7.98	NA		GBT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure
Gu Yuchen 2020[29]	32/32	15/17	18/14	53.06 ± 7.84	52.61 ± 7.34	NA		GBT + CT	CT	2 mo	Systolic blood pressure Diastolic blood pressure
Wang Kui 2019[30]	43/43	23/20	24/19	50.62 ± 6.51	50.27 ± 6.39	12.03 ± 3.84	11.76 ± 3.64	GBT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure
Wang Lu 2023[31]	99/99	46/53	43/56	71.14 ± 9.83	73.79 ± 7.33	10.09 ± 4.51	10.35 ± 5.65	GBT + CT	CT	NA	Systolic blood pressure Diastolic blood pressure Total effective rate NO ET-1
Han Wei 2023[32]	40/40	26/14	23/17	67.12 ± 5.12	68.32 ± 5.43	7.87 ± 5.83	7.42 ± 5.43	GBT + CT	CT	1 mo	Systolic blood pressure Diastolic blood pressure Total effective rate NO ET-1
Li Juan 2017[33]	26/24	16/10	13/11	64.22 ± 1.62	64.91 ± 1.35	7.60 ± 0.66	7.08 ± 0.91	GBT + CT	CT	2 mo	Systolic blood pressure Diastolic blood pressure Total effective rate
Chen Yue 2017[34]	150/150	81/69	78/72	73.51 ± 3.89	74.15 ± 4.13	NA		GBT + CT	CT	6 mo	Systolic blood pressure Diastolic blood pressure Adverse events
Huang Chunmei 2015[35]	125/125	68/57	70/55	67.0 ± 4.8	66.8 ± 4.7	6.6 ± 2.3	6.5 ± 2.3	GBT + CT	CT	3 mo	Systolic blood pressure Diastolic blood pressure Total effective rate NO

(*Continued*)

Table 1

(*Continued*)

Included studies	Sample (E/C)	(Sex (M/F)		Age		Course of disease		Intervention		Disease duration	Outcomes
		E	C	E	C	E	C	E	C		
Guo Wei 2013[36]	42/42	20/22	21/21	68.8 ± 7.7	67.5 ± 7.4	7.8 ± 5.7	7.5 ± 5.5	GBT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure Total effective rate NO ET-1
Han Xiangrui 2014[37]	30/30	33/27		67.31 ± 5.24		15.33 ± 6.18		GBT + CT	CT	8 wk	Total effective rate
Wang Hongli 2016[38]	3030	18/12	16/14	6.37 ± 3.32	67.13 ± 3.53	16.55 ± 5.6	6.13 ± 5.53	GBT + CT	CT	8 wk	Total effective rate
Du Chunhua 2014[39]	50/50	24/26	25/25	69.2 ± 6.7	68.7 ± 7.1	25.1 ± 3.5	25.6 ± 3.1	GBT + CT	CT	10 wk	Total effective rate
Yang Yuanfen 2014[40]	30/30	17/13	16/14	66.61 ± 5.47	67.31 ± 5.24	15.17 ± 6.54	15.33 ± 6.18	GBT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure Total effective rate
Wang Xuemei 2015[41]	48/48	26/22	26/22	53. 2 ± 3. 7	53. 6 ± 3. 2	8. 1 ± 3. 5	8. 3 ± 3. 4	GBT + CT	CT	24 wk	Systolic blood pressure Diastolic blood pressure Total effective rate TC TG
Zhou Jincai 2007[42]	56/60	36/20	40/20	49.7 ± 3.2	48.7 ± 3.0	8.6 ± 2.0	8.4 ± 2.7	GBT + CT	CT	24 wk	Total effective rate TC TG
Kong Chunhui 2016[43]	75/75	71/79		68.25		NA		GBC + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure Total effective rate
Pan Feng 2015[44]	30/30	34/26		67.82 ± 5.36		15.63 ± 6.93		GBC + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure Total effective rate
Zhou Jian 2017[45]	118/118	NA		51.2	50.9	7.83		GBC + CT	CT	2 mo	Systolic blood pressure Diastolic blood pressure Total effective rate
Zhou Tianming 2023[46]	50/50	26/24	25/25	NA		NA		GBD + CT	CT	NA	Systolic blood pressure Diastolic blood pressure Total effective rate Adverse events
Liu Ning 2023[47]	58/58	39/19	38/20	70.92 ± 3.67	70.23 ± 3.51	7.13 ± 1.18	7.41 ± 1.26	GBD + CT	CT	60 d	Total effective rate Adverse events
Hong Yan 2014[48]	65/65	33/32	32/33	70.4 ± 5.1	70.3 ± 5.5	10.1		GBD + CT	CT	12 wk	Systolic blood pressure Diastolic blood pressure TC TG
Fang Runbo 2019[49]	100/100	64/36	64/36	56.7 ± 5.8	55.9 ± 5.6	5.5 ± 2.3	5.3 ± 2.5	GBD + CT	CT	3 mo	Systolic blood pressure Diastolic blood pressure TC TG
Cheng Ruixue 2016[50]	107/107	50/57	56/51	70.55 ± 5.24	71.13 ± 4.61	NA		GBD + CT	CT	6 mo	Systolic blood pressure Diastolic blood pressure

(*Continued*)

Table 1
(*Continued*)

Included studies	Sample (E/C)	(Sex (M/F)		Age		Course of disease		Intervention		Disease duration	Outcomes
		E	C	E	C	E	C	E	C		
Cai Jianhua 2012[51]	80/80	42/38	43/37	NA		NA		GBD + CT	CT	NA	Systolic blood pressure Diastolic blood pressure Total effective rate
Ren Qianling 2018[18]	45/45	47/43		65.1 ± 2.8		6.2 ± 1.5		GBKED + CT	CT	6 mo	Systolic blood pressure Diastolic blood pressure Total effective rate TC TG
Yang Jingnuo 2019[52]	60/60	32/28	34/26	63.25 ± 3.28	62.12 ± 2.89	6.24 ± 2.78	6.78 ± 2.54	GBKED + CT	CT	6 mo	Adverse events
Liu Yang 2022[53]	52/52	23/29	24/28	69.81 ± 8.41	69.28 ± 8.12	7.18 ± 5.08	7.15 ± 4.91	GBKED + CT	CT	6 mo	Systolic blood pressure Diastolic blood pressure Total effective rate TC TG
Wei Yihong 2016[54]	29/29	16/13	14/15	51.97 ± 11.44	52.86 ± 11.20	NA		FFYX + CT	CT	1 mo	Systolic blood pressure Diastolic blood pressure
Li Guanghao 2018[55]	29/29	16/13	14/15	40~75	41~75	NA		FFYX + CT	CT	4 wk	Total effective rate
Yang Haiyan 2012[56]	40/40	36/44		52.14 ± 6.50	50.93 ± 4.44	NA		FFYXTM + CT	CT	4 wk	Systolic blood pressure Diastolic blood pressure Total effective rate
Huang Junfang 2018[57]	53/53	38/25	29/24	54.43 ± 2.82	54.27 ± 2.68	6.45 ± 1.72	6.29 ± 1.57	FFYXTM + CT	CT	4 wk	Systolic blood pressure Diastolic blood pressure Total effective rate NO ET-1
Zheng Xuejing 2020[58]	34/34	22/12	18/16	56.85 ± 5.56	57.36 ± 5.46	5.58 ± 1.38	5.78 ± 1.45	YXMH + CT	CT	3 mo	Systolic blood pressure Diastolic blood pressure Total effective rate
Chen Ying 2020[59]	46/46	24/22	25/21	72.8 ± 5.2	73.2 ± 4.9	NA		YXMH + CT	CT	2 mo	Systolic blood pressure Diastolic blood pressure Total effective rate
Guo Yongli 2023[60]	28/28	15/13	17/11	75.62 ± 2.17	75.45 ± 2.58	5.26 ± 0.51	5.26 ± 0.51	YDXNT + CT	CT	1 mo	Systolic blood pressure Diastolic blood pressure
Gui Xiang 2017[61]	101/100	47/54	50/50	60.71 ± 11.58	61.08 ± 12.07	NA		YDXNT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure Total effective rate Adverse events
Gao Hui 2012[62]	57/61	31/26	34/25	68.42 ± 8.85	67.69 ± 8.67	NA		YDXNT + CT	CT	6 mo	Systolic blood pressure Diastolic blood pressure TC TG
Lin Guizhen 2011[63]	38/38	23/15	25/13	68.2 ± 9.8	67.8 ± 10.3	NA		YDXNT + CT	CT	3 mo	Systolic blood pressure Diastolic blood pressure NO ET-1

(*Continued*)

Table 1
(Continued)

Included studies	Sample (E/C)	(Sex (M/F))		Age		Course of disease		Intervention		Disease duration	Outcomes
		E	C	E	C	E	C	E	C		
Wang Mingjian 2012[64]	40/37	24/16	37/23	64 ± 9	62 ± 10	3~3.5	2.5~3.5	YDXNT + CT	CT	12 wk	Systolic blood pressure Diastolic blood pressure TC TG
Bai Yang 2016[65]	40/40	23/17	22/18	57 ± 8	55 ± 9	6~30	8~29	YDXNT + CT	CT	8 wk	Systolic blood pressure Diastolic blood pressure TC TG Adverse events
Wang Zhouyuan 2019[66]	45/45	25/20	24/21	32.45 ± 2.98	33.65 ± 3.22	4.14 ± 1.36	3.68 ± 1.54	YDXNT + CT	CT	2 mo	Systolic blood pressure Diastolic blood pressure TC TG

C = control, CT = conventional treatment, E = experimental group, ET-1 = endothelin-1, F = female, M = male, NO = nitric oxide, TC = Total cholesterol, TG = Triglyceride.

dice, 1 study[46] used 2-color random draws, and 27 studies[18,22–26,29,30,33,34,37–39,41,43,44,47,51,52,61,62,64–66] mentioned "random" but did not explicitly describe how it was done. None of the 46 studies mentioned allocation concealment. Forty-six studies reported comparable baseline information between groups. Forty-four studies[18,22–41,43–57,59–66] did not mention blinding, 1 study[58] utilized double blinding, and 1 study[42] was single blinded. Regarding the outcome section, 45 studies[22–28,30–50] used tables combined with text to record the outcome indicators of the researchers, and 1 study[29] used textual descriptions, and none of them had missing outcome data. Forty-six studies[18,22–66] described in detail the methods of measuring the outcome indicators, and there were no multiple methods of outcome measurements and no multiple ways of analyzing them. The details of risk of bias evaluation are shown in Figure 2.

3.3. Network meta-analysis

3.3.1. Primary outcomes. Thirty-six studies (78.26%) and 4342 participants (83.77%) assessed systolic blood pressure involving 8 CPMs, forming 8 direct comparisons with no closed loops (Fig. 3A). Compared with CT, 6 proprietary Chinese medicines significantly improved systolic blood pressure, GBD + CT (MD = −13.50, 95% CI [−19.39 to −7.62]), GBT + CT (MD = −12.00, 95% CI [−15.56 to −8.44]), YXMH + CT (MD = −11.13, 95% CI [−20.73 to −1.54]), YDXNT + CT (MD = −10.51, 95% CI [−15.61 to −5.41]), FFYXTM + CT (MD = −10.05, 95% CI [−19.44 to −0.67]), and GBC + CT (MD = −9.66, 95% CI [−17.26 to −2.07]) were superior to CT (Table 2). The rank probability ranking of SUCRA showed that GBD + CT (SUCRA = 78.7%) was the most effective and CT (SUCRA = 4.7%) was the worst (Fig. 4A). A two-by-two comparison showed no significant difference in the comparison between CPMs combined with CT (Table 2).

Thirty-six studies (78.26%) and 4342 participants (83.77%) assessed diastolic blood pressure involving 8 CPMs, forming 8 direct comparisons with no closed loops (Fig. 3B). Compared with CT, 6 CPMs significantly improved diastolic blood pressure, GBC + CT (MD = −10.38, 95% CI [−15.38 to −5.81]), YXMH + CT (MD = −6.88, 95% CI [−12.76 to −1.00]), GBD + CT (MD = −6.63, 95% CI [−10.28 to −2.98]), GBT + CT (MD = −6.29, 95% CI [−8.46 to −4.11]), FFYXTM + CT (MD = −6.30, 95% CI [−11.92 to −0.69]), and YDXNT + CT (MD = −4.70, 95% CI [−7.92 to −1.49]) outperformed CT (Table 3). The rank probability ranking of SUCRA showed that GBC + CT (SUCRA = 92.6%) was the most effective and CT (SUCRA = 7.4%) was the worst (Fig. 4B). The two-by-two comparison showed that GBC + CT was superior to YDXNT + CT (MD = −5.89, 95% CI [−11.65 to −0.12]), GBKED + CT (MD = −9.64, 95% CI [−17.21 to −2.08]), and there was no significant difference in the comparison between the rest of the combinations (Table 3).

3.4. Secondary outcomes

Twenty-nine studies (63.04%) and 3021 participants (58.28%) assessed the total effective rate involving 8 CPMs, forming 8 direct comparisons with no closed loops (Fig. 3C). Compared with CT, 5 CPMs significantly improved the overall effective rate, GBD + CT (OR = 7.26, 95% CI [3.54 to 14.89]), FFYX + CT (OR = 7.69, 95% CI [2.13 to 27.79]), YXMH + CT (OR = 5.24, 95% CI [1.86 to 14.80]), GBT + CT (OR = 4.52, 95% CI [3.25 to 6.30]), GBC + CT (OR = 3.35, 95% CI [1.93 to 5.84]) were superior to CT (Table 4). The rank probability ranking of SUCRA showed that GBD + CT (SUCRA = 86.7%) was the most effective and YDXNT + CT (SUCRA = 0.1%) was the worst (Fig. 4C). Two-by-two comparisons showed that GBD + CT (OR = 62.05, 95%

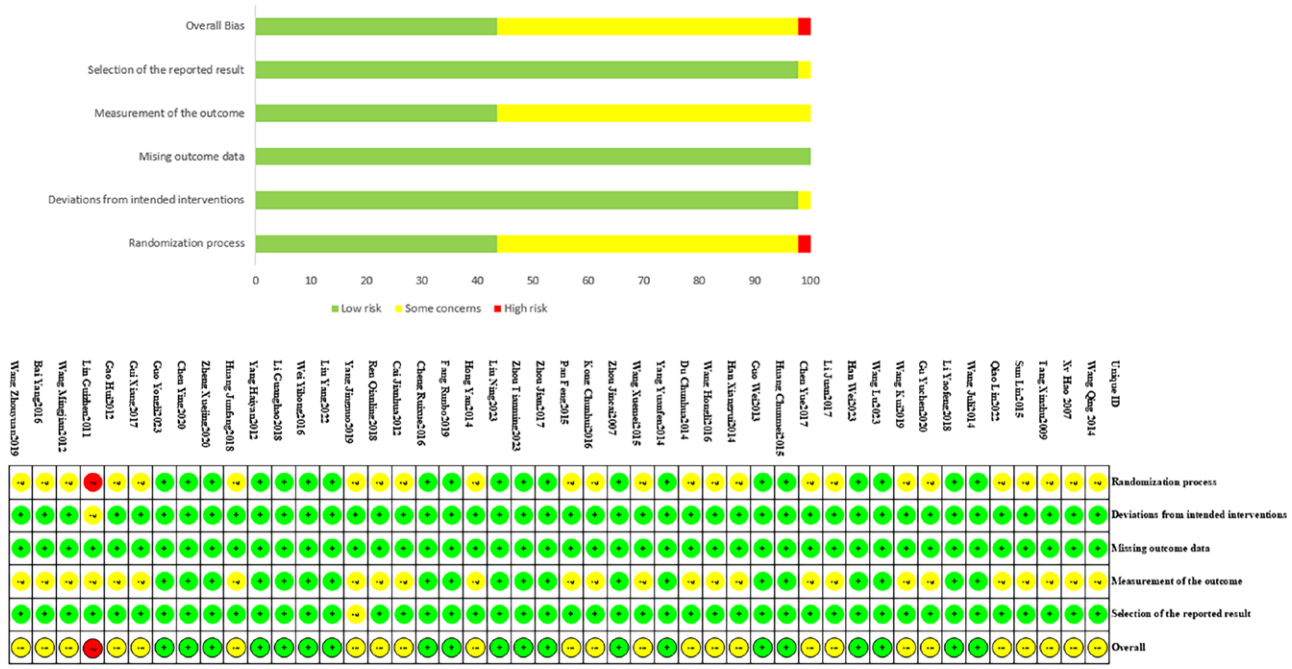

Figure 2. Results of risk of bias evaluation of included studies.

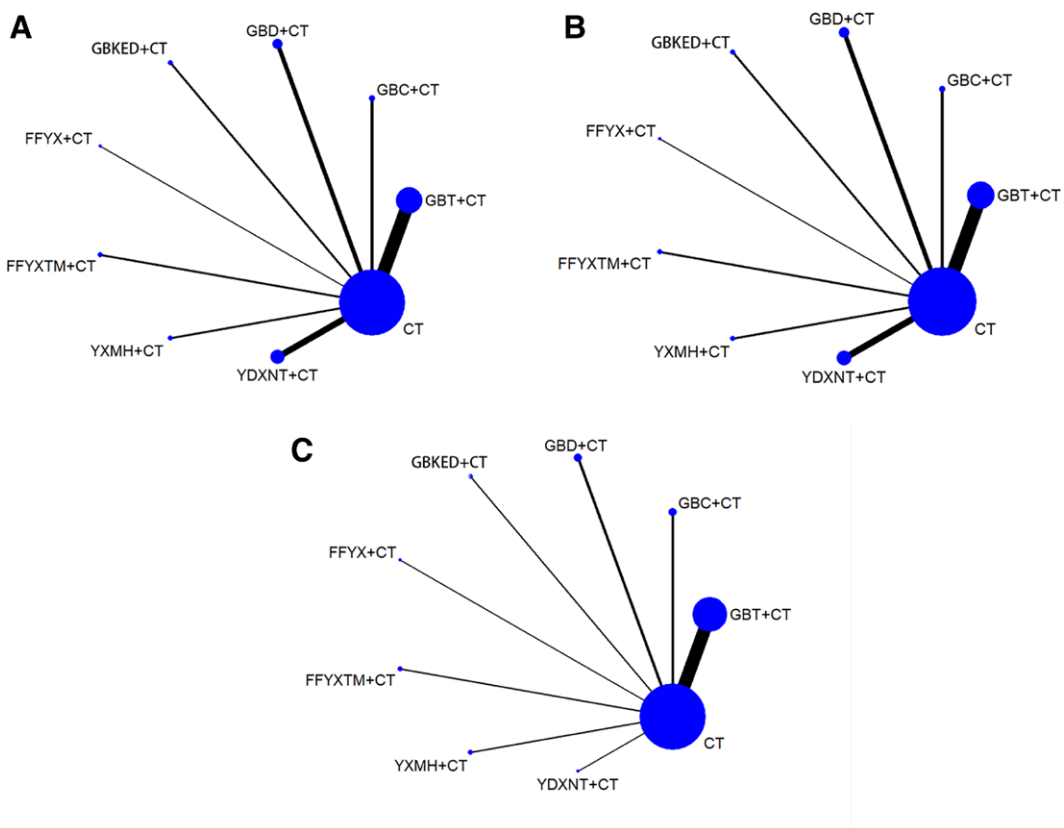

Figure 3. Network diagrams of comparisons on different outcomes of treatments in different groups of patients with hypertension. (A) Systolic blood pressure. (B) Diastolic blood pressure. (C) Total effective rate.

CI [11.72 to 328.36]), FFYX + CT (OR = 65.74, 95% CI [9.10 to 474.88]), YXMH + CT (OR = 44.80, 95% CI [7.21 to −278.43]), GBT + CT (OR = 38.65, 95% CI [8.29 to 180.25]), GBC + CT (OR = 28.65, 95% CI [5.77 to 142.24]), GBKED + CT (OR = 18.64, 95% CI [3.22 to 108.03]), FFYXTM + CT (OR = 14.15, 95% CI [2.00 to 99.94]) were superior to YDXNT + CT, and CT (OR = 8.55, 95% CI [1.90 to 38.43]) was also superior to YDXNT + CT. GBD + CT was superior to GBKED + CT (OR = 3.33, 95% CI [1.04 to 10.60]) and FFYXTM + CT (OR = 4.39, 95% CI [1.04 to 18.54]), and there was no significant difference in the comparison between the remaining combinations (Table 4).

Table 2

Network meta-analysis of systolic blood pressure.

Intervention	GBD + CT	GBT + CT	YXMH + CT	YDXNT + CT	FFYXTM + CT	FFYX + CT	GBC + CT	GBKED + CT	CT
GBD + CT	0								
GBT + CT	−1.50 (−8.38, 5.38)	0							
YXMH + CT	−2.37 (−13.62, 8.89)	−0.87 (−11.10, 9.37)	0						
YDXNT + CT	−2.99 (−10.78, 4.80)	−1.49 (−7.71, 4.73)	−0.62 (−11.49, 10.25)	0					
FFYXTM + CT	−3.45 (−14.53, 7.63)	−1.95 (−11.99, 8.09)	−1.08 (−14.50, 12.34)	−0.46 (−11.14, 10.23)	0				
FFYX + CT	−3.63 (−18.67, 11.41)	−2.13 (−16.42, 12.16)	−1.26 (−18.11, 15.58)	−0.64 (−15.39, 14.11)	−0.18 (−16.91, 16.54)	0			
GBC + CT	−3.84 (−13.45, 5.77)	−2.34 (−10.73, 6.05)	−1.47 (−13.71, 10.77)	−0.85 (−10.00, 8.30)	−0.39 (−12.47, 11.69)	−0.21 (−16.00, 15.58)	0		
GBKED + CT	−10.55 (−21.66, 0.56)	−9.05 (−19.12, 1.02)	−8.18 (−21.63, 5.27)	−7.56 (−18.27, 3.16)	−7.10 (−20.40, 6.20)	−6.92 (−23.66, 9.83)	−6.71 (−18.81, 5.39)	0	
CT	−13.50 (−19.39, −7.62)	−12.00 (−15.56, −8.44)	−11.13 (−20.73, −1.54)	−10.51 (−15.61, −5.41)	−10.05 (−19.44, −0.67)	−9.87 (−23.72, 3.97)	−9.66 (−17.26, −2.07)	−2.95 (−12.37, 6.47)	0

CT = conventional treatment, FFYX = fufangyinxing capsule, FFYXTM = fufangyinxingtongmai oral liquid , GBC = ginkgo biloba capsule, GBD = ginkgo biloba drop, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule, YXMH = Yinxingmihuan oral liquid.

Eleven studies (23.91%) and 1159 participants (22.36%) assessed TC involving 4 CPMs, forming 4 direct comparisons with no closed loops (Fig. 5D). Compared with CT, the 4 CPMs significantly improved the overall effectiveness rate, GBT + CT (MD = −1.46, 95% CI [−1.49 to −1.43]), GBD + CT (MD = −1.13, 95% CI [−1.32 to −0.95]), GBKED + CT (MD = −0.76, 95% CI [−1.07 to −0.45]), and YDXNT + CT (MD = −0.65, 95% CI [−0.75 to −0.56]) were superior to CT (Table 5). The rank probability ranking of SUCRA showed that GBT + CT (SUCRA = 100%) had the last effect and CT (SUCRA = 0.0%) the worst (Fig. 4D). A two-by-two comparison showed that GBT + CT was superior to GBD + CT (MD = −0.33, 95% CI [−0.52 to −0.14]), GBKED + CT (MD = −0.70, 95% CI [−1.02, −0.39]) and YDXNT + CT (MD = −0.81, 95% CI [−0.90, −0.71]), the GBD + CT was superior to GBKED + CT (MD = −0.37, 95% CI [−0.74, −0.01]) and YDXNT + CT (MD = −0.48, 95% CI [−0.68, −0.27]), and there were no significant differences in the remaining comparisons between combinations (Table 5).

Eleven studies (23.91%) and 1159 participants (22.36%) assessed TG, involving 4 CPMs, forming 4 direct comparisons with no closed loops (Fig. 5E). Compared with CT, GBT + CT (MD = −0.54, 95% CI [−0.91, −0.17]), and YDXNT + CT (MD = −0.79, 95% CI [−1.14, −0.44]) were superior to CT (Table 6). The rank probability ranking of SUCRA showed that YDXNT + CT (SUCRA = 92.2%) was the most effective and CT (SUCRA = 4.1%) was the worst (Fig. 4E). A two-by-two comparison showed no significant difference between the combinations (Table 6).

Eight studies (17.39%) and 1004 participants (19.37%) assessed NO, involving 3 CPMs, forming 3 direct comparisons with no closed loops (Fig. 5F). Compared with CT, YDXNT + CT (MD = 26.10, 95% CI [6.21,45.99]), FFYXTM + CT (MD = 14.38, 95% CI [8.05,20.72]), and GBT + CT (MD = 9.50, 95% CI [6.65,12.35]) were superior to CT (Table 7). The rank probability ranking of SUCRA showed that YDXNT + CT (SUCRA = 93.9%) was the most effective and CT (SUCRA = 0.2%) was the worst. A two-by-two comparison showed no significant difference between the combinations (Table 7).

Seven studies (15.22%) and 754 participants (14.55) evaluated the ET-1, involving 3 CPMs, forming 3 direct comparisons with no closed loops (Fig. 5G). Compared with CT, FFYXTM + CT (MD = −13.95, 95% CI [−22.79, −5.12]), and GBT + CT (MD = −13.48, 95% CI [−17.89, −9.06]) were superior to CT when compared with conventional treatment (Table 8). The rank probability ranking of SUCRA showed that YDXNT + CT (SUCRA = 67.5%) and FFYXTM + CT (SUCRA = 67.5%) were relatively the best and CT (SUCRA = 0.2%) was the worst. A two-by-two comparison showed no significant difference between the combinations (Table 8).

3.5. Adverse reactions

A total of 14 studies in this NMA included adverse reactions in their observations, involving GBTs, GBDs, GBKEDs, and Gindan Xinguangtong capsules. Ten of the studies mentioned specific symptoms and number of patients, and the remaining studies did not report any serious adverse events (Table 9). In terms of adverse effects, the results of descriptive analysis suggested that the occurrence of adverse effects of CPMs in combination with conventional treatment was less and the safety profile was better compared to CT alone. Symptoms are mainly headache, dizziness, panic and chest tightness as well as edema. Adverse reaction symptoms are mostly mild and can be relieved on their own after stopping the drug.

3.6. Cluster analysis

We performed a cluster analysis of the outcome indicators included in this study to derive the results of 2 outcome indicators doing well at the same time for different CPMs. We clustered systolic blood pressure with diastolic blood pressure, systolic blood pressure with total efficiency, diastolic blood pressure and total efficiency, TC with TG, and NO with ET-1, respectively. Clustering of systolic and diastolic blood pressure showed that GBD + CT, GBT + CT, YXMH + CT, FFYX + CT, and GBC + CT were located in the upper right corner relatively well (Fig. 6A). The clustering of systolic blood pressure and total effective rate showed that GBD + CT, YXMH + CT, and GBT + CT were located in the upper right corner relatively well (Fig. 6B). Cluster analysis of diastolic blood pressure and total effective rate showed that GBD + CT, YXMH + CT, and GBT + CT were relatively well located in the upper right corner (Fig. 6C). Clustering analysis of TC and TG showed that GBT + CT was relatively well located in the upper right corner (Fig. 6D). Clustering analysis of NO and ET-1 showed that YDXNT + CT was relatively well located in the upper right corner (Fig. 6E).

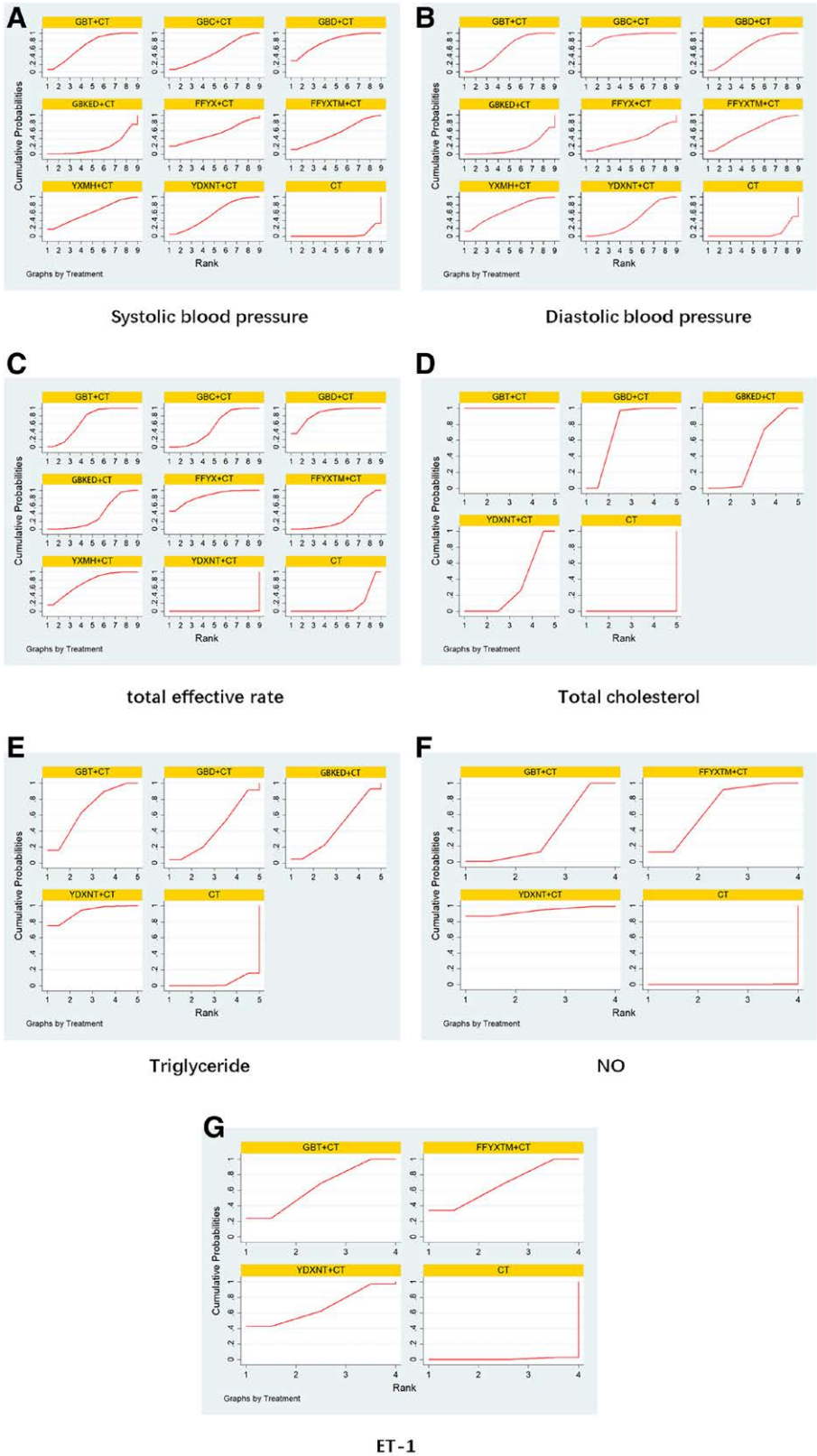

Figure 4. SUCRA of comparisons on different outcomes of treatments in different groups of patients with hypertension. SUCRA = surface under the cumulative ranking.

3.7. Publication bias

The funnel plots of the 7 outcomes are shown in Figure 7. The symmetry of the comparative adjusted funnel plots for the 4 indicators of TC, TG, NO, and ET-1 was poor, and there may have been a publication bias which may be related to the small number of included studies and the small total sample size. Adjusted funnel plots by comparing the 3 outcome measures of systolic blood

Table 3

Network meta-analysis of diastolic blood pressure.

Intervention	GBC + CT	YXMH + CT	GBD + CT	GBT + CT	FFYXTM + CT	YDXNT + CT	FFYX + CT	GBKED + CT	CT
GBC + CT	0								
YXMH + CT	−3.72 (−11.30, 3.86)	0							
GBD + CT	−3.96 (−9.98, 2.06)	−0.25 (−7.17, 6.67)	0						
GBT + CT	−4.30 (−9.56, 0.95)	−0.59 (−6.86, 5.68)	−0.34 (−4.59, 3.91)	0					
FFYXTM + CT	−4.29 (−11.67, 3.09)	−0.57 (−8.70, 7.56)	−0.33 (−7.03, 6.37)	0.01 (−6.01, 6.04)	0				
YDXNT + CT	−5.89 (−11.65, −0.12)	−2.17 (−8.88, 4.53)	−1.93 (−6.79, 2.94)	−1.58 (−5.47, 2.30)	−1.60 (−8.07, 4.87)	0			
FFYX + CT	−6.66 (−16.95, 3.63)	−2.95 (−13.79, 7.90)	−2.70 (−12.51, 7.11)	−2.36 (−11.72, 7.01)	−2.37 (−13.07, 8.33)	−0.77 (−10.43, 8.89)	0		
GBKED + CT	−9.64 (−17.21, −2.08)	−5.93 (−14.23, 2.37)	−5.68 (−12.59, 1.22)	−5.34 (−11.59, 0.91)	−5.36 (−13.47, 2.76)	−3.76 (−10.44, 2.93)	−2.98 (−13.81, 7.85)	0	
CT	−10.59 (−15.38, −5.81)	−6.88 (−12.76, −1.00)	−6.63 (−10.28, −2.98)	−6.29 (−8.46, −4.11)	−6.30 (−11.92, −0.69)	−4.70 (−7.92, −1.49)	−3.93 (−13.04, 5.18)	−0.95 (−6.81, 4.91)	0

CT = conventional treatment, FFYX = fufangyinxing capsule, FFYXTM = fufangyinxingtongmai oral liquid , GBC = ginkgo biloba capsule, GBD = ginkgo biloba drop, GBKED = ginkgo biloba ketone ester drop, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule, YXMH = Yinxingmihuan oral liquid.

Table 4

Network meta-analysis of total effective rate.

Intervention	GBD + CT	FFYX + CT	YXMH + CT	GBT + CT	GBC + CT	GBKED + CT	FFYXTM + CT	CT	YDXNT + CT
GBD + CT	0								
FFYX + CT	0.94 (0.22, 4.11)	0							
YXMH + CT	1.38 (0.39, 4.89)	1.47 (0.28, 7.65)	0						
GBT + CT	1.61 (0.73, 3.54)	1.70 (0.45, 6.41)	1.16 (0.39, 3.45)	0					
GBC + CT	2.17 (0.87, 5.37)	2.29 (0.57, 9.30)	1.56 (0.48, 5.07)	1.35 (0.71, 2.57)	0				
GBKED + CT	3.33 (1.04, 10.60)	3.53 (0.73, 17.01)	2.40 (0.60, 9.55)	2.07 (0.79, 5.46)	1.54 (0.53, 4.46)	0			
FFYXTM + CT	4.39 (1.04, 18.54)	4.65 (0.77, 27.89)	3.17 (0.62, 16.08)	2.73 (0.75, 9.96)	2.03 (0.52, 7.95)	1.32 (0.28, 6.18)	0		
CT	7.26 (3.54, 14.89)	7.69 (2.13, 27.79)	5.24 (1.86, 14.80)	4.52 (3.25, 6.30)	3.35 (1.93, 5.84)	2.18 (0.88, 5.42)	1.66 (0.47, 5.78)	0	
YDXNT + CT	62.05 (11.72, 328.36)	65.74 (9.10, 474.88)	44.80 (7.21, 278.43)	38.65 (8.29, 180.25)	28.65 (5.77, 142.24)	18.64 (3.22, 108.03)	14.15 (2.00, 99.94)	8.55 (1.90, 38.43)	0

CT = conventional treatment, FFYX = fufangyinxing capsule, FFYXTM = fufangyinxingtongmai oral liquid, GBC = ginkgo biloba capsule, GBD = ginkgo biloba drop, GBKED = ginkgo biloba ketone ester drop, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule, YXMH = Yinxingmihuan oral liquid.

pressure, diastolic blood pressure total effective rate showed that all studies were symmetrically distributed on both sides of the midline, suggesting a low risk of publication bias.

3.8. Inconsistency check

The included studies were all comparisons of CPMs in combination with CT versus CT, and the lack of direct comparisons between interventions failed to close the loop, so no inconsistency comparisons were needed. Therefore, this study was analyzed using a consistent random-effects model.

4. Discussion

4.1. Implications of our study and comparison with other studies

The main bioactive components of ginkgo-based CPMs are ginkgo flavonoids, ginkgolides, ginkgolide, ginkgolide terpene lactones and ginkgolic acid, which have antiinflammatory, antioxidant, neuroprotective, lipid-lowering, antiplatelet agglutination, and other pharmacological effects.[67,68] Hypertension belongs to the category of "vertigo" and "headache" in TCM, and its main pathogenesis includes internal obstruction of phlegm and stasis, deficiency of liver and kidney, and hyperactivity of liver yang. Pathological products such as turbid lipid, phlegm and stasis obstruct the blood vessels, damaging blood vessels and reducing vascular compliance, which in turn leads to target organ damage. And Ginkgo biloba as a TCM has the efficacy of resolving turbidity and lowering lipids, activating blood circulation and removing blood stasis, and clearing collaterals and relieving pain. Ginkgo-based CPMs not only lower blood pressure and improve its risk factors, but also protect target organs. Previous studies have found that Ginkgo biloba extract can inhibit angiotensin-converting enzyme, thereby reducing the secretion of catecholamines and aldosterone, and then achieve vasodilatation and lower blood pressure.[69] Secondly, Ginkgo biloba extract can modulate vascular endothelial cell function

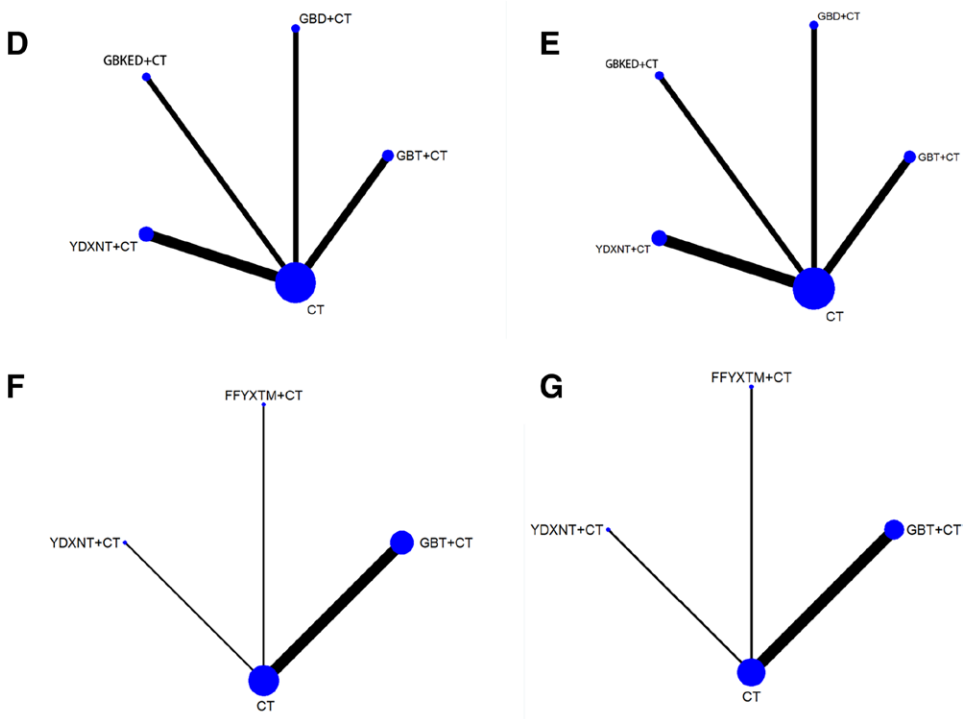

Figure 5. Network diagrams of comparisons on different outcomes of treatments in different groups of patients with hypertension. (D) Total cholesterol (TC). (E) Triglyceride. (F) NO. (G) ET-1. ET-1 = endothelin-1, NO = nitric oxide, TC = total cholesterol.

Table 5

Network meta-analysis of total cholesterol.

Intervention	GBT + CT	GBD + CT	GBKED + CT	YDXNT + CT	CT
GBT + CT	0				
GBD + CT	−0.33 (−0.52, −0.14)	0			
GBKED + CT	−0.70 (−1.02, −0.39)	−0.37 (−0.74, −0.01)	0		
YDXNT + CT	−0.81 (−0.90, −0.71)	−0.48 (−0.68, −0.27)	−0.10 (−0.43, 0.22)	0	
CT	−1.46 (−1.49, −1.43)	−1.13 (−1.32, −0.95)	−0.76 (−1.07, −0.45)	−0.65 (−0.75, −0.56)	0

CT = conventional treatment, GBD = ginkgo biloba drop, GBKED = ginkgo biloba ketone ester drop, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule.

Table 6

Network meta-analysis of triglyceride.

Intervention	GBT + CT	GBD + CT	GBKED + CT	YDXNT + CT	CT
GBT + CT	0				
GBD + CT	−0.21 (−0.80, 0.39)	0			
GBKED + CT	−0.19 (−0.79, 0.41)	0.02 (−0.65, 0.68)	0		
YDXNT + CT	0.25 (−0.26, 0.76)	0.46 (−0.13, 1.04)	0.44 (−0.15, 1.03)	0	
CT	−0.54 (−0.91, −0.17)	−0.33 (−0.80, 0.13)	−0.35 (−0.82, 0.12)	−0.79 (−1.14, −0.44)	0

CT = conventional treatment, GBD = ginkgo biloba drop, GBKED = ginkgo biloba ketone ester drop, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule.

to improve vascular stenosis,[70] and stabilize microRNA-21, matrix metalloprotein-9, and hypersensitive C-reactive protein by reducing atherosclerotic plaques.[71] Meanwhile, other studies have found that the flavonoid glycosides and ginkgolides in ginkgo biloba can inhibit the phenotypic transformation of vascular epicardial fibroblasts in rats with essential hypertension, and have a certain effect on the prevention of vascular wall thickening and atherosclerosis.[15] In terms of target organs, Ginkgo biloba extract can counteract myocardial remodeling,[72] and inhibit cardiomyocyte apoptosis,[73] and in the case of cerebrovascular diseases, it can prevent thrombosis and promote thrombolysis.[17] It can inhibit signaling in the p38 MAPK and nuclear factor-kappa B p65 pathway, and reduce the levels of tumor necrosis factor- α (TNF-α) and interleukin-1β to protect the brain tissue.[74] A large body of evidence exists for the efficacy of ginkgo-related preparations in the treatment of hypertension, but clinicians are still unable to choose from a wide range of ginkgo preparations.

As of now, we have identified 4 meta-analysis studies focused on the treatment of hypertension using CPMs, out of which, 2 studies[75,76] were classified as ordinary meta-analysis while the remaining 2 studies[77,78] were categorized as NMA. Ordinary meta-analysis solely focused on comparing a specific ginkgo-based CPM in combination with western medicine against the

Table 7

Network meta-analysis of NO.

Intervention	YDXNT + CT	FFYXTM + CT	GBT + CT	CT
YDXNT + CT	0			
FFYXTM + CT	11.72 (–9.15, 32.59)	0		
GBT + CT	16.60 (–3.49, 36.69)	4.88 (–2.06, 11.83)	0	
CT	26.10 (6.21, 45.99)	14.38 (8.05, 20.72)	9.50 (6.65, 12.35)	0

CT = conventional treatment, FFYXTM = fufangyinxingtongmai oral liquid, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule.

Table 8

Network meta-analysis of ET-1.

Intervention	YDXNT + CT	FFYXTM + CT	GBT + CT	CT
YDXNT + CT	0			
FFYXTM + CT	–0.55 (–17.55, 16.45)	0		
GBT + CT	–1.02 (–16.21, 14.16)	–0.48 (–10.35, 9.40)	0	
CT	–14.50 (–29.03, 0.03)	–13.95 (–22.79, –5.12)	–13.48 (–17.89, –9.06)	0

CT = conventional treatment, FFYXTM = fufangyinxingtongmai oral liquid, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule.

use of western medicine alone, and all these studies demonstrated the effectiveness of combining the medicines. However, they were unable to establish the comparative advantages and disadvantages among different ginkgo-based CPMs. The 2 NMAs encompassed all CPMs rather than focusing solely on ginkgo-based CPMs, and both studies included CPMs that contained ginkgo biloba extract as one of the types of CPM. Thus, the purpose of this study was to employ NMA as a means to compare the efficacy differences between various ginkgo-based CPMs, aiming to address the existing dearth of direct comparative studies in clinical settings.

4.2. Results of the study

Our study included the results of 46 ginkgo-based PCMs studies and 8 outcome indicators using NMA, which provided a comprehensive assessment of the efficacy and safety of different CPMs + CT in the treatment of hypertensive patients. We found that GBT + CT was superior to CT in improving blood pressure, total efficiency, TC, TG, NO, and ET-1. Cluster analysis showed that GBT + CT was the best in improving both TC and TG, and was at the top of the list in the rest of the outcome measures. GBD + CT was the most effective in improving systolic blood pressure and overall efficiency and ranked third in improving diastolic blood pressure. GBC + CT was the most effective only in diastolic blood pressure, but was a relative laggard in total efficiency and systolic blood pressure. YDXNT + CT was the most effective in improving TG, NO, and ET-1. Adverse reactions involve 4 CPMs, GBT, GBD, GBKED, and YDXNT, and we can see that CPMs have a lower number of adverse reactions and a better safety profile compared to CTs. Synthesizing the outcome indicators, we found that GBD, GBT, and YDXNT were more effective in improving the primary and secondary outcome indicators, which is of great clinical value.

With the continuous deepening of pharmacological research and clinical trials, the mechanism of ginkgo-based CPMs has been gradually discovered. It has been found that GBT can lower serum TC and TG, reduce plaque area, and

Table 9

Adverse reactions.

CPMs	Included studies	Clusters	Adverse reactions												
			Aggregate	Headaches	Spin	Chest distress	Tachycardia	Vomiting	Diarrhea	Gastrointestinal discomfort	Insomnia	Liver dysfunction	Neutropenia	Wearily	Arteriosclerosis
GBT	Sun Lin 2015[25]	C	1	1											
		E	0	0											
	Qiao Lin 2022[26]	C	39	12		16		11							
		E	9	3		4		2							
GBD	Zhou Tianming 2023[46]	C	18	5	6										7
		E	9	2	3										4
	Liu Ning 2023[47]	C	6		2			2			2				
		E	10		2			6			2				
GBKED	Ren Qianling 2018[48]	C	6		3										2
		E	3		3										0
	Yang Jingnuo 2019[52]	C	8		1		2								3
		E	2		1		0								1
	Liu Yang 2022[53]	C	13	3						3				3	4
		E	4	1						1				1	1
YDXNT	Gui Xiang 2017[61]	C	23	7					4			6	6		
		E	7	2					1			2	2		
	Bai Yang 2016[65]	C	0						0						
		E	1						1						
	Wang Zhouyuan 2019[66]	C	8		4				1	3					
		E	2		0				1	1					

GBD = ginkgo biloba drop, GBKED = ginkgo biloba ketone ester drop, GBT = ginkgo biloba tablet, YDXNT = Yindanxinanotong softgel capsule.

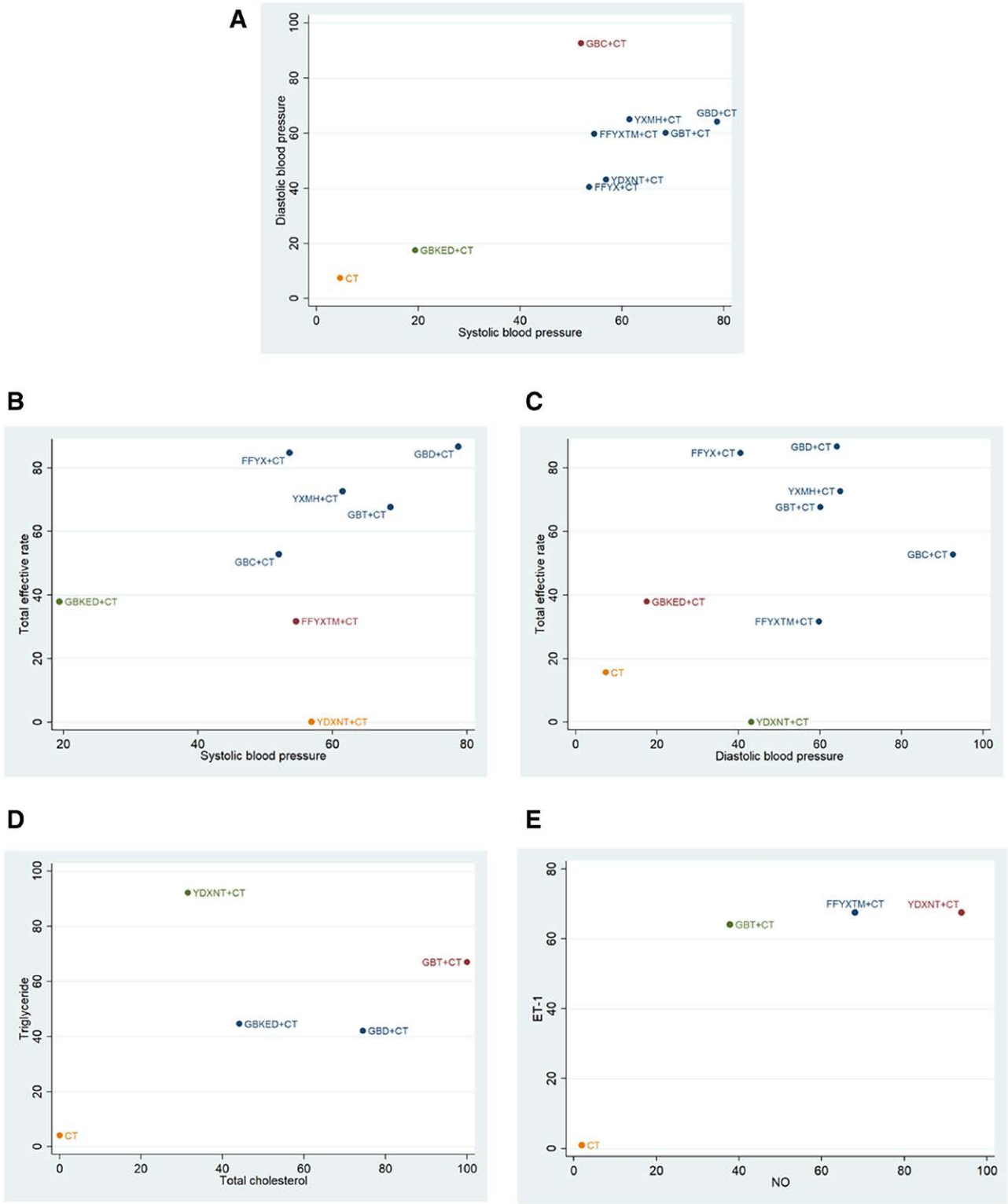

Figure 6. Cluster analysis of comparisons on different outcomes of treatments in different groups of patients with hypertension.

have a significant effect on the recovery of neurological function in patients with cerebral infarction.[79] GBT can reduce oxidative stress and improve the body's antioxidant capacity by decreasing maleicdialdehyde (MDA) and increasing superoxide dismutase, which can better protect the function of vascular endothelial cells.[80] Secondly, GBT may inhibit the formation and development of atherosclerosis and protect blood vessels by inhibiting serum inflammatory factors and decreasing macrophage scavenger receptor A expression.[81] These reasons make GBT superior to conventional treatment alone in all other respects while improving TC and TG, as the best measures.

GBD was best in improving systolic blood pressure and total effective rate.The main active ingredients in GBD are terpene lactones, mainly ginkgolide A, ginkgolide B and ginkgolide K.[82] It was found that ginkgolide B could effectively improve blood

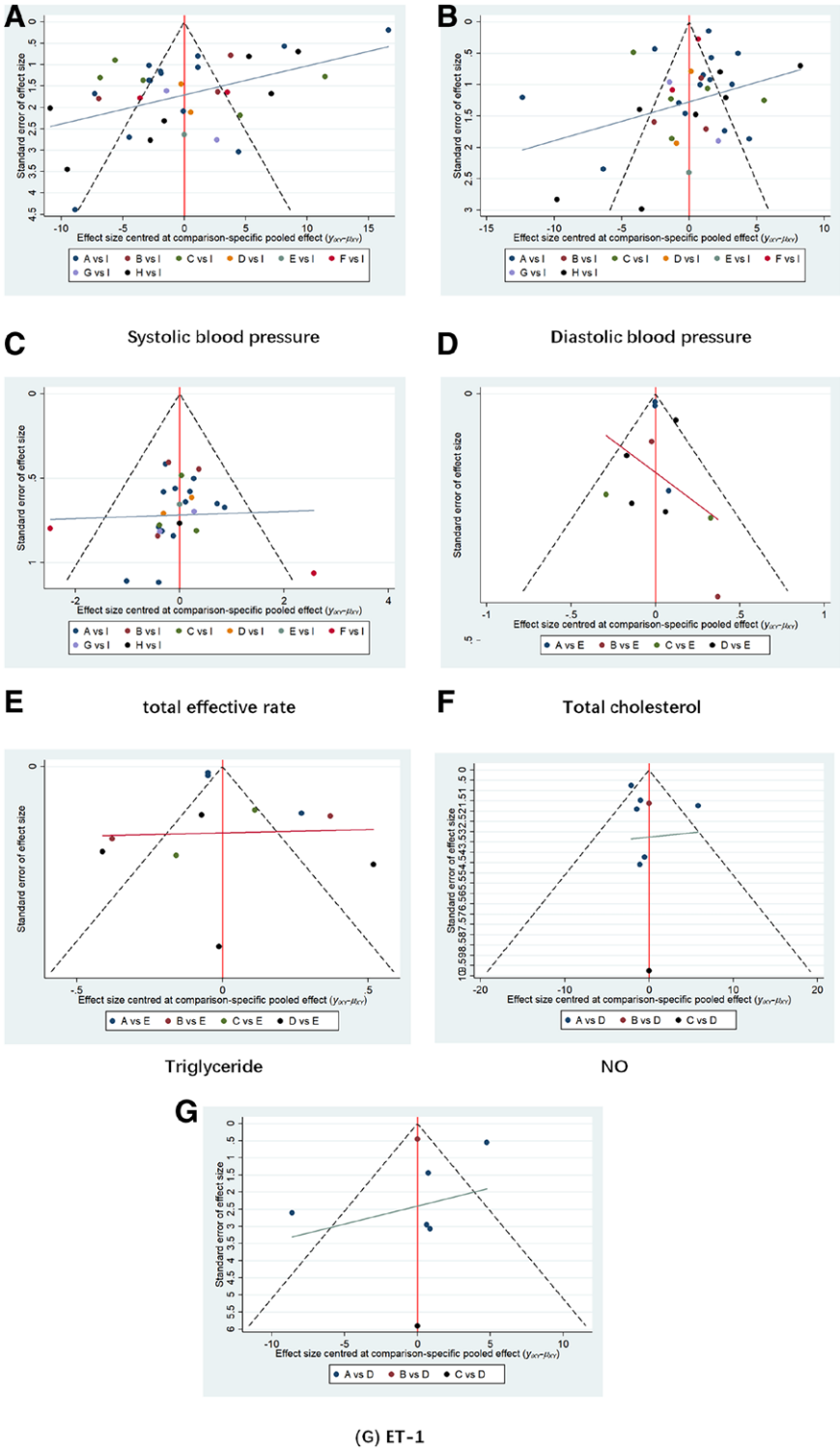

Figure 7. Comparison-correction funnel chart for ending indicators.

pressure and lipid levels, promote hemodynamic improvement and delay disease progression. Meanwhile, ginkgolide B can reduce TG, TC and low-density lipoprotein cholesterol in serum of obese mice.[83] Ginkgolide A inhibits the expression of pro-inflammatory mediators cyclooxygenase-2, NO and pro-inflammatory cytokines TNF-α, IL-6 and interleukin-1 β.[84] Pro-inflammatory cytokines are closely associated with blood pressure regulatory systems, such as the sympathetic nervous system and the renin-angiotensin-aldosterone system,[85] and thus are closely related to the development of hypertension.[86] Moreover, compared with tablets and capsules, pill formulations have the advantages of high concentration, fast action and long duration of efficacy.[87] Therefore, these may also be the reasons why GBD are so effective in lowering blood pressure.

YDXNT was best at improving NO and ET-1. It was found that YDXNT could significantly improve lipid indices (TG, TC, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol [HDL-C]) as well as vascular endothelial function indices (NO, H_2S, ET-1), which in turn improved endothelial cell function.[88] And it was found that H_2S protects

endothelial cells and improves endothelial function by activating peroxisome proliferator-activated receptor δ,[89] which in turn is responsible for improving NO and ET-1 levels. Thus, the role of YDXNT in improving NO and ET-1 optimally may be due to the fact that YDXNT can improve endothelial cell function.

5. Limitation

There are some limitations of this study, mainly: the low quality of the literature for most of the studies, and the fact that 46 studies were not explicitly and specifically blinded, which may have some small-sample effect and publication bias. The incomplete range of CPMs included in the study and the indirect comparisons between all the studies and the lack of direct comparisons may affect the accuracy and credibility of the results. There was inconsistency in treatment regimens, with treatment cycles ranging from 1 month to 6 months for the included studies, which may have had some impact on the results. The relatively small number of studies GBC + CT (3 cases), GBKED + CT (3 cases), FFYX + CT (2 cases), FFYXTM + CT (2 cases), and YXMH + CT (2 cases) may have had an impact on the rating of outcome indicators. Proprietary Chinese medicines are used only in China and there may be some restrictions on their use. The low reporting of adverse reactions in most of the literature may have influenced the judgment of adverse reactions, which were reported with a predominantly symptomatic description and fewer reports of safety indicators.

In response to the aforementioned issues, future research should pay attention to several aspects. It is crucial to improve the methodological quality of RCTs, such as employing rigorous randomization methods. Incorporating the double-blind principle in trials is essential. It is prudent to determine the appropriate sample size using the sample size calculation formula. Conducting comparative studies with multiple groups, allowing for direct comparison among them, is warranted. Considering Traditional Chinese medicinal preparations, significant progress still needs to be made. Therefore, a greater number of rigorously designed studies with multi-centers and large sample sizes need to be conducted in future research to provide evidence in support of promoting Traditional Chinese medicinal preparations.

6. Conclusion

In this study, we evaluated 8 commonly used ginkgo-based CPMs in terms of 8 outcome indicators to provide a comprehensive assessment of the efficacy and safety of ginkgo-based CPMs for the treatment of hypertension. Ginkgo-based CPMs + CT may be an effective and safe intervention for the treatment of hypertension. GBD have the best effect in lowering systolic blood pressure and increasing total effective rate, GBC have the best effect in lowering diastolic blood pressure, GBT have the best effect in lowering TC, and YDXNT has the best effect in improving TG, NO, and ET-1. The results of adverse reactions suggest that the combination of CPMs with conventional treatment has less occurrence of adverse reactions and better safety compared to CT alone. The conclusions of this study are limited to the results of the literature analysis, which may not fully explain the clinical efficacy and safety of ginkgo-based CPMs in the treatment of hypertensive disorders and have some limitations. Better designed double-blind, multicenter, large-sample RCTs are needed to address the problems of blinding, selective reporting, and allocation concealment.

Author contributions

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