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A Network Meta-Analysis of the Efficacy and Safety of Chinese Patent Medicines Combined with Calcium Dobesilate for Treating Diabetic Retinopathy

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ABSTRACT

In China, clinicians often use Chinese patent medicines (CPMs) as supportive therapy for diabetic retinopathy (DR). This study employed a network meta-analysis (NMA) to evaluate the comparative efficacy and safety of three CPMs combined with calcium dobesilate (CD) and to identify the most effective adjunctive treatment for DR.A Bayesian NMA framework was applied to examine both therapeutic outcomes and safety profiles of different CPM regimens in DR. The review protocol was registered in PROSPERO (CRD42022323996).Twenty-three randomized controlled trials involving 1,824 patients met the inclusion criteria. When compared with CD monotherapy, Compound Danshen Dripping Pills (DS) + CD and Qiming Granule (QM) + CD showed marked improvements in best-corrected visual acuity (BCVA). DS + CD and Compound Xueshuantong Capsule (XST) + CD led to significant reductions in macular thickness, while all CPM + CD combinations effectively decreased VEGF levels. Among the treatments, DS + CD and XST + CD outperformed QM + CD in lowering macular thickness. Safety analysis revealed no significant differences in adverse events among the CPMs or when compared with CD alone.DS + CD or QM + CD appear more effective for enhancing BCVA, while DS + CD and XST + CD show greater efficacy in reducing macular thickness. All CPM combinations were effective in lowering VEGF without increasing adverse events, suggesting DS + CD as a potentially preferred adjuvant therapy for DR.

Keywords: Network meta-analysis, Systematic review, Calcium dobesilate, Diabetic retinopathy, Chinese patent medicine

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Introduction

Diabetes mellitus (DM) affects approximately 463 million individuals worldwide, and this number is projected to rise to 700 million by 2045 [1]. Chronic hyperglycemia can damage retinal blood vessels, causing fluid accumulation in the light-sensitive tissue at the back of the eye [2]. Consequently, at least one-third of diabetic patients develop complications that threaten vision, a condition known as diabetic retinopathy (DR) [1, 3]. DR represents the leading cause of vision impairment among working-age adults globally, with an estimated 103.12 million affected individuals, expected to increase to 160.50 million by 2045 [1, 3]. The early stages of DR are often asymptomatic, yet progressive neural retinal damage occurs [4], underscoring the importance of timely intervention to reduce disease burden and improve patient outcomes.

Calcium dobesilate (CD) is a common pharmacological treatment for DR, acting to decrease blood hyperviscosity, inhibit platelet aggregation, and improve retinal microcirculation, thereby ameliorating microvascular disturbances [5, 6]. Nevertheless, CD monotherapy may be ineffective in some patients [7]. According to traditional Chinese medicine (TCM), DR falls under the category of “wasting thirst disorder eye disease,” typically caused by deficiencies in qi and yin. These deficiencies can result in blood stasis, obstructing ocular pathways, leading to insufficient retinal nourishment, blurred vision, and eventual disease progression [8]. Therefore, TCM treatment strategies focus primarily on promoting blood circulation.

Recent clinical practice has demonstrated that combining Chinese patent medicines (CPMs) aimed at enhancing blood flow with CD can improve therapeutic outcomes in DR [9–11]. Among these, Compound Danshen Dripping Pills (DS), Qiming Granule (QM), and Compound Xueshuantong Capsule (XST) are widely employed in clinical settings. Despite their widespread use, direct comparative studies among these CPMs are limited. To address this, we conducted a network meta-analysis (NMA) to integrate data from randomized controlled trials (RCTs). NMA allows for both direct and indirect comparisons, providing a framework to rank interventions and establish evidence-based hierarchies of comparative efficacy [12]. This study aimed to evaluate the effectiveness and safety of various CPMs combined with CD and identify the optimal CPM for DR management.

Materials and Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] and was registered with PROSPERO (registration number CRD42022323996).

Search strategy

A comprehensive literature search was performed across four English-language databases (PubMed, Cochrane Library, Web of Science, Embase) and four Chinese-language databases (CNKI, Wanfang, SinoMed, VIP) from inception to August 12, 2023. Search terms included “diabetic retinopathy,” “DR,” “Compound Danshen Dripping Pills,” “Qiming Granule,” and “Compound Xueshuantong Capsule.”

Selection criteria

Inclusion criteria were: (1) patients diagnosed with DR according to current or past clinical criteria, with no restrictions on gender or nationality; (2) interventions involving DS, QM, or XST combined with CD; (3) RCT study design; and (4) reporting efficacy and/or safety outcomes, including best-corrected visual acuity (BCVA), macular thickness, plasma vascular endothelial growth factor (VEGF) levels, or adverse events. Exclusion criteria included reviews, duplicates, preclinical studies, case reports, editorials, letters, studies with incomplete data, or treatment duration less than two months.

Data extraction and quality assessment

Two investigators (XY Zhu and SM Liang) independently extracted data using a predesigned form. Study quality was assessed independently by the same investigators using the Cochrane Collaboration’s risk-of-bias tool (version 5.1.0, http://handbook-5-1.cochrane.org/). Discrepancies were resolved through discussion or consultation with a third reviewer (XY Deng).

Statistical analysis

For binary outcomes, risk ratios (RR) were calculated; for continuous outcomes, weighted mean differences (WMD) with 95% confidence intervals (CIs) were used. Analyses and graphical presentations were conducted using Stata 15.1. Network diagrams illustrated relationships between interventions, and the node-splitting method assessed local inconsistencies within closed loops. Surface under the cumulative ranking (SUCRA) probabilities were calculated to rank treatments (100% = most effective, 0% = least effective). Funnel plots were used to evaluate potential publication bias.

Results and Discussion

Study selection

The database search identified 1,282 records. After removing duplicates, 516 studies remained. Screening titles, abstracts, and full texts yielded 23 RCTs evaluating CPMs for DR. The included CPMs were DS, QM, and XST. The study selection process is summarized in **Figure 1.**

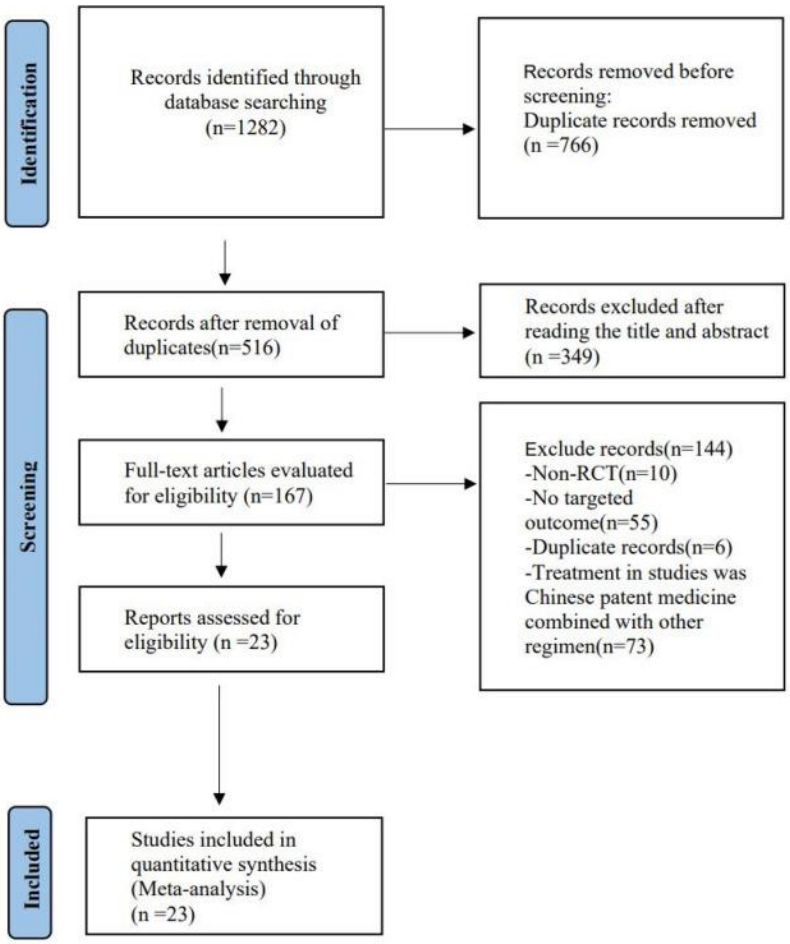
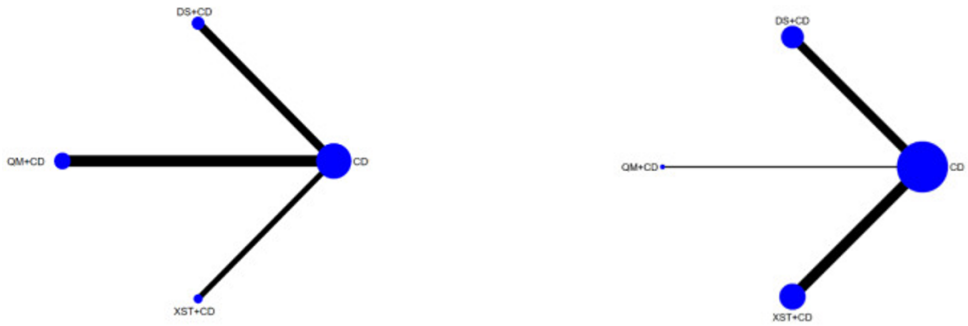


Figure 1. Flowchart illustrating the study identification and screening process.

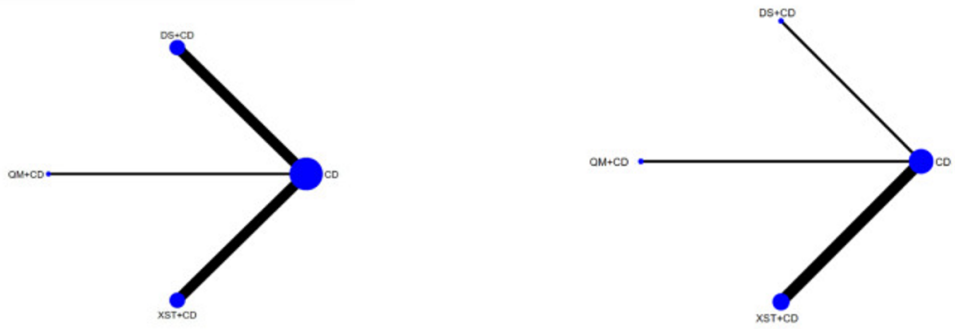
Study characteristics

A total of 1,824 patients with diabetic retinopathy were included across 23 RCTs in this NMA analysis [14–35]. Of these, 919 patients received CPMs combined with CD, while 905 patients were treated with CD alone. The treatment duration in the included trials ranged from 2 to 6 months. Key characteristics of the individual studies are summarized in **Table 1.**

The network graphs depicting comparisons among interventions for each outcome are shown in **Figure 2**. Specifically, **Figure 2a** illustrates the network of interventions for best-corrected visual acuity (BCVA), **Figure 2b** for macular thickness, **Figure 2c** for vascular endothelial growth factor (VEGF) levels, and **Figure 2d** for adverse events. Notably, the network graphs do not contain any closed loops, indicating that no inconsistencies are expected in the theoretical framework.



a) b)



c) d)

Figure 2. Network diagrams for the analyzed outcomes. (a) Best-corrected visual acuity (BCVA); (b) Macular thickness; (c) Vascular endothelial growth factor (VEGF); (d) Adverse events. Abbreviations: DS, Compound Danshen Dripping Pills; QM, Qiming Granule; XST, Compound Xueshuantong Capsule; CD, calcium dobesilate.

Table 1. Characteristics of the included studies.

Study ID	Age (years) (E/C)	Sex (M/F)	N (E/C)	I (E)	I (C)	Cs (month)	Outcome
Sun Y, 2023	57.82 ± 4.91/58.12 ± 4.95	53/31	42/42	DS 0.81 g + CD 1.5 g	CD 1.5 g	4	②③
Huang YX *et al*., 2021	67.5 ± 5.3/67.3 ± 5.1	57/33	45/45	DS 0.81 g + CD 1.5 g	CD 1.5 g	6	①②③④
Huang W *et al*., 2021	52.85 ± 6.38/51.86 ± 6.16	35/25	30/30	XST 4.5 g + CD 0.75 g	CD 0.75 g	5	②④
Yan H *et al*., 2020	48.5 ± 4.9/47.4 ± 4.6	52/40	46/46	XST 4.5 g + CD 1.5 g	CD 1.5 g	3	④
Yan JH,2020	56.65 ± 4.02/56.96 ± 4.59	49/33	41/41	QM 13.5 g + CD 1.5 g	CD 1.5 g	2	①④
Wang J *et al*., 2020	69.52 ± 7.11/68.35 ± 6.82	48/38	44/42	XST 4.5 g + CD 1.5 g	CD 1.5 g	5	②④
Miao CX,2020	57.33 ± 4.26/57.46 ± 4.41	29/19	24/24	DS 0.81 g + CD 1.5 g	CD 1.5 g	4	①②
Xu HT,2019	53.11 ± 4.41/53.06 ± 4.39	49/37	43/43	DS 0.81 g + CD 1.5 g	CD 1.5 g	4	②④
Wang SQ *et al*., 2019	66.7 ± 6.2/66.8 ± 6.3	60/40	52/48	QM 13.5 g + CD 1.5 g	CD 1.5 g	6	④
Wang DQ *et al*., 2019	/	27/21	24/24	DS 0.81 g + CD 1.5 g	CD 1.5 g	3	②③
Yin XD,2018	54.63 ± 5.28/55.27 ± 5.42	49/47	50/46	QM 13.5 g + CD 1.5 g	CD 1.5 g	3	①④
Ma JP,2018	53.02 ± 4.13/53.08 ± 4.25	31/23	27/27	XST 4.5 g + CD 2.25 g	CD 2.25 g	5	②④

Li Q,2018	56.68 ± 2.52/55.72 ± 2.31	35/25	30/30	XST 1.5 g + CD 2.25 g	CD 2.25 g	5	②③
Ge AL,2018	51.25 ± 3.64/50.87 ± 3.71	54/52	53/53	QM 13.5 g + CD 1.5 g	CD 1.5 g	6	②
Chai F *et al*., 2018	61.11 ± 6.01/61.19 ± 6.03	62/45	54/53	XST 4.5 g + CD 0.75 g	CD 0.75 g	3	②③
Yu W *et al*., 2017	57.4 ± 8.3/58.1 ± 7.9	36/32	34/34	XST 1.5 g + CD 1.5 g	CD 1.5 g	3	②③
Wang ZZ,2017	54.5 ± 4.8/54.3 ± 4.9	55/39	47/47	QM 13.5 g + CD 1.5 g	CD 1.5 g	3	③④
Bai YX,2017	/	41/35	38/38	DS 0.81 g + CD 1.5 g	CD 1.5 g	4	①②③④
Feng JL *et al.*, 2016	55.26 ± 6.29/55.89 ± 6.13	56/27	42/41	QM 13.5 g + CD 2 g	CD 2 g	3	①
Bai YX,2016	50.63 ± 5.51/51.08 ± 4.73	41/35	38/38	XST 4.5 g + CD 1.5 g	CD 1.5 g	6	①④
Pei R *et al*., 2015	56.4 ± 2.1/55.3 ± 1.2	33/31	32/32	XST 1.5 g + CD 2.25 g	CD 2.25 g	5	②③④
Sui HL *et al.*, 2014	50.22 ± 14.82/50.53 ± 11.28	45/41	43/43	QM 13.5 g + CD 1.5 g	CD 1.5 g	6	①④
Wang QF *et al.*, 2013	40~70/41~69.4	41/37	40/38	XST 4.5 g + CD 1.5 g	CD 1.5 g	3	1

Note: ①BCVA; ②macular thickness; ③vascular endothelial growth factor; ④adverse events. Abbreviations: C, control group; Cs, course; E, experimental group; F, female; I, intervention; M, male; CD: calcium dobesilate.

Quality assessment

The methodological rigor of the included RCTs was critically examined using the Cochrane risk of bias tool. While all studies mentioned randomization, only 12 trials [14–20, 22, 24, 28, 30, 36] detailed the use of a random number table for sequence generation, earning a low-risk rating for this domain. The remaining studies provided no specifics beyond stating "randomization," and were therefore judged as having an unclear risk.

None of the trials reported allocation concealment, resulting in an unclear risk of selection bias across all studies. Only one study [35] implemented single blinding, which led to a low-risk classification for performance bias in that trial. The rest, lacking blinding measures, were rated as unclear risk for performance bias. Detection bias was considered low risk overall, since outcome assessments were unlikely to be influenced by knowledge of the treatment assignments. All trials had complete outcome data, so attrition bias was uniformly rated as low risk. Reporting bias could not be fully assessed because detailed protocols were unavailable, and thus it was classified as unclear risk. No additional sources of bias were identified in any study, which were rated as low risk.

An overview of the risk of bias for all included RCTs is summarized in **Figure 3.**

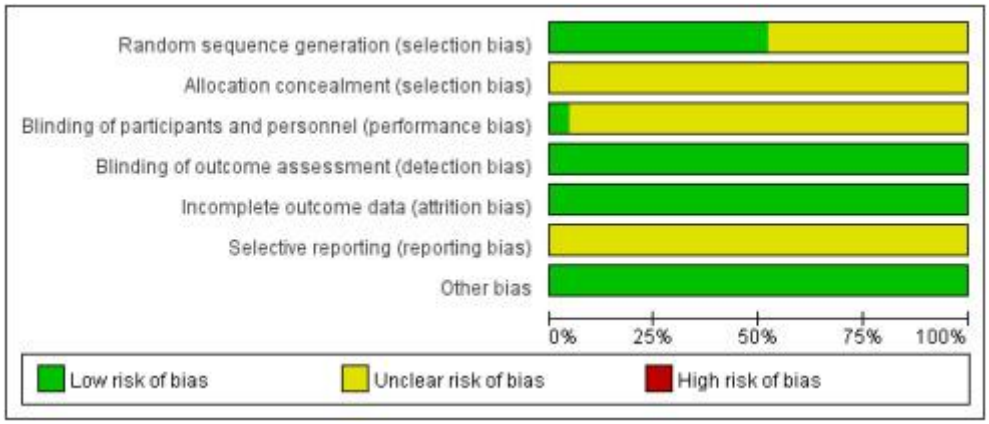


Figure 3. Risk of bias summary for the included studies.

Outcomes

Best-Corrected Visual Acuity (BCVA)

Nine RCTs [14, 16, 19, 23, 30–32, 34, 35] contributed data for the analysis of BCVA. As shown in **Table 2**, patients treated with DS + CD or QM + CD experienced significantly greater improvements in BCVA compared to those receiving CD alone, with WMDs of −0.12 (95% CI: −0.22 to −0.04) and −0.13 (95% CI: −0.21 to −0.05), respectively. In contrast, the combination of XST + CD did not produce a statistically meaningful improvement in BCVA relative to CD monotherapy. No significant differences were observed when comparing DS + CD directly with QM + CD.

Table 2. Weighted mean difference (95%CIs) of BCVA and macular thickness.

		macular thickness (Right upper part)		
BCVA (Left lower part)	CD	**−52.56 (-60.95, -44.17)**	−7.38 (−23.49., 8.73)	**−62.08 (-69.01, -55.16)**
	−0.12 (-0.22, -0.04)	DS plus CD	**45.18 (27.03, 63.35)**	−9.52 (−20.08, 1.04)
	−0.13 (-0.21, -0.05)	−0.01 (−0.13, 0.12)	QM plus CD	**−54.70 (-72.24, -37.17)**
	−0.11 (−0.25, 0.03)	0.01 (−0.15, 0.18)	0.02 (−0.14, 0.18)	XST plus CD

The numbers in bold in the table indicate that there are statistically significant differences between this group and the CD group.

Macular thickness

Fourteen RCTs [14, 15, 18–20, 22, 24–28, 30, 33, 36] provided data for macular thickness analysis. Indirect comparisons indicated that DS + CD and XST + CD significantly reduced macular thickness compared with CD alone, with WMDs of −52.56 (95% CI: −60.95 to −44.17) and −62.08 (95% CI: −69.01 to −55.16), respectively **(Table 2)**. Furthermore, both DS + CD and XST + CD showed superior efficacy compared to QM + CD, with WMDs of 45.18 (95% CI: 27.03 to 63.35) and −54.70 (95% CI: −72.24 to −37.17), respectively. By contrast, QM + CD did not demonstrate a statistically significant effect in improving macular thickness relative to CD monotherapy.

Vascular Endothelial Growth Factor (VEGF) levels

Nine RCTs [14, 22, 25, 27–30, 33, 36] reported VEGF outcomes. Indirect comparisons revealed that DS + CD, QM + CD, and XST + CD all significantly reduced VEGF levels compared with CD alone, with WMDs of 17.38 (95% CI: 13.99 to 20.76), 17.10 (95% CI: 4.75 to 29.45), and 17.12 (95% CI: 12.57 to 21.67), respectively **(Table 3).** No significant differences were observed among the three combination therapies when compared with each other.

Table 3. Weighted mean difference/Risk Ratios (95%CIs) of VEGF and adverse events.

		adverse events (Right upper part)		
VEGF (Left lower part)	CD	1.35 (0.2, 10.13)	0.22 (0.02, 1.35)	0.5 (0.22, 1.19)
	17.38 (13.99, 20.76)	DS plus CD	0.16 (0.01, 2.26)	0.37 (0.04, 2.97)

	17.10 (4.75, 29.45)	−0.28. (−13.08, 12.52)	QM plus CD	2.31 (0.31, 26.16)
	17.12 (12.57, 21.67)	−0.26. (−5.93, 5.42)	0.02 (−13.14, 13.18)	XST plus CD

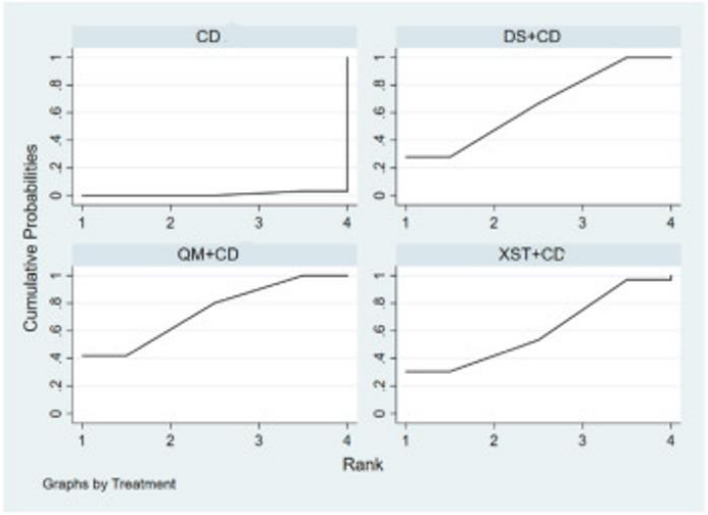
Values highlighted in bold within the table represent statistically significant differences compared with the CD group.

Adverse events

Fourteen studies [14–18, 20, 21, 23, 24, 29, 30, 32–34] provided data on adverse events. Among them, eight studies reported no adverse events during the treatment period. The remaining six studies provided detailed accounts of side effects, with the most frequently observed being reduced appetite, nausea, and mild gastrointestinal discomfort. Comparisons among the different CPM combinations revealed no statistically significant differences, and none of the CPM + CD regimens showed significant safety concerns compared with CD alone **(Table 3).**

SUCRA rankings for clinical outcomes

Based on SUCRA probabilities **(Figure 4)**, DS + CD (64.8%) and QM + CD (74.0%) were associated with the highest likelihood of improving BCVA among the CPM interventions **(Figure 4a)**. For reducing macular thickness, DS + CD (67.8%) and XST + CD (98.8%) ranked highest **(Figure 4b)**. Regarding VEGF reduction, XST + CD (66.3%), DS + CD (68.6%), and QM + CD (65.0%) demonstrated favorable probabilities **(Figure 4c).** In terms of safety, QM + CD (90.3%) and XST + CD (68.3%) were most likely to be well tolerated **(Figure 4d).** The detailed SUCRA values for each CPM across all outcomes are presented in **Table 4.**



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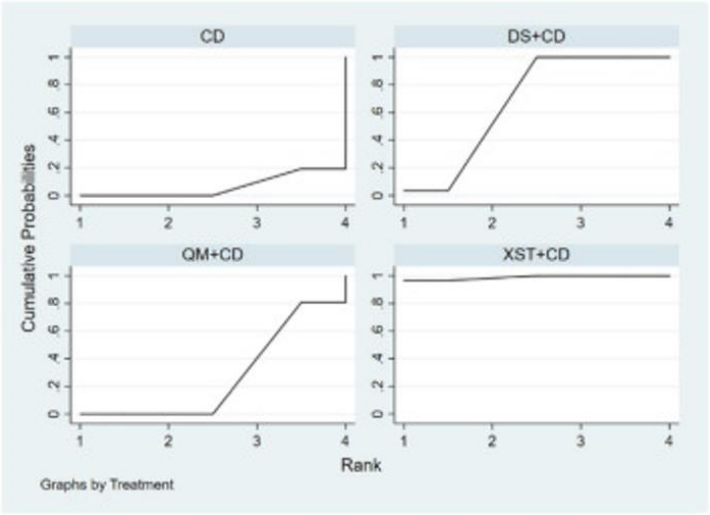

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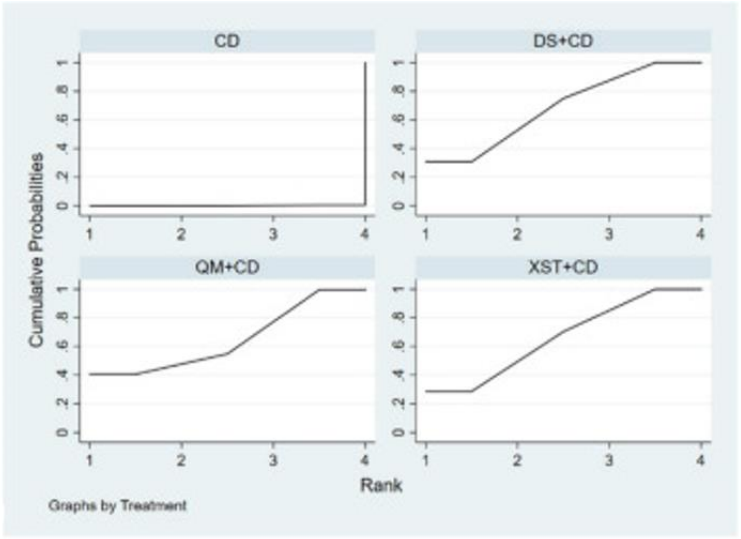

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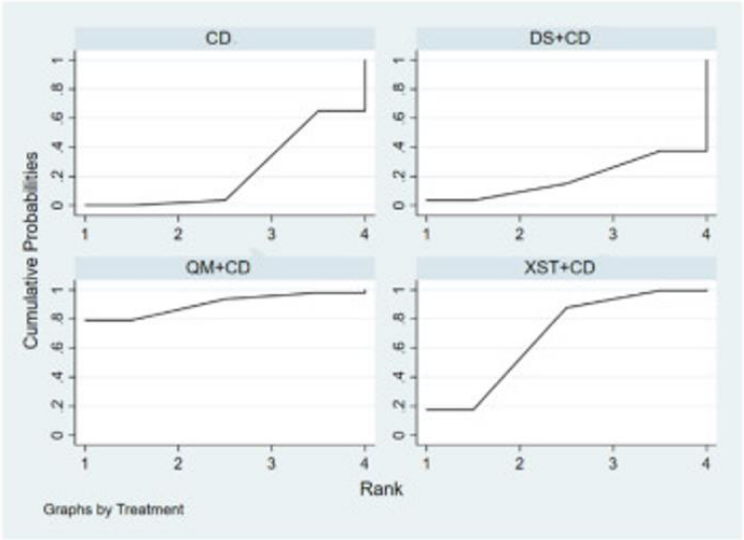


d)

Figure 4. Rankings based on cumulative probabilities for each outcome: (a) Best-corrected visual acuity (BCVA); (b) Macular thickness; (c) Vascular endothelial growth factor (VEGF); (d) Adverse events.

Table 4. SUCRA values of different groups for outcomes.

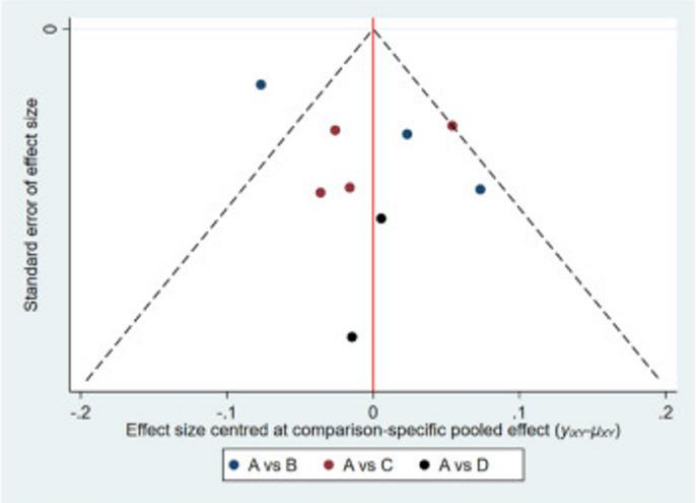
	BCVA	**macular thickness**	**VEGF**	**adverse events**
CD	1.0 %	6.4 %	0.2 %	22.9 %
DS plus CD	**64.8 %**	**67.8 %**	**68.6 %**	18.6 %
QM plus CD	**74.0 %**	26.9 %	65.0 %	**90.3 %**
XST plus CD	60.2 %	**98.8 %**	**66.3 %**	**68.3 %**

Note: Bolded values represent the two interventions with the highest SUCRA rankings for each outcome.
Abbreviations: DS, Compound Danshen Dripping Pills; QM, Qiming Granule; XST, Compound Xueshuantong Capsule; CD, calcium dobesilate; BCVA, best corrected visual acuity; VEGF, vascular endothelial growth factor.

Publication bias

Funnel plots were generated using STATA software to evaluate potential publication bias, with different colors representing comparisons among interventions. As shown in **Figure 5**, asymmetry was observed across the funnel plots for all outcomes, indicating possible bias. Specifically, **Figure 5a** displays the funnel plot for BCVA, **Figure**

5b for macular thickness, **Figure 5c** for vascular endothelial growth factor (VEGF), and **Figure 5d** for adverse events, suggesting that some degree of publication bias may exist.



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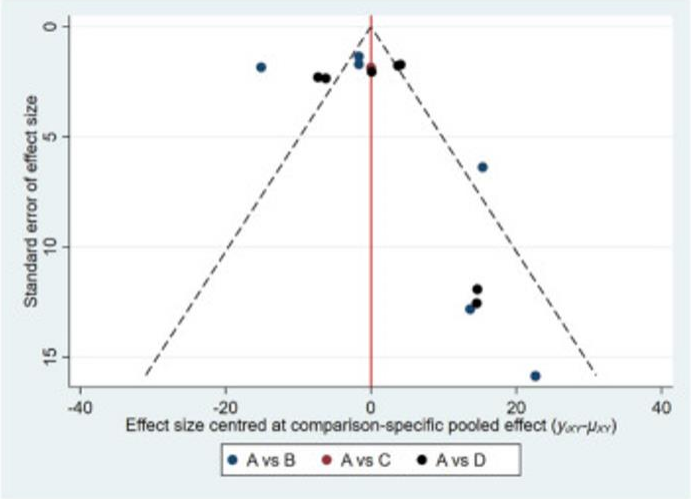

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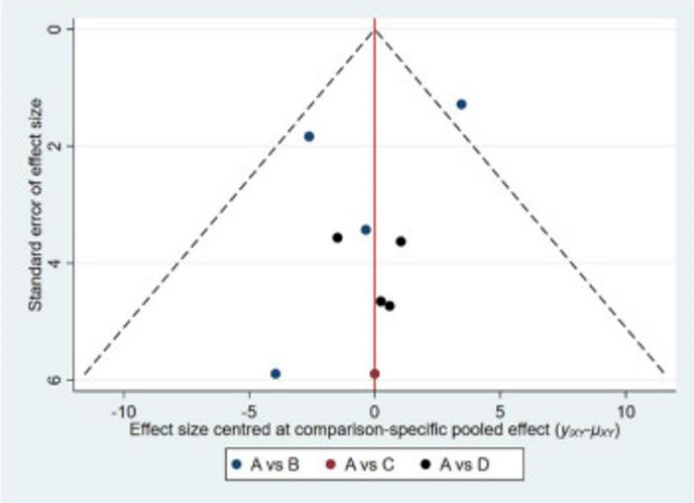

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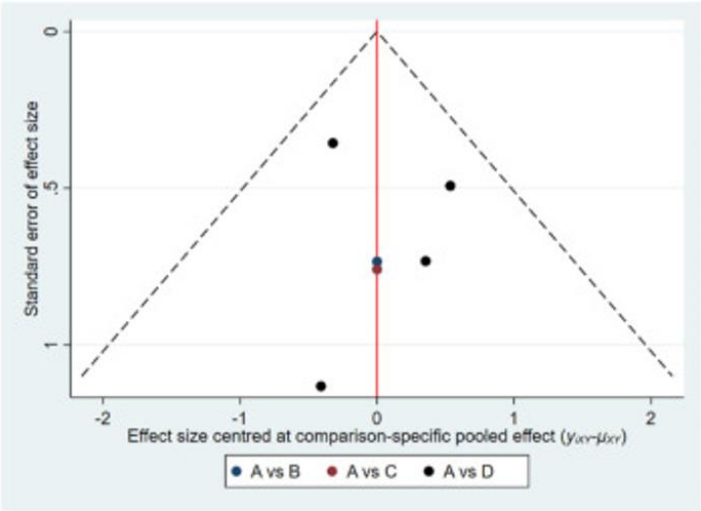

d)

Figure 5. Funnel plots illustrating potential publication bias for each outcome: (a) BCVA; (b) Macular thickness; (c) Vascular endothelial growth factor; (d) Adverse events. a, Compound Danshen Dripping Pills (DS); b, Qiming Granule (QM); c, Calcium dobesilate (CD); d, Compound Xueshuantong Capsule (XST).

The development of diabetic retinopathy (DR) is multifactorial, primarily involving retinal microangiopathy, endothelial cell apoptosis, disruption of the blood-retinal barrier, inflammation, oxidative stress, activation of the polyol and hexosamine pathways, cytokine imbalances, and dysregulation of the renin-angiotensin system [37–39]. Chinese patent medicines (CPMs), formulated according to traditional Chinese medicine principles and modern biotechnology, have been widely applied in China for DR management.

DS is mainly composed of Salviae Miltiorrhizae Radix et Rhizoma, Notoginseng Radix et Rhizoma, and borneol, which collectively improve local blood flow, protect vascular endothelial cells, and alleviate vascular congestion [40, 41]. QM contains Astragali Radix, Pueraria lobata, Rehmannia glutinosa, Lycium chinense, Cassiae Semen, and Hirudo, exerting effects through anti-inflammatory, antioxidant, anti-angiogenic, and anti-apoptotic mechanisms [42, 43]. XST, consisting of Notoginseng Radix et Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Astragali Radix, and Scrophulariae Radix, mitigates retinal edema, suppresses neovascularization, and counters inflammation and oxidative stress induced by DR [44, 45]. Collectively, these CPMs demonstrate substantial potential in preventing DR progression.

Our analysis indicated that, compared with CD monotherapy, DS + CD or QM + CD significantly improved BCVA, DS + CD or XST + CD effectively reduced macular thickness, and all three combinations (DS, QM, XST + CD) decreased VEGF levels. No significant differences in adverse events were observed between the combination therapies and CD alone. Considering efficacy, safety, and SUCRA rankings, DS + CD may represent the most favorable regimen. Mechanistically, DS primarily enhances local microcirculation and protects vascular endothelial cells [46], while CD improves microvascular circulation by inhibiting vasoactive substances [47]. The combination of DS and CD likely produces synergistic effects, resulting in superior clinical outcomes.

However, some results should be interpreted cautiously. Improvements in BCVA with XST + CD and reductions in macular thickness with QM + CD were based on only one or two RCTs [26, 32, 35]. Compared with previous meta-analyses [9, 11, 48, 49], which established the general superiority of CPMs combined with western medicine over western medicine alone, our study further ranked individual CPMs. Prior network meta-analyses [50] suggested DS and XST combined with CD as optimal for certain visual and anatomical outcomes, but differences in outcome measures and stricter inclusion criteria in our analysis provide a more objective evaluation. Notably, we included studies with a minimum treatment duration of two months to minimize the influence of treatment course on efficacy.

This study offers evidence-based guidance for clinicians in selecting CPMs for DR treatment. Nonetheless, limitations exist. First, funnel plots for all outcomes indicated potential publication bias, reflecting the moderate quality of included trials; only one study reported blinding, and only 12 described random sequence generation. Second, direct head-to-head comparisons among CPMs were lacking. Third, all trials were conducted in China, limiting generalizability to other populations. Future high-quality, multicenter RCTs are warranted to confirm and

extend these findings. Despite these limitations, this NMA provides a comprehensive assessment of CPMs plus CD in DR management.

Conclusion

DS + CD or QM + CD appears most effective for improving BCVA, while DS + CD or XST + CD is likely more beneficial for reducing macular thickness. All three combinations (DS, QM, XST + CD) show promise in lowering VEGF levels. No increase in adverse events was observed with combination therapy. These findings suggest that DS + CD may be considered a preferred adjuvant treatment option for patients with DR.

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Conflict of Interest: None

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

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