Contents lists available at ScienceDirect

Chinese Herbal Medicines

Original Article

Systematic review and Meta-analysis of 26 randomized controlled clinical trials of Compound Danshen Dripping Pill for non-proliferating diabetic retinopathy

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A B S T R A C T

Objective: Diabetic retinopathy (DR) is the retinal consequence of chronic progressive diabetic microvascular leakage and occlusion. Non-proliferating diabetic retinopathy (NPDR) is the early stage of DR. It eventually occurs to some degree in all patients with diabetes mellitus. In recent years, many clinical trials have shown that Compound Danshen Dripping Pill (CDDP) may be associated with the improvement of NPDR symptoms. The aim of this study was to quantitatively summarize the association between CDDP and the therapeutic effects of NPDR.
Methods: It was conducted that a systematic literature search of PubMed, Web of Science, CNKI, VIP and Wanfang Data updated in June 2020 with the following search terms: "diabetic retinopathy" or "retinopathy" or "DR" or "NPDR", in combination with "Compound Danshen Dripping Pill" or "*Salvia miltiorrhiza*" or "Danshen". Risk ratio (RR) and weighted mean difference (WMD) with their 95% confidence interval (CI) was calculated between treatment and control groups. The sensitivity analyses were undertaken by removing each individual study when high heterogeneity appeared. Subgroup analysis, Meta-regression, and publication bias analysis were also conducted. The strength of evidence was evaluated with the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) method.
Results: Twenty-six RCTs involving 2047 subjects were included to conduct a Meta-analysis after screening the studies, extracting the data, and assessing the study quality. The Stata15.0 software was utilized for processing. Meta-analysis indicated that curative effects of treatment group with CDDP was significantly better than control [RR = 0.54, 95% CI (0.40, 0.73); moderate-quality evidence]. In addition, the results showed that CDDP was significantly associated with improving retinal hemorrhages [WMD = −0.62, 95% CI (−0.78, −0.46); low-quality evidence], the vision [WMD = 0.14, and 95% CI (0.09, 0.19), low-quality evidence], fundus fluorescence angiography [RR = 0.37 and 95% CI (0.23, 0.60); low-quality evidence], reduction of retinal microaneurysm [WMD = −3.74 and 95% CI (−4.38, −3.11); moderate-quality evidence], hemangioma volume [WMD = −3.15, 95%CI (−3.45, −2.85); moderate-quality evidence], macular thickness [WMD = −5.52, 95%CI = (−64.27, −48.78); low-quality evidence], mean defect [WMD = −1.65 and 95% CI (−1.95, −1.34); very low-quality evidence], fasting blooding glucose [WMD = −0.95, 95% CI (−1.19, −0.70); low-quality evidence), hemoglobin A1c [WMD = −0.62, 95% CI (−0.93, −0.30); low-quality evidence], high sensitive C reaction protein [WMD = −5.66, 95% CI (−8.01, −3.31); low-quality evidence]. Sensitivity, subgroup, and Meta-regression analyses were also assessed.
Conclusion: The study demonstrated that CDDP has beneficial clinical effects for treating NPDR and improve the vision. Moreover, it indicated that oral CDDP in NPDR patients led to significant regulation of serum level of fasting blooding glucose, hemoglobin A1c and high sensitive C reaction protein, which was associated with the pathogenesis of NPDR. However, high-quality and large randomized clinical trials will be needed to prove the consequence in future.

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1. Introduction

Diabetes mellitus (DM), one of the most common chronic metabolic diseases currently in the world, is characterized by hyperglycemia which results from the deficiency of insulin secretion or resistance to the action of insulin, or both (Amer Diabet, 2013). The International Diabetes Federation estimates that there are approximately 425 million adults (20–79 years) who were suffered from DM in 2017 with a projected increase of 592 million by the year 2035 (Guariguata et al., 2014). Numerous studies have demonstrated that DM is a risk factor for the development of microvascular complications, which can remarkably decrease the quality of life of diabetes patients with abnormal blood glucose.

Diabetic retinopathy (DR) is a common microvascular complication of diabetes, characterized by microaneurysm, lipid exudation, macular edema, capillary occlusion and neovascularization, vitreous hemorrhage. DR has become a significant public health problem that affects more than 90% of diabetic patients, which can cause different degrees of vision loss and ultimate blindness in working-aged individuals worldwide (Kowluru & Chan, 2007). DR has a complex process, which can be divided into two stages clinically: non-proliferating diabetic retinopathy (NPDR) and proliferating diabetic retinopathy (PDR) (Wilkinson et al., 2003). NPDR is the early stage of DR and is characterized by damaging retinal vasculature, increasing vascular permeability, thickening of the basement membrane, formation of the microangioma, loss of pericytes and neovascularization (Arroba & Valverde, 2017). The pathology of PDR is more severe than that of NPDR, which is defined by vitreous hemorrhage, retinal scars and detachment (Das, Stroud, Mehta, & Rangasamy, 2015).

It is gradually discovered that DR is a chronic inflammation and retinal neurodegeneration, which may be associated with local microvascular injury and microcirculation disorders (Altmann & Schmidt, 2018; Ji et al., 2019). For NPDR, surgical treatment and laser photocoagulation are the most commonly used therapeutic methods in clinical treatment (Abu El-Asrar, 2013; Sato et al., 2013), and increased physical activity is associated with less severe levels of DR as well (Praidou, Harris, Niakas, & Labiris, 2017). In patients with DR, several oral medications such as protein kinase C inhibitor (Aiello et al., 2011), Candesartan (Tillin, Orchard, Malm, Fuller, & Chaturvedi, 2011) and renin-angiotensin blockade (Wilkinson-Berka, Rana, Armani, & Agrotis, 2013) can effectively control the progression of DR and inhibit early lesions. However, these treatments cannot completely reverse retinal damage in patients with DR. Also, the visual acuity of patients could be severely damaged if NPDR is not successfully prevented and cured. Therefore, it is necessary to develop a new therapeutic strategy for DR progression at an early stage.

In traditional Chinese medicine (TCM) theory, DR is developed because of blood stasis, which causes hemorrhage and angiogenesis (Duan, Jin, Jie, & Ye, 2011). Compound Danshen Dripping Pill (CDDP, obtained from Tasly Pharmaceutical, Tianjin, China), the first traditional Chinese medicine to complete Phase III clinical trials by the US Food and Drug Administration (FDA), consists of *Salvia miltiorrhiza* Bunge, *Panax notoginseng* and Borneol. Animal experiment results showed that CDDP had retinal neuroprotective effects that were independent of blood glucose levels. These CDDP-induced neuroprotective effects may be mediated by retinal cell apoptosis inhibition and increased neuropeptide Y expression (Zhang et al., 2018). Furthermore, as Chinese herb medicine, CDDP can be used extensively to treat blood stasis and improve blood circulation including angina pectoris, hyperlipidemia and myocardial infarction (Chu et al., 2011; Yao, Feng, & Lin, 2015).

In recent years, several reports demonstrate that CDDP has noticeable curative effect on early DR, including the control of microaneurysm and hemorrhage and the improvement of visual acuity and visual field. Based on the data from related randomized controlled trials, we conducted Meta-analysis to further confirm the efficacy of CDDP, which may be helpful in the management of NPDR.

2. Methods

2.1. Databases and search strategy

Relevant literatures were systemically retrieved from the database inception to June 2020 without language restriction, including English databases PubMed, Web of Science, the Chinese databases China National Knowledge Infrastructure (CNKI), the VIP information resource integration service platform (VIP), and Wanfang Data knowledge service platform (Wanfang Data). The search terms utilized were ("diabetic retinopathy" or "retinopathy" or "DR" or "NPDR") and ("Compound Danshen Dripping Pill" or "*S. miltiorrhiza*" or "Danshen"). Furthermore, the references of eligible studies and previously systematic reviews were manually searched to identify further relevant studies.

2.2. Inclusion criteria

All studies selected were designed to be clinical randomized controlled trials (RCTs). Included studies were selected to meet the following criteria: (1) Patients were diagnosed and confirmed as NPDR; (2) CDDP was used as an intervention, and a placebo or conventional medication was used as a control; (3) The outcome included macular thickness, vision, mean defect (MD) of visual field, microaneurysms, hemangioma volume, hemorrhage improvements as well as fundus fluorescence angiography (FFA), fasting blooding glucose (FBG), hemoglobin A1c (HbA1c), high sensitive C reaction protein (hs-CRP); (4) Treatment lasted four weeks or more.

2.3. Exclusion criteria

The criteria to exclude studies were as follows: (1) Study of the control groups with unclear treatment strategy or the treatment groups using interventions other than CDDP; (2) Duplicate publications, and literature on nonclinical studies such as medical record reviews, retrospective clinical studies and animal experiments; (3) Clinical studies with unclear statistical analysis; (4) Patients were taking DR medications, such as intravitreal anti-VEGF, statin, fibrates; (5) Patients were treated with photocoagulation; (6) Patients had liver and kidney dysfunction; (7) Patients were pregnant or lactating.

2.4. Data extraction and quality assessment

Two authors (Lei Hao and Yu-jing Sun) independently reviewed the retrieved studies to filter and extract information according to the inclusion and exclusion criteria, and any disagreements were resolved through group discussion and consensus with the third reviewer (Yuan-xue Liu). According to the Jadad scale, the studies were graded as low quality (scores of 0–2) or high quality (scores of 3–5). If there was a disagreement during cross-checking, it was further discussed with or dealt by a third-party researcher. The detailed scoring criteria were as follows: (1) application of a randomized method, (2) application of blinding method, and (3) application of withdrawal and loss to follow-up. The extracted data from each study included author, year of publication, study

population, age, sex, number of participants in treatment and control groups, interventions, duration, macular thickness, vision, MD, microaneurysm number, hemangioma volume, hemorrhage improvements, FFA, FBG, HbA1c and hs-CRP. We assessed the quality of the evidence supporting study findings by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (risk of bias, imprecision, inconsistency, indirectness and publication bias) (Gordon, Andrew, Regina, Gunn, & Holger, 2008). According to GRADE, RCTs were considered higher-quality evidence, and observational studies were of lower quality. The quality of the evidence for each outcome was rated high, moderate, low or very low.

2.5. Statistical analysis

The Stata15.0 was used to carry out the Meta-analysis. Heterogeneity among studies was assessed by the chi-square test, with the I^2 statistic. If the I^2 > 50% and P < 0.10, the heterogeneity among studies existed, and the random-effects model was used for data analysis. Otherwise, the fixed-effect model was adopted. The analyses of count data were presented as the risk ratios (RR) or values with 95% confidence interval (95%CI), and the continuous data were presented as weighted mean difference (WMD) and their 95% CI. The evidence of heterogeneity was necessitated further subgroup analysis and Meta-regression to determine the possible factors underlying the heterogeneity. Besides, sensitivity analyses were undertaken by removing each individual study from the Meta-analysis when high heterogeneity appeared ($I^2 \geq 75\%$). The Peters, Egger test and the Funnel plot were used to test publication bias. Egger test (P < 0.05) was considered to be representative of statistically significant publication bias, and there was no publication bias if the P value was more than 0.05 in Peters test.

3. Results

3.1. Search results

A total of 233 studies were identified from the five electronic bibliographic databases, among which 81 duplicate studies were removed. Based on the review of titles and abstracts, 16 non-RCTs, 15 animal trials, 26 reviews or commentaries, and 47 studies that combined with other interventions were excluded. Eventually, 26 eligible studies were identified as prospective randomized controlled trials for further Meta-analysis. Fig. 1 had depicted the detailed selection process for study identification.

3.2. Characteristics of included studies

The characteristics of the included articles in this Meta-analysis were summarized in Table 1, including author and publication year, sample size, participant age, treatment duration, treatment and control group, outcome measures and Jadad score. In the 26 trials (Bai, 2017; Bao, Yang, & Wang, 2006; W.F. Chen, 2019; Y. Chen & Zhong, 2006; Ding & Chen, 2012; Fu, Ruan, & Liu, 2017; He & Zhen, 2013; Jin, Deng, Yuan, & Yang, 2009; L. Li, 2019; Y. Li, 2017; Lian et al., 2015; J. Liu, 2018; M.Y. Liu & Hao, 2011; Luo et al., 2015; Meng, Zhang, & Duan, 2011; Qi, Tan, Li, & Wang, 2007; Ruan et al., 2017; Shi, 2010; D.Q. Wang, Guan, Wang, Li, & Wan, 2019; H.M. Wang, Tian, & Han, 2016; H. Xu, 2011; H.T. Xu, 2019; Yan & Yuan, 2014; Zhao, 2019; Zhou, 2008; Zhu, 2018) between 2006 and 2019, 2047 participants between the age of 32 and 78 years old were included: The treatment group of CDDP and the control group with calcium dobesilate (six studies); The treatment group of CDDP combined with calcium dobesilate and the control group with calcium dobesilate (10 studies); The treatment group of CDDP and the control group with placebo (six studies); The treatment group of CDDP and the control group with Vitamin B1 and/or Vitamin C and/or inosine tablets and/or Luding Tablets and/or Panshending Tablets (three studies); The treatment group of CDDP + Alprostadil and the control group with Alprostadil (one study). The course of treatment ranged from one month to six months.

3.3. Primary outcome

3.3.1. Clinical therapeutic effectiveness

The efficacy evaluation criteria was based on guiding principles of clinical research on traditional Chinese medicine new drugs for diabetic retinopathy (Zheng, 2002). A Meta-analysis of the 15 articles (Bai, 2017; Chen & Zhong, 2006; Fu et al., 2017; Li, 2017; Li, 2019; Lian et al., 2015; Meng et al., 2011; Ruan et al., 2017; Shi, 2010; Wang et al., 2016; Xu, 2011; Xu, 2019; Zhao, 2019; Zhou, 2008; Zhu, 2018) showed that, for the total effective treatment rate, the homogeneity test results were I^2 = 0% and P = 0.657, indicating no significant heterogeneity. Thus, the fixed-effect model was adopted and further subgroup analysis showed that the clinical effective rate of participants only with CDDP was significantly better than placebo [RR = 0.54, 95% CI (0.40, 0.73)], CDDP was also significantly better than Calcium dobesilate (Cd) [RR = 0.26, 95% CI (0.13, 0.52)], and CDDP combining with Cd was more effective than Cd alone [RR = 0.31, 95% CI (0.20, 0.47)], as shown in Fig. 2A. The publication bias was evaluated using funnel plot and Peters test. There was no publication bias analyzed by Peters test for the clinical efficacy rate of CDDP (P = 0.287), and the funnel plot was shown in Fig. 3A.

3.3.2. Hemorrhage

Thirteen studies (Bai, 2017; Fu et al., 2017; He & Zhen, 2013; Jin et al., 2009; Li, 2019; Lian et al., 2015; Luo et al., 2015; Ruan et al., 2017; Wang et al., 2019; Xu, 2019; Yan & Yuan, 2014; Zhao, 2019; Zhu, 2018) involving 1053 participants with 537 in the treatment group and 516 in control group were included in Meta-analysis for hemorrhage. The total results showed that the improvement of hemorrhage in treatment group was significantly better than controls [WMD = −0.62, 95% CI (−0.78, −0.46)] with significant heterogeneity (I^2 = 87.7%), using a random-effects model (Fig. 2B). The results of subgroup analysis indicated that the hemorrhages area of participants only used CDDP was significantly decrease compared with placebo [WMD = −0.42, 95% CI (−0.77, −0.07)] and Cd [WMD = −0.62, 95% CI (−1.24, −0.00)], and combining CDDP with Cd was more effective than Cd [WMD = −0.77, 95% CI (−0.90−0.63)]. The sensitivity analysis further showed that there was no significant change between the total effect amount and the combined effect amount after excluding each certain study, suggesting a stable result from the Meta-analysis (Fig. 4A). The funnel plot and further Egger test were used to evaluate publication bias. As a result, though, the funnel plot showed a left–right asymmetry (Fig. 3B), but P = 0.423, suggesting that there was no sign of publication bias analyzed for the effect of CDDP on NPDR. Moreover, the individual associations between hemorrhage area and study-level variables were evaluated by univariable Meta-regression using restricted maximum likelihood method. The prespecified variables included gender (male *vs* female), number of participants, mean age and duration. According to the univariable Meta-regression, the results indicated that the heterogeneity could not be well explained by each of the prespecified variables (Table 2).

3.3.3. Vision

Eight studies (Bai, 2017; Jin, Deng, Yuan, & Yang, 2009; Li, 2019; Liu & Hao, 2011; Luo et al., 2015; Qi, Tan, Li, & Wang, 2007; Yan &
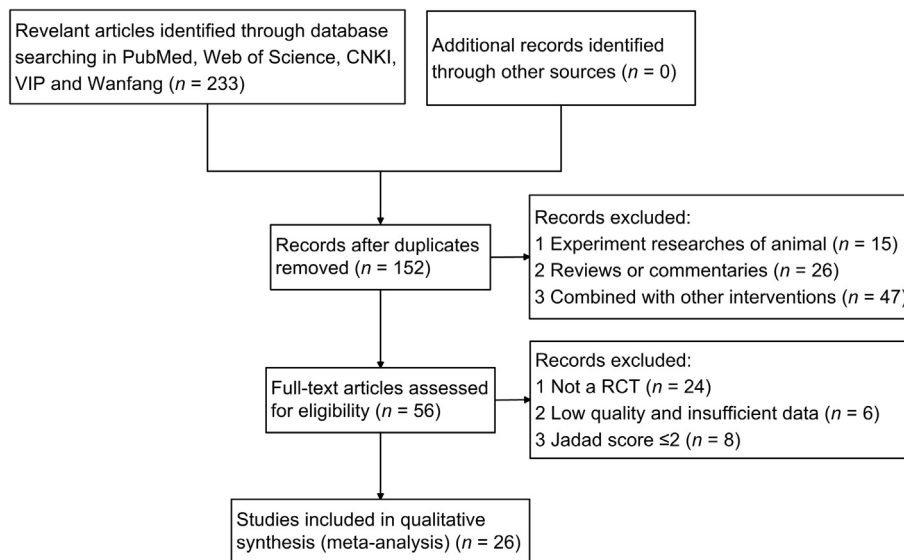
Fig. 1. Flowchart and strategy of Meta-analysis.

Yuan, 2014; Zhu, 2018) with a total of 579 participants were included to investigate the difference of visual acuity between two groups. Moderate heterogeneity was found in these articles ($P = 0.018$, $I^2 = 58.6\%$), and the evaluation by the random-effects model revealed that there were significant differences among these studies. The pooled WMD estimate showed a much higher value of visual acuity in the treatment group taking CDDP compared with control group [WMD = 0.14, and 95% CI (0.09, 0.19)] (Fig. 2C).

3.3.4. Microaneurysm number

Eight studies (Chen, 2019; He & Zhen, 2013; Jin, Deng, Yuan, & Yang, 2009; Li, 2019; Liu & Hao, 2011; Luo et al., 2015; Qi, Tan, Li, & Wang, 2007; Yan & Yuan, 2014) reported microaneurysm number involving 555 participants with 290 in the treatment group and 265 in control group, and significant heterogeneity difference did not exist ($P = 0.274$, $I^2 = 19.6\%$). Thus, the fixed-effect model was used to statistical analysis, and the result in Fig. 2D showed that microaneurysm number significantly decreased in the treatment group compared with controls [WMD = −3.74 and 95% CI (−4.38, −3.11)].

3.3.5. FFa

The heterogeneity analysis based on the three trials (Ding & Chen, 2012; Lian et al., 2015; Wang et al., 2016) reporting relevant data showed that there was no heterogeneity among these studies ($P = 0.551$, $I^2 = 0\%$), and the fixed effect model was adopted to analyze data. The results suggested that the patients taking CDDP had a noticeable advantage in changing the FFA of diabetic retinopathy compared with those who do not take CDDP [RR = 0.37 and 95% CI (0.23, 0.60)] (Fig. 5A).

3.3.6. Hemangioma volume

In this Meta-analysis, six studies (Bai, 2017; Fu et al., 2017; Ruan et al., 2017; Wang et al., 2019; Xu, 2019; Zhao, 2019) involving 448 participants reported the hemangioma volume. A fixed-effects model was used to analyze the data due to no heterogeneity ($P = 0.78$, $I^2 = 0\%$). The results indicated that the volume of the hemangioma has dramatically improved after taking CDDP in the treatment group compared with controls [WMD = −3.15, 95%CI (−3.45, −2.85)] (Fig. 5B).

3.3.7. Macular thickness

Six RCTs (Bai, 2017; Fu et al., 2017; Ruan et al., 2017; Wang et al., 2019; Xu, 2019; Zhao, 2019) with a total of 448 participants were included to investigate the changes of macular thickness between the treatment group and controls. Significant heterogeneity was found ($P = 0.000$, $I^2 = 96.8\%$) among the trials, and the random-effects model revealed that the macular thickness changed significantly after taking CDDP [WMD = −56.52, 95% CI = (−64.27, −48.78)] (Fig. 5C), suggesting that CDDP showed favorable effects in decreasing macular thickness of NPDR. Although substantial heterogeneity was observed in the magnitude of the effect amount, the conclusion was not affected after sequential exclusion of any specific study (Fig. 4B).

3.3.8. MD

Eleven studies (Bai, 2017; Fu, Ruan, & Liu, 2017; Jin, Deng, Yuan, & Yang, 2009; Li, 2019; Liu & Hao, 2011; Qi, Tan, Li, & Wang, 2007; Ruan et al., 2017; Xu, 2019; Yan & Yuan, 2014; Zhao, 2019; Zhu, 2018) with a total of 845 participants provide data to observe the difference of MD between treatment and control groups, and they did not show homogeneity ($I^2 = 98.3\%$). A random-effects model showed that there were remarkable differences among these studies. Compared with those who do not take CDDP in the control group, the MD value of the visual field notably decreased in the treatment group [WMD = −1.65 and 95% CI (−1.95, −1.34)] (Fig. 5D). The results of sensitivity analysis did not show any significant differences after excluding any study from this Meta-analysis (Fig. 4C). Furthermore, a Meta-regression analysis were conducted to explore heterogeneity based on gender, number of participants, mean age, duration and allocation. Overall, gender ($P = 0.181$), number ($P = 0.937$), mean age ($P = 0.055$), duration ($P = 0.393$) and allocation ($P = 0.693$) did not significantly affect the relationship between MD and NPDR (Table 3).

3.3.9. FBg

Four studies (Chen, 2019; Li, 2017; Liu, 2018; Ruan et al., 2017) among 508 participants reported on changes in fasting blooding glucose (mmol/L), and the pooled standardized mean difference showed a statistically significant reduction in fasting blooding glucose in CDDP group (WMD = −0.95, 95% CI (−1.19, −0.70)) compared with the control group, with a high heterogeneity ($I^2 = 92.8\%$) (Fig. 6A).

Table 1
Characteristic of included studies.

Included studies	Sample size (T/C)	Age /years	Duration /months	Treatment groups	Control groups	Outcomes	Jadad scores
Liu & Hao, 2011	52 (26/26)	39–76	3	CDDP	Vitamin B1 + Vitamin C + Inosine tablets	Hemorrhage, vision, MD, microaneurysm	3
He & Zhen, 2013	84 (42/42)	32–70	2	CDDP	Placebo	Hemorrhage, microaneurysm	3
Zhu, 2018	114 (57/57)	52–73 52–74	2	CDDP	Placebo	Efficacy, hemorrhage, vision, MD	4
Yan & Yuan, 2014	60 (40/20)	65.60 68.80	6	CDDP	Placebo	Hemorrhage, vision, MD, microaneurysm	4
Liu, 2018	178 (89/89)	49–78 45–76	1	CDDP	Placebo	FBG, HbA1c, hs-CRP	3
Xu, 2011	80 (40/40)	52.30 54.50	3	CDDP	Luding tablets + Vitamin C + Panshending tablets	Efficacy	3
Chen & Zhong, 2006	63 (31/32)	54.60 ± 10.40 58.12 ± 9.31	3	CDDP	Calcium dobesilate	Efficacy	3
Wang et al., 2016	90 (45/45)	57.15 ± 6.68 57.06 ± 6.72	2	CDDP	Calcium dobesilate	Efficacy, FFA	3
Qi, Tan, Li, & Wang, 2007	42 (23/19)	36–72	3	CDDP	Vitamin B1 + Luding tablets	Hemorrhage, vision, MD, microaneurysm	3
Li, 2019	120 (60/60)	58.11 ± 3.43 58.00 ± 3.56	4	CDDP	Calcium dobesilate	Efficacy, hemorrhage, vision, MD, microaneurysm	4
Jin et al., 2009	58 (30/28)	62.78 ± 7.69 61.11 ± 7.27	3	CDDP	Calcium dobesilate	Hemorrhage, vision, MD, microaneurysm	3
Bao et al., 2006	67 (37/30)	47–70 48–69	6	CDDP	Calcium dobesilate	HbA1c	3
Fu et al., 2017	62 (31/31)	43.70 ± 4.50 44.30 ± 4.10	2	CDDP + Alprostadil	Alprostadil	Efficacy, hemorrhage, MD, hemangioma volume, macular thickness, hs-CRP	4
Bai, 2017	76 (38/38)	40–72 39–71	4	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy, vision, MD, hemorrhage, hemangioma volume, macular thickness, hs-CRP	4
Zhou, 2008	46 (28/18)	50.40 ± 8.70 50.50 ± 9.36	6	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy	4
Chen, 2019	82 (41/41)	36–74 35–72	2	CDDP + Calcium dobesilate	Calcium dobesilate	Microaneurysm, FBG, HbA1c, hs-CRP	4
Xu, 2019	86 (43/43)	53.11 ± 4.41 53.06 ± 4.39	4	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy, MD, hemorrhage, hemangioma volume, macular thickness	4
Wang et al., 2019	48 (24/24)	41–62 40–64	3	CDDP + Calcium dobesilate	Calcium dobesilate	Hemorrhage, hemangioma volume, macular thickness	4
Shi, 2010	68 (35/33)	38–76	3	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy	3
Ruan, 2017	70 (35/35)	52.50 ± 1.10 52.80 ± 1.70	4	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy, hemorrhage, hemangioma volume, MD, macular thickness, FBG, HbA1c	4
Zhao, 2019	106 (53/53)	38–75 40–76	2	CDDP	Placebo	Efficacy, hemorrhage, MD, macular thickness, hemangioma volume, hs-CRP	4
Meng et al., 2011	58 (30/28)	50.60 ± 8.70 51.20 ± 7.90	6	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy	4
Li, 2017	178 (89/89)	56.50 ± 7.20 55.80 ± 6.80	2	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy, FBG, HbA1c	3
Ding et al., 2012	76 (38/38)	45–66 42–60	2	CDDP + Calcium dobesilate	Calcium dobesilate	Efficacy	3
Lian et al., 2015	112 (56/56)	58.90 ± 8.10 58.90 ± 7.60	6	CDDP	Placebo	Efficacy, hemorrhage, exudate, FFA	4
Luo et al., 2015	57 (28/29)	59.54 ± 7.46 57.80 ± 10.03	3	CDDP	Calcium dobesilate	Hemorrhage, vision, microaneurysm	4

3.3.10. HbA1c

Among all enrolled studies, five trials (Bao et al., 2006; Chen, 2019; Li, 2017; Liu, 2018; Ruan et al., 2017) involving 575 participants with 291 in the treatment group and 284 in control group had evaluated the HbA1c. Compared with the control group, the result showed a weak trend toward in HbA1c in treatment group taking CDDP [WMD = −0.62, 95% CI (−0.93, −0.30)], with a high level of heterogeneity (I^2 = 93.1%) (Fig. 6B).

3.3.11. hs-CRP

Five of the enrolled articles (Bai, 2017; Chen, 2019; Fu et al., 2017; Liu, 2018; Zhao, 2019) including 504 participants had assessed the hs-CRP, and the pooled data demonstrated that the treatment group showed a statistically significant reduction in hs-CRP [WMD = −5.66, 95% CI (−8.01, −3.31)] compared with patients without taking CDDP in control group, and high statistical heterogeneity could be detected (I^2 = 98.9%) (Fig. 6C).
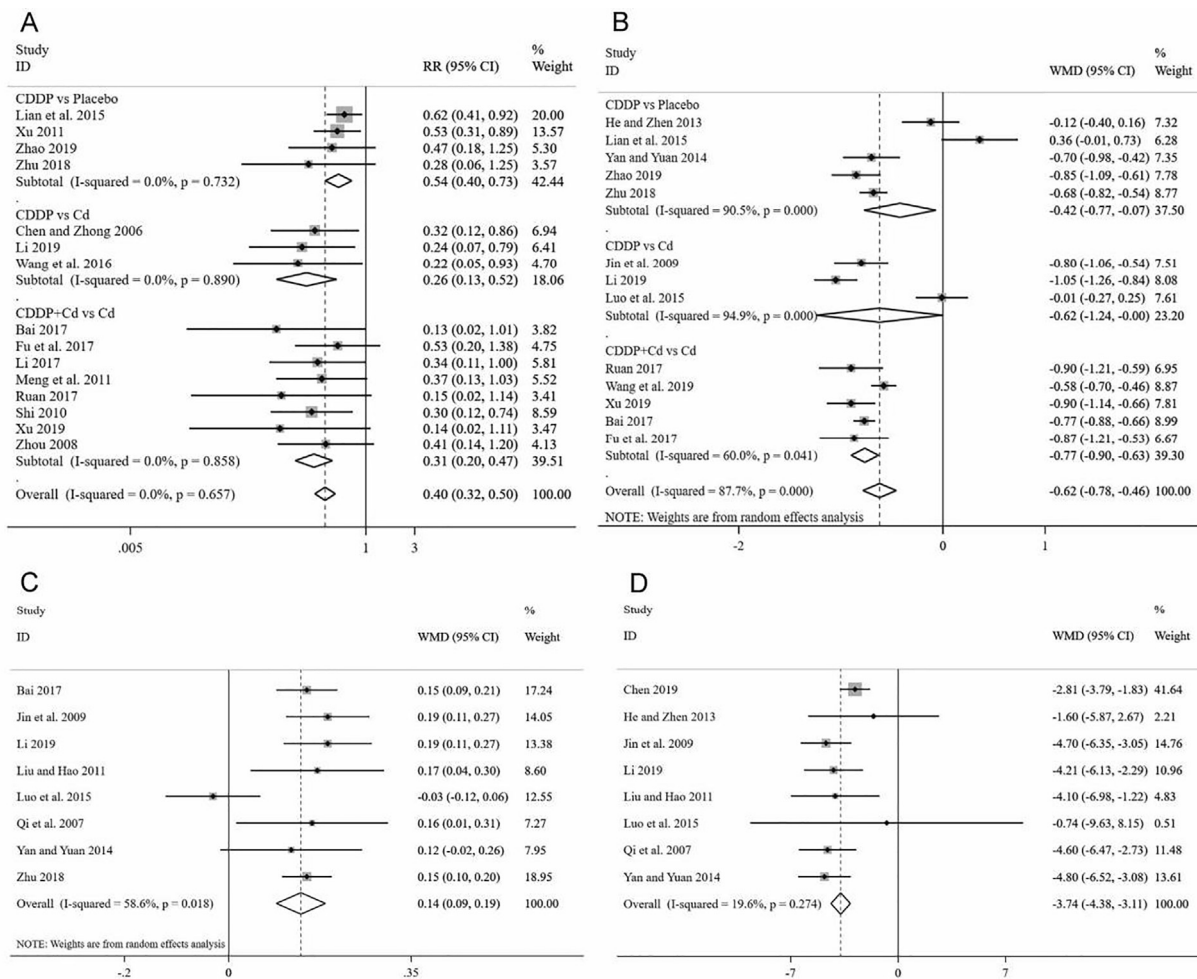
Fig. 2. Forest plot of clinical therapeutic effectiveness (A), hemorrhage (B), vision (C), microaneurysms (D).
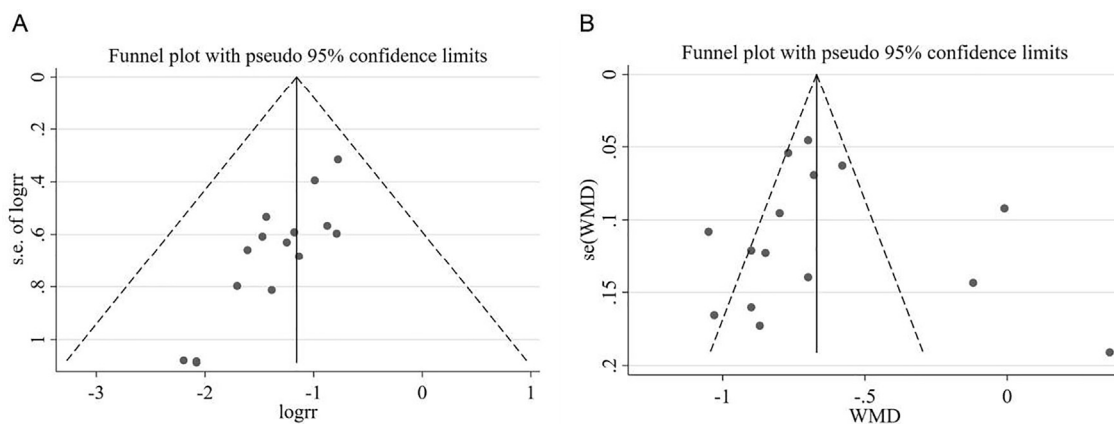

Fig. 3. Funnel plot of clinical efficacy rate (A) and hemorrhage (B).

3.4. Grading quality of evidence

GRADE was used to evaluate the level of evidence in the Meta-analysis. Table 4 presented the results of all outcomes in GRADE summary-of-finding tables. The quality of the evidence for the clinical therapeutic effectiveness, microaneurysm number, and hemangioma volume was moderate because of high risk of bias. Only the MD was judged as very low-quality evidence because of high risk of bias, inconsistency and publication bias, and the others were judged as low-quality evidence due to high risk of bias, inconsistency or publication bias.
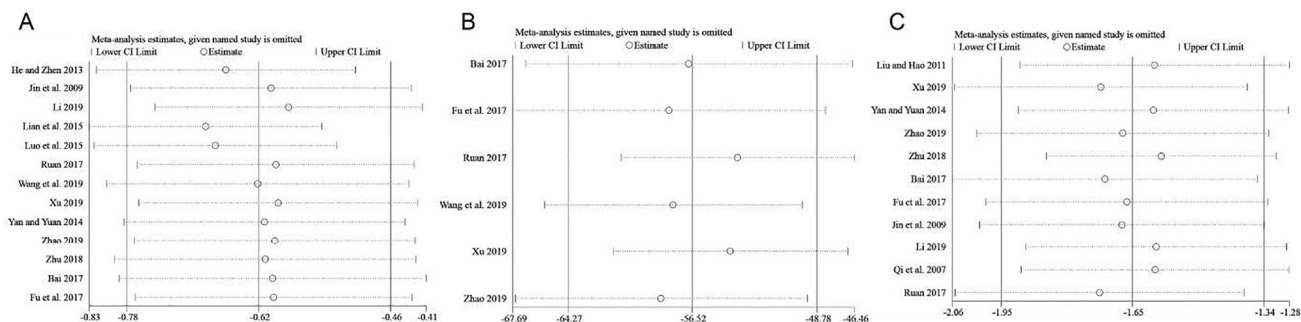
Fig. 4. Sensitivity analysis result of hemorrhage area (A), macular thickness (B) and MD (C).

Table 2
Results of Meta-regression analysis of hemorrhage.

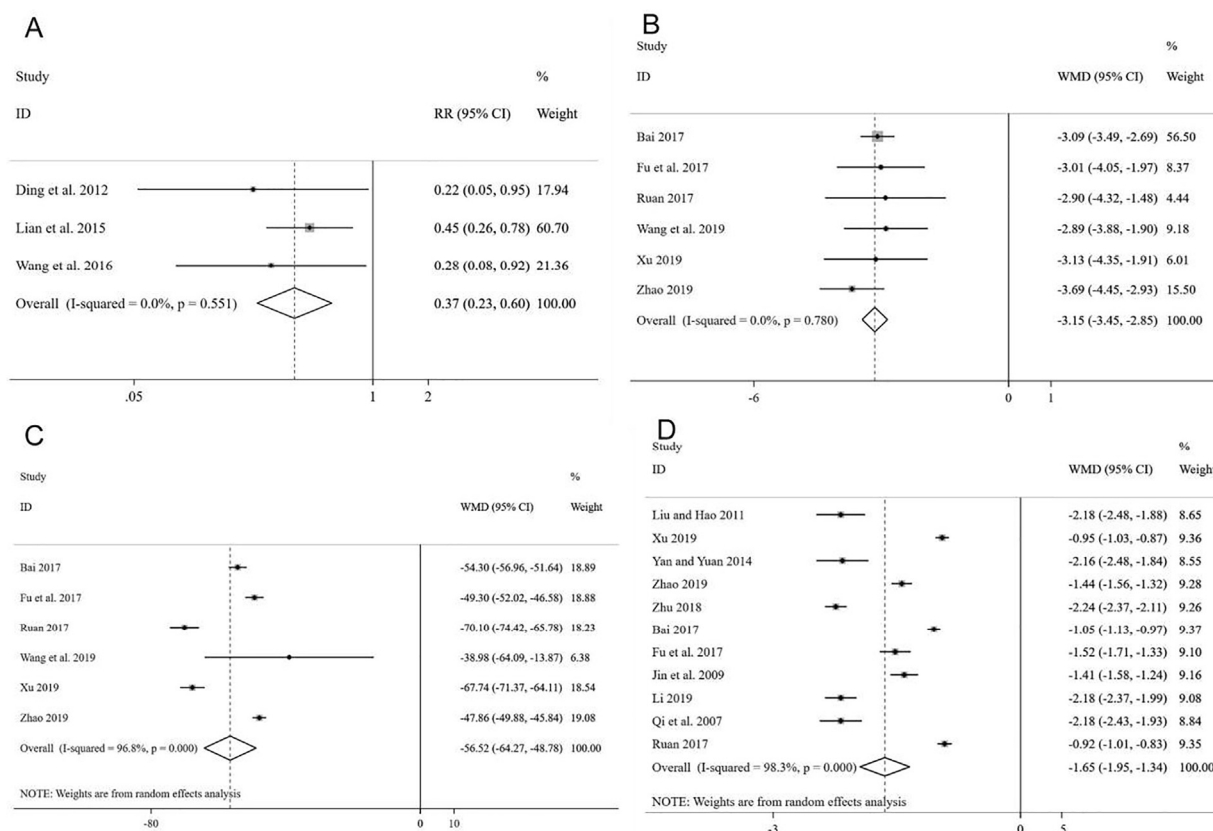| ES	Exp(b)	Std. Err.	t	P>|t|	95% Conf. Interval	
Gender	1.084278	0.3182035	0.28	0.788	0.5683549	2.06853
Number	0.999757	0.0051021	−0.05	0.963	0.9885902	1.01105
Age	1.01234	0.0210653	0.59	0.568	0.9670209	1.059782
Duration	1.057154	0.0934905	0.63	0.543	0.8701703	1.284316

Fig. 5. Forest plot of FFA (A), hemangioma volume (B), macular thickness (C) and MD (D).

4. Discussion

DR is a leading cause of visual impairment in people of working age. The prevalence rate of DR for all adults with DM is estimated to be 34.6%, and an estimate of the prevalence rate for vision-threatening diabetic retinopathy is 10.2% (Kempen et al., 2004; Zhang et al., 2010). Based on both clinical trials and epidemiologic studies, it is generally believed that duration of diabetes and severity of hyperglycemia are the major risk factors for developing retinopathy, and excessive oxidative stress reaction will undergo in retinal cells under the high glucose concentration, and this series of reactions will lead to damage and loss of peripheral cell, and

Table 3
Results of Meta-regression analysis of MD.

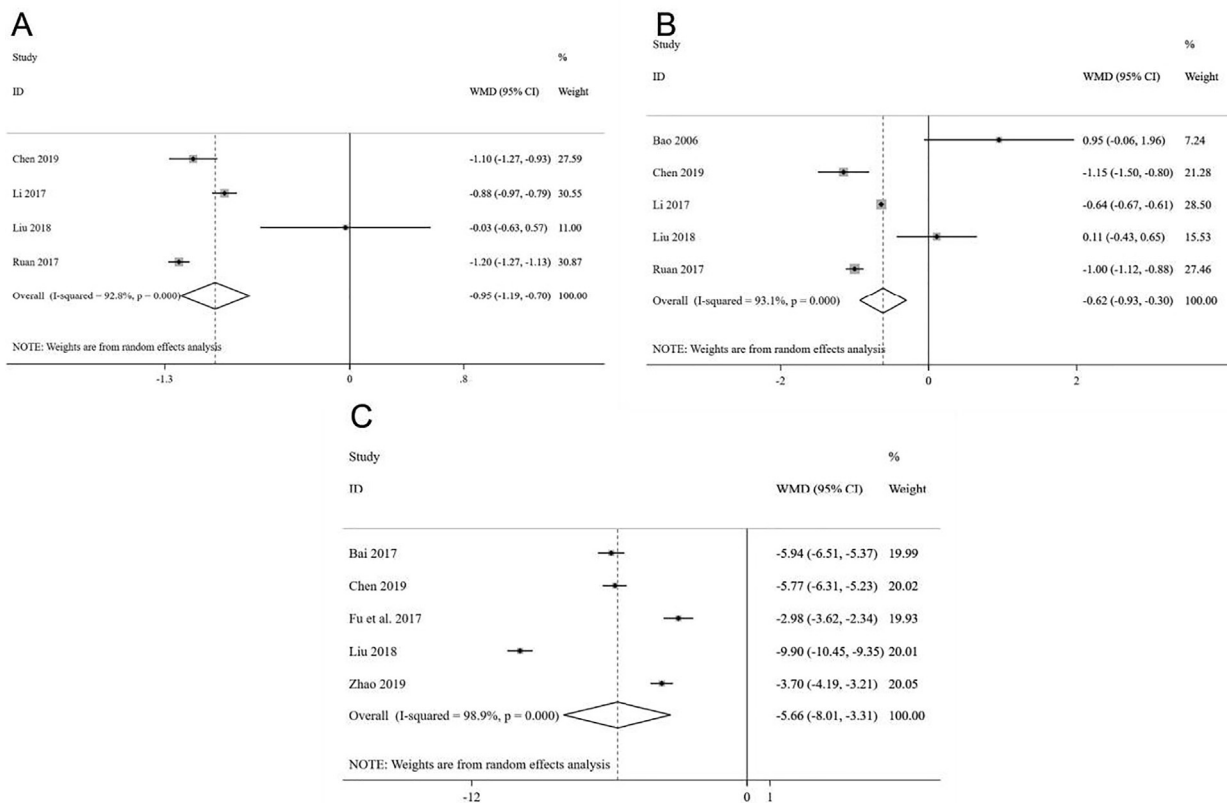| ES	Exp(b)	Std. Err.	t	P>|t|	95% Conf. Interval	
Gender	0.588972	0.2152843	−1.45	0.181	0.2576243	1.346488
Number	0.999438	0.0069255	−0.08	0.937	0.9838937	1.015228
Age	1.053794	0.0250609	2.20	0.055	0.9986002	1.112038
Duration	1.137683	0.1636272	0.90	0.393	0.8217155	1.575146
Allocation	0.221476	0.5390795	0.41	0.693	−1.053244	1.496196

Fig. 6. Forest plot of FBG (A), HbA1c (B), and hs-CRP (C).

even damage to retinal endothelial cells and promote apoptosis finally (Wong et al., 2008). Clinically, the therapy of western medicine is considered as the conventional treatment for diabetic retinopathy. Most patients are usually treated by calcium dobesilate, anti-VEGF therapy, retinal laser photocoagulation, and even vitreous retinal surgery, but noninvasive treatment is not very effective.

According to the theory of traditional Chinese medicine, the pathogenesis of DR is a deficiency of *qi* and *yin* and *qi* failing to circulate blood. So the principle of treatment is to nourish *qi* and *yin* and promote blood circulation to resolve blood stasis (Ou, Yang, & Peng, 2019). The previous studies of the CDDP method for NPDR have been conducted in clinical. However, due to variations in the sample size and methodological quality of these researches, the efficacy of CDDP for NPDR is still not fully understood. Therefore, a systematic review and Meta-analysis were conducted to compare the clinical efficacy of patients who were treated with CDDP and combined with conventional western drugs, placebo, and other medicine. This Meta-analysis included 26 randomized clinical studies, and the results showed that, compared with the control group, CDDP has obvious clinical curative effect in visual function recovery by decreasing macular thickness, retinal microaneurysm number and hemangioma volume, promoting the control

of hemorrhage, improving FFA, visual acuity and visual field, FBG, HbA1c and hs-CRP. The results suggested that CDDP may delay retinopathy progression at the early stage of DR and enhance the vision and quality of life through the microcirculation improvement further. In addition, no serious adverse drug reactions were observed during all the studies, which suggested that CDDP was safe for the treatment of NPDR. What is different from the previous research (Huang, Bao, Jin, & Lian, 2017) is that more new articles are included in this study, and sensitivity analyses are undertaken to explore the influence on the overall results by each individual study. Furthermore, Meta-regression are performed to search for the potential source of heterogeneity and we did not observe evidence that any prespecified variables represented the cause of the observed heterogeneity.

CDDP, a modern Chinese medicine preparation listed in the Chinese Pharmacopeia, is now widely applied for the clinical prevention and treatment of coronary heart disease, angina pectoris and other cardiovascular conditions. CDDP is composed of the mixed extracts of *S. miltiorrhiza*, *P. notoginseng* and Borneol. Among them, *S. miltiorrhiza* possesses remarkable antioxidant properties owing to its ability to upregulate endogenous antioxidant enzymes and induce free radical scavenging (Lin & Hsieh, 2010). Salvianolic acid A, a chemical constituent with antioxidant properties in *S. miltior-*

Table 4
Assessment of quality of evidence.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates /%		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With treatment		Risk with control	Risk difference with treatment (95% CI)
Efficacy (Critical outcome)											
1380 (15 RCTs) range 2–6 months	serious[1]	not serious	not serious	not serious	undetected	⊕⊕⊕◯ MODERATE[1] due to risk of bias	446/683 (65.3%)	616/697 (88.4%)	RR 1.35(1.28 to 1.43)	653 per 1,000	229 more per 1000 (from 183 more to281 more)
Hemorrhage (Better indicated by lower values)											
1053 (13 RCTs) range 2–6 months	serious[1]	serious[2]	not serious	not serious	undetected	⊕⊕◯◯ LOW[1,2] due to risk of bias, inconsistency	516	537	–		MD 0.65 lower (0.8 lower to 0.5 lower)
Vision (Better indicated by higher values)											
579 (eight RCTs) range 2–6 months	serious[1]	serious[2]	not serious	not serious	undetected	⊕⊕◯◯ LOW[1,2] due to risk of bias, inconsistency	277	302	–		MD 0.14 higher (0.1 higher to 0.18 higher)
Microaneurysm number (Better indicated by lower values)											
555 (eight RCTs) range 2–6 months	serious[1]	not serious	not serious	not serious	undetected	⊕⊕⊕◯ MODERATE[1] due to risk of bias	265	290	–		MD 3.74 lower (4.38 lower to 3.11 lower)
FFA (Better indicated by lower values)											
278 (three RCTs) range 2–6 months	serious[1]	not serious	not serious	not serious	publication bias strongly suspected[3]	⊕⊕◯◯ LOW due to risk of bias, publication bias[1,2]	64/139 (46.0%)	18/139 (12.9%)	RR 0.28(0.18 to 0.44)	460 per 1000	332 fewer per 1000 (from 378 fewer to 258 fewer)
Hemangioma volume (Better indicated by lower values)											
448 (six RCTs) range 2–4 months	serious[1]	not serious	not serious	not serious	undetected	⊕⊕⊕◯ MODERATE[1] due to risk of bias	224	224	–		MD 3.15 lower (3.45 lower to 2.85 lower)
Macular thickness (Better indicated by lower values)											
448 (six RCTs) range 2–4 months	serious[1]	serious[2]	not serious	not serious	undetected	⊕⊕◯◯ LOW[1,2] due to risk of bias, inconsistency	224	224	–		MD 56.52 lower (64.27 lower to 48.78 lower)
MD (Better indicated by lower values)											
845 (11 RCTs) range 2–6 months	serious[1]	serious[2]	not serious	not serious	publication bias strongly suspected[3]	⊕◯◯◯ VERY LOW due to risk of bias, inconsistency, publication bias[1,2,3]	409	436	–		MD 1.64 lower (1.95 lower to 1.34 lower)
FBG (Better indicated by lower values)											
508 (four RCTs) range 1–4 months	serious[1]	serious[2]	not serious	not serious	undetected	⊕⊕◯◯ LOW[1,2] due to risk of bias, inconsistency	254	254	–		MD 0.95 lower (1.19 lower to 0.7 lower)
Hb A1c (Better indicated by lower values)											
575 (five RCTs) range 1–4 months	serious[1]	serious[2]	not serious	not serious	undetected	⊕⊕◯◯ LOW[1,2] due to risk of bias, inconsistency	284	291	–		MD 0.62 lower (0.93 lower to 0.3 lower)
hs-CRP (Better indicated by lower values)											
504 (five RCTs) range 1–6 months	serious[1]	serious[2]	not serious	not serious	undetected	⊕⊕◯◯ LOW[1,2] due to risk of bias, inconsistency	252	252	–		MD 5.66 lower (8.01 lower to 3.31 lower)

The quality assessment is shown both graphically by the number of + signs and as high, moderate, low, or very low quality.
[1] Risk of bias: (a) lack of allocation concealment; (b) lack of blinding of participants and personnel (c) lack of blinding of outcome assessment; (d) Incomplete accounting of patients and outcome events; (e) Selective outcome reporting; (f) including non-randomized controlled trial. Lack of allocation concealment and inadequate blinding caused risk of bias.
[2] The inconsistency was considered serious because significant heterogeneity.
[3] The publication bias was assessed via the Eggers test, Peters test and the funnel plot.

rhiza, has been shown to inhibit phosphorylation of Src and Akt directly, thereby prevent endothelial cell proliferation and angio-genesis during proliferative diabetic retinopathy (Yang et al., 2012). Rosmarinic acid, another phytoconstituent of *S. miltiorrhiza*, inhibits retinal neovascularization by causing cell cycle arrest at G2 and M phase (Kim et al., 2009). Since oxidative stress-induced reti-nal neurodegeneration is one of the critical pathological events involved in the pathogenesis of DR, *S. miltiorrhiza* may be utilized for preventing apoptosis of retinal neuron. In addition, *S. miltior-rhiza* can be used to treat blood stasis and improve blood circula-tion due to its positive effects on myocardial energy metabolism improvement, antiplatelet aggregation and neuroprotective effects (Pills, 2017; Zhang et al., 2018).

P. notoginseng extracts have an effect of anti-coagulation, anti-inflammation, antioxidant, and inhibition of lipid deposition and platelet aggregation, owing to several kinds of saponin, such as gin-senoside Re 14, ginsenoside Rk1, ginsenoside Rg1, ginsenoside Rb1 and notoginsenoside R1 (Bermudez et al., 2010). Retinopathy mac-ular edema is a common cause of vision impairment in DR patients with the presence of hard exudates. VEGF is one of the most potent pro-angiogenic agents, which can induce the proliferation, migra-tion and angiogenesis of endothelial cells, and the inhibition of its release attenuates retinal neovascularization in proliferative diabetic retinopathy (Godoy, Betts-Obregon, & Tsin, 2014). Recent studies have shown that oxidative stress and inflammation were involved in the pathogenesis of DR (Gao et al., 2013), these benefi-cial effects of saponins can be utilized in the treatment of DR. According to the report, ginsenoside Rk1 showed significant inhibi-tion in VEGF-induced and AGE induced retinal endothelial perme-ability, thereby reducing retinal edema, which indicating that *P. notoginseng* extracts could attenuate symptoms associated with diabetic retinopathy (Maeng et al., 2013). Borneol has the effect of promoting coronary dilating and analgesic, as an adjuvant and guiding drug, contributes to the entry of active ingredients of *S. miltiorrhiza* and *P. notoginseng* into the body tissues and organs (Zhang, Gao, Shang, Zhao, & Wang, 2003). More broadly, these Chi-nese herbs can be used for the treatment of diabetic retinopathy owing to the active ingredients by which they alleviate pathologi-cal occurrences in retina caused by hyperglycaemia. Consequently, the CDDP treatment may be used as one of the effective and safe therapy for DR.

An increasing number of epidemiological evidences had identi-fied several factors associated with the DR, such as blood glucose level, duration of diabetes and obesity (Atchison & Barkmeier, 2016). It has been reported that the elevated FBG level and higher HbA1c concentration were associated with the risk factors for DR (Corcóstegui et al., 2017). In the Diabetes Control and Complications Trial (DCCT) study of patients with type 1 diabetes, intensive therapy to maintain normal glucose blood and HbA1c levels reduced the risk for the development of retinopathy and the progression of retinopa-thy (Nathan et al., 1993). It also has been confirmed that hs-CRP is one of the inflammation markers for consideration as a predictor of cardiovascular risk (Rifai & Ridker, 2001). With population-based studies, the inflammation assessed by the measurement of serum hs-CRP is associated with the development of diabetes (Tan et al., 2003) Furthermore, it also has been reported that DR is nega-tively associated with serum hs-CRP level with the mechanism of this phenomenon is that some humoral factors related to DR might negatively modulate the CRP production (Keiko et al., 2005). All this suggested that CDDP might have positive effect on glycemic control, serum inflammatory factors reduction and inflammation inhibition to retard the progression of DR and improve of the symptom of patients. Notably, significant heterogeneity was observed in the Meta-analysis of FBG, HbA1c and hs-CRP. There are several sources of heterogeneity, including differences in the treatment, the treated population, the study design, or the data analysis method. We could

not be able to estimate heterogeneity precisely because of the small sample size Meta-analysis provides the little information about heterogeneity (Paul, 2015)

Nevertheless, there are several limitations in this study. First, in view of the fact that CDDP is a kind of TCM preparation, all literatures for this Meta-analysis were from China, among which two were in English and the rest were in Chinese. Therefore, lacking relevant for-eign experiments, the systematic review and Meta-analysis of this study were regional and may be cause selection bias. Second, most studies only mentioned the random trials, but the specific method of random sequence generation used, RCTs of allocation conceal-ment and blinding of outcome assessment is unknown. Further-more, the methodological quality of many of the included RCTs was generally low and might have a high risk of bias. Third, most of the articles were related to positive results, which would likely lead to the overestimation of actual treatment effects. Fourth, the heterogeneity was still very high though we considered different methods of administration in the subgroup analysis. Furthermore, the source of heterogeneity could not be detected by Meta-regression, and the high heterogeneity might be due to the study designs and methods and methodological qualities as well. We also found that the association between CDDP and the severity level of NPDR was not analyzed because of a lack of enough data. Therefore, more multicenter RCTs with large sample and high quality are needed to confirm the beneficial effects of CDDP or CDDP combined with conventional treatments on NPDR treatment.

5. Conclusion

In summary, this systemic review demonstrated the therapeutic effects of CDDP treatment in NPDR patients, which was involved decreasing macular thickness, retinal microaneurysm number and hemangioma volume, promoting the control of hemorrhage, improving FFA, visual acuity and visual field. Moreover, our find-ings conclusively demonstrated that oral CDDP in NPDR patients led to significant regulation of serum level of fasting blooding glu-cose, hemoglobin A1c and high sensitive C reaction protein, which was associated with the pathogenesis of NPDR. According to GRADE, the quality of the evidence for each outcome was moderate to very low. Taking account of the limits in this study, to investi-gate the effect of CDDP on NPDR for providing some guidance sug-gestions in the clinical practice, more rigorous RCTs of the long-term with a large sample size and high methodological standards are needed to enhance the strength of evidence.

Declaration of Competing Interest

The authors declare that they have no known competing finan-cial interests or personal relationships that could have appeared to influence the work reported in this paper.

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