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WORD COUNT

6383

TIME SUBMITTED

15-JUN-2023 01:57PM

PAPER ID

100523050

**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 85187

**Manuscript Type:** META-ANALYSIS

**Effectiveness and safety of traditional Chinese medicine for diabetic retinopathy: A <sup>16</sup> systematic review and network meta-analysis of randomized clinical trials**

Complementary replacement **therapy** for diabetic retinopathy

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## **Abstract**

### **BACKGROUND**

Diabetic retinopathy (DR) is currently recognized as one of the most serious diabetic microangiopathies and a major cause of adult blindness. Commonly used clinical approaches include etiological control, microvascular improvement, and surgical intervention, but they are ineffective and have many side effects. Oral Chinese medicine (OCM) has been used for thousands of years to treat DR and is still widely used today, but it is unclear which OCM is more effective for DR.

### **AIM**

To estimate relative effectiveness and safety profiles for different classes of OCMs for DR, and provide rankings of the available OCMs.

### **METHODS**

The search time frame was from the creation of the database to January 2023. RevMan 5.3 and Stata 14.0 software were used to perform the systematic review and Network meta-analyses (NMA).

### **RESULTS**

A total of 107 studies and 9710 patients were included, including 4767 cases in the test group and 4973 cases in the control group. Based on previous studies and clinical reports, and combined with the recommendations of Chinese guidelines for the prevention and treatment of DR, 9 OCMs were finally included in this study, namely Compound Xueshuantong Capsules (XST), Qiming Granules (QM), Compound Danshen Dripping Pills (DS), Hexue Mingmu Tablets(HXMM), Qiju Dihuang Pills(QJDH), Shuangdan Mingmu Capsules(SDMM), Danguai Buxue Decoction(DGBX), Xuefu Zhuyu Decoction(XFZY) and Buyang Huanwu Decoction (BYHW). When these nine OCMs were analyzed in combination with conventional western medicine treatment (CT) compared with CT alone, the NMA results showed that HXMM+CT has

better intervention effect on the overall efficacy of DR patients, HXMM+CT has better effect on improving patients' visual acuity, SDMM+CT has better effect on inhibiting VEGF, DGBX+CT has better effect on reducing fundus hemorrhage area, HXMM+CT has better effect on reducing fasting blood glucose, and QJDH+CT has better effect on reducing glycated hemoglobin. When there are not enough clinical indicators for reference, SDMM+CT or HXMM+CT treatments can be chosen because they are effective for more indicators and demonstrate multidimensional efficacy.

## CONCLUSION

This study provides evidence that combining OCMs with western drugs leads to better outcomes in all aspects of DR compared to using western drugs alone. Based on the findings, we highly recommend the use of SDMM or HXMM for the treatment of DR. These two OCMs have demonstrated outstanding efficacy across multiple indicators.

**Key Words:** diabetic retinopathy; network meta-analysis; Traditional Chinese Medicine; therapeutic effect; systematic review

Li H, Li M, Zhang W, Zhang S, Gong Y. Effectiveness and safety of traditional Chinese medicine for diabetic retinopathy: <sup>14</sup> A systematic review and network meta-analysis of randomized clinical trials. *World J Diabetes* 2023; In press

**Core Tip:** To our knowledge, this study represents the first network meta-analysis (NMA) examining the effectiveness of traditional Chinese medicine in treating diabetic retinopathy (DR). Notably, this NMA includes the largest number of original studies, subjects, and variety of Chinese medicines to date. While the efficacy of Chinese medicine for DR has been widely recognized in China, no previous studies have systematically evaluated which Chinese medicine treatment is the most effective. Therefore, this study fills an important gap in the field.

## INTRODUCTION

Diabetic retinopathy (DR) is currently recognized as one of the serious diabetic microangiopathies and is the leading cause of blindness in adults. According to the International Diabetes Federation, it is estimated that the number of people with diabetes will reach 642 million worldwide in 2040, and 34.6% of these patients will have DR as a complication<sup>[1]</sup>. DR causes irreversible visual impairment, including abnormal vision, blurred vision, and even blindness. In addition, the presence of DR implies an increased risk of life-threatening systemic vascular complications<sup>[2]</sup>. Currently, the main treatments for DR include retinal laser photocoagulation, pharmacotherapy, hormonal therapy, and surgery. However, these treatments may lead to adverse effects such as increased angiogenesis, increased intraocular pressure, and retinal hemorrhage<sup>[3,4]</sup>. Studies have shown that age is a key factor affecting DR, and the number of DR patients in the elderly population will reach new highs as the world ages<sup>[5]</sup>. In view of the current situation, the pathogenesis of DR is being actively explored around the world and effective therapeutic drugs are being explored.

In fact, Traditional Chinese Medicine (TCM) has long been considered a promising complementary therapy that dates back more than 1,000 years. In China, many facts have proven that herbal medicine can effectively improve the fundus condition of patients, relieve the pain of the disease, and obtain a better quality of life for patients through multi-target and multi-path interventions in DR<sup>[6]</sup>. Many Oral Chinese medicine (OCM), including proprietary Chinese medicine preparations and herbal granules are widely used in the treatment of DR. For example, Qiming Granules(QM), the first OCM approved by the State Food and Drug Administration for the treatment of DR, whose main ingredients are *Hedysarum Multijugum Maxim.* (Huangqi in chinese), *Radix Puerariae*(Gegen in chinese), *Lycii Fructus*(Gouqizi in chinese), and *Cassiae Semen* (Juemingzi in chinese), etc, were shown to alleviate retinal hypoxia and ischemia by increasing retinal blood flow and improving blood circulation in a multicenter, randomized, parallel controlled clinical trial<sup>[7]</sup>. Then for example, Compound Xueshuantong Capsules(XST), an OCM commonly used for DR, was shown to

effectively improve the disorder of retinal structure and edema in streptozotocin-induced type 2 diabetic rats by activating the PPAR signaling pathway, reversing the reduction in retinal thickness and retinal ganglion cell number, and reducing the apoptotic index of retinal cells<sup>[8]</sup>. Compound Danshen dripping pills, an oral proprietary Chinese medicine containing Danshen, was found to improve vision and clinical symptoms and reduce the incidence of macular edema compared to captopril in a retrospective study<sup>[9]</sup>.

In addition to these well known OCMs, there are many lesser known OCMs that are widely used in clinical practice. However, the selection of these OCMs remains a challenge for patients with different disease states. Network meta-analyses (NMA) allow for the comparison of multiple treatments (i.e. three or more) using both direct comparisons of interventions within randomized controlled trials (RCT) and indirect comparisons across trials based on a common comparator<sup>[10]</sup>. To date, there are no studies comparing different types of OCMs used for the treatment of DR. Therefore, we searched all RCTs of OCMs used for the treatment of DR and initiated this NMA to compare the efficacy between them, hoping to provide some suggestions for clinical practice.

## **MATERIALS AND METHODS**

The study protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews). Registration No. CRD42022352250 (<https://www.crd.york.ac.uk/PROSPERO/#myprosperoID=CRD42022352250>). This program was developed in accordance with the Preferred Reporting Items For Systematic Review And Meta-analysis Protocols (PRISMA-P)<sup>[11]</sup>. The PRISMA Extension Statement is used to ensure that all aspects of the methods and results are reported<sup>[12]</sup>.

### **Eligibility criteria**

The Population-Intervention-Comparators-Outcomes-Studydesign(PICOS) framework was adopted as the eligibility criteria for the review as following.

## Study Type

The RCT is the original study that we agreed to include. We did not place any restrictions on the language, country, publication date, or phase of the RCT. Duplicate publications, summaries of personal experience, purely theoretical studies, reviews, animal or cellular experiments, and original studies with incorrect or incomplete data in the literature should also be excluded.

## Population

Patients with DR who meet the standard diagnosis rely on fundus fluorescence angiography and fundus signs to detect microangiomas, exudates, hemorrhages, neovascularization, and other fundus changes. No restriction of age, gender, occupation and region. No concomitant ocular diseases caused by non-hyperglycemic factors, such as primary glaucoma and senile cataract; no acute metabolic diseases, such as diabetic ketoacidosis, within a short period of time before enrollment.

## Intervention

Regarding the RCT of OCM for DR, the blinding and language are not limited. The control group received only oral western medicine, conventional western medicine treatment (CT) mainly included hypoglycemic drugs, lipid-lowering drugs and antihypertensive drugs, among which hypoglycemic drugs could include subcutaneous injection of insulin, in addition, other injectable drugs were not acceptable; antioxidant and microcirculation improvement drugs, such as calcium dobesilate, pancreatic kininogenase; drugs to promote retinal metabolism and nerve nutrition of the eye, such as lecithin complex iodine, *etc.* The test group was added to the control group with OCM. by combining previous studies and actual clinical observations, and also referring to the latest published Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition)<sup>[13]</sup>, we decided to study the 9 most commonly used OCMs which are Compound Xueshuantong Capsules (XST, composed of *Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow/ Figwort Root/ Hedysarum Multijugum Maxim./ Radix Salviae*), Compound Danshen Dripping Pills(DS, composed of *Radix Salviae/ Borneolum Syntheticum/Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow*),

Qiming Granules (QM, composed of *Hedysarum Multijugum Maxim./ Radix Puerariae/ Rehmanniae Radix Praeparata/ Lycii Fructus/ Leonuri Fructus/ Cassiae Semen/ Pollen Typhae/ Whitmaniana Pigra Whitman*), Hexue Mingmu Tablets (HXMM, *Pollen Typhae/ Rehmanniae Radix Praeparata/ Radix Salviae/ Ecliptae Herba/ Chrysanthemi Flos/ Scutellariae Radix/ Cassiae Semen/ Plantaginis Semen/ Leonuri Fructus/ Fructus Ligustri Lucidi/ Prunellae Spica/ Gentianae Radix Et Rhizoma/ Curcumae Radix/ Equiseti Hiemalis Herba/ Radix Paeoniae Rubra/ Cortex Moutan/ Angelicae Sinensis Radix/ Chuanxiong Rhizoma*), Qiju Dihuang Pills (QJDH, *Lycii Fructus/ Rehmanniae Radix Praeparata/ Chrysanthemi Flos/ Cornus Officinalis Sieb. Et Zucc./ Rhizoma Dioscoreae/ Poria Cocos (Schw.) Wolf./ Alisma Orientale (Sam.) Juz./ Cortex Moutan*), Shuangdan Mingmu Capsules (SDMM, *Ecliptae Herba/ Fructus Ligustri Lucidi*), Danggui Buxue Decoction (DGBX, *Hedysarum Multijugum Maxim./ Angelicae Sinensis Radix*), Xuefu Zhuyu Decoction (XFZY, *Persicae Semen/ Carthami Flos/ Radix Paeoniae Rubra/ Chuanxiong Rhizoma/ Radix Bupleuri/ Platycodon Grandiflorus/ Licorice/ Angelicae Sinensis Radix/ Rehmanniae Radix Praeparata/ Achyranthis Bidentatae Radix/ Aurantii Fructus*) and Buyang Huanwu Decoction (BYHW, *Hedysarum Multijugum Maxim./ Angelicae Sinensis Radix/ Radix Paeoniae Rubra/ Chuanxiong Rhizoma/ Persicae Semen/ Carthami Flos/ Pheretima*). To obtain the most accurate efficacy results for OCM, all studies performing non-oral treatments such as laser photocoagulation, surgery, injectable fluids, acupuncture, tui-na, and traditional Chinese gongfu were excluded from this study.

### **Outcome measures**

The main efficacy indicators in this study encompass total clinical effectiveness and visual acuity. Following the IDR efficacy determination criteria, the efficacy after treatment was categorized into three groups: significantly effective, effective, and ineffective. Significantly effective cases were identified based on two criteria: ① improvement in visual acuity by  $\geq 2$  Lines, and ② improvement in two or more of the three fundus indices (microvessel count, hemorrhage, and exudation), or significant improvement in one or more of the three indices without deterioration in the remaining indices. Effective cases were determined by improvement in visual acuity and



improvement in at least one of the three fundus indices without deterioration in the remaining indices. Ineffective cases were those that did not meet the criteria for effectiveness based on the indices. For assessing visual acuity, the international standard visual acuity table was utilized, where the counting included 2 rows for no light perception to light perception, and 1 row for each interval including light perception, manual, index, 0.02, 0.04, 0.06, 0.08, and 0.1, while refractive error measurements accounted for corrected visual acuity. The efficacy index considered the total clinical efficiency (comprising significantly effective and effective populations), reflecting the actual determination of clinical effects. Secondary indicators include fundus hemorrhagic area (FHA), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), vascular endothelial growth factor(VEGF).

#### **Data sources and search strategy**

A total of seven databases were searched by computer: China national knowledge infrastructure, Wanfang Database, Weipu Journal Database (VIP), Chinese Biomedical Literature Database, PubMed, Cochrane Library, and Web of Science database, and the search time of each database was built until January 2023. In addition, references to the literature were incorporated retrospectively to supplement access to relevant literature. The search takes a combination of subject terms and free words. English search terms include: "Diabetic Retinopathy", " Diabetic Retinopathies ", " Traditional Chinese medicine ", " Compound Xueshuantong Capsules ", " Compound Danshen Dripping Pills ", "Qiju Dihuang Pills", " Qiming Granules ", "Hexue Mingmu Tablets", "Randomized Controlled Trial", *etc.* The detailed search strategy is described in

#### **Supplementary Material 1.**

#### **Data Screening and Quality Evaluation**

Two investigators (LMX and LHD) performed literature screening and data extraction, excluding duplicates and then first read the title and abstract to exclude literature that clearly did not meet the requirements, and then read the remaining literature in full to clarify whether it met the inclusion criteria, and if there was disagreement, a third investigator (AD) had to be consulted for a decision after

discussion. Data extraction was performed using Microsoft Excel 2019 to collect relevant information. Data extraction included: ①basic information: article title, first author, publication time, country/region, *etc.*; ②study characteristics: interventions in the trial and control groups, number of cases, age, duration of intervention, and adverse effects in the study subjects; ③key information required for risk of bias evaluation in the literature; ④outcome indicators included in the test and control groups.

Quality evaluation of RCTs was performed using RevMan 5.3 (Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre). Assessed by 2 investigators (HL and ML) using the tool for assessing risk of bias recommended in the Cochrane systematic reviewers' handbook 5.1<sup>[14]</sup>, including the following 7 aspects: random-sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); others bias. Each aspect can be further categorized as "low risk of bias", "unclear risk of bias", and "high risk of bias". When there is a disagreement, it can be decided by mutual discussion or by consulting 3 investigators (SZ).

### **Statistical analysis**

Stata 14.0 (MRC Biostatistics Unit, Cambridge, UK) software was used to implement the statistical process. The odds ratio (OR) and its 95% confidence interval (CI) were used for statistical data, and the mean difference (MD) and its 95% CI were used for measurement data. Data were preprocessed using the "Network" command, and two comparisons were made between different interventions, according to this case there is no closed loop, so the consistency model is used. The efficacy was ranked according to the surface under the cumulative ranking curve (SUCRA), and the results of the NMA analysis were finally presented in tabular form to obtain the relatively best interventions. Considering the inclusion of multiple observations, we combined the individual observations two by two and used a multivariate approach to determine the dependencies between the results. Use the "Clustering" command to obtain a clustering ranking chart<sup>[15]</sup>. Sensitivity analysis is performed for factors that may affect the

stability of the results. Finally, "correction-comparison" funnel plots were drawn for publication bias assessment.

## **RESULTS**

### ***Literature search results and basic characteristics***

A total of 1,667 relevant papers were identified and screened for inclusion in 107 randomized controlled trials, involving a total of 9,710 patients (4,767 in the trial group and 4,973 in the control group). Baseline characteristics were carefully matched between the groups. The individual sample sizes of the trials ranged from 30 to 256 individuals, and the observation periods varied from 4 wk to 24 wk. The trials encompassed 9 different OCMs, namely XST (26 studies<sup>[16-41]</sup>), QM (23 studies<sup>[42-64]</sup>), DS (21 studies, references<sup>[65-85]</sup>), HXMM (9 studies<sup>[86-94]</sup>), QJDH (6 studies<sup>[95-100]</sup>), SDMM (5 studies<sup>[101-105]</sup>), DGBX (6 studies<sup>[106-111]</sup>), XFZY (7 studies<sup>[112-118]</sup>), and BYHW (4 studies<sup>[119-122]</sup>). All studies evaluated at least one of the two primary efficacy measures, namely total clinical effectiveness and visual acuity. Importantly, it should be noted that all included studies were conducted exclusively in China. The literature screening process is shown in **Figure 1**, the characteristics of the literature are shown in **Table 1**, and the OCMs involved in the study and their details are shown in **Supplementary Material 2 and 3**, respectively.

### ***Risk of bias evaluation results***

The quality of the included literature was evaluated using the "Risk Assessment Tool" recommended by the Cochrane Collaboration: 33 studies<sup>[16,19,22,28,29,35,37,39,43,45,49,51,55,69,72,73,78,83,85,88,89,92,94,98,102,104,106,111-115,120]</sup> mentioned the specific randomization method used and therefore assessed as "Low risk". The other 74 studies only mentioned the randomized grouping without mentioning the specific method used for allocation and were therefore evaluated as "Unclear risk". None of the included studies mentioned allocation concealment and blinding, and were evaluated as "Unclear risk". All studies had clear outcome indicators and were evaluated as "Low risk"; no duplicate publications or published biases were found in any of the studies

and were evaluated as "Low risk"; other biases were unknown and were evaluated as "Unclear risk". All data were reported completely and were comparable between groups (Figure 2 and Supplementary Material 4).

### Results of Reticulated Meta-Analysis

#### Mesh Relationship Diagram and Consistency Testing

The reticulation between the nine included OCM is shown in Figure 3. The total number of arms in the 107 papers totals 214. Lines between nodes indicate direct comparative evidence between the two interventions, no lines indicate no direct comparison, indirect comparisons can be made through reticulated Meta-analysis. The thickness of the line represents the number of included studies comparing each treatment, and the circular area represents the sample size of the population using the measure. All interventions involved in this study did not form a closed loop and did not require consistency testing.

#### Total effective rate

A total of 89 studies<sup>[16-20,22-25,27-31,33-37,39-69,72,74,75,77,79-81,83,87-99,102-111,113,116-122]</sup> were included to compare the total effective rate after OCM+CT treatment. The evidence diagram is shown in Figure 4A. The difference was statistically significant ( $P < 0.05$ ) for the total effective rate for these nine OCMs+CT treatments compared with CT (Figure 5A). The nine OCMs+CT total effective rate in descending order are: DS( SUCRA = 75.0%) > DGBX( SUCRA = 72.8%) > SDMM( SUCRA = 71.4%) > QM( SUCRA = 66.4%) > QJDH( SUCRA = 62.4%) > XST = HXMM( SUCRA = 52.5%) > BYHW( SUCRA = 26.8%) > XFZY( SUCRA = 20.1%) > CT(SUCRA = 0.0%). The probability ranking is shown in Figure 6A.

#### Visual acuity

A total of 34 studies<sup>[16-18,21,23,25,26,29,37,38,44,46,47,49,51,55,56,59,60,65,71,73,76,78,81,83,91,100,108,110,112,114,115,120]</sup> with 8 OCMs were included to compare visual acuity after OCM+CT treatment. The evidence diagram is shown in Figure 4B. In terms of visual acuity, supplemental XST, QM, DS, HXMM, QJDH, DGBX and XFZY treatments were statistically significant

compared with CT treatment alone ( $P < 0.05$ ) (Figure 5B). The eight OCMs+CT in order of highest to lowest improvement in visual acuity are: HXMM( SUCRA = 76.3%) > XST( SUCRA = 67.4%) > DS( SUCRA= 67.2%) > DGBX( SUCRA = 64.8%) > BYHW( SUCRA = 50.3%) > XFZY( SUCRA = 44.4%) > QM(SUCRA = 40.1%) > QJDH(SUCRA = 36.2%) > CT (SUCRA = 3.4%). The probability ranking is shown in Figure 6B.

#### *Vascular endothelial growth factor(VEGF)*

A total of 18 studies<sup>[16,25,29,31,33,35,55,58,66,69,73,83,96,97,100,102,104,107]</sup> with 6 OCMs were included to compare VEGF after OCM+CT treatment. The evidence diagram is shown in Figure 4C. In terms of VEGF, supplemental XST, DS, QJDH and SDMM were statistically significant compared with CT treatment alone ( $P < 0.05$ ) (Figure 5C). The seven OCMs+CT in order of VEGF reduction from highest to lowest are: SDMM( SUCRA = 97.7%) > DS( SUCRA = 74.4%) > QJDH( SUCRA= 57.9%) > DGBX( SUCRA = 45.9%) > XST( SUCRA = 44.8%) > QM( SUCRA = 24.7%) > CT (SUCRA = 4.7%). The probability ranking is shown in Figure 6C.

#### *Fundus hemorrhage area (FHA)*

A total of 32 studies<sup>[16,20,21,31,32,35,37,39-41,60,65,69,71,72,76,78-81,83,86,88-90,96,97,100,102,104,106,109]</sup> with 7 OCMs were included to compare FHA after OCM+CT treatment. The evidence diagram is shown in Figure 4D. These seven OCM+CT were statistically significant ( $P < 0.05$ ) compared with CT for FHA, respectively (Figure 5D). The seven OCMs+CT reduce FHA in the following order from highest to lowest: DGBX( SUCRA = 87.5%) > SDMM( SUCRA = 77.7%) > XST( SUCRA= 67.9%) > QJDH( SUCRA = 58.8%) > DS( SUCRA = 45.9%) > QM( SUCRA = 45.1%) > HXMM (SUCRA = 17.0%) > CT (SUCRA = 0.0%). The probability ranking is shown in Figure 6D.

#### *Fasting blood glucose(FBG)*

A total of 21 studies<sup>[47,49,51,61,65,70,75,79,82,84,85,92,97-99,101,108,113,114,116,120]</sup> with 8 OCMs were included to compare FBG after OCM+CT treatment. The evidence diagram is shown in Figure 4E. In terms of FBG, supplemental DS, HXMM, QJDH and SDMM treatments were statistically significant compared with CT treatment alone ( $P < 0.05$ ) (Figure 5E). The eight OCMs+CT lower FBG in the following order from highest to lowest: HXMM(

SUCRA = 91.1%) > SDMM( SUCRA = 86.4%) > QJDH( SUCRA= 73.8%) > DS( SUCRA = 54.2%) > XFZY( SUCRA = 36.1%) > BYHW( SUCRA = 34.0%) > DGBX (SUCRA = 33.2%)> QM (SUCRA =27.8%)> CT (SUCRA =13.5%). The probability ranking is shown in Figure 6E.

#### *Glycated hemoglobin (HbA1c)*

A total of 17 studies<sup>[47,49,51,61,65,70,75,79,82,84,85,92,97,99,108,113,114]</sup> with 6 OCMs were included to compare HbA1c after OCM+CT treatment. The evidence diagram is shown in Figure 4F. In terms of HbA1c, supplemental DS and QJDH treatments were statistically significant compared with CT treatment alone ( $P<0.05$ ) (Figure 5F). The six OCMs+CT lower HbA1c in the following order from highest to lowest: QJDH( SUCRA = 95.5%) > HXMM( SUCRA = 65.3%) > XFZY( SUCRA= 50.8%) > QM( SUCRA = 45.0%) > DS( SUCRA = 43.6%) > DGBX( SUCRA = 42.2%) > CT (SUCRA =7.6%). The probability ranking is shown in Figure 6F.

#### *Cluster analysis and meta-analysis two-by-two comparison results*

The key outcome indicators included in this study were cluster analyzed to derive the intervention of different OCMs+CT for two outcome indicators at the same time. In terms of total effective rate and visual acuity, HXMM, XST, DS and DGBX in the upper right corner of Figure 7A performed better; in terms of total effective rate and VEGF, SDMM and DS performed better ( Figure 7B); in terms of total effective rate and FHA, DGBX and SDMM in the upper right corner of Figure 7C performed better; in terms of FBG and HbA1c, QJDH and HXMM in the upper right corner of Figure 7D performed better.

A two-by-two comparison of the nine OCMs+CT and CT was performed at each index. The total clinical efficiency of DR treatment with all 9 OCMs + CT was found to be higher than that of CT alone; CT in combination with XST, QM, DS, HXMM, DGBX and XFZY were superior to CT alone in improving visual acuity, respectively; in anti-VEGF, CT in combination with XST,DS,QJDH and SDMM were better than CT alone, respectively; CT in combination with XST, QM, DS, HXMM, QJDH,SDMM and DGBX were superior to CT alone in reducing FHA, respectively; CT in combination with DS,

HXMM, QJDH and SDMM were superior to CT alone in lowering FBG, respectively; CT in combination with DS and QJDH were superior to CT alone in lowering HbA1c, respectively. All results are plotted as forest plots shown in **Supplementary Material 5**.

### **Sensitivity analysis**

To verify the stability of the above results, we performed NMA with sample size and duration of treatment as sensitivity factors that may affect the results. Of the total 107 studies, 54 studies<sup>[16-18,20,21,23,27,31-36,38,40,42,44,46,52,54,60,61,63-68,71,76-79,82,83,87,89,91,93-96,98,99,101,105,106,108,110,113,116,120-122]</sup> with a case load of no more than 80<sup>2</sup> were included in the sensitivity analysis. The results revealed that there was no significant difference in total effective rate for CT+SDMM compared with CT (OR: 0.94, 95%CI: 0.94-23.98,  $P > 0.05$ ), unlike the original NMA; for HbA1c, DGBX+CT was effective in reducing HbA1c compared with CT (OR: 0.67, 95%CI: 0.48-0.94,  $P < 0.05$ ), unlike the original NMA. There was no significant change in the remaining indicators, so the sample size was considered as a possible factor influencing the results (**Figure S1 A-F in Supplementary Material 6**). When using duration of treatment as a sensitivity factor, we divided all studies according to 12 wk of treatment, and a total of 65 studies<sup>[16,19,22,24,26-31,33,34,37,38,41-45,47-49,51,56,58-61,66,69,71,72,75,80-82,85-95,98,100,102,106-113,116-122]</sup> with no more than 12 wk of treatment were included in the sensitivity analysis. Results found that DGBX+CT was more effective than CT in terms of VEGF (OR: 0.29, 95%CI: 0.16-0.53,  $P < 0.05$ ), unlike the original NMA; for FBG, CT+QJDH was not significantly different from CT (OR: 0.67, 95%CI: 0.39-1.16,  $P > 0.05$ ), unlike the original NMA; for HbA1c, the effect of DS+CT was not significantly different from CT (OR: 0.77, 95%CI: 0.38-1.57,  $P > 0.05$ ), unlike the original NMA. Consideration of sample size may have influenced this result (**Figure S2 A-F in Supplementary Material 6**).

**1**

### **The Small Sample Effect and Publication Bias**

The total effective rate (significantly effective + effective), visual acuity, VEGF, FHA, FBG and HbA1c were used as evaluation indicators to produce a comparative corrected funnel plot of the study<sup>1</sup> to assess the small sample effect, see **Figure 8**. The results

showed that the total effective rate and FBG comparison corrected funnel plots showed basic symmetry, with studies roughly symmetrically distributed on both sides of the midline, suggesting that a small sample effect is less likely. The poor symmetry of the corrected funnel plot for visual acuity, VEGF, FHA, and HbA1c comparisons suggests the possibility of a small sample effect. The reasons may be related to the mixed quality of included studies, small sample size, inconsistent treatment regimens, and different pathological stages of study subjects. Further analysis of publication bias using Begg's and Egger's tests revealed the presence of publication bias for total clinical effectiveness ( $P_{Begg} < 0.001$ ,  $P_{Egger} < 0.001$ ). Additionally, there was a potential publication bias for FBG ( $P_{Begg} = 0.01$ ;  $P_{Egger} = 0.151$ ) and FHA ( $P_{Begg} = 0.224$ ,  $P_{Egger} = 0.041$ ). However, no publication bias was observed for visual acuity, VEGF, and HbA1c ( $P_{Begg} > 0.05$ ;  $P_{Egger} > 0.05$ ). The presence of bias in these particular outcomes may be attributed to various factors, including the mixed quality of the included studies, small sample sizes, variations in treatment regimens, and differences in the pathological stages of the study subjects. These factors could contribute to heterogeneity and potential reporting biases within the literature.

### **Adverse reactions**

Of the total 107 RCTs, 47 mentioned adverse reactions, but only 20 of these studies<sup>[17,19,33,37,39,43,51,55,73,86-88,90,93,99,101-103,109,111]</sup> had patients with adverse reactions, and the other 26 studies<sup>[30,34,35,40,46,47,57-61,67-70,72,79,83,94-98,104,106,108,113]</sup> in which all patients had no adverse reactions. A total of 76 patients in the experimental group had adverse reactions during the treatment, and 127 patients in the control group had adverse reactions. A total of 7 OCMs were involved, and the results are shown in Table 2.

### **DISCUSSION**

To the best of our knowledge, this study is the first NMA focused on the combination of OCM with conventional Western medicine for the treatment of DR, and is the NMA with the largest number of original studies included, the largest number of subjects, and the largest variety of OCM included to date. Only five NMAs<sup>[123-127]</sup> have reported



the therapeutic effect on DR, and only one<sup>[125]</sup> of them is about the efficacy of herbal injections for DR. This study comprehensively collected RCTs involving 9 commonly used OCMs in China and included 6 clinical indicators commonly used to evaluate the efficacy of DR, the largest number of included indicators we are aware of to date in a similar report.

Although surgical treatment and intravitreal drug injection for DR are becoming popular, there are still some problems that are difficult to solve in a short period of time. First, invasive therapies have a limited audience. Total retinal photocoagulation is the primary treatment for proliferative diabetic retinopathy and is not advocated for the treatment of non-proliferative diabetic retinopathy; Intraocular injections of VEGF inhibitors are more effective primarily in the treatment of DR with macular edema. In some forms of non-clearing vitreous hemorrhage, vitrectomy has been shown to remain the only method for removing fibrous proliferation and relieving traction detachment, with mixed results<sup>[128]</sup>. Second, safety issues need to be kept in mind, for example, one study found that although intraocular steroid injections led to rapid regression of dimethyl ether, however, this improvement did not persist and was associated with a significant increase in the incidence of elevated intraocular pressure and cataracts<sup>[129]</sup>. Furthermore, we must take into account the additional financial burden incurred by this type of treatment. A study from Canada reported that Grid laser therapy adds an additional cost benefit per quality of life adjusted year<sup>[130]</sup>. In contrast, OCM is not only increasingly proving to have surprising clinical efficacy<sup>[131]</sup>, is affordable<sup>[132]</sup>, and is indicated for patients in almost all stages of DR with a broad universal indication. Therefore, a systematic and comprehensive evaluation of the therapeutic efficacy of OCM for DR is essential.

This study found that DS showed excellent efficacy in improving visual acuity levels and total clinical effectiveness. DS is composed of three herbs *Radix Salviae* (Danshen in Chinese), *Panax notoginseng* (Burkill) F. H. Chen ex C. H. (Sanqi in Chinese) and *borneol* (bingpian in Chinese). According to Chinese medicine, Danshen and Sanqi have the effect of activating blood circulation and dispelling blood stasis, and are commonly

used herbs for treating diseases of blood stasis and obstruction; Bingpian is obtained from the stem of *Blumea balsamifera* (L.) DC. or the leaves of *Cinnamomum camphora* by water steam distillation and recrystallization, and is documented in the famous Chinese medical work *Annotation of Materia Medica* from the Tang Dynasty (about 659 AD) as a treatment for eye diseases. Each of the three herbs has its own characteristics and at the same time exerts the effect of activating blood circulation and removing blood stasis, which is in line with modern pharmacological research. It was found<sup>[133]</sup> that Tanshinone IIA (the main active component of Danshen) promoted phosphorylation of AMP-activated protein kinase AMPK at T172 in retinal pigment epithelial cells and inhibited monolayer permeability of human retinal epithelial cells under high glucose conditions, similar to that under normal glucose, while apparently preventing colocalization of NF- $\kappa$ B and p300 and inhibiting their binding, thereby reducing ARPE-19 cell monolayer permeability. A study by Fan *et al* <sup>[134]</sup> found that Tanshinone IIA significantly downregulated the expression levels of VEGF and intercellular adhesion molecule-1 (ICAM-1) in a dose-dependent manner under HG conditions, probably by mediating proliferation, migration and inhibition of angiogenesis in human retinal endothelial cells. Sanqi and its extracts have anti-inflammatory<sup>[135-138]</sup>, antioxidant, inhibit platelet aggregation, regulate blood glucose<sup>[139,140]</sup>, regulate blood pressure<sup>[141-143]</sup>, improve insulin resistance <sup>[144,145]</sup>, inhibit neuronal apoptosis<sup>[146-148]</sup> and neuronal protection<sup>[149-152]</sup>. In particular, ginsenoside Rb1 (the main active compound extracted from the rhizome of Sanqi) has been widely demonstrated to be promising as an antidiabetic and its complications, improving diabetes-related complications by regulating oxidative stress, apoptosis, inflammatory response, enhancing insulin sensitivity, improving leptin resistance, activating the activation of lipocalin signaling pathway, and inhibiting fibronectin expression<sup>[153-161]</sup>. In addition to showing good clinical treatment rates, DGBX has shown excellent performance in improving the fundus hemorrhage area. According to TCM theory, DGBX is mainly used for treating diseases caused by fatigue and internal injury, blood deficiency and qi weakness. Although there are only two herbs in the formula, Radix Astragali Mongolici

(Huangqi in Chinese) and *Angelicae Sinensis Radix* (Danggui in Chinese), the formula is short but powerful and can promote the production of tangible blood from invisible qi, which is a classic OCM with the effect of tonifying qi and promoting blood production. It is a classic OCM with the effect of nourishing Qi and promoting blood circulation. DGBX <sup>10</sup> was found to affect lipid metabolism in the early stages of atherosclerosis in diabetic Goto-Kakizaki rats, and the mechanism may be related to the regulation of intravascular lipid metabolism genes<sup>[162]</sup>. Astragalus polysaccharides are the main active components of Huangqi, can reduce the levels of tumor necrosis factor- $\alpha$ , ICAM-1, vascular VEGF and p-Akt in the retina of diabetic rats, and affect the Akt-VEGF signaling pathway by anti-inflammatory and reducing the adhesion of leukocytes to the diabetic retina<sup>[163]</sup>, while inhibiting peripapillary cell apoptosis and basement membrane thickening<sup>[164]</sup>. Dangui and its active ingredients were able to inhibit the VEGF- $\alpha$  pathway to improve the inflammatory response and apoptosis in the retina of diabetic rats <sup>[165]</sup>, and inhibit  $\alpha$ -glucosidase, protein tyrosine phosphatase 1B, rat lens aldose reductase, acetylcholinesterase, butyrylcholinesterase and  $\beta$ -site amyloid precursor protein cleaving enzyme 1 to exert antidiabetic effects<sup>[166]</sup>.

An interesting finding is that SDMM, QJDH and HXMM are all OCMs with the main effect of nourishing the Yin of the liver and kidney, and they all showed good results in lowering glucose. Chinese medicine theory believes that diabetes is a disease with Yin deficiency as the fundamental pathogenesis, and DR develops from diabetes, so the treatment should focus on replenishing Yin. *Ligustrum lucidum* (Nvzhenzi in Chinese) and *Ecliptae Herba* (Mohanlian in Chinese) are common components of HXMM and SDMM, which are widely used in China for the treatment of liver-kidney yin deficiency syndrome<sup>[167]</sup> ( A TCM pathological diagnostic pattern caused by the imbalance of yin and yang<sup>[168-170]</sup>, which is closely related to the development of diabetes<sup>[167]</sup> ). They were found to increase insulin sensitivity, enhance <sup>17</sup> the function of islet  $\beta$ -cells INS-1 and  $\beta$ -tc-6<sup>[171]</sup>, reduce retinal oxidative stress levels, repair diabetes-induced abnormal transcriptome<sup>[172]</sup>, improve retinal cell apoptosis<sup>[173]</sup>, inhibit NLRP3 inflammasome and autophagy signaling pathways<sup>[175]</sup>, regulate homocysteine pathway, reduce lipid

peroxidation and scavenge free radicals<sup>[176]</sup>, thereby reducing fundus microangiopathy and protecting normal retinal barrier function in diabetic mice. Meanwhile, SDMM was confirmed to be the most effective complementary and alternative drug for inhibiting VEGF in this study, exerting anti-VEGF effects by inhibiting VEGF-induced RF/6A cell tube formation<sup>[174]</sup>, inhibiting NF-κB activity to regulate advanced glycosylation end-product accumulation, oxidative stress and mitochondrial function, and thus improving retinal cell apoptosis by downregulating PKCδ, P47phox and ERK1/2<sup>[177,178]</sup>. QJDH is a very well known Chinese OCM for the treatment of eye diseases, which is composed of Liuwei Dihuang Pills (an ancient remedy with very good treatment of diabetes and its complications) plus *Chrysanthemi Flos* and *Lycii Fructus*, and has been shown to possibly inhibit the development of DR by interfering with multiple biological pathways such as regulation of response to insulin, glucose homeostasis, and angiogenesis<sup>[179]</sup>. It was found that *Lycii Fructus* extract and the active ligand taurine dose-dependently enhanced cell viability, reduced apoptosis, downregulated caspase-3 protein expression and caspase-3 enzymatic activity, and downregulated mRNA encoding pro-inflammatory mediators of MMP-9 and fibronectin as well as COX-2 and iNOS protein expression in human retinal epithelial cell lines after HG treatment in order to achieve a protective effect on human retinal epithelial cell lines under HG exposure, thereby delaying the progression of DR<sup>[180,181]</sup>. Several network pharmacological and experimental validations found that chemical components such as luteolin, kaempferol, beta-sitosterol, and thymol were able to improve apoptosis-related protein expression by regulating the NLRP/NOX4 signaling pathway, downregulate network hub genes of TNF, and other multibiological pathways, inhibit VEGF-induced RF/6A cell tube formation, and slow down the DR process<sup>[182-185]</sup>, and these chemicals were also found in *Chrysanthemi Flos*.

It is noteworthy that metabolic diseases, such as hyperglycemia, hyperlipidemia, and hypertension, serve as crucial risk factors contributing to the development of diabetic retinopathy (DR) <sup>[186]</sup>. Effective management of these risk factors is imperative in the prevention and treatment of DR. In this regard, incorporating exercise training and

neuromuscular electrical stimulation [187,188] can prove to be a valuable strategy. The guidelines<sup>13</sup> established by the American College of Sports Medicine and the American Diabetes Association emphasize the significance of initial guidance from a qualified exercise trainer for individuals with type 2 diabetes [189]. These guidelines advocate for the implementation of appropriate exercise training to optimize outcomes related to glycemic control, blood pressure, lipid levels, and cardiovascular risk management.

Despite the clear strengths of this study, there are some limitations. First, the quality of the included studies in this study warrants improvement, as most of them were short-term, single-center, and had small sample sizes. Second, clinical effectiveness, being a commonly used measure in clinical practice, may vary slightly in its definition across different randomized controlled trials, leading to a certain degree of heterogeneity in the results. And then, due to the relatively strict inclusion criteria applied in this study, some high-quality individualized TCM treatment studies were excluded, which may limit the comprehensive representation of the characteristics of TCM. Finally, the included literature lacked direct comparisons between different traditional Chinese medicines, and a closed loop was not formed in the evidence network, thereby allowing only indirect comparisons to assess the efficacy advantages and disadvantages of different interventions. Despite these limitations, the present study remains one of the most comprehensive studies available and holds significant clinical reference value.

This study aims to optimize patient outcomes by tailoring treatment strategies to each patient's unique condition. We recommend the utilization of SDMM+CT or HXMM+CT for treatment due to their demonstrated efficacy across multiple indicators. Specifically, HXMM+CT has shown greater effectiveness in improving patients' visual acuity, while SDMM+CT exhibits stronger inhibitory effects on VEGF. Furthermore, DGBX+CT has proven to be more effective in reducing FHA, HXMM+CT excels in reducing FBG, and QJDH+CT demonstrates superior efficacy in reducing HbA1c. Additionally, we suggest combining OCMs with western drugs for the treatment of DR, as this combination has been shown to yield superior outcomes compared to interventions with western drugs

alone. Hence, it is crucial to select appropriate treatment methods in clinical practice based on the individual circumstances of patients with DR to attain maximum benefits from combined Chinese and Western medicine interventions.

## **CONCLUSION**

This study provides evidence that combining OCMs with western drugs leads to better outcomes in all aspects of DR compared to using western drugs alone. Based on the findings, we highly recommend the use of SDMM or HXMM for the treatment of DR. These two OCMs have demonstrated outstanding efficacy across multiple indicators.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Diabetic retinopathy is one of the most important factors in adult blindness, yet rationalized DR treatment protocols are currently not systematically updated.

### ***Research motivation***

Current traditional Chinese medicine treatment options for diabetic retinopathy need to be re-evaluated.

### ***Research objectives***

To investigate which complementary alternative treatment with herbs is the most effective for the different clinical characteristics of DR patients.

### ***Research methods***

Alternative treatment options to TCM were incorporated and assessed by employing a mesh meta-analysis to prioritize the therapeutic effects of these options based on various clinical observations.

### ***Research results***

When these nine OCMs were analyzed in combination with conventional western medicine treatment (CT) compared with CT alone, the results showed that Hexue Mingmu Tablets has better intervention effect on the overall efficacy, visual acuity and reducing fasting blood glucose, Shuangdan Mingmu Capsules has better effect on inhibiting VEGF, Danggui Buxue Decoction has better effect on reducing fundus hemorrhage area, and Qiju Dihuang Pills has better effect on reducing glycated hemoglobin.

***Research conclusions***

SDMM or HXMM in combination with western drugs for DR may be the ideal treatment option.

***Research perspectives***

Bringing guidance to the clinical use of DR, as well as providing direction to basic experiments.

**ACKNOWLEDGEMENTS**

Special thanks to the National administration of Traditional Chinese Medicine for providing us with funding and support for this study.

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