Evaluation of Therapeutic Effect and Mechanism of Traditional Chinese Medicine on Non-Proliferative Diabetic Retinopathy

Xuedong an

China Academy of Chinese Medical Sciences Guanganmen Hospital <https://orcid.org/0000-0002-2787-1645>

De Jin

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Liyun Duan

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Yiru Zhao

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Shenghui Zhao

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Rongrong Zhou

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Yingying Duan

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Fengmei Lian

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Xiaolin Tong (✉ tongxiaolin66@sina.com)

China Academy of Traditional Chinese Medicine Guanganmen Hospital: China Academy of Chinese Medical Sciences Guanganmen Hospital

Research

Keywords: Traditional Chinese Medicine, Non-proliferative Diabetic Retinopathy, Efficacy, Safety, Mechanism

Posted Date: September 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-72183/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective: To review the therapeutic effect and mechanism of traditional Chinese medicine (TCM) on non-proliferative diabetic retinopathy (NPDR).

Methods: Randomized controlled studies (RCTs) on NPDR treatment with TCM was conducted by searching China National Knowledge Internet, Wanfang Database, Chinese Biomedical Literature Database, PubMed, EMBASE, Cochrane database. The search date was up to December 24, 2019. At the same time, the mechanism of NPDR with TCM include studies was conducted by searching China National Knowledge Internet, Wanfang Database, PubMed.

Results: 3208 related literatures were retrieved and 36 RCTs were included, including 3691 patients. The overall curative effect was significant [$n = 4028$, $RR 1.20 (1.16, 1.25)$, $P < 0.00001$, $I^2 = 35\%$] with Qiming granule, Compound Xueshuantong capsule, no matter treated with TCM alone or combined with chemical drugs, it could show significant advantages. At the same time, TCM can effectively improve the fundus, and vision, reduce macular thickness, and microangioma of NPDR patients. TCM can reduce the generation of vascular endothelial growth factor and improve the blood retinal barrier through polyol pathway, oxidative stress pathway, etc.

Conclusion: Our study shows that TCM has a significant effect on NPDR, and can significantly improve vision, reduce microangioma and macular thickness, and is safe. TCM mainly protects retinal neurons and blood retinal barrier through polyol pathway, which suggests that TCM can prevent macular edema and neovascularization in NPDR patients. However, in consideration of the quality of literature, the results of this study should be carefully considered.

1. Introduction

According to International Diabetes Federation, the number of diabetes mellitus (DM) in the world has reached 415 million, and by 2040, the total number will exceed 600 million. Compared with simple hyperglycemia, diabetic complications will bring more economic and social burden. Diabetic complications include macrovascular complications (such as cardiovascular disease, stroke) and microvascular complications (such as diabetic nephropathy, diabetic retinopathy (DR), diabetic peripheral neuropathy). DR is a continuous process of microcirculation, which has typical retinal microvascular damage, including microangioma, hemorrhage, hard exudation, neovascularization and many other pathological changes. According to the clinical guidelines for ophthalmology compiled by the American Academy of ophthalmology in 2006, DR is mainly divided into non-obvious diabetic retinopathy, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), which is often accompanied by diabetic macular edema (DME). The Wisconsin experimental study of diabetic retinopathy (WESDR) reported that about 75% of DM patients would develop to DR 10 years after diagnosis, while for those who developed DR at baseline, about two-thirds of patients developed more severe DR stage (1). With the rapid growth of DM incidence, the number of DR patients is expected to increase from 126.6 million in 2010 to 191 million in 2030 (2). For PDR patients, the quality of life, psychology and social behavior are affected to varying degrees, and more medical expenses are needed (3). The decrease of visual acuity often occurs in the late stage of DME or PDR, and DR is also one of the main causes of blindness in many countries (4).

The main causes of DR are duration of DM, heredity, hyperglycemia, hyperlipidemia and hypertension (5, 6). Five main pathogenic pathways have been identified in vivo and in vitro, including accumulation of advanced glycation end products, activation of polyol pathway, hexosamine pathway, protein kinase C pathway, and activation of poly polymerase. These pathways together induce oxidative stress, inflammation, microvascular dysfunction and mitochondrial damage, and then up regulate inflammatory mediators, transcription factors, chemokines and adhesion molecules, damage the blood retinal barrier, leading to the production of angiogenic growth factors (7). According to the current treatment, in the non-proliferative stage, the main treatment is oral drugs, including calcium dobesilate and intestinal kallidinogenase; in the proliferative stage, laser surgery often used, when accompanied with DME, anti-vascular endothelial growth factor (VEGF) are needed. But the real clinical research shows that there are still some disadvantages in the current treatment, such as oral drugs, not suitable for all patients, and the effect is not good; Laser surgery is a destructive treatment, which can only block the occurrence of blindness, and cannot improve the vision and fundus lesions of DR patients, although recent experiments show that laser therapy can actually improve the vision of some DR patients (8). A relatively high proportion of patients (46%) injected with anti-VEGF may still need local or grid laser therapy (9). Therefore, at present, the treatment task of NPDR is still very arduous, and it still needs a significant alternative drug for treatment.

TCM has a history of nearly 2000 years for the prevention and treatment of chronic diseases. TCM has made important progress in the treatment of DM and its complications. Now, many studies have shown that it can effectively reduce blood sugar and regulate blood fat (10), and can be used to treat DR and other diabetic complications (11). In view of the more and more extensive application of TCM in the treatment of DR, and there is no systematic evaluation of the effectiveness of TCM in the treatment of DR and the relevant mechanisms (12), so it is necessary to systematically review the existing evidence to clarify the potential benefits and hazards of TCM in the treatment of DR, so as to provide higher quality for clinical practice.

2. Methods

This study was conducted and reported in accordance with the preferred reporting project (PRISMA) guidelines for system evaluation and meta-analysis (13). The registration number is CRD4201913636363.

2.1 Retrieval Strategy and Data Sorting

We searched the related Randomized controlled trials (RCTs) in China National Knowledge Internet (CNKI), Wanfang Database, Chinese Biomedical Literature Database (CBM), PubMed, EMBASE, and Cochrane Database. Three aspects are considered: patients (NPDR), treatment (with TCM), and study type (RCTs). Free words & subject words are used, including "early or non-proliferative phase" and "diabetic retinopathy" and "randomized controlled trial or

randomized". If necessary, we would contact the author for more information. The retrieval date is until December 24, 2019. The title, abstract and full text of the reading research were selected, and the related work was completed by Xuedong An and Rongrong Zhou. Different opinions can be settled through consultation or consultation with Fengmei Lian.

2.2 Inclusion criteria

- ☐ RCTs;
- ☐ Type 2 DM patients and diagnosed as NPDR;
- ☐ The treatment group was treated with TCM, while the control group was not with TCM (including chemical drugs or none or placebo);
- ☐ The intervention time was 3 months (or 12 weeks) or more.

2.3 Data extraction

Data were extracted by Xuedong An and Rongrong Zhou respectively, including basic information such as gender, age, duration of disease, basic treatment, main outcome indicators (clinical efficacy, vision, microangioma, macular thickness, etc.), medication and dosage, intervention time, adverse reactions.

2.4 Assessment the risk of bias and the quality of evidence

The RCTs included in this evaluation were evaluated by Cochrane bias risk tool (CRBT), including random sequence generation, assignment concealment, blind method, incomplete data of results, selective reporting and other biases, and each of these aspects was evaluated as low, high or uncertain bias risk. Xuedong An and Rongrong Zhou independently applied CRBT to assess the bias risk of each study. Any dispute shall be solved through consultation with Fengmei Lian.

2.5 Statistics

All results were analyzed using Revman 5.2 software provided by Cochrane Collaboration (14). The results of continuous variables were analyzed by mean difference (MD) and 95% confidence interval (CI), while the results of classification were analyzed by relative risk (RR) and 95% CI, and I2 statistics were used to evaluate heterogeneity. If $I2 \leq 50\%$, the fixed effect model is used, $I2 > 50\%$, the random effect model is used. In addition, if the main outcome data is missing or the test is incomplete, the corresponding authors will be contacted. According to the Cochrane manual, funnel plots were used to assess potential publication bias (15).

2.6 Mechanism of TCM on NPDR

In CNKI, Wanfang Database and PubMed database, the mechanism of TCM on NPDR involved in the research is searched, and relevant information such as composition, main efficacy and mechanism of TCM are retained.

3. Results

3.1 Basic information and quality evaluation

In the literature search, 3208 articles were found (PubMed: 648, EMBASE: 480, Cochrane: 1346, CNKI: 461, Wanang: 155, CBM: 118) (Fig 1). According to the inclusion criteria, 36 articles were selected. The basic information of the studies is summarized in Table 1, including the diagnostic criteria for DM and NPDR, clinical efficacy evaluation criteria, outcome indicators, basic interventions, number of patients, gender, age, intervention measures and duration of the treatment group and the control group. In Table 2, the TCM included in the study include Qiming granules, Compound Xueshuantong capsules, Qizhen Jiangtang granules, Mimenghua Fang, Tangwangkang capsules, Quyadi capsules, Tincture of Ginkgo biloba leaves, Zhenwu Decoction, Compound Danshen dropping pills, Tangluotong capsules, Danshen injection, Yougui pills, Jinlida granules & Tongxinluo capsules, Qizhi Tongluo capsules & Qiju Dihuang pills, Danggui Buxue Decoction. According to the results of subgroup analysis of different TCM, the results were summarized. In Fig 2, the quality of the included studies was evaluated. Three of the included studies were of high quality (16-18), a total of 13 studies described random (16-28), and three studies adopted blind method (16-18).

Table 1 Basic characteristics of included studies

Reference	diagnostic criteria	Efficacy criteria	Outcome	Basic treatment	Number	Sex(M/F)	Age (years)	Intervention measures	Duration
SONG JT 2004(25)	1997 WHO	2002 GNCM	VisionFFA Fundus photography FFA	CBS	T:231	160/71	59.85±10.52	Qiming granule(4.5g tid)	3/6mo
	1985 SFC				C:111	40/51	59.29±7.62	CH(0.5g bid)	
LI R 2006(21)	1997 WHO	2002 GNCM	VisionFFA	CBS	T:30	NA	61.37±9.19	Tangwangkang capsule(1.5g tid)	3mo
	1985 SFC				C:24		59.33±10.91	CH(0.5g tid)	
DUAN JG 2005(18)	1999 WHO	2002 GNCM	VisionFFA Fundus photography	CBS	T:107	42/65	59.617±8.463	Qiming granule(4.5g tid) +CH placebo(0.5g bid)	3mo
	1984 FCDC				C:105	45/60	58.733±9.411	CH(0.5g bid)+ Qiming granule placebo(4.5g tid)	
WU L 2009(17)	NA	NA	curative effect	NA	T:20	11/9	55.04±7.05	Qihuangmingmu capsule (4 grains tid)+ CH (2 grains tid)	12w
	PPP				C:24	8/16	56.07±6.82	Qihuangmingmu capsule placebo(4 grains tid) + CH(2 grains tid)	
LIN WX 2011(29)	NA	2002 GNCM	VisionEOF	NA	T:60 120v	16/14	52.656	Compound Xueshuantong capsule2 grains tid	3mo
	1984 FCDC				C:3060 eyes	14/16	54	Pancreatic kininogenase120U tid	
ZANG LH 2011(30)	NA	2002 GNCM	VisionEOF FFA	NA	T:4182 eyes	48/34	36-63	Qiming granule 4.5g tid	3mo
	1984 FCDC				C:4182 eyes			CH0.5g tid	
YAN J 2013(31)	NA	2002 GNCM	VisionEOF FFA	NA	T:124	NA	NA	Mi Meng Hua Fang 0.5 agents bid	3mo
	1984 FCDC				C:121			CH0.5g,bid	
YANG L 2013(32)	1999 WHO	NA	VisionEOF	CBS	T:35	17/18	50.23±7.15	Qiming granule 4.5g tid	6mo
	1984 FCDC				C:36	18/18	50.94±8.01	—	
SUI HL 2014(33)	NA	NA	VisionEOF FFA	CBS	T:43	22/21	50.22±14.82	Qiming granule 4.5g tid	3mo
	NA				C:43	23/20	50.53±11.28	CH0.5g tid	
LIAN FM 2015(16)	NA	NA	FFAEOF	CBS	T:56	27/29	58.9±8.1	Compound Danshen dropping pills20 pills tid	12w
	AAO				C:56	25/31	58.9±7.6	Placebo20 pills tid	
LIU SL 2015(34)	NA	NA	curative effect	CBS	T:40	23/17	55.63±12.28	Qiming Jiangtang granules(10g tid)	6mo
	2002				C:40	21/19	57.15±13.62	VitC,vitb12Rutin Tablets	
KONG WJ 2015(35)	NA	DCOC	VisionEOF Retinal circulation time	NA	T:36	24/12	45.15±3.26	Qiming granule 4.5g tid	180d
	Practical Ophthalmology (3rd Edition)				C:36	22/14	46.77±4.06	CH (0.5g, tid)	
LI WJ 2015(24)	NA	GPTDF	VisionEOF	NA	T:38	32/44	57.4±2.8	CH(2 grains tid) + Qihuangmingmu capsule(4 grains,tid)	3mo

	PPP				C:38			CH(2 grains/tid)	
SHI JC	NA	SDCTC	VisionEOF	CBS	T:28	14/14	56.3±5.8	Quyidi capsule	24w
2015(36)	NA				C:28	15/13	54.3±4.6	—	
CHEN XL	NA	NA	VisionFFAEOF	NA	T:60 114 eyes	46/74	52	Whole retinal photocoagulation + Huo Xue Ming Mu Pian(1.5g/tid)	3mo
2016(19)	2001 International Conference on ophthalmology (Sydney)				C:60 112 eyes			Whole retinal photocoagulation	
ZHU CY	1999 WHO	NA	VisionFFA	CBS	T:4178 eyes	21/20	62.64±3.80	Aspirin enteric coated tablets(100mgqd)+ Tincture of Ginkgo biloba leaves(2ml tid)	6mo
2016(37)	2014 FOCMA				C:3972 eyes	20/19	61.37±5.63	Aspirin enteric coated tablets(100mgqd)	
LIU X	NA	NA	VisionEOF	CBS	T:49	55/43	65.6±2.9	CH(1gbid) or Pancreatic kininogenase(120IU tid)+ Zhenwu Decoction(0.5 agentsbid)	3mo
2016	DCCR				C:49			CH(1gbid) or Pancreatic kininogenase(120IU tid)	
YAO YK	NA	NA	VisionEOF	CBS, BP, blood lipid	T:40	22/18	51	CH(0.5g/tid) + Sanqi powder(2g/tid)	3mo
2016	1985 SFC				C:40	19/21	50	CH(0.5g/tid)	
SUN GX	1999 WHO	2002 GNCM	VisionEOF FFAOCT	NA	T:64 128 eyes	32/32	48.98±9.34	Compound Xueshuantong capsule(1.5g/tid)	6mo
2016	Global diabetic retinopathy project 2002				C:64(120 eyes	36/28	49.81±8.55	CH(600mg/tid)	
ZHANG Y	NA	NA	VisionEOF FFA	CBS	T:45	44/47	45-70	Qiming granule 4.5g/tid	6mo
2016	NA				C:46			—	
LUO D	1999 WHO	NA	Vision Fundus examination	Diet and sports education	T:3060 eyes	13/17	58.5	Tangluotong granules, 0.5 agents/tid	12w
2016	1985 SFC				C:3060 eyes	16/14	57.8	CH0.5g/tid	
XIAO LP	NA	NA	VisionSlit lamp Intraocular pressureEOF	CBS, Blood pressure, blood lipid	T:110 216 eyes	69/41	49.5±5.9	CH0.5g/0.25g/tid + Compound Xueshuantong capsule 3 capsules/tid	6mo
2016	1985				C:110 214 eyes	68/42	50.2±6.4	CH0.5g/0.25g/tid	
ZHENG Q	NA	NA	EOFmacular edema	NA	T:47	29/18	44.94±5.36	Qiming granule 4.5g/tid	180d
2016	NA				C:41	25/16	46.72±5.43	CH0.5g/tid	
WANG ZZ	NA	NA	curative effectVision Fundus photography Visual field sensitivity	Diet and sports education	T:4747 eyes	29/18	54.5±4.8	CH0.5g/tid + Qiming granule 4.5g/tid	3mo
2017	GDTDR				C:4747 eyes	26/21	54.3±4.9	CH0.5g/tid	

ZHANG Y 2017	1999 WHO	2002 GNCM	Vision EOF	CBS	T:40	24/16	48.55±11.17	Qizhen Jiangtang granules 1 bag tid	3mo
	2014 FOCMA				C:40	27/13	48.61±11.26	—	
DAI GL 2017	NA	NA	Vision EOF	CBS	T:40	45/35	52.24±4.75	CH 0.5g tid + Danhong injection 40ml qd	3mo
	NA				C:40			CH 0.5g tid	
LI C 2017	1999 WHO	NA	Vision Macular thickness	CBS	T:58	32/26	62.23±7.54	Photocoagulation + Compound Xueshuantong capsule 3 capsules tid	3mo
	NA				C:58	28/30	61.57±6.89	Photocoagulation	
HU XD 2017	NA	SDCTC	Vision EOF	NA	T:40	23/17	52.35±3.11	CH 2 tablets bid + Mi Meng Hua Fang 0.5 agents bid	3mo
	Practical Ophthalmology				C:40	24/16	52.31±3.07	CH 2 tablets bid	
YIN XD 2018	NA	NA	Vision EOF	CBS	T:50	24/26	54.63±5.28	CH 2 tablets tid + Qiming granule 4.5g tid	3mo
	NA				C:46	25/21	55.27±5.42	CH 2 tablets tid	
WEI G 2018	1999 WHO	2002 GNCM	Vision Fundus photography FFA	CBS	T:30	12/18	58.13±8.42	CH 0.5g tid + Jinlida granules(0.5g,tid) + Tongxinluo capsule(1.04g,tid)	12w
	1985 SFC				C:32	14/18	58.29±7.56	CH 0.5g tid	
LIU D 2018	NA	NA	curative effect	CBS	T:45	27/16	48.34±6.49	CH (500mg /250mg,tid)+ Compound Xueshuantong capsule(3 capsules tid)	3mo
	NA				C:45	25/20	48.56±7.64	CH (500mg /250mg, tid)	
YANG M 2018	NA	NA	Vision EOF	CBS	T:32	42/22	65.8±3.4	CH (1 tablets tid)or Pancreatic kininogenase(120IU tid) + YouguiWan(0.5 agents bid)	3mo
	2014 FOCMA				C:32			CH (1 tablets tid)or Pancreatic kininogenase(120IU tid)	
WANG Q 2018	NA	NA	curative effect	NA	T:44	22/22	57.8±6.2	CH 0.5g tid + Qiming granule 4.5g tid	3mo
	NA				C:44	18/26	58.4±7.5	CH 0.5g tid	
FAN YP 2018	NA	2002 GNCM	Macular thickness Retinal circulation time Vision	CBS	T:47 60 eyes	26/21	48.6±5.1	CH 0.5g tid + Qiming granule 4.5g tid	6mo
	Practical Ophthalmology				C:47 60 eyes	27/20	47.5±4.9	CH 0.5g tid	
LIU LW 2019	NA	2002 GNCM	Vision EOF Hemorheology	CBS	T:30	14/16	51.2±3.9	CH 0.5g tid + Qizhi Tongluo Capsule (4 pills, bid)+ Qiju Dihuang pill(8 pills, tid)	3mo
	2014 FOCMA				C:32	15/17	52.5±5.1	CH 0.5g tid	
SUN XH,2019	GPTDC	2002 GNCM	Vision Fundus examination	CBS	T:48 92 eyes	30/18	55.9±3.5	CH 0.5g tid + Danggui Buxue Decoction(0.5 agents bid)	3mo

NA	macular edema	C:48% eyes	31/17	55.3±3.7	CH0.5g/tid
----	---------------	---------------	-------	----------	------------

Abbreviation: 1999 WHO (1999 world health organization diagnostic Standard); 2002 GNCM (Guiding principles for clinical research of new Chinese Medicine); DCOC:Diagnostic criteria for clinical efficacy of ophthalmology in China; GPTDF:Guidelines for the prevention and treatment of diabetic fundus diseases; SDCTC :The standard of diagnosis and curative effect of traditional Chinese Medicine; AAO :American Association of Ophthalmology, 2006; GPTDC: Guidelines for the prevention and treatment of type 2 diabetes in China (2017); GDTDR:Guidelines for clinical diagnosis and treatment of diabetic retinopathy in China ; DCDR :Diagnostic criteria of diabetic retinopathy;EOFexamination of ocular fundus; SFC:The standard of fundus diseases group in China; FCDC: The first Chinese Fundus Disease ConferenceFOCMA:Fundus lesions group, ophthalmology society, Chinese Medical Association; CH:Calcium hydroxybenzenesulfonate; CBS:Control blood sugar;PPP: Preferred Practice Pattern;BP: blood pressure;BL: blood lipidTTTest groupC: control group;

Table 2 Composition and function of included TCM

TCM	Compose	Main functions	Reference	Results (efficiency)
Qiming granule	<i>Astragaluspropinquus</i> Schischkin❏ <i>Puerariamontana</i> var. <i>lobate</i> (Willd.) Sanjappa & Pradeep❏ <i>Rehmannia glutinosa</i> (Gaetn.) Libosch. ex Fisch. et Mey.❏FRUCTUS LYCI❏Seed of <i>Cassia tora</i> Linn❏Seed of <i>Leonurus japonicus</i> Houtt.❏ <i>Typha angustifolia</i> L.❏ <i>Whitmania pigra</i> Whitman	Replenishing qi and promoting body fluid, nourishing liver and kidney, clearing collaterals and brightening eyes	(18, 20, 25, 27, 30, 32, 33, 35, 38-41)	n=1594❏ RR 1.30 (1.18, 1.43), P<0.00001, I2=67%
Compound Xueshuantong capsule	<i>Panaxnotoginseng</i> (Burk.)F.H.Chen❏ <i>Astragaluspropinquus</i> Schischkin❏ <i>Salvia miltiorrhiza</i> Bge.❏ <i>Scrophularia ningpoensis</i> Hemsl.	Promoting blood circulation and removing blood stasis, benefiting qi and nourishing yin	(17, 22, 24, 26, 29, 42, 43)	n=1064❏ RR 1.20 (1.12, 1.29), P<0.00001, I2=0%
Qizhen Jiangtang granules	<i>Astragaluspropinquus</i> Schischkin❏ <i>Ligustrum thibeticum</i> Decne.❏ <i>Cornus officinalis</i> Sieb. et Zucc.❏ <i>Coptis chinensis</i> Franch.❏ <i>Rhus chinensis</i> Mill.	Nourishing liver and kidney	(34, 44)	n=160❏ RR 1.32 (1.11, 1.58), P=0.002, I2=0%
Mi Meng Hua Fang	<i>Buddleja officinalis</i> Maxim.❏ <i>Coptis chinensis</i> Franch.❏ <i>Cinnamomum cassia</i> Presl❏ <i>Astragaluspropinquus</i> Schischkin❏ <i>Ligustrum thibeticum</i> Decne.❏ <i>Leonurus artemisia</i> ❏Laur. ❏S. Y. Hu F	Invigorating qi and Yin, promoting blood circulation and eyesight	(45)	NA
Tangwangkang capsule	<i>Astragaluspropinquus</i> Schischkin❏ <i>Ligustrum thibeticum</i> Decne.❏ <i>Angelica sinensis</i> ❏ <i>Salvia miltiorrhiza</i> Bge.❏ <i>Carthamus tinctorius</i> L.❏FRUCTUS LYCI❏ <i>Panaxnotoginseng</i> (Burk.)F.H.Chen❏ <i>Ligusticum chuanxiong</i> hort	Invigorating Qi, nourishing Yin, removing blood stasis and brightening eyes	(21)	NA
Quyidi capsule	<i>Astragaluspropinquus</i> Schischkin❏ <i>Panax ginseng</i> C. A. Mey.❏ <i>Rehmannia glutinosa</i> (Gaetn.) Libosch. ex Fisch. et Mey.❏ <i>Atractylodes lancea</i> (Thunb.) DC.❏ <i>Poria cocos</i> (Schw.) Wolf❏ <i>Scrophularia ningpoensis</i> Hemsl.❏ <i>Polygonatum sibiricum</i> ❏ <i>Polygonatum odoratum</i> ❏Mill.❏Druce❏ <i>Pinellia ternata</i> ❏Broiled❏ <i>Coptis chinensis</i> Franch.❏ <i>Whitmania pigra</i> Whitman❏ <i>Scolopendridae</i>	Invigorating Qi, nourishing Yin, promoting blood circulation and eliminating phlegm	(36)	NA
Tincture of Ginkgo biloba leaves	<i>Ginkgo biloba</i> L.	Promoting blood circulation, removing blood stasis and unblocking collaterals	(37)	NA
Zhenwu Decoction	<i>Poria cocos</i> (Schw.)Wolf❏ <i>Paeonia lactiflora</i> Pall.❏ <i>Zingiber officinale</i> Roscoe❏ <i>Aconitum camichaelii</i> Debx❏ <i>Atractylodes macrocephala</i> Koidz.	Warming Yang, benefiting qi and benefiting water	(46)	NA
Compound Danshen Dropping Pill	<i>Panaxnotoginseng</i> (Burk.)F.H.Chen❏ <i>Salvia miltiorrhiza</i> Bge.❏ <i>Borneolum</i> Syntheticum	Promoting blood circulation and removing blood stasis, regulating qi and relieving pain	(16)	NA
Tangluotong granules	<i>Rehmannia glutinosa</i> (Gaetn.) Libosch. ex Fisch. et Mey.❏ <i>Dioscoreaoppositifolia</i> L.❏ <i>Panax quinquefolius</i> ❏ <i>Cornus officinalis</i> Sieb. et Zucc.❏CORTEX MOUTAN❏ <i>Cuscuta chinensis</i> Lam.❏ <i>Cistanche deserticola</i> Ma❏ <i>Angelica sinensis</i> ❏ <i>Leonurus artemisia</i> ❏Laur. ❏S. Y. Hu F❏twig of <i>Winged Euonymus</i> ❏ <i>Ligustrum thibeticum</i> Decne.❏FRUCTUS LYCI❏ <i>Panaxnotoginseng</i> (Burk.) F.H.Chen	Invigorating Qi, nourishing Yin, promoting blood circulation and removing stasis	(47)	NA
Danhong injection	<i>Salvia miltiorrhiza</i> Bge.❏ <i>Carthamus tinctorius</i> L.	Promoting blood	(48)	NA

			circulation and removing blood stasis		
You Gui pill	Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. Aconitum carmichaeli Debx. Cinnamomum cassia Presl Dioscorea oppositifolia L. Cornus officinalis Sieb. et Zucc. processing with wine Cuscuta chinensis Lam. Colla Corni Cervi FRUCTUS LYCII Angelica sinensis Eucommia ulmoides Oliver Salt making		Warming the kidney yang, filling the essence and stopping the remaining	(28)	NA
Jinlida granule, Tongxinluo capsule	Panax ginseng C. A. Mey. Polygonatum sibiricum Atractylodes lancea (Thunb.) DC. bran-fry Radix Sophorae Flavescentis Ophiopogon japonicus (Linn. f.) Ker-Gawl. Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. Cinnamomum cassia Presl Fallopia multiflora (Thunb.) Harald. Cornus officinalis Sieb. et Zucc. Poria cocos (Schw.) Wolf Eupatorium fortunei Turcz. Coptis chinensis Franch. Anemarrhena asphodeloides Bunge. Epimedium brevicornu Maxim. Salvia miltiorrhiza Bge. Pueraria montana var. lobata (Willd.) Seed of Litchi chinensis Sonn. Lycium chinense Mill. Panax ginseng C. A. Mey. Whitmania pigra Whitman Buthus martensii Karsch Paeonia lactiflora Pall. Periostracum Cicadae Eupolyphaga sinensis Walker Scolopendridae Santalum album L. Dalbergia odorifera T. Chen Boswellia carterii Birdw. Seed of Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chow Borneolum Syntheticum		Invigorating qi and Yin, strengthening the spleen and promoting the circulation of Tianjin Invigorating qi and promoting blood circulation, unblocking collaterals and relieving pain	(49)	NA
Qizhi Tongluo capsule, Qiju Dihuang Pill	Whitmania pigra Whitman Geosaurus Buthus martensii Karsch Eupolyphaga sinensis Walker Bombyx mori Linnaeus Borneolum Syntheticum Astragalus propinquus Schischkin Salvia miltiorrhiza Bge. Carthamus tinctorius L. Aconitum gymnanthum Maxim. Curcuma renyujin Y. H. Chen et C. Ling Angelica sinensis Spatholobus suberectus Dunn Panax ginseng C. A. Mey. Rhizoma Arisaematis Cum Bile Paeonia lactiflora Pall. Gastrodia elata Bl. Curcuma longa L. Ligusticum chuanxiong hort. Ilex pubescens Hook. et Arn. Ophiopogon japonicus (Linn. f.) Ker-Gawl. Schisandra chinensis Turcz. Baill. Fructus Gleditsiae Abnormalis Notopterygium incisum Ting ex H. T. Chang Cinnamomum cassia Presl Fallopia multiflora (Thunb.) Harald. FRUCTUS LYCII Dendranthema morifolium Ramat. Tzvel. Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. Cornus officinalis Sieb. et Zucc. CORTEX MOUTAN Dioscorea oppositifolia L. Poria cocos (Schw.) Wolf Alisma plantago-aquatica Linn.		Invigorating Qi, promoting blood circulation and unblocking collaterals Nourishing the kidney and nourishing the liver	(23)	NA
Danggui Buxue Decoction	Astragalus propinquus Schischkin Angelica sinensis		Invigorating qi and generating blood	(50)	NA

Abbreviation: NA:Not applicable.

3.2 Outcome

3.2.1 Overall efficacy

3.2.1.1 Subgroup analysis based on different TCM

The data were statistically analyzed by the random effect model. The results showed that the total curative effect of TCM in the treatment of NPDR was significant [n = 4028, RR 1.20 (1.16, 1.25), P < 0.00001, I² = 35%], among which Qiming granule, Compound Xueshuantong capsule, Qizhen Jiangtang capsule, Mimenghua formula, Zhenwu Decoction, Danggui Buxue Decoction showed obvious therapeutic advantage, Qihuang Mingmu capsule, Tangwangkang capsule, Quyadi capsule, Tincture of Ginkgo biloba leaves, Danhong injection, Yougui Pill, Jinlida granule & Tongxinluo capsule, Qizhi Tongluo Capsule & Qiju Dihuang pill had no significant effect. (Fig 3)

3.2.1.2 Subgroup analysis on the combined use of drugs

The data were statistically analyzed by fixed effect model. The results showed that the total effect of TCM or with other treatment measures (including calcium dobesilate, aspirin, photocoagulation, calcium dobesilate or pancreatic kininogenase) on the treatment of NPDR was significant [n = 4028, RR 1.21 (1.17, 1.25), P < 0.00001, I² = 35%], TCM alone, or plus calcium hydroxybenzene sulfonate, or photocoagulation, or calcium hydroxybenzene sulfonate or Pancreatic Kallidinogenase showed significant effect, among which Tincture of Ginkgo biloba leaves & aspirin had no significant effect. (Fig 4)

3.2.2 Fundus effect

The results of fundus efficacy showed heterogeneity (I² = 93%). The data were statistically analyzed by random effect model. The results showed that the efficacy of TCM in the treatment of fundus was significant [n = 1901, RR 1.38 (1.15, 1.67), P = 0.0008, I² = 93%]. (Fig 5)

3.2.3 Vision

The results of vision showed heterogeneity (I² = 93%). The data were statistically analyzed by random effect model. The results showed that TCM treatment could significantly improve the vision of NPDR patients [n = 806, MD 0.17 (0.08, 0.25), P = 0.0002, I² = 93%]. (Fig 6)

3.2.3 Macular thickness

The results of macular thickness showed heterogeneity ($I^2 = 94\%$). The data were statistically analyzed by random effect model. The results showed that TCM could significantly reduce macular thickness of the NPDR patients [$n = 396$, $md-19.33$ ($- 32.24, - 6.41$), $P = 0.003$, $I^2 = 94\%$]. (Fig 7)

3.2.4 Microangioma

The results of microangioma showed heterogeneity ($I^2 = 95\%$). The data were statistically analyzed by random effect model. The results showed that TCM could significantly reduce the micro angioma of NPDR patients [$n = 352$, $md-1.40$ ($- 2.15, - 0.65$), $P = 0.0002$, $I^2 = 95\%$]. (Fig 8)

3.2.5 Retinal circulation time

The results of retinal circulation time showed heterogeneity ($I^2 = 77\%$), and the random effect model was used. The results showed that the effect of TCM on retinal circulation time was not significant [$n = 280$, $md-0.34$ ($- 0.86, - 0.18$), $P = 0.20$, $I^2 = 77\%$]. (Fig 9)

3.2.6 Adverse events

A total of 15 studies mentioned adverse events (16-18, 20, 21, 25, 26, 33, 38, 39, 43-45, 49, 50) and 9 studies reported adverse events (16, 18, 20, 21, 25, 44, 45, 49, 50). The results showed heterogeneity ($I^2 = 29\%$), and the data were statistically analyzed with fixed effect model. The results showed that TCM was safer [$n = 1243$, $MD 0.45$ ($0.29, 0.69$), $P = 0.0002$, $I^2 = 29\%$]. (Fig 10)

3.3 Publication bias

The funnel chart shown in Fig 11 and Fig 12 is basically symmetrical, indicating the potential publication bias. Unpublished research may be considered a factor in publication bias.

3.3 Mechanism summary

The mechanism included in the treatment of NPDR with TCM mainly involves the intervention of polyol pathway (Qiming granules), oxidative stress (Compound Xueshuantong capsule, Qihuangmingmu capsule, Qiju Dihuang pill), reduction of VEGF (Compound Xueshuantong capsule, Qihuangmingmu capsule, Danhong injection), reduction of neuron damage (Mimenghua formula, Tincture of Ginkgo biloba leaves, Danhong injection), and improvement blood retinal barrier, reduce capillary permeability (Tangwangkang capsule, Tongxinluo capsule, Dangguibuxue Decoction), reduce advanced glycosylation accumulation (Qizhen Jiangtang granules), inflammation (Tongxinluo capsule).(Table 3, Fig 13)

Table 3 Mechanism of TCM in treating DR

TCM	Mechanism
Qiming granule	Qiming granule can reduce the content of malondialdehyde in serum and retina, increase the activity of superoxide dismutase and glutathione peroxidase(51), inhibit the abnormal activity of polyol pathway in retina of diabetic rats, promote the increase of inositol synthesis, reduce the content of sorbitol, glucose and fructose (52), and reduce the expression of collagen IV in retinal vascular basement membrane(53).
Compound xueshuantong capsule	Compound xueshuantong capsule can reduce oxidative stress injury, decrease the expression of bioactive factor, VEGF and inducible nitric oxide synthetase, and up regulate the expression of pigment epithelium derived factor (54, 55)[]
Qihuangmingmu capsule	Qihuangmingmu capsule can inhibit the expression of VEGF, recombinant human VEGF receptor-1, fetal liver kinase-1, transforming growth factor - β , insulin-like growth factor-I in diabetic mice, interfere with the signal transduction pathway of VEGF receptor, inhibit the phosphorylation level of p38 mitogen activated protein kinase (56-58), and reduce the visual net of diabetic mice expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin (59).
Mimenghua formula	Mimenghua formula can reduce the damage of retinal nerve cells in early stage of diabetic rats through the mechanism of glutamate and sigma-1r (60, 61); the serum containing Mimenghua formula can inhibit the apoptosis and damage of retinal ganglion-5 cells under the condition of high glucose, and its mechanism may be related to the regulation of brain-derived neurotrophic factor, the expression of ciliary neurotrophic factor and sigma-1r (62).
Tangwangkang capsule	Tangwangkang capsule can reduce blood glucose and capillary permeability of rats (63)[]
Qizhen Jiangtang granule	Qizhen Jiangtang granule can reduce blood glucose, increase superoxide dismutase level and reduce the accumulation of advanced glycation end products (64)[]
Quyidi capsule	None
Tincture of Ginkgo biloba leaves	Ginkgo biloba extract can effectively protect retinal ganglion cells, which may be related to the activation of NF-E2-related factor 2 / extracellular regulatory protein kinase pathway and the expression of Bcl-2 and p53 protein (65); increase the expression level of matrix metalloproteinase 9 and inducible nitric oxide synthetase, and reduce the damage of retinal ganglion cells (66).
Zhenwu Decoction	None
Tangluotong granules	None
Danhong injection	Danhong injection improves retinal ischemia and hypoxia by reducing VEGF, reduces retinal neovascularization, and can reduce retinal nerve cell apoptosis to a certain extent (67).
Jinlida granule & Tongxinluo capsule	Jinlida granules: None. Tongxinluo capsule can reduce the pathological damage of retina in diabetic mice, and its mechanism may be related to the reduction of p38 mitogen-activated protein kinase protein phosphorylation (68); Expression can improve retinopathy (69); can significantly improve retinopathy in KK / Upj-Ay mice, with inhibition inhibitor of nuclear factor kappa-B kinase / human nuclear factor kappa inhibitory protein α / NF-kB (IKK β / IKBa / NF-kB pathway (70-72).
Qizhi Tongluo Capsule & Qiju Dihuang Pills	Qizhi Tongluo Capsule: None; Qiju Dihuang Pills can significantly prove retinopathy in rats by increasing antioxidant enzyme activity and inhibiting aldose reductase activation (73).
Danggui Buxue Decoction	Danggui Buxue Decoction can reduce blood-retinal barrier leakage in GK rats (74).

Abbreviation: QM: Qiming granule; QZJT: Qizhen Jiangtang Capsule; CXST: Compound Xueshuantong capsule; QHMM: qihuangmingmu capsule; TXL: Tongxinluo capsule; MMH: mimenghua formula; DHI: Danhong injection; TGBL: ginkgo leaf tincture; PARP: Poly ADP ribose polysaccharide

4. Discussion

In this study, 3208 related literatures were retrieved, and 36 studies were selected according to patients (NPDR), treatment (TCM), and studies (RCTs). The overall quality of literatures was low, including 3 literatures (16-18), which described not only randomization, but also placebo control and blind operation, and the results were more representative. All the therapeutic effects included in the study were more focused on the improvement of overall symptoms (including vision, fundus hemorrhage, retinal microangioma, etc.). Based on the subgroup analysis of different TCM or combined with chemical drugs, although the overall results show that the curative effect is significant, the results of Qihuang Mingmu capsule, Tangwangkang capsule, Quyidi capsule, Tincture of Ginkgo biloba leaves, Danhong injection, Yougui Pill, Jinlida granule & Tongxinluo capsule, Qizhi Tongluo Capsule & Qiju Dihuang pill are all efficacy but not significant, which may not be connected with the number of cases included in the study is less related. After treatment with TCM, the results of fundus effect (including hemorrhage, microangioma), vision, macular thickness, microangioma were significant, but not including retinal circulation time. Because of the lack of literature, subgroup analysis was not conducted. A total of 15 studies mentioned adverse events, 9 studies had adverse events, the results show that the application of TCM safety, but the relevant literature did not trace the causes of adverse events. Publication bias analysis of the overall efficacy showed that funnel diagram was basically symmetrical, and there might be potential publication bias. Finally, the mechanism of TCM in the treatment of DR was summarized, which showed that the main ways of action of TCM include polyol pathway, oxidative stress, VEGF reduction, neuron damage reduction, improvement of blood retinal barrier, AGEs reduction, inflammation and so on. On the whole, TCM is effective and safe in the treatment of NPDR, and its mechanism is diversified, which provides an alternative treatment for clinical treatment of NPDR.

Comparison of similar studies

A meta-analysis was conducted to evaluate the efficacy and harm of single TCM on DR, involving 754 participants. The evaluation indexes were progression of DR, vision, retinal microangioma and hemorrhage, glycosylated hemoglobin-1c and adverse events. The results showed that single TCM could significantly improve vision, while only a few studies have reported adverse events. In conclusion, based on the current evidence, the effect of single TCM on DR was inconclusive (75).

Based on the analysis of TCM compound prescription, we selected the more standardized and representative TCM for evaluation for the first time, and added additional information, including the composition of TCM, the mechanism of TCM on NPDR. In view of the increasing number of patients with NPDR, at the same time, there is still no safe and effective treatment for NPDR, including targeted treatment (calcium dobesilate) or treatment for risk factors (hypoglycemia, hypotension, etc.), which can be widely used in clinical. Our results show that TCM (including Qiming granule, Compound xueshuantong capsule, Compound Danshen dropping pill, etc.) can significantly improve NPDR in vision, microangioma, macular thickness, and can play a role through polyol pathway, oxidative stress pathway, etc. This provides a series of alternative treatment measures for clinical treatment of NPDR.

Limitations

Limitations of statistical methods: Due to the lack of information provided by the included studies, or the possibility of selective reports in many studies, it is not possible to conduct subgroup analysis on the risk factors of the population, and it is not clear that the precise applicable population included in the TCM. For example, we don't know the applicable population, with which risk factors, of Qiming granules. At the same time, many studies just discussed the efficacy, including the improvement of vision, fundus, and so on. The baseline level and diagnostic criteria of the patients were also different, but there were significant statistical differences compared with the control group, which also showed that TCM treatment still had significant efficacy.

Limitations of the inclusion studies: Although the inclusion study describes the randomization and we tried to eliminate the false randomization, some included studies may still with incorrect randomization. At the same time, most of the studies did not have placebo control, which could not exclude the placebo effect. None of the included studies had long-term follow-up results, and then to evaluate the long-term efficacy of TCM on NPDR.

Future perspective

In view of the problem that DR still brings us huge social and economic burden, early screening is the most important, and more effective therapeutic drugs still need to be developed. For the curative effect of TCM, although it is concluded that TCM can treat NPDR effectively and safely. But the quality of literature is low, and there is still a lack of large-scale and long-term follow-up RCTs to evaluate the long-term benefits of TCM on NPDR. More clinical data are needed to support the clinical effectiveness and mechanism of action of TCM on NPDR.

Conclusion

Our study shows that TCM has a significant effect on NPDR, which can significantly improve vision, reduce microangioma and macular thickness, and is safe. TCM mainly protects retinal neurons and blood retinal barrier through polyol pathway, AGEs pathway, oxidative stress, inflammation and other pathways, which has obvious protective effects on DME and neovascularization. However, in consideration of the quality of literature, the results of this study should be carefully considered.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

None

Author contributions

XLT and FML designed the review protocol. DJ and LYD carried out the literature search. RRZ and XDA contributed to data extraction and quality assessment. YRZ, YYD and SHZ provided statistical supports for meta-analysis. All authors approved the final version of the manuscript.

Competing Interests

Not Applicable

Funding section

This work was supported by the National Public Welfare Industry Special (201507001-11), National Traditional Chinese Medicine Administration of Traditional Chinese Medicine Science and Technology Research Project (2016ZX03). The funders had no role in the study design, data collection, data

analysis, interpretation, or writing of the report.

Acknowledgements

Not Applicable

References

1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1984;102(4):520-6.
2. Zheng Y, He M, Congdon N. The worldwide epidemic of diabetic retinopathy. *Indian J Ophthalmol*. 2012;60(5):428-31.
3. Fenwick EK, Pesudovs K, Rees G, Dirani M, Kawasaki R, Wong TY, et al. The impact of diabetic retinopathy: understanding the patient's perspective. *The British journal of ophthalmology*. 2011;95(6):774-82.
4. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *The New England journal of medicine*. 2012;366(13):1227-39.
5. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556-64.
6. Perrone L, Matrone C, Singh LP. Epigenetic modifications and potential new treatment targets in diabetic retinopathy. *J Ophthalmol*. 2014;2014:789120.
7. Wang JH, Ling D, Tu L, van Wijngaarden P, Dusting GJ, Liu GS. Gene therapy for diabetic retinopathy: Are we ready to make the leap from bench to bedside? *Pharmacol Ther*. 2017;173:1-18.
8. Aiello LP, Edwards AR, Beck RW, Bressler NM, Davis MD, Ferris F, et al. Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2010;117(5):946-53.
9. Elman MJ, Qin H, Aiello LP, Beck RW, Bressler NM, Ferris FL, 3rd, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119(11):2312-8.
10. Yu X, Xu L, Zhou Q, Wu S, Tian J, Piao C, et al. The Efficacy and Safety of the Chinese Herbal Formula, JTTZ, for the Treatment of Type 2 Diabetes with Obesity and Hyperlipidemia: A Multicenter Randomized, Positive-Controlled, Open-Label Clinical Trial. *Int J Endocrinol*. 2018;2018:9519231.
11. Lian F, Wu L, Tian J, Jin M, Zhou S, Zhao M, et al. The effectiveness and safety of a danshen-containing Chinese herbal medicine for diabetic retinopathy: a randomized, double-blind, placebo-controlled multicenter clinical trial. *Journal of ethnopharmacology*. 2015;164:71-7.
12. Vasant More S, Kim IS, Choi DK. Recent Update on the Role of Chinese Material Medica and Formulations in Diabetic Retinopathy. *Molecules*. 2017;22(1).
13. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *Jama*. 2015;313(16):1657-65.
14. Godlee F. The Cochrane collaboration. *BMJ (Clinical research ed)*. 1994;309(6960):969-70.
15. Furlan AD, Pennick V, Bombardier C, van Tulder M. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine*. 2009;34(18):1929-41.
16. Lian F, Wu L, Tian J, Jin M, Zhou S, Zhao M, et al. The effectiveness and safety of a danshen-containing Chinese herbal medicine for diabetic retinopathy: a randomized, double-blind, placebo-controlled multicenter clinical trial. *Journal of ethnopharmacology*. 2015;164:71-7.
17. Wu L, Yan F, Su H, Jian L. Clinical study of qihuangmingmu capsule in the treatment of non proliferative diabetic retinopathy. *Chinese Journal of Ophthalmology of traditional Chinese Medicine*. 2009;19(02):74-8.
18. Duan J, Liao P, Wu L, Li Y, Yu Y, Qiu B, et al. Multi center clinical study on the treatment of diabetic retinopathy with Qiming granule. *Journal of Chengdu University of traditional Chinese Medicine*. 2006(02):1-5.
19. Chen XL, Tao LM, Xu Y, Zhou Q. Effect of 532nm laser combined with a traditional Chinese patent drug in the treatment of severe non proliferative diabetic retinopathy. *International eye science*. 2016;16(12):2268-71.
20. Fan Y, Li Y, Chen G, Wang H, Li Y. Effect and safety of Qiming Granule on non proliferative diabetic retinopathy. *International Journal of Ophthalmology*. 2018;18(12):2260-3.
21. Li R. The clinical effect of Tangwangkang Capsule on simple Dr [master]: xinjiang medical university; 2006.
22. Liu D, Zhou Q, Zhang Y. The effect of compound Xueshuantong combined with calcium hydroxybenzoate on the levels of HIF-1 α and SDF-1 in non proliferative diabetic retinopathy. *Hebei medicine*. 2018;40(12):1838-41.
23. Liu L. Qizhi Tongluo capsule and Qiju Dihuang Pill in the treatment of non proliferative diabetic retinopathy. *Guangming Chinese Medicine*. 2019;34(14):2152-4.
24. Li J. Qihuangmingmu capsule in the treatment of 38 cases of non proliferative diabetic retinopathy. *Hunan Journal of traditional Chinese Medicine*. 2015;31(03):72+83.
25. Song J. Qiming granule in the treatment of diabetic retinopathy [doctor]: Chengdu University of TCM; 2004.
26. Sun G. Clinical observation on the therapeutic effect of compound Xueshuantong Capsule on non proliferative diabetic retinopathy [master]: zhejiang chinese medical university; 2016.

27. Wang Q. Effect of Qiming Granule on nonproliferative diabetic retinopathy. *Shenzhen Journal of Integrated Chinese and Western Medicine*. 2018;28(10):48-9.
28. Yang M, Luo X, Kang L, Guo M. Clinical observation on the treatment of non proliferative retinopathy of type 2 diabetes mellitus with YouguiWan. *Chinese Journal of traditional Chinese Medicine*. 2018;36(07):1613-6.
29. Lin WX, Zang J, Bao JL, Zhou BB, Zhu YD, Li Q. Clinical study of the combined application of xueshuantong complex capsule and pan-creokinin on nonproliferative diabetic retinopathy. *International journal of ophthalmology*. 2011;11(4):625-7.
30. Zang L, Yang Y. Effect of Qiming Granule on non proliferative diabetic retinopathy. *Shaanxi Chinese Medicine*. 2011;32(04):429-30.
31. Yan J, Gao J, Jie C, Guo X, Jin M, Xu B, et al. Study on the effect of MI Meng Hua Fang on non proliferative diabetic retinopathy. *World Journal of Integrated Chinese and Western Medicine*. 2013;8(03):246-8.
32. Yang L, Zhang G, Quan X, Jia N. Qiming granule in the treatment of non proliferative diabetic retinopathy. *Journal of Aerospace Medicine*. 2013;24(06):686-7.
33. Sui H, Yu C, Xue H, Wang R. Clinical observation of Qiming granule combined with calcium dobesilate capsule in the treatment of non proliferative diabetic retinopathy. *Chinese medical innovation*. 2014;11(20):99-102.
34. Liu S. Clinical observation of Qizhen Jiangtang granule in the treatment of nonproliferative diabetic retinopathy with deficiency of liver and kidney yin. *Introduction to traditional Chinese Medicine*. 2015;21(22):64-6.
35. Kong W, Shan J. Effect of Qiming Granule on non proliferative diabetic retinopathy. *Pharmacology and clinic of traditional Chinese Medicine*. 2015;31(05):145-7.
36. Shi J, Qiu Y, Han Y, Li D, Zhang Z. Clinical observation of quyidi capsule in 56 cases of nonproliferative diabetic retinopathy. *New world of diabetes*. 2015(11):40-1.
37. Zhu CY, Yi Q, Ma JL, Wei QP. Clinical evaluation of Ginkgo biloba extract for diabetic retinopathy. *International eye science*. 2016;16(2):361-4.
38. Wang ZZ. Qi Ming granule combined with calcium dobesilate in treatment of non-proliferative diabetic retinopathy. *International eye science*. 2017;17(4):702-5.
39. Yin X. Efficacy and safety of Qiming granule combined with calcium dobesilate in the treatment of nonproliferative diabetic retinopathy. *Medical theory and Practice*. 2018;31(01):83-4.
40. Zhanb Y, Ma J, Wang C. Effect of Qiming Granule on non proliferative diabetic retinopathy. *Chinese Practical Medicine*. 2016;11(12):151-2.
41. Zheng Q. Effect of Qiming Granule on non proliferative diabetic retinopathy. *Modern drug application in China*. 2016;10(17):181-2.
42. Li C, Qiao S. 58 cases of non proliferative diabetic retinopathy treated by retinal laser photocoagulation combined with compound Xueshuantong. *Western Traditional Chinese Medicine*. 2017;30(10):90-2.
43. Xiao L. Clinical effect of compound Xueshuantong combined with calcium dobesilate in the treatment of non proliferative diabetic retinopathy. *Jilin medicine*. 2016;37(09):2254-5.
44. Zhang Y. Clinical study on Qi Zhen Jiang Tang granule in the treatment of non proliferative liver kidney yin deficiency of diabetic retinopathy. *Journal of traditional Chinese Medicine*. 2017;32(12):2354-8.
45. Hu X, Ren F, Nan Y. Observation on the curative effect of the combination of MI Meng Hua Fang and calcium dobesilate capsule in the treatment of non proliferative diabetic retinopathy. *Journal of modern integrated Chinese and Western Medicine*. 2017;26(18):1945-7+51.
46. Liu X, Li X. Clinical observation of Zhenwu Decoction in the treatment of non proliferative retinopathy of type 2 diabetes mellitus. *Chinese herbal medicine*. 2016;39(02):431-3.
47. Luo D, Xu Y. Therapeutic effect of Tangluotong Granule on non proliferative diabetic retinopathy. *Journal of practical Chinese Medicine*. 2016;32(10):955-6.
48. Dai G. Clinical analysis of calcium dobesilate combined with Danhong injection in the treatment of non proliferative diabetic retinopathy. *New world of diabetes*. 2017;20(11):170-1.
49. Wei G, Xing Y, Cao L, Zhang S, He S. Clinical observation on the treatment of diabetic retinopathy with Jinlida granule and Tongxinluo capsule. *Chinese Journal of experimental prescriptions*. 2018;24(18).
50. Sun X, Qian K, Zhou Y, Gu H. Study on the therapeutic effect and mechanism of Danggui Buxue Decoction in the treatment of diabetic retinopathy. *Journal of modern integrated Chinese and Western Medicine*. 2019;28(28):3152-5+70.
51. Liu A, Liao P, Zheng Y, Duan J. Effect of Qiming Granule on Antioxidation of retina in diabetic rats. *Chinese Journal of Ophthalmology of traditional Chinese Medicine*. 2003(03):7-9.
52. Ye H, Duan J, Liao P, editors. Effect of Qiming Granule on polyol pathway in retina of experimental diabetic rats. *The 9th Academic Symposium on experimental medicine of Integrated Chinese and Western Medicine*; 2009; Changchun, Jilin, China.
53. Liao P, Liu L, Duan J, Liu A, Liu W, Lu X, editors. Effect of Qiming on type Ⅱ collagen of retinal vascular basement membrane in experimental diabetic rats. *The Seventh National Academic Conference on diabetes in traditional Chinese Medicine*; 2003; Nanning, Guangxi, China.
54. Xing Y. Protective effect and mechanism of compound Shuantong Capsule on microvascular in diabetic rats [master]: *Second Military Medical University*; 2010.
55. Xing Y, Zou J, Shi Y, Liu Z. Protective effect of compound Shuantong Capsule on oxidative stress injury of retina in diabetic rats. *Journal of medical research*. 2016;45(01):40-3.

56. Zhang H, Wang H, Zhao S, Zhu H, Cui Q, Qi X. The effect and mechanism of qihuangmingmu Capsule on oxidative stress of retina in diabetic mice. *Chinese Journal of basic Chinese Medicine*. 2012;18(11):1216-8.
57. Zhu H, Wei G, Zhang H, He Q, Gao X, Qi X, et al. Effect of qihuangmingmu Capsule on retinopathy and growth factor expression in diabetic mice. *Chinese general medicine*. 2012;15(30):3551-4.
58. Wang H, Wang C, Zhu H, Wei G, Zhao S, Qi X, et al. Effect of qihuangmingmu Capsule on retinal protection and VEGF expression in diabetic mice. *Chinese Journal of traditional Chinese Medicine*. 2012;37(22):3481-5.
59. Zhang H, Zhang H, Wei G, Zhao S, He Q, Qi X, et al. Effect and mechanism of qihuangmingmu Capsule on retinal adhesion molecules in diabetic mice. *Shizhen national medicine*. 2012;23(08):1876-8.
60. Bao Y, Wu Z, Jie C, Gao J, Yan J. Effect of MI Meng Hua Fang on the proliferation of retinal m ü ller cells in high glucose condition. *Chinese Journal of Ophthalmology of traditional Chinese Medicine*. 2014;24(01):18-21.
61. Yan J, Yan H, Wang Q, Ge D, Wu Z, Jie C, et al. Study on the protective mechanism of MI Meng Hua Fang on early retinal nerve cell injury in diabetic rats. *New progress in ophthalmology*. 2018;38(12):1109-13.
62. Wu Z, Yan H, Ge D, Wang Q, Yan J, Gong X, et al. Study on the mechanism of preventing and treating the injury of retinal ganglion cells under high glucose. *Chinese Journal of Ophthalmology of traditional Chinese Medicine*. 2018;28(05):297-302.
63. Yin L. Experimental study of Tangwangkang capsule in the treatment of non proliferative diabetic retinopathy [master]: xinjiang medical university; 2006.
64. Hu X. Effect of Qizhen Jiangtang Granule on early diabetic retinopathy with deficiency of liver and kidney yin and oxidative stress of retina in rats [master]: Anhui University of traditional Chinese Medicine; 2018.
65. Xiang N, Lin H, Li G, Liu H. Effects of Ginkgo biloba extract on Bax and bcl-2 gene expression in retinal ganglion cells of diabetic rats. *Journal of Huazhong University of science and Technology (Medical Edition)*. 2008(02):243-6+81.
66. Qi R, Zhou L, Gu Z, Huo Y. Protective effect and mechanism of Ginkgo biloba polysaccharide on diabetic retinopathy induced by high fat diet. *Chinese Journal of Gerontology*. 2018;38(09):2200-2.
67. Fan H, Wang J, Li Z, Chen Z. Protective effect of Danhong Injection on retina of diabetic rats. *International Journal of Ophthalmology*. 2019;19(06):895-900.
68. Zhang Z, Wang C. Effect of Tongxinluo Capsule on p38MAPK signal pathway in retina of diabetic mice. *Hebei medicine*. 2015;37(04):504-7.
69. Liu M, Wang C, Xing D, Wang X. The effect of Tongxinluo Capsule on the expression of LN and FN in the retina of diabetic mice. *Hebei medicine*. 2015;37(02):174-6.
70. Wang C, Xing D, Wang X, Liu M, Zhang Z. Effect of Tongxinluo Capsule on the expression of inflammatory factors in blood and retina of diabetic retinopathy KK / UPJ ay mice. *Chinese general medicine*. 2014;17(27):3264-8.
71. Wang C, Xing D, Wang X, Liu M, Zhang Z. Inhibition of NF - κ B pathway by Tongxinluo Capsule on adhesion molecules in diabetic retinopathy mice. *Hebei medicine*. 2014;36(15):2245-7.
72. Wang X, Wang C, Xing D, Liu M, Zhang Z. Effect of Tongxinluo Capsule on IKK β / IKB α / NF - κ B pathway in retina of diabetic mice. *New progress in ophthalmology*. 2014;34(11):1005-8.
73. Liu G. The protective effect of Qiju Dihuang Pill on diabetic retinopathy. *Hebei Journal of traditional Chinese Medicine*. 2012;27(01):45-6.
74. Guo Y, Gao D, Liu S, Li X, Yang S. Experimental study on the protective effect of Danggui Buxue Decoction on blood retinal barrier in GK rats. *Chinese Journal of basic Chinese Medicine*. 2013;19(04):400-1.
75. Zhang HW, Zhang H, Grant SJ, Wan X, Li G. Single herbal medicine for diabetic retinopathy. *Cochrane Database Syst Rev*. 2018;12:Cd007939.

Figures

Figure 1

Selection process

	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)	Other bias
CHEN XL 2016	●	●	●	●	?	?	?
DAI GL 2017	?	●	●	●	?	?	?
DUAN JC 2005	●	●	●	●	?	?	?
FAN YP 2018	●	?	●	●	?	?	?
HU XD 2017	?	●	●	?	?	?	?
KONG WJ 2015	?	●	●	●	?	?	?
LIAN FM 2015	●	●	●	●	●	●	●
LI C 2017	?	●	●	?	?	?	?
LIN WX 2011	?	●	●	●	?	?	?
LI R 2006	●	?	●	●	?	?	?
LIU D 2018	●	?	●	●	?	?	?
LIU LW 2019	●	?	●	●	?	?	?
LIU SL 2015	?	●	●	●	?	?	?
LIU X 2016	?	●	●	●	?	?	?
LI WJ 2013	●	?	?	●	?	?	?
LUO D 2016	?	●	●	●	?	?	?
SHI JC 2015	?	●	●	●	?	?	?
SONG JT 2004	●	●	●	●	?	?	?
SUN HL 2014	?	●	●	●	?	?	?
SUN GX 2016	●	●	●	●	?	?	?
SUN XH 2019	?	●	●	●	?	?	?
WANG Q 2018	●	●	●	●	?	?	?
WANG ZZ 2017	?	●	●	●	?	?	?
WEI C 2018	?	●	●	●	?	?	?
WU L 2009	●	●	●	●	?	?	?
XIAO LP 2016	?	●	●	●	?	?	?
YANG L 2013	?	●	●	●	?	?	?
YANG M 2018	●	●	●	●	?	?	?
YAN J 2013	?	●	●	●	?	?	?
YAO YK 2016	?	●	●	●	?	?	?
YIN XD 2018	?	●	●	●	?	?	?
ZANG LH 2011	?	●	●	●	?	?	?
ZHANG Y 2016	?	●	●	●	?	?	?
ZHANG Y 2017	?	●	●	●	?	?	?
ZHENG Q 2016	?	●	●	●	?	?	?
ZHU CY 2016	?	●	●	●	?	?	?

Figure 2

Assessment of the quality of the included literature, showing the risk of bias

Figure 3

Fig 3

Figure 4

Fig 4

Figure 5

Fig 5

Figure 6

Figure 7

Figure 8

Figure 9

Fig 9

Figure 10

Fig 10

Figure 11

Fig 11

Figure 12

Fig 12

Figure 13

Fig 13