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Single herbal medicine for diabetic retinopathy (Review)

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[Intervention Review]

Single herbal medicine for diabetic retinopathy

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ABSTRACT

Background

Diabetic retinopathy is one of the major causes of blindness and the number of cases has risen in recent years. Herbal medicine has been used to treat diabetes and its complications including diabetic retinopathy for thousands of years around the world. However, common practice is not always evidence-based. Evidence is needed to help people with diabetic retinopathy or doctors to make judicious judgements about using herbal medicine as treatment.

Objectives

To evaluate the effectiveness and harm of single herbal medicine for diabetic retinopathy.

Search methods

We searched CENTRAL, which contains the Cochrane Eyes and Vision Trials Register, MEDLINE, Embase, OpenGrey, the ISRCTN registry, ClinicalTrials.gov and the ICTRP. The date of the search was 12 June 2018. We also searched the following Chinese databases in June 2013: Chinese BioMedical Literature Database (CBM), Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), Wanfang China Dissertation Database (CDDB), Wanfang China Conference Paper Database (CCPD) and the Index to Chinese Periodical Literature.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs that investigated the effects of any single herb (or extracts from a single herb) as a treatment for people with diabetic retinopathy. We considered the following comparators: placebo, no treatment, non-herbal (conventional) medicine or surgical treatment.

Data collection and analysis

Two review authors independently extracted data and assessed the risk of bias in the studies. Our prespecified outcomes were: progression of diabetic retinopathy, visual acuity, microaneurysms and haemorrhages in the retina, blood glycated haemoglobin A1c (HbA1c) (%) and adverse effects. We performed meta-analyses using risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI). We assessed the certainty of the evidence using GRADE.

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Main results

We included 10 studies involving 754 participants, of which nine were conducted in China and one in Poland. In all studies, participants in both groups received conventional treatment for diabetic retinopathy which included maintaining blood glucose and lipids using medicines and keeping a stable diabetic diet. In three studies, the comparator group also received an additional potentially active comparator in the form of a vasoprotective drug. The single herbs or extracts included Ruscus extract tablet, Sanqi Tongshu capsule, tetramethylpyrazine injection, Xueshuantong injection, Puerarin injection and Xuesaitong injection. The Sanqi Tongshu capsule, Xueshuantong injection and Xuesaitong injection were all made from the extract of Radix Notoginseng (San qi) and the main ingredient was sanchinoside. The risk of bias was high in all included studies mainly due to lack of masking (blinding). None of the studies reported the primary outcome of this review, progression of retinopathy.

Combined analysis of herbal interventions suggested that people who took these herbs in combination with conventional treatment may have been more likely to gain 2 or more lines of visual acuity compared to people who did not take these herbs when compared to conventional intervention alone at the end of treatment (RR 1.26, 95% CI 1.08 to 1.48; 5 trials, 541 participants; low-certainty evidence). Subgroup analyses based on the different single herbs found no evidence for different effects of different herbs, but the power of this analysis was low. One study reported Sanqi Tongshu capsule might be associated with a greater reduction in microaneurysms and haemorrhages in the retina (very low-certainty evidence). The pooled analysis of two studies on tetramethylpyrazine or Xueshuantong injection showed such herbs may have had little effect on lowering HbA1c (MD 0.00, 95% CI -0.58 to 0.58; 215 participants; low-certainty evidence).

There was very low-certainty evidence on adverse events. Two studies reported minor adverse events such as uncomfortable stomach, urticaria, dizziness and headache. There was no report of observation on adverse events in the other studies.

Authors' conclusions

No conclusions could be drawn about the effect of any single herb or herbal extract on diabetic retinopathy from the current available evidence. It was difficult to exclude the placebo effect as a possible explanation for observed differences due to the lack of placebo control in the included studies. Further adequately designed trials are needed to establish the evidence.

PLAIN LANGUAGE SUMMARY

Herbal medicine for people with diabetic retinopathy

What was the aim of this review?

The aim of this Cochrane Review was to find out if herbal medicine is useful for people with diabetic retinopathy when compared with placebo, no treatment, non-herbal (conventional) medicine or surgical treatment. Cochrane researchers collected and analysed all relevant studies to answer this question and found 10 studies.

Key messages

It is not certain if herbal medicine is of benefit to people with diabetic retinopathy.

What did this review study?

Diabetes is a life-long condition that means that there is too much sugar in the blood. Usually, our bodies regulate the levels of sugar in the blood with a hormone called insulin. In diabetes, either there is not enough insulin to deal with the sugar, or the insulin does not work. People with diabetes can experience problems with their eyes. High blood sugar can affect the blood vessels at the back of the eye. This is known as diabetic retinopathy and can lead to problems with vision, including blindness in severe cases.

Worldwide, many medicinal herbs or herbal extracts are used to treat diabetic retinopathy. The Cochrane researchers looked at six different types of herbal medicines: Ruscus extract tablet, Sanqi Tongshu capsule, tetramethylpyrazine injection, Xueshuantong injection, Xuesaitong injection and Puerarin injection. These treatments lasted from two weeks to 12 months.

What were the main results of the review?

The Cochrane researchers found 10 relevant studies involving 754 participants; nine studies were from China and one was from Poland.

These studies compared herbal medicine combined with conventional treatment with conventional treatment alone for people with diabetic retinopathy. None of the studies reported where the funding for the study came from. The findings were as follows.

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• None of the studies reported on the progression of diabetic retinopathy.

• The studies provided low-certainty evidence that herbal extracts may have increased the chances of visual improvement (being able to read 2 or more additional lines on an Eye chart, which is used to measure visual acuity).

• The Cochrane researchers judged the evidence on some of the signs of diabetic retinopathy (such as reduction in blood vessels bleeding at the back of the eye) as being very low-certainty.

• Similarly, there was low-certainty evidence as to the effect of herbal extracts on blood sugar levels but the available evidence suggested little effect.

• Most of the studies did not report on side effects. Two studies reported minor side effects such as uncomfortable stomach, itching, dizziness and headache.

How up-to-date is this review?

The Cochrane researchers searched for studies that had been published up to June 2018.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Single herb plus conventional intervention versus conventional intervention for diabetic retinopathy

Patient or population: people with diabetic retinopathy
Settings: hospital
Intervention: single herbal medicine plus conventional intervention[a]
Comparison: conventional intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Single herbal medicine				
Progression of retinopathy	-	-	-	-	-	None of the studies reported this outcome.
Visual acuity (gain of ≥ 2 lines) (end of treatment)	250 per 1000	315 per 1000 (270 to 370)	**RR 1.26** (1.08 to 1.48)	541 (5 studies)	⊕⊕◯◯ **Low**[b,c]	-
Reduction in microaneurysms	1 per 1000	18 per 1000 (1 to 205)	**RR 17.9** (1.05 to 305.26)	146 (1 study)	⊕◯◯◯ **Very low**[b,d]	None of the control group experienced a reduction. We estimated risk of 1 per 1000 in the control group for illustrative purposes
Observations in retina: reduction in haemorrhages	1 per 1000	26 per 1000 (2 to 438)	**RR 26.3** (1.59 to 437.56)	146 (1 study)	⊕◯◯◯ **Very low**[b,d]	None of the control group experienced a reduction. We estimated risk of 1 per 1000 in the control group for illustrative purposes

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HbA1c (%)	The mean HbA1c ranged across control groups from 7.5% to 8.3%	The mean HbA1c in the intervention groups was on average the same as the control group (i.e. MD 0, 95% CI -0.58 to 0.58)	-	215 (2 studies)	⊕⊕◯◯ **Low**[b,c]	-
Adverse outcomes	-	-	-	687 (6 studies)	⊕◯◯◯ **Very low**[b,d]	In 8/10 included studies, there was no report of observation on adverse outcomes. 2/80 (2.5%) participants reported uncomfortable stomach and 1/80 (1.25%) participants reported urticaria who orally took Sanqi Tongshu capsule. 2/52 (3.85%) participants reported dizziness and headache who received intravenous drip infusion of tetramethylpyrazine injection

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HbA1c:** glycated haemoglobin A1c; **RR:** risk ratio.

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Single herbal medicines include Puerarin, tetramethylpyrazine and Radix Notoginseng extract. The conventional intervention generally included oral medicine or insulin for maintaining blood glucose and lipid and maintaining a stable diabetic diet.

[b]Downgraded 1 level for high risk of bias because of lack of masking (particularly with subjective outcomes) and lack of allocation concealment.

[c]Downgraded 1 level for imprecision as the confidence intervals include, or are close to, null effect

[d]Downgraded 2 levels for imprecision as very few events.

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BACKGROUND

Description of the condition

Diabetic retinopathy is a disease of the retina that occurs as a complication of diabetes mellitus. It is characterised by progressive microvascular complications, such as microaneurysms, inter-retinal oedema, haemorrhages, hard exudates and intraocular pathological neovascularisation. Diabetic retinopathy is the leading cause of blindness among people of working age in high-income countries (Bunce 2006). It accounted for 1.9% of moderate or severe visual impairment and 2.6% of blindness globally in 2010 (Bourne 2013). The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5%, and an estimated 422 million adults were living with diabetes in 2014 (WHO 2016). The prevalence of any retinopathy in people with diabetes is 35% while proliferative (vision-threatening) retinopathy is 7% in 2010 (Yau 2012).

Diabetic retinopathy is classified and graded using two main scales, the Early Treatment Diabetic Retinopathy Study (ETDRS) staging system and, more recently, the scale developed by the International Council of Ophthalmology. The ETDRS severity scale is based on the modified Airlie House classification of diabetic retinopathy, and is used to grade fundus photographs (Fong 2004a). Although ETDRS is recognised as the gold standard for grading the severity of diabetic retinopathy, the ETDRS staging system is not suited to population screening. To facilitate communication among global ophthalmologists and physicians, and provide a common, user-friendly terminology to describe disease severity, the International Council of Ophthalmology developed an international scale (ICO 2002). This scale grades the severity of diabetic retinopathy on five levels based on findings observed through dilated ophthalmoscopy. The first level, 'no apparent retinopathy,' has no abnormal findings. The second level, 'mild non-proliferative diabetic retinopathy (NPDR),' which is characterised by increased vascular permeability, has microaneurysms only; then it progresses to the third and fourth levels of 'moderate and severe NPDR,' characterised by vascular closure with findings of intraretinal microvascular abnormalities. The fifth level is 'proliferative diabetic retinopathy (PDR),' characterised by the growth of new blood vessels on the retina and posterior surface of the vitreous, with findings of neovascularisation or vitreous/preretinal haemorrhage (Fong 2004a; ICO 2002). Macular oedema, characterised by retinal thickening from leaky blood vessels, can develop at all stages of retinopathy (Fong 2004b).

Although it is an important cause of blindness, diabetic retinopathy has few visual or ophthalmic symptoms until visual loss develops (Fong 2004b). Therefore, it is very important to detect retinopathy early in people with diabetes. There are many techniques used in the detection: direct and indirect ophthalmoscopy, fluorescein angiography, stereoscopic digital and colour film-based fundus photography, and mydriatic or non-mydriatic digital colour or monochromatic single-field photography. Ophthalmoscopy is the most commonly used technique to monitor for diabetic retinopathy (ICO 2017).

Description of the intervention

Large clinical trials have shown that glycaemic and blood pressure control can prevent and delay the progression of diabetic retinopathy (DCCTRG 1993; Frank 2004; UK PDSG 1998). Timely laser photocoagulation therapy can prevent vision loss in a large proportion of people with severe NPDR and PDR, macular oedema, or both. Vitrectomy, removal of the whole or part of the vitreous body, reduces visual loss of severe vitreous haemorrhage and proliferative retinopathy (Fong 2004b; Harding 2003). Intravitreal triamcinolone acetonide seems to improve visual acuity and reduce macular thickness in eyes with macular oedema refractory to previous macular laser photocoagulation, but may be associated with a significant risk of adverse effects (Jonas 2006a; Jonas 2006b; Lam 2007). Although the mechanism of diabetic retinopathy is not well known, some putative mechanisms have been proposed, some of which have led to the development of new drugs. However, none of these drugs has been effective in randomised controlled trials (RCTs) (Frank 2004). Other approaches to treat and prevent diabetic retinopathy, especially in the early stages, are needed.

Herbal medicine has a long history of treating diabetes and its complications around the world. This may provide an alternative therapy for preventing or delaying the progression of diabetic retinopathy (Head 1999). In China and some other Asian countries, traditional Chinese herbal medicine is widely used for treating diabetic retinopathy in clinical practice. Besides the traditional herbal decoction (remaining liquid prepared by boiling a mixture of different herbal medicine), various forms of herbal medicine such as patent medicine (fixed formula of Chinese medicine in different forms, such as granule, tablet, capsule or liquid) (Sun 2007), extract of herbal medicine (Song 2006), or Chinese medicine combined with laser treatment have been explored to treat diabetic retinopathy (Gong 2007).

According to Chinese medicine theory, diabetes mellitus is mainly due to the insufficiency of the essence of spleen and kidney. The main treatment principle of Chinese medicine is to invigorate spleen and replenish kidney. So it is mainly the regulation of whole body through which Chinese medicine takes effect on diabetic retinopathy.

How the intervention might work

Some RCTs on diabetic retinopathy reported that herbal medicine may have an effect on reducing the symptoms, improving visual acuity and visual field, and improving the observations under ophthalmoscopy (Ma 2004; Song 2006). For example, the compound

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Danshen dripping pill improved ischaemia of the retina and the visual field in early diabetic retinopathy, and reduced the number of microaneurysms (Deng 2005). When combined with laser photocoagulation therapy, ginkgo dipyridolum injection had an add-on effect, reduced the related adverse effect and improved the patients' satisfaction (Wei 2005).

Some active ingredients from medicinal herbs have been identified. Many preclinical and clinical studies have been conducted to explore the possible effect mechanism. Ginkgo biloba extract (EGb 761) improved abnormal haemorrheological parameters (Huang 2004), cleared free radicals (Doly 1986), and was a good adjuvant in people with long-lasting diabetes mellitus (Bernardczyk-Meller 2004). Ginkgo applanatum not only inhibited aldose reductase in vitro, but also suppressed the serum glucose concentration and sorbitol accumulation in the tissues of streptozotocin (STZ)-induced diabetic rats (Jung 2005). Anisodamine increased tissue oxygen tension, and may therefore be useful in treating clinical conditions thought to be secondary to tissue hypoxia, such as diabetic retinopathy (Linsenmeier 1989). *Stephania Tetrandra S. Moore* (Han Fang Ji) had a direct effect on the retinal capillary of the posterior ocular region and suppressed neovascularisation of the retinal capillary in diabetic rats through the activation of tetrandrine (Liang 2002). Saptamrita Lauha could hasten the process of retinal haemorrhage absorption and prevent its recurrence (Sharma 1992). The combination therapy comprising of plant-derived extracts and sulindac sulfone may have an antiangiogenic effect (Skopinski 2004).

Why it is important to do this review

Given the increasingly widespread use of herbal medicine for treating diabetic retinopathy, the concerns about its effectiveness and safety are increasing, and to date there has been no conclusive evidence (Parveen 2018; Vasant 2017). A systematic review of the available evidence is needed to elucidate the potential benefit and harm of herbal medicine treatment for diabetic retinopathy. Due to the large number of mixed Chinese herbal prescriptions presenting a great challenge on the identification of effective ingredients and mechanisms on diabetic retinopathy, this review focused on single herbal medicine.

OBJECTIVES

To evaluate the effectiveness and harm of single herbal medicine for diabetic retinopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and quasi-RCTs irrespective of masking (blinding), publication status or language. The allocation method of quasi-randomisation is not truly random; for example, allocation by date of birth, day of the week, medical record number, month of the year or the order in which participants are included in the study (e.g. alternation). We included quasi-RCTs in order to retrieve more potentially eligible studies in this field.

Types of participants

We included trials with participants with type I or type II diabetes diagnosed with diabetic retinopathy in at least one eye.

Types of interventions

Interventions included any single herb or extracts originated from any single herb regardless of their compositions, formula forms or administration route. The comparator included placebo, no treatment, conventional intervention or surgical treatment. Other herbal medicines or complementary medicines without validated effectiveness were not accepted as comparators.

Conventional intervention was accepted as the cointerventions among groups when all arms of the trial received the same cointerventions.

Types of outcome measures

Primary outcomes

- Progression of retinopathy, defined as any clinically meaningful progression from the baseline (based on the ETDRS severity scale, Airlie House classification, International Clinical Diabetic Retinopathy Disease Severity Scale, or similar) from stereoscopic colour fundus photographs.

If a study used any other classification system for progression of retinopathy, we sought and verified justification for its use and validation of the system compared to the ETDRS classification. The primary outcome was collected immediately after the treatment and at the end of follow-up.

Secondary outcomes

- Visual acuity, measured by an ETDRS chart. The improvement of visual acuity was gain of 2 or more lines on the chart.

If a study used any other visual acuity chart, we sought and verified justification for its use and validation of the chart compared to the ETDRS chart.

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Visual acuity might be measured as the numerical value on the chart or dichotomous data (change of 2 or more lines of acuity or not) after the treatment.

- Observations in retina detected by ophthalmoscopy or stereoscopic fundus photography, such as microaneurysms, haemorrhages, hard exudates, new vessels, fibrous proliferations, photocoagulation scars, etc.
- Visual field (measured by manual or automated perimetry).
- Quality of life (assessed by validated scales).
- Blood glycated haemoglobin levels (HbA1c), fasting blood glucose, postprandial two-hour blood glucose.
- Blood pressure.

All the secondary outcomes were collected immediately after the treatment and at the end of follow-up. The value at such particular time points was used.

Adverse outcomes

We recorded the number and type of adverse events (serious and less serious ones). Serious adverse events were any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of hospitalisation, resulted in persistent or significant disability, was a congenital anomaly/birth defect or was an event that may have jeopardised the participant or required interventions to prevent one of the former serious adverse events.

Both types of adverse events were classified into the clinical manifestation mainly related to respiratory, digestive, circulatory, neurological, urological, blood system or others. We reported them separately and calculated the incidence rate.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for RCTs and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 12 June 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 5), which contains the Cochrane Eyes and Vision Trials Register, in the Cochrane Library (Appendix 1).
- MEDLINE Ovid (1946 to 12 June 2018) (Appendix 2).
- Embase Ovid (1947 to 12 June 2018) (Appendix 3).
- Allied and Complementary Medicine Database (AMED) (1970 to 12 June 2018) (Appendix 4).
- System for Information on Grey Literature in Europe (OpenGrey) (www.opengrey.eu; to 12 June 2018) (Appendix 5).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 12 June 2018) (Appendix 6).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 12 June 2018) (Appendix 7).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 12 June 2018) (Appendix 8).

We also searched the following Chinese databases in June 2013: Chinese BioMedical Literature Database (CBM), Traditional Chinese Medical Literature Analysis and Retrieval System (TCM-LARS), Wanfang China Dissertation Database (CDDB), Wanfang China Conference Paper Database (CCPD) and the Index to Chinese Periodical Literature. There were no date or language restrictions in the electronic search for trials. The search strategy used to search CBM was slightly modified to search the other Chinese databases (Appendix 9).

Searching other resources

We scanned the references of all included studies and relevant reviews to identify any trials that met our inclusion criteria.

Data collection and analysis

Selection of studies

Two review authors (HWZ and RT) independently assessed the title or abstract of each retrieved record to select potential eligible studies. We graded each record as include, exclude or unclear. We retrieved full-text copies for further assessment if they were graded as include or unclear.

The same two review authors independently assessed the full-text copies to decide which ones met the inclusion criteria. We labelled each record as include, exclude or unclear. We resolved any disagreements including unclear issues by discussion and consensus. We summarised reasons for exclusion in the Characteristics of excluded studies table. If necessary, we attempted to contact the study authors to obtain further information.

Data extraction and management

Two review authors (HWZ and HYZ) independently extracted data from the included studies using a data extraction form which had been piloted on seven studies. We resolved any discrepancies by discussion, and consulted a third review author (XW) if consensus was not possible. The data extraction form included the following data.

- General information: published/unpublished, country, publication language, publication year.
- Trial design: comparison groups, method of randomisation, allocation concealment, masking (participants, intervention

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administrators, outcome assessors), evaluation of masking by trialists.

- Participants: inclusion and exclusion criteria, total number and number in comparison groups, baseline characteristics, setting.
- Interventions: the composition or ingredients, preparation method, dose, route, timing of intervention, comparison intervention and cointervention, expertise of practitioner.
- Outcomes: outcomes specified under Primary outcomes; Secondary outcomes, any other outcomes assessed, adverse events.
- Follow-up: length of follow-up; reason and number of dropouts and withdrawals, method of analysis.

If the above data were missing in the trial report, we contacted the corresponding author of the study for further information. If the data were not available, we reported the results of the correspondence in the review.
One review author (HWZ) entered data into Review Manager 5 (Review Manager 2014) and another review author (HYZ) checked them.

Assessment of risk of bias in included studies

Two review authors (HWZ and RT) independently assessed the risk of bias of the included studies. We resolved any discrepancies by discussion. When needed, a third review author (HYZ) assisted in making the final decision.
To detect potential selection bias, performance bias, attrition bias and detection bias, we addressed the following six domains in the assessment of risk of bias: sequence generation, allocation concealment, masking, incomplete outcome data, selective outcome reporting and other sources of bias. Baseline comparability was considered as one of the 'other sources of bias.'
We assessed each domain as yes: indicating a low risk of bias, no: indicating a high risk of bias and unclear where we could not tell due to unclear information or domain not reported.

Measures of treatment effect

Dichotomous outcomes

- Progression of retinopathy. The proportion of participants who showed improved progression or not was calculated.
- Visual acuity. The proportion of people who had a change of 2 lines or more on the acuity chart or not in each group was calculated and compared within groups.
- Observations in retina. The proportion of participants who showed improved observations or not in retina detected by ophthalmoscopy or stereoscopic fundus photography was calculated.
- Visual field. The proportion of participants who had a 10-degree increment or not in visual field was collected.

For dichotomous outcomes, we calculated the RR with its 95% CI.

Continuous data

- Quality of life.
- Blood HbA1c, fasting blood glucose, postprandial two-hour blood glucose.
- Blood pressure.

For continuous data, we calculated the MD between groups with its 95% CI when the same measurement scale was used.
The meta-analysis of continuous data was based on an underlying assumption that the outcomes had a normal distribution. We assessed the distribution of each continuous variable mainly based on previous knowledge of the variable. If the mean was smaller than twice the standard deviation (SD) in each intervention group, the data were likely to be skewed (Altman 1996).

Unit of analysis issues

The unit of analysis was the randomised participant. The included studies all used random allocation based on participants. However, four studies reported results based on eyes (Dou 1998; Ren 2000; Yin 2012; Yuan 2012). In two studies, approximately correct analyses were performed to adjust for within-person correlation between eyes (Armstrong 2013; Tuft 2005). The idea of an approximately correct analysis was to reduce the size of each trial to its 'effective sample size,' that is, its original sample size divided by a quantity called the 'design effect.' The design effect is calculated as 1 + (M - 1) ICC, where M is the mean cluster size and the intracluster (or intraclass) correlation coefficient (ICC) is an estimate of the relative variability within and between clusters (Higgins 2011). It was estimated that the ICC was 0.22 based on related studies (Armstrong 2013; Tuft 2005).
In the case of multiple intervention groups within a trial, we used only relevant single pair-wise comparisons for analysis.

Dealing with missing data

We conducted available-case analyses. We addressed the potential impact of the missing data on the results in the assessment of risk of bias. We calculated the proportion of missing data, and explored possible reasons.
Sensitivity analyses based on missing data were not conducted due to the deficiency of necessary data.

Assessment of heterogeneity

To investigate possible heterogeneity, we first reviewed the study components such as participants, interventions and outcomes in the included studies to decide if the heterogeneity was substantially large. If not, heterogeneity was further detected by visual inspection of the forest plots. If the CIs for the results of included studies

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had poor overlap, heterogeneity might have been present. We used a Chi² test to test for heterogeneity. We set the significance level at 0.1 in view of its low statistical power. We also used the I² statistic to quantify inconsistency, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A value of more than 50% may indicate substantial heterogeneity.

Assessment of reporting biases

We did not produce a funnel plot to detect reporting biases due to the small number of included studies. In future, if 10 or more studies are included, we will construct a funnel plot.

Data synthesis

We conducted meta-analyses on several reported important secondary outcomes including visual acuity, observations in retina and blood HbA1c. We used the random-effects model for analysis unless there were fewer than three trials in which case we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to undertake subgroup analysis on the duration of treatment and severity of diabetic retinopathy but there was not enough information. We performed subgroup analysis based on each single herbal extract.

Sensitivity analysis

We planned to conduct sensitivity analysis to explore the influence of study quality and severity of diabetic retinopathy. However, as there was not enough information available on study quality influencing factors, such as adequacy of sequence generation, allocation concealment and masking, and the severity level of diabetic retinopathy, no sensitivity analysis was conducted.

RESULTS

Description of studies

See: Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

The electronic searches run by the Cochrane Information Specialist (CIS) yielded 761 records (Figure 1). After removal of 128 duplicates, the CIS screened the remaining 633 records and removed 182 records that were not relevant to the scope of the review, leaving a total of 451 records to be screened by the review authors. We conducted searches on five Chinese databases and retrieved 654 records, after removal of 227 duplicates, 427 records were identified for assessment. We merged the results from both searches and two review authors independently screened 878 records by reading the titles or abstracts. A total of 184 studies were potentially relevant, and we retrieved their full-texts for further assessment. We included 10 studies in the review; of which eight studies with prespecified outcomes were included in meta-analyses.

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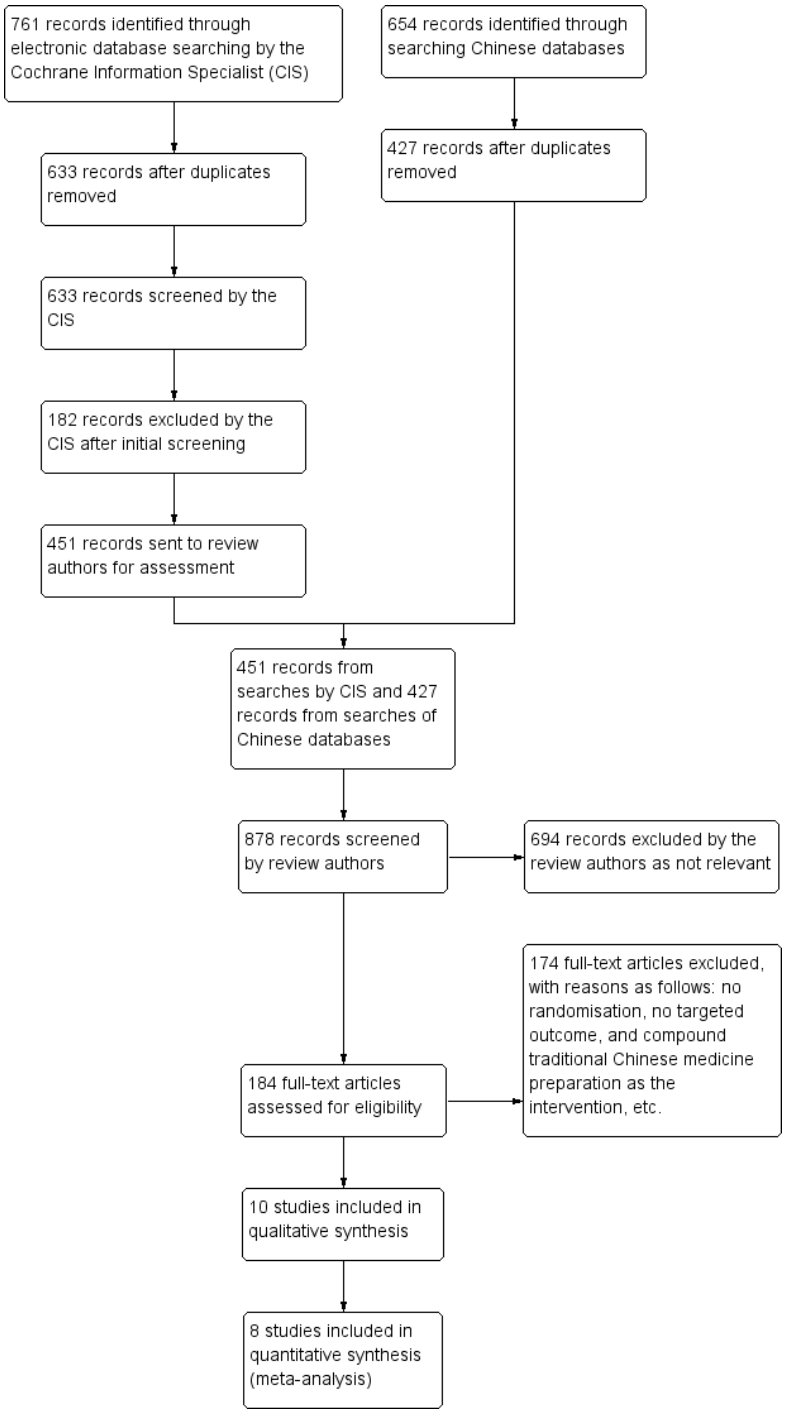
Figure 1. Study flow diagram.



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Included studies

We included 10 RCTs in the review (Archimowicz-Cyrylowska 1996; Chen 2009; Dou 1998; Li 2007; Ren 2000; Xu 2003; Yang 2005; Yin 2012; Yuan 2012; Zhao 2009). The source of all data presented in the review was obtained from published literature.

Design

The 10 included studies were all RCTs.

Sample sizes

The 10 included studies involved 754 participants with diabetic retinopathy, and the sample sizes ranged from 30 to 158. The eight studies included for meta-analysis involved 665 participants.

Setting

Nine studies were conducted in China and published in Chinese, and one was conducted in Poland and published in English (Archimowicz-Cyrylowska 1996). All the studies were conducted in hospitals. None of the studies reported the funding sources.

Participants

The studies included 754 participants with diabetic retinopathy. The population was evenly spread with 374 (49.6%) males and 386 (51.2%) females. In most studies, participants with NPDR or PDR were all recruited. For eight studies that had data available about the participants' age range, the range was from 20 to 85 years.

Interventions

Seven studies compared single herb plus conventional intervention to the same conventional intervention alone (Chen 2009; Dou 1998; Li 2007; Xu 2003; Yin 2012; Yuan 2012; Zhao 2009), and three studies compared single herbal medicine plus conventional intervention to western medicine plus the same conventional intervention (Archimowicz-Cyrylowska 1996; Ren 2000; Yang 2005).

The single herbs or extracts included Ruscus extract tablet (Archimowicz-Cyrylowska 1996), Sanqi Tongshu capsule (Chen 2009), tetramethylpyrazine injection (Dou 1998), Xueshuantong injection (Li 2007; Yuan 2012), Puerarin injection (Ren 2000; Xu 2003; Yin 2012; Zhao 2009), and Xuesaitong injection (Yang 2005). The Sanqi Tongshu capsule, Xueshuantong injection and Xuesaitong injection were all made from the extract of Radix Notoginseng (San qi) and the main ingredient was sanchinoside. The herbal extract injections of tetramethylpyrazine and Puerarin were administered by intravenous drip infusion. Three studies used western medicine: Troxerutin tablet (Archimowicz-Cyrylowska 1996), mecobalamin intramuscular injection (Ren 2000), and oxerutins (Venoruton forte) intravenous drip infusion (Yang 2005). All the studies provided the conventional intervention, generally including maintaining the level of blood glucose and lipid using medicine and keeping a stable diabetic diet. Two studies used laser photocoagulation (Li 2007; Xu 2003). The treatment duration in the included studies ranged from two weeks to 12 months.

Outcome measures

No included study reported the primary outcome of progression of retinopathy. Six studies reported the results of visual acuity immediately after the end of treatment (Dou 1998; Li 2007; Ren 2000; Yin 2012; Yuan 2012; Zhao 2009). One study reported the follow-up data three months after treatment (Li 2007).

Two studies reported outcomes about visual acuity and some observations in retina, but they used self-developed criteria to indicate the treatment effect, such as the percentage of participants with increased visual acuity more than 0.1 or the effective rate indicated by the percentage of patients with new vessels (Xu 2003; Yang 2005). Their outcomes were not pooled in the meta-analysis. The synthesis of predefined outcome measures, but not all available relevant outcome measures, may not present a relatively unbiased result. The standardisation of outcome report in clinical trials is important for improving the validity of pooled analysis.

Excluded studies

We excluded 174 articles excluded after careful examination of the full-text copies. Common reasons for study exclusion included: no random allocation; traditional Chinese medicine (TCM) as the control intervention; compound TCM preparation as the treatment intervention; TCM as one of the cointerventions; and the reported outcomes were not relevant to the review scope, such as blood rheology indexes, haemodynamic indexes, thromboxane B_2 (TxB_2) and 6-keto prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) (Feng 2007; Liu 2005). Some excluded studies that may represent the common reasons for exclusion and be easily considered for inclusion are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

See: Figure 2; Figure 3.

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Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

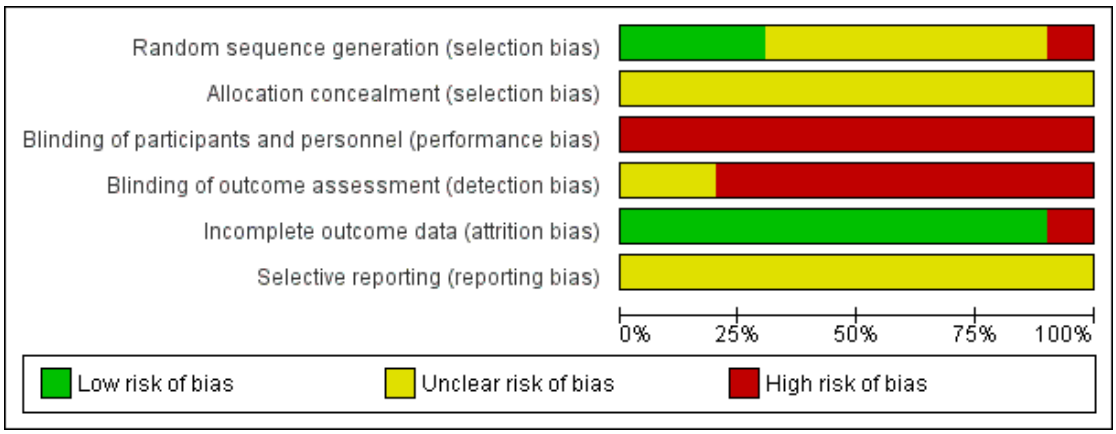

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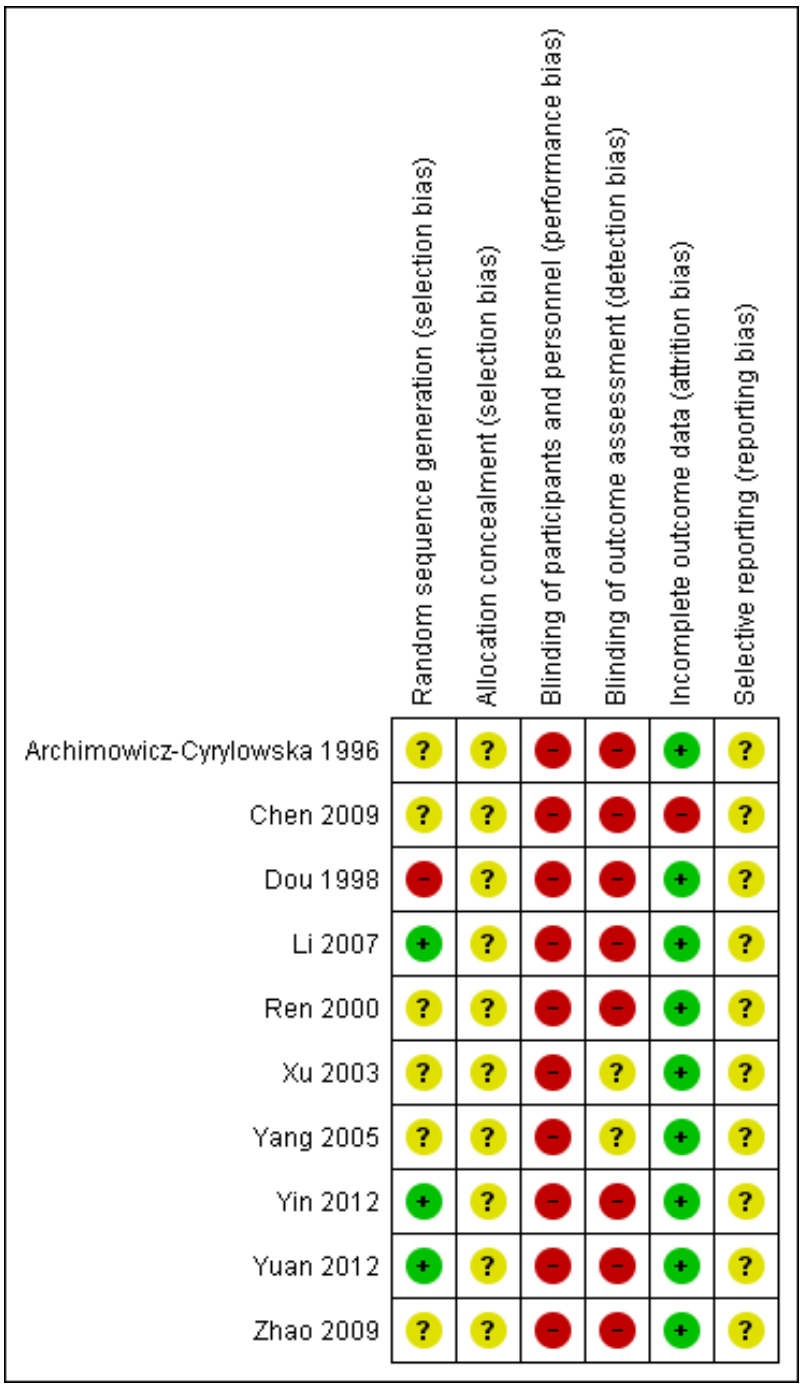
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Of the included studies, only three mentioned using a random numbers table to generate random numbers (low risk of bias; Li 2007; Yin 2012; Yuan 2012). The other studies mentioned random allocation but with no detailed information about the method. In one study, the obvious imbalance in the case number between two groups (52 in tetramethylpyrazine injection group versus 35 in no treatment group) may suggest improper randomisation method used (high risk of bias; Dou 1998). None of the studies reported information on allocation concealment (unclear risk of bias).

Blinding

None of the included studies masked personnel, participants or outcome assessors (high risk of bias). When many cointerventions are administered, the knowledge of intervention assignment may potentially influence the participant's behaviour. Furthermore, for the assessment of some outcome measures involving subjective judgement, such as the observations in retina detected by ophthalmoscopy or visual acuity, unmasking may induce performance bias and detection bias.

Incomplete outcome data

Nine studies reported no missing data and conducted analysis based on the initial random allocation (low risk of bias). Only one study, with 12 months of treatment duration, reported withdrawals with 9/80 participants (11.2%) in the Sanqi Tongshu capsule group and 3/78 (3.8%) in the no intervention group who experienced some adverse effects (high risk of bias; Chen 2009).

Selective reporting

None of the studies had published protocols and only some studies reported limited outcome measures, therefore the possibility of selective reporting was unknown (unclear risk of bias).

Other potential sources of bias

Although most included studies stated that the baseline characteristics between treatment and control group were comparable, only one study provided detailed information, which presented comparable baseline characteristics (Dou 1998). The possibility of imbalance in baseline characteristics in 9/10 of the included studies was unknown.

In summary, we judged the risk of bias overall as high in all of the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Single herb plus conventional intervention versus conventional intervention for diabetic retinopathy

Herb and conventional intervention versus conventional intervention alone

Seven studies compared herb and conventional intervention versus conventional intervention alone (Chen 2009; Dou 1998; Li 2007; Xu 2003; Yin 2012; Yuan 2012; Zhao 2009).

The conventional intervention generally included maintaining blood glucose and lipid using medicines and keeping a stable diabetic diet.

Primary outcome: progression of retinopathy

None of the seven studies reported progression of retinopathy.

Secondary outcome: visual acuity

A combined analysis showed that people treated with herbal medicine in addition to conventional intervention were more likely to gain 2 or more lines of visual acuity compared to people treated with conventional intervention alone after the end of treatment with no heterogeneity (5 trials, 541 participants; RR 1.26, 95% CI 1.08 to 1.48) (Figure 4). There were similar effects for each individual herb; however, with few trials, the power to detect differences between trials was too low.

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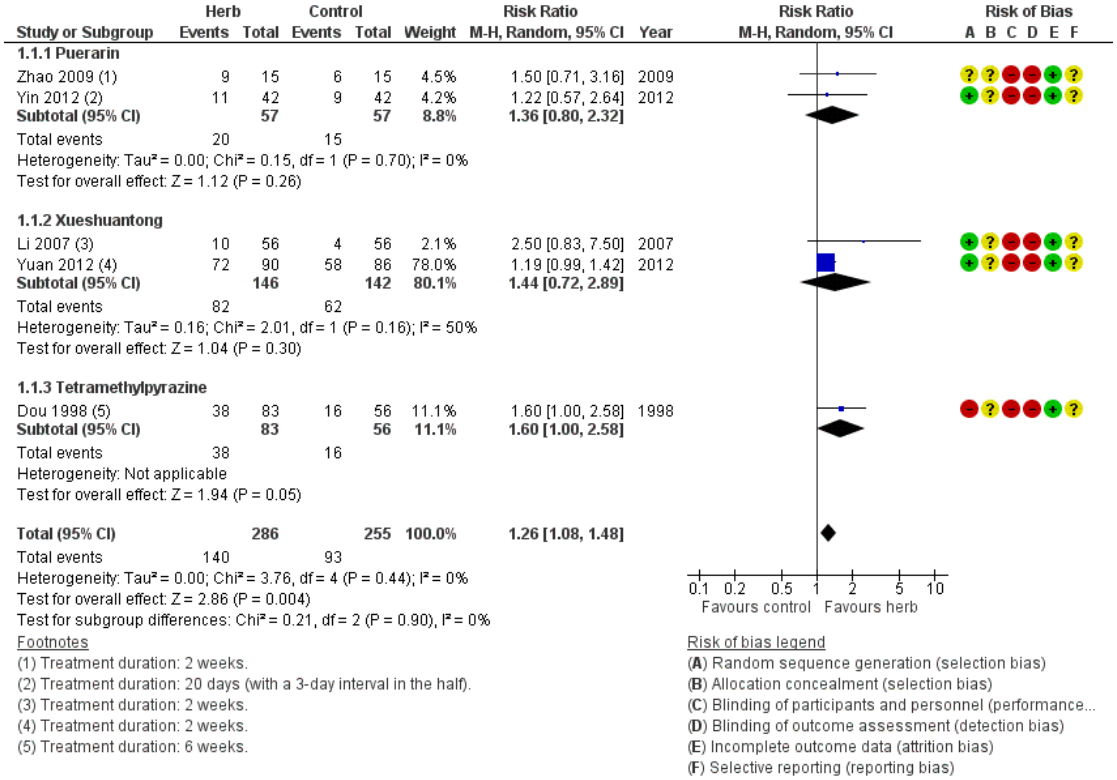
Figure 4. Forest plot of comparison: 1 Herb plus conventional intervention versus conventional intervention, outcome: 1.1 Visual acuity (gain of 2 or more lines) (end of treatment).



One study reported a follow-up benefit on visual acuity three months after the Xueshuantong injection treatment (112 participants; RR 2.33, 95% CI 0.97 to 5.64) (Li 2007).
Two studies did not report visual acuity (Chen 2009; Xu 2003).

Secondary outcome: observations in retina

One study reported that Sanqi Tongshu capsule might reduce microaneurysms (146 participants; RR 17.94, 95% CI 1.05 to 305.26) and haemorrhages (146 participants; RR 26.39, 95% CI 1.59 to 437.56) in the retina (Chen 2009). The other six studies did not report reduction in microaneurysms and haemorrhages in retina.

Secondary outcome: visual field

None of the seven studies reported visual field.

Secondary outcome: Quality of life

None of the seven studies reported quality of life.

Secondary outcome: blood glycated haemoglobin levels

The pooled analysis of two studies on tetramethylpyrazine or Xueshuantong injection showed herbs had no effect on lowering HbA1c with slight heterogeneity (2 trials, 215 participants; MD 0.00, 95% CI -0.58 to 0.58; I^2 = 11%) (Dou 1998; Yuan 2012). The other five studies did not report HbA1c.

Secondary outcome: fasting blood glucose and postprandial two-hour blood glucose

None of the seven studies reported fasting blood glucose or postprandial two-hour blood glucose.

Blood pressure

None of the seven studies reported blood pressure.

Adverse outcomes

In one study, the were digestive adverse events (uncomfortable stomach) in 2/80 (2.5%) participants and urticaria in 1/

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80 (1.25%) participants who took Sanqitongshu capsule (Chen 2009). In another study, there was dizziness and headache 2/52 (3.85%) participants who received intravenous drip infusion of tetramethylpyrazine injection, which was relieved after slowing the dripping speed (Dou 1998).
In the other five studies, there was no report of adverse events.

Herb and conventional intervention versus Troxerutin or vitamin B and conventional intervention

Three studies compared herb and conventional intervention versus Troxerutin or vitamin B and conventional intervention (Archimowicz-Cyrylowska 1996; Ren 2000; Yang 2005).

Primary outcome: progression of retinopathy

None of the three studies reported progression of retinopathy.

Secondary outcome: visual acuity

One study showed that, compared to mecobalamin (nerve protective agent), Puerarin had an effect on improving visual acuity (50 participants; RR 15, 95% CI 0.9 to 249.3) (Ren 2000). The other two studies did not report visual acuity.

Secondary outcome: observations in retina

None of the three studies reported observations in retina.

Secondary outcome: visual field

None of the three studies reported visual field.

Secondary outcome: quality of life

None of the three studies reported quality of life.

Secondary outcome: blood glycated haemoglobin levels

One study which compared Ruscus extract with troxerutin (vasoprotective agent) found a reduction on HbA1c (40 participants; MD 0.9, 95% CI 0.67 to 1.13) (Archimowicz-Cyrylowska 1996). It reported a slight, statistically insignificant increase in visual acuity in all participants treated with troxerutin and Ruscus extract for three months. Such data were reported in numbers that were not eligible for inclusion in data analysis in the review. The other two studies did not report HbA1c.

Secondary outcome: fasting blood glucose and postprandial two-hour blood glucose

None of the three studies reported fasting blood glucose or postprandial two-hour blood glucose.

Secondary outcome: blood pressure

None of the three studies reported blood pressure.

Adverse outcome

None of the three studies reported adverse events.
Following the GRADE approach, the certainty of evidence was low on visual acuity (gain of 2 or more lines) at the end of treatment and HbA1c, and very low on reduction in microaneurysms and haemorrhages and adverse outcomes (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

The review included 10 trials recruiting 754 participants, studying four types of herb extracts including Puerarin injection, Radix Notoginseng (San qi), tetramethylpyrazine and Ruscus extract. Nine of the included studies were conducted in China and one in Poland. Seven studies compared herb extract plus cointervention to the same cointervention. The combined analysis suggested herb extract was associated with the increased likelihood of improving visual acuity (Summary of findings for the main comparison); however, it should be noted that it was related to evidence with low-or very-low certainty. A pooled analysis of two studies found no effect on HbA1c. It should be noted that the observed effect of the interventions could be due to the placebo effect alone due to the lack of placebo control.
The single herbs or extracts included Ruscus extract tablet (Archimowicz-Cyrylowska 1996), Sanqi Tongshu capsule (Chen 2009), tetramethylpyrazine injection (Dou 1998), Xueshuantong injection (Li 2007; Yuan 2012), Puerarin injection (Ren 2000; Xu 2003; Yin 2012; Zhao 2009), and Xuesaitong injection (Yang 2005). The Sanqi Tongshu capsule, Xueshuantong injection and Xuesaitong injection were all made from the extract of Radix Notoginseng (San qi) and the main ingredient was sanchinoside. The herbal extract injections of tetramethylpyrazine and Puerarin were administered by intravenous drip infusion.
Two studies reported some adverse events, such as uncomfortable stomach, urticaria, dizziness and headache.
The risk of bias in all the included studies was high. Due to the low quality and small number of included studies and the slight beneficial effect in the results, we could not conclude any conclusion on the beneficial effect or harm of any herb or herb extract on diabetic retinopathy.

Overall completeness and applicability of evidence

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The combined analysis of eight studies involving 665 participants did not provide substantial evidence to support or refute the use of any herb or herbal extract in people with diabetic retinopathy. Some of the included studies reported only data on visual acuity, observations in the retina and blood HbA1c. The improvement in visual acuity was demonstrated in the pooled analysis, but not in the subgroup analyses, which may be due in part to the small number and the small sample size of included studies. Some herbs, such as Radix Notoginseng, Puerarin and tetramethylpyrazine, improved the blood rheology indices at the same time in some included studies (Dou 1998; Li 2007; Ren 2000; Yin 2012). However, no study reported any data on the progression of diabetic retinopathy, visual field, quality of life and blood pressure.

Some herbal extract injections such as tetramethylpyrazine and Puerarin injection are generally not allowed to be used outside of China. Exploration on the other administration routes of herb or herbal extract is needed.

Quality of the evidence

The report and quality of the included studies were generally poor. No study included masking, and, as such, trial participants may have behaved differently between groups when multiple cointerventions were administered, which may introduce performance and detection bias especially for subjective outcomes. Most studies provided no details on random allocation, and minimal details on baseline characteristics, and as such, selection bias may exist. Therefore, considering the potentially high risk of bias induced from unmasking and improper random allocation, we downgraded the quality of a body of evidence. The results of included studies were generally consistent. For the data analysis, a unit of analysis issue should be noted. Four of the 10 included studies did analysis based on eyes, which did not take into account the level at which randomisation occurred. The eyes were used as the denominator without adjustment for the non-independence between eyes. An approximately correct analysis is suggested, which is to reduce the size of each trial to its 'effective sample size' (Higgins 2011). Overall, the certainty of the evidence in GRADE approach was low.

Potential biases in the review process

We did not pool the studies that used change of 1 or more lines on the visual chart to measure visual acuity or other ways to measure observations in retina, into the meta-analysis. These studies may provide potential evidence to demonstrate the effectiveness and safety of single herb or herbal extract on diabetic retinopathy.

The reporting of most included studies was unsatisfactory without proper descriptions of random allocation and outcome measurement. Additionally, the potential publication bias could not be excluded based on the current available studies.

Agreements and disagreements with other studies or reviews

We could not find any other systematic review covering this topic although there have been a couple of narrative reviews focused on pharmacological properties (Behl 2017; More 2017).

AUTHORS' CONCLUSIONS

Implications for practice

We were unable to draw any conclusions on the effect of any single herb or herbal extract on diabetic retinopathy as an added medicine to the conventional intervention due to the lack of good-quality studies. There was no substantial evidence to support or refute the use of some single herbs to treatment diabetic retinopathy.

Implications for research

Based on the available evidence, further clinical trials with scientifically rigorous methodology are justified to clarify the effect of some single herbs or herbal extract on diabetic retinopathy. Specifically, Ruscus extract, Radix Notoginseng (San qi), Tetramethylpyrazine and Puerarin are potentially promising agents.

Based on the design drawbacks of the current studies included in this review, the following points are suggested for consideration.

- Use proper placebo control to evaluate the possible placebo effect.
- Choose proper analysis methods when using an eye as the analysis unit and participant as the randomisation unit.
- Describe clearly the method of random number generation and allocation concealment.
- Mask all the trial participants and evaluate the degree of masking.
- Recruit enough participants based on proper calculation of sample size.
- Use some widely accepted outcome measurements, such as the progression of retinopathy, visual field and quality of life.
- Make follow-up visits to know the long-term result of herbal treatment.

It is recommended that all studies comply with the CONSORT statement in reporting results (www.consort-statement.org/).

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Archimowicz-Cyrylowska 1996

Methods	**Design:** parallel group RCT **Randomisation method:** not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** no specific information was provided regarding 1 eye or both eyes. Mean change of visual acuity was reported on the group level without information on the calculation. Individual data on HbA1c reported
Participants	**Inclusion criteria:** non-proliferative diabetic retinopathy. **Exclusion criteria:** diseases of the kidney and the liver, allergy, venous abnormalities and psychosis **Number of participants:** 60 **Mean age (range):** NR (20 to 75) **Gender (M/F):** 32/28 **Setting:** hospital in Szczecin, Poland
Interventions	**Intervention:** • oral Ruscus (Ruscus aculeatus Linne) extract, containing 0.0375 g of extract, twice a day **Comparator:** • oral Troxerutin, 1 tablet, twice a day. 1 tablet containing 0.5 g of 0-(beta-hydroxyethy1)-rutoside **Participants in both groups received conventional intervention** in the form of a stable diabetic diet and hypoglycaemic medication **Treatment duration:** 3 months There was a further intervention in this study, oral pressed buckwheat herb, which was not included in this review
Outcomes	HbA1c Visual acuity **Follow-up:** 3 months
Notes	**Date of study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	Authors' judgement	Support for judgement

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Archimowicz-Cyrylowska 1996 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of generating random number not described.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking, and subjective outcome measures were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

Chen 2009

Methods	**Design:** parallel group RCT **Randomisation method:** not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** total 12/158 (7.6%); treatment 9/80 (11.2%); control group 3/78 (3.8%). Among 9 participants in the treatment group who withdrew from the study, 2 experienced an uncomfortable stomach and 1 developed urticaria. There were no reasons given for the remaining 7 **Eyes:** no report about the involvement of 1 or 2 eyes during evaluation, and the evaluation report was based on the people randomised
Participants	**Inclusion criteria:** diabetic retinopathy diagnosed through fundus photography without any chronic serious complications **Number of participants:** 158 **Average age (range):** 62 (54 to 85) years **Gender (M/F):** 90/68 **Setting:** hospital in Shantou, Guangdong Province, China
Interventions	**Intervention:** • oral Sanqi Tongshu capsule, 400 mg, 3 times daily **Comparator:** • no intervention **Participants in both groups received conventional intervention** to control serum glucose (fasting blood glucose < 6.5 mmol/L), antiplatelet aggregation treatment and symptomatic treatment

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Chen 2009 (*Continued*)

	Treatment duration: 12 months	
Outcomes	Observations in retina (microaneurysms and haemorrhages) **Follow-up:** 12 months	
Notes	**Date of study conducted:** October 2007 to October 2008 **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of generating random number not described.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions administered
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking, and subjective outcome measures used.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants withdrew from study, 9 from treatment group.
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures reported, but there was insufficient information to permit judgement of relevant risk of bias

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Dou 1998

Methods	**Design:** parallel group RCT **Randomisation method**: not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no. 2 participants in the treatment group experienced dizziness and headaches during intravenous infusion drip of tetramethylpyrazine, and the symptoms resolved after slowing the speed of dripping **Eyes:** 2 eyes included in study and both eyes received same treatment, with a mixture of 1 eye and 2 eyes. The selection of eye was based on the judgement of DR stage I to VI. The visual acuity results were reported based on the eye level and not adjusted for within-person correlation. An approximately correct analysis was used for a meta-analysis
Participants	**Inclusion criteria:** DR diagnosed based on China National criteria, including non-proliferative and proliferative DR **Number of participants:** 87 **Mean age:** 54 years **Gender (M/F):** 39/48 **Setting:** hospital in Xinxiang, Henan Province, China
Interventions	**Intervention:** • tetramethylpyrazine injection 280-400 mg (5 mg/kg) in 500 mL sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • no treatment **Participants in both groups received conventional intervention** in the form of oral antidiabetic drug or insulin and diabetic diet **Treatment duration:** 6 weeks
Outcomes	Visual acuity (change of ≥ 2 lines of acuity or not) HbA1c **Follow-up:** 6 weeks
Notes	**Date study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of generating random number not described. The imbalance in the number of cases between 2 groups may have suggested improper random allocation (52 in tetramethylpyrazine group vs 35 in no treatment group)

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Dou 1998 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

Li 2007

Methods	**Design:** parallel group RCT **Randomisation method:** random number table **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment, with a mixture of 1 eye and 2 eyes. The selection of eye was based on the judgement of DR stage II to VI. The visual acuity results were reported based on the individual level
Participants	**Inclusion criteria:** DR diagnosed based on China National criteria **Number of participants:** 112 **Average age (range):** 64 (45-76) years **Gender (M/F):** 45/67 **Setting:** hospital in Lanzhou, Gansu Province, China
Interventions	**Intervention:** • Xueshuantong injection 500 mg in 250 mL 0.9% sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • no treatment **Participants in both groups received conventional intervention** in the form of laser photocoagulation and control of blood glucose and lipid **Treatment duration:** 2 weeks
Outcomes	Visual acuity (change of $\geq$ 2 lines of acuity or not) **Follow-up**: 2 weeks and 3 months

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Li 2007 (*Continued*)

Notes	**Date study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

Ren 2000

Methods	**Design:** parallel group RCT **Randomisation method:** not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment, without mixture of 1 eye and 2 eyes. The visual acuity results were reported based on the eye level and not adjusted for within-person correlation. An approximately correct analysis was used for a meta-analysis
Participants	**Inclusion criteria:** DR diagnosed based on China National criteria. **Number:** 30 **Mean age (range):** 63 (39-72) years **Gender (M/F):** 17/13 **Setting:** hospital in Shenyang, Liaoning Province, China

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Ren 2000 (*Continued*)

Interventions	**Intervention:** • Puerarin injection 400 mg for intravenous drip infusion, once a day **Comparator:** • Mecobalamin 500 μg for intramuscular injection, once a day **Participants in both groups received conventional intervention** in the form of antidiabetic drug to control serum glucose. **Treatment duration:** 6 weeks
Outcomes	Visual acuity (change of $\geq$ 2 lines of acuity or not) **Follow-up:** 6 weeks
Notes	**Date study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of generating random number not described.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

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Xu 2003

Methods	**Design:** parallel group RCT **Randomisation method:** not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment, with a mixture of 1 eye and 2 eyes. The visual acuity results were reported based on the eye level and not adjusted for within-person correlation
Participants	**Inclusion criteria:** participants with preproliferative DR **Number:** 37 **Mean age (range):** 63 (27-80) years **Gender (M/F)**: 17/20 **Setting:** hospital in Lishui, Zhejiang Province, China
Interventions	**Intervention:** • Puerarin injection 200-500 mg in 500 mL sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • No treatment **Participants in both groups received conventional intervention** in the form of laser photocoagulation therapy. **Treatment duration:** 2 weeks
Outcomes	Visual acuity (percentage of participants with increased visual acuity > 0.1) Observation in retina (percentage of participants with disappeared microaneurysms and retinal oedema) **Follow-up:** 2 weeks
Notes	**Date study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of generating random number not described.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No masking

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Xu 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

Yang 2005

Methods	**Design:** parallel group RCT **Randomisation method:** not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment. There was no report of single or both eyes. The outcome was reported based on the individual level
Participants	**Inclusion criteria:** DR diagnosed based on China National criteria. **Number:** 52 **Mean age (range):** 51 (35-67) years **Gender (M/F):** 28/24 **Setting:** hospital in Dandong, Liaoning Province, China
Interventions	**Intervention:** • Xuesaitong injection 400 mg in 250 mL 0.9% sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • oxerutins (Venoruton forte) 0.2 g in 250 mL 0.9% sodium chloride for intravenous drip infusion, once a day. **Participants in both groups received conventional intervention** in the form of antidiabetic drug to control serum glucose. **Treatment duration:** 30 days (5 interval days between 2 courses of 15 days)
Outcomes	Observation in retina (percentage of participants with atrophy new vessels and increased or original visual acuity) **Follow-up:** 30 days
Notes	**Date study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

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Yang 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of generating random number not described.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

Yin 2012

Methods	**Design:** parallel group RCT **Randomisation method:** random number table **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment, with a mixture of 1 eye and 2 eyes. The selection of eye was based on the judgement of DR stage I to IV. The visual acuity results were reported based on the eye level and not adjusted for within-person correlation. An approximately correct analysis was used for a meta-analysis
Participants	**Inclusion criteria:** DR diagnosed based on WHO criteria. **Number:** 60 **Mean age (range):** 63 (49-76) years **Gender (M/F):** 37/33 **Setting:** hospital in Longhua County, Hebei Province, China
Interventions	**Intervention:** • Puerarin injection 400 mg in 250 mL 0.9% sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • no treatment

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Yin 2012 (*Continued*)

	Participants in both groups received conventional intervention in the form of antidiabetic drug or insulin to control serum glucose **Treatment duration:** 20 days (with a 3-day interval in the middle)
Outcomes	Visual acuity (change of ≥ 2 lines of acuity or not) **Follow-up:** 20 days
Notes	**Date study conducted:** July 2008 to June 2011 **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

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Yuan 2012

Methods	**Design:** parallel group RCT **Randomisation method:** random number table **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment, with a mixture of 1 eye and 2 eyes. No information was provided on the selection of eye. The visual acuity results were reported based on the eye level and not adjusted for within-person correlation. An approximately correct analysis was used for a meta-analysis
Participants	**Inclusion criteria:** DR diagnosed based on China National criteria. **Number:** 128 **Mean age (range):** NR (46-69) years **Gender (M/F):** 66/62 **Setting:** hospital in Guangzhou, Guangdong Province, China
Interventions	**Intervention:** • Xueshuantong injection 450 mg in 250 mL 0.9% sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • no treatment **Participants in both groups received conventional intervention** to control glucose, blood pressure and lipids. **Treatment duration:** 2 weeks.
Outcomes	Visual acuity (change of ≥ 2 lines of acuity or not) HbA1c **Follow-up**: 2 weeks
Notes	**Date study conducted:** December 2008 to September 2011 **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table was used.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered

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Yuan 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

Zhao 2009

Methods	**Design:** parallel group RCT **Randomisation method:** not specified **Unit of randomisation:** participant **Masking:** no **Power calculation:** no **Dropouts/withdrawals:** no **Eyes:** 2 eyes included in study and both eyes received same treatment. There was no report about the involvement of 1 or 2 eyes during evaluation. The visual acuity results were reported based on the individual level
Participants	**Inclusion criteria:** DR **Number:** 30 **Mean age:** 58 years **Gender (M/F):** 13/17 **Setting:** hospital in Mianchi, Henan Province, China
Interventions	**Intervention:** • Puerarin injection 300 mg in 250 mL 0.9% sodium chloride solution for intravenous drip infusion, once a day. **Comparator:** • no treatment **Participants in both groups received conventional intervention** in the form of symptomatic and supportive treatments. **Treatment duration:** 2 weeks
Outcomes	Visual acuity (change of ≥ 2 lines of acuity or not) **Follow-up:** 2 weeks
Notes	**Date study conducted:** NR **Funding source:** NR **Declaration of interest:** NR **Trial registration ID:** not registered
Risk of bias	

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Zhao 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of generating random number not described.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of placebo control and masking. Multiple conventional interventions were administered
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of masking. For the outcome assessment, subjective influence could not be excluded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported, but there was insufficient information to permit judgement of relevant risk of bias

DR: diabetic retinopathy; F: female; HbA1c: glycated haemoglobin A1c; M: men; NR: not reported; RCT: randomised controlled trial; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Feng 2007	Relevant outcomes not measured. Blood rheology indexes and haemodynamic indexes were measured
Gao 2012	Different doses of ligustrazine (Chuanxiongqin) injection compared between groups
Jiang 2006a	Chinese medicine used in both groups.
Jiang 2006b	2 single herbal preparations combined in treatment group.
Lanthony 1988	No targeted outcome measures. Colour saturation was studied.
Liu 2005	Relevant outcomes not measured. Measured thromboxane B_2 and 6-keto prostaglandin $F_{1\alpha}$.
Lu 2017	Not a single herb extract.

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(*Continued*)

Ma 2008	Chinese medicine used in both groups.
Scorolli 1997	Relevant outcomes not measured. Colour saturation was studied
Tang 2009	Different administration routes of liquid ambaris fructus compared between groups
Wang 2006	Chinese medicines used in both groups.
Wang 2017	Treatment was a compound Chinese medicine preparations in which astragali was 1 ingredient
Wu 2005	Treatment was a compound Chinese medicine preparations in which Notoginseng was the main ingredient
Wu 2017	Not a single herb extract.
Xia 2012	Compound Chinese herbal medicines used in treatment group.
Xu 2010	Chinese medicine combined with Xuesaitong injection was used in treatment group

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DATA AND ANALYSES

Comparison 1. Herb plus conventional intervention versus conventional intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity (gain of ≥ 2 lines) (end of treatment)	5	541	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.08, 1.48]
1.1 Puerarin	2	114	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.80, 2.32]
1.2 Xueshuantong	2	288	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.72, 2.89]
1.3 Tetramethylpyrazine	1	139	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.00, 2.58]
2 Visual acuity (gain of ≥ 2 lines) (end of follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Observations in retina: reduction in microaneurysms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Observations in retina: reduction in haemorrhages	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Glycated haemoglobin A1c (%)	2	215	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.58, 0.58]

Comparison 2. Herb plus conventional intervention versus Troxerutin or vitamin B and subgroup plus conventional intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity (gain of ≥ 2 lines)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Glycated haemoglobin A1c	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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CONTRIBUTIONS OF AUTHORS

Conceiving the review: HWZ.

Designing the review: HWZ.

Co-ordinating the review: HWZ, HYZ.

Data collection for the review:

- designing search strategies: HWZ, HYZ;
- undertaking searches: HWZ, HYZ, SG;
- screening search results: HWZ, HYZ;
- organising retrieval of papers: HWZ, HYZ;
- screening retrieved papers against inclusion criteria: HWZ, HYZ, SG;
- appraising quality of papers: HWZ, HYZ;
- extracting data from papers: HWZ, HYZ;
- writing to authors of papers for additional information: HWZ, XW;
- providing additional data about papers: HWZ, HYZ;
- obtaining and screening data on unpublished studies: HWZ, HYZ.

Data management for the review:

- entering data into Review Manager 5: HWZ, HYZ
- Analysis of data: HWZ, XW.

Interpretation of data:

- providing a methodological perspective: HWZ, XW, SG;
- providing a clinical perspective: HYZ, HWZ, XW;
- providing a policy perspective: HWZ;
- providing a consumer perspective: XW, SG.

Writing the review: HWZ, SG, HYZ.

Providing general advice on the review: SG, XW.

Securing funding for the review: HWZ.

Performing previous work that was the foundation of the current study: HWZ.

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DECLARATIONS OF INTEREST

HYZ: none known.

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SG: none known.

XW: none known.

GL: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We initially intended to review all the herbal treatment including single herb and herbal mixtures as detailed in the protocol. However, because there was a heterogeneous mixture of interventions, we decided to focus this review on the efficacy of single herbs. The review title has also been changed accordingly. The mixture of many herbs prepared in decoction, tablet or injection is the most commonly used treatment approach for diabetic retinopathy in China. Further reviews to summarise those studies may be needed in the future.

The planned subgroup analysis in the protocol was not conducted due to the insufficient relevant information. We performed subgroup analysis based on each single herbal extract to explore possible difference between them.

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