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Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

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Title

Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

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ABSTRACT

Objectives

To provide a broad evaluation of the efficacy and safety of oral Chinese herbal medicine (CHM) as an adjunctive treatment for diabetic kidney disease (DKD), including mortality, progression to end stage renal disease (ESKD), albuminuria, proteinuria and kidney function.

Design

A systematic review and meta-analysis.

Methods

Randomised controlled trials (RCTs) comparing oral CHM with placebo as an additional intervention to conventional treatments were retrieved from five English (CENTRAL, MEDLINE, Embase, AMED and CINAHL) and four Chinese databases (CBM, CNKI, CQVIP and Wanfang) from inception to May 2018. RCTs recruiting adult DKD patients induced by primary diabetes were considered eligible, regardless of the form and ingredients of oral CHM. Mean difference (MD) or standardized mean difference (SMD) was used to analyze continuous variables and risk ratio (RR) for dichotomous data, both with 95% confidence intervals (CIs).

Results

From 7,255 reports retrieved, 20 eligible studies involving 2,719 DKD patients were included. CHM was associated with greater reduction of albuminuria than placebo, regardless of whether angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) were concurrently administered (SMD -0.56, 95%CI [-1.04,

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-0.08], *P*=0.002) or not (SMD -0.92, 95%CI [-1.35, -0.51], *P*<0.0001). When CHM was used as an adjunct to ACEi/ARB, serum creatinine was lower (MD, -4.02 μmol/L; 95%CI [-7.81, -0.23], *P*=0.15) and glomerular filtration rate was improved (MD, 5.8 mL/min; 95%CI [2.42, 10.14], *P*=0.001) in the CHM group than placebo group. The effects of CHM on progression to ESKD and mortality were uncertain due to low event rates. CHM appeared to be well-tolerated, with low reported rates of adverse events.

Conclusions

With moderate to low quality evidence, CHM may have beneficial effects on renal function and albuminuria beyond that afforded by conventional treatment in adults with DKD. Further well-conducted, adequately powered trials are warranted to confirm the long-term effect of CHM.

PROSPERO registration number: CRD42015029293

Index words: diabetic kidney disease (DKD); Chinese herbal medicine (CHM); complementary and alternative medicine; systematic review; meta-analysis

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ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review and meta-analysis provided a broad review of the efficacy and safety of oral Chinese herbal medicine for diabetic kidney disease, with patient-oriented outcomes such as mortality, progression to ESKD and quality of life.
- Only randomised controlled trials applied matched placebo to achieve blinding were included, to avoide potential risk of performance bias which may exaggerate the CHM effect.
- The search strategy was comprehensive and over 7,000 articles were screened, as a result 20 studies with a large total sample size of 2,719 participants were collected.
- A priori subgroups analysis was planned and completed to provide potential candidate formulae and frequently used herbs for further investigation.
- The overall quality of evidence was moderate to very low mainly due to unclear randomization procedures, wide confident interval and heterogeneity in outcome measures.

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INTRODUCTION

Diabetic kidney disease (DKD) is one of the most common complications of diabetes. As the prevalence of diabetes continues to grow globally, it is estimated that the number of DKD patients will double by 2025.[1] Since patients with DKD are at markedly higher risks of progression to end stage kidney disease (ESKD) and cardiovascular disease (CVD), the socioeconomic and public health burden of DKD is significant.[2, 3] Effective therapies in preventing and treating DKD are therefore of critical importance.

Risk factor management, including glycemic and blood pressure control, is one of the mainstays of treatment of DKD and has been successful in reducing its progression and complications.[4, 5] However, such treatments have only been partially successful. Moreover, the optimal interventions for these risk factors remain unclear, including the appropriate choice of anti-diabetic agents, and the optimal targets for glycemic and blood pressure levels for various subgroups. Renin-angiotensin system (RAS) blockade is partially effective in reducing the progression and complications of DKD in those with increased albuminuria excretion, although its role is less certain in those with deteriorating glomerular filtration rate (GFR) without albuminuria.[6-8] Some promising therapies addressing novel targets, such as sulodexide and bardoxolone methyl, have been found to be ineffective and/or harmful, whilst several others, including mineralocorticoid receptor antagonist and phosphodiesterase inhibitors, are still under evaluation.[9-11]

To facilitate the discovery of new therapeutic agents for patients with diabetes and

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impaired renal function, screening candidates from natural products including Chinese herbal medicine (CHM) which have been traditionally used for symptoms associated with this indication, may offer insights into a more targeted approach for therapeutic development. With respect to CHM, relevant records of treatment of DKD symptoms in Chinese classical literature date back to the *Han* dynasty (AD 202–220) and it has evolved to contemporary literature including RCTs concerning the use of CHM for diabetes and its complications.[12] Some herbal formulae and manufactured medicines have been recommended for patients with DKD in the clinical practice guidelines of Chinese Medicine.[13-15] However, these guidelines were based on experts' consensus rather than outcomes of systematically evaluated best available clinical evidence. Moreover, safety concerns existed due to the potential for aristolochic-acid nephrotoxicity with some herbal products.[6, 16] Even though legislation and quality control have been reinforced in recent years, the general lacks of information regarding the safety profiles of some herbal formulae due to their multi-compound nature have limited their application.[6, 17]

In recent years, there have been a growing number of clinical trials of CHM and related systematic reviews of CHM as adjunctive treatment for DKD. Unfortunately, most of these systematic reviews included original studies lack of blinding and focusing on specific CHM formulae, with poor report completeness.[18] As unmasking was associated with exaggeration of intervention effects,[19] we therefore undertook a systematic review and meta-analysis of randomized, placebo-controlled trials to evaluate the efficacy and safety of oral CHM as adjunctive treatment for DKD.

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METHODS

This systematic review was conducted followed the Cochrane handbook of systematic reviews of interventions and reported in accord with the PRISMA guidelines.[20, 21] The protocol was registered in the PROSPERO database and can be accessed online (Registry number: CRD42015029293).

Search Strategy

A comprehensive search was conducted in the following databases irrespective of publication status or language: MEDLINE, EMBASE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine Database (AMED), China BioMedical Literature (CBM), China National Knowledge Infrastructure (CNKI), Chonqing VIP (CQVIP) and Wanfang. The former five databases were in English while the later four were in Chinese. Databases were searched from inception to May 2018. The U.S.A. National Institutes of Health register (ClinicalTrials.gov), the Australian New Zealand Clinical Trial Registry (ANZCTR), the Chinese Clinical Trial Registry (ChiCTR), and the European Union Clinical Trials Register (EU-CTR) were searched for completed but unpublished trials. Further, reference lists of related systematic reviews were reviewed for additional publications.

Search terms included “diabetic nephropathy”, “diabetic kidney disease”, “albuminuria”, “Traditional Chinese Medicine”, “randomized controlled trial” and their synonyms. All terms were mapped to controlled vocabulary (where applicable) in addition to being searched as keywords. A sample of search strategy of MEDLINE

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has been provided (**Table S1**).

Eligibility criteria

Eligible studies had to fulfill the following criteria: (1) randomized controlled trial design; (2) included primary diabetes adults with persistent increased albuminuria/proteinuria excretion, which was defined as an albumin excretion rate (AER) more than 20 μg/min, an albumin-to-creatinine ratio (ACR) larger than 30 mg/g or 24-hour proteinuria over 0.5 g/d;[6, 7] (3) intervention was oral Chinese herbal medicine, which could have been either single or multiple ingredients in any form (decoction, granules, capsules etc.); (4) CHM matched placebo was applied in the control group; (5) both intervention and control groups received the same conventional treatments of DKD, including comprehensive management of glycaemia, blood pressure, serum lipid level, life-style and nutrition in accordance with Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines' recommendation;[6, 7] and, (6) the study reported at least one of the primary outcomes. Studies including patients with albuminuria that was not caused by diabetes, patients who already had ESKD, or those receiving renal replacement therapy were excluded.

Outcomes of Interest

Primary outcomes of interest included albuminuria/proteinuria, kidney function, number of participants progressing to ESKD, all-cause mortality and adverse events, at the end of treatment or follow-up. Progression to ESKD was defined as initiation of renal replacement therapy or estimated GFR (eGFR) lower than 15 mL/min/1.73m^2. Kidney function was reflected by the measurement of serum creatinine concentration

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(Scr) and glomerulus filtration rate (GFR). Likewise, quantitative measurement of albuminuria and proteinuria included urinary albumin excretion rate (AER), albumin-to-creatinine ratio (ACR), 24-hour urine protein excretion (UP) and protein-to-creatinine ratio (PCR).

Secondary outcomes included cardiovascular mortality, all-cause hospitalization, quality of life measured by validated scales, indicators of risk factor control (such as fasting blood glucose, glycated haemoglobin [HbA1c], blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]). All outcomes were reported with specified units at the end of treatment or at the end of follow-up.

Safety outcomes included numbers of any adverse events and serious adverse events during the study period.

Study Selection and Data Extraction

Titles and abstracts identified in searching were screened by one reviewer and then checked by another investigator (L.Z. and X.Q.) against the predefined criteria. After titles and abstracts screening, possibly relevant studies underwent full-text review by L.Z. and cross checked by L.Y. to confirm their eligibility. Any disagreement was resolved by consensus and discussion with a third reviewer (J.S. or AL.Z.).

Two reviewers (L.Z and L.Y.) independently extracted data from eligible studies into a pre-designed spreadsheet. A third reviewer (J.S.) cross checked the data. Study design characteristics, trial locations, demographic features (age, types of diabetes, baseline albuminuria, kidney function, etc.), intervention and control protocol (herbal

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ingredients, dosage, frequency, treatment duration, follow-up period, etc.), and outcome measures were recorded. Authors of studies with missing data were contacted by email or telephone to obtain additional data.

Data Synthesis and Analysis

All studies satisfying the eligibility criteria were included for qualitative synthesis. For continuous variables, mean and standard deviation of each study were obtained and pooled as mean difference (MD) or standardized mean differences (SMD) with a 95% confidence interval (CI). For dichotomous data, risk ratios (RR) were calculated with a 95% CI. Considering the diversity of interventions and potential heterogeneity among included studies, a random-effect model was applied in all meta-analyses. Review Manager Software (RevMan, version 5.3) was used to perform the statistical analysis.[22]

Pre-defined subgroup analysis included baseline DKD severity and CHM formulae. Heterogeneity between studies was detected by using the Cochrane Q statistic and I^2 test. For outcomes with substantial heterogeneity (I^2 levels >50%), subgroup analyses were performed to explore potential sources, whereby results were stratified by factors, such as different measured approaches for the same outcome. Sensitivity analysis was performed by excluding studies with high/unclear risk of bias in the domain of random sequence generation. Publication bias was explored when 10 or more studies were included in one meta-analysis by visual inspection of funnel plots for asymmetry.

Quality Assessment

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The methodologic quality of each individual study was assessed by two reviewers (L.Z. and L.Y.) in parallel according to the Cochrane Risk of Bias (ROB) tool.[23] For the domain of other sources of bias, baseline imbalance and conflicts of interest were evaluated. Each domain was judged as high, low or unclear risk of bias with justifications. The consistency was checked by a third reviewer (L.Z.) and disagreements were resolved by discussion with methodologists (AL.Z. and X.G.).

To evaluate the overall quality of evidence for primary outcomes, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied.[24] A panel group was formed to make the GRADE evaluation, which included methodologists, CM practitioners and conventional medicine physicians. The assessments of evidence started at 'high quality', and were downgraded when significant risk of bias, indirectness, inconsistency, imprecision of estimated effect or publication bias were detected.

Patient and Public Involvement

Patients or public were not directly involved in this systematic review.

RESULTS

Description of Studies

The comprehensive search retrieved over 50 thousand citations and 7,255 of them were examined in full-text (**Figure 1**). Eighty-five percent of the studies were excluded due to lack of a placebo control. As a result, 20 eligible studies with 23 publications involving 2,719 DKD participants were included.[25-47] For studies with

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multiple reports, the most recent publication or the one with primary outcomes was used, and complementary outcomes data from other reports were extracted and merged.

Characteristics of the included studies are summarized in **Table 1**. All 20 studies were conducted in China. Except for one study[34] written in English, all others were published in Chinese language between 2000 and 2017. Enrolled participants were all diabetic patients with exceeded albuminuria or proteinuria but varied in baseline kidney function. The mean of age was 55.1 years old (range 20 to 79). Three studies[27-29] used herbal compounds or a single herb as intervention while the remaining 17 studies used CHM formulae with multi-ingredients. The ingredients of CHM used in each study are provided in **appendix Table 2**. The most common herbal ingredients used by ten or more studies were *Astragali Radix, Rehmanniae Radix* and *Rhei Radix et Rhizoma.* All studies applied CHM matched placebo, except for one [47] which made Captopril (comparator) identical in appearance to CHM (intervention). Treatment duration ranged from 4 weeks to 2 years (median 3 months). There were no outcome data with respect to cardiovascular mortality and all-cause hospitalisation among all included studies.

Quality of Studies

Generally, the quality of included studies was fair with low or unclear risk of bias, especially regarding blinding and outcome data completeness (**Figure 2**). Two studies were judged as high risk of bias with respect to blinding of patients and personnel because blinding may have been compromised by prescription of unequal

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numbers/amounts of medication between groups.[43, 45] Twelve studies reported correct procedures for random sequence generation,[25, 27, 28, 30, 32, 34, 36-38, 43-45] whereas eight studies did not provide adequate details. For the domain of allocation concealment, one study did not conceal the allocation to researchers thus was judged with high risk.[37] Seven studies were considered with high risk of selection reporting bias (mainly incomplete reporting in secondary outcomes),[25, 30, 35, 38, 41, 44, 45] whilst unclear risk in 13 other studies since protocols were not found. Other biases included baseline balance and conflict of interest assessment. Two high risk studies included pharmaceutical industry employees as co-authors thereby introducing conflicts of interest.[27,28] Seven studies which either without baseline statistical test results or without information regarding sources of funding were ranked as unclear risk.[29, 31, 32, 36, 41, 43, 45]

Effect Evaluation of CHM Therapy

Considering the uses of RAS blockage may affect the primary outcomes, studies were categorized and separated into three groups according to trial application of RAS blockade (angiotensin converting enzyme inhibitors [ACEi] and/or angiotensin receptor blockers [ARB]) in each arm prior to meta-analysis. It should be noted that conventional concurrent treatments of DKD recommended by guidelines were applied equally in both groups in all included studies, such that these conventional treatments are not separately mentioned henceforth. The three groups were:

- CHM versus placebo; [25-33]
- CHM plus ACEi/ARB versus placebo plus ACEi/ARB;[34-38] and,

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- CHM versus placebo plus ACEi/ARB.[38-47]

Mortality and progression to ESKD

Though all-cause mortality was measured in a study [45] comparing CHM with matched placebo plus Irbesartan, no deaths observed amongst the 315 participants during the two-year follow-up (**Table 2**). Within the same trial,[45] the number of patients that progressed to ESKD was reported as part of the composite outcome, measuring with the number of patients with microalbuminuria progressing to macroalbuminuria, doubling serum creatinine from baseline, or initiating dialysis. Compared with placebo plus Irbesartan, the risk of experienced this composite outcome may be 66% lower in the CHM group (RR: 0.34, 95%CI [0.15, 0.77], P=0.01; low quality evidence).

Albuminuria

Fourteen studies reported albuminuria outcome at the end of treatment (**Figure 3a)**. Based on meta-analysis of eight studies[25-29, 31-33] involving 1,021 participants, the CHM group experienced lower end of study albuminuria than the placebo group (SMD -0.92, 95%CI [-1.35, -0.51], I^2=87%, P<0.0001; moderate quality evidence). Subgroup analysis suggested different CHM formulae could be the sources of heterogeneity (**Table S3**). The estimate of effect with the least heterogeneity was observed in the Qi Wei granule CHM subgroup[26, 33] in which albuminuria was 70.06 mg/24h lower compared to placebo after 3 months (95%CI [-88.84, -51.28], I^2=0%, P<0.0001). Likewise, the Arctiin granule[27,28] probably reduced albuminuria greater than placebo group after 2 months intervention (SMD -0.38, 95% CI [-0.56, -0.20],

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I^2=0%, *P*<0.0001).

When used in combination with ACEi/ARB, lower end of treatment albuminuria level was still observed in the CHM rather than in the placebo group (SMD -0.56, 95%CI [-1.04, -0.08], I^2=64%, *P*=0.002; moderate quality evidence).[34, 36, 37] However, though lower albuminuria excretion was observed in the CHM group,[41, 42, 47] the effect of CHM in decreasing albuminuria compared to ACEi/ARB was uncertain because of the very low quality of evidence (**Table 2**).

Proteinuria

Nine studies measured end of treatment 24-hour proteinuria (**Figure 3b**). The pooled estimated effect favored CHM over placebo in reducing proteinuria, although heterogeneity was marked (SMD -1.34, 95%CI [-2.18, -0.51], I^2=94%, *P*=0.002; low quality evidence).[26-28, 33] Subgroup analysis revealed that different formulae and proteinuria measured approaches may have been the source of heterogeneity (**Table S3**). Pooled estimates of effect of Qi Wei granule[26, 33] and Arctiin granule[27, 28] both showed that CHM may lead to greater reductions in proteinuria than placebo. Subgroup of measurements unit of microgram per 24-hour showed the proteinuria was 324.42 mg/24h lower (95%CI, [-485.15, -163.69]; I^2=30%; *P*<0.0001) in the CHM than the placebo group.[27, 28, 33]

However, favorable effect of CHM disappeared when combination used with ACEi/ARB in proteinuria outcome. Meta-analysis of four studies with 489 participants[34-36, 38] reporting proteinuria showed little between group difference with significant heterogeneity (SMD -0.15, 95%CI [-0.52,0.23], I^2=72%, *P*=0.44; low

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quality evidence). Sources of heterogeneity were not identified (**Table S3**). Likewise, it remained unknown whether CHM reduced more proteinuria than ACEi/ARB based on current low quality of evidence of uncertain effect (**Table 2**).[38, 43]

Serum Creatinine Level

Ten studies provided end of treatment data of serum creatinine (Scr) level (**Figure 3c**). Pooled estimation of two small studies[30, 33] showed that the additional CHM intervention may have made little difference to Scr compared with placebo (MD 5.75 μmol/L, 95%CI [-2.06, 13.57], I^2=0%, *P*=0.15; moderate quality of evidence). In contrast, an average 4.02 μmol/L lower (95%CI [-7.81, -0.23], I^2=0%, *P*=0.15; moderate quality evidence) end of treatment Scr level was observed in the CHM plus ACEi/ARB group compared to the ACEi/ARB alone group.[34-38] Subgroup analysis found that the lowering Scr effect of CHM was evident in patients with abnormal baseline Scr (MD -9.99 μmol/L, 95%CI [-17.71, -2.26], I^2=0%, *P*=0.01).[36, 38]

Though lower Scr level was observed in the CHM group when directly compared to ACEi/ARB group, the confidence was compromised due to the conflict sensitivity analysis result (**Table S4**).[38, 41-43] Subgroup analysis found that the superiority of CHM in reducing Scr was the most apparent in patients with normal baseline Scr (MD -4.07 μmol/L 95%CI [-6.13, -2.01], I^2=0%, *P*=0.0001) [41-43] or using the Tang Shen Ning formula (MD -3.96 μmol/L, 95%CI [-6.13, -1.78], I^2=6%, *P*=0.0004).[41, 42]

Estimated Glomerular Filtration Rate

Of the eight studies, the glomerular filtration rate (GFR) was estimated by either Cockcroft-Gault equation or other serum creatinine-based equations (**Figure 3d**).

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Benefits of CHM was observed when adding on ACEi/ARB, with an average 6.28 mL/min higher estimated GFR (eGFR) than placebo plus ACEi/ARB (95%CI [2.42, 10.14], I^2=0%, *P*=0.001; moderate quality evidence).[34, 36-38] Subgroup analysis of specific formula showed the end of treatment eGFR was 5.22 mL/min higher (95%CI [0.69, 9.74], I^2=0%, *P*=0.02) in the Tang Shen Fang formula plus ACEi/ARB group than the ACEi/ARB alone group.[34, 38]

One small study (44 participants)[33] provided low quality of evidence that CHM was not superior to placebo in terms of eGFR (**Table 2**). When compared to active control (ACEi/ARB), pooled estimation indicated that no significant differences between the CHM group and the ACEi/ARB group for improving eGFR (low quality evidence; **Table 2**).[38, 41, 42, 44]

Secondary Outcomes

Meta-analysis results of secondary outcomes were summarized in **appendix Table S5**. When compared to placebo, the pooled estimated effects for both fasting blood glucose (FBG)[25, 30-33, 36, 37, 42, 47] and HbA1c[30, 31, 33, 34, 36, 37, 42, 47] did not show additional benefit of CHM in lowering blood glucose. Likewise, summarized effects from three studies showed no statistical differences between the CHM and placebo groups for systolic and diastolic blood pressure.[31, 33, 34] CHM resulted in lower levels of total cholesterol,[29-32, 34, 36, 37, 47] triglycerides[29-32, 34, 36, 37, 47] and LDL-C[29-32, 34, 36, 37], although HDL-C levels[29-32, 34, 36, 37, 47] were not statistically significantly different compared to placebo. However, the results were limited by substantial heterogeneity and the reason was not found. Three studies [34, 38, 45]measured patients' quality of life by questionnaire

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at the end of treatment but only two of them applied Diabetes QoL tool provided usable data. The pooled estimation suggested no statistically significant differences between the CHM and the placebo group regarding the quality of life.[34, 45]

Safety Evaluation of CHM Therapy

Data on adverse events were provided in 14 studies. Of these, seven studies stated no adverse events were observed during study period.[26, 30, 33, 35, 42, 44, 47] In total, 53 cases of adverse events were reported in seven studies with 1,445 participants. Except for Li's study,[45] details of AEs in each group were reported. The most common AE of CHM was digestive system disorders (18 cases), including abdominal pain, diarrhea or sloppy stool.[27, 28, 37] Both the CHM and control groups reported a modest number of cases of elevated liver enzyme levels (11 cases), infection (2 cases) or anemia (3 cases).[34, 38, 43] In a three-arm study,[38] one case of hypertension in the CHM group, one case of hypotension in losartan group and one case of hyperkalemia in CHM plus losartan group were reported. All participants experienced above AEs recovered after discontinuation of the tested interventions. Three cases of serious AEs, including two cases of death and a case of acute myocardial infarction (AMI), were reported in Li's trial.[34] One participant in the CHM group died due to subarachnoid hemorrhage while another participant died after AMI. The researchers reported that these serious AEs were not related to the study agent.

Sensitivity and Subgroup Analysis

The sensitivity analysis of excluding studies with substantial risk of bias regarding randomization showed consistency results with the primary analysis, except for the

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comparison of CHM versus placebo plus ACEi/ARB in terms of Scr level (**Table S4**). Subgroup analysis indicated that baseline kidney function, different CHM formulae and outcome measured methods could partially explain the variant treatment effect of primary outcomes (**Table S3**). Publication bias was not evaluated due to the limited number of studies included in each outcome.

DISCUSSION

This review included 20 RCTs involving 2,719 participants to evaluate the effects and safety of CHM or placebo in addition to conventional therapies of DKD. As an adjunctive therapy, CHM favorably decreased proteinuria (either measured as urinary albumin or protein excretion) in patients with DKD compared with placebo, regardless of concomitant use of ACEi/ARB or not. When CHM and ACEi/ARB were used simultaneously, beneficial effects of CHM on Scr and eGFR were observed. In addition, CHM appeared to play a role in regulating blood lipids in the DKD population. These results suggest potential additional renal protective benefit by adding CHM to other conventional pharmacotherapies in DKD populations. However, due to the short follow-up periods and small numbers of clinical events (such as mortality and progression to ESKD) in included studies, the long-term clinical benefit of CHM is yet to be determined.

Findings from this review were basically in line with those of previous reviews focusing on single herbs or particular formulae. Li et.al reviewed the clinical effect of preparations of *Astragali Radix* in DKD patients, finding that *Astragali* injection

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lowered Scr, increased eGFR and reduced urinary protein based on data from 21 randomized controlled trials and 4 non-randomised controlled trials.[48] In published reviews of *Ginkgo Folium* extract and Xue Zhi Kang capsules, lower fasting blood glucose and HbA1c levels in the CHM group were reported.[49, 50] The inconsistency in terms of the glycemic outcomes may have been due to differences in ingredients amongst the included studies. In our review, only two trials applied either *Ginkgo Folium* extract or Xue Zhi Kang capsules as interventions. The glycemic control effect may have been diluted by other trials using various herbal ingredients, which targeting on kidney rather than glycemic control. It should also be noted that the studies included in the previous reviews of *Ginkgo Folium* extract and Xue Zhi Kang capsules resulted in significant risk of bias (including publication bias). Thus, rigorous and large scale clinical trials are needed to confirm the glycemic control effects of CHM.

The renal protective effect of CHM may be related to particular bioactive compounds contained in the herbal ingredients included in these RCTs. The most frequently used herb was *Astragali Radix*. Both *in vitro* and *in vivo* studies have indicated that chemical components of *Astragali Radix, such as* Astragaloside IV and Astragalus Saponin I, exert anti-oxidative and anti-inflammatory properties in diabetic models.[51,52] These chemicals can prevent and restore kidney tissue injury related to oxidative stress. Additionally, Astragaloside IV can reduce endoplasmic reticulum stress and increase podocyte integrity, which is the therapeutic target for decreasing albuminuria.[53, 54] The second most frequently used herb, *Rehmanniae Radix*, also

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upregulates anti-inflammatory and antioxidant effects in diabetic rats.[55] Furthermore, anti-diabetic properties were observed in its constituent compound (catalpol) and ethanolic extract.[56] Although the glucose lowering effect of *Rehmanniae Radix* was not superior to metformin, its use was associated with higher anti-inflammatory activity, lower oxidative stress levels, and restoration of diabetes-induced kidney lesions. The third most frequent herb was *Rhei Radix et Rhizoma*. Active compounds of *Rhei Radix et Rhizoma,* including anthraquinones (rhein and emodin) and phenolic acids (gallic acid and ferulic acid), have been shown to protect the kidneys by reducing oxidative stress, inflammation, fibronectin and extracellular matrix accumulation.[57-59] Furthermore, *in vitro* experiments have demonstrated that extracts of *Rhei Radix et Rhizoma* can inhibit lipid peroxidation and lower serum lipid levels, which are risk factors for diabetes and DKD progression.[60,61]

This study demonstrated that CHM may be applied as an add-on treatment for DKD to achieve better renal outcomes. For those patients with DKD who are on ACEi/ARB, CHM may improve kidney function, albuminuria, proteinuria and blood lipids. For the subgroup of patients with DKD who are intolerant to ACEi/ARB, CHM can be applied with standard care to decrease urinary protein excretion. Since the participants in most included trials were older adults with a GFR greater than 60 mL/min, the renal protective effect of CHM in younger individuals and in advanced kidney disease is less uncertain. Moreover, all included studies were conducted in China, such that the effect of CHM reported in this review may not be generalizable to other population groups. It should further be noted that, in most of the included studies, the

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forms of CHM used were multi-ingredients herbal formulae, which were constructed based on traditional Chinese medicine theory and experts' clinical experience. While indicative from pharmacological studies, the most frequently used ingredients discussed above may not necessarily be relevant to the observed effects reported in this study.

Renal toxicity induced by aristolochic acid (AA) has been alerted since a series of renal failure cases caused by AA contaminated products were reported.[62, 63] In our review, the CHM used in included studies appeared to be well-tolerated and safety signals were not identified. This could be related to the fact that all herbal ingredients investigated were free from AA, and some of the studies mentioned a strict quality control processes regarding the CHM raw material and manufactured procedures.[34, 40, 45] Mortality risk reduction effect of non-AA prescribed CHM was indicated in a Chronic Kidney Disease population study, but for DKD patients, the long-term safety of CHM requires further studies to confirm.[64]

Although this review was conducted in a systematic and comprehensive manner, there are limitations that should be taken into account when interpreting the findings. Firstly, the number of included studies was relatively small and few studies measured and reported the same outcomes consistently. This caused difficulty in meta-analysis and introduced heterogeneity across studies and led to downgrade in quality of evidence. Core outcome sets with standardized measurements are needed in future studies to determine the effect of CHM. Secondly, most of the studies had short follow-up periods (1-3 months) and small sample sizes, leading to imprecision of the estimated

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effect and low confidence with regard to long-term benefit and effect on renal function. Thirdly, more than half of the included studies did not provide information on randomization and allocation procedures, such that the impact of potential selection bias was unclear. In addition, although the CHM formulae were processed as granules or capsules in order to achieve blinding, quality assurance information for each CHM preparation was not provided in most of the studies. Further studies are strongly encouraged to report following the CONSORT reporting guidelines.[65-67] Finally, although we did not limit the CHM interventions in terms of herbal composition, five included studies shared highly homologous CHM ingredients synthesis,[26, 33, 34, 38, 45] thereby limiting the diversity of CHM treatments evaluated.

CONCLUSION

In conclusion, combination of CHM with conventional RAS blockade pharmacotherapy showed promise as an add-on treatment for improving renal function and decreasing urinary albumin and protein excretion in patients with DKD. The rate of occurrences adverse events was low and the tested CHM appeared to be well-tolerated. This systematic review also provided potential candidate formulae and frequently used herbs for further investigation. Well-designed RCTs following reporting guidelines with adequate sample sizes and follow-up periods are warranted to confirm the long-term efficacy and safety of CHM, especially with respect to patient-oriented outcomes such as mortality, disease progression, and quality of life.

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Competing Interests

None declared.

Data Sharing Statement

No additional data are available.

Contributions

Research idea and study design: LZ, CL, CCX, WM; data collection and screening: LZ, LY, JS, XQ, ALZ; data extraction: LZ, LY, JS; data analysis: LZ, JS; ROB assessment: LZ, LY, XG, ALZ; GRADE assessment: WM, LZ, LY, JS, and DJ; Manuscript writing: all authors; supervision and mentorship: CCX, XL, CL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately

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investigated and resolved.

Supplementary Appendix

Table S1: Search strategy of MEDLINE.

Table S2: Herbal Ingredients used in included studies

Table S3: Subgroup Analysis of primary outcomes

Table S4: Sensitivity Analysis of primary outcomes

Table S5: Meta-analysis results of secondary outcomes

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References

[1]. White SL, Chadban S. KinD Report (Kidneys in Diabetes): temporal trends in the epidemiology of diabetic kidney disease and the associated health care burden in Australia. *Report of the Kidney in Diabetes*. Melbourne, Australia: Kidney Health Australia; 2014.

[2]. Saran R, Li Y, Robinson B, et al. US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2015;66 (1) (suppl 1):S1-S305.

[3]. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension*. 2003;42(5):1050-1065.

[4]. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA*. 2003;290(16):2159-2167.

[5]. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317(7160):703-713.

[6]. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

[7]. Fingerhut D. KDOQI Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis*. 2007;49(2)(suppl 2):S12-S154.

[8]. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA*. 2016;316(6):602-610.

[9]. Packham DK, Wolfe R, Reutens AT, et al. Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy. *J Am Soc Nephrol*. 2012;23(1):123-130.

[10]. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013;369(26):2492-2503.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[11]. Brenneman J, Hill J, Pullen S. Emerging therapeutics for the treatment of diabetic nephropathy. *Bioorg Med Chem Lett*. 2016;26(18):4394-4402.

[12]. Zhang L, Li Y, Guo X, et al. Text mining of the classical medical literature for medicines that show potential in diabetic nephropathy. *Evid Based Complement Alternat Med*. 2014; 2014:189125.

[13]. Gao YB, Liu TH, Nan Z, Zhen Z, Zhou Q. The Chinese medicine diagnosis and treatment standards of diabetic nephropathy. *World Journal of Integrated Traditional and Western Medicine.* 2011;6(6):548-552. (in Chinese)

[14]. China Academy of Chinese Medical Sciences. Evidence-based guidelines of clinical practice in Chinese medicine- internal medicine. *Beijing: China Press of Traditional Chinese Medicine;* 2011. (in Chinese)

[15]. China Association of Chinese Medicine. Guideline for TCM diabetes prevention and treatment. *Beijing: China Press of Traditional Chinese Medicine;* 2007. (in Chinese)

[161. Lord GM, Cook T, Arlt VM, Schmeiser HH, Williams G, Pusey CD. Urothelial malignant disease and Chinese herbal nephropathy. *Lancet*. 2001;358(9292):1515-1516.

[17]. Stanifer JW, Kilonzo K, Wang D, et al. Traditional medicines and kidney disease in low-and middle-income countries: opportunities and challenges. *Semin Nephrol*. 2017;37(3):245-259.

[18]. Abstracts of the 24th Cochrane Colloquium, 23-27 October 2016, Seoul, South Korea. Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 2). dx.doi.org/10.1002/14651858.CD20160

[19]. Savović J, Jones H E, Altman D G, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials[J]. *Annals of internal medicine*, 2012, 157(6): 429-438.

[20]. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions 5.1. 0[J]. The Cochrane Collaboration, 2011: 33-49.

[21]. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement[J]. International journal of surgery, 2010, 8(5): 336-341.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[22]. The Nordic Cochrane Centre, The Cochrane Collaboration. *Review Manager (RevMan)*. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.

[23]. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

[24]. Schünemann H, Brozek J, Guyatt G. GRADE handbook for grading quality of evidence and strength of recommendation. https://gdt.gradepro.org/app/handbook/handbook.html. Accessed October 19, 2017.

[25]. Fan Y. Clinical study of Qi Kwai granules in early type 2 diabetic nephropathy. *Nanjing: Nanjing University medicin;* 2010. (in Chinese)

[26]. Jia XL. Study on clinic effect and experiment research of Qiwei treating the DN. *Beijing: Beijing University of Chinese Medicine;* 2012. (in Chinese)

[27]. Ma ST, Liu DL, Niu R, et al. Double -blind randomized placebo-controlled multi-centre phase □ clinical trial of Arctiin granule in the treatment of diabetic nephropathy. *Chin J Clin Pharmacol.* 2011;27(1):15-18. (in Chinese)

[28]. Ma ST, Liu DL, Niu R, et al. Tangjiangshekang granule in treatment of diabetic nephropathy: a double -blind, randomized, placebo-controlled multicentre clinical trial. *Chin J New Drugs Clin Rem.* 2011;30(1):16-19. (in Chinese)

[29]. Wei N, Chang WS, Xue DZ, Shen XF. Effect of Xuezhikang on oxidative stress in early diabetic nephropathy. *Chinese General Practice.* 2012;15(18):2085-2087. (in Chinese)

[30]. Wei X, Yao HJ, Liu Y, Zhang J. Efficacy observation of adjunctive treatment of gandi capsules for diabetic nephropathy. *China Pharmacy.* 2016;27(2):225-227. (in Chinese)

[31]. Xie SF, Huang LJ, Liu JS, Yu JY, Wang XC. The long-term effect of Yang yin he luo medicinals for reducing urinary albumin to creatinine ratio in early diabetic nephropathy patients. *Jiangsu J Tradit Chin Med.* 2011;43(9):19-20. (in Chinese)

[32]. Yang L, Tan ZH, Li YK. The clinical effect observation of Qiming granules with standard care for early diabetic nephropathy. *Guiding Journal of Traditional Chinese Medicine and Pharmacy.* 2014;20(6):52-53. (in Chinese)

[33]. Zhou JX. Effect and safety of Qiwei granule on diabetic nephropathy and podocyte. *Beijing: Beijing University of Chinese medicine*; 2014. (in Chinese)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[34]. Li P, Chen Y, Liu J, et al. Efficacy and safety of tangshen formula on patients with type 2 diabetic kidney disease: a multicenter double-blinded randomized placebo-controlled trial. *PLoS One*. 2015;10(5):e0126027.

[35]. Liu YF. Qihuang capsule in treatment of diabetic nephropathy Qi and Yin deficiency syndrome clinical. *Harbin: Heilongjiang University Of Chinese Medicine;* 2015. (in Chinese)

[36]. Ni Q, Jiang S, Xiao YX, et al. A clinical observation on Qiyao Xiaoke capsule combined with western medicine for 146 cases of Diabetic Nephropathy. *Journal of Traditional Chinese Medicine.* 2013;54(6):484-487. (in Chinese)

[37]. Yang M. Study on the clinical exploratory study of Qizhu granule in the treatment of early type 2 diabetic nephropathy. Beijing: China Academy of Chinese Medical Sciences; 2017. (in Chinese)

[38]. Zhang LF, Zhao JX, Lv RH, et al. Study on the effectiveness and safety of optimum program of prevention and treatment of renal insufficiency of diabetic nephropathy. *China Foreign Medical Treatment.* 2006;47(10):755-758. (in Chinese)

[39]. Zhang LF, Lv RH, Zhao JX, Wang SR. Effect of TCM treatment on quality of life in diabetic nephropathy patients with renal failure: a multi-centered clinical study. *Journal of Traditional Chinese Medicine.* 2008;49(2):119-122. (in Chinese)

[40]. Zhang LF, Zhao JX, Lv RH, et.al. The effect of Differiation Chinese Medicine Treatment on Syndrome Improvement in diabetic nephropathy patients with renal failure. Abstract of the forth International Integration Medicine Conference of Kidney Diseases. 2006. (in Chinese)

[41] Gao YB, Zhao HL, Guan S, et al. Clinical research of Tang Shen Ning in treating early stage of diabetic nephropathy with types of deficiency of both vital energy and yin and collaterals si ltation and stagnant. *China Journal of Traditional Chinese Medicine and Pharmacy.* 2006;21(7):409-411. (in Chinese)

[42]. Gao YB, Zhou H, Guan S, et,al..Multicenter randomized and double-blind controlled clinical trial of Tang Shen Ning Granules in treating diabetic kidney disease. *Chinese Journal of Traditional Chinese Medicine.* 2017;32(11):5212-215. (in Chinese)

[43] Han YL, Liu HF, Lou XE, Miao GZ, Wang XQ. Method of combination of disease and syndrome in treating stage IV proteinuria in diabetic nephropathy of Qi-Yin deficiency. *Journal of Changchun University of Traditional Chinese Medicine.* 2014;30(5):903-905. (in Chinese)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[44]. Jia M, Zhao JX, Dong C, Feng R. Clinical research of Sanhuang Yishen granule on patients diabetic nephropathy in □ stage. *World Chinese Medicine.* 2015;10(6):845-848. (in Chinese)

[45] Li J, Zhao JX, Wang SD, et al. Effect of the whole course intervention program of combined therapy of TCM on the endpoint events of diabetic nephropathy. *Journal of Traditional Chinese Medicine.* 2012;53(7):568-571. (in Chinese)

[46]. Zhou X, Zhao JX, Wang SD, et al. Effect of TCM Comprehensive Treatment Program on Quality of Life in Patients With Diabetic Nephropathy. *Journal of Traditional Chinese Medicine.* 2014;55(6):473-477. (in Chinese)

[47]. Lin L, Ni Q, Gao QJ et al. Clinical study on Tangweikang capsule in treating diabetic nephropathy. *Chinese Journal of Integrated Traditional and Western Medicine.* 2000;20(11):811-814. (in Chinese)

[48]. Li M, Wang W, Xue J, Gu Y, Lin S. Meta-analysis of the clinical value of Astragalus membranaceus in diabetic nephropathy. *J Ethnopharmacol*. 2011;133(2):412-419.

[49]. Zhang L, Mao W, Guo XF, et al. Ginkgo biloba extract for patients with early diabetic nephropathy: a systematic review. *Evid Based Complement Alternat Med*. 2013;2013:689142.

[50]. Wang F, Wu HM. Xuezhikang for diabetic kidney disease: a systematic review of randomized controlled trials. *Chin J Evid-based Med.* 2009;9(1):63-70. (in Chinese)

[51]. Gui D, Huang J, Guo Y, et al. Astragaloside IV ameliorates renal injury in streptozotocin-induced diabetic rats through inhibiting NF-kappaB-mediated inflammatory genes expression. *Cytokine*. 2013;61(3):970-977.

[52]. Qi W, Niu J, Qin Q, Qiao Z, Gu Y. Astragaloside IV attenuates glycated albumin-induced epithelial-to-mesenchymal transition by inhibiting oxidative stress in renal proximal tubular cells. *Cell Stress Chaperones*. 2014;19(1):105-114.

[53]. Gui D, Guo Y, Feng W, et al. Astragaloside IV, a novel antioxidant, prevents glucose-induced podocyte apoptosis in vitro and in vivo. *PLoS One*. 2012;7(6):e39824.

[54]. Wang ZS, Xiong F, Xie XH, Chen D, Pan JH, Cheng L. Astragaloside IV attenuates proteinuria in streptozotocin-induced diabetic nephropathy via the inhibition of endoplasmic reticulum stress. *BMC Nephrol*. 2015;16:44.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[55]. Waisundara VY, Huang M, Hsu A, Huang D, Tan BK. Characterization of the anti-diabetic and antioxidant effects of rehmannia glutinosa in streptozotocin-induced diabetic Wistar rats. *Am J Chin Med*. 2008;36(6):1083-1104.

[56]. Yang SS, Deng HC, Zhang QZ, et al. Amelioration of diabetic mouse nephropathy by catalpol correlates with down-regulation of Grb10 expression and activation of insulin-like growth factor 1 / insulin-like growth factor 1 receptor signaling. *PLoS One*. 2016;11(3):e0151857.

[57]. Zeng CC, Liu X, Chen GR, et al. The molecular mechanism of rhein in diabetic nephropathy. *Evid Based Complement Alternat Med*. 2014;2014:487097.

[58]. Ahad A, Ahsan H, Mujeeb M, Siddiqui WA. Gallic acid ameliorates renal functions by inhibiting the activation of p38 MAPK in experimentally induced type 2 diabetic rats and cultured rat proximal tubular epithelial cells. *Chem Biol Interact*. 2015;240:292-303.

[59]. Zhang ZH, Wei F, Vaziri ND, et al. Metabolomics insights into chronic kidney disease and modulatory effect of rhubarb against tubulointerstitial fibrosis. *Sci Rep*. 2015;5:14472.

[60]. Punithavathi VR, Prince PS, Kumar R, Selvakumari J. Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats. *Eur J Pharmacol*. 2011;650(1):465-471.

[61]. Hosseini A, Mollazadeh H, Amiri MS, Sadeghnia HR, Ghorbani A. Effects of a standardized extract of Rheum turkestanicum Janischew root on diabetic changes in the kidney, liver and heart of streptozotocin-induced diabetic rats. *Biomed Pharmacother*. 2017;86:605-611.

[62]. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet*. 1993;341(8842):387-391.

[63]. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). *N Engl J Med*. 2000;342(23):1686-1692.

[64]. Hsieh CF, Huang SL, Chen CL, Chen WT, Chang HC, Yang CC. Non-aristolochic acid prescribed Chinese herbal medicines and the risk of mortality in patients with chronic kidney disease: results from a population-based follow-up study. *BMJ Open*. 2014;4(2):e004033.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[65]. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *BMJ*. 2010;340:c332.

[66]. Gagnier JJ, Boon H, Rochon P, et al. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. *Ann Intern Med*. 2006;144(5):364-367.

[67]. Gagnier J, Boon H, Rochon P, et al. Improving the quality of reporting of randomized controlled trials evaluating herbal interventions: implementing the CONSORT statement [corrected]. *Explore (NY)*. 2006;2(2):143-149.

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Table 1 Characteristics of Included Studies

Study	Sample Size (M/F)	Age	Inclusion criteria of kidney function	Intervention and Control Protocol	Duration	Reported Outcomes
Fan YW (2010) [25]	61 (28/33)	59.6	Albuminuria 30-300 mg/g or 30-300 mg/24h	T: Qi Kui granule 1 bag bid C: placebo	12m	UAE; FBG
Jia XL (2012) [26]	60 (29/31)	58.3	Proteinuria < 3.5 g/24h; Normal Scr level	T: Qi Wei granule 4.5g tid C: placebo	3m	UAE; 24hUP;
Ma ST (2011a) [27]	414 (186/ 228)	56.6	Proteinuria ≤ 4.5 g/24h; Scr ≤ 190 μmol/L	T: Arctiin granule 1 bag tid C: placebo	2m	UAE; 24hUP;
Ma ST (2011b) [28]	186 (78/108)	55.3	Proteinuria ≤ 3.5 g/24h; Scr < 176 μmol/L	T1: Arctiin granule 2 bag bid + placebo 2 bag qd T2: Arctiin granule 1 bag tid + placebo 1 bag tid C: placebo 2 bag tid	2m	UAE; 24hUP;
Wei N (2012) [29]	56 (24/32)	50.6	Albuminuria 30-300 mg/24h; Scr ≤ 1.2 mg/dL	T: Xue Zhi Kang capsule 0.6g tid C: placebo	3m	UAE; TC; TG; LDLC; HDLC
Wei X (2016) [30]	41 (32/9)	61.8	Albuminuria > 30 mg/g and Proteinuria ≤ 3.5 g/24h GFR ≥ 30 mL/min	T: Gan Di capsue 3# tid C: placebo	6m	Scr; FBG; A1C; TC; TG; LDLC; HDLC
Xie SF (2011) [31]	67 (30/37)	62.3	Albuminuria 30-299 μg/mg	T: Liu Wei Di Huang pill 3g tid + Ginkgo biloba tablet 19.2mg tid C: LWDHW placebo + GBT placebo	24m	UAE; FBG; A1C; TC; TG; LDLC; HDLC; SBP; DBP
Yang L (2014) [32]	142 (80/62)	48.5	Albuminuria 30-300 mg/24h; Normal Scr level	T: Qi Ming granule 4.5g tid C: placebo	3m	UAE; FBG; TC; TG; LDLC; HDLC
Zhou JX (2014) [33]	48 (27/21)	58.5	Proteinuria ≤ 3.5 g/24h; Normal Scr level	T: Qi Wei granule 6g tid C: placebo	3m	UAE; 24hUP; Scr; GFR; FBG; A1C; SBP; DBP
Li P (2015) [34]	180 (100/80)	59.0	Albuminuria > 20 μg/min or Proteinuria 0.5-2 g/24h GFR 60-130 mL/min	T: Tang Shen granule 8g bid + ACEi/ARB C: placebo + ACEi/ARB	6m	UAE; 24hUP; Scr; GFR; A1C; TC; TG; LDLC; HDLC; SBP; DBP;QoL
Liu YF (2015) [35]	60 (NS)	20-70	Albuminuria 20-200 μg/min or Proteinuria ≤ 3.5 g/24h GFR > 60 mL/min	T: Qi Huang capsule 1.9g tid + losartan C: placebo + losartan	6m	24hUP; Scr
Ni Q (2013) [36]	224 (112/112)	54.7	Albuminuria 20-200 μg/min or Proteinuria ≤ 3.5 g/24h GFR 60-130 mL/min	T: Qi Yao Xiao Ke capsule 2.4g tid + benazepril C: placebo + benazepril	3m	UAE; 24hUP; Scr; GFR; FBG; A1C; TC; TG; LDLC; HDLC

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Yang M (2017) [37]	25 (23/2)	59.3	Albuminuria 20-200 μg/min or 30-300 mg/24h	T: Qi Zhu granule 1 bag bid + irbesartan C: placebo + irbesartan	6m	UAE; Scr; GFR FBG; A1C; TC; TG; LDLC; HDLC
Zhang LF (2006) [38-40]	221 (119/102)	61.9	Proteinuria < 10g/24h; Scr 133-354 μmol/L or Ccr 30-70 mL/min	T 1: Modified Qi Wei granule 1 bag bid + losartan T 2: Modified Qi Wei granule 1 bag bid + losartan simulant C: placebo + losartan	3m	24hUP; Scr; GFR; QoL
Gao YB (2006) [41]	90 (NS)	35-70	Albuminuria 20-200 μg/min or 30-300 mg/24h	T: Tang Shen Ning granule 5g tid + benazepril simulant C: placebo + benazepril	2m	UAE; Scr;
Gao YB (2017) [42]	250 (116/134)	52.3	Albuminuria 30-300 mg/24h	T: Tang Shen Ning granule 8g tid + losartan simulant C: placebo + losartan	3m	UAE; Scr; FBG; A1C
Han YL (2014) [43]	104 (NS)	30-78	Proteinuria ≥ 0.5 g/24h Scr < 265 μmol/L	T1: Bao Shen pill 1 bag bid + Tripterygium glycosides 20mg tid T2: Bao Shen pill 1 bag bid C: BS placebo + valsartan	1m	24hUP; Scr
Jia M (2015) [44]	56 (31/25)	59.6	Proteinuria < 10g/24h; Scr < 265 μmol/L	T: San Huang Yi Shen granule 1 bag bid + irbesartan simulant C: placebo + irbesartan	3m	GFR
Li J (2012) [45, 46]	315 (194/121)	58.1	Proteinuria <10g/24h; Scr < 265 μmol/L or GFR > 40 mL/min;	T: Modified Qi Wei granule 4.5g bid C: placebo + irbesartan	24m	Mortality; Composite endpoints; QoL
Lin L (2000) [47]	119 (46/73)	55.3	Proteinuria < 0.5 g/24h; Normal Scr level	T: Tang Wei Kang capsule 2g tid C: Captopril (same appearance as herbal capsule)	3m	UAE; FBG; A1C; TC; TG; HDLC

Abbreviation: M/F, male versus female; NS, not specified in the original reports; T, tested group; C, control group; qd, once daily; bid, twice daily; tid, thrice daily; m, months; Scr, serum creatinine concentration; Ccr, creatinine clearance rate; GFR, glomerular filtration rate; UAE, urinary albuminuria excretion;24hUP, 24-hour proteinuria; FBG, fasting blood glucose; A1C, glycated haemoglobin; TC, total cholesterol; TG, triglycerides; LDLC, low-density lipoprotein cholesterol; HLDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; QoL, quality of life.

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Table 2: Summary of Findings Table

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with Placebo	Risk with CHM			
Comparison 1: CHM versus Placebo					
Albuminuria follow up: range 2 to 12 months	-	SMD 0.92 lower (1.35 lower to 0.51 lower)	-	1021 (8 RCTs)	⊕⊕⊕◯ MODERATE [a, b]
24-hour proteinuria follow up: range 2 to 3 months	-	SMD 1.34 lower (2.18 lower to 0.51 lower)	-	699 (4 RCTs)	⊕⊕◯◯ LOW [a, b, c]
Serum creatinine (Scr) follow up: range 3 to 6 months	The mean Scr was 77.41 µmol/L	The mean Scr in the intervention group was 5.75 µmol/L higher (2.06 lower to 13.57 higher)	-	85 (2 RCTs)	⊕⊕⊕◯ MODERATE [a, d]
Estimated glomerular filtration rate (eGFR) follow up: mean 3 months	The mean eGFR was 96.24 mL/min	The mean eGFR in the intervention group was 10.71 mL/min lower (23.93 lower to 2.51 higher)	-	44 (1 RCT)	⊕⊕◯◯ LOW [a ,d]
Comparison 2: Placebo + ACEi/ ARB versus CHM +ACEi/ARB					
Albuminuria follow up: range 3 to 6 months	-	SMD 0.56 lower (1.04 lower to 0.08 lower)	-	330 (3 RCTs)	⊕⊕⊕◯ MODERATE [d, e]
24h-proteinuria follow up: range 3 to 6 months	-	SMD 0.15 lower (0.52 lower to 0.23 higher)	-	489 (4 RCTs)	⊕⊕◯◯ LOW [b, d, e]
Serum creatinine (Scr) follow up: range 3 to 6 months	The mean Scr was 88.13 µmol/L	The mean Scr in the intervention group was 4.02 µmol/L lower (7.81 lower to 0.23 lower)	-	595 (5 RCTs)	⊕⊕⊕◯ MODERATE [a, c]
Estimated glomerular filtration rate (eGFR) follow up: range 3 to 6 months	The mean eGFR was 79.27 mL/min	The mean eGFR in the intervention group was 6.28 mL/min higher (2.42 higher to 10.14 higher)	-	535 (4 RCTs)	⊕⊕⊕◯ MODERATE [c, e]
Comparison 3: CHM versus Placebo + ACEi/ ARB					
All-cause mortality follow up: mean 24 months	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	315 (1 RCT)	⊕⊕⊕◯ MODERATE [f]
Composite end-points events follow up: mean 24 months	133 per 1,000	45 per 1,000 (20 to 102)	RR 0.34 (0.15 to 0.77)	315 (1 RCT)	⊕⊕◯◯ LOW [d, g]
Albuminuria follow up: mean 3 months	-	SMD 6.38 lower (9.01 lower to 3.75 lower)	-	499 (3 RCTs)	⊕◯◯◯ VERY LOW [a, b, d]
24h-proteinuria follow up: range	-	SMD 0.00 lower (0.32 lower to 0.32 higher)	-	260 (2 RCTs)	⊕⊕⊕◯ LOW [d, h]

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1 to 3 months					
Serum creatinine (Scr) follow up: range 1 to 3 months	The mean Scr was 105.52 μmol/L	The mean Scr in the intervention group was 4.05 μmol/L lower (6.09 lower to 2.01 higher)	-	590 (4 RCTs)	⊕⊕⊕◯ MODERATE [a, c]
Estimated glomerular filtration rate (eGFR) follow up: range 1 to 3 months	The mean eGFR was 97.24 mL/min	The mean eGFR in the intervention group was 0.57 mL/min lower (11.01 lower to 9.88 higher)	-	542 (4 RCTs)	⊕⊕◯◯ LOW [a, b, c]

*The risk in the intervention group (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).
Abbreviation: Confidence interval (CI); Mean difference (MD); Standardised mean difference (SMD); Risk ratio (RR)
GRADE justification: a. Unclear risk of bias of randomization and allocation concealment; b. Significant heterogeneity; c Wide confidence interval; d Small sample size and wide confidence interval; e. High or unclear risk of attrition bias; f. Low events rate lead to imprecise estimation and small simple size; g. Number of patients progressed to ESRD were included in composite outcomes, not solely reported; h. Unclear risk of attrition bias and potential selecting report bias;

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Figure Legends

Figure 1. PRISMA flowchart of searching and screening.

Figure 2. Risk-of-bias summary

Figure 3. Forest plot of primary outcomes

Note: Panel (a) albuminuria outcomes; (b) proteinuria outcomes; (c) serum creatinine outcomes; (d) estimated glomerulus filtration rate outcomes.

Abbreviation: CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standard.

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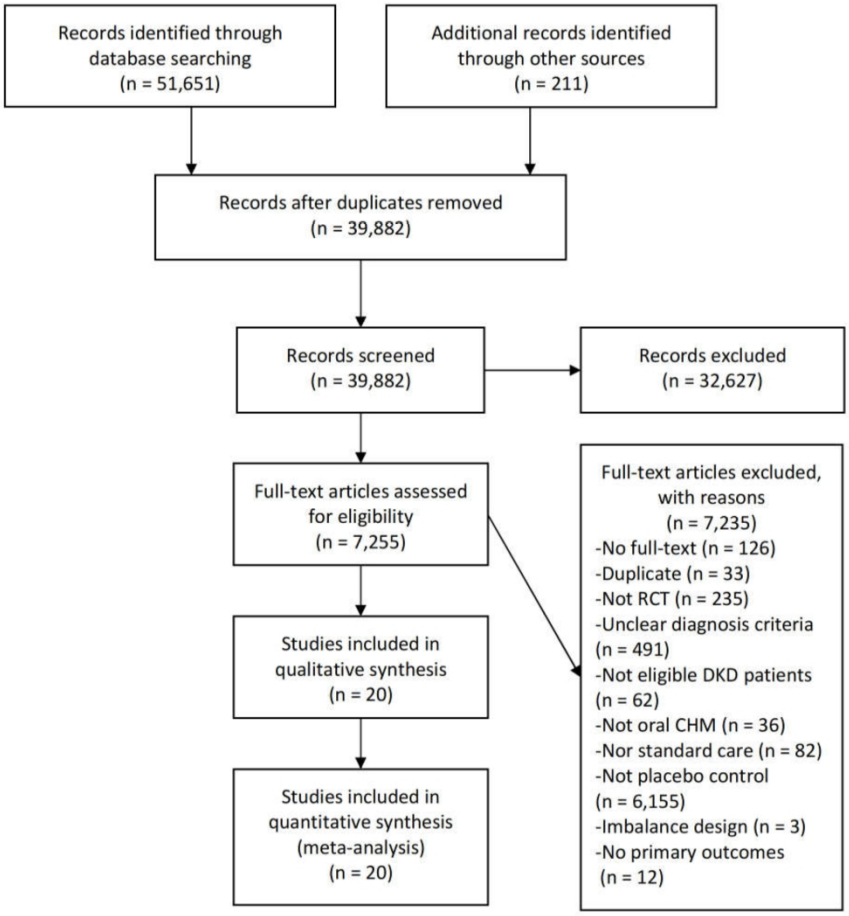

Figure 1. PRISMA flowchart of searching and screening.

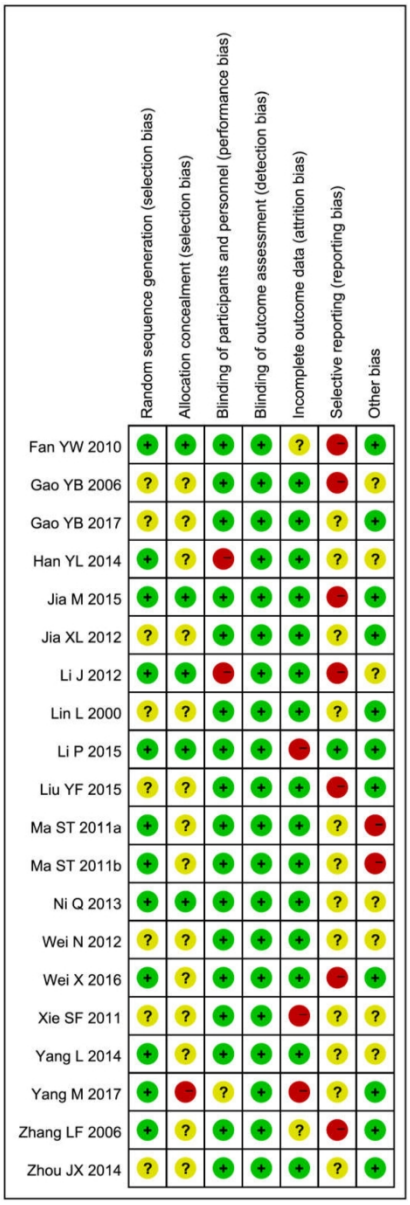

Figure 2. Risk-of-bias summary

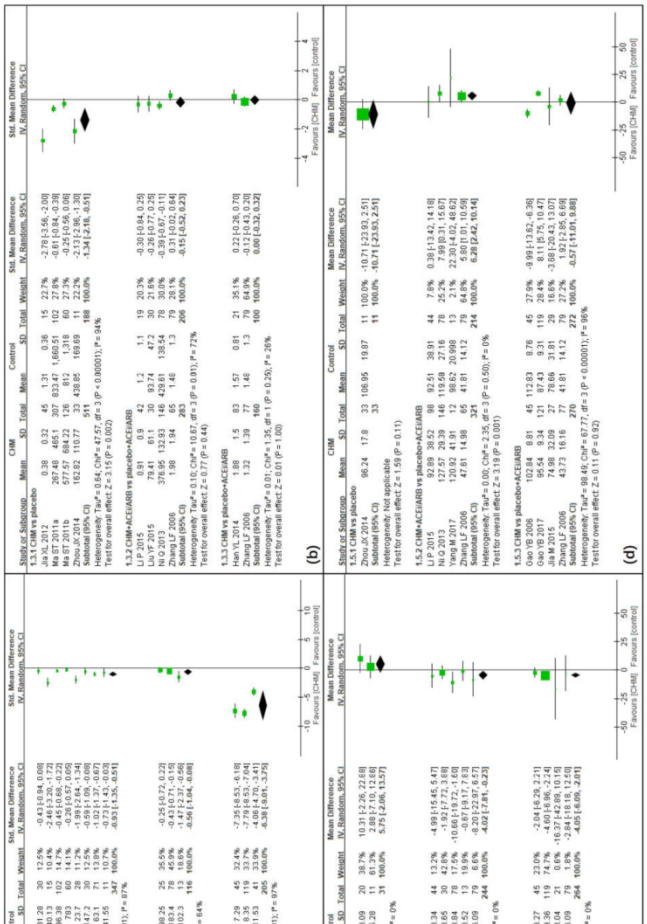

Figure 3. Forest plot of primary outcomes

Note: Panel (a) albuminuria outcomes; (b) proteinuria outcomes; (c) serum creatinine outcomes; (d) estimated glomerulus filtration rate outcomes. Abbreviation: CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standard.

Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

Supplementary Appendix

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Table S1: Search strategy of MEDLINE.
Table S2: Herbal ingredients used in included studies
Table S3: Subgroup analysis of primary outcomes
Table S4: Sensitivity analysis of primary outcomes
Table S5: Meta-analysis results of secondary outcomes

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Table S1: Search Strategy of MEDLINE

Search Block	Search terms
Intervention	Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs, Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Chinese Medicine Herb OR Herbal Medicine OR Herbs
Condition	Diabetic Nephropathies OR Diabetic Nephropathy OR Diabetic Kidney Disease OR Diabetic Kidney Diseases OR Kimmelstiel Wilson Syndrome OR Kimmelstiel Wilson Disease OR Diabetic Glomerulosclerosis OR Nodular Glomerulosclerosis OR Intracapillary Glomerulosclerosis OR albuminuria OR Microalbuminuria OR proteinuria OR Glomerulosclerosis OR Glomerulonephritis OR Kimmelstiel wilson nephropathy OR diabetic nephrosclerosis
Study design	Systematic[sb] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab] OR "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] OR "case series"[tw]

Note: The three search blocks were connected with Boolean operators 'AND' to build the overall search terms.

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Table S2. Herbal Ingredients Used in Included Studies

Study	Formulae Name	Ingredients
Fan YW (2010)	Qi Kui granule	Astragali Radix; Polygoni Multiflori Radix; Abelmoschi Corolla
Jia XL (2012)	Qi Wei granule	Astragali Radix; Rehmanniae Radix; Rhei Radix et Rhizoma; Prunellae Spica; Curcumae Rhizoma; Euonymus Alatus; Notoginseng Radix et Rhizoma
Ma ST (2011a)	Arctiin granule	Arctii Fructus
Ma ST (2011b)	Arctiin granule	Arctii Fructus
Wei N (2012)	Xue Zhi Kang capsule	*Fermentum Rubrum**
Wei X (2016)	Gan Di capsue	Scutellariae Radix; Astragali Radix; Corni Fructus; Rehmanniae Radix Phylianthi Fructus; Leonuri Herba Leonuri Herba; Bombyx Batryticatus; Sophorae Flos (stir fry processed)
Xie SF (2011)	Liu Wei Di Huang pill Ginkgo biloba tablet	Rehmanniae Radix; Corni Fructus; Dioscoreae Rhizoma; Alismatis Rhizoma; Moutan Cortex; Poria; Ginkgo Folium
Yang L (2014)	Qi Ming granule	Astragali Radix; Puerariae Lobatae Radix; Rehmanniae Radix; Lycii Fructus; Cassiae Semen; Leonuri Fructus; Typhae Pollen; Hirudo
Zhou JX (2014)	Qi Wei granule	Astragali Radix; Rehmanniae Radix; Rhei Radix et Rhizoma; Prunellae Spica; Curcumae Rhizoma; Euonymus Alatus; Notoginseng Radix et Rhizoma
Li P (2015)	Tang Shen granule	Astragali Radix; Rehmanniae Radix; Rhei Radix et Rhizoma; Notoginseng Radix et Rhizoma; Euonymus Alatus; Corni Fructus; Aurantii Fructus
Liu YF (2015)	Qi Huang capsule	Astragali Radix; Rehmanniae Radix; Ligustri Lucidi Fructus; Hirudo; Bombyx Batryticatus; Eupolyphaga Steleophaga; Rhei Radix et Rhizoma; *Gymnema sylvestre**; Sinomenii Caulis; Plantaginis Semen
Ni Q (2013)	Qi Yao Xiao Ke capsule	Panacis Quinquefolii Radix; Astragali Radix; Rehmanniae Radix; Dioscoreae Rhizoma; Corni Fructus; Lycii Fructus; Ophiopogonis Radix; Anemarrhenae Rhizoma; Trichosanthis Radix; Puerariae Lobatae Radix; Schisandrae Chinensis Fructus Schisandrae Chinensis Fructus; Galla Chinensis
Yang M (2017)	Qi Zhu granule	Astragali Radix; Ligustri Lucidi Fructus; Atractylodis Macrocephalae Rhizoma; Abelmoschi Corolla; Rosae laevigatae Fructus Dioscoreae Spongiosae Rhizoma; Paeoniae Radix Rubra; Coptidis Rhizoma

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Zhang LF (2006) [37, 38]	Modified Qi Wei granule	Astragali Radix; Rehmanniae Radix; Prunellae Spica; Rhei Radix et Rhizoma; Euonymus Alatus; Epimedii Folium; Corni Fructus; Curcumae Longae Rhizoma
Gao YB (2006)	Tang Shen Ning granule	Astragali Radix; Rehmanniae Radix; Euryales Semen; Corni Fructus; Rhei Radix et Rhizoma; Chuanxiong Rhizoma
Gao YB (2017)	Tang Shen Ning granule	Astragali Radix; Euryales Semen; Rosae laevigatae Fructus; Rhei Radix et Rhizoma; Chuanxiong Rhizoma
Han YL (2014)	Bao Shen pill; Tripterygium glycosides	Not given.
Jia M (2015)	San Huang Yi Shen granule	Astragali Radix; Curcumae Longae Rhizoma; Rhei Radix et Rhizoma; Chuanxiong Rhizoma; Angelicae Sinensis Radix; Salviae Miltiorrhizae Radix et Rhizoma; Cervi Cornu; Anemarrhenae Rhizoma; Arctii Fructus
Li J (2012)	Modified Qi Wei granule	Astragali Radix; Rehmanniae Radix; Prunellae Spica; Rhei Radix et Rhizoma; Euonymus Alatus; Epimedii Folium; Corni Fructus; Curcumae Longae Rhizoma
Lin L (2000)	Tang Wei Kang capsule	Astragali Radix; Ligustri Lucidi Fructus; Rhei Radix et Rhizoma

Note: All ingredients were standarised based on the Chinese Pharmacopoeia 2015 version. * Latin names were given due to not included in the Chinese Pharmacopoeia 2015.

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Table S3: Subgroup Analysis of Primary Outcomes

Outcome or Subgroup	Studies	Pts	Statistical Method	Effect Estimate (95%CI)	I^2	*p* value
Urinary albumin excretion						
Subgroup-CHM formulae						
4.2.1 Qiwei Granules	2	104	MD	-70.06 [-88.84, -51.28]	0%	p<0.0001
4.2.2 Arctiin Granules	2	595	Std. MD	-0.38 [-0.56, -0.20]	0%	p<0.0001
4.2.4 Tang shen ning Formulae group	2	330	MD	-48.16 [-55.12, -41.20]	95%	p<0.0001
Subgroup-Measurements						
5.2.1 CHM vs placebo-AER	1	186	MD	-149.48 [-362.79, 63.83]	NA	p=0.17
5.2.2 CHM vs placebo-ACR	2	124	MD	-30.53 [-76.59, 15.53]	66%	p=0.19
5.2.3 CHM vs placebo-UAE	5	711	MD	-60.91 [-76.82, -45.01]	53%	p<0.0001
5.2.4 CHM vs placebo + ACEi/ARB-AER	1	119	MD	-48.85 [-53.30, -44.40]	NA	p<0.0001
5.2.5 CHM vs placebo + ACEi/ARB-UAE	2	330	MD	-48.16 [-55.12, -41.20]	95%	p<0.0001
24-hour proteinuria						
Subgroup-baseline UP						
3.3.1 CHM vs placebo-baseline UP < 0.5g/d	2	453	MD	-378.34 [-649.90, -106.77]	63%	p=0.006
3.3.2 CHM vs placebo-baseline UP > 0.5g/d	2	246	Std. MD	-1.49 [-3.97, 0.99]	97%	p=0.24
3.3.3 CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline UP < 0.5g/d	2	284	MD	-31.30 [-68.61, 6.02]	61%	p=0.10
3.3.4 CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline UP > 0.5g/d	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
Subgroup-CHM formulae						
4.3.1 Qiwei Granules	2	104	Std. MD	-2.47 [-3.11, -1.83]	21%	p<0.0001
4.3.2 Arctiin Granules	2	595	MD	-407.65 [-732.24, -83.05]	45%	p=0.01
4.3.3 Tang shen fang group	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
Subgroup-Measurements	8					
5.3.1 CHM vs placebo-g/24h	1	60	MD	-0.93 [-1.13, -0.73]	NA	p<0.0001
5.3.2 CHM vs placebo-mg/24h	3	639	MD	-324.42 [-485.15, -163.69]	30%	p<0.0001

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5.3.3 CHM + ACEi/ARB vs placebo + ACEi/ARB-g/24h	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
5.3.4 CHM + ACEi/ARB vs placebo + ACEi/ARB-mg/24h	2	284	MD	-31.30 [-68.61, 6.02]	61%	p=0.10
Serum creatinine level						
Subgroup-baseline Scr						
3.4.1 CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline Scr normal	3	227	MD	-2.12 [-6.48, 2.23]	0%	p=0.34
3.4.2 CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline Scr abnormal	2	368	MD	-9.99 [-17.71, -2.26]	0%	p=0.01
3.4.3 CHM vs placebo + ACEi/ARB-baseline Scr normal	3	434	MD	-4.07 [-6.13, -2.01]	0%	p=0.0001
3.4.4 CHM vs placebo + ACEi/ARB-baseline Scr abnormal	1	156	MD	-2.84 [-18.18, 12.50]	NA	p=0.72
Subgroup-CHM formulae						
4.4.2 Tang shen fang group	2	286	MD	-6.06 [-14.60, 2.47]	0%	p=0.16
4.4.3 Tang shen ning Formulae group	2	330	MD	-3.96 [-6.13, -1.78]	6%	p=0.0004
Glomerular filtration rate						
Subgroup-baseline GFR						
3.5.1 CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline GFR>90	2	249	MD	9.38 [1.07, 17.70]	4%	p=0.03
3.5.2 CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline GFR<90	2	286	MD	5.22 [0.69, 9.74]	0%	p=0.02
3.5.3 CHM vs placebo + ACEi/ARB-baseline GFR>90	1	90	MD	-9.99 [-13.62, -6.36]	NA	p<0.0001
3.5.4 CHM vs placebo + ACEi/ARB-baseline GFR<90	3	452	MD	4.48 [-1.32, 10.28]	70%	p=0.13
Subgroup-CHM formulae						
4.5.2 Tang shen fang group	2	286	MD	5.22 [0.69, 9.74]	0%	p=0.02
4.5.3 Tang shen ning Formulae group	2	330	MD	-0.89 [-18.62, 16.85]	99%	p=0.92
Subgroup-Measurements						
5.5.1 CHM + ACEi/ARB vs placebo + ACEi/ARB-Ccr	1	144	MD	5.80 [1.01, 10.59]	NA	p=0.02
5.5.2 CHM + ACEi/ARB vs placebo + ACEi/ARB-eGFR	3	391	MD	7.13 [-0.29, 14.56]	11%	p=0.06
5.5.3 CHM vs placebo + ACEi/ARB-Ccr	2	246	MD	-4.14 [-15.81, 7.53]	93%	p=0.49
5.5.4 CHM vs placebo + ACEi/ARB-eGFR	2	296	MD	5.25 [-4.65, 15.15]	46%	p=0.30

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Abbreviation: Pts, patients; CI, confident interval; NA, not applicable. CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MD, mean differences; Std, standard.; AER, albuminuria excretion rate; ACR, albuminuria to creatinine ratio; UAE, urinary albuminuria excretion; UP, urinary proteinuria; GFR, glomerular filtration rate; Scr, serum creatinine concentration; Ccr, creatinine clearance.

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Table S4: Sensitivity Analysis of Primary Outcomes

Outcomes	Studies	Participants	Statistical Method	Effect Estimate (95% CI)	I^2	*p* value
Urinary albumin excretion						
CHM vs placebo	4	798	Std. Mean Difference	-0.54 [-0.85, -0.22]	73%	p=0.0009
CHM+ACEi/ARB vs placebo+ACEi/ARB	3	330	Std. Mean Difference	-0.56 [-1.04, -0.08]	64%	p=0.02
24-hour proteinuria						
CHM vs placebo	2	595	Mean Difference	-407.65 [-732.24, -83.05]	45%	p=0.01
CHM+ACEi/ARB vs placebo+ACEi/ARB	3	429	Std. Mean Difference	-0.12 [-0.60, 0.37]	81%	p=0.63
CHM vs placebo+ACEi/ARB	2	260	Std. Mean Difference	0.00 [-0.32, 0.32]	26%	p=1.00
Serum creatinine level						
CHM vs placebo	1	41	Mean Difference	10.31 [-2.26, 22.88]	NA	p=0.11
CHM+ACEi/ARB vs placebo+ACEi/ARB	4	535	Mean Difference	-5.59 [-10.61, -0.58]	0%	p=0.03
CHM vs placebo+ACEi/ARB	2	260	Mean Difference	-6.23 [-19.51, 7.05]	0%	p=0.36
Glomerular filtration rate						
CHM+ACEi/ARB vs placebo+ACEi/ARB	4	535	Mean Difference	6.28 [2.42, 10.14]	0%	p=0.001
CHM vs placebo+ACEi/ARB	2	212	Mean Difference	1.50 [-3.08, 6.09]	0%	p=0.52

Abbreviation: NA, not applicable. CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standard.

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Table S5: Meta-analysis Results of Secondary Outcomes

Outcome	Studies	Participants	Statistical Method	Effect Estimate (95% CI)	I2	p value
2.1 Fasting blood sugar	9	962	Mean Difference	-0.45 [-1.15, 0.25]	93%	p=0.21
2.2 Haemoglobin A1c	8	901	Mean Difference	0.04 [-0.17, 0.24]	59%	p=0.73
2.3 Total cholesterol	8	815	Mean Difference	-0.96 [-1.70, -0.21]	95%	p=0.01
2.4 Triglyceride	8	815	Mean Difference	-0.60 [-1.01, -0.19]	90%	p=0.004
2.5 Low-density lipoprotein	7	696	Mean Difference	-0.51 [-0.93, -0.09]	92%	p=0.02
2.6 High-density lipoprotein	8	815	Mean Difference	0.14 [-0.04, 0.33]	93%	p=0.12
2.7 Systolic blood pressure	3	252	Mean Difference	0.64 [-0.90, 2.17]	0%	p=0.43
2.8 Diastolic blood pressure	3	252	Mean Difference	0.14 [-2.02, 2.29]	52%	p=0.90
2.9 Diabetes quality of life score	2	461	Mean Difference	0.07 [-3.87, 4.00]	54%	p=0.97

Abbreviation: CI, confident interval.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P10-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P10

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P11-12 Fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P12 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P12-13, Fig2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P13-18, Fig 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P13-18, Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P18-19 Appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P22-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P24

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PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

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Title

Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

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[2] Charlie Changli Xue and Wei Mao contributed equally to this paper as corresponding authors.

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ABSTRACT

Objectives

To provide a broad evaluation of the efficacy and safety of oral Chinese herbal medicine (CHM) as an adjunctive treatment for diabetic kidney disease (DKD), including mortality, progression to end stage renal disease (ESKD), albuminuria, proteinuria and kidney function.

Design

A systematic review and meta-analysis.

Methods

Randomised controlled trials (RCTs) comparing oral CHM with placebo as an additional intervention to conventional treatments were retrieved from five English (CENTRAL, MEDLINE, Embase, AMED and CINAHL) and four Chinese databases (CBM, CNKI, CQVIP and Wanfang) from inception to May 2018. RCTs recruiting adult DKD patients induced by primary diabetes were considered eligible, regardless of the form and ingredients of oral CHM. Mean difference (MD) or standardised mean difference (SMD) was used to analyse continuous variables and risk ratio (RR) for dichotomous data, both with 95% confidence intervals (CIs).

Results

From 7,255 reports retrieved, 20 eligible studies involving 2,719 DKD patients were included. CHM was associated with greater reduction of albuminuria than placebo, regardless of whether renin-angiotensin system (RAS) inhibitors were concurrently administered (SMD -0.56, 95%CI [-1.04, -0.08], I^2=64%, p=0.002) or not (SMD -0.92, 95%CI [-1.35, -0.51], I^2=87%, p<0.0001). When CHM was used as an adjunct to RAS inhibitors, estimated glomerular filtration rate (eGFR) was higher in the CHM than placebo group (MD 6.28 mL/min; 95%CI [2.42, 10.14], I^2=0%, p=0.001). The effects

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of CHM on progression to ESKD and mortality were uncertain due to low event rates. The reported adverse events in CHM group included digestive disorders, elevated liver enzyme level, infection, anemia, hypertension and subarachnoid hemorrhage, but the report rates were low and similar to control groups. The favourable results of CHM should be balanced with the limitations of the included studies such as high heterogeneity, short follow-up periods, small numbers of clinical events, and older patients with less advanced disease.

Conclusions

Based on moderate to low quality evidence, CHM may have beneficial effects on renal function and albuminuria beyond that afforded by conventional treatment in adults with DKD. Further well-conducted, adequately powered trials with representative DKD populations are warranted to confirm the long-term effect of CHM, particularly on clinically relevant outcomes.

PROSPERO registration number: CRD42015029293

Index words: diabetic kidney disease (DKD); Chinese herbal medicine (CHM); complementary and alternative medicine; systematic review; meta-analysis

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ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review and meta-analysis provided a broad review of the efficacy and safety of oral Chinese herbal medicine (CHM) for diabetic kidney disease.
- Randomised controlled trials comparing CHM to placebo were included to avoide potential risk of bias that may exaggerate the estimated effect of CHM.
- The search strategy was comprehensive, over 7,000 articles were screened and 20 studies included with a total of 2,719 participants.
- A priori subgroups analysis was performed to provide potential candidate formulae and frequently used herbs for further investigation.
- Overall the evidence was moderate to very low quality due to unclear randomisation procedures, wide confident interval and substantial heterogeneity in outcome measures. The external validity was compromised by multi-ingredients herbal formulae, short follow-up periods, small numbers of clinical events, and includsion of older patients with less advanced disease.

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INTRODUCTION

Diabetic kidney disease (DKD) is one of the most common complications of diabetes. As the prevalence of diabetes continues to grow globally, it is estimated that the number of DKD patients will double by 2025 [1]. Since patients with DKD are at markedly higher risks of progression to end stage kidney disease (ESKD) and cardiovascular disease (CVD), the socioeconomic and public health burden of DKD is significant [2 3]. Effective therapies that prevent and treat DKD are of critical importance.

Glycemic management, blood pressure control and the renin-angiotensin system (RAS) inhibitors are the mainstay of treatment for DKD and have been successful in reducing risk of disease onset or progression [4 5]. However, an unmet need exists in DKD patients intolerant or unresponsive to current pharmacotherapies, and those patients with deteriorating renal function yet normo-albuminuria [6-8]. Some promising therapies addressing novel targets, such as sulodexide and bardoxolone methyl, have been found to be ineffective and/or harmful, whilst several others, including sodium-glucose cotransporter 2 (SGLT-2) inhibitors and mineralocorticoid receptor antagonist are still under evaluation [9-11].

To facilitate the discovery of new therapeutic agents for patients with diabetes and impaired renal function, screening candidates from natural products including Chinese herbal medicine (CHM) that have traditionally been used for symptoms associated with DKD, may offer insights into a more targeted approach for therapeutic development. With respect to CHM, records dating to the Han dynasty (AD 202–220) indicate the treatment of DKD symptoms in Chinese medicine literature and contemporary literature including RCTs indicating CHM is used for diabetes and its complications [12]. Multi-ingredient herbal

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decoctions and manufactured products of *Abelmoschi Corolla* and *Cordyceps* have been recommended for patients with DKD in the practice guidelines of Chinese medicine [13 14]. However, these guidelines were based on experts' consensus rather than outcomes of systematically evaluated best available clinical evidence. Moreover, safety concerns exist due to the potential for aristolochic-acid nephrotoxicity with some herbal products [5 15]. Even though legislation and quality control have been reinforced in recent years, the general lack of information regarding the safety profiles of herbal formulae due to their multi-compound nature have limited their application [5 16].

In recent years, there have been a growing number of clinical trials and systematic reviews of CHM for DKD but not of placebo-controlled trials. We therefore undertook a systematic review and meta-analysis of randomised, placebo-controlled trials to evaluate the efficacy and safety of oral CHM as adjunctive treatment for DKD.

METHODS

This systematic review was conducted following the Cochrane Handbook of Systematic Reviews of Interventions and reported in accord with the PRISMA guidelines [17 18]. The protocol was registered in the PROSPERO database and can be accessed online (Registry number: CRD42015029293).

Search Strategy

A comprehensive search was conducted in the following databases irrespective of publication status or language: MEDLINE, EMBASE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials

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(CENTRAL), Allied and Complementary Medicine Database (AMED), China BioMedical Literature (CBM), China National Knowledge Infrastructure (CNKI), Chonqing VIP (CQVIP) and Wanfang. The former five databases were in English while the later four were in Chinese. Databases were searched from inception to May 2018. The U.S.A. National Institutes of Health register (ClinicalTrials.gov), the Australian New Zealand Clinical Trial Registry (ANZCTR), the Chinese Clinical Trial Registry (ChiCTR), and the European Union Clinical Trials Register (EU-CTR) were searched for completed but unpublished trials. Further, reference lists of related systematic reviews were reviewed for additional publications.

Search terms included "diabetic nephropathy", "diabetic kidney disease", "albuminuria", "Traditional Chinese Medicine", "randomised controlled trial" and their synonyms. All terms were mapped to controlled vocabulary (where applicable) in addition to being searched as keywords. The MEDLINE search strategy is provided in **Table S1**.

Eligibility criteria

Eligible studies had to fulfill the following criteria: (1) randomised controlled trial design; (2) included primary diabetes adults with persistent albuminuria/proteinuria, which was defined as an albumin excretion rate (AER) more than 20 μg/min, an albumin-to-creatinine ratio (ACR) larger than 30 mg/g [4 5] or 24-hour proteinuria over 0.5 g/d (the overt DKD stage defined by Mogensen and used as in DKD diagnostic criteria in China) [19 20]; (3) oral Chinese herbal medicine as intervention, which could have been either single or multiple ingredients in any form (decoction, granules, capsules etc.); (4) CHM matched placebo was applied in the control group; (5) both intervention and control groups received the same conventional treatments of DKD, including comprehensive management of glycaemia,

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blood pressure, serum lipid level, life-style and nutrition in accordance with Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines' recommendation [4 5]; and, (6) the study reported at least one of the primary outcomes. Studies including patients with albuminuria that was not caused by diabetes, patients who already had ESKD, or those receiving renal replacement therapy were excluded.

Outcomes of Interest

Primary outcomes of interest included albuminuria/proteinuria, kidney function, number of participants progressing to ESKD, all-cause mortality and adverse events, at the end of treatment or follow-up. Progression to ESKD was defined as initiation of renal replacement therapy or estimated GFR (eGFR) lower than 15 mL/min/1.73m^2. Kidney function was reflected by the measurement of serum creatinine concentration (Scr) and glomerulus filtration rate (GFR). Likewise, quantitative measurement of albuminuria and proteinuria included urinary albumin excretion rate (AER), albumin-to-creatinine ratio (ACR), 24-hour urine protein excretion (UP) and protein-to-creatinine ratio (PCR).

Secondary outcomes included cardiovascular mortality, all-cause hospitalization, quality of life measured by validated scales, indicators of risk factor control (such as fasting blood glucose, glycated haemoglobin [HbA1c], blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]). All outcomes were reported with specified units at the end of treatment or at the end of follow-up.

Safety outcomes included numbers and type of adverse events and serious adverse events during the study period.

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Study Selection and Data Extraction

Titles and abstracts identified in searching were screened by one reviewer and then checked by another (La Z. and X.Q.) against the predefined criteria. After titles and abstracts screening, possibly relevant studies underwent full-text review by La Z. and cross checked by L.Y. to confirm their eligibility. Any disagreement was resolved by consensus and discussion with a third reviewer (J.S. or AL.Z.).

Two reviewers (La Z and L.Y.) independently extracted data from eligible studies into a pre-designed spreadsheet. A third reviewer (J.S.) cross checked the data. Study design characteristics, trial locations, demographic features (age, types of diabetes, baseline albuminuria, kidney function, etc.), intervention and control protocol (herbal ingredients, dosage, frequency, treatment duration, follow-up period, etc.), and outcome measures were recorded. Authors of studies with missing data were contacted by email or telephone to obtain additional data.

Data Synthesis and Analysis

All studies satisfying the eligibility criteria were included for qualitative synthesis. For continuous variables, mean and standard deviation of each study were obtained and pooled as mean difference (MD) or standardized mean differences (SMD) with a 95% confidence interval (CI). SMD was used in the meta-analysis of albuminuria and proteinuria outcomes due to the different scales used in the included studies such as microgram per minute (μg/min), milligram to gram (mg/g) and milligram per day (mg/24 hours). For dichotomous data, risk ratios (RR) were calculated with a 95% CI. Considering the diversity of interventions and potential heterogeneity among included studies, a random-effect model was applied in all meta-analyses. Review Manager Software (RevMan, version 5.3) was

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used to perform the statistical analysis [21].

Pre-defined subgroup analysis included baseline DKD severity and CHM formulae. Heterogeneity between studies was detected by using the Cochrane Q statistic and I^2 test. For outcomes with substantial heterogeneity (I^2 levels >50%), subgroup analyses were performed to explore potential sources, whereby results were stratified by factors, such as different measured approaches for the same outcome. Sensitivity analysis was performed by excluding studies with high/unclear risk of bias in the domain of random sequence generation. Publication bias was explored when 10 or more studies were included in one meta-analysis by visual inspection of funnel plots for asymmetry.

Quality Assessment

The methodologic quality of each individual study was assessed by two reviewers (La Z. and L.Y.) in parallel according to the Cochrane Risk of Bias (ROB) tool [22]. For the domain of other sources of bias, baseline imbalance and conflicts of interest were evaluated. Each domain was judged as high, low or unclear risk of bias with justifications. The consistency was checked by a third reviewer (Lei Z.) and disagreements were resolved by discussion with methodologists (AL.Z. and X.G.).

To evaluate the overall quality of evidence for primary outcomes, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied [23]. A panel group was formed to make the GRADE evaluation, which included methodologists, CM practitioners and conventional medicine physicians. The assessments of evidence started at 'high quality', and were downgraded when significant risk of bias, indirectness, inconsistency, imprecision of estimated effect or publication bias were detected.

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Patient and Public Involvement

Patients or public were not directly involved in this systematic review.

RESULTS

Description of Studies

The comprehensive search retrieved over 50 thousand citations and 7,255 of them were examined in full-text (**Figure 1**). Eighty-five percent of the studies were excluded due to lack of a placebo control. As a result, 20 eligible studies with 23 publications involving 2,719 DKD participants were included [24-46]. For studies with multiple reports, the most recent publication or the one with primary outcomes was used, and complementary outcomes data from other reports were extracted and merged.

Characteristics of the included studies are summarised in **Table 1**. All 20 studies were conducted in China. Except for one study [24] written in English, all others were published in Chinese language between 2000 and 2017. Enrolled participants were all diabetic patients with persistent albuminuria or proteinuria but varied in terms of baseline kidney function. The mean of age was 55.1 years old (range 20 to 79 years). Three studies [34 35 37] used herbal compounds or a single herb as intervention while the remaining 17 studies used CHM formulae with multi-ingredients. The ingredients of CHM used in each study are provided in **Table 2**. The most common herbal ingredients used by ten or more studies was *Astragali Radix, Rehmanniae Radix* and *Rhei Radix et Rhizoma.* All studies applied CHM matched placebo, except for one [32] which made Captopril (comparator) identical in appearance to CHM (intervention). Treatment duration ranged from 4 weeks to 2 years

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(median 3 months). There were no outcome data with respect to cardiovascular mortality and all-cause hospitalisation among the included studies.

Quality of Studies

Generally, the quality of included studies was fair with low or unclear risk of bias, especially regarding blinding and outcome data completeness (**Figure 2**). Two studies were judged at high risk of bias with respect to blinding of patients and personnel because blinding may have been compromised by prescription of unequal numbers/amounts of medication between groups [28 31]. Twelve studies reported correct procedures for random sequence generation [24 25 28-30 34-36 38 41 44], whereas eight studies did not provide adequate details. For the domain of allocation concealment, one study did not conceal the allocation to researchers thus was judged at high risk of bias [41]. Seven studies were considered at high risk of selection reporting bias (mainly incomplete reporting in secondary outcomes) [25 26 29 31 33 38 44], whilst 13 studies were at unclear risk because protocols were not found. Other bias assessment included baseline balance and conflict of interest. Two studies included pharmaceutical industry employees as co-authors without statements regarding their roles in the study, thereby these two trials were judged as high risk for potential conflicts of interest [34 35]. Seven studies without baseline statistical test results or without information regarding sources of funding were judged to be at unclear risk [26 28 31 36 37 39 40].

Effecacy of Chinese herbal medicine

Considering the uses of RAS blockage may affect the primary outcomes, studies were categorised and separated into three groups according to trial application of RAS blockade (angiotensin converting enzyme inhibitors [ACEi] and/or angiotensin receptor blockers [ARB]) in each arm prior to meta-analysis. It should be noted that conventional concurrent

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treatments of DKD recommended by guidelines were applied equally in both groups in all included studies, such that these conventional treatments are not separately mentioned henceforth. The three groups were:

- CHM versus placebo [25 30 34 35 37-40 45];
- CHM plus ACEi/ARB versus placebo plus ACEi/ARB [24 33 36 41 44]; and,
- CHM versus placebo plus ACEi/ARB [26-29 31 32 44 46]

Mortality and progression to ESKD

Though all-cause mortality was measured in a study [31] comparing CHM with matched placebo plus Irbesartan, no deaths were observed amongst the 315 participants during the two-year follow-up (**Table 3**). Within the same trial, the number of patients that progressed to ESKD was reported as part of a composite outcome, measuring the number of patients with microalbuminuria progressing to macroalbuminuria, doubling serum creatinine from baseline, or initiating dialysis. Compared with placebo plus Irbesartan, the risk of experiencing this composite outcome may be 66% lower in the Chinese herbal medicine (CHM) group over two-year period (RR: 0.34, 95%CI [0.15, 0.77], p=0.01; low quality evidence).

Albuminuria

Fourteen studies reported albuminuria at the end of treatment (**Figure 3a)**. Based on meta-analysis of eight studies [25 30 34 35 37 39 40 45] involving 1,021 participants, use of CHM probably lowered albuminuria compared to placebo over 2 to 12 months intervention (SMD -0.92, 95% CI [-1.35, -0.51], I^2 = 87%, p < 0.0001; moderate quality evidence). Subgroup analysis suggested different CHM formulae could be the sources of

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heterogeneity (**Table S2**). The estimate of effect with the least heterogeneity was observed in the Qi Wei granule CHM subgroup [30 45] in which albuminuria was 70.06 mg/24h lower compared to placebo after 3 months (95% CI [-88.84, -51.28], I^2 = 0%, p < 0.0001). Likewise, the Arctiin granule [34 35] reduced albuminuria more than placebo after 2 months intervention (SMD -0.38, 95% CI [-0.56, -0.20], I^2 = 0%, p < 0.0001).

When used in combination with ACEi/ARB, slightly lower end of treatment albuminuria level was still observed in the CHM rather than in the placebo group over a 3 to 6 month intervel (SMD -0.56, 95% CI [-1.04, -0.08], I^2 = 64%, p = 0.002; moderate quality evidence) [24 36 41]. Although lower albuminuria excretion was observed in the CHM group [26 27 32], the effect of CHM in decreasing albuminuria compared to ACEi/ARB was uncertain because of the very low quality of evidence (**Table 3**).

Proteinuria

Nine studies measured end of treatment 24-hour proteinuria (**Figure 3b**). The pooled estimated effect showed CHM may reduce proteinuria compared to placebo after 2 to 3 months intevention, although heterogeneity was high (SMD -1.34, 95% CI [-2.18, -0.51], I^2 = 94%, p = 0.002; low quality evidence) [30 34 35 45]. Subgroup analysis revealed that different formulae and proteinuria scales may have been the source of heterogeneity (**Table S2**). Pooled estimates of effect of Qi Wei granule [30 45] and Arctiin granule [34 35] both showed that CHM may lead to greater reductions in proteinuria than placebo. Subgroup of measurements unit of milligram per 24-hour showed the proteinuria was 324.42 mg/24h lower (95% CI, [-485.15, -163.69]; I^2 = 30%; p < 0.0001) in the CHM group than the placebo group [34 35 45].

When used in combination with ACEi/ARB, meta-analysis of four studies with 489

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participants [24 36 44] showed that CHM may make little or no difference to proteinuria compared to placebo after 3 to 6 months of intervetions (SMD -0.15, 95% CI [-0.52,0.23], I^2 = 72%, p = 0.44; low quality evidence). Sources of heterogeneity were not identified (**Table S2**). Likewise, low quanlity evidence suggested that CHM may make no differences to end of treatment proteinuria compared to placebo plus ACEi/ARB after 1 to 3 months intervention (**Table 3**) [28 44].

Serum Creatinine Level

Ten studies provided end of treatment data of serum creatinine (Scr) level (**Figure 3c**). Pooled estimation of two small studies [38 45] showed that the additional CHM intervention probably made little difference to Scr levels compared with placebo after 3 to 6 months (MD 5.75 μmol/L, 95% CI [-2.06, 13.57], I^2 = 0%, p = 0.15; moderate quality evidence). When used in combination with ACEi/ARB, end of treatment Scr level was slightly lower in the CHM group compared to the placebo group over 3 to 6 months, but was not clinically significant (MD -4.02 μmol/L, 95% CI [-7.81, -0.23], I^2 = 0%, p = 0.15; moderate quality evidence) [24 33 36 41 44]. Subgroup analysis found that the lowering Scr effect of CHM was evident in patients with abnormal baseline Scr after 3 months intevention (MD -9.99 μmol/L, 95% CI [-17.71, -2.26], I^2 = 0%, p = 0.01) [36 44].

Slightly lower Scr levels were observed in the CHM group compared to placebo plus ACEi/ARB group after 1 to 3 months intervention, but the difference was not clinically significant [26-28 44]. A similar effect was found in the subgroup analysis of Tang Shen Ning formula compared to placebo plus ARB after 2 to 3 months treatment (MD -3.96 μmol/L, 95% CI [-6.13, -1.78], I^2 = 6%, p = 0.0004) [26 27].

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Estimated Glomerular Filtration Rate

Of the eight studies, the glomerular filtration rate (GFR) was estimated by either Cockcroft-Gault equation or other serum creatinine-based equations (**Figure 3d**). When used in combination with ACEi/ARB, the end of treatment eGFR was slightly higher in the CHM group compared to placebo group after 3 to 6 intervention (MD 6.28 mL/min, 95% CI [2.42, 10.14], $I^2 = 0\%$, $p = 0.001$; moderate quality evidence) [24 36 41 44]. Subgroup analysis of specific formula showed that the end of treatment eGFR was 5.22 mL/min higher (95% CI [0.69, 9.74], $I^2 = 0\%$, $p = 0.02$) in the Tang Shen Fang formula plus ACEi/ARB group than the placebo plus ACEi/ARB group [24 44]. It should be noted that Cockcroft-Gault equation may overestimate eGFR, leading to 10-20% higher value in pooled estimation of eGFR than the actual eGFR and these positive results should be interpreted cautionsly.

One small study (44 participants) provided low quality of evidence that CHM made no difference to placebo in terms of eGFR after 3 months intervention (**Table 3**) [45]. When comparing CHM to placebo plus ACEi/ARB, meta-analysis results indicated that no significant difference in eGFR over 1 to 3 months treatment (low quality evidence; **Table 3**) [26 27 29 44].

Secondary Outcomes

Meta-analysis results of secondary outcomes are summarised in **Table S3**. When compared to placebo, the pooled estimated effects for both fasting blood glucose (FBG) [25 27 32 36 38-41] and HbA1c [24 27 32 36 38 39 41 45] did not show additional benefit of CHM in lowering blood glucose. Likewise, summarised effects from three studies showed no statistical differences between the CHM and placebo groups for systolic and diastolic blood pressure [24 39 45]. CHM resulted in lower levels of total cholesterol [24 32 36-41], triglycerides [24 32 36-41] and LDL-C

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[24] [36-41], although HDL-C levels [24] [32] [36-41] were not statistically significant compared to placebo. However, the results were limited by substantial heterogeneity and the reason was not found. Three studies [24] [42] [46] measured patients' quality of life by questionnaire at the end of treatment but only two studies used the Diabetes QoL tool and provided usable data. The pooled estimation suggested no statistically significant differences between the CHM and the placebo group regarding quality of life [24] [46].

Safety Evaluation of CHM Therapy

Data on adverse events was provided in 14 studies. Of these, 7 studies stated no adverse events (AEs) were observed during study period [27] [29] [30] [32] [33] [38] [45]. In total, 53 cases of adverse events were reported in seven studies with 1,445 participants. Except for Li's study [31], details of AEs in each group were reported. The most common AE of CHM was digestive system disorders (18 cases), including abdominal pain, diarrhea or sloppy stools [34] [35] [41]. Both the CHM and control groups reported a modest number of cases of elevated liver enzyme levels (11 cases), infection (2 cases) or anemia (3 cases) [24] [28] [44]. In a three-arm study [44], one case of hypertension in the CHM group, one case of hypotension in losartan group and one case of hyperkalemia in CHM plus losartan group were reported. All participants that experienced the AEs recovered after discontinuation of the tested interventions. Three cases of serious AEs, including two cases of death and a case of acute myocardial infarction (AMI), were reported in Li's trial [24]. One participant in the CHM group died due to subarachnoid hemorrhage while another participant died after AMI. The researchers reported that these serious AEs were not related to the study agent.

Sensitivity and Subgroup Analysis

Sensitivity analysis by excluding studies with substantial risk of bias regarding

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randomisation showed consistent results with the primary analysis, except for the comparison of CHM versus placebo plus ACEi/ARB in terms of Scr level (**Table S4**). Subgroup analysis indicated that baseline kidney function, different CHM formulae and outcome measurement scales could partially explain the variant treatment effect of primary outcomes (**Table S2**). Publication bias was not evaluated due to the limited number of studies included in each outcome.

DISCUSSION

This review included 20 RCTs involving 2,719 participants and evaluated the effects and safety of CHM in addition to conventional therapies for DKD. As an adjunctive therapy, CHM may decrease proteinuria (either measured as urinary albumin or protein excretion) in DKD patients compared with placebo, regardless of concomitant use of ACEi/ARB. When CHM and ACEi/ARB were used simultaneously, eGFR improved compared to ACEi/ARB alone but studies had measurement shortfalls that may have overestimated the effect. CHM appeared to be well tolarated in DKD patients and no significant adverse events causal to CHM interventions were reported. These results suggest potential short-term renal benefit by adding CHM to conventional pharmacotherapies in DKD populations. However, due to the short follow-up periods and small numbers of clinical events in terms of mortality and progression to ESKD, the long-term benefit of CHM is yet to be determined.

This study demonstrated that CHM may be applied as an adjunctive treatment for DKD to achieve better renal outcomes. From the clinical perspective, the short-term

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albuminuria/proteinuria reduction effect of CHM identified in this review is moderate when compared to placebo. In patients with chronic kidney disease, the early reduction in albuminuria is associated with lower risk of ESKD or doubling Scr level, particulally in those patients with baseline albuminuria greater than 30mg/g [47]. Therefore, for the subgroup of DKD patients who are contraindicated for ACEi/ARB use, CHM may offer some benefit. When used in combination with ACEi/ARB, the lowering albuminuria effect of CHM is mild to moderate from a clinical perspective. Considering the failure of dual RAS inhibitors therapy, CHM could be a potential option for those DKD patients who are on ACEi/ARB to achieve greater albuminuria reduction in the short-term. The combination of CHM and ACEi/ARB may also be benefitial in improving eGFR, especially for patients experiencing acute drop of eGFR after early RAS inhibitors initiation.

Findings from this review are in line with those of previous reviews focusing on single herbs or particular formulae. Li et.al reviewed the clinical effect of preparations of *Astragali Radix* in DKD patients, finding that *Astragali* injection lowered Scr, increased eGFR and reduced proteinuria based on data from 21 RCTs and 4 non-randomised controlled trials [48]. In published reviews of *Ginkgo Folium* extract and *Xue Zhi Kang* capsules, lower fasting blood glucose and HbA1c levels in the CHM group were reported [49] [50]. The inconsistency in terms of the glycemic outcomes may have been due to differences in ingredients amongst the included studies. In our review, only two trials applied either *Ginkgo Folium* extract or *Xue Zhi Kang* capsules as interventions. The glycemic control effect may have been diluted by other trials using various herbal ingredients, which targeted on kidney rather than glycemic control. It should also be noted

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that the studies included in the previous reviews of *Ginkgo Folium* extract and *Xue Zhi Kang* capsules resulted in significant risk of bias (including publication bias). Thus, rigorous and large scale clinical trials are needed to confirm the glycemic control effects of CHM in DKD patients.

The renal protective effect of CHM may be related to particular bioactive compounds contained in the herbal ingredients included in these RCTs. The most frequently used herb was *Astragali Radix*. Both *in vitro* and *in vivo* studies have indicated that chemical components of *Astragali Radix,* such as Astragaloside IV and Astragalus saponin I, exert anti-oxidant and anti-inflammatory properties in diabetic models [51 52]. These chemicals can prevent and restore kidney tissue injury related to oxidative stress. Additionally, Astragaloside IV can reduce endoplasmic reticulum stress and increase podocyte integrity, which is the therapeutic target for decreasing albuminuria [53 54]. The second most frequently used herb, *Rehmanniae Radix*, also upregulates anti-inflammatory and antioxidant effects in diabetic rats [55]. Furthermore, anti-diabetic properties were observed in its constituent compound (catalpol) and ethanolic extract [56]. Although the glucose lowering effect of *Rehmanniae Radix* was not superior to metformin, its use was associated with higher anti-inflammatory activity, lower oxidative stress levels, and restoration of diabetes-induced kidney lesions. The third most frequent herb was *Rhei Radix et Rhizoma*. Active compounds of *Rhei Radix et Rhizoma,* including anthraquinones (rhein and emodin) and phenolic acids (gallic acid and ferulic acid), have been shown to protect the kidneys by reducing oxidative stress, inflammation, fibronectin and extracellular matrix accumulation [57-59]. Furthermore, *in vitro* experiments have demonstrated that extracts of *Rhei Radix et*

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Rhizoma can inhibit lipid peroxidation and lower serum lipid levels, which are risk factors for diabetes and DKD progression [60 61].

Renal toxicity induced by aristolochic acid (AA) has been a concern since a series of renal failure cases caused by AA contaminated products were reported [62 63]. In our review, the CHM used in included studies appeared to be well-tolerated and safety signals were not identified. This could be related to the fact that all herbal ingredients investigated were free from AA, and some of the studies mentioned a strict quality control processes regarding the CHM raw material and manufacturing procedures [24 31 44]. Mortality risk reduction effect of non-AA prescribed CHM was indicated in a chronic kidney disease population study, but for DKD patients, the long-term safety of CHM requires further studies to confirm [64].

Although this review was conducted in a systematic and comprehensive manner, there are limitations that should be taken into account when interpreting the findings. Firstly, the number of included studies was relatively small, and few studies measured and reported the same outcomes consistently. This caused difficulty in meta-analysis and introduced heterogeneity across studies and led to downgrading in quality of evidence. Even meta-analyses with low heterogeneity may not be reliable because there were only a very small number of included studies in the subgroup analyses (less than or equal to three studies in each subgroup). In addition, the positive effect of CHM in eGFR outcomes is dominated by a study using Cockcroft-Gault equation (64.8% weight), leading to possible overestimation of eGFR value [65]. Core outcome sets with standardised measurements are needed in future studies to rigorously assess the effect of CHM. Secondly, most of the

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studies had short follow-up periods (1-3 months) and small sample sizes, leading to imprecision of the estimated effect and low centainty with regard to long-term benefit and effect on renal function and clinical outcomes. Thirdly, more than half of the included studies did not provide information on randomisation and allocation procedures, such that the impact of potential selection bias was unclear. Although the CHM formulae were processed as granules or capsules in order to achieve blinding, quality assurance information for each CHM preparation was not provided in most of the studies. Further studies are strongly encouraged to report following the CONSORT reporting guidelines with sufficient details regarding the manufacture and quality control of investigated CHM [66-68]. Finally, although we did not limit the CHM interventions in terms of herbal composition, five included studies shared highly homologous CHM ingredients synthesis [24 30 31 44 45], thereby limiting the diversity of CHM treatments evaluated.

Since the participants in most included trials were older adults with a GFR greater than 60 mL/min, the renal protective effect of CHM in younger individuals and in advanced kidney disease is uncertain. Moreover, all included studies were conducted in China, such that the effect of CHM reported in this review may not be generalisable to other population groups. It should further be noted that, in most of the included studies, the forms of CHM used were multi-ingredients herbal formulae, which were developed based on traditional Chinese medicine theory and experts' clinical experience. While indicative from pharmacological studies, the most frequently used ingredients and formulae discussed above may not necessarily be relevant to the observed effects reported in this study.

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CONCLUSION

In conclusion, combination of CHM with conventional RAS inhibitors showed promise as an adjunctive treatment for improving renal function and decreasing urinary albumin and protein excretion in patients with DKD. The rate of occurrences of adverse events was low and the tested CHM appeared to be well-tolerated. This systematic review also provided potential candidate formulae and frequently used herbs for further investigation. Well-designed RCTs following reporting guidelines with adequate sample sizes and longer follow-up periods are warranted to confirm the long-term efficacy and safety of CHM, especially with respect to patient-oriented outcomes such as mortality, disease progression, and quality of life.

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Competing Interests

None declared.

Data Sharing Statement

Data extracted from original studies and data used for meta-analysis are available upon request.

Contributions

Research idea and study design: La Z, CL, CCX, WM; data collection and screening: La Z, LY, JS, XQ, ALZ; data extraction: La Z, LY, JS; data analysis: La Z, JS; Risk of bias assessment: La Z, LY, Lei Z, XG, ALZ; GRADE assessment: WM, Lei Z, LY, JS, and DJ; Manuscript writing: all authors; supervision and mentorship: CCX, XL, CL. Each author contributed important intellectual content during manuscript drafting and revision and

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accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Supplementary Material

Table S1: Search strategy of MEDLINE.

Table S2: Subgroup Analysis of primary outcomes

Table S3: Meta-analysis results of secondary outcome

Table S4: Sensitivity Analysis of primary outcomes

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References

1. White SL, Chadban S. KinD Report (Kidneys in Diabetes): temporal trends in the epidemiology of diabetic kidney disease and the associated health care burden in Australia. *Report of the Kidney in Diabetes*. Melbourne, Australia: Kidney Health Australia, 2014.
2. Saran R, Li Y, Robinson B, et al. US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2015;66(1) (suppl 1):S1-305.
3. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation.* 2003;108(17):2154-2169.
4. Kidney Disease Outcomes Quality Initiative. Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis.* 2007;49(2) (suppl 2):S12-154.
5. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis.* 2012;60(5):850-886.
6. Kramer H, Boucher RE, Leehey D, et al. Increasing mortality in adults with diabetes and low estimated glomerular filtration rate in the absence of albuminuria. *Diabetes Care.* 2018;41:775-781.
7. Krolewski AS, Skupien J, Rossing P, Warram JH. Fast renal decline to end-stage renal disease: an unrecognized feature of nephropathy in diabetes. *Kidney Int* 2017;91(6):1300-1311.
8. Afkarian M, Zelnick LR, Hall YN, et al. Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. *JAMA.* 2016;316(6):602-610.
9. Muskiet MHA, Wheeler DC, Heerspink HJL. New pharmacological strategies for protecting kidney function in type 2 diabetes. *The Lancet Diabetes & Endocrinology.* 2018; doi: https://doi.org/10.1016/S2213-8587(18)30263-8.
10. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med.* 2013;369(26):2492-2503.
11. Packham DK, Wolfe R, Reutens AT, et al. Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy. *J Am Soc Nephrol.* 2012;23(1):123-130.
12. Zhang L, Li Y, Guo XF, et al. Text mining of the classical medical literature for medicines that show potential in diabetic nephropathy. *Evid Based Complement Alternat Med.* 2014;2014:189125.
13. China Academy of Chinese Medical Sciences. Evidence-based guidelines of clinical practice in Chinese medicine-internal medicine. *Beijing: China Press of Traditional Chinese Medicine*; 2011. (in Chinese) 中国中医科学院. 中医循证临床实践指南: 中医内科分册. 北京: 中国中医药出版社, 2011
14. Gao YB, Liu TH, Nan Z, Zhen Z, Zhou Q. The Chinese medicine diagnosis and treatment standards of diabetic nephropathy. *World Journal of Integrated Traditional and Western Medicine.* 2011;6(6):548-552. (in Chinese) 高彦彬, 刘铜华, 南征, et al. 糖尿病肾脏疾病中医诊疗标准. *世界中西医结合杂志* 2011;6(6):548-52
15. Lord GM, Cook T, Arlt VM, Schmeiser HH, Williams G, Puesy CD. Urothelial

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

malignant disease and Chinese herbal nephropathy. *Lancet.* 2001;358(9292):1515-1516.

16. Stanifer JW, Kilonzo K, Wang D, et al. Traditional medicines and kidney disease in low- and middle-income countries: opportunities and challenges. *Semin Nephrol.* 2017;37(3):245-259.
17. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions (Version 5.1.0). The Cochrane Collaboration, 2011.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-269.
19. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal-disease - with emphasis on the stage of incipient diabetic nephropathy. *Diabetes.* 1983;32:64-78.
20. Yang NZ, Liu XS. Diagnosis, syndrome diffeciation and treatment effect eveluation of diabetic nephropathy (protocal). *Shanghai Journal of Traditional Chinese Medicine*. 2007;41(7):7-8. 杨霓芝, 刘旭生. 糖尿病肾病诊断, 辨证分型及疗效评定标准 (试行方案). *上海中医药杂志* 2007;41(7):7-8.
21. The Nordic Cochrane Centre, The Cochrane Collaboration. *Review Manager (RevMan)*. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014
22. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
23. Schünemann H, Brozek J, Guyatt G. GRADE handbook for grading quality of evidence and strength of recommendation. https://gdt.gradepro.org/app/handbook/handbook.html. Accessed October 19, 2017.
24. Li P, Chen YP, Liu JP, et al. Efficacy and safety of tangshen formula on patients with type 2 diabetic kidney disease: a multicenter double-blinded randomized placebo-controlled trial. *Plos One.* 2015;10(5): e012602710.
25. Fan YW. Clinical study of Qi Kwai granules in early type 2 diabetic nephropathy. *Naijing: Nanjing University of Chinese Medicine*; 2010. (in Chinese) 范译文. 芪葵颗粒干预早期 2 型糖尿病肾病的临床研究. 南京中医药大学, M1 - 硕士, 2010.
26. Gao YB, Zhao HL, Guan S, et al. Clinical research of Tang Shen Ning in treating early stage of diabetic nephropathy with types of deficiency of both vital energy and yin and collaterals siltation and stagnant. *China Journal of Traditional Chinese Medicine and Pharmacy*. 2006(07):409-411.高彦彬, 赵慧玲, 关崧, et al. 糖肾宁治疗气阴两虚、络脉瘀滞型早期糖尿病肾病临床研究. *中华中医药杂志* 2006(07):409-411.
27. Gao YB, Zhou HL, Guan S, et al. Multicenter randomized and double-blind controlled clinical trial of Tang Shen Ning Granules in treating diabetic kidney disease. *Chinese Journal of Traditional Chinese Medicine.* 2017;32(11):5212-5215. (in Chinese) 高彦彬, 周晖, 关崧, et al. 糖肾宁颗粒治疗糖尿病肾病多中心随机双盲对照临床试验. *中华中医药杂志* 2017;32(11):5212-5215.
28. Han YL, Liu HF, Lou XE, Miao GZ, Wang XQ. Method of combination of disease and syndrome in treating stage IV proteinuria in diabetic nephropathy of Qi-Yin deficiency. *Journal of Changchun University of Traditional Chinese Medicine.* 2014;30(5):903-905. (in Chinese) 韩玉岭, 柳红芳, 娄锡恩, et al. 病

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

证结合法治疗气阴两虚型糖尿病肾病Ⅳ期蛋白尿. *长春中医药大学学报* 2014(05):903-905.

29. Jia M, Zhao JX, Dong C, Feng R. Clinical research of Sanhuang Yishen granule on patients diabetic nephropathy in Ⅳ stage. *World Chinese Medicine.* 2015;10(6):845-848. (in Chinese) 贾冕, 赵进喜, 董超, et al. 三黄益肾颗粒干预糖尿病肾病Ⅳ期的临床研究. *世界中医药* 2015(06):845-848.
30. Jia XL. Study on clinic effect and experiment research of Qiwei treating the DN. *Beijing: Beijing University of Chinese Medicine;* 2012. (in Chinese) 贾晓蕾. 芪卫颗粒干预糖尿病肾病临床及实验研究. 北京中医药大学, M1 - 硕士, 2012.
31. Li J, Zhao JX, Wang SD, et al. Effect of the whole course intervention program of combined therapy of TCM on the endpoint events of diabetic nephropathy. *Journal of Traditional Chinese Medicine.* 2012;53(7):568-571+580. (in Chinese) 李景, 赵进喜, 王世东, et al. 中医药综合治疗方案全程干预对糖尿病肾病终点事件的影响. *中医杂志* 2012(07):568-71+80.
32. Lin L, Ni Q, Gao QJ et al. Clinical study on Tangweikang capsule in treating diabetic nephropathy. *Chinese Journal of Integrated Traditional and Western Medicine.* 2000;20(11):811-814. (in Chinese) 林兰, 倪青, 高齐健, et al. 糖微康胶囊治疗糖尿病肾病的临床观察. *中国中西医结合杂志* 2000(11):811-814.
33. Liu YF. Qihuang capsule in treatment of diabetic nephropathy Qi and Yin deficiency syndrome clinical. *Harbin: Heilongjiang University Of Chinese Medicine;* 2015. (in Chinese) 刘羽飞. 芪黄胶囊治疗糖尿病肾病气阴两虚型的临床观察. 黑龙江中医药大学, M1 - 硕士, 2015.
34. Ma ST, Liu DL, Niu R, et al. Double -blind randomized placebo-controlled multi-centre phase Ⅲ clinical trial of Arctiin granule in the treatment of diabetic nephropathy. *Chin J Clin Pharmacol.* 2011;27(1):15-18. (in Chinese) 马松涛, 刘冬恋, 牛锐, et al. 牛蒡子苷治疗糖尿病肾病的随机双盲安慰剂多中心III期临床试验. *中国临床药理学杂志* 2011(01):15-18.
35. Ma ST, Liu DL, Niu R, et al. Tangjiangshekang granule in treatment of diabetic nephropathy: a double -blind, randomized, placebo-controlled multicentre clinical trial. *Chin J New Drugs Clin Rem.* 2011;30(1):16-19. (in Chinese) 马松涛, 刘冬恋, 牛锐, et al. 糖降肾康颗粒治疗糖尿病肾病随机双盲安慰剂对照多中心临床试验. *中国新药与临床杂志* 2011(01):16-19.
36. Ni Q, Jiang S, Xiao YX, et al. A clinical observation on Qiyao Xiaoke capsule combined with western medicine for 146 cases of Diabetic Nephropathy. *Journal of Traditional Chinese Medicine.* 2013;54(6):484-487. (in Chinese) 倪青, 姜山, 肖月星, et al. 芪药消渴胶囊联合西药治疗糖尿病肾病 146 例临床观察. *中医杂志* 2013(06):484-487.
37. Wei N, Chang WS, Xue DZ, Shen XF. Effect of Xuezhikang on oxidative stress in early diabetic nephropathy. *Chinese General Practice.* 2012;15(18):2085-2087. (in Chinese) 魏娜, 常万松, 薛迪中, et al. 血脂康对早期糖尿病肾病患者氧化应激的影响. *中国全科医学* 2012(18):2085-2087.
38. Wei X, Yao HJ, Liu Y, Zhang J. Efficacy observation of adjunctive treatment of gandi capsules for diabetic nephropathy. *China Pharmacy.* 2016;27(2):225-227. (in Chinese) 魏昕, 姚慧娟, 刘艳, et al. 甘地胶囊辅助治疗糖尿病肾病的疗效观察. *中国药房* 2016(02):225-227.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

39. Xie SF, Huang LJ, Liu JS, Yu JY, Wang XC. The long-term effect of Yang yin he luo medicinals for reducing urinary albumin to creatinine ratio in early diabetic nephropathy patients. *Jiangsu J Tradit Chin Med.* 2011;43(9):19-20. (in Chinese) 谢绍锋, 黄莉吉, 刘敬顺, et al. 长期应用养阴和络中药对早期糖尿病肾病患者尿微量白蛋白肌酐比值的影响. *江苏中医药* 2011(09):19-20.
40. Yang L, Tan ZH, Li YK. The clinical effect observation of Qiming granules with standard care for early diabetic nephropathy. *Guiding Journal of Traditional Chinese Medicine and Pharmacy.* 2014;20(6):52-53. (in Chinese) 杨力, 檀增桓, 李玉坤, et al. 芪明颗粒配合常规疗法治疗早期糖尿病肾病 71 例临床观察. *中医药导报* 2014(06):52-53.
41. Yang M. Study on the clinical exploratory study of Qizhu granule in the treatment of early type 2 diabetic nephropathy. *Beijing: China Academy of Chinese Medical Sciences*; 2017. (in Chinese) 杨明. 芪术颗粒治疗早期 2 型糖尿病肾病临床探索性试验研究 [硕士]. 中国中医科学院, 2017.
42. Zhang LF, Lv RH, Zhao JX, Wang SR. Effect of TCM treatment on quality of life in diabetic nephropathy patients with renal failure: a multi-centered clinical study. *Journal of Traditional Chinese Medicine.* 2008;49(2):119-122. (in Chinese) 张丽芬, 吕仁和, 赵进喜, et al. 中医辨证治疗方案对糖尿病肾病肾功能不全患者生存质量的影响——多中心临床研究. *中医杂志* 2008(02):119-122.
43. Zhang LF, Zhao JX, Lv RH, et.al. The effect of Differiation Chinese Medicine Treatment on Syndrome Improvement in diabetic nephropathy patients with renal failure. Abstract of the forth International Integration Medicine Conference of Kidney Diseases. Tian jin, China; 2006. (in Chinese) 中医辨证论治糖尿病肾病肾功能不全证候疗效评价研究. 第四届国际中西医结合肾脏病学术会议; 2006; 中国天津.
44. Zhang LF, Zhao JX, Lv RH, et al. Study on the effectiveness and safety of optimum program of prevention and treatment of renal insufficiency of diabetic nephropathy. *China Foreign Medical Treatment.* 2006;47(10):755-758. (in Chinese) 张丽芬, 赵进喜, 吕仁和, et al. 糖尿病肾病肾功能不全防治优化方案的有效性和安全性研究. *中医杂志* 2006(10):755-758.
45. Zhou JX. Effect and safety of Qiwei granule on diabetic nephropathy and podocyte. *Beijing: Beijing University of Chinese medicine*; 2014. (in Chinese) 周静鑫. 芪卫颗粒干预糖尿病肾病临床疗效及其保护足细胞作用机制研究. 北京中医药大学, M1 - 博士, 2014.
46. Zhou X, Zhao JX, Wang SD, et al. Effect of TCM Comprehensive Treatment Program on Quality of Life in Patients With Diabetic Nephropathy. *Journal of Traditional Chinese Medicine.* 2014;55(6):473-477. (in Chinese) 周鑫, 赵进喜, 王世东, et al. 中医药综合治疗方案对糖尿病肾病患者生存质量的影响. *中医杂志* 2014(06):473-477.
47. Heerspink HJL, Greene T, Tighiouart H, et al. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *The Lancet Diabetes & Endocrinology.* 2019;7(2):128-139.
48. Li MX, Wang WX, Xue J, Gu Y, Lin SY. Meta-analysis of the clinical value of Astragalus membranaceus in diabetic nephropathy. *J Ethnopharmacol*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2011;133(2):412-419.
49. Wang F, Wu HM. Xuezhikang for diabetic kidney disease: a systematic review of randomized controlled trials. *Chin J Evid-based Med.* 2009;9(1):63-70. (in Chinese) 王锋, 吴红梅. 血脂康治疗糖尿病肾病的系统评价, 2009.
50. Zhang L, Mao W, Guo XF, et al. Ginkgo biloba extract for patients with early diabetic nephropathy: a systematic review. *Evid Based Complement Alternat Med* 2013;2013:689142.
51. Gui D, Huang JH, Guo YP, et al. Astragaloside IV ameliorates renal injury in streptozotocin-induced diabetic rats through inhibiting NF-κB-mediated inflammatory genes expression. *Cytokine.* 2013;61(3):970-977.
52. Qi WW, Niu JY, Qin QJ, Qiao ZD, Gu Y. Astragaloside IV attenuates glycated albumin-induced epithelial-to-mesenchymal transition by inhibiting oxidative stress in renal proximal tubular cells. *Cell Stress Chaperones.* 2014;19(1):105-114.
53. Gui D, Guo Y, Wang F, et al. Astragaloside IV, a novel antioxidant, prevents glucose-induced podocyte apoptosis in vitro and in vivo. *PloS one.* 2012;7(6):e39824.
54. Wang ZS, Xiong F, Xie XH, Chen D, Pan JH, Cheng L. Astragaloside IV attenuates proteinuria in streptozotocin-induced diabetic nephropathy via the inhibition of endoplasmic reticulum stress. *BMC nephrol.* 2015;16(1):44.
55. Waisundara VY, Huang M, Hsu A, Huang D, Tan BK. Characterization of the anti-diabetic and antioxidant effects of rehmannia glutinosa in streptozotocin-induced diabetic Wistar rats. *Am J Chin Med.* 2008;36(6):1083-1104.
56. Yang SS, Deng HC, Zhang QZ, et al. Amelioration of diabetic mouse nephropathy by catalpol correlates with down-regulation of Grb10 expression and activation of insulin-like growth factor 1/insulin-like growth factor 1 receptor signaling. *PLoS One.* 2016;11(3):e0151857.
57. Zhang ZH, Wei F, Vaziri ND, et al. Metabolomics insights into chronic kidney disease and modulatory effect of rhubarb against tubulointerstitial fibrosis. *Sci Rep.* 2015;5:14472.
58. Ahad A, Ahsan H, Mujeeb M, Siddiqui WA. Gallic acid ameliorates renal functions by inhibiting the activation of p38 MAPK in experimentally induced type 2 diabetic rats and cultured rat proximal tubular epithelial cells. *Chem Biol Interact.* 2015;240:292-303.
59. Zeng CC, Liu X, Chen GR, et al. The molecular mechanism of rhein in diabetic nephropathy. *Evid Based Complement Alternat Med.* 2014;2014:487097.
60. Hosseini A, Mollazadeh H, Amiri MS, Sadeghnia HR, Ghorbani A. Effects of a standardized extract of Rheum turkestanicum Janischew root on diabetic changes in the kidney, liver and heart of streptozotocin-induced diabetic rats. *Biomed Pharmacother* 2017;86:605-11.
61. Punithavathi VR, Prince PS, Kumar R, Selvakumari J. Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats. *Eur J Pharmacol* 2011;650(1):465-471.
62. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet.* 1993;341(8842):387-391.
63. Nortier JL, Martinez MCM, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). *New Engl J Med.* 2000;342(23):1686-1692.

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64. Hsieh CF, Huang SL, Chen CL, Chen WT, Chang HC, Yang CC. Non-aristolochic acid prescribed Chinese herbal medicines and the risk of mortality in patients with chronic kidney disease: results from a population-based follow-up study. *Bmj Open.* 2014;4(2):e004033.
65. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis.* 2010;55(4):622-627.
66. Gagnier JJ, Boon H, Rochon P, et al. Improving the quality of reporting of randomized controlled trials evaluating herbal interventions: implementing the CONSORT statement. *Explore(NY).* 2006;2(2):143-149.
67. Gagnier JJ, Boon H, Rochon P, et al. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. *Ann Intern Med.* 2006;144(5):364-367.
68. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.

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Table 1 Characteristic of Included Studies

Study	Sample Size (M/F)	Age	Diabetes Type	Inclusion criteria of kidney function	Intervention and Control Protocol	Duration	Reported Outcomes
Fan, 2010 [25]	61 (28/33)	59.6	2	Albuminuria 30-300 mg/g or 30-300 mg/24h	T: Qi Kui granule 1 bag bid C: placebo	12m	UAE; FBG
Jia, 2012 [30]	60 (29/31)	58.3	2	Proteinuria < 3.5 g/24h; Normal Scr level	T: Qi Wei granule 4.5g tid C: placebo	3m	UAE; 24hUP;
Ma, 2011a [34]	414 (186/ 228)	56.6	NS	Proteinuria ≤ 4.5 g/24h; Scr ≤ 190 μmol/L	T: Arctiin granule 1 bag tid C: placebo	2m	UAE; 24hUP;
Ma, 2011b [35]	186 (78/108)	55.3	NS	Proteinuria ≤ 3.5 g/24h; Scr < 176 μmol/L	T1: Arctiin granule 2 bag bid + placebo 2 bag qd T2: Arctiin granule 1 bag tid + placebo 1 bag tid C: placebo 2 bag tid	2m	UAE; 24hUP;
Wei, 2012 [37]	56 (24/32)	50.6	NS	Albuminuria 30-300 mg/24h; Scr ≤ 105 μmol/L	T: Xue Zhi Kang capsule 0.6g tid C: placebo	3m	UAE; TC; TG; LDLC; HDLC
Wei, 2016 [38]	41 (32/9)	61.8	2	Albuminuria > 30 mg/g and Proteinuria ≤ 3.5 g/24h GFR ≥ 30 mL/min	T: Gan Di capsule 3# tid C: placebo	6m	Scr; FBG; A1C; TC; TG; LDLC; HDLC
Xie, 2011 [39]	67 (30/37)	62.3	2	Albuminuria 30-299 μg/mg	T: Liu Wei Di Huang pill 3g tid + Ginkgo biloba tablet 19.2mg tid C: LWDHW placebo + GBT placebo	24m	UAE; FBG; A1C; TC; TG; LDLC; HDLC; SBP; DBP
Yang, 2014 [40]	142 (80/62)	48.5	NS	Albuminuria 30-300 mg/24h;	T: Qi Ming granule 4.5g tid C: placebo	3m	UAE; FBG; TC; TG; LDLC; HDLC

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				Normal Scr level			
Zhou, 2014 [45]	48 (27/21)	58.5	2	Proteinuria ≤ 3.5 g/24h; Normal Scr level	T: Qi Wei granule 6g tid C: placebo	3m	UAE; 24hUP; Scr; GFR; FBG; A1C; SBP; DBP
Li, 2015 [24]	180 (100/80)	59.0	2	Albuminuria > 20 μg/min or Proteinuria 0.5-2 g/24h GFR 60-130 mL/min	T: Tang Shen granule 8g bid + ACEi/ARB C: placebo + ACEi/ARB	6m	UAE; 24hUP; Scr; GFR; A1C; TC; TG; LDLC; HDLC; SBP; DBP; QoL
Liu, 2015 [33]	60 (NS)	20-70	2	Albuminuria 20-200 μg/min or Proteinuria ≤ 3.5 g/24h GFR > 60 mL/min	T: Qi Huang capsule 1.9g tid + losartan C: placebo + losartan	6m	24hUP; Scr
Ni, 2013 [36]	224 (112/112)	54.7	NS	Albuminuria 20-200 μg/min or Proteinuria ≤ 3.5 g/24h GFR 60-130 mL/min	T: Qi Yao Xiao Ke capsule 2.4g tid + benazepril C: placebo + benazepril	3m	UAE; 24hUP; Scr; GFR; FBG; A1C; TC; TG; LDLC; HDLC
Yang, 2017 [41]	25 (23/2)	59.3	2	Albuminuria 20-200 μg/min or 30-300 mg/24h	T: Qi Zhu granule 1 bag bid + irbesartan C: placebo + irbesartan	6m	UAE; Scr; GFR FBG; A1C; TC; TG; LDLC; HDLC
Zhang, 2006 [42-44]	221 (119/102)	61.9	NS	Proteinuria < 10g/24h; Scr 133-354 μmol/L or Ccr 30-70 mL/min	T 1: Modified Qi Wei granule 1 bag bid + losartan T 2: Modified Qi Wei granule 1 bag bid + losartan simulant C: placebo + losartan	3m	24hUP; Scr; GFR; QoL
Gao, 2006 [26]	90 (NS)	35-70	2	Albuminuria 20-200 μg/min or 30-300 mg/24h	T: Tang Shen Ning granule 5g tid + benazepril simulant C: placebo + benazepril	2m	UAE; Scr;
Gao, 2017	250	52.3	2	Albuminuria 30-300	T: Tang Shen Ning granule 8g tid	3m	UAE; Scr; FBG; A1C

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[27]	(116/134)			mg/24h	+ losartan simulant C: placebo + losartan		
Han, 2014 [28]	104 (NS)	30-78	2	Proteinuria ≥ 0.5 g/24h Scr < 265 μmol/L	T1: Bao Shen pill 1 bag bid + Tripterygium glycosides 20mg tid T2: Bao Shen pill 1 bag bid C: BS placebo + valsartan	1m	24hUP; Scr
Jia, 2015 [29]	56 (31/25)	59.6	NS	Proteinuria < 10g/24h; Scr < 265 μmol/L	T: San Huang Yi Shen granule 1 bag bid + irbesartan simulant C: placebo + irbesartan	3m	GFR
Li, 2012 [31 46]	315 (194/121)	58.1	NS	Proteinuria <10g/24h; Scr < 265 μmol/L or GFR > 40 mL/min;	T: Modified Qi Wei granule 4.5g bid C: placebo + irbesartan	24m	Mortality; Composite endpoints; QoL
Lin, 2000 [32]	119 (46/73)	55.3	NS	Proteinuria < 0.5 g/24h; Normal Scr level	T: Tang Wei Kang capsule 2g tid C: Captopril (same appearance as herbal capsule)	3m	UAE; FBG; A1C; TC; TG; HDLC

Abbreviation: M/F, male versus female; NS, not specified in the original reports; T, tested group; C, control group; qd, once daily; bid, twice daily; tid, thrice daily; m, months; Scr, serum creatinine concentration; Ccr, creatinine clearance rate; GFR, glomerular filtration rate; UAE, urinary albuminuria excretion;24hUP, 24-hour proteinuria; FBG, fasting blood glucose; A1C, glycated haemoglobin; TC, total cholesterol; TG, triglycerides; LDLC, low-density lipoprotein cholesterol; HLDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; QoL, quality of life.

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Table 2 Herbal Ingredients Used in Included Studies

Study	Formulae Name	Ingredients
Fan, 2010 [25]	Qi Kui granule	Astragali Radix; Polygoni Multiflori Radix; Abelmoschi Corolla
Jia, 2012 [30]	Qi Wei granule	Astragali Radix; Rehmanniae Radix; Rhei Radix et Rhizoma; Prunellae Spica; Curcumae Rhizoma; Euonymus Alatus; Notoginseng Radix et Rhizoma
Ma, 2011a [34]	Arctiin granule	Arctii Fructus
Ma, 2011b [35]	Arctiin granule	Arctii Fructus
Wei, 2012 [37]	Xue Zhi Kang capsule	Fermentum Rubrum*
Wei, 2016 [38]	Gan Di capsue	Scutellariae Radix; Astragali Radix; Corni Fructus; Rehmanniae Radix Phylianthi Fructus; Leonuri Herba Leonuri Herba; Bombyx Batryticatus; Sophorae Flos (stir fry processed)
Xie, 2011 [39]	Liu Wei Di Huang pill Ginkgo biloba tablet	Rehmanniae Radix; Corni Fructus; Dioscoreae Rhizoma; Alismatis Rhizoma; Moutan Cortex; Poria; Ginkgo Folium
Yang, 2014 [40]	Qi Ming granule	Astragali Radix; Puerariae Lobatae Radix; Rehmanniae Radix; Lycii Fructus; Cassiae Semen; Leonuri Fructus; Typhae Pollen; Hirudo
Zhou, 2014 [45]	Qi Wei granule	Astragali Radix; Rehmanniae Radix; Rhei Radix et Rhizoma; Prunellae Spica; Curcumae Rhizoma; Euonymus Alatus; Notoginseng Radix et Rhizoma
Li, 2015 [24]	Tang Shen granule	Astragali Radix; Rehmanniae Radix; Rhei Radix et Rhizoma; Notoginseng Radix et Rhizoma; Euonymus Alatus; Corni Fructus; Aurantii Fructus
Liu, 2015 [33]	Qi Huang capsule	Astragali Radix; Rehmanniae Radix; Ligustri Lucidi Fructus; Hirudo; Bombyx Batryticatus; Eupolyphaga Steleophaga; Rhei Radix et Rhizoma; *Gymnema sylvestre**; Sinomenii Caulis; Plantaginis Semen
Ni, 2013 [36]	Qi Yao Xiao Ke capsule	Panacis Quinquefolii Radix; Astragali Radix; Rehmanniae Radix; Dioscoreae Rhizoma; Corni Fructus; Lycii Fructus; Ophiopogonis Radix; Anemarrhenae Rhizoma; Trichosanthis Radix; Puerariae Lobatae Radix; Schisandrae Chinensis Fructus Schisandrae Chinensis Fructus; Galla Chinensis
Yang, 2017 [41]	Qi Zhu granule	Astragali Radix; Ligustri Lucidi Fructus; Atractylodis Macrocephalae Rhizoma; Abelmoschi Corolla; Rosae laevigatae Fructus Dioscoreae Spongiosae Rhizoma; Paeoniae Radix Rubra; Coptidis Rhizoma

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Zhang, 2006 [42-44]	Modified Qi Wei granule	Astragali Radix; Rehmanniae Radix; Prunellae Spica; Rhei Radix et Rhizoma; Euonymus Alatus; Epimedii Folium; Corni Fructus; Curcumae Longae Rhizoma
Gao, 2006 [26]	Tang Shen Ning granule	Astragali Radix; Rehmanniae Radix; Euryales Semen; Corni Fructus; Rhei Radix et Rhizoma; Chuanxiong Rhizoma
Gao, 2017 [27]	Tang Shen Ning granule	Astragali Radix; Euryales Semen; Rosae laevigatae Fructus; Rhei Radix et Rhizoma; Chuanxiong Rhizoma
Han, 2014 [28]	Bao Shen pill; Tripterygium glycosides	Not given.
Jia, 2015 [29]	San Huang Yi Shen granule	Astragali Radix; Curcumae Longae Rhizoma; Rhei Radix et Rhizoma; Chuanxiong Rhizoma; Angelicae Sinensis Radix; Salviae Miltiorrhizae Radix et Rhizoma; Cervi Cornu; Anemarrhenae Rhizoma; Arctii Fructus
Li, 2012 [31 46]	Modified Qi Wei granule	Astragali Radix; Rehmanniae Radix; Prunellae Spica; Rhei Radix et Rhizoma; Euonymus Alatus; Epimedii Folium; Corni Fructus; Curcumae Longae Rhizoma
Lin, 2000 [32]	Tang Wei Kang capsule	Astragali Radix; Ligustri Lucidi Fructus; Rhei Radix et Rhizoma

Note: All ingredients are the standarised pharmaceutical name from the Chinese Pharmacopoeia 2015. * *Monascus purpureus* Went. (Red Rice Yeast); pharmaceutical name not included in Chinese Pharmacopoeia 2015.

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Table 3 Summary of Findings Table

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with Placebo	Risk with CHM			
Comparison 1: CHM versus Placebo					
Albuminuria follow up: range 2 to 12 months	-	SMD 0.92 lower (1.35 lower to 0.51 lower)	-	1021 (8 RCTs)	⊕⊕⊕◯ MODERATE [a, b]
24-hour proteinuria follow up: range 2 to 3 months	-	SMD 1.34 lower (2.18 lower to 0.51 lower)	-	699 (4 RCTs)	⊕⊕◯◯ LOW [a, b, c]
Serum creatinine (Scr) follow up: range 3 to 6 months	The mean Scr was 77.41 μmol/L	The mean Scr in the intervention group was 5.75 μmol/L higher (2.06 lower to 13.57 higher)	-	85 (2 RCTs)	⊕⊕⊕◯ MODERATE [a, d]
Estimated glomerular filtration rate (eGFR) follow up: mean 3 months	The mean eGFR was 96.24 mL/min	The mean eGFR in the intervention group was 10.71 mL/min lower (23.93 lower to 2.51 higher)	-	44 (1 RCT)	⊕⊕◯◯ LOW [a, d]
Comparison 2: Placebo + ACEi/ ARB versus CHM +ACEi/ARB					
Albuminuria follow up: range 3 to 6 months	-	SMD 0.56 lower (1.04 lower to 0.08 lower)	-	330 (3 RCTs)	⊕⊕⊕◯ MODERATE [d, e]
24h-proteinuria follow up: range 3 to 6 months	-	SMD 0.15 lower (0.52 lower to 0.23 higher)	-	489 (4 RCTs)	⊕⊕◯◯ LOW [b, d, e]
Serum creatinine (Scr) follow up: range 3 to 6 months	The mean Scr was 88.13 μmol/L	The mean Scr in the intervention group was 4.02 μmol/L lower (7.81 lower to 0.23 lower)	-	595 (5 RCTs)	⊕⊕⊕◯ MODERATE [a, c]
Estimated glomerular filtration rate (eGFR) follow up: range 3 to 6 months	The mean eGFR was 79.27 mL/min	The mean eGFR in the intervention group was 6.28 mL/min higher (2.42 higher to 10.14 higher)	-	535 (4 RCTs)	⊕⊕⊕◯ MODERATE [c, e]
Comparison 3: CHM versus Placebo + ACEi/ ARB					
All-cause mortality follow up: mean 24 months	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	315 (1 RCT)	⊕⊕⊕◯ MODERATE [f]
Composite end-points events follow up: mean 24 months	133 per 1,000	45 per 1,000 (20 to 102)	RR 0.34 (0.15 to 0.77)	315 (1 RCT)	⊕⊕◯◯ LOW [d, g]
Albuminuria follow up: mean 3 months	-	SMD 6.38 lower (9.01 lower to 3.75 lower)	-	499 (3 RCTs)	⊕◯◯◯ VERY LOW [a, b, d]
24h-proteinuria follow up: range 1 to 3 months	-	SMD 0.00 lower (0.32 lower to 0.32 higher)	-	260 (2 RCTs)	⊕⊕⊕◯ LOW [d, h]
Serum creatinine (Scr)	The mean Scr was	The mean Scr in the intervention group was	-	590 (4 RCTs)	⊕⊕⊕◯ MODERATE

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follow up: range 1 to 3 months	105.52 µmol/L	4.05 µmol/L lower (6.09 lower to 2.01 lower)			a, c
Estimated glomerular filtration rate (eGFR) follow up: range 1 to 3 months	The mean eGFR was 97.24 mL/min	The mean eGFR in the intervention group was 0.57 mL/min lower (11.01 lower to 9.88 higher)	-	542 (4 RCTs)	⊕⊕◯◯ LOW a, b, c

*The risk in the intervention group (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).
Abbreviation: Confidence interval (CI); Mean difference (MD); Standardised mean difference (SMD); Risk ratio (RR)
GRADE justification: a. Unclear risk of bias of randomization and allocation concealment; b. Significant heterogeneity; c Wide confidence interval; d Small sample size and wide confidence interval; e. High or unclear risk of attrition bias; f. Low events rate lead to imprecise estimation and small simple size; g. Number of patients progressed to ESRD were included in composite outcomes, not solely reported; h. Unclear risk of attrition bias and potential selecting report bias;

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Figure Legends

Figure 1 PRISMA flowchart of searching and screening

Figure 2 Risk-of-bias of included studies

Note: The red dot indicates high risk of bias, yellow indicates unclear risk of bias anf green dot indicates low risk of bias.

Figure 3. Forest plot of primary outcomes

Note: Panel (a) albuminuria outcomes; (b) proteinuria outcomes; (c) serum creatinine outcomes; (d) estimated glomerulus filtration rate outcomes.
Abbreviation: CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standard.

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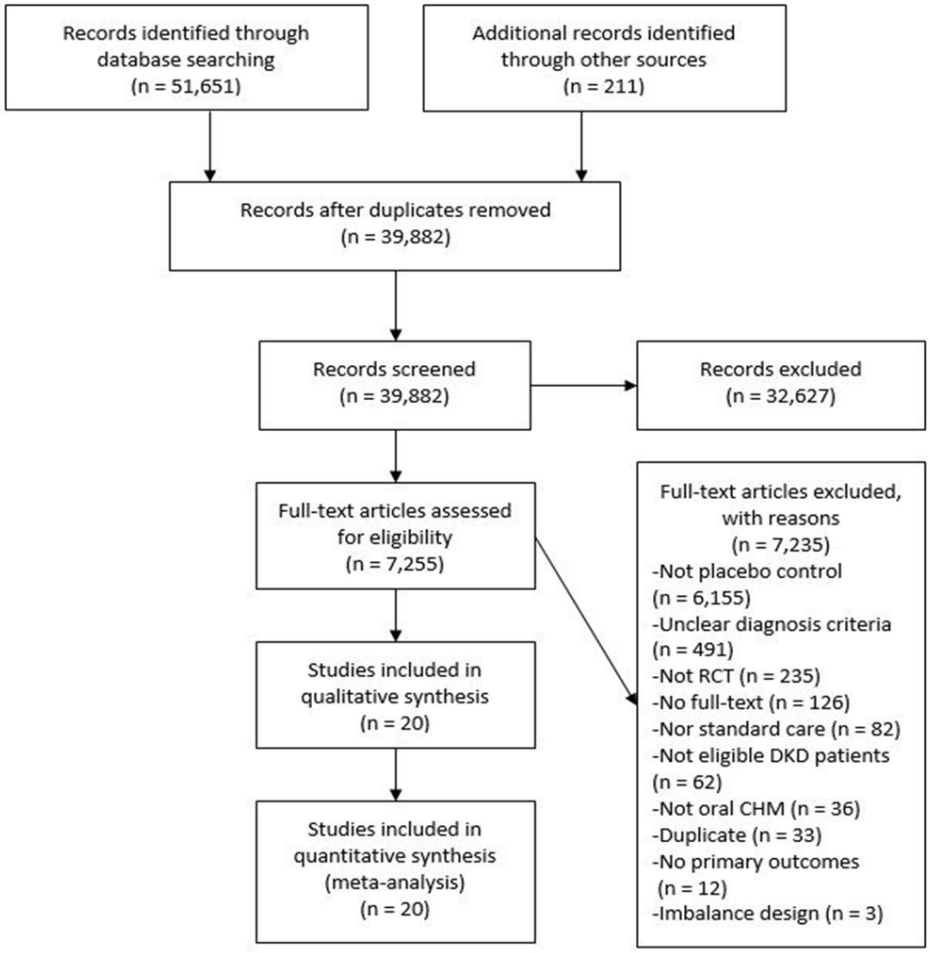

Figure 1 PRISMA flowchart of searching and screening

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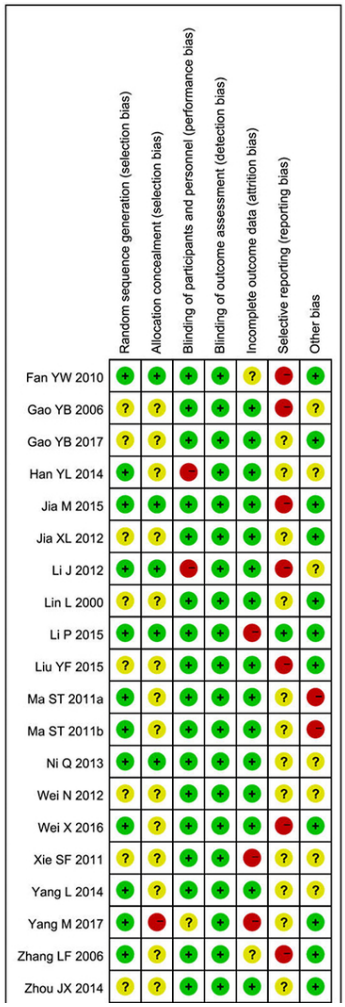

Figure 2 Risk-of-bias of included studies
Note: The red dot indicates high risk of bias, yellow indicates unclear risk of bias anf green dot indicates low risk of bias.

89x89mm (300 x 300 DPI)

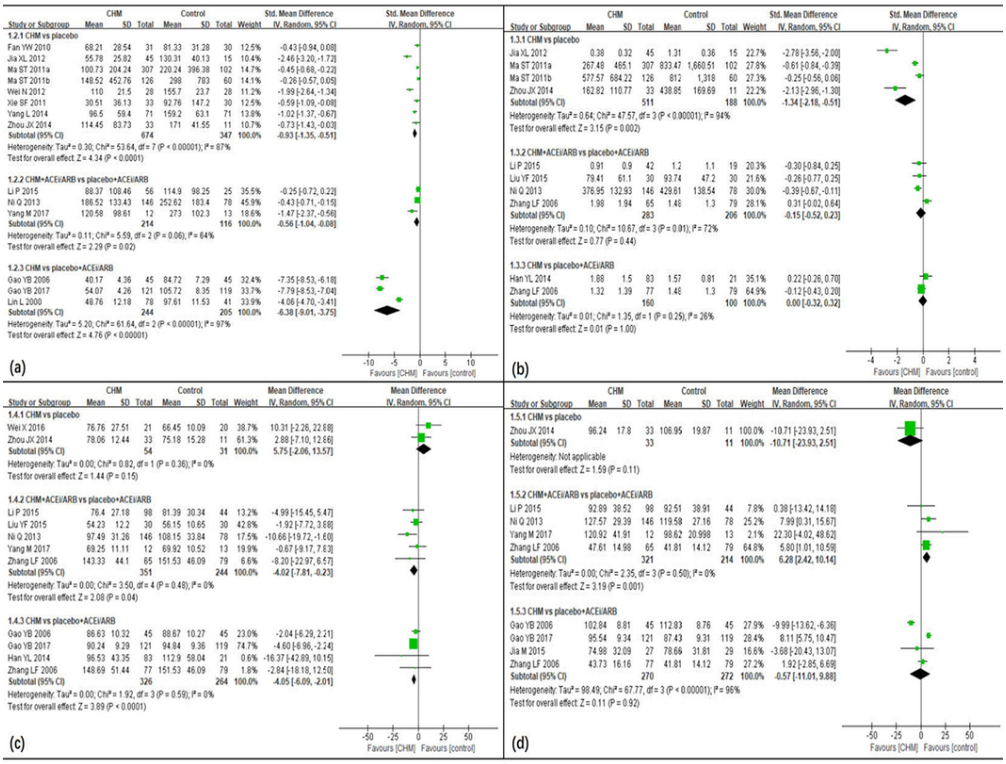

Figure 3. Forest plot of primary outcomes
Note: Panel (a) albuminuria outcomes; (b) proteinuria outcomes; (c) serum creatinine outcomes; (d) estimated glomerulus filtration rate outcomes.
Abbreviation: CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standard.

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Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

Supplementary Appendix

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Table S1: Search strategy of MEDLINE.
Table S2: Subgroup analysis of primary outcomes
Table S3: Meta-analysis results of secondary outcomes
Table S4: Sensitivity analysis of primary outcomes

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Table S1: Search Strategy of MEDLINE

Search Block	Search terms
Intervention	Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs, Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Chinese Medicine Herb OR Herbal Medicine OR Herbs
Condition	Diabetic Nephropathies OR Diabetic Nephropathy OR Diabetic Kidney Disease OR Diabetic Kidney Diseases OR Kimmelstiel Wilson Syndrome OR Kimmelstiel Wilson Disease OR Diabetic Glomerulosclerosis OR Nodular Glomerulosclerosis OR Intracapillary Glomerulosclerosis OR albuminuria OR Microalbuminuria OR proteinuria OR Glomerulosclerosis OR Glomerulonephritis OR Kimmelstiel wilson nephropathy OR diabetic nephrosclerosis
Study design	Systematic[sb] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab] OR "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] OR "case series"[tw]

Note: The three search blocks were connected with Boolean operators 'AND' to build the overall search terms.

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Table S2: Subgroup Analysis of Primary Outcomes

Outcome or Subgroup	Studies	Pts	Statistical Method	Effect Estimate (95%CI)	I^2	*p* value
Urinary albumin excretion						
Subgroup-CHM formulae						
Qiwei Granules	2	104	MD	-70.06 [-88.84, -51.28]	0%	p<0.0001
Arctiin Granules	2	595	Std. MD	-0.38 [-0.56, -0.20]	0%	p<0.0001
Tang shen ning Formulae group	2	330	MD	-48.16 [-55.12, -41.20]	95%	p<0.0001
Subgroup-Measurements						
CHM vs placebo-AER	1	186	MD	-149.48 [-362.79, 63.83]	NA	p=0.17
CHM vs placebo-ACR	2	124	MD	-30.53 [-76.59, 15.53]	66%	p=0.19
CHM vs placebo-UAE	5	711	MD	-60.91 [-76.82, -45.01]	53%	p<0.0001
CHM vs placebo + ACEi/ARB-AER	1	119	MD	-48.85 [-53.30, -44.40]	NA	p<0.0001
CHM vs placebo + ACEi/ARB-UAE	2	330	MD	-48.16 [-55.12, -41.20]	95%	p<0.0001
24-hour proteinuria						
Subgroup-baseline UP						
CHM vs placebo-baseline UP < 0.5g/d	2	453	MD	-378.34 [-649.90, -106.77]	63%	p=0.006
CHM vs placebo-baseline UP > 0.5g/d	2	246	Std. MD	-1.49 [-3.97, 0.99]	97%	p=0.24
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline UP < 0.5g/d	2	284	MD	-31.30 [-68.61, 6.02]	61%	p=0.10
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline UP > 0.5g/d	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
Subgroup-CHM formulae						
Qiwei Granules	2	104	Std. MD	-2.47 [-3.11, -1.83]	21%	p<0.0001
Arctiin Granules	2	595	MD	-407.65 [-732.24, -83.05]	45%	p=0.01
Tang shen fang group	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
Subgroup-Measurements						
CHM vs placebo-g/24h	1	60	MD	-0.93 [-1.13, -0.73]	NA	p<0.0001
CHM vs placebo-mg/24h	3	639	MD	-324.42 [-485.15, -163.69]	30%	p<0.0001

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CHM + ACEi/ARB vs placebo + ACEi/ARB-g/24h	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
CHM + ACEi/ARB vs placebo + ACEi/ARB-mg/24h	2	284	MD	-31.30 [-68.61, 6.02]	61%	p=0.10
Serum creatinine level						
Subgroup-baseline Scr						
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline Scr normal	3	227	MD	-2.12 [-6.48, 2.23]	0%	p=0.34
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline Scr abnormal	2	368	MD	-9.99 [-17.71, -2.26]	0%	p=0.01
CHM vs placebo + ACEi/ARB-baseline Scr normal	3	434	MD	-4.07 [-6.13, -2.01]	0%	p=0.0001
CHM vs placebo + ACEi/ARB-baseline Scr abnormal	1	156	MD	-2.84 [-18.18, 12.50]	NA	p=0.72
Subgroup-CHM formulae						
Tang shen fang group	2	286	MD	-6.06 [-14.60, 2.47]	0%	p=0.16
Tang shen ning Formulae group	2	330	MD	-3.96 [-6.13, -1.78]	6%	p=0.0004
Glomerular filtration rate						
Subgroup-baseline GFR						
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline GFR>90	2	249	MD	9.38 [1.07, 17.70]	4%	p=0.03
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline GFR<90	2	286	MD	5.22 [0.69, 9.74]	0%	p=0.02
CHM vs placebo + ACEi/ARB-baseline GFR>90	1	90	MD	-9.99 [-13.62, -6.36]	NA	p<0.0001
CHM vs placebo + ACEi/ARB-baseline GFR<90	3	452	MD	4.48 [-1.32, 10.28]	70%	p=0.13
Subgroup-CHM formulae						
Tang shen fang group	2	286	MD	5.22 [0.69, 9.74]	0%	p=0.02
Tang shen ning Formulae group	2	330	MD	-0.89 [-18.62, 16.85]	99%	p=0.92

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Subgroup-Measurements						
CHM + ACEi/ARB vs placebo + ACEi/ARB-Ccr	1	144	MD	5.80 [1.01, 10.59]	NA	p=0.02
CHM + ACEi/ARB vs placebo + ACEi/ARB-eGFR	3	391	MD	7.13 [-0.29, 14.56]	11%	p=0.06
CHM vs placebo + ACEi/ARB-Ccr	2	246	MD	-4.14 [-15.81, 7.53]	93%	p=0.49
CHM vs placebo + ACEi/ARB-eGFR	2	296	MD	5.25 [-4.65, 15.15]	46%	p=0.30

Abbreviation: Pts, patients; CI, confident interval; NA, not applicable. CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MD, mean differences; Std, standard.; AER, albuminuria excretion rate; ACR, albuminuria to creatinine ratio; UAE, urinary albuminuria excretion; UP, urinary proteinuria; GFR, glomerular filtration rate; Scr, serum creatinine concentration; Ccr, creatinine clearance.

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Table S3 Meta-analysis Results of Secondary Outcomes

Outcome	Studies	Participants	Effect Estimate (95% CI)	I^2	*p* value
Fasting blood sugar	9	962	-0.45 [-1.15, 0.25]	93%	p=0.21
Haemoglobin A1c	8	901	0.04 [-0.17, 0.24]	59%	p=0.73
Total cholesterol	8	815	-0.96 [-1.70, -0.21]	95%	p=0.01
Triglyceride	8	815	-0.60 [-1.01, -0.19]	90%	p=0.004
Low-density lipoprotein	7	696	-0.51 [-0.93, -0.09]	92%	p=0.02
High-density lipoprotein	8	815	0.14 [-0.04, 0.33]	93%	p=0.12
Systolic blood pressure	3	252	0.64 [-0.90, 2.17]	0%	p=0.43
Diastolic blood pressure	3	252	0.14 [-2.02, 2.29]	52%	p=0.90
Diabetes quality of life score	2	461	0.07 [-3.87, 4.00]	54%	p=0.97

Note: All outcomes analysed with mean difference. Abbreviation: CI, confident interval

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Table S4: Sensitivity Analysis of Primary Outcomes

Outcomes	Studies	Participants	Statistical Method	Effect Estimate (95% CI)	I^2	*p* value
Urinary albumin excretion						
CHM vs placebo	4	798	Std. Mean Difference	-0.54 [-0.85, -0.22]	73%	p=0.0009
CHM+ACEi/ARB vs placebo+ACEi/ARB	3	330	Std. Mean Difference	-0.56 [-1.04, -0.08]	64%	p=0.02
24-hour proteinuria						
CHM vs placebo	2	595	Mean Difference	-407.65 [-732.24, -83.05]	45%	p=0.01
CHM+ACEi/ARB vs placebo+ACEi/ARB	3	429	Std. Mean Difference	-0.12 [-0.60, 0.37]	81%	p=0.63
CHM vs placebo+ACEi/ARB	2	260	Std. Mean Difference	0.00 [-0.32, 0.32]	26%	p=1.00
Serum creatinine level						
CHM vs placebo	1	41	Mean Difference	10.31 [-2.26, 22.88]	NA	p=0.11
CHM+ACEi/ARB vs placebo+ACEi/ARB	4	535	Mean Difference	-5.59 [-10.61, -0.58]	0%	p=0.03
CHM vs placebo+ACEi/ARB	2	260	Mean Difference	-6.23 [-19.51, 7.05]	0%	p=0.36
Glomerular filtration rate						
CHM+ACEi/ARB vs placebo+ACEi/ARB	4	535	Mean Difference	6.28 [2.42, 10.14]	0%	p=0.001
CHM vs placebo+ACEi/ARB	2	212	Mean Difference	1.50 [-3.08, 6.09]	0%	p=0.52

Abbreviation: NA, not applicable. CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standar

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P9-10

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P11 Fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P11-12 Table1, 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P12, Fig2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P12-16, Fig 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P12-16, Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P16-18 Appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P18-19,22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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