Systematic Review and Meta-Analysis

Medicine

OPEN

The effect and safety of low-dose *Tripterygium wilfordii* in patients with type 2 diabetic nephropathy

A meta-analysis

Yixuan Chen, MM[a], Meiqi Lu, MM[b], Yiting Feng, MM[c], Qing Gao, MD[a,b,*]

Abstract

Background: This review aims to assess the efficacy and safety of low-dose *Tripterygium wilfordii* Hook F (TWHF) in treating type 2 diabetic nephropathy (DN) and provide high-level evidence supporting its normalized application.

Methods: Seven electronic databases were queried to locate trials that qualify. Randomized controlled trials (RCTs) about low-dose TWHF long-term treatment of type 2 DN are included. After data extraction and quality evaluation of the clinical studies that met the inclusion criteria, a meta-analysis was performed using RevMan 5.4 and Stata 14.

Results: A total of 23 RCTs were included. For the patients in the trial group, the effective rate [confidence interval (CI), odd ratio] [odd ratio = 1.38, 95% CI (1.22–1.56), $P < .001$], albumin [standard mean difference (SMD) = 0.58, 95% CI (0.18–0.98), $P = .004$], 24-hour urine total protein [SMD = –1.329, 95% CI = (–1.647 to –1.012), $P < .001$], serum creatinine [SMD = –0.64, 95% CI = (–0.86 to –0.31), $P < .001$], and the untoward effect [RR = 2.43 95% CI = (1.23–4.82), $P = .01$] were significantly higher than those in the control group. However, in white blood cell [Weighted mean difference = –0.27, 95% CI (–0.54 to 0.01), $P = .06$] and blood urea nitrogen [Weighted mean difference = –0.11, 95% CI (–0.42 to 0.21), $z = 0.67$, $P = .50$], none of the differences were significant compared with the control group.

Conclusion: This suggests that low-dose TWHF positively affects patients with type 2 DN after a long course of treatment. Although there are some side effects, symptoms can improve after medication suspension or symptomatic treatment. Limited by the methodological quality of the included studies, this conclusion needs to be verified by more large-sample RCTs with rigorous design and long-term follow-up.

Abbreviations: 24h UTP = 24-hour urine total protein, ALB = albumin, BUN = blood urea nitrogen, CI = confidence interval, DN = diabetic nephropathy, RCT = randomized controlled trial, Scr = serum creatinine, SMD = standard mean difference, TWHF = *Tripterygium wilfordii* Hook F.

Keywords: clinical efficacy, diabetes mellitus, diabetic nephropathy, *Tripterygium wilfordii* Hook F

1. Introduction

Diabetic nephropathy (DN) estimated to affect nearly 40% of diabetic patients, is the leading cause of chronic kidney disease globally.[1,2] Researchers have discovered that a variety of pathways and/or multiple targets, including aberrant glucose and lipid metabolism, chronic inflammation, oxidative stress, immunological activation, and podocyte dysfunction, are related to the pathogenesis of DN.[3–5] Current treatments are mainly for the comprehensive management of patients suffering from type 2 DN, such as the adjustment of poor lifestyle, control of risk factors (hyperglycemia, hypertension, lipid metabolism disorders,

YC and ML contributed equally to this work.

This study was supported by Fujian Provincial Nature and Science Foundation (Grant No. 2020J011206).[47]

The authors have no conflict of interest to disclose.

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

This systematic review evaluates the effect and safety of low-dose Tripterygium wilfordii in patients with type 2 diabetic nephropathy. Because all of the data used in this systematic review and meta-analysis have been published, this review does not require ethical approval. Furthermore, all data will be analyzed anonymously during the review process trial.

Supplemental Digital Content is available for this article.

[a] The School of Clinical Medicine, Fujian Medical University, Fuzhou, China, [b] Department of Nephrology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China, [c] Department of Anesthesiology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China.

** Correspondence: Qing Gao, Department of Anesthesiology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, NO.201-209 Hubinnan Road, Siming District, Xiamen 361000, China (e-mail: qinggao_neph1@163.com).*

How to cite this article: Chen Y, Lu M, Feng Y, Gao Q. The effect and safety of low-dose Tripterygium wilfordii in patients with type 2 diabetic nephropathy: A meta-analysis. Medicine 2022;101:52(e32504).

Received: 28 September 2022 / Received in final form: 7 December 2022 / Accepted: 8 December 2022

http://dx.doi.org/10.1097/MD.0000000000032504

etc), and education of diabetic patients. Renin-angiotensin system inhibitors, which are frequently used as first-line treatments, include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[6] Therefore, to treat DN effectively, further research is required.

Traditional Chinese medicine has recently demonstrated distinct benefits and opportunities in the detection and treatment of diabetes and has been widely used to treat and control diabetes and its complications in many scientific studies and has gradually built a more thorough theoretical framework.[7] *Tripterygium wilfordii* Hook F (TWHF), a traditional Chinese herb, is the only plant drug with immunosuppressive qualities. It acts as an anti-inflammatory, antiproliferative, antioxidant, and immunosuppressive agent, reducing urine protein excretion in several primary and secondary glomerular disorders.[8,9] However, research on its efficacy and safety is lacking. A systematic review and meta-analysis was conducted to evaluate the effectiveness and safety of TWHF for the treatment of DN, which may be a potential supplemental therapy for DN.

2. Material and Methods

2.1. Inclusion and exclusion criteria

1.2.1. Inclusion criteria. Randomized controlled trials (RCT) conducted in the study; the subjects of observation are type 2 DN, which was diagnosed according to clear definitions or internationally recognized standards, and there were no requirements for the race, age, geography, etc; the intervention was low-dose TWHF (i.e., <60 mg/d or <1 mg/kg d) for a duration of six months, with consistency between groups of basic therapy.

2.2.1. Exclusion criteria. Studies that were repeated publications; studies that were non-randomized controlled trials and quasi-randomized controlled trials; the dose and duration of the studies did not meet the inclusion criteria; studies that combined treatments with further traditional Chinese medicine treatments including acupuncture, acupoint injections, and herbal extracts.

3.2.1. Outcomes. Effective rate, 24-hour urine total protein (24h UTP), serum creatinine (Scr), albumin (ALB), WBC, blood urea nitrogen (BUN), and safety indicators (including visceral damage, reproductive toxicity and hematological damage, etc).

2.2. Search strategy

Searches were conducted in electronic databases such as Chinese National knowledge infrastructure (CNKI), Wanfang, China Biology Medicine disc (CBM), PubMed, Embase, and Cochrane Library to find studies that would be included in the database after it was established in April 2020. We searched papers using MeSH terms and/or keywords like "randomized controlled trial" and "*Tripterygium wilfordii* Hook F" or "*Tripterygium wilfordii*" and "Diabetic nephropathy" or "Diabetic Kidney Diseases" or "DN" or "DKD."

Only human subjects were used in the investigations. In addition, a comprehensive search for the included literature was done. After many preliminary searches, all search techniques were defined, and retrieval methods were integrated with free-text retrieval. The title and abstracts were independently reviewed by two reviewers. The full text of the articles were reviewed by a third reviewer if there was a disagreement between the two. Inter-investigator reliability was measured utilizing kappa (κ) statistics.[10]

2.3. Data extraction

A data extraction form was developed based on the Cochrane Handbook[11] checklist for data gathering considerations. The author, year, sample size, duration of therapy, outcome measures, and adverse effects were extracted by two independent reviewers. Disagreements were settled by dialogue between the two reviewers and a study of the trial data. When clarifications were required, study authors were contacted. And data was recorded data in an Excel spreadsheet.

2.4. Quality assessment

Two independent reviewers assessed the methodological quality of randomized controlled trials using the Risk of Bias instrument developed by the Cochrane Collaboration.[11] Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcomes assessment (detection bias), incomplete outcomes data (attrition bias), selective reporting (reporting bias), and other biases were assessed using the Cochrane Handbook. Quality assessment was performed using GRADE[12] Criteria for (Grading of Recommendations Assessment, Development, and Evaluation) designed to assess the overall reliability of a body of information. This method comprises five important domains: risk of bias, inconsistency, indirectness, imprecision of the evidence, and reporting bias. In addition, it takes into account additional optional domains that may be important in certain cases. These included plausible confounding that would decrease the observed effect and strength of association (i.e., magnitude of effect) or factors that would increase the strength of association (i.e., dose-response effect). The risk of bias and quality assessment information were considered in the interpretation of findings.

2.5. Data synthesis

We analyzed the data using Review Manager 5.4 https://en.freedownloadmanager.org/Windows-PC/Review-Manager.html and Stata 14 https://www.stata.com/stata14/. The binary categorical variable data results are presented as the risk ratios (RR) with 95% CI and standard mean difference (SMD) with the 95% confidence interval (CI) in continuity variable data. I^2 statistics were used for the heterogeneity assessment. In the absence of significant data heterogeneity ($I^2 > 50\%$), a model with fixed effects was used. However, considerable heterogeneity was observed ($I^2 > 50\%$), subgroup analysis, meta-regression, and sensitivity analysis can be performed to eliminate heterogeneity. If heterogeneity persists but clinically suggests homogeneity (patient age, sex, course, underlying condition, etc, baseline conditions are substantially consistent between groups), random-effects model analysis was used. Finally, publication bias was evaluated using funnel charts and Egger tests in Stata 14.

3. Results

3.1. Study selection

Computer and manual searches yielded a total of 1218 papers; after deleting 578 duplicates, 640 articles remained; 120 articles were read in full after reading the title and abstract; 98 pieces were eliminated; and finally, 22 articles were included in the meta-analysis. The entire study selection procedure is presented in the PRISMA flowchart. Inter-rater agreement was excellent at the full-text review ($\kappa = 1$) stages.

3.2. Data extraction

Table 1 displays the fundamental content and features of the selected studies. Twenty-two studies have been published between 2012 and 2022. Twenty articles were published in Chinese, while two were published in English. All studies examined the effects of TWHF on DKD and reported at least one

clinical measure, such as the efficacy rate, 24h UTP, Scr, ALB, WBC, and BUN levels, as well as safety signs. The duration of the intervention was six months, and the dosage of TWHF was <60 mg/d or <1 mg/kg d (see Table S1, Supplemental Digital Content 1, http://links.lww.com/MD/I229, which includes all the data we extracted from the included literature for the meta-analysis).

3.3. Risk of bias and quality assessment

Using the Cochrane risk of the bias assessment instrument, two researchers (Yixuan Chen and Meiqi Lu) independently analyzed all included studies. Figures 1 and 2 provide comprehensive findings of the bias analysis. As a consequence of the variability and publication bias in the majority of research, the GRADE criteria for assessing the quality of evidence revealed that the overall analyses yielded low-quality evidence[12] (see Table S2, Supplemental Digital Content 2 , http://links.lww.com/MD/I230, which illustrates the GRADE criteria for assessing the quality of evidence) (see Powerpoint, Supplemental Digital Content 3, http://links.lww.com/MD/I231, which illustrates the risk of bias for all literature included in this meta-analysis).

3.4. Meta-analysis

3.4.1. Effective rate. Five articles[13–17] reported efficacy outcomes. Because there was no significant heterogeneity in the data (I^2 < 50%), a fixed-effect model was selected for the pooled effect quantity. Figure 3 shows a forest plot for the efficacy comparison. The results show that patients in the TWHF group had significantly higher efficacy than those in the control group [RR = 1.38 (1.22–1.56), P < .001].

3.4.2. Effects on the changes of ALB or proteinuria. Effect of TWHF on ALB. Thirteen articles[13,14,17–24] reported ALB outcomes after TWHF therapy after the heterogeneity test, I^2 = 87% >50%, suggesting significant heterogeneity in the selected study. Due to the clinical homogeneity of the trials (the baseline conditions of patients, such as age, sex, course,

Table 1

Characteristics of included studies.

Author	Year	n (E/C)	Experimental group	Control group	Outcomes	Untoward effect (E/C)
Wang	2018	20/20	Conventional treatment + TWHF	Conventional treatment	②③④	1/0
Xiong	2020	62/62	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③④⑧⑨	12/4
Diao	2010	33/32	Conventional treatment + ACEI/ARB + TWHF	Conventional treatment + ACEI/ARB	②⑤⑥⑩	-
Yu	2011	65/64	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②④⑦	-
Sun	2014	74/76	Conventional treatment + Metformin + TWHF	Conventional treatment + Metformin	②④⑦⑧	-
Song	2014	40/40	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②④⑦	1/2
Chang	2012	22/23	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②④	-
Zhang	2012	50/50	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③④	-
Zhang	2010	28/30	Conventional treatment + TWHF	Conventional treatment	②③④⑦⑩	-
Xu	2017	36/36	Conventional treatment + TWHF	Conventional treatment	④⑩	-
Li	2014	48/48	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③④	-
Wang	2013	32/30	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②④⑦⑨	-
Wang	2011	20/20	Conventional treatment + TWHF	Conventional treatment	②③	-
Wang	2012	52/30	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③⑤⑥⑧⑨⑩	3/0
Shi	2006	23/20	Conventional treatment + TWHF	Conventional treatment	②③④⑤⑧⑨	2/0
Cai	2012	35/30	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③④⑤⑥	-
Tan	2010	25/23	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③	3/0
He	2010	31/29	Conventional treatment + ARB + TWHF	Conventional treatment + ARB	②③④⑤⑧⑨	-
Wu	2011	52/48	Conventional treatment + TWHF	Conventional treatment	⑩	4/3
Zheng	2009	30/30	Conventional treatment + ACEI/ARB + TWHF	Conventional treatment + ACEI/ARB	②③④⑤⑥⑦	-
Guo	2007	24/20	Conventional treatment + TWHF	Conventional treatment	②④⑤⑧	-
Gao	2012	40/40	Conventional treatment + ACEI/ARB + TWHF	Conventional treatment + ACEI/ARB	②④⑦	-

① Effective rate; ② Urine protein; ③ ALB; ④ Scr; ⑤ ALT; ⑥ WBC; ⑦ BUN; ⑧ FBG; ⑨ HBA1c; ⑩ Ccr. Experimental group: intervention measures in the experimental group; Control group: intervention measures in the control group.

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, TWHF = *Tripterygium wilfordii* Hook F.

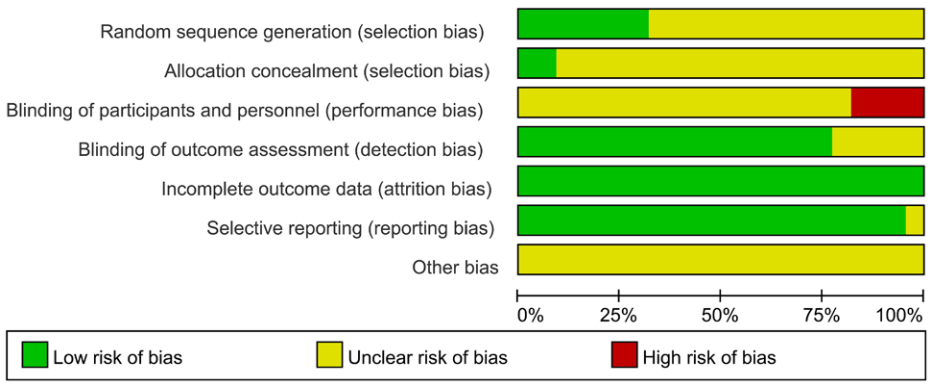

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

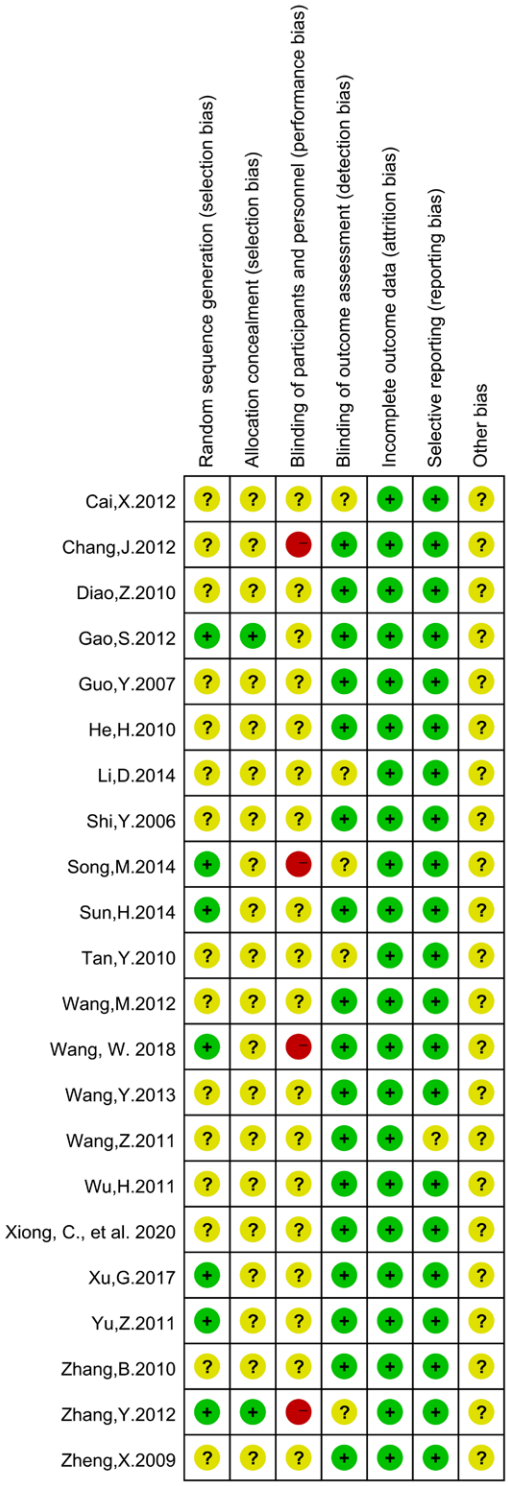

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

and underlying condition of patients, were consistent between groups), random effects models were selected. Figure 4 shows a forest plot for ALB comparison. Patients in the TWHF group had markedly higher ALB levels than those in the control group, according to the findings [SMD = 0.58 (0.18–0.98), $z = 2.86$, $P = .004$].

Effect of TWHF on 24h UTP. Twenty-one[13–32] articles reported on 24h UTP outcome, and significant heterogeneity was present ($I^2 = 86.9\% > 50\%$). However, subgroup and sensitivity analyses found that none of the studies substantially impacted the results. Due to the clinical homogeneity of the trials, random effects models were selected for effect-size pooling. Compared with patients in the TWHF group, those in the TWHF group had significantly lower urine protein levels. [SMD = −1.329(−1.647 to −1.012), $z = 8.21$, $P < .001$] (Fig. 5).

3.4.3. Effects on kidney function changes. Effect of TWHF on Scr. In the included studies, Scr and BUN levels indicated the function of the kidney.

Eighteen articles had reported on Scr[13–15,17–19,21–25,27–29,32,33] outcome. Due to the significant heterogeneity of the experiments selected in this study, our sensitivity analysis of the 18 studies found that the two studies by "He, 2010" and "Zhang, 2010" significantly impacted the results. After removing the two studies, the heterogeneity decreased ($I^2 = 68\%$); however, the results did not change significantly. Indicating that although the heterogeneity was significant, the results were stable. Random effects models were selected for effect-size pooling. According to the findings, TWHF group patients had considerably lower Scr than the control group's patients. [SMD = −0.64 (−0.86 to −0.31), $z = 3.20$, $P < .001$] (Fig. 6).

Effect of TWHF on BUN. Seven RCTs[15,23,24,27,29,30,32] reported the BUN outcomes after TWHF therapy. Our findings demonstrated no significant differences between experimental and control groups concerning BUN change from baseline ($P = .50$, I2 = 59%) (Fig. 7).

3.4.4. Effects on inflammation and immunity. Effect of TWHF on WBC. Four RCTs,[13,20,24,26] including 268 participants, reported WBC outcomes after TWHF therapy. Our results indicated no significant difference in WBC change from baseline between the experimental and control groups ($P = .06$) with no significant heterogeneity ($I^2 = 0\%$) (Fig. 8).

One study showed significantly lower IL-6[33] levels. Whereas two studies showed substantially lower TNF-α levels,[21,33] one study showed that the improvement in CD4/CD8 inversion in the trial group was better than in the control group.[33]

3.4.5. Untoward effect. Adverse reactions were reported in seven trials,[15,16,19–22,34] including 26 out of 270 cases in the treatment group and 9 out of 247 patients in the control group.[15,16,19–22,34] The meta-analysis results suggested more adverse reactions than conventional therapy (RR = 2.43 (1.23–4.82), $P = .01$, I^2=0%), including visceral damage, reproductive toxicity, and hematological damage. See Figure 9 for details.

3.4.6. Publication bias. The funnel plot was drawn with the effect of TWHF treatment on Scr, and the funnel plot was roughly symmetrical (Fig. 10). A bias test was performed, and $P = .157 > 0.005$. Therefore, it can be concluded that the literature in the current study had no publication bias, respectively (Fig. 11).

4. Discussion

Microvascular complications of diabetes and diabetic kidney disease (DKD) are the primary cause of the end-stage renal disease (ESRD) worldwide. High glomerular filtration rate (GFR) is followed by microalbuminuria, albuminuria, and end-stage renal failure (ESRD).[35] Uremia can have grave consequences if left untreated. DKD has a complicated pathogenesis characterized by inflammation and invasion of the kidney by an immune cell. Recent techniques for the treatment of DN include anti-inflammatory treatments, cytokine suppression, and the avoidance of podocyte harm. However, no new therapeutics for DKD has been available for nearly 20 years.

In this systematic review, 22 studies were included to analyze the effectiveness of TWHF, an extract of a traditional Chinese

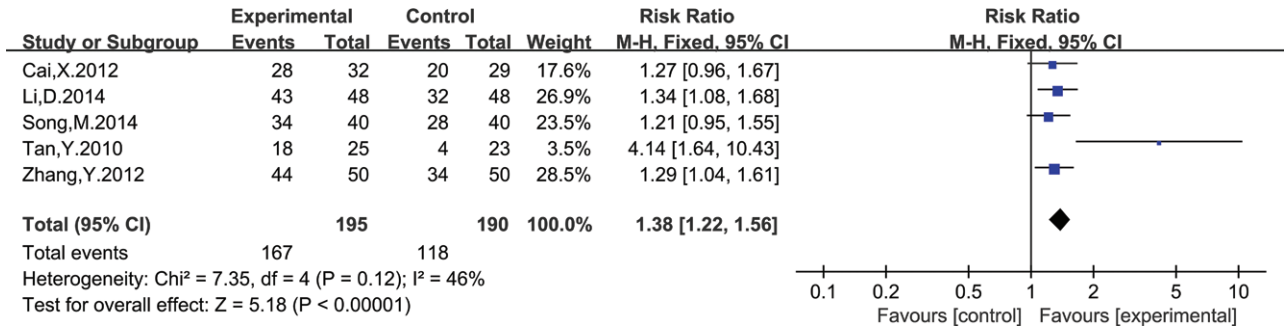

Figure 3. Results of meta-analysis for effective rate.

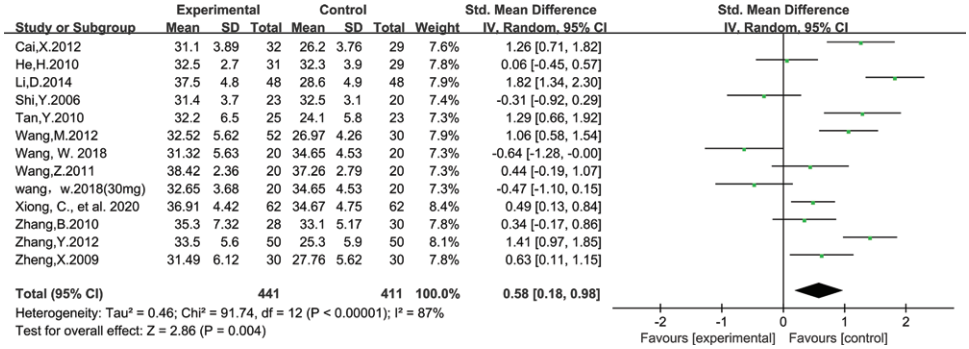

Figure 4. Results of meta-analysis for the effect of TWHF on ALB. ALB = albumin, TwHF = *Tripterygium wilfordii* Hook F.

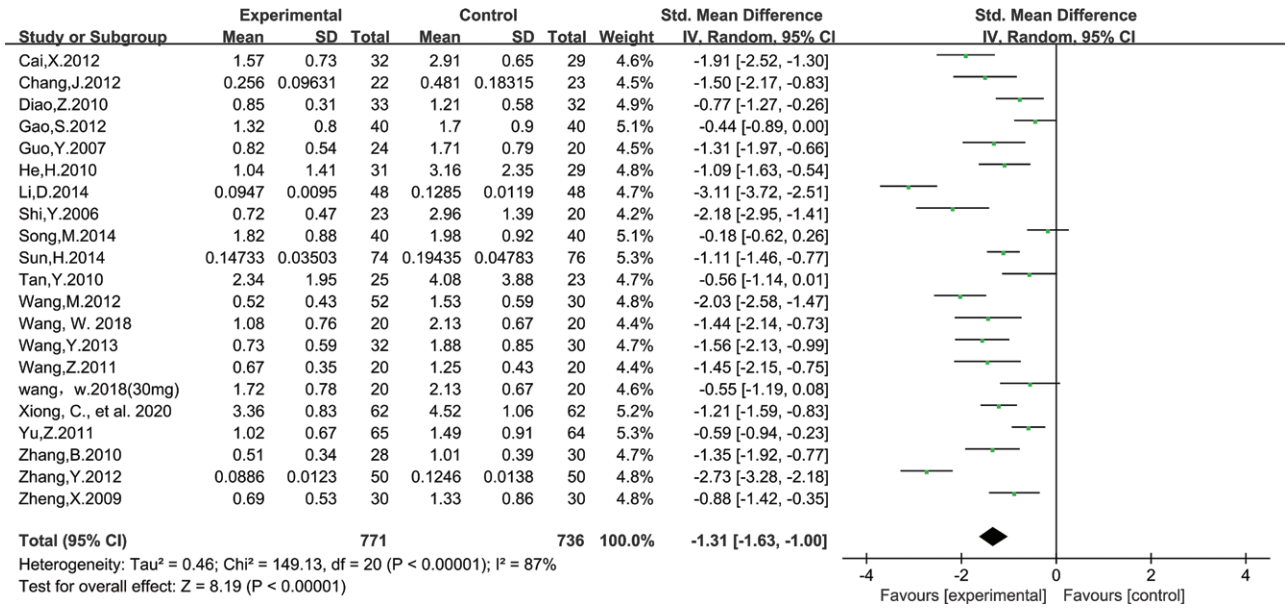

Figure 5. Results of meta-analysis for the effect of TWHF on 24h UTP. 24hUTP = 24-hour urine total protein, TWHF = *Tripterygium wilfordii* Hook F.

herb, in treating DKD. We identified most treatment markers utilized in DKD diagnosis or clinical response assessment, such as albuminuria, proteinuria, Scr, BUN, and other immunoinflammatory signs. Multiple studies have shown that the rate of decline in renal function after the appearance of a large amount of urine protein is greatly accelerated.[36] Therefore, it is recommended that proteinuria should be routinely tested in diabetic patients at risk of potential renal impairment. Moreover, to increase the sensitivity of screening tests, Scr and BUN are valuable markers that correlate well with renal function assessment

The present meta-analysis results showed that the total efficiency of the TWHF group was significantly better than that of the traditional treatment group. It also delayed the decline in renal function (e.g., effectively reducing proteinuria, SCR, and improving ALB level), suggesting that the effect of low-dose TWHF in treating type 2 DN is worthy of affirmation. The mechanism by which TWHF protects the kidneys is as follows: Anti-inflammatory, suppression of humoral immunity, and cellular immunity: In the study performed by Fevziye Burcu Sirin et al, positive correlations were observed between IL-6 levels and blood glucose, HbA1c, creatinine, urine albumin, and protein excretion, whereas negative

correlations were observed with GFR.[37] In patients with high levels of blood glucose maintained for a long time, kidney cells release TNF-α free radicals and accumulate in the body, increase lipid metabolites, cellular intima damage, glomeruli keep a hypertonic state, and promote the production of albuminuria.[38] In this study, we observed a decrease in IL-6 and TNF-α after treatment,[39] which may reduce the local inflammatory response in the kidney and delay renal cell sclerosis and interstitial fibrosis in diabetic patients. CD4 and CD8 are a significant subset of T lymphocytes, which antagonize each other to maintain the balance of immune response in vivo and affect the mechanism of the immune response.[33] Our study suggests that it can correct cellular immune abnormalities to a certain extent. However, owing to the small number of included studies, more in-depth studies are needed. Improvement of podocyte injury: Hyperglycemia induces podocyte transdifferentiation and causes albuminuria.[40] This may be effective in preventing podocyte damage in DKD, which may be mediated at least in part by the downregulation of CTGF, OPN, and TGF expression.[41] Thus delaying the deterioration of renal function and reducing proteinuria. Protection of glomerular endothelial cell function: Hyperglycemic stimulation can increase the production of VEGF in the kidney, leading to endothelial activation followed by macrophage infiltration, which compromises glomerular endothelial cell structure and function, increases glomerular permeability, and causes proteinuria.[42] The primary method of preventing DKD may include preventing VEGFA overexpression, which inhibits a cascade of pro-inflammatory proteins and intracellular signaling, thereby relieving kidney injury under diabetic conditions.[43] Inhibition of extracellular matrix and mesangial cell proliferation: Chronic hyperglycemia and excessive development of advanced glycation end products (AGEs) produce anomalies in VEGFA synthesis and release in many signaling pathways, including inflammation, excessive ROS production, TGF- and CTGF activation, and foot process effacement, and disrupts VEGFA overexpression and inhibits mesangial cell proliferation and extracellular matrix proliferation.[44]

However, this meta-analysis cannot provide reliable evidence on whether it has anti-inflammatory effects, inhibiting humoral immunity and cellular immunity. The meta-analysis also suggested some side effects, mainly visceral damage, reproductive toxicity, and hematological damage. Symptoms can improve after medication suspension or symptomatic treatment. Some investigators stated that the immunosuppressive effect of TWHF is different from that of all other immunosuppressants and that TWHF has an immunosuppressive unique impact.[45] Tripterygium glycosides have powerful immunosuppressive effects without causing significant harm to the normal immune system, malignancies, or infections. Tripterygium glycosides efficiently suppressed T-cells but had little impact on resting cells. Therefore, short delivery of tripterygium glycosides to DKD patients would not have serious side effects.[46]

The above outcome measures were statistically heterogeneous in the different studies, and neither our sensitivity analysis nor our regression analysis was eliminated. The source of heterogeneity may be related to the TWHF dose, the baseline level of patient renal function, the different included populations, or the very low quality of evidence included in the analysis.

The meta-analysis also has some other limitations: most included studies were mainly Chinese and of low quality. The

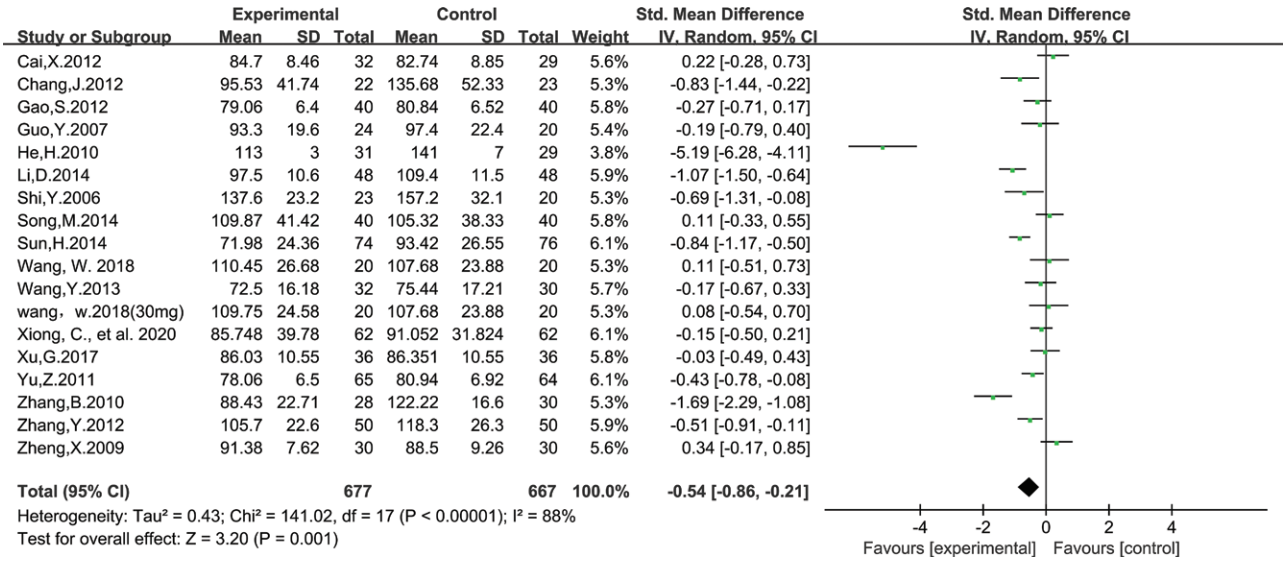

Figure 6. Results of meta-analysis for the effect of TWHF on Scr. Scr = Serum creatinine, TWHF = *Tripterygium wilfordii* Hook F.

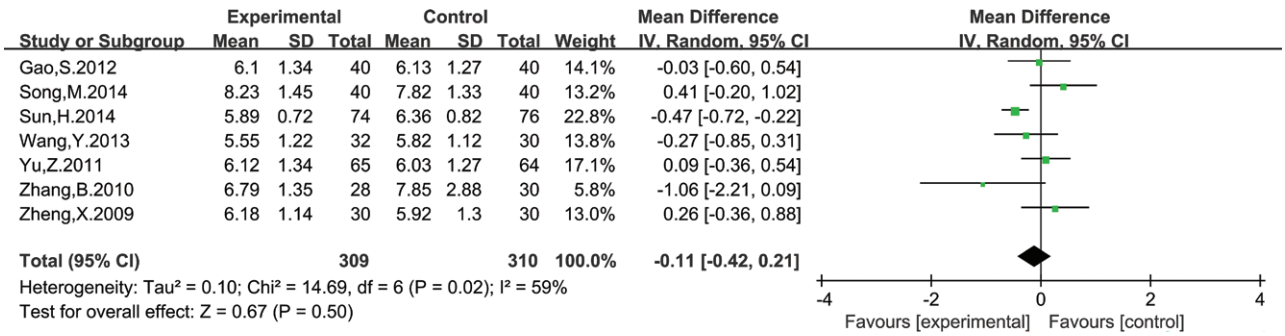

Figure 7. Results of meta-analysis for the effect of TWHF on BUN. BUN = Blood urea nitrogen, TWHF = *Tripterygium wilfordii* Hook F.

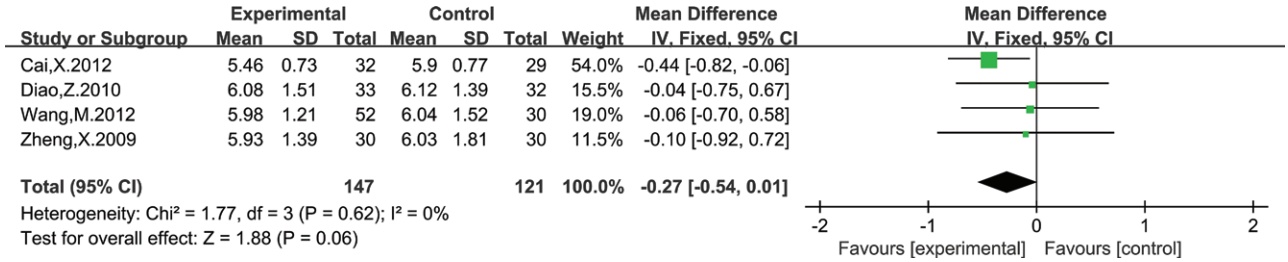

Figure 8. Results of meta-analysis for the effect of TWHF on WBC. TWHF = *Tripterygium wilfordii* Hook F, WBC = white blood cell.

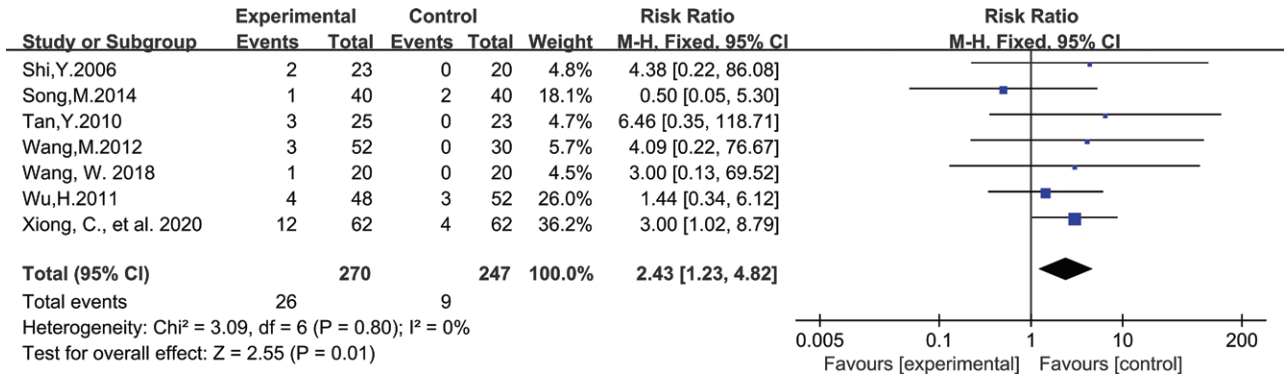

Figure 9. Untword effect.

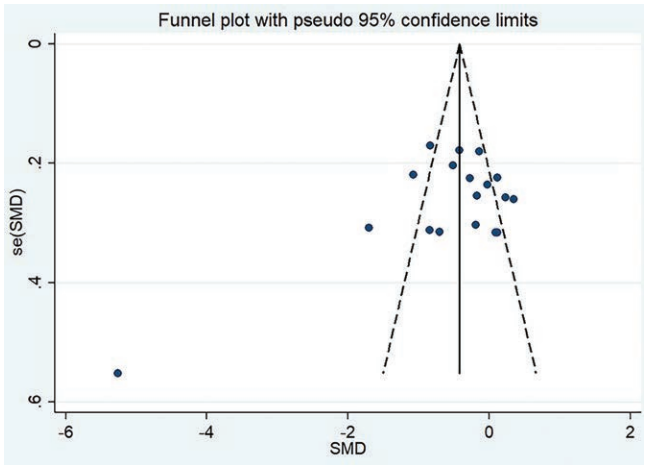

Figure 10. Publication bias.

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.5141759	.6507901	0.79	0.441	-.8654376	1.893789
bias	-4.012727	2.700583	-1.49	0.157	-9.737707	1.712253

Figure 11. Egger test.

description of random and blind methods is too vague and prone to bias. The majority of indications described in the literature are favorable outcomes; however, there is a possibility that the negative findings were not publicized. Several studies show better double-dose efficacy over smaller doses, but only small doses are discussed in this paper. An agreement has been pre-registered for this review (as in PROSPERO), but because the review time is too long, we have tried our best and failed to register as soon as possible. Nevertheless, we believe that this research presents a novel therapeutic intervention technique for patients with DN and a better therapy base to enhance these patients' prognosis.

5. Conclusion

In conclusion, the efficacy of TWHF in treating DKD is positive, and it can effectively reduce urine protein and blood creatinine levels and improve ALB levels. However, they also have some side effects. It is recommended that future clinical studies consider the following: The literature included in this study are of low quality, so patients with type 2 DN need more high-quality, large-sample, multicenter, randomized, double-blind controlled studies to validate the efficacy and safety of low-dose *T. wilfordii*. Fixed treatment course and dose to reduce heterogeneity. We also excluded retrospective data from the combined analysis to prevent them from affecting the outcome judgment. While focusing on efficacy, reducing toxicity is one of the key research directions in the future.

Author contributions

Yixuan Chen: Data curation; Formal analysis; Investigation; Validation; Visualization; Writing – original draft; Writing – review & editing.
Meiqi Lu: Conceptualization; Data curation; Methodology; Validation; Writing – review & editing.
Yiting Feng: Conceptualization; Methodology; Validation; Writing – review & editing.
Qing Gao: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Writing – review & editing.
Conceptualization: Meiqi Lu, Qing Gao, Yiting Feng.
Data curation: Meiqi Lu, Yixuan Chen.
Formal analysis: Yixuan Chen.
Funding acquisition: Qing Gao.
Investigation: Yixuan Chen.
Methodology: Meiqi Lu, Yiting Feng.
Project administration: Qing Gao.
Resources: Qing Gao.
Supervision: Qing Gao.

Validation: Meiqi Lu, Yiting Feng, Yixuan Chen.
Visualization: Yixuan Chen.
Writing – original draft: Yixuan Chen.
Writing – review & editing: Meiqi Lu, Qing Gao, Yiting Feng, Yixuan Chen.

References

[1] Valencia WM, Florez H. How to prevent the microvascular complications of type 2 diabetes beyond glucose control. BMJ (Clinical research ed.). 2017;356:i6505.
[2] Xue R, Gui D, Zheng L, et al. Mechanistic insight and management of diabetic nephropathy: recent progress and future perspective. J Diabetes Res. 2017;2017:1839809.
[3] Muayad Shukur Al Obaidi R. The physiological effects of Visfatin on immune response and inflammatory impacts on nephropathy. Archives of Razi Institute 2021;76:639–47.
[4] Adnan Khalaf M, Ghassan Zainal I. Investigation of antioxidant markers in diabetic patients. Arch Razi Inst. 2021;76:1453–60.
[5] Donate-Correa J, Luis-Rodríguez D, Martín-Núñez E, et al. Inflammatory targets in diabetic nephropathy. J Clin Med. 2020;9:458.
[6] Doshi SM, Friedman AN. Diagnosis and management of type 2 diabetic kidney disease. Clin J Am Soc Nephrol. 2017;12:1366–73.
[7] Wang XQ, Wang L, Tu YC, et al. Traditional Chinese medicine for refractory nephrotic syndrome: strategies and promising treatments. Evid-based Complement Altern Med. 2018;2018:8746349.
[8] Xu X, Li QJ, Xia S, et al. Tripterygium glycosides for treating late-onset rheumatoid arthritis: a systematic review and meta-analysis. Altern Ther Health Med. 2016;22:32–9.
[9] Ho LJ, Chang WL, Chen A, et al. Differential immunomodulatory effects by Tripterygium wilfordii Hook f-derived refined extract PG27 and its purified component PG490 (triptolide) in human peripheral blood T cells: potential therapeutics for arthritis and possible mechanisms explaining in part Chinese herbal theory "Junn-Chenn-Zuou-SS". J Transl Med. 2013;11:294.
[10] Chmura Kraemer H, Periyakoil VS, Noda A. Kappa coefficients in medical research. Stat Med. 2002;21:2109–29.
[11] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:Ed000142.
[12] Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64:669–77.
[13] Cai X. ARB combined with tripterygium glycosides regimen for treatment of patients with diabetic nephropathy(ARB制剂联合雷公藤多甙治疗糖尿病肾病). J Clin Med Pract. 2012;16:112–14.
[14] Li D. Clinical observation of irbesartan combined with tripterygium glycosides in type 2 diabetic nephropathy(厄贝沙坦联合雷公藤多苷治疗2型糖尿病肾病的临床观察). J Yichun College. 2014;36:31–2.
[15] Song M. Effect of valsartan and triptolide in diabetic nephropathy proteinuria(缬沙坦分散片与雷公藤多甙在治疗糖尿病肾病蛋白尿中的效果分析). China Med Engineer. 2014;22:154–56.
[16] Tan Y, Wang M. Clinical observation on triptolide combined with irbitartan for massive albuminuria in diabetic nephropathy(雷公藤多苷与厄贝沙坦联合治疗糖尿病肾病大量蛋白尿临床观察). National Med Front China. 2010;5:32–3.
[17] Zhang Y, Sun Y, Liu D. Observation of curative effect on type 2 diabetic nephropathy treated with Tripterygium Glycosides and Irbesartan (雷公藤多苷和厄贝沙坦治疗2型糖尿病肾病的效果观察). China Med Herald. 2012;9:73–4.
[18] He H, Wang W, Chen Z, et al. Efficacy of tripterygium glycosides combined with valsartan in stage 1-3 diabetic nephropathy of chronic kidney disease(雷公藤多苷联合缬沙坦治疗慢性肾脏病1~3期糖尿病肾病疗效观察). Lishizhen Med Materia Medica Res. 2010;21:3032–33.
[19] Shi Y, Liu Z, Wang C, et al. Clinical study of triptolide in the treatment of early-and middle-term diabetic nephropathy(雷公藤多苷治疗早中期糖尿病肾病的临床研究). Mod J Integrat Tradit Chin West Med. 2006;15:987–88.
[20] Wang M, Zhang C. Clinical observation on Valsartan combined with triptolide in type 2 diabetic nephropathy(缬沙坦联合雷公藤多苷治疗2型糖尿病肾病蛋白尿临床观察). Chin J Clin Rational Drug Use. 2012;5:84–5.
[21] Wang W. Different doses of tripterygium glycosides in the treatment of diabetic nephropathy: effects on blood lipids. Kidney Blood Pressure Res. 2018;43:931–7.
[22] Xiong C, Li L, Bo W, et al. Evaluation of the efficacy and safety of TWHF in diabetic nephropathy patients with overt proteinuria and normal eGFR. J Formos Med Assoc. 2020;119:685–92.
[23] Zhang B. Effects of Triperygium glucosides on diabetic nephropathy(雷公藤多甙治疗糖尿病肾病疗效观察). J China Tradit Chin Med Informat. 2010;2:23–4.
[24] Zheng X. Effects of Triperygium glucosides on diabetic nephropathy(雷公藤多甙治疗糖尿病肾病的疗效观察). J Clin Experiment Med. 2009;8:134–35.
[25] Chang J, Shi L, Song H. Clinical study of Tripterygium wilfordii in the treatment of the senile diabetic nephropathy(雷公藤多甙对老年性糖尿病肾脏疾病患者肾功能的影响). World Clin Drugs. 2012;33:96–8.
[26] Diao Z, Wang Z, Xu Y. Clinical effects of Triperygium glucosides on diabetic nephropathy(雷公藤多苷治疗糖尿病肾病临床疗效观察). Med Innovat China 2010;7:45–7.
[27] Gao S. Randomized controlled study of tripterygium glycosides in diabetic nephropathy(雷公藤多苷治疗糖尿病肾病的随机对照研究). Hainan Med J. 2012;23:31–2.
[28] Guo Y, Zuo Y. Clinical analysis of effect of Tripterysium glucosides in treatment of diabetic nephron(雷公藤多甙片治疗糖尿病肾病的临床分析). Clin Nephrol. 2007;7:198–99.
[29] Sun H, Li C. Clinical observation on tripterygium glycosides combined with metformin in treating diabetic nephropathy(雷公藤多苷联合二甲双胍治疗糖尿病肾病临床观察). West J Tradit Chin Med. 2014;27:82–4.
[30] Wang Y, Xiao Q. Efficacy of triptolide combined with telmisartan in proteinuria of type 2 diabetic nephropathy (雷公藤多苷联合替米沙坦治疗2型糖尿病肾病蛋白尿疗效观察). Chinese Med Mod Distance China. 2013;11:45–6.
[31] Wang Z, Liu J. Effect of tripteride in diabetic nephropathy (雷公藤治疗糖尿病肾病的疗效观察). Chinese Foreign Women Health. 2011;19:227.
[32] Yu Z. Clinical effects of tripterygium for diabetic nephropathy (雷公藤多苷片治疗糖尿病肾病的临床效果探讨). Med Informat. 2011;24:2440–41.
[33] Xu G, Dejun C, Weizhen C. Effect of Tripterygium wilfordii polyglycoside on inflammatory factor level in patients with diabetic nephropathy (雷公藤多苷片对糖尿病肾病患者临床疗效及炎症因子水平影响研究). Chinese Archives Tradit Chin Med. 2017;35:2206–08.
[34] Wu H, Liu C, Liu J. Mechanism and safety of triptolide in diabetic nephropathy (雷公藤多苷片治疗糖尿病肾病的机制及安全性探讨). Mod Pract Med. 2011;23:389–91.
[35] Anders HJ, Huber TB, Isermann B, et al. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. Nat Rev Nephrol. 2018;14:361–77.
[36] Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014;37:2864–83.
[37] Sirin FB, Korkmaz H, Eroglu I, et al. Serum zonulin levels in type 2 diabetes patients with diabetic kidney disease. Endokrynol Pol. 2021;72:545–9.
[38] Bonner R, Albajrami O, Hudspeth J, et al. Diabetic kidney disease. Primary Care. 2020;47:645–59.
[39] Tang Y, Liu Q, Feng Y, et al. Tripterygium ingredients for pathogenicity cells in rheumatoid arthritis. Front Pharmacol. 2020;11:583171.
[40] Reidy K, Kang HM, Hostetter T, et al. Molecular mechanisms of diabetic kidney disease. J Clin Invest. 2014;124:2333–40.
[41] Ma RX, Zhao N, Zhang W. The effects and mechanism of Tripterygium wilfordii Hook F combination with irbesartan on urinary podocyte excretion in diabetic nephropathy patients. Zhonghua Nei Ke Za Zhi. 2013;52:469–73.
[42] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed.). 2021;372:n71.
[43] Wang Y, Liu T, Ma F, et al. A network pharmacology-based strategy for unveiling the mechanisms of Tripterygium wilfordii Hook F against diabetic kidney disease. J Diabetes Res. 2020;2020:2421631.
[44] Zhao T, Jin Q, Kong L, et al. microRNA-15b-5p shuttled by mesenchymal stem cell-derived extracellular vesicles protects podocytes from diabetic nephropathy via downregulation of VEGF/PDK4 axis. J Bioenerg Biomembr. 2022;54:17–30.
[45] Nong C, Wang XZ, Jiang ZZ, et al. Progress of effect and mechanisms of Tripterygium wilfordii on immune system. Zhongguo Zhong Yao Za Zhi. 2019;44:3374–83.
[46] Ziaei S, Halaby R. Immunosuppressive, anti-inflammatory and anti-cancer properties of triptolide: a mini review. Avicenna J Phytomed 2016;6:149–64.
[47] Wang Y, Zhao B, Liu L, et al. Progress of tripterygium glycosides in the treatment of diabetic nephropathy (雷公藤多苷治疗糖尿病肾病的研究进展). Chin J Cardiovasc Med. 2021;26:193–96.