META-ANALYSIS

Meta-analysis of Huangqi (*Astragalus membranaceus*) and Chinese Yam (*Rhizoma Dioscoreae*) for Diabetic Nephropathy

Chaozhen Wang, MM; Shubing Li, BS; Jie Meng, MD; Meiling Xia, MM; Qin Bo, BS; Weifeng Ying, BS

ABSTRACT

Context • Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), has caused enormous economic pressure and serious health problems worldwide. TCM practitioners commonly use a combination of *Astragalus membranaceus* (*A. membranaceus*) and *Rhizoma Dioscoreae* (*R. Dioscoreae*) in the treatment of DN. Research is still lacking on the therapeutic effects of TCM for DN.

Objective • The systematic review and meta-analysis intended to evaluate whether the combination of *A. membranaceus* and *R. Dioscoreae* together with Western medicine can provide better efficacy against DN than treatment with traditional Western medicine alone, to provide a clinical medical basis for the use of the TCM combination.

Design • The research team performed a performed a systematic narrative review by searching the Web of Science, Science Direct, Pubmed, China National Knowledge Infrastructure (CNKI), VIP, Wanfang, Chinese Science and Technology Journal Database, and Biomedical Literature Chinese Database from databases' inceptions to May 2023. The team used the keywords astragalus and yam, diabetic nephropathy, antidiabetic, and 24-h urinary protein.

Setting • The review and meta-analysis occurred at Jiangxi Hospital of Integrated Traditional China and Western Medicine in Nanchang, Jiangxi, China.

Intervention • To perform a subgroup analysis, the research team divided the studies into two groups based on the TCM treatment course, with one subgroup receiving treatment for ≤4 weeks and the second receiving treatment for >4 weeks, to judge whether a time-dependence existed for the effects of the TCM combination on UP.

Outcome Measure • All studies used 24-h urinary protein (UP) as the outcome measure.

Results • In all studies, all heterogeneous ($P < .01$, $I^2 = 94\%$, the intervention groups had a significantly greater reduction in 24-h UP than the control groups did ($P < .05$). The heterogeneity for a treatment course of ≤4 weeks was $P < .01$, $I^2 = 97\%$, and for a course of >4 weeks was $P < .01$, $I^2 = 87\%$. For both ≤4 weeks and >4 weeks, the intervention groups had a significantly greater reduction in 24-h UP than the control groups did, with $P < .01$ and $P < .01$, respectively. The protein effect wasn't time dependent.

Conclusions • *A. membranaceus* and *R. Dioscoreae* can significantly reduce UP production, and inhibition of UP wasn't time-dependent. (*Altern Ther Health Med.* 2023;29(8):840-845).

Chaozhen Wang, MM, Attending physician, Preventive Medicine Department, Jiangxi Hospital of Integrated Traditional China and Western Medicine, Nanchang, Jiangxi, China. **Shubing Li,** BS, Deputy chief physician; **Jie Meng,** MD, Attending physician; **Meiling Xia,** MM, Attending physician; and **Qin Bo,** BS, Deputy chief physician; Department of Endocrinology, Jiangxi Hospital of Integrated Traditional China and Western Medicine, Nanchang, Jiangxi, China. **Weifeng Ying,** BS, Attending physician, Information Center, Jiangxi Hospital of Integrated Traditional China and Western Medicine, Nanchang, Jiangxi, China.

Corresponding author: Weifeng Ying, BS
E-mail: ewf4418@163.com

Diabetes nephropathy (DN), also known as diabetic kidney disease (DKD), is a chronic metabolic disease that not only creates the hyperglycemic state that plagues diabetics around the world but also is potentially life-threatening, with dire complications being associated with the disease. Clinicians recognize it as a serious microvascular complication of type 1 and type 2 insulin-dependent diabetes mellitus (DM) and a major pathogenic factor in end-stage renal disease (ESRD), and its incidence is increasing rapidly in developed and developing countries. DN has caused enormous economic pressure and serious health problems worldwide.

DN's main pathological features are glomerulosclerosis and tubulointerstitial fibrosis, and the clinical manifestations are edema, increases in urinary protein, and azotemia. As the

condition worsens, the patient gradually develops chronic renal failure.

According to the classic description of DN,[1] histopathological changes occur in a patient's kidneys. In the glomeruli, clinicians commonly observe capillary lumen extension, extracellular-matrix dilation, podocyte injury, an increase in basement-membrane thickness, and fibrosis, whereas in the tubulointerstitium, they observe a degeneration of the vacuoles, presenting a loose arrangement and fibrosis.[2-4]

Usually DN patients have glomerular hyperfiltration and microalbuminuria, and as the disease progresses, they experience a decreased glomerular filtration rate (GFR).[5] Clinicians often consider the main indicator of DN to be urinary protein (UP) levels, including those identified using the urinary albumin excretion rate (UAER) or the 24-h urinary protein of patients with macroalbuminuria.[6] The most commonly used rating index for renal impairment is 24-h urinary protein. Other measures can include measurements of kidney function, blood glucose or lipid levels, and overall symptoms. In addition, a certain number of patients will develop end-stage renal disease (ESRD).

Therapeutic Methods

The current conventional therapy in Western medicine for managing DN mainly relies on the effect of drugs—mainly controlling a patient's blood sugar, lowering his or her blood pressure, regulating fat, and decreasing inflammation—and other methods of symptomatic treatment. However, this treatment often doesn't achieve the desired effect, and side effects can occur after the drugs' long-term administration.

Nowadays, healthcare practitioners are widely promoting and using Western medicine combined with traditional Chinese medicine (TCM), which can relieve clinical symptoms, especially by improving patients' quality of life of and delaying the disease's development. Tu et al and Xiao et al found that medical practitioners widely use Chinese herbal medicine (CHM) as an adjuvant or independent treatment for DN, which clinicians have found to be efficacious.[8,9]

Chinese Herbal Medicine

Liu et al found that many studies nowadays have focused on natural products with renal protection; however, high-quality, large-sample studies are lacking on the therapeutic effects of TCM on DN.[7]

The World Health Organization (WHO) recommends some herbal remedies as adjunctive therapies for diabetes and its associated complications.[26,27] Wu and Liang found that TCM, as a holistic and comprehensive treatment method, has significant advantages of better curative effect in DN's treatment as compared to Western medicine.[28]

Diet therapy has been a part of Chinese medicine for thousands of years.[29] Although no historical record exists for treatment of DN in Chinese medicine, the descriptions for kidney elimination, kidney fatigue, turbid urine, fullness, edema, and diabetes in TCM are similar to DN's clinical manifestations. According to the syndrome differentiation and treatments in TCM, the disease is mostly the syndrome of deficiency in origin and excess in superficiality.

Deficiency, stasis, and turbidity are the basic pathogenesis. The superficiality manifests as blood stasis and turbid toxin accumulation. Blood stasis runs through the whole process of DN, and treatments mainly invigorate vitality deficiency, activate blood circulation, and dredge collaterals, diuresis and dampness, detoxification, blood stasis, and turbidity.

Astragalus Membranaceus

TCM practitioners widely use a decoction prepared from the root of *Astragalus membranaceus* (*A. membranaceus*), known as Huangqi in TCM, to treat bacterial infections and viruses, inflammation, and cancer. The herb has the effects of promoting body fluid to quench thirst, nourishing vitality and yin, decreasing diuresis, and reducing swelling. It can dilate blood vessels, improve microcirculation, increase renal blood flow, and thus, improve the protein and lipid metabolism disorders of DN.

Zhang et al indicates that records in historical documents and pharmacological studies have found that A. membranaceus may have benefits for patients with DKD, a growing burden in society with limited validated options for renoprotection.[10]

One of the main components of *A. membranaceus*' aqueous extract is astragaloside IV (AS-IV), which is a cycloartane triterpene glycoside compound.

Tang et al found that *A. membranaceus*, when used as an adjuvant therapy, can exert a significant antidiabetic effect during treatment, by reducing fasting blood glucose (FPG) and glycosylated hemoglobin A2c (HbA_{1c}), and that it can have protective effects for the kidneys.[11]

Rhizoma Dioscoreae

Traditional Asian medicine has widely used yam, *Rhizoma Dioscoreae* (*R. Dioscoreae*), to promote health and to relieve the symptoms of, decrease the effects of, and treat many diseases, such as hypertension, diabetes, inflammation, cancer, asthma, abscesses, chronic diarrhea, and ulcers.[12,13] Belonging to the Dioscoreaceae family, the main components of yam are allantoin, diosgenin, saponin, polysaccharide, proto-dioscorea, gracillin, choline, and protein.[14]

R. Dioscoreae has the functions of invigorating the middle and replenishing vitality, nourishing kidney vitality, and invigorating the spleen and stomach, and it can promote kidney regeneration and repair.

The polysaccharides of Chinese yam have attracted much attention in the field of biomedicine because of their immunomodulatory and antitumor effects. Zhang et al found that the mucopolysaccharides in *R. Dioscoreae* have immunostimulatory biological activities, including enhancement of splenic lymphocytes, stimulation of phagocytosis, and creation of helper macrophages.[15]

Allantoin in yam is natural, safe, and nontoxic; moreover, the substance can be effective in treating diabetes, high blood

pressure, and cancer and can relieve common pain.[16] Go et al found that *R. Dioscoreae* has antidiabetic effects and can improve kidney function.[17]

Herbal Combination

TCM practitioners commonly use and prefer a combination of *A. membranaceus* and *R. Dioscoreae* in the treatment of DN.

Wang's study evaluated the active ingredients and targets of the combination of A. membranaceus and R. Dioscoreae for the treatment of immunoglobulin A (IgA) nephropathy (IgAN) to determine their correlation with the clinical characteristics of IgAN patients.[30] Wang carried out a molecular docking simulation to find network predictions, and the study's model verification provided new evidence for the use of the combination in the treatment of IgAN.

Current Study

Research is still lacking on the therapeutic effects of TCM for DN. The current systematic review and meta-analysis intended to evaluate whether the combination of *A. membranaceus* and *R. Dioscoreae* together with Western medicine can provide better efficacy against DN than treatment with traditional Western medicine alone, to provide a clinical medical basis for the use of the TCM combination.

METHODS

Procedures

The review and meta-analysis occurred at Jiangxi Hospital of Integrated Traditional China and Western Medicine in Nanchang, Jiangxi, China.

Search strategy. The research team performed a performed a systematic narrative review by searching the Web of Science, Science Direct, Pubmed, China National Knowledge Infrastructure (CNKI), VIP, Wanfang, Chinese Science and Technology Journal Database and Biomedical Literature Chinese Database. The team searcher for articles published from the databases' inceptions to May 2023. The team used the key words astragalus and yam, diabetic nephropathy, antidiabetic, and 24-h urinary protein. At the same time, the team carried out manual retrieval of articles by reading relevant monographs and reviewing references.

Literature selection. The research team included studies if: (1) they were randomized controlled trials (RCTs); (2) they provided complete clinical data; (3) their participants had DM, diagnosed using a diagnostic method for DM that met the World Health Organization's (WHO's) or the American Diabetes Association's (ADA's) diagnostic criteria; (4) they had a control group that received conventional western medicine for lowering blood sugar, lipids, and blood pressure, without limitations to the type or dose of a drug; and (5) they had an intervention group that received treatment based on a combination of *A. membranaceus* and *R. Dioscoreae*, with no limitations on dosage, dosage form, or course of treatment, and the same Western medicine treatment as the control group. The team placed no limitations on the characteristics of the studies' participants, including the stage of diabetes, disease duration, age, gender, or race. The team placed no restrictions on the use of blinding.

The research team excluded studies if: (1) they used unclear outcome measures; (2) the team couldn't extract the data; (3) their participants had types of kidney disease other than DN, such as urinary tract infections, kidney stones, or nephrotic syndrome; or (4) the articles involved dissertations, were basic, or were literature reviews.

Two members of the research team: (1) independently screened each eligible article according to the literature inclusion and exclusion criteria, (2) extracted the data, (3) evaluated the study's quality, (4) cross-checked each other's data, and (5) listed each study's relevant characteristics, including the title, first author, year of publication, research design, each group's intervention, research quality, diagnostic criteria, number of participants, participants' age range, and other relevant data. They resolved any disagreements by discussion and sought the opinion of a third team member when necessary.

Quality assessment. The previously mentioned members of the research team assessed the methodological quality of the included literature using an assessment method that determined risk of bias, as recommended by the Cochrane Assistance Network.

The research team adopted the Cochrane Collaboration's definitions and the seven criteria for assessment: (1) random sequence generation, (2) blinding of participants and personnel, (3) allocation concealment, (4) incomplete outcome data, (5) blinding of outcome assessments, (6) selective reporting. For each study, the team recorded whether each study met those criteria.

Additionally, the team expressed its assessments as low risk, high risk, or unclear risk. According to the above standards, the research team divided the studies into three grades. Those that met all of the above standards = A grade; those that met three or more of the above standards = B grade; and those that met two of the above criteria or fewer = C grade.

Meta-analysis. A meta-analysis is the use of statistical techniques to integrate the results of studies included in a systematic review.[18]

All studies used 24-h urinary protein (UP) as the outcome measure.

The research team performed a subgroup analysis for the TCM treatment course, with one subgroup receiving treatment for ≤4 weeks and the second receiving treatment for >4 weeks, to judge whether a time-dependence existed for the effects of the TCM combination on UP and whether confounding factors and differential factors could be ruled out.

Statistical Analysis

The research team analyzed the data using the RevMan5.4 software. The team analyzed the heterogeneity of the included research data using the Chi Square (χ^2) test and corresponding

p value. The team used I^2 to represent heterogeneity. When $I^2 > 50\%$, statistical heterogeneity existed among the studies, and the team used the random effects model for analysis. When $I^2<50\%$, no heterogeneity existed among the studies, and the team used the fixed effects model to analyze the data.

The team expressed the data as weighted mean differences (WMDs) and 95% confidence intervals (95% CIs). The specific methods to calculate the means and standard deviations of the intervention group and the control group at baseline and postintervention were: (1) Mean=X1-X2, where X1 was the mean at baseline and X2 was the mean postintervention and (2) SD=S1-S2, where S1 was the standard deviation at baseline and S2 was the standard deviation. P<0.05 indicated statistically significant difference.

RESULTS

Literature Search

In the preliminary search, the research team screened 181 relevant studies (Figure 1). The team removed 174 studies: (1) 89 after reading the abstract, (2) 14 after reading the introduce, (3) four studies for repeated content, (4) 16 animal studies, (5) eight that were controlled studies without use of Western medicine, and (6) 43 after reading the full text. Seven studies met the screening criteria.[19-25]

Table 1 shows the studies' basic characteristics—number of participants in the intervention and control groups, types of treatment, and course of treatment. of the included studies are shown.

Quality assessment

The assessment of risk of bias (Figures 2 and 3, Table 2) found: (1) three studies with random sequence generation,[22,23,25] (2) six studies with allocation concealment,[19-21,23-25] (3) three studies with blinding of participants and personnel,[22,23,25] and (4) three with blinding of outcome assessments.[19,21,22] The bias was unclear for the studies not meeting each criteria. All studies had complete outcome data, and the presence of selective reporting was unclear for all studies.

The results were well documented, and the selection bias was unknown. No studies had withdrawal or loss to follow-up. The quality grade for all studies was a B grade.

Meta-analysis of 24-h UP

The seven included studies reported the changes in the 24-h UP between baseline and postintervention, with 289 participants in the intervention groups and 267 in the control groups (Figure 4). Heterogeneity existed among the studies ($P < .01$, $I^2 = 96\%$), and the random model analysis showed that the intervention groups had a significantly greater reduction in 24-h UP than the control groups did [SMD = 1.60, 95%CI (0.29, 2.90), $P < .01$].

These findings suggest that treatment with *A. membranaceus* and *R. Dioscoreae* in addition to Western medicine can significantly affect DN.

Figure 1. Literature Screening Process

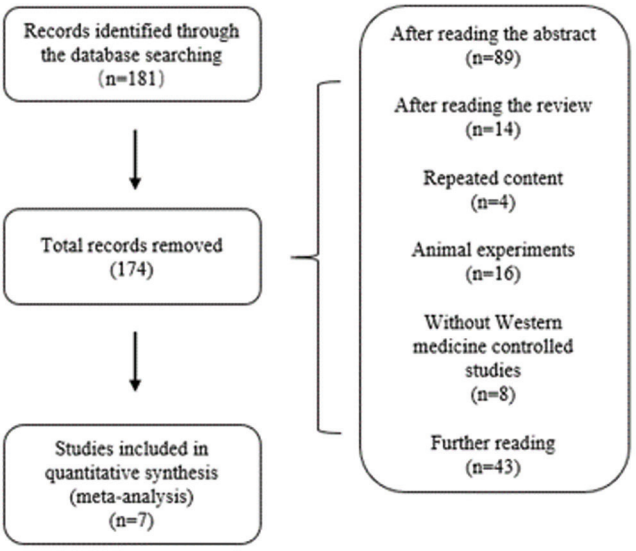


Table 1. Basic Characteristics of the Included Studies

Included Studies	Participants		Treatments		Course of Treatment Wks
	Intervention Group n (%)	Control Group n (%)	Intervention Group	Control Group	
Li, 2009[19]	30 (50.00)	30 (50.00)	Activating blood and tonifying kidney decoction + conventional treatment	Nephritis recovery pills + conventional treatment	12
Xu, 2010[20]	60 (50.00)	60 (50.00)	Benazepril hydrochloride + tonifying kidney and activating blood decoction + conventional treatment	Benazepril Hydrochloride + conventional treatment	6
Zhou, 1999[21]	36 (64.29)	20 (35.71)	Chinese medicine + conventional treatment	Conventional treatment	3
Song, 2014[22]	48 (53.33)	42 (46.67)	Prescription for strengthening the root and promoting blood circulation + conventional treatment	Conventional treatment	4
Zhou and Sun, 2004[24]	25 (50.00)	25 (50.00)	Vitalitydan Dihuang decoction + conventional treatment	Conventional treatment	3
Zhao and Guo, 2008[23]	60 (50.00)	60 (50.00)	Detoxifying decoction + conventional treatment	Conventional treatment	8
Dai, 2010[25]	30 (50.00)	30 (50.00)	Shejing Xiaobai capsules + conventional treatment	Benazepril + conventional treatment	8

Figure 2. Summary of Risk of Bias in Seven Studies

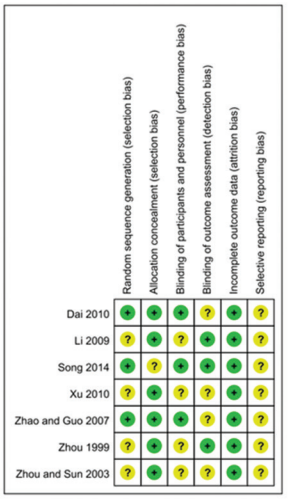


Table 2. Quality Assessment of Seven Included Studies

Included studies	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Dai, 2010[25]	Correct	Correct	Correct	Not described	Incorrect	Not described
Li, 2009[19]	Not described	Correct	Not described	Correct	Incorrect	Not described
Song, 2014[22]	Correct	Not described	Correct	Correct	Incorrect	Not described
Xu, 2010[20]	Not described	Correct	Not described	Not described	Incorrect	Not described
Zhao and Guo, 2007[23]	Correct	Correct	Correct	Not described	Incorrect	Not described
Zhou, 1999[21]	Not described	Correct	Not described	Correct	Incorrect	Not described
Zhou and Sun, 2003[24]	Not described	Correct	Not described	Not described	Incorrect	Not described

Meta-analysis of Different Treatment Courses

Figure 5 shows that heterogeneity existed among the three studies[21,22,24] with a treatment course of ≤4 weeks, with 109 participants in the intervention groups and 87 in the control groups ($P < .01$, $I^2 = 97\%$). The analysis showed that the intervention groups had a significantly greater reduction in 24-h UP than the control groups did [SMD = 0.24, 95%CI (-1.72, 2.20), $P < .01$].

Figure 5 shows that heterogeneity existed among the four studies[19,20,23,25] with a treatment course of >4 weeks, with 180 participants in the intervention groups and 180 in the control groups ($P < .01$, $I^2 = 87\%$). The analysis showed that the intervention groups had a significantly greater reduction in 24-h UP than the control groups did [SMD = 2.59, 95%CI (1.61; 3.56) $P < .01$].

The protein effect wasn't time dependent, which suggests that treatment with *A. membranaceus* and *R. Dioscoreae* in addition to Western medicine can significantly affect DN.

DISCUSSION

The current study's results provide medical evidence that Chinese medicine can treat DN, finding that the combined treatment, regardless of the dosage, can reduce the production of urinary protein and that the effects weren't time-dependent.

With 24-h urinary protein as the outcome measure, the meta-analysis found that I2 was greater than 50% for all studies, suggesting that no risk of bias existed. The reasons for the heterogeneity may be that: (1) the severity of DN for patients in the seven studies was different, and a significant differences in the 24-h urinary protein existed before the DN treatment; (2) the current study based the treatment on a TCM prescription of A. membranaceus and R. Dioscoreae, and great differences existed in the prescriptions in the seven studies; (3) although the control and intervention groups in each study received the same Western medicine, great differences existed in the Western medicine used in the different studies; and (4) some differences existed in the quality evaluations of the seven studies. However, no significant differences existed between the control and the intervention groups in the current study, and the risk of bias should have had a low impact on the results.

The current research team drew the following conclusions: the TCM combination of *A. membranaceus* and *R. Dioscoreae* can assist Western medicine in reducing the content of urinary protein and serum urea nitrogen, thereby delaying the occurrence and development of DN. However, to obtain more reliable evidence-based medical data, more high-quality studies need to occur, including strict, double-blind, controlled and randomized trials, consistent DN staging, and the same Western medicine and TCM intervention. In the future, the current research team hopes that more researchers can do more research on Chinese herbal medicine and its effects on the treatment of DN and other diseases, based on evidence-based and reliable medical data.

Figure 3. Risk of Bias Ratio for Seven Studies

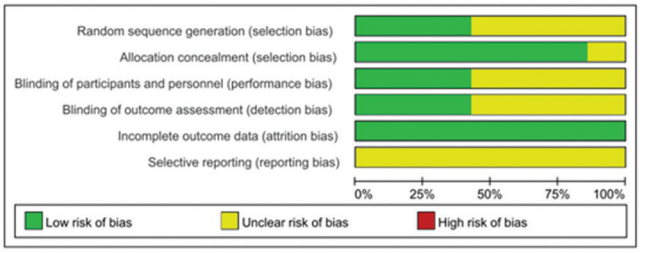
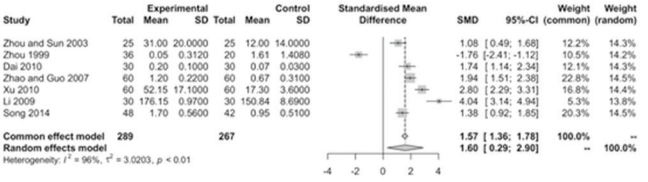
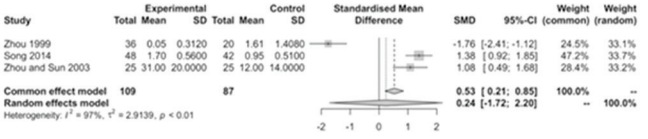


Figure 4. Meta-analysis of the Mean Difference in 24-h Proteinuria Protein Between Baseline and Postintervention for the Intervention and Control Groups



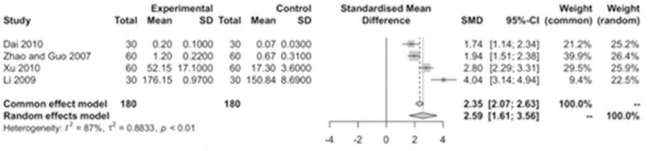
Abbreviations: DN, diabetic nephropathy.

Figure 5. Meta-analysis of the Mean Difference in 24-h Proteinuria Protein Between Baseline and Postintervention for the Intervention and Control Groups after ≤4 Weeks of Treatment



Abbreviations: DN, diabetic nephropathy.

Figure 6. Meta-analysis of the Mean Difference in 24-h Proteinuria Protein Between Baseline and Postintervention for the Intervention and Control Groups after >4 Weeks of Treatment



Abbreviations: DN, diabetic nephropathy.

CONCLUSIONS

A. membranaceus and *R. Dioscoreae* can significantly reduce UP production, and inhibition of UP wasn't time-dependent.

REFERENCES

1. Tang G, Li S, Zhang C, Chen H, Wang N, Feng Y. Clinical efficacies, underlying mechanisms and molecular targets of Chinese medicines for diabetic nephropathy treatment and management. *Acta Pharm Sin B*. 2021a;11(9):2749-2767. doi:10.1016/j.apsb.2020.12.020
2. Anders HJ, Huber TB, Isermann, B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nature Reviews Nephrology* 2018 14:6, 14(6), 361–377. doi:10.1038/s41581-018-0001-y
3. Jiang G, Luk AOY, Tam CHT, et al; Hong Kong Diabetes Register TRS Study Group. Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with Type 2 diabetes. *Kidney Int*. 2019;95(1):178-187. doi:10.1016/j.kint.2018.08.026
4. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm, KAM, Zoungas S, Rossing P, Groop PH, Cooper ME. Diabetic kidney disease. *Nature Reviews Disease Primers* 2015 1:1, 1(1), 1–20. doi:10.1038/nrdp.2015.18
5. Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: a mechanistic viewpoint. *Kidney Int*. 2008;74(1):22-36. doi:10.1038/ki.2008.128
6. de Zeeuw D, Renfurm RW, Bakris G, et al. Efficacy of a novel inhibitor of vascular adhesion protein-1 in reducing albuminuria in patients with diabetic kidney disease (ALBUM): a randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol*. 2018;6(12):925-933. doi:10.1016/S2213-8587(18)30289-4
7. Tu X, Ye X, Xie C, Chen J, Wang F, & Zhong S. Combination Therapy with Chinese Medicine and ACEI/ARB for the Management of Diabetic Nephropathy: The Promise in Research Fragments. *Herbal Medicine: Biomolecular and Clinical*. 2012. doi:https://doi.org/10.1016/J.JFF.2015.01.034.
8. Xiao Y, Liu Y, Yu K, et al. The effect of chinese herbal medicine on albuminuria levels in patients with diabetic nephropathy: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2013;2013:937549. doi:10.1155/2013/937549
9. Liu JY, Chen XX, Tang SCW, et al. Edible plants from traditional Chinese medicine is a promising alternative for the management of diabetic nephropathy. *J Funct Foods*. 2015;14:12-22. doi:10.1016/j.jff.2015.01.034
10. Cefalu WT, Stephens JM, Ribnicky DM. Diabetes and Herbal (Botanical) Medicine. *Herbal Medicine: Biomolecular and Clinical*. 2011:405–418. doi:10.1201/b10787-20
11. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137-149. doi:10.1016/j.diabres.2013.11.002
12. Wen Y, Yan M, Zhang B, Li P. Chinese medicine for diabetic kidney disease in China. *Nephrology (Carlton)*. 2017;22(suppl 4):50-55. doi:10.1111/nep.13149
13. Wu Q, Liang X. Food therapy and medical diet therapy of Traditional Chinese Medicine. *Clin Nutr Exp*. 2018;18:1-5. doi:10.1016/j.yclnex.2018.01.001
14. Zhang J, Wu C, Gao L, Du G, Qin X. Astragaloside IV derived from Astragalus membranaceus: A research review on the pharmacological effects. *Adv Pharmacol*. 2020;87:89-112. doi:10.1016/bs.apha.2019.08.002
15. Tang G, Li S, Zhang C, Chen H, Wang N, Feng Y. Clinical efficacies, underlying mechanisms and molecular targets of Chinese medicines for diabetic nephropathy treatment and management. In Acta Pharmaceutica Sinica B. *Chinese Academy of Medical Sciences*. 2021;1109:2749-2767. doi:10.1016/j.apsb.2020.12.020
16. McAnuff MA, Harding WW, Omoruyi FO, Jacobs H, Morrison EY, Asemota HN. Hypoglycemic effects of steroidal sapogenins isolated from Jamaican bitter yam, Dioscorea polygonoides. *Food Chem Toxicol*. 2005;43(11):1667-1672. doi:10.1016/j.fct.2005.05.008
17. Miyoshi N, Nagasawa T, Mabuchi R, et al. Chemoprevention of azoxymethane/dextran sodium sulfate-induced mouse colon carcinogenesis by freeze-dried yam sanyaku and its constituent diosgenin. *Cancer Prev Res (Phila)*. 2011;4(6):924-934. doi:10.1158/1940-6207.CAPR-10-0279
18. Liu JY, Yang FL, Lu CP, et al. Polysaccharides from Dioscorea batatas induce tumor necrosis factor-α secretion via Toll-like receptor 4-mediated protein kinase signaling pathways. *J Agric Food Chem*. 2008;56(21):9892-9898. doi:10.1021/jf8018722
19. Zhang L, Liu Y, Chen G. Simultaneous determination of allantoin, choline and L-arginine in Rhizoma Dioscoreae by capillary electrophoresis. *J Chromatogr A*. 2004;1043(2):317-321. doi:10.1016/j.chroma.2004.06.003
20. Chen MF, Tsai JT, Chen LJ, et al. Antihypertensive action of allantoin in animals. *BioMed Res Int*. 2014;2014:690135. doi:10.1155/2014/690135
21. Go HK, Rahman MM, Kim GB, et al. Antidiabetic effects of yam (Dioscorea batatas) and its active constituent, allantoin, in a rat model of streptozotocin-induced diabetes. *Nutrients*. 2015;7(10):8532-8544. doi:10.3390/nu7105411
22. Wang WX. Exploring the potential mechanism of A. membranaceus and R. Dioscoreae in the treatment of IgA nephropathy based on network pharmacology. *Herald of Traditional Chinese Medicine*. 2023.
23. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341. doi:10.1016/j.ijsu.2010.02.007
24. Li JL. Clinical Observation on 30 Cases of Diabetic Nephropathy Treated by Activating Blood and Tonifying Kidney. *Herald of Traditional Chinese Medicine*. 2009.
25. Xu HL. 60 Cases of Diabetic Nephropathy Treated with Bushen Huoxue Decoction. *Shaanxi Traditional Chinese Medicine*. 2010:31-38.
26. Zhou XY. 36 Cases of Diabetic Nephropathy Treated with Combination of Traditional Chinese and Western Medicine. *Shaanxi Traditional Chinese Medicine*. 1999:20-26.
27. Song ZL. 48 Cases of Early Diabetic Nephropathy Treated by Guben Huoxue Decoction. *Shaanxi Traditional Chinese Medicine*. 2014:35.
28. Zhao LX. 60 Cases of Diabetic Nephropathy Treated with Paidu Huoxue Decoction Combined with Western Medicine. *Herald of Traditional Chinese Medicine*. 2008.
29. Zhou ZH, Sun BQ. 25 Cases of Diabetic Nephropathy Treated by Qidan Dihuang Decoction. *Herald of Traditional Chinese Medicine*. 2004.
30. Dai M. 30 Cases of Diabetic Nephropathy Treated by Shejing Xiaobai Capsule. *Herald of Traditional Chinese Medicine*. 2010. .