Chinese medicinal herbs for idiopathic membranous nephropathy in adults with nephrotic syndrome

A systematic review of effectiveness and safety

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Abstract

To assess the benefits and harms of Chinese medicinal herbs formulae for the treatment of idiopathic membranous nephropathy in adult patients with primary nephrotic syndrome.

Only randomized controlled trials were included. We searched the Cochrane Central Register of Controlled Trials database, PubMed, EMBASE, Chinese National Knowledge Internet, Chinese Biomedicine Database, and VIP. All studies were analyzed using the criteria of the Cochrane Handbook and were assessed in terms of quality and the risk of bias. Review Manager ver. 5.3.5 software was used for the data analysis, and GRADE profiler software was employed to evaluate quality.

Two studies were included (n = 126 Chinese participants). We found that compared with against conventional treatment, one Chinese medicinal herbs formula plus conventional treatment reduced 24-hours urinary total protein (mean differences –3.16 g/24 h, 95% confidence intervals –4.03 to –2.29), and two Chinese medicinal herbs formulae increased serum albumin levels (mean differences 3.18 g/L, 95% confidence intervals 1.12 to 5.52; $I^2 = 0\%$).

Chinese medicinal herbs formulae may reduce 24-hours urinary total protein and increase serum levels of albumin. However, larger and multicenter studies with high methodological quality are still needed.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, Alb = serum levels of albumin, ARBs = angiotensin II receptor blockers, BUN = blood urea nitrogen, CI = confidence intervals, IMN = idiopathic membranous nephropathy, MD = mean differences, RCTs = randomized controlled trials, RR = risk ratios, SCr = serum levels of creatinine, TC = total cholesterol, TCM = traditional Chinese medicine, TG = triglycerides, UTP = urinary total protein.

Keywords: Chinese medicinal herbs, membranous nephropathy, meta-analysis, nephrotic syndrome, treatment

1. Introduction

Idiopathic membranous nephropathy (IMN) is an autoimmune disease which is the most common type of nephrotic syndrome in the world for adults.[1–4] More than 75% of membranous nephropathy cases are suffering from IMN.[5] IMN involves functional damage of glomerular capillary wall characterized by the deposition of immune complexes and complement activation on the sub-epithelial space between glomerular basement membrane and the glomerular podocytes. Approximately 30% of the patients with IMN experience spontaneous complete or partial remission,[6,7] while 30% to 40% ultimately develop end-stage kidney disease within 5 to 15 years.[1,8,9] From 2009 to

2018, the rate of IMN in China increased from 7.1% to 22.7% in the patients with primary or idiopathic nephrotic syndrome.[10,11] In Japan, 443 of 1,203 the patients with primary or idiopathic nephrotic syndrome had IMN.[12] IMN accounted for 12.3% of all kidney biopsies in Korea and 12.0% in Oman.[13,14] The prevalence of IMN in the patients with primary or idiopathic nephrotic syndrome ranged from 11.2% to 29.4% in Europe.[12,15] In elderly (≥60 years old) Chinese patients, IMN is the most common type of primary nephrotic syndrome. In China, the median age of the patients with new-onset IMN in 2005 to 2014 was 52.91 ± 15.30 years, whereas in 1995 to 2004 it was 48.29 ± 13.81 years.[11] In comparison, the incidence of membranous nephropathy is comparatively low in children, accounting for less than 5% of kidney biopsy diagnoses.[16] The treatment of IMN involves both general and specific approaches. The general therapeutic principles include the use of statins to reduce cholesterol, angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) to reduce proteinuria, and antiplatelet adhesion drugs to prevent thrombosis, especially renal vein thrombosis. ARBs or ACEIs are often used to protect the kidney function and decrease proteinuria.[12] In one study, 36% of the patients in China with IMN had venous thromboembolism, 33% had kidney vein thrombosis, and 17% had a pulmonary embolism.[17] Therefore, adult IMN patients with normal kidney function, proteinuria < 4 g/d, and serum levels of albumin (Alb) > 25 g/L should be treated with an ARB or ACEI combined with a preventative antiplatelet drug.[16] According to Kidney Disease Improving Global Outcomes, a combination of cytotoxic agents (e.g., oral cyclophosphamide or chlorambucil) and corticosteroids can induce the remission of the primary nephrotic syndrome in patients with IMN.[18] A placebo-controlled study reported that tacrolimus monotherapy was effective for the adult patients with IMN.[19] Another study suggested that earlier initiation of tacrolimus combined with prednisone therapy for more than 24 weeks was beneficial for ameliorating the severity of urine protein in Chinese adult patients with IMN.[20] Although tacrolimus induces remission for the most adult patients with IMN, however the kidney toxicity, heavy cost burden, and higher recurrence rates after treatment are main causes of drug withdrawal in the adult patients with IMN.[21] Hence, it is necessary to explore alternative treatment strategies for IMN.

According to traditional Chinese medicine (TCM) basic theory, Chinese medicinal herbs have been widely used in China to therapy nephropathy for thousands of years.[22] TCM internal medicine theory shows that IMN belongs to the TCM categories of "edema (*shui zhong*)" (e.g., any disease is characterized by subcutaneous fluid retention), "consumptive disease (*xu lao*) " (e.g., a common term for a chronic deficiency disease because the consumption of qi, blood, yin, and yang), and "turbid urine disease (*niao zhuo*)" (such as the discharge of turbid urine, with no difficulty or/and pain during urination, white rice-like water, a condition which differs from unctuous strangury). The Chinese medicinal herb radix astragali (*huang qi*: the root of *Astragalus membranaceus* Bge. or *Astragalus mongholicus* Bge.) is a primary tonic herb in China. One research showed that *Astragalus* polysaccharide derived from a water extract of *A. membranaceus* roots improved kidney function and proteinuria, however the level of nuclear IkappaB mRNA expression increased and factor-kappaB mRNA in the kidney cortex reduced.[23] Rhubarb (*Rheum* spp.), a well-known natural drug, has various pharmacological characteristics, including nephron-protective,

diuretic, lipid purgative, lowering, and anti-inflammatory activities.[24] Although the clinical effects of rhubarb for the kidney disease has been confirmed, but the biochemical mechanism underlying its clinical efficacy remains unclear. Various components of natural drug can act concurrently on many targets involved in the mechanism of kidney disease.[24]

Although Chinese medicinal herb formulae and other Chinese herbal medicine preparations have been used widely to treat IMN in China, their effects and safety have not been reviewed systematically.

2. Methods and material

2.1. Inclusion, exclusion and outcomes criteria

Randomized controlled trials (RCTs) were included only. We included studies that involved patients aged ≥18 years of either sex who with a histologically proven diagnosis of IMN (including stages 1–4), a cut-off proteinuria level of 3.5 g/24 h was used, and a diagnosis of nephrotic syndrome (as defined by the authors). Studies were excluded if they involved secondary forms of membranous nephropathy (e.g., diabetes mellitus, lupus erythematosus, viral infection, paraproteinemia, any malignant tumor, and amyloidosis), other kinds of membranous nephropathy, including rapidly progressive membranous nephropathy (defined as a rapid loss of the kidney function; more than 50% descend (within 3 months) in the eGFR [estimated glomerular filtration rate]), a hemoglobin A1c level >6.2 mmol/L and/or diabetes, pregnancy, treatment with hormone in the previous 6 months or/ and with immunosuppressive agents for more than 4 weeks, uncontrolled hypertension (systolic pressure of blood >190 mm Hg, diastolic >105 mm Hg), abnormal liver function (elevated serum levels of gamma glutamic transpeptidase, alkaline phosphatase, bilirubin, albumin, aspartate aminotransferase [AST; >38 U/L] or alanine aminotransferase [ALT; >40 U/L]), treatment with ARBs or ACEIs unless treatment was inconsecutive for more than 2 weeks before the study. Treatment with other Chinese patent medicine or/and Chinese herbal medicines that lack of vaildation as the control intervention, and incomplete data or data not extractable from the original trial were excluded.

Primary outcomes included all-cause mortality, end-stage kidney disease or a requirement for renal replacement therapy, and remission: complete/partial (Cure identified as normal kidney and liver function, plasma albumin ≥ 35 g/L, proteinuria < 0.3 g/d, disappearance of all the IMN signs and symptoms (e.g. edema, hypertension). Markedly effective was identified as plasma albumin ≥ 30 g/L, proteinuria < 0.3 g/d, disappearance of most the IMN signs and symptoms (e.g. edema, hypertension). Effective was identified as proteinuria <2 g/d, but ≥ 0.3 g/d and a reduce more than 50% from baseline, accompanied by an improvement in or normalization of the serum concentration of albumin and stable kidney function such as change in serum levels of creatinine < 25%. Secondary outcomes included kidney function (e.g. blood urea nitrogen [BUN], and serum levels of creatinine [SCr]), proteinuria (assessed based on 24 h urinary total protein (UTP) excretion), nutritional status (measured using Alb, serum levels of total cholesterol [TC], and triglycerides [TG]), adverse effects (toxicities), TCM outcomes (including tongue status, pulse status, and symptoms), economic index, relapse rate, and withdrawal. This study has been approved by the Chinese Clinical Trial Registry.

2.2. Literature search

We searched the following electronic databases and a series of related terms: All the searches ended at 31th March 2017. The Cochrane Central Register of Controlled Trials (to March 2017), PubMed (1966–March 2017), EMBASE (1967–March 2017), the Chinese Biomedicine Database (1978 – March 2017), Chinese National Knowledge Internet (1979–March 2017), and Chinese Science and Technology Periodical Database (VIP) (1989–March 2017). All studies included were analyzed according to Cochrane Handbook criteria. The following search terms were used: (Traditional Chinese Medicine OR Chinese Medicine OR Traditional Chinese and Western Medicine OR Traditional Chinese Pharmacy OR Integrated Chinese and Western Medicine OR Chinese herbology OR Chinese Materia Medica OR Chinese Patent Medicine OR Chinese Patent Drugs OR Chinese Tradition-al Patent Medicine OR Chinese traditional herbs OR Chinese medicinal herbs OR Chinese herbal medicines) AND (idiopathic membranous nephropathy OR membranous nephropathy OR IMN OR membranous glomerulonephritis OR membranous GN). We manually searched the Journal of Guangzhou University of Traditional Chinese Medicine. We attempted to contact all original authors to obtain study protocols for the review.

2.3. Data collection

Data were extracted by using a pre-tested data extraction form, including study characteristics, including methods, participants, interventions, and outcomes. No disagreements developed among the authors. Further information required from the original authors was requested by telephone if necessary. Issues raised by missing data and the imputation methods employed were critically appraised. We extracted the Chinese herbal formulations used in the included studies; Table 1 gives the names of the herbs in Chinese, Latin, and English.

2.4. Bias risk assessment

According to the risk for bias assessment tool, the following items were evaluated including generation of random sequence, assignment concealment, blinding of patients and researchers, blinding of outcome evaluators, incomplete result data, selective reporting, and other biases.

2.5. Statistical analysis

Data analyses were performed using Cochrane Collaboration RevMan software ver. 5.3.5. Results are expressed as risk ratios

(RR) and 95% confidence intervals (CI) for dichotomous outcomes (e.g., mortality, remission: complete/partial, adverse effects, relapse rate, and withdrawal), and as mean differences (MD) with 95% CI for continuous outcomes (such as SCr, BUN, Alb, TC, TG, and 24 hour UTP).

3. Results

3.1. Selection of studies

According to the retrieval strategy, a total of 444 related articles were obtained by preliminary retrieval, and 115 were obtained after endnote de-duplication. After reading the titles and abstracts, we excluded the basic animal research, non-RCT, other interventions and disease, and read the remaining 42 articles in full. Finally, 2 studies were included, with a total of 126 Chinese patients (Fig. 1).

The ratio of male to female participants in the two studies was 75/51.[27,28] Participants' ages ranged from 18 to 78 years. Course of disease was not reported. The intervention was oral administration or/and as intravenous drips of the Chinese medicinal herb formulae plus conventional treatment. The longest therapy duration was 22 months and the shortest was 6 months. The 24 hours UTP, BUN, SCr, Alb, TC, TG, remission: complete/partial and relapse rate were summarized. (Table 2).

3.2. Bias risk assessment of inclusion research

The methodological quality of each study's randomization sequence, allocation concealment, blinding (including blinding of participants and personnel, blinding of outcome assessment), incomplete outcome data, selective outcome reporting, and other bias were evaluated (Figs. 2 and 3). Overall, the two studies were considered as moderate-quality studies.

3.3. Efficiency of meta-analysis results

The results showed that Chinese medicinal herbs plus conventional treatment did not significantly increase remission when compared to conventional treatment (RR= 1.09, 95% CI [0.92, 1.29]; $I^2 = 34\%$) in two included studies (Fig. 4), while it also did not significantly decrease SCr and BUN when compared to conventional treatment (MD 0.13 μmol/L, 95% CI [−3.55, 3.80]; $I^2 = 0\%$ and MD –0.09 mmol/L, 95% CI [−0.53, 0.34]; $I^2 = 0\%$ respectively) in two included studies (Fig. 5).

Chinese medicinal herbs plus conventional treatment did not significantly reduce 24-hours UTP when compared with conventional treatment (MD −1.57g/24h, 95% CI [⁻4.64, 1.49]; I^2=97%). *Han* reported that a Self-Developed Qi Xue Shui

Table 1

Contents of the formulations (in Chinese, English and Latin) used in the included studies.

| Study ID	Herbs (Composition)
Han 2013 [27]	Self-Developed Qi Xue Shui Mo Shen Prescription: Huangqi (Radix Astragali/Membranous Milkvetch Root), Taizishen (Radix Pseudostellariae/Heterophylly Falsestarwort Root), Baizhu (Rhizoma Atractylodis Macrocephalae/Largehead Atractylodes Rhizome), Danggui (Radix Angelicae Sinensis/Chinese Angelica), Chishao (Radix Paeoniae Rubra/Red Paeony Root), Baishao (Radix Paeoniae Alba/White Paeony Root), Chuanxiong (Rhizoma Chuanxiong/ Szechuan Lovage Rhizome), Dilong (Lumbricus/Earthworm), Fuling (Poria /Indian Buead), Zexie (Alismatis/Oriental Waterplantain Rhizome), Cheqianzi (Semen Plantaginis/Plantain Seed), Gancao (Radix Glycyrrhizae/Liquoric Root).
Yang 2016 [28]	Self-Developed Ye Shi Yi Shen Xiao Bai Formula: Huangqi (Radix Astragali/Membranous Milkvetch Root), Dihuang (Radix Rehmanniae/Rehmannia Root), Baizhu (Rhizoma Atractylodis Macrocephalae/Largehead Atractylodes Rhizome), Quanxie (Scorpio/Scorpion), Danshen (Radix Salviae Miltiorrhizae/ Danshen Root), Fuling (Poria/Indian Buead), Chantui (Periostracum Cicadae/Cicada Slough), Jiangcan (Bombyx Batryticatus /Stiff Silkworm), Dilong (Lumbricus/Earthworm), Shuizhi (Hirudo/Leech), Danggui (Radix Angelicae Sinensis /Chinese Angelica), Honghua (Flos Carthami/Safflower), Taoren (Semen Persicae/Peach Seed), Chuanxiong (Rhizoma Chuanxiong/Szechuan Lovage Rhizome).
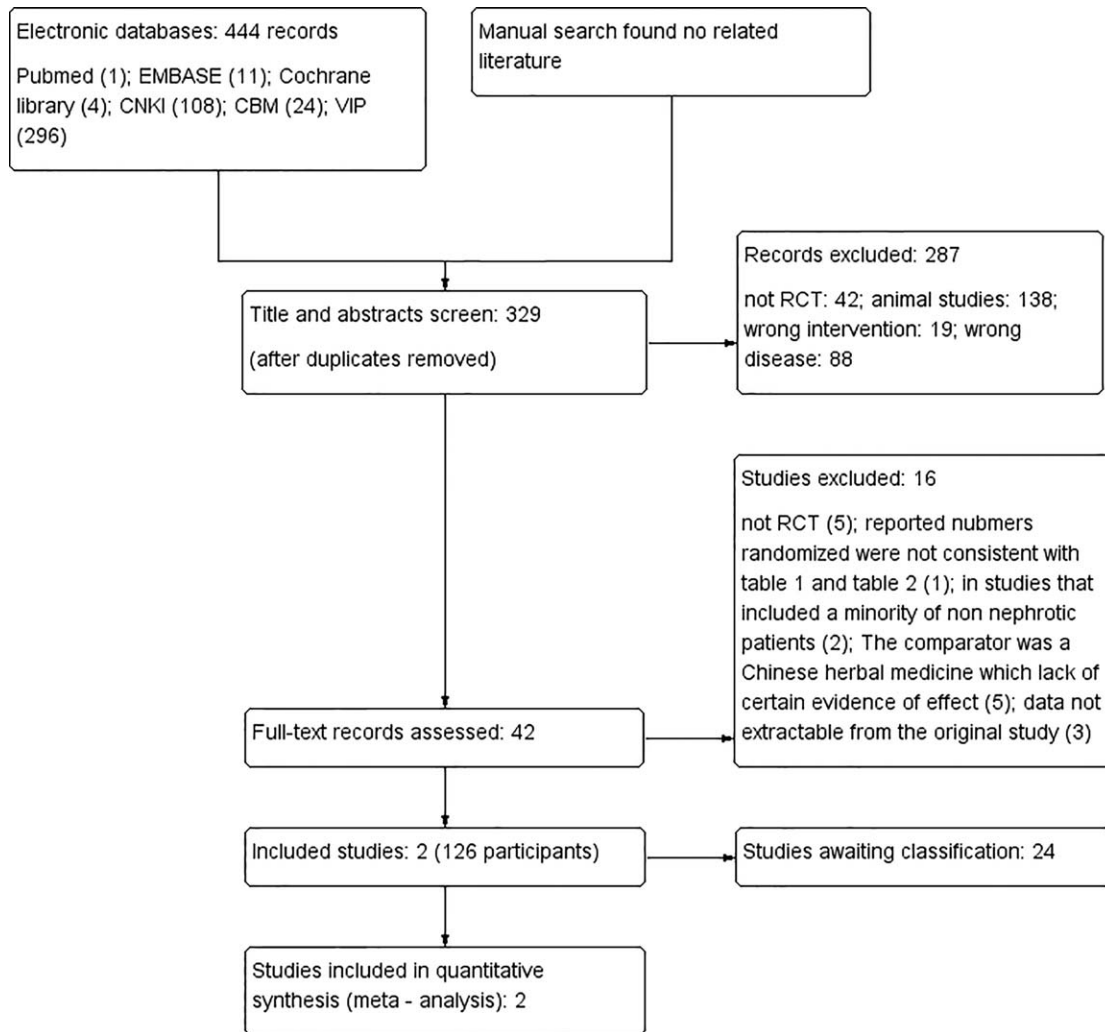
Figure 1. Summary of the search results in a flow diagram.

Mo Shen Prescription plus conventional treatment did not significantly reduce 24-hours UTP when compared with conventional treatment (MD −0.03 g/24 h, 95% CI [−0.56, 0.50]). However, Yan greported that significantly reduced 24-h UTP [MD-3.16 g/24h, 95% CI (−4.03,−2.29)] (Fig. 6).

Chinese medicinal herbs plus conventional treatment significantly increased Alb when compared with conventional treatment (MD 3.18 g/L, 95% CI [1.26, 5.11]; I^2=0%). *Han* reported that a Self-Developed Qi Xue Shui Mo Shen Prescription plus conventional treatment did not significantly increase Alb when compared with conventional treatment (MD 2.73 g/L, 95% CI [−1.28, 6.74]). However, *Yang* showed that a Self-Developed Ye Shi Yi Shen Xiao Bai Prescription plus conventional treatment significantly increased Alb when compared against conventional treatment (MD 3.32 g/L, 95% CI [1.12, 5.52]) (Fig. 7).

That study showed that Chinese medicinal herbs plus conventional treatment did not significantly decrease TC and TG when compared against conventional treatment (MD −0.35 mmol/L, 95% CI [−1.49, 0.79]) and (MD −0.23 mmol/L, 95% CI [−0.81, 0.35]), respectively[27] (Fig. 8).

Besides, Chinese medicinal herbs plus conventional treatment did not significantly decrease relapse rate when compared with conventional treatment (RR = 0.07, 95% CI [0.00,1.12]) (Fig. 9).

Overall, the "GRADE profiler" of the Cochrane Collaboration Network was used to classify the systematic review results. The quality of evidence was moderate (Table 3).

4. Discussion

Based on two RCTs[27,28] conducted in China, we found limited evidence that Chinese medicinal herbs formulae (including Self-Developed Qi Xue Shui Mo Shen Prescription and Self-Developed Ye Shi Yi Shen Xiao Bai Formula) plus conventional treatment had equal effects in increasing remission and decreasing the level of renal function (SCr and BUN) when compared against conventional treatment. Based upon one study Chinese medicinal herbs might increase the serum Alb level and decrease 24-hours UTP in idiopathic membranous nephropathy in adults with nephrotic syndrome, Chinese medicinal herbs might be an adjunct in treating idiopathic membranous nephropathy in adults with nephrotic syndrome. However, there was no sufficient evidence to confirm whether Chinese medicinal herbs increase complete/partial remission, improve kidney function (*e.g.*, BUN, and SCr), and nutritional status (including reduction in TC and TG), and/or decrease mortality. All of the results reported herein were from studies with two moderate methodological quality.

Table 2

Characteristics of included studies.

Study ID	Han 2013[27]	Yang 2016[28]
Methods	RCT: randomized, open-label RCT. Allocation concealment: not mentioned. Follow-up: not mentioned. Study duration: 6 months. Parallel/crossover/factorial RCT: open-label parallel RCT. Randomization method: random number table. Blinding: single-blinding was used. ITT: not mentioned.	RCT: a random sequence generated by a random number table. Allocation concealment: allocation concealment was done by phone to confirm. Follow-up: 12 months. Study duration: 16–22 months. Parallel/crossover/factorial RCT: parallel RCT. Randomization method: random number table. Blinding: single-blinding was used by phone to confirm. ITT: not mentioned.
Participants	Setting: inpatients and outpatients. Country: China. Number (randomized/analyzed): treatment group (35/35); control group (25/25). Treatment group 35 patients and control group 25 patients; 30 males (50%) and 30 females (50%); age 18 − 75 (average 52) years; disease duration: not mentioned. Biopsy proven membranous nephropathy (stages 1 − 3).	Setting: inpatients. Country: China. Number (randomized/analyzed): treatment group (33/33); control group (33/33). Treatment group: 33 (23 males; 70%; 10 females; 30%), age 20–78 (average 44) years; Control group: 33 (22 males; 66.7%; 11 females; 33.3%), age 21–76 (average 42) years. Biopsy proven membranous nephropathy, but not described the staging.
Interventions	Treatment group: Self-Developed Qi Xue Shui Mo Shen Prescription plus conventional treatment. Self-Developed Qi Xue Shui Mo Shen Prescription: Huangqi 30 − 60 g, Taizishen 15 − 30 g, Baizhu 10 g, Danggui 10 − 20 g, Chishao 10 g, Baishao 10 g, Chuanxiong 10 g, Dilong 6 g, Fuling 10 − 15 g, Zexie 15 − 25 g, Cheqianzi 15 − 25 g, Gancao 3 g (not described in detail in the original study). Conventional treatment was the same as that used in the control group. Control group: low-salt, high-quality protein diet, control blood pressure, control infection, and angiotensin converting enzyme inhibitor (ACEI) (routine dose, but there was specific drug in detail).	Treatment group: Self-Developed Ye Shi Yi Shen Xiao Bai Prescription plus conventional treatment. Self-Developed Ye Shi Yi Shen Xiao Bai Formula: Huangqi 45 g, Dihuang 24 g, Baizhu 9 g, Quanxie 9 g, Danshen 30 g, Fuling 20g, Chantui 20 g, Jiangcan 20 g, Dilong 20 g, Shuizhi 5 g, Danggui 15 g, Honghua 15 g, Taoren 15 g, Chuanxiong 15 g (not described in detail in the original study). Conventional treatment was the same as that used in the control group. Control group: including control blood pressure, control blood lipid, and anticoaguate therapy (not described in detail in the original study); prednisone 0.8 − 1.0 mg/kg orally once daily (qd); once liver function is impaired, changed to oral methylprednisolone for 8 weeks; after 3 months reduced to 5 mg. Study duration: 16 − 22 months. Months 1 − 6 intravenous cyclophosphamide once a month 0.75 g/m² cumulative dose ≤ 12 g.
Outcomes	1. 24-h UTP; 2. Complete remission and/or partial remission; 3. BUN and SCr; 4. Alb, TC, TG.	1. Complete remission and partial remission; 2. 24-h UTP; 3. Alb; 4. SCr and BUN; 5. Relapse rate.
Notes	1. All-cause mortality: not mentioned; 2. ESKD or requirement for renal replacement therapy: not mentioned; 3. TCM outcomes: tongue coat and pulse condition: not mentioned; 4. Economic index: not mentioned; 5. Adverse effects (leucopenia, herpes zoster virus infection, bone toxicity, hemorrhagic cystitis, sustained amenorrhea, development of any malignancy, alopecia): not mentioned; 6. Source of funding: Project support, Project Number: Guanganmen Hospital of China Academy of Chinese Medicine Funded Projects, 2009s209; 7. The protocol: not mentioned, but it was clear that the published reports included all expected outcomes, including those that were pre-specified; 8. Overall, participant demographic data were similar between groups; 9. Although not mentioned informed consent form, but an informed consent form was obtained from each participant by telephone confirmed; 10. Ethics committee approval: not mentioned; 11. Relapse rate: not mentioned; 12. Withdrawal: not mentioned.	1. All-cause mortality: not mentioned; 2. ESKD or requirement for renal replacement therapy: not mentioned; 3. TC and TG: not mentioned; 4. TCM outcomes: tongue coat and pulse condition: not mentioned; 5. Economic index: not mentioned; 6. Adverse effects (leucopenia, herpes zoster virus infection, bone toxicity, hemorrhagic cystitis, sustained amenorrhea, development of any malignancy, alopecia): not mentioned; 7. Project support, Project Number: Shanxi Provincial Authority of Chinese Medicine Projects, 13-LC043; 8. Overall, participant demographic data were similar between groups; 9. The protocol: not mentioned; 10. Informed consent: not mentioned; 11. Ethics committee approval: not mentioned; 12. Withdrawal: not mentioned.

24-h UTP - 24-hour urinary protein excretion, Alb = serum albumin, BUN = urea nitrogen, ESKD – end-stage kidney disease, ITT – intention-to-treat, RCTs = randomized controlled trials, SCr - serum creatinine, TC = serum total cholesterol, TCM = traditional Chinese medicine, TG = triglyceride, WBC - white blood cell.
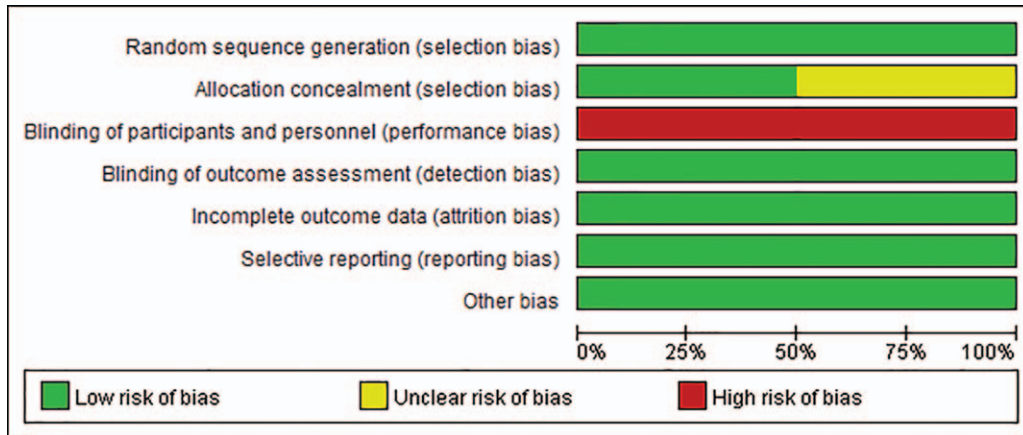
Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
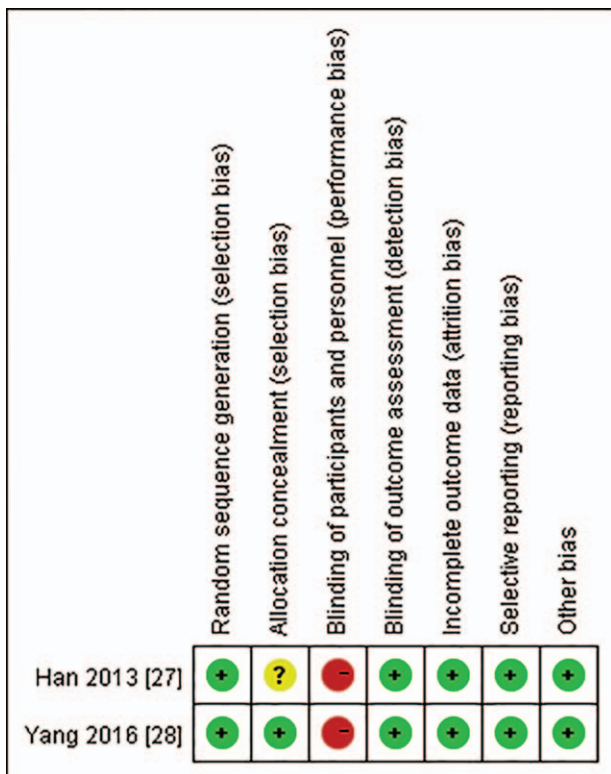

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Zheng 2017 conducted a review which compared Chinese medicinal herbs formulae plus conventional treatment use for the treatment of Chinese patients with IMN while focusing on China. Similar methodological approaches were applied in both reviews, and both focus on Chinese medicinal herbs formulae plus conventional treatment versus conventional treatment and measures of kidney function, blood lipid levels, and Alb correction (including SCr, BUN, TC, and TG). There were differences in study inclusion criteria: we included patients aged ≥18 years of either sex who with a histologically proven diagnosis of IMN (including stages 1–4), however which were eligible for all age by Zheng 2017; we included two studies (126 participants) and Zheng 2017 included 11 studies (725 participants). Only two studies were common to both reviews;[27,28] in our review, the original authors were contacted by telephone to confirm whether the studies included were RCTs and to resolve all methodological doubts, but in Zheng 2017 review the original authors were not contacted by telephone to prove if the studies included were RCTs and to resolve all methodological tissues.

We evaluated that the two included studies were moderate methodological quality, it was possible that these deficits might relate partly or wholly to absence of adequate reporting. The number of literature and patients included in this study was small for the lack of large samples of RCTs, more high-quality studies were needed to confirm the utility of Chinese medicinal herbs for idiopathic membranous nephropathy in adults with nephrotic syndrome. Future studies with a cohort treated with only Chinese medicinal herbs and conventional but without immunosuppressants was needed to fully assess the efficiency.
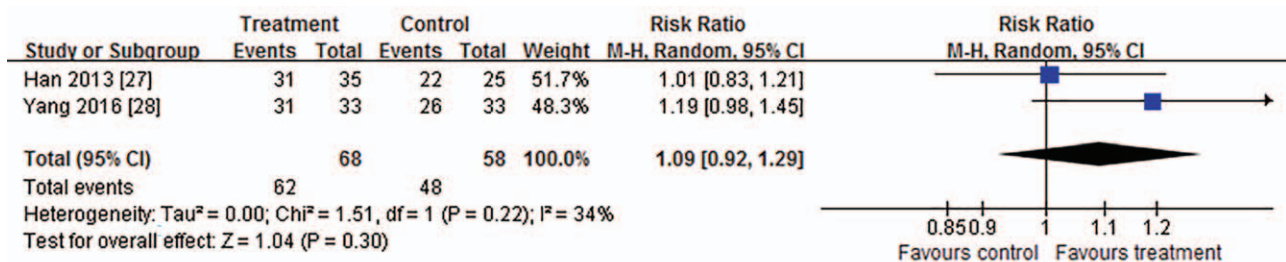

Figure 4. (analysis 1.1): Comparison. Chinese medicinal herbs plus conventional treatment versus conventional treatment: outcome 1 remission: complete/partial.
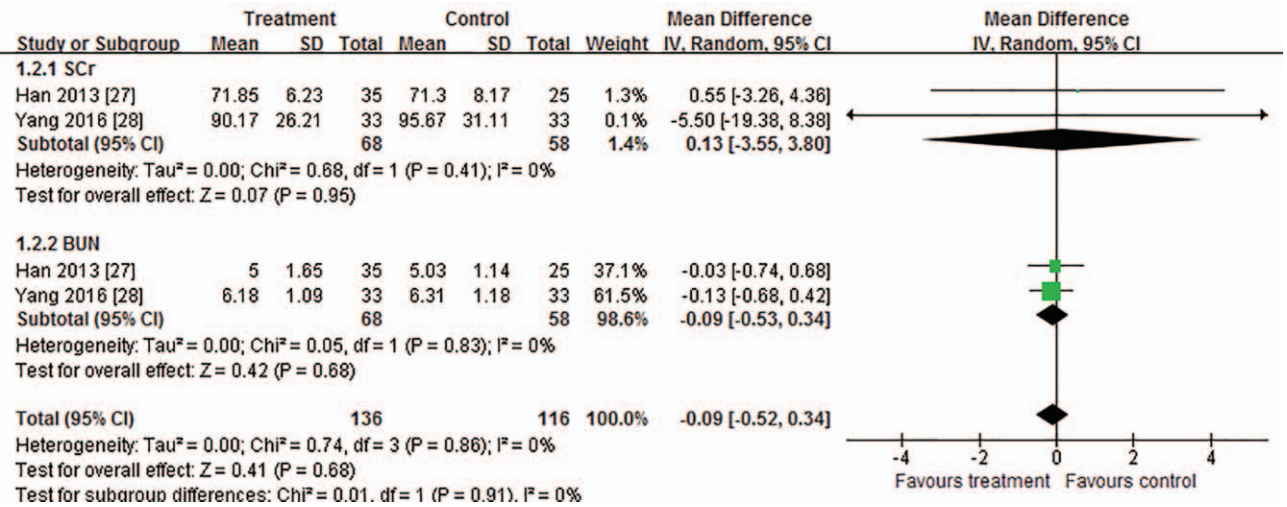
Figure 5. (analysis 1.2): Comparison. Chinese medicinal herbs plus conventional treatment versus conventional treatment: outcome 2 Kidney function (SCr and BUN).
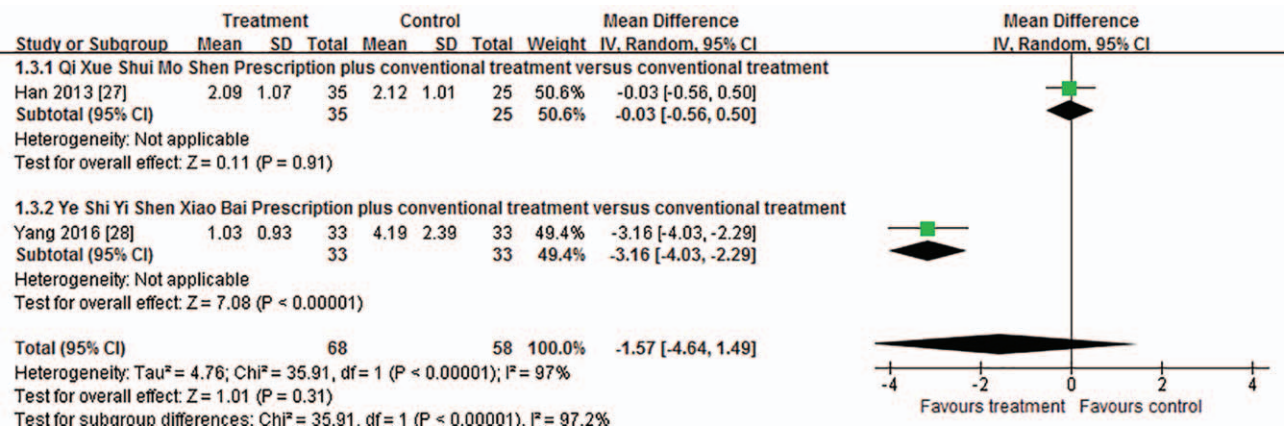

Figure 6. (analysis 1.3): Comparison. Chinese medicinal herbs plus conventional treatment versus conventional treatment: outcome 3 24 h UTP.
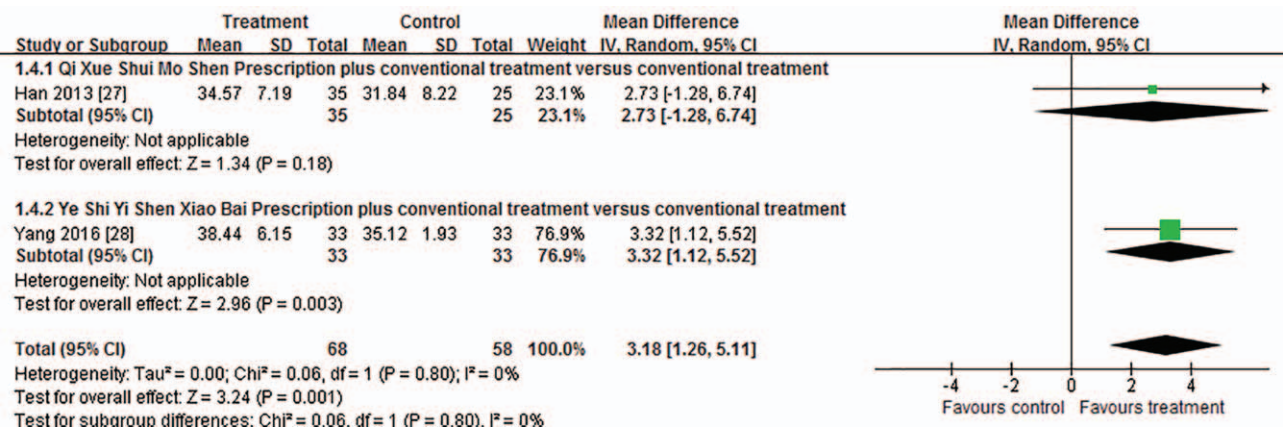

Figure 7. (analysis 1.4): Comparison. Chinese medicinal herbs plus conventional treatment versus conventional treatment: outcome 4 Alb.
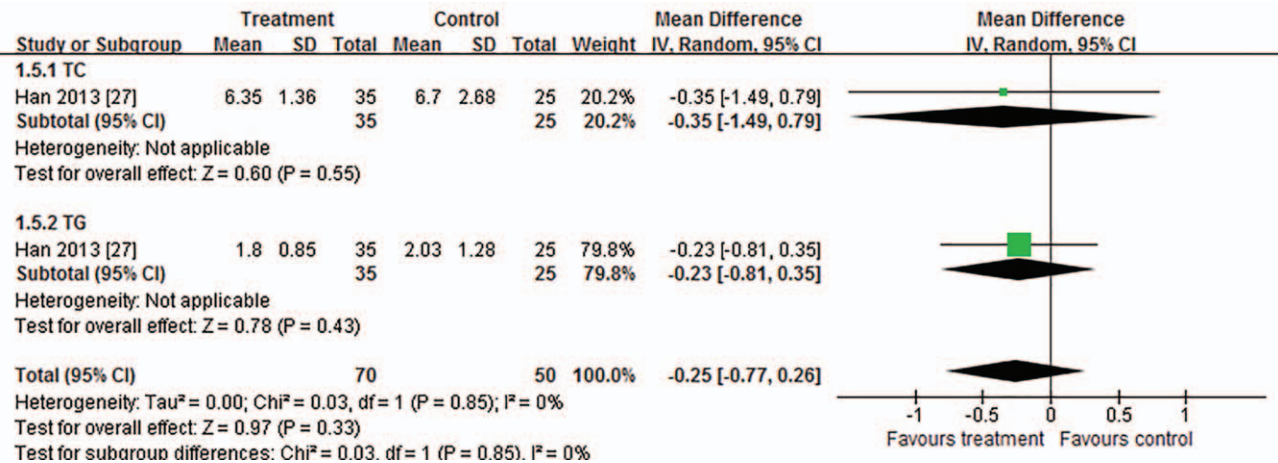
Figure 8. (analysis 1.5): Comparison. Chinese medicinal herbs plus conventional treatment versus conventional treatment: outcome 5 Blood lipid level (TC and TG).
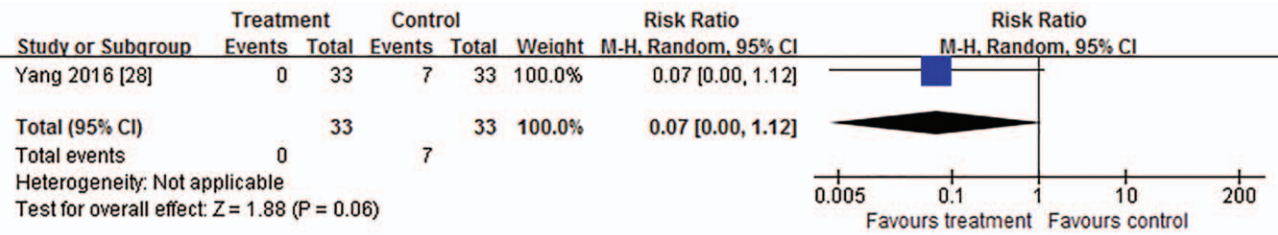

Figure 9. (analysis 1.6): Comparison. Chinese medicinal herbs plus conventional treatment versus conventional treatment: outcome 6 Relapse.

Table 3

GRADE quality of evidence.

Chinese medicinal herbs plus conventional treatment versus conventional treatment for idiopathic membranous nephropathy in adults patients

Patient or population: patients with idiopathic membranous nephropathy in adults patients
Settings: inpatients or outpatients
Intervention: Chinese medicinal herbs plus conventional treatment versus conventional treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Chinese medicinal herbs plus conventional treatment versus conventional treatment				
Total effective rate	Study population		RR 1.09 (0.92 to 1.29)	126 (2 studies)	⊕⊕⊖⊖ low[1,2]	Important
	828 per 1000	902 per 1000 (761 to 1000)				
	Moderate 834 per 1000	909 per 1000 (767 to 1000)				
Kidney function (SCr and BUN)		The mean kidney function (scr and bun) in the intervention groups was 0.09 lower (0.52 lower to 0.34 higher)		252 (2 studies)	⊕⊕⊖⊖ low[1,2]	Important
24-h UTP		The mean 24-h utp in the intervention groups was 1.57 lower (4.64 lower to 1.49 higher)		126 (2 studies)	⊕⊖⊖⊖ very low[1,2,3]	Important
Alb		The mean alb in the intervention groups was 3.18 higher (1.26 to 5.11 higher)		126 (2 studies)	⊕⊖⊖⊖ very low[1,2,3]	Important
Blood lipid level						Important

(continued)

Table 3

(continued).

Chinese medicinal herbs plus conventional treatment versus conventional treatment for idiopathic membranous nephropathy in adults patients

Patient or population: patients with idiopathic membranous nephropathy in adults patients
Settings: inpatients or outpatients
Intervention: Chinese medicinal herbs plus conventional treatment versus conventional treatment

| Outcomes | Illustrative comparative risks[*] (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
	Assumed risk Control	Corresponding risk Chinese medicinal herbs plus conventional treatment versus conventional treatment				
		The mean blood lipid level in the intervention groups was 0.25 lower (0.77 lower to 0.26 higher)		120 (1 study)	⊕⊕⊝⊝ low[1,4]	
Relapse	Study population		RR 0.07 (0 to 1.12)	66 (1 study)	⊕⊕⊝⊝ low[4,5]	Important
	280 per 1000	14 per 1000 (0 to 227)				
	Moderate					
	280 per 1000	14 per 1000 (0 to 227)				

[*] The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect. Handbook description: randomized controlled trial.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Cochrane Handbook description: relegation randomized controlled trial.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Cochrane Handbook description: two or more degradation factors of randomized controlled trials.

Very low quality: We are very uncertain about the estimate. Cochrane Handbook description: more than three degradation factors of randomized controlled trials.

Reduce the evidence quality factors: methodology defect, included in the research results of the inconsistency, indirect evidence, inexactness, and publication bias.

Increase the level of evidence factor: large effect quantity, confounding factors cannot change effect quantity, or the existing concentration-response relationship.

[1] There is high risk of performance bias.

[2] Only two studies included.

[3] One study showed a significant difference, but one study showed no significant difference.

[4] Only one study included.

Acknowledgments

Author contributions

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References

[1] Choi JY, Kim DK, Kim YW, et al. The effect of mycophenolate mofetil versus cyclosporine as combination therapy with low dose corticosteroids in high-risk patients with idiopathic membranous nephropathy: a multicenter randomized trial. J Korean Med Sci 2018;33:e74.

[2] Naumovic R, Pavlovic S, Stojkovic D, Basta-Jovanovic G, Nesic V. Renal biopsy registry from a single centre in Serbia: 20 years of experience. Nephrol Dial Transpl 2009;24:877–85.

[3] Hou JH, Zhu HX, Zhou ML, et al. Changes in the Spectrum of kidney diseases: an analysis of 40,759 biopsy-proven cases from 2003 to 2014 in China. Kidney Dis (Basel) 2018;4:10–9.

[4] Tang Z, Wang Y, Tao L, Guo Y, Zheng Y, Zheng D. Correction to: the elevated levels of urinary angiotensinogen are correlated with the severity of idiopathic membranous nephropathy. BMC Nephrol 2019;20:50.

[5] Radice A, Trezzi B, Maggiore U, et al. Clinical usefulness of autoantibodies to M-type phospholipase A2 receptor (PLA2R) for monitoring disease activity in idiopathic membranous nephropathy (IMN). Autoimmun Rev 2016;15:146–54.

[6] Liu S, Li X, Li H, Liang Q, Chen J, Chen J. Comparison of tripterygium wilfordii multiglycosides and tacrolimus in the treatment of idiopathic membranous nephropathy: a prospective cohort study. BMC Nephrol 2015;16:200.

[7] Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med 1993;329: 85–9.

[8] Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol 2007;18:1899–904.

[9] Cortazar FB, Leaf DE, Owens CT, Laliberte K, Pendergraft WF, Niles JL. Combination therapy with rituximab, low-dose cyclophosphamide, and prednisone for idiopathic membranous nephropathy: a case series. BMC Nephrol 2017;18:44.

[10] Lin L, Wang WM, Pan XX, et al. Biomarkers to detect membranous nephropathy in Chinese patients. Oncotarget 2016;7:67868–79.

[11] Pan X, Xu J, Ren H, et al. Changing spectrum of biopsy-proven primary glomerular diseases over the past 15 years: a single-center study in China. Contributions to nephrology 2013;181:22–30.

[12] Xu J, Hu X, Xie J, Chen N. Management of membranous nephropathy in Asia. Kidney Dis (Basel) 2015;1:119–25.

[13] Alwahaibi NY, Alhabsi TA, Alrawahi SA. Pattern of glomerular diseases in Oman: a study based on light microscopy and immunofluorescence. Saudi J Kidney Dis Transpl 2013;24:387–91.

[14] Chang JH, Kim DK, Kim HW, et al. Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. Nephrol Dial Transplant 2009;24:2406–10.

[15] Hanko JB, Mullan RN, O'Rourke DM, McNamee PT, Maxwell AP, Courtney AE. The changing pattern of adult primary glomerular disease. Nephrol Dial Transplant 2009;24:3050–4.

[16] Xie J, Chen N. Primary glomerulonephritis in mainland China: an overview. Contrib Nephrol 2013;181:1–11.

[17] Li SJ, Guo JZ, Zuo K, et al. Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome – a prospective study. Thrombosis Research 2012;130:501–5.

[18] Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide) lines–application to the individual patient. Kidney Int 2012;82:840–56.

[19] Praga M, Barrio V, Juarez GF, Luno J, Grupo Espanol de Estudio de laNefropatia M. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. Kidney Int 2007;71:924–30.

[20] Li XY, Lv R, He Q, et al. Early initiation of tacrolimus or cyclophosphamide therapy for idiopathic membranous nephropathy with severe proteinuria. J Nephrol 2008;21:584–91.

[21] Segarra A, Vila J, Pou L, et al. Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. Nephrology Dialysis Transplantation 2002;17:655–62.

[22] Nowack R, Birck R. Complementary and alternative medicine is popular among chronic renal failure patients—renal teams must increase their competence to advise patients with respect to efficacy and safety. Evidence-Based Nursing 2012;15:29–30.

[23] Zhang YW, Wu CY, Cheng JT. Merit of Astragalus polysaccharide in the improvement of early diabetic nephropathy with an effect on mRNA expressions of NF-kappaB and IkappaB in renal cortex of streptozotoxin- induced diabetic rats. J Ethnopharmacol 2007;114:387–92.

[24] Zhang ZH, Vaziri ND, Wei F, Cheng XL, Bai X, Zhao YY. An integrated lipidomics and metabolomics reveal nephroprotective effect and biochemical mechanism of Rheum officinale in chronic renal failure. Sci Rep 2016;6:22151.

[25] Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available at: www.cochrane-handbook.org.

[26] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. BMJ 2003;327:227–60.

[27] Han DY, Zhao C, Rao XR, Wang L, Zhang GH, Zhan YL. The treatment from gas blood water for idiopathic membranous nephropathy clinical observation. Chinese Journal of Basic Medicine in Traditional Chinese Medicine 2013;19:1311–3.

[28] Yang YC, Wang CL, Li J, Ma H, Ma BM. Replenishing the kidney and eliminating urinary protein prescription for idiopathic membranous nephropathy observation of curative effect. Shanxi Journal of Traditional Chinese Medicine 2016;37:1140–1.