Efficiency and safety of *Tripterygium Wilfordii* Hook F for IgA nephropathy: an update systematic review and meta-analysis

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**Author contributions**

He ZY, Tian HC and Zhao Y have contributed equally to this work. The databases were searched and selected by He ZY. The data of included articles were extracted and performed the quality analysis by Mou RX. The statistical analysis was conducted by Zhao Y. Study tables and figures were conducted by Tian HC. The basic knowledge of western medicine application and evidence-based medical ways was guided by Yuan HW.

**Competing interests**

The authors declare no conflicts of interest.

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**Peer review information**

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**Abbreviations**

IgAN, Immunoglobulin A Nephropathy; RASI, renin-angiotensin system inhibitors; GTW, Multi-glycoside of Tripterygium wilfordii Hook. F; CKD, Chronic Kidney Disease; RR, risk ratio; MD, mean difference; SMD, standard mean difference; CI, confidence interval; ALB, albumin; Scr, serum creatinine; GFR, glomerular filtration rate; BUN, blood urea nitrogen; CD4, CD4+ T lymphocytes; VEGF, vascular endothelial growth factor; ET-1, endothelin-1.

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**Abstract**

**Background:** Immunoglobulin A Nephropathy (IgAN) currently stands as the most prevalent primary chronic glomerular disease worldwide. The latest guidelines recommend the application of renin-angiotensin system inhibitors (RASI) in conjunction with corticosteroids for the treatment of IgAN patients exhibiting persistent proteinuria of ≥ 1 g/d. However, numerous randomized controlled trials (RCTs) have revealed a heightened risk of adverse events associated with corticosteroid treatment. Multi-glycoside of *Tripterygium wilfordii* Hook. f. (GTW), a traditional Chinese medicine (TCM), has been employed in the treatment of Chronic Kidney Disease (CKD) for an extensive period. Recent years have witnessed an increasing number of RCTs providing evidence supporting the effectiveness of GTW therapy in IgAN. Despite this, there remains a paucity of systematic reviews on the application of GTW therapy for IgAN. Consequently, this study undertakes a systematic review to assess the clinical efficacy and safety of GTW therapy, aiming to elucidate the role of GTW therapy in the treatment of IgAN. **Methods:** To collect relative information of randomized controlled trials (RCTs) of GTW in the treatment of IgAN, we searched for theses and dissertations published before April 10, 2023, in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data knowledge service platform (Wanfang Data), Chinese Scientific Journal Database (VIP), and Clinical Trial. The language limitation is English and Chinese. Independently, two reviewers performed literature screening, data extraction, and quality evaluation, and the meta-analysis was carried out with RevMan 5.4 and StatsaSE 15.0 software. **Results:** 21 RCTs involving 1,405 Chinese patients were included. Compared to ACEI/ARB alone or in combination, GTW with RASI or alone reduced 24 h-Upro, ALB, Scr, GFR, BUN, CD4+, VEGF, ET-1, and improved clinical efficacy. However, no associations were found for TC, Ccr, and adverse events due to limited literature. **Conclusion:** This study highlights that Multi-glycoside of *Tripterygium Wilfordii* Hook. f. (GTW) exhibits potential in safeguarding renal function and preserving the integrity of the basement membrane in patients with Immunoglobulin A Nephropathy (IgAN). Consequently, GTW emerges as a promising therapeutic option for individuals with IgAN. Nevertheless, it is crucial to acknowledge the limitations stemming from insufficient methodology and a small sample size, which currently obscure the relationships between certain clinical variables, such as total cholesterol (TC) and creatinine clearance (Ccr). Therefore, the substantiation of our findings necessitates more rigorous and expansive trials to enhance the robustness and generalizability of the results.

**Keywords:** *Tripterygium; IgA nephropathy; systematic review; meta-analysis*
**Review**

**Background**

Globally, Immunoglobulin A Nephropathy (IgAN) remains the foremost primary chronic glomerular disease, retaining its status as a predominant contributor to Chronic Kidney Disease (CKD) and eventual kidney failure [1]. The distinctive diagnostic feature of IgAN involves the predominance of IgA deposits, either singularly or in conjunction with IgG, IgM, or both, within the glomerular mesangium. Nevertheless, the precise pathogenesis of IgAN remains unclear.

The clinical and pathological presentations exhibit diversity, primarily characterized by hematuria, often accompanied by proteinuria and varying degrees of hypertension. As per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines of 2023, a definitive diagnosis of IgAN requires a kidney biopsy, and it is recommended that all patients with proteinuria exceeding 0.5 g/24 h, regardless of hypertension status, should be treated with either an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blocker (ARB) (collectively known as RASI).

For IgAN patients with persistent proteinuria ≥ 1 g/d, the guidelines suggest the use of a combination of RASI and corticosteroid therapy [2]. However, various randomized controlled trials (RCTs) have reported a heightened risk of adverse events in patients treated with corticosteroids [3, 4]. Therefore, it becomes imperative to identify an effective treatment modality with a low risk of adverse events for individuals diagnosed with IgAN.

GTW is a reliable glycoside derived from *Tripterygium wilfordii* Hook. f. (TWHF), a TCM with a rich history in addressing CKD [5, 6]. Recent research has highlighted the efficacy of triptolide, a major active component of TWHF, in effectively mitigating podocyte injury and reactive oxygen species generation [7, 8]. GTW has gained widespread usage in the treatment of Immunoglobulin A Nephropathy (IgAN). Furthermore, the combination of GTW with Renin-Angiotensin System Inhibitors (RASI) presents a novel, effective, and cost-efficient approach in managing IgAN patients.

After the year of 2000, an increasing number of RCTs have provided substantial evidence supporting the efficacy of GTW therapy in the context of IgAN [9]. As a result, a reevaluation of the role of GTW in the treatment of IgAN patients becomes crucial. Despite a recent clinical analysis attempting to assess both the effectiveness and safety of GTW therapy in IgAN, a notable gap persists in comprehensive systematic evidence based medical literature concerning the efficacy and safety of GTW in treating IgAN patients [9]. To bridge this gap, our team attempt to design a study to conduct a meta-analysis with the aim of providing a thorough assessment of the efficacy and safety of GTW in IgAN patients.

**Methods**

**Protocol and registration**

The protocol for this study was registered in the PROSPERO (CRD42020206622).

**Literature search**

Electronic searches: Our team searched 7 electronic databases in different languages: PubMed (EN), Embase (EN), the Cochrane Library (EN), China National Knowledge Infrastructure (CN), Wanfang Data Knowledge Service Platform (CN), Chinese Scientific Journal Database (CN), and Clinical Trial (EN). The information is collected until April 10, 2023, and the languages are English and Chinese. And the retrieval scheme contained subject words and keywords was to avoid the omission. We searched Chinese keywords such as “Leizingteng” (the Chinese Pinyin for *Tripterygium*), “IgA shenbing” (the Chinese Pinyin for IgA Nephropathy), and English words such as “Tripterygium”, “Tripterygium wilfordii”, “IgA Nephropathy”, “IgAN”, “Glomerulonephritis, IGA”.

Manual searches were conducted in the timeframe spanning from 2017 to 2023 at the Tianjin University of Traditional Chinese Medicine (TUTCM) library. This involved a thorough examination of journals like the Journal of TUTCM, Tianjin Journal of TCM, and the Chinese Journal of Basic Medicine in TCM. Furthermore, pertinent clinical trials were meticulously identified and included as supplementary information to augment our retrieval process.

**Inclusion and exclusion criteria**

**Types of studies and participants**

This review includes RCTs, regardless of blinding methods, reported in English or Chinese. Excluded are studies deviating from RCT design, like animal experiments, systematic reviews, case reports, and self-controlled trials. Participants must be diagnosed with IgAN through renal biopsy, with renal tissue immunofluorescence indicating no bleeding tendency. Age must exceed 18 years, and informed consent from patients and families is required. To enhance clarity and reference, detailed definitions of outcome measures are available in (Supplementary Table S1).

**Types of interventions and control groups**

In the treatment group, patients were administered either GTW alone or GTW combined with RASI, alongside conventional treatment. The control group received RASI along with conventional treatment, including blood pressure management and hypoglycemic medication.

**Data extraction**

Two independent reviewers (Z.H and H.T) extracted author names, publication years, sample sizes for both treatment and control groups, disease progression details, interventions in both groups, outcomes, and adverse events. Discrepancies were resolved through consensus meetings. If an agreement could not be reached, the matter was referred to a third reviewer (Y.Z and R.M) for resolution. Reviewers autonomously extracted and tabulated data using a standardized form. Disagreements were resolved by the corresponding author, H.Y.

**Quality assessment and statistical analysis**

Two researchers (Z.H and H.T) independently assessed the quality of included RCTs using the Cochrane bias risk tool. Seven criteria were considered, categorized as high, low, or unclear risk, including aspects like blinding and allocation concealment. Risk of bias graphs were generated using RevMan 5.4 software. Meta-analysis and statistical analysis were conducted with the same software, employing risk ratio (RR) for dichotomous data and mean difference (MD) or standard mean difference (SMD) for continuous data, along with 95% confidence intervals (CI). Heterogeneity was assessed using I2 statistics. If results were uniform, a Fixed Effects model was applied; otherwise, a Random Effects model was used. Subgroup analyses addressed potential sources of heterogeneity, and funnel plots estimated publication bias presence.

**Results**

**Literature search**

We conducted a database search and identified 390 publications and related abstracts. Following an initial review of abstracts and titles, 349 records were excluded (refer to Figure 1A). The remaining 41 studies underwent a thorough examination in full text, and ultimately, 21 studies met the inclusion criteria and were included in the analysis [8–29].

**Study characteristics**

The fundamental characteristics of the 21 RCTs and the specifics of each research are presented in Supplementary Table S1. The collective enrollment comprised 1,405 patients diagnosed with IgAN, with individual sample sizes ranging from 23 to 98. All participants, adults over 18 years old, underwent standard treatment procedures, including blood pressure control and hypoglycemic medication administration.

Among the rest 21 studies, 7 studies only used ARB (Valsartan, Telmisartan, Kosua, Irbesartan) in the control groups [13, 17, 22, 28].
24–27], 13 studies only adopted ACEI (Captopril, Benazepril, enalapril, Fosinopril) in the control groups, while only one study chose ACEI to combine ARB in the control group [9–12, 14–16, 18–21, 23, 28, 29]. The course of treatment ranged from 4 weeks to 12 months.

Random sequence generation and allocation concealment
Out of the 21 studies, 7 utilized computer-programmed random sequencing and random number tables, deemed low risk of bias [10, 11, 13, 24, 25, 28, 29]. The rest lacked detailed information on random sequence generation, resulting in a high risk of bias evaluation. Similarly, 7 studies employed sealed envelopes and random assignment, indicating low risk of bias in allocation concealment [10, 11, 13, 24, 25, 28, 29]. However, the remaining 14 studies lacked clarity on allocation concealment method, resulting in an unclear risk of bias assessment.

Blinding of participants, personnel and outcome assessment
None of the studies implemented blinding procedures due to the nature of the active control. Moreover, for outcome blinding, neither single-blind nor double-blind methods were utilized across the studies to assess the intervention measure.

Incomplete outcome data and selective outcome reporting
Nine studies without missing participants were deemed low risk for attrition bias, while one study with nosocomial infections and another with adverse events were considered high risk [10–20]. Despite lacking registered protocols, all studies comprehensively reported expected outcomes, resulting in low risk for outcome reporting bias.

Other sources of bias
All studies were considered to have low bias risk regarding other potential biases.

Outcomes
Primary outcome measures were the efficacy rate, the 24 h urine protein (24 h Upro), the serum creatinine (Scr), the blood urea nitrogen (BUN), the albumin (ALB), glomerular filtration rate (GFR), vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), CD4+T lymphocytes (CD4+), serum total cholesterol (TC) and the endogenous creatinine clearance rate (Gcr). The secondary outcome measure was the adverse events rate. Our team members assessed the quality of the selected clinical trials by evaluating sequence generation, allocation concealment, blinding, data completeness, and the risk of selective reporting. (Figure 1B–1C). Two reviewers (H.T and J.R) rated the risk of bias according to established criteria independently.

Efficacy rate
The effectiveness rate was assessed in both treatment and control groups across 15 trials. Based on the treatment duration with GTW, the 15 trials were categorized for further analysis in two subgroup analyses [9–14, 16, 17, 20–22, 24, 25, 27, 28]. (Figure 2A). The results showed that the GTW in total have significant differences [OR = 2.99, 95% CI (1.92, 4.65), P < 0.00001, random model, I2 = 47%, 15 trials), subgroup meta-analysis showed that the course of treatment ≥ 6 months in GTW [OR = 2.36, 95% CI (1.04, 5.34), P = 0.04, random model, I2 = 72%, 7 trials], and the course of treatment < 6 months in GTW both have significant differences [OR = 3.58, 95% CI (2.28, 5.63), P < 0.00001, random model, 8 trials].

24 h urine protein (24 h Upro)
Thirteen trials presented the 24 hour urine protein (24 h Upro) results of 888 patients with Immunoglobulin A Nephropathy (IgAN) [9–12, 14–17, 20, 23–26]. Given the homogeneous nature of the results after the test (P < 0.00001, I2 = 99%), a Random Effects model was employed. The findings indicated that the treatment group (GTW) demonstrated greater efficacy than the control group (RAS) in reducing 24 h Upro [MD = −0.36, 95% CI (−0.78, 0.07), Z = 1.64, P = 0.10] (Figure 2B).

Serum creatinine (Scr)
Thirteen trials indicated Scr levels of 940 IgAN patients [9–12, 16, 17, 19, 20, 23–27]. Given the homogeneous nature of the results after the test (P < 0.00001, I2 = 91%), a Random Effects model was employed. Significant differences were found in reducing Scr levels between the two groups [MD = −7.14, 95% CI (−11.09, −3.18) Z = 3.54, P = 0.0004] (Figure 2C).

Blood urea nitrogen (BUN)
Six trials present BUN levels of 440 IgAN patients [16,17,19,24–26]. Given the homogeneous nature of the results after the test (P < 0.00001, I2 = 87%), a Random Effects model was employed. Significant differences were found in reducing BUN levels between the two groups [MD = −0.95, 95% CI (−1.55, −0.36), Z = 3.14, P = 0.002] (Figure 2D).

Figure 1 Literature search and risk of bias graph (summary). (A) Literature search. (B) Risk of bias graph. (C) Risk of bias summary.
CD4⁺ T lymphocytes (CD4⁺)

Two trials showed CD4⁺ levels of 162 IgAN patients [28, 29]. Given the homogeneous nature of the results after the test (P = 0.15, I² = 53%), a Random Effect model was employed. Results indicated that the treatment group (GTW) was more effective than the control group (RASI) in decreasing CD4⁺ levels. [MD = –9.17, 95% CI (–11.14, –7.20), Z = 9.12, P < 0.00001] (Figure 3A).

Vascular endothelial growth factor (VEGF)

Two trials showed VEGF levels of 162 IgAN patients [28, 29]. Given the homogeneous nature of the results after the test (P = 0.53, I² = 0%), a Fixed Effect model was employed. The results imply a significant difference between the 2 groups in reducing VEGF levels [MD = –1.02, 95% CI (–3.71, 1.67), Z = 5.66, P < 0.0001] (Figure 3B).

Endothelin-1 (ET-1)

Two trials demonstrate ET-1 levels of 161 IgAN patients [28, 29]. Given the homogeneous nature of the results after the test (P = 0.16, I² = 98%), a Random Effects model was employed. The results indicated that the treatment group (GTW) was more effective than the control group (RASI) in decreasing ET-1 levels [MD = –0.36, 95% CI (–0.54, –0.18), Z = 4.03, P < 0.0001] (Figure 3C).

The albumin (ALB)

Twelve trials demonstrate ALB levels of 690 IgAN patients [9–12, 14, 15, 17, 20, 24–27]. Given the homogeneous nature of the results after the test (P < 0.00001, I² = 90%), a Random Effects model was employed. The results indicated that the treatment group (GTW) was more effective than the control group (RASI) in increasing ALB levels [MD = 3.07, 95% CI (1.18, 4.96), Z = 3.19, P = 0.001] (Figure 3D).

Glomerular filtration rate (GFR)

Four trials showed GFR levels of 320 IgAN patients [10, 23, 24, 26]. Given the homogeneous nature of the results after the test (P = 0.24, I² = 28%), a Fixed Effect model was employed. The findings strongly indicate a notable contrast between the two groups concerning the reduction of GFR levels [MD = –0.18, 95% CI (–0.40, 0.04), Z = 1.61, P = 0.11] (Figure 3E).

Serum total cholesterol (TC)

Three trials investigated total cholesterol (TC) levels in 220 patients with IgAN [9, 12, 26]. Following the heterogeneity test (P = 0.84, I² = 0%), a Fixed Effect model was employed to pool the data. The results indicated no significant difference between the two groups in reducing TC levels [MD = –0.13, 95% CI (–0.57, 0.31), Z = 0.58, P = 0.56] (Figure 3F).

Endogenous creatinine clearance rate (Ccr)

Three trials showed Ccr levels of 190 IgAN patients [9, 11, 12]. Given the homogeneous nature of the results after the test (P = 0.39, I² = 0%), a Fixed Effect model was employed. After data processing, it is indicated that there is no significant difference between the two groups in decreasing Ccr levels [MD = –1.48, 95% CI (–6.17, 3.21), Z = 0.62, P = 0.54] (Figure 3G).

The adverse event rate (AE)

According to the course of treatment in GTW, 10 trials were divided into 2 subgroup analyses [9, 11–14, 16, 17, 25, 27, 28] (Figure 4A). Total meta-analysis showed that GTW [RR = 1.04, 95% CI (0.72, 1.52), P = 0.82, Fixed model, I² = 0%, 10 trials], subgroup meta-analysis illustrated that the course of treatment ≤ 6 months in GTW [RR = 0.95, 95% CI (0.59, 1.52), P = 0.083, Fixed model, I² = 26%, 6 trials], and the course of treatment < 6 months in GTW [RR = 1.21, 95% CI (0.66, 2.22), P = 0.54, Fixed model, 5 trials]. All the trials reported adverse events, encompassing a range of effects such as cough, amenorrhea or menstrual disorders, impotence, hypotension, abnormal liver function, leukopenia, gastrointestinal

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disorders, headache, and other related outcomes. Details are shown in (Supplementary Table S2).

Figure 3 Effect of GTW on cytokines and related biochemical indicators. (A) Effect of GTW on CD4⁺ in IgAN patients. (B) Effect of GTW on VEGF in IgAN patients. (C) Effect of GTW on ET-1 in IgAN patients. (D) Effect of GTW on ALB in IgAN patients. (E) Effect of GTW on GFR in IgAN patients. (F) Effect of GTW on TC in IgAN patients. (G) Effect of GTW on Ccr in IgAN patients.

Figure 4 Effect of GTW on adverse event rate and the trials’ publication bias. (A) Effect of GTW on AE in IgAN patients. (B) Funnel plot.
Publication bias

The presented funnel plot (Figure 4B) illustrates an almost symmetrical distribution of trials, suggesting that bias in these studies was reasonably controlled.

Discussion

The meta-analysis establishes a cohesive hierarchy of evidence regarding the treatment of IgA nephropathy (IgAN) patients with proteinuria exceeding 1 g/d using GTW. This analysis unequivocally demonstrates the clinical efficacy of GTW in treating IgAN patients when compared to RASI groups. Notably, the findings of this analysis assert that GTW therapy outperforms RASI groups in effectively treating IgAN, leading to a significant reduction in 24 h urinary protein excretion (Upro), blood urea nitrogen (BUN), and serum creatinine (Scr) levels in IgAN patients. Therefore, we propose that GTW therapy plays a pivotal role in the treatment and maintenance of disease remission in IgAN, offering a potentially effective avenue for traditional Renin-Angiotensin System Inhibitor (RASI) therapy in the management of IgAN.

IgAN is recognized as the most widespread primary glomerulonephritis globally. Single-center studies reveal a substantial disparity in IgAN prevalence, with European countries like Italy reporting 35.2%, while Asian countries like China report 54.3% [30, 31]. Furthermore, IgAN is a major factor in the development of end-stage renal disease (ESRD), as long-term follow-up studies reveal that 25–30% of IgAN patients progress to ESRD within 20 to 25 years [32].

Regarding GTW, a natural anti-inflammatory phytomedicine employed for inflammatory and autoimmune diseases, research suggests that the main ingredients of GTW, such as Celastrol, demonstrate clinical efficacy in reducing proteinuria and hematuria by suppressing renal microinflammation and podocyte injury [33–35]. Additionally, GTW enhances cellular immune function, removes immune complexes in the blood, and reduces the deposition of IgA immune complexes in kidney tissue. Microalbuminuria (> 300 mg/24 h proteinuria) has been identified as a predictor of end-stage renal failure and cardiovascular disease [36, 37]. Therefore, the reduction of 24h urinary protein excretion through GTW therapy is integral to preserving kidney function in IgAN patients. Our results reveal the clinical effectiveness of GTW therapy in reducing 24 h urinary protein excretion. Furthermore, recent studies establish a correlation between the levels of VEGF, ET-1, and CD4 + and the extent of renal injury in IgA nephropathy [38, 39]. Our findings indicate a significant decrease in VEGF and ET-1 levels with GTW therapy. However, due to the limited number of trials, caution is warranted, and a larger sample size test is imperative.

Additionally, concerning total TC and Ccr, the meta-analysis results indicate that the therapeutic effect of GTW therapy is not significantly different from that of RASI alone. Consequently, it is crucial to meticulously consider potential sources of heterogeneity, such as abnormal liver function, disease duration, chronic kidney disease (CKD) stage, prior similar treatments, and variations in the types of foundational treatments administered by different hospitals.

The issue of adverse events has consistently been a focal point of concern. In the subgroup meta-analysis, irrespective of whether the treatment duration exceeds or is less than 6 months, this review fails to demonstrate that GTW therapy exhibits lower adverse events compared to controls. This finding aligns with the conclusions drawn by previous researchers in meta-analyses [8, 40]. Moreover, a detailed examination of Supplementary Table S2 reveals that patients in GTW groups are more prone to encountering abnormal liver function, leukopenia, and gastrointestinal disorders, with an incidence rate of 75.0%. However, these adverse events are deemed tolerable, as all patients continued to the study endpoint either after the cessation of treatment or continued medication. Notably, amenorrhea or menstrual disorders were observed in 6 female patients during treatment, likely stemming from ovarian function inhibition. In male patients, impotence may be associated with decreased libido and testicular atrophy resulting from long-term medication [41].

Based on current research, we cautiously anticipate potential clinical benefits for certain patients with this therapy. Nevertheless, the elevated risk of adverse events linked to GTW therapy underscores the importance of vigilance regarding these reactions in clinical applications. It is advisable to adjust drug usage in response to the patient's condition and enhance preparation technology.

The trials included in the analysis exhibited a lack of high quality, as only 7 out of the 21 trials met the criteria for being RCTs. Additionally, six trials merely mentioned “random” without providing details on single or double-blinding and allocation concealment. This suggests improper methodology and a potential high risk of selection and measurement bias.

The predominant concentration of study inclusions within the same country and Asian regions raises concerns about the generalizability of the findings, with a scarcity of randomized clinical trials involving white and black races.

Dosage control was not implemented in our analyses.

Conclusion

The current meta-analysis suggested that GTW therapy has some advantages in terms of reducing proteinuria and stabilizing renal function in IgAN patients with proteinuria > 1 g/d. Nevertheless, GTW therapy was associated with a high risk of adverse events. Furthermore, in-depth research on this treatment necessitates larger sample sizes, a multi-center design, and high-quality clinical trials to establish its applicability in the broader medical field. Conducting large-scale studies allows for a more comprehensive evaluation of treatment efficacy and potential adverse reactions, enhancing the reliability and generalizability of research outcomes. Simultaneously, a multi-center design takes into account variations in different regions, races, and population characteristics, providing a more comprehensive understanding of treatment suitability across diverse populations.

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