Clinical Effect of Tripterygium Glycosides Combined with Glucocorticoids in the Treatment of Refractory Nephrotic Syndrome Patients: A Systematic Review and Meta-Analysis

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Abstract

The objective of this study is to evaluate the effectiveness and safety of *Tripterygium* glycosides combined with glucocorticoids for the treatment of refractory nephrotic syndrome (NS). Computer search of Chinese and English databases, including CNKI, VIP, Wan Fang Database, PubMed, Cochrane Library, Embase, and Sinomed, for randomized controlled trials (RCTs) of *Tripterygium* glycosides combined with glucocorticoids for refractory NS (RNS) was conducted. Meta-analysis was performed using RevMan 5.3. Thirteen RCTs comprising 994 patients were included in the study. *Tripterygium* glycosides combined with glucocorticoids had a statistical significance on the effective rate (odds ratio [OR] = 4.69, 95% confidence interval [CI] 3.29, 6.67, P < 0.0001), 24-h urine protein (Weighted mean difference (MD) = −0.57, 95% CI [−0.62, −0.51], P = 0.00001), serum albumin (MD = 4.77, 95% CI [4.30, 5.24], P < 0.00001), total serum protein (MD = 9.45, 95% CI [8.73, 10.17], P < 0.00001), urea nitrogen (MD = −0.53, 95% CI [−0.90, −0.17], P = 0.005), and serum creatinine (MD = −8.45, 95% CI [−15.32, −1.57], P = 0.02). There was no statistical significance on adverse reactions (OR = 0.68, 95% CI [0.41, 1.12], P = 0.13). *Tripterygium* glycosides combined with glucocorticoids could improve clinical effective rate, reduce 24-h urine protein, improve serum albumin and total serum protein, and reduce urea nitrogen and serum creatinine levels in patients with RNS. However, the quality of the included literature is poor, and conclusion still needs further verification using larger samples and high-quality randomized, double-blind controlled trials.

Keywords: Glucocorticoids, meta-analysis, refractory nephrotic syndrome, *Tripterygium* glycosides

INTRODUCTION

Nephrotic syndrome (NS) is a group of clinical syndromes caused by a variety of glomerular diseases, about 75% caused by the primary glomerular disease primary NS (PNS); the main clinical manifestations are massive proteinuria (>3.5 g/24 h), hypoalbuminemia (<30 g/L), hyperlipidemia, and edema. The first two are essential for diagnosis. Secondary NS and hereditary diseases need to be excluded. In addition to meeting the diagnostic criteria of PNS, refractory NS (RNS) should be satisfied: (1) Hormone Resistance: The standardization treatment with hormones for 8 weeks (FSGS cases require 16 weeks) is still invalid; (2) Hormone Dependence: Hormone treatment remission in the hormone withdrawal process or within 14 days after withdrawal, NS recurrence; (3) Frequent Recurrence: Recurrence ≥2 times within 6 months after treatment remission or ≥3 times within 1 year. The prevalence of RNS is about 30%–50% in patients with PNS, and the renal damage is progressively aggravated. If the long-term large amounts of proteinuria are not well controlled, it can gradually develop into glomerular sclerosis and renal interstitial fibrosis, which eventually leads to end-stage kidney disease. This
imposes a great burden on families and society. Therefore, it is extremely urgent to find a practical treatment.

NS is mainly caused by abnormal immune-inflammatory reaction, which leads to glomerular injury. Hence, the main purpose of treatment is to suppress immune-inflammatory response, reduce glomerular damage, and delay the disease process. Glucocorticoids are still the preferred treatment strategy for RNS. They are generally combined with other immunosuppressive agents to enhance efficacy. However, the side effects are numerous, and the cost is high, the cycle is long, and difficult for an average family to accept. In recent years, Chinese medicine has made good progress in the prevention and treatment of RNS. Among them, Tripterygium wilfordii has attracted the attention of the majority of researchers. It was first recorded in “Shen Nong’s Herbal Classic.” It can control rheumatism and relieve pain. Li Leishi first discovered the effect of T. wilfordii in nephritis diseases in 1980, and after a large number of animal experiments and clinical validations, and clarified that its treatment range played a unique advantage in the treatment of RNS.

The combination of traditional Chinese and Western medicine is a major feature of the treatment of diseases in China. Chinese herbal medicine or its preparations combined with Western medicine in the treatment of RNS has played a huge role in reducing side effects and urine protein and improving hypoproteinemia. At present, research on Tripterygium preparations has become a hot topic, which has attracted the attention of researchers, home and abroad, but it also has its limitations. For example, the sample size is small and the single sample size research is hardly convincing. There is still an insufficient evidence-based basis for foreign promotion. Therefore, this study intends to conduct a meta-analysis of Tripterygium glycosides combined with glucocorticoid treatment of RNS, providing better evidence support for a wide range of clinical applications.

**METHODS**

**Search strategy**

The scope of the search included the following databases: CNKI, VIP Database, Wan Fang Data, PubMed, Cochrane Library, Embase, and Sinomed. The specific retrieval strategies are as follows: (1) “Tripterygium or Tripterygium glycosides or T. wilfordii;” (2) “NS or RNS;” (3) “Hormone or Glucocorticoids;” (4) 1 and 2 and 3. The time frame ranged from database construction to June 2019, and the search language was not limited.

**Inclusion criteria**

The following types of research studies were included: clinical randomized controlled trials (RCTs), with or without blind study designs. The subjects of the studies included patients who met the diagnostic criteria for RNS, including hormone-resistant, hormone-dependent, and frequently recurrent PNS. There were no requirements for age, gender, length of disease, and pathological type. The interventions for the experimental group were Tripterygium glycosides combined with glucocorticoids (including prednisone, etc.), while the control group was treated with glucocorticoids alone. Both included the basic treatment (low-salt and low-protein diet, antihypertensive, diuresis, anticoagulation, kidney preservation, etc.). The main research indicator was the effective rate. The secondary indicators were 24-h urine protein, serum albumin, total serum protein, urea nitrogen, serum creatinine, and adverse reactions.

**Exclusion criteria**

Exclusion criteria included the following: (1) Secondary NS, including lupus nephritis, purpural nephritis, genetic nephropathy, diabetic nephropathy, and so on; (2) non-RCTs, including semi-randomized and pseudo-randomized, incomplete data indicators, repeated income literature, retrospective studies, review studies, cell and animal experiments, and so on; and (3) the experimental group used nontripterygium preparations combined with glucocorticoids (including alkylating agents and other regimens), and the control group used nonglucocorticoids.

**Evaluation standard of curative effect**

According to the thematic discussion on the 7th National Conference on Nephrology of Integrated Traditional Chinese and Western Medicine, the Efficacy Judgment Criteria: (1) Complete remission: Multiple routine urine protein examinations were negative, urine protein <0.3 g/d, NS performance eliminated, normal renal function; (2) significant relief: Multiple 24 h urine protein determinations <1 g, serum albumin significantly improved, normal or near-normal renal function; (3) partial relief: Multiple routine urine protein determinations were reduced, 24 h urine protein <3 g, serum albumin was better than before, renal function improved; and (4) invalid: Urine protein and serum albumin levels were not significantly improved than before, the clinical manifestations of NS were not eliminated, and renal function was not improved.

**Methodology quality assessment**

The improved JADAD scale was used for quality evaluation: (1) Random sequence generation method, (2) random concealment method, (3) blind method, and (4) exit and withdrawal. Among them, 1–3 were divided into low-quality studies and 4–7 high-quality studies. The items recommended by Cochrane Assistance Network were used for bias risk assessment: (1) Random allocation program, (2) covert group, (3) blinded patients and doctors, (4) blinded result evaluation, (5) incomplete results data, (6) selective results report, and (7) other biases. These seven items were mainly evaluated from five aspects: Selection bias, implementation bias, measurement bias, loss of bias, and reporting bias. “Low risk” indicated low bias risk; “high-risk” indicated high bias risk; and “Unclear risk” indicated that the study did not provide sufficiently or provided uncertain information for the bias assessment, and finally drew the result as a bias risk map.

**Data extraction and analysis**

Two personnel screened independently; the first read the
title and abstract of the literature, excluded those that did not meet the inclusion and exclusion criteria, carefully read the full text of those who met the criteria, and further screened, according to the criteria. If there was any disagreement, it was discussed first. If it could not be resolved, it was evaluated by a third party. Then, author, year, sample size, experimental group, control group interventions, research indicators (effective rate, 24 h UTP, AL, TP, BUN, Cr, etc.), course of treatment, and adverse reaction information were extracted from the selected literature. Then, a data extraction form was created.

Statistical analyses
Meta-analysis was performed using RevMan5.3 software provided by the Cochrane collaboration network. Heterogeneity Analysis: Heterogeneity test, also known as the homogeneity test, generally used the Chi-Square test method to study heterogeneity. According to the analysis of $P$ value and $I^2$ value, if $P \geq 0.10$ and $I^2 \leq 50\%$, it meant that the homogeneity between the studies was good and should be analyzed by a fixed-effect model. If $P < 0.10$ and (or) $I^2 > 50\%$, it meant that there was heterogeneity between the studies and subgroup analysis, meta-regression, or sensitivity analysis were needed to find the source of the heterogeneity. If the source of heterogeneity was not clear, a random-effect model was used for analysis. The second categorical variable data used odds ratio (OR). If the unit and measurement method are the same, weighted mean difference was used. If they are different, standardized mean difference (normalized mean difference) was used. Confidence intervals (CI) were expressed as 95% CI. Publication bias analysis: Using the funnel plot analysis, the abscissa was the effect of the original study and the ordinate the sample size or standard error or precision of the original study. If it was a symmetrical funnel type, it was considered a small publication bias. If the pattern was asymmetrical or biased, it indicated that there was a high possibility of publication bias.

Results

Search results
A total of 219 articles were preliminarily retrieved. After initial screening and re-screening, a total of 13 RCTs were included [Figure 1].

Study description
A total of 13 RCTs were included,[5-17] published from 2002 to 2017, a total of 994 patients, including 504 in the experimental group and 490 in the control group. All the literatures mentioned that the baseline was comparable, and the course of treatment lasted 8–48 weeks [Table 1].

Quality assessment
The improved JADAD scale was used to assess the quality of the included studies. According to the improved JADAD scale, 10 articles scored 2 points, two scored 3, and one scored 1, all of which were low-quality literature [Table 2].

Bias risk assessment
Among the 13 articles included, only two used appropriate random methods, which had a low-risk bias, one article used the order of medical treatment and had a high-risk bias, while the other 10 articles only mentioned the use of random methods, but did not discuss them in detail, and the risk of bias was not clear. One of the literatures included did not use the blind method and the others did not describe the distributive concealment and blind method, which are high-risk biases. The outcome data of the 13 articles were complete. None of them described selective reports and other biases, and were not clear about the risks of bias [Figure 2].

Meta-analysis results
Effective rate
The heterogeneity index was $P = 0.97$ and $I^2 = 0\%$, indicating a small heterogeneity and the data were analyzed by a fixed-effect model. The results of the analysis were OR = 4.69, 95% CI (3.29, 6.67), and $P < 0.00001$, indicating that the Tripterygium glycoside combinations with hormones were more effective than hormone therapy alone.

![Figure 1: Flow chart of inclusion studies](image_url)
The difference between the two groups was statistically significant [Figure 3].

**Twenty-four-hour urine protein**

The heterogeneity analysis index ($P < 0.00001$ and $I^2 = 97\%$) indicates that the 24 h urine protein quantification data of 10 articles was relatively heterogeneous and a random-effects model was used to analyze the data. The results were $MD = -0.79, 95\% CI (-1.12, -0.47)$, and $P < 0.00001$, indicating that the 24 h urine protein quantitation in the *Tripterygium* glycosides combinations was lower than that of the hormone therapy alone. The difference between the two groups was statistically significant [Figure 5].

**Serum albumin**

The heterogeneity analysis index ($P = 0.18$ and $I^2 = 28\%$) indicates that the data heterogeneity of serum albumin in 11 articles was small, and the data were analyzed using a fixed-effect model. The results were $MD = -0.79, 95\% CI (-1.12, -0.47)$ and $P < 0.00001$, indicating that the serum albumin in *Tripterygium* glycoside combinations was lower than that in the hormone therapy alone. The difference between the two groups was statistically significant [Figure 6].

**Total serum protein**

The heterogeneity index ($P = 0.71$ and $I^2 = 0\%$) indicates

| Table 1: Basic content of the included studies |
|-----------------------------------------------|
| **Author** | **Years** | **Sample size (E/C)** | **Intervention** | **Control group** | **Course of treatment (week)** | **Adverse reactions (E/C)** |
|------------|-----------|-----------------------|-----------------|-------------------|-------------------------------|--------------------------|
| FDY        | 2014      | 48/48                 | Tripterygium glycosides + control | Prednisone + basic treatment | 12                            | 3/8                      |
| HJ         | 2015      | 50/50                 | Tripterygium glycosides + control | Prednisone + basic treatment | 48                            | Not described            |
| LQ         | 2017      | 41/41                 | Tripterygium glycosides + control | Prednisone + basic treatment | 24                            | 5/10                     |
| LY         | 2017      | 42/42                 | Tripterygium glycosides + control | Prednisone + basic treatment | 48                            | Not described            |
| LZH        | 2010      | 30/30                 | Tripterygium glycosides + control | Prednisone + basic treatment | 24                            | 3/2                      |
| PCM        | 2015      | 49/49                 | Tripterygium glycosides + control | Prednisone + basic treatment | 48                            | Not described            |
| TW         | 2014      | 15/15                 | Tripterygium glycosides + control | Prednisone                | 48                            | 2/6                      |
| WMH        | 2014      | 33/33                 | Tripterygium glycosides + control | Prednisone + basic treatment | 48                            | Not described            |
| WXX        | 2016      | 40/40                 | Tripterygium glycosides + control | Prednisone + basic treatment | 12                            | Not described            |
| XQY        | 2016      | 40/40                 | Tripterygium glycosides + glucocorticoid | Prednisone | 8                             | 1/4                      |
| YGF        | 2009      | 40/32                 | Tripterygium glycosides + control | Prednisone + basic treatment | 24                            | 13/Not described         |
| ZB         | 2016      | 44/44                 | Tripterygium glycosides + control | Prednisone + basic treatment | 48                            | 6/8                      |
| ZZH        | 2002      | 32/26                 | Tripterygium glycosides + control | Prednisone                | 36                            | 14/6                     |

| Table 2: Document quality evaluation form |
|-------------------------------------------|
| **Author** | **Years** | **Random sequence generation method** | **Random concealment method** | **Blind method** | **Exit and withdrawal** | **Incomplete results data** | **Incomplete results report** | **Selective results report** | **Other biases** | **Improved JADAD scale score** |
|------------|-----------|-----------------------------------|-------------------------------|-----------------|------------------------|-----------------------------|-------------------------------|-----------------------------|-----------------|-------------------------------|
| FDY        | 2014      | Unclear                           | Unclear                       | No blinding     | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| HJ         | 2015      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| LQ         | 2017      | Random number tables              | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 3                             |
| LY         | 2017      | Inappropriate                      | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 1                             |
| LZH        | 2010      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| PCM        | 2015      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| TW         | 2014      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| WMH        | 2014      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| WXX        | 2016      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| XQY        | 2016      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| YGF        | 2009      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
| ZB         | 2016      | Random number tables              | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 3                             |
| ZZH        | 2002      | Unclear                           | Unclear                       | Not described   | Not described          | Not described               | Not described                 | Not described               | Not described   | 2                             |
that the data heterogeneity of total serum protein in nine literatures was small, and the data were analyzed using a fixed-effect model. The results of the analysis were MD = 9.45, 95% CI (8.73, 10.17), and \( P < 0.00001 \), indicating that the serum total protein in *Tripterygium* glycoside combinations was higher than that in the hormone alone. The difference between the two groups was statistically significant [Figure 7].

**Urea nitrogen**

The heterogeneity index (\( P = 0.03 \) and \( I^2 = 59\% \)) indicates that the data heterogeneity of urea nitrogen in six literatures was large. Further reading the literature, no heterogeneity source was found, so the data were analyzed using the random-effects model. The results of the analysis were MD = 9.45, 95% CI (8.73, 10.17), and \( P < 0.00001 \), indicating that the urea nitrogen in *Tripterygium* glycosides combinations was lower than that in the hormone alone. The difference between the two groups was statistically significant [Figure 8].
Serum creatinine
The heterogeneity index \((P < 0.00001\) and \(I^2 = 91\%\)) indicates that the data heterogeneity of serum creatinine in seven articles was large. Further reading the literature, no heterogeneity source was found, so the data were analyzed using the random-effects model. The results of the analysis were \(MD = -8.45, 95\% CI (-15.32, -1.57)\), and \(P = 0.02\), indicating that the serum creatinine in Tripterygium glycoside combinations was lower than that in the hormone alone. The difference between the two groups was statistically significant [Figure 9].

Adverse reactions
The heterogeneity index \((P = 0.13, I^2 = 39\%)\) indicates that the data heterogeneity of adverse reactions in seven articles was small and the data were analyzed using a fixed-effect model. The analysis results were \(OR = 0.68, 95\% CI (0.41, 1.12)\), and \(P = 0.13\), indicating that the incidence of adverse

Figure 5: Meta-analysis of 24-hour urine protein quantitation in the experimental and control groups

Figure 6: Meta-analysis of serum albumin in the experimental and control groups

Figure 7: Meta-analysis of serum total protein in experimental and control groups
reactions in *Tripterygium* glycoside combination treatments and hormone therapy alone was similar, and the difference was not statistically significant [Figure 10].

**Publication bias assessment**
The funnel plot was used to assess the publication bias of the included studies. The results showed that the publication biased funnel plots of improving clinical efficacy, reducing adverse reactions, and elevating serum albumin and total protein were roughly symmetrical, indicating that the published literatures in these four aspects were less likely biased, so the conclusions were more reliable. The asymmetry of the funnel plot in reducing 24 h UTP, serum creatinine, and urea nitrogen levels suggested that there was a publication bias, which may be related to large heterogeneity, small sample size, low literature quality evaluation, and excluded unpublished literature [Figures 11-17].

**Discussions**
RNS means that there is no significant remission after conventional hormone therapy, which is mainly characterized by severe massive proteinuria, hypoalbuminemia, hyperlipidemia, or systemic edema. In addition, RNS easily induces infection and other complications and the disease is progressive, which eventually leads to glomerulosclerosis, renal interstitial fibrosis, and gradually develops into end-stage renal disease. At present,
it is considered closely related to immunity. A large amount of proteinuria is its main clinical feature and also an independent risk factor for the continuous progression of the disease. Proteinuria can lead to glomerular damage and accelerate glomerular sclerosis. In addition, studies have shown that proteinuria can also contribute to renal tubulointerstitial fibrosis occurrence. It significantly increases the incidence and mortality of end-stage renal disease. This is mainly related to gene expression regulation in the renal tubular epithelial cells through the Fas pathway and activation of the complement pathway.\[19\]

RNS is currently treated with glucocorticoids combined with other immunosuppressants. At the same time, combined with diet, antihypertensive, lipid-lowering, anticoagulation,
diuresis, kidney protection, and other basic treatment measures. Therefore, to reduce the recurrence rate in patients and improve the sensitivity of its effect, it is generally necessary to use combined drugs in clinics. Glucocorticoid therapy is still the main means of RNS treatment. Studies have shown that glucocorticoids control inflammation by inhibiting cellular and humoral immunity. At the same time, it can reduce the secretion of hormones related to water-sodium balance and reduce the permeability of the glomerular basement membrane.[20] However, because the traditional immunosuppressive drugs such as glucocorticoids, cyclophosphamide, and cyclosporine, have poor efficacy and adverse reactions in RNS treatment, optimizing the immunosuppressive regimen is the fundamental way to treat RNS.[21] A large number of clinical studies have shown that glucocorticoids can reduce the level of proteinuria and delay the progression of renal failure in patients with RNS, but the effect of hormone therapy alone is not significant.[22]

In recent years, more attention has been paid to the development of traditional Chinese medicine, and treatment with integrated traditional Chinese and Western medicine has given full play to its unique advantages. A large number of clinical studies have shown that Tripterygium glycosides play a very important role in the treatment of RNS. Some studies have shown that the effective rate of Tripterygium glycosides combined with glucocorticoid for RNS treatment can be more than 90%.[23] It can significantly improve patients’ symptoms, reduce urine protein, increase albumin, and reduce the incidence of adverse reactions.[23] Presently, the Tripterygium extract called Tripterygium glycosides is commonly used in clinics. Through the study of modern pharmacology, it is mainly used to curb inflammation, inhibit immune response, and so on. The main mechanism of Tripterygium glycosides is to reduce urinary protein by inhibiting renal tubular antigen presentation, inflammatory cell reaction, and renal tubulointerstitial fibrosis, scavenging oxygen-free radicals, and protecting the permeability of the glomerular basement membrane charge barrier.[23] Besides, it is also related to the kidney pathological types in glomerular disease treatment. Many clinical studies are showing that it is better for minimal change nephrosis, mesangial proliferative nephritis, and IgA nephropathy.[24] Li Leishi fully verified the effect of T. wilfordii in the treatment of nephropathy through animal experiments. Studies have shown that T. wilfordii can reduce the degree and duration of animal proteinuria, renal damage, and pathological changes of renal tissue.[25] Professor Wang Yongjun, a well-known nephropic expert, believes that NS is closely related to rheumatism. Therefore, curbing rheumatism is the main treatment principle for this disease.[26] Tripterygium glycosides are one of the wind-dispelling and dampness-removing preparations that are widely used in clinics. Kidney disease develops into end-stage renal insufficiency, which causes renal tubulointerstitial damage, and gradually into renal interstitial fibrosis. Yang et al.[27] used unilateral ureteral ligation (Unilateral Ureteral Obstruction [UUO] model) in mice, Tripterygium glycosides as the experimental group, and Angiotensin converting enzyme inhibitor (ACEI) MengNuo as the control group; the results showed that Tripterygium and MengNuo treatment can significantly improve renal pathological damage, reduce interstitial fibrosis in UUO mice, and decrease alpha smooth muscle actin and Vimentin protein expression in renal tubulointerstitial, and the effect in the Tripterygium glycoside group was significantly better than in the MengNuo group. This experiment illustrates the role of Tripterygium glycosides in delaying the progression of kidney disease, and further proves the significance of rheumatism and the importance of anti-rheumatic treatment of chronic kidney disease.

Tripterygium glycosides are effective in the treatment of renal disease, but adverse reactions are also reported frequently. Studies have shown that one or more abnormal or conventional doses can cause single or multiple organ damage or even death within a few to dozen hours.[28] A recent meta-analysis of Tripterygium glycosides in the treatment of kidney disease showed that about 11.7% of patients had adverse events such as 2469 patients with gastrointestinal reactions and 4843 with elevated alanine aminotransferase, after taking the drug.[29] About 12.7% of female patients had menstrual disorders, and 4.9% of patients had cardiovascular events.[29] Patients with blood system damage and skin and mucous membrane damages accounted for about 6.5% and 7.8%, respectively.[29] There were 43 reports of kidney damage in 193 patients and also adverse reactions such as severe hair loss, weight loss, and fatigue.[29] Therefore, how to increase efficiency and decrease the toxicity of Tripterygium glycosides should be the focus of future research.

The combination of traditional Chinese and Western medicine for the treatment of diseases is characteristic of medical development in China. The combination of traditional Chinese medicine or traditional Chinese medicine preparations with Western medicine has been increasing. It has also been affirmed by researchers at home and abroad. In this study, the RCT of
Tripterygium glycosides combined with glucocorticoids in the treatment of RNS in the past 10 years were collected and analyzed by meta-analysis to evaluate the efficacy and safety of Tripterygium glycosides combined with glucocorticoid. A total of 13 RCT articles were included in this study, published from 2002 to 2017, including a total of 994 patients. The experimental group was treated with Tripterygium glycosides combined with glucocorticoids and the control group with hormone alone. Both groups were treated with western medicine basic treatment for 8–48 weeks. The results showed that Tripterygium glycosides combined with glucocorticoids could increase the effective rate (OR = 4.69, 95% CI [3.29, 6.67], and P < 0.00001), reduce urine protein (MD = −0.57, 95% CI [−0.62, −0.51], and P < 0.00001), increase serum albumin (MD = 4.77, 95% CI [4.30, 5.24], and P < 0.00001) and total protein (MD = 9.45, 95% CI [8.73, 10.17], and P < 0.00001), and decrease creatinine (MD = −8.45, 95% CI [−15.32, −1.57] and P = 0.02) and urea nitrogen (MD = −0.53, 95% CI [−0.90, −0.17], and P = 0.005) levels. Compared with simple hormone therapy, it has certain advantages, which provides an evidence-based basis for the treatment of RNS with Tripterygium glycosides and hormone combinations in the future. In the case of adverse reactions, the combination of Tripterygium glycosides was similar to the treatment with hormone alone (OR = 0.68, 95% CI [0.41, 1.12], and P = 0.13). Since there is no blank control, the conclusion of similar adverse reactions is yet to be verified.

According to the results of meta-analysis, Tripterygium glycosides combined with glucocorticoids can improve efficiency, reduce urine protein, increase albumin and total protein, and reduce creatinine and urea nitrogen, and the differences are statistically significant. However, at the same time, this study has its limitations: (1) The literatures included in this study were all low-quality literature. Only two articles used the correct random method. The random method of one article was inappropriate. One article mentioned that the blind method was not used, the rest did not mention randomized blindness, and loss of follow-up and withdrawal during follow-up; (2) The literatures included did not mention the pathological type of patients included and could not analyze the therapeutic effect of Tripterygium preparation on different pathological types. At the same time, dehumidification drugs are mainly used for patients with rheumatism syndrome. However, none of the 13 articles included mentioned the syndrome differentiation of patients, which may have a certain influence on the treatment results. (3) The research of meta-analysis and evidence-based medicine requires high-quality and large-sample RCT, however, the 13 articles included in this study are all Chinese, low-quality literature, no blank or placebo controls, and all combined with Western medicine basic treatment. It may have a certain impact on the results. Hence, more randomized double-blind controlled trials with large sample size and high literature quality are needed to obtain more evidence. (4) There was no statistically significant difference between the experimental and control groups in adverse reactions, which may be related to the small sample size and low literature quality. More clinical evidence-based medicine is needed to guide the clinical use of drugs. (5) The treatment goal of RNS is to prevent disease recurrence as much as possible, delay the progress of the disease, improve the quality of life of patients. However, the study showed that the treatment group can reduce creatinine levels, compared with the control group, the difference is statistically significant, but the heterogeneity is higher, the follow-up time is limited, and it is not clear whether it will be truly beneficial. Therefore, more comprehensive clinical evidence-based medical evidence is needed to support the efficacy of Tripterygium glycosides combined with glucocorticoids in treating RNS.

**Conclusion**

Tripterygium glycosides combined with glucocorticoids has certain advantages in the treatment of RNS compared with hormone therapy alone. This has a certain guiding significance for the clinical treatment of RNS.

**Financial support and sponsorship**

National Nature Fund Youth funding Project (81603570).

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Zhang Y. Research on TCM Syndromes and Drug Use Characteristics of Refractory Nephrotic Syndrome Based on Data Mining. Jinan University; 2018.
2. Chen YP. Nephrology. Beijing: People’s Medical Publishing House; 2015. p. 7.
3. Li XH, Lei GP, Pan DH. Progress in research on traditional Chinese medicine and Western medicine for refractory nephrotic syndrome. Chinese J Integr Tradit West Med Nephrol 2013:87-9.
4. Chen XM. Classical questions and answers about clinical kidney disease 800 questions. Beijing: People's Medical Publishing House; 2014. p. 59.
5. Fan DY, Xu CG. Therapeutic effect of tripterygium glycosides combined with glucocorticoid on refractory nephrotic syndrome. Chinese J Tradit Chinese Med Pharm 2014;32:958-60.
6. Hao J, Su M. Clinical study of treatment of refractory nephrotic syndrome with tripterygium wilfordii combined with glucocorticoids. Shenzhen J Integr Tradit Chinese West Med 2015;25:46-7.
7. Liu Q, Lu H, Guo GX, Zhang Y, Zhang XL. Effects of tripterygium glycosides combined with hormones on glucocorticoid resistance and HSP90 in adults. Genomics Appl Biol 2017;36:4485-90.
8. Liu Y. Therapeutic effect of tripterygium glycosides combined with glucocorticoid on refractory nephrotic syndrome. World Clin Med 2017;11:107-111.
9. Liu ZH, Yuan F, Wang YF. Observation of 30 cases of refractory nephrotic syndrome treated with tripterygium wilfordii combined with prednisone. Med Innov China 2010;7:1-2.
10. Pu CM. Clinical observation of refractory nephrotic syndrome treated with tripterygium wilfordii combined with glucocorticoids. Appl Mod Med China 2015;9:135-6.
11. Tan W. Clinical observation of 30 cases of tripterygium wilfordii combined with drug diagnosis and treatment of nephrotic syndrome. Chinese Med Guide 2014:140-1.
12. Wang MH, Qin M. Analysis of the effect of using tripterygium glycosides combined with glucocorticoids in the treatment of refractory nephrotic syndrome. J Contemp Med 2014;129-30.
13. Wang XX. Analysis of the effect of prednisone combined with
Tripterygium for RNS

1. Cheng, et al. Tripterygium for RNS in the treatment of refractory nephrotic syndrome. Chinese Pract Med 2016;136-7.
2. Xu QY. Clinical analysis of glucocorticoid combined with tripterygium glycosides in the treatment of refractory nephrotic syndrome. New World Diabetes 2016;19:33-4.
3. Yuan GF, Yuan SG. Clinical observation of tripterygium glycosides combined with prednisone in the treatment of refractory nephrotic syndrome. Chinese J Integr Tradit Wes Med Nephrol 2009;10:246-7.
4. Zhou B. Therapeutic effect of tripterygium wilfordii combined with glucocorticoid on refractory nephrotic syndrome. J Hunan Univ Tradit Chinese Med 2016;36:62.
5. Zhong ZH, Lu JJ, Cai JD. Clinical analysis of 30 patients with recurrent nephrotic syndrome treated with hormone combined with tripterygium wilfordii. China Compr Clin 2002:53-4.
6. Jiang LZ. Effect of tacrolimus combined with glucocorticoid on refractory nephrotic syndrome. Med Inf 2014:433.
7. Liu J, Chen XM. Mechanism of proteinuria accelerating renal tubular injury. Chinese J Nephrol Ejournal 2014:99-103.
8. Xie DD. Clinical Study on the Treatment of Refractory Nephrotic Syndrome with Integrated Traditional Chinese and Western Medicine. Southern Medical University; 2017.
9. Li XY, Chen JH. Immunosuppressive therapy for refractory nephrotic syndrome. J Clin Nephrol 2012;12:100-1.
10. Du PJ, Liu J, Wang L, Pan CQ. Evaluation of the effect of tacrolimus on refractory nephrotic syndrome. Chinese Contin Med Educ 2019;11:110-2.
11. Yang DM, Liu J. Research progress in clinical application and adverse reactions of tripterygium glycosides. Chinese J Hosp Pharm 2018;38:2185-90.
12. Yu DR, Hong YZ, Wang YJ. Application and mechanism of tripterygium wilfordii in the field of kidney disease. Chinese J Integr Tradit West Nephrol 2002;3:554-8.
13. Li LS, Zhang X, Chen HP. Clinical and experimental study of tripterygium wilfordii in the treatment of nephritis. Chinese J Med 1982;62:581-2.
14. Chen HY. Professor Wang Yongjun's experience in the treatment of primary nephrotic syndrome. Chinese J Integr Tradit West Med Nephrol 2007;8:438-9.
15. Yang RC, Wang YJ, Zhou DW, Lin JL, Wang J, Zhu XL. Effect of tripterygium glycosides on phenotypic transformation of renal tubulointerstitial cells in unilateral ureteral obstruction mice. Chinese J Tradit Chinese Med 2007;25:290-2.
16. Yang F. The side effects and research status of tripterygium wilfordii. The institute of evidence law and forensic science, China University of Political Science and Law. Second Evid Theory Sci Int Proc Symp 2009;2:7.
17. Lu Y, Yan XQ. Toxic side effects of tripterygium wilfordii and its rational application in nephropathy. Chinese J Nephrol Res 2018;7:17-22.