A meta-analysis of effects and safety of *Tripterygium wilfordii* polyglycoside in the treatment of IgA nephropathy

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Abstract. – OBJECTIVE: To evaluate the effects and safety of *Tripterygium wilfordii* polyglycoside (TWP) in the treatment of immunoglobulin A (IgA) nephropathy.

SUBJECTS AND METHODS: A computer-assisted study search of Chinese Biomedical Database (CBM), Chinese Journal Full-text Database (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP), PubMed, Medline, EMBASE and Cochrane Library was performed, with the time range of retrieval set between the establishment of the database to December 31, 2019. Articles of randomized controlled trials on the treatment of IgA nephropathy by *Tripterygium wilfordii* polyglycoside were collected, and then screened according to the inclusion and exclusion criteria. Next, the quality of the papers was assessed, effective data were extracted, and a meta-analysis of the included studies was conducted using the Review Manager 5.3 software provided by the Cochrane Collaboration.

RESULTS: Thirty randomized controlled trials (RCT) were included ultimately, and the meta-analysis showed that 1) Single (Sgl) TWP group was superior to angiotensin-converting enzyme inhibitor/angiotension receptor blocker (ACEI/ARB) group in terms of complete remission [odds ratio (OR) = 4.74, *p*-value < 0.00001], total remission (OR = 3.90, *p*-value < 0.0001), 24-hour proteinuria [mean difference (MD) = 1.18, *p*-value < 0.00001], and serum albumin (MD = -8.23, *p*-value < 0.00001), and no significant difference in serum creatinine (MD = 2.09, *p*-value = 0.08) was found between Sgl TWP and control groups; TWP + ACEI/ARB group was superior in complete remission (OR = 2.57, *p*-value < 0.00001), total remission (OR = 4.36, *p*-value < 0.00001), serum albumin [standardized mean difference (SMD) = -0.68, *p*-value = 0.0005], 24-hour proteinuria (SMD = 1.24, *p*-value < 0.00001) and serum creatinine (SMD = 0.48, *p*-value = 0.006);

2) TWP group was superior to glucocorticoid group in complete remission (OR = 1.93, *p*-value < 0.0010), total remission (OR = 3.71, *p*-value < 0.00001), serum albumin (MD = -3.50, *p*-value = 0.002), 24-hour proteinuria (SMD = 0.93, *p*-value < 0.0001) and serum creatinine (SMD = 0.88, *p*-value = 0.006); 3) TWP group was better than mycophenolate mofetil (MMF) group in complete remission (OR = 2.05, *p* = 0.005), total remission (OR = 3.30, *p*-value = 0.002), 24-hour proteinuria (MD = 2.61, *p*-value < 0.0001), and serum albumin (MD = -6.43, *p*-value < 0.00001), but the differences in serum creatinine (MD = 1.28, *p*-value = 0.89) between TWP and control groups were not significant. Besides, TWP + ACEI/ARB group had a higher adverse reaction rate than the control group (OR = 2.21, *p*-value = 0.04), but there was no significant difference in the adverse reaction rate between other control and experimental groups (*p*-value > 0.05).

CONCLUSIONS: The present evidence shows that *Tripterygium wilfordii* polyglycoside can effectively improve the remission rate, reduce proteinuria, and protect kidney function of IgA nephropathy patients, and also has good safety. However, limited by the quality of the included studies, the effects and safety of *Tripterygium wilfordii* polyglycoside in the treatment of IgA nephropathy need to be verified by more high-quality, large-scale, multi-center RCTs.

Key Words:
 Tripterygium wilfordii polyglycoside, IgA nephropathy, Meta-analysis.

Introduction

immunoglobulin A (IgA) nephropathy (IgAN) is one of the most common primary glomeru-

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lar diseases worldwide at present, accounting for 30-40% of the total primary glomerular diseases in China[1]. Its pathogenic manifestation is featured by the deposition of IgA-dominant immunocomplexes in the glomerular mesangial area. IgAN progresses slowly in most patients, but 30-40% of the patients can develop into end-stage renal disease (ESRD) in 20 years after the diagnosis[2], so it becomes one of the main causes of ESRD in China. Therefore, effective control and treatment of IgAN is of great significance. However, there is no unified treatment plan at IgAN due to the unclear etiology and pathogenesis and diversified clinical symptoms and renal pathology. The main treatment methods for IgAN include angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), glucocorticoid, tonsillectomy, fish oil, traditional Chinese medicine, immunosuppressant, etc[3]. Individual treatment is usually made according to the clinical manifestation, laboratory test and pathology feature in clinical practice.

Tripterygium wilfordii preparations are the most widely used Chinese patent medicine immunosuppressants in the treatment of IgAN[4]. *Tripterygium wilfordii* polyglycoside is an active ingredient extracted from the plant *Tripterygium wilfordii*. It is cheap and has the effects of resisting inflammation, immunomodulation, protecting intrinsic renal cell function, easing pain, anti-rejection and anti-tumor[5-8]. Since traditional Chinese medicine *Tripterygium wilfordii* was used by Li et al[9] to treat glomerulonephritis, it has been gradually applied to the treatment of various primitive and secondary glomerulonephritis, including IgAN. *Tripterygium wilfordii*'s clinical use is restricted due to its toxic side effects although it has extensive pharmacological actions. As a refined preparation of the *Tripterygium wilfordii* extract, *Tripterygium wilfordii* polyglycoside has enhanced curative effects, reduced toxic side effects and adverse reactions, but there is controversy over its effects and toxicity. The purpose of this paper is to provide evidence to prove the effects and safety of *Tripterygium wilfordii* polyglycoside in the treatment of IgAN by studying the randomized controlled trials on the treatment of IgAN with *Tripterygium wilfordii* polyglycoside.

Subjects and Methods

Research Design
The study included randomized controlled trials (RCT), with the language limited to Chinese and English whether the blind method was employed or not.

Research Object
Patients selected were confirmed to have primary IgA nephropathy by renal needle biopsy regardless of gender, age, ethnicity and nationality.

Treatment
The treatment group mainly received *Tripterygium wilfordii* polyglycoside tablets, which could be supplemented by other non-*Tripterygium wilfordii* drugs, and the control group was treated with other drugs. Basic treatment like blood pressure control, diet control and redressing water-electrolyte balance disorder was given to both groups.

Outcome Index
The primary indices included complete remission (CR), partial remission (PR), and total remission (TR), TR = CR + PR. CR was defined as proteinuria < 0.15-0.40 g/24 h, and PR was defined as proteinuria between 0.15-0.40 g/24 h to 1.0 g-3.0/24 h and reduced protein excretion > 50%. The secondary indices were 24-hour proteinuria, serum creatinine, serum albumin, and adverse reaction rate.

Exclusion Criteria
1) Secondary IgAN; 2) The treatment was the *Tripterygium wilfordii* herb or dispensing granules; 3) In addition to basic treatment, other treatment methods were used to affect the outcome; 4) Other traditional Chinese medicine was taken besides *Tripterygium wilfordii*; 5) Studies that were duplicated and data could not be extracted; 6) Studies with unreasonable effect indices or less detailed treatment results; 7) Random grouping was not mentioned or the experimental process was unclear.

Search Strategy
PubMed, Medline, EMBASE, Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Internet (CNKI), Wanfang Database, and China Science and Technology Journal Database (CSTJ) were computer-searched, with the retrieval time ranging from the establishment of the database to December 2019. Search terms included Glomerulonephritis, IGA; Berger's Disease; IgA Glomerulonephritis; IgA Nephropathy; Tripterygium; *Tripterygium wilfordii*; *Tripterygium wilfordii* polyglycoside; *Tripterygium wilfordii* Hook F etc.

Data Extraction and Quality Evaluation
Two reviewers independently screened documents according to inclusion and exclusion crite-

ria, and then cross-checked them. In case of disagreement, discuss settlement or refer to a third researcher. The Cochrane manual 5.1.0 was used to evaluate the methodology quality of the included studies, including random grouping method, concealment of grouping plan, application of blinding researchers and subjects, blind evaluation of outcomes, integrity of result data, selective reporting of outcomes, and other sources of bias.

Statistical Analysis

The Meta-analysis was carried out using RevMan 5.3 software (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark). The dichotomous variables between treatment methods were compared using odds ratio (OR) and 95% confidence interval (CI); the continuous variables were expressed as mean difference (MD) and its 95% CI. Standardized mean difference (SMD) was selected when the mean difference between different studies was large. The heterogeneity of the results between studies was analyzed with χ^2 test. A low heterogeneity (p-value ≥ 0.10 or $I^2 \leq 50\%$) indicated that the fixed effect model should be used to merge the data, while a high heterogeneity (p-value < 0.10 or $I^2 > 50\%$) suggested the random effect model was used to merge the data.

Results

Characteristics and Quality Evaluation of the Included Studies

A total of 1,266 related articles[10-39] were initially selected, and after several times of screening, 30 RCTs were finally included. The control group in 18 RCTs was treated with ACEI/ARB[10-27], and ACEI/ARB group was further divided into single (Sgl) *Tripterygium wilfordii* polyglycoside (TWP) group[10-13] and TWP + ACEI/ARB group[14-27] according to different types of drugs used in the treatment group. Glucocorticoid and mycophenolate mofetil (MMF) were taken as the control in 7 RCTs[28-34] and 5 RCTs[35-39] respectively. A total of 1,858 IgAN patients were enrolled ultimately. Figure 1 shows the study screening process, and the basic characteristics of the study are presented in Table I. The quality evaluation results are shown in Table II and Figure 2, from which it can be seen that the quality of the included studies is medium. In this study, 6 effect indices were compared among 3 drugs. The analysis results of the primary indices (complete remission and total re-

mission) are shown in Figures 3-8, and the analysis results of the secondary indices are shown in Table III.

Comparison of Tripterygium Wilfordii Polyglycoside and ACEI/ARB

The complete remission of the TWP and ACEI/ARB groups was compared in 17 RCTs[10-16,18-27]. Since both groups had a low heterogeneity after data merging, the fixed effect model was used for the meta-analysis, which showed that the complete remission in both Sgl TWP group[10-13] [OR = 4.74, 95% CI (2.72, 8.27), Z = 5.49, p-value < 0.00001] and TWP + ACEI/ARB group[14-16,18-27] [OR = 2.57, 95% CI (1.88, 3.51), Z = 5.89, p-value < 0.00001] was higher than that in the control group, and the differences were significant (Figure 3). 16 RCTs[10,12-16,18-27] compared the total remission of the TWP and ACEI/ARB groups. The meta-analysis was performed using the fixed effect model because the merged results showed both groups had a low heterogeneity, indicating that the total remission in both Sgl TWP group[10,12,13] [OR = 3.90, 95% CI (1.98, 7.66), Z = 3.94, p-value < 0.0001] and TWP + ACEI/ARB group[14-16,18-27] [OR = 4.36, 95% CI (2.98, 6.36), Z = 7.62, p-value < 0.00001] was higher than that in the control group, and the differences were significant (Figure 4). 12 RCTs meta-analysis[11-14,16,17,19,20,22,23,25,27] of TWP + ACEI/ARB group[14,16,17,19,20,22,23,25,27] was carried out by the standardized mean difference random effect model owing to a high heterogeneity after data merging. The results suggested that the 24-hour proteinuria in both Sgl TWP group [MD = 1.18, 95% CI (0.93, 1.43), Z = 9.22, p-value < 0.00001] and TWP + ACEI/ARB group [SMD = 1.24, 95% CI (0.80, 1.67), Z = 5.61, p-value < 0.00001] decreased more than that in the control group, and the differences were significant (Table III). 10 RCTs[10-14,17,20,22,25,26] compared the serum creatinine of TWP and ACEI/ARB groups. Due to the low heterogeneity after data merging, the fixed effect model was used for the meta-analysis of Sgl TWP group[10-13], showing that the serum creatinine in Sgl TWP group [MD = 2.09, 95% CI (-0.21, 4.39), Z = 1.78, p-value = 0.08 > 0.05] was not significantly different from that in the control group (Table III). The meta-analysis of TWP + ACEI/ARB group[14,17,20,22,25,26] was made using the standardized mean difference random effect model because the merged data showed a high heterogeneity, indicating that the serum creatinine in TWP + ACEI/ARB group (SMD = 0.48, 95% CI (0.14, 0.82), Z = 2.75, p-value = 0.006) decreased more than
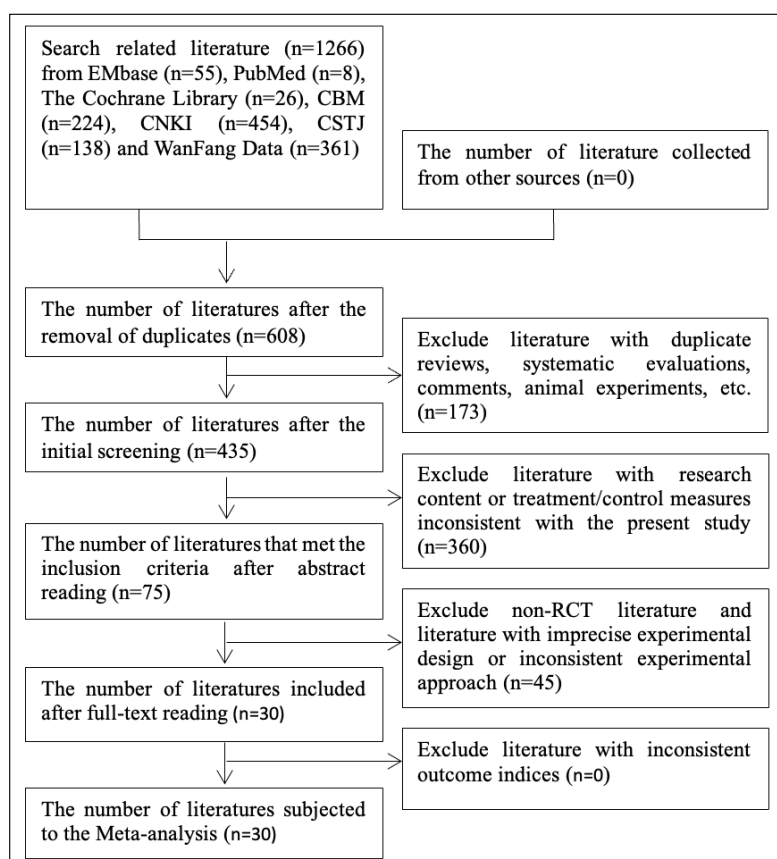
Figure 1. Study selection flow diagram. 1) After searching in the database, delete the duplicate files, and finally get 608 literatures. 2) After excluding duplicate reviews, systematic evaluations, comments, animal experiments, 435 literatures were obtained. 3) After excluding literature with research content or treatment/control measures inconsistent with the present study, 75 literatures remain. 4) After excluding non-RCT literature, literature with imprecise experimental design or inconsistent experimental approach and literature with inconsistent outcome indices, 30 literatures remain.

that in the control group, and the differences were significant (Table III). The serum albumin of the TWP and ACEI/ ARB groups was compared in 10 RCTs[10-14,17,20,22,25,26]. The fixed effect model was applied to the meta-analysis of Sgl TWP group[10-13] due to a low heterogeneity after data merging, while the standardized mean difference random effect model was applied to the meta-analysis of TWP + ACEI/ARB group[14,17,20,22,25,26] which had a high heterogeneity after data merging. The results showed that the serum albumin in both Sgl TWP group [MD = -8.23, 95% CI (-9.65, -6.81), Z = 11.34, p-value < 0.00001] and TWP + ACEI/ ARB group [SMD = -0.68, 95% CI (-1.07, -0.30), Z = 3.48, p-value = 0.0005] increased more than that in the control group, and the differences were significant (Table III). The adverse reaction rate of the TWP and ACEI/ARB groups was compared in 8 RCTs[11-13,20,22-24,26]. Both groups had a low heterogeneity after data merging, so the fixed effect

model was used for the meta-analysis. It was indicated that no significant difference between the adverse reaction rate in Sgl TWP group[11-13] [OR = 0.86, 95% CI (0.32, 2.30), Z = 0.29, p-value = 0.77 > 0.05]] and that in the control groups was observed (Table III), and the adverse reaction rate in TWP + ACEI/ARB group[20,22-24,26] [OR = 2.21, 95% CI (1.03, 4.77), Z = 2.03, p-value = 0.04] was higher than that in the control group (Table III).

Comparison of Tripterygium Wilfordii Polyglycoside and Glucocorticoid

7 RCTs[28-34] compared the complete remission of TWP and glucocorticoid groups, whose meta-analysis was performed with the fixed effect model because of a low heterogeneity after data merging. The results showed that the complete remission in TWP group [OR = 1.93, 95% CI (1.31, 2.85), Z = 3.30, p-value < 0.0010] was higher than that in the control group (Figure 5). The to-

Table I. Basic features of the included literature.

Ref. number	Samples (T/C)	Sample gender (M/F)		Age (years old)		Follow-up period (Month)	Intervening measure		Intervening Outcome
		T	C	T	C		T	C	
30	18/18	12/6	14/4	22.3±1.8		6	TWP	PN	a
20	12/11	9/14		21-50		3	TWP+VST	VST	a, f
35	20/19	Not mentioned		40.7±5.3	38.8±7.5	6	TWP+MMF	MMF	a, c, d, e, f
21	8/7	11/7		Not mentioned		6	TWP+PN+EN-P+VST	PN+EN-P+VST	a, c, d, e, f
25	25/24	16/9	17/7	9.1±1.1	9.3±1.2	3	TWP+PN	PN	a, d, e
10	34/34	19/15	18/16	46.1±9.1	45.8±8.8	6	TWP+TMST	TMST	a, c, d, e, f
13	40/40	19/21	18/22	66.2±4.1	65.2±4.0	12	TWP+LSTP	LSTP	a, e
11	15/15	9/6	10/5	54.1±8.9	53.7±8.5	3	TWP+TMST	TMST	a
16	34/31	18/16	17/14	37.3±6.7	36.7±5.9	3	TWP+BNP	BNP	a, c, d, e, f
17	42/44	22/20	23/21	39.6±1.3	40.3±1.6	3	TWP+BNP	BNP	a
12	30/30	Not mentioned		14-65		4	TWP+BNP	BNP	a, c
31	30/30	29/31		71.5±8.8		6	TWP+MMF	MMF	a
34	40/36	41/35		44.7±7.9		6	TWP+MMF	MMF	a
7	36/32	39/29		16-38		6	TWP	VST	a, d, e, f
22	26/26	26/26		32.5±10.1		6	TWP+BNP	BNP	a, c, d, e, f
24	34/34	19/15	20/14	42.8±5.6	42.9±4.4	12	TWP+PN	PN	a, c, d, e, f
6	35/35	19/16	21/14	39.57±5.2	37.7±5.6	3	TWP	IBST	a, d, e
27	58/62	36/22	36/26	33.5±6.2	34.8±7.6	3	TWP+PN+LSTP	PN+LSTP	a, e
32	30/30	35/25		60 ± 1. 2		6	TWP+MMF	MMF	a
14	41/41	23/18	21/20	33.5±5.30	35.2±4.5	3	TWP+BNP	BNP	a
28	50/50	57/43		36.9±4.4		6	TWP+PN	PN	a
29	25/25	15/10	16/9	33.5±12.4	34.1±13.2	3	TWP+PN	PN	a, c, e
18	30/30	18/12	19/11	50.3± 9.6	51.3±8.2	3	TWP+TMST	TMST	a, c, d, e, f
9	39/39	27/12	28/11	33.5±12.7	32.2±13.5	12	TWP	CTP	a, c, d, e, f
23	38/40	Not mentioned		Not mentioned		6	TWP+BNP+VST	BNP+VST	a
26	30/30	15/15	12/18	41.2 ± 7.0	43.2 ± 6.4	1.3	TWP	PN	a, c, e, f
15	30/30	15/15	16/14	46.1±9.4	45.2±5.7	3	TWP+BNP	BNP	a, c
19	32/31	17/15	17/14	49.3±10.6	50.0±10.1	3	TWP+BNP	BNP	a, c, f
33	22/20	Not mentioned		65.4±4.3	66.6±6.6	6	TWP+MMF	MMF	a, c, d, e, f
8	30/30	16/14	17/13	33.2±11.8	32.8±12.6	12	TWP	ENP	a, c, d, e, f

T: Treat; C: Control; M: male; F: female; TWP: *Tripterygium wilfordii* polyglycoside; PN: Prednisone; VST: valsartan; MMF: Mycophenolate mofetil; ENP: Enalapril; TMST: Telmisartan; LSTP: Losartan potassium; BNP: Benazepril; IBST: Irbesartan; CTP: Captopril; a: Complete remission; b: Total remission; c: 24-hours proteinuria; d: Albumen; e: Serum creatinine; f: Adverse event.

tal remission of TWP and glucocorticoid groups was also compared in 7 RCTs[28-34]. Data merging showed a low heterogeneity, so the fixed effect model was employed to the meta-analysis, indicating that the total remission in TWP group [OR = 3.71, 95% CI (2.21, 6.25), Z = 4.95, *p*-value < 0.00001] was higher than that in the control group

(Figure 6). 4 RCTs[28-30,33] compared the 24-hour proteinuria of TWP and glucocorticoid groups. A high heterogeneity was showed after merging, so the standardized mean difference random effect model was used for meta-analysis, which suggested that the 24-hour proteinuria in TWP group [SMD = 0.93, 95% CI (0.49, 1.37), Z = 4.16,

Table II. Detailed assessment of bias in each literature.

Ref. number	Allocation plan	Allocation concealment	Blind method	Data integrity	Selective reporting	Other bias
30	RNT	NM	NM	Yes	No	No
20	RNT	NM	NM	Yes	No	No
35	NM	NM	NM	Yes	No	No
21	RNT	NM	NM	Incomplete	No	No
25	NM	NM	NM	Yes	No	No
10	RNT	NM	NM	Yes	No	No
13	RNT	NM	NM	Yes	No	No
11	NM	NM	NM	Yes	No	No
16	NM	NM	NM	Yes	No	No
17	NM	NM	NM	Yes	No	No
12	NM	NM	NM	Yes	No	No
31	RNT	NM	NM	Incomplete	No	No
34	NM	NM	NM	Yes	No	No
7	NM	NM	NM	Incomplete	No	No
22	NM	NM	NM	Yes	No	No
24	NM	NM	NM	Yes	No	No
6	NM	NM	NM	Yes	No	No
27	CT	NM	NM	Yes	No	No
32	NM	NM	DB	Yes	No	No
14	NM	NM	NM	Yes	No	No
28	NM	NM	NM	Yes	No	No
29	NM	NM	NM	Yes	No	No
18	NM	NM	NM	Yes	No	No
9	NM	NM	NM	Yes	No	No
23	NM	NM	NM	incomplete	No	No
26	NM	NM	NM	Yes	No	No
15	NM	NM	NM	Yes	No	No
19	RNT	NM	NM	Yes	No	No
33	NM	NM	NM	Yes	No	No
8	NM	NM	NM	Yes	No	No

RNT: Random number table; NM: Not mentioned; CT: Coin-tossing; DB: Double-blind.

p-value < 0.0001] decreased more than that in the control group, and the differences were statistically significantly (Table III). In the comparison of serum creatinine between TWP and glucocorticoid groups in four RCTs[28,30,31,33], the meta-analysis was carried out using the standardized mean difference random effect model because of a high heterogeneity after data merging, indicating that the serum creatinine in experimental groups [SMD = 0.88, 95% CI (0.38, 1.39), Z = 3.42, *p*-value = 0.006] decreased more than that in the con-

trol group, and the differences were statistically significantly (Table III). 2 RCTs[28,29] compared the serum albumin of TWP and glucocorticoid groups. Data merging revealed a low heterogeneity, so the fixed effect model was used for the meta-analysis, which showed that the serum albumin in the experimental groups [MD = -3.50, 95% CI (-5.70, -1.29), Z = 3.11, *p*-value = 0.002] increased more than that in the control group, and the differences were statistically significantly (Table III). In the comparison of adverse reaction

rate between TWP and glucocorticoid groups in 4 RCTs[28,30,31,33], the meta-analysis was conducted using the random effect model due to a high heterogeneity after data merging. The results showed that there was no statistically significant difference in the adverse reaction rate between the experimental groups [OR = 0.48, 95% CI (0.17, 1.35), Z = 1.39, *p*-value = 0.16 > 0.05] and the control group (Table III).

Comparison of Tripterygium Wilfordii Polyglycoside and MMF

The complete remission of TWP and MMF groups was compared in 5 RCTs[35-39], and the meta-analysis was conducted with the fixed effect model owing to a low heterogeneity after data merging. The results revealed that the complete remission in TWP group [OR = 2.05, 95% CI (1.24, 3.37), Z = 2.82, *p*-value = 0.005] was higher than that in the control group (Figure 7). In the comparison of total remission of TWP and MMF groups in 5 RCTs[35-39], the fixed effect model was also applied to the meta-analysis because of a low heterogeneity indicated by the data merging, showing that total remission in TWP group [OR = 3.30, 95% CI (1.57, 6.95), Z = 3.14, *p*-value = 0.002] was higher than that in the control group (Figure 8). The meta-analysis of 2 RCTs[37,39], which compared the 24-hour proteinuria of TWP and MMF groups, was carried out using the fixed effect model owing to a low heterogeneity after data merging. The results suggested that the 24-hour proteinuria in TWP group [MD = 2.61, 95% CI

(1.43, 3.79), Z = 4.34, *p*-value < 0.0001] decreased more than that in the control group, and the differences were statistically significantly (Table III). 2 RCTs[37,39] also compared the serum creatinine of TWP and MMF groups. In view of a low heterogeneity after data merging, the fixed effect model was used for the meta-analysis, which revealed that no significant difference in the serum creatinine between the experimental group [MD = 1.28, 95% CI (-16.85, 19.42), Z = 0.14, *p*-value = 0.89 > 0.05] and control group was found (Table III). The serum albumin was compared between TWP and MMF groups in 2 RCTs[37,39]. The merged results showed a low heterogeneity, so the fixed effect model was employed to the Meta-analysis, which suggested that the serum albumin of the experimental groups [MD -6.43, 95% CI (-8.29, -4.57), Z = 6.78, *p*-value < 0.00001] increased more than that of the control group, and the differences were statistically significantly (Table III). 2 RCTs[37,39] also compared the adverse reaction rate between TWP and MMF groups. Since a high heterogeneity was found, the meta-analysis was made using the random effect model, which indicated that the adverse reaction rate in the experimental groups [OR = 0.92, 95% CI (0.29, 2.92), Z = 0.14, *p*-value = 0.88] was not statistically significantly different from that in the control group (Table III).

Publication Bias Analysis

The risk of bias of the included study was assessed by drawing the funnel plot with Revman 5.3. The inverted funnel plot was drawn with the
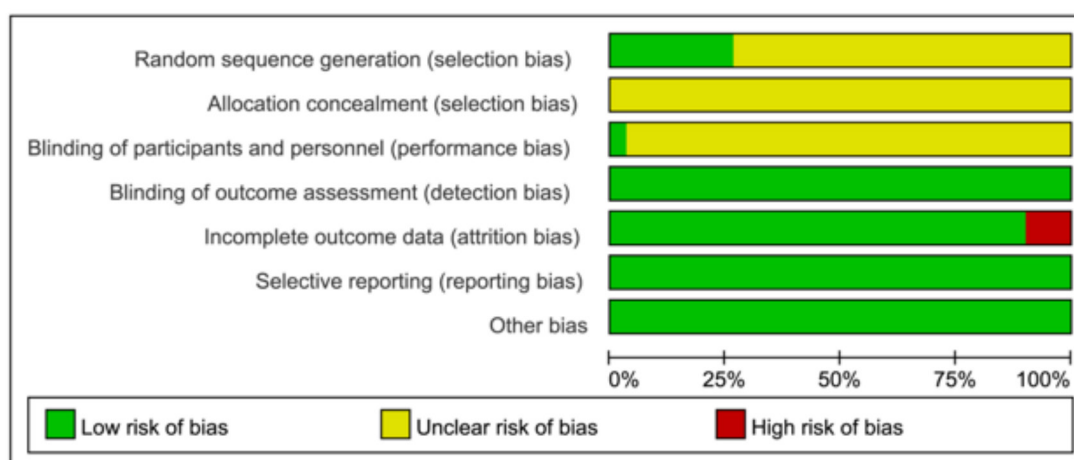

Figure 2. Overall quality assessments. In this figure, selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias in the included literature were summarized and analyzed, from which it can be seen that the quality of the included studies is medium.

Table III. Summary of analysis results (secondary indices).

Comparison of medication regimens	Literature numbers	T/C	p-value	I² (%)	Analytical model	Meta-analysis results		
						OR/MD/ SMD	95% CI	p-value
TWP *vs.* ACEI/ARB								
Sgl TWP								
Urine protein (g/24 h)	3	103/101	1.00	0	Fixed	1.18	(0.93, 1.43)	<0.00001
Serum creatinine (μmol/L)	4	138/136	0.17	41	Fixed	2.09	(-0.21, 4.39)	0.08
Albumen (g/L)	4	138/136	0.99	0	Fixed	-8.23	(-9.65, -6.81)	<0.00001
Adverse reaction	3	105/101	0.38	0	Fixed	0.86	(0.32, 2.30)	0.77
2) TWP+ACEI/ARB								
Urine protein (g/24 h)	9	264/259	<0.00001	79	Random	1.24	(0.80, 1.67)	<0.00001
Serum creatinine (μmol/L)	6	172/168	0.04	57	Random	0.48	(0.14, 0.82)	0.006
Albumen (g/L)	6	172/168	0.02	64	Random	-0.68	(-1.07, -0.30)	0.0005
Adverse reaction	5	135/129	0.70	0	Fixed	2.21	(1.03, 4.77)	0.04
TWP *vs.* Glucocorticoids								
Urine protein (g/24 h)	4	114/113	0.06	60	Random	0.93	(0.49, 1.37)	<0.0001
Serum creatinine (μmol/L)	4	147/151	0.006	76	Random	0.88	(0.38, 1.39)	0.0006
Albumen (g/L)	2	59/58	0.16	48	Fixed	-3.50	(-5.70, -1.29)	0.002
Adverse reaction	4	147/151	0.08	56	Random	0.48	(0.17, 1.35)	0.16
TWP *vs.* Mycophenolate Mofetil								
Urine protein (g/24 h)	2	42/39	0.94	0	Fixed	2.61	(1.43, 3.79)	<0.0001
Serum creatinine (μmol/L)	2	42/39	0.99	0	Fixed	1.28	(-19.85, 19.42)	0.89
Albumen (g/L)	2	42/39	0.14	53	Fixed	-6.43	(-8.29, -4.57)	<0.00001
Adverse reaction	2	42/39	0.97	0	Fixed	0.92	(0.29, 2.92)	0.88

TWP: *Tripterygium wilfordii* polyglycoside; ACEI: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; Sgl: Single; T: Treat; C: Control; CI: Confidence interval; OR: Odds ratio; MD: Mean difference; SMD: Standardized mean difference.
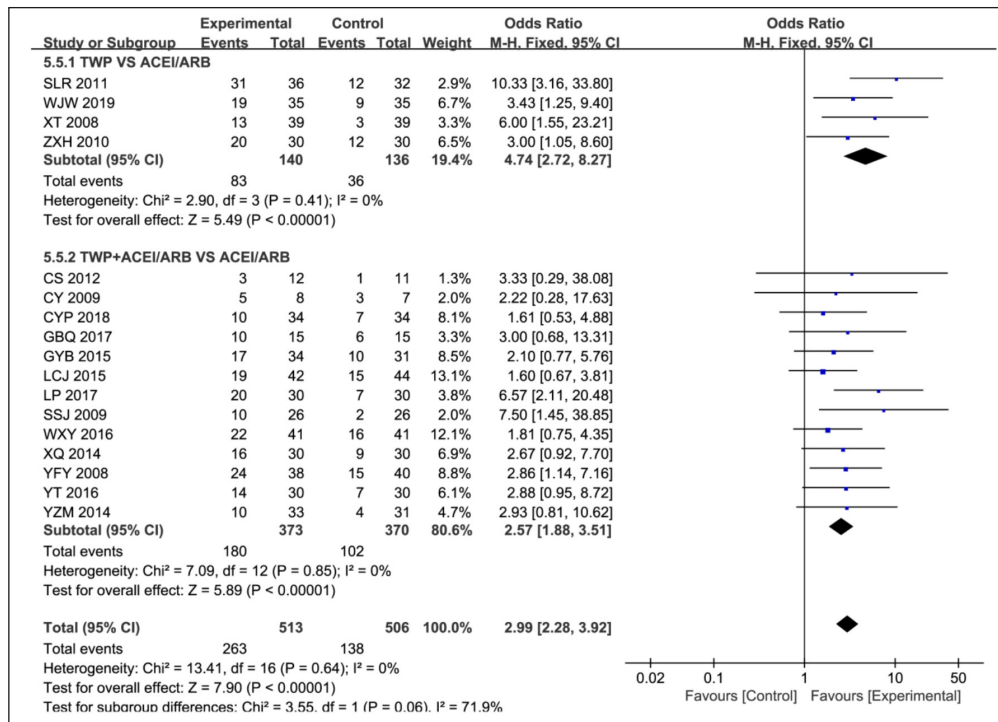
Figure 3. Comparison of TWP *vs.* ACEI/ARB on complete remission. The figure showed that the complete remission in both Sgl TWP group [OR = 4.74, 95% CI (2.72, 8.27), Z = 5.49, *p*-value < 0.00001] and TWP + ACEI/ARB group [OR = 2.57, 95% CI (1.88, 3.51), Z = 5.89, *p*-value < 0.00001] was higher than that in the ACEI/ARB group, and the differences were significant.

complete remission as the evaluation index, the logarithm value of OR of each research as the ordinate, and the OR value as the abscissa. The results showed that the funnel plot was not well symmetrical, suggesting the possibility of publication bias (Figure 9).

Discussion

In recent years, the treatment of IgAN has gradually enriched. The most common ones include ACEI/ARB, glucocorticoid, immunosuppressant, etc. ACEI/ARB is commonly used in the treatment of IgAN, having the effects of reducing the risk factors that promote disease progression, lowering the proteinuria of IgAN patients and protecting their renal function. Glucocorticoid is one of the common drugs for the treatment of IgAN, which is proved by clinical research[36] to be able to reduce the level of proteinuria and slow the progression of IgAN[40]. Nevertheless, it was only used to treat special subtype IgAN in the past, but it has a larger application range with the increased incidence of ESRD. Immunosuppressant is the main treatment for IgAN, and much progress has been made in the IgAN treatment by mizoribine (MZR), cyclosporine A (CSA), mycophenolate mofetil (MMF) and other immunosuppressants[41-44]. In contrast with immunesuppressants made from western medicine, which are generally expensive, TWP has small toxic side effects and a low price, so it is considered the optimal TCM immunosuppressant for the treatment of IgAN.

The mechanism of TWP in the treatment of IgAN remains controversial and unclear. With the deepening of the knowledge about the mechanism, *Tripterygium wilfordii* is suggested to have many therapeutic effects on IgAN. On the one hand, triptolide can directly regulate the expression of podocyte-associated proteins (such as E-cadherin, P-cadherin, nephrin, podocin, etc.) to stabilize the podocyte cytoskeleton, maintain the integrity of the glomerular charge barrier, and reduce proteinuria[45,46]. On the other hand, *Tripterygium wilfordii* can exert effects indirectly: 1) Triptolide can inhibit the activated human proximal renal tubular epithelial cells to express B7-H1, MHC-II, ICAM-1 and other costimulatory factors, thereby weakening
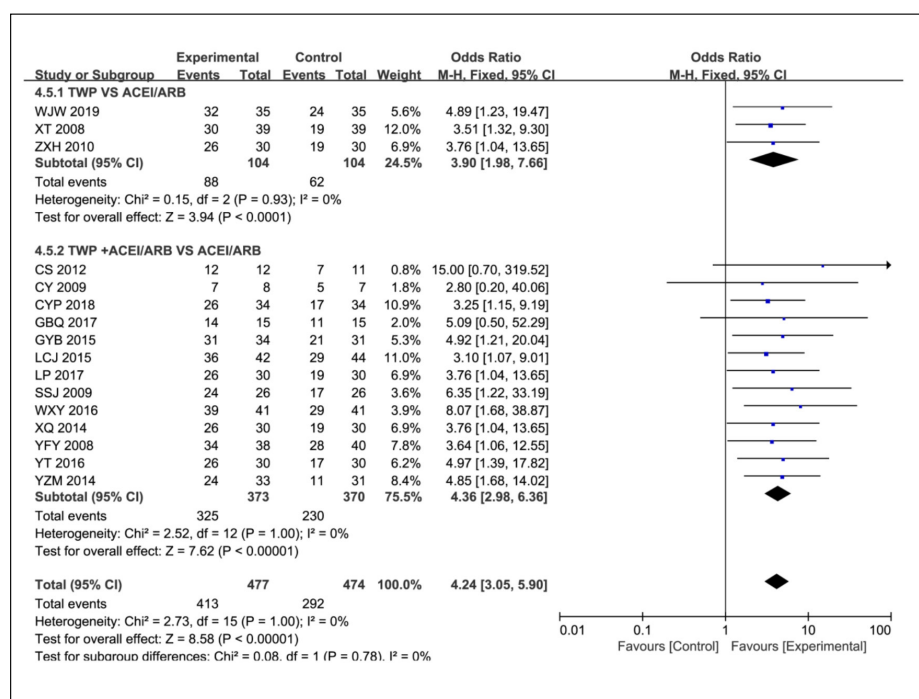
Figure 4. Comparison of TWP *vs.* ACEI/ARB on total remission. The figure showed that the total remission in both Sgl TWP group [OR = 3.90, 95% CI (1.98, 7.66), Z = 3.94, *p*-value < 0.0001] and TWP + ACEI/ARB group [OR = 4.36, 95% CI (2.98, 6.36), Z = 7.62, *p*-value < 0.00001] was higher than that in the ACEI/ARB group, and the differences were significant.
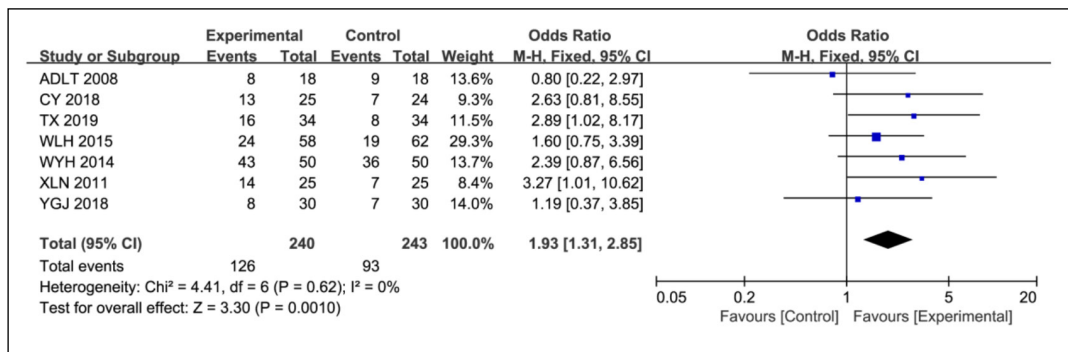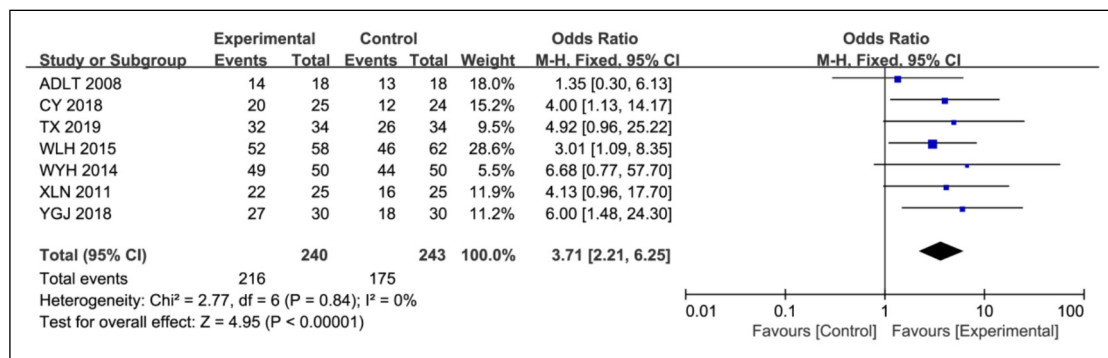
Figure 5. Comparison of TWP *vs.* Glucocorticoid on complete remission. The figure showed that the complete remission in TWP group [OR = 1.93, 95% CI (1.31, 2.85), Z = 3.30, *p*-value < 0.0010] was higher than that in the glucocorticoid group, and the differences were significant.

the antigen presentation effect of renal tubular epithelial cells, preventing the activation of T cells and reducing inflammation[47]; 2) Triptolide can reduce the generation of the membrane attack complex C5b-9 by immunosuppression to inhibit the fusion of podocytes and protect podocytes[48]; 3) Triptolide can suppress the secretion of inflammatory cytokines such as interleukin-13 (IL-13), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and tumor necrosis factor beta (TNF-β), and prevent their destruction to podocyte cytoskeleton protein and their stimulation of mesangial proliferation[49-52]; 4) *Tripterygium wilfordii* T4 can significantly reduce IgA fibronectin, the deposition of IgA in glomerular mesangial membrane, and thus lessen mesangial cell proliferation[53].

The comparative studies of ACEI/ARB and TWP showed that TWP was superior to ACEI/ARB in terms of complete remission, total re-

mission, proteinuria and serum albumin. Serum creatinine could be effectively lowered by the TWP + ACEI/ARB, but not by TWP alone, indicating that the combination of TWP and ACEI/ARB had a better protective effect on the kidney in the treatment of IgA nephropathy. However, TWP + ACEI/ARB had a higher adverse reaction rate than TWP alone, but the liver defunction, reproductive inhibition and gastrointestinal reaction caused by the use of TWP are reversible after drug withdrawal, and the side effects can be significantly reduced by the liver protection drugs and acid inhibitors during the use of TWP. Meanwhile, the improved drug extraction and refining technology enables to remove most of the harmful ingredients and retain effective ingredients in TWP in its preparation, thus minimizing the side effects. Therefore, the combination of TWP and ACEI/ARB is recommended for the IgAN treatment.

Figure 6. Comparison of TWP *vs.* Glucocorticoid on total remission. The figure showed that the total remission in TWP group [OR = 3.71, 95% CI (2.21, 6.25), Z = 4.95, *p*-value < 0.00001] was higher than that in the glucocorticoid group, and the differences were significant.
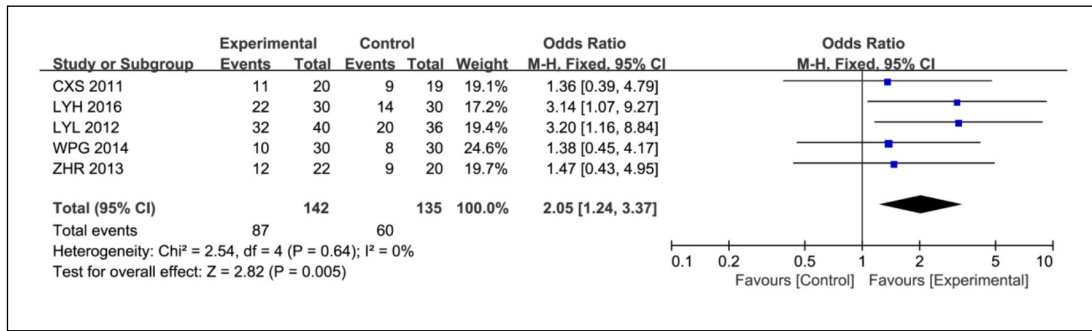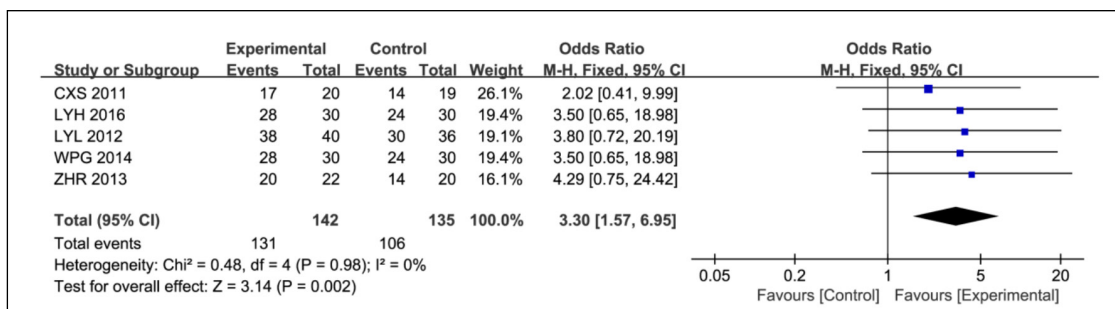
Figure 7. Comparison of TWP *vs.* MMF on complete remission. The figure showed that the complete remission in TWP group [OR = 2.05, 95% CI (1.24, 3.37), Z = 2.82, *p*-value = 0.005] was higher than that in the MMF group, and the differences were significant.

According to the comparative studies[30,34] of TWP and glucocorticoid, TWP group was superior to glucocorticoid group in complete remission, total remission, serum albumin, proteinuria and serum creatinine, and no significant difference between the adverse reaction rate was observed between the two groups. Therefore, TWP may be an alternative of glucocorticoid in the treatment of IgA nephropathy in the future, which will help achieve a better treatment effect, make it safer for treating patients with contra-indications or serious adverse reactions to glucocorticoid, and avoid unnecessary side effects caused by irrational dosage or non-standard dose reduction of glucocorticoid.

The comparative studies[35-39], of TWP and MMF showed that TWP was better than MMF in terms of complete remission, total remission, 24-hour proteinuria and serum albumin, but there was no significant difference in serum creatinine and adverse reaction rate between TWP and MMF. TWP tablets are much cheaper than mainstay immunosuppressants such as MMF. It generally costs 2-3,000 yuan per month when using MMF or tacrolimus to treat chronic kidney diseases, while TWP costs less than 100 yuan per month, which greatly reduces the economic burden of patients and the occurrence of drug withdrawal caused by it. However, the conclusion still needs to be further verified due to the small number of articles included in this paper.

Based on the analysis of this paper, TWP was capable of effectively improving the remission, reducing proteinuria and protecting renal function, and it was not inferior to glucocorticoid and MMF in safety. It is urgent to enhance the efficacy and reduce the toxic side effects of TWP in its clinical use. With the high-efficiency and low-toxicity TWP coming on the market

Figure 8. Comparison of TWP *vs.* MMF on total remission. The figure showed that total remission in TWP group [OR = 3.30, 95% CI (1.57, 6.95), Z = 3.14, *p*-value = 0.002] was statistically significantly higher than that in the MMF group, and the differences were significant.
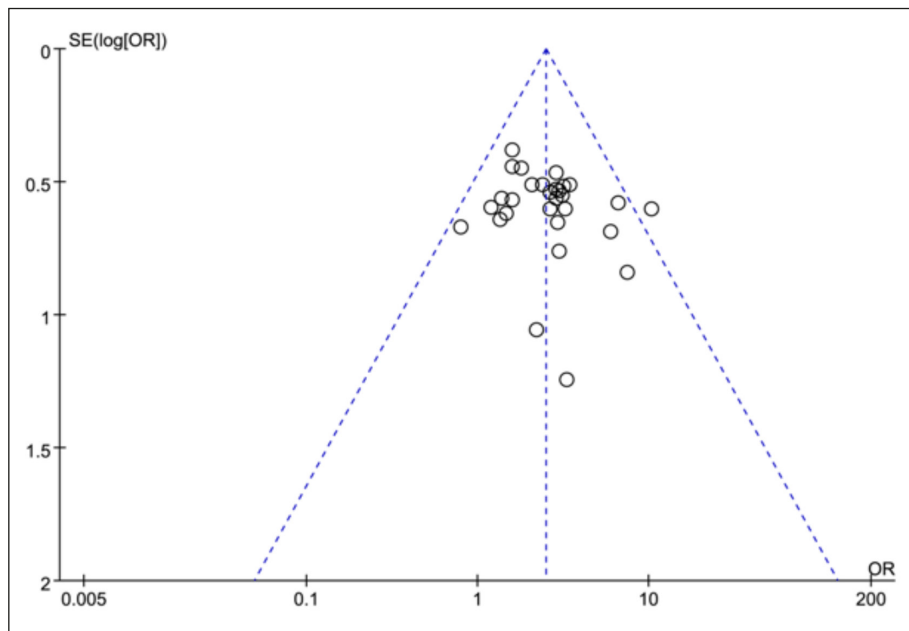
Figure 9. Funnel plot of publication bias. The inverted funnel plot was drawn with the complete remission as the evaluation index, the logarithm value of OR of each research as the ordinate, and the OR value as the abscissa. The results showed that the funnel plot was not well symmetrical, suggesting the possibility of publication bias.

and wide spread of rational drug use, TWP, as a cheap TCM immunosuppressant, has great potential in the treatment of IgA nephropathy in clinical practice.

Limitations

This study has some limitations. Firstly, 30 RCTs included were all conducted by domestic scholars, and had poor quality. Secondly, among the 30 RCTs that mentioned the random grouping, only 8 RCTs described the method in detail, and only 1 RCT described the implementation of blind method. Thirdly, the inconsistency in administration dosage, frequency and treatment course among the included RCTs might influence the meta-analysis results. Fourthly, all 30 RCTs did not report relapse of the disease, so it was impossible to evaluate the long-term effect of TWP. To conclude, the effects and safety of TWP in the treatment of IgA nephropathy still need to be further verified by multi-center and large-scale RCT research before it is widely applied in clinical practice.

Conclusions

In summary, our present evidence shows that TWP can effectively improve the remission rate, reduce proteinuria, and protect kidney function of IgA nephropathy patients, and also has good safety.

Informed Consent

Subjects followed the principle of voluntary participation and signed a study consent form.

Ethics Approval

The study was approved by the Ethics Committee of the First Affiliated Hospital, Gannan Medical University. The privacy and safety of subjects were adequately protected in accordance with clinical study guidelines.

Authors' Contributions

R.-X. Wang: searched the literatures and wrote this article. B.-Q. Liao: screened the literatures for statistically analysis. W. Chen: helped R.-X. Wang searching the literatures. Y.-M. Zhang: edited the figures and tables. X.-H. Tang: evaluated the screened literature. F.-H. Xie: designed the project and constructed the article framework.

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