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Original Article

Combination therapy of tripterygium glycosides plus valsartan in diabetic nephropathy treatment: A systematic review and meta-analysis

Wan-chun Ye[a], Jian-zhong Ye[b,c], Cheng Zheng[d], Xiao-wei He[e], Jia-jie Huang[f], Ren Ye[f,*]

[a] Department of Chemotherapy 2, Wenzhou Central Hospital, Wenzhou 325000, China
[b] State Key Laboratory for Diagnosis and Treatment of Infectious Disease, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310000, China
[c] Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Zhejiang University, Hangzhou 310000, China
[d] Department of Cardiology, The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, China
[e] Zhuang Medical College, Guangxi University of Chinese Medicine, Nanning 530000, China
[f] Department of Traditional Chinese Medicine, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, China

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ABSTRACT

Objective: To assess the efficacy and safety of the combination therapy of Chinese herbal medicines, tripterygium glycosides, plus valsartan for the treatment of diabetic nephropathy (DN).
Methods: A comprehensive research of 12 electronic databases was performed. Data of the included studies were extracted and analyzed independently by two authors, and were synthesized using Review Manager (version 5.2) and Stata (version 12.0).
Results: A total of 12 randomized controlled trials (RCTs) involving 829 patients were included. Pooled results showed that the combination therapy significantly increased total efficacy of DN patients [RR = 1.35, 95% CI (1.22, 1.50), $P < 0.001$], the level of serum albumin [Mean difference (MD) = 3.87, 95% CI (3.12, 4.62), $P < 0.001$], and significantly decreased 24 h urinary protein level [MD = −0.97, 95% CI (−1.19, −0.76), $P < 0.001$], urinary albumin-excretion rate [MD = −145.53, 95% CI (−227.95, −63.11), $P < 0.001$], and urinary β2-microglobuli level [MD = −11.86, 95% CI (−13.02, −10.69), $P < 0.001$]. No significant differences were found in levels of serum creatinine [MD = −0.26, 95% CI (−7.52, 7.00), $P > 0.05$), blood urea nitrogen [MD = 0.25, 95% CI (−0.23, 0.74), $P > 0.05$], and endogenous creatinine clearance rate [MD = −0.43, 95% CI (−3.48, 2.62), $P > 0.05$]. However, tripterygium glycosides plus valsartan seemed to exert higher adverse reaction rate than valsartan monotherapy [MD = 3.41, 95% CI (1.34, 8.66), $P < 0.05$]. There were no publication bias for all of the pooled effect sizes.
Conclusion: Combination therapy of tripterygium glycosides plus valsartan may be effective for the treatment of DN. However, the safety of the combination therapy need to be further confirmed.

1. Introduction

Diabetic nephropathy (DN) is one of the most severe microvascular complications in patients with diabetes mellitus (DM). The early pathological characterizations of DN include glomerular mesangial expansion and hypertrophy, as well as extracellular matrix accumulation and podocyte disappearance (Kato et al., 2016). It is estimated that about 20%–40% of patients with diabetes mellitus are at risk of developing DN (Xu, Diao, Liu, & Liu, 2017). Persistent proteinuria has been shown as an independent risk factor for the progression of DN (Remuzzi, Ruggenenti, & Benigni, 1997). Therefore, reducing the proteinuria level has become an important strategy to improve the prognosis.

Angiotensin II receptor blockers (ARB), such as valsartan, confer renoprotection role to improve proteinuria level in patients with DN (Viberti & Wheeldon, 2002). Tripterygium glycosides is extracted from *Tripterygium wilfordii* Hook. f., a Chinese herbal medicine. It has been widely used in rheumatoid arthritis treatment for its immunosuppressive and anti-inflammatory effects (Goldbach-Mansky et al., 2009; Zhang, Wang, & Liu, 2014). In addition, it has been demonstrated that tripterygium glycosides is a promising renoprotective drug for the treatment of DN in attenuating albuminuria (Ge et al., 2013; Jiang, 2015).

Recently, several single-center, prospective, randomized controlled trials indicate that addition of tripterygium glycosides

* Corresponding author.
E-mail address: yeren601@sina.com (R. Ye).

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might achieve better effectiveness than valsartan monotherapy in DN treatment. However, evidences for the combination therapy remain insufficient. Hence, we conducted this quantitative meta-analysis to assess the efficacy and safety of combination therapy of tripterygium glycosides and valsartan for DN comparing to valsartan monotherapy.

2. Materials and methods

2.1. Publication searching

A systematic search of 12 databases was carried out for clinical trials up to January 14, 2018, including PubMed, Web of Science, Cochrane Library Databases, OVID, EBSCO, EMBASE, CNKI, CNKI Master Degree Dissertation Databases of China, Wan Fang Databases, Wan Fang Master Degree Dissertation Databases of China, Weipu Databases, and Chinese Biomedical Literature Database. The following formula was conducted for English databases, ("tripterygium glycosides" OR tripterygium*) AND (Valsartan) AND ("diabetic nephropathy" OR "DN" OR "diabetic kidney disease"), while for Chinese databases, terms "lei gong teng duo gan" (for tripterygium glycosides), "xie sha tan" (for valsartan), and "tang niao bing shen bing" (for diabetic nephropathy) were adopted in the formula (lei gong teng duo gan) AND (xie sha tan) AND (tang niao bing shen bing). All references of relevant publications were also searched for additional analysis. Two authors (Wan-chun Ye and Jian-zhong Ye) independently completed the literature searches, discrepancies were settled by discussion or a third author (Ren Ye). Our study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.2. Inclusion and exclusion criteria

The following inclusion criteria were adopted: (1) Clinical randomized controlled trials (RCTs). (2) Patients receiving a diagnosis of DM according to the WHO diagnostic criteria for diabetes mellitus in 1999 (Alberti & Zimmet, 1998), and DN according to the Mogensen's criteria (Mogensen, Christensen, & Vittinghus, 1983). (3) Quantitative urinary protein of patients with DN was greater than 1.0 g/24 h, while serum creatinine was less than 442.0 μmol/L. (4) Combination therapy of tripterygium glycosides plus valsartan was chosen as intervention group for treatment of DN. Parallel control trials received valsartan monotherapy. Both intervention and control groups were given the same basic therapy (oral hypoglycaemic agents, anti-hypertension drugs, diet, exercise, etc.). (5) The data of interest were available.

The exclusion criteria were: (1) non-RCTs, (2) Patients received an ambiguous diagnosis, (3) There was no control group, control group did not meet the inclusion criteria, less reasonable study design or inappropriate statistical method, (4) Duplicated or incomplete publications, and (5) published in other languages (not Chinese or English).

2.3. Data extraction and quality assessment

Data of each included study were independently extracted by two authors (Wan-chun Ye and Jian-zhong Ye). Any discrepancies were consulted for consensus with the corresponding author (Ren Ye). Clinical characteristics of included publications were summarized, the main outcomes and adverse events (AEs) of each study were also extracted.

The methodological quality of each included study was evaluated by two reviewers according to the Cochrane Reviews Handbook standards.

2.4. Statistical analysis

Rev Man 5.2 Software and Stata 12.0 Software were used to perform the statistical analyses. If there were multiple measurement data, only the most long-term treatment data were adopted in the analyses. Dichotomous data were presented as risk ratio (RR) and its corresponding 95% confidence interval (CI). As for continuous data, mean value and its standard deviation were presented. The measurement data were presented as weighted mean difference (WMD).

Tau^2, Chi^2, and I^2 tests were adopted to evaluate statistical heterogeneity. The random-effect model was used to pool studies when substantial heterogeneity existed ($I^2 > 50\%$ or $P < 0.10$). Otherwise, a fixed-effect method was employed. When the heterogeneity was high, heterogeneity analysis including sensitivity analysis, subgroup analysis, and meta-regression analysis were conducted to track heterogeneous sources. The publication biases were evaluated by Begg's tests.

3. Results

3.1. Publication characteristics

The study selection process was illustrated in Fig. 1. Initially, 2653 publications were identified through searching databases, after browsing the title and abstract, 18 articles were reviewed with full texts. Finally, 12 completed RCTs ($n = 829$) were included in the current meta-analysis. The dose of valsartan and tripterygium glycosides differed among the included studies, with a range of 40–160 mg/d for valsartan and a range of 20–180 mg/d for tripterygium glycosides. The treatment duration range was 4 – 24 weeks. The main characteristics of the included studies were summarized in Table 1.

3.2. Study quality assessment

The methodological quality of the included studies was generally poor. Although all the 12 studies were RCTs, only one study mentioned the appropriate method of random sequence generation, and the allocation concealment was not reported in all articles. Moreover, none of included studies mentioned blinding of

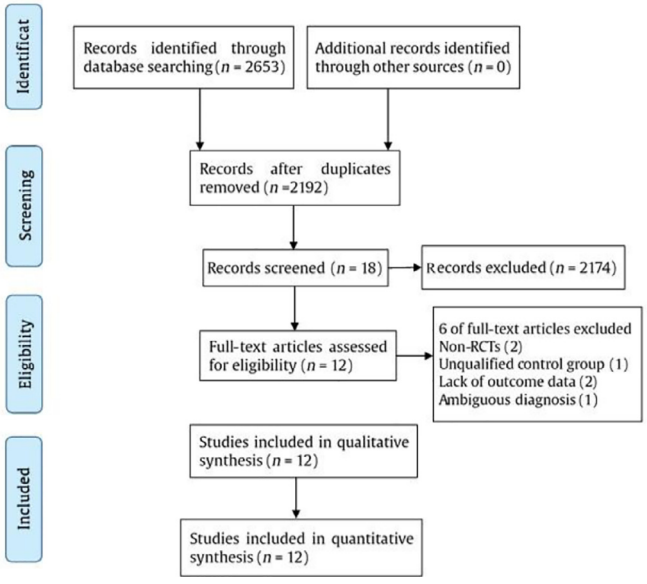

Fig. 1. Flow chart of publication searching.

Table 1
Details of included studies.

Studies	*n*/patients		Dose/(mg·d^{-1})		Duration/weeks	Indexes
	Val	Val + TG	Val	Val + TG		
Li (2011)	20	20	160	60	14	1, 2, 3, 6, 7, 9, 17, 21, 24
Zhao et al. (2011)	23	23	160	160 + 60	12	2, 3, 6, 8, 9
Cai (2012)	35	30	40–80	40–80 + 60	24	1, 2, 3, 6, 9
Wang and Zhang (2012)	52	30	160	160 + 20–60	24	2, 3, 4, 5, 6, 8, 9, 17, 18, 19, 20, 21, 22, 23
Wu et al. 2012	33	32	80–160	80–160 + 30–60	24	1, 2, 3, 6, 9, 13, 14, 15
Pu, Zou, and Pu (2013)	98	98	80–160	80–160 + 60	4	1, 2, 4, 5
Zhou (2013)	15	15	80–160	80–160 + 60–120	8	2, 3, 6, 9
Chi (2014)	25	24	160	160 + 60	12	2, 3, 8, 25
Song (2014)	40	40	40–80	40–80 + 60	24	1, 2, 6, 7, 10, 11, 12
Liu (2015)	42	42	160	160 + 20–60	24	2, 6
Wang (2016)	26	26	80	80 + 60–90	12	1, 2, 16
Xu (2016)	20	20	80	80 + 180	8	2, 3, 6, 9, 10

1. Total efficacy 2. 24 h urinary protein; 3. Serum albumin; 4. Urinary albumin-excretion rate; 5. Urinary β2-microglobulin; 6. Serum creatinine; 7. Blood urea nitrogen; 8. Endogenous creatinine clearance rate; 9. Abnormal liver function; 10. Nausea; 11. Dizzy; 12. Leucopenia; 13. Ig G; 14. C3; 15. C4; 16. Urinary microalbumin; 17. ALT; 18. ALP; 19. HbAlc (%); 20. FBG; 21. WBC; 22. RBC; 23. PLT; 24: ASI; 25. Ser; Val: valsartan; TG: tripterygium glycosides; \: Not available.

participants and personnel. However, included articles showed relatively low risk of detection bias, attrition bias, reporting bias, and other bias. The outcome of methodological quality of the included studies was shown in Fig. 2.

3.3. Outcomes

3.3.1. Total efficacy

A total of six studies reported the total clinical efficacy of tripterygium glycosides plus valsartan in the treatment of DN when compared with valsartan monotherapy. Significant statistical heterogeneity was not found in the meta-analysis ($Chi^2 = 4.57$, $I^2 = 0\%$, $P > 0.05$), thus the risk ratio (RR) was pooled by a fixed effect model, results indicated a better clinical efficacy of combination therapy than that of monotherapy [RR = 1.35, 95% Confidential Interval (CI) (1.22, 1.50), $P < 0.001$] (Fig. 3A).

3.3.2. 24 h urinary protein

All of the 12 included studies researched the 24 h urinary protein quantity of post-treatment. As significant heterogeneity existed across the studies ($Chi^2 = 105.93$, $I^2 = 90\%$, $P < 0.001$), overall effect was pooled by a random effect model. The meta-analysis showed that therapeutic method of tripterygium glycosides plus valsartan significantly decreased 24 h urinary protein level in DN treatment when compared with valsartan monotherapy [Mean difference (MD) = −0.97, 95% CI (−1.19, −0.76), $P < 0.001$] (Fig. 3B).

Five covariates were investigated as potential sources of heterogeneity using meta-regressions, but no significant variation was found (Table 2). In sensitivity analysis, the pooled MD ranged from −0.91 to −1.02 by removing every single study, indicating that none of the studies would influence the stability of summarized results, which consolidated the robustness of this meta-analysis (Fig. 4A). The results of subgroup analysis regarding publication year, sample size, follow-up periods, valsartan dosages, and tripterygium glycosides dosages further confirmed that the basic clinical characteristics of included studies were not the sources of heterogeneity (Table 3).

3.3.3. Serum albumin

There were eight studies which compared the serum albumin level of tripterygium glycosides plus valsartan treatment with valsartan monotherapy. Overall effects pooled by a fixed effect model showed that combination therapy significantly increased the serum albumin than monotherapy [MD = 3.87, 95% CI (3.12, 4.62), $P < 0.001$; heterogeneity $Chi^2 = 12.27$, $I^2 = 43\%$, $P > 0.05$] (Fig. 3C).

3.3.4. Albumin-excretion rate

Only two studies reported significant reduction of urinary albumin-excretion rate of the combination therapy, and pooled effects calculated by a random effect model further supported the conclusion [MD = −145.53, 95% CI (−227.95, −63.11), $P < 0.001$; heterogeneity $Chi^2 = 119.93$, $I^2 = 99\%$, $P < 0.001$] (Fig. 5A). Sensitivity analysis, subgroup analysis, and meta-regression analysis

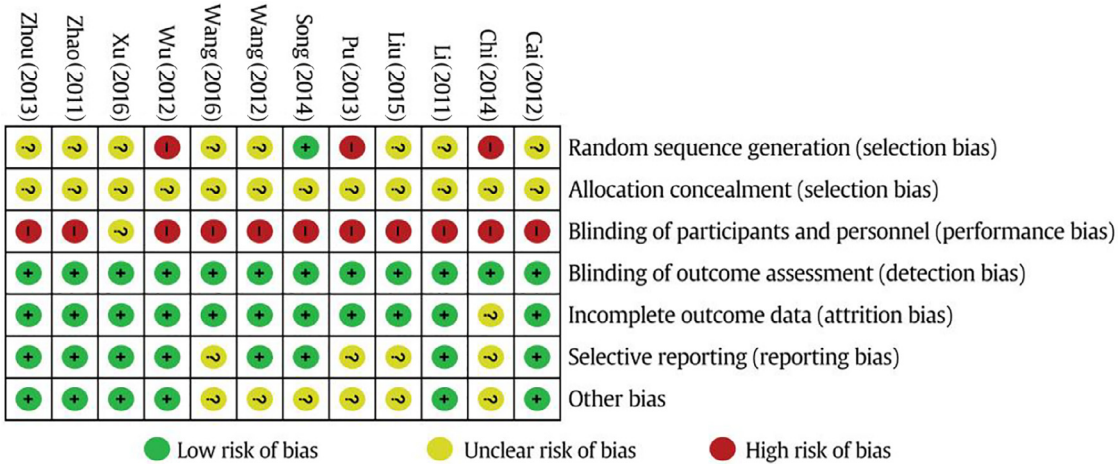

Fig. 2. Study quality assessment.

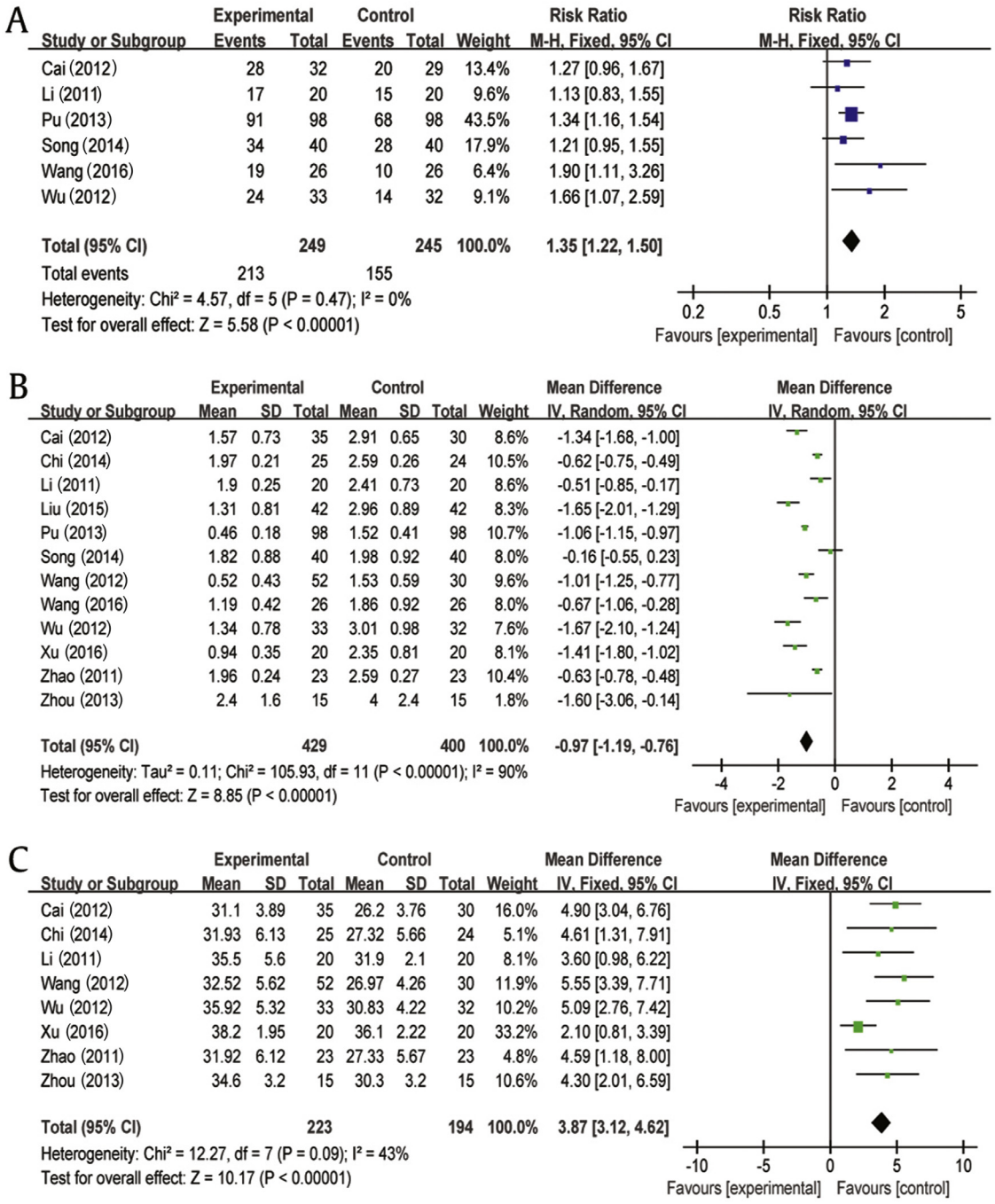

Fig. 3. Forest plot of tripterygium glycosides plus valsartan in treatment of diabetic nephropathy for (A) total efficacy, (B) 24 h urinary protein, and (C) serum albumin.

Table 2
Meta-regression based on RCT characteristics.

Outcomes	*n* / RCTs	Covariates	Coefficient	*P*
24 h urinary protein	12	Year	−0.39	0.705
		Sample size	−0.33	0.749
		Mean dose of Val	−0.41	0.693
		Mean dose of TG	−0.32	0.754
		Course	−0.53	0.608
Serum creatinine	9	Year	−0.43	0.681
		Sample size	−0.66	0.533
		Mean dose of Val	−0.26	0.803
		Mean dose of TG	−0.27	0.797
		Course	0.06	0.955

Val: valsartan; TG: tripterygium glycosides.

cannot be conducted because of limited study numbers, though significant heterogeneity presented in the pooled effects.

3.3.5. Urinary β2-microglobulin

Similarly, two studies reported urinary β2-microglobulin level of the post-treatment. Compared with valsartan monotherapy, tripterygium glycosides plus valsartan treatment significantly reduced urinary β2-microglobulin level for DN patients. [MD = −11.86, 95% CI (−13.02, −10.69), $P < 0.001$; heterogeneity $Chi^2 = 0.04$, $I^2 = 0\%$, $P > 0.05$] (Fig. 5B).

3.3.6. Serum creatinine

Serum creatinine was observed in nine studies. As illustrated in Fig. 5C, meta-analysis of the included studies showed that serum

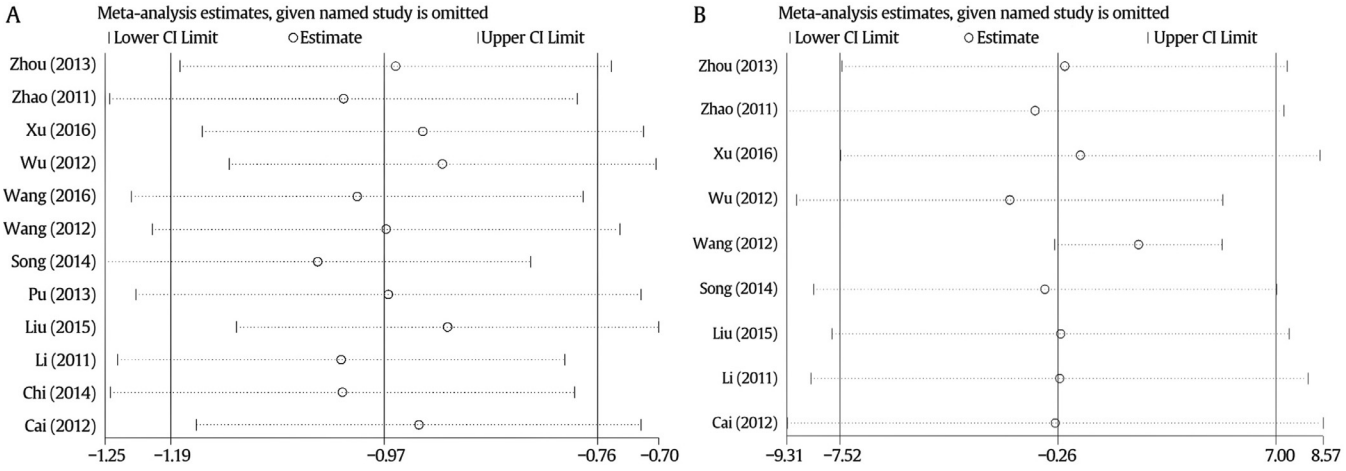

Fig. 4. Sensitivity analyses of tripterygium glycosides plus valsartan in treatment of diabetic nephropathy for (A) 24 h urinary protein and (B) serum creatinine.

creatinine level was not significantly different between combination therapy and monotherapy [MD = −0.26, 95% CI (−7.52, 7.00), $P > 0.05$; heterogeneity $Chi^2 = 49.08$, $I^2 = 84\%$, $P < 0.001$].

Similar to 24 h urinary protein, meta-regression analysis was conducted based on five covariates, and no significant variation was found (Table 2). In sensitivity analysis, the heterogeneity was significantly reduced when Wang's study (2012) was removed [MD = 2.43, 95% CI (−0.36, 5.22), $P > 0.05$; heterogeneity $Chi^2 = 6.82$, $I^2 = 0\%$, $P > 0.05$] (Fig. 4B). Heterogeneity was significantly reduced when similar publication year, valsartan dosages, and tripterygium glycosides dosages were pooled in the subgroup analysis, however, the effect sizes of subgroup analysis were similar, which were not significantly affected (Table 3).

3.3.7. Blood urea nitrogen

Two studies reported blood urea nitrogen level of the post-treatment. As shown in Fig. 6A, results of meta-analysis indicated that combination therapy did not significantly reduce the blood urea nitrogen level when compared with monotherapy [MD = 0.25, 95% CI (−0.23, 0.74), $P > 0.05$; heterogeneity $Chi^2 = 0.70$, $I^2 = 0\%$, $P > 0.05$].

3.3.8. Endogenous creatinine clearance rate

A comparison of endogenous creatinine clearance rate between combination therapy of tripterygium glycosides and valsartan with valsartan monotherapy was made in three studies (Chi, 2014; Wang & Zhang, 2012; Zhao et al., 2011) Results suggested no significant improvement regarding to the combination therapy [MD = −0.43, 95% CI (−3.48, 2.62), $P > 0.05$, heterogeneity $Chi^2 = 0.52$, $I^2 = 0\%$, $P > 0.05$] (Fig. 6B).

3.3.9. Adverse reaction rate

We pooled abnormal liver function, nausea, dizzy, leucopenia together as the whole adverse reaction because of limited available data. Meta-analysis results indicated that tripterygium glycosides plus valsartan seemed to exert higher adverse reaction rate than valsartan monotherapy [RR = 3.41, 95% CI (1.34, 8.66), $P = 0.01$, heterogeneity $Chi^2 = 3.16$, $I^2 = 0\%$, $P > 0.05$] (Fig. 6C).

3.4. Publication bias

The funnel plots for evaluating publication bias regarding to all of the pooled effects showed symmetrical distribution (Fig. 7), and Begg's tests were also not significant for publication bias ($P = 0.452$

Table 3
Subgroup analyses on outcome measures.

Outcomes	Covariates	Subgroup	*n*/RCTs	Pooled effects			Heterogeneity	
				Mean difference	95% CI	*P*	I^2/%	*P*
24 h urinary protein	Year	≤ 2013	7	−1.02	[−1.28, −0.77]	< 0.01	87.2	< 0.01
		> 2013	5	−0.90	[−1.19, −0.76]	< 0.01	89.6	< 0.01
	Sample size	≤ 70	8	−0.97	[−1.24, −0.69]	< 0.01	86	< 0.01
		> 70	4	−0.98	[−1.37, −0.60]	< 0.01	90	< 0.01
	Mean dose of Val	≤ 80 mg/d	4	−0.90	[−1.47, −0.33]	< 0.01	89.3	< 0.01
		> 80 mg/d	8	−1.00	[−1.25, −0.75]	< 0.01	91.0	< 0.01
	Mean dose of TG	≤ 60 mg/d	9	−0.94	[−1.18, −0.71]	< 0.01	91.8	< 0.01
		> 60 mg/d	3	−1.12	[−1.74, −0.49]	< 0.01	73.5	0.023
	Course	≤ 3 months	6	−0.88	[−1.14, −0.62]	< 0.01	90.2	< 0.01
		> 3 months	6	−1.05	[−1.50, −0.61]	< 0.01	90.1	< 0.01
Serum creatinine	Year	≤ 2013	6	0.22	[−8.88, 9.33]	0.962	89.6	< 0.01
		> 2013	3	−1.80	[−10.99, 7.40]	0.702	0	0.675
	Sample size	≤ 70	6	2.27	[−1.59, 6.12]	0.249	25.1	0.246
		> 70	3	−6.18	[−19.25, 2.88]	0.354	59.6	0.084
	Mean dose of Val	≤ 80 mg/d	3	1.37	[−2.53, 5.26]	0.491	0	0.528
		> 80 mg/d	6	0.11	[−11.05, 11.27]	0.984	87.8	< 0.01
	Mean dose of TG	≤ 60 mg/d	7	0.79	[−7.40. 8.97]	0.851	87.7	0
		> 60 mg/d	2	−5.32	[−17.06, 6.43]	0.375	0	0.872
	Course	≤ 3 months	3	2.29	[−3.18, 7.76]	0.412	8.5	0.335
		> 3 months	6	0.27	[−9.45, 9.99]	0.957	86.9	< 0.01

Val: valsartan; TG: tripterygium glycosides.

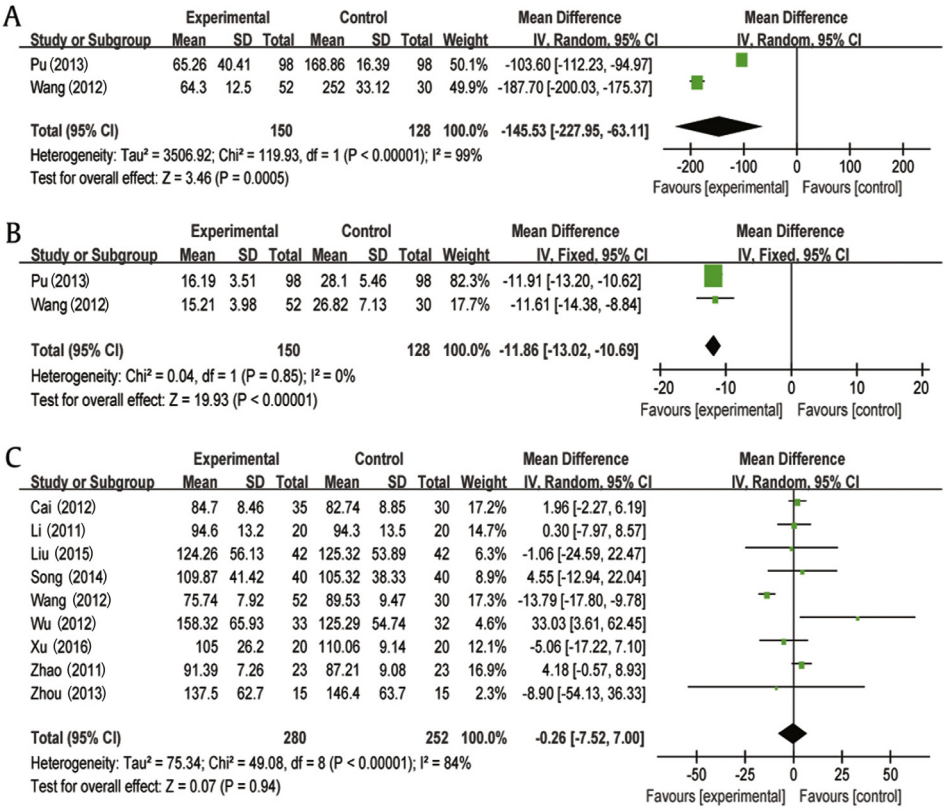

Fig. 5. Forest plot of tripterygium glycosides plus valsartan in treatment of diabetic nephropathy for (A) urinary albumin-excretion rate, (B) urinary β2-microglobulin, and (C) Serum creatinine.

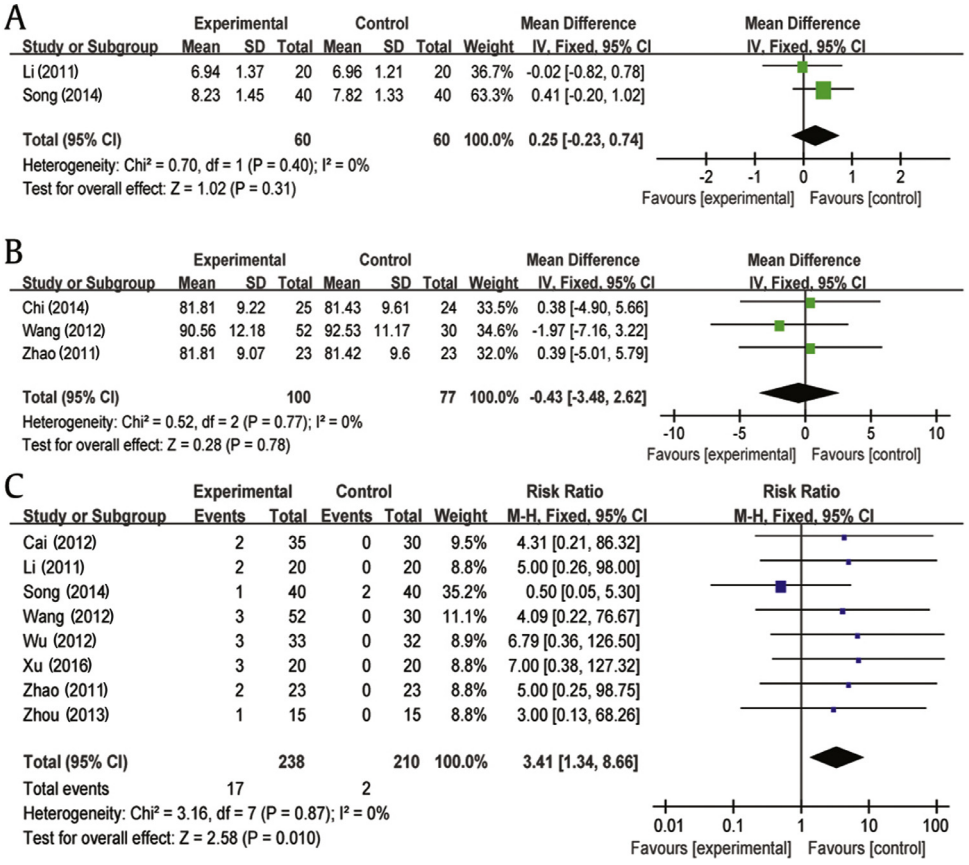

Fig. 6. Forest plot of tripterygium glycosides plus valsartan in treatment of diabetic nephropathy for (A) blood urea nitrogen, (B) endogenous creatinine clearance rate, and (C) adverse reaction rate.

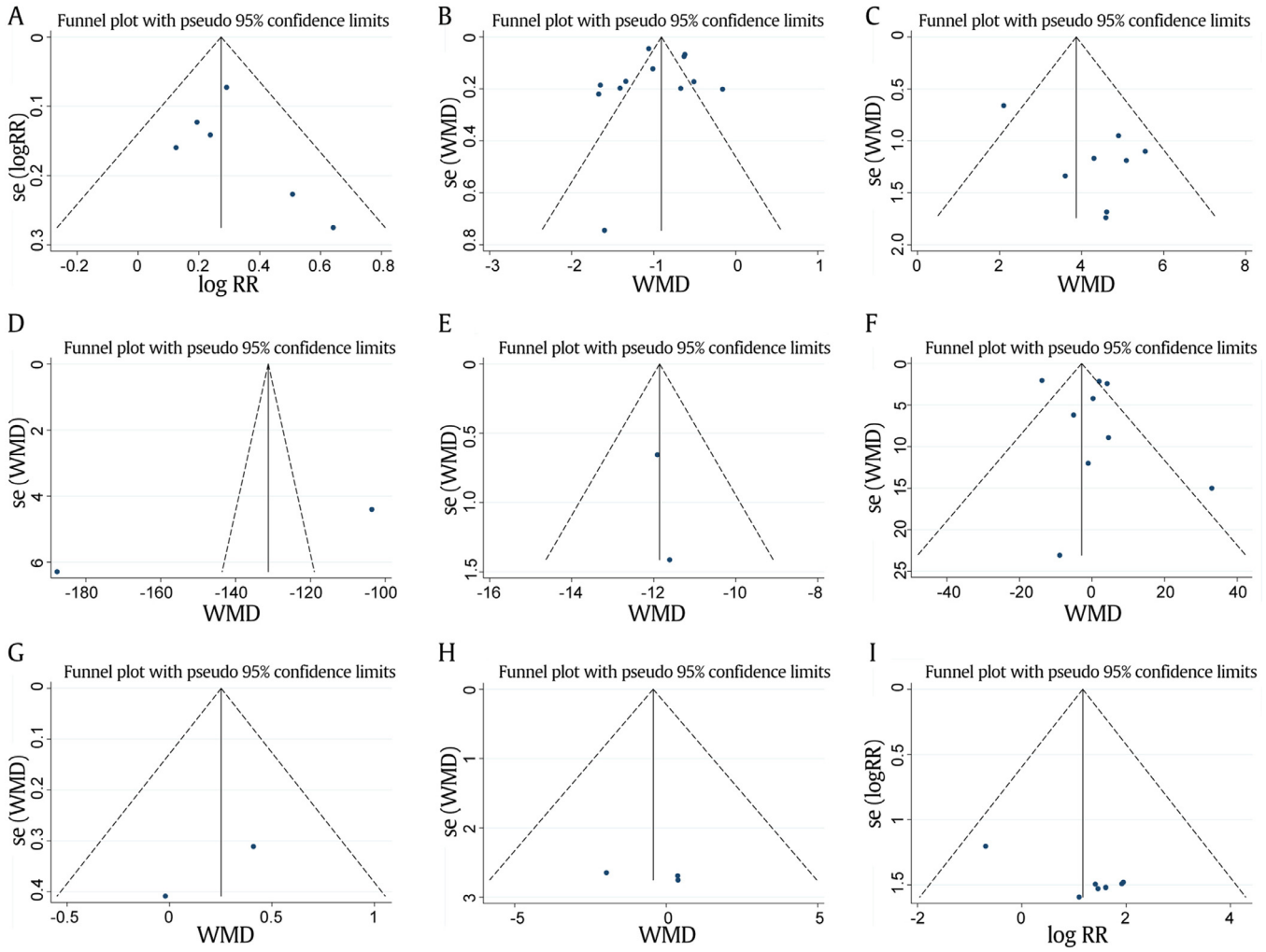

Fig. 7. Funnel plot for publication bias of meta-analysis of (A) total efficacy; (B) 24 h urinary protein; (C) serum albumin; (D) urinary albumin-excretion rate; (E) urinary β2-microglobulin; (F) serum creatinine; (G) blood urea nitrogen; (H) endogenous creatinine clearance rate; (I) adverse reaction rate.

for total efficacy; $P = 0.631$ for 24 h urinary protein; $P = 0.902$ for serum albumin; $P = 1.000$ for urinary albumin-excretion rate; $P = 1.000$ for urinary β2-microglobulin; $P = 0.917$ for serum creatinine; $P = 1.000$ for blood urea nitrogen; $P = 1.000$ for endogenous creatinine clearance rate, and $P = 0.386$ for adverse reaction rate).

4. Discussion

Traditional Chinese medicine (TCM) has been nourished by Chinese culture for thousands of years and it is generally practiced and delivered by qualified practitioners (Jin et al., 2016). Tripterygium glycosides has various TCM effects including dispelling wind, detoxification, eliminating dampness, subsidence of swelling, and dredging collaterals according to the theory of Chinese medicine (Li et al, 2015). While for the Western medical theory, tripterygium glycosides not only have potent anti-inflammatory and immunomodulatory effects, but also has a direct analgesic effect (Raphaela et al., 2009). Tripterygium glycosides has been widely used for the long-term treatment of inflammatory disorders, including chronic nephritis, ankylosing spondylitis, and rheumatoid arthritis (Ji et al., 2015). More recently, tripterygium glycosides has been used in treatment of diabetic nephropathy (DN) with satisfactory efficacy (Wu et al., 2017). A systematic review and meta-analysis of effectiveness and safety of tripterygium glycosides for DN treatment has been conducted (Hong, Gui, Cai, & Lan, 2016). However, this study was insufficient to evaluate the clinical efficiency: (1) Only 211 publications in two databases (Pubmed and CNKI) were initially identified, which could not guide clinical practice and leading to a significant publication bias regarding to tripterygium glycoside-related toxicity. (2) The study only reported four outcomes including clinical efficacy, 24 h urinary protein, serum creatinine, and toxicity, so more detailed outcomes need to be disclosed. (3) Heterogeneous sources were not traced in the meta-analysis. (4) It has been more than two years (before 2014) since the study conducted. After that, new randomized controlled trials (RCTs) have been published.

In this meta-analysis of 829 patients from 12 studies, we found that tripterygium glycosides plus valsartan significantly increased the total efficacy when compared with valsartan monotherapy [RR = 1.35, 95% CI (1.22, 1.50), $P < 0.001$; heterogeneity $Chi^2 = 4.57$, $I^2 = 0\%$, $P > 0.05$]. This result confirms a certain application value of tripterygium glycosides in DN treatment. Furthermore, the combination therapy significantly reduced 24 h urinary protein level, with significantly lower urinary albumin-excretion rate and urinary β2-microglobulin, and unexpectedly, with significantly higher serum albumin in patients with DN. However,

there were no significant differences in reduction of serum creatinine, blood urea nitrogen, and endogenous creatinine clearance rate.

Obviously, heterogeneity existed when effects were pooled regarding to outcomes of 24 h urinary protein level, urinary albumin-excretion rate and serum creatinine. However, no factors were found that may significantly affect the heterogeneity and effect sizes for 24 h urinary protein level by sensitivity analysis and subgroup analysis. In addition, meta-regression analysis also failed to trace the factors that contributed to the heterogeneity. Similarly, no significant variation was found in meta-regression analysis with regarding to serum creatinine, but heterogeneity significantly reduced when Wang's study (2012) was excluded in the sensitivity analysis, and no significant variation was found when similar publication year, valsartan dosages, and tripterygium glycosides dosages were pooled in the subgroup analysis, this may due to limited included studies and small sample size in the subgroup. However, certain set of confounders which might be one of the heterogeneity sources did not significantly affect the effect sizes (Table 3). Heterogeneous sources of pooled effects with urinary albumin-excretion rate were not found because of limited study numbers.

Among 12 included studies, adverse events were reported in eight studies, which included abnormal liver function, nausea, dizzy, and leucopenia. There was significant difference between tripterygium glycosides plus valsartan and valsartan monotherapy in occurrence of adverse events. No withdrawal from clinical studies was reported due to the adverse events in all the eight included studies, which indicated a plausible slight influence of tripterygium glycosides on patients. However, more safe and stable process of pharmaceutical preparations remains to be developed.

Several limitations in this study should be addressed: (1) All of the included studies were limited in Chinese population, which indicated a high risk of selection bias, therefore the pooled effects from these trials should be interpreted with caution. (2) Significant clinical heterogeneity existed in some outcomes, and sources of heterogeneity could not be traced by meta-regression, sensitivity analysis, or subgroup analysis. (3) The methodological quality of included studies with small sample size was generally poor, with most studies did not mention random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments. It is partially because the Chinese journal editors usually encourage authors to focus on the research results and discussion sections of their manuscripts and shorten the methods section of their papers (Jin et al., 2016), with limited length to elaborate the detailed methodological design, including abovementioned blinding of participants and personnel.

5. Conclusion

Our study suggested that the combination therapy of tripterygium glycosides and valsartan may be effective in DN treatment and can be used as a promising strategy for enhancing total efficacy, increasing serum albumin, and decreasing 24 h urinary protein, urinary albumin-excretion rate, and urinary β2-microglobulin level. However, the adverse reaction rate should not be neglected, more stable pharmaceutical procedures for Chinese herbal medicine need to be developed. Furthermore, due to the low methodological quality of included trials, rigorous multi-center and large sample size clinical studies are proposed to further verify the efficacy and safety.

Conflict of interest

The authors declare no conflict of interest.

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