

Efficacy and safety of tripterygium glycosides in the treatment of hyperthyroidism

A systemic review and meta-analysis

Chunyan Xie, MN^a, Chaozhu He, PhD^a, Jun Gao, PhD^b, Shulei Jia, MM^{a,*}

Abstract

Background: Hyperthyroidism is a condition in which the thyroid gland is overreactive and produces excess amounts of thyroid hormone. Tripterygium glycosides, traditional Chinese medicine has been widely used in the treatment of rheumatoid arthritis, nephrotic syndrome, hyperthyroidism and other diseases due to its anti-inflammatory and immunosuppressive effects. Evidence-based research is becoming popular especially with the application of Chinese traditional medicine. This paper systematically reviews and evaluates existing clinical data on the efficacy and safety of Tripterygium glycosides in the treatment of hyperthyroidism.

Materials and methods: PubMed, Cochrane library and EMBase, Chinese biomedical literature database (CBM), Chinese journal full-text database (CNKI), Wan fang digital periodical full-text database and China Science and Technology Journal Database (VIP) were searched based on the defined inclusion and exclusion criteria. Data extraction, research quality assessment and meta-analysis were conducted with RevMan5.3 software. Trial sequential analysis (TSA) was used to evaluate information size and treatment benefits.

Results: Seventeen randomized controlled clinical trials with 1536 participants were included in the systematic review. In the meta-analysis, there were two subgroups: Tripterygium glycosides combined with thiamazole and prednisone group; Tripterygium glycosides combined with thiamazole group. The study results revealed that the degree of exophthalmos, FT3, FT4, BGP, and AKP decreased while TSH, SOD, GSH-PX increased after the addition of Tripterygium glycosides. This study results suggested that Tripterygium glycosides combined with western medicine are an effective therapy for hyperthyroidism.

Conclusion: This study indicates that Tripterygium glycosides enhances the effect of thiamazole and prednisone in the treatment of hyperthyroidism and without increasing the risk of adverse events.

Abbreviations: RCT = randomized controlled trial, RIS = required information size, TAO = thyroid associativity ophthalmocace, TSA = trial sequential analysis, TWP = Tripterygium Wilfordii Polyglycosides.

Keywords: hyperthyroidism, meta-analysis, prednisone, thiamazole, Tripterygium Wilfordii

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Hyperthyroidism is a clinical condition which is characterized by the production of excess thyroid hormone.^[1,2] In recent years, the incidence rate of hyperthyroidism has increased.

The clinical manifestations of hyperthyroidism comprise of a series of symptoms such as hypermetabolic syndrome, goiter, exophthalmos, insomnia, and increased heart rate.^[3] The effects of hyperthyroidism in humans are multifaceted affecting the heart, blood, nerves, circulatory system, and also important organs such as the eyes, intestines, and ovaries. In particular, eyelid retraction, and eye movement disorders caused by exophthalmos affect the patients' appearance and even cause blindness.^[4,5] The most commonly used treatment for hyperthyroidism exophthalmus is immunosuppression. Currently, available conventional therapeutic drugs are mainly glucocorticoids which cause a reduction in the infiltration of inflammatory cells, improve the edema and inflammatory reactions of the tissues around the eyelids and the extraocular muscles,^[6,7] thereby reducing the pressure on the eyes. Thioureas are the most commonly used anti-thyroid drugs.^[8] However, these drugs are associated with adverse effects such as liver damage, allergic reactions and leukopenia.

Tripterygium is a vine-like plant growing in the Southeast parts of China and has been used in both ancient and modern times.^[9] Tripterygium wilfordii polyglycosides (TWP) is a glycoside extracted from the roots of tripterygium, and its main component is epoxy diterpene lactones. TWP possess a number of pharmacological effects such as detoxification, promoting blood circulation, inflammation prevention, immunosuppression, anti-tumor and anti-fertility.^[10]

Modern pharmacological research indicates that TWP has significant inhibition on T-lymphocyte.^[11] It has a regulatory effect on the body's autoimmunity,^[12] hence used for the treatment of autoimmune diseases such as rheumatoid arthritis,^[13] Crohn disease,^[14] systemic lupus erythematosus^[15] and connective tissue diseases.^[16] TWP has been widely used in clinical trials for the treatment of hyperthyroidism in China.

Unlike traditional Chinese medicine decoctions, TWP is mostly made in the form of tablets. It has the advantages of convenient storage and portability, and the amount used each time is much smaller than that of traditional Chinese medicine decoction.^[17] The dosage of TWP for treating hyperthyroidism is 3 times a day, 30 mg for each time.^[22,33] Furthermore, the TWP tablets eliminate the peculiar smell of traditional Chinese medicine decoction and also help the patients to accurately control the dosage of the medicine, hence it is easily accepted by the general public.^[18,19] This paper presents a meta-analysis to evaluate the efficacy and safety of TWP combined with thiamazole and prednisone in the treatment of hyperthyroidism based on randomized controlled trials.

2. Methods

2.1. Eligibility criteria

Studies were included if the design was an RCT with TWP used in the treatment of hyperthyroidism, and the studies reported either in Chinese or English literature.

Studies were excluded if the course of treatment lasted less than three months or the therapeutic effects could not be judged due to incomplete information. Repeated studies were also excluded.

2.2. Patients

Patients were included if they had typical clinical symptoms such as hypermetabolic syndrome (irritability, obvious emaciation, fast heartbeat, diarrhea, low fever, exophthalmos, etc.), thyromegaly, and thyroid hormone met the diagnostic criteria for hyperthyroidism.^[20]

Patients were excluded if they had thyrotoxic storm, thyroid tumors, bone marrow suppression, mental illness, fertility requirements, exophthalmos caused by intracranial tumors, contraindications to glucocorticoids and allergic reactions to the drugs used in this study.

2.3. Interventions

The control group used thiamazole or a combination of prednisone whereas the intervention group had TWP administered. The study was divided into two subgroups based on the combination regimen: TWP combined with thiamazole group (test group) versus thiamazole group (control group); TWP combined with thiamazole and prednisone (test group) versus thiamazole combined with prednisone group (control group). The dose and usage of the two groups of drugs were almost similar.

2.4. Ethical review

Ethical approval and patient consent were not applied because the meta-analysis was based on published research.

2.5. Primary outcomes

Thyroid hormone indicators, such as serum-free triiodothyronine (FT3), serum-free thyroxine (FT4), thyroid-stimulating hormone (TSH); other disease-related biochemical indicators such as superoxide dismutase (SOD), Glutathione peroxidase (GSH-Px), plasma osteocalcin (BGP), alkaline phosphatase (AKP) and other outcomes such as the degree of thyrotoxic exophthalmos, curative effect of hyperthyroidism and adverse reactions.

2.6. Literature search strategy

A systematic search of articles was conducted using the following English databases; PubMed, Cochrane library, EMBase and Chinese database; China biomedical literature database (CBM), China Science and Technology Journal Database (VIP), Chinese journal full-text database (CNKI) and Wan-Fang digital periodical full-text database. The search timelines were from the establishment of the databases up to July 2019. English search keywords used included: "Hyperthyroidism" and "Tripterygium". The search strategy for PubMed is shown at the end of the article. Keywords used in Chinese were "Lei gong Teng", "Jia Kang". All animal experiments were excluded from the study.

2.7. Literature selection and data management

Studies that are noticeably inapplicable based on reading the titles and abstracts will be deleted. In addition, any duplicated articles were eliminated. A final screening was done by reading the full text of the selected articles. The main data included baseline data of patients, medication information and reported outcomes. The studies selection and data management processes were independent of each other and data cross-checking was done. The literature selection process is as shown in the Figure 1.

2.8. Statistical analysis

RevMan5.3 software was used for meta-analysis. To analyze the heterogeneity of the clinical methodologies (age, gender, drug type, usage, and dosage) included in the study, the χ^2 test and the I^2 test were used.^[21] When $P > .1$, $I^2 < 50\%$, the trial did not show any significant heterogeneity and the fixed effect model was used. When $P < .1$, $I^2 > 50\%$, there was significant clinical heterogeneity hence subgroup analysis or sensitivity analysis was conducted. Risk ratio (RR) was used to analyze the statistics for categorical variable whereas the mean difference (MD) was used to analyze the statistic for the continuous variable. For the combined analysis, 95% confidence interval was used. When $P < .05$, there was a significant difference between the two groups. The U test was used to prove the hypothesis test while the forest plot presented the meta-analysis results and trial sequential analysis (TSA) was used to evaluate information size and treatment benefits.

3. Results

3.1. Characteristics of patients

After careful selection and evaluation, 17 studies were considered for the systematic review. These studies were published in Chinese.

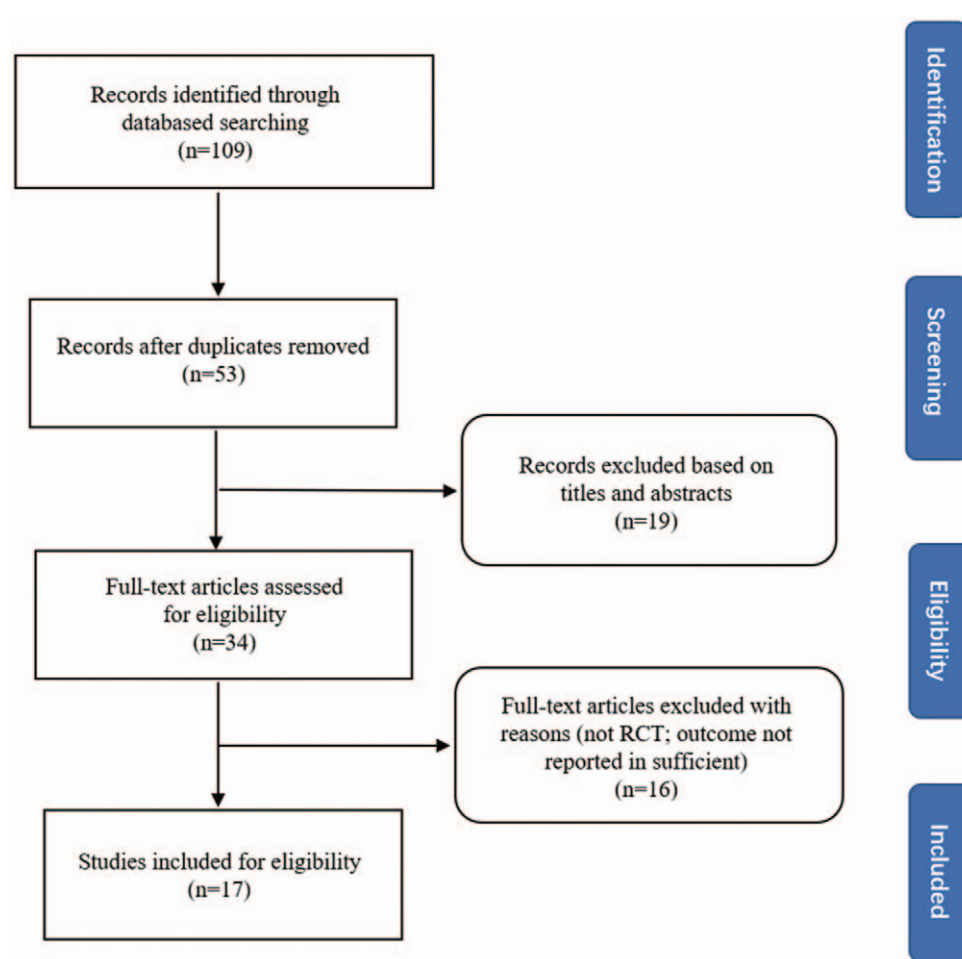


Figure 1. Flowchart of study selection process.

The patients' characteristics are shown in Table 1. The patients included in the study were 1536 from randomized controlled trials. Based on the symptoms of hyperthyroidism, the types of drugs, and the reported outcomes, 17 studies were divided into two subgroups for meta-analysis: TWP combined with thiamazole group; TWP combined with thiamazole, Prednisone group. All studies showed that the baseline data for the experimental group and the control group were comparable.

3.2. Quality assessment

The Cochrane reviewers' handbook was used to conduct a quality assessment of RCTs, which is a multi-verified scale having good reliability and validity. The methodological quality of the 17 articles included was not all high. For the included studies, fourteen of seventeen articles (82.4%) described the randomized methods.^[22,23,25,26,28-31,33-38] We judged three study to be at high risk of bias for this part because of allocation based on the date of admission or different drugs.^[24,27,32] As for allocation concealment, we classified their risks are unclear because all studies did not contain enough details to allow us to judge this field. All studies had not mentioned the specific detail of blinding. In addition, considering that it was difficult to achieve a blinded study of participants and personnel because clinical trials involve

ethical issues, researchers need to explain the study methods and processes to participants and obtain informed consent from them before the study began, so we judged the risk as unclear. Considering that the blinding of outcome assessment has little effect on the results, we consider that all studies in this part as low risk. Only one article had not provided information on the loss of cases and the reasons why participants withdrew, so we classified it existed a high risk of attrition bias.^[38] Other studies have retained the full sample size, so we rated it as low risk in this area. Figures 2 and 3 show the risk of bias in the included studies.

3.3. Outcomes

3.3.1. TWP combined with thiamazole, prednisone group

3.3.1.1. Curative effect on TAO. Nine studies reported the efficacy of TWP combined with thiamazole and prednisone in the treatment of TAO. There were 380 patients in the combined group and 274 patients in the control group.^[23-31] The results showed no statistical heterogeneity ($P=.35$, $I^2=10\%$) and therefore the fixed effect model was used for meta-analysis. The results further indicated that TWP combined with thiamazole and prednisone was more effective in the treatment of TAO (efficacy was assessed by NOSPECS) [RR=1.38, 95% CI (1.28, 1.49), $P<.00001$] (Fig. 4A).

Table 1
Characteristics of participants in included studies.

Included trials	Sample size (n)	Mean Age (yr)	Gender (Male/female) (n)	Duration of Hyperthyroidism (years)		The degree of exophthalmos (mm)		Treatment (months)	Outcomes
				Exp/Cor	Exp/Cor	Exp/Cor	Exp/Cor		
TWP combined with Thiamazole, Prednisone group (9 trials)									
Li et al, 2017	40/40	32.2±3.5;31.5±3.2	18/22;17/23	0.2–1.1; 0.3–1.0	20.22±1.77; 20.85±1.73	3	AB		
Jiang, 2013	42/42	38.6±1.8;38.3±1.7	9/33;12/30	1–13; 1–10	N/A	3	A		
Zhang et al, 2010	50/48		The average age was 33.5 years; the course of disease was 6.5 years			3	AO		
Gao, 2018	45/45	40.91±10.11;40.95±10.21	27/18;28/17	1–9; 1–9	20.01±1.19; 20.03±1.15	N/A	A		
Li, 2015	57/57	35.7±8.2;35.5±8.4	20/37;21/36	0.4–12; 0.4–11	N/A	3	AB		
Chi, 2017	54/54	33.1±5.6;33.9±5.3	27/27;28/26	0.6–11; 0.5–12	20.9±1.7; 20.3±1.8	3	AB		
Liao, 2012	33/33		The mean age was(32.6±2.9)years; the course of disease was 0.5–9 years			3	A		
AO, 2015	40/40	33.2±2.4;32.9±3.5	15/25;16/24	0.3–10; 0.5–9	20.92±1.78; 20.79±1.62	3	AB		
Xue et al, 2019	50/50		No details are described, only the baseline is comparable			3	AB		
TWP combined with Thiamazole group (8 trials)									
Chen et al, 1998	30/30		The average age was 26 years old and no other details			3	EFKLM		
Li et al, 2013	30/30	35.5±9.5;34.8±9.1	12/18;11/19	0.4–1.2; 0.5–1.3	N/A	3	CDN		
Wang, 2015	42/42	36.45±6.15;35.98±7.74	20/22;17/25	0.4–6.25; 0.25–6	N/A	3	DEFGHU		
Wang, 2014	46/46	37.5±6.9;37.4±7.1	17/29;18/28	0.3–6.6; 0.3–6.5	N/A	3	CGHU		
Zhang, 2015	45/45	46.7±1.2;45.7±1.2	28/17;30/15	0.4–5; 0.4–5.4	N/A	N/A	CDN		
Peng, 2017	65/65	42.5±9.4;41.8±9.1	28/37;25/40	0.4–9; 0.4–8	N/A	3	CDEFHINJ		
Zhang et al, 2016	42/42	36.8±6.5;36.4±7.2	18/24;20/22	0.4–6.5; 0.3–6.4	N/A	3	CGHU		
Li, 2017	58/58	36.78±5.19;37.25±6.34	23/35;21/37	0.25–4.8; 0.3–4.6	N/A	3	CGHU		

Note: BEF: A: Curative effect of TAO; B: The degree of exophthalmos; C: Curative effect of hyperthyroidism; D: TSH; E: FT3; F: FT4; G: SOD; H: GSH-Px; I: BGP; J: AKP K: TGAB; L: TMAB; M: TS; N: Adverse reaction; O: Quality of life; N/A: Not mentioned.

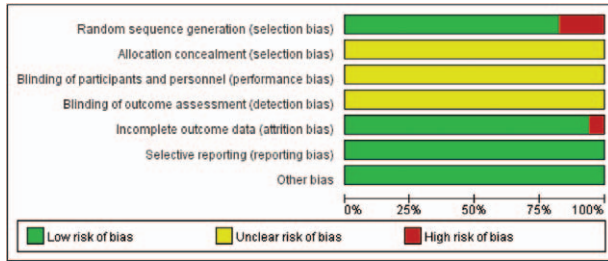


Figure 2. Risk of bias graph.

TSA suggested that the calculated sample size was RIS (required information size)=148 [the control event rate=66.5%, RRR (relative risk reduction)=−30%, two-sided test, $\alpha=0.05$, Power=80%, $I^2=10\%$]. The cumulative Z-curve crosses the vertical axis of RIS=148, and also crosses trial sequential monitoring boundary and the traditional boundary value ($z=-1.96$), indicating that the sample size included in this meta-analysis is sufficient to reach a firm conclusion (Fig. 4B).

3.3.1.2. The degree of thyrotoxic exophthalmos. Five trials were used in comparing the effect of TWP combined with thiamazole and prednisone on the degree of thyrotoxic exophthalmos.^[23,24,27,28,30] The test group and the control groups each had 241 participants. The results showed statistical heterogeneity ($P=.007$, $I^2=71\%$) since each trial did not demonstrate clinical heterogeneity (patients' age, sex, course of treatment into the subgroups being similar at baseline data between the two groups). Therefore, the random-effects model was used for analysis. The results showed statistically significant effects on the experimental group on the degree of thyrotoxic exophthalmos [MD=−4.01 mm, 95% CI(−4.26, −3.76), $P<.00001$] as shown in Figure 5.

TSA showed that the RIS=14 (mean difference=−4.011, variation=1.954, two-sided test, $\alpha=0.05$, Power=80%, $I^2=71\%$). Each RCT sample size included in this meta-analysis is more than the RIS, indicating that current evidence was sufficient to reach a firm conclusion.

3.3.2. TWP combined with thiamazole group

3.3.2.1. Curative effect on hyperthyroidism. As shown in Figure 6A, seven trials reported the effectiveness of TWP combined with thiamazole in the treatment of hyperthyroidism.^[22,32–37] The criteria for determining efficacy in clinically controlled experiments included: the patient's symptoms disappeared, the heart rate was normal, and related indicators of thyroid hormone returned to normal. The significant effects observed were when the symptoms and signs were improved, the heart rate was normal, and related indicators were normal. If the symptoms and signs were improved, the heart rate had slowed down, and the thyroid hormone and other related indicators were recovered, we consider it effective. It was judged to be ineffective when the symptoms, the thyroid hormone and other related indicators had not improved significantly after treatment. The test group had 314 patients while the control group had 261 patients. there was no significant heterogeneity between the results ($P=.76$, $I^2=0\%$), therefore a fixed-effects model was used for the analysis. All articles showed similar results, with a combined RR of 1.2 which showed that TWP combined with thiamazole and prednisone was more effective than thiamazole [RR=1.2, 95% CL (1.13, 1.28), $P<.00001$].

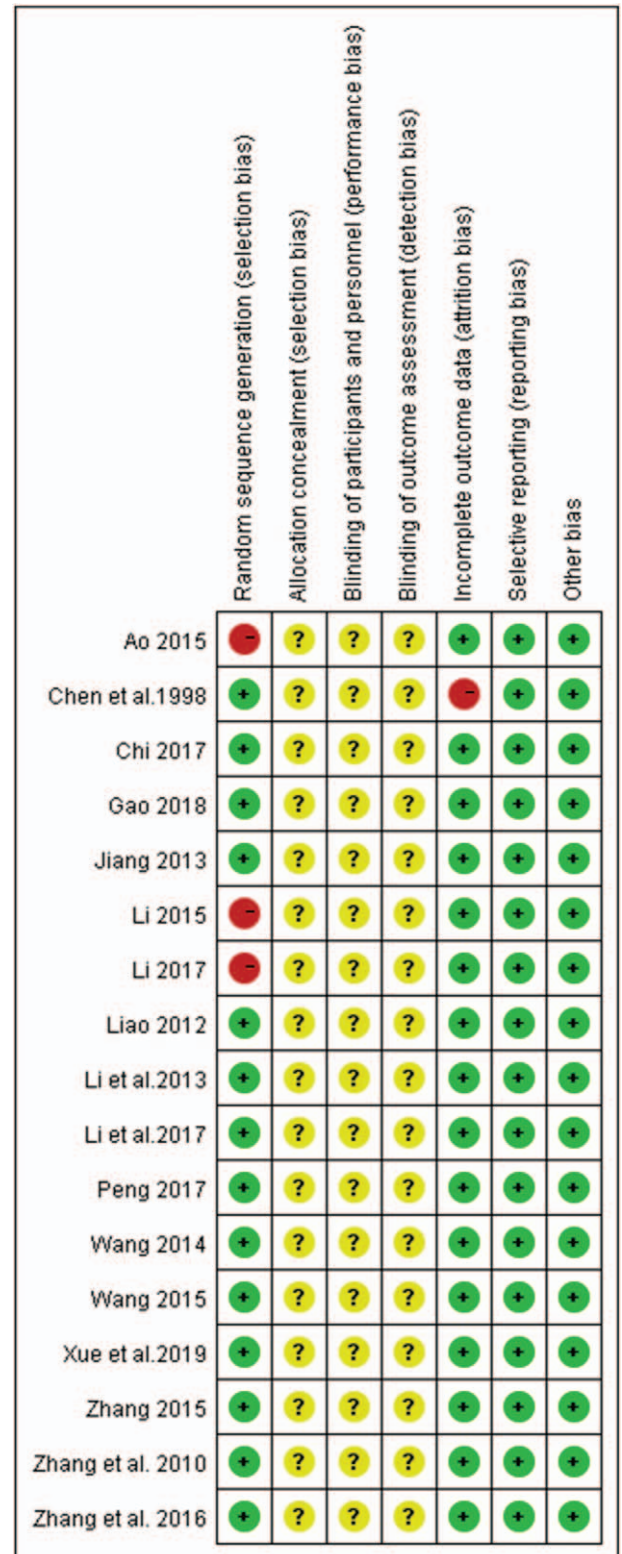
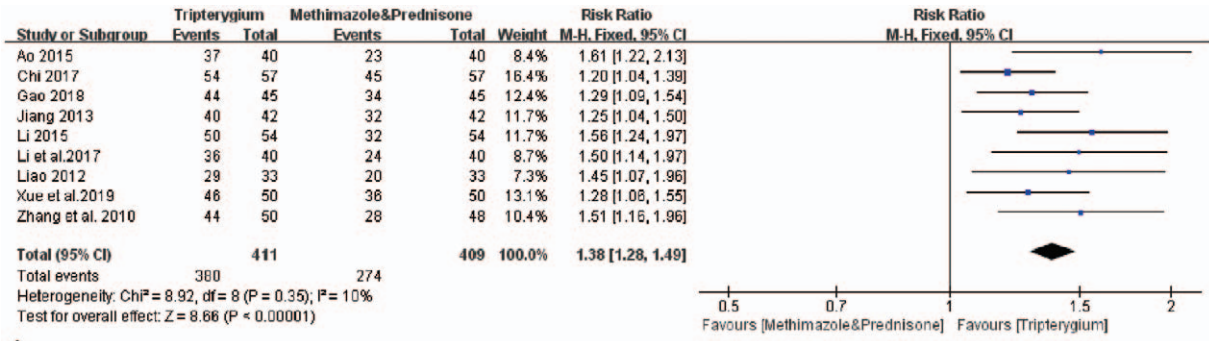
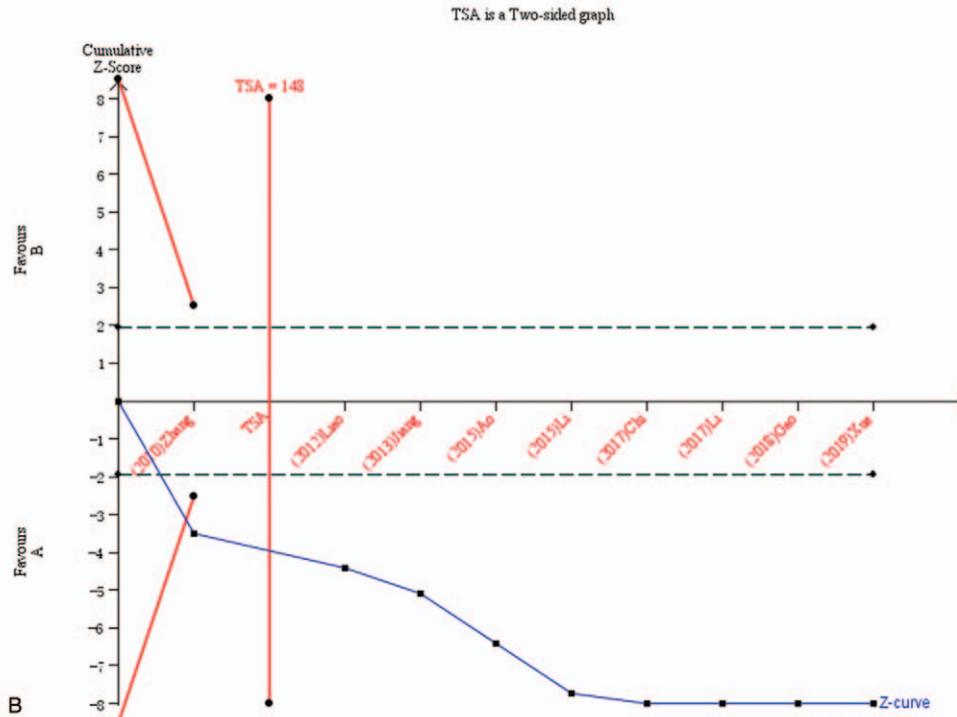


Figure 3. Risk of bias summary.

TSA showed that the RIS=153 (the experimental event rate in our meta-analysis=95%, the control event rate in our meta-analysis=80%, RRR=−18.75%, two-sided test, $\alpha=0.05$, Power=80%, $I^2=0$). The cumulative Z-curve crosses the vertical



A



B

Figure 4. A: Curative effect on TAO. B: Trial sequential analysis of curative effect on TAO.

axis of RIS=153, and also crosses the TSA boundary value and the traditional boundary value ($z = -1.96$), indicating that the sample size included in this meta-analysis was sufficient (Fig. 6B).

3.3.2.2. *Effects on thyroid hormone.* Four studies reported higher TSH after using TWP combined with thiamazole. The

treatment groups comprised of 182 patients while the control group had 182 patients.^[33,34,36,37] There was no statistical heterogeneity ($P = .63$, $I^2 = 0\%$) in the 2 groups, hence a fixed effect model was used for the analysis. The results showed that TSH was more effectively elevated in a combination of TWP and thiamazole [MD=0.23 (mU/L), 95% CL (0.20, 0.26), $P < .00001$] (Fig. 7).

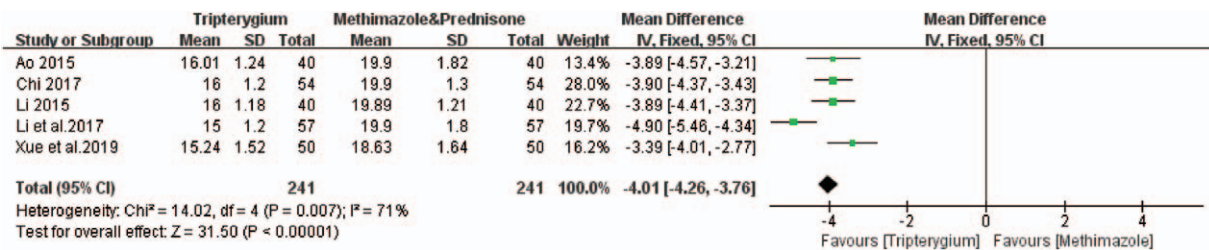
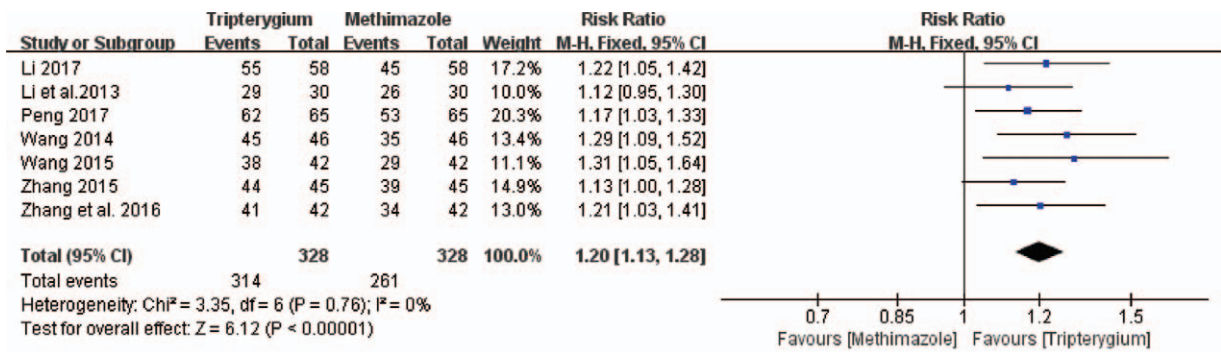
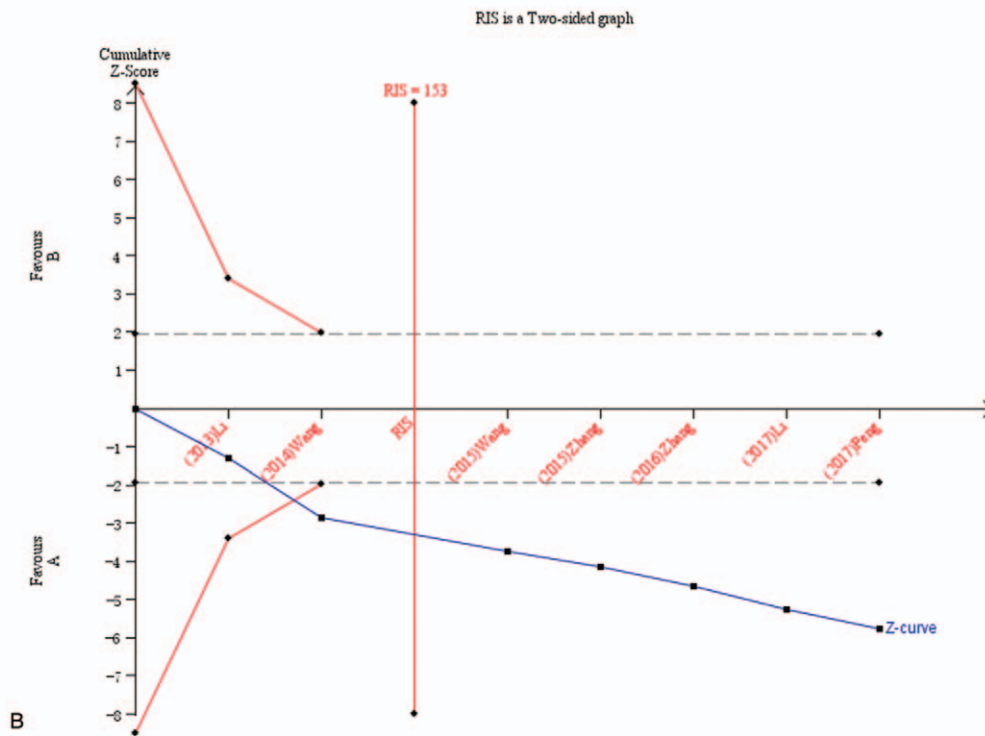


Figure 5. Effect of the degree of exophthalmos.



A



B

Figure 6. A: Curative effect on hyperthyroidism. B: Trial sequential analysis of curative effect on hyperthyroidism.

TSA showed that the RIS=15 (mean difference=0.2286, variance=0.186, two-sided test, $\alpha=0.05$, Power=80%, $I^2=0$). Each RCT sample included in this meta-analysis was more than the required information size, and the accumulated evidence is sufficient for the conclusion.

Only three trials reported FT3 and FT4 and both the test group and the control group included 137 patients.^[34,36,38] The results of FT3 and FT4 showed statistically significant heterogeneity (FT3: $P<.00001$, $I^2=92\%$; FT4: $P<.0001$, $I^2=90\%$). The studies were divided into subgroups, and the patient's age, sex,

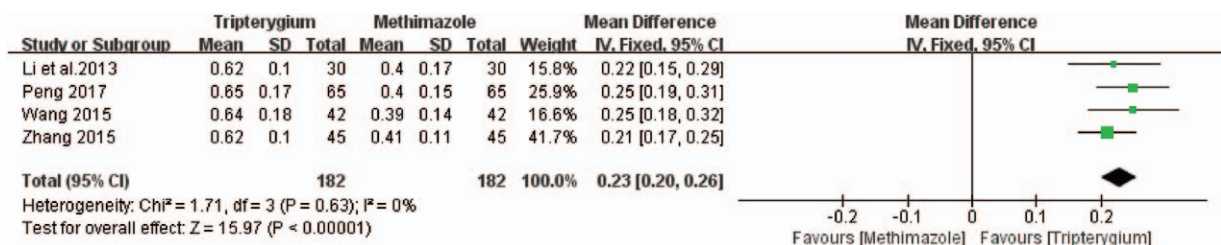
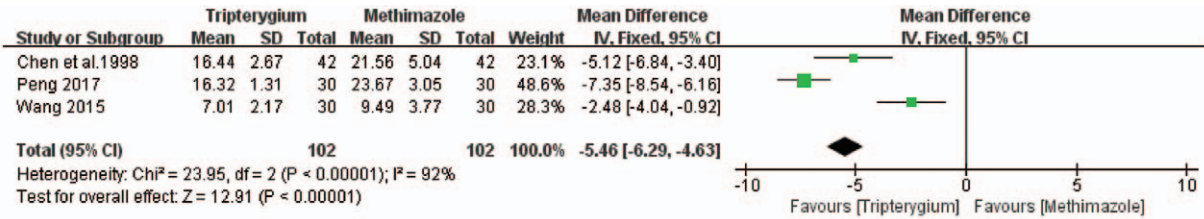
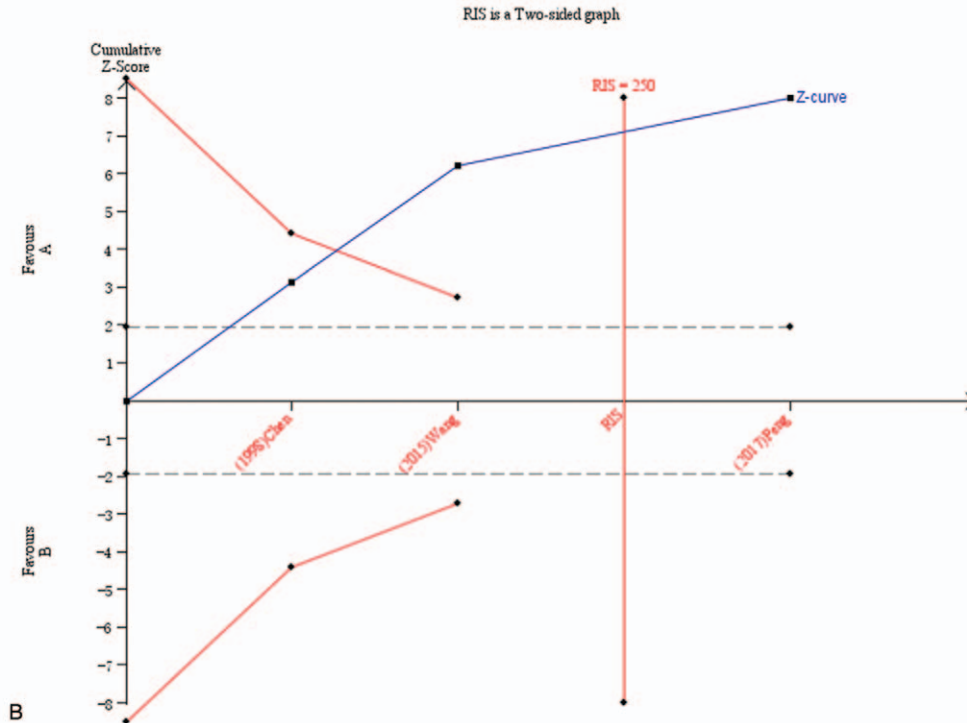


Figure 7. Thyroid-stimulating hormone.



A



B

Figure 8. A: Serum-free triiodothyronine. B: Trial sequential analysis of FT3.

course of treatment was all similar at baseline level hence a fixed-effects model was used for meta-analysis. The results showed that TWP combined with thiamazole decreased FT3/FT4 levels than thiamazole [FT3: MD = -5.46 (pmol/L), 95% CL (-6.26, -4.63), $P < .00001$; FT4: MD = -7.3 (pmol/L), 95% CL (-7.96, -6.65), $P < .00001$] (Figs. 8A and 9A).

TSA suggested that the RIS of FT3 = 250 (mean difference = -4.3259, variation = 11.371, two-sided test, $\alpha = 0.05$, Power = 80%, $I^2 = 92\%$). RIS of FT4 = 68 (mean difference = -7.3027, variation = 7.684, two-sided test, $\alpha = 0.05$, Power = 80%, $I^2 = 90\%$). The cumulative Z-curve crosses the vertical axis of RIS, and also crosses the TSA threshold and the traditional threshold ($z = -1.96$), indicating that the sample size included in this meta was sufficient (Figs. 8B and 9B).

3.3.2.3. Effect on the biochemical indicators. Five studies with 253 patients in the test group and 253 patients in the control group reported SOD, GSH-Px, BGP, and AKP.^[22,32,34-36] There was no significant heterogeneity shown among the study results (SOD: $P = .99$, $I^2 = 0\%$; GSH-Px: $P = .8$, $I^2 = 0\%$; BGP: $P = .43$, $I^2 = 0\%$; AKP: $P = .77$, $I^2 = 0\%$) and the fixed effect model was used for analysis. The combined MD showed that TWP combined with thiamazole increased SOD and GSH-Px level and reduced BGP and AKP compared with the control group

[SOD: MD = 6.31 (NU/mL), 95% CL (4.72, 7.89), $P < .00001$; GSH-Px: MD = 5.07 (U/L), 95% CL (3.63, 6.52), $P < .00001$; BGP: MD = -1.79 (ng/mL), 95% CL (-1.86, -1.72), $P < .00001$; AKP: MD = -16.36 (U/L), 95% CL (-18.03, -14.69), $P < .00001$] (Figs. 10-13).

TSA showed that the RIS of SOD = 66 (mean difference = 6.3052, variation = 82.7335, two-sided test, $\alpha = 0.05$, Power = 80%, $I^2 = 0$); the RIS of GSH-Px = 83 (mean difference = 5.1349, variation = 69.0906, two-sided test, $\alpha = 0.05$, Power = 80%, $I^2 = 0$); the RIS of BGP = 20 (mean difference = -1.7883, variation = 0.1583, two-sided test, $\alpha = 0.05$, Power = 80%, $I^2 = 0$); the RIS of AKP = 11 (mean difference = -16.3731, variation = 92.1461, two-sided test, $\alpha = 0.05$, Power = 80%, $I^2 = 0$). Each RCT sample included in this study is more than the required information size, and the accumulated evidence is sufficient for the reliable conclusion.

3.3.3. Other indicators. Gao reported the scores of quality of life (QOL) after the treatment.^[25] In comparison to the control group, the scores of QOL the experimental group were higher (89.04 ± 5.66) ($P < .05$). Chen found that the levels of TMAB and TGAB in the experimental group were significantly decreased after treatment, and the chronic inflammatory of the thyroid were alleviated.^[38] In addition, the TSI decreased rapidly in the

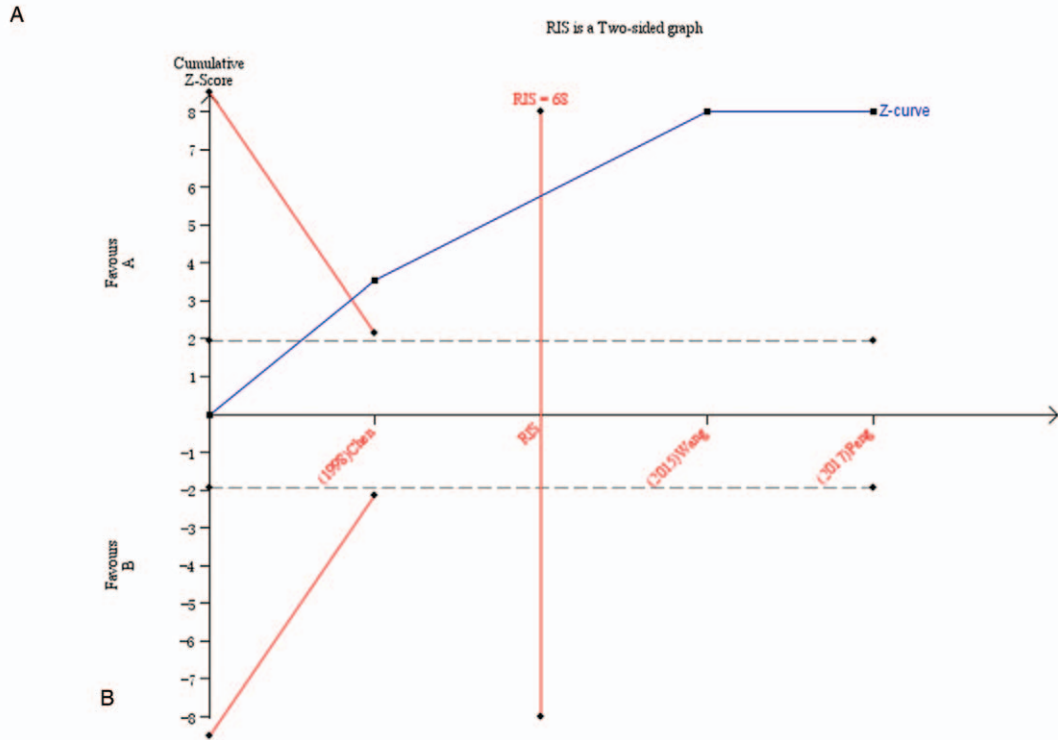
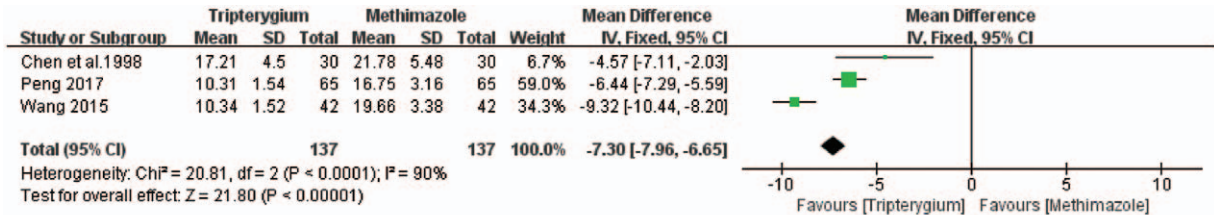


Figure 9. A: Serum-free thyroxine; B: Trial sequential analysis of FT4.

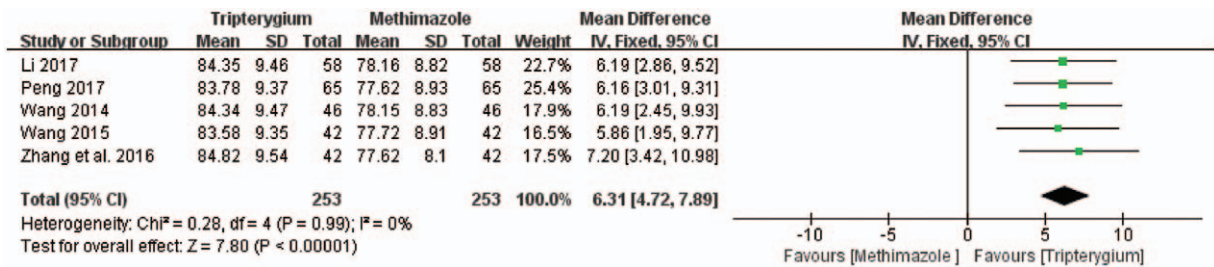


Figure 10. Superoxide dismutase.

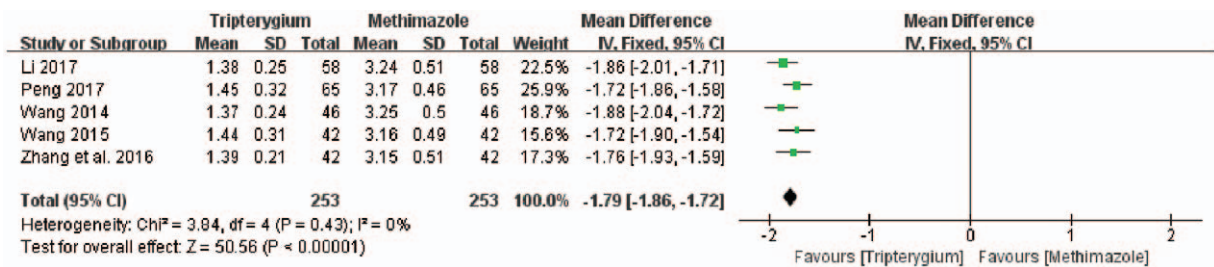


Figure 11. Glutathione peroxidase.

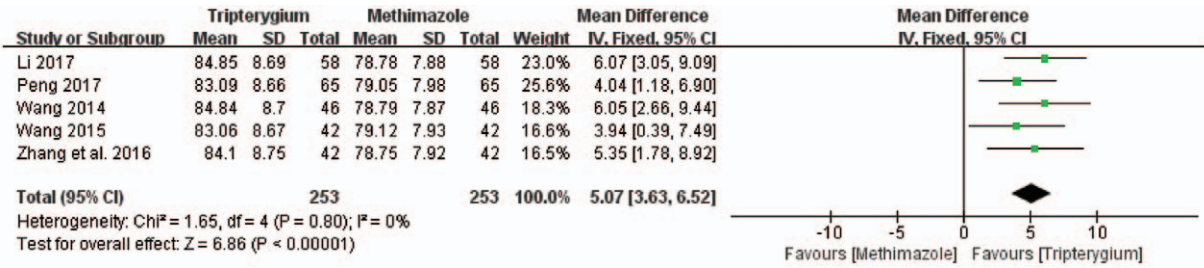


Figure 12. Plasma osteocalcin.

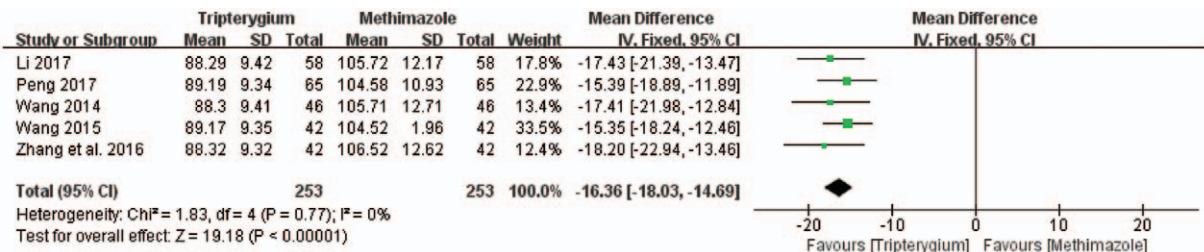


Figure 13. Alkaline phosphatase.

experimental group, indicating that the immune factors causing hyperthyroidism were effectively controlled.

3.3.4. Adverse reactions. Three articles reported the adverse reactions including gastrointestinal discomfort, drug eruption, leukopenia, liver damage, nephrotoxicity, and menstrual disorders after adding TWP while other articles lacked clear data showed that the TWP is safe in the treatment process and the incidence of adverse reactions is low, without occurrence or no serious adverse reactions that effects important organs occurred in the course of the experiment.^[30,31,34] And in contrast with the adverse reactions of control group, there was no statistical significance in those three studies. We sorted out the data and listed into a table and figure (Table 2 and Fig. 14).

4. Discussion

The combined use of TWP to treat hyperthyroidism raises a lot of questions: what is the exact curative effect and safety of TWP? How much can patients benefit from Chinese medicine? Meta-analysis or systematic reviews are needed to answer these questions. As far as we know, it will be the first attempt to perform a systematic review and meta-analysis of practical effects of TWP combined with thiamazole and prednisone for the

treatment of hyperthyroidism. What is more, the results will provide a useful and referable evidence for clinicians to develop treatment options.

The levels of FT3 and FT4 in patients with hyperthyroidism increased significantly. Due to the feedback effect on the thyroid and pituitary axis, TSH was reduced, and abnormal bone metabolism occurred. The expression of BGP and AKP was abnormally elevated, therefore these indicators should be controlled actively in therapy.^[39] The patient's SOD and GSH-Px levels were relatively low, indicating that the antioxidant capacity was damaged, and required repair.^[40] One of the most commonly used antithyroid drugs is thiamazole, which inhibits peroxidase in the thyroid gland and inhibits the synthesis of thyroxine (T4) and triiodothyronine (T3), but many side effects

Table 2

Adverse reactions (n).

Adverse Reactions	Intervention Group	Control Group
Drug allergy	5	2
Liver damage	2	1
Leukopenia	1	1
Digestive discomfort	3	2
Menstrual disorders	1	2
Nephrotoxicity	1	0

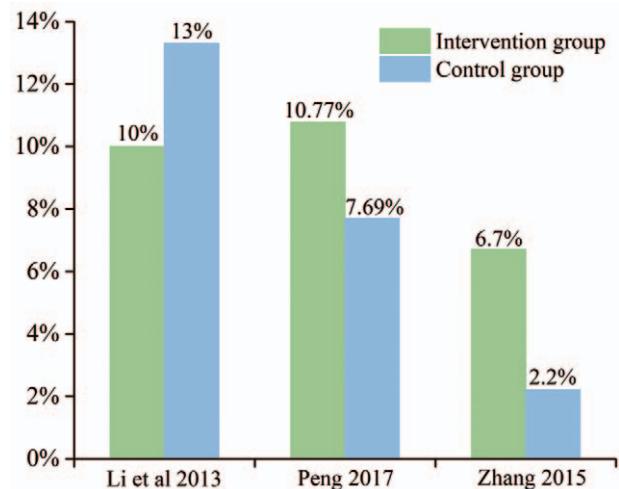


Figure 14. The incidence of adverse reactions.

may affect its therapeutic effect. TWP is known as “Chinese herbal hormone” and its anti-immune effect may be consistent with the mechanism in modern pharmacology.^[9] TWP exerts immunomodulatory effects by reducing the proliferation and infiltration of T-lymphocytes and macrophages, and inhibiting the synthesis and expression of adhesion molecules and chemokines, thereby reducing the damage of autoimmunity.^[41] For autoimmune diseases, TWP can replace most glucocorticoids or be used in combination with them to play a complementary role to improve clinical efficacy, and will not have drug resistance for long-term use.^[42] There will be no bounce after sudden withdrawal as well. For example, TWP can effectively suppress the occurrence of exophthalmos by suppressing the formation of eyeball tissue autoantigens.^[43]

More and more trials have shown that TWP can effectively treat hyperthyroidism and improve its side effects. For example, one study showed that TWP reduced the levels of TGAB and TMAB in the treatment of Hashimoto’s hyperthyroidism resulting in a reduction in chronic inflammation and volume of the thyroid gland.^[38] Due to significant decrease in TSI, there was improved abnormal immune mechanism. Similarly, TWP also indicated its therapeutic effect in nonclinical trials. A laboratory study found that the application of different concentrations of TWP to fibroblasts significantly inhibited the proliferation of fibroblasts and the secretion of hyaluronan in a concentration- and time-dependent manner.^[44] This experiment also showed that the synthesis of glucocorticoids in the adrenal gland was promoted and an increase in the function of the adrenal cortex.^[44] Therefore, TWP may serve well as a therapeutic treatment for hyperthyroidism.

However, the associated adverse drug reactions should not be ignored. In this meta-analysis, only three trials reported adverse events without significant difference between the two groups. But it is well known that the active ingredients in TWP are also toxic components, which could impact including the digestive system (including nausea, vomiting, abdominal pain, and diarrhea), the genital system (including sperm reduction, paramenia), the blood system (including white blood cells, red blood cells, thrombocytopenia, and secondary granulocytes) and other reactions (including bone thinning, drug rash, facial erythema, and pigmentation).^[45,46] Patients should discontinue medication immediately, and clinicians should address these events as necessary when adverse reactions appear.

4.1. Study strengths and limitations

This study is the first systematic review and meta-analysis of the effect and safety of TWP in the treatment of hyperthyroidism which included 17 trials with 1536 patients and TSA revealed that the trials were of sufficient standard to draw reliable conclusions. To increase the homogeneity of the study and make the conclusion more credible, we divided the studies into two subgroups according to the different focus of the treatment. We got a conclusion from this meta-analysis that TWP combined with thiamazole and prednisone has a therapeutic effect on hyperthyroidism and without increasing the incidence of adverse reactions.

However, the study was not without limitations.^[21] The previous evidence reported that the adverse reactions of TWP mainly included leukopenia, gastrointestinal reactions, irregular menstruation and abnormal liver function.^[42] These studies further suggested that the combination of TWP should consider irregular menstruation while treating immune system diseases

attention should be paid to leukopenia and liver damaged.^[47] In the meta-analysis, the adverse reactions of TWP combined with thiamazole or prednisone were insufficiently reported, as only 4 articles mentioned the side effects. Since TWP are crude extracts rather than monomers, there is no uniform standard for the dosage and course of treatment.^[48] A further study of its mechanism of action is needed to provide a reliable basis for the development of uniform standards for clinical safety medications. The studies included were all RCTs which concealment of allocation were not mentioned clearly and as a result of the review has the possibility of selection bias, detection bias, implementation bias which could result in a deviation to the true therapeutic effect in the meta-analysis.^[21] In addition, meta-analysis is a retrospective study, which cannot completely eliminate the heterogeneity of the combined studies. So we suggest that future researches should be based on RCTs with multi-center, large sample and rigorous design in order to provide greater evidence for the clinical applications of TWP.

5. Conclusion

This study revealed that Tripterygium glycosides enhances the effect of thiamazole and prednisone in the treatment of hyperthyroidism. TWP combined with thiamazole improved thyroid hormone levels and restored normal bone metabolism and antioxidant capacity. Therefore, the addition of TWP to thiamazole and prednisone is effective in the treatment of hyperthyroidism. However, its adverse events have not been reported adequately, and more attention and significant data should be paid in future preclinical and clinical studies research to monitor the incidences of adverse reactions.

5.1. Search strategy (PubMed)

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(((((Hyperthyroid[Title/Abstract] OR Hyperthyroids[Title/Abstract]) OR Primary Hyperthyroidism[Title/Abstract]) OR (“hyperthyroidism”[Mesh Terms] OR “hyperthyroidism”[All Fields]) AND Primary[Title/Abstract])) OR “Hyperthyroidism”[-Mesh]) AND (((((((((Tripterygium hypoglauca[Title/Abstract] OR Tripterygium wilfordii[Title/Abstract] OR Lei gong Teng [Title/Abstract]) OR (Lei gong[All Fields] AND Tengs[Title/Abstract])) OR (Teng[All Fields] AND Leigong[Title/Abstract])) OR (Tengs[All Fields] AND Leigong[Title/Abstract])) OR Thundergod Vine[Title/Abstract]) OR (Thundergod[All Fields] AND Vines[Title/Abstract])) OR (Vine[All Fields] AND Thundergod[Title/Abstract])) OR (Vines[All Fields] AND Thundergod [Title/Abstract])) OR “Tripterygium”[Mesh])
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Author contributions

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Writing – original draft: Chunyan Xie.

Writing – review & editing: Chunyan Xie, Chaozhu He, Shulei Jia, Jun Gao.

Correction

When originally published, Shulei Jia's degree appeared incorrectly as PhD and should be MM.

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