Original Article

A systematic review and meta-analysis of the clinical efficacy and safety of Chinese patent medicines in treating subacute thyroiditis

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Background: This meta-analysis was performed to evaluate the clinical efficacy and safety of Chinese patent medicines in the treatment of subacute thyroiditis (SAT).

Methods: Chinese databases were searched using a combination of "patent Chinese medicine", "traditional Chinese medicine", "traditional Chinese and western medicine", "sub-thyroiditis", and "subacute thyroiditis". Studies that set Chinese patent medicine treatment of SAT as the experimental group were selected. Then, meta-analysis was performed by RevMan 5.3.

Results: A total of 12 studies were included, and most of them had a high risk of bias (low quality). The heterogeneity test results of clinical efficacy showed that Chi^2=6.21, df=7, P=0.52>0.1, and I^2=0%<50%. Then, the fixed effects model (FEM) was used, with OR =2.80; 95% confidence interval (CI): 1.89–4.13. The heterogeneity test of recurrence rate showed that Chi^2=10.69, df=9, P=0.30>0.1, and I^2=16%<50%. The heterogeneity test of erythrocyte sedimentation rate showed that I^2=97%, P<0.00001, MD =–10.02; 95% CI: –12.88 to –7.16, and P<0.00001. The heterogeneity test of free triiodothyronine showed that Chi^2=500.75, I^2=99%>50%, P<0.00001, MD =–2.88; 95% CI: –3.85 to –1.91; Z=5.83, and P<0.00001. The heterogeneity test of free thyroid hormone showed that Chi^2=25.15, I^2=72%>50%, P=0.0007, MD =–2.48; 95% CI: –3.69 to –1.26; Z=3.99, and P<0.0001. The heterogeneity test of the occurrence of adverse reactions showed that Chi^2=11.28, df=11, P=0.42>0.1, and I^2=3%<50%, and the combined effect size was Z=6.49 and P<0.00001, with OR =0.21; 95% CI: 0.13–0.34.

Discussion: The meta-analysis of this study confirms that Chinese patent medicines have considerable clinical effects in the treatment of SAT. They can reduce the recurrence rate, adjust the levels of free triiodothyronine and free thyroid hormone, and have good safety.

Keywords: Chinese patent medicine; subacute thyroiditis (SAT); randomized controlled trial; meta-analysis; safety

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Introduction

Subacute thyroiditis (SAT) is a self-recoverable non-bacterial infectious disease of the thyroid. SAT is also a self-limited non-suppurative thyroid inflammatory disease that can be self-alleviated or cured. It is characterized by transient painful destructive thyroid tissue damage and systemic inflammatory responses. Moreover, it is the most common thyroid pain disease (1). The prevalence of SAT has obvious seasonality, with a high prevalence in winter and spring. The incidence is high in young and middle-aged women aged 30 to 50, and is 3–6 times that of men (2).

The main clinical manifestations are fever, goiter pain, and abnormal thyroid function (3,4). SAT is not uncommon in clinical practice, and diagnosis is not difficult when the manifestations are typical. However, due to the sometimes atypical manifestations or doctors' insufficient understanding of the disease, misdiagnosis often occurs, and the misdiagnosis rate in domestic reports is 12–48%.

SAT belongs to the categories of "gall disease" and "gall carbuncle" in traditional Chinese medicine (5). Traditional Chinese medicine has a considerable clinical effect in the treatment of SAT with low toxicity and side effects (6). Ancient medical records suggest that gall carbuncle is a disease of external infection, internal injury, or lack of vital energy, leading to qi, blood, and body fluid operation disorders. Deficiency, phlegm, "qi", and blood stasis are the "persistent roots" of the development of SAT (7). SAT is classified into exogenous wind-heat syndrome, exogenous wind-cold syndrome, syndrome of heat accumulation in liver depression, syndrome of mutual combination of deficiencies in "qi" and "Yin", spleen and kidney "Yang" deficiency syndrome, and "qi" stagnation and blood stasis syndrome (8).

The treatment of SAT with traditional Chinese medicine can alleviate local symptoms, enhance drug absorption, has fewer adverse reactions, easy operation, and high patient acceptance, it can significantly shorten the course of disease and reduce the recurrence rate (9). According to the clinical characteristics of SAT, the primary symptoms are fever and pain. The anterior neck mass starts with obvious tenderness, and the treatment is aimed at clearing heat and relieving the surface and pain by dispersing nodules. In the middle period, fever is gradually reduced, and the anterior neck mass is hard and painful. The treatment involves cooling the blood, dispersing nodules, relieving pain, and detumescence. Hypothyroidism occurs in the late stage of the disease, which may be due to mistreatment. When symptoms such as fear of cold, edema, and abdominal distension are the main symptoms, treatment should be given by warming the kidneys, strengthening the spleen, dispersing nodules, and reducing swelling.

In this study, a meta-analysis was performed to collect randomized controlled trials related to Chinese patent medicines from large domestic Chinese databases. The search time was up to December 2020. The quality evaluation was based on the Cochrane Review Handbook 5.0. Statistical analysis was performed using RevMan 5.3. The purpose was to explore the clinical efficacy of Chinese patent medicines in the treatment of SAT, so as to fully understand the problems in the clinical research of SAT. It is hoped that this work can provide a scientific theoretical basis for the later clinical treatment of Chinese patent medicines, and can promote the development of Chinese patent medicines in wider medicine.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2248).

Methods

Literature search

CNKI, China Biomedical Literature Database, VIP, Wanfang, and Baidu Academic were searched by computer from their establishment to December 20, 2020. Chinese databases were searched by a combination of "patent Chinese medicine", "traditional Chinese medicine", "traditional Chinese and western medicine", "subthyroiditis", and "subacute thyroiditis". All search words were combined freely. Databases were searched many times to screen literature that set Chinese patent medicine treatment of SAT as the experimental group. Search engines were used to track down the literature. Experts and researchers in the field were contacted to keep up to date with the latest research progress.

Literature inclusion and exclusion criteria

The inclusion criteria were as follows: (I) articles were clinical randomized controlled trials of Chinese patent medicine in the treatment of SAT published before December 20, 2020; (II) the studies clarified the diagnostic criteria for SAT; (III) the general data of the experimental group and the control group (Ctrl) were well balanced and comparable; (IV) for pathological control analysis, the index comparison was reliable within the 95% confidence interval (CI).

The exclusion criteria were as follows: (I) studies that were not randomized controlled trials; (II) the treatment method was not Chinese patent medicine; (III) repeated published literature; (IV) individual cases, false cases , verified reports, and animal experiments; (V) literature for which complete data could not be obtained by contacting the original author.

Clinical evaluation indicators of SAT

The clinical evaluation indicators of SAT included clinical

Table 1 Jadad scale rating standards

Element	Evaluation criterion	Scores
Random sequence generation	Using computer to use random number table method	2 points
	Randomized controlled experiment was used, but the specific method of random allocation was not described in detail	1 point
	The confidence of the estimated value of the effect is limited, and it is completely irrelevant to the actual value	0 point
Allocation concealment	Using the computer to control the consistent numbering of containers, the signal is strictly sealed, and the research object cannot predict the sequence allocation mode	2 points
	The random number table method is described, but it is not further elaborated	1 point
	Random number table method is not used	0 point
Blinding	The experiment is blind, and the operation method is described in detail	2 points
	The experiment was blind, but the operation method was not described	1 point
	The experiment did not use the blind method, or used the blind method	0 point

efficacy, recurrence rate, erythrocyte sedimentation rate, free triiodothyronine (FT3), free thyroxine (FT4), and adverse reactions.

Data extraction

Two experts used a unified Excel table to screen the titles, abstracts, and full texts. Three preliminary experiments were required. For inconsistencies between experts, a consensus conclusion was reached through discussion, or was dealt with by a third expert. The extracted data were (I) title, first author, and publication year; (II) the name or source of the publication; (III) the time when the research was published; (IV) general information of the research subjects such as the average age; (V) intervention measures and treatment methods; (VI) the therapeutic effect comparison.

Bias risk assessment

The risk of bias was assessed by 2 experts, and if the 2 disagreed, the outcome was determined through discussion or a third expert was asked to arbitrate. Cochrane Collaboration's Oxford Scoring System (JADAD) scale was used as a tool for "bias risk assessment" in randomized controlled trials, and RevMan 5.3 was employed to evaluate the quality of the literature. The evaluation criteria included random sequence generation, blinding method, allocation concealment, integrity of data results, and integrity of research results. The literature was judged as high, low, or unclear risk of bias according to the above 5 aspects.

Literature quality assessment

The risk of bias was assessed by 2 experts at the same time. If the 2 disagreed, the outcome was determined through discussion. In this work, the Jadad scale of the Cochrane Collaboration was used for quality grading. The specific Jadad quality grading method is shown in *Table 1*. A Jadad score of 4–7 was considered high-quality research (low risk bias), and a score within 0–3 was considered low-quality research (high risk bias).

Statistical analysis

RevMan 5.3 was employed for statistical analysis. The odds ratio (OR) was utilized to evaluate the clinical efficacy, recurrence rate, and adverse reactions. The mean difference (MD) was used to evaluate the erythrocyte sedimentation rate, FT3, and FT4. RevMan 5.3 was also used to generate the risk of bias assessment charts to assess the risk of bias. Each effect was expressed using a 95% CI. If the heterogeneity test showed that $P>0.1$ and $I^2<50\%$, the fixed effects model (FEM) was used. If the heterogeneity test showed that $P<0.1$ and $I^2>50\%$, the random effects model (REM) was used.

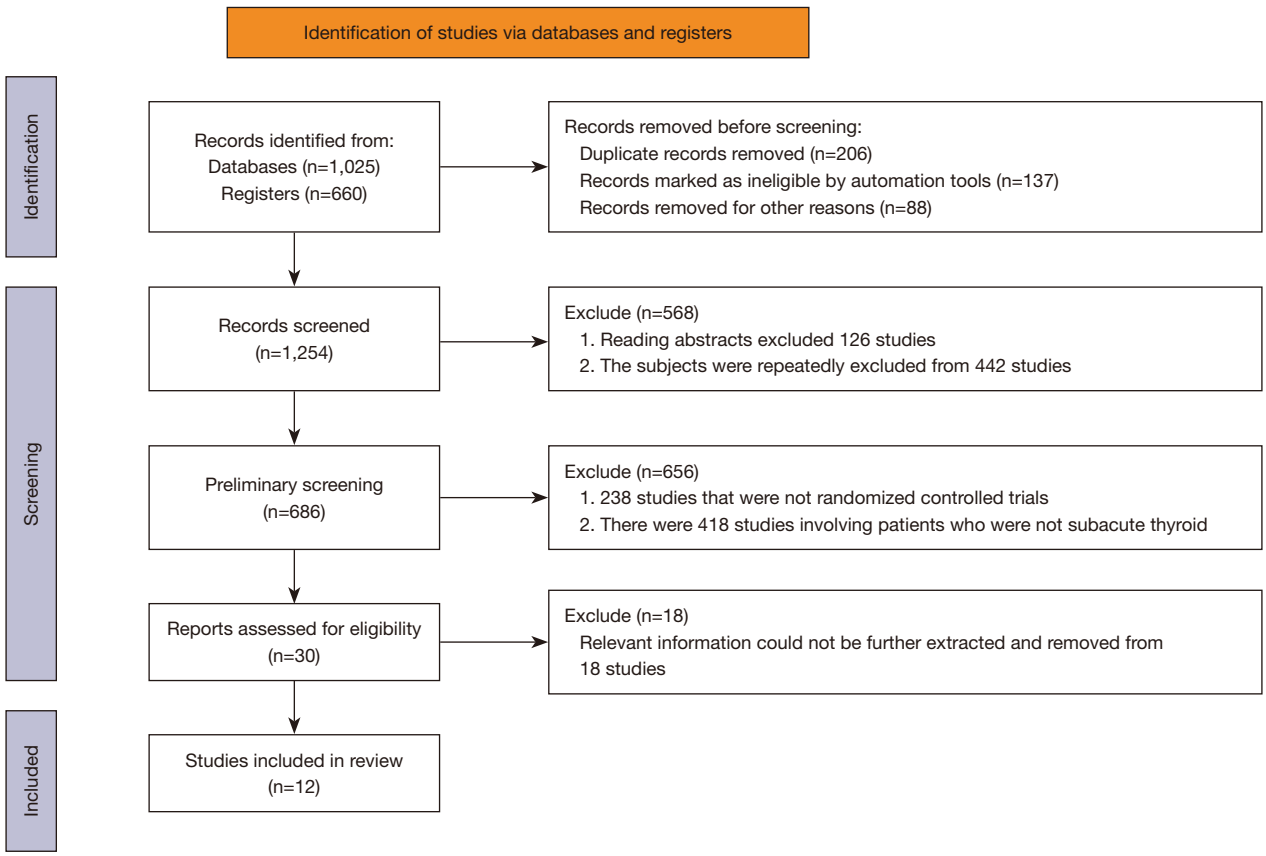

Figure 1 Literature search flowchart.

Results

Search results and basic information of literature

A total of 1,685 articles were obtained, and the remaining 1,254 articles were selected through the title selection. Through reading abstracts, 126 articles were deleted, 442 articles were repeatedly deleted, leaving 686 articles. After reading the full text, 238 literatures that were not randomized controlled trials and 418 literatures that were not subacute thyroid patients were excluded, leaving 30 literatures. The relevant information of the study could not be further extracted and excluded 18 articles, and 12 articles were finally included in the meta-analysis (*Figure 1*). There were 9 articles with 4–7 points and 3 articles with 0–3 points.

There were 12 articles meeting the inclusion criteria (all of which were small sample studies) involving 781 patient cases. The sample size ranged from 35 to 150, and the study subjects were all over 18 years old. All of the included studies described in detail the gender, age, and disease course of patients. The basic information is shown in *Table 2*.

Results of the literature risk of bias evaluation

Figures 2 and *3* show the risk of bias evaluations of the literature generated by RevMan 5.3. Among the 12 included randomized controlled trials, four described the correct random allocation method. Two of them described the correct random allocation method and described the concealment of allocation plan in detail. One article was evaluated by blinding, and the other articles were not. However, the measurement indicators in this study were laboratory indicators determined by computer, which deemed that all articles were blinded correctly.

Clinical efficacy comparison between groups

A total of 8 randomized controlled trials performed a comparison of clinical efficacy, with 341 experimental cases and 257 Ctrls. The overall heterogeneity test showed

Table 2 General information of the research subjects in the included literature

Author	Year	Cases	Interventions		Course of treatment
			Experimental group	Control group	
Su LF (10)	2012	60	Oral Chinese medicine	Prednisone	12 weeks
Sun XQ (11)	2012	70	Oral Chinese medicine, external application	Prednisone	4–8 weeks
Xia ZY (12)	2009	150	Oral Chinese medicine	Fenbid	8 weeks
Xu XH (13)	2011	40	Oral Chinese medicine	Prednisone	6–8 weeks
Yao MC (14)	2007	62	Oral Chinese medicine, external application	Prednisone	4 weeks
Zhang MH (15)	2011	35	Oral Chinese medicine	Prednisone	8 weeks
Zheng L (16)	2011	44	Oral Chinese medicine, external application	Prednisone	–
Zhou WH (17)	2008	60	Oral Chinese medicine	Prednisone	6–8 weeks
Zhu DJ (18)	2001	50	Oral Chinese medicine	Methylprednisolone	5–6 weeks
Zou XL (19)	2009	40	Oral Chinese medicine	Methylprednisolone	4–6 weeks
Gao QL (20)	2005	102	Oral Chinese medicine, external application	Xiaoyantong, prednisone	4–6 weeks
Li MN (21)	2010	68	Oral Chinese medicine	Prednisone, antibiotic	6 weeks

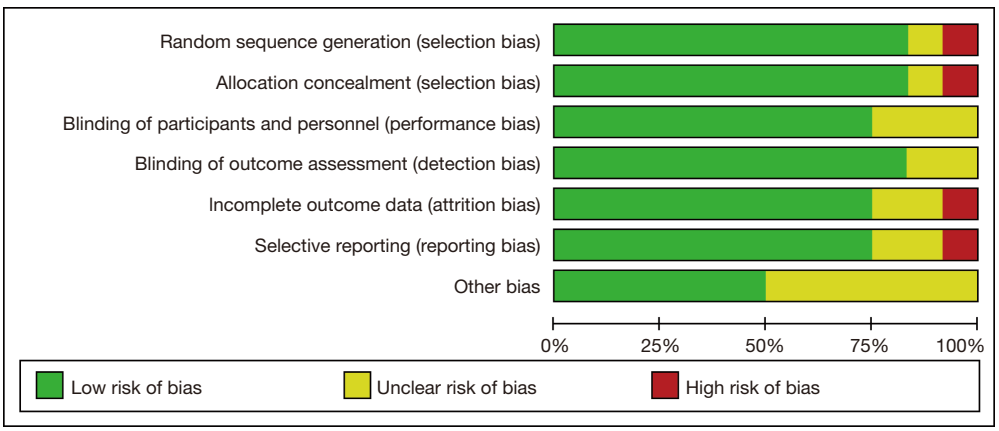

Figure 2 Literature risk of bias evaluation results.

that Chi^2=6.21, df=7, P=0.52>0.1, and I^2=0%<50%. The combined effect size test showed that Z=5.15 and P<0.00001. The 12 studies were homogeneous, and the combined effect size was analyzed using the FEM. *Figure 4* showed that the clinical effect of Chinese patent medicine (experimental group) in treating SAT was more obvious than the Ctrls (OR =2.80, 95% CI: 1.89–4.13). The horizontal line (HL) of the 95% CI of most studies intersected the invalid vertical line (IVL), and a few fell to the right of the IVL. The FEM was adopted, and the difference between groups was significant.

The funnel plot of clinical efficacy (*Figure 5*) showed that the circles of some studies were basically symmetrical with the midline, reflecting high research accuracy and no publication bias.

Recurrence rate

In 8 literatures, the recurrence rate in randomized controlled trials was analyzed. The total number of cases was 895, including 447 cases in experimental group and 448 cases in control group. The overall heterogeneity test showed that Chi^2=10.69, df=9, P=0.30, I^2=16%<50%. Test of combined effect quantity Z=8.38, P<0.00001.

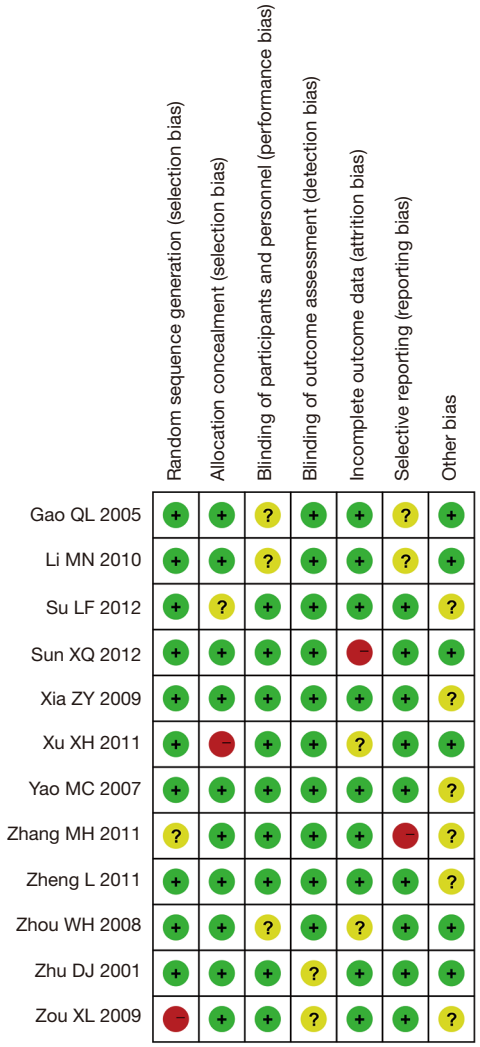

Figure 3 Bias evaluation results of the included literature corresponding to multiple risks.

According to the analysis of the above results, the included 12 references are homogeneous, and the combined effect amount uses the fixed effect model, OR =0.22, 95% CI: 0.16–0.31, indicating that the recurrence rate of subacute thyroiditis treated with Chinese patent medicine is lower than that of the control group (*Figure 6*). In most studies, the horizontal line of 95% CI is located on the left side of the intersection of invalid vertical lines. The fixed effect model was used to analyze the whole, which showed that the difference between the experiment and the control group was statistically significant.

A total of 10 randomized controlled trials analyzed the most studies fell to the left of the IVL, and a few intersected the IVL. The difference between groups was significant.

The funnel plot of the recurrence rate indicated that the circles of some studies were asymmetrical with the midline (*Figure 7*), indicating that the research accuracy was low and there was a certain degree of bias in the publications.

Erythrocyte sedimentation rate

A total of 6 randomized controlled trials analyzed the erythrocyte sedimentation rate, with 210 experimental cases and 164 Ctrls. It was found that I^2=97% and P<0.00001, and the heterogeneity was large. The HL of the 95% CI of most studies fell to the left of the IVL. Through REM analysis, the difference between groups was not significant, with MD =–10.02; 95% CI: –12.88 to –7.16, and P<0.00001 (*Figure 8*).

The funnel plot of the erythrocyte sedimentation rate showed that the circles of some studies were on the midline (*Figure 9*), but were asymmetrical to the midline, suggesting

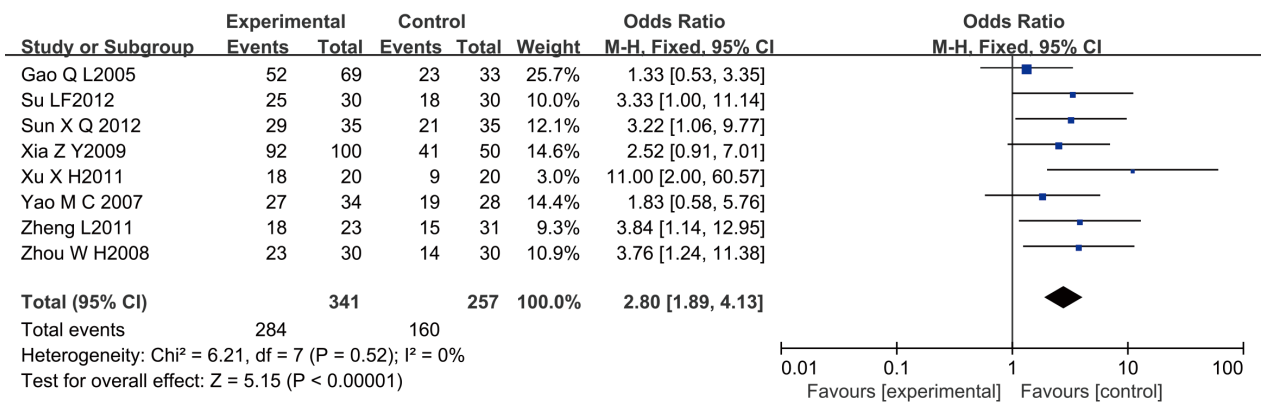

Figure 4 Forest plot of clinical efficacy.

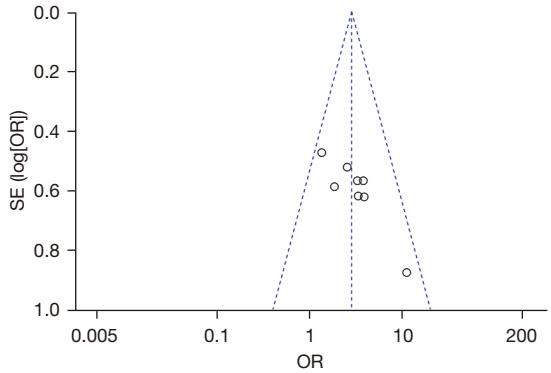

Figure 5 Funnel plot of clinical efficacy.

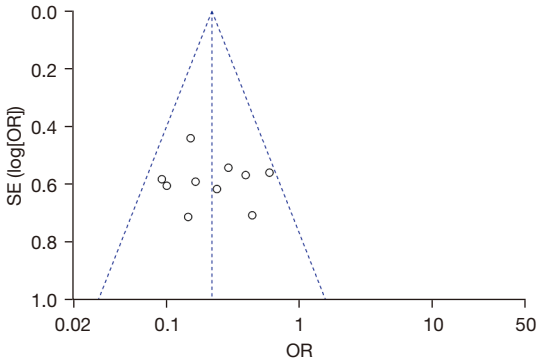

Figure 7 Funnel plot of recurrence rate.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gao Q L2005	5	69	15	33	14.0%	0.09 [0.03, 0.29]
Li M N2010	3	22	12	46	5.0%	0.45 [0.11, 1.79]
Su LF2012	6	30	18	30	10.7%	0.17 [0.05, 0.53]
Sun X Q 2012	7	35	16	35	9.5%	0.30 [0.10, 0.86]
Xia Z Y2009	10	100	21	50	18.7%	0.15 [0.06, 0.36]
Yao M C 2007	6	34	19	28	12.8%	0.10 [0.03, 0.33]
Zheng L2011	9	23	16	31	6.2%	0.60 [0.20, 1.80]
Zhou W H2008	7	30	13	30	7.4%	0.40 [0.13, 1.21]
Zhu D J2001	6	23	16	27	8.1%	0.24 [0.07, 0.81]
Zou X L2009	5	22	12	18	7.6%	0.15 [0.04, 0.60]
Total (95% CI)		**388**		**328**	**100.0%**	**0.22 [0.16, 0.31]**
Total events	64		158			

Heterogeneity: Chi² = 10.69, df = 9 (P = 0.30); I² = 16%
Test for overall effect: Z = 8.38 (P < 0.00001)

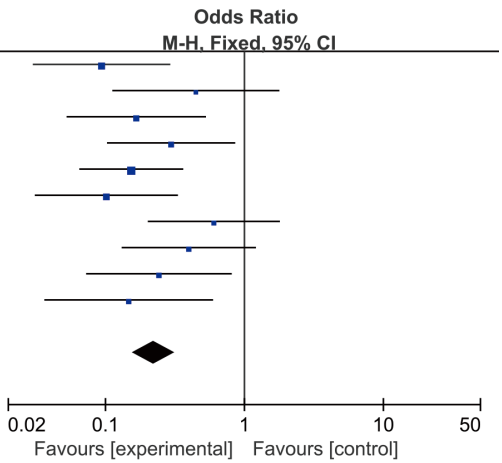

Figure 6 Forest plot of recurrence rate.

low research accuracy and a certain degree of publication bias in the studies.

FT3

A total of 8 randomized controlled trials analyzed FT3, with 323 experimental cases and 279 Ctrls. The overall heterogeneity test showed that Chi^2=500.75, I^2=99%>50%, and P<0.00001. The heterogeneity between each experimental group was relatively large. The HL of the 95% CI of most studies fell to the left of the IVL. REM analysis showed that the difference in FT3 levels between groups was significant, with MD =−2.88; 95% CI: −3.85 to −1.91, Z=5.83, and P<0.00001 (*Figure 10*).

The funnel plot of FT3 in *Figure 11* showed that the circles of some studies were concentrated on the midline, and were basically symmetrical to the midline, indicating high research accuracy and no publication bias.

FT4

A total of 8 randomized controlled trials analyzed FT4, with 413 experimental subjects and 411 Ctrls. The overall heterogeneity test showed that Chi^2=25.15, I^2=72%>50%, and P=0.0007, indicating large heterogeneity among experimental groups. The HL of the 95% CI of most studies fell to the left of the IVL, and a few intersected the IVL. Through REM analysis, the difference in FT4 between groups was significant, with MD =−2.48; 95% CI: −3.69 to −1.26, Z=3.99, and P<0.0001 (*Figure 12*).

The funnel plot of FT4 showed that the circles of some studies were concentrated on the midline (*Figure 13*), and

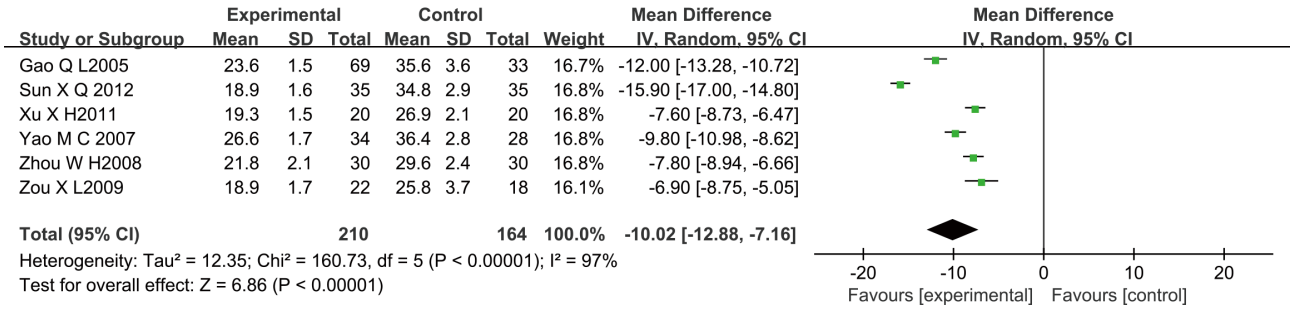

Figure 8 Forest plot of erythrocyte sedimentation rate.

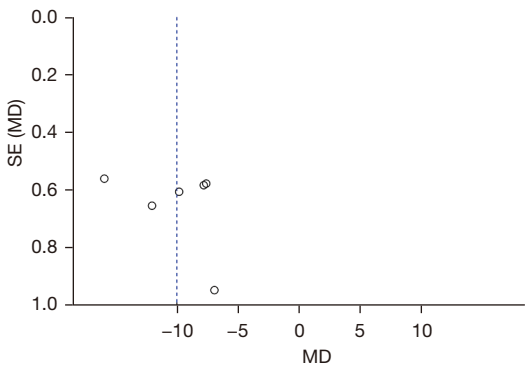

Figure 9 Funnel plot of erythrocyte sedimentation rate.

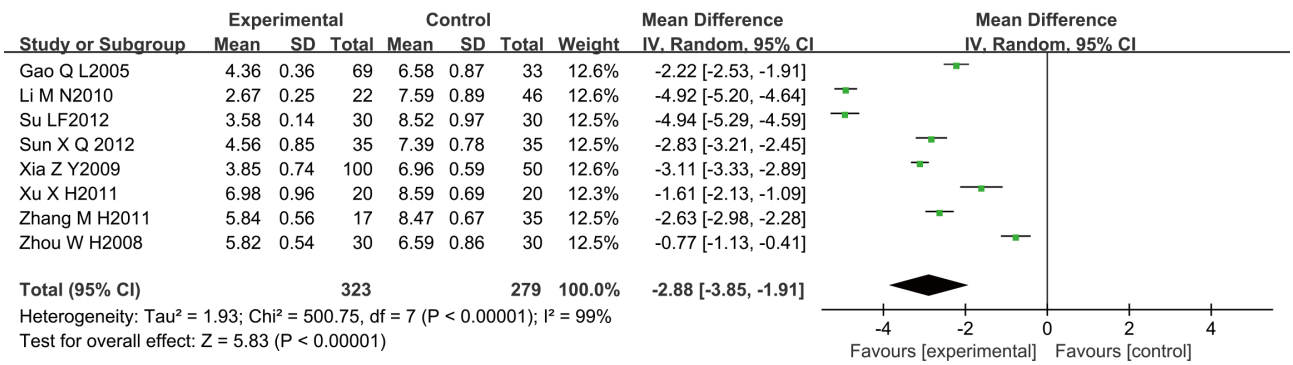

Figure 10 Forest plot of free triiodothyronine.

were basically symmetrical to the midline, reflecting high research accuracy and no publication bias.

Adverse reactions

A total of 12 randomized controlled trials analyzed adverse reactions, with 674 experimental cases and 667 Ctrls. The overall heterogeneity test showed that Chi^2=11.28, df=11, P=0.42>0.1, and I^2=3%<50%. The combined effect size was Z=6.49 and P<0.00001. The 12 included studies were homogeneous. FEM analysis showed that OR =0.21; 95% CI: 0.13–0.34. There was no significant difference between different studies (*Figure 14*). The HL of the 95% CI of most studies fell to the left of the IVL, and a few intersected the IVL. The FEM was adopted, and the difference between groups was significant (Z=6.49, P<0.00001).

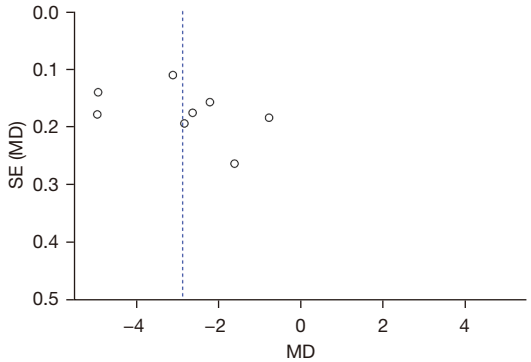

Figure 11 Funnel plot of free triiodothyronine.

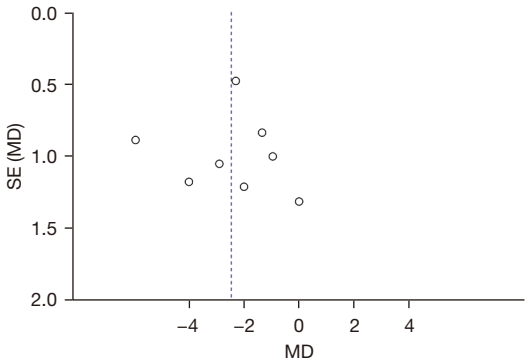

Figure 13 Funnel plot of free thyroid hormone.

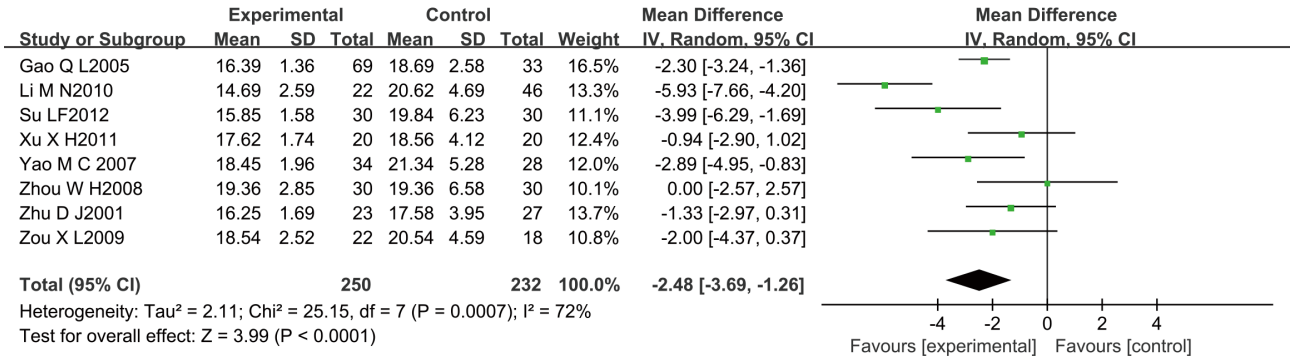

Figure 12 Forest plots of free thyroid hormone in the two groups.

The funnel plot of adverse reactions (*Figure 15*) showed that the circles of some studies were asymmetrical to the midline, suggesting low research accuracy and a certain degree of publication bias.

Discussion

SAT is a self-limited non-suppurative thyroid inflammatory disease that can be self-alleviated or cured. It is not uncommon in clinical practice, and the diagnosis is not difficult when the manifestations are typical. However, due to the sometimes atypical manifestations or doctors' insufficient understanding of the disease, misdiagnosis often occurs, and the misdiagnosis rate in domestic reports is 12–48%. SAT is characterized by transient painful destructive thyroid tissue damage and systemic inflammatory responses. The pathogenesis of SAT lies in exogenous wind-heat, liver qi stagnation, and phlegm and blood stasis. Traditional Chinese medicine has a considerable clinical effect in the treatment of SAT with low toxicity and side effects. Ancient medical records suggest that gall carbuncle is a disease of external infection, internal injury, or lack of vital energy, leading to qi, blood, and body fluid operation disorders. Deficiency, phlegm, "qi", and blood stasis are the "persistent roots" of the development of SAT. Therefore, most experts of traditional Chinese medicine believe that it is important to relieve the exterior, clear heat and detoxify, reduce phlegm, and resolve masses in the treatment of SAT. In this study, the efficacy and safety of Chinese patent medicine in the treatment of SAT were systematically evaluated. A total of 12 studies were included, including 9 high-quality studies and 3 low-quality studies. The analysis results show that Chinese patent medicine treatment of SAT can reduce the recurrence rate, improve the levels of FT3 and FT4, and reduce the occurrence of adverse reactions. The results are consistent with the study of Ma *et al.* [2006] (22).

The severity of SAT lies between acute suppurative thyroiditis and chronic thyroiditis. The main clinical features are goiter and pain, accompanied by fever or even high fever. If not actively and correctly treated, it can lead

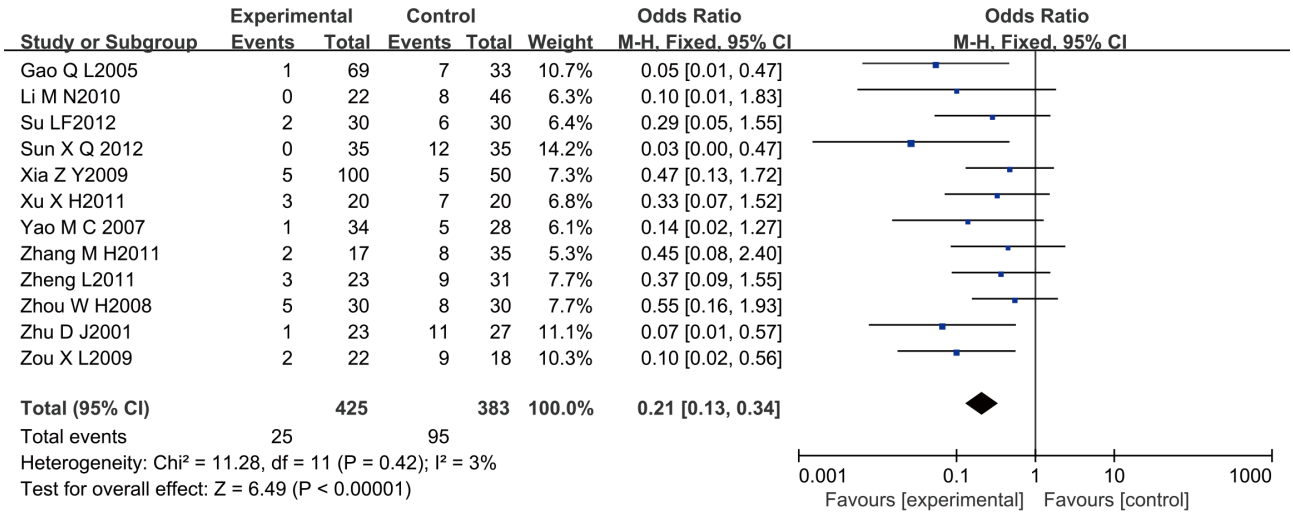

Figure 14 Forest map of adverse reactions of two groups of patients.

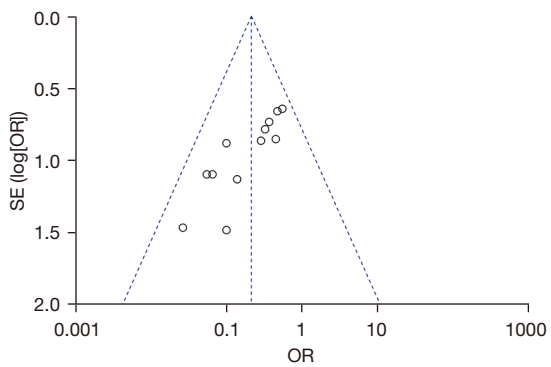

Figure 15 Funnel diagram of adverse reactions in two groups.

to permanent hypothyroidism. Due to the variety of clinical changes of this disease, misdiagnosis and missed diagnosis can easily occur. The curative effect of traditional Chinese medicine on SAT is considerable, with fewer side effects and low recurrence rate. Hypothyroidism occurs at a later stage of the disease, which may be due to improper treatment. The main symptoms of SAT are fever, pain, fearing the cold, edema, and abdominal distension, with obvious tenderness starting from the anterior cervical mass. The treatment methods are clearing heat, relieving the surface, dispersing nodules, and relieving pain. In metaphase of subacute thyroiditis, fever gradually alleviates, and the anterior neck mass is hard and painful. The treatment focuses on cooling the blood, relieving pain, and detumescence.

In this study, it aimed to explore the therapeutic efficacy of Chinese patent medicines in the treatment of SAT. The meta-analysis of this study confirmed that Chinese patent medicines have considerable clinical effects in the treatment of SAT. They were shown to reduce the recurrence rate, adjust the levels of FT3 and FT4, and have good safety. The clinical efficacy, recurrence rate, erythrocyte sedimentation rate, FT3, FT4, and adverse reactions between groups were compared to evaluate the treatment effect of Chinese patent medicines for SAT. The heterogeneity test of clinical efficacy showed that Chi^2=6.21, df=7, P=0.52>0.1, and I^2=0%<50%. Then, the FEM was adopted, with OR =2.80, and (95% CI: 1.89–4.13). The heterogeneity test of recurrence rate showed that Chi^2=10.69, df=9, P=0.30>0.1, and I^2=16%<50%. The circles of the included studies were asymmetrical with the midline, suggesting low accuracy of these studies, and there was a certain degree of bias in the publications. The above results show that the effect of Chinese patent medicines in treating SAT is more obvious than the Ctrls, which is consistent with the research results of Martino *et al.* [1987] (23).

Conclusions

In this study, 12 literatures on the treatment of SAT with Chinese patent medicine as the experimental group were included for meta-analysis. This meta-analysis aimed to explore the therapeutic efficacy of Chinese patent medicines in the treatment of SAT. The meta-analysis of this study confirms that Chinese patent medicines have considerable

clinical effects in the treatment of SAT, and can reduce the recurrence rate, adjust the levels of FT3 and FT4, and have good safety. This work still has the following shortcomings. The number of included studies was small, the funnel plots were asymmetrical, and there might have an impact on publication bias. Therefore, the sample size needs to be expanded in the future to conduct clinical randomized controlled trials for further verification. In short, this study shows that Chinese patent medicines can considerably reduce the recurrence rate of SAT, and provides a reliable reference for the clinical treatment of SAT.

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Footnote

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