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Zeng X, Yuan Y, Wu T, Yan L, Su H

Zeng X, Yuan Y, Wu T, Yan L, Su H.  
Chinese herbal medicines for hyperthyroidism.  
*Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD005450.  
DOI: [10.1002/14651858.CD005450.pub2](https://doi.org/10.1002/14651858.CD005450.pub2).

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**Chinese herbal medicines for hyperthyroidism (Review)**  
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[Intervention Review]

# Chinese herbal medicines for hyperthyroidism

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**Editorial group:** Cochrane Metabolic and Endocrine Disorders Group.

**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2010.

**Citation:** Zeng X, Yuan Y, Wu T, Yan L, Su H. Chinese herbal medicines for hyperthyroidism. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD005450. DOI: [10.1002/14651858.CD005450.pub2](https://doi.org/10.1002/14651858.CD005450.pub2).

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## ABSTRACT

### Background

Hyperthyroidism is a disease in which excessive amounts of thyroid hormones circulate in the blood. Patients, among other things suffer from tachycardia, warm moist skin and raised body temperature. The treatment of hyperthyroidism includes symptom relief and therapy with antithyroid medications, radioiodine and thyroidectomy. Medicinal herbs are used alone or in combination with antithyroid agents to treat hyperthyroidism in China and some other countries.

### Objectives

To assess the effects of Chinese herbal medicines for treating hyperthyroidism.

### Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE, *The Cochrane Library*, the Chinese Biomedical Database.

### Selection criteria

Randomised controlled trials comparing the effects of Chinese herbal medicines alone with Chinese herbal medicines combined with antithyroid drugs, radioiodine or both.

### Data collection and analysis

Three authors interviewed authors of all potentially relevant studies by telephone to verify randomisation procedures. One author entered data into a data extraction form and another author verified the results of this procedure.

### Main results

Thirteen relevant trials with 1770 participants were included. All of them were of low quality. Fifty-two studies still need to be assessed because the original authors could not be interviewed. None of these trials analysed mortality, health related quality of life, economic outcomes or compliance. Compared to antithyroid drugs alone the results showed that Chinese herbal medicines combined with antithyroid drugs may offer benefits in lowering relapse rates, reducing the incidence of adverse effects, relieving symptoms, improving thyroid antibody status and thyroid function. Two trials investigated Chinese herbal medicine versus radioiodine and reported improvements in anxiety, tachycardia and heat intolerance. However, thyroid function - with the exception of restored thyroid stimulating hormone (TSH) - was not significantly altered.

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**Authors' conclusions**

The results suggest that traditional Chinese herbal medicines added to other routine treatment have a therapeutic potential for people with hyperthyroidism. However, due to methodological limitations, we could not identify a well-designed trial to provide strong evidence for Chinese traditional herbal medicine in the treatment of hyperthyroidism. Thus, we currently cannot recommend any single preparation or formulation for clinical use.

**PLAIN LANGUAGE SUMMARY****Chinese herbal medicines for hyperthyroidism**

Hyperthyroidism is a common illness in which excessive amounts of thyroid hormones circulate in the blood. Affected people, among other things suffer from increased heart beats, warm moist skin and raised body temperature. A large number of Chinese herbal medicines are used to treat this condition in China. Thirteen relevant trials with 1770 participants were analysed. All of them were of low quality. None of these trials analysed mortality, health related quality of life, economic outcomes or compliance with treatments. Some of these herbs may show benefits in improving symptoms, thyroid function and adverse effects. Unfortunately, we were unable to find reliable evidence to recommend a specific herbal preparation from 103 investigated formulations.

## BACKGROUND

### Description of the condition

Both hyperthyroidism and thyrotoxicosis describe a syndrome in which excessive amounts of thyroid hormones circulate in the blood because of an overactive thyroid gland or due to other causes leading to tachycardia, warm moist skin and raised body temperature.

The most frequent cause of hyperthyroidism is Graves's disease followed by non-cancerous growths of the thyroid or pituitary gland, tumours of the testes or ovaries, inflammation of the thyroid due to viral infections or other causes, ingestion of excessive amounts of thyroid hormone and ingestion of excessive amounts of iodine. Graves's disease accounts for 85% of all cases of hyperthyroidism (Brown 2002).

Hyperthyroidism is a common disorder: Unsuspected and undiagnosed hyperthyroidism was found in roughly 0.5% of women in a large population-based British survey, done in the 1970s (Cooper 2003). Approximately 2% of women and 0.2% of men in the general population are affected by hyperthyroidism (Farling 2000). Hyperthyroidism can occur at all ages, but is less common before the age of 15. At the other extreme, hyperthyroidism is one of the major causes of morbidity in the elderly. Graves's disease can occur at any age, whereas toxic multinodular goitre is more common in people older than 60 years (John 1997).

Clinical features of hyperthyroidism are all mainly caused by an excess of thyroid hormones. The most common manifestations include hyperkinesia, weight loss, sweating, palpitations and nervousness. Other manifestations include atrial fibrillation, cardiac failure, tremor and weakness with general fatigue etc. However, not all the patients show these symptoms or signs but present with varying disorders like menstrual irregularities, vomiting or diarrhoea, psychotic illness, proximal myopathy or pruritus. A proportion of patients have negligible or no symptoms with the diagnosis discovered only during screening (John 1997). Ophthalmic and cardiovascular complications are two clinically significant complications caused by hyperthyroidism. Thyroid-associated eye disease may occur before, after or contemporary with hyperthyroidism in different patients. It may result in diplopia, increased intraocular pressure, soft-tissue signs, marked congestive ophthalmopathy and even sight loss (John 1997). Clinically evident ophthalmopathy occurs in about 50% of patients, however, imaging studies like ultrasonography and computed tomography reveal evidence of ophthalmopathy, in the form of enlarged extraocular muscles, in most patients without clinical signs (Weetmen 2000). The cardiovascular complications of hyperthyroidism are common and sometimes life-threatening. Most patients with hyperthyroidism complain of palpitations and breathlessness on exertion. A variety of atrial and ventricular tachycardias have been described in hyperthyroidism and the most common one is atrial fibrillation. Overt cardiac failure is rare in hyperthyroidism and usually occurs in the context of rapid atrial fibrillation in elderly patients with pre-existing ischaemic or valvular heart disease (Toft 2000).

The actual diagnosis of hyperthyroidism is easy to establish once its possibility is entertained. Accurate and widely available blood tests can confirm or rule out the diagnosis. In most patients, free tri-iodothyronine (FT3) and thyroxine (FT4) concentrations in

serum are raised and serum thyroid-stimulating hormone (TSH) or thyrotropin might be undetectable. The 24-hour radioactive iodine uptake is a measure of the iodine avidity of the thyroid gland. In most hyperthyroid diseases, including Graves's disease, toxic multinodular goitre and toxic adenoma, the results are at the higher end of normal or raised. But this test is generally not needed to arrive at the diagnosis. However, it can be very useful in distinguishing mild Graves's disease from silent or postpartum thyroiditis in which the 24-hour uptake of radioactive iodine will be low (Cooper 2003).

### Description of the intervention

#### Description of treatment options

The treatment of hyperthyroidism includes symptom relief and therapy with antithyroid medications, use of radioiodine (radioactive iodine 131 or I-131) and thyroidectomy. The extrathyroidal manifestations are not improved by treatment directed at hyperthyroidism and specific treatment is needed (McKenna 2001).

#### Medications for symptom relief

Many of the neurological and cardiovascular symptoms such as tremor, palpitation and anxiety following thyrotoxicosis are relieved by beta-blocker therapy because these medicines can block the peripheral effects of the excess amounts of thyroid hormones (Cheetham 1998). Those with a longer duration of action such as propranolol, metoprolol, atenolol and nadolol are usually preferred. Beta-antagonists are generally well tolerated, but can cause depression, nausea, headache, and fatigue. Furthermore, these drugs should be used cautiously in patients with asthma, congestive heart failure, or Raynaud's phenomenon (Cooper 2003). Calcium channel blockers can be used for the same purposes when beta-blockers are contraindicated or poorly tolerated.

#### Antithyroid medications

Antithyroid drugs (thioamides: carbimazole, methimazole or propylthiouracil) are used for almost all patients with thyrotoxicosis in European countries. Carbimazole 0.5 to 1.0 mg/kg/day or propylthiouracil 5 to 10 mg/kg/day in divided doses usually control hyperthyroidism in about 4 to 8 weeks. In practice, antithyroid drugs are usually given for 12 to 24 months when used alone. When the circulating thyroid hormone levels are restored to normal, treatment can be reduced to a single daily dose and titrated against regular thyroid function tests to maintain euthyroidism (McKenna 2001). As with any long term treatment, patients' compliance is not good because many patients and their families find it remarkably difficult to remember to take the drugs regularly. Some 2% to 5% of patients will develop minor side effects with an antithyroid drug, such as rash, nausea, headache, or arthralgia. Usually, such symptoms are transient but if they persist the patient may take another major agent, as cross sensitivity is unusual. Serious adverse effects are rare, but include neutropenia, agranulocytosis (which is nearly always reversible) and hepatotoxicity, all of which need to be dealt with immediately once the effect is discovered (Cheetham 1998).

#### Radioactive iodine

Radioactive iodine therapy is the most common treatment of hyperthyroidism in US adults. It is easy to administrate, lacks significant adverse effects and is relatively inexpensive. Those who

relapse after a course of antithyroid drugs are usually prescribed radioactive iodine or undergo partial thyroidectomy. About 20% of patients will require a second dose of radioactive iodine. Around 50% become hypothyroidal within five years irrespective of the dose (McKenna 2001).

### Thyroidectomy

Surgery for hyperthyroidism is used infrequently all over the world (Cooper 1998). Thyroidectomy is mainly used in specific situations including patient preference, poor response to antithyroid drugs (especially in pregnancy), presence of a very large goitre and the presence of a co-existing potentially malignant thyroid nodule (Cooper 2003). The amount of thyroid tissue to be removed is not easy to decide on: A too conservative operation will result in a high rate of recurrent hyperthyroidism and an overly radical thyroidectomy in hypothyroidism. Either of these two problems could occur unpredictably many years later. Besides, a short hospital stay is needed and potential problems of the operation include the discomfort of the operation, the scar (which may form keloid), the risk of general anaesthesia and surgical complications like the risk of damage to the recurrent laryngeal nerves and transient or permanent hypoparathyroidism (Cheetham 1998).

All currently available therapies are effective, but all the three options have problems as well. Antithyroid drugs usually do not cure the patient, need to be used for long time and have rare but potentially life-threatening adverse effects. Surgery is expensive, may cause permanent hypothyroidism and can be a source of significant morbidity from complications. Radioiodine necessitates radiation exposure, may almost inevitably cause hypothyroidism and may be associated with exacerbation of Graves ophthalmopathy in certain patient subsets (Cooper 1998).

### Medicinal herbs

Medicinal herbs are widely used to treat many diseases including hyperthyroidism in China and many other countries. Chinese herbs including membranous milk vetch root, begonia, tangshen, common anemarrhena rhizome, dwarf lilyturf tuber, Chinese magnoliavine fruitfigwort, rehmannia dride rhizome, common selfheal fruit-spike etc. have been used to treat hyperthyroidism. These herbs are able to decrease the raised affinity of alpha-adrenergic receptors in hyperthyroidism, weaken the biological effects of thyroxine and inhibit the transformation of T4 to T3 (Yao 1998). Some are said to be able to modulate the function of sympathetic nerves or the immune system (Li 1998). The contents of traditional Chinese herbal preparations are variable depending on traditional Chinese medicine syndromes of patients. They are used to treat hyperthyroidism along or in combination with other anti-hyperthyroidism drugs.

### Adverse effects of the intervention

There is evidence that not all herbs are risk-free. In particular, there are concerns about allergic reactions as well as nephropathy (Lampert 2002; Lord 2001; Nortier 2000).

### Why it is important to do this review

Up to now, a lot of studies have been published about the effects of Chinese herbal medicines for hyperthyroidism. These studies showed marked benefits with treatment and indicated that various Chinese herbal medicine preparations are widely used clinically. However, the quality and the effects of these trials have

not been systematically reviewed and assessed. Therefore, this review aims to summarise the existing evidence of the comparative effects and safety of Chinese herbal medicines in the treatment of hyperthyroidism.

## OBJECTIVES

To assess the effects of Chinese herbal medicines for treating hyperthyroidism.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled clinical trials, irrespective of blinding, publication status or language.

#### Types of participants

Participants were males or females of any age or ethnic origin with hyperthyroidism. Participants were excluded if they had acute myocardial infarction, heart failure, hepatic or renal failure.

Diagnostic criteria:

- clinical manifestations, such as weight loss, heat intolerance, irritability, anxiety, palpitations and tremor;
- laboratory abnormalities, such as increase of free triiodothyronine (FT3), free thyroxine (FT4) and decrease of thyroid-stimulating hormone (TSH) in the serum;
- complications, such as ophthalmopathy and pretibial myxoedema.

#### Types of interventions

Therapy with Chinese medicinal herbs alone or Chinese medicinal herbs in combination with antithyroid drugs or radioactive iodine. The following comparisons were acceptable for evaluation:

- antithyroid drugs without Chinese herbal medicines;
- radioactive iodine without Chinese herbal medicines;
- another Chinese herbal medicines preparation.

#### Types of outcome measures

##### Primary outcomes

- mortality;
- relapse rates (recurrence of hyperthyroidism) at least one year after completion of drug treatment;
- incidence of hypothyroidism.

##### Secondary outcomes

- course of ophthalmopathy (need for corticosteroids, radiotherapy, visual compromise);
- adverse effects (for example agranulocytosis, drug rash, hepatitis, vasculitis);
- symptoms of hyperthyroidism (for example anxiety, tachycardia, heat intolerance, diarrhoea, oligomenorrhoea);
- thyroid antibody status;
- weight change;
- thyroid function tests and serum levels of thyroid hormones;

- health-related quality of life;
- economic outcomes;
- compliance rates (for example by calculations of pharmacy prescription, pill counts).

## Search methods for identification of studies

### Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (issue 2, 2006);
- MEDLINE (until July 2006);
- EMBASE (until July 2006);
- Science Citation Index Expanded (until July 2006);
- The Chinese Biomedical Database (until August 2006);
- VIP Chinese Science and Technique Journals Database (until August 2006);
- China National Infrastructure (CNKI) (until August 2006).

The described search strategy (see [Appendix 1](#) for a detailed search strategy) was used for MEDLINE. For use with EMBASE and the other databases this strategy was slightly adapted. There were no language restrictions when searching for trials.

## Data collection and analysis

### Selection of studies

Zeng Xiaoxi (ZXX) scanned the results of the search strategy for potentially relevant studies and retrieved the full articles for all potentially relevant trials. We scrutinized each trial report for multiple publications from the same data set. ZXX, Yuan Yong (YY) and Liu Yan (LY) interviewed the original authors by telephone in order to find out whether participants were really randomised. ZXX and YY independently assessed each of these trials for inclusion in the review using an eligibility form based on the contents of the section 'Criteria for considering studies for this review'. We excluded studies that failed to meet the inclusion criteria and stated the reason in [Characteristics of excluded studies](#). There was no disagreement for study selection.

### Data extraction and management

ZXX entered data into a data extraction form and YY examined these. We extracted data on study characteristics including methods, participants, interventions and outcomes. We resolved any disagreements by referring back to the original trial report and through discussion. If data from the trial reports were insufficient or missing, we contacted the authors for additional information. Where possible, we extracted data to allow an intention-to-treat analysis. For binary outcomes, we recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes, we extracted the arithmetic means and standard deviations for each group.

## Assessment of risk of bias in included studies

According to empirical evidence ([Jadad 1996](#); [Juni 2001](#); [Kjaergard 2001](#); [Moher 1998](#); [Schulz 1995](#)), we assessed the methodological quality as described in *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2005](#)):

- generation of the allocation sequence: adequate (computer generated random numbers, table of random numbers or similar) or inadequate (other methods or not described);
- allocation concealment: adequate (central independent unit, sealed envelopes or similar) or inadequate (not described or open table of random numbers or similar);
- double blinding: adequate (identical placebo tablets or similar) or inadequate (not performed or tablets versus injections or similar);
- follow up: adequate (number and reasons for dropouts and withdrawals described) or inadequate (number or reasons for dropouts and withdrawals not described).

Based on these criteria, we assigned studies to one of the following three categories:

A - all quality criteria met: low risk of bias;

B - one or more of the quality criteria only partly met: moderate risk of bias;

C - one or more criteria not met: high risk of bias.

This classification was used as the basis of a sensitivity analysis. Additionally, we assessed individual quality criteria.

Each trial was assessed independently by two authors (ZXX, LY). There was no disagreement.

## Data synthesis

We did not perform meta-analysis since the herbal medicines used in the evaluated studies were different to each other.

We provide a qualitative description of studies relating to adverse effects.

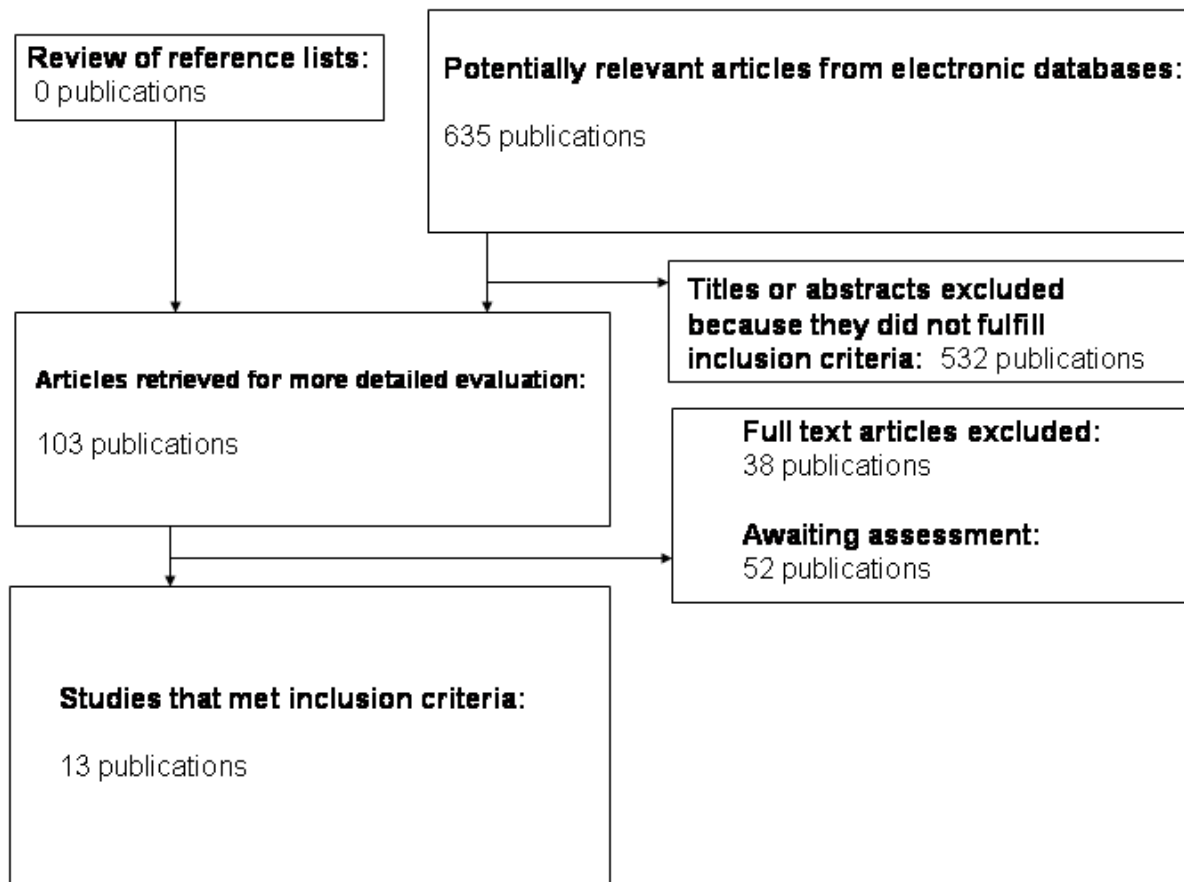
## RESULTS

### Description of studies

#### Results of the search

The electronic searches revealed 635 studies. After reading the titles and abstracts, 103 potential RCTs were retrieved for further assessment. We interviewed the original authors of these 103 studies and discovered that 13 trials turned out to be real RCTs. The authors of 52 studies could not be contacted, these are named under 'Studies awaiting assessment'. Thirty-eight studies were excluded, the reasons for exclusion are listed under 'Characteristics of excluded studies'. In total, 13 trials were included in this review. For an overview ([Figure 1](#)), please see the adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection ([Moher 1999](#)).

**Figure 1. Adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection**



**Included studies**

**Participants**

Altogether 1770 patients with hyperthyroidism participated in the 13 trials. The proportion of males to females was 437 to 1333. All of them were Chinese with an average age of 32 years, ranging from 12 to 68 years. Seven studies (Chen 2004, Dai 2000, Ding 2001a, Ding 2005, Huang 2003, Zhang 2003a and Zhu 2005) described disease duration, which ranged from one month to longer than 10 years. The average number of participants was 136 individuals (ranging from 62 to 368 participants per trial).

Eleven trials enrolled patients with hyperthyroidism alone. Among them, the participants were diagnosed with Graves's disease in two trials (Chen 2004, Fang 2003), diffuse goitre in one trial (Ding 2001b) and diffuse toxic goitre or subacute thyroiditis in one trial (Ding 2005). Two trials enrolled patients with hyperthyroidism accompanied by other co-morbidities (Graves's disease with liver impairment (Yu 2002a) and Graves's disease with proteinuria (Yu 2002b)).

The diagnostic criteria were based on clinical symptoms, physical signs and laboratory tests (mainly thyroid gland function tests). However, four studies (Huang 2003, Qiu 2003, Yan 1999 and Yu 2002b) did not describe exact diagnostic criteria.

**Interventions**

The 13 included RCTs used the following Chinese herbal preparations:

**Chen 2004:** Consisted of a three-arm comparison. The therapeutic effects of herbal oral liquid Jiakangxin Koufuye combined with radioiodine versus methimazole and radioiodine were tested. Jiakangxin koufuye was prepared by the trialists' hospital.

**Dai 2000:** The therapeutic effects of self-prepared herbal tea (Jia 1 formulation) combined with methimazole versus methimazole were compared.

**Ding 2001a:** The therapeutic effects of self-prepared herbal medicine (herbal tea in the beginning and later on Longdanxiegan Wan, Chenxiangshuqi Wan, Zhibaidihuang Wan) combined with radioiodine versus radioiodine were evaluated.

**Ding 2001b:** The therapeutic effects of self-prepared herbal tea (Jiakangping formulation) combined with methimazole versus methimazole were compared.

**Ding 2005:** The therapeutic effects of the herbal capsule Jiakangmianyi Jiaonang combined with propylthiouracil versus another herbal pill Jiakangning Pian combined with propylthiouracil were analysed. Jiakangmianyi Jiaonang was prepared by the trialists' hospital, while Jiakangning Pian was manufactured by a pharmaceutical company.

**Fang 2003:** Consisted of a three-arm comparison. The therapeutic effects of Huangqi injection combined with methimazole versus



another herbal medicine Jiakangling Pian and methimazole were tested.

**Huang 2003:** The therapeutic effects of the herbal medicine pill Yikang Wan which was manufactured by a pharmaceutical company combined with methimazole, propranolol and thyroxine were compared versus methimazole, propranolol and thyroxine.

**Qiu 2003:** The therapeutic effects of self-prepared herbal tea Erdongtang with Xiaoyingwan Jiawei (Yangyinqingre and huatansanjie formulation) combined with methimazole or propylthiouracil versus methimazole or propylthiouracil were evaluated.

**Yan 1999:** The therapeutic effects of self-prepared herbal tea combined with methimazole versus methimazole were compared.

**Yu 2002a:** The therapeutic effects of self-prepared herbal medicine (Qingganjeyu formulation) combined with methimazole or propylthiouracil versus methimazole or propylthiouracil were investigated. The intervention group used herbal tea in the beginning, later on herbal pills.

**Yu 2002b:** The therapeutic effects of self-prepared herbal pills (Qinglihuoxue formulation) combined with propylthiouracil versus propylthiouracil were investigated.

**Zhang 2003a:** The therapeutic effects of Huangqi and Shengmai injection combined with methimazole versus methimazole were compared.

**Zhu 2005:** The therapeutic effects of self-prepared herbal tea (Jiakangxiao formulation) combined with methimazole and propranolol versus methimazole and propranolol were analysed.

The formulations, dosages, methods of administration and course of treatment varied in these trials. The raw Chinese herbal medicines used, formulations and methods of administration are listed in [Appendix 2](#) and 'Chinese herbs terminology in three languages' in [Appendix 3](#), as well as in the table [Characteristics of included studies](#).

### Outcomes

The outcome 'relapse rates' was reported in three trials ([Ding 2001b](#), [Qiu 2003](#) and [Zhu 2005](#)).

The incidence of hypothyroidism was reported in one trial ([Ding 2001a](#)).

Five trials reported adverse effects ([Ding 2001b](#), [Ding 2005](#), [Huang 2003](#), [Qiu 2003](#) and [Zhang 2003a](#)).

Clinical symptoms, physical signs (ophthalmopathy and weight change) and thyroid function tests (including free serum thyroxine (FT3), free triiodothyronine (FT4) and thyroid-stimulating hormone (TSH)) were reported in every trial. The outcomes were divided into recovery, marked improvement, improvement and inefficiency in three trials ([Chen 2004](#), [Ding 2005](#) and [Zhu 2005](#)), while division into recovery or control, improvement and inefficiency was observed in four trials ([Dai 2000](#), [Ding 2001a](#), [Ding 2001b](#) and [Zhang 2003a](#)).

Five trials tested the thyroid antibody status ([Ding 2005](#), [Fang 2003](#), [Qiu 2003](#), [Yu 2002a](#) and [Yu 2002b](#)).

No trial reported on the outcomes mortality, health-related quality of life, costs and compliance rates.

### Risk of bias in included studies

None of the included trials was considered as a high quality study with regards to the components allocation concealment, double blinding and dropouts. As the publications did not provide enough information about design and methodology, we tried to acquire additional data by interviewing the authors, but some of them did

not supply further relevant facts. Details of the individual studies are listed in [Characteristics of included studies](#).

Due to the overall low methodological quality we did not perform sensitivity analyses on the basis of quality.

### Allocation

Three of the 13 studies used computer software to generate randomisation ([Ding 2005](#); [Fang 2003](#); [Qiu 2003](#)), while ten studies used random number tables. None of the 13 trials used allocation concealment.

### Blinding

None of the trials used double blinding. Only four studies used a single blind design ([Ding 2005](#); [Fang 2003](#); [Yu 2002a](#); [Yu 2002b](#)). In these four trials, the patients were not aware of their allocated treatment.

### Incomplete outcome data

Withdrawals and losses to follow-up were described in one study ([Fang 2003](#)). None of the studies performed an intention-to-treat analysis.

### Other potential sources of bias

#### Assessment of compliance

None of the studies mentioned any method of assessing compliance.

#### Similarity of comparison groups at baseline

Age and gender were considered important factors and appeared to be balanced across study groups.

### Effects of interventions

#### Primary outcomes

##### Mortality

None of the studies analysed mortality.

##### Relapse rates

Three studies showed significant differences in relapse rates which were lower after treatment with traditional Chinese herbal medicines in combination with antithyroid drugs than after antithyroid drugs alone:

- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole ([Ding 2001b](#)): RR 0.36, 95% confidence interval (CI) 0.22 to 0.58;
- self-prepared herbal tea Erdongtang with Xiaoyingwan Jiawei (Yangyinqingre and huatansanjie formulation) combined with methimazole or propylthiouracil versus methimazole or propylthiouracil ([Qiu 2003](#)): RR 0.46, 95% CI 0.28 to 0.75;
- Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol ([Zhu 2005](#)): RR 0.35, 95% CI 0.16 to 0.80.

#### Incidence of hypothyroidism

Weak evidence from one study ([Ding 2001a](#)) showed that self-preparation of herbal tea (in the beginning, later on Longdanxiegan Wan, Chenxiangshuqi Wan, Zhibaidihuang Wan) combined with

radioiodine was better at lowering the incidence of late-onset hypothyroidism than radioiodine alone (RR 0.57, 95% CI 0.34 to 0.97). However, the same study showed no statistical significance at reducing the sub-category of early-onset hypothyroidism (RR 0.36, 95% CI 0.12 to 1.09).

## Secondary outcomes

### Course of ophthalmopathy

One study listed ophthalmopathy as an outcome and showed that Chinese herbal medicines combined with antithyroid drugs were not significantly better at modifying ophthalmopathy:

Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000): RR 1.07, 95% CI 0.86 to 1.34.

### Adverse effects

Three studies showed borderline trends or statistical significant differences in reducing the incidence of agranulocytosis with Chinese herbal medicines combined with antithyroid drugs compared to antithyroid drugs alone:

- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole (Ding 2001b): RR 0.02, 95% CI 0.00 to 0.28;
- self-prepared herbal tea Erdongtang with Xiaoyingwan Jiawei (Yangyingqingre and huatansanjie formulation) combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Qiu 2003): RR 0.62, 95% CI 0.47 to 0.83;
- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 0.04, 95% CI 0.00 to 0.75.

However, two other studies did not demonstrate statistical significant differences in reducing the agranulocytosis rate:

- herbal medicine pill Yikang Wan combined with methimazole, propranolol and thyroxine versus methimazole, propranolol and thyroxine (Huang 2003): RR 0.56, 95% CI 0.15 to 2.15;
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 0.48, 95% CI 0.04 to 5.07.

Data from two studies showed that traditional Chinese herbal medicines combined with antithyroid drugs had no significantly better effect in reducing the incidence of hepatitis than antithyroid drugs:

- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 0.28, 95% CI 0.01 to 6.78;
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 1.91, 95% CI 0.18 to 20.28.

Chinese herbal medicines combined with antithyroid drugs did not significantly reduce the incidence of drug rash compared to antithyroid drugs alone:

- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole (Ding 2001b): RR 0.14, 95% CI 0.01 to 1.42;
- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 0.12, 95% CI 0.01 to 2.29;

- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 1.91, 95% CI 0.01 to 3.87.

### Symptoms of hyperthyroidism (anxiety, tachycardia, heat intolerance, diarrhoea)

#### Category 'symptoms subsided'

Four studies of traditional Chinese herbal medicines in combination with antithyroid drugs versus antithyroid drugs alone did not show significant differences:

- Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000): RR 1.40, 95% CI 0.92 to 2.13;
- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole (Ding 2001b): RR 1.23, 95% CI 0.87 to 1.73;
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 1.10, 95% CI 0.60 to 2.03;
- Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol (Zhu 2005): RR 1.71, 95% CI 0.61 to 4.81.

Two studies demonstrated significant effects in favour of the control intervention:

- self-prepared herbal tea Erdongtang with Xiaoyingwan Jiawei (Yangyingqingre and huatansanjie formulation) combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Qiu 2003): RR 1.31, 95% CI 1.08 to 1.58;
- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 2.47, 95% CI 1.52 to 4.02.

#### Category 'symptoms were markedly improved'

Traditional Chinese herbal medicines in combination with antithyroid drugs had no significant better effect than antithyroid drugs alone:

- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 1.06, 95% CI 0.67 to 1.66;
- One study showed better control of symptoms after the control intervention: Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol (Zhu 2005): RR 2.34, 95% CI 1.37 to 4.01.

#### Category 'symptoms were improved'

One study showed statistical significant differences in favour of herbal medicines: Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 0.47; 95% CI 0.25 to 0.86.

However, the other four studies showed no statistical significant differences in improving symptoms:

- Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000): RR 0.80, 95% CI 0.52 to 1.24;
- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole (Ding 2001b): RR 0.55, 95% CI 0.19 to 1.61;

- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 0.95, 95% CI 0.30 to 3.06;
- Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol (Zhu 2005): RR 0.74, 95% CI 0.041 to 1.35.

#### Category 'symptoms were improved'

Evidence from two studies showed statistical significant differences in the number of participants whose symptoms remained unimproved being smaller in the intervention than in the control groups:

- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 0.23, 95% CI 0.07 to 0.78;
- Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol (Zhu 2005): RR 0.29, 95% CI 0.13 to 0.62.

Three other studies revealed no statistical significant differences:

- Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000): RR 0.40, 95% CI 0.08 to 1.97;
- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole (Ding 2001b): RR 0.55, 95% CI 0.11 to 2.74;
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 0.57, 95% CI 0.15 to 2.25.

#### Heart rate

One study (Zhu 2005) investigated heart rates. Jiakangxiao formulation combined with methimazole and propranolol was significantly better than methimazole and propranolol in reducing heart rates by 20 beats/min (RR 2.34, 95% CI 1.37 to 4.01); however, there was no statistically significant difference in normalisation of heart rates (RR 1.71, 95% CI 0.61 to 4.81) and reduction of heart rates by 10 beats/min (RR 0.74, 95% CI 0.41 to 1.35).

#### Pulse rate

- One study (Ding 2005) showed that Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil had similar effects in restoring pulse rates to normal (RR 1.10, 95% CI 0.60 to 2.03), near normal (RR 1.06, 95% CI 0.67 to 1.66) and in reducing pulse rates (RR 0.95, 95% CI 0.30 to 3.06).
- Data from another study (Zhang 2003a) showed statistically significant differences: Huangqi and Shengmai injection combined with methimazole had better effects in restoring pulse rates to normal levels (RR 2.47, 95% CI 1.52 to 4.02) and was less likely not to improve pulse rates (RR 0.23, 95% CI 0.07 to 0.78) than methimazole alone. However, there was no statistically significant difference in reducing pulse rates (RR 0.47, 95% CI 0.25 to 0.86).

#### Anxiety, tachycardia, heat intolerance, diarrhoea

- One study (Ding 2001a) showed that self-prepared herbal medicine (herbal tea in the beginning and later Longdanxiegan Wan, Chenxiangshuqi Wan, Zhibaidihuang Wan) combined with radioiodine was statistically significantly better in improving the

symptoms of anxiety (RR 1.63, 95% CI 1.38 to 1.93), tachycardia (RR 1.21, 95% CI 1.06 to 1.38) and heat intolerance (RR 1.45, 95% CI 1.23 to 1.71) than radioiodine alone.

- Another study (Chen 2004) showed no statistically significant differences in improving anxiety and tachycardia by treatment of Jiakangxin Koufuye combined with radioiodine versus methimazole and radioiodine or radioiodine alone (RR 1.05, 95% CI 0.94 to 1.16 and RR 1.04, 95% CI 0.94 to 1.16, respectively).
- One study (Dai 2000) showed that the Jia 1 formulation combined with methimazole was better in improving the symptoms of tachycardia than methimazole. However, the same could not be demonstrated for weight change and diarrhoea.

#### Thyroid antibody status

Several studies investigated the effects of herbal medicine on thyroid antibodies:

- one study (Yan 1999) showed statistically significant restoration of thyroglobulin antibodies (TGAb) and thyroid microsomal autoantibodies (TMAB) after self-prepared herbal-tea combined with methimazole compared to methimazole alone (RR 4.22, 95% CI 1.84 to 9.69);
- statistically significant improvements of TGAb after herbal medicine were demonstrated by two further studies: Self-prepared herbal-tea combined with methimazole versus methimazole (Yan 1999) and Huangqi injection combined with methimazole versus Jiakangling Pian and methimazole (Fang 2003);
- two studies did not show significant improvements in TGAb after herbal medicine: Self-prepared Qingganjeyu formulation combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Yu 2002a) and self-prepared herbal pills Qinglihuoxue formulation combined with propylthiouracil versus propylthiouracil (Yu 2002b);
- regarding restoration of TMAB, two studies revealed significant differences: Self-prepared herbal-tea combined with methimazole versus methimazole (Yan 1999) and Huangqi injection combined with methimazole versus Jiakangling Pian and methimazole (Fang 2003); self-prepared Qingganjeyu formulation combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Yu 2002a) did not show significant differences;
- one study (Fang 2003) showed that Huangqi injection combined with methimazole was significantly better at restoration of TGAb and TMAB than Jiakangling Pian and methimazole;
- another study (Qiu 2003) showed that self-prepared herbal tea erdongtang with Xiaoyingwan Jiawei (Yangyingqingre and huatansanjie formulation) combined with methimazole or propylthiouracil was followed by a statistically better restoration of thyroid stimulating antibodies (TSAb) than methimazole or propylthiouracil (RR 1.31, 95% CI 1.08 to 1.58).

#### Weight change

Traditional Chinese herbal medicines combined with antithyroid drugs were significantly better in reducing weight than antithyroid drugs in two studies:

- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 2.47, 95% CI 1.52 to 4.02;

- Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol (Zhu 2005): RR 2.17, 95% CI 1.42 to 3.31.

Two studies did not demonstrate significant differences:

- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 1.07, 95% CI 0.86 to 1.34;
- Another study (Dai 2000) showed that Jia 1 formulation combined with methimazole was not statistically significantly better at improving a weight index than methimazole alone.

### Thyroid function tests and thyroid hormone levels

Several studies investigated a variety of outcomes of thyroid function tests as well as thyroid hormone levels.

One study (Huang 2003) showed that herbal medicine pill Yikang Wan combined with methimazole, propranolol and thyroxine was better than methimazole, propranolol and thyroxine at restoration of free triiodothyronine (FT3) (RR 61.06, 95% CI 3.90 to 954.85), free thyroxine (FT4) (RR 2.81; 95% CI 1.40 to 5.64), total triiodothyronine (TT3) (RR 34.76, 95% CI 2.19 to 552.42) and total thyroxine (TT4) (RR 1.41, 95% CI 1.01 to 1.95).

Significant restoration of thyroid stimulating hormone (TSH) was shown in the following studies:

- Huangqi injection combined with methimazole versus Jiakangling Pian and methimazole (Fang 2003);
- Jiakangxin Koufuye combined with radioiodine versus methimazole and radioiodine (Chen 2004);
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005).

Other studies did not demonstrate significant differences:

- self-prepared herbal-tea combined with methimazole versus methimazole (Yan 1999);
- self-prepared Qingganjieyu formulation combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Yu 2002a).

Significant restoration of FT3 was shown in the following studies:

- Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000);
- Huangqi injection combined with methimazole versus Jiakangling Pian and methimazole (Fang 2003);
- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a);
- Jiakangxin Koufuye combined with radioiodine versus methimazole and radioiodine (Chen 2004).

Other studies did not demonstrate significant differences:

- Self-prepared Qingganjieyu formulation combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Yu 2002a);

- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005).

Significant restoration of FT4 was shown in the following studies:

- Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000);
- Huangqi injection combined with methimazole versus Jiakangling Pian and methimazole (Fang 2003);
- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a);
- Jiakangxin Koufuye combined with radioiodine versus methimazole and radioiodine (Chen 2004).

Other studies did not demonstrate significant differences:

- Self-prepared Qingganjieyu formulation combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Yu 2002a);
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005).

Significant restoration of total triiodothyronine (TT3) and thyroxine (TT4) was shown in the following study:

- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a).

Another study did not demonstrate significant differences:

- Self-prepared herbal-tea combined with methimazole versus methimazole (Yan 1999).

Significant normalisation of thyroid hormone levels was demonstrated in two studies:

- Self-prepared herbal tea Erdongtang with Xiaoyingwan Jiawei (Yangyinqingre and huatansanjie formulation) combined with methimazole or propylthiouracil versus methimazole or propylthiouracil (Qiu 2003): RR 1.31, 95% CI 1.08 to 1.58;
- Huangqi and Shengmai injection combined with methimazole versus methimazole (Zhang 2003a): RR 2.47, 95% CI 1.52 to 4.02.

However, several studies showed no statistically significant differences:

- Jia 1 formulation combined with methimazole versus methimazole alone (Dai 2000): RR 1.40, 95% CI 0.92 to 2.13;
- self-prepared herbal tea Jiakangping formulation combined with methimazole versus methimazole (Ding 2001b): RR 1.23, 95% CI 0.87 to 1.73;
- Jiakangmianyi Jiaonang capsule combined with propylthiouracil versus Jiaokangning Pian pill combined with propylthiouracil (Ding 2005): RR 1.10, 95% CI 0.06 to 2.03;
- Jiakangxiao formulation combined with methimazole and propranolol versus methimazole and propranolol (Zhu 2005): RR 1.71, 95% CI 0.61 to 4.81;
- self-prepared herbal medicine (herbal tea in the beginning and later Longdanxiegan Wan, Chenxiangshuqi Wan, Zhibaidihuang Wan) combined with radioiodine ((Ding 2001a) (RR 0.97, 95% CI 0.83 to 1.14).

In one study (Yu 2002b), FT3 and FT4 were measured twice, after 4 and 8 weeks respectively. No statistically significant differences could be demonstrated.

One study (Fang 2003) showed that Huangqi injection combined with methimazole was significantly better at restoration of TSH, FT3 and FT4 than Jiakangling Pian combined with methimazole.

One study (Chen 2004) showed that Jiakangxin Koufuye combined with radioiodine versus methimazole and radioiodine were significantly better at restoration of TSH and FT4 but not at restoration of FT3 compared to radioiodine alone.

#### **Health-related quality of life**

None of the studies analysed health-related quality of life.

#### **Economic outcomes**

None of the studies analysed economic outcomes.

#### **Compliance rates**

None of the studies analysed compliance rates.

## **DISCUSSION**

Studies of Chinese herbal medicine for hyperthyroidism lack sufficient power to provide reliable estimates of the effects of treatment with herbal medicines, due to poor study design and low methodological quality of publications.

Certain important clinical criteria were not clearly defined in our included studies. Except for three studies (Dai 2000, Ding 2005 and Zhu 2005), which provided diagnostic criteria, most included studies did not mention or failed to provide sufficient details on diagnosis. Only two studies (Ding 2005 and Fang 2003) supplied exclusion criteria.

Furthermore, the included studies assessed different outcome measures and some endpoints were only mentioned in one or two publications. Often, the descriptions of the effects were ambiguous and qualitative, which made comparisons difficult.

Formulations of herbal medicines were prepared by the trial authors themselves or associates in ten studies (Chen 2004; Dai 2000; Ding 2001a; Ding 2001b; Ding 2005; Qiu 2003; Yan 1999; Yu 2002a; Yu 2002b; Zhu 2005). The fact that in these ten studies, the trialists acted as the main players, including formulation designer, trial designer and performer, could have introduced bias

Although Chinese herbal medicine as a treatment for hyperthyroidism and its method of manufacturing are widely accepted in China, most of the constituents of the pharmacologically prepared drugs used in trials cannot be clearly specified. In contrast, in pharmacological agents like antithyroid drugs, the chemical constituents, their quantities, the percentage of any impurities or contaminants are precisely known; and the variation between different production batches is kept within specified limits. Variation between formulations and batches of herbal treatments are an inevitable consequence of Traditional Chinese Medicine (TCM), though the Chinese Government also specifies tolerable limits of variation. This variation is a factor that may contribute to heterogeneity between the studies. One

formulation of Chinese herbal medicine was tested by one study only.

Furthermore, one must accept that the overall treatment concept of TCM is different to that used in a pharmacological approach by means of antithyroid drugs. When a study uses a self-prepared herbal formulation, the quality of herbs and the methods of preparation should nevertheless be stated in detail, in order to achieve consistent effects.

A large number of the trials claimed to be RCTs, but when we phoned the trial authors and asked them about the method of randomisation they used, we found that in about 88% (93/106) of publications the authors misunderstood the concept of randomisation. In addition, some of the studies were conducted several years ago and the trial authors may have forgotten the details of the methodology they employed, again increasing the probability of bias.

Two studies (Ding 2001b; Qiu 2003) used unequal arms in their design. Of these studies, Ding 2001b applied a ratio of 3:1 and only 18 patients were included in the control group (66:18). In addition, calculation of sample sizes was not reported.

Hyperthyroidism is a pathological syndrome caused by different causes. Only four studies (Chen 2004, Ding 2005, Yu 2002a and Yu 2002b) pointed out the exact causes. Therefore, it was difficult to associate the effects of herbal therapy with different causes of hyperthyroidism.

On the other hand, traditional Chinese herbal medicine should be used according to the "bian zheng lun zhi" rule. According to TCM theory, hyperthyroidism is recognised as nearly 40 types of "zheng". These different types of "zheng" need to be treated by different herbal medicine formulations. But no study reported in detail what type of "zheng" led to certain preparations making it difficult to judge whether the formulations used were appropriate or not.

Finally, half of studies (52/103) could not be evaluated because the original authors could not be interviewed with regards to the methodological issues. There is a potential risk of analysis bias regarding the results, although we think that only a few of these studies were real RCTs. We will try to contact the authors in the future and will update this review as soon as the interviews are completed.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

According to our findings, traditional Chinese herbal medicines in combination with other routine treatment may show some benefit for people with hyperthyroidism in improving their symptoms, signs, thyroid function and in avoiding or reducing some adverse effects, such as agranulocytosis, drug rash caused by antithyroid drugs and hypothyroidism caused by treatment with radioiodine and thyroidectomy.

However, due to methodological limitations, we could not find a well-designed trial to provide strong evidence for Chinese traditional herbal medicine in the treatment of hyperthyroidism. Thus, we currently cannot recommend any single preparation or formulation for clinical use.

### Implications for research

High quality randomised controlled trials (RCT) are still needed for assessing the effects of Chinese herbal medicines combined with other routine treatment for hyperthyroidism. Especially, randomisation and allocation concealment should be done by independent individuals like a statistician. The authors should report the exact methods of randomisation and blinding (in particular who was blinded, for example outcomes assessors) as

well as for allocation concealment to ensure quality and more rigorous reporting according to the CONSORT statement. The formulation for which "zheng" and the patients' "zheng" as well as details about the herbal medicines should be clearly specified and reported.

### ACKNOWLEDGEMENTS

We thank all the original authors who agreed to be interviewed by telephone.

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**Li 2003c** {published data only}

**Lin 1999** {published data only}

**Liu 1998** {published data only}

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**Wang 2000** {published data only}

**Wang 2001b** {published data only}

**Wang 2003a** {published data only}

**Wang 2003b** {published data only}

**Wang 2004b** {published data only}

**Wang 2004c** {published data only}

**Wu 2000** {published data only}

**Wu 2004** {published data only}

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

**Chen 2004**

Methods	Parallel design. Due to the randomisation method was not mentioned in original article, we telephone interviewed the trialist. The randomisation method was made clear that allocation sequence was generated by random number table. No blinding was performed.
Participants	147 cases of Grave's disease were included (M/F=38/109, aged between 21 and 68, 31.4+/-4.8 years old on average, with the length of the disease between 2 months and 6 years, 17 months on average). 49

**Chinese herbal medicines for hyperthyroidism (Review)**

**Chen 2004** (Continued)

cases were in radioiodine group (I), 49 cases were in tapazole group (T) and 49 cases were in jiakangxin with radioiodine group (J).

Interventions	Radioiodine was used in both I and J groups, p.o., 3.70~5.55 MBq, only once. The second day after taking radioiodine, Jiakangxin Koufuye was additionally given to the latter group, p.o., t.i.d., 20 mL each time, for 2 weeks. Tapazole was used in T group, p.o., 15~30 mg/d, decreased the dosage 2 months later according to the changes of thyroxin.
Outcomes	<p>The outcomes were evaluated by total effective rate, on the basis of improvement of principal symptoms, body weight, thyroid hormones after 6 months.</p> <ol style="list-style-type: none"> <li>1. Recovery: T/I/J=10/23/24;</li> <li>2. Improvement: T/I/J=7/18/19;</li> <li>3. Moderate improvement: T/I/J=11/1/4;</li> <li>4. No improvement: T/I/J=21/7/2;</li> <li>5. Total effective rate: T/I/J=57.1%/85.7%/91.7%. I group and J group had better effect than T group (P&lt;0.05);</li> <li>6. Improvement of principal symptoms (including hidrosis, inertia, hyposomnia, dysphoria and limbs jitter): there was statistical significance between two groups, showing that 1~3 months after the treatment, J group had better effects than I group. But there was no statistical significance between two groups 6 months after the treatment;</li> <li>7. The level of FT3, FT4, TSH was better improved in I and J group than T group. There was statistical significance between two groups.</li> </ol>
Notes	<ol style="list-style-type: none"> <li>1. Jiakangxin Koufuye was prepared by the author's hospital;</li> <li>2. There's potential conflict of interest in the study.</li> </ol>

**Dai 2000**

Methods	Parallel design. Due to the randomisation method was not mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.
Participants	<p>100 patients of hyperthyroidism were included. 50 cases were in intervention group (M/F=9/41, aged between 16 and 65, 35 years old on average, with the length of disease between 1 month and 2 years, 1.2 years on average). 50 cases were in control group (M/F=11/39, aged between 15 and 66, 36 years old on average, with the length of disease between 1 month and 2 years, 1.1 years on average). Diagnosis criterion: symptoms: heat intolerances, polyphagia, emaciation, fatigue, sweating, palpitation, increased frequency of defecation, irregular menstruation;</p> <p>signs: tachycardia, enhanced heart sound, increased pulse pressure, enlarged thyroid gland, vascular murmur and tremor, hand and tongue tremor, damp skin and exophthalmos, obviously increased TT3,TT4,FT3,FT4 concentration ,decreased TSH concentration, increased 99MTc intaking function, no tuberosity or tumor. Including criterion: according with diagnosis criterion, with no severe diseases of heat, brain and kidney, aged between 12 and 75. Excluding criterion: suffering from cerebrovascular accidents in half a year, with severe heart or kidney diseases.</p>
Interventions	Tapazole was used in both groups, p.o., 10 mg each time, t.i.d., for 2 months. Intervention group additionally used Chinese medicine, 1 ampoule/day, decocted with water, for 2 months.
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical recovery: the symptoms and signs subsided completely, concentration of FT3, FT4, TT3, TT4 came to the normal level, radioiodine intaking rate turned to be normal and/or T3 suppressive test was suppressed (I/C=28/20);</li> <li>2. Improvement: the symptoms and signs were improved, not all the concentration of FT3, FT4, TT3, TT4 reached normal level (I/C=20/25);</li> <li>3. No improvement: no change on the symptoms, sighs and the concentration of TT3, TT4, FT3, FT4 (I/C=2/5);</li> <li>4. Total effective rate: I/C=96%/90%. There was statistical significance between two groups, showing that the effect of intervention group was better than control group;</li> </ol>

**Dai 2000** (Continued)

5. The effect of intervention group on improving three symptoms, including tachycardia, body weight and frequency of defecation, was better than control group. There was statistical significance between two groups;
6. The effect of intervention group on decreasing concentration of FT3, FT4 was better than control group.

- |       |  |
|-------|--|
| Notes | <ol style="list-style-type: none"> <li>1. The formulation of Chinese medicine used in the intervention group was provided by the trialist;</li> <li>2. There was potential conflict of interest in the study.</li> </ol> |
|-------|--|

**Ding 2001a**

- |               |   |
|---------------|---|
| Methods       | Parallel design. Due to the randomisation method was not mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.  |
| Participants  | 312 cases which were diagnosed as diffuse goitre by clinical symptoms and laboratory examination (including radioiodine, TT3, TT4, FT3, FT4, TSH, TGA, TMA, ect.) were included. Cases with obvious exophthalmos and hyperthyroidism complication were excluded. 150 cases were in the intervention group (M/F=48/114, patients' age: 20~29/30~39/40~49/50~59=23/45/63/19, first onset/recurrence after operation/recurrence after treatment with drugs=72/22/56). 162 cases were in the control group (M/F=38/112, patients' age: 20~29/30~39/40~49/50~59=24/45/66/27, first onset/recurrence after operation/recurrence after treatment with drugs=78/26/58). Baseline of two groups were similar.  |
| Interventions | Radioiodine and Chinese medicine was used in the intervention group. The radioiodine was given once, p.o., 74~148 MBq. The 2nd week after taking radioiodine, Chinese medicine was used, p.o., for 3 months. Then Chinese formulated products Longdanxiegan Wan, Chenxiangshuqi Wan, Zhibaidihuang Wan was used. Control group used radioactive iodine. The whole course of treatment lasted 6 months~1 year. The patients were followed up in 1~4 years.   |
| Outcomes      | <ol style="list-style-type: none"> <li>1. Recovery: symptoms, signs almost subsided or subsided completely, the results of laboratory examination turned normal (I/C=98/109);</li> <li>2. Improvement: symptoms almost subsided, signs were markedly lightened, the results of laboratory examination were almost normal (I/C=40/38);</li> <li>3. No improvement: symptoms was lightened, but signs and the results of laboratory examination remained the same (I/C=12/15);</li> <li>4. Improvement of symptoms (including palpation, hyposomnia, polyphagia, restlessness, heat intolerance, sweating, ect.): there was statistical significance between two groups, showing that the effect of the intervention group was better than the control group;</li> <li>5. The incidence of hypothyroidism: there was statistical significance between two groups, showing that the incidence of the intervention group was lower than that of the control group.</li> </ol> |
| Notes         | <ol style="list-style-type: none"> <li>1. The formulation of Chinese medicine used in the intervention group was provided by the original authors themselves;</li> <li>2. There was potential conflict of interest in the study.</li> </ol>   |

**Ding 2001b**

- |              |   |
|--------------|---|
| Methods      | Parallel design. Due to the randomisation method was not mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.  |
| Participants | 84 patients of hyperthyroidism were included. The symptoms and laboratory examinations: polyphagia, irritability or depression, emaciation, fatigue, sweating, palpitation, dizziness, enlarged thyroid gland, thyroid murmur and vascular murmur, hand tremor, tachycardia (HR>90/min), exophthalmos, carmoisine tongue, increased T3,T4 and decreased TSH concentration. 36 cases were with liver func- |

**Ding 2001b** (Continued)

tion impairment, 24 were with decrease of WBC, 18 were with decrease of platelets. 66 cases were in the intervention group (M/F=12/54, 30.8 years old on average, 1.4 years on average of the length of disease). 18 were in the control group (M/F=3/15, 31.4 years old on average, 1.6 years on average of the length of disease).

Interventions	Tapazole and Chinese medicine was used in the intervention group, 1 ampoule/day, decocted with water, b.i.d.; Tapazole was used in the control group, 5~10 mg each time, t.i.d., for 2 months, examined FT3, FT4, TSH, liver function and blood routine test once a month.
Outcomes	<ol style="list-style-type: none"> <li>Control: FT3, FT4 turned to normal level and symptoms of hyperthyroidism disappeared (I/C=54(81.8%)/12(22.2%));</li> <li>Improvement: FT3, FT4 decreased by more than 50%, symptoms improved obviously (I/C=8(12.1%)/4(22.2%));</li> <li>No improvement: FT3, FT4 decreased by less than 50% or increased, symptoms didn't improve (I/C=4(6.1%)/2(11.1%));</li> <li>Total effective rate: I/C=93.9%/88.9%. There was no statistical significance between two groups;</li> <li>Adverse effects: in the control group, WBC decrease/platelets decrease/tetter and exophthalmos aggravation=8/3/2; in the intervention group, only 1 case appeared to have tetter and exophthalmos aggravation;</li> <li>Relapse rate within 1 year: I/C=16(29.6%)/10(83.3%). There was statistical significance between two groups, showing that the recurrence rate of the intervention group was lower than the control group.</li> </ol>
Notes	<ol style="list-style-type: none"> <li>Chinese medicine used in the intervention group was prepared by the trialist;</li> <li>There was potential conflict of interest in the study;</li> <li>Two cases in control group were withdrawn from the study for aggravation of the disease.</li> </ol>

**Ding 2005**

Methods	Parallel design. Due to the randomisation method did not be mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by randomisation computer software. Single blindness: the patients didn't know which group they were in.
Participants	86 diagnosed patients were included. Among them, 76 were suffered from diffuse toxic goitre and the rest were at the early stage of subacute thyroiditis. 44 cases were in the intervention group (M/F=18/26, aged between 18 and 65, 35.6+/-12.0 years old on average, with the length of the disease between 1 month and 8 years, 4.5+/-8.6 months on average). 42 cases were in the control group (M/F=15/27, aged between 15 and 67, 30.6+/-14.1 years old on average, with the length of disease between 2 months and 5 years, 3.5+/-6.8 months on average). Baseline of two groups were similar.
Interventions	Propylthiouracil was used in both groups, t.i.d., 100 mg each time. Decreased the dosage to 50~100 mg/d. Jiakangmianyi Jiaonang were used in the intervention group, p.o., t.i.d., 4 capsules each time, for 90 days. The control group used Jiakangning Pian, p.o., t.i.d., 6 tablets each time, for 90 days.
Outcomes	<ol style="list-style-type: none"> <li>Clinical control: the symptoms subsided completely, body weight increased, sphygmus turned to be normal, tremor of the thyroid gland and vascular murmur disappeared, goitre and exophthalmos was lightened and the concentration of TSH, FT3, FT4 came to the normal level (I/C=15/13);</li> <li>Improvement: Main symptoms subsided, body weight increased, sphygmus was almost normal, thyroid tremor and vascular murmur disappeared, goitre and exophthalmos was lightened and the concentration of TSH, FT3, FT4 became almost normal (I/C=21/19);</li> <li>Moderate improvement: The symptoms were improved, sphygmus slowed down, the vascular murmur was lightened, goitre became smaller and the concentration of TSH, FT3, FT4 was almost normal (I/C=5/5);</li> <li>No improvement: No change on the symptoms, signs and laboratory examination (I/C=5/5);</li> <li>Total effective rate: I/C=93.2%/88.1% and there was no statistical significance between two groups;</li> </ol>

**Ding 2005** (Continued)

6. Adverse effects: Decreasing of WBC and impairment of the liver function was observed in one and two cases in the intervention group respectively. In the control group, two patients got iatric tetters, two had WBC decreasing and one patient's liver function was impaired.

Notes

1. The drug was made and provided by the author's hospital;
2. It was a local government supported project.

**Fang 2003**

Methods

Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author and made clear that the allocation sequence was generated by computer software. Single blindness: the patients didn't know which group they were in.

Participants

123 diagnosed GD patients (M/F=33/90, 32+/-7 years old on average) were included. The diagnoses was based on typical hypermetabolic symptoms, enlargement of thyroid gland, exophthalmos and high concentration of T3,T4. All the patients had light symptoms and short length of disease. The enlargement of thyroid gland was within 60 degree and the increase of T3, T4 was less than 20%. Excluding criterion: hyperthyroidism crisis, recurrence cases after treatment of radioiodine or operation, pregnancy, cases accompanied by heart disease, 60 degree or more severe exophthalmos and cases with other chronic and endocrine diseases.

The patients were divided into three groups. 41 cases for each group. Baseline of two groups were similar.

Interventions

Tapazole and Huangqi injection was given in the intervention group. The usage of Tapazole was similar to control 2 group, 60 ml/day Huangqi injection diluted in 500 ml 5% glucose infusion, venous transfusing for 15 days. In diapause, Tapazole was used; Jiakangling was used in control 1 group, p.o., t.i.d., 2 tablets each time; Tapazole was used in control 2 group, p.o., t.i.d., 10 mg each time.

Outcomes

The outcomes were evaluated by function of thyroid gland (FT3,FT4,TSH), TGA, TMA, T lymphocytes, blood routine test and liver function.

1. The changes of WBC amount, liver function and thyroid gland function: The liver function of the patients in control 1 group improved, but little improvement was seen on their WBC amount and thyroid gland function; in control 2 group, liver function and thyroid gland function of the patients improved; in the intervention group, liver function, thyroid gland function, WBC amount and concentration of TGA, TMA improved obviously. And the result showed that the effects of intervention group were better than other groups;
2. The changes of T lymphocytes: In control 1 group, the T lymphocytes almost stayed the same; in control 2 group, CD4 decreased and CD8 increased a little so that CD4/CD8 decreased; in the intervention group, CD4 and CD8 improved so that CD4/CD8 decrease obviously. The result showed that there was statistical significance between intervention group and other groups.

Notes

1. 'Positive drug' jiakangling was used to be the control but there was no any record about its effect;
2. Two cases in control 1 group quit the study for aggravation of the disease.

**Huang 2003**

Methods

Parallel design. Due to the randomisation method was not mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.

Participants

All patients included were inpatients or outpatients who were diagnosed as hyperthyroidism by clinical and laboratory examination. 32 cases were in the intervention group (M/F=8/24, aged between 15 and 61, 26+/-9.8 years old on average, with the length of disease between 2 and 36 months, 14+/-5.2 months on average). 30 cases were in the control group (M/F=7/23, aged between 19 and 57, 25+/-9.2 years old

**Huang 2003** (Continued)

on average, with the length of disease between 2 and 24 months, 12+/-5.6 months on average). Baseline of two groups were similar.

Interventions	Yikang Wan and Tapazole was used in the intervention group, Yikang Wan: p.o., 1 pill(9 g) each time, t.i.d., Tapazole: p.o., 5 mg each time, t.i.d. Tapazole was used in the control group, p.o., 5 mg each time, t.i.d. Propranolol (10 mg each time, t.i.d.) and Jiazhuangxian Pian (30 mg each time, q.d.) was used in both groups.
Outcomes	<p>The outcomes were evaluated by clinical symptoms, signs, blood routine test, FT3, FT4, TT4, TT3 concentration. They were examined 2, 3, 4 weeks after the treatment and before the treatment.</p> <ol style="list-style-type: none"> <li>1. The hyperthyroidism diagnoses index of the intervention group was lower than the control group. There was statistical significance;</li> <li>2. Two and three weeks after treatment, FT3 concentration of the intervention group turned to be normal, while FT3 concentration of the control group was still above the normal level;</li> <li>3. FT4 concentration of 21 cases in the intervention group turned to be normal, while only 7 cases in the control group was normal;</li> <li>4. TT3 concentration of 18 cases in the intervention group turned to be normal, while no one in the control group turned to be normal;</li> <li>5. TT4 concentration of 27 cases in the intervention group turned to be normal, while 18 cases in the control group turned normal;</li> <li>6. Adverse effect: temple WBC increasing was observed in 3 cases in the intervention group and 5 cases in the control group. Taking drugs that could increase WBC, the symptom subsided and the cases continued the study.</li> </ol>
Notes	<ol style="list-style-type: none"> <li>1. Yikang Wan was provided by the company that was the sponsor of the magazine in which the article was published;</li> <li>2. There was potential conflict of interest in the study.</li> </ol>

**Qiu 2003**

Methods	Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author and made clear that the allocation sequence was generated by computer software. No blindness.
Participants	368 cases were included (M/F=82/286, aged between 18 and 62, 35.6 years old on average). The diagnoses criterion included FT3>10 pmol/L, FT4>30 pmol/L, or TT3>3.0 pmol/L, TT4>155 nmol/L and sTSH<0.5 mU/L. 260 were in the intervention group (34.8 years old on average). 108 were in control group (36.2 years old on average). Baseline of two groups were similar.
Interventions	The intervention group was treated by Erdong Tang with Xiaoluowan Jiawei (ETXJ) on the basis of west medicine treatment. 1 ampoule/day, decocted with water, b.i.d. When the symptoms were lightened, decreased the dosage to 1 ampoule/3-day and keep the minimum dosage of 1 ampoule/15-day for 1.5~2 years; Tapazole (p.o., 30~40 mg/day) or Propylthiouracil (p.o., 300~450 mg/day) was used in control group. The dosage was decreased when the symptoms were lightened. Then the patients were treated by the minimum dosage (tapazole: 5 mg/day, propylthiouracil: 50 mg/day) for 1.5~2 years.
Outcomes	<ol style="list-style-type: none"> <li>1. Recovery: The symptoms subsided completely, thyroid gland shank, negative TSAb and T3, T4, TSH sustained the normal level for 1 year after discontinuing drugs. (I/C=186(71.5%)/59(54.6%)) There was statistical significance between two groups, showing that the effect of intervention group was better than control group;</li> <li>2. Relapse Rate: Hyperthyroidism was ameliorated but then relapsed within 1 year after discontinuing drugs, symptoms recurred and FT3, FT4 (or TT3,TT4) increased. (I/C=29(15.6%)/20(33.9%)) There was statistical difference between two groups that was the recurrence rate of intervention group was lower than control group;</li> <li>3. Granulocytes decreasing: WBC&lt;4*10<sup>9</sup>/L and neutrophils were the mainly cells that decreased. (I/C=72(27.7%)/48(44.4%)) There was statistical difference between two groups, showing that the adverse effect of intervention group was less than control group.</li> </ol>



**Qiu 2003** (Continued)

Notes	<ol style="list-style-type: none"> <li>1. Funded by patients themselves.</li> <li>2. Both the Xiaying Wan and Erdongtang decoction were prepared by the original authors themselves;</li> <li>3. There was potential conflict of interest in the study.</li> </ol>
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**Yan 1999**

Methods	Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.
Participants	105 in-patients of hyperthyroidism were included. 62 cases were in intervention group (M/F=22/40, aged between 15 and 57, 29.1+/-10.8 years old on average). 43 cases were in control group (M/F=14/29, aged between 14 and 56, 28.3+/-11.2 years old on average). Baseline of two groups were similar.
Interventions	Tapazole was used in both groups, 30 mg/day, for 28 days. Besides tapazole, Chinese medicine was additionally used in the intervention group, 1 ampoule/day, decocted with water.
Outcomes	<ol style="list-style-type: none"> <li>1. Symptoms (including palpitation, fatigue, emaciation, heat intolerance) of both groups improved obviously. There was statistical significance between two groups;</li> <li>2. Concentration of T3, T4 decreased and concentration of TSH increased obviously in both groups. There was no statistical significance between two groups;</li> <li>3. TGAb (TGAb&gt;30%) / TMAb (TMAb&gt;15%) negative turning rate of intervention group was better than control group. There was statistical significance between two groups. (I/C=31 (65.9%) / 5 (15.6%) )</li> </ol>
Notes	<ol style="list-style-type: none"> <li>1. The formulation of Chinese medicine used in the intervention group was provided by the original authors;</li> <li>2. There was potential conflict of interest in the study.</li> </ol>

**Yu 2002a**

Methods	Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. Single blindness: the patients didn't know which group they were in.
Participants	73 patients that suffered from Grave's disease with light to moderate liver impairment were included. The patients whose liver were impairment by virus hepatitis or the causes were excluded. 38 cases were in the intervention group (M/F=8/30, aged between 18 and 60, 31.2 years old on average). 35 cases were in the control group (M/F=6/29, aged between 19 and 63, 32.7 years old on average). Baseline of two groups were similar.
Interventions	Chinese medicine and anti-thyroid drugs (ATD, including Tapazole and Propylthiouracil) was used in the intervention group. Chinese medicine was decocted with water, 1 ampoule/d, for 4 weeks. Then take the pills made by Chinese herb, 1 ampoule/d, for 4~8 weeks; Tapazole (5 mg/d, t.i.d.) or Propylthiouracil (50 mg/d, t.i.d.) was also used in the control group. Change the dosage from the 5th weeks after the function of thyroid gland turned to normal. The control group only used ATD. The method was similar to the intervention group.
Outcomes	<p>Thyroid gland function (including T3, T4, TSH, FT3, FT4), thyroid gland auto-antibody (including TGA, TMA) and liver function (including ALT, AST, TBil) was taken into consideration.</p> <ol style="list-style-type: none"> <li>1. The decrease of ALT and AST: The intervention group (ALT: from 67.2+/-20.3 IU/L to 30.6+/-4.5 IU/L, AST: from 54.6+/-13.7 IU/L to 29.3+/-5.1 IU/L, TBil: from 23.1+/-7.3 IU/L to 12.3+/-4.7 IU/L) had better effects than the control group after 12 weeks;</li> </ol>

### Yu 2002a (Continued)

2. The time needed for liver function's improvement: The intervention group (it took 25.7+/-9.2 days to be normal and 94% cases turned to be normal within 8 weeks.) was better than the control group (It took 36.8+/-12.4 days to be normal and only 57.1% cases turned to be normal within 8 weeks);
3. The improvement of the thyroid gland and the changes of relative antibody: The improvement of FT3, FT4, TGA, TMA and TSH showed no statistical significance between two groups.

#### Notes

1. We telephone interviewed the pharmaceutical company and learned that the formulation of the Chinese medicine and the pills made by Chinese herb used in the intervention group was provided by the authors themselves, and the company provided processed raw material needed;
2. There was potential conflict of interest in the study.

### Yu 2002b

#### Methods

Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. Single blindness: the patients didn't know which group they were in.

#### Participants

93 patients who were diagnosed as Grave's disease and PCI>150 were included. The patients whose kidney were impaired other causes were excluded. 46 cases were in the intervention group (M/F=9/37, aged between 18 and 71, 38.1+/-12.4 years old on average). 47 cases were in the control group (M/F=8/39, aged between 17 and 68, 36.4+/-11.2 years old on average). Baseline of two groups were similar.

#### Interventions

Propylthiouracil was used in both groups, p.o., 100 mg/day, b.i.d. Chinese medicine was additionally used in the intervention group. Chinese medicine was made into pills, 1 ampoule/d, for 4 weeks.

#### Outcomes

The outcomes were evaluated by  $PCI=(\text{uria protein}/\text{uria creatinine}) \times 10$ , uria NAG/PNP method, blood/uria  $\beta_2$ -MG, thyroid gland function and relative antibody (FT3, FT4, TGA).

1. The changes of uria protein and NAG: After 4 and 8 weeks, uria protein and NAG of both groups decreased. There was statistical significance between two groups, showing that the decrease of intervention group was more obviously than control group. And the decrease of PCI was in correlation of NAG;
2. The changes of blood/uria  $\beta_2$ -MG:  $\beta_2$ -MG of both groups decreased to normal level. After 4 weeks, both blood and uria  $\beta_2$ -MG of the intervention group decreased more obviously than control group;
3. The changes of thyroid gland function: After 8 weeks, FT3, FT4 of both groups improved obviously.

#### Notes

1. We telephone interviewed the pharmaceutical company and learned that the formulation of the Chinese medicine and the pills made by Chinese herb used in the intervention group was provided by the authors themselves, and the company provided processed raw material needed;
2. There was potential conflict of interest in the study.

### Zhang 2003a

#### Methods

Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.

#### Participants

96 diagnosed patients were included. 52 cases were in the intervention group (M/F=11/41, aged between 18 and 66, 38.5+/-3.6 years old on average; the length of disease within 0.5 year /within 10 years/ longer than 10 years=38/11/3; first on set/recurrence after discontinuing drugs=42/10). 44 cases were in the control group (M/F=9/35, aged between 19 and 65, 40.5+/-2.4 years old on average, with the length of disease between 2 months and 5 years, 3.5+/-6.8 months on average; the length of disease within 0.5 year /within 10 years/longer than 10 years=32/10/2; first on set/recurrence after discontinuing drugs=36/8). Baseline of two groups were similar.

**Zhang 2003a** (Continued)

Interventions	Tapazole was used in both groups, p.o., t.i.d., 10 mg each time, decreased the dosage to 5~15 mg/day; Tapazole, Huangqi injection and Shengmai injection was given in the intervention group. The usage of Tapazole was similar to control 2 group. 20 ml/day Huangqi injection diluted in 250 ml 5% GNS infusion and 30 mL/day Shengmai injection diluted in 250 5% GNS was transfused through veins.
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical recovery: The symptoms subsided completely, body weight increased, sphygmus turned to be normal, thyroid gland function and the results of immunology test turned to be normal. (I/C=38 (73.1%) / 13 (29.5%) )</li> <li>2. Improvement: The symptoms were improved, sphygmus slowed down, thyroid gland function was almost normal. (I/C=11 (94.23%) / 20 (45.5%) )</li> <li>3. Inefficacy: The results didn't reach improvement criterion or discontinued the drugs because of adverse effects or accepted other treatment. (I/C=3 (5.7%) / 11 (25%) )</li> <li>4. Total effective rate: I/C=94.23%/75.00%. There was statistical significance between two groups, showing that the effect of intervention group was better than control group;</li> <li>5. Comparison of changes of T3, T4, FT3, FT4 before and after the treatment: both groups decreased. There was statistical between two groups, showing that intervention group decreased more obviously than control group;</li> <li>6. Adverse effects: Decreasing of WBC, tetter and impairment of the liver function was observed in 9, 3 and 1 cases in the intervention group respectively. In the control group, no adverse effect was observed;</li> <li>7. The dates for thyroid gland function turned to be normal: I/C=25.96+/-3.84/30.77+/-3.61. There was statistical significance between two groups, showing that the time needed of intervention group was shorter than control group.</li> </ol>
Notes	<ol style="list-style-type: none"> <li>1. The study was a local government support project.</li> <li>2. Both Huangqi injection and Shengmai injection were made by pharmaceutical company.</li> </ol>

**Zhu 2005**

Methods	Parallel design. Due to the randomisation method wasn't mentioned in original article, we telephone interviewed the original author. The randomisation method was made clear that allocation sequence was generated by random number table. No blindness.
Participants	121 cases that were diagnosed as hyperthyroidism were included. 62 cases were in the intervention group (M/F=15/47, aged between 12 and 53, 30 years old on average; with the length of disease between 3 months and 6 years, 1.2 years on average; ¶ all had the symptoms of sweating, dysphoria, palpitation, hard breath and emaciation; ¶ 41 cases had thyroid gland tremor; ¶ The cases of ¶, ¶, ¶ degree of thyroid gland enlargement=12/48/2; ¶ 53 cases were accompanied by sinus arrhythmia, and ¶ 1 cases was atrial fibrillation; ¶ The concentration of TSH, T3, T4, FT3 and FT4 increased lightly in 11 cases, moderately in 31 cases and obviously in 20 cases; ¶ 20 cases' BMR>30%, 42 cases' BMR>60%.) 59 were in the control group (M/F=13/46, aged between 13 and 51, 29.5 years old on average; with lengths of disease between 4 months and 5 years, 1.3 years on average; ¶ all had the symptoms of sweating, dysphoria, palpitation, hard breath and emaciation; ¶ 40 cases had thyroid gland tremor; ¶ The cases of ¶, ¶, ¶ degree of thyroid gland enlargement=11/46/2; ¶ 48 cases were accompanied by sinus arrhythmia, and ¶ 2 cases was atrial fibrillation; ¶ The concentration of TSH, T3, T4, FT3 and FT4 increased lightly in 10 cases, moderately in 30 cases and obviously in 19 cases; ¶ 21 cases' BMR>30%, 38 cases' BMR>60%. ) Baseline of two groups were similar.
Interventions	Tapazole and Propranolol was used in the control group. Tapazole: 30 mg/d, t.i.d. The dosage was decreased to 5~15 mg/d. For 1.5~2 years. Propranolol:30 mg/d,t.i.d. and discontinued using it when HR<80/min; Besides the drugs listed above, Chinese medicine was used in the intervention group. 1 ampoule/d, decocting with water, and orally drank 200 ml in the morning and evening respectively.
Outcomes	<p>The outcomes were evaluated after 50 days. The patients were followed up for 1 year.</p> <ol style="list-style-type: none"> <li>1. Clinical recovery: The symptoms subsided completely, body weight increased, the size of tyroid gland reduced by 30% or more, the concentration of thyroxin came to the normal level and gained the normal ECG and BMR. (I/C=9/5)</li> </ol>

**Zhu 2005** (Continued)

2. obviously improvement: Symptoms were obviously alleviated, body weight increased, sphygmus reduced by more than 20/min, the size of thyroid gland reduced by 20% or more, the concentration of thyroxin obviously decreased and BMP<=30%. (I/C=32/13)
3. Improvement: The symptoms were improved, sphygmus slowed down by more than 10/min, the concentration of thyroxin decreased and BMR<=40%. (I/C=14/18)
4. Inefficacy: No change on the symptoms, the concentration of thyroxin and BMR stay the same. (7/23)
5. Total effective rate: I/C=88.6%/36.1%. There's statistical significance between two groups, showing that the effect of intervention group was better than the control group's.
6. Relapse Rate: After taking Chinese medicine and using tapazole alone, the symptoms recurred in once recovery and obviously improving cases or the improving cases' weight gained and concentration of thyroxin increased. (I/C=7/13) There was statistical significance between two groups, showing that the recurrence of intervention group was lower than control group.

**Notes**

1. The formulation of Chinese medicine used in the intervention group was provided by the original authors;
2. There was potential conflict of interest in the study.

**Abbreviations**

P.O.=per os (orally)  
 B.i.d.=Eis in die (two times a day)  
 T.i.d.=Ter in die (three time a day)  
 Q.d.=Quaque die (one time a day)  
 MBq = megabecquerel  
 T3 = triiodothyronine  
 T4 = thyroxine  
 FT3 = free triiodothyronine  
 FT4 = free thyroxine  
 TT3 = total triiodothyronine  
 TT4 = total thyroxine  
 TSH = thyroid stimulating hormone  
 TGA = anti-thyroglobulin antibody  
 TMA = anti-thyroid-microsome antibody  
 ATD = anti-thyroid drugs  
 GNS = glucose and sodium chloride  
 NAG = N-acetyl- $\beta$ -D-glucosaminidase  
 BMR = basic metabolic rate  
 WBC = white blood cell  
 GD = grave's disease

**Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
Du 2003	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Fei 2004	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The allocation procedure was described as that the patients decided which treatment would be accepted by themselves.

Study	Reason for exclusion
Feng 1998	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Ge 2004	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The trialist decided which remedy would be allocated to the patient in a non-random way.</p>
Hu 2005	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>Chinese medicine was used by in-patients and western medicine was used by out-patients.</p>
Huang 2002	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The trialist decided which remedy would be allocated to the patient in a non-random way.</p>
Huang 2004	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Huang 2005	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were allocated to the intervention and control group by their registration sequence, depending on the even or odd number.</p>
Li 2003a	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>Which remedy would be taken was decided by the patients.</p>
Liang 2000	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Liao 1999	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The trialist decided which remedy would be allocated to the patient in a non-random way.</p>
Liao 2000	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The trialist decided which remedy would be allocated to the patient in a non-random way.</p>
Lv 1997	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p>

Study	Reason for exclusion
	The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Nie 1997	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Shi 2002	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were allocated to the intervention and control group by their registration number at libitum.</p>
Sun 1999	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Tang 2003	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Wang 1999a	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The trialist decided which remedy would be allocated to the patient in a non-random way.</p>
Wang 2001a	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were allocated to the intervention group and the control group by the method of self-drawing lots.</p>
Wang 2004a	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and control group by their registration sequence.</p>
Xiao 2004	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>Which remedy would be taken was decided by the patients.</p>
Xing 2003	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p> <p>The patients were alternately allocated to the intervention and the control group by their visiting sequence.</p>
Xu 2003a	<p>Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature.</p>

Study	Reason for exclusion
	The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Yang 2004a	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were allocated to the intervention and the control group by the date of visit.
Yao 1997	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and control group.
Yuan 2002	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The trialist decided which remedy would be allocated to the patient in a non-random way.
Zeng 1998	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were allocated to the intervention and the control group by the method of drawing lots.
Zhang 2000	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Zhang 2001	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Zhang 2002	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Zhang 2003b	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The trialist decided which remedy would be allocated to the patient in a non-random way.
Zhang 2004a	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. Which remedy would be taken was decided by the patients.
Zhang 2005	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were allocated to the intervention and control group by their registration sequence depending on the even or odd number.

Study	Reason for exclusion
Zhao 2001	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by their visiting sequence.
Zhao 2003	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by the date on which they visited the doctor.
Zhao 2004a	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by the date on which they visited the doctor.
Zhao 2004b	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by the date on which they visited the doctor.
Zhao 2005	Authors described their study as a randomised controlled trial. We interviewed the original author(s) by telephone to identify which method of randomisation was used. According to authors' description, we decided that this trial was of a non-randomised nature. The patients were alternately allocated to the intervention and the control group by the date on which they visited the doctor.

## DATA AND ANALYSES

### Comparison 1. Chinese herbs versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thyroid antibody status	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Thyroglobulin antibody (TGAb)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Thyroid microsomal antibodies (TMAB)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Relapse rates	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Thyroid function tests (di-chotamous data)	7		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected



Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Normalisation of free triiodothyronine (FT3)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Normalisation of free thyroxine (FT4)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Normalisation of total triiodothyronine (TT3)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Normalisation of total thyroxine (TT4)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Normalisation of thyroid hormones	6		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>4 Thyroid function tests (continuous data)</b>	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Thyroid-stimulating hormone (TSH)	5		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Thyroid-stimulating hormone (TSH)(Huangqi injection versus Jiahangling)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Free triiodothyronine (FT3)	6		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Free triiodothyronine (FT3) (Huangqi injection versus Jiakangling)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Free triiodothyronine (FT3) at 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Free triiodothyronine (FT3) at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Free thyroxine (FT4)	6		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.8 Free thyroxine (FT4)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.9 Free thyroxine (FT4) at 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.10 Free thyroxine (FT4) at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.11 Total triiodothyronine (TT3)	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.12 Total thyroxine (TT4)	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>5 Thyroid antibody status</b>	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

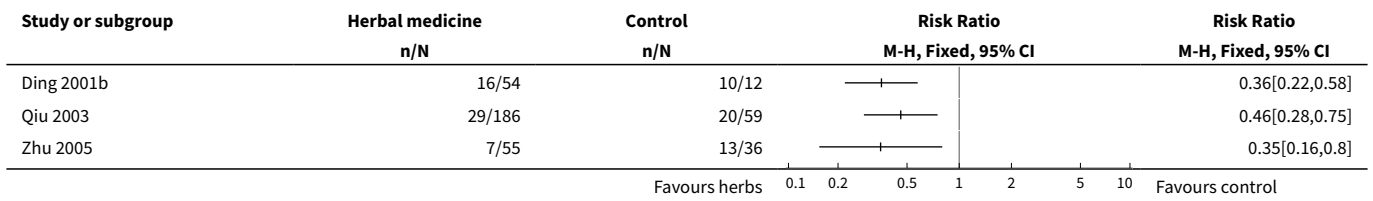
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Thyroglobulin antibodies (TGAbs)	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Thyroglobulin antibody (TGAbs)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Thyroid microsomal autoantibodies (TMAB)	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Thyroid microsomal antibodies (TMAB)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>6 Symptoms of hyperthyroidism</b>	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Symptoms subsided	6		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Symptoms were markedly improved	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Symptoms were improved	5		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 No improvement of symptoms	5		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>7 Weight change (improvement)</b>	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
<b>8 Adverse effects</b>	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Agranulocytosis	5		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Hepatitis	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Drug rash	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>9 Tachycardia</b>	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Normalisation of heart rate	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Decrease in heart rate by 20 beats/min	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Decrease in heart rate by 10 beats/min	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 No improvement of heart rate	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.5 Normalisation of pulse rate	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.6 Near normalisation of pulse rate	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.7 Decrease in pulse rate	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.8 No improvement of pulse rate	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>10 Thyroid antibody status</b>	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Reduction in thyroglobulin antibodies (>30%) and thyroid microsomal autoantibodies (>15%)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Normalisation of thyroid-stimulating antibodies (TSAb)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>11 Improvement of ophthalmopathy</b>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
<b>12 Weight change ( weight index )</b>	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
<b>13 Symptoms of hyperthyroidism</b>	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Tachycardia (heart rate)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Diarrhoea ( frequency of stools)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

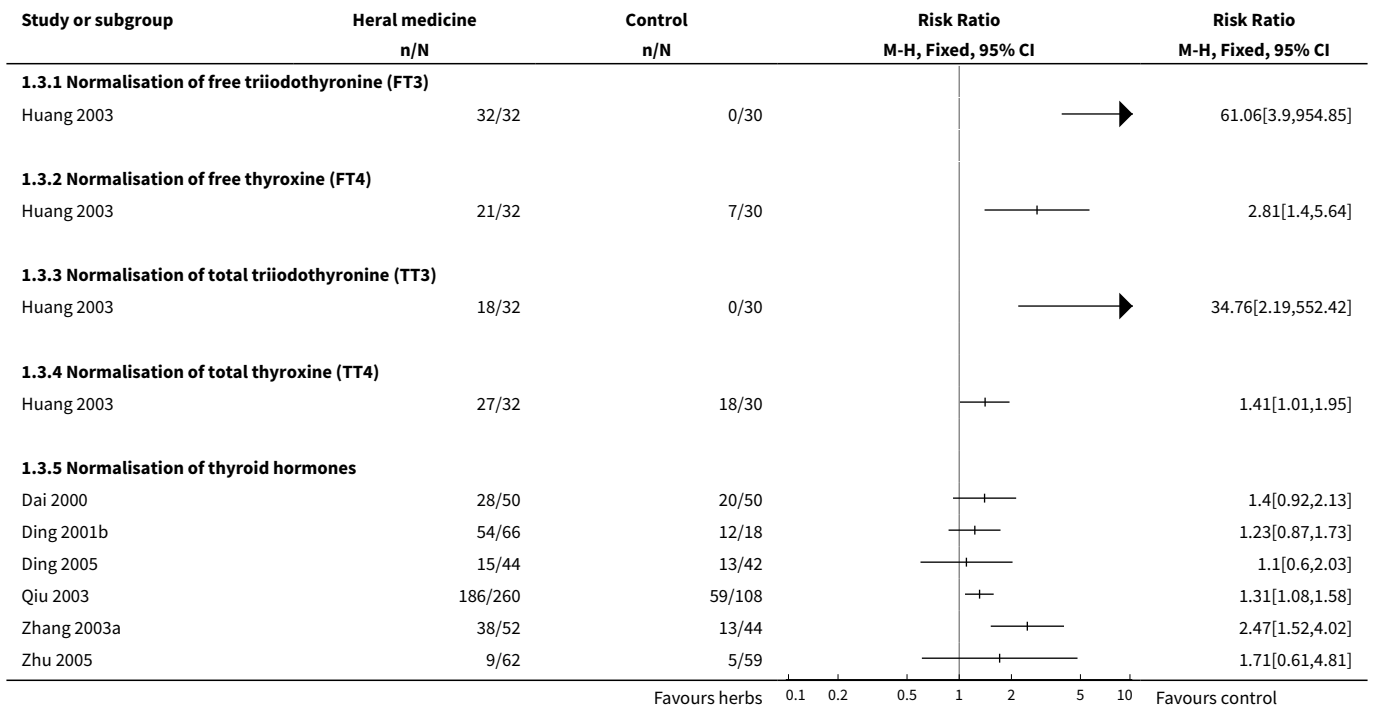
**Analysis 1.1. Comparison 1 Chinese herbs versus control, Outcome 1 Thyroid antibody status.**

Study or subgroup	Herbal medicine		Control		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
<b>1.1.1 Thyroglobulin antibody (TGAb)</b>						
Fang 2003	41	5.9 (2.3)	41	14.6 (6.4)		-8.7[-10.78,-6.62]
<b>1.1.2 Thyroid microsomal antibodies(TMAb)</b>						
Fang 2003	41	2.1 (1.1)	41	7.3 (3.6)		-5.24[-6.38,-4.1]

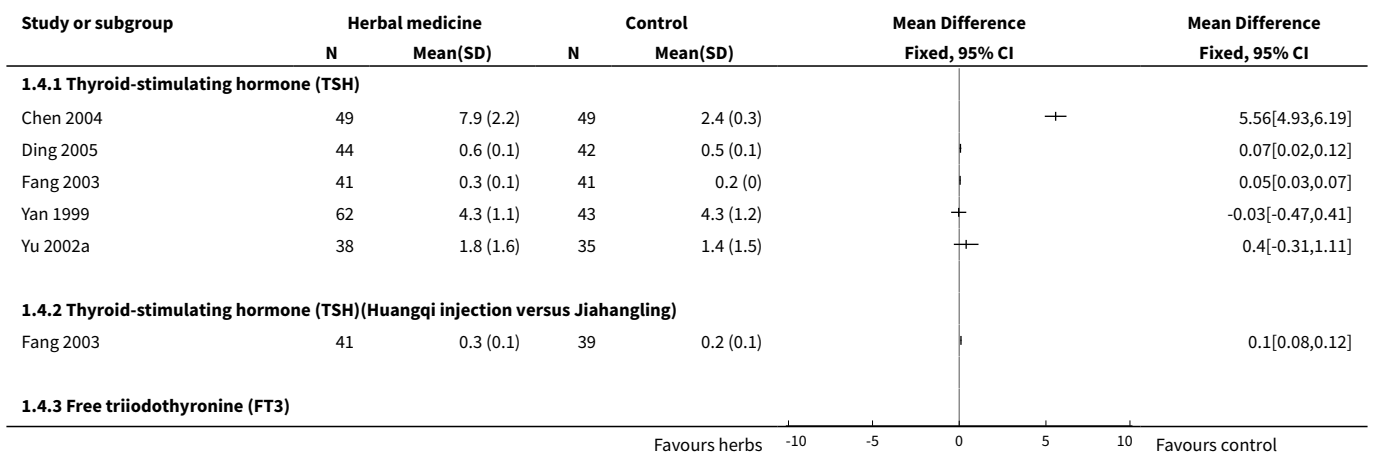
**Analysis 1.2. Comparison 1 Chinese herbs versus control, Outcome 2 Relapse rates.**

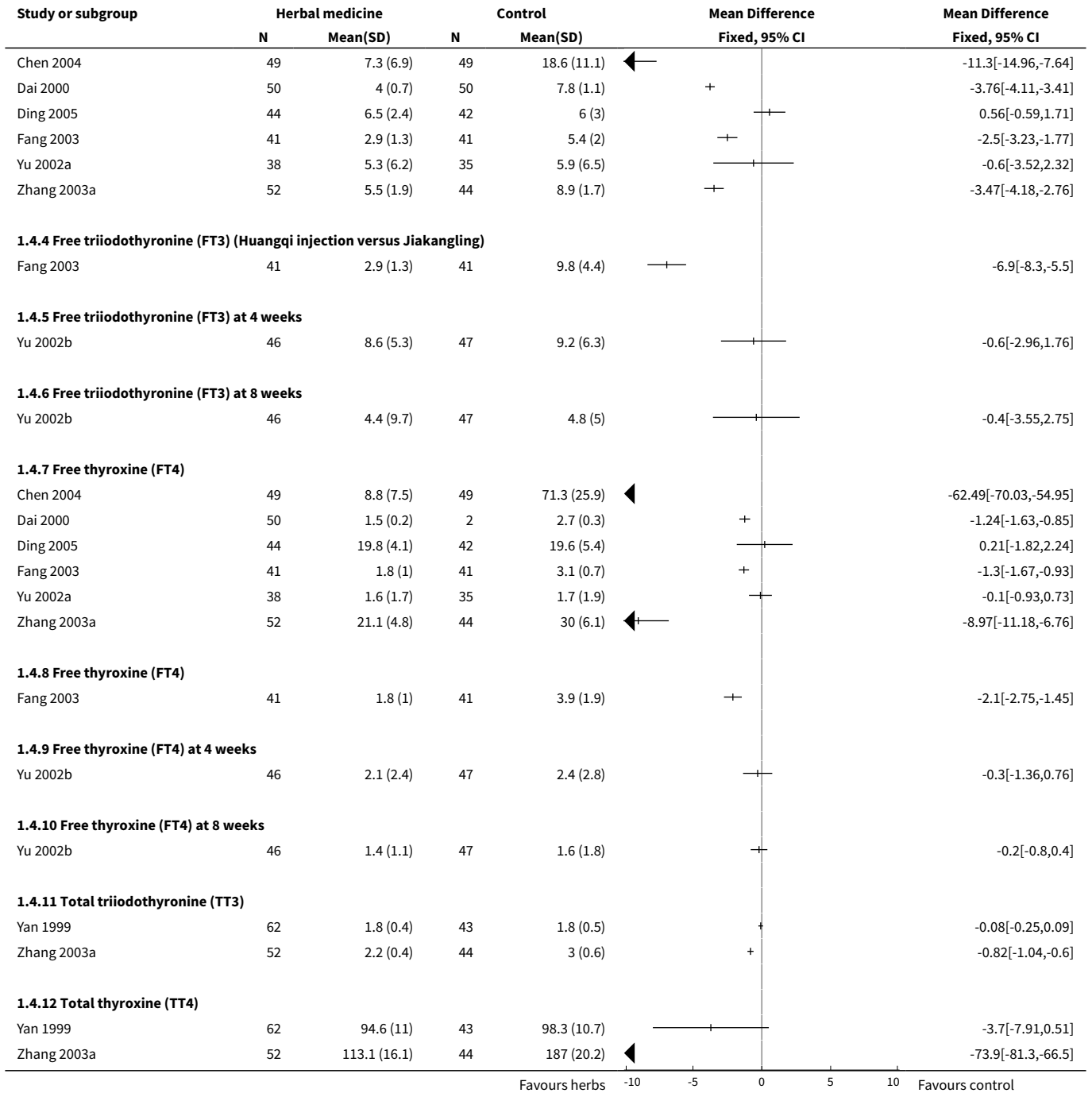


**Analysis 1.3. Comparison 1 Chinese herbs versus control, Outcome 3 Thyroid function tests (dichotomous data).**

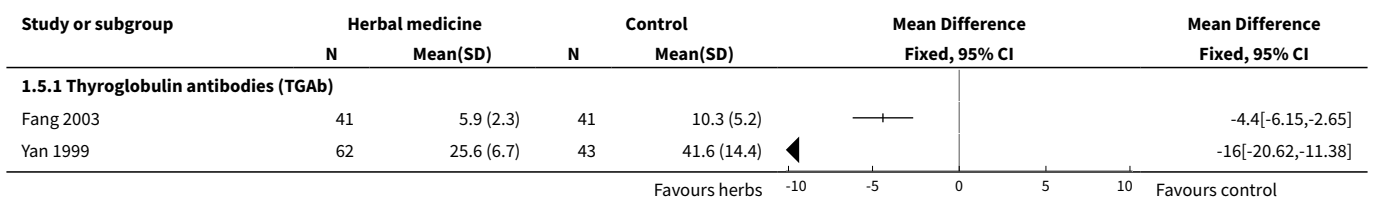


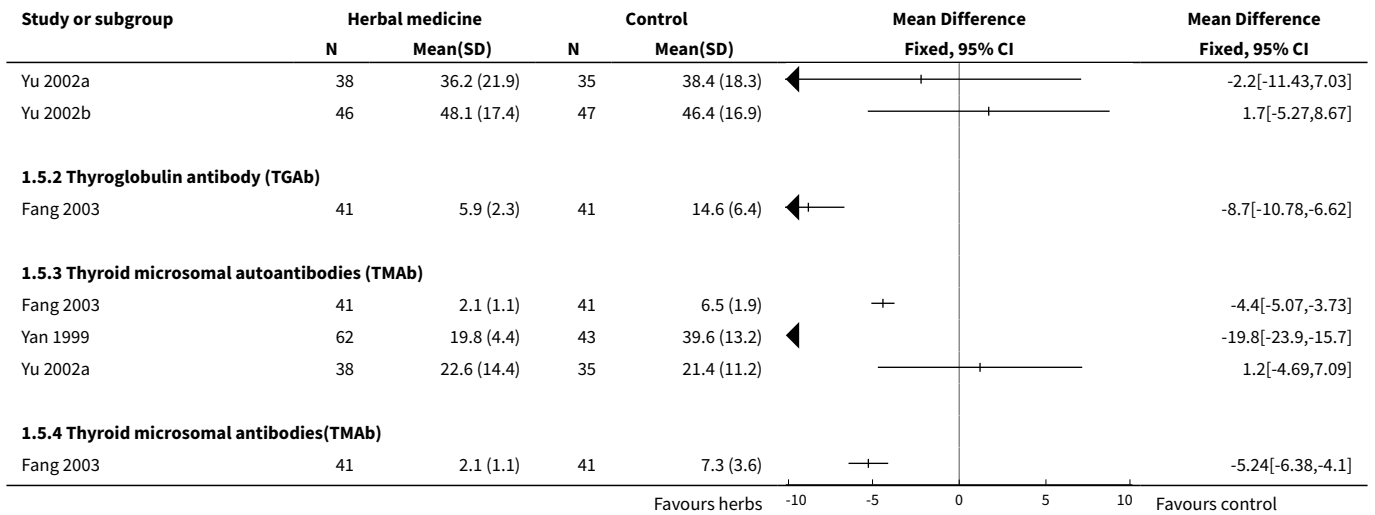
**Analysis 1.4. Comparison 1 Chinese herbs versus control, Outcome 4 Thyroid function tests (continuous data).**



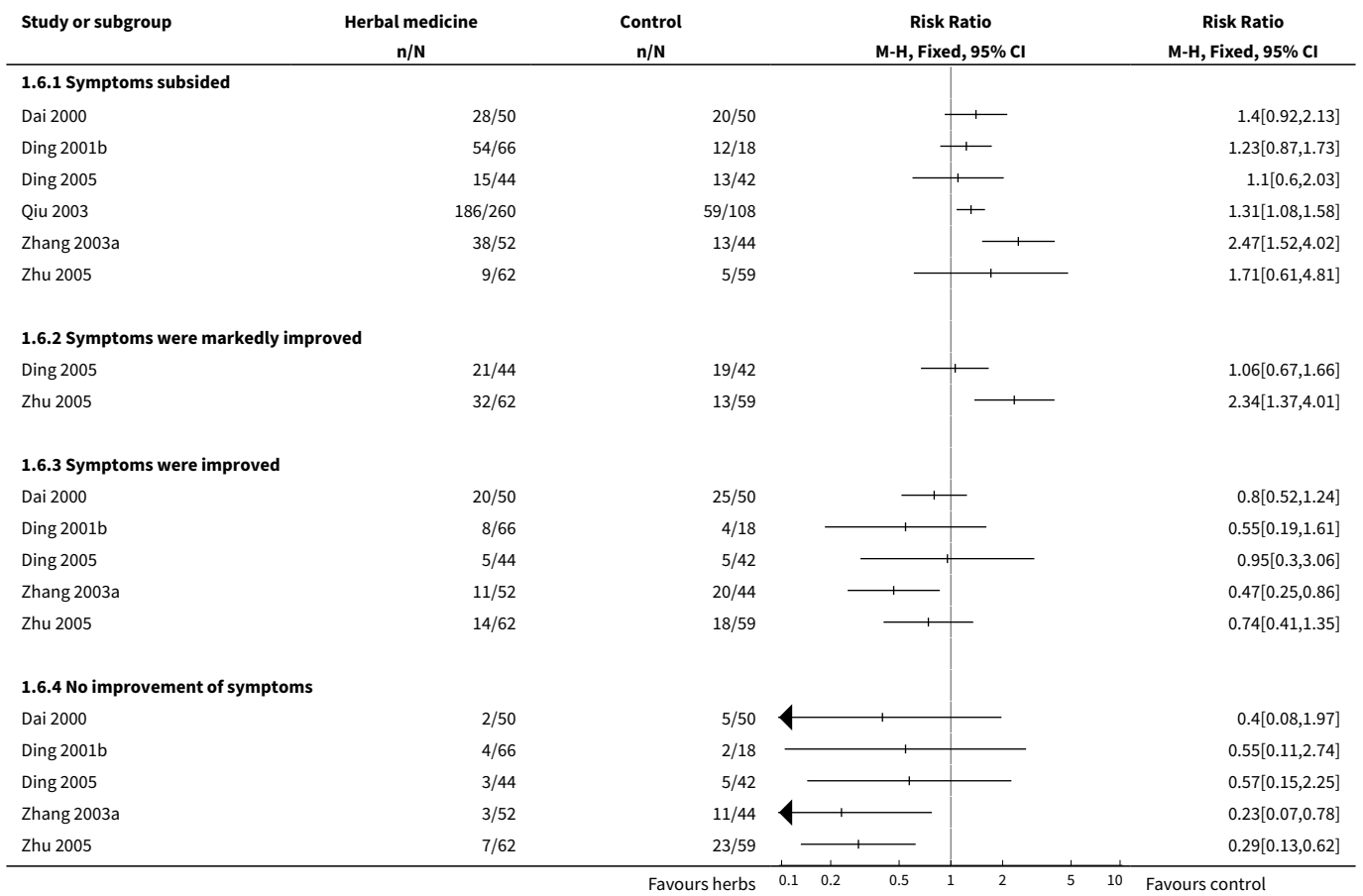


**Analysis 1.5. Comparison 1 Chinese herbs versus control, Outcome 5 Thyroid antibody status.**

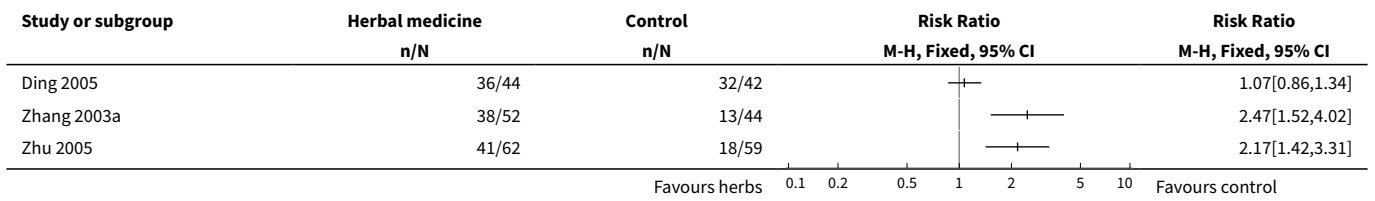




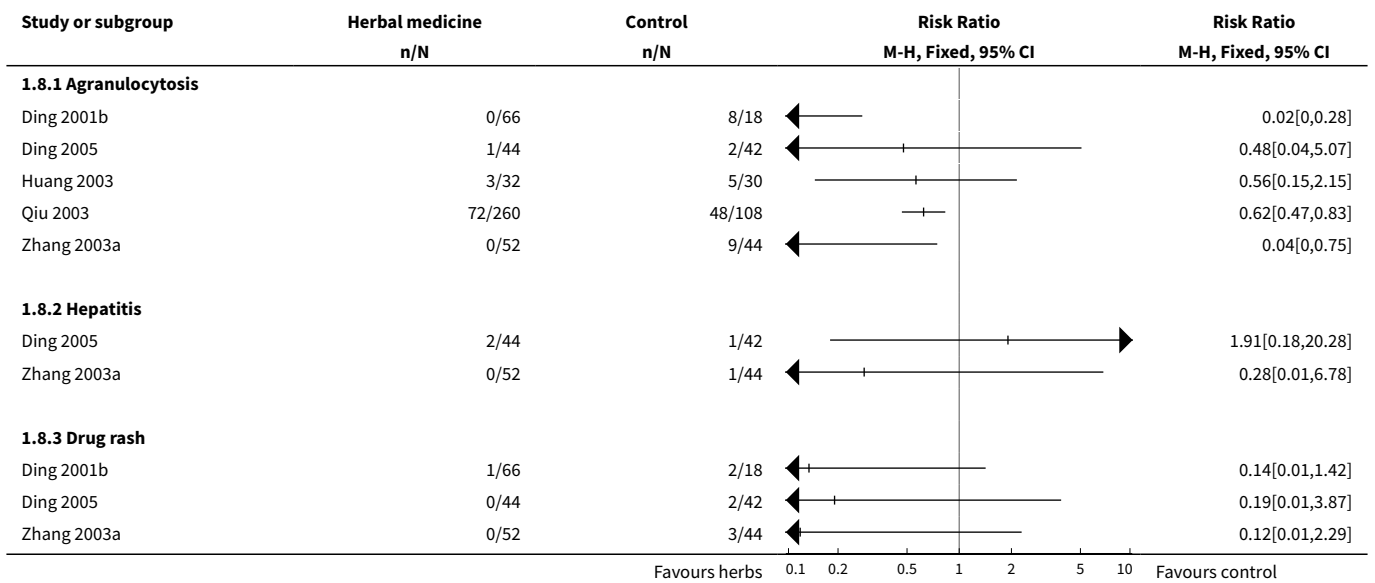
**Analysis 1.6. Comparison 1 Chinese herbs versus control, Outcome 6 Symptoms of hyperthyroidism.**



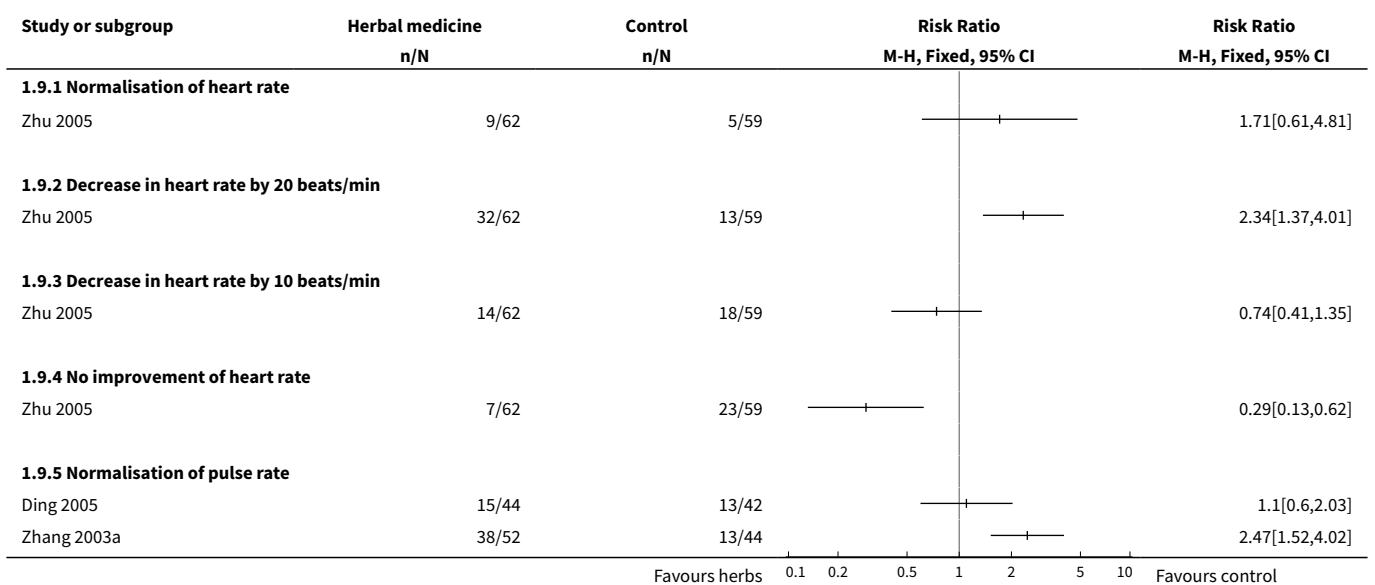
**Analysis 1.7. Comparison 1 Chinese herbs versus control, Outcome 7 Weight change (improvement).**

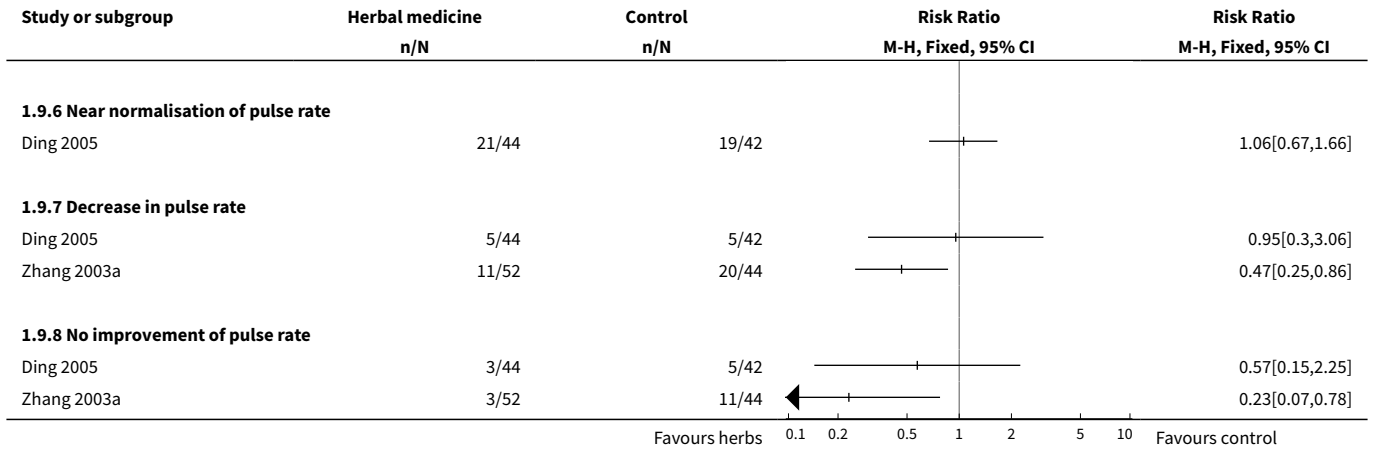


**Analysis 1.8. Comparison 1 Chinese herbs versus control, Outcome 8 Adverse effects.**

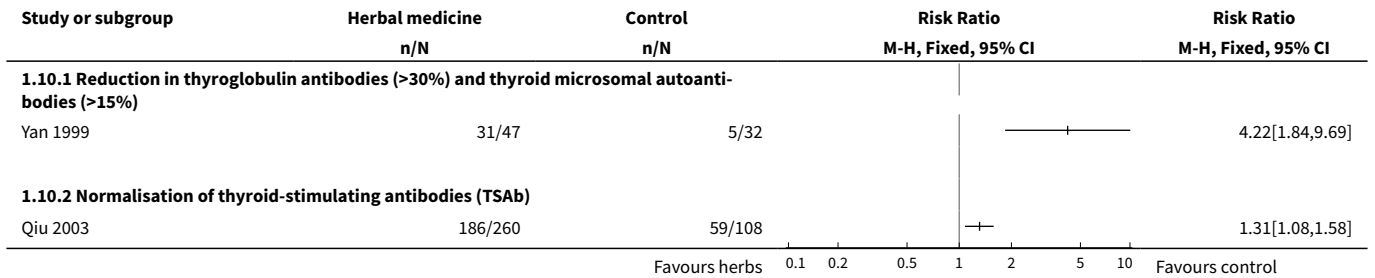


**Analysis 1.9. Comparison 1 Chinese herbs versus control, Outcome 9 Tachycardia.**

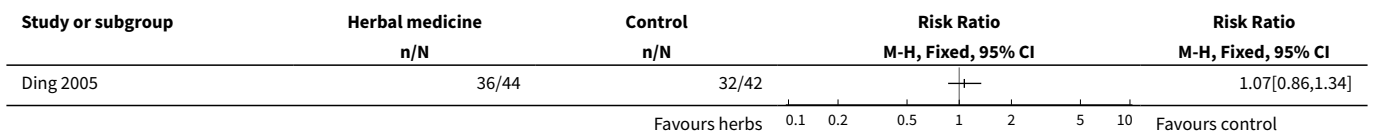




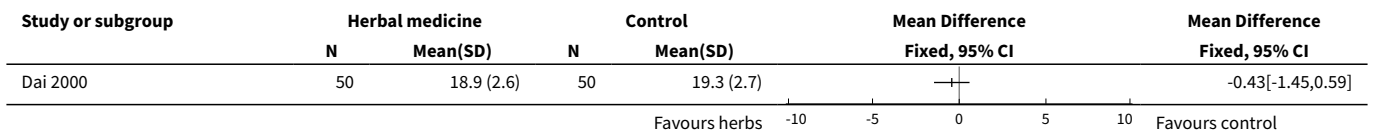
**Analysis 1.10. Comparison 1 Chinese herbs versus control, Outcome 10 Thyroid antibody status.**



**Analysis 1.11. Comparison 1 Chinese herbs versus control, Outcome 11 Improvement of ophthalmopathy.**



**Analysis 1.12. Comparison 1 Chinese herbs versus control, Outcome 12 Weight change ( weight index ).**





**Analysis 1.13. Comparison 1 Chinese herbs versus control, Outcome 13 Symptoms of hyperthyroidism.**

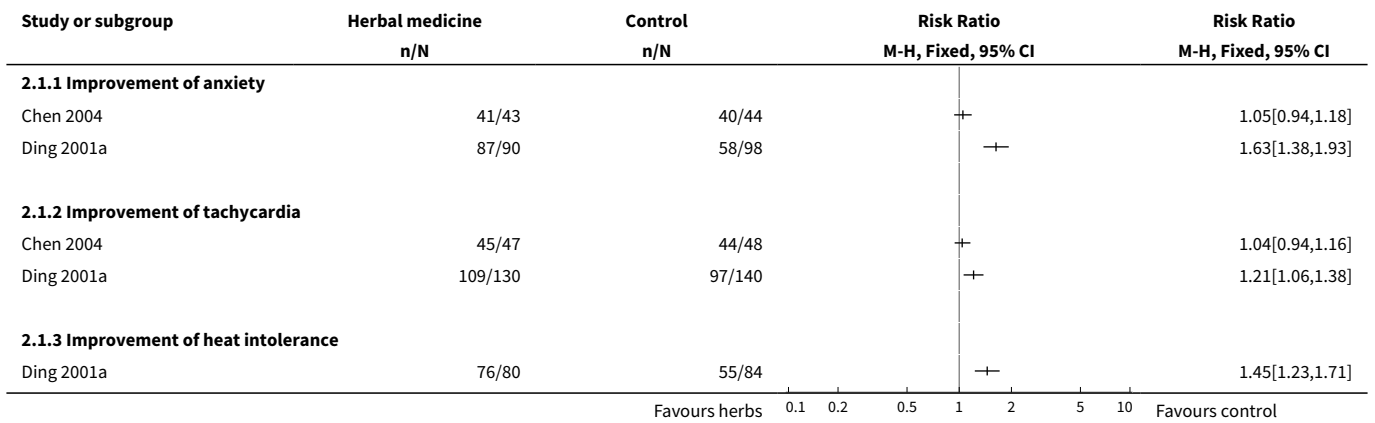
Study or subgroup	Herbal medicine		Control		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
<b>1.13.1 Tachycardia (heart rate)</b>						
Dai 2000	50	80.6 (0.2)	50	82.8 (2.7)	+-	-2.2[-2.95,-1.45]
<b>1.13.2 Diarrhoea ( frequency of stools)</b>						
Dai 2000	50	1.1 (0.2)	50	1 (0.6)		0.03[-0.15,0.21]

Favours herbs    -10    -5    0    5    10    Favours control

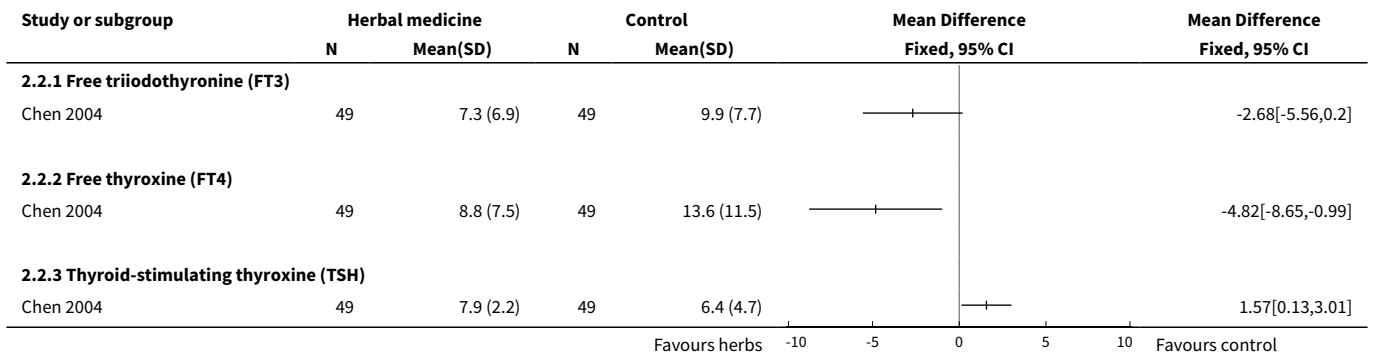
**Comparison 2. Chinese herbs versus radioiodine**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Symptoms of hyperthyroidism</b>	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Improvement of anxiety	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Improvement of tachycardia	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Improvement of heat intolerance	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>2 Thyroid function tests</b>	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Free triiodothyronine (FT3)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Free thyroxine (FT4)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Thyroid-stimulating thyroxine (TSH)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>3 Thyroid function tests</b>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Normalisation of thyroid hormones	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>4 Hypothyroidism</b>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Early onset	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Late onset	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

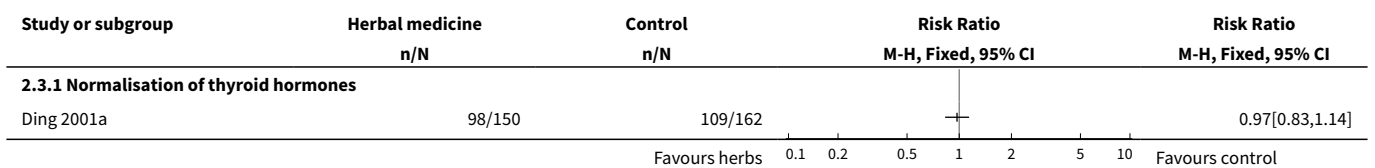
**Analysis 2.1. Comparison 2 Chinese herbs versus radioiodine, Outcome 1 Symptoms of hyperthyroidism.**



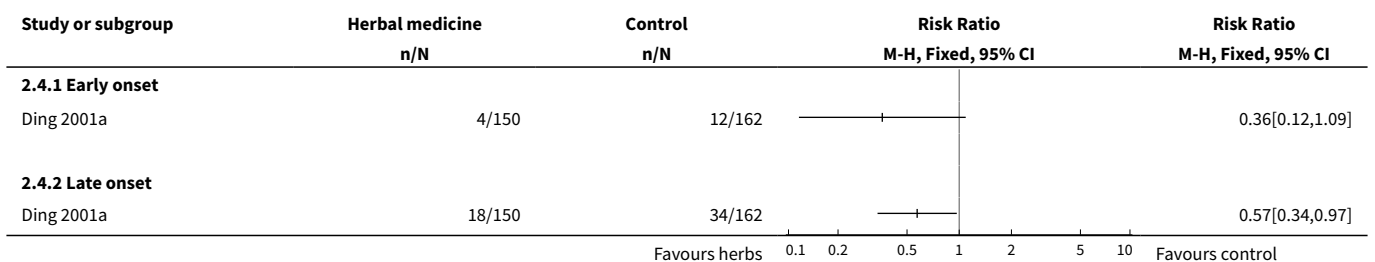
**Analysis 2.2. Comparison 2 Chinese herbs versus radioiodine, Outcome 2 Thyroid function tests.**



**Analysis 2.3. Comparison 2 Chinese herbs versus radioiodine, Outcome 3 Thyroid function tests.**



**Analysis 2.4. Comparison 2 Chinese herbs versus radioiodine, Outcome 4 Hypothyroidism.**



## APPENDICES

### Appendix 1. Search strategy

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#### Search terms

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Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign (\$) stands for any character(s); the question mark (?) = to substitute for one or no characters; ti = title; ab = abstract; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

- #1 Complementary Therapies
  - #2 alternative medicine\$.ti,ab.
  - #3 Plant Extracts
  - #4 plant extract\$.ti,ab.
  - #5 botanical extract\$.ti,ab.
  - #6 Plants, Medicinal
  - #7 medicinal plant\$.ti,ab.
  - #8 Medicine, Kampo/ or Phytotherapy/ or Drugs, Chinese Herbal
  - #9 Medicine, Chinese Traditional/ or Medicine, Oriental Traditional
  - #10 (Chinese adj3 medicin\$).ti,ab.
  - #11 phytodrug\$.mp.
  - #12 phytomedicine\$.ti,ab.
  - #13 phytopharmaceutical\$.ti,ab.
  - #14 herbal medicine\$.ti,ab.
  - #15 (complementary adj3 medicine\$).ti,ab.
  - #16 non-prescription drug\$.mp. or Drugs, Non-Prescription
  - #17 (Chinese adj3 herb\$).mp.
  - #18 herbal remed\$.mp.
  - #19 herbal extract\$.mp.
  - #20 herbal preparation\$.mp.
  - #21 botanical preparation\$.mp.
  - #22 (herb\$ adj3 mixture\$).mp.
  - #23 exp medicine, traditional/ or exp medicine, african traditional/ or exp medicine, arabic/ or exp medicine, unani/ or exp medicine, ayurvedic/ or exp medicine, kampo/ or exp medicine, oriental traditional/ or exp medicine, chinese traditional/ or exp medicine, tibetan traditional/ or exp shamanism
  - #24 #1- #23/or
  - #25 exp hyperthyroidism
  - #26 exp thyrotoxicosis
  - #27 exp Graves' disease
  - #28 #25 - #27/or
  - #29 #24 and #28
- 

### Appendix 2. Contents of the formulations used in the included studies

Study ID	Contents	Treatment
Ding 2005	Jiakangmianyi Jiaonang: Chuanshanlong, Huangqi, Huangjing, Xiakucao, Cebaiye	p.o.,t.i.d.,4 capsules each time,for 90 days
Zhu 2005	Chaihu 10 g, Zhishi 10 g, Baishao 12 g, Shengmuli (fried) 20 g, Baitouweng 20 g, Zhebeimu 20 g, Zidan-shen 20 g, Zhimu 15 g, Huangbai 15 g	1 ampoule/d, decocted with water and getting 400mL liquid from each ampoule, orally drank 200ml in the morning and evening respectively.

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(Continued)

Chen 2004	Jiakangxin Koufuye: Taizishen 6 g, Shengshigao 10 g, Zhimu 6 g, Maidong 6 g, Shanyao 7 g, Huangqi 8 g, Wuweizi 5 g, Gegen 8 g, Cishi 7 g	P.o.,t.i.d.,20 ml each time,for 2 weeks
Zhang 2003a	The author didn't mention contents of Huangqi Injection and Shengmai Injection.	1.Huangqi injection:20mL huangqi injection was diluted with 250mL 5% GNS and transfused intravenously once a day;2.Shengmai injection:30mL shengmai injection was diluted with 250 5% GNS and transfused intravenously once a day.
Fang 2003	Jiakangning pian: Mohanlian, Danshen, Shaoyao, Longgu, Muli. The author didn't mention contents of shengmai injection.	1.Jiakangling pian:p.o.,t.i.d.,2 tablets each time;2.Shengmai injection:60mL shengmai injection was diluted with 500mL 5% GNS and transfused intravenously for 15 days.
Qiu 2003	Erdong Tang with Xiaoluowan Jiawei: Tiandong 15 g, Maidong 15 g, Shashen 15 g, Tianhuafen 15 g, Zhimu 15 g, Shengdihuang 15 g, Xuanshen 15 g, Gancao 6 g, Longdancao 10 g, Xiakucao 10 g, Wuweizi 10 g, Xiyangshen 10 g, Zhebeimu 5 g	1 ampoule/day was decocted with water and orally taken in the morning and evening.When the symptoms were modified,decrease the dosage to 1 ampoule/3 days and kept the minimum dosage of 1 ampoule/15 days for 1.5~2 years.
Huang 2003	Yikang wan: Lingyangjiao, Shengbaoshao, Shengdi, Xiangfu, Tiandong, Huangjing, Shijueming, Xuanshen, Chaihu, Nvzhenzi	The materials were made into pills.1 pill contained 9g raw material.p.o.,t.i.d.,1 pill for each time.
Dai2000	Fabanzia 15 g, Fuling 15 g, Zhebei 12 g, Gualoupi 15 g, Hanliancao 15 g, Danshen 30 g, Tianqipian 5 g, Maozhuacao 15 g, Yujin 12 g	1 ampoule/day,decocted with water.
Yan 1999	Xuanshen 15 g, Huangqi 15 g, Xiakucao 15 g, Chuan-shanjia 15 g, Taizishen 15 g, Sanleng 12 g, Eshu 12 g, Maidong 15 g, Huhuanglian 12 g, Wuweizi 10 g	1 ampoule/day,decocted with water,one course of treatment was 28 days.
Yu 2002a	Zhizi 10 g, Pugongying 30 g, Banzhilian 30 g, Lianqiao 9 g, Yujin 10 g, Wuweizi 15 g, Chuanlianzi 10 g, Zhike 5 g, Juhua 10 g, Gouqizi 12 g, Baihuashehecao 30 g	1 ampoule of raw material was needed for a day ,decocted with water,for 4 weeks.Then orally took pills made by the raw materials,1 amoule/day,for 4~8 weeks.
Ding 2001a	chaihu 12 g, baishao 12 g, zhizi 10 g, shandougen 10 g, Shashen 15 g, Maidong 15 g, Gouqizi 15 g, Wuweizi 10 g, Baijili 10 g, Juemingzi 10 g, Chaozaoren 30 g, Gancao 6 g	1 ampoule/day decocted with water,p.o.,b.i.d.
Yu 2002b	Liuyuexue 30 g, Fuling 10 g, Banzhilian 30 g, Shengdi 10 g, Yimucao 20 g, Baihuashehecao 30 g, Danshen 12 g, Danggui 15 g	Raw material was made into granules,1 ampoule/day,for 8 weeks.
Ding 2001b	Shenghuangqi 15~30 g, Taizishen 10 g, Shengdi 10 g, Shengbaishao 10 g, Xiakucao 10 g, Maidong 10 g, Wuweizi 10 g, Chaozaoren 10 g, Jiugancao 10 g, Shenglonggu 25 g, Shengmuli 25 g, Caojueming 25 g	The authors didn't give details on the usage of the Chinese medicine used in the intervention group.

### Appendix 3. Chinese herbs terminology in three languages

<b>Pinyin name</b>	<b>Latin name</b>	<b>English name</b>
Chaihu	Radix Bupleuri	Chinese Thorowax Root
Baishao	Radix Paeoniae Alba	White Paeony Root
Zhizi	Fructus gardeniae	Cape Jasmine Fruit
Shandougen	Radix Sophorae Tonkinensis	Vietnamese Sophora Root
Shashen	Radix Adenophorae	Ladybell Root
Maidong	Radix Ophiopogonis	Dwarf Lilyturf Tuber
Gouqizi	Fructus Lycil	Barbary Wolfberry Fruit
Wuweizi	Fructus Schisandrae	Chinese Magnoliavine Fruit
Baijili	Fructus Tribuli	Puncturevine Caltrop Fruit
Juemingzi	Semen Cassiae	Cassia Seed
Chaozaoren		Stir-baked Semen Ziziphi Spinosa
Gancao	Radix Glycyrrhizae	Liquoric Root
Taizishen	Radix Pseudostellariae	Heterophylly Falsestarwort Root
Zhimu	Rhizoma Anemarrhenae	Common Anemarrhena Rhizome
Shengshigao	Gypsum Fibrosum	Gypsum
Shanyao	Rhizoma Dioscoreae	Common Yam Rhizome
Huangqi	Radix Astragali	Membranous Milkvetch Root
Gegen	Radix Puerariae	Kudzuvine Root
Lingyangjiao	Cornu Saigae Tataricae	Antelope Horn
Cishi	Magnetitum	Magnetite
Shengbaishao		
Shengdi		Rehmannia Dried Rhizome
Xiangfu	Rhizoma Cyperi	Nutgrass Galingale Rhizoma
Tiandong	Radix Asparagi	Cochinchinese Asparagus Root
Huangjing	Rhizoma Polygonati	Manyflower Solomonseal Rhizome
Shijueming	Concha Haliotidis	Sea-ear Shell
Xuanshen	Radix Scrophulariae	Figwort Root

(Continued)

Nvzhenzi	Fructus Liguistri Lucidi	Glossy Privet Fruit
Mohanlian	Herba Ecliptae	Yerbadetajo Herb
Danshen	Radix Salviae Miltiorrhizae	Danshen Root
Xiakucao	Spica Prunellae	Common Selfheal Fruit-spike
Longgu	Os Draconis	Drgon's Bones
Muli	Concha Ostreae	Oyster Shell
Chuanshanjia	Squama Manitis	Pangolin Scales
Sanling	Rhizoma Sparganii	Common Burreed Rhizome
Huhuaglian	Rhizoma Picrorhizae	FigwortflowerPicrorhizaRhizome
Eshu	Rhizoma Curcumae	Zedoary
Pugongying	Herba Taraxaci	Mongolian Dandelion Herb
Banzhilian	Herba Scutellariae Barbatae	Barbed Skullcap Herb
Lianqiao	Fructus Forsythiae	Forsythia Suspensa
Yujin	Radix Curcumae	Turmeric Root-tuber
Zhike	Fructus Aurantii	Bitter Orange
Chuanlianzi	Fructus Toosendan	Szechwan Chinaberry Fruit
Juhua	Flos Chrysanthemi	Chrysanthemum
Baihuasheshecao	Herba Hedyotidis Diffusae	Spreading Hedyotis Herb
Liuyuexue	Herba Serissae	Snow of June Herb
Fuling	Poria	Indian Buead
Yimucao	Herba Leonuri	Motherwort Herb
Danggui	Radix Angelicae Sinensis	Chinese Angelica
Tianhuafen	Radix Trichosanthis	Mongolian Snakegourd Root
Shengdihuang	Radix Rehmanniae	Rehmannia Root
Longdancao	Radix Gentianae	Chinese Gentian
Xiyangshen	Radix Panacis Quinquefolii	American ginseng
Zhebeimu	Bulbus Fritillariae Thunbergii	Thunberg Fritillary Bulb
Zhishi	Fructus Aurantii Immaturus	Immature Bitter Orange

(Continued)

Baitouweng	Radix Pulsatillae	Chinese Pulsatilla Root
Zidanshen		
Huangbai	Cortex Phellodendri	Amur Corktree Bark
Chuanshanlong	Rhizoma Dioscoreae Nipponicae	Dioscorea Nipponica Dioscorea nipponica
Cebaiye	Cacumen Platycladi	Chinese Arborvitae Tops
Fabanxia	Rhizoma Pinelliae	Pinellia Tuber
Gualoupi	Pericarpium Trichosanthis	
Hanliancao	Herba Ecliptae	Yerbadetajo Herb
Maozhuacao	Radix Ranunculus Ternati	
Tianqi	Radix Notoginseng	Panax Pseudo-ginseng

## WHAT'S NEW

Date	Event	Description
7 July 2008	Amended	Converted to new review format.

## CONTRIBUTIONS OF AUTHORS

Han S and Wu TX contributed to develop the protocol  
 Zen XX, Yuan Y and Liu Y interviewed the original authors of claimed randomised controlled trials and contributed to data extraction, quality assessment, data input and analysis  
 Zen XX and Wu TX were responsible for developing the review

## DECLARATIONS OF INTEREST

None known.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Phytotherapy [adverse effects]; Drugs, Chinese Herbal [adverse effects] [\*therapeutic use]; Hyperthyroidism [complications] [\*drug therapy]; Randomized Controlled Trials as Topic; Thyroid Hormones [blood]

### MeSH check words

Humans