Heliyon 10 (2024) e35114

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Clinical comparative efficacy and therapeutic strategies for the Hashimoto's thyroiditis: A systematic review and network meta-analysis

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ARTICLE INFO

Keywords:
Hashimoto's thyroiditis
Oral medications
TPOAb
TgAb
Network meta-analysis

ABSTRACT

Ethnopharmacological relevance: Vitamin D (VD), selenium preparations (Se), and thyroid hormone replacement therapy are commonly used to treat Hashimoto thyroiditis (HT). Increasing evidence suggests that traditional Chinese medicine (TCM) is an effective therapeutic strategy in the treatment of HT.

Aim of the study: This study aimed to investigate the efficacy and safety of commonly-used drugs for HT.

Materials and methods: A literature search was performed using PubMed, Web of Science, Cochrane Library, EMBASE, Chinese China National Knowledge Infrastructure (CNKI), Clinical Trial Registry (Chi CTR), China Science and Technology Journal Database (the VIP), Wanfang Database, and China Chinese Biomedical Database (CBM) from January 1, 2003, to December 31, 2022. The outcomes included TPOAb, TgAb, TSH, FT3, FT4, and adverse events. Our study was registered in PROSPERO (CRD42023449705).

Results: Sixty trials and 4719 participants were included, comparing 16 treatments: VD, Se, LT-4, Se + LT-4, HM, placebo + LT-4, HM + LT-4, Se + myolnositol, Se + VD, HM + Se, mannan peptide, LT-4+prednisone, Methimazole, Methimazole + HM, Tapazole + Propranolol, and placebo. We found that Chinese herbal medicine has significant effect *vs*. LT-4 [MD 0.10, 95 % confidence interval 0.02 to 0.50]) and LT-4+placebo [MD 0.10, 95 % confidence interval 0.01 to 0.77]) in reducing TPOAb. Although receiving LT-4+prednisone was not statistically significant, the treatment ranking showed that this combination therapy had the highest probability of reducing TPOAb levels (72.8 %). In addition, the effect of Se plus LT-4 was not statistically significant; however, the treatment ranking showed that this combination therapy had the highest

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https://doi.org/10.1016/j.heliyon.2024.e35114
Received 5 May 2024; Received in revised form 17 July 2024; Accepted 23 July 2024
Available online 31 July 2024

probability (78.6 %) of reducing TgAb levels, followed by HM (64.0 %). Reports on side effects have mainly focused on the digestive and cardiovascular systems.
Conclusion: Our analyses showed that HM alone or in combination with other treatments for patients with HT can improve the side effects of other drugs, enhance efficacy, and maybe the most effective option for treating HT. However, there still need further verified using high-quality evidence.

1. Introduction

Hashimoto's thyroiditis (HT) is an autoimmune disorder that attacks and destroys the thyroid gland, leading to elevated levels of thyroid autoantibodies. It is the primary cause of hypothyroidism [1]. HT is characterized by an enlarged thyroid gland, lymphocytic infiltration. HT is a common cause of hypothyroidism in iodine-replete settings, and the first-line treatment for HT patients is thyroid hormone replacement [2] About 0.3–1.5 cases per 1000 people suffer HT, which is one of the most common forms of chronic autoimmune thyroiditis [3]. This disease is more likely to affect women than men, and most often middle-aged women. The risk of its development increases with age [4]. Moreover, patients with HT are more likely to have cardiovascular diseases and malignant neoplasms [5,6]. In addition, hypothyroidism affects all organ systems. Moreover, the most common symptoms that burden patients with HT are weight gain, constipation, lethargy, fatigue etc. [7].

Numerous studies have shown that there were lower life quality scores in euthyroid HT patients with high thyroid antibody levels [8,9]. A population-based cohort study of 22 million individuals in the UK showed that autoimmune diseases affect approximately one in ten individuals, and their burden continues to increase over time at varying rates across individual diseases [10]. Furthermore, low-to-middle-income areas have a higher prevalence of HT, especially in Africa [11]. Therefore, HT not only harms health but also imposes a serious medical burden.

Hormone replacement therapy is a common treatment for hypothyroidism caused by HT. The synthetic hormone LT-4 is recommended as a therapy for hypothyroidism-related conditions [12]. Moreover, research has found that patients with HT may have a two-fold lower level of vitamin D in the blood than healthy individuals [13,14]. Supplementation of blood with vitamin D can reduce the risk of developing hypothyroidism in patients with HT [15]. In addition, the thyroid gland is characterized by a high concentration of selenium, which is incorporated into several selenoproteins with key functions in the gland [16]. Se deficiency may impair thyroid function [17]. Many studies have shown that selenium supplementation may restore euthyroidism in patients with SCH and HT [18,19]. However, the above therapies still have limitations.

Thyroid disease, known as yingbing in ancient China, has a long history of treatment with Chinese herbal medicines. Oral traditional Chinese medicine (TCM) decoctions such as Chaihu Shugan powder, Xiaoyao powder, and Longdan Xiegan decoction are the most commonly used. In addition to the traditional internal treatment of TCM, there are special external treatments that can effectively improve the clinical symptoms caused by HT, such as acupoint catgut embedding, acupuncture and moxibustion, auricular point plaster therapy, and treatment of the thyroid projection area in front of the neck with the external application of a Chinese herbal paste [20]. Modern pharmacological experiments and clinical trials have shown that herbs have unique advantages and curative effects for the treatment of thyroid diseases [21–23]. However, the effect of combining Chinese herbal medicine with vitamin D, levothyroxine, or selenium preparation have not been confirmed. Therefore, we conducted a network meta-analysis of RCTs.

2. Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for Network Meta-Analyses (PRISMA-NMA) guidelines [24]. The PROSPERO number is CRD42023449705. The plant name has been checked with MPNS (http://mpns.kew.org) in December 21, 2023.

2.1. Search strategy and selection criteria

A literature search was performed according to the search strategy for randomized controlled trials published by the Cochrane Collaboration [25]. We searched PubMed, Web of Science, Cochrane Library, EMBASE, CNKI, Chi CTR, VIP, CBM, and Wanfang Database. To avoid bias, we did not limit the date of publication in our search. We used the search terms "Hashimoto thyroiditis" OR "chronic lymphadenoid thyroiditis" OR "chronic lymphocyte thyroiditis" OR "chronic lymphocytic thyroiditis" OR "Hashimoto's Thyroiditis" OR "Autoimmune thyroiditis" combined with a list of all included drugs for HT. The search strategy was shown in Appendix 1.

2.2. Inclusion criteria

(1) study type: randomized controlled trial. (2) Study subjects: Patients with HT. (3) Intervention: The treatment group included herbal medicine, vitamin D, levothyroxine, LT4, selenium preparation, myoinositol, and prednisone, which could also be combined on these bases. The control group was either a placebo or conventional treatment (Thyropathy Committee of Beijing Association of the Integrating of Traditional and Western Medicine, 2022). The treatment dose and course were not restricted. (4) Outcome indicators:

primary outcomes, TPOAb, and TgAb; secondary outcomes, TSH, FT3, and FT4 levels.

2.3. Exclusion criteria

We excluded duplicate publications, articles with insufficient data, studies in which the full text was not available, interventions with non-drug therapies, studies in which the baseline characteristics between the experimental and control groups were inconsistent, comparative studies of different doses of the same drug, studies published in non English or Chinese, and studies in which the control groups were followed up.

2.4. Bias risk assessment

Risk of bias assessment was performed using the Cochrane Handbook 6.0 [26], which was classified into "low risk," "high risk," and "some concerns." ROB 2 was used to summarize and map biased risk assessment results. The quality of evidence was assessed for pairwise meta-analyses and NMAs using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach [27,28].

2.5. Data extraction and quality assessment

Luo and Zhou performed literature screening based on inclusion and exclusion criteria. Discrepancies were resolved by Han. The risk of bias in the included RCTs was assessed using the ROB 2.

2.6. Statistical analyses

Data from each eligible study were extracted and entered into a standardized spreadsheet. We analyzed the results for all outcome indicators. Random-effects Bayesian NMAs were performed using Stata 15.1 (StataCorp, TX, USA) and OpenBUGS version 3.2.3 [29] to

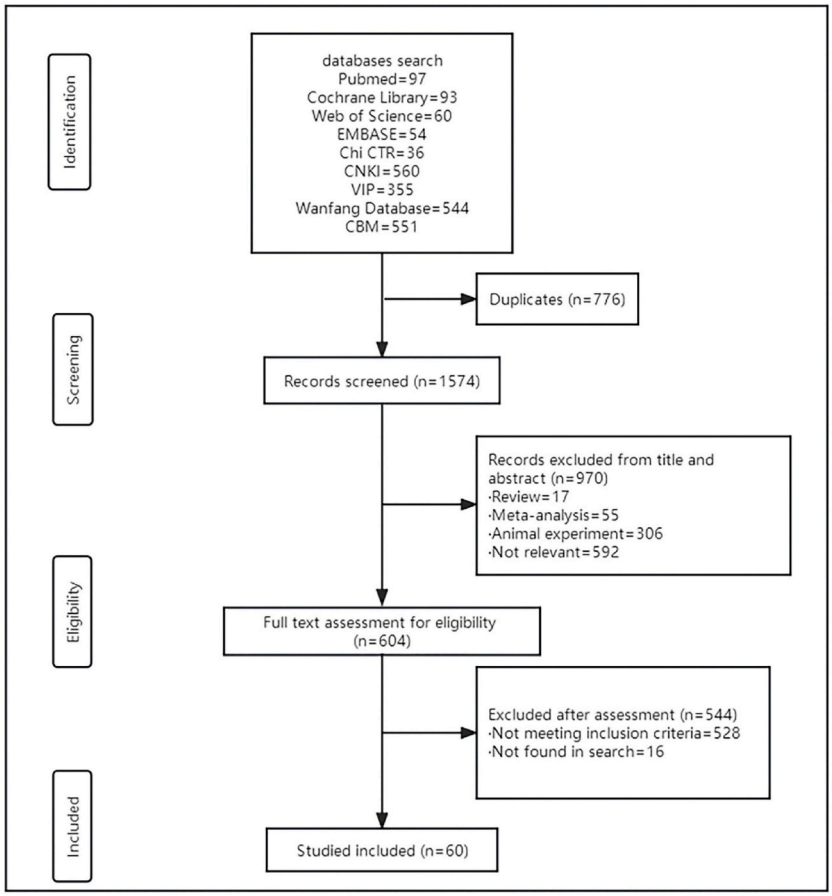

Fig. 1. Summary of trial identification and selection.

Table 1
General information of included studies.

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
R Chahardoli 2019 [33]	Vitamin D (50 000 IU cholecalciferol [1,25(OH) 2D3])	placebo	/	treatment group:21/19 Control group:21/21	Treatment group:0/21 Control group:0/21	Hypothyroidism	3 months (3 months)	Not reported(N/R)	Reduction of TPOAb、TGAb improvement of Calcium、25(OH)D
P.V Anaraki 2017 [34]	Vitamin D (50 000 IU cholecalciferol [1,25(OH) 2D3])	placebo	/	treatment group:33/30 Control group:32/26	Treatment group:9/21 Control group:11/15	Hypothyroidism or euthyroidism	12 weeks (12 weeks)	N/R	improvement of 25(OH) D Reduction of PTH
L.H Duntas 2003 [35]	Seme (200 μg, Lamberts, Athens, Greece) with LT-4	Placebo with LT-4	/	treatment group:34/34 Control group:31/31	All patients: 9/56	Subclinical hypothyroidism	6 months (6 months)	N/R	Reduction of TPOAb
Robert Krysiak 2012 [36]	treatment group 1: LT-4 (0.5–1 μg/kg per day) treatment group 2: Selenomethionine (200 μg daily) treatment group 3: LT-4 (0.5–1 μg/kg) with Selenomethionine (200 μg daily)	placebo	/	treatment group 1: 39/38 treatment group 2: 39/37 treatment group 3: 40/38 Control group: 37/36	treatment group 1: 0/38 treatment group 2: 0/37 treatment group 3: 0/38 Control group: 0/36	Subclinical hypothyroidism or euthyroidism	6 months (6 months)	treatment group 1: 1 patient reported hyperthyroidism; treatment group 2: 1 patient reported nausea and vomiting; 1 patient reported headaches; treatment group 3: 1 patient reported rash; 1 patient reported abdominal pain and diarrhea;	treatment group 1–3: Reduction of TPOAb、TGAb、hsCRP treatment group 1/3: Reduction of TSH improvement of FT4、FT3
L. Yu 2017 [37]	selenium yeast capsule (200 μg daily) with L-T4 (25–150 μg)	LT-4	/	All patients: 61/60 treatment group: 34 Control group: 26	All patients: 4/56	Subclinical hypothyroidism or euthyroidism	3 months (3 months)	N/R	improvement of Se Reduction of TPOAb、TGAb、IL-2
M. NORDIO 2017 [38]	L-selenomethionine (16.6 μg) with myoinositol (600 mg)	L-selenomethionine	/	treatment group: 84/84 Control group: 84/84	Treatment group:9/75 Control group:10/74	Subclinical Hypothyroidism	6 months (6 months)	N/R	Reduction of TPOAb、TGAb、TSH improvement of FT4
W. Bonfig 2010 [39]	treatment group 1: LT-4 with 100 μg sodium-selenite treatment group 2: LT-4 with 200 μg sodium-selenite	LT-4	/	treatment group 1: 13/13 treatment group 2: 18/18 Control group: 18/18	treatment group 1: 4/9 treatment group 2: 8/18 Control group: 4/14	Hypothyroidism	12 months (12 months)	N/R	Control group: Reduction of TGAb
Robert Krysiak 2019 [40]	Selenomethionine with Vitamin D (4000 IU once-daily)	Selenomethionine	/	treatment group: 23/23 Control group: 24/24	treatment group: 0/23 Control group: 0/24	Euthyroidism	6 months (6 months)	N/R	Reduction of TPOAb、TGAb improvement of 25-hydroxyvitamin D

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Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
M.A. Farhangi 2016 [41]	Nigella sativa powder (2 g per day)	Placebo	/	treatment group: 23/20 Control group: 24/20	treatment group: 3/17 Control group: 3/17	N/R	8 weeks (8 weeks)	Treatment group: 3 patients reported itching and nausea	Reduction of TPOAb、TSH improvement of T4
X.F. Meng 2022 [42]	Bupleurum inula flower soup (decoction-free granulestwice a day) with LT-4	Placebo with LT-4	soothing the liver, regulating qi, resolving phlegm, and dispersing stasis	treatment group: 25/24 Control group: 25/24	treatment group: 4/20 Control group: 2/22	Hypothyroidism	8 weeks (8 weeks)	N/R	Symptom improvement Reduction of TPOAb、TGAb、TSH、Depression scores、anxiety scores
C.P. Sun 2021 [43]	selenium (50 μg, twice a day) with LT-4 (1–2 μg/(kg·d))	LT-4		treatment group: 69/65 Control group: 69/64	treatment group: 23/46 Control group: 21/48	Hypothyroidism	3 months (3 months)	treatment group: 1 patient reported nausea; 1 patient reported fever; 1 patient reported dizziness; 2 patient reported chest tightness; 2 patient reported bloating; Control group: 2 patient reported nausea; 3 patient reported fever; 2 patient reported dizziness; 1 patient reported chest tightness; 3 patient reported bloating;	Symptom improvement Reduction of TPOAb、TGAb、IL-2、TNF-α、SAS Scores、SDS Scores improvement of IL-10
T. He 2016 [44]	Corbrin Capsule, [*Cordyceps sinensis (ascomycetes)*, powder] (2.0 g tid) with LT-4	LT-4	Tonifying the kidneys and lungs, stopping bleeding and resolving phlegm	treatment group: 39/39 Control group: 17/17	N/R	Hypothyroidism	24 weeks (24 weeks)	N/R	Reduction of TSH、TPOAb、TGAb、$CD8^+$ improvement of FT4、CD4/CD8 ratio
M.A. Farhangi 2018 [45]	Nigella sativa powder (2 g per day)	Placebo		treatment group: 23/20 Control group: 24/20	treatment group: 3/17 Control group: 3/17	N/R	8 weeks (8 weeks)	Treatment group: 3 patients reported itching and nausea	Reduction of TSH、TPOAb、AIP improvement of T4、Insulin、HDL、HOMA-IR
B.J. Fang 2006 [46]	Ruanjian Xiaoying decoction, 10-fold volume of water, extracting twice with 1 h for each time., 250 ml twice a day) with LT-4	Prednisone with LT-4	Regulating Qi, resolving phlegm, and promoting blood circulation	treatment group: 40/40 Control group: 40/40	treatment group: 5/35 Control group: 6/34	N/R	16 weeks (16 weeks)	N/R	Symptom improvement improvement of FT3、FT4 Reduction of TGAb, TMAb titers
Y.H. Li 2015 [47]	treatment group 1: HM (produced by Guizhou Tongjitang Traditional Chinese Medicine Decoction Co., Ltd. (batch number: 140301, expiration date: 160311), with 9 g of traditional Chinese medicine granules per bag, twice a day)	placebo	NA	treatment group 1: 55/55 treatment group 2: 57/57 Control group: 54/54	treatment group 1: 1: 4.6 treatment group 2: 1: 10.4 Control group: 1: 6.7	Euthyroidism	90 days (90 days)	N/R	treatment group 1: Reduction of TPOAb titers

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Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
	treatment group 2: LT-4 (12.5 μg/d)								
L. Mahmoudi 2021 [48]	selenium capsule (200 μg/d)	placebo		treatment group: 25/21 Control group: 25/21	treatment group: 1/20 Control group: 4/17	Subclinical hypothyroidism	8 weeks (8 weeks)	N/R	selenium supplementation has no significant effect on serum anti-TPO Ab and TSH levels in the patients with subclinical hypothyroidism
R. L 2021 [49]	Xiaoyaosan Jiawei Granules (produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd, granules 3 times per day, 2 bags per time)	placebo	Soothing the liver and regulating qi, strengthening the spleen and tonifying the spleen	treatment group:40/40 Control group:40/40	Treatment group:18/22 Control group:13/27	Euthyroidism	30 days(30 days)	N/R	Symptom improvement Reduction of TGAb, TPOAb titers
WS. L 2019 [50]	Xiaoying forrmula, produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd, granules 2 times per day, 1 bag per time) with Selenium yeast flakes	Selenium yeast flakes	Soothing the liver and strengthening the spleen, regulating qi and resolving phlegm	treatment group:28/28 Control group:28/28	Treatment group:1/27 Control group:3/25	Euthyroidism	2 months(2 months)	N/R	Symptom improvement Reduction of TGAb、TPOAb、TSH improvement of FT4 Reduce the thickness of the thyroid gland
SR. Z 2020 [51]	Xiaoying Mixture (30 ml twice a day, produced by Shanghai University of Traditional Chinese Medicine Affiliated Shuguang Hospital Intrahospital Preparation [Hu Z04100928])	Selenium yeast flakes	Nourishing Qi and Yin, Soothing Qi and Resolving Phlegm	treatment group:50/44 Control group:50/45	Treatment group:7/37 Control group:9/36	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb, TPOAb、IFN-γ、IL-2、IL-4、IL-10
XM. C 2019 [52]	Modified Shenling Baizhu San (200 ml twice a day) with LT-4	LT-4	replenishing qi to invigorate the spleen, Clearing heat and dispersing nodules	treatment group:34/34 Control group:34/34	Treatment group:7/27 Control group:9/25	N/R	3 months(3 months)	Treatment group: 1 patients reported Tachycardia; Control group:3 patients reported Tachycardia; 2 patients reported Diarrhea	Symptom improvement Reduce the size of the thyroid gland Reduction of TGAb, TPOAb、TSH improvement of FT3、FT4
XY. W 2018 [53]	Qiaoben Fang, water extraction, 200 ml twice a day)	Selenium yeast capsules	Nourishing Qi and Yin, Resolving Phlegm and Stasis	treatment group:35/35 Control group:35/35	Treatment group:1/34 Control group:3/32	N/R	6 months(6 months)	N/R	Reduction of TPOAb、IL-6 improvement of TGF-β
QJ. X 2018 [54]	Shugan Sanjie decoction, (water extraction, 300 ml three times a day)	placebo	Soothing the liver and dispersing nodules	treatment group:60/60 Control group:60/60	Treatment group:12/48 Control group:11/49	Euthyroidism	N/R(treatment group and control group Intervention time and number were consistent)	N/R	Symptom improvement Reduction of TRAb、TGAb, TPOAb
YL. Z 2018 [55]	Jiuwei Sanjie capsules (produced by the Preparation Room of Shanxi Academy of Traditional Chinese Medicine,	Mannan peptide tablets	Regulating Qi and promoting blood circulation, resolving	treatment group:60/60 Control group:60/60	Treatment group:3/57 Control group:5/55	Hypothyroidism	8 weeks(8 weeks)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb improvement of TT3、

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Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
	with the Jin Yao Zhi Zi AZ20080291, 2.0g per dose, 3 times per day.)		phlegm and dispersing nodules						TT4、FT3、FT4、$CD4^+$、$CD4^+/CD8^+$
D. Z 2018 [56]	Qiaojiafang Granule (Produced by Guizhou Tongjitang Traditional Chinese Medicine Decoction Co., Ltd., batch number: 140301, twice a day)	Selenium yeast flakes	Tonifying Qi and Soothing Liver, Clearing heat and dispersing nodules	treatment group:35/35 Control group:35/35	Treatment group:5/30 Control group:4/31	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb
J. H 2017 [57]	Erxian decoction combined Qihai Xiaoying decoction, (250 ml twice a day) with LT-4	LT-4	Promoting Qi and Resolving Phlegm, disperse blood stasis and dredge collateral	treatment group:40/40 Control group:40/40	Treatment group: 7/33 Control group:5/35	Hypothyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb improvement of FT3、FT4 Reducing the size of the thyroid gland
ZY. F 2017 [58]	Xiakucao capsule (produced by Beijing Xiehe Kangyou Pharmaceutical Co., Ltd, 0.7g per time twice a day) with LT-4	LT-4	Clearing heat and purging fire, dispersing nodules and eliminating carbuncle	treatment group:36/36 Control group:36/36	Treatment group: 9/27 Control group:5/31	Hypothyroidism	8 weeks(8 weeks)	Treatment group:1 patients reported Insomnia; 1 patients reported Vomiting; Control group:1 patients reported Headaches; 1 patients reported Diarrhea; 1 patients reported Flushed face	Reduction of TSH、TGAb、TPOAb improvement of FT4 Reduce the thickness of the thyroid gland
YJ. C 2016a [59]	Rhizoma Dioscoreae Nipponicae granules (10g twice a day) with LT-4 (50–200 μg/d)	LT-4		treatment group:32/32 Control group:32/32	Treatment group:N/R Control group:N/R All patients: 16/48	Hypothyroidism or Subclinical hypothyroidism	6 months(6 months)	N/R	Reduction of TGAb、TPOAb、Th17、IL-6 improvement of Treg
Y. H 2016 [60]	Selenium Yeast (10 μg/d) with LT-4 (50–100 μg/d)	LT-4		treatment group:32/32 Control group:32/31	Treatment group: 9/23 Control group:6/25	Hypothyroidism	3 months(3 months)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb、$CD4^+$、$CD4^+/CD8^+$ improvement of FT3、$CD8^+$、NK Reducing the size of the thyroid gland
YJ. C 2016b [61]	Rhizoma Dioscoreae Nipponicae granules (10g twice a day) with LT-4 (50–200 μg/d)	LT-4		treatment group:24/24 Control group:24/24	Treatment group: N/R Control group:N/R	Hypothyroidism or Subclinical hypothyroidism	6 months(6 months)	N/R	Reduction of TGAb、TPOAb
XC. Z 2016 [62]	HM (TCM decoction, 250 ml twice a day)	LT-4	Soothing the liver and regulating qi, clearing heat and dispersing nodules	treatment group:40/40 Control group:40/40	Treatment group: 0/40 Control group:2/38	Subclinical hypothyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb

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Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
GQ. H 2015 [63]	Shugan Sanjie Prescription (water extraction 300 ml, three times a day)	placebo	Soothing the liver and dispersing nodules	treatment group:54/54 Control group:54/54	Treatment group:29/25 Control group:27/27	Euthyroidism	3 months(3 months)	N/R	Symptom improvement Reduction of TRAb、TGAb、TPOAb
YJ. C 2013 [64]	Rhizoma Dioscoreae Nipponicae granules (10g twice a day)	LT-4		treatment group:24/24 Control group:24/24	Treatment group:4/20 Control group:4/20	Hypothyroidism or Subclinical hypothyroidism	3 months(3 months)	N/R	Reduction of TSH、TGAb、TPOAb Reduce the dose of LT-4 required to maintain thyroid function
SL.C 2013 [65]	Reinforcing kidney and strengthening spleen and soothing liver prescription (extracts water solvent prepared into granules, twice a day) with LT-4 (25 μg/d)	LT-4	Tonifying the Kidney, Strengthening the Spleen, and Soothing the Liver	treatment group:27/25 Control group:27/25	Treatment group: 1/24 Control group:2/23	Subclinical hypothyroidism	3 months(3 months)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb
HK. X 2022 [66]	Yiqi Huatan decoction (water extraction,200 ml twice a day) with Selenium yeast flakes (100 μg twice day)	Selenium yeast flakes	Strengthening the spleen and soothing the liver, regulating qi, resolving phlegm, and dispersing nodules	treatment group:30/30 oup:30/30	Treatment group: 5/25 Control group:4/26	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb Reducing the size of the thyroid gland
YP. D 2021 [67]	Shugan Lipi decoction (granules produced by Tianjiang Pharmaceutical Co., Ltd, three times a day)	LT-4	Eliminating galls and dispersing nodules, harmonizing the liver and spleen	treatment group:36/35 Control group:36/34	Treatment group: 5/30 Control group:6/28	Subclinical hypothyroidism	8 weeks(8 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb
YX. S 2017 [68]	Xiaojin Pills, ((produced by Chengdu Yongkang Pharmaceutical Co., Ltd. with approval number: National Pharmaceutical Approval Z20013119, 1.2g per time, twice a day)	Selenium yeast flakes	Dispelling blood stasis and dispersing nodules	treatment group:60/58 Control group:60/57	Treatment group: 13/45 Control group:13/44	Euthyroidism	8 weeks(8 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb Decreased thyroid ultrasound score
ZY. Y 2020 [69]	Jiawei Xiaoying decoction (water extraction, 150 ml twice a day)	Selenium yeast flakes	Soothing the liver and regulating qi, resolving phlegm and nodules, promoting blood circulation and removing blood stasis	treatment group:30/30 Control group:30/30	Treatment group: 1/29 Control group:2/28	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reducing the size of the thyroid gland Reduces thyroid hardness Reduction of TGAb、TPOAb、IFN-γ
SY. W 2020 [70]	Shugan Jianpi Huatan decoction (water extraction, 250 ml twice a day) with Selenium yeast capsules (100 μg twice day)	Selenium yeast capsules	Soothing the liver and strengthening the spleen, resolving phlegm and dispersing nodules, promoting qi and blood circulation	treatment group:30/28 Control group:30/29	Treatment group:5/23 Control group:6/23	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TPOAb
K. X 2020 [71]	Chaigui decoction (water extraction, 150 ml twice a day)	Selenium yeast flakes	Soothing the liver and relieving	treatment group:36/31	Treatment group:3/28	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、

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Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
			depression, tonifying qi and strengthening the spleen, and unblocking collaterals and meridians	Control group:36/32	Control group:4/28				TPOAb Reducing the size of the thyroid gland
QH. X 2020 [72]	Xiaoying decoction (water extraction, 160 ml twice a day) with Selenium Yeast (100 μg twice day)	Selenium Yeast	Nourishing Qi and Yin, Resolving phlegm and eliminating galls	treatment group:44/41 Control group:44/41	Treatment group: 8/33 Control group:10/31	Euthyroidism	3 months(3 months)	N/R	Symptom improvement Reduction of TGAb、TPOAb Reduce the thickness of the thyroid gland
Y. C 2019 [73]	Qiaojiafang granules (produced by Guizhou Tongjitang Traditional Chinese Medicine Decoction Co., Ltd, twice a day)	placebo	Replenishing qi to invigorate the spleen, Soothing liver and clearing heat, reducing swelling and dispersing nodules	treatment group:30/30 Control group:30/30	Treatment group: 10/20 Control group:9/21	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb
JR. S 2019 [74]	Chaishao Xiaoying decoction (water extraction, 150 ml three times a day) with LT-4 (12.5 μg/d)	LT-4	Soothing the liver and regulating the spleen, resolving phlegm and removing blood stasis	treatment group:40/40 Control group:40/40	Treatment group: 3/27 Control group:2/38	Euthyroidism or Subclinical hypothyroidism	4 weeks(4 weeks)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb Reducing the size of the thyroid gland
YL. L 2019 [75]	Shugan Jianpi Xiaoying decoction, dose unknow, 250 ml twice a day) with LT-4 (25 μg/d)	LT-4	Soothing the liver and strengthening the spleen, resolving phlegm and dispersing nodules	treatment group:63/60 Control group:63/61	Treatment group: 11/49 Control group:13/48	Hypothyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb、IL-17 improvement of FT4 Reducing the size of the thyroid gland Reducing the thickness of the isthmus of the thyroid gland
HL. Z 2018 [76]	Shugan Jianpi decoction, (water extraction, 250 ml twice a day) with Selenium yeast flakes (150 μg twice day)	Selenium yeast flakes	Soothing the liver and relieving depression, strengthening the spleen and promoting qi circulation	treatment group:24/19 Control group:22/18	Treatment group: 4/15 Control group:0/18	Euthyroidism	8 weeks(8 weeks)	Treatment group:1 patients reported hypothyroidism Control group:3 patients reported hypothyroidism	Symptom improvement Reduction of neck enlargement
YM. S 2017 [77]	Haizao Yuhu decoction (water extraction, 250 ml twice a day) with Selenium yeast flakes (100 μg twice day)	Selenium yeast flakes	Soothing the liver and relieving depression, resolving phlegm and dispersing nodules	treatment group:25/25 Control group:25/25	Treatment group: 3/22 Control group:2/23	N/R	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb Reducing the thickness of the isthmus of the thyroid gland

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Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
XX. L 2013 [78]	Shugan Jianpi Xiaoying decoction (water extraction, 250 ml twice a day) with LT-4 (25 μg/d)	LT-4	Soothing the liver and strengthening the spleen, resolving phlegm and galls, clearing heat and detoxifying	treatment group:30/30 Control group:30/30	Treatment group: 5/25 Control group:7/23	Subclinical hypothyroidism	8 weeks(8 weeks)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb
Y. Z 2015 [79]	Compound Jiakang tablets (made by the Pharmacy Department of Hubei Provincial Hospital of Traditional Chinese Medicine, 5 tablets/time, 3 times a day) with Methimazole tablets (15–25 mg/d)	Methimazole tablets	Tonifying Qi and nourishing Yin, resolving phlegm and dispersing nodules	treatment group:30/30 Control group:30/30	Treatment group: 5/25 Control group:6/24	Hyperthyroidism	6 months(6 months)	Treatment group:1 patients reported hepatic disfunction Control group:1 patients reported skin itch; 1 patients reported hepatic disfunction; 1 patients reported Leukopenia	Reducing the size of the thyroid gland
YL. T 2005 [80]	Danzhi Xiaoyao powder, (water extraction, 250 ml twice a day)	Tapazole and Propranolol	Soothing the liver and relieving depression, clearing heat and strengthening the spleen	treatment group:30/30 Control group:30/30	Treatment group: 5/25 Control group:4/26	Hyperthyroidism	4 weeks(4 weeks)	Treatment group:1 patients reported hypothyroidism Control group:9 patients reported Leukopenia ;4 patients reported hypothyroidism	Symptom improvement Reduction of TGAb、TPOAb Maintain white blood cell level and thyroid function
XL. C 2022 [81]	Shugan Qingre decoction (water extraction, 300 ml twice a day) with LT-4 (50 μg/d)	LT-4	Soothing Liver and Strengthening Spleen, replenishing qi and activating blood, clearing heat and dispersing nodules	treatment group:40/40 Control group:40/40	Treatment group: 11/29 Control group:12/28	N/R	12 weeks(12 weeks)	N/R	Symptom improvement improvement of FT3、FT4 Reduction of TSH、TGAb、TPOAb Reducing the size of the thyroid gland Reducing the thickness of the isthmus of the thyroid gland
NJ. X 2019 [82]	Xiaojin capsule (produced by Jianmin Pharmaceutical Group Co., Ltd., National Pharmaceutical, approval No. Z10970132, 4 pills each time twice a day) with Selenium yeast flakes (100 μg twice day)	Selenium yeast flakes	Warm circulation, promoting blood circulation, reducing swelling, dispersing nodules, and resolving phlegm	treatment group:32/32 Control group:28/28	Treatment group: 10/22 Control group:12/16	Euthyroidism	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb Reducing the size of the thyroid gland
YP. W 2019 [83]	Modified Mendong Qingfei decoction (water extraction, 250 ml twice a day) with LT-4 (12.5 μg/d)	LT-4	Nourishing Qi and Yin, Promoting Qi and Resolving Phlegm	treatment group:35/35 Control group:35/35	Treatment group: 6/29 Control group:8/27	N/R	3 months(3 months)	Treatment group:1 patients reported Transient palpitations; Control group:2 patients reported Arrhythmia; 1 patients reported vomiting;	Symptom improvement Reducing the size of the thyroid gland improvement of FT3、FT4 Reduction of TSH、IgG4、TGAb、TPOAb
J. W 2020 [84]	Shugan Sanjie formula (water extraction, 250 ml twice a day)	LT-4	Promoting blood circulation and removing blood	treatment group:35/35	Treatment group: 16/19	Euthyroidism	6 months(6 months)	N/R	Reduction of TGAb、TPOAb

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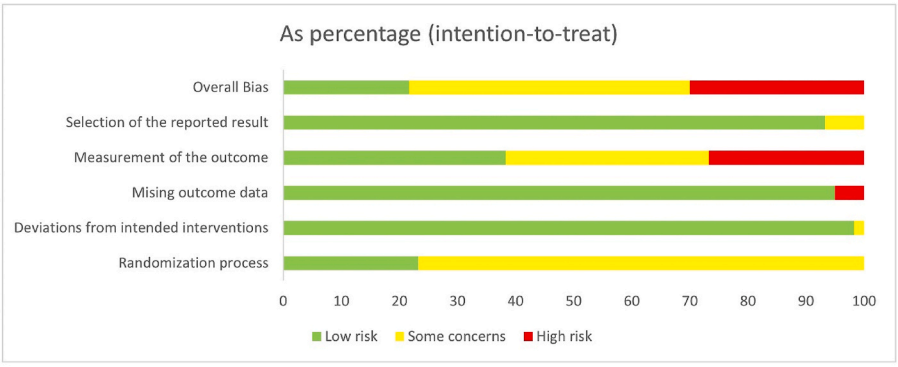
Table 1 (*continued*)

Reference	Treatment group (dosage)	Control group	Traditional use	Number of participants R/A	Sex(M/F)	Thyroid function	Treatment duration (Length of follow-up)	Adverse effects	Outcome
			stasis, soothing the liver and dispersing nodules	Control group:35/35	Control group:15/20				Reduction of thyroid volume
H. C 2021 [85]	Shugan Wenshen Recipe (water extraction, 400 ml twice a day) with LT-4 (25 μg/d)	LT-4	Soothing the liver and promoting qi, resolving phlegm and promoting blood circulation	treatment group:68/68 Control group:69/69	Treatment group: 13/55 Control group:13/56	Subclinical hypothyroidism	12 weeks(12 weeks)	N/R	improvement of FT3、FT4、HDL-C Reduction of TSH、TGAb、TPOAb、TC、TG、LDL-C
SW. C 2021 [86]	Yiqi Yangyin decoction (water extraction, 250 ml twice a day) with Selenium yeast capsules (100 μg twice day)	Selenium yeast capsules	Nourishing Qi and Yin, Resolving Phlegm and Stasis	treatment group:40/40 Control group:40/40	Treatment group: N/R Control group:N/R	Euthyroidism	6 months(6 months)	N/R	Reduction of TGAb、TPOAb
HJ. Y 2021 [87]	Jianpi Xiaoying decoction (water extraction, 400 ml twice a day) with Selenium Yeast (100 μg twice day)	Selenium Yeast	Strengthening the spleen and tonifying qi, clearing heat and dispersing blood stasis	treatment group:50/50 Control group:50/50	Treatment group: 7/43 Control group:9/41	N/R	12 weeks(12 weeks)	N/R	Symptom improvement Reduction of TGAb、TPOAb
P. L 2015 [88]	Huatan Sanjie decoction (water extraction, 250 ml twice a day) with Selenium yeast flakes (50 μg/d)	Selenium yeast flakes	Dispelling phlegm and nodules, soothing the liver and promoting blood circulation	treatment group:30/29 Control group:30/30	Treatment group:4/25 Control group:3/27	Subclinical hypothyroidism or hypothyroidism	2 months(2 months)	N/R	Symptom improvement Reduction of TSH、TGAb、TPOAb
DM. X 2021 [89]	Jianpi Xiaoying decoction (water extraction, 250 ml twice a day) with Selenium yeast capsules (0.143g twice day)	Selenium yeast capsules	Strengthening the spleen, tonifying qi, clearing heat and dispersing nodules	treatment group:26/26 Control group:26/26	Treatment group: 9/17 Control group:10/16	N/R	12 weeks(12 weeks)	Treatment group:1 patients reported liver damage; 1 patients reported hair loss Control group:2 patients reported liver damage; 2 patients reported hair loss	Symptom improvement Reduction of IFN-γ、TGAb、TPOAb improvement of IL-10 Maintain thyroid function
ZM. W 2022 [90]	Bailing capsule (produced by Hangzhou Zhongmei East China Pharmaceutical Co., Ltd., with the national drug approval number Z10910036)	Methimazole tablets	Invigorating qi and essence	treatment group:49/49 Control group:49/49	Treatment group: 21/28 Control group:19/30	N/R	6 months(6 months)	N/R	Maintain FT4 levels Reduction of TRAb、TGAb、TPOAb
TQ. SG 2021 [91]	Shugan Jianpi decoction (water extraction, 250 ml twice a day) with LT-4 (12.5–75 μg/d)	LT-4	Dispelling galls and dispersing nodules, Relieving Qi Stagnancy in Liver	treatment group:35/35 Control group:35/35	Treatment group: 14/21 Control group:16/19	N/R	3 months(3 months)	N/R	Symptom improvement Reduction of TGAb、TPOAb Reducing the size of the thyroid gland
AC. Y 2016 [92]	Danggui Liuhuang decoction (water extraction, 250 ml twice a day) with LT-4 (12.5–75 μg/d)	LT-4	Strengthening the spleen and tonifying qi, promoting blood circulation and removing blood stasis, clearing heat and detoxifying	treatment group:36/36 Control group:36/36	Treatment group: 15/21 Control group:16/20	N/R	3 months(3 months)	Treatment group: N/R Control group:2 patients reported palpitation	Symptom improvement Reduction of TGAb、TPOAb Reducing the size of the thyroid gland



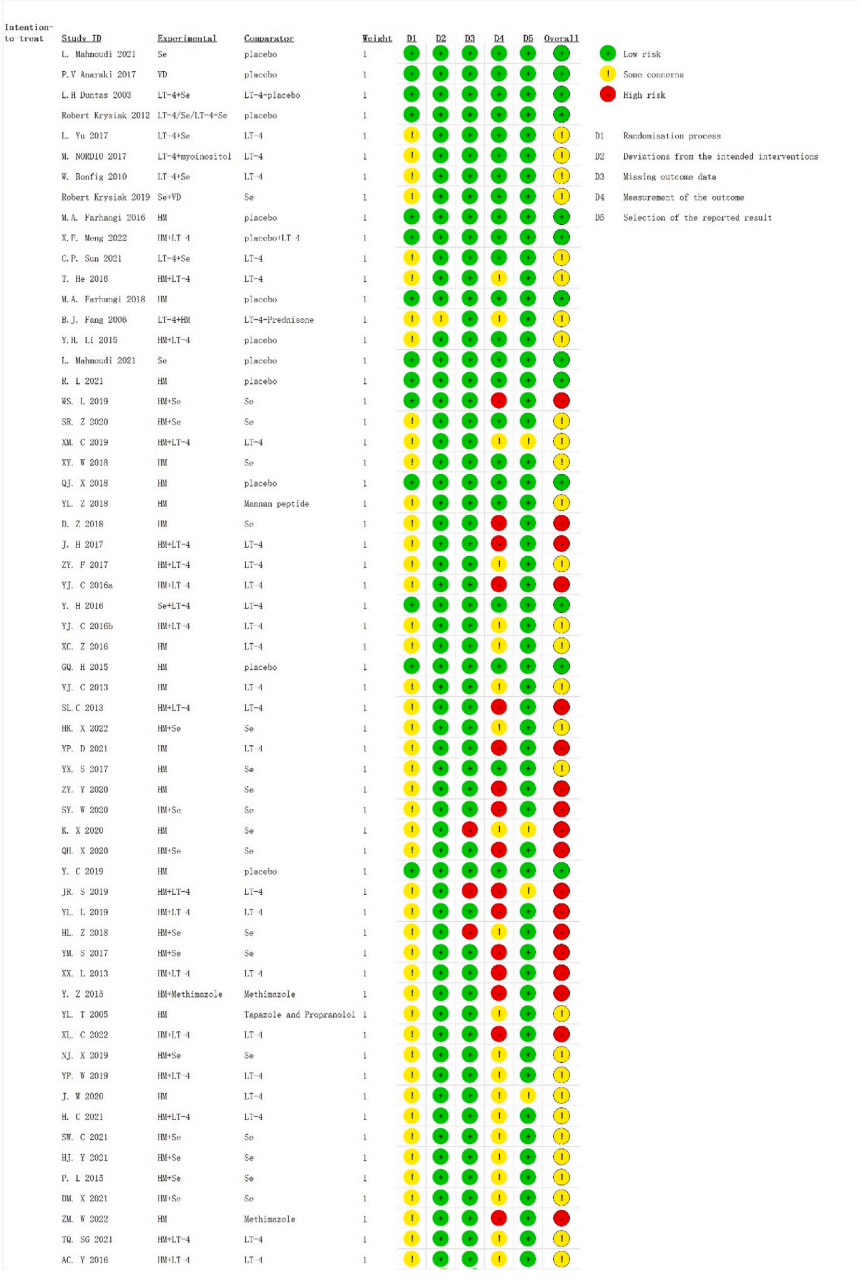


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Fig. 2. Risk of bias summary and risk of bias graph.

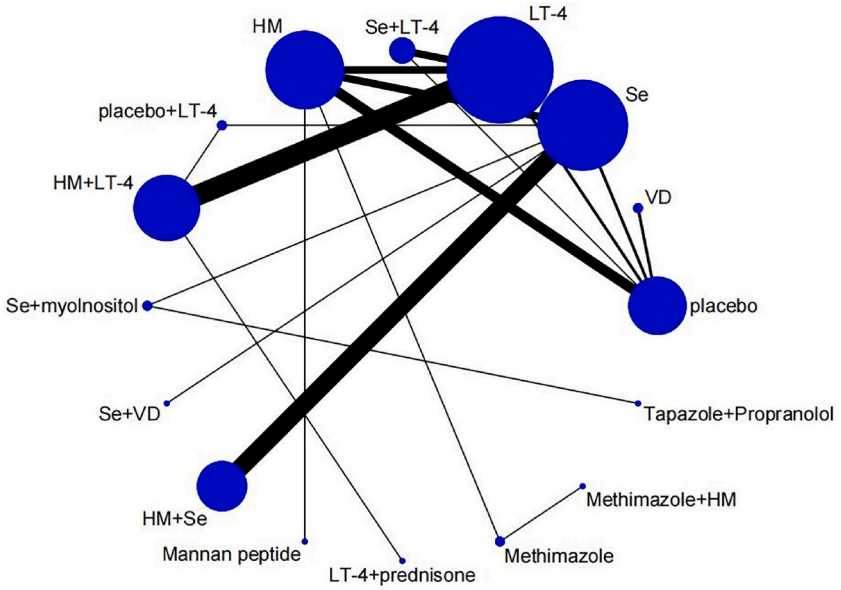

Fig. 3. Network meta-analysis of available comparisons in TPOAb.

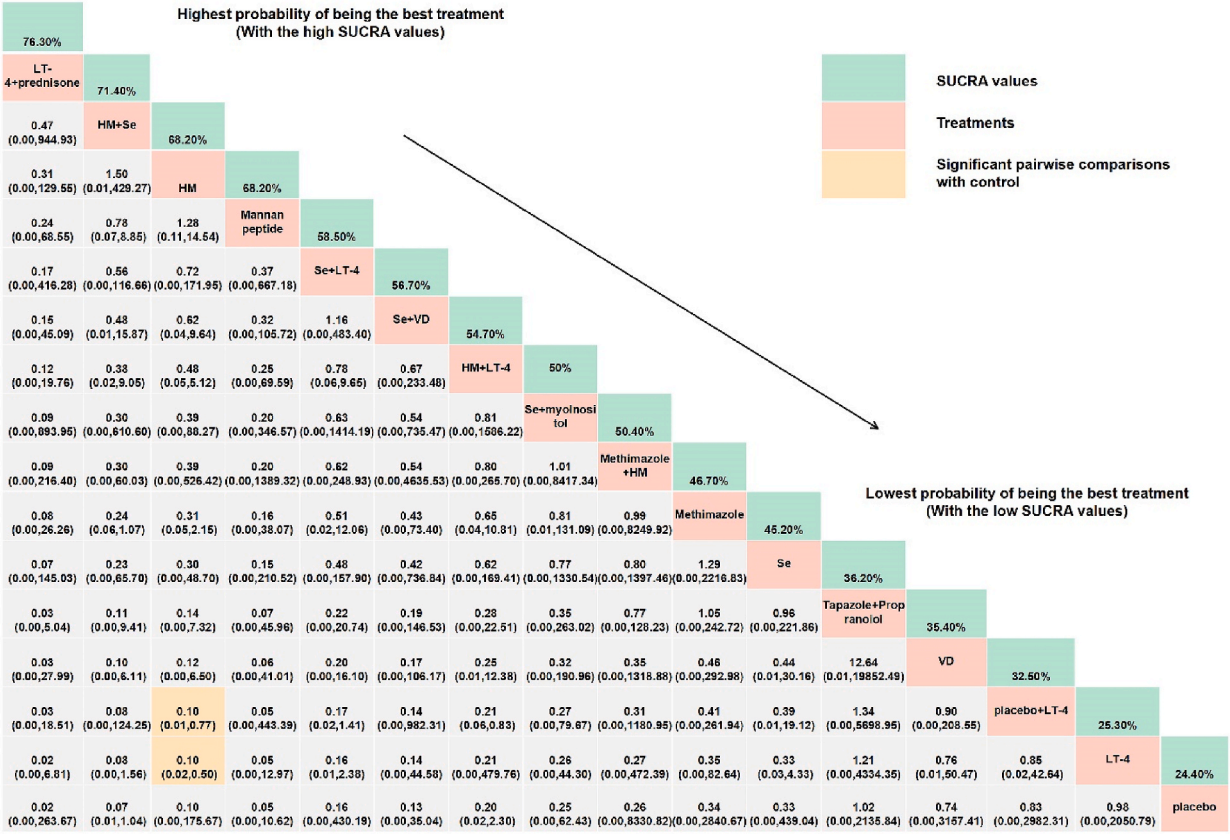

Fig. 4. Legend relative effects size of efficacy at TPOAb according to NMA. Numbers in the green boxes are the values of SUCRA, which represents the rank of treatment in TPOAb. Significant pairwise comparisons with control treatment are highlighted in orange.

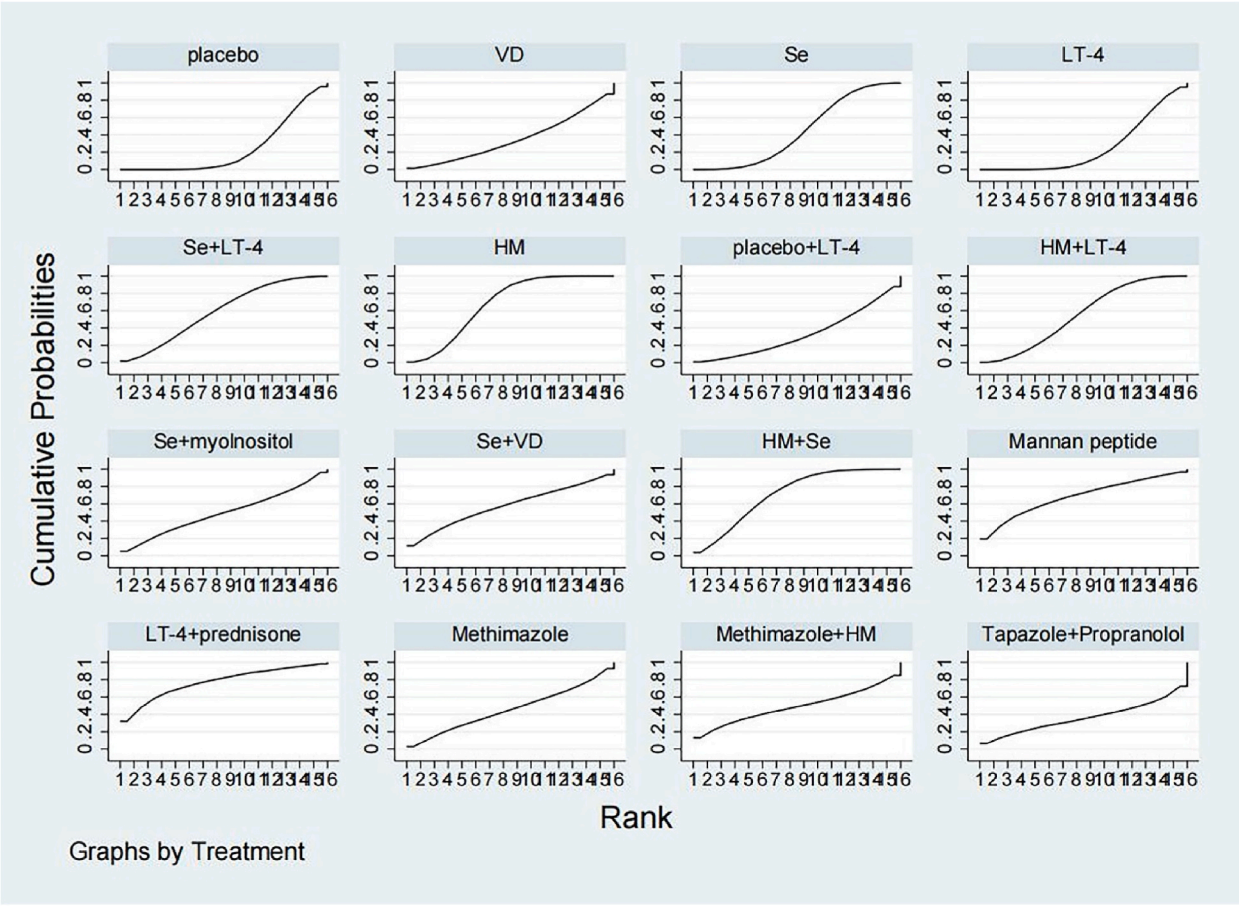

Fig. 5. Ranking of treatment strategies based on the probability in terms of reducing TPOAb.

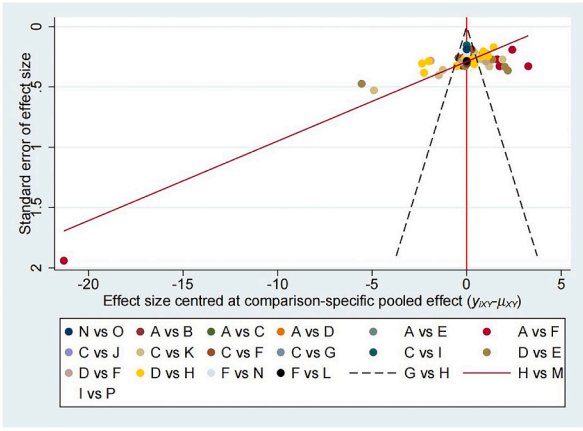

Fig. 6. Comparison-specific funnel chart in terms of reducing TPOAb. A, placebo; B, VD; C, Se; D, LT-4; E, Se + LT-4; F, HM; G, placebo + LT-4; H, HM + LT-4; I, Se + myolnositol; J, Se + VD; K, HM + Se; L, Mannan peptide; M, LT-4+prednisone; N, Methimazole; O, Methimazole + HM; P, Tapazole + Propranolol.

evaluate the comparative effectiveness of each treatment. The results for all outcome indicators were analyzed using normal likelihood models [30]. Continuous outcomes are expressed as odds ratios (OR) with 95 % confidence intervals (CI) and mean differences (MD) with 95 % CI. We compared the posterior distribution of the estimated heterogeneity variance with its predictive distribution to assess the degree of heterogeneity. Heterogeneity was assessed using the I^2 test with the significance level set at $I^2 > 50$ %. If there was no

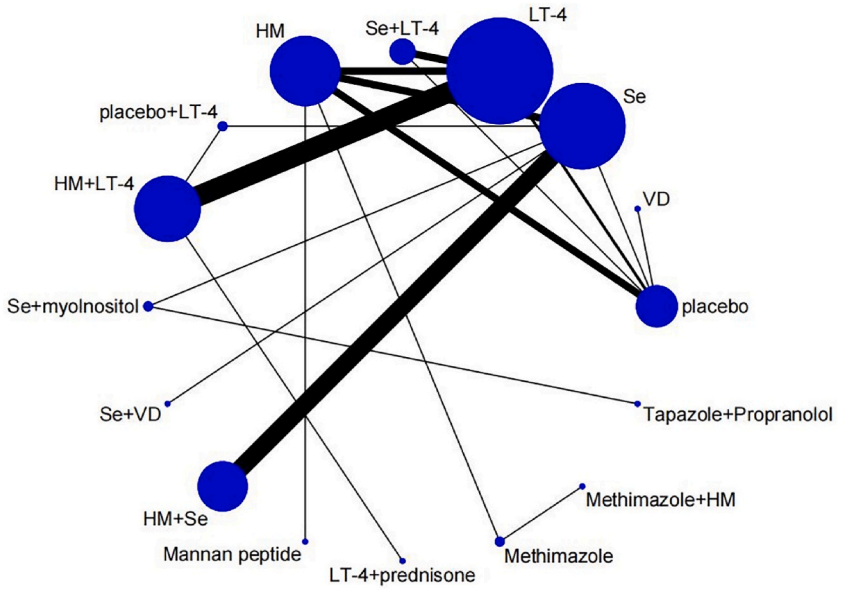

Fig. 7. Network meta-analysis of available comparisons in TgAb.

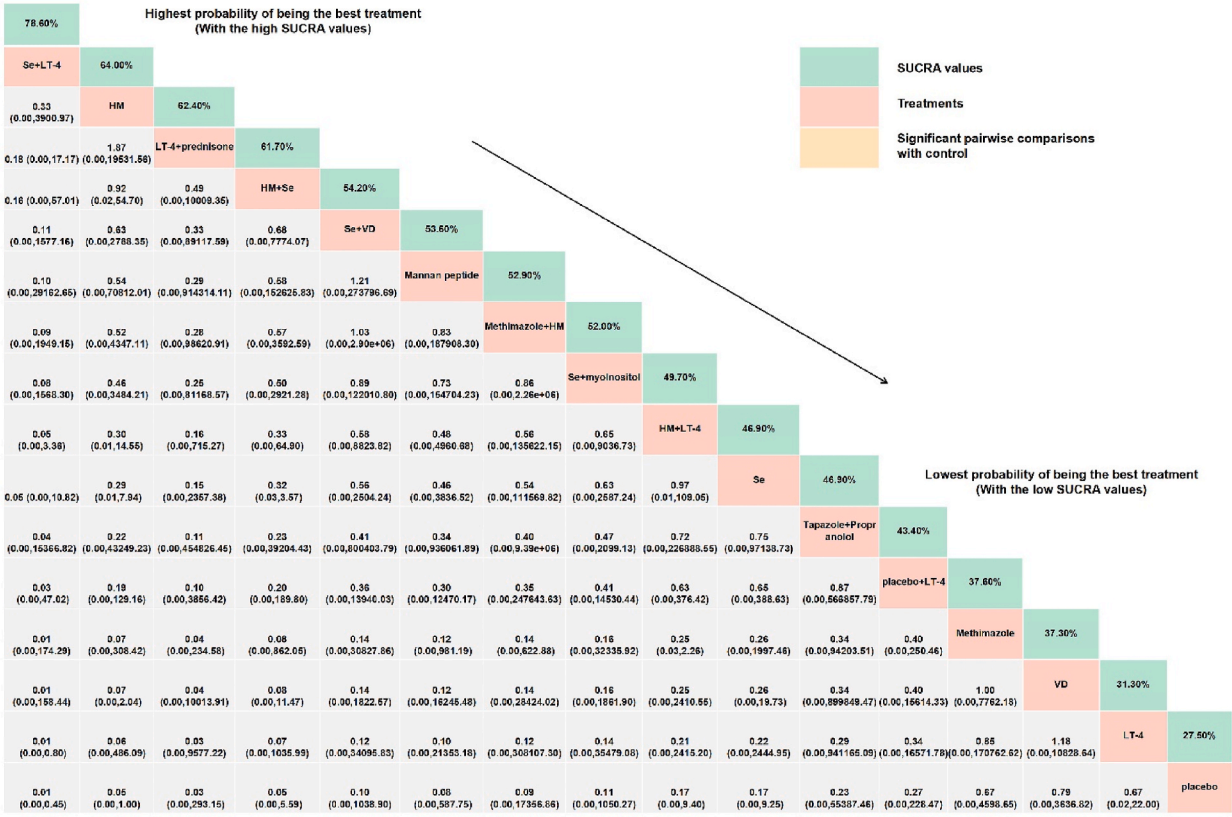

Fig. 8. Legend relative effects size of efficacy at TgAb according to NMA. Numbers in the green boxes are the SUCRA values, which represent the treatment rank in TgAb.

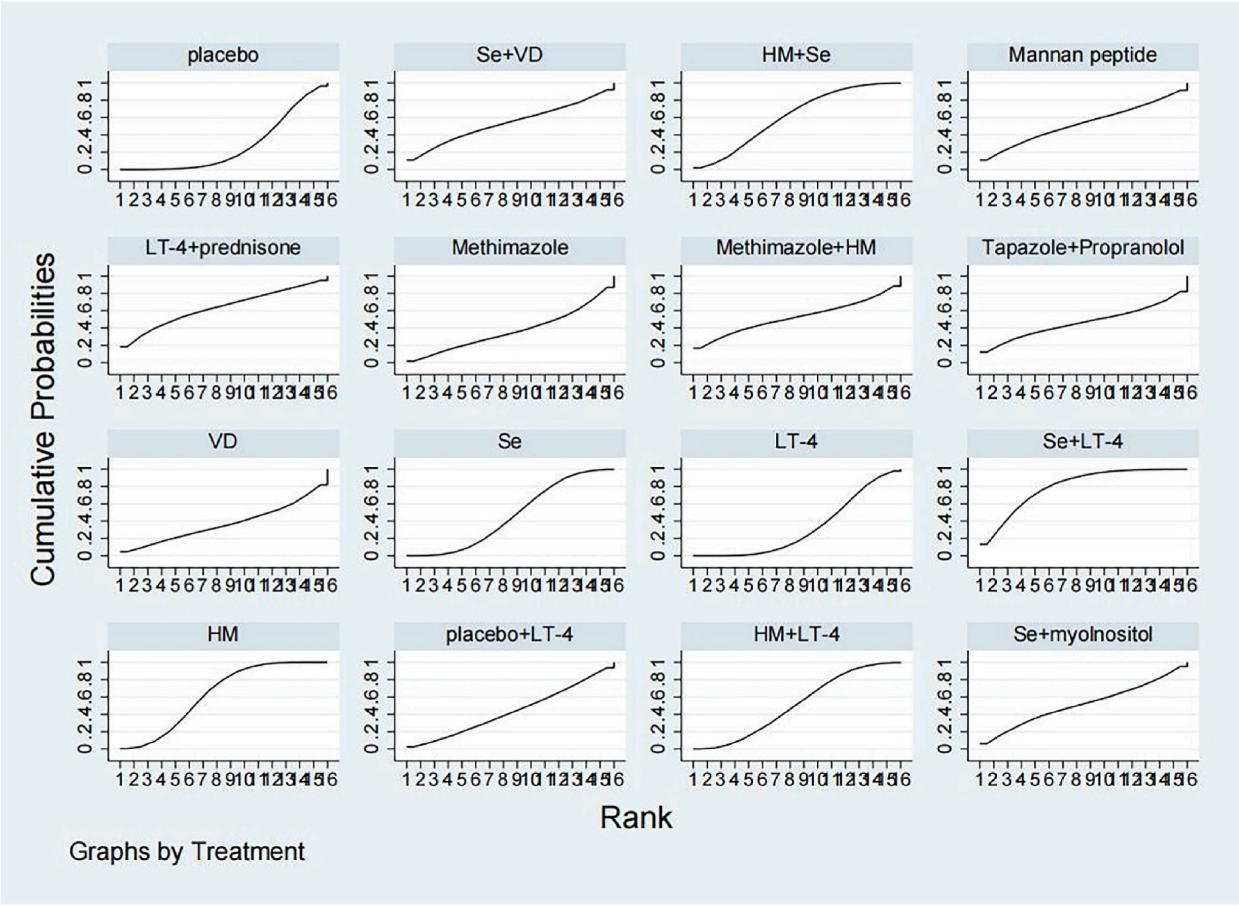

Fig. 9. Ranking of treatment strategies based on the probability in terms of reducing TgAb.

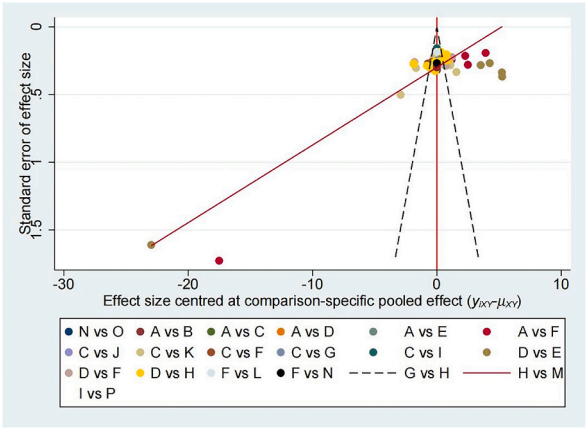

Fig. 10. Comparison-specific funnel chart in terms of reducing TgAb. A, placebo; B, VD; C, Se; D, LT-4; E, Se + LT-4; F, HM; G, placebo + LT-4; H, HM + LT-4; I, Se + myolnositol; J, Se + VD; K, HM + Se; L, Mannan peptide; M, LT-4+prednisone; N, Methimazole; O, Methimazole + HM; P, Tapazole + Propranolol.

heterogeneity ($I^2 < 50$ %), we selected the fixed effects model; otherwise, we used the random effects model to explain the possible causes of heterogeneity ($I^2 > 50$ %). Sensitivity analyses were also performed to assess the robustness of the results [31]. Moreover, we used the surface under the cumulative ranking curve (SUCRA) [32]. The larger the SUCRA value, the better the intervention efficacy.

3. Results

3.1. Study characteristics

We obtained 2350 citations through a literature search of nine databases above. 1574 titles and abstracts were screened for deduplication. A total of 604 full texts were subjected to further eligibility assessment. At last, 60 RCTs conducted between 2003 and 2022 were included. (Fig. 1).

The 60 included studies enrolled a total of 4719 patients and evaluated 9 drugs and 16 intervention strategies, including VD, Se, LT-4, Se + LT-4, HM, placebo + LT-4, HM + LT-4, Se + myolnositol, Se + VD, HM + Se, mannan peptide, LT-4+prednisone, Methimazole, Methimazole + HM, Tapazole + Propranolol, and placebo. No statistically significant differences were observed between the baseline values for all study descriptions (Table 1).

3.2. Risk of bias assessment

The results of the risk of bias for the included studies are in Fig. 2. Most of study designs had a low risk of selection of the reported result, deviation from intended interventions, randomization process. Partial studies had a high risk of measurement of the outcome and missing outcome data. All studies had complete primary outcome data.

3.3. TPOAb

3.3.1. Evidence network

Sixty studies reported TPOAb involving 16 medication strategies, including VD, Se, LT-4, Se + LT-4, HM, placebo + LT-4, HM + LT-4, Se + myolnositol, Se + VD, HM + Se, mannan peptide, LT-4+prednisone Methimazole, Methimazole + HM, Tapazole + Propranolol, and placebo in all patients. The evidence network is shown in Fig. 3. Among these, the number of studies comparing LT-4 with HM + LT-4, Se with HM + Se, and HM with placebo was the highest.

3.3.2. Network meta-analysis and SUCRA ranking

A network meta-analysis of the reduction of TPOAb levels and produced 120 pairwise comparisons, of which two were statistically significant. The combination of MD and 95 % CI showed that the efficacy of HM was higher than that of placebo + LT-4 and LT-4 alone. The ranking of probability was LT-4+prednisone > HM + Se > HM > Mannan peptide > Se + LT-4 > Se + VD > HM + LT-4 > Se + myolnositol > Methimazole + HM > Methimazole > Se > Tapazole + Propranolol > VD > placebo + LT-4 > LT-4 > placebo (Fig. 4). The SUCRA ranking showed that LT-4+prednisone was most likely the best intervention in reducing TPOAb (Fig. 5).

3.3.3. Publication bias assessment

As shown in Fig. 6, each dot represents the included studies, and different colors indicate different interventions. The comparison-correction funnel chart showed a publication bias, especially in the comparison between HM and placebo.

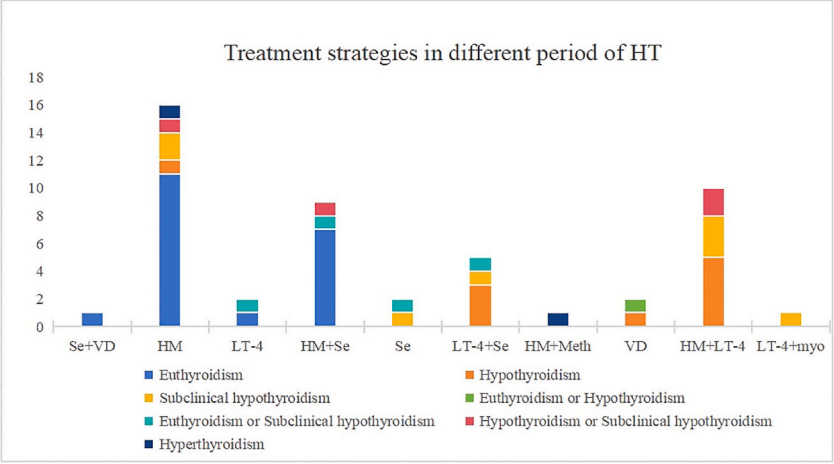

Fig. 11. The treatment strategies in different period of HT.

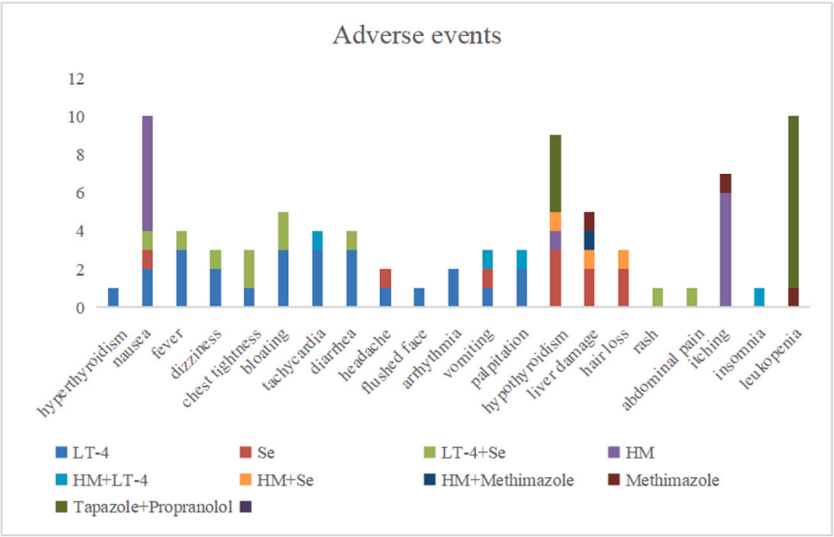

Fig. 12. The frequency adverse reactions in different treatments.

3.4. TgAb

3.4.1. Evidence network

Fifty-five studies reported TgAb involving 16 medication strategies, including VD, Se, LT-4, Se + LT-4, HM, placebo + LT-4, HM + LT-4, Se + myolnositol, Se + VD, HM + Se, mannan peptide, LT-4+prednisone Methimazole, Methimazole + HM, Tapazole + Propranolol, and placebo in all patients. Among these, the number of studies comparing LT-4 with HM + LT-4, Se with HM + Se, and HM with placebo were the highest (Fig. 7).

3.4.2. Network meta-analysis and SUCRA ranking

A network meta-analysis of the reduction of TgAb levels and produced 120 pairwise comparisons, none of which were statistically significant. The ranking of probabilities was as follows: Se + LT-4 > HM > LT-4+prednisone > HM + Se > Se + VD > Mannan peptide > Methimazole + HM > Se + myolnositol > HM + LT-4 > Se > Tapazole + Propranolol > placebo + LT-4 > Methimazole > VD > LT-4 > placebo (Fig. 8). The SUCRA ranking showed that Se + LT-4 was most likely the best intervention (Fig. 9).

3.4.3. Publication bias assessment

As shown in Fig. 10, each dot represents the included studies, and different colors indicate different interventions. The comparison-correction funnel chart showed that there was a publication bias, especially in the comparison of HM with placebo and LT-4 with Se + LT-4.

3.5. Effects on thyroid function

The heterogeneity of TSH, FT3, and FT4 levels was computed (Appendix 2-4). The effect of TSH, including VD, Se, LT-4, Se + LT-4, HM, placebo + LT-4, HM + LT-4, Se + myolnositol, Se + VD, HM + Se, Mannan peptide, LT-4+prednisone Methimazole, Methimazole + HM, and Tapazole + Propranolol, was reported in 49 studies. There is significant heterogeneity among the studies ($P < 0.00001$, $I^2 = 98\,\%$). A random-effects model combined with effect size was used for the analysis. With oral medicine treatment, TSH was significantly lower than that of the control group (MD = −0.658, 95 % CI: −0.95 to −0.35, Z = 4.25, $P < 0.00001$). The effect of FT3 in patients with HT treated with HM has been reported in 41 studies. Significant heterogeneity was observed among the studies ($P < 0.00001$, $I^2 = 82\,\%$). The random effect model combined effect size was used for analysis, and significant differences were found between the treatment and control groups (MD = 0.16, 95 % CI: 0.06 to 0.26, Z = 3.21, $P = 0.001$). Forty studies reported the effect of FT4. Significant heterogeneity was observed among the studies ($P < 0.00001$, $I^2 = 94\,\%$). The random effect model combined effect size was used for analysis, and no significant difference was found between the treatment and control groups (MD = 0.28, 95 % CI: 0.09 to 0.48, Z = 2.87, $P = 0.04$).

3.6. Treatment strategies in different periods of HT

Thyroid function at presentation may vary, ranging from a transient hyperthyroid phase to frank hypothyroidism. In our study, thyroid function was reported in 47 trials, including 19 on euthyroidism, 10 on hypothyroidism, 8 on subclinical hypothyroidism, 1 on euthyroidism or hypothyroidism, 3 on euthyroidism or subclinical hypothyroidism, 4 on hypothyroidism or subclinical

hypothyroidism, and 2 on hyperthyroidism. HM can be used during various periods of HT, including euthyroidism, hypothyroidism, subclinical hypothyroidism, and hyperthyroidism, especially in patients with HT and euthyroidism. Furthermore, LT-4, HM, Se, and VD alone or in pairwise combinations could be used in hypothyroidism or subclinical hypothyroidism (Fig. 11).

3.7. Adverse events

Adverse events encompassed 12 trials (n = 74 patients) with 9 treatments. No serious adverse events were reported (Table 1 and Fig. 12). Common adverse reactions to LT-4 treatment alone included hyperthyroidism, nausea, fever, dizziness, chest tightness, bloating, tachycardia, diarrhea, headache, flushed face, arrhythmia, vomiting, palpitations, and hypothyroidism. Common adverse reactions to Se included nausea, headache, vomiting, hypothyroidism, liver damage, and hair loss. Treatment with LT-4 + Se resulted in occasional nausea, fever, dizziness, chest tightness, bloating, diarrhea, rashes, and abdominal pain. The adverse reactions to LT-4+Se were similar to those to LT-4 or Se alone; however, the frequency and severity of adverse reactions decreased in the following order: LT-4 > LT-4+Se > Se. Common adverse reactions of methimazole include liver damage, itching, and leukopenia. In terms of adverse reactions to Tapazole + Propranolol, four patients experienced hypothyroidism, and nine patients experienced leukopenia. As for HM, there are a few reports of occasional hypothyroidism, and six patients experienced nausea and itching in the literature. HM + LT-4 treatment resulted in occasional tachycardia, vomiting, palpitation, and insomnia; HM + Se treatment resulted in occasional hypothyroidism, liver damage, and hair loss; and HM + Methimazole treatment resulted in liver damage. There were no adverse reports regarding the use of VD therapy.

4. Discussion

We reviewed the effects of VD, Se, LT-4, HM, myelositol, mannan peptide, Methimazole, Propranolol, and combination therapy strategies on the main thyroid antibody outcome indicators of HT. We found that HM was a more effective treatment method than LT-4 or LT-4+placebo. HM effectively reduced the TPOAb levels. It has been suggested that in terms of reducing TPOAb, we found that HM may be more effective than LT-4+placebo and LT-4 alone. In addition, the beneficial effects of various treatment options compared with the placebo did not reach statistical significance both in TPOAb and TgAb; however, the SUCRA probability of LT-4+prednisone being dominant in all results was the highest in TPOAb, followed by HM + Se and HM. The SUCRA probability of Se + LT-4 being in the dominant position in all results was the highest in TgAb, followed by HM.

HT is characterized by the presence of autoantibodies [93]. Antibody titers are positively correlated with hypothyroidism [94], but no specific drug reduces antibody titers. Moreover, several studies from a Posish team have reported that disorders of the brain's bioelectrical activity in the course of HT may be associated with an autoimmune process, and patients with HT even in the euthyroid phase have both abnormalities of bioelectrical brain function and changes in the metabolic composition of the brain found in neuroimaging studies [95–97]. Currently, the main treatments for HT are follow-up observation and thyroid hormone replacement therapy for secondary hypothyroidism. However, thyroid hormone replacement therapy cannot reduce the high titers of autoantibodies in the serum or correct immune abnormalities. Although glucocorticoids can correct immune abnormalities, they are generally not recommended for clinical use due to adverse reactions after administration and high recurrence after withdrawal. Therefore, there is a lack of treatment measures for HT that can ameliorate immune abnormalities with fewer side effects and recurrences.

HM has been widely used in the treatment of thyroid dysfunction, and there have been an increasing number of reports of HM alone or in combination with other oral medicines for the treatment of HT. Several studies have shown that HM, whether used alone or in combination with other drugs, has a potent therapeutic effect in the treatment of HT. A systematic review of patients with HT showed that the use of HM in combination with Western Medicine (WM) may result in improved clinical efficacy in the treatment of hypothyroidism compared to WM alone [98]. Various HM are widely used in HT, such as phlegm-dispersing and knot-dispersing, tonifying and benefiting, and blood-activating and pain-relieving medicines. A randomized trial that used a placebo-controlled approach found that the Bupleurum inula flower soup, which can sooth the liver, promote qi and blood circulation, and relieve pain widely used for treatment, can effectively reduce thyroid titers. The soup can also relieve emotional and clinical symptoms, and improve health-related quality of life among patients with HT [38]. *Prunella vulgaris* L. [Lamiaceae] (PVL), a perennial herb mainly clearing heat and purging fire, dispersing nodules and reducing swelling, has been used to treat thyroid diseases in China for over 2000 years. Its therapeutic effects have been described for HT, including reducing autoantibodies titers against thyroid peroxidase, thyroglobulin, and T helper 17 (Th17) cells and protecting thyrocytes by suppressing both innate and adaptive immune responses and cell death [99]. *Sargassum pallidum (Turn.) C. Ag.*, which can resolve phlegm and softening hardness, regulate qi and disperse nodules derived from the classic formula Seaweed Yuhu Decoction. It has been found that *Sargassum pallidum (Turn.) C. Ag.* effectively reduced serum T3, T4, TgAb, and TPOAb levels and downregulated TRAIL protein expression, which increases thyroid fibrosis and apoptosis and promotes thyroid follicle destruction in EAT rats. Saikosaponin-d (SSd), an active component of *Bupleurum chinense DC.* [Apiaceae] which is the most widely used TCM for soothing the liver and relieving depression has anti-inflammatory and immunomodulatory effects [100]. In addition, SSd can regulate Th1/Th2 and Th17/Treg imbalances and reduce the severity of HT in mice by promoting the polarization of M2 macrophages [101]. Xiaoying Daotan decoction contains *Prunella vulgaris* L. [Lamiaceae] and *Bupleurum chinense DC.* [Apiaceae], *Dioscorea nipponica Makino* [Dioscoreaceae], *Cyperus rotundus* L. [Cyperaceae] and *Angelica sinensis (Oliv.) Diels* [Apiaceae], *Paeonia lactiflora Pall.* [Paeoniaceae], *Conioselinum anthriscoides 'Chuanxiong'* [Apiaceae], could be related to the immune inflammatory response of the Treg/Th17 cell axis mediated by the Notch protein pathway of HT [102]. Our results are consistent with these studies in certain aspects. Although HM is not the most effective treatment method according to SUCRA, its advantages are its few side effects and fewer adverse events than other treatments. In addition, different herbal treatments have slightly different modes of action, such as

decoctions, capsules, and granules, as listed. Decoctions are suitable for patients with severe or unstable conditions and can be adjusted conveniently; capsules are ideal for drugs that are odorous and bitter and improve their bioavailability; and granules are suitable for drugs that require quick onset, convenient portability, and easy preparation. When selecting dosage forms, comprehensive consideration should be given to the patient's condition, the nature of the drug, and the need for treatment.

The ultimate outcome of Hashimoto's thyroiditis is hypothyroidism [103]. Although thyroid hormone replacement therapy counteracts some of the symptoms, it does not cure the disease. Thyroid function at presentation may vary, ranging from a transient hyperthyroid phase to frank hypothyroidism. Treatment with LT-4 should be promptly initiated in the presence of frank hypothyroidism. Therefore, synthetic LT-4 is the therapy the patient must take daily for their entire life. LT-4 may be given at doses of 1.5–1.7 μg per kg [104]. Many studies have shown that patients with HT who are euthyroid with LT-4 medical treatment still have persistent symptoms, such as chronic fatigue, weakness, nervousness, irritability, frequent mood swings, and impaired sexual activity, indicating that supplementing thyroid hormones is not the fundamental treatment for HT [105]. Correction of thyroid hormone deficiency cannot alleviate high levels of circulating TPOAb [106].

Furthermore, it was reported that LT-4 may be the optimal form of management for asymptomatic patients or those with a normal free thyroxine level but with a slightly elevated TSH level between the upper reference level [107]. For HT patients with obvious thyroid goiter and cervical lymphadenopathy, Lyu et al. found that combination therapy with levothyroxine and prednisone is effective for cervical lymphadenopathy in HT patients [108]. In our network meta-analysis, LT-4 alone or in combination slightly reduced the TPOAb and TgAb titers in patients with HT; however, the difference was insignificant. Compared with other treatments, LT-4 alone or in combination resulted in more adverse events. Therefore, more therapeutic targets need to be explored, especially in HT patients with euthyroidism and only elevated antibody levels.

Vitamin D and selenium preparations are two drug classes with well-documented thyroid protective effects, and adequate levels of vitamin D and selenium (Se) may help prevent or delay the onset of HT [109,110]. A meta-analysis involving 26 observational studies found that the 25-hydroxyvitamin D (25(OH)D) level was significantly lower in patients with HT than in healthy controls [111]. However, the mechanism through which vitamin D affects HT remains unclear. Previous studies have reported that supplementation with 25(OH)D3 in patients with HT and vitamin D deficiency significantly decreased the titer of thyroid autoantibodies, demonstrating the curative effect of vitamin D in treating HT [112,113]. Interestingly, other studies have reached the opposite conclusion, that vitamin D supplementation has no effect on thyroid antibodies [33,34]. In our network meta-analysis, vitamin D supplementation reduced the TPOAb and TgAb titers in patients with HT; however, the difference was not statistically significant. Compared to other oral drugs, such as LT-4 and prednisone, vitamin D has a milder effect; therefore, it is relatively lower in the SUCRA rankings. Se, which is widely detected in the environment, is critical for thyroid function and is particularly abundant in the thyroid gland [114,115]. In addition, Wang et al. found a general selenium deficiency in patients with autoimmune thyroiditis (AITD) with a normal thyroid reference range; however, selenium supplementation may be effective in reducing the titers of TgAb and TPOAb after six months of treatment [116]. The efficacy of VD in treating HT remains unclear, and its SUCRA rankings are lower than those of most strategies. However, there were no adverse reports regarding VD therapy in our study.

Myoinositol (Myo) plays a key role in thyroid function and autoimmune diseases by regulating iodine organization and thyroid hormone biosynthesis through the formation of hydrogen peroxide in thyrocytes [117]. Recently, several studies have explored a significant decrease in TSH and antithyroid autoantibody levels in patients with subclinical hypothyroidism, with or without autoimmune thyroiditis, after treatment with Myo plus selenium [12,38]. Thiel et al. [118] reviewed that a lack of Mannan-binding lectin (MBL) has been associated with autoimmune diseases, and the production of MBL is stimulated by thyroid hormones [119]. Although hypothyroidism and AITD are associated with decreased MBL levels, relevant clinical research on MBL treatments for HT is still lacking. Studies have shown that hyperthyroidism is associated with elevated methimazole levels. Methimazole (MMI), also known as tapazole, has an immunomodulatory effect in Graves' disease (GD). It is the mainstay of therapy for GD [12,120]. In the early stages of HT, mild and transitory hyperthyroidism may occur because of thyroid cell destruction and the release of thyroid hormones into the bloodstream [121]. The short-term use of MMI can improve thyrotoxicosis in patients with transient hyperthyroidism caused by HT. However, further clinical studies are needed to determine whether MMI can be used for the treatment of HT, to reduce thyroid antibodies, and to delay disease progression. Propranolol, a non-selective beta-adrenergic receptor antagonist, is currently used to treat arrhythmias and is commonly used to treat patients with HT accompanied by palpitations [122]. Painful Hashimoto's thyroiditis (pHT) is a rare variant of HT that mostly affects women and typically features elevated serum levels of TPOAb or TgAb and a firm, painless goiter [123]单击或点击此处输入文字。. Oral corticosteroids, primarily prednisone, are widely used to treat pHT (Peng et al., 2020). 50%–75 % of patients still experience neck pain despite the administration of corticosteroids, even develop Cushing syndrome [124] 单击或点击此处输入文字。. Unfortunately, Myo, prednisone, MMI, and Propranolol are mainly limited to a certain stage or symptom of HT, and further research is needed to determine whether they can effectively treat HT in the long term.

In this review, we systematically combine the existing research and comprehensively summarize the evidence. We analyzed the ranking probability of different treatment effects using the Bayesian method to facilitate the evaluation of the comparative effectiveness of different treatments for HT. We preliminarily evaluated the most recommended treatment method for HT to assist clinicians in decision-making.

However, this study has a number of limitations. The original study did not subdivide patients at different stages; thus, we only evaluated the effects of the main drug in the treatment of HT. In the included RCTs, the severity of TPOAb and TgAb was different, and the patients included may have been in the stages of hypothyroidism, hyperthyroidism, or normal thyroid function, resulting in inconsistent treatment effects, causing heterogeneity and affecting the results of the study. Finally, there is heterogeneity in TCM. Although we limited TCM to commonly used herbal medicines, TCM formulas have complex effects involving multiple components, targets, and systems, which cannot be avoided. In addition, owing to the insufficient number of other drugs available for HT

treatments, such as Myo and MMI, we did not analyze them further, which is a limitation of this study.

5. Conclusion

This is the first review of the various medications used for the treatment of HT using a network meta-analysis. Our network meta-analysis showed that both LT-4+prednisone and HM reduced TPOAb levels, thereby improving thyroid damage in patients with HT. Although the SUCRA ranking showed that LT-4+prednisone was most likely the best intervention, it did not reach statistical significance when compared with the placebo. Hence, among the treatment strategies mentioned above, HM may be the optimal choice for HT treatment. However, it is still necessary to further observe the long-term effectiveness and safety, to clarify the clinical medication strategy. Therefore, larger, double-blind, placebo-and randomized controlled trials are required to verify the efficacy, safety, tolerability, and recurrence rates of herbs for the treatment of HT.

Author contributions

LJL, ZL and HL contributed to the conception of the study and its design. SAR and MY designed the search strategy and completed the literature search. LJL and ZL screened studies for eligibility. LYQ extracted the data and assessed the risk of bias. LJL and ZL performed the data analysis. LYQ and HL conducted the GRADE assessment. LJL and ZL drafted the manuscript. HL revised the manuscript. All other authors revised the manuscript. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Funding

This study was supported by grants from the Clinical Research Center Construction Project of Guang'anmen Hospital, CACMS (No. 2022LYJSZX15) and Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No: ZYYCXTD-D-202001).

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35114.

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