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Nutraceuticals in Hypothyroidism, Hyperthyroidism, Hashimoto's Thyroiditis and Graves'' Disease: Biological Rationale and Critical Appraisal of Clinical Evidence

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Abstract

Background: Nutraceutical interventions have been investigated in thyroid dysfunction, but biological plausibility, antibody responses, and clinical efficacy are often interpreted as equivalent outcomes.

Objective: To critically examine their mechanisms and clinical effects of nutraceuticals for hypothyroidism, hyperthyroidism, Hashimoto's thyroiditis, and Graves'' disease.

Methods: A structured narrative review integrated human studies identified through directed searches of bibliographic records, accessible primary publications, regional literature, and gray sources. Selected primary studies and relevant evidence syntheses were prioritized. Outcomes were interpreted according to diagnosis, nutritional status, concurrent treatment, comparator, and clinical relevance.

Results: Selenium studies demonstrate a separation between immunological and clinical responses. Meta-analytic reductions in thyroid peroxidase antibodies coexist with substantial heterogeneity, while CATALYST trial found no improvement in quality of life or levothyroxine requirements. GRASS trial did not improve Graves' remission, and selenium findings in orbitopathy varied between settings. Myo-inositol plus selenium, Aloe vera, Nigella sativa, and selected botanical preparations showed preliminary biochemical or symptomatic effects. Brazil nuts increased T3 and free T4 in selenium-deficient hemodialysis patients, representing indirect evidence for primary thyroid disease. L-carnitine primarily targets peripheral hormone action. Pharmacological iodine suppresses thyroid activity in selected Graves' settings, whereas desiccated thyroid extract is hormonal treatment.

Conclusions: The evidence supports intervention-specific and outcome-specific interpretation. Nutrient repletion, immunomodulation, altered drug absorption, and symptom relief are distinct therapeutic effects. Most preparations lack replicated evidence for sustained recovery of endogenous thyroid function or durable remission. Future trials should test defined clinical phenotypes, standardized formulations, and patient-relevant outcomes.

Keywords: nutraceuticals, thyroid dysfunction, Hashimoto's thyroiditis, Graves' disease, selenium, dietary supplements

Introduction

Hypothyroidism and hyperthyroidism comprise clinically heterogeneous disorders in which nutritional factors, hormone metabolism, and autoimmunity may contribute differently to disease expression. Hashimoto's thyroiditis can present with preserved thyroid function, subclinical dysfunction, or established hormone deficiency, whereas Graves' disease involves antibody-mediated thyroid stimulation and may also affect orbital tissues. These distinctions are essential when evaluating interventions intended to improve thyroid function, attenuate autoimmunity, or relieve symptoms, because an effect on one disease component does not necessarily translate into improvement in another. [1–3]

Nutraceuticals have attracted interest because several nutrients and bioactive compounds participate in pathways relevant to thyroid physiology. Selenium contributes to antioxidant defense and thyroid hormone metabolism, while L-carnitine has been investigated for its ability to attenuate peripheral manifestations of hormone excess. [1, 2] Food-based interventions, including Brazil nuts as a source of selenium, have also produced favorable hormonal findings in selected populations. However, improvements observed in selenium-deficient hemodialysis patients cannot be directly extrapolated to primary hypothyroidism or autoimmune thyroid disease. [6]

The clinical evidence remains heterogeneous, with important differences between biochemical, immunological, and patient-reported outcomes. Selenium supplementation has reduced thyroid peroxidase antibody concentrations in some studies, yet the CATALYST trial found no corresponding improvement in quality of life or levothyroxine requirements. [4] Similarly, favorable findings in mild Graves' orbitopathy concern ocular outcomes and should be distinguished from control of hyperthyroidism. [5] The subsequent GRASS trial did not demonstrate improved remission or quality of life with selenium added to antithyroid treatment, highlighting the need to interpret efficacy according to the population and outcome studied. [7]

This review critically examines the biological rationale and clinical evidence for nutraceutical interventions in hypothyroidism, hyperthyroidism, Hashimoto's thyroiditis, and Graves' disease. It considers nutrients, foods, probiotics, and botanical preparations, distinguishing nutritional repletion, immunomodulation, symptom relief, and effects on conventional treatment. Pharmacological iodine preparations are discussed separately from nutritional supplementation, while thyroid extracts are identified as hormonal interventions. The objective is to clarify the clinical significance of reported benefits, explain discrepancies between studies, and identify priorities for research on sustained thyroid function and patient-relevant outcomes.

Methods

Review Design and Information Sources

A structured narrative review was developed from directed, iterative searches conducted through October 30, 2026. Sources included PubMed-indexed records, accessible primary publications, regional Chinese journal pages and records associated with CNKI, SinoMed, and VIP, Indian Ayurveda publications, trial registries, conference abstracts, and institutional repositories. Public regional records were consulted rather than complete exports from every native database interface. Searches combined thyroid diagnoses with intervention terms, including selenium, Brazil nut, iodine, Lugol, myo-inositol, Aloe vera, Nigella sativa, ashwagandha, L-carnitine, vitamins, minerals, probiotics, guggulu, Prunella, and Xiakucao. Reference lists and relevant evidence syntheses supported additional study identification.

Selection and Organization of Evidence

Human interventional evidence was considered regardless of the direction of the reported result. Randomized trials, nonrandomized comparative studies, and uncontrolled interventions were evaluated according to their design. Representative primary studies were retained for interventions with overlapping reports, while relevant systematic reviews were used to summarize larger bodies of evidence without treating them as additional cohorts. The bibliography prioritizes studies that define the intervention, establish a clinically important result, or explain a substantive disagreement. It is therefore a selective critical synthesis rather than a complete study-by-study inventory. Protocols without results and redundant reports were not retained as clinical efficacy evidence.

Studies with a confirmed autoimmune etiology were assigned to Hashimoto's thyroiditis or Graves' disease; other or incompletely specified etiologies were discussed under general hypothyroidism or hyperthyroidism. Graves' orbitopathy was distinguished from Graves' hyperthyroidism. Findings from euthyroid nutritional populations and hemodialysis patients were designated indirect evidence. Traditional multicomponent preparations were identified separately from isolated nutrients, and multimodal interventions were not interpreted as tests of a single nutraceutical.

Outcomes and Critical Synthesis

The synthesis distinguished thyroid function, autoantibodies, symptoms and quality of life, medication requirements, remission or relapse, and safety. Between-group effects were separated from changes within a treatment arm. Particular attention was given to baseline thyroid status, nutrient status, concurrent treatment, intervention composition, follow-up, attrition, and potential cohort overlap. Mechanistic findings were used to formulate explanations rather than establish clinical efficacy. Formal instrument-based risk-of-bias scoring, certainty grading, and meta-analysis were not performed. Because retrieval and selection were not conducted as a completed systematic process with a reproducible screening denominator, this manuscript is reported as a narrative clinical review rather than a completed scoping review.

Biological Rationale

Selenium Redox Regulation and Immune Activity

Selenium links nutrient availability to both thyroid hormone metabolism and antioxidant defense. Iodothyronine deiodinases participate in hormone activation and inactivation, whereas glutathione peroxidases and other selenoproteins contribute to control of oxidative stress. This creates a plausible route by which correcting deficiency could change circulating hormones without directly modifying the autoimmune process. It also explains why improved selenium status or glutathione peroxidase activity is an intermediate physiological response, not in itself evidence of improved thyroid health. The Brazil nut dialysis study is relevant to this distinction because participants had both selenium deficiency and low T3 at baseline. [6]

An immune pathway has also been examined in humans. In a randomized study of 90 patients with autoimmune thyroiditis, selenium yeast supplementation was associated with increased glutathione peroxidase 3 and selenoprotein P1, lower autoantibodies, and changes in activated regulatory T cells and Helios expression. These observations support a hypothesis connecting antioxidant capacity and immune regulation. However, parallel changes in selenium markers, regulatory T cells, and antibodies do not demonstrate that a

specific cellular change mediated the thyroid response. The study lacked a placebo-treated control, and its immunological findings cannot be assumed to predict prevention of gland failure. [9]

Two biological questions consequently need separate testing: whether supplementation corrects a functional limitation caused by inadequate selenium, and whether additional selenium alters autoimmune disease when nutritional requirements are already met. A trial combining these populations may obscure a benefit restricted to deficiency, while a positive biomarker result in sufficient patients may have limited clinical consequences. Importantly, subgroup differences must be demonstrated within an adequately designed study rather than inferred from comparisons between unrelated trials. [1, 4]

Signaling Substrates and Residual Gland Function

Myo-inositol has been proposed to influence the phosphoinositide-dependent component of thyrotropin receptor signaling. This provides a rationale for studying it in patients with mild biochemical dysfunction and retained thyroid tissue. The clinical hypothesis is improved responsiveness of residual gland function, not generation of new thyroid tissue. Combination trials with selenium cannot determine whether any effect is attributable to myo-inositol, selenium, or their interaction without appropriate component comparisons. [10]

Similarly, the availability of a biosynthetic precursor does not demonstrate that it is the limiting determinant of hormone production. Tyrosine has been evaluated in a physiological research setting involving euthyroid Antarctic residents, but such a study cannot establish efficacy in destructive autoimmune hypothyroidism. The relevant clinical question is whether supplementation increases endogenous hormone output in a defined deficient or dysfunctional population while improving patient outcomes. Its participation in hormone biosynthesis is insufficient to answer that question. [11]

Peripheral Hormone Action and Intestinal Mechanisms

L-carnitine was investigated as a peripheral antagonist of thyroid hormone action, with experimental rationale involving reduced nuclear access of thyroid hormone. This predicts improvement in tissue manifestations despite persistence of elevated circulating hormone exposure. A trial demonstrating symptom reduction under a fixed suppressive levothyroxine dose tests this peripheral mechanism directly, but it does not test suppression of thyroid synthesis or autoimmune remission. [2]

Vitamin C addresses a different pathway: the gastrointestinal conditions affecting oral levothyroxine exposure. In patients with gastritis, administration in an acidic solution was associated with improved biochemical compensation. Any resulting reduction in TSH may reflect greater delivery of exogenous hormone rather than restoration of thyroid function. [12] Microbiota-directed interventions could, in principle, influence intestinal physiology, nutrient handling, metabolites, or immune signaling. However, clinical studies must distinguish these possibilities, because altered microbiota composition can also follow changes in thyroid status, diet, or concomitant methimazole treatment. An association between microbiome change and improvement is not evidence of its direction or causal mediation. [13]

Clinical Evidence

Hypothyroidism

Botanical Interventions and Symptom Directed Treatment

Table 1 summarizes evidence in general hypothyroidism and explicitly identified indirect populations. In the placebo-controlled ashwagandha trial, 50 participants with TSH of 4.5–10 mIU/L were randomized to root extract or placebo for eight weeks. The extract improved TSH, T3, and T4 measurements. The result is a clinically relevant signal, but the small sample, short exposure, and mild baseline dysfunction do not establish benefit in overt or longstanding autoimmune hypothyroidism. A report of painless thyroiditis associated with the same botanical category also demonstrates why increased thyroid hormone availability cannot always be classified as a desirable effect. [14, 15]

Ginger was studied in 60 patients with persistent symptoms during controlled levothyroxine treatment. Thirty days of supplementation improved selected symptoms and metabolic measurements, placing the intervention in the category of adjunctive symptom management. The study did not demonstrate recovery of gland function or justify withdrawing replacement. [16] A trial involving 72 patients evaluated a mixture of Nigella sativa, Trachyspermum ammi, and Citrus aurantifolia. Anthropometric, depression, and quality-of-life findings were favorable, whereas the accessible results did not establish a convincing hormonal effect. Because this was a mixture, its response should not be attributed to Nigella alone or equated with the separate Hashimoto's trial. [17]

Indian traditional preparations warrant inclusion because they have been evaluated clinically. In a comparative study, TSH decreased by 16.61% in patients receiving Vyoshadi Guggulu and by 26.29% in those receiving Shadushana Churna. However, the difference between treatments was not statistically significant, and only 21 of the 30 registered participants completed treatment. The absence of a placebo or usual-care control, together with substantial attrition, limits attribution of these changes to either preparation. [18] A whole-system Ayurveda trial involving 46 patients with a suboptimal response to stable levothyroxine treatment reported a greater reduction in TSH with the comprehensive program than with Kanchanara Guggulu alone. Because the program combined several therapeutic components, the findings cannot establish the independent efficacy of any individual oral ingredient. [19] In an uncontrolled study involving 15 patients, combined treatment with Triphaladya Guggulu and Punarnavadi improved symptoms, but changes in laboratory measurements were not statistically significant. Reported discontinuation of thyroid medication in this setting does not demonstrate sustained biochemical control or establish that these preparations can safely replace levothyroxine. [20]

Micronutrients Oxidative Outcomes and Intestinal Interventions

In a four-arm trial of 68 overweight or obese hypothyroid women, zinc with or without selenium increased free T3 in selected comparisons, but TSH and free T4 did not show a consistent between-group benefit. These results are compatible with a limited metabolic effect but do not establish correction of thyroid failure. [21] A zinc, magnesium, and vitamin A combination produced free T4 and

inflammatory changes in another small trial. The combination design and emphasis on changes within treatment arms prevent attribution to an individual component and weaken claims of generalized thyroid improvement. [22]

Fermented papaya and alpha-lipoic acid were investigated principally for oxidative stress and vascular physiology. The papaya preparation improved redox measurements during treatment of mild or subclinical hypothyroidism. Alpha-lipoic acid improved flow-mediated dilation in a short study of women with subclinical disease. These are potentially relevant secondary physiological outcomes, but neither study demonstrates prevention of cardiovascular events, reversal of hypothyroidism, or a reduction in replacement requirements. [23, 24]

The vitamin C study provides a more specific pharmacological explanation for a biochemical response. Among 31 patients with hypothyroidism and gastrointestinal pathology, median TSH declined from 11.1 to 4.2 mIU/L during coadministration of vitamin C with levothyroxine, and 17 patients achieved normalization. Its sequential design limits causal certainty, but the population, formulation, and response are coherent with improved replacement exposure. The appropriate inference is an absorption-related adjunct in a selected setting rather than a general thyroid-stimulating action. [12]

Microbiota-directed trials produced a further separation between symptoms and laboratory outcomes. A synbiotic trial involving 56 randomized patients found improvements in selected quality-of-life domains without a significant TSH effect. [25] In the 80-patient VSL#3 study, thyroid function and mean levothyroxine dose did not differ, although the frequency of dose adjustments did. Fewer adjustments may indicate a difference in short-term biochemical stability, but it cannot be equated with lower hormone requirements or recovery of endogenous secretion. These findings also do not establish a probiotic class effect. [26]

Brazil Nuts and Iodine Exposure

The Brazil nut pilot is a positive clinical study in a specific phenotype. Forty selenium-deficient hemodialysis patients consumed one nut daily for three months. T3 increased from 27.3 to 50.2 ng/dL and free T4 increased from 0.87 to 0.98 ng/dL. Nevertheless, T3 remained below the normal range and TSH did not decrease significantly. The measured daily portion supplied approximately 290.5 µg selenium. The findings establish a favorable uncontrolled association in dialysis-associated low-T3 illness and should neither be omitted nor generalized to primary hypothyroidism or Hashimoto's thyroiditis. [6]

Iodine studies demonstrate that nutritional context can reverse the direction of an appropriate intervention. Supplementation with 150 µg/day in mildly iodine-deficient euthyroid adults reduced thyroglobulin without changing TSH or free T4. This supports a nutritional-status effect rather than treatment of established hypothyroidism. [27] Conversely, avoiding iodine-rich products in 33 hypothyroid patients reduced median TSH from 21.9 to 5.3 mIU/L, and 11 became euthyroid. The observational design and population limit generalizability, but the result directly contradicts the assumption that all patients with hypothyroidism require more iodine. It instead identifies iodine-associated reversible dysfunction in a subset. [28]

Hyperthyroidism Outside Confirmed Graves' Disease

Table 2 summarizes the comparatively sparse evidence outside confirmed Graves' disease. The randomized L-carnitine trial enrolled 50 women receiving a fixed TSH-suppressive levothyroxine dose. Doses of 2 or 4 g/day improved or prevented several manifestations of hormone excess during a six-month protocol. Because the hormone exposure was maintained, the design supports an effect on peripheral manifestations. It does not establish control of endogenous hormone synthesis, reduction of arrhythmic events, or remission of an autoimmune process. [2]

An open Lycopus europaeus study reported increased urinary T4 excretion and improvement in selected symptoms. However, eligibility based on TSH below 1 mIU/L encompasses values that may remain within the reference interval. The population is therefore insufficiently specific to infer efficacy in overt hyperthyroidism. The proposed renal mechanism also remains distinct from direct inhibition of the thyroid gland. [29]

A one-month observational study of L-carnitine plus selenium enrolled participants with TSH of 0.1–0.4 mIU/L and positive antibodies. Symptoms improved while the hormonal profile did not. The result is coherent with a peripheral or nonspecific symptomatic effect, but the combination prevents component attribution, and the antibody description does not establish Graves' disease in every participant. The brief follow-up cannot address atrial fibrillation, bone outcomes, or progression of subclinical disease. [30]

Graves' Disease

Selenium and Vitamin D in Graves' Hyperthyroidism

Table 3 distinguishes hyperthyroidism, orbitopathy, and pharmacological iodine. In the 41-patient study of recurrent Graves' hyperthyroidism, selenium added to methimazole was associated with earlier biochemical improvement, lower TRAb, and a favorable remission curve. TRAb at six months was 2.4 versus 5.6 IU/L. The study is relevant because it identifies a specific recurrent-disease population, but its pilot design does not establish that the result extends to newly diagnosed disease or routine long-term supplementation. [31]

GRASS subsequently evaluated 430 participants with newly diagnosed Graves' hyperthyroidism using selenium or placebo for 24–30 months. Nonremission occurred in 54.6% and 53.3%, respectively; the odds ratio was 1.0, with a 95% confidence interval of 0.7–1.5. TRAb and thyroid-related quality of life were also similar. The point estimate provides no support for a remission benefit, while the interval cautions against claiming strict equivalence. The difference between recurrent-disease pilot findings and GRASS may involve population, design, or chance; it does not demonstrate a proven selenium-responsive subgroup. [7]

Vitamin D also failed to improve the clinically meaningful endpoint in DAGMAR. Failure to achieve or sustain remission occurred in 42% of the vitamin D group and 32% of controls, corresponding to a relative risk of 1.30 with a 95% confidence interval of 0.95–1.78. The study does not support benefit, but the interval and endpoint definition do not justify converting the numerical imbalance into an established harmful effect. Its practical contribution is to separate a plausible immunological rationale from demonstrated prevention of Graves' relapse. [32]

Selenium in Orbitopathy

The earlier 159-patient placebo-controlled trial in mild Graves' orbitopathy found improvements in eye-related quality of life and ocular course after six months of selenium. Because participants were euthyroid, the benefit concerns orbital disease rather than control of hormone excess. [5] SeGOSS later investigated a selenium-sufficient setting and found no difference in the primary quality-of-life outcome at six months: the between-group difference was 0.9 points, with a 95% confidence interval from −9.3 to 11.3. Favorable findings at three months were not sustained at the primary endpoint. These trials support a context-dependent interpretation, but nutritional status, disease severity, and trial design differ together, preventing attribution of the disagreement to selenium sufficiency alone. [33]

Combination Products Microbiota and Traditional Formulas

A randomized study of L-carnitine plus selenium added to methimazole in 60 patients found earlier TRAb negativity and lower drug exposure without an overall difference in the trajectory of circulating hormones. The reported hazard ratio for TRAb negativity was 2.35, with a 95% confidence interval of 1.14–4.81. That time-to-event effect is not equivalent to a remission probability. The absence of placebo, inability to isolate components, short treatment-free remission criterion, and internally inconsistent remission totals limit disease-modifying conclusions. [34]

The small Bifidobacterium longum study reported normalization of TRAb with adjunctive treatment and concurrent microbiome changes. The reported treatment groups sum to 26 participants, whereas another passage reports 25. [13] Berberine added to methimazole also produced favorable biochemical and microbiome findings in a small comparative study. Possible shared controls between these reports require clarification before they are treated as independent evidence. In both cases, background antithyroid treatment and limited allocation information prevent confident attribution of the response to microbiota modulation. [35]

Pingkang was studied in a multicenter, double-blind, three-arm trial with 186 randomized participants and 150 in the efficacy analysis. Hormone concentrations declined in all treatment arms, with selected antibody and symptom benefits reported for combination therapy. The difference between randomized and analyzed populations requires attention, and within-group significance cannot establish that botanical monotherapy is noninferior to methimazole. [36] For Prunella vulgaris or Xiakucao, a systematic review summarized 17 studies involving 1,366 patients and reported favorable hormonal, antibody, and other outcomes with add-on treatment. However, the review itself judged the underlying evidence weak. Its aggregate findings identify a research signal and a broader regional literature, not confirmation that heterogeneous preparations have an established class effect. Because the synthesis pooled hyperthyroidism studies, its results cannot be assumed to apply exclusively to confirmed Graves' disease. [37]

Pharmacological Iodine

Lugol solution has a different dose range, mechanism, and clinical purpose from nutritional iodine repletion. In a 27-patient rescue series, free T4 fell from 53 to 20 pmol/L and free T3 from 20 to 6.5 pmol/L after five to nine days before definitive treatment. Adverse effects occurred in four patients. This is evidence of rapid biochemical suppression in a selected preoperative setting, with limitations inherent to an uncontrolled series. [38]

The 56-patient randomized preoperative trial reported hormonal suppression but no significant improvement in its principal blood-loss outcome, vascularity, operating time, or morbidity. Median blood loss was 80.5 versus 94 mL and operating time was 75 minutes in both groups. Thus, a biological effect did not translate into demonstrated surgical superiority. [39] In the 504-patient Japanese potassium iodide cohort, free T4 became normal or low in 83.7%; 92 patients developed a high-TSH hypothyroid response. Escape and resistance required additional management. The composite normal-or-low free T4 outcome therefore cannot be presented as an 83.7% rate of stable euthyroidism or cure. [3]

Hashimoto's Thyroiditis

Selenium from Pooled Biomarkers to Clinical Outcomes

Table 4 summarizes the autoimmune-thyroiditis evidence. The selenium meta-analysis included 35 unique studies. Among patients not receiving replacement, the pooled TSH effect was small, with a standardized mean difference of −0.21 and a 95% confidence interval of −0.43 to −0.02. TPOAb showed a larger standardized reduction of −0.96, but heterogeneity was substantial at $I^2 = 90\%$. Free T4, free T3, thyroglobulin antibodies, and thyroid volume did not show significant overall changes. The standardized antibody effect cannot be translated into a universal absolute reduction or a probability of clinical improvement because assays, baselines, and populations differ. [1]

CATALYST directly addressed whether selenium improves the experience of treated autoimmune hypothyroidism. Among 412 randomized adults, 332 completed the intervention. At 12 months, thyroid-related composite quality-of-life scores were similar with selenium and placebo, approximately 28.8 and 28.0, while TPOAb was lower in the selenium group. Levothyroxine requirements and the free T3/free T4 ratio did not improve. Stratification by baseline selenium status, antibody level, or disease duration did not reveal a significant change in the main conclusion. The trial therefore provides direct evidence that an antibody response need not produce measurable symptomatic or replacement-dose benefit. [4]

The regulatory T-cell findings in the 90-patient selenium-yeast trial remain biologically informative, especially because a larger TSH response was reported in the subclinical subgroup. However, the subgroup signal and cellular measurements require replication under placebo-controlled conditions. Together, the meta-analysis, mechanistic study, and CATALYST address different questions: average biomarker response, possible immune pathways, and clinically relevant benefit during hormone replacement. They should be integrated without treating any one outcome as a substitute for the others. [9]

Myo Inositol Aloe Vera and Nigella Sativa

In a comparative study involving 168 patients, myo-inositol plus selenium produced favorable TSH, antibody, free T4, and well-being findings relative to selenium alone. However, entry TSH of 3–6 mIU/L encompasses both mild elevation and values within some reference intervals. The term restoration of euthyroidism therefore requires patient-level baseline classification and a predefined biochemical

threshold. An active selenium comparator tests incremental benefit from the combination but not its absolute benefit over an inactive preparation. The study does not establish prevention of overt hypothyroidism or durable avoidance of levothyroxine. [10]

The Aloe study involved 30 treated women with subclinical autoimmune hypothyroidism and a nonrandomized untreated comparison group. TSH decreased from 5.19 to 2.01 mIU/L, TPOAb by approximately 56%, and free T4 increased. Free T3, however, decreased by approximately 16%. This pattern is not evidence that all components of thyroid hormone metabolism improved uniformly, and an increased free T4/free T3 ratio cannot establish direct inhibition of deiodination without more specific measurement. The abstract also differs internally on dose, describing 50 mL/day in the methods and 100 mL/day in its conclusion. Despite the favorable TSH result, nonrandomization, baseline mild dysfunction, and formulation uncertainty preclude a definitive replacement claim. [40]

Nigella sativa was tested as an adjunct to stable levothyroxine in a double-blind trial, with 40 of 47 randomized participants completing eight weeks. Lower TSH and TPOAb and higher T3 were reported, together with anthropometric changes. Three active-group withdrawals were associated with itching and nausea. Its randomized design makes the signal more informative than an uncontrolled before-and-after observation, but the small sample, brief follow-up, and concomitant replacement still leave long-term clinical benefit unresolved. [41]

Vitamin D and Emerging Preparations

In an Indian randomized open study, 100 analyzed patients with autoimmune thyroid disease showed a TPOAb reduction of 46.73% with vitamin D versus 16.6% with control treatment. Vitamin D insufficiency was present in 93%, making deficiency correction an important part of the interpretation. [42] In contrast, a placebo-controlled trial of 42 women with Hashimoto's thyroiditis did not show a significant between-group TPOAb benefit, despite some favorable within-group changes in TSH or thyroglobulin antibodies. These findings do not establish uniform disease modification by vitamin D, but they also do not justify ignoring nutritional deficiency when present. [43]

Curcumin added to an anti-inflammatory diet in a 57-patient trial reduced TPOAb compared with placebo, whereas adjusted thyroid-function differences were nonsignificant. The trial estimates the additional effect of curcumin within that dietary program, not a combined treatment effect relative to usual care. [44] Genistein was associated with hormonal and antibody changes and changes in interferon-γ and interleukin-2 consistent with a proposed Th1-related action. However, cytokine changes measured alongside clinical outcomes do not prove mechanistic mediation, and the discrepancy between enrolled and completing populations requires scrutiny. [45]

Additional studies evaluated an enzyme-containing supplement, Lactiplantibacillus plantarum 299v, Chaihu Xuanfuhua decoction, selenium yeast plus vitamin D, and resveratrol. The enzyme study was open and did not isolate components. [46] The probiotic study reported quality-of-life benefits during nutritional education without improvement in TPOAb or body mass index, supporting a potentially non-antibody-mediated symptomatic pathway. [47] Regional Chinese studies reported selected hormonal or antibody benefits with the decoction and selenium–vitamin D combination, but incomplete formulation and methodological information limit quantitative interpretation. [48, 49] Resveratrol was investigated in euthyroid autoimmune thyroiditis with ischemic heart disease, providing indirect evidence for overt hypothyroidism rather than proof of reversal of gland failure. [50]

Discussion

Distinct Therapeutic Mechanisms Require Distinct Efficacy Claims

The principal scientific implication is that nutraceutical interventions act, or are proposed to act, at different levels of the thyroid system. An intervention may alter substrate availability, redox balance, immune activity, gland responsiveness, gastrointestinal drug exposure, or tissue response to circulating hormones. These are separate causal pathways. Their clinical evaluation should therefore begin with a specified mechanism and target population rather than a broad expectation of thyroid improvement.

The available studies illustrate why this framework matters. Brazil nuts changed thyroid hormone measurements in selenium-deficient dialysis patients; vitamin C improved biochemical compensation during continued levothyroxine; L-carnitine improved manifestations during maintained exogenous hormone exposure; and selenium changed antibodies without improving the principal clinical outcomes in CATALYST. Each result may be valid within its own estimand, but none can be substituted for the others. A review that labels all such outcomes as successful treatment of hypothyroidism or hyperthyroidism would overstate the evidence. [2, 4, 6, 12]

The distinction also changes how combination trials should be interpreted. A myo-inositol–selenium preparation may show incremental benefit over selenium, yet this does not identify the relative contribution of both components compared with no supplementation. A curcumin trial with dietary treatment in both arms estimates the curcumin effect conditional on that diet. A whole-system Ayurveda program estimates the effect of a therapeutic package. These designs answer legitimate but different questions and cannot support ingredient-specific claims without additional comparisons. [10, 19, 44]

The Antibody Response and Clinical Benefit Are Biologically Separable

Autoantibodies serve different roles in Hashimoto's and Graves' disease. TPOAb reflects thyroid autoimmunity, but its circulating concentration is not a direct measure of viable follicular mass or of an individual's capacity to maintain euthyroidism. Reducing an immune marker may occur after substantial tissue damage has already taken place. Consequently, even a true antibody-lowering effect may have little influence on replacement requirements in established hypothyroidism. This interpretation is consistent with the dissociation between antibody and clinical outcomes in CATALYST rather than proof that selenium has no biological activity. [4]

TRAb has a closer relationship to the pathogenic stimulation underlying Graves' hyperthyroidism, but an observed fall during methimazole treatment still requires careful attribution. The relevant treatment effect is the difference in a prespecified outcome between randomized groups, and the relevant disease-modifying endpoint is sustained remission

after withdrawal of antithyroid treatment. An earlier time to TRAb negativity may be prognostically interesting without establishing a reduced probability of relapse. GRASS and the smaller L-carnitine–selenium study therefore cannot be reconciled simply by comparing whether antibodies decreased. Their designs, combination exposures, and remission definitions differ. [7, 34]

Mechanistic immune observations require the same discipline. Increased activated regulatory T cells or altered Th1-associated cytokines are compatible with immunomodulation, but mediation requires more than a significant association after treatment. Temporality, specificity, and analysis linking the proposed mediator to the outcome are needed. Otherwise, the immune measurement may be an associated response or a consequence of changing disease activity. Clinical mechanistic studies are valuable, but they should generate testable pathways rather than be used to infer efficacy beyond the outcomes measured. [9, 45]

Statistical Significance Does Not Define Clinical Relevance

The selenium meta-analysis illustrates the difference between a statistically detectable change and a clinically interpretable effect. A standardized TSH difference of −0.21 is a small average separation on a scale expressed in standard deviations, not an absolute change in mIU/L. It does not establish how many patients crossed a clinically meaningful threshold or avoided future replacement. For TPOAb, the larger standardized effect coexisted with I^2 of 90%, indicating substantial inconsistency in relative study findings. A pooled result under this degree of heterogeneity requires explanation of populations and methods rather than a universal efficacy statement. [1]

Multiple outcomes and time points create further interpretive problems. A trial may yield a favorable secondary marker or a short-lived response while remaining negative for its principal endpoint. In SeGOSS, selected three-month findings did not translate into superiority on the primary six-month quality-of-life outcome. In the Lugol surgical trial, reduced hormone measurements did not translate into less bleeding or lower morbidity. Both patterns show why the hierarchy and timing of outcomes must be retained in the synthesis. [33, 39]

Failure to reach statistical significance also has different implications depending on precision. GRASS provides a reasonably informative estimate centered near no remission benefit, but its confidence interval does not prove exact equivalence. DAGMAR does not establish benefit, yet its numerical excess of failures is not sufficient to establish harm. Small nutraceutical trials often produce much wider uncertainty than either study. Their negative results should be described as inconclusive when imprecise, while their positive results require attention to the same instability and to possible multiplicity. [7, 32]

Within-group improvement is particularly vulnerable to overinterpretation. Patients selected because of an elevated TSH may have a lower value on repeat measurement even without an effective intervention. Symptoms may improve through contextual care, adherence, or expectations. Concurrent thyroid medication can dominate the biological response. Therefore, the relevant contrast is usually the baseline-adjusted difference between groups, with its confidence interval, rather than significance before and after treatment in one group. The active-comparator Guggulu trial and three-arm Pingkang trial illustrate why improvement in all arms does not establish efficacy over no treatment or noninferiority to standard therapy. [18, 36]

Nutritional Status Phenotype and Transportability

Biological responsiveness is likely to depend on what is limiting function at baseline. Selenium deficiency in dialysis, vitamin D insufficiency in autoimmune thyroid disease, and iodine excess in reversible hypothyroidism are different phenotypes. Correcting one abnormality cannot be generalized to supplementation of an already sufficient population. Likewise, the thyroid may retain substantial functional reserve in mild subclinical disease but little recoverable output after extensive autoimmune destruction. Trials should characterize these states prospectively rather than rely on a broad diagnosis alone. [6, 28, 42]

However, a plausible effect modifier should not be declared established because one study was positive and another negative. The orbitopathy trials differ in selenium environment but also in other aspects of eligibility and design. Cross-trial comparisons cannot isolate the nutritional explanation. CATALYST did not demonstrate a different primary conclusion after stratification by baseline selenium status, which further cautions against assuming that every discordant result can be explained by deficiency. A credible precision-treatment claim requires a prespecified interaction, adequate power, and external replication. [4, 5, 33]

Diagnostic thresholds also determine transportability. A TSH range of 3–6 mIU/L does not define the same population as overt hypothyroidism, while TSH below 1 mIU/L does not necessarily define hyperthyroidism. The thyroid axis, reference interval, assay, age distribution, and ongoing treatment all affect interpretation. Studies using broad or nonstandard thresholds may still inform symptom or physiological hypotheses, but their findings should not be transferred to patients with more severe disease merely because the authors use the same diagnostic label. [10, 29]

Product Identity and Safety Are Part of the Causal Question

The intervention must be sufficiently defined for its effects to be reproducible. Brazil nuts vary in selenium content, making one nut an unreliable universal dose unit. The concentration measured in the dialysis intervention cannot be applied automatically to other food sources. Probiotic findings belong to a strain and formulation rather than to all probiotics. Botanical preparations vary by plant material, extraction, dose, and coingredients; a multicomponent formula may also contain ingredients with competing actions. These issues affect both external validity and the interpretation of apparently conflicting studies. [6, 26, 36]

Safety cannot be inferred from the adjective natural or from the absence of events in a small trial. The ashwagandha-associated thyroiditis case, active-group withdrawals with Nigella, and adverse events during Lugol rescue treatment document different categories of risk. Small trials can identify common intolerance but have limited capacity to detect rare hepatic, endocrine, or interaction-related harms. A benefit assessment should therefore include formulation, exposure duration, coadministered drugs, and adverse-event ascertainment rather than compare reported symptom improvements alone. [15, 38, 41]

Iodine is especially informative because its direction of effect depends on dose and context. Nutritional replacement

addresses substrate inadequacy; pharmacological iodide can suppress thyroid activity; persistent exposure can be followed by escape or hypothyroidism. The 504-patient iodide cohort therefore supports a monitored treatment strategy in a defined Graves' population, not unrestricted supplementation for autoimmune thyroid disease. The iodine-restriction study demonstrates the converse situation, in which reducing exposure improved function. These findings are coherent when the intervention is defined physiologically rather than grouped under iodine supplementation. [3, 28]

Implications for Clinical Interpretation

The current evidence is most useful when organized into therapeutic roles. Nutritional repletion may be appropriate to a documented inadequacy, but that indication is separate from disease modification. Absorption-directed interventions may improve the effectiveness of ongoing levothyroxine without changing the underlying gland disorder. Symptom-directed interventions may improve well-being without normalizing hormones, while an immunological signal may not alter either symptom burden or replacement requirements. The literature supports discussing these possibilities individually, with different thresholds of evidence for each proposed clinical claim.

Substitution for indicated thyroid treatment requires stronger evidence than adjunctive benefit. The necessary outcome would include maintained biochemical control under a prespecified medication-reduction protocol, adequate observation after withdrawal, and assessment of clinical safety. A small uncontrolled study reporting lower TSH or reduced drug use cannot establish these conditions. Similarly, desiccated thyroid extract is not evidence for successful hormone-free treatment. In the 75-patient crossover study, overall outcomes were similar across hormone regimens, with exploratory signals in the most symptomatic subgroup. Because the extract supplies T3 and T4, the trial concerns alternative hormone delivery, not nutraceutical replacement of hormone therapy. [8]

Research Priorities and Limitations

Future research should specify whether the objective is biochemical normalization, preservation of thyroid reserve, reduction of symptoms, improvement of orbitopathy, or sustained remission. Hashimoto's trials should distinguish euthyroid autoimmunity from untreated subclinical dysfunction and established replacement dependence. Graves' trials should define remission after antithyroid withdrawal and follow participants long enough to detect relapse. Where medication adjustment is an outcome, clinicians should follow a common blinded algorithm so that lower prescribed doses do not merely reflect discretionary management. Candidate benefits from Aloe, Nigella, myo-inositol combinations, and microbiota-directed treatment warrant independent replication under these conditions. [10, 13, 40, 41]

Standardized preparations, baseline nutrient measurements, repeated thyroid assessment, prespecified primary outcomes, and complete adverse-event reporting are essential. Factorial or component-controlled designs would clarify combination effects. Mechanistic substudies should be embedded within adequately powered clinical trials, with mediation analyses specified prospectively when appropriate. An observed change in a biomarker should lead to a test of the proposed pathway rather than serve as its confirmation.

This review retains a broad clinical scope and includes regional evidence, but its retrieval was directed rather than a completed systematic process. The selective bibliography emphasizes pivotal studies, representative intervention reports, and syntheses of larger research bodies. Some regional publications remain incompletely characterized, and no formal risk-of-bias or certainty ratings were assigned. Consequently, the review cannot establish an exhaustive inventory, quantify all intervention effects, or rank preparations with a common certainty scale. Its contribution is a mechanistically informed interpretation of the available clinical signals and their practical limits.

Proposed Clinical Framework for Adjunctive Nutraceutical Use

The available evidence supports a selective approach to adjunctive nutraceutical use based on thyroid disease etiology, functional status, nutritional context, and the outcome being targeted. Before selecting an intervention, clinicians should review conventional treatment, current supplement exposure, potential absorption problems, and clinically relevant nutritional deficiencies. The options discussed below include interventions with preliminary signals for symptoms, thyroid function, autoantibodies, or other surrogate outcomes; these endpoints should not be considered interchangeable. Tables 1–4 summarize the studied populations, doses, treatment durations, outcomes, and limitations. The proposed pathways represent an interpretation of the available literature by the authors and have not been prospectively validated. Individual substances have been investigated, but their inclusion within a broader decision framework does not establish the efficacy or safety of combining them. Nutraceuticals should remain adjuncts to indicated thyroid hormone replacement, antithyroid treatment, and management of clinically significant orbitopathy.

Hypothyroidism

In overt hypothyroidism, appropriate levothyroxine treatment remains the initial priority, together with assessment of adherence, administration timing, interacting substances, and gastrointestinal conditions that may impair absorption. Subsequent nutraceutical selection should address a defined residual problem. For persistent symptoms despite biochemical euthyroidism, ginger at 500 mg twice daily for 30 days produced symptomatic improvements in a small placebo-controlled trial and represents a candidate for further evaluation. Its proposed role is adjunctive symptom management, rather than restoration of thyroid hormone production. [16] In patients with gastrointestinal pathology and suspected impaired levothyroxine absorption, vitamin C at 500 mg taken with levothyroxine has supportive findings from a small sequential study. Thyroid function requires reassessment because improved absorption may change replacement requirements. [12]

Micronutrient interventions should be considered in their nutritional context. Zinc, alone or combined with selenium, and a combination of zinc, magnesium, and vitamin A produced selected biochemical or inflammatory changes, but these studies do not establish reliable reversal of hypothyroidism or identify which component accounts for the observed effects. [21, 22] Brazil nuts also warrant consideration within the evidence map: one nut daily improved selected thyroid hormone measurements in

selenium-deficient hemodialysis patients, although this population provides indirect evidence for primary hypothyroidism. Their highly variable selenium content prevents extrapolation of the study exposure to a standardized daily nut prescription. [6] Fermented papaya and alpha-lipoic acid have been studied for oxidative balance and endothelial function, respectively; these findings support investigation of associated metabolic disturbances rather than a claim of thyroid recovery. [23, 24] Synbiotic preparations have shown selected patient-reported benefits, whereas probiotic findings do not establish a consistent improvement in thyroid function or levothyroxine requirements. [25, 26]

Additional botanical candidates include ashwagandha and Indian traditional preparations. Ashwagandha root extract at 600 mg/day for eight weeks improved thyroid measurements in a small subclinical hypothyroidism trial, but reported thyrotoxicosis requires particular caution and prevents its presentation as a routine treatment option. [14, 15] Guggulu-based preparations and whole-system Ayurveda programs have also produced selected symptom or TSH signals, although active comparators, attrition, small samples, and multicomponent treatment packages limit attribution of benefit. [18–20] The interventions relevant to hypothyroidism and related clinical settings are summarized in Table 1, and their proposed placement within an adjunctive assessment pathway is illustrated in Figure 1.

Hashimoto Thyroiditis

Management should distinguish euthyroid autoimmunity, subclinical hypothyroidism, and overt hypothyroidism. In euthyroid patients, functional surveillance is generally more relevant than treatment directed exclusively at antibody concentrations. For selected adults with mild subclinical hypothyroidism who do not otherwise require immediate levothyroxine treatment, myo-inositol plus selenium represents a studied investigational combination. The reported regimen of myo-inositol 600 mg plus selenium 83 µg daily for six months requires verification of product composition and the original dosing instructions before implementation. Favorable biochemical findings do not establish durable prevention of gland failure or avoidance of future hormone replacement. [10] Selenium alone may reduce antibody concentrations, but CATALYST demonstrated that this response did not translate into improved quality of life or reduced levothyroxine requirements. [4]

Other candidates broaden the research options available for Hashimoto thyroiditis. Nigella sativa seed powder at 2 g/day for eight weeks produced short-term improvements in TSH and antibody measurements, supporting further investigation without establishing sustained disease modification. [41] Curcuminoids administered alongside an anti-inflammatory diet reduced TPOAb concentrations in a randomized trial, but the adjusted thyroid-function findings did not demonstrate recovery of gland function. [44] Lactiplantibacillus plantarum 299v produced selected quality-of-life benefits without a corresponding TPOAb benefit, suggesting a possible symptom-directed role that requires distinction from an autoimmune or hormonal effect. [47] Vitamin D findings are mixed; correction of deficiency remains conceptually separate from prescribing vitamin D specifically to modify Hashimoto thyroiditis. [42, 43]

Aloe vera produced a preliminary functional and antibody signal in a nonrandomized study, but the discrepancy between the dose reported in the abstract and that described in the methods limits its inclusion in a reproducible dosing pathway. [40] Genistein, enzyme-containing preparations, Chaihu Xuanfuhua decoction, selenium yeast combined with vitamin D, and resveratrol have also been investigated. Their findings justify inclusion in the evidence map, but limitations involving dose verification, study design, population applicability, or component attribution prevent their positioning as established treatment choices. [45, 46, 48–50] Table 4 presents the Hashimoto-specific evidence and study regimens; Figure 1 distinguishes nutritional correction, symptom-directed adjuncts, and exploratory functional or antibody targets.

Graves Disease

Nutraceutical selection should distinguish control of hyperthyroidism from treatment of thyroid-associated orbitopathy. For Graves hyperthyroidism, routine selenium supplementation is not supported as a remission-inducing strategy by the negative GRASS findings. [7] Vitamin D should similarly be selected for an appropriate nutritional or skeletal indication rather than an expectation of improved Graves remission. [32] Mild, active orbitopathy of recent onset constitutes a separate clinical setting in which a six-month course of selenium may be considered, particularly in regions of selenium insufficiency. The formulation and dose must correspond to the intended regimen, and this ocular indication should not be extrapolated to moderate-to-severe or sight-threatening disease. [5]

Several additional interventions can be identified as exploratory adjuncts to conventional Graves treatment. L-carnitine combined with selenium produced favorable antibody and treatment-related findings in a small randomized study, but the design does not establish superiority over either component alone. [34] Berberine and Bifidobacterium longum, each investigated alongside methimazole, produced selected biochemical, antibody, or microbiome findings. These small studies support further trials rather than routine use or substitution for antithyroid medication. [13, 35] Pingkang granules have been evaluated in a multicenter trial, with selected symptom and antibody findings, although improvement within treatment groups does not establish comparative superiority. [36] Prunella vulgaris preparations have favorable pooled adjunctive findings, but methodological limitations and variation in formulations and doses restrict their clinical interpretation. [37] These Graves-related interventions, including the distinction between ocular and thyroid outcomes, are detailed in Table 3 and organized into proposed clinical and research pathways in Figure 2.

Other Causes of Hyperthyroidism or Thyrotoxicosis

Treatment should remain etiologically directed. In iatrogenic thyrotoxicosis, correction of excessive thyroid hormone exposure is the primary intervention. L-carnitine at 2–4 g/day improved selected peripheral manifestations in a small randomized trial and represents a possible specialist-supervised symptomatic adjunct. These findings do not demonstrate suppression of thyroid hormone synthesis or

autoimmune remission. [2] A lower-dose combination of L-carnitine and selenium has also shown a short-term symptomatic signal in subclinical hyperthyroidism, without corresponding hormonal improvement or a definitive etiological classification. [30] Lycopus europaeus has preliminary clinical findings, but uncertainty regarding the administered regimen and the studied population prevents its incorporation into a reproducible treatment pathway. [29] Evidence remains insufficient to propose a standardized nutraceutical combination for toxic nodular disease or destructive thyroiditis. Pharmacological iodine, including Lugol solution and potassium iodide, belongs to specific medical treatment pathways and should be distinguished from nutritional iodine supplementation. [3, 38, 39] Table 2 summarizes the evidence for non-Graves-specific hyperthyroidism and thyrotoxicosis, while Figure 2 places these options within an etiologically directed framework.

Combination Selection and Reassessment

The proposed figures provide a range of options for individualized assessment and future investigation; they do not imply that all listed substances should be prescribed together. Myo-inositol plus selenium and L-carnitine plus selenium are examples of combinations that have been studied in particular thyroid settings. [10, 34] By contrast, adding ginger, Nigella sativa, curcuminoids, probiotics, or other ingredients to these combinations would generate a new regimen whose efficacy, interactions, and cumulative exposure have not been established in the cited trials. Where an adjunct is considered, selection should follow a defined target outcome, a verifiable formulation and dose, and a planned reassessment point. Overlapping selenium and iodine exposure should be avoided, and Brazil nuts should not be treated as a precisely dosed selenium preparation. Symptoms, thyroid function, tolerability, and treatment requirements should guide reassessment; antibody reduction alone should not justify withdrawal of conventional therapy. Lack of meaningful benefit, adverse effects, or deterioration in thyroid function should prompt discontinuation and clinical review.

Conclusions

Nutraceutical research in thyroid disease demonstrates several biological and clinical signals, but the strongest interpretation is intervention-specific and outcome-specific. Selenium can alter selected immune measurements without consistently improving thyroid-related quality of life, replacement requirements, or Graves' remission. Myo-inositol plus selenium, Aloe vera, Nigella sativa, and several botanical or microbiota-directed preparations remain candidates for further controlled investigation. Brazil nuts have positive clinical evidence in selenium-deficient dialysis patients, which is indirect for primary hypothyroidism and Hashimoto's thyroiditis. L-carnitine chiefly addresses peripheral manifestations of hormone excess, and pharmacological iodine has a distinct role in selected Graves' settings. Scientific appraisal should distinguish nutrient repletion, symptom management, altered drug exposure, and disease modification, requiring durable patient-relevant outcomes before claims of treatment substitution.

References

1. Huwiler VV, Maissen-Abgottspon S, Stanga Z, Mühlebach S, Trepp R, Bally L, Bano A. Selenium Supplementation in Patients with Hashimoto's Thyroiditis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Thyroid. 2024 Mar;34(3):295-313. doi: 10.1089/thy.2023.0556. Epub 2024 Feb 16. PMID: 38243784; PMCID: PMC10951571.
2. Benvenga S, Ruggeri RM, Russo A, Lapa D, Campenni A, Trimarchi F. Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2001 Aug;86(8):3579-94. doi: 10.1210/jcem.86.8.7747. PMID: 11502782.
3. Okamura K, Sato K, Fujikawa M, Bandai S, Ikenoue H, Kitazono T. Iodide-sensitive Graves'' hyperthyroidism and the strategy for resistant or escaped patients during potassium iodide treatment. Endocr J. 2022 Aug 29;69(8):983-997. doi: 10.1507/endocrj.EJ21-0436. Epub 2022 Mar 24. PMID: 35321988.
4. 4Larsen C, Winther KH, Cramon PK, Rasmussen ÅK, Feldt-Rasmusssen U, Knudsen NJ, Bjorner JB, Schomburg L, Demircan K, Chillon TS, Gram J, Hansen SG, Brandt F, Nygaard B, Watt T, Hegedus L, Bonnema SJ. Selenium supplementation and placebo are equally effective in improving quality of life in patients with hypothyroidism. Eur Thyroid J. 2024 Feb 5;13(1):e230175. doi: 10.1530/ETJ-23-0175. PMID: 38215286; PMCID: PMC10895332.
5. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, Nardi M, Pitz S, Boboridis K, Sivelli P, von Arx G, Mourits MP, Baldeschi L, Bencivelli W, Wiersinga W; European Group on Graves'' Orbitopathy. Selenium and the course of mild Graves'' orbitopathy. N Engl J Med. 2011 May 19;364(20):1920-31. doi: 10.1056/NEJMoa1012985. PMID: 21591944.
6. Barcza Stockler-Pinto M, Carrero JJ, De Carvalho Cardoso Weide L, Franciscato Cozzolino SM, Mafra D. EFFECT OF SELENIUM SUPPLEMENTATION VIA BRAZIL NUT (BERTHOLLETIA EXCELSA, HBK) ON THYROID HORMONES LEVELS IN HEMODIALYSIS PATIENTS: A PILOT STUDY. Nutr Hosp. 2015 Oct 1;32(4):1808-12. doi: 10.3305/nh.2015.32.4.9384. PMID: 26545554.
7. Cramon PK, Winther KH, Boesen VB, Larsen CB, Bjorner JB, Nordqvist SF, Forman JL, Juul AB, Bach-Mortensen P, Knudsen N, Nolsøe RL, Vilsbøll T, Andries A, Gram J, Nygaard B, Demircan K, Chillon TS, Schomburg L, Hegedüs L, Bonnema SJ, Feldt-Rasmussen U, Rasmussen ÅK, Watt T. Selenium supplementation in individuals with newly diagnosed Graves'' hyperthyroidism: a double-blind, multi-centre RCT. Eur Thyroid J. 2026 Jan 6;15(1):ETJ250264. doi: 10.1530/ETJ-25-0264. PMID: 41384622; PMCID: PMC13156667.
8. Shakir MKM, Brooks DI, McAninch EA, Fonseca TL, Mai VQ, Bianco AC, Hoang TD. Comparative

Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine+Liothyronine in Hypothyroidism. J Clin Endocrinol Metab. 2021 Oct 21;106(11):e4400-e4413. doi: 10.1210/clinem/dgab478. PMID: 34185829; PMCID: PMC8530721.

9. Hu Y, Feng W, Chen H, Shi H, Jiang L, Zheng X, Liu X, Zhang W, Ge Y, Liu Y, Cui D. Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. Clin Transl Sci. 2021 Jul;14(4):1390-1402. doi: 10.1111/cts.12993. Epub 2021 Apr 9. PMID: 33650299; PMCID: PMC8301566.
10. Nordio M, Basciani S. Myo-inositol plus selenium supplementation restores euthyroid state in Hashimoto's patients with subclinical hypothyroidism. Eur Rev Med Pharmacol Sci. 2017 Jun;21(2 Suppl):51-59. PMID: 28724185.
11. Palinkas LA, Reedy KR, Smith M, Anghel M, Steel GD, Reeves D, Shurtleff D, Case HS, Van Do N, Reed HL. Psychoneuroendocrine effects of combined thyroxine and triiodothyronine versus tyrosine during prolonged Antarctic residence. Int J Circumpolar Health. 2007 Dec;66(5):401-17. PMID: 18274206.
12. Jubiz W, Ramirez M. Effect of vitamin C on the absorption of levothyroxine in patients with hypothyroidism and gastritis. J Clin Endocrinol Metab. 2014 Jun;99(6):E1031-4. doi: 10.1210/jc.2013-4360. Epub 2014 Mar 6. PMID: 24601693.
13. Huo D, Cen C, Chang H, Ou Q, Jiang S, Pan Y, Chen K, Zhang J. Probiotic Bifidobacterium longum supplied with methimazole improved the thyroid function of Graves'' disease patients through the gut-thyroid axis. Commun Biol. 2021 Sep 7;4(1):1046. doi: 10.1038/s42003-021-02587-z. PMID: 34493790; PMCID: PMC8423791.
14. Sharma AK, Basu I, Singh S. Efficacy and Safety of Ashwagandha Root Extract in Subclinical Hypothyroid Patients: A Double-Blind, Randomized Placebo-Controlled Trial. J Altern Complement Med. 2018 Mar;24(3):243-248. doi: 10.1089/acm.2017.0183. Epub 2017 Aug 22. PMID: 28829155.
15. Hayashi M, Hamada H, Azuma SI, Hayashi K. Painless Thyroiditis by Withania somnifera (Ashwagandha). Cureus. 2024 Mar 1;16(3):e55352. doi: 10.7759/cureus.55352. PMID: 38559552; PMCID: PMC10981964.
16. Ashraf H, Heydari M, Shams M, Zarshenas MM, Tavakoli A, Sayadi M. Efficacy of Ginger Supplementation in Relieving Persistent Hypothyroid Symptoms in Patients with Controlled Primary Hypothyroidism: A Pilot Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Evid Based Complement Alternat Med. 2022 Jan 20;2022:5456855. doi: 10.1155/2022/5456855. PMID: 35096113; PMCID: PMC8794674.
17. Javidi N, Mazloum Khorasani Z, Salari R, Niroumand S, Yousefi M. Investigation the effect of a herbal composition based on blackseed on patients with primary hypothyroidism: A randomized controlled trial. Avicenna J Phytomed. 2024 May-Jun;14(3):325-337. doi: 10.22038/AJP.2024.23984. PMID: 39086868; PMCID: PMC11287032.
18. Sharma VB, Padhar BC, Meena HML, Mathur SK. Efficacy of *Vyoshadi Guggulu* and *Shadushana Churna* in the management of subclinical hypothyroidism: An open labelled randomized comparative pilot clinical trial. Ayu. 2020 Jul-Sep;41(3):181-187. doi: 10.4103/ayu.ayu_359_20. Epub 2022 Feb 24. PMID: 35370380; PMCID: PMC8966764.
19. Vivek, Chougale A, Joshi H, Tubaki BR. Add on effect of Whole System Ayurveda protocol in suboptimal controlled Primary Hypothyroidism - A randomized controlled trial. J Ayurveda Integr Med. 2025 Jan-Feb;16(1):101052. doi: 10.1016/j.jaim.2024.101052. Epub 2025 Jan 10. PMID: 39798266; PMCID: PMC11773014.
20. Singh K, Thakar AB. A clinical study to evaluate the role of *Triphaladya Guggulu* along with *Punarnavadi Kashaya* in the management of hypothyroidism. Ayu. 2018 Jan-Mar;39(1):50-55. doi: 10.4103/ayu.AYU_62_17. PMID: 30595635; PMCID: PMC6287405.
21. Mahmoodianfard S, Vafa M, Golgiri F, Khoshniat M, Gohari M, Solati Z, Djalali M. Effects of Zinc and Selenium Supplementation on Thyroid Function in Overweight and Obese Hypothyroid Female Patients: A Randomized Double-Blind Controlled Trial. J Am Coll Nutr. 2015;34(5):391-9. doi: 10.1080/07315724.2014.926161. Epub 2015 Mar 11. PMID: 25758370.
22. Rabbani E, Golgiri F, Janani L, Moradi N, Fallah S, Abiri B, Vafa M. Randomized Study of the Effects of Zinc, Vitamin A, and Magnesium Co-supplementation on Thyroid Function, Oxidative Stress, and hs-CRP in Patients with Hypothyroidism. Biol Trace Elem Res. 2021 Nov;199(11):4074-4083. doi: 10.1007/s12011-020-02548-3. Epub 2021 Jan 7. PMID: 33409923.
23. Tomella C, Catanzaro R, Illuzzi N, Cabeca A, Zerbinati N, Celep G, Milazzo M, Sapienza C, Italia A, Lorenzetti A, Marotta F. The hidden phenomenon of oxidative stress during treatment of subclinical-mild hypothyroidism: a protective nutraceutical intervention. Rejuvenation Res. 2014 Apr;17(2):180-3. doi: 10.1089/rej.2013.1495. Epub 2014 Apr 8. PMID: 24050492; PMCID: PMC3995355.
24. G D X, J H P, H L S, L S Z. Alpha-lipoic acid improves endothelial dysfunction in patients with subclinical hypothyroidism. Exp Clin Endocrinol Diabetes. 2010 Oct;118(9):625-9. doi: 10.1055/s-0029-1237702. Epub 2010 Feb 16. PMID: 20162509.
25. Ramezani M, Reisian M, Sajadi Hezaveh Z. The effect of synbiotic supplementation on hypothyroidism: A randomized double-blind placebo controlled clinical trial. PLoS One. 2023 Feb 6;18(2):e0277213. doi: 10.1371/journal.pone.0277213. PMID: 36745650; PMCID: PMC9901790.
26. Spaggiari G, Brigante G, De Vincentis S, Cattini U, Roli L, De Santis MC, Baraldi E, Tagliavini S, Varani M, Trenti T, Rochira V, Simoni M, Santi D. Probiotics Ingestion Does Not Directly Affect Thyroid Hormonal Parameters in Hypothyroid Patients on Levothyroxine Treatment. Front Endocrinol (Lausanne). 2017 Nov 14;8:316. doi: 10.3389/fendo.2017.00316. PMID: 29184537; PMCID: PMC5694461.

27. Ma ZF, Venn BJ, Manning PJ, Cameron CM, Skeaff SA. Iodine Supplementation of Mildly Iodine-Deficient Adults Lowers Thyroglobulin: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2016 Apr;101(4):1737-44. doi: 10.1210/jc.2015-3591. Epub 2016 Feb 18. PMID: 26891118.
28. Kasagi K, Iwata M, Misaki T, Konishi J. Effect of iodine restriction on thyroid function in patients with primary hypothyroidism. Thyroid. 2003 Jun;13(6):561-7. doi: 10.1089/105072503322238827. PMID: 12930600.
29. Beer AM, Wiebelitz KR, Schmidt-Gayk H. Lycopus europaeus (Gypsywort): effects on the thyroidal parameters and symptoms associated with thyroid function. Phytomedicine. 2008 Jan;15(1-2):16-22. doi: 10.1016/j.phymed.2007.11.001. PMID: 18083505.
30. 30Nordio M. A novel treatment for subclinical hyperthyroidism: a pilot study on the beneficial effects of l-carnitine and selenium. Eur Rev Med Pharmacol Sci. 2017 May;21(9):2268-2273. PMID: 28537653.
31. Wang L, Wang B, Chen SR, Hou X, Wang XF, Zhao SH, Song JQ, Wang YG. Effect of Selenium Supplementation on Recurrent Hyperthyroidism Caused by Graves'' Disease: A Prospective Pilot Study. Horm Metab Res. 2016 Sep;48(9):559-64. doi: 10.1055/s-0042-110491. Epub 2016 Jul 8. PMID: 27392116.
32. Grove-Laugesen D, Ebbehoj E, Watt T, Riis AL, Østergård T, Bruun BJ, Juel Christiansen J, Hansen KW, Rejnmark L. Effect of Vitamin D Supplementation on Graves'' Disease: The DAGMAR Trial. Thyroid. 2023 Sep;33(9):1110-1118. doi: 10.1089/thy.2023.0111. Epub 2023 Jun 26. PMID: 37218433.
33. Ahn HY, Lee MJ, Jung KY, Kim HJ, Jung EH, Chung CW, Kim K, Jang J, Park YJ, Lee JK, Cho SW. Selenium vs Control for Graves' Ophthalmopathy in a Selenium-Sufficient Area: A Randomized Clinical Trial. JAMA Ophthalmol. 2025 Feb 27;143(4):287–94. doi: 10.1001/jamaophthalmol.2024.6337. Epub ahead of print. PMID: 40014353; PMCID: PMC11869097.
34. Rossi M, Meomartino L, Zavattaro M, Selvatico G, Rossetto Giaccherino R, Pagano L. Adding L-Carnitine and Selenium to Methimazole in Graves'' Disease: A Prospective Randomized Trial on Thyroid Markers and Quality of Life. Nutrients. 2025 Aug 20;17(16):2693. doi: 10.3390/nu17162693. PMID: 40871722; PMCID: PMC12389566.
35. Han Z, Cen C, Ou Q, Pan Y, Zhang J, Huo D, Chen K. The Potential Prebiotic Berberine Combined With Methimazole Improved the Therapeutic Effect of Graves'' Disease Patients Through Regulating the Intestinal Microbiome. Front Immunol. 2022 Jan 10;12:826067. doi: 10.3389/fimmu.2021.826067. PMID: 35082799; PMCID: PMC8785824.
36. Gan D, Gao TS, Ma L, Lu H, Dai H, Liu QY, Lai YW, Liu XH, Peng ZD, Chen RY, Qiu ZY, Tong Y, Yan RX, Liu JH, Shen Q, Wang C, Yu SS, Chen SW, Liu XW, Chen XY, Zhang FN, Wang ZM, Wang YN, Yang X. Clinical efficacy of Chinese herbal medicine formula for Graves'' hyperthyroidism: A multicentre, randomized, double-blind, placebo-controlled clinical trial. J Ethnopharmacol. 2025 Feb 10;338(Pt 3):119106. doi: 10.1016/j.jep.2024.119106. Epub 2024 Nov 15. PMID: 39550016.
37. Wei M, Zhao Q, Yuan M, Fan Y, Li M. Efficacy and safety of *Prunella vulgaris* L. combined with antithyroid drugs for hyperthyroidism: a systematic review and meta-analysis. Front Pharmacol. 2025 Feb 27;16:1530152. doi: 10.3389/fphar.2025.1530152. PMID: 40083379; PMCID: PMC11903460.
38. Calissendorff J, Falhammar H. Rescue pre-operative treatment with Lugol's solution in uncontrolled Graves'' disease. Endocr Connect. 2017 May;6(4):200-205. doi: 10.1530/EC-17-0025. Epub 2017 Mar 21. PMID: 28325735; PMCID: PMC5434745.
39. Metro D, Cernaro V, Papa M, Benvenga S. Marked improvement of thyroid function and autoimmunity by *Aloe barbadensis* miller juice in patients with subclinical hypothyroidism. J Clin Transl Endocrinol. 2018 Feb 14;11:18-25. doi: 10.1016/j.jcte.2018.01.003. PMID: 29527506; PMCID: PMC5842288.
40. Farhangi MA, Dehghan P, Tajmiri S, Abbasi MM. The effects of Nigella sativa on thyroid function, serum Vascular Endothelial Growth Factor (VEGF) - 1, Nesfatin-1 and anthropometric features in patients with Hashimoto's thyroiditis: a randomized controlled trial. BMC Complement Altern Med. 2016 Nov 16;16(1):471. doi: 10.1186/s12906-016-1432-2. PMID: 27852303; PMCID: PMC5112739.
41. Chaudhary S, Dutta D, Kumar M, Saha S, Mondal SA, Kumar A, Mukhopadhyay S. Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial. Indian J Endocrinol Metab. 2016 May-Jun;20(3):391-8. doi: 10.4103/2230-8210.179997. PMID: 27186560; PMCID: PMC4855971.
42. Chahardoli R, Saboor-Yaraghi AA, Amouzegar A, Khalili D, Vakili AZ, Azizi F. Can Supplementation with Vitamin D Modify Thyroid Autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and Thyroid Profile (T3, T4, TSH) in Hashimoto's Thyroiditis? A Double Blind, Randomized Clinical Trial. Horm Metab Res. 2019 May;51(5):296-301. doi: 10.1055/a-0856-1044. Epub 2019 May 9. PMID: 31071734.
43. Bourbour F, Mahdavi B, Naghshi N, Yari Z, Hosseini SM, Kalbasi S, Sohrab G. The Combined Effects of an Anti-Inflammatory Diet and Curcumin Supplementation on Thyroid Function and Lipid Profile in Patients With Hashimoto's Thyroiditis: A Double Blind Randomised Clinical Trial. Endocrinol Diabetes Metab. 2026 Jan;9(1):e70138. doi: 10.1002/edm2.70138. PMID: 41329567; PMCID: PMC12671534.
44. Zhang K, Wang Y, Ma W, Hu Z, Zhao P. Genistein improves thyroid function in Hashimoto's thyroiditis patients through regulating Th1 cytokines. Immunobiology. 2017 Feb;222(2):183-187. doi: 10.1016/j.imbio.2016.10.004. Epub 2016 Oct 4. PMID: 27729167.
45. Nordio M, Basciani S. Efficacy of a food supplement in patients with Hashimoto's thyroiditis. J Biol Regul Homeost Agents. 2015 Jan-Mar;29(1):93-102. PMID: 25864745.
46. Osowiecka K, Skrypnik D, Myszkowska-Ryciak J. Probiotic Supplementation Enhances the Effects of a Nutritional Intervention on Quality of Life in Women

with Hashimoto's Thyroiditis-A Double-Blind Randomised Study. Nutrients. 2025 Oct 28;17(21):3387. doi: 10.3390/nu17213387. PMID: 41228460; PMCID: PMC12609251.
47. Wang JZ, Zhang N, Meng XF, et al. A randomized controlled blind study of Chaihu Xuanfuhua Decoction for intervention of Hashimoto's thyroiditis. Beijing J Tradit Chin Med. 2021;40:1183–1186.
48. Hou LP, et al. Effects of selenium yeast and vitamin D on thyroid function, autoantibodies, and inflammation in adolescents and adults with Hashimoto's thyroiditis. Chin J Clin Pharm. 2022;31:676–682. doi:10.19577/j.1007-4406.2022.09.007.
49. Chekalina N. Influence of resveratrol on the structural and functional state of the thyroid gland in patients with autoimmune thyroiditis combined with stable ischemic heart disease. J Clin Med Kaz. 2017;1(43):48–55. DOI 10.23950/1812-2892-JCMK-0044

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