

The Applications of *Prunella Vulgaris* L. and Its Compound Formulations in the Treatment of Hashimoto Thyroiditis

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Received: 28 October 2025; **Accepted:** 19 November 2025; **Published:** 1 December 2025

Abstract:

Prunella vulgaris L. is a Chinese herbal medicine used to clear excessive heat and fire, which manifested as inflammation and irritability, dissipate nodules, and reduce swelling. Hashimoto Thyroiditis (HT) is a common autoimmune disease characterized by a chronic immune attack on the thyroid gland, leading to progressive hypothyroidism. To investigate the applications of *Prunella vulgaris* L. and its compound formulations in the treatment of Hashimoto Thyroiditis (HT), this article summarizes the pathogenesis of HT and the limitations in current clinical practice. Meanwhile, the mechanism by which *Prunella vulgaris* L. and its compound formulations cure HT are analyzed. Moreover, the clinical applications including Huayu Xiaoying Decoction, Bupleurum Inula flower soup and other Chinese Herbal Formula have developed a lot. This article also outlines key points for the treatment of patients with Yang Deficiency Syndrome or in special physiological periods such as during pregnancy and lactation. The results demonstrate that *Prunella vulgaris* L. and its compound formulations can not only modulate the immune-inflammatory response through pleiotropic mechanisms which is of practical value in management of HT, but also provide direction for the treatment for special populations with HT and inform future efforts in related research. Follow-up studies require undertaking more in-depth research in order to verify efficacy and safety of *Prunella vulgaris* L. and its compound formulations.

Keywords:

Prunella Vulgaris L., Hashimoto Thyroiditis, Compound Formulations

1. Introduction

Hashimoto Thyroiditis (HT) is one of the most common autoimmune disease [1], which is characterized by diffuse thyroid enlargement, firm and rubbery consistency, nodular surface associated with an elevation of Anti-thyroid peroxidase antibody (TPOAb) and Anti-thyroid globulin antibody (TgAb) and defined by the pathological hallmarks of lymphocytic infiltration of the thyroid gland [2]. In recent years, the incidence of HT showed a significant increasing trend. Statistical studies have shown

that the incidence rate ranged from 0.3-1.5 cases per 1000 people. Besides, the incidence of HT is markedly elevated in women, who accounted for over 10% of the clinical data exhibited a positive reaction. Clinical symptoms were observed in 2% of the female participants. However, the incidence rate among men was tenfold lower than that among women. In addition, older age groups demonstrated a higher incidence compared to younger cohorts and the peak incidence among women occurred in the 30-50 age range [3].

On the basis of clinical features including diffuse, painless goiter and a firm texture, Traditional Chinese Medicine (TCM) categorizes HT as Ying Liu (Goiter and Tumor) or Luo Bing (Scrofulous Masses). Commonly used herbal formulas in TCM include Bupleurum Inula flower soup, Ruanjian Xiaoying Decoction, Shugan Qingre Decoction etc. These formulations have the function of activate blood and resolve stasis, and resolve goiter. Evidence from scientific investigations suggests that *Prunella vulgaris* L. is recommended by TCM to treat HT [4]. However, few studies have specifically analyzed the therapeutic efficacy of *Prunella vulgaris* L. formulations for HT. This article aims to investigate mechanism and clinical application of *Prunella vulgaris* L. and its compound formulations in the treatment of HT, informing decision-making process for optimizing the therapeutic strategies.

2. Pathogenesis of HT

Although the exact pathogenesis of HT remains incompletely understood, it is hypothesized that the pathogenesis may be caused by the interaction of genetics, environment, emotion, diet, and infectious factors. Its fundamental mechanism underlying the pathogenesis is that immune imbalance mediated by T lymphocytes and B lymphocytes leads to the autoimmune response, stimulating B cells to proliferate and produce antibodies, which disrupts the immune homeostasis of thyroid tissue [3], ultimately leading to its destruction [5].

Elevation of TPOAb and TgAb can not only be widely used in the diagnosis of HT as the main clinical characteristics [2], but also related to the autoimmune pathogenesis of HT. TPOAb targeted Thyroid Peroxidase (TPO), which is a key enzyme for the synthesis of thyroid hormones. As an autoimmune antigen, TPO stimulates the body to produce TPOAb to attack its own thyroid target tissue during thyroid disease. TgAb targets the precursor protein of thyroid hormone synthesis-Thyroglobulin (Tg). After TgAb binds to Tg, it destroys thyroid cells by activating natural killer cells (NK cells) [6]. Autoantibodies represented by TPOAb and TgAb are a major cause of thyroid follicular destruction. TPOAb and TgAb activate complements to enhance T lymphocyte toxicity and induce killer T cells to destroy thyroid follicles.

In addition, the thyroid tissue of HT patients is mainly infiltrated by T helper cell 1 (Th1). By secreting Interferon Gamma (IFN- γ) and Tumor Necrosis Factor- α (TNF- α), Th1 induces abnormal expression of Major Histocompatibility Complex ClassII (MHCII) antigens in thyroid cells and enhances its own antigen delivery ability. Recent studies have shown T helper cell 17 (Th17) participate in the inflammatory process by producing pro-inflammatory factors such as Interleukin-17 (IL-17), thus aggravating tissue damage [7]. Besides, the dysfunction or decrease in the number of Regulatory T cells (Treg) results in insufficient immunosuppression and further promotes the occurrence of disease [5].

3. Clinical Therapeutics and Relevant Limitation in HT

The clinical treatment of HT is mainly for addressing hypothyroidism, with levothyroxine sodium serving as the standard alternative therapy. The major obstacle to long-term treatment is the requirement for indefinite use of levothyroxine sodium. Furthermore, existing studies have confirmed that long-term use of levothyroxine sodium is associated with altered bone metabolism and may even induce hyperthyroidism [8]. The Pharmacopoeia of the People's Republic of China also notes the difficulty in precisely controlling the I-131 dosage, which carries the risk of inducing permanent hypothyroidism. Therefore, there is a pressing need to identify safer and more effective therapeutic strategies. *Prunella vulgaris* L. and its related formulations have gained recognition for their therapeutic advantages, which include multi-target effects and a good safety profile. Accordingly, the aim of the following discussion is to clarify its mechanism of action.

4. The Therapeutic Mechanism of *Prunella vulgaris* L. and Its Compound Formulations

The Therapeutic Mechanism of *Prunella vulgaris* L. and its compound formulations primarily involve immunomodulatory balance and suppression of the inflammatory response. Patients with HT often own a symptom of presenting imbalance between Th1 and Th2. Clinical observations indicate that thyroid tissue of patients with HT is characterized by a predominant infiltration of Th1 cells and expression of their related cytokines [9]. By secreting IFN- γ and IL-2, Th1 cells enhance lymphocytic infiltration, leading to the destruction of thyroid follicles. In contrast, Th2 cells function by secreting cytokines such as IL-4 and IL-10, thereby suppressing the activation and proliferation of Th1 cells. According to the experimental results of Yu Lingying et al., *Prunella vulgaris* L. reduce IFN- γ levels and lowers the Th1/Th2 ratio, suppresses TPOAb production, and improve thyroid function in experimental autoimmune thyroiditis (EAT) rats, with particularly significant effects observed in preventive intervention [10].

Besides, *Prunella vulgaris* L. exerts the function by inhibiting the Nuclear factor kappa-B (NF- κ B) signaling pathway, reducing the secretion of pro-inflammatory factors (e.g., TNF- α , IL-6, IL-8), blocking the inflammation-NF- κ B-inflammation positive feedback loop, and inhibiting the production of TPOAb and TgAb it ultimately alleviates thyroid tissue inflammation [11].

Clinical studies also found that HT patients demonstrate significantly elevated serum Th17 levels, indicating an imbalance between Th17 and Treg cells. Th17 cells primarily secrete pro-inflammatory factors such as IL-17 and IL-23, amplifying the inflammatory response. Notably, IL-17 plays a pivotal role in driving the early inflammatory progression of HT. Treg cells exert their immunosuppressive function by two primary mechanisms. Firstly, suppressing target cell activation through direct cell contact. Secondly, inhibiting T-cell activation via the secretion of soluble factors such as TGF- β , IL-10, and IL-35 [7]. Experiments by Chen Xiaowei et al. have demonstrated that Ruanjian Xiaoying Granules, primarily composed of *Prunella vulgaris* L., ultimately exert anti-inflammatory effects by correcting the Treg/Th17 imbalance, increasing the overactivation and proliferation of Th17 cells, and reducing the secretion of IL-17 and IL-23 [12].

5. The Clinical Application of *Prunella Vulgaris* L.

The clinical of *Prunella vulgaris* L. in HT treatment is primarily achieved through compound formulation. Historical records of TCM document the use of oral decoctions and topical ointments for the prevention and treatment of goiter. Chai Shufang et al. employed a combined administration of Huayu Xiaoying Decoction with Xiaoying Sanjie Ointment. The formula Huayu Xiaoying Decoction employs a multi-component strategy to address the pathology systematically. (1) The combination of *Pinelliae Rhizoma* (Banxia), *Magnoliae Officinalis Cortex* (Houpu), and *Poria* (Fuling) acting to eliminating the pathogenic factor of phlegm-dampness at its root. (2) *Angelicae Sinensis Radix* (Danggui), *Chuanxiong Rhizoma* (Chuanxiong), and *Paeoniae Radix Rubra* (Chishao) function to activate blood circulation, move Qi (the vital energy that governs physiological functions), resolve blood stasis, and reduce swelling, thereby ensuring the free flow of Qi and blood. (3) *Fritillariae Thunbergii Bulbus* (Zhebeimu) and *Cremastrea Pseudobulbus* (Shancigu) function to clear heat, resolve toxicity, dissipate phlegm, disperse nodules, and reduce goiter. (4) In TCM, the thyroid gland is associated with the liver meridian, which explains the close connection between thyroid disorders and liver function. *Bupleuri Radix* (Chaihu) and *Paeoniae Radix* (Baishao) act to regulate Qi of liver and balance the dynamics of Qi and blood throughout the blood, thereby ensuring their free flow. (5) *Prunella vulgaris* L. (Xiakucao) serves as a dual role: it acts as a guiding herb to direct the effects of all other components to the liver meridian, while concurrently exerting its own detoxifying, nodule-resolving, and goiter-reducing effects. (6) *Glycyrrhizae Radix* (Gancao) serves to harmonize the actions of all other components in the prescription, while also providing heat-clearing, detoxifying and mild stasis-resolving effects. This internal decoction is synergistically combined with the topical application of Xiaoying Sanjie Ointment, which also contains *Prunella vulgaris* L., thereby significantly improving the therapeutic effect through the dual-pathway treatment mechanism.

Research of Chai Shufang et al. showed that *Prunella vulgaris* L. and its formulations exhibit anti-inflammatory activity, as evidenced by a significant reduction in serum TPOAb, TgAb, and IL-8 and increase IL-10 levels post-treatment [13].

Bupleurum Inula flower soup is a modified formula derived from the combination of Minor *Bupleurum* Decoction and *Inula* Decoction. The main components and functions are illustrated below. (1) *Bupleuri Radix* (Chaihu) primarily targets the liver and gallbladder system. Its key function is to ease constraints in the liver, often associated with stress or emotional imbalance, and to promote the smooth flow of Qi throughout the body. (2) *Inulae Flos* (Xuanfuhua) primarily acts on the digestive system. Its key functions are to direct downward rebellious energy (reflux or hiccups) and resolve mucus accumulation (phlegm). (3) *Pinelliae Rhizoma* (Banxia), *Fritillariae Thunbergii Bulbus* (Zhebeimu), and *Prunella vulgaris* L. functions to resolve phlegm and dissipate nodules. (4) *Paeoniae Radix Rubra* (Chishao) functions to improve blood quality and circulation (nourish and activate blood), while also calming an overly excited or hyperactive state of liver system (pacify liver yang). Meanwhile, *Cyperus Rhizoma* (Xiangfu) works synergistically with *Bupleuri Radix* (Chaihu) to alleviate functional disharmony of liver often associated with constrained energy flow and emotional stress (move Qi and soothe the liver). (5) *Codonopsis Radix* (Dangshen) acts to tonify the body's energy and support its metabolic warmth, which in turn improves the transformation and absorption of nutrients (spleen function).

Collectively, the formula works synergistically to regulate liver and spleen function (soothe the liver and fortify the spleen), resolve phlegm, and dissipate nodules by promoting the smooth flow of Qi.

Wang Jiazhe et al. conducted a parallel, randomized, double-blind, placebo-controlled study. The results indicated that Bupleurum Inula flower soup counteracts the immune-mediated injury in HT and slows the progression of hypothyroidism. Long-term follow-up revealed that patients receiving Bupleurum Inula flower soup maintained significantly lower serum TPOAb levels than the control group, suggesting that the formula provides a sustained intervention against the immune injury in HT [14].

6. Discussion

Current conventional monotherapy for the treatment of HT faces limitations, and the therapeutic effect needs to be further improved. Therefore, combination therapy represents a critical pathway for enhanced treatment effect. By integrating the advantages of TCM and Western medicine, while overcoming the limitations of single therapy, this comprehensive strategy can significantly improve the treatment effect [15].

Compound TCM formulations demonstrate multi-dimensional therapeutic effects in HT, which can not only reduce autoantibody titers, improve clinical symptoms, and fewer adverse reactions, but also delaying disease progression through immunomodulation [12]. Studies have confirmed that *Prunella vulgaris* L. as a recommended option for HT. *Prunella vulgaris* L. has the medicine effect of improving vision, eliminating nodules, and reducing inflammation. For HT patients presenting with heat syndrome (such as irritability, dry mouth, heat intolerance), *Prunella vulgaris* L. can serve as a key ingredient in the treatment compound. However, for HT patients exhibiting marked Yang deficiency patterns or distinct Spleen-Stomach cold deficiency, the use of *Prunella vulgaris* L. should be strictly avoided. Its cooling nature may further consume the energy of human body and affect the digestive function, potentially worsening debilitating cold intolerance and loose stools. Therefore, the application of *Prunella vulgaris* L. and its compound formulations for treating HT must strictly adhere to precise pattern differentiation, demanding special caution in individuals exhibiting Yang deficiency or Spleen-Stomach cold deficiency. To minimize risks, *Prunella vulgaris* L. should be use in combination with warm and spleen deficiency tonic drugs to obtain better therapeutic of personalized medical treatment.

Additionally, pregnant and lactating women demand heightened attention due to their unique physiology and heightened sensitivity. The cooling nature of *Prunella vulgaris* L. may irritate the digestive system of pregnant women, potentially weakening digestive function and leading to discomfort as loose stools, and may even have potential adverse effect on the generation of development of fundamental metabolic energy and the establishment of digestive function of fetus. Owing to insufficient safety data of the application of *Prunella vulgaris* L. in pregnant and lactating HT patients, and a lack of clinical evidence to guarantee absolute safety, the application of *Prunella vulgaris* L. necessitates extreme caution in its use.

7. Conclusions

Prunella vulgaris L. and its compound formulations are gradually becoming a research focus based on their treatment ability of HT. The pathogenesis of HT involves elevated levels of thyroid autoantibodies, an imbalance between Th1 and Th2 cells and their associated cytokines, and dysregulation of Th17/Treg axis and related cytokines. Current clinical management of HT has certain limitations. However, integrating TCM and WM can effectively harness the strengths of both systems to overcome the shortcoming of either approach used alone. *Prunella vulgaris* L. and its compound formulations exert anti-inflammatory effects by modulating immune balance, suppressing NF- κ B signaling pathway and restoring the Th17/Treg equilibrium, thereby alleviating HT symptoms. The clinical application of Bupleurum Inula flower soup combined with the topical Xiaoying Sanjie Ointment significantly reduces serum TPOAb and TgAb levels and improves thyroid function in HT patients. Furthermore, this research extended the investigation to special populations, such as HT patients with Yang deficiency pattern and pregnant or lactating women. Through a multi-dimensional analysis of their mechanisms of action and clinical efficacy, the critical importance of accurate pattern distinction and rational medication use in these cases is emphasized. *Prunella vulgaris* L. and its compound formulations demonstrate significant therapeutic value in treating HT, but further rigorous studies remain essential to comprehensively verify their efficacy and safety.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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