Review

Emerging therapeutic role of *Prunella vulgaris* in thyroid disease

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\textbf{ABSTRACT}

Thyroid disease is characterized by unusual levels of thyroid hormones, which results in either hyperthyroidism or hypothyroidism. The pathology of a particular type or stage of thyroid disease is very complicated, and always linked to a variety of biological functions. Although the mortality rate is not high, thyroid dysfunction could lead to metabolic and immunological disorders that can subsequently cause discomfort. To date, many drugs are suggested to have curative effects on thyroid disease, however, drug toxicity and long treatment periods encourage the search for more promising ones. *Prunella vulgaris* L. (Labiatae) is a popular herb that has shown great potential for improving human immunity and organ protection. It has been extensively used in the treatment of many diseases but its ability to treat specific diseases has not been fully reported. In this review, a literature search regarding herbs and herbal recipes for treating thyroid disease were carried out, organized, and summarized. In addition, this study conducted a literature search on the current situation and progress of *P. vulgaris* treatment for various diseases. Finally, this study discussed studies regarding *P. vulgaris* treatment of goiter, and the mechanism of treatment through the regulation of apoptosis. Accordingly, a combination therapy of herbs and Western medicine can provide significant therapeutic effects in the clinical treatment of thyroid disease. Furthermore, the association between *P. vulgaris* and various diseases suggests that *P. vulgaris* is rich in a variety of active substances that can fight oxidation and participate in the regulation of apoptosis, thus having a protective effect on the thyroid. Here, a comprehensive literature review regarding the application of herbs or herbal recipes in the treatment of thyroid disease was presented. It is concluded that there is strong evidence for further research regarding the use of *P. vulgaris* in the treatment of thyroid diseases.

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1. Introduction

As the largest endocrine gland in human body, the thyroid plays a vital role in regulating human growth and metabolism through synthesizing thyroid hormones (Fig. 1). Malfunctions of the thyroid can cause serious thyroid related diseases including goiter, autoimmune thyroid disease (AITD), and thyroid cancer. In recent years, the relative incidences of AITD and thyroid cancer have increased up to 5% (Antonelli, Ferrari, Corrado, Domenicantonio, & Fallahi, 2015) and 20% (Kim, Gosnell, & Roman, 2020), respectively. Among these thyroid-related diseases, goiter is commonly found in the general population. Clinically, it involves either diffuse or nodular goiters based on the thyroid histology (Studer & Ramelli, 1982). The cause of goiter is complicated and can be associated with a euthyroid, hyperthyroid, or hypothyroid metabolic state (Fuhrer, Bockisch, & Schmid, 2012). People with goiter tend to have a normal life, but some suffer from discomfort, such as pain, airway blockage and esophageal blockage. In addition, nodules may form in the later stage of goiter that can aggravate the disease and even lead to thyroid cancer. Therefore, medications for the prevention and early intervention of goiter and its development are urgently required.

In terms of treatment, the corresponding medication and surgeries can be applied depending on the stages and types of goiter. Antithyroid drugs such as propylthiouracil (PTU), methimazole (MMI), carbimazole (Cooper, 2005), and levothyroxine (LT4) (Kuang, 2018) are commonly used drugs. Combination therapies of these individual drugs with iodine (Kuang, 2018) or selenium (Osadtsiv, Kravchenko, & Andrusyshyna, 2014) have been effective in reducing the size of thyroid nodules. For euthyroid goiter, drugs, surgery or radioactive iodine therapy are normally used to reduce the size of the gland. However, there are limitations in their application. The mechanisms of drug therapies are still unclear and relative data on long-term usage is limited. In addition, for large and more nodular goiters, drug therapy may be inadequate. Although surgery is a rapid mean of mechanical symptom removal and provision of tissues for histological examination, it is invasive and carries the risks of recurrent laryngeal nerve palsy or hypoparathyroidism. Radioactive therapy is a good alternative to goiter surgery, but it requires a longer period of hospitalization and clinical follow-up after treatment (Fuhrer, Bockisch, & Schmid, 2012).

*Prunella vulgaris* L. is a very popular herb in China, and has great potential for improving human immunity. It belongs to the Lamiaceae family, genus *Prunella*, and its medical components are accumulated mainly in either the dry fruit-spike or the whole herb. This plant has a wide spectrum of biological effects, including antimicrobial (Li et al., 2019), anti-inflammatory (Zaka, Sehgal, ...
to treat thyroid-related disease, including thyroiditis (Bright, 2007; Sa et al., 2007), goiter (Kiseleva, Teplaia, & Kaminskii, 2012; Kvakeniuk & Kvachenkui, 2013; Turchaninova, 2014), hyperthyroidism (Eiling, Wieland, & Niestroy, 2013; Guo, Chen, & Li, 2009; Kim & Kim, 2018), and thyroid cancer (Chou et al., 2018; Ruan, Jia, & Li, 2017; Yang, Ji, Guan, Shi, & Hou, 2013; Yu et al., 2018; Zhang, Sun, Huang, Zhao, & Zeng, 2018). Eight articles involved the specific herb-derived compound used, including curcumin (Bright, 2007), ginsenoside (Chen, Feng, & Huang, 2016), evodiamine (Yang, Ji, Guan, Shi, & Hou, 2013; Yu et al., 2018), shikonin (Bai et al., 2018), honokiol (Chou et al., 2018), harmine (Ruan, Jia, & Li, 2017), rosmarinic acid (Qi, Zhang, Guo, Zhang, & Zhong, 2020). There are eight articles involving P. vulgaris and most of them were thyroiditis-related. In these studies, the application of P. vulgaris was favored by in combination with western medicines, including prednisolone (PSL) (Li, Wu, Chen, Hu, & Liu, 2019), betamethasone (Li, Wang, & Zhao, 2017), and Euthyrox (Fan, Zhang, & Mi, 2017), and the treatments showed good efficacy. Some articles (10/35) involved herbal recipes (containing P. vulgaris or not) in the treatment of thyroid disease. MMI was a frequently used drug in combination therapy with herbal recipes and most of these studies have suggested that the combination therapy was better than MMI alone (Han et al., 2009; Yang et al., 2017). In terms of goiter studies, herbs including Potentilla alba L. (Turchaninova, 2014) and P. vulgaris (Yang, Guo, & Wu, 2007; Yin, 2016), and herbal recipes including Ying Liu mixture (YL) (Yang et al., 2017), Xing Qi Hu Ying Tang (XQHYT) (Yang & Lu, 2018), Kang Jia Wan (KJW) (Han et al., 2009) were analyzed. The efficacy of using combination therapy or herbs alone were the most studied. These results indicated that the combination therapy has significant therapeutic effects on the clinical treatment of thyroid disease, which also suggests that plant drugs are multi-targeting and have gentle efficacy. Therefore, they are more suitable to coordinate with Western drugs for a safe and more rapid treatment of disease.

4. Effectiveness of P. vulgaris in thyroid-related diseases

As both an edible and a medicinal herb, P. vulgaris has been found to be effective in a variety of thyroid-related human disorders (Ahmad, Masoodi, Tabassum, Mir, & Iqbal, 2020; Feng, Jia, Shi, & Chen, 2010; Gao, Hua, Li, Liu, & Xu, 2019; Lin et al., 2020). P. vulgaris is suggested to have protective roles against oxidation and inflammation in general (Hu, Yu, Wu, Yu, & Zhong, 2016; Hwang et al., 2012). It has also been reported to have curative effects on a variety of abnormal physiological conditions including hepatic fibrosis (Hu, Yu, Wu, Yu, & Zhong, 2016), rheumatoid arthritis (Zaka, Sehgal, Shafique, & Abbasi, 2017), and diabetic diseases (Hwang et al., 2012). Based on this evidence, we performed a general literature search on P. vulgaris. Research articles relating to ‘P. vulgaris’ from WOS and BIOSIS Previews were categorized by either ‘Research direction’ or ‘Country’ (Fig. 2). A totals of 43 and 376 research articles were identified through WOS and BIOSIS Previews, respectively. Most articles including Plant Science (21/43), Pharmacology Pharmacy (19/43), Biochemistry vs Molecular Biology (11/43) and Integrative Complementary Medicine (9/43) were found in WOS. BIOSIS Previews provided most articles belonging to the category of Pharmacology Pharmacy (165/376), Environmental Science Ecology (104/376), Biochemistry vs Molecular Biology (103/376), Biodiversity Conservation (49/376), Genetics Heredity (47/376) and Agriculture (40/376). The countries studying P. vulgaris were mainly in Asia and USA, with UK, Germany, and Russia also having some records. In addition, we also collected the data on the incidence of cancer around the worldwide and in China in 2018, and found that thyroid cancer was among the top 10 most
Table 1
List of publications applying herbs or herbal recipes to treat thyroid disease.

| Types               | Herb/Herbal recipe                  | Active ingredient | Thyroid disorders | Finding                                                                 | Refs                                      |
|---------------------|-------------------------------------|-------------------|-------------------|--------------------------------------------------------------------------|-------------------------------------------|
| Herbs               | *Launaea procumbens* (L.) Amin (LP) | 70% Methanol      | Thyroid hormonal  | LPME can protect thyroid tissue against oxidative damage, possibly through the antioxidant effects of its bioactive compounds. | (Khan, 2017)                             |
|                     | *Curcuma longa* L. Curcumin          | –                 | Thyroiditis       | Regulation of inflammatory cytokines.                                   | (Bright, 2007)                           |
|                     | *Gamung Tang* (GGT)                  | –                 | Thyroiditis       | Down-regulation of T helper cell 1 cytokines and enhancement of T helper cell 2 cytokine production, playing an important role in the control of T-cell-mediated autoimmunity. | (Sa et al., 2007)                         |
|                     | *Potentilla alba* L.                 | –                 | Goiter with iodine and selenium deficiency | Application of Alba in patients showed reduced volume of thyroid, normalized function, reduced levels of thyroid stimulating hormone (TSH) receptor. | (Kiseleva, Teplaia, & Kaminskii, 2012; Kvachenkova & Kvachenkova, 2013; Turchaninova, 2014) |
|                     | *Nigella Sativa* Powder (NSP)        | –                 | Hashimoto’s thyroiditis (HT) | Patients received NSP showed improved thyroid status. | (Farhangi, Dehghan, Tajmiri, & Abbasi, 2016) |
|                     | *Panax ginseng C. A. Meyer* Ginsenoside | –                 | Thyroiditis       | Down-regulation of T helper cell 1 cytokines and enhancement of T helper cell 2 cytokine production, playing an important role in the control of T-cell-mediated autoimmunity. | (Kvacheniuk & Kvacheniuk, 2013; Turchaninova, 2014) |
|                     | *Lycopus europaeus* L. *Jia Jian Yu Nu Jian* (JYNJ) granules | –                 | Mild hyperthyroidism | Mild symptomatic hyperthyroidism significantly improved. | (Eiling, Wieland, & Niestroj, 2013) |
|                     | *Ahu Jeon Baek Ho Tang* (AJBHT)      | –                 | Hyperthyroidism   | Improving symptomatic effects, but not working through iodine blocking. | (Guo, Chen, & Li, 2009) |
|                     | *Astragali Radix* (AR)               | –                 | Hyperthyroidism   | Supressing T4 synthesis by modulating cAMP and Tg expression. | (Lee, Kang, Ahn, Doo, & Ahn, 2008) |
|                     | *Anemarrhena Bunge*                  | –                 | Hyperthyroidism   | No adverse effects and achieving euthyroidism, normalization of T3, T4 levels. | (Kim & Kim, 2018) |
|                     | *Tetradium L. erythrorhizon Sieb. et Zucc.* Evediamine | –                 | Thyroid cancer    | Evediamine status showed significant changes. | (Yu et al., 2018) |
|                     | *Lithospermum erythrorhizon Sieb. et Zucc.* Shikonin | –                 | Thyroid cancer    | Suppression of cell migration by modulating epithelial-mesenchymal transition and downregulating expression of Slug and MMP-2, MMP-9, and MMP-14. | (Yang, Ji, Guan, Shi, & Hou, 2013) |
|                     | *Magnolia species* Honokiol          | –                 | Thyroid cancer    | Suppression of cell migration by modulating epithelial-mesenchymal transition and downregulating expression of Slug and MMP-2, MMP-9, and MMP-14. | (Chou et al., 2018) |
|                     | *Peganum harmala* L. *Erythrorhizon* Shikonin | –                 | Thyroid cancer    | Suppression of cell migration by modulating epithelial-mesenchymal transition and downregulating expression of Slug and MMP-2, MMP-9, and MMP-14. | (Ruan, Jia, & Li, 2017) |
|                     | *Jiayan Kangtai Granules* (JYKT)     | –                 | Thyroiditis       | Regulating the Th17 cell/T-reg imbalance in AIT. | (Shi & Zhang, 2017)* |
| Herbal recipes      | *Jiayan Kangtai Granules* (JYKT)     | –                 | Thyroiditis       | Regulating the Th17 cell/T-reg imbalance in AIT. | (Shi & Zhang, 2017)* |
|                     | *Haizao Yuhu Decoction* (HYD)        | –                 | Hypothyroidism    | Pharmacokinetic profile of different HYD prescriptions was obtained in hypothyroidism rat. | (Ma et al., 2016)* |
|                     | *Xiakucao Oral Liquid* (XOL)         | –                 | SAT               | Combination using Betamethasone showed improved clinical symptoms, reduced inflammatory response. | (Li, Wang, & Zhao, 2017)* |
|                     | *Prunellae Oral Liquid* (POL)        | –                 | SAT               | Combined treatment using POL and thiamazole is superior to thiamazole alone. | (Yang, Guo, & Wu, 2007)* |
|                     | *Xiakucao Capsule*                   | –                 | HT                | Combination with Euthyrox improved thyroid function of patients, reduced levels of thyroid antibodies. | (Fan, Zhang, & Mi, 2017)* |
|                     | *Xiakucao granules*                  | –                 | HT                | Combined with Euthyrox showed significant good treatment effects. | (Yin, 2016)* |
|                     | *Xiakucao granules*                  | –                 | Diffuse goiter with hyperthyroidism | Combined with Thiamazole Tablets showed good efficacy in treatment of hyperthyroidism with little adverse reaction. | (Yin, 2016)* |
|                     | *Jiayan Kangtai Granules* (JYKT)     | –                 | Thyroiditis       | Regulating the Th17 cell/T-reg imbalance in AIT. | (Hou et al., 2018)* |
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Thyroid disorders | Finding | Refs |
--- | --- | --- |
Shuganjianpihuatanxingqi /C0 | Diffuse Goiter with YL-MMI combination can improve thyroid function, and decrease autoantibodies, cytokines, and clinical symptoms. | (Yang et al., 2015)* |
Graves Combination with MMI has improved treatment outcome of Graves. (Yang et al., 2015)* |
Xing Qi Hua Ying Tang /C0 | Achieving better treatment effect using the combination therapy. (Liu & Liao, 2016)*# |
JC | Hypothyroidism Combined with Euthyrox reduced dose of thyroid hormone, and lowered the lipids levels in blood. |
Kang Jia Wan (KJW) | goiter KJW markedly increased the caspase-3 and Fas protein expression than MMI. (Han et al., 2009)* |
Hui Kang Ling (HKL) | Thyroid cancer HKL inhibited peripheral blood micro-metastasis of differentiated thyroid carcinoma (DTC) patients. (Liu, Wang, Tian, Wang, Dong, & Deng, 2015) |

Note: Studies were grouped into three parts: herbs having no association with P. vulgaris, P. vulgaris, and herbal recipes. Studies which include the use of both herbs and western drugs to treat thyroid disease, are labelled with ‘*’at the end of the related references; Herbal recipes containing P. vulgaris are labelled with ‘#’.

4.1. Metabolic disease

Thyroid hormone plays an important role in regulating human body metabolism. Therefore, it is of great reference value to explore the therapeutic effect of P. vulgaris in treating metabolic diseases in the future. P. vulgaris has been studied for its protective role in various metabolic disorders, including diabetes. P. vulgaris is suggested to be a good therapeutic inhibitor for diabetic vascular disease through exerting anti-inflammatory effects via the ROS/NF-κB pathway (Hwang et al., 2012). The caffeic acid extracts of P. vulgaris are known to increase serum insulin levels, and attenuate alpha-amylase and alpha-glucosidase, therefore P. vulgaris is suggested to be a potential agent for ameliorating type I diabetes (Raafat, Wurglics, & Schubert-Zsilavecz, 2016). Studies used P. vulgaris to treat diabetic nephropathy cell lines and found that P. vulgaris extracts suppressed renal inflammation and fibrosis through disrupting the TGF-β/Smad signaling pathway (Namgung et al., 2017).

4.2. Immunological disease

There are many research studies addressingAITD, which is a type of organ specific immune disease that can be tightly linked to thyroiditis, HT, GD, osteoarthritis, and arthritis. SKI 306X, an anti-arthritic agent derived from P. vulgaris has shown good effect on osteoarthritis (Jung et al., 2001). Aqueous extract of P. vulgaris has been reported to treat rheumatoid arthritis owing to its anti-inflammatory, anti-arthritic, and anti-rheumatic properties (Zaka, Sehgal, Shafique, & Abbasi, 2017). P. vulgaris is combined with LT4 produced a significant improvement in the clinical efficiency in HT (Zhang et al., 2020b). The polysaccharides of P. vulgaris have also been found to have a therapeutic effect on thyroid-associated ophthalmopathy (TAO) by inhibiting the proliferation and promoting the apoptosis of orbital fibroblasts (Li, Guo, Wang, Cheng, & Zeng, 2020). However, there is no clear evidence of how P. vulgaris participates in immune-regulatory function in the diseased condition.

4.3. Cancer

P. vulgaris extracts are suggested to have profound anticancerous effects, including for thyroid cancer (Yin et al., 2017), breast cancer (Gao, Hua, Li, Liu, & Xu, 2019), hepatocellular carcinoma (Su, Lin, Siao, Liu, & Yeh, 2016), and uterine myoma (Lin et al., 2020). The root extracts of P. vulgaris are found to have anti-cancer effects relating to apoptosis induction, inhibition of angiogenesis, cell cycle arrest, and modulation of the PI3K/AKT signaling pathway in MCF-7 human BC cells (Gao, Hua, Li, Liu, & Xu, 2019). Supercritical fluid extraction of P. vulgaris has the ability to promote cell growth by negative regulation of surviving and Bcl-2, inducing caspase-3 and Bax through mitochondrial apoptotic pathway (Lin et al., 2020). Flavonoids have been found to exert an anti-hepatocarcinoma effect through the PI3K/Akt/mTOR pathway.
pathway (Song et al., 2021). On the other hand, studies used network pharmacology and bioinformatics to evaluate the potential of *P. vulgaris* and identified that AKT1, EGFR, MYC, and VEGFA are important gene targets for *P. vulgaris* in breast cancer (Zhang et al., 2020a) and TP53, MYC, MAPK8 and CASP3 are key proteins involved in *P. vulgaris* regulation in colon adenocarcinoma (COAD) (Lei, Yuan, Gai, Wu, & Luo, 2021). In summary, *P. vulgaris* is rich in the active compounds triterpenes, essential oils and polysaccharides. These molecules have inhibitory effects on the proliferation of cancerous cells (Gao, Hua, Li, Liu, & Xu, 2019; Lin et al., 2020) via either triggering particular signaling pathways or inducing apoptosis (Yin et al., 2017).

### 4.4. Other diseases

Some diseases have not been associated with thyroid disorders. However, studies on using *P. vulgaris* to treat these diseases are important for understanding the phenotypic complications that thyroid disease may cause. Herbal recipe LA16001 containing *P. vulgaris* in breast cancer (Zhang et al., 2020a) and TP53, MYC, MAPK8 and CASP3 are key proteins involved in *P. vulgaris* regulation in colon adenocarcinoma (COAD) (Lei, Yuan, Gai, Wu, & Luo, 2021). In summary, *P. vulgaris* is rich in the active compounds triterpenes, essential oils and polysaccharides. These molecules have inhibitory effects on the proliferation of cancerous cells (Gao, Hua, Li, Liu, & Xu, 2019; Lin et al., 2020) via either triggering particular signaling pathways or inducing apoptosis (Yin et al., 2017).

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therapy of *P. vulgaris* extracts and taxane showed high efficacy and
good treatment of patients with BC (Zhao et al., 2018). These
results indicate that *P. vulgaris* can act as a suitable adjuvant med-
icine either within herbal recipes or with Western medicine by
effectively reducing the toxic effect of drugs, which also suggests
that *P. vulgaris* has a certain protective effect on the disease pathol-
ogy. Some studies have indicated that *P. vulgaris* extracts can offer
protections against certain factor-induced physiological condi-
tions. For example, *P. vulgaris* has been found to alleviate carbon
tetrachloride-induced hepatic fibrosis by inhibiting the activation
of hepatic stellate cells, promoting collagenolysis and regulating
fibrosis-related microRNAs (Hu, Yu, Wu, Yu, & Zhong, 2016). *P. vul-
garis* can also protect against UVB-induced photoaging and photo-
inflammation through regulating the production of radical oxygen
species (Zhang et al., 2018). Furthermore, flavonoid and phenolic
extracts of *P. vulgaris* provided hepatoprotective activity on parac-
etamol induced liver toxicity (Ahmad, Masoodi, Tabassum, Mir, &
Iqbal, 2020). Based on these evidences, *P. vulgaris* works through
improving the immunity and has a protective effect on particular
organs during the progress of many diseases.

A recently published paper summarized the research progress
of the clinical application of *P. vulgaris* in the treatment of thyroid
disease over the past 10 years. There were 998 herbal recipes for
thyroid disease and 65.53% of them contained *P. vulgaris* (Tang
et al., 2020). By comparing the numbers of *P. vulgaris* containing
herbal recipes, the numbers retrieved in our paper is far from that.
One of the possible explanations is the methodology for the litera-
ture search of ‘applying herbs or herbal recipes on thyroid disease’
was not perfect. Because *P. vulgaris* is a popular herb in China, other
Chinese electronic libraries such as WanFang Database, CNKI, and
some university resources should also be considered. In addition,
herbal recipes are characterized by the complexity. Some recipes
may differ by one or two kinds of herbs. Furthermore, for the vast
majority of clinical herbal recipes, the exact compounds have not
been fully published. *P. vulgaris* is a plant with intricate biological
properties that enable it to be of potential medical use. Therefore,
it is important to maintain a detailed record of the extraction and
purification methods for already published *P. vulgaris*-derived
active compounds. Regarding the content, the article discussed
the clinical treatment of different types of thyroid disease follow-
ing treatment with herbal recipes containing *P. vulgaris*. However,
we described the potential of *P. vulgaris* in thyroid disease from a
different angle. In addition to summarizing the herbal recipes con-
taining *P. vulgaris*, *P. vulgaris* alone and other herbs rather than *P.
vulgaris* used for thyroid disease, we also discussed the progress
of *P. vulgaris* research in metabolic diseases, immunological dis-
eases, cancers, and other diseases. Although the use of *P. vulgaris*
on thyroid disease is the major topic of this article, there is limited
information regarding the actual mechanism. In addition, goiter is
a complicated phenotype of the thyroid gland, its physiology is
linked to both metabolism and immunology. Therefore, in order
to improve our understanding of *P. vulgaris* on thyroid disease,
especially regarding goiter, it is necessary to investigate goiter
and its related functions.

5. Goiter, apoptosis and relevant apoptotic signaling pathways

Goiter is the most common type of thyroid disorder and the
majority of them are found to be harmless. In general, the histology
of goiter can be grouped into diffuse goiter, nodular goiter, and
combined cases. Goiters that develop over a long period of time

![Fig. 3. Estimated age-standardized incidence rates of cancer worldwide and in China in 2018. The data obtained from the GLOBOCAN 2018, the International Agency for
Research on Cancer 2018. The incidence of estimated age-standardized incidence rates (ASR) of cancer were analyzed and categorized into either Worldwide (A and B) or in
China (C and D). For each of them, the comprehensive cancer ASR (A and C) and ASR found in female (B and D) were also presented. The horizontal axis shows the rate of
specific cancers per 10,000 people.](image-url)
Fig. 4. Regulation of apoptosis under activation of TNF-α. The signaling pathway triggered by TNF-α can be either pro-apoptotic or anti-apoptotic. The caspase family plays a vital role during the process of apoptosis. Activation of caspase proteins and subsequent proteins could induce a cascade amplification of apoptosis. The apoptotic pathway can be triggered by the activation of Caspase-8, which then activates Caspases 3, 6, and 7, leading to apoptosis. The anti-apoptotic pathway is triggered through recognition of TNF-α and its receptor. Activation of TRAF2, TRADD or CYLD can cause subsequent activation of nuclear factor kappa-B (NF-κB), which is responsible for the activation of the transcription of anti-apoptotic proteins, such as BCL-2, Fas, and Bim under the extracellular stimuli of cytokines.

6. Feasible research options for P. vulgaris

Herbs such as P. vulgaris have great potential for treating thyroid disorders owing to their anti-oxidation and immunological effects and are frequently used as ingredients in herbal recipes. P. vulgaris is thought to combat drug toxicity within the body, therefore its own active ingredients have attracted much attention. In a survey of herbal recipes used for thyroid disease, P. vulgaris was frequently included owing to its efficacy. The use of P. vulgaris with other drugs resulted in significant elimination of swollen nodules, reduced inflammatory response, and improved thyroid function. These effects of P. vulgaris benefit the clinical treatment of thyroid disease while having reduced drug-induced side effects and have the following characteristics: increased numbers of epithelial cells and follicles, imbalance among thyroglobulin and colloid content, reduced thyroglobulin iodination and stored iodine content, and complicated interfollicular heterogeneity. Further development of goiter can lead to euthyroid, hyperthyroidism, and hypothyroidism (Antonelli, Ferrari, Corrado, Domenicantonio, & Fallahi, 2015; Fuhrer, Bockisch, & Schmid, 2012). Therefore, no matter what types of drugs are applied, the apoptosis pathway is affected in goiter. In addition, a study compared the apoptosis of thyrocyte cells among euthyroid goiter, lymphocytic thyroiditis (LT) and HT, and goiter is not serious than LT and HT; this may indicate that apoptosis-related pathogenesis is quite distinct in goiter (Todorovic, Nesovic, Opric-Ostojic, Dundjerovic, Bozic, & Markovic, 2014). Despite this evidence, some studies focus on the apoptosis-related genes in goiter. The role of Fas has been studied in rat models of goiter and it was found to act as a key regulator during Fas-mediated apoptosis (Andrikoula & Tsatsoulis, 2001). Survivin 2α was found to play a protective effect in goiter through survivin quenching, owing to its high expression in normal tissue compared with lesions (Kyani et al., 2014). The expression of Bad is also found to be correlated with goiter. Its expression is linked with the size of benign thyroid nodules and also its relatively lower expression in nodules (Gol et al., 2018). TNF-α is one of the most studied genes in goiter-related apoptosis. This controls cellular signaling proteins generated during systemic inflammation. It has been implicated in the pathogenesis of numerous inflammatory conditions, and its inhibition has proven efficacious in the treatment of autoimmune diseases including goiter (Mitsiades, Poulaki, Mitsiades, Koutras, & Chrousos, 2001). A Meta-analysis of the TNF-α gene identified that its promoter, SNPs rs1800629, is associated with increased risk for developing Graves’ Disease (GD) (Tu, Fan, Zeng, Cai, & Kong, 2018). Clinical studies have also found significant elevated levels of TNF-α in GD and HT (Antonelli, Ferrari, Corrado, Domenicantonio, & Fallahi, 2015). For people with nonthyroidal illness, administration of TNF-α produced significant alternations in thyroid hormones (Diez, Hernanz, Medina, Bayon, & Iglesias, 2002). Based on this evidence, TNF-α is tightly linked with the abnormal thyroid function. Therefore, it is necessary to investigate the regulatory function of P. vulgaris from the aspect of apoptosis inhibition, especially its action on TNF-α induced apoptosis (Fig. 4). Because this induction signaling pathway affects both activation and inhibition of apoptotic function, it is possible to investigate the expression of specific genes involved in the pathway. For example, inhibition of apoptosis can be detected through the TNFR-1/TRAF-2/TRADD/NF-κB/BCL-2 signaling pathway. In addition, the pathway of TNFR-1/C YLD/Caspase-8/Caspase-3/Caspase-6 is found in apoptosis activation. By applying specific inhibitors, the signaling transduction of particular gene up-regulation and down-regulation can be investigated. However, the role of apoptosis in the pathogenesis of goiter and in goitrogenesis is still not understood.
improved therapeutic effects. Therefore, an in-depth exploration of the molecular mechanism of this herb is of great importance to the treatment and prognosis of thyroid disease.

Nevertheless, only a few studies address *Prunella vulgaris* alone in the treatment of thyroid disease. The detailed working mechanisms on either tissue protection from drug toxicity or anti-oxidation, regulation of the immunological function, control of thyroxin, and its treatment effects are completely unknown. Therefore, it is necessary to design a systematic experimental strategy for further investigating how *Prunella vulgaris* affects thyroid disease and the relevant physiological mechanism. Many web tools can be used, including PubMed and WOS. Moreover, small molecule databases such as DrugBank and MMDB are important tools to reveal the already published active ingredients. Because *Prunella vulgaris*-derived active ingredients have not been fully identified, it may be necessary to repeat the search process and analysis. After obtaining the newly identified active ingredients of *Prunella vulgaris*, conjoint analysis of identified active ingredients can be carried out based on the network pharmacology analysis. Molecules of interest and their biological activities can be involved in suppressing inflammation, proliferation, and promoting apoptosis through the PI3K-AKT pathway (Zhang, Li, Guo, Dong, & Liao, 2020).

Another means of studying *Prunella vulgaris* effects on the thyroid gland may start with the preparation of *Prunella vulgaris* extracts. There are already cancerous thyroid-derived cell lines for studying the specific molecular function of *Prunella vulgaris* under the extreme conditions of thyroid disorder, for example, TPC-1, BCPCP, Nthy-ori 3-1 and FTC-133. Animal models of thyroiditis can also be used to study the biological function of *Prunella vulgaris*. In addition, the serum or tissues of patients suffering from thyroid disorders before and after taking oral *Prunella vulgaris* extracts could be used for sequencing analysis. Through identifying the differently expressed genes, potential candidates of *Prunella vulgaris* targeted genes could be validated. This approach may help to understand why using *Prunella vulgaris* with other drugs improves treatment effects. Such a network would enable us to better understand the treatment effects of *Prunella vulgaris* extracts.

**Declaration of Competing Interest**

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

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2021.12.005.

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