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Review

Emerging therapeutic role of *Prunella vulgaris* in thyroid disease

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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.

Contents

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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,

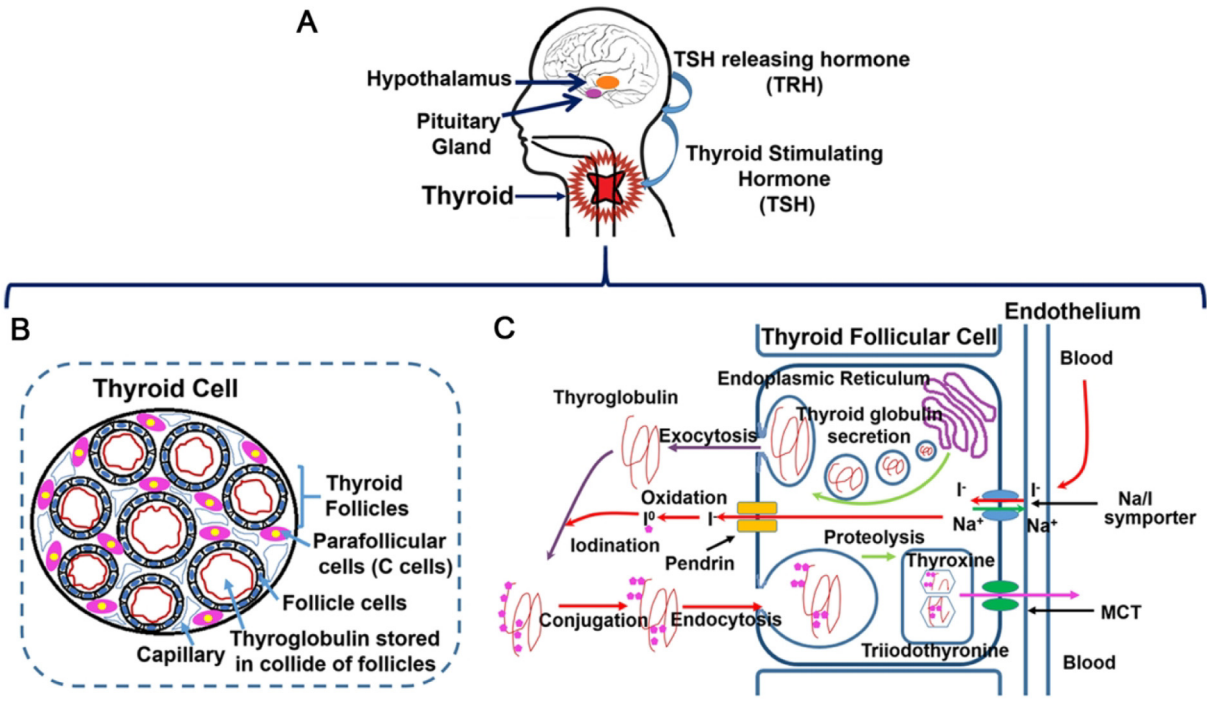

Fig. 1. Schematic diagram of thyroid and its biological function. A. Thyrotropin releasing hormone (TRH) is secreted by the hypothalamus and acts on the pituitary gland causing the release of TSH. TSH acts on the thyroid gland, stimulating the release of thyroid hormone. TRH and TSH are synergistically regulated and the thyroid and the pituitary gland are working under a feedback loop. B. Detailed presentation of a thyroid cell. C. Specific illustration of iodine uptake by thyroid follicular cells. Thyroid epithelial cells take up iodine via sodium-iodine symporters. It is secreted into the follicle through the chloride or iodine transporter pendrin on the apical side. Thyroglobulin secretion is processed based on the uptake of amino acids on the basolateral side. Thyroglobulin within thyroid follicles is then iodinated and subsequently taken up by follicular cells via endocytosis. After treatment with proteases, thyroid hormones are released into the blood.

Shafique, & Abbasi, 2017), antioxidant (Xia et al., 2018), antiestrogenic (Kim et al., 2014), and immunomodulatory actions (Kim, Cho, & Choung, 2019). Because of these beneficial medical applications, *P. vulgaris* is popularly consumed as a tea in China and some European countries. To date, many studies have been carried out on the active ingredients of *P. vulgaris*. Important constituents include polysaccharides (Gu, Li, Mu, & Zhang, 2013), ursolic acids (Li et al., 2019), phenolic acids, triterpenoids (Wang, Zhao, Chen, & Ma, 2000), flavonoids (Xia et al., 2018), and tannins (Lei, Yuan, Gai, Wu, & Luo, 2021)). Some of these have notable effects on particular biological functions. For example, the inhibition of inflammatory response caused by rosmarinic acid (Huang et al., 2009), antioxidant effects of phenols (Feng, Jia, Shi, & Chen, 2010), and anti-tumor effects of caffeic acid (Zhao et al., 2018). Clinically, many studies have used *P. vulgaris* to treat a variety of diseases, including many types of thyroid disease (Zhang et al., 2018). Yet, despite its promising nature as a drug resource, information related to its effect on thyroid malfunction and the mechanism is still limited.

In this review, literatures regarding the treatment of thyroid disease using herbs or herbal recipes, both with *P. vulgaris* as an ingredient and without, are comprehensively summarized. The therapeutic roles of *P. vulgaris* in treating various diseases are discussed. Furthermore, recent studies that used *P. vulgaris* to treat goiter are discussed. Genes and signaling pathways regarding apoptosis in *P. vulgaris* treatment are also discussed. This review provides a basis for further research of the use of herbal recipes on treatment of the thyroid gland.

2. Literature retrieval regarding *P. Vulgaris* and thyroid disease

Literature searches were implemented using online databases including PubMed (From 1900 to 2020), Web of Science (WOS) (From 1900 to 2020) and BIOSIS Previews (From 1944 to 2020).

Searches related to '*Prunella vulgaris* Labiatae', 'thyroid disease', 'herbal recipe', and 'applying herbs or *Prunella vulgaris* Labiatae to treat thyroid malfunction' were performed and the relevant information was collected from each research platform (Table S1). HistCite (only applicable to WOS and BIOSIS previews) was used to analyze the identified research articles in terms of research direction and country. Because *P. vulgaris* is a popular herb in Asia and some European countries, the key words for searching for *P. vulgaris* have also included 'self-heal' and 'Xiakucao', so as to gather a more comprehensive list of information. In addition, some articles published in Chinese, French, and Germany were also included.

3. Herbs or herbal recipes to combat thyroid disease

Many excellent records were found regarding the application of herbal extracts for thyroid-related disease around the world. A comprehensive literature search of studies under the term 'herbal medicines and thyroid diseases' from PubMed obtained 149 articles. Among them, 35 studies were clinical trials and randomized controlled trials (Table 1) and these were selected for further analysis. Twenty-five of the 35 studies involved herbs and eight studies involved herbal recipes. In addition, there were 12 articles that used a combination of herbs and Western medicine. Regardless of the type of thyroid disease, the application of herbs or herbal recipes revealed beneficial treatments that gave rise to symptom improvement. Because this article mainly discusses *P. vulgaris* treatment of thyroid disease, the information was grouped into three categories based on the types of herbs applied: 'herbs', '*P. vulgaris*', and 'herbal recipe containing *P. vulgaris* or not'. Approximately half of the articles (16/35) involved herbs (no *P. vulgaris*) to treat thyroid-related disease, including thyroiditis (Bright, 2007; Sa et al., 2007), goiter (Kiseleva, Teplaia, & Kaminskii, 2012; Kvacheniuk & Kvacheniuk, 2013; Turchaninova, 2014), hyperthyroidism (Eiling, Wieland, & Niestroj, 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 (Qiu, 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 Hua 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 extract (LPME)	Thyroid hormonal dysfunction	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)
	Gamgung 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) (Kvacheniuk & Kvacheniuk, 2013; Turchaninova, 2014)
	Nigella Sativa L. Powder (NSP)	–	Hashimoto's thyroiditis (HT)	Patients received NSP showed improved thyroid status.	(Farhangi, Dehghan, Tajmiri, & Abbasi, 2016)
	Panax ginseng C. A. Meyer	Ginsenoside	HT	It can decrease peripheral blood IFN-γ levels, and reduce level of T-bet and increased GATA-3.	(Chen, Feng, & Huang, 2016)
	Lycopus europaeus L.	–	Mild hyperthyroidism	Mild symptomatic hyperthyroidism significantly improved.	(Eiling, Wieland, & Niestroj, 2013)
	Jia Jian Yu Nu Jian (JJYNJ) granules	–	Hyperthyroidism graves	Improving symptom effects, but not working through iodine blocking.	(Guo, Chen, & Li, 2009)
	Ahn Jeon Baek Ho Tang (AJBHT)	–	Hyperthyroidism graves	Suppressing T4 synthesis by modulating cAMP and Tg expression.	(Lee, Kang, Ahn, Doo, & Ahn, 2008)
	Astragali Radix (AR)	–	Hyperthyroidism graves	Significantly relieving the symptoms and regulating the immune function of patients with graves.	(Wu, Liu, & Chen, 2011)
	Anemarrhena Bunge	–	Hyperthyroidism Graves	No adverse effects and achieving euthyroidism, normalization of T3, T4 levels.	(Kim & Kim, 2018)
	Tetradium	Evodiamine	Thyroid cancer	Evodiamine status showed significant changes.	(Yu et al., 2018)
	Lithospermum erythrorhizon Sieb. et Zucc.	Shikonin	Thyroid cancer	Inhibition of cell migration and invasion by suppressing 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	Identified 178 proteins	(Chou et al., 2018)
	Peganum harmala L.	Harmine	Thyroid cancer	Inhibition of the growth of thyroid cancer.	(Ruan, Jia, & Li, 2017)
	L. erythrorhizon	Shikonin	Thyroid cancer	Suppressing the expression of DNMT1, reducing PTEN gene methylation, and increasing PTEN protein expression, leading to the inhibition of TPC-1 cell migration.	(Zhang, Sun, Huang, Zhao, & Zeng, 2018)
P. vulgaris	*P vulgaris*	Rosmarinic acid	Autoimmune thyroiditis	Rosmarinic acid has effects of promoting splenic Tregs, IL-10, and TGF-β expression in rats with autoimmune thyroiditis.	(Qiu, Zhang, Guo, Zhang, & Zhong, 2020)
	P. vulgaris	–	Subacute thyroiditis (SAT)	Low dose of *P. vulgaris* combined with prednisolone (PSL) showed effective and safe treatment effects.	(Li, Wu, Chen, Hu, & Liu, 2019)*
	Xiakucao Oral Liquid (XOL)	–	SAT	XOL combined with prednisone revealed very effective treatment effects.	(Wei, 2018)*
	XOL	–	SAT	Combination with Betamethasone showed improved clinical symptoms, reduced inflammatory response.	(Li, Wang, & Zhao, 2017)*
	Prunellae Oral Liquid (POL)	–	Goiter	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.	(Shi & Zhang, 2017)*
	Xiakucao granules	–	Diffuse goiter with hyperthyroidism	Combined with Thiamazole Tablets showed good efficacy in treatment of hyperthyroidism with little adverse reaction.	(Yin, 2016)*
Herbal recipes (containing *P. vulgaris* or not)	Jiayan Kangtai Granules (JYKT)	–	Thyroiditis	Regulating the Th17 cell/T-reg imbalance in AIT.	(Hou et al., 2018)#
	Haizao Yuhu Decoction (HYD)	–	Hypothyroidism	Pharmacokinetic profile of different HYD prescriptions was obtained in hypothyroidism rat	(Ma et al., 2016)#

Table 1 (*continued*)

Types	Herb/Herbal recipe	Active ingredient	Thyroid disorders	Finding	Refs
	Shuganjianpihuatanxingqi Decoction (SD)	–	Hypothyroidism	Improving symptoms and reducing TSH levels.	(Bai et al., 2018)#
	Yingliu Mixture (YL)	–	Diffuse Goiter with Hyperthyroidism	YL-MMI combination can improve thyroid function, and decrease autoantibodies, cytokines, and clinical symptoms.	(Yang et al., 2017)*
	Yingliu Mixture (YL)	–	Graves	Combination with MMI has improved treatment outcome of Graves.	(Yang et al., 2015)*
	Jiakangling Capsule (JC)	–	Hyperthyroidism graves	Achieving better treatment effect using the combination therapy.	(Liu & Liao, 2016)*#
	Xing Qi Hua Ying Tang (XQHYT)	–	Multinodular goiter or diffuse goiter	Reducing goiter size and alleviating symptoms.	(Yang & Lu, 2018)#
	JC	–	Graves' Disease (GD)	Reducing thyroid hormone levels of GD mice and lowering expression levels of mTOR.	(Li, Wei, Li, & Meng, 2015)#
	Fuzheng Fujia Mixture (FFM)	–	Hypothyroidism	Combined with Euthyrox reduced dose of thyroid hormone, and lowered the lipids levels in blood.	(Liu, Chen, & Zhai, 2012)*
	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 '#'.

common cancers in the world (Fig. 3). It also found that thyroid cancer was the top five cancers among various high incidence women cancers. These results indicate that *P. vulgari* has attracted much research attentions around the world, indicating the important role it plays in treating human diseases. The thyroid plays a central role in homeostatsis, and any type of abnormality in this organ can lead to homeostasis imbalance, which can lead to various diseases. Therefore, understanding *P. vulgaris* treatment in many diseases is of great significance to further explore how *P.* vulgars treats thyroid disease. The diseases treated by *P. vulgaris* are divided into the following categories: metabolic disease, immunological disease, cancers and other kinds of diseases.

4.1. Metabolic disease

Thyroid hormone plays an important role in regulating huamn 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 addressing AITD, 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 anti-cancerous effects, including for thyroid cancer (Yin et al., 2017), breast cancer (Gao, Hua, Li, Liu, & Xu, 2019), hepatocellular carcinomac (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

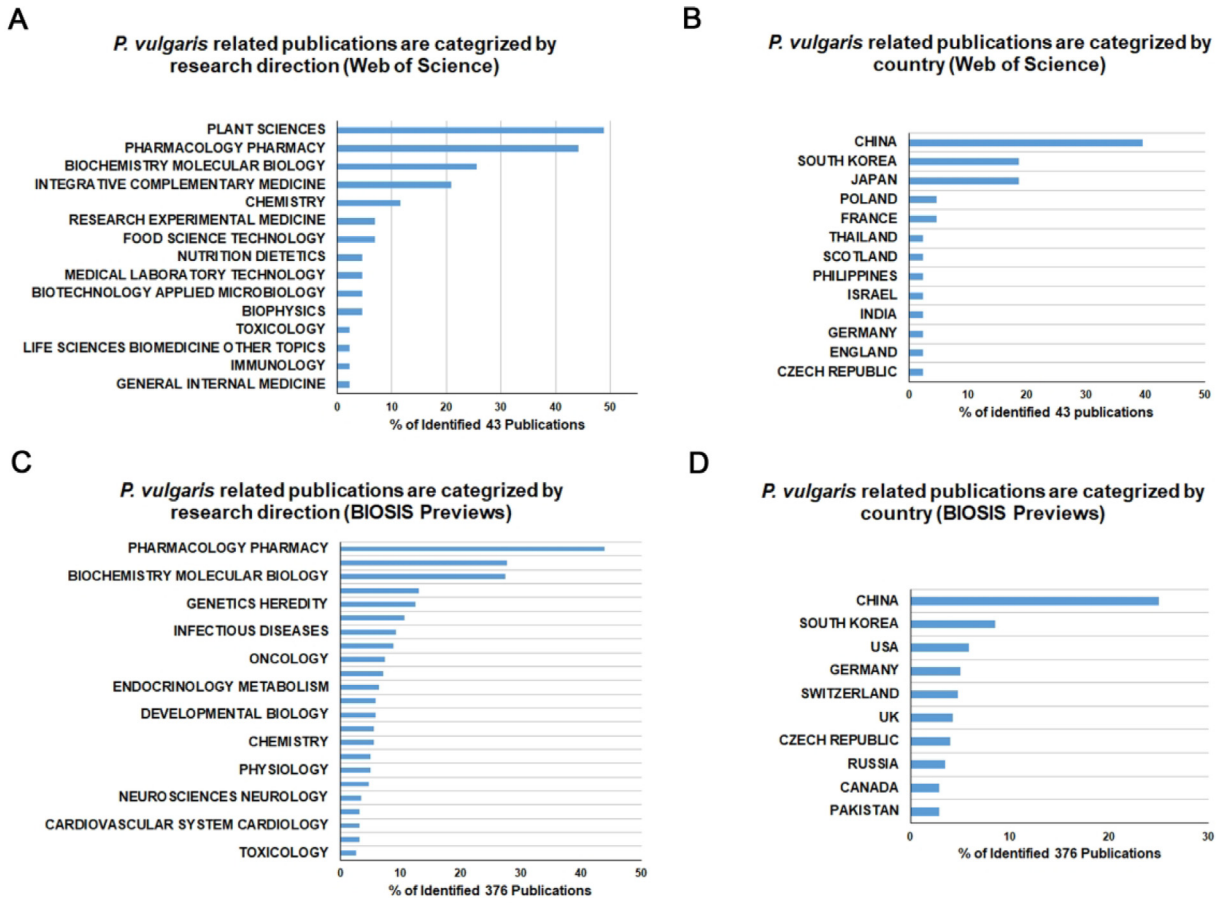

Fig. 2. Literature analysis of *P. vulgaris* using WOS and BIOSIS Previews. *P. vulgaris* as a key word was searched in both WOS and BIOSIS Previews. The identified research articles were categorized by research direction and country using the HistCite. *P. vulgaris* related articles in WOS are classified by either research direction (A) or by country (B); whereas *P. vulgaris* related articles in BIOSIS Previews are presented in C and D, respectively.

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. vuglaris* to treat these diseases are important for understanding the phenotypic complications that thyroid disease may cause. Herbal recipe LA16001 containing *P. vulgaris* has been studied for its potential application in the prevention of chemotherapy-induced anorexia (Woo et al., 2018). *P. vulgaris* is reported to have protective effects on age-related macular degeneration by inhibiting nuclear translocation of nuclear factor kappa beta (NF-kB) (Kim, Cho, & Choung, 2019). In addition, *P. vulgaris* has been used alongside Banxia (*Pinellia ternata* Thunb. Breit.) to treat sleep disorders (Guo, Lou, Hu, & Zhang, 2020). A herbal complex extract containing *P. vulgaris* has been reported to alleviate MK-801 induced cognitive malfunction (Koo et al., 2020). A Korean medical formula containing *P. vulgaris* was found to have anti-angiogenic activity through inhibiting the cell adhesion-related FAK signaling pathway (Yi, Bang, & Kim, 2015).

The above evidence suggests that *P. vulgaris* is an herb that can potentially be used in the treatment of various diseases. Its antioxidation and anti-inflammation properties receive the most attention. In addition, its effects on apoptosis and metastatic functions in various cancers are also recognized.

4.5. Protective role of P. vulgaris and its usage in thyroid disease

P. vulgaris is generally used as a component of an herbal recipe or in combination with western medicines. Several herbal recipes exist that contain *P. vulgaris* and are used to combat a variety of diseases. Here, we have summarized herbal recipes related to the treatment of different thyroid disease patterns, including Jiayan Kangtai Granules (JYKT) (Hou et al., 2018), Haizao Yuhu Decoction (HYD) (Ma et al., 2016), Shugan Jianpi Huatan Xingqi Decoction (SD) (Bai et al., 2018), Jiakangling Capsule (JC) (Li, Wei, Li, & Meng, 2015; Liu & Liao, 2016), HKL (Liu et al., 2015) and XQHYT (Yang & Lu, 2018). This indicates that the combination of *P. vulgaris* with different types of herbs could offer distinctive treatment effects. Western medicines such as thiamazole (Yang, Guo, & Wu, 2007) and methimazole (Yang et al., 2015) are used in combination with *P. vulgaris* to promote a significant improvement in hyperthyroyditis. Combined therapy of *P. vulgaris* with PSL (Li, Wu, Chen, Hu, & Liu, 2019) or betamethasone (Li, Wang, & Zhao, 2017) are also effective and safe in the treatment of SAT. The combination

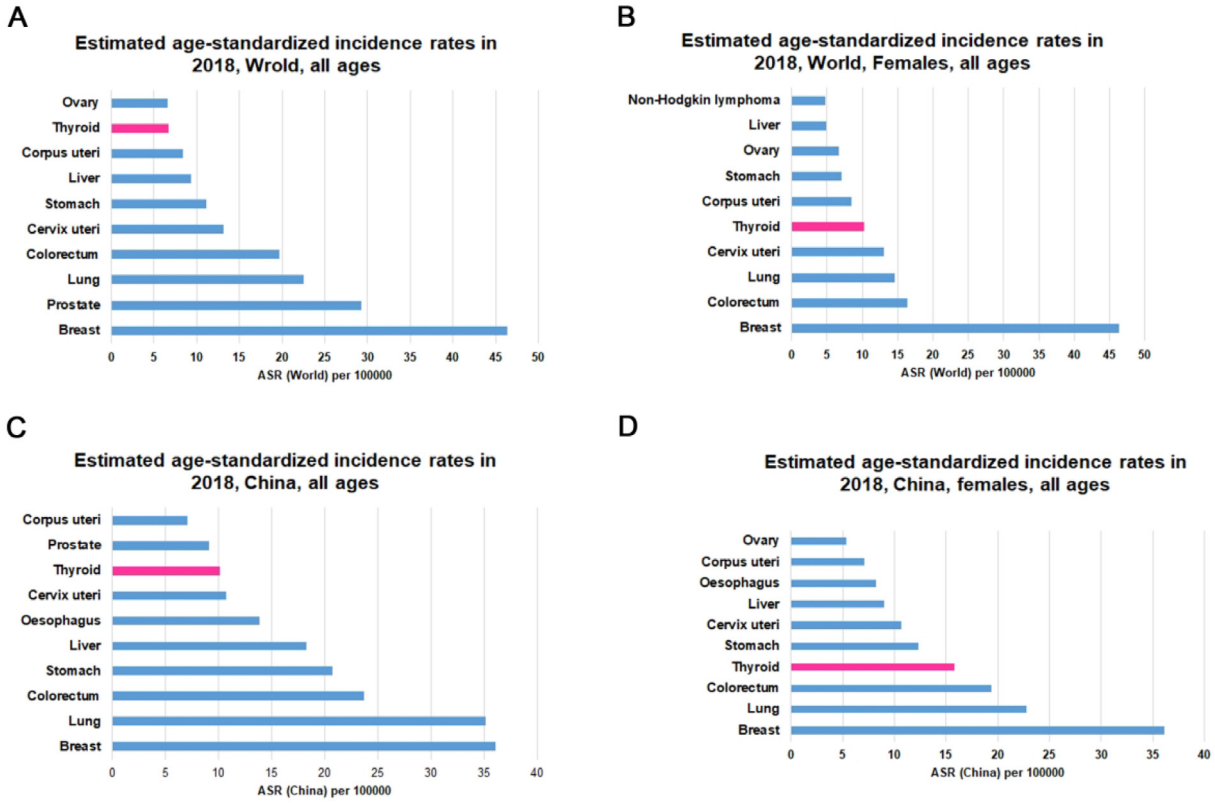

Fig. 3. Estimated age-standarized incidence rates of cancer worldwide and in China in 2018. The data obtained from the GLOBOCAN 2018, the International Agency for Research on Cancer 2018. The incidence of estimated age-standarized incidence rates (ASR) of cancer were analyzed and categorized into either 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.

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 medicine 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 pathology. Some studies have indicated that *P. vulgaris* extracts can offer protections against certain factor-induced physiological conditions. 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. vulgaris* can also protect against UVB-induced photoaging and photoinflammation through regulating the production of radical oxygen species (Zhang et al., 2018). Furthermore, flavonoid and phenolic extracts of *P. vulgaris* provided hepatoprotective activity on paracetamol 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 literature 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 following 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 containing *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 diseases, 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

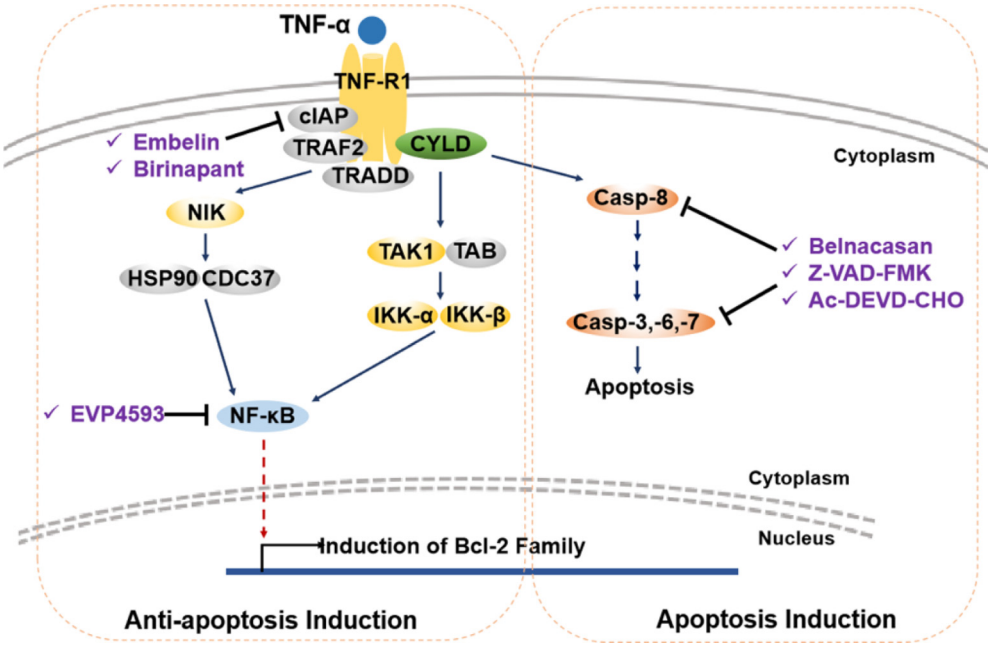

Fig. 4. Regulation of apoptosis under activation of TNF-α. The signaling pathway triggered by TNF-α can be either pro-apoptotic or anti-apoptotic. The caspase family plays a vital role during the process of apoptosis. Activation of caspase proteins and subsequent proteins could induce a cascade amplification 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.

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).

Goiter is suggested to be associated with apoptosis. Application of arachidonic acid (IL-d) in a goiter rat model showed that IL-d affects on cell proliferation inhibition and causes transient stimulation of apoptosis, and its action is not related to the oxidative stress (Thomasz et al., 2010). Iodolipids are potential inhibitors for goiter growth because they are known to modulate cell responses to growth factors and to trigger apoptosis in some cell types (Swietaszczyk & Pilecki, 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 (Gul 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, SNPrs1800629, 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/NIK/NF-κB/BCL-2 signaling pathway. In addition, the pathway of TNFR-1/CYLD/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.

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

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 *P. 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 *P. 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 *P. 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 *P. vulgaris*, conjoint analysis of identified active ingredients can be carried out based on the network pharmacology analysis. Molecules of interest and their biological targets and joined signaling pathways can be further validated through experimental methods. For example, by analyzing the activity of microvesicles captured biomolecules in the blood circulation before and after antithyroid treatment, the levels of microvesicles could provide additional information on underlying immunological disturbances (Mobarrez et al., 2016). Another example is to apply network pharmacology approach and identified *P. vulgaris* 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 *P. vulgaris* effects on the thyroid gland may start with the preparation of *P. vulgaris* extracts. There are already cancerous thyroid-derived cell lines for studying the specific molecular function of *P. 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 *P. vulgaris*. In addition, the serum or tissues of patients suffering from thyroid disorders before and after taking oral *P. vulgaris* extracts could be used for sequencing analysis. Through identifying the differently expressed genes, potential candidates of *P. vulgaris* targeted genes could be validated. This approach may help to understand why using *P. vulgaris* with other drugs improves treatment effects. Such a network would enable us to better understand the treatment effects of *P. 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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