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Review

Review of Phytochemical Composition and Impact of *Potentilla alba* Extracts on Thyroid Health and Immunity

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Abstract

Thyroid disorders are an actual global health concern requiring diverse therapeutic strategies. *Potentilla alba* (*P. alba*), commonly known as White cinquefoil, has been used in folk medicine for its rich composition of microelements and pharmacologically essential phytocompounds. It has now also gained recognition in evidence-based medicine for its potential to treat thyroid dysfunction, particularly hypothyroidism and nodular goiter. However, the complicated composition of *P. alba* extracts makes it difficult to predict the final results of such treatment and to understand its therapeutic mechanisms. The review aims to synthesize the current knowledge of the phytochemical composition of *P. alba* extracts and to analyze the mechanisms underlying its complex effects on thyroid health. Additionally, the analysis reviews the efficacy and side effects of *P. alba* extracts in preclinical and clinical research, highlighting key challenges and proposing approaches to address them.

Keywords
Potentilla alba; root extracts; phytochemical composition; micronutrients; dietary supplements; thyroid health; thyroid diseases; immunity

1. Introduction

Thyroid diseases, including thyroid cancer, hypothyroidism, hyperthyroidism, and goiter, are among the most common endocrine disorders worldwide. At this, hypothyroidism alone affects about 5% of the global population. The incidence rate of diffuse, mixed, and nodular goiter is also steadily increasing among all aging groups, reaching 100% at 80-90 years old. According to published reports, grade I-III goiter is diagnosed in 66.2% of patients, nodular goiter in 12.7%, thyroiditis in 8.4%, hypothyroidism in 7.9%, diffuse toxic goiter in 2.9%, and cancer in 1.7% [1-4].

While the main causes of thyroid diseases are the inherent factors and iodine deficiency, the essential factors that critically impact pathological changes in thyroid function are currently also given to environmental pollution from technogenic, industrial, and household waste, as well as the quality of diet and nutrition, impacting the gut microbiome-associated metabolism and immunity [3, 5, 6]. The impact of adverse environmental factors is especially critical for Europe, given the legacy of the Chernobyl disaster [5], as well as ongoing hostilities in Ukraine and other parts of the continent, which exacerbate the negative impact of environmental factors and soil iodine deficiency on food quality. This may be a cause of uncontrolled immunomodulation and an increased risk of allergic and autoimmune disorders, including autoimmune thyroiditis [6-9].

Some environmental pollutants, such as phthalates, Bisphenol A, and Polychlorinated Biphenyls, may affect the thyroid and immune systems by disrupting thyroid hormone production and altering immunological responses. These chemicals can mimic or block thyroid hormones, promoting inflammation and autoimmunity. In particular, elevated levels of anti-thyroid peroxidase antibodies are associated with exposure to Bisphenol A. The accumulation of heavy metals in the thyroid, such as mercury and cadmium, causes oxidative stress and exacerbates autoimmune processes. Infections also impact the pathophysiology of thyroid autoimmunity. Bacterial and viral infections can trigger autoimmunity through molecular mimicry, activating cross-reactive immune reactions. Recent evidence suggests that diet and nutrition impact microbiome-associated changes, and an elevated consumption of animal fat stimulates increased production of thyroid autoantibodies [3, 8-10].

The treatment of thyroid disorders is to prevent the growth of nodules, control hypothyroidism, normalize the size of the thyroid gland, and mitigate the negative impact of autoimmune reactions. The most common treatment for hypothyroidism is preparations of thyroid hormones, which lead to the normalization of the thyrotropin level and blood thyroxine, reducing the size of the thyroid gland and eliminating clinical signs of hypothyroidism. However, replacement therapy has a range of limitations and side effects, including increased risk of heart arrhythmia and osteoporosis. Thyrotoxicosis is controlled with thyrostatic therapy. The main drawback of this therapy is the high relapse rate after thyrostatic drug discontinuation [11].

A promising method for the prevention and treatment of thyroid diseases is phytotherapy, which utilizes plants capable of accumulating essential microelements and natural biologically active

compounds in significant quantities, offering fewer side effects and comparable therapeutic effects [12-18].

A large number of herbal plants are known as having anti-thyroid effects and are suitable for thyroid therapy [19-21]. Among these, *Potentilla alba* L. (*P. alba*), Rosaceae family, also known as White cinquefoil, a medicinal herb traditionally used in Eastern Europe and parts of Asia, attracts the attention of researchers and physicians due to its expressed thyroid-modulating and immunomodulating effects [21-29]. In folk medicine, the raw material of *P. alba* has been used to treat thyroid diseases since the 18th century. Evidence-based medicine mainly uses extracts from the roots and rhizomes of this plant, alone or as a part of comprehensive therapy [12-14, 22-29].

The biologically active phytocomponents of *P. alba* may have multiple physiological effects: flavonoids regulate the permeability and elasticity of the walls of blood vessels, prevent atherosclerotic changes, and neutralize free radicals; phenolic acids have antimutagenic and diuretic properties, and saponins (glycosides) have cardiotonic, neurotropic, hypocholesterolemic, corticotropic, adaptogenic, and sedative effects [14, 15, 30-32]. *P. alba* extracts also exhibit antibacterial activity. Therefore, they are used for colitis, enterocolitis, dysentery, and other gastrointestinal diseases, for the prevention and treatment of liver diseases, and also as a local wound healing agent for abscesses, furuncles, and carbuncles [15, 22, 30, 33, 34]. In addition, flavonoids, phenolic acids, saponins, and carbohydrates, contained in different herbal plants, including *P. alba*, have multiple immunoregulatory effects on innate and adaptive components of the immune system [35-39]. Although *P. alba* is not in the list of traditional immunomodulating herbal plants, *P. alba* extracts contain these phytocompounds at therapeutic concentrations. Therefore, they may have significant beneficial potential for autoimmune thyroiditis.

The first clinical studies, using *P. alba* root extracts for thyroid dysfunctions, began in Ukraine in the 1970s and showed hopeful results. However, at this stage, the application of *P. alba* was empirical and based solely on folk medicine knowledge. From 1977 to 2004, intensive studies were conducted on the application of *P. alba* in patients with thyroid hyperfunction, hypofunction, and autoimmune processes; and the plant itself was subjected to detailed spectral biochemical analysis. According to these observations and patient reviews, significant positive changes were noted in both hyper- and hypothyroid conditions [12, 13, 22, 23]. A new series of clinical studies using *P. alba* extracts from the underground parts of this plant was carried out from 2012 to 2025 [22-24, 26-29]. These studies confirm primary clinical observations and create the ground for the extended application of *P. alba* root extracts in various forms of thyroid pathologies.

Despite the long history and great potential that has been revealed in clinical studies with use of *P. alba* root extracts, conducted mainly in Ukraine, Russia, and Belarus [12-14, 22-29], and the availability of methods enabling solid dosage forms [40], in the European Union trademark of a dietary supplement, containing dry extract from the roots of *P. alba*, intended to normalize the volume and functional state of the thyroid gland, Alb-Eurika, was registered only in 2025 (IK Eurika Ltd, Limassol, Cyprus) [41]. A few other dietary supplements, containing *P. alba* root and rhizome extracts, imported from Eastern Europe, have also gained popularity in European Union pharmacies and online nutraceutical markets [30, 42]. Therefore, due to the expansion of *P. alba* preparations, there is a need for a revision of current knowledge and experience in the therapeutic application of *P. alba* extracts in thyroid health.

This review assesses the factors that impact thyroid dysfunction, analyzes the phytochemical composition of *P. alba* and the impact of its individual compounds, as well as whole extracts, mainly

from the underground part, on thyroid health in the context of thyroid hormone synthesis and immune system regulation. Since, *P. alba* extracts that are used in pre-clinical and clinical studies still do not include the detail description of quantitative and quality composition of its compounds, the review provide the first critical systemic analysis of potential combinate effects of such extracts on thyroid gland from the point of functional effects its individual components and provide new insight for researchers, pharmacologist and clinicians to control and mitigate potential risks and predict the phytotherapeutic effect. This analysis includes selected articles from 1970 to 2026, accessible in PubMed, Scopus, Web of Science, Open Research Europe, Google Scholar, and other international databases, as well as in Ukrainian and Russian national digital libraries. The search was based on keywords related to the whole *P. alba* plant, its extracts, and individual components, as well as their impact on thyroid glands, thyroid pathologies, and associated functional systems and organs in basic research, pre-clinical, and clinical studies. About 30 publications cited in some other articles were not included in the final reference list because they were not accessible in the mentioned sources, did not include sufficient information for analysis, or were presented only by abstracts.

2. Natural and Renewable Resources of *Potentilla alba*

P. alba preferably grows in temperate and subarctic climatic zones of central Europe and West Asia. The plant is distributed in a variety of environments, including deciduous forests, grasslands, heaths, and alpine slopes. This species is indigenous to France, Germany, Italy, Albania, Romania, Poland, the Baltic states, the central and southern parts of Russia, Belarus, and Ukraine [25, 30, 34, 43]. In Ukraine, *P. alba* grows in the Polesie, the forest-steppe, and in the foothills of the Carpathians [44].

P. alba is a perennial, low (no more than 30 centimeters) herbaceous medicinal plant with a branched rhizome, ending in a rosette of palmate dissected leaves with 5 leaflets. It blooms from April to June, grows very slowly, and usually does not form thickets. The seeds have a low germination rate, and seedlings take 10 to 15 years to develop. The rhizome of an adult *P. alba* has many dormant buds, due to which, using vegetative propagation, a whole plant can be grown from a 1-1.5 cm long cutting. Several dozen cuttings can be obtained from one rhizome. Cuttings are planted in spring or autumn. The plants become suitable for subsequent planting and harvesting of medicinal raw materials after 3-5 years. By this time, the underground part (rhizome and roots) has reached an optimal weight and can be used as a medicinal raw material. The rhizomes and roots are harvested in the fall when the above-ground parts die off. The grass of *P. alba* (above-ground part) does not have thyroid-stimulating activity [45-47].

Currently, biotechnological methods of *P. alba* cultivation have been developed, and the phytochemical composition of these materials has been well evaluated. This allows for greater standardization of raw materials with higher maturation rates and content of active components [40, 45, 46, 48-52]. To get biotechnologically mature raw materials, it is enough to cultivate *P. alba* for 3-4 years. During this period, polyphenolic compounds and tannins accumulate in the underground part in sufficient amounts [45, 46, 49].

The extensive demand for *P. alba* rhizomes for medical purposes threatens this species, causing it to become endangered in natural habitats [42]. Currently, *P. alba* is listed in various regional Red

Books, and therefore, the use of new biotechnological methods and renewable technologies is extremely relevant.

3. Phytochemical Composition of *Potentilla alba*

P. alba contains a complex array of bioactive compounds contributing to its medicinal properties. Major classes of phytochemicals include polyphenols (flavonoids and phenolic acids), tannins, and saponins, as well as microelements such as manganese (Mn), zinc (Zn), copper (Cu), selenium (Se), cobalt (Co), iron (Fe), silicon (Si), magnesium (Mg), aluminum (Al), sodium (Na), calcium (Ca), nickel (Ni), bismuth (Bi), lanthanum (La), molybdenum (Mo), lithium (Li), silver (Ag), iodine (I) and the anion of iodic acid, iodide (I^-). *P. alba* is a concentrator of microelements Mn, Zn, Cu, Se, Co, Fe, Si, Al, and elemental iodine. At this, for Si, Al, Zn, and Mn, their content exceeds the criterion for the degree of concentration of mineral elements for medical plants by 1.7, 2.5, 3.0, and 4.0 times, respectively [34, 42, 45, 46, 49] (Figure 1).

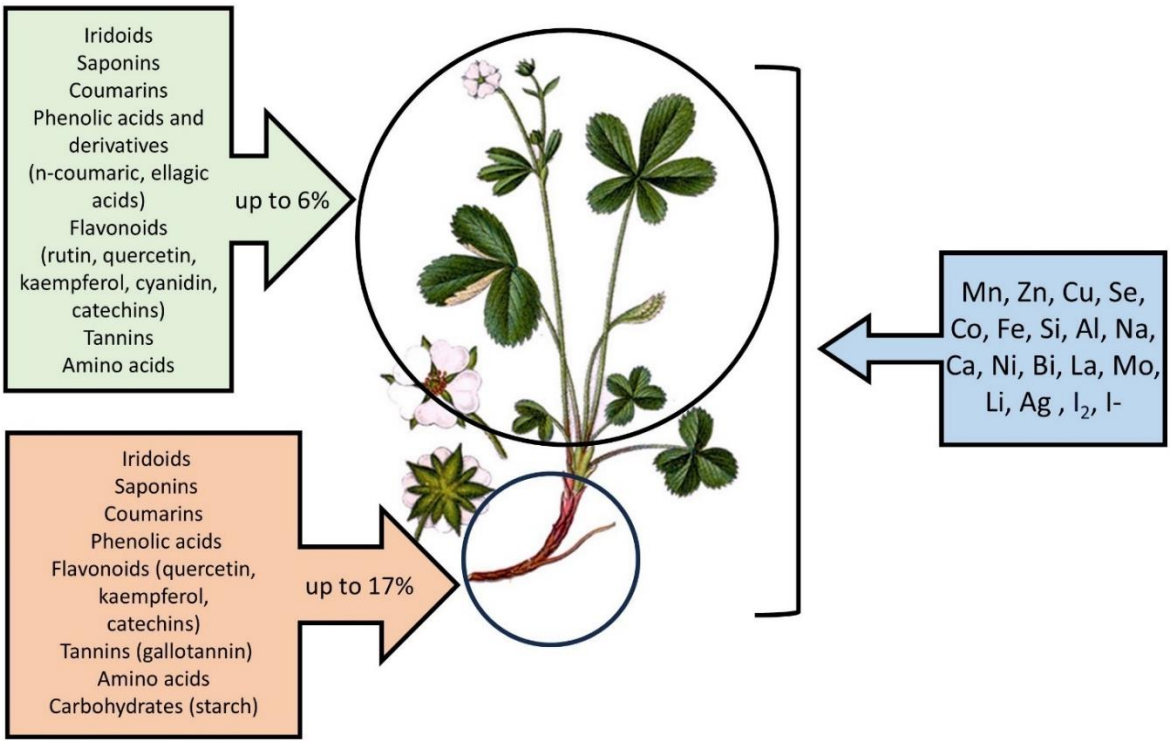

Figure 1 Phytochemical composition of *Potentilla alba*. This illustration was created using the standard Microsoft PowerPoint 12 package. The *Potentilla alba* illustration was adopted from the public domain https://ecotopia.ru/p/10465/.

P. alba contains at least 47 compounds completely identified by chromatographic and spectral methods. The underground part is rich in carbohydrates (starch), iridoids, saponins, phenolic acids, flavonoids (quercetin), and especially tannins (gallotannins). And therefore, *P. alba* belongs to the tanning plants. The tannin complex of *P. alba* consists of polyphenols and condensed tannins. At this, the underground part of *P. alba* contains 9-17% tannins, and the above-ground part 3-6%. Behind tannins, the above-ground part also contains iridoids, saponins, phenolic acids, and flavonoids (rutin). Moreover, phenolic acids and their derivatives (n-coumaric, ellagic acids), and

flavonoids (quercetin, kaempferol, cyanidin) were also found in the leaves [15, 25, 42, 45, 46, 49, 53-56].

A comparative study of the composition of biologically active compounds and the dynamics of tannin accumulation in different growth phases of wild and cultivated *P. alba* revealed a complete qualitative identity. The maximum accumulation of tannins in the roots was observed during the mass flowering phase, and amounted to 16.4% for samples in nature and 14.1% for samples in culture. The biologically active compounds are located mainly in the underground part of *P. alba* [45, 49, 52].

We must remember that the action of the whole medical plant or its extracts may differ from that of its individual components. With *P. alba* raw materials, the presence of many compounds in an extract may lead to a synergy or antagonistic effect, which can result in different biological effects than those observed with isolated substances. Therefore, a reliable assessment of the qualitative composition and quantitation content of therapeutically significant components in *P. alba* extracts is critically important for the creation of new dietary supplements or dosage forms with a predictable effect.

4. Potential Immunoregulatory Properties of *Potentilla alba* Phytochemical Complex

Plant-derived immunomodulators consist of polyphenolics, carbohydrates, terpenoids, alkaloids, lipids, organosulfur, and nitrogen-containing chemicals. The immunomodulatory activity of phytocompounds is mediated through the activation and stimulation of macrophages and lymphoid cells, as well as the suppression or enhancement of innate and adaptive parts of immune systems via impact on signaling pathways [37, 38, 57-59]. However, the mechanisms of the immunomodulation effects of most phytocompounds have not yet been fully elucidated.

Dietary polyphenols, particularly flavonoids, contained in *P. alba* extracts, may impact multiple aspects of immune function by regulating key immune cells. They can regulate the activity of immune cells, including macrophages, dendritic cells, neutrophils, NK cells, T cells, and B cells. Flavonoids inhibit the polarization of macrophages toward the pro-inflammatory M1 phenotype and facilitate their conversion to the anti-inflammatory M2 type. They can reduce neutrophil activation and modulate dendritic cell maturation and antigen presentation. Furthermore, flavonoids influence T-cell differentiation, particularly by modulating Th17/Treg balance, and suppress B-cell activation and autoantibody production, and stimulate innate immune responses by activating NK cells [35, 36, 39, 60]. Therefore, immunomodulatory properties of polyphenols can contribute to the prevention and treatment of a range of immune-dependent diseases, including autoimmune thyroiditis.

Chronic inflammation is a major driver of many diseases, including thyroiditis [61, 62]. Polyphenols play a crucial role in modulating the inflammatory response by affecting the production of cytokines that regulate immune and inflammatory responses. Polyphenols, particularly quercetin, reduce the secretion of TNF-α, IL-6, and IL-1β, which are associated with prolonged inflammatory responses. At the same time, polyphenols promote the generation of IL-10, which helps mitigate excessive immune responses and prevent the inflammatory tissue damage. Therefore, the ability of polyphenols to regulate the balance of inflammatory reactions helps maintain immune homeostasis and prevents the immune system from becoming more activated, which can lead to autoimmune disorders or chronic inflammation [35, 36, 39, 60].

The immunomodulatory and antioxidant properties of dietary polyphenols suggest their synergistic use with conventional therapies to mitigate adverse effects associated with drug therapies, which may compromise the immune system [39].

Beyond their direct interactions with immune cells, polyphenols can modulate immune responses at the epigenetic level, modifying histone methylation, acetylation, and DNA methylation, which are crucial for regulating gene expression. Dietary polyphenols can reverse these modifications, thereby restoring normal cellular functions and immune reactions [39, 60, 63]. For example, quercetin regulates histone acetylation and modulates macrophage subtype switching [39].

Saponins and carbohydrates exhibit immunosuppressive properties [37, 58] and may help reduce autoimmune symptoms. Moreover, anti-inflammatory, antioxidant, and antimicrobial properties of saponins and flavonoids (quercetin and kaempferol) [37, 64] may directly impact immune system activity and thyroid tissue functionality, as well as via the gut microbiota-immune system and thyroid-gut axis [65, 66].

In addition, trace elements, which are also essential components of *P. alba* extracts, such as Cu, Se, Zn, and Fe, are effective immunomodulatory and can prevent bacterial and viral infections and, thereby, critically impact thyroid health, especially of autoimmune thyroiditis [58, 67-70] (Figure 2).

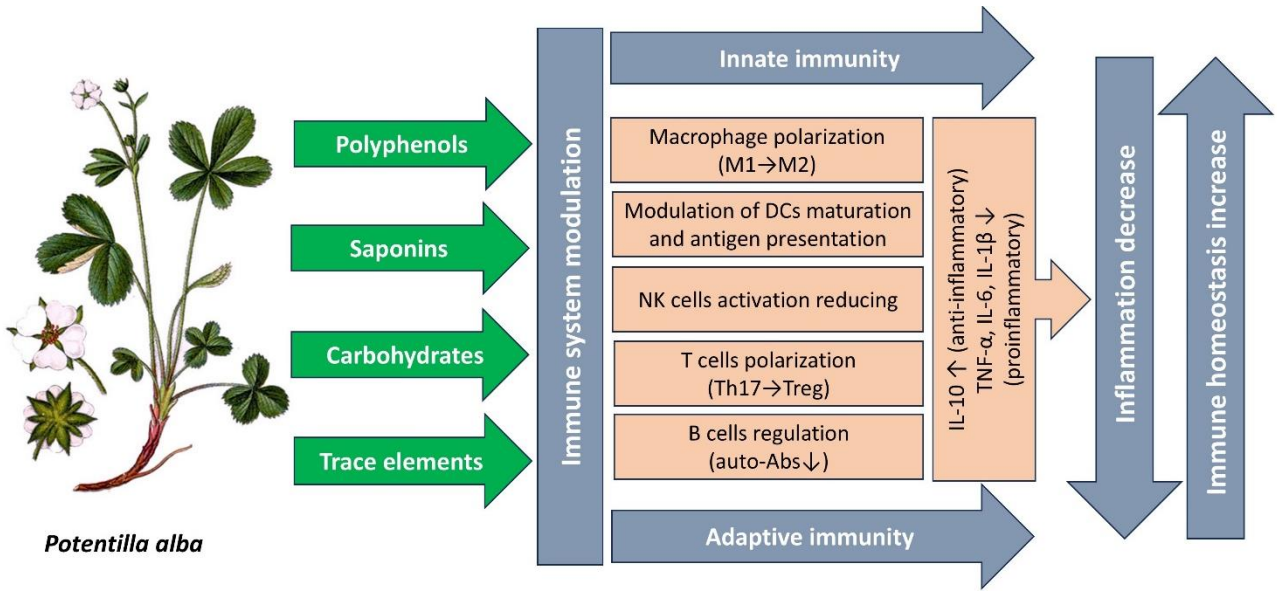

Figure 2 Potential immunoregulatory properties of *Potentilla alba* phytochemical complex. Polyphenols (flavonoids) inhibit the activation of M1-type macrophages and promote their polarization to M2-type, reduce the maturation and differentiation of dendritic cells (DCs), and activate natural killer (NK) cells and thus stimulate innate immunity. In addition, flavonoids regulate adaptive immunity by facilitating the proliferation and polarization of regulatory T cells (Treg) and suppressing the activation and proliferation of Th17 helper cells, and enhancing the activity of cytotoxic T cells. On B cells, flavonoids exhibit a dual effect. They can inhibit the production of autoantibodies (auto-Abs), as well as stimulate the production of normal IgG, IgM, and IgA. Flavonoids (quercetin) promote the secretion of IL-10 and inhibit the secretion of proinflammatory cytokines and thus reduce the inflammatory response. Saponins and carbohydrates exhibit immunosuppressive properties and may contribute to reducing autoimmune

reactions. Trace elements (Cu, Se, Zn, and Fe) suppress bacterial and viral infections, reducing inflammatory and autoimmune reactions. ↓, decrease; ↑, increase. This illustration was created using the standard Microsoft PowerPoint 12 package. The *Potentilla alba* illustration was adopted from the public domain https://ecotopia.ru/p/10465/.

5. Thyroid Pathologies

The thyroid gland is a crucial component of the human endocrine system. It regulates cellular metabolism in the body through two thyroid hormones, triiodothyronine (T3) and thyroxine (T4). Their serum concentrations are controlled by the thyrotropin-releasing hormone (TRH) secreted from the hypothalamus and by the anterior pituitary thyroid-stimulating hormone, thyrotropin (TSH) [71].

Thyroid pathologies (thyroiditis) present disorders caused by thyroidal inflammation, but appear in different ways and are separated into euthyroidism, hyperthyroidism, and hypothyroidism. The most common causes of thyroiditis are autoimmune diseases (Hashimoto thyroiditis, Graves' disease, postpartum thyroiditis, or painless sporadic thyroiditis), infection (painful subacute thyroiditis or suppurative thyroiditis), drugs (amiodarone, lithium, interferons, interleukin-2, checkpoint inhibitors), and fibrosis (Riedel thyroiditis) [2, 72-75].

Painful thyroiditis encompasses infectious subacute thyroiditis and traumatic or irradiation-induced thyroiditis; painless thyroiditis encompasses autoimmune, postpartum, and drug-induced thyroiditis. Painful thyroiditis can be classified into acute, subacute, and chronic. Bacterial infections of the thyroid gland cause acute thyroiditis, and viral infections cause subacute, also known as granulomatous thyroiditis [2, 72] (Figure 3).

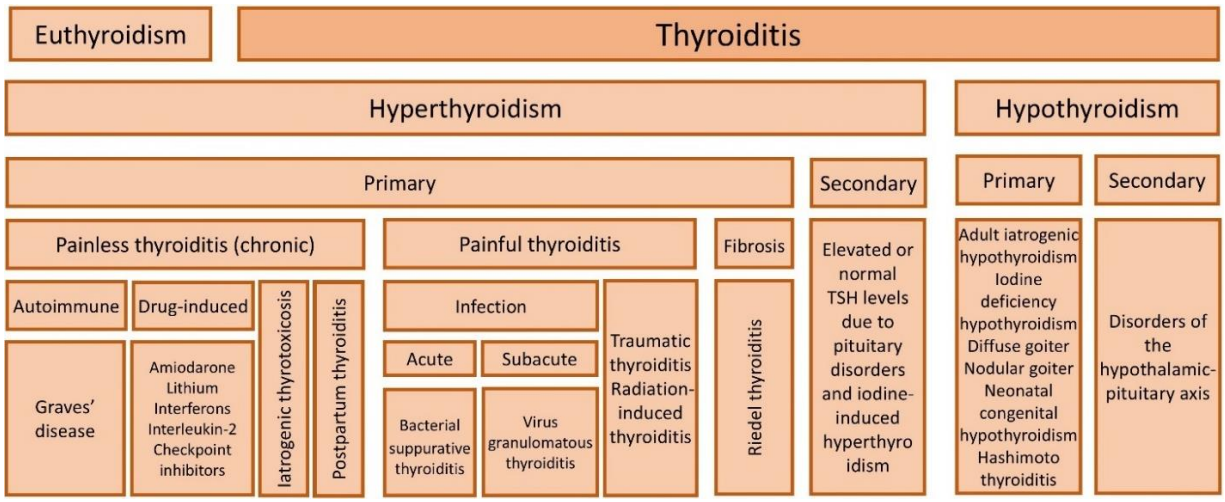

Figure 3 Various forms of thyroid dysfunction. TSH, thyroid-stimulating hormone. This illustration was created using the standard Microsoft PowerPoint 12 package.

Euthyroidism is characterized by normal thyroid function without symptoms of hypo- or hyperthyroidism and normal levels of thyroid hormones in the blood. This condition is usually associated with iodine deficiency and is characterized by an enlarged thyroid gland (euthyroid goiter) [2, 72, 73].

The overproduction of thyroid hormones leads to primary hyperthyroidism, which can be caused by diffuse hyperthyroid goiter (Graves' disease). This condition is an autoimmune disorder in which antibodies directed against the TSH receptor on thyroid follicular cells overstimulate the thyroid gland. This antibody stimulates iodine uptake, thyroid hormone generation and release, and thyroid gland growth. Secondary hyperthyroidism occurs with elevated or normal TSH levels due to pituitary disorders and iodine-induced hyperthyroidism [1, 2, 76].

Hypothyroidism can also be divided into primary and secondary, with the manifestation of decreased thyroid hormone production. Primary hypothyroidism includes iatrogenic and iodine deficiency hypothyroidism, diffuse and nodular goiters in adults, as well as neonatal congenital hypothyroidism. Secondary hypothyroidism occurs mainly due to disorders of the hypothalamic-pituitary axis function [1, 2, 72, 73].

6. Mechanisms and Cofactors of Thyroid Dysfunction

The development of thyroid dysfunction is a multifactorial process that involves both hereditary and environmental factors, acting as triggers that activate specific genes and modulate immunity [3, 6-9, 77-83] (Figure 4).

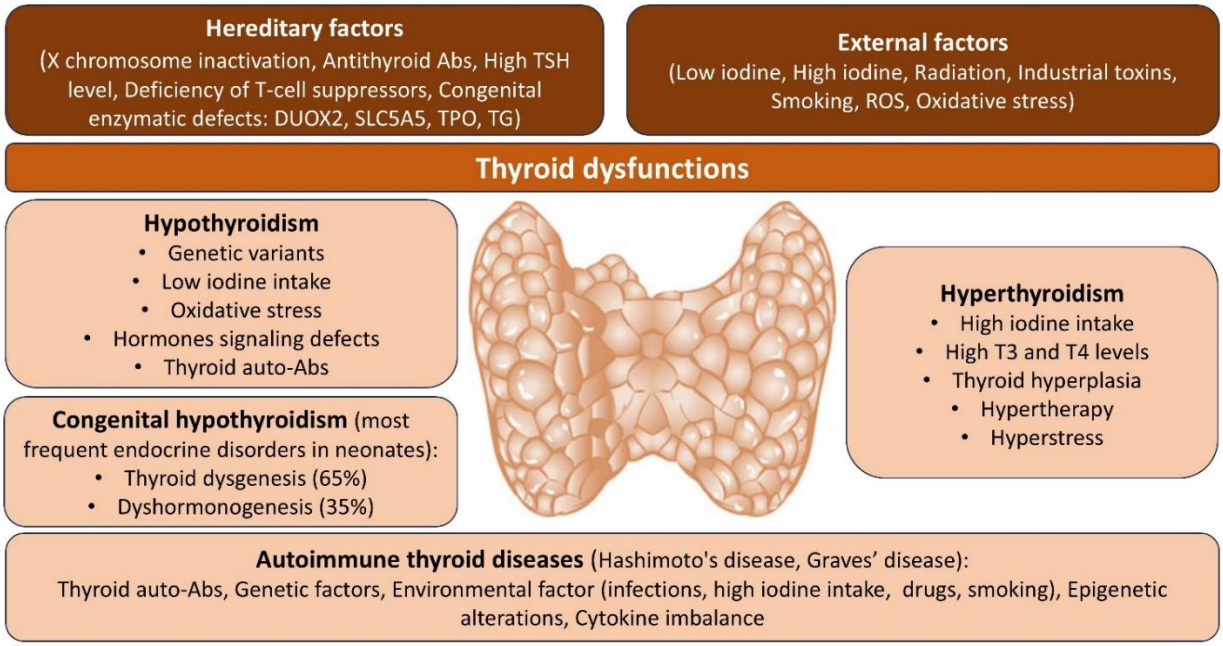

Figure 4 Impact of hereditary and external factors on thyroid dysfunction. Environmental pollutants and industrial toxins may induce oxidative stress, modulate immune response, and impair thyroid function. Radiation may induce cellular necrosis and amplify the inflammatory response. Cigarette smoke promotes oxidative stress, inflammation, and facilitates the production of autoantibodies and pro-inflammatory cytokines. D1, deiodinases 1; DUOX2, dual oxidase 2; ROS, reactive oxygen species; SLC5A5, solute carrier family 5 member 5; TPO, thyroid peroxidase; TG, thyroglobulin; TSH, thyroid-stimulating hormone. This illustration was created using the standard Microsoft PowerPoint 12 package. The thyroid gland illustration was adopted from the public domain https://centr-hirurgii-spb.ru/diseases/adenoma-paraschitovidnoy-zhelezy/.

Genetically determined mechanisms of thyroid dysfunction include inactivation of the X chromosome, the presence of microsomal antibodies, a high titer of circulating antithyroid antibodies, a deficiency of T-cell suppressors, and congenital defects of enzymatic systems and carrier proteins [77-82].

Congenital hypothyroidism is the most frequent endocrine disorder in neonates. It may be due to developmental or functional thyroid defects (primary or peripheral congenital hypothyroidism) or be hypothalamic-pituitary in origin (central hypothyroidism). In most cases, primary congenital hypothyroidism is caused by a developmental malformation of the gland (thyroid dysgenesis) or by a defect in thyroid hormone synthesis (dyshormonogenesis). Thyroid dysgenesis represents about 65% of congenital hypothyroidism, and a genetic cause is currently identified in fewer than 5% of patients. The remaining 35% are cases of dyshormonogenesis and are explained at the molecular level in more than 50% of cases [80-83].

The development and function of the thyroid gland are directed by the expression of specific transcription factors in the thyroid follicular cells, which mediate hormone biosynthesis. Membrane transporters limit the rate of cellular entry of thyroid hormones T3 and T4 into tissues, and selenium-cysteine-containing deiodinase enzymes (DIO1 and DIO2, or D1 and D2, respectively) convert T4 to the biologically active hormone T3. In turn, thyroid hormones regulate the expression of target genes via hormone-inducible nuclear receptors TRα and TRβ. Defects in thyroid transcription factors or impaired TSH receptor function may mediate primary congenital dyshormonogenesis due to mutations in genes mediating thyroidal iodide transport or iodotyrosine synthesis and recycling [79]. Thus, disorders of thyroid hormonal signaling are associated with defects in membrane thyroid hormone transporters, impaired hormone metabolism due to deiodinase deficiency, and resistance to thyroid hormones due to pathogenic variants in TRα or TRβ.

In autoimmune thyroid diseases, infection, in combination with genetic and environmental factors, may trigger an autoimmune reaction to the TSH receptor and different thyroid antigens, as well as lymphocytic infiltration of thyroid tissue. Graves' and Hashimoto's diseases are autoimmune disorders with a genetic predisposition. They are associated with the *CD40* gene, which, along with the *PTPN22* gene, is an immunomodulator for the TSH receptor and thyroglobulin [78, 83]. Graves' disease is the most common cause of hyperthyroidism and has a strong female predominance [77]. Clinical practice and twin studies show that family and genetic factors account for 60-80% of the Graves' disease risk. Variants in genes of *HLA*, *CTLA4*, and *PTPN22* have been shown to have a substantial effect on individual susceptibility to this disease [82, 83].

Infections implicated in the pathogenesis of autoimmune thyroiditis include *Coxsackie virus*, *Yersinia enterocolitica*, *Borrelia burgdorferi*, *Helicobacter pylori*, and retroviruses (HTLV-1, HFV, HIV, and SV40). Among these, infectious hepatitis C agents have the strongest affiliation with autoimmune thyroiditis. The essential triggers of autoimmune thyroiditis are also iodine, drugs, smoking, and perhaps stress [2, 3, 78, 83].

A 2024 meta-analysis of the polygenic risk score for thyroid function in up to 271040 individuals of European ancestry showed the effects of genetically determined variation in thyroid function on various clinical outcomes, including cardiovascular risk factors and diseases, autoimmune diseases, and cancer [81]. Thus, the results of genetic and population studies suggest that thyroid pathologies develop against the background of hereditary predisposition and environmental factors, and correlate with iodine intake, a key component in thyroid hormone synthesis [78-82].

Most researchers associate the prevalence of thyroid gland disease with chronic iodine deficiency, primarily in the diet [2, 84-87]. Approximately one-third of the world population lives in iodine-deficient areas, which is associated with the risk of hypothyroidism [87, 88]. The prevalence of hypothyroidism in Europe ranges from 0.2 to 5.3% [1]. Contrarily, in areas with high iodine intake, a considerable number of thyroid disorders are due to hyperthyroidism and autoimmune thyroiditis [10, 89, 90]. A 2014 meta-analysis of 17 European studies revealed a mean prevalence rate of overt hyperthyroidism of 0.75% [91].

In Ukraine, morbidity is characterized by various nosological forms. Most frequently (in 66.2% of cases) diffuse nontoxic goiter of I-III degree is developed; nodular forms of goiter are diagnosed in 12.7% of patients; autoimmune thyroiditis - in 8.4%; hypothyroidism - in 7.9%; diffuse toxic goiter - in 2.9%; cancer - in 1.7% of patients [12, 13, 22-24].

Understanding the mechanisms and factors underlying the initiation and development of thyroid dysfunction is key to effective, safe means of long-term disease control.

7. Progression of Thyroid Nodules with Aging and Thyroid Cancer

With age, the number of thyroid nodules increases by an average of 10% every 10 years. It is detected by ultrasound in 80% of women and 74% of men over 60 years old, as well as more than 60% of the general population [92-95]. The vast majority of these nodules are benign, and thyroid cancer, according to various estimates, is diagnosed in only 5-15% of cases [92, 95]. There is an association between an increase in the number of benign nodules and the incidence of thyroid cancer, the mechanisms of which remain unclear [93]. However, a direct cause-and-effect relationship between these two processes is absent. Scientific and clinical data do not support the direct transformation of benign nodules to thyroid cancer. Moreover, the scientific community adheres to the point of view that thyroid cancer arises under multiple factors from newly formed nodules with an initially existing precancerous potential [96].

Regarding the association between a significant age-related increase in the frequency of benign nodules and diagnosed cancer cases, an opposite trend has been observed, as confirmed by a well-designed academic clinical study, published in 2015, on a cohort of 6391 patients aged 20 to 95 years [97]. According to this study, in patients over 70 years of age, despite a significantly higher frequency of benign nodules (43% more than the youngest group of 20-29 years old), the incidence of diagnosed thyroid-related cancer cases was only 5.6%, compared to 14.8% in the younger patient population. In the age range of 20 to 60 years, each advancing year was associated with a 2.2% reduction in the risk that a newly evaluated thyroid nodule was malignant. After age 60, the risk of malignancy remained stable. However, diagnosed high-aggressive cancer cases in the older population were more frequent, ranging from 0% in the youngest group to 16% in the oldest group [94, 97], which is likely primarily due to the aging process of the immune system and its insufficient functionality, which allows transformed cells to escape immune surveillance and evolve towards greater aggressiveness.

8. Potential Impact of *Potentilla alba* Micronutrients on Thyroid Health

The thyroid gland function is closely connected to nutrients via the diet-gut-thyroid axis. Such micronutrients as I, Se, Zn, Fe, Cu, Mg, as well as vitamin A, and vitamin B12 influence thyroid hormone synthesis and their metabolism throughout life. An unbalanced diet can alter the gut

microbiota, leading to micronutrient deficiency, dysbiosis, and changes in thyroid function that impact nutrient absorption, epigenetic modifications, and immune system modulation [65]. These changes finally result in hypothyroidism or hyperthyroidism and possibly contribute to the initiation of autoimmune diseases and thyroid cancer [83, 86].

The manifestations of thyroid disease depend on age and correlate with iodine deficiency [87]. At this, the goiter formation is a universal compensatory reaction of thyroid tissue to iodine deficiency. A significant role in the development of thyroid pathologies is played by deviations from the norm (deficiency or excess) in the levels of iodine and other essential elements, as well as their correlations [89, 90]. Many diseases of the thyroid gland not only arise under the influence of these deviations but also contribute to their appearance. In this regard, the effectiveness of treatment and preventive measures can be significantly reduced [86].

Recent studies have demonstrated that iodine-deficient thyroid pathology is significantly aggravated by deficiencies of Se, Fe, and Zn, as the main molecular synergists of iodine, necessary for the implementation of biological effects on the pathway of thyroid hormone synthesis and metabolism [84-86]. Therefore, *P. alba*, which is rich in these, as well as other essential microelements, may benefit thyroid health by directly impacting this crucial mechanism (Figure 5).

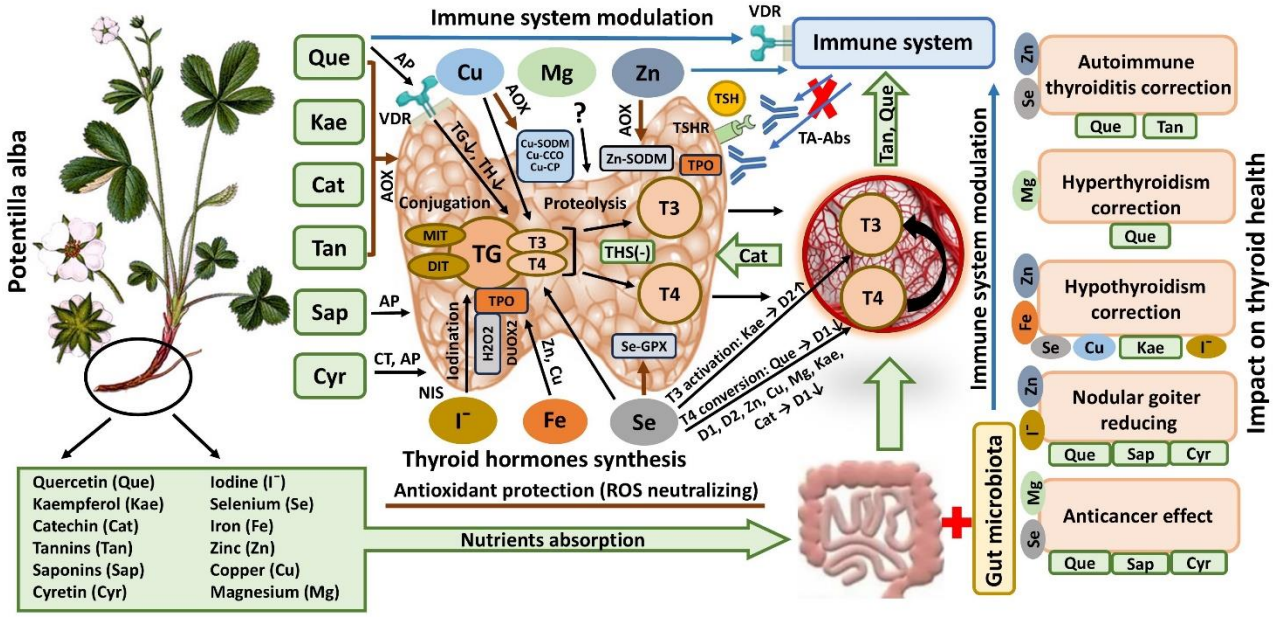

Figure 5 The potential effects of *Potentilla alba* phytochemical composition on thyroid function and health. Description in the text. Abs, antibodies; AOX, antioxidant; AP, antiproliferative; CT, cytotoxic; Cu-CCO, copper-dependent cytochrome C oxidase; Cu-CP, copper-dependent ceruloplasmin; Cu-SODM, copper-dependent superoxide dismutase; D1 and D2, deiodinases 1 and 2; DIT, diiodotyrosine; DUOX2, dual oxidase 2; H_2O_2, hydrogen peroxide; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; ROS, reactive oxygen species; Se-GPX, selenium-dependent glutathione peroxidase; T3, triiodothyronine; T4, thyroxine; TA-Abs thyroid autoantibodies; TG, thyroglobulin; TH, thyroid hormones; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TSHR, thyroid stimulating hormone receptor; Zn-SODM, zinc-dependent superoxide dismutase; VDR, vitamin D receptor. ↓, decrease; ↑, increase. This illustration was created using the standard Microsoft PowerPoint 12 package. The *Potentilla alba* illustration was

adopted from the public domain https://ecotopia.ru/p/10465/. The thyroid gland illustration was adopted from the public domain https://centr-hirurgii-spb.ru/diseases/adenoma-paraschitovidnoy-zhelezy/.

Iodine is key to the synthesis of thyroid hormones. It is absorbed in the small intestine and is transported via the bloodstream to the thyroid gland. Sodium-iodide symporter (NIS) transports circulating I^- into thyrocytes, where I^- is oxidized in the presence of hydrogen peroxide (H_2O_2), generated by dual oxidase (DUOX2) and its accessory protein, DUOXA2. Thyroperoxidase (TPO) catalyzes the oxidation of I^- into I^+, the iodination of tyrosyl residues on the surface of thyroglobulin (TG) to form monoiodotyrosine (MIT) and diiodotyrosine (DIT), and the coupling of MIT and DIT to produce thyroid hormones T4 and T3. TG-bound T3 and T4 are cleaved and secreted into the circulation. T4 enters the liver and skeletal muscle, where deiodinases D1 and D2, respectively, deiodinate it and catalyze the conversion of T4 to T3 and T3 activation [86]. Iodine deficiency results in hypothyroidism and nodular goiter, while supporting physiological balance is crucial for normalizing thyroid hormone synthesis and thyroid health [87, 88].

Se is another essential trace element crucial for the thyroid gland. Se-cysteine-containing proteins convey cellular protection along with H_2O_2-dependent biosynthesis and the deiodinase-mediated inactivation/activation of thyroid hormones. Se-dependent glutathione peroxidase (Se-GPX) catalyzes the breakdown of H_2O_2, providing antioxidant protection to thyroid glands [86]. Se deficiency is associated with hypothyroidism, thyroid cancer, and autoimmune thyroid diseases [98], while Se supplementation reduces anti-TPO-Abs levels and may help normalize thyroid function [86].

The microelement pair “I and Se” is of utmost importance in the functioning of the thyroid gland. Iodine is necessary as a building material from which two main thyroid hormones are formed, T3 and T4, while selenocysteine is part of the enzyme iodothyronine-5’-deiodinase, which provides peripheral activation of thyroid hormones. Thus, even under conditions of adequate I^- supply, with Se deficiency, the imbalance of thyroid hormones may persist. At the same time, Se-dependent peroxidases provide antioxidant protection for the thyroid gland. As an antioxidant, Se protects cytoplasmic membranes, and counteracts damage to chromosomes. Se impacts also immunity modeling. Se-cysteine-containing proteins provide cellular protection, impacting H_2O_2-dependent biosynthesis and the deiodinase-mediated inactivation/activation of thyroid hormones, which is critical for their receptor-mediated mechanism of action [86, 98].

The role of I and Se deficiency in thyroid pathology differs. Iodine deficiency provokes proliferative and hyperplastic processes in thyroid tissue, such as diffuse nontoxic goiter, nodular goiter, toxic adenoma, and cancer [10, 84-87]. Se deficiency increases the risk of thyroid autoimmune processes activation, particularly chronic autoimmune thyroiditis and toxic diffuse goiter [70, 98].

Zn plays a critical role in the TPO activity. It decreases the oxidation of DNA/RNA and proteins through Zn-dependent superoxide dismutase (Zn-SODM) and decreases the formation of reactive oxygen species (ROS). Zn acts as a link between T3 and its nuclear receptor in the hypothalamus to stimulate the synthesis of thyrotropin-releasing hormone (TRH), which in turn stimulates the synthesis and release of TSH in the pituitary glands. TSH stimulates the synthesis of T4 and T3, which are released into the bloodstream [86].

The Zn deficiency affects the function of the thyroid gland, and vice versa, thyroid hormones impact Zn metabolism [86]. Since Zn is a component of multiple proteins, the molecular mechanisms

of its effect on the thyroid gland vary. The so-called zinc fingers were found in the structure of the T3 receptor. These are specialized protein fragments that chelate Zn. The Zn-containing enzyme Zn-SODM provides antioxidant protection for the thyroid gland. A decrease in this enzyme's activity increases the risk of thyroid hyperplasia [99, 100].

Higher dietary Zn intake [69], as well as Zn deficiency [68], may increase the risk of autoimmune thyroiditis. However, Zn supplementation does not affect serum thyroid autoantibody levels in individuals with autoimmune thyroiditis [67].

Zn, likely, may impact the intensity of iodine metabolism [84, 86]. However, there is still little evidence that the metabolic interaction between iodine and Zn may have an impact on thyroid function.

Fe is the central atom in the active sites of TPO. Fe deficiency is associated with hypothyroidism due to the reduced biosynthesis of the TPO. Randomized controlled trials in I and Fe-deficient human populations showed that providing Fe together with iodine results in a more effective improvement of thyroid function and volume than iodine alone [84]. Disbalances in the thyroidal content of I^-, Fe, and Se negatively impact the regulation of the hypothalamic-pituitary-thyroid axis, facilitating metabolic disorders and autoimmune thyroid diseases [84-86]. Fe deficiency decreases the total T3 level by 43% and the total T4 level by 67% [86].

Thus, it is now believed that Se, Zn, and Fe deficiency aggravate the course of iodine deficiency processes. Replenishing these trace elements with *P. alba* extracts may be important for preventing and treating thyroid diseases.

Cu is a trace microelement involved in several key processes related to thyroid hormone synthesis and regulation. It is a cofactor for tyrosinase and is involved in the conversion of inactive T4 to the biologically active T3. Cu is necessary for the TPO synthesis, a precursor to thyroid hormones, and the subsequent coupling of iodotyrosine residues to form T4 and T3 [100, 101]. Moreover, Cu is an antioxidant, and its imbalance may lead to oxidative stress and thyroid dysfunction [86]. Antioxidant actions occur through Cu's role in Cu-dependent superoxide dismutase, which mitigates oxidative stress, and Cu-dependent enzymes cytochrome C oxidase and ceruloplasmin [102]. Cu also contributes to calcium level regulation in the body, which, in turn, prevents the overabsorption of T4 in blood cells and is important for hormone level regulation and supporting optimal thyroid function [100]. A deficiency of Cu is related to subclinical hypothyroidism [103] or hypothyroidism [104].

Mg is involved in various aspects of thyroid function, as it is required for activation of adenosine triphosphate, DNA replication, and transcription. Mg is a cofactor of several enzymes and enzymatic reactions and is involved in the metabolism of thyroid hormones. It can indirectly influence deiodination, which catalyzes the conversion of T4 to the more active T3 form [101, 105]. Additionally, as a second messenger, Mg is involved in the regulation of thyroid hormone receptor sensitivity, affecting the receptivity of target tissues to thyroid hormones and balancing oxidative phosphorylation [106]. Mg deficiency is associated with impaired thyroid function, metabolic disorders, and carcinogenesis. It is linked to inflammation and free radicals, which can cause oxidative DNA damage and cancer [86]. In combination with coenzyme Q10 and Se and inefficient oxidative phosphorylation, Mg deficiency may lead to mitochondrial dysfunction and the development of hyperthyroidism. Therefore, a balanced Mg level may be beneficial for supporting thyroid and overall health [107].

Exploring the relationships among iodine metabolism, thyroid function, and other significant micronutrients based on molecular biology, physiology, biochemistry, pharmacology, and evidence-based medicine is relevant and necessary to develop a more effective, comprehensive approach for patients with thyroid dysfunctions.

9. Potential Impact of *Potentilla alba* Phytochemical Compounds on Thyroid Health

The presence of flavonoids, saponins, and tannins in the extracts of *P. alba* roots and rhizomes, in combination with essential microelements and a significant number of hydroxyl groups, confers thyroid-specific biological activity of *P. alba,* supported by experimental and clinical studies. These studies demonstrate that *P. alba* may impact thyroid health through several mechanisms associated with its phytochemical composition, including antioxidant defense, modulation of immune function, regulation of thyroid hormone synthesis, and inhibition of thyroid nodular growth. These properties of *P. alba* can be used in the complex therapy of thyroid pathologies as a thyroid-stimulating, antioxidant, anti-inflammatory, immunomodulating, and anticancer agent [12, 13, 18, 23, 30, 64, 108-122] (Figure 5).

Recent studies with the use of animal models reported the positive influence of the balm containing iodine, starch, ascorbic acid, sodium chloride, and glycerin in combination with a *P. alba* root extract on the condition of adrenergic innervation of the thyroid gland, thyroid blood vessels, lymph nodes, and lymphatic vessels in an induced hypothyroidism rat model. The *P. alba* extract increased the levels of the thyroid hormones T3 and T4 by 34% and 30%, respectively, restored morphological structure, and reduced proliferative processes in the thyroid gland [109]. These *P. alba* effects are possible due to the presence of ellagic acid in the extract, which is capable of binding to TSH, as well as the content of phenolic compounds, iodine, and iodic acid anion, and trace elements Zn and Se, the presence of which is necessary for the functioning of thyroid hormones. Iodine compounds in *P. alba* may stimulate or regulate the synthesis of T3 and T4 hormones [85]. Several studies demonstrate that *P. alba* can restore normal thyroid function by supporting natural thyroid hormone production, especially in iodine-deficient conditions [12, 13, 22-24, 26-29].

Thyroid cells are highly susceptible to oxidative stress due to their role in hormone synthesis, which involves the reactive oxygen species (ROS). *P. alba's* polyphenols, flavonoids, and tannins neutralize ROS, reducing oxidative damage to thyroid cells. This antioxidant activity is particularly relevant for Hashimoto's thyroiditis and other inflammatory thyroid disorders. Several reports verified the high antioxidant properties of various extracts from the herbal parts of *P. alba* [108]. Similar significant antioxidant activity was also reported for water and methanol extracts obtained from rhizomes and roots of *P. alba* [64].

Such flavonoids, as quercetin, kaempferol, catechins, and tannins contained in *P. alba*, play a crucial role in reducing oxidative stress in the thyroid gland [14, 15, 85, 110]. At this, quercetin is highly tropic to the vitamin D nuclear receptor (VDR) [110, 111] via which vitamin D regulates gene expression responsible for thyroid hormone synthesis, influences the immune system, and overall thyroid health [123]. Vitamin D deficiency is considered a risk factor for the development of many thyroid disorders, including thyroid cancer and hypothyroidism caused by autoimmune processes [123, 124]. The immune-mediated properties of vitamin D decrease anti-thyroid antibody levels and reduce the symptoms of hypothyroidism caused by autoimmune factors. Maintaining adequate vitamin D levels improves thyroid gland function and prevents disease-related complications [124].

Results of a recent randomization study published in 2024 support a suggestive causal effect that higher genetically predicted vitamin D concentration lowers the odds of having high TSH or autoimmune hypothyroidism [125].

Quercetin, one of the main *P. alba* polyphenolic compounds, directly interacts with VDR and has antiproliferative, antiviral, anti-inflammatory, and antioxidant properties [111], reducing the production of thyroid auto-antibodies, such as anti-TPO and anti-TSHR (thyroid-stimulating hormone receptor).

I*n vitro* studies demonstrated that quercetin inhibits the growth and function of normal thyroid cells and may therefore act as a thyroid disruptor. This effect has been confirmed *in vivo* on rodent models [112]. A molecular mechanism of this antiproliferative effect of quercetin is the inhibition of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway [113]. Some studies reported that quercetin can interfere with thyroid hormone metabolism. In particular, quercetin inhibits 5-deiodinase type 1 (D1) activity [114] and iodide uptake by thyroid glands, and this downregulates the expression of the *NIS* gene. It was reported that 14-day quercetin treatment significantly decreased radioiodine uptake by thyroid glands in rats [112]. Contrary to the expected effect, which is analogous to the action of vitamin D, quercetin reduces the expression of TSH receptors as well as TG and TPO genes [113]. This effect of quercetin may be due to its dose-dependent action [114] on the thyroid gland and high binding constant with VDR [111].

Besides the destructive effects on normal thyroid cells, experiments *in vitro* reported a potential therapeutic role of quercetin in thyroid cancer, since quercetin inhibits the growth, adhesion, and migration of cancer cells. Quercetin also shows redifferentiation properties in some thyroid cancer cell lines [113]. Together, these data suggest that, although the effects of quercetin can benefit hyperthyroidism and thyroid cancer, caution is required when using long-term high doses of quercetin due to its anti-thyroid properties [115].

Another small polyphenolic molecule, kaempferol, unlike quercetin, demonstrated impressive thyroid-stimulation properties, activating the cAMP-responsive gene for type 2 iodothyronine deiodinase (D2), an intracellular enzyme that activates thyroid hormone T3. At this, kaempferol dramatically and selectively increases the D2 half-life and the rate of T3 production, which persists even 24 h after kaempferol is removed from the system [116]. However, few publications report the effect of kaempferol on thyroid health. It was reported that there is a link between consuming foods high in kaempferol and lowering the risk of acquiring cardiovascular disease, diabetes, obesity, and cancer [117].

The effect of catechin on thyroid physiology has been little investigated. In the experiment on rats, catechin decreased the activities of TPO and D1, while significantly increasing the Na(+), K(+) ATP activity in a dose-dependent manner. It was also noted that there was a substantial decrease in serum T3 and T4 levels, coupled with a significant elevation in serum TSH. Histological examinations of the thyroid gland revealed marked hypertrophy and hyperplasia of the thyroid follicles with depleted colloid content [118].

P. alba is rich in hydrolyzable tannins (belonging to the polyphenol group), which exert antioxidant, anti-inflammatory, and immunomodulatory effects. These properties are beneficial in autoimmune thyroid disorders, such as Hashimoto's thyroiditis and Graves' disease, where oxidative stress and inflammation play significant roles, resulting in immune dysregulation [2, 78, 112]. *P. alba* exhibits immunomodulatory effects, helping to balance Th1/Th2 responses and modulating antibody production, and blocking their connection with the TSH receptor and thus

potentially reducing autoimmune reaction in Hashimoto's and Graves' diseases [15, 30, 119]. However, there is still little evidence supporting this assertion.

Saponins are an important group of natural glycosidic compounds. They possess high structural diversity, which is linked to their anticancer activities. Several studies reported mechanisms of anticancer action, including cell-cycle arrest, antioxidant activity, inhibition of cellular invasion, induction of apoptosis, and induction of autophagy. However, despite the significant anticancer effect, no saponin-based anticancer drugs are currently known. This can be attributed to several limitations, including toxicities and drug-like properties [120, 121]. *P. alba* saponins are linked to anti-inflammatory and antitumor properties, which can impact thyroid nodules' growth and prevent their progression [42, 53, 108]. In cases of nodular goiter, *P. alba* has demonstrated anti-proliferative effects on thyroid cells, potentially slowing the progression or reducing the size of thyroid nodules. Saponins and polyphenols may contribute to this effect by regulating cell proliferation and apoptosis pathways [15, 26, 30, 54, 55, 117].

Finally, *P. alba* extracts abundant in caffeoylquinic acid and its derivative cyretin (cynarin), demonstrate cytotoxic properties and display the highest antineoplastic activity due to their ability to modulate the cell cycle and thus increase apoptosis [108].

Summarizing the above sections, we note that this knowledge is highly relevant to creating *P. alba* preparations with a targeted effect. However, to achieve the desired result, it is necessary to consider the potential synergistic and antagonistic effects of various components of *P. alba* when they are used together. In this aspect, it would be interesting to explore the combined effect of selected compounds of *P. alba* extracts with the vitamin B5 and vitamin U combination [126]. While vitamin B5 (pantothenic acid) and vitamin U (S-methylmethionine) are not directly linked to thyroid hormone production, they play remarkable roles in overall health that can indirectly impact thyroid function. Vitamin B5 is crucial for energy production and hormone synthesis, including those related to the adrenal glands, which can influence thyroid hormone regulation. Vitamin U, on the other hand, is known for its protective and regenerative effects on the gastrointestinal mucosa and gut microbiota [126], which can be beneficial for thyroid health through its impact on the gut-thyroid axis [66].

10. *Potentilla alba* Clinical Efficacy and Toxicity in Thyroid Diseases

P. alba extracts (roots and rhizomes) are currently used in traditional medicine, mainly in Eastern Europe, preferably in Ukraine, either alone or as a comprehensive therapy against thyroid gland impairments [12, 13, 30].

Several independent controlled clinical studies using *P. alba* root extract, 300 mg, twice a day for 2-6 months in single or combined therapies to treat diagnosed hyperthyroidism, hypothyroidism, chronic autoimmune thyroiditis, subclinical autoimmune thyroiditis, diffuse nontoxic and toxic goiters, mixed diffuse and benign goiter, and nodular formations in the thyroid gland were carried out from 2012 to 2025 in Ukraine. These treatments demonstrated reductions in thyroid size and normalization of thyroid function, decreased serum antibody levels against TSH receptors, and shorter time to stabilize TSH serum levels [21-24, 26-29, 127].

In clinical studies published in 2012, 2013 and 2017, the use of *P. alba* root dry extract in adult patients, compared to the control groups (total 178 participants), resulted in significantly decreased somatic symptoms of hypo- and hyperthyroidism, as well as a reduction in the volume of the

nodules, improved the morphological structure and function of the thyroid gland, reduced antibody levels to TSH receptors, and normalized TSH levels to the average population level against the background of a decrease in the total volume of the thyroid gland. The normalization of TSH levels was accompanied by an improvement in general well-being and correlated with reduced risk of further disease progression. As underlined in these studies, intolerance, side effects, or treatment refusal were not observed [22-24, 26].

One clinical observation, published in 2014, demonstrated the efficacy of the *P. alba* root dry extract in children aged from 9 to 18 years (35 participants). The highest efficiency was observed in children with diffuse toxic goiter and nodular formations in the thyroid gland, who received *P. alba* treatment for 6 months. After 6 months of using the preparation, the thyroid gland volume decreased by 24.2%, the TSH level increased 3-fold, and stable remission occurred in these patients [27].

The use of *P. alba* extract in two independent clinical studies, published in 2017 and 2019, in adult patients with subclinical (100 patients) and chronic (60 patients) autoimmune thyroiditis, in addition to standard therapy, resulted in a reduction in somatic disorders and normalization of the thyroid gland functional state. An analysis of the tolerability and clinical safety of herbal therapy in addition to standard therapy showed that this treatment was well tolerated and safe in 100% of cases [28, 29].

The results of these studies indicate the clinical efficacy of the *P. alba* preparation in adults, children, and adolescents with thyroid diseases of normal, decreased, or increased function. Good tolerability to the *P. alba* preparations was noted with long-term use (3-6 months) and the absence of side effects [22-24, 26-29].

In a 2020 clinical study, the combined herbal complex with 80 mg of *P. alba* extract was administered for 3-4 weeks to 11 sick women working in chemical factories. This study demonstrated progressive improvement in the general condition of thyroid patients, as well as a decrease in the manifestations of lesions in the cardiovascular system, hepatobiliary system, digestive tract, and central nervous system, which made it possible to reduce the dose of anti-ischemic, antiarrhythmic, and hypotensive drugs. Three months after the treatment, TSH levels were within normal limits [127].

The clinical study of 2025, which included 147 adult patients with nodular goiter and different thyroid functional state demonstrated that dietary supplement, containing *P. alba* root and rhizome dry extract alone or in combination with dry extract of black chokeberry fruits (*Aronia melanocarpa*), dry extract of flowers and fruits of red haw hawthorn (*Crataegus sanguinea*), and sodium selenite is more effective in nodular goiter with hyperthyroidism and euthyroidism for 6-month administration. The best effect for endemic and mixed goiter without thyroid dysfunction was due to undergoing combined therapy for 3 months. As reported, thyroid status in these patients remained normal, antibody levels were unchanged, and there was a tendency to a decrease in the size of thyroid nodules, as well as a significant decrease in the volume of the thyroid gland [21].

Finally, a 3-month open-label pilot study published in 2025 used a complex, which included extracts of *P. alba*, *Rhodiola rosea*, and *Feijoa* along with small amounts of vitamins B1, B2, and B6 in patients aged 18 to 65 (16 women and 11 men) with subclinical hypothyroidism. A three-month course of using this dietary complex contributed to a noticeable normalization of thyroid indicators. There was a tendency to reduce the levels of TSH, a significant increase in the level of free T4 and T3, and a decrease in the anti-TPO antibody levels. Biochemical changes were accompanied by a

tendency to improve well-being, activity, and mood. In accordance to authors' conclusion, the results demonstrated the effectiveness of the complex dietary supplement and the prospects for its preventive and therapeutic use in people with thyroid dysfunction [128].

It should be noted that all these clinical studies and observations, involving *P. alba* extracts, included only individuals whose levels of thyroid hormones and TSH were within the reference values or had insignificant deviation. Patients with clinically pronounced dysfunction of the thyroid gland who were on drug treatment were not included in the studies. Therefore, the conducted studies suggest the essential prophylactic and therapeutic value of *P. alba* root extracts in the subclinical stage of thyroid pathology. Additional well-designed studies are required to assess the therapeutic potential of *P. alba* preparations for clinically expressed symptoms confirmed by laboratory indicators. We should also underline that these studies used the dry extract of *P. alba* as a diet supplement, which does not require detailed characterization but still raises questions, especially with the development of *P. alba*-based drugs.

11. Safety and Side Effects

Despite the long-time usage of *P. alba* preparations in medicine, the full toxicological profile has not been fully explored through studies in humans. However, animal rodent models are an acceptable alternative to assess the toxicological potential of herbal formulations. For the aerial parts of *P. alba*, the LD_{50} value of 2359.9 mg/kg body weight was calculated based on acute toxicity testing in mice at the dose range of 1000-4000 mg/kg body weight. In a chronic 3-month toxicity study in rats, the administration of 239 mg/kg body weight (i.e., 1/10 of LD50) showed no negative impact on the laboratory animals. According to the Organization for Economic Co-operation and Development (OECD) classification, the authors classified the aerial part of *P. alba* as virtually nontoxic [129].

The toxicity of *P. alba* rhizome extract was evaluated in mice and rats. Single intraperitoneal and 3-month multiple administration did not cause toxicity or mortality in the tested rodents [130]. The extract prepared from the underground parts of *P. alba* showed an LD_{50} value of 6500 mg/kg body weight in male and female rats. Immunotoxicity studies in the two mouse breeds revealed that the dry rhizome extract from *P. alba*, at a dose of 50 mg/kg body weight, had no negative impact on humoral, cellular, or macrophage immunity. One study reported that *P. alba* rhizome extract administered to albino guinea pigs at 3 mg/kg body weight stimulated the primary humoral response. The tested sample had no sensitizing effect in tests of systemic or active skin anaphylaxis or delayed hypersensitivity [131].

However, *P. alba* preparations administered orally affect the natal and postnatal periods in rat offspring, resulting in delayed ossification in fetuses, decreased sperm motility and a higher number of pathological spermatozoa in male rats [132]. Despite these observations, the authors concluded that the extract did not significantly affect rodent fertility or offspring development [133].

Similar results were published in 2025 by another research grope used the *P. alba* dry extract, containing mainly 61.29% phenolic compounds (catechins, gallic acid, p-coumaric acid), 25% polysaccharides, and 2% phytosterols (beta-sitosterol). Male Wistar rats were orally treated with a standardized drug preparation for 60 consecutive days, at doses 8 and 40 times the median therapeutic dose recommended for the clinical trials. Treatment significantly decreased the motility of the sperm and increased the number of pathological spermatozoa. Additionally, a dose-

dependent effect on Leydig cells was observed. However, these *P. alba* effects did not significantly affect male fertility nor fetal and offspring development when treated males were mated with intact females [134].

Long-term administrations of the dry extract of *P. alba* into the stomachs of clinically healthy rats of both sexes in 2.5, 12.5-37.5 times therapeutic doses caused hypothyroidism and hypolipidemic action. The dry extract at all tested doses showed no toxic effects on the blood, cardiovascular, and nervous systems of rats. Prolonged administration of the studied extract at the maximum tested dose (375 mg/kg) resulted in a moderate damaging effect on the liver and kidneys of rats of both sexes, as well as the testes. The threshold dose was 25 mg/kg [135].

A toxicity study of tablets containing 150 mg of dry extract of the roots and rhizomes of *P. alba* was conducted in 2023 on 15 male rabbits, which received tablets at doses of 37.5 and 75 mg/kg for 90 days. Control animals received placebo tablets. Administration of tablets at 9- and 17-fold therapeutic doses did not affect the hematological, biochemical, or electrocardiographic parameters characterizing the functional state of the liver, kidneys, and cardiovascular system. A histopathological examination revealed a dose-dependent suppression of thyroid function and spermatogenesis. At the maximum tested dose of 75 mg/kg, the drug exerted a selective pharmacological effect on the pituitary gland, reducing the size of basophilic cells. No adverse changes in the gastrointestinal mucosa were noted [136].

Thus, the safety profile of *P. alba* appears favorable, with minimal reported adverse effects when used at recommended doses. However, patients with hyperthyroidism or those already on thyroid medication should use *P. alba* in consultation with their physician to avoid potential drug interactions and hormonal imbalances. Additional toxicological studies are recommended to establish *P. alba's* long-term safety profile, especially for individuals with underlying health conditions.

12. Conclusion

The complex phytochemical composition of *P. alba* roots and rhizomes, encompassing polyphenols, flavonoids, tannins, saponins, polysaccharides, and microelements, has a multifactorial impact on thyroid health, supported by experimental and clinical studies.

Low toxic profile and absence of side effects at long-term application support the use of *P. alba* extracts as a promising herbal therapy, both as a monotherapy and part of comprehensive treatment for various forms of hypo- and hyperthyroid disorders associated with increased growth of thyroid nodules and their potential transformation into malignancy.

While published evidence suggests that extracts prepared from *P. alba* roots and rhizomes are a promising herbal therapy, the underlying mechanisms of action, bioavailability, pharmacokinetics, and cumulative effects of the main active compounds remain to be assessed. Furthermore, the resulting action of these components can be both synergistic and antagonistic, as between these components and with thyroid hormones. Therefore, to achieve optimal results and avoid unwanted side effects, it is essential to control the phytochemical composition of the manufacturing process and standardize extracts to maintain the certified bioactive compound composition and concentration.

Large-scale, randomized, well-designed clinical trials are needed to verify efficacy across different thyroid disorders with varying degrees of severity and to evaluate the long-term consequences of such treatments.

As a potential natural adjunct or alternative to conventional treatments, *P. alba* may be considered for integration into management strategies for thyroid disease, taking into account the phytochemical composition of the preparation, disease specificity, as well as age, gender, dietary habits, and lifestyle of patients.

The high demand for underground parts of *P. alba* requires further efforts to develop efficient renewable biotechnological raw materials with compositions similar to or improved upon those of underground parts of P. alba.

Noted aspects have to be the main focus of ongoing studies to fully reveal *P. alba's* potential, create targeted preparations, and further substantiate the use of *P. alba* extracts for various thyroid pathologies.

Author Contributions

V.P. Shichkin has done all parts of this manuscript (conceptualization, literature search, formal analysis, manuscript writing, illustrations creation, manuscript edition, submission, and revision). O.V. Kurchenko has done conceptualization, literature search, formal analysis, and revision.

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