



Review Article

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# Insight into Therapeutic Role of Plant-derived Medicines in Thyroid Dysfunction

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## Abstract

Endocrine disorders are very common in Asia of which the thyroid dysfunction (TD) represents a major subset. The prevalence of TD is rising to an alarming rate. The thyroid gland (TG) is morphologically a butterfly-shaped organ, located anterior to the trachea, just inferior to the larynx and flanked by wing-shaped left and right lobes with the medial region called isthmus. TG produces thyroid hormones (TH), mainly triiodothyronine (T3) and thyroxine (T4). TH action is mediated by multiple TH receptors belonging to a nuclear receptor superfamily that also includes receptors for other small lipophilic hormones. TH receptors function by binding to specific TH-responsive sequences in promoters of target genes and by regulating transcription. Regulation of TH is followed by the hypothalamic-pituitary-thyroid axis. TD can be due to overproduction or under production of TH; i.e. hyperthyroidism and hypothyroidism respectively. Hyperthyroidism is characterized by weight loss, heat intolerance, palpitation, increased sweating, warm soft skin, increased heart rate and blood pressure. Whereas; in hypothyroidism, the facial expressions become dull, the voice becomes husky, speech is slow, the eyes and face become puffy. Hormone replacement therapy has been a standard approach to TD. However, herbal approach for the treatment of thyroid dysfunction is gaining popularity as it is proved to be effective, safe and devoid of any or at least lesser side effects. According to the world health organization (WHO), about three-quarters of the world population depends upon natural remedies, including herbal medicine. Plants possess several secondary metabolites like phenols, phenolic acids, flavonoids, alkaloids, tannins, quinones, coumarins, saponins, terpenoids, triterpenoids, glycosides and organic acids, which affect thyroid dysfunction by different mechanisms. Therefore, this review aims to provide comprehensive information regarding various herbal drugs used in the management of thyroid dysfunction.

**Keywords:** Endocrine system, Thyroid gland, Hyperthyroidism, Hypothyroidism, T3 (Triiodothyronine), T4 (Thyroxine), TSH (Thyroid Stimulating Hormone), TPO (Thyropoxidase), Natural products

## Introduction

### Endocrine system

Endocrine system comprises of the endocrine glands and the hormones they produce; and it is intimately related to the hormone secretion, its actions and principles of feedback mechanisms [1,2]. Endocrine glands are richly vascularized, ductless organs that secrete hormones into the interstitial spaces and circulatory system. Endocrine system maintains homeostasis through the collaborative function of various endocrine glands, including pituitary gland, thyroid gland, parathyroid gland, adrenal gland, gonads, pancreas, gut endocrine cells and adipose tissues [3]. Endocrine glands not only communicate with each other but are also linked with immune system, stress system and gut microbial

flora. All this communication occurs through chemical mediators called hormones [4].

### Thyroid gland

The thyroid gland is morphologically a butterfly-shaped organ, located anterior to the trachea, just inferior to the larynx. It is flanked by wing-shaped left and right lobes and the medial region called isthmus [5]. The thyroid gland produces thyroid hormones, mainly triiodothyronine (T3) and thyroxine (T4). Thyroid hormone action is mediated by multiple thyroid hormone receptor isoforms derived from two distinct genes. The thyroid hormone receptors belong to a nuclear receptor superfamily that also includes receptors for other small lipophilic hormones. Thyroid hormone receptors function



by binding to specific thyroid hormone-responsive sequences in promoters of target genes and by regulating transcription. Regulation of thyroid hormone is followed by the hypothalamic-pituitary-thyroid axis [6]. Thyroid hormone exerts both positive and negative feedback mechanism by the hypothalamus as well as anterior pituitary, which controls the release of both TRH from hypothalamus and TSH from anterior pituitary gland [7].

### Thyroid dysfunction

Thyroid disease is very common worldwide affecting 5-15% of general population. Women are 3-4 times more susceptible to experience any type of thyroid disease. Thyroid dysfunction can be due to overproduction or under production of thyroid hormones; i.e. hyperthyroidism and hypothyroidism respectively. Hyperthyroidism is characterized by weight loss, heat intolerance, warm soft skin, increased heart rate and blood pressure, palpitation and hyper-sweating. Hyperthyroidism can be caused by graves' disease, painless thyroiditis or postpartum thyroiditis, painful subacute thyroiditis, toxic multinodular goiter or toxic adenoma and exogenous thyroid hormone excess [8]. Whereas, hypothyroidism is characterized by dull facial expressions, husky voice, slow speech, puffy eyes and face. The clinical manifestations of hypothyroidism include cretinism and myxedema [9]. Diagnosis of thyroid dysfunction is based on the clinical features and laboratory findings of T3, T4 and TSH [10]. Healthcare physicians follow the guidelines of the "American Thyroid Association" for the management of thyroid disorders [11]. Pharmacological treatment of thyroid dysfunction varies according to the condition. Levothyroxine sodium is the drug of choice for the management of hypothyroidism [12,13]. Whereas the treatment of hyperthyroidism includes antithyroid drugs; i.e. propylthiouracil, carbimazole, methimazole, radioactive iodine and thyroidectomy [14,15].

### Natural products in medicine

According to the world health organization (WHO), about three-quarters of the world population depends upon natural remedies, including herbal medicine [16]. Throughout the entire history, natural products including plants, marine organisms, animal products and products of microorganism fermentation have been used in traditional medicines. This historical experience with natural products as therapeutic agents has evolved to isolate active chemical constituents from ethnopharmacological plants which help in further drug discovery [17]. The traditional Chinese medicine, Kampo, Ayurveda, traditional Korean medicine and Unani have been practiced in different areas of the world and played a great role into the wellbeing of mankind since centuries. Natural products, which evolved millions of years ago, have a

unique chemical diversity, which results in diversity in their biological activities and drug-like properties. These products have become one of the most important source for developing new lead compounds. Their efficacy is related to the complexity of their well-organized three-dimensional chemical and steric properties, which offer many advantages in terms of efficiency and selectivity of molecular targets. As a successful example of drug development from natural products, artemisinin and its analogs are presently in wide use for malaria treatment. This shows how research using natural products has made a significant contribution in drug development [18].

The use of plants for the management and treatment of various health disorders is very common worldwide. People utilize various parts; i.e. leaves, bark, flowers, fruits and stalks of the plants [16]. Whereas, biological oils and venoms are also used for various ailments. Insulin, heparin, adrenaline, thyroxin, musk, beeswax, enzymes, and antitoxins sera are some examples of drugs obtained from animal sources. Fermentation is an indispensable traditional technology for improving the efficacy or reducing adverse effects of herbal medicines. The fermentation process has been shown to improve biological properties of plants, vegetables, and herbs. More specifically, fermentation causes decomposition and biotransformation of complex substrates into compatible components, thereby modulating product properties or changing the quantity of certain bioactive compounds [19].

### Plants and thyroid dysfunction

Plants possess several secondary metabolites like phenols, phenolic acids, flavonoids, alkaloids, tannins, quinones, coumarins, saponins, terpenoids, triterpenoids, glycosides and organic acids which affect the biological system in different ways [20]. Flavonoids are polyphenolic compounds of natural occurrence produced by plants that are largely consumed for therapeutic purposes. Experimental data have shown that many flavonoids could inhibit thyroperoxidase activity, decreasing thyroid hormones levels thus increasing TSH and causing goiter. In thyroid tumor cell line, flavonoids were shown to inhibit cell growth, but they can also decrease radioiodine uptake and that could reduce the efficacy of radioiodine therapy. Flavonoids also affect the availability of thyroid hormones to target tissues, by inhibiting deiodinase activity or displacing T4 from transthyretin. Thus, flavonoids have been shown to interfere with many aspects of the thyroid hormones synthesis and availability in in vivo and in vitro models [21]. Thyroid peroxidase, also called thyroperoxidase (TPO) or iodide peroxidase, is an enzyme participating in the synthesis of thyroid hormones, which is reported to be inhibited by polyphenolic compounds [22] (Table 1).

**Table 1:** Various Plants Reported to Possess Therapeutic Efficacy against Thyroid Dysfunction.

Plant	Part Used	Extraction Method	Animal Model	Parameters Observed	Reference
<b>Plants Used Against Hyperthyroidism</b>					
Aegle marmelos (L.) Corrêa	Leaves	28% Aqueous extract by boiling	1.0 g/kg for 15 days	T3, T4	[27]
Allium sativum L.	Bulbs	Dry powder by lyophilization	L-thyroxine (300 µg/kg/d for 12 consecutive days) induced hyperthyroidism	TSH, T3, T4	[28]
Aloe vera (L.) Burm.f.	Parenchyma	10% Aqueous extract by blending and centrifugation	125 mg/kg for 15 days	T3, T4	[27]
	Gel	Petroleum ether, chloroform and methanolic extract by maceration and evaporation	L-thyroxin (0.5 mg/kg, i.p for 14 days) induced hyperthyroidism	TSH, T3, T4	[29]
Althaea officinalis L.	Flowers	Hydro-alcoholic extract by evaporation	Scopoletin (7-hydroxy-6-methoxy coumarin) 1.00 mg/kg, p.o. daily for 7 days	TSH, T3, T4, lipid peroxidation and blood glucose	[30]
Carica papaya L.	Seeds	96% Ethanolic extract by evaporation	50, 200 mg/kg, p.o extract for 1 and 8 weeks	Pituitary and thyroids	[31]
Emblica officinalis Gaertn	Fruits	95% ethanolic extract by soxhlation	L-thyroxine (0.5 mg/kg/day, i.p for 30 days) induced hyperthyroidism	T3, T4, hepatic LPO, SOD and CAT	[32]
Moringa oleifera Lam.	Leaves	Aqueous extract by evaporation	350 mg/kg/ 0.2ml/day for 10 days	T3, T4	[27]
Nigella sativa L.	Dry seeds	96% Ethanolic extract by evaporation	Alloxan monohydrate (150 mg/kg, i.p once) induced diabetes + 1 g/kg extract for 14 day	TSH, T3, T4	[23]
Trigonella foenum-graecum L.	Seeds	Powder extracted with 20% ethanol by the cold percolation	L-thyroxine (300 µg/kg body wt./d for 12 consecutive days) induced hyperthyroidism	TSH, T3, T4	[28]
<b>Plants Used Against Hypothyroidism</b>					
Bacopa monnieri (L.) Wettst.	Leaves	50% ethanolic extract by evaporation	PTU (10 mg/kg) + 200 mg/kg for 15 days	T3, T4	[27]
Citrullus vulgaris	Dried peels	Methanolic extract by evaporation	PTU (10 mg/kg/day, i.p for 10 days) induced hypothyroidism+ 100 mg/kg, p.o for 10 days	T3, T4, fasting glucose, serum insulin and tissue peroxidation	[34]
Cucumis melo L.	Dried peels	Methanolic extract by evaporation	PTU (10 mg/kg/day, i.p for 10 days) induced hypothyroidism+ 100 mg/kg, p.o for 10 days	T3, T4, fasting glucose, serum insulin and tissue peroxidation	[34]
Curcuma longa L.	Rhizome	Curcumin	Lithium carbonate (14.4 mg/kg b.wt/day for 6 weeks) induced thyroid dysfunction	TSH, T3, T4, pro-inflammatory cytokines, thyroid lipid nitric oxide and levels peroxidation	[35]
Fucus vesiculosus L.	Algae	Aqueous extract and isolated flavonoid	25,50 and 75 mg/kg/day of aqueous extract and 25,50 and 75 mg/kg/day of isolated flavonoids	TSH, T3, T4	[36]
	Whole Sea weed	Powder	Propylthiouracil (15 mg/kg for 3 weeks) induced hypothyroidism	TSH, T3, T4	[37]
Mangifera indica L.	Dried peels	Methanolic extract by evaporation	PTU (10 mg/kg/day, i.p for 10 days) induced hypothyroidism+ 200 mg/kg, p.o for 10 days	T3, T4, fasting glucose, serum insulin and tissue peroxidation	[34]
Melissia Officinalis	Whole plant	96 % Ethanolic extract by centrifugation and evaporation	2% Cholesterol added in diet to induce Hypercholesterol rat+treatment for 21 days	TSH, T3, T4	[38]

Withania somnifera (L.) Dunal	Roots	Aqueous extract	1.4 g/kg body weight daily for 20 days	T3, T4 and lipid peroxidation	[39]
	Roots	Aqueous methanolic extract by evaporation	Propylthiouracil (PTU, 0.05% w/v) in drinking water for 6 weeks) induced hypothyroidism	TSH, total T3, free T3, free T4, total T4 and serum glucose	[40,42]

Resveratrol, genistein and curcumin have been reported to reduce cell proliferation, viability and growth in diverse thyroid cancer cell lines [23]. Piperine, the main alkaloid of Piper nigrum fruits, reported to lower the serum levels of both the thyroid hormones, thyroxin (T4) and triiodothyronine (T3) [24]. Recently, a series of saponins are proved to exert their physiological activities through binding to nuclear receptors. As thyroid hormone receptors belong to nuclear receptor family, so saponins can alter thyroid hormone activity by binding to these receptors [25]. Quercetin, naringenin, p-coumaric acid, cinnamic acid and scopoletin are known to possess thyroid inhibitory properties [26]. Hence, different secondary metabolites affect thyroid dysfunction by different mechanisms.

## Conclusion

The review provides comprehensive information regarding various herbal drugs used in the management of thyroid dysfunction, Hyperthyroidism and Hypothyroidism.

## Conflict of Interest

Authors declare no conflict of interest.

## Author Contributions

Ms. Maaria Anwaar is M.Phil. (Pharmacology) scholar and the article is a part of her research project. H.M. Farhan Rasheed is Ph.D. (Pharmacology) scholar who helped Maaria in article write-up. Prof. Dr. Qaiser Jabeen is the research supervisor of both the students and designed the project.

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