Effects of Substances on Plants’ Active Compounds on Changes in the Hormone Levels of the Pituitary–Thyroid Axis in Hyperthyroidism and Hypothyroidism

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ABSTRACT
The roles of thyroid glands in different functions of the body have been well explained such that hypothyroidism and hyperthyroidism can impair the metabolism and normal functions of the body's tissues. Recently, using medicinal plants and their active compounds in treating diseases has attracted attention, and the people's tendency to use these compounds, which are considered to be low risk and to cause no side effect, is increasing. Because changes in the levels of thyroid hormones have considerable effects on body physiology and play a substantial role in the pathogenesis of different diseases, it is necessary to conduct further studies on hyperthyroidism and hypothyroidism and also the effects of plants and their compounds on thyroid hormone secretion rates. This review was conducted to present the information on thyroid hormones, as metabolism-regulating agents, and their association with different diseases as well as the effects of plant-based active compounds on changes in the hormone levels of the pituitary–thyroid axis in hyperthyroidism and hypothyroidism. Results indicated that disrupted serum levels of the thyroid hormones lead to increased incidence of cardiovascular disease, diabetes, depression, menstrual disorders, and kidney disease. The most important effective compounds on these hormones include flavonoids, coumarins, alkaloids, minerals, essential oil components, such as terpinene, gamma-terpinene, and limonene, and antioxidant compounds that directly influence thyroid and change serum levels of the thyroid hormones through inhibiting thyroid peroxidase. Other mechanisms of change in thyroid hormone levels by plant-based compounds are related to decrease in lipooxygenase activity and increase in the activities of catalase and dismutase. It can therefore be argued that using medicinal plants and their compounds can be a novel and efficient approach to develop drugs for thyroid diseases.

Key words: Herbal medicines, hyperthyroidism, hypothyroidism, medicinal plants, pituitary–thyroid axis

INTRODUCTION
Thyroid gland that is responsible for producing and secreting thyroid hormones is a blood-rich gland of the body that its dysfunction leads to disruption of energy production and fatigue. These hormones cause the metabolism to speed up, which affects almost all parts of the body including the gastrointestinal system (metabolism of fats and carbohydrates, synthesis of protein), adjusting body weight, heart rate and blood pressure, muscle strength, and regulating sleep and sexual function. Thyroid hormones also affect human mood and mental states. The secretion rate of thyroid-stimulating hormone (TSH) is regulated based on the levels of thyroid hormones in the blood.[⁷-⁹] Hypothyroidism and hyperthyroidism are two of the most important thyroid disorders. Hypothyroidism is characterized by thyroid underactivity and is classified into different types. Hypothyroidism is a disorder caused by iodine deficiency, which has endangered the health of over 800 million people worldwide, including Iran.⁶ Iodine is an essential element required for human survival, and iodine deficiency can lead to irreversible complications due to its role in the production of essential hormones and the physiological effects of these hormones on the functions of the body's cells. Iodine is essentially required for growth even before birth such that its deficiency in pregnancy leads to a type of mental retardation in the fetus called cretinism and causes reduced mental activity and depression in children. Disorders are developed most frequently when the amounts of iodine in pregnant woman decrease, and due to lack of sufficient iodine for the fetus, the production of thyroid hormones decreases, which impairs the growth of brain cells and therefore causes postnatal neurological–mental disorders.⁹ Goiter gets enlarged and developed into nodular goiter with increasing age. Thyroid overactivity, commonly referred to as hyperthyroidism, can affect the fetus and lead to low birth weight. In patients with hyperthyroidism, the levels of oxidants increase and those of antioxidants decrease.⁹¹ Currently, the roles of medicinal plants in treating and maintaining health are being emphasized. These plants have long been commonly used in traditional medicine such that they have been the primary sources for traditional drugs; since chemical drugs are associated with several side effects, using medicinal plants and active plant-based compounds that are efficient and cause comparatively...
fewer side effects is a new therapeutic approach. In modern medicine, many positive pharmaceutical effects of medicinal plants have been demonstrated in various studies such that the results have shown that these plants are effective in treating various diseases including thyroid disorders. Diets containing plant-based nutrients not only provide essential vitamins and minerals required by the body but also have effective compounds with biological effects and properties. This review was conducted to present the information on thyroid hormones, as metabolism-regulating agents, and their association with different diseases as well as the effects of plant-based active compounds on changes in the hormone levels of the pituitary–thyroid axis in hyperthyroidism and hypothyroidism.

THYROID HORMONES AND THEIR FUNCTIONS

Thyroid is one of the most important endocrine glands, which regulates almost all body functions and produces and secretes two hormones, thyroxin (T₄) and triiodothyronine (T₃). These hormones are derived from tyrosine and contribute greatly to metabolism. The thyroid hormone secretion is regulated by the pituitary gland thyrotropin (TSH), which is itself stimulated by the hypothalamic thyrotropin-releasing hormone (TRH), released from the paraventricular nucleus of the hypothalamus and less regulated by the serum concentrations of thyroid hormones. The most abundantly released thyroid hormone is T₄, and a large proportion of T₄ in the bloodstream is obtained from the peripheral metabolism of T₃ in the liver. Increasing T₄ and T₃ levels inhibits TSH and TRH secretion through the negative feedback of thyroid hormones.

HYPOTHYROIDISM AND HYPERTHYROIDISM

Hyperthyroidism occurs due to excessive production of T₄ by the thyroid, and hypothyroidism is a condition due to the thyroid’s failure to produce sufficient amounts of the thyroid hormone. If the rate of T₄ production is too low, the rate of metabolism in the body decreases and hypothyroidism is developed. Hypothyroidism is caused by antibodies attack on the thyroid. In this condition, the thyroid cannot produce sufficient amounts of thyroid hormone as much as before. Approximately 3% of the general population suffers from hypothyroidism. The symptoms of hypothyroidism are fatigue, muscle weakness, cold sensitivity, depression, muscle cramps, goiter, thin and brittle nails, thin and fragile hair, pallor, sweating, dry and itchy skin, weight gain, water retention, low heart rate (<60 beats/min), and constipation. If these symptoms are overlooked, conditions are exacerbated and lead to slow speech, hoarse voice, osteoporosis, and hypercholesterolemia. Certain other symptoms such as memory impairment, hair loss, irritability and anger, and dyspnea are comparatively less common. Conventional diagnosis of hypothyroidism is made by measuring TSH. When the thyroid is overactive, hypothyroidism is developed leading to excessive elevation of thyroid hormones. When excessive amounts of thyroid hormones are secreted, the body operates at a higher rate and certain symptoms such as increased heart rate, neurologic tremor and anxiety, diarrhea, and weight loss appear. Other symptoms such as heat intolerance, hair loss, weakness, irritability, osteoporosis, and tremor may also appear. Hyperthyroidism can be diagnosed by measuring TSH.

THE ROLES OF HYPOTHYROIDISM AND HYPERTHYROIDISM IN SOME DISEASES

Heart diseases

Longitudinal studies have indicated that thyroid diseases affect cardiovascular system adversely. The association between low T₃ levels and increased mortality rate has also been reported. It has been demonstrated that many cardiac function-related parameters such heart rate, cardiac output, and vascular resistance are closely associated with thyroid function. T₄ decreases vascular resistance through directly influencing smooth muscle cells of the arterioles. Hyperthyroidism leads to myocardial necrosis through causing mild fibrosis, increase in ionic sensitivity in response to local effects of catecholamines due to increased number of beta-adrenergic receptors, increase in B-MHC, decrease in resting time, and increase in the frequency of calcium release from the sarcoplasmic network. Overall, in hyperthyroidism, heart rate, blood pressure, and pulse pressure elevate, resulting in increased coronary blood flow. In this disease, bradycardia, mid (diastolic) hypertension, fatigue due to low blood pressure, and cold intolerance appear due to heart symptoms.

Diabetes

It has been determined that insulin metabolism is slower in the people with hypothyroidism, which causes decrease in the need for insulin in the short term. However, hyperthyroidism can exacerbate impaired glucose tolerance and make the control of diabetes more challenging. Hyperthyroidism can affect the control of diabetes and can make it more difficult to control blood sugar. Hyperthyroidism also intensifies the need for insulin due to increased liver gluconeogenesis, increased rate of intestinal glucose absorption, and possibly increased insulin resistance. Hyperthyroidism may indeed turn hidden diabetes into obvious diabetes. It has been reported that thyroid function influences the production, secretion, metabolism, and serum concentrations of many hormones; since thyroid hormones play a role in ghrelin secretion from the stomach, they can cause diabetes through affecting obesatin secretion. In addition, several esterase enzymes such as butyrylcholinesterase and carboxylesterase that are activated by thyroid hormones contribute to ghrelin degradation such that the activities of these enzymes decline in thyroid diseases such as dysthyroidism. It has also been observed that serum obesatin levels (obestatin receptors are found in gastric, intestinal, pancreatic, pituitary, hypothalamic, and lipid tissues and are involved in the metabolism and secretion of insulin) are associated with hypothyroidism and hyperthyroidism and that thyroid diseases lead to significant decrease in the serum levels of these hormones. Evidence indicates that there is an inverse correlation between cholesterol and thyroid hormones levels. Increasing dietary cholesterol causes significant decrease in the T₄ and T₃ levels and therefore development of hypothyroidism. The study of Chin et al. showed that serum lipid levels were inversely correlated with thyroid hormones levels and decreased with increasing the thyroid hormones levels. On the other hand, the activities of lipolytic enzymes, lipoprotein lipase, and hepatic lipase are varied by thyroid hormones, which is considered one of the factors for changes in lipid profile in hypothyroidism and hyperthyroidism. Thyroid hormone, indeed, changes the levels of these enzymes through influencing the expression rates of their genes. There is also a close association between thyroid autoantibodies, especially microsomal antibodies and peroxidase, and anti-pancreatic beta-cell autoantibodies. Research findings have indicated that the incidence rate of thyroid dysfunction is high in the type I diabetes patients who have anti-thyroid antibodies at onset of disease. A study showed that subclinical hypothyroidism, increased levels of TSH, and normal levels of free thyroid hormones in the bloodstream were observed in 17% of the women with type I diabetes and in 6.1% of the men with this disease that are high rates compared to the general population. In type I diabetic patients, leaving hypothyroidism untreated leads to congestive heart failure, dyslipidemia, infertility, and mental retardation in children, and leaving hyperthyroidism untreated causes certain complications such as sudden weight loss, congestive heart failure, and eye complications in adults.
Kidney diseases
Hypothyroidism and hyperthyroidism affect renal function through directly affecting the hemodynamic, metabolic, and vascular systems. Hypothyroidism is associated with increased serum creatinine levels and decreased glomerular filtration rate with feedback and toxicotic effects. Nephrotic syndrome is associated with fluctuations in the thyroid hormone concentrations. Hypothyroidism is developed by affecting renal function through direct mechanisms and indirectly through inducing changes in cardiovascular function and impairing the renin-angiotensin system. Hypertension is the result of reduced systemic activity of the renin-angiotensin system that can be due to kidney self-regulation.

A study on the effects of thyroid hormones on the activity of the adrenal cortex showed that the thyroid hormone secretions were effective on the adrenal cortex; it can be argued that increased levels of thyroid hormones represent a burden on the adrenal system, and the regulation of the thyroid gland may be effective in reducing the secretion of the hormones of the adrenal cortex. It therefore seems that if the control of thyroid hormones is accompanied by the regulation of adrenal cortex secretions, better results can be achieved.

Menstrual disorders
Menstrual disorders including prolonged menstrual periods, reduced lifespan, and increased or decreased blood volume in menstrual flow can be caused by thyroid disorders. A study showed that approximately 25% of female infertility and 15% of menstrual disorders were due to thyroid dysfunction. Therefore, the women with infertility for unspecified reasons or menstrual disorders should be examined for thyroid hormones.

Depressive disorders
Thyroid hormone is one of the major factors for brain chemical imbalance so that in any of these disorders, thyroid hormone imbalance may have serious effects on patients’ emotions and behaviors until treatment is done. Hypothyroidism is usually associated with mood disorders, anxiety, depression, psychotic disorders, and dementia, while in patients with hyperthyroidism, reduced sleep, restlessness, inner turmoil, and irritability appear. Ample evidence indicates that mood swings are associated with thyroid problems. 50%–10% of the people examined for depression had thyroid dysfunction. In addition, declined quality of life and general health, numerous emotional problems, and limitations in social activities have been reported in these patients. The results, including increased levels of T3 and TSH, are inconsistent. Some studies have demonstrated lower levels of T4 and increased levels of TSH. Some studies have attributed the high levels of T4 in secondary depression to the effect of TSH on T4 retention.

THE EFFECTS OF PLANTS’ ACTIVE COMPOUNDS ON THYROID HORMONES
As it was mentioned, the roles of thyroid in body metabolic activities are highly important and effective. Thyroid disorders, such as hypothyroidism and hyperthyroidism, cause change in normal functioning and impair the main activities and metabolism of the body. Therefore, the successful treatment of hypothyroidism and hyperthyroidism requires the level of thyroid hormones in the peripheral tissues to reach normal levels. Researches have indicated that many of the plants contain certain compounds that are effective on thyroid hormone levels. Flavonoids are one of the important phenolic groups that are made up of two aromatic six-carbon rings A and B. Pharmacological effects of flavonoids are mostly attributed to their antioxidant properties. These natural compounds are abundantly found in fruits, vegetables, seeds, roots, and stems. Certain plant-based flavonoids induce certain changes in the production of thyroid hormones through inhibiting thyroid peroxidase. Hops, botanically referred to as Humulus lupulus, contains flavonoid compounds that affect the function of pituitary–thyroid axis and the levels of thyroid hormones. A study showed that Dorema aucheri contains flavonoids and that its hydroalcoholic extract can be effective on thyroid function in a dose-dependent manner, which can help treat thyroid disorders. The flavonoids can decrease the levels of the thyroid hormones through inhibiting thyroperoxidase. Besides that, these compounds trigger changes in the thyroid hormone levels through inhibiting the activation of type I deiodinase that is specifically activated by TSH and also preventing the mineralization of iodine in the thyroid cells. As natural antioxidants, plant flavonoids help modulate the levels of hormones through inducing variations in O2 levels in the body and changing ATP metabolism. In addition, the protective effects of antioxidants on methimazole-induced hypothyroidism have been demonstrated. The flavonoids of Chelidonium majus are effective on the thyroid hormones. Alkaloids, flavonols, and phenols are the important pharmaceutical compounds of C. majus. Besides that, this plant contains sterol, saponin, vitamin, calcium salts, magnesium, resinous substances, and mucilage. The flavonoids of C. majus cause increase in TRH through inhibiting catechol-O-methyltransferase, which causes the breakdown of norepinephrine, and therefore increasing this hormone. This can lead to increase in the synthesis and release of TSH. Given that C. majus contains calcium and magnesium, it can contribute to producing and therefore increasing TSH as a mediator of second messenger through calcium-phosphatidylinositol mechanism. The antioxidants present in Cucurbita longa have positive direct effects on the thyroid.

A study on the effects of Aegle marmelos and Bacopa monnieri extracts on fluctuations in thyroid hormones concentrations has shown that the extracts of these two plants’ leaves exert antiperoxidase properties and that B. monnieri is used in hypothyroidism regulation. The study of Peepre et al. on the roles of antioxidants in the secretion rates of thyroid hormones showed that serum T3 and T4 levels increased in the rats fed with natural antioxidant-containing diets, which was attributed to the direct effects of the antioxidants on the thyroid.

The study of Souza et al. with rats on the effect of omega 3-containing diet on thyroid hormone signaling indicated that the activities of the mitochondrial enzymes involved in the lipid metabolism were normally stimulated by T3 hormones through thyroid hormone receptor-beta 1, which was much more marked in the omega 3-receiving group. Coumarin is another compound of D. aucheri that affects thyroid function through inhibiting the conversion of T3 to T4. Coumarins are simple phenolic compounds whose pharmacological properties are highly important and that are mainly found in the plants from the family Apiaceae. Furancoumarins are one of the most important groups of coumarins that are present in A. majus, Pimpinella anisum, and Heracleum persicum. Umbelliferone is another type of coumarins which is found in A. majus and Apium graveolens. Studies have shown that coumarin derivatives have increasing effect on thyroid hormones. A. dorema, therefore, induces change in these hormones due to containing flavonoids and coumarins.

Table 1 enlists a number of the most important plants that have coumarins and flavonoids. Because D. aucheri contains calcium and magnesium, it can contribute to producing and therefore increasing TSH as a mediator of second messenger through calcium-phosphatidylinositol mechanism. Oat, botanically referred to as Avena sativa, is the other plant that can affect the levels of the thyroid hormones due to containing certain compounds including iodine. This plant contains fatty substances, nitrogen, and carbon hydrates. Palmitic acid, oleic acid, linoleic acid, arsenic acid, and oxalic acid are the fatty acids of A. sativa. This plant also contains iodine, nitrogenous compounds, saponins (steroids,
Table 1: A number of most important coumarin and furanocoumarin-containing plants

<table>
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<tr>
<th>Row</th>
<th>Scientific name</th>
<th>English name</th>
<th>Family</th>
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<tr>
<td>1</td>
<td>Ruta graveolens</td>
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<td>Ammi majus</td>
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<td>Heracleum persicum</td>
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<td>Ackeri dorema</td>
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<td>27</td>
<td>Artemisia dracunculus</td>
<td>Tarragon</td>
<td>Compositae</td>
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triterpenes), avenacosides,avenacin, and alkaloids. In A. sativa, carotenes and Vitamins D, C, B₁, B₂, and E and minerals such as silicium and potassium. A. sativus is the richest plant source of zinc.[84,85] Souza et al. argued that increased thyroid hormone signaling pathway in the liver can represent one of the mechanisms through which omega 3 affects lipid metabolism.[86] The study of Mirazi et al. with male rats with hypothyroidism on the effect of hydroalcoholic H. persicum extract on serum thyroid hormone level showed that plasma T₄, T₃, and TSH concentrations were significantly different between the extract-treated groups with hypothyroidism and the control group.[87] The study of Zarei and Taheri, with hypercholesterolemic rats on the effect of Berberis root extract on serum thyroid hormones concentrations, demonstrated that no significant change was observed in the extract-treated groups. Zarei and Taheri argued that increased T₄ and T₃ levels and lack of their effects on the TSH levels in the extract-treated groups represent euthyroid hyperthyroxinemia.[88] Steroids cause decrease in thyroid hormone-transferring proteins in the blood. The fibers present in plant extracts exert inhibitory effects on the activities of the neuropeptide Y-producing neurons through increasing leptin secretion; due to the stimulatory effects of neuropeptide Y on the secretion of TRH, T₄, and T₃, the serum levels of these hormones increase.[89] Peganum harmala extract declines pituitary–thyroid axis function. Certain compounds of P. harmala inhibit neuropeptide Y activity through secreting leptin, and therefore, the levels of neuropeptide Y and TSH decrease through declining the activities of the neuropeptide Y-producing neurons that stimulate the secretion of the TRH. The action mechanisms of the compounds of this plant including alkaloids such as harmaline have been demonstrated. Harmaline exerts inhibitory effect on monoamine oxidase. Indole amine (serotonin) levels increase through inhibiting monoamine oxidase because serotonin is considered an inhibitory neurotransmitter of TRH secretion.[89,90] Then, it can cause decrease in the secretion of the thyroid hormones.

CONCLUSION

Overall, hypothyroidism and hyperthyroidism can be effective on the pathogenesis of various diseases and cause impairment of body tissues. Since the treatment with chemical drugs is often associated with adverse side effects, the use of plant substances can have beneficial effects without inducing damage to the body. The active compounds of medicinal plants, including flavonoids, antioxidants, alkaloids, and essential oils as well as coumarins and furanocoumarins, can directly affect thyroid hormones and cause them to function better under different physiological conditions. It is therefore essential to conduct additional clinical trials regarding the roles and functions of the active compounds of medicinal plants to determine their precise formulations.

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Conflicts of interest
There are no conflicts of interest.

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