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REVIEW ARTICLE

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 lipoxygenase 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.[1-4] 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.[5,6] Iodine is an essential element required for human survival, and iodine deficiency can lead to irreparable 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.[7-9] 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.[10-12] 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

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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.[13-19] 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 (T_4) and triiodothyronine (T_3). 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.[20,21] The most abundantly released thyroid hormone is T_4 and a large proportion of T_3 in the bloodstream is obtained from the peripheral metabolism of T_4 in the liver. Increasing T_3 and T_4 levels inhibits TSH and TRH secretion through the negative feedback of thyroid hormones.[22,23]

HYPOTHYROIDISM AND HYPERTHYROIDISM

Hyperthyroidism occurs due to excessive production of T_4 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 T_4 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.[24-27] 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.[28-30]

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 T_3 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. T_3 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.[31-34]

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.[35,36] 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 obestatin 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 obestatin 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.[37-40] Evidence indicates that there is an inverse correlation between cholesterol and thyroid hormones levels. Increasing dietary cholesterol causes significant decrease in the T_3 and T_4 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.[41] 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.[42] 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.[43-47]

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 toxicosic 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.[48-50]

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.[51,52]

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 T_4 and TSH, are inconsistent. Some studies have demonstrated lower levels of T_3 and increased levels of TSH. Some studies have attributed the high levels of T_4 in secondary depression to the effect of TSH on $T_{4\,sec}$retion.[53-56]

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 hyperthyroidism and hypothyroidism, 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.[57] Researches have indicated that many of the plants contain certain compounds that are effective on thyroid hormone levels.[58-60] 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.[61-64] Hops, botanically referred to as *Humulus lupulus*, contains flavonoid compounds that affect the function of pituitary–thyroid axis and the levels of thyroid hormones.[65,66] 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 1 deiodinase that is specifically activated by TSH and also preventing the mineralization of iodine in the thyroid cells.[20,67] As natural antioxidants, plant flavonoids help modulate the levels of hormones through inducing variations in O_2 levels in the body and changing ATP metabolism. In addition, the protective effects of antioxidants on methimazole-induced hypothyroidism have been demonstrated.[68] 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 via calcium-phosphatidylinositol mechanism.[69-72] The antioxidants present in *Curcuma longa* extract have positive direct effects on the thyroid.[73] 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.[74] The study of Peepre *et al*. on the roles of antioxidants in the secretion rates of thyroid hormones showed that serum T_3 and T_4 levels increased in the rats fed with natural antioxidant-containing diets, which was attributed to the direct effects of the antioxidants on the thyroid.[75] 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 T_3 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 T_4 to T_3. Coumarins are simple phenolic compounds whose pharmacological properties are highly important and that are mainly found in the plants from the family *Apiaceae*. Furanocoumarins 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.[76,77] 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[78-83]

Row	Scientific name	English name	Family
1	*Ruta graveolens*	Rue	*Rutaceae*
2	*Ammi visnaga*	Visnaga	*Apiaceae*
3	*Petroselinum crispum*	Percile	*Apiaceae*
4	*Ammi majus*	Ajowan	*Apiaceae*
5	*Pimpinella anisum*	Anise	*Apiaceae*
6	*Heracleum persicum*	Cow parsnip	*Apiaceae*
7	*Althaea officinalis*	Marshmallow	*Malvaceae*
8	*Cinnamomum zeylanicum*	Cinnamon	*Lauraceae*
9	*Ferula gummosa*	Galbanum	*Apiaceae*
10	*Chamomilla recutita*	Common chamomile	*Asteraceae*
11	*Apium graveolens*	Celery	*Apiaceae*
12	*Foeniculum vulgare*	Fennel	*Apiaceae*
13	*Trigonella foenum-graecum*	Fenugreek	*Apiaceae*
14	*Aucheri dorema*	Bilhar	*Apiaceae*
15	*Anethum graveolens*	Dill	*Apiaceae*
16	*Coriandrum sativum*	Coriander	*Apiaceae*
17	*Datura stramonium*	Thornapple	*Solanaceae*
18	*Achillea millefolium*	Yarrow	*Asteraceae*
19	*Glycyrrhiza glabra*	Licorice	*Papilionaceae*
20	*Lavandula officinalis*	Lavender	*Lamiaceae*
21	*Urtica dioica*	Common nettle	*Urticaceae*
22	*Lawsonia inermis*	Garden balsam	*Lythraceae*
23	*Carum carvi*	Caraway seed	*Apiaceae*
24	*Artemisia aucheri*	Mugwort	*Asteraceae*
25	*Passiflora incarnata*	Passion flower	*Passifloraceae*
26	*Panax ginseng*	Ginseng	*Araliaceae*
27	*Artemisia dracunculus*	Tarragon	*Compositae*

triterpenes), avenacosides, avenacin, and alkaloids. In *A. sativa*, carotenes and Vitamins D, C, B_2, B_1, and E and minerals such as silicium and potassium. *A. sativa* 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 T_4, T_3, 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 T_3 and T_4 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, T_3, and T_4, 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 harmala have been demonstrated. Harmala 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.[89-91] 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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REFERENCES

1. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, *et al.* Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304:1365-74.
2. Völzke H, Schwahn C, Wallaschofski H, Dörr M. Review: The association of thyroid dysfunction with all-cause and circulatory mortality: Is there a causal relationship? J Clin Endocrinol Metab 2007;92:2421-9.
3. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008;29:76-131.
4. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, *et al.* Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.
5. Philips J. Thyroid hormone disorder. Endocrinol J 2002;49:100-7.
6. Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, *et al.* Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab 2004;89:3365-70.
7. Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet 2008;372:1251-62.
8. Wilders-Truschnig MM, Warnkross H, Leb G, Langsteger W, Eber O, Tiran A, *et al.* The effect of treatment with levothyroxine or iodine on thyroid size and thyroid growth stimulating immunoglobulins in endemic goitre patients. Clin Endocrinol (Oxf) 1993;39:281-6.
9. Morreale de Escobar G. The role of thyroid hormone in fetal neurodevelopment. J Pediatr Endocrinol Metab 2001;14 Suppl 6:1453-62.
10. Abraham-Nordling M, Byström K, Törring O, Lantz M, Berg G, Calissendorff J, *et al.* Incidence of hyperthyroidism in Sweden. Eur J Endocrinol 2011;165:899-905.
11. Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, *et al.* Hyperthyroidism and other causes of thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract 2011;17:456-520.
12. Jansen J, Friesema EC, Milici C, Visser TJ. Thyroid hormone transporters in health and disease. Thyroid 2005;15:757-68.
13. Al-Snafi A. Therapeutic properties of medicinal plants: A review of their effect on reproductive systems (part 1). Indian J Pharm Sci Res 2015;5:240-8.
14. Al-Snafi AE. Therapeutic properties of medicinal plants: A review of their immunological effects (part 1). Asian J Pharm Res 2015;5:208-16.
15. van der Heide D, Kastelijn J, Schröder-van der Elst JP. Flavonoids and thyroid disease. Biofactors 2003;19:113-9.
16. May BH, Lit M, Xue CC, Yang AW, Zhang AL, Owens MD, *et al.* Herbal medicine for dementia: A systematic review. Phytother Res 2009;23:447-59.
17. Sadati SN, Ardekani MR, Ebadi N, Yakhchali M, Dana AR, Masoomi F, *et al.* Review of scientific evidence of medicinal convoy plants in traditional Persian medicine. Pharmacogn Rev 2016;10:33-8.
18. Moloudizargari M, Mikaili P, Aghajanshakeri S, Asghari MH, Shayegh J. Pharmacological and therapeutic effects of *Peganum harmala* and its main alkaloids. Pharmacogn Rev 2013;7:199-212.

19. Jana S, Shekhawat GS. *Anethum graveolens*: An Indian traditional medicinal herb and spice. Pharmacogn Rev 2010;4:179-84.
20. Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. J Ethnopharmacol 2002;81:281-5.
21. Ott J, Promberger R, Kober F, Neuhold N, Tea M, Huber JC, *et al.* Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: A prospective case-control study in women undergoing thyroidectomy for benign goiter. Thyroid 2011;21:161-7.
22. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG, *et al.* Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004;292:2591-9.
23. Harvey CB, Williams GR. Mechanism of thyroid hormone action. Thyroid 2002;12:441-6.
24. Dhingra S, Singh U, Bansal MP. Protective role of selenium status on T3/T4 kinetics in rats under hyperlipidemia. Indian J Biochem Biophys 2003;40:260-4.
25. Bhandarkar SD, Retnam VJ. Hyperthyroidism following hypothyroidism. J Postgrad Med 1980;26:90-4.
26. Chung YH, Ou HY, Wu TJ. Development of hyperthyroidism following primary hypothyroidism: A case report. Kaohsiung J Med Sci 2004;20:188-91.
27. Biondi B. Endogenous subclinical hyperthyroidism: Who, when and why to treat. Expert Rev Endocrinol Metab 2011;6:785-92.
28. Torlak V, Zemunik T, Modun D, Capkun V, Pesutić-Pisać V, Markotić A, *et al.* 131 I-induced changes in rat thyroid gland function. Braz J Med Biol Res 2007;40:1087-94.
29. Champion B, Gopinath B, Ma G, El-Kaissi S, Wall JR. Conversion to Graves' hyperthyroidism in a patient with hypothyroidism due to Hashimoto's thyroiditis documented by real-time thyroid ultrasonography. Thyroid 2008;18:1135-7.
30. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011;99:39-51.
31. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, *et al.* Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 2005;165:2467-72.
32. Asvold BO, Bjøro T, Nilsen TI, Gunnell D, Vatten LJ. Thyrotropin levels and risk of fatal coronary heart disease: The HUNT study. Arch Intern Med 2008;168:855-60.
33. Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, *et al.* Initial thyroid status and cardiovascular risk factors: The EPIC-Norfolk prospective population study. Clin Endocrinol (Oxf) 2010;72:404-10.
34. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. Nat Rev Endocrinol 2010;6:431-43.
35. Kordonouri O, Charpentier N, Hartmann R. GADA positivity at onset of type 1 diabetes is a risk factor for the development of autoimmune thyroiditis. Pediatr Diabetes 2011;12:31-3.
36. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, *et al.* Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009;160:785-90.
37. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid 2008;18:141-4.
38. Kundu S, Pramanik M, Roy S, De J, Biswas A, Ray AK, *et al.* Maintenance of brain thyroid hormone level during peripheral hypothyroid condition in adult rat. Life Sci 2006;79:1450-5.
39. Iglesias P, Díez JJ. Influence of thyroid dysfunction on serum concentrations of adipocytokines. Cytokine 2007;40:61-70.
40. De Vriese C, Gregoire F, Lema-Kisoka R, Waelbroeck M, Robberecht P, Delporte C, *et al.* Ghrelin degradation by serum and tissue homogenates: Identification of the cleavage sites. Endocrinology 2004;145:4997-5005.
41. Chin KY, Ima-Nirwana S, Mohamed IN, Aminuddin A, Johari MH, Ngah WZ, *et al.* The relationships between thyroid hormones and thyroid-stimulating hormone with lipid profile in euthyroid men. Int J Med Sci 2014;11:349-55.
42. Diekman T, Lansberg PJ, Kastelein JJ, Wiersinga WM. Prevalence and correction of hypothyroidism in a large cohort of patients referred for dyslipidemia. Arch Intern Med 1995;155:1490-5.
43. Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A, *et al.* Thyroid dysfunction in patients with type 1 diabetes: A longitudinal study. Diabetes Care 2003;26:1181-5.
44. Roldán MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Diabetes Nutr Metab 1999;12:27-31.
45. McCanlies E, O'Leary LA, Foley TP, Kramer MK, Burke JP, Libman A, *et al.* Hashimoto's thyroiditis and insulin-dependent diabetes mellitus: Differences among individuals with and without abnormal thyroid function. J Clin Endocrinol Metab 1998;83:1548-51.
46. Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P, Pappas S, *et al.* Prevalence of thyroid dysfunction among Greek type 2 diabetic patients attending an outpatient clinic. J Clin Med Res 2010;2:75-8.
47. Gray RS, Borsey DQ, Seth J, Herd R, Brown NS, Clarke BF, *et al.* Prevalence of subclinical thyroid failure in insulin-dependent diabetes. J Clin Endocrinol Metab 1980;50:1034-7.
48. Bando Y, Ushiogi Y, Okafuji K, Toya D, Tanaka N, Miura S, *et al.* Non-autoimmune primary hypothyroidism in diabetic and non-diabetic chronic renal dysfunction. Exp Clin Endocrinol Diabetes 2002;110:408-15.
49. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G, *et al.* Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1296-300.
50. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005;67:1047-52.
51. Check JH, Mitchell-Williams J. Failure to have menses following progesterone withdrawal in a normal estrogenic woman with polycystic ovarian syndrome who menstruates with oral contraceptives. Clin Exp Obstet Gynecol 2009;36:141-2.
52. Maruna P. Gynecological aspects of thyroid disorders. A review. Ceska Gynekol 2006;71:332-8.
53. Arem R. The Thyroid Solution: A Mind-Body Program for Beating Depression and Regaining Your Emotional and Physical Health. Trade Paperback Edition. United States: Ballantine Books; 2007.
54. Kirkegaard C, Faber J. Influence of free thyroid hormone levels on the TSH response to TRH in endogenous depression. Psychoneuroendocrinology 1986;11:491-7.
55. Chakrabarti K, Singh PM, Joshi SP. Thyroid function in depression. Nepal Med Coll J 2006;8:47-8.
56. Demartini B, Masu A, Scarone S, Pontiroli AE, Gambini O. Prevalence of depression in patients affected by subclinical hypothyroidism. Panminerva Med 2010;52:277-82.
57. Mistry D, Atkin S, Atkinson H, Gunasekaran S, Sylvester D, Rigby AS, *et al.* Predicting thyroxine requirements following total thyroidectomy. Clin Endocrinol (Oxf) 2011;74:384-7.
58. Berrougui H, Martín-Cordero C, Khalil A, Hmamouchi M, Ettaib A, Marhuenda E, *et al.* Vasorelaxant effects of harmine and harmaline extracted from *Peganum harmala* L. Seeds in isolated rat aorta. Pharmacol Res 2006;54:150-7.
59. Deshpande UR, Joseph LJ, Patwardhan UN, Samuel AM. Effect of antioxidants (Vitamin C, E and turmeric extract) on methimazole induced hypothyroidism in rats. Indian J Exp Biol 2002;40:735-8.
60. Parmar HS, Kar A. Medicinal values of fruit peels from *Citrus sinensis*, *Punica granatum*, and *Musa paradisiaca* with respect to alterations in tissue lipid peroxidation and serum concentration of glucose, insulin, and thyroid hormones. J Med Food 2008;11:376-81.
61. Wollenweber E, Dorr M, Rustiyan A. *Dorema aucheri*, the first umbelliferous plant found to produce exudate flavonoids. Phytochemistry 1995;38:1417.
62. Ferreira AC, Neto JC, da Silva AC, Kuster RM, Carvalho DP. Inhibition of thyroid peroxidase by *Myrcia uniflora* flavonoids. Chem Res Toxicol 2006;19:351-5.
63. Anand David AV, Arulmoli R, Parasuraman S. Overviews of biological importance of quercetin: A Bioactive flavonoid. Pharmacogn Rev 2016;10:84-9.
64. Basri AM, Taha H, Ahmad N. A review on the pharmacological activities and phytochemicals of *Alpinia officinarum* (Galangal) extracts derived from bioassay-guided fractionation and isolation. Pharmacogn Rev 2017;11:43-56.
65. Román GC. Autism: Transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. J Neurol Sci 2007;262:15-26.
66. Tanaka Y, Yanagida A, Komeya S, Kawana M, Honma D, Tagashira M, *et al.* Comprehensive separation and structural analyses of polyphenols and related compounds from bracts of hops (*Humulus lupulus* L.). J Agric Food Chem 2014;62:2198-206.
67. Robbins J, Rall JE. Proteins associated with the thyroid hormones. Physiol Rev 1960;40:415-89.
68. Gholamzadeh S, Behbahani M, Fattahi A, Sajjadi S, Shokoohinia Y. Antiviral evaluation of coumarins from *Prangos ferulacea* L. (Lindl). Res Pharm Sci 2012;7:S783.
69. Biswas SJ, Bhattacharjee N, Khuda-Bukhsh AR. Efficacy of a plant extract (*Chelidonium majus* L.) in combating induced hepatocarcinogenesis in mice. Food Chem Toxicol 2008;46:1474-87.
70. de Souza Dos Santos MC, Gonçalves CF, Vaisman M, Ferreira AC, de Carvalho DP. Impact of flavonoids on thyroid function. Food Chem Toxicol 2011;49:2495-502.
71. Weiss R, Volker F. Herbal Medicine. Germany: Thieme Verlag; 2001. p. 181, 330.
72. Qin LP, Zhang HM, Zhang WD. Effect of osthol and total coumarins of *Fructus cnidii* on thyroid hormone and thyrotropic hormone in kidney-yang deficiency rats. Zhongguo Zhong Xi Yi Jie He Za Zhi 1996;16:552-3.

73. Sies H, editor. Antioxidants in Disease, Mechanisms and Therapy. New York: Academic Press; 1996.
74. Petrulea MS, Duncea I, Hazi G, Dragotoiu G, Decea N, Mureşan A. Oxidative stress in experimental hypothyroidism: Effect of Vitamin E supplementation. Clujul Med 2010;83:245-9.
75. Kelly GE, Husband AJ. Flavonoid compounds in the prevention and treatment of prostate cancer. Prostate Cancer Methods and Protocols. Springer; 2003. p. 377-94.
76. Massumi MA, Fazeli MR, Alavi SH, Ajani Y. Chemical constituents and antibacterial activity of essential oil of *Prangos ferulacea* (L.) Lindl. fruits. Iran J Pharm Sci 2007;3:171-6.
77. Maji AK, Banerji P. *Chelidonium majus* L. (Greater celandine)- a review on its phytochemical and therapeutic perspectives. Int J Herb Med 2015;3:10-27.
78. Sutovska M, Nosalova G, Franova S, Kardosova A. The antitussive activity of polysaccharides from *Althaea officinalis* l. var. Robusta, *Arctium lappa* L. var. Herkules, and *Prunus persica* L. Batsch. Bratisl Lek Listy 2007;108:93-9.
79. Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. 4th ed. St. Louis, MO.: Mosby; 2010.
80. Duke JA. CRC Handbook of Medicinal Herbs. Boca Raton: CRC Press; 1990. p. 74.
81. Peroutka R, Schulzova V, Botek P, Hajslova J. Analysis of furanocoumarins in vegetables (Apiaceae) and citrus fruits (Rutaceae). J Sci Food Agric 2007;87:2152-63.
82. Singh LR, Singh OM. *Datura stramonium*: An overview of its phytochemistry and pharmacognosy. J Pharmacogn Phytochem 2013;5:143-8.
83. Souri E, Farsam H, Sarkheil P, Ebadi F. Antioxidant activity of some furanocoumarins isolated from *Heracleum persicum*. Pharm Biol 2004;42:396-9.
84. Peepre K, Deshpandey U, Choudhary P. Role of antioxidants on thyroid hormones in Wistar rats. Int J Sci Res 2014;3:34-8.
85. Ulianich L, Secondo A, De Micheli S, Treglia S, Pacifico F, Liguoro D, *et al.* TSH/cAMP up-regulate sarco/endoplasmic reticulum Ca2+-ATPases expression and activity in PC Cl3 thyroid cells. Eur J Endocrinol 2004;150:851-61.
86. Souza LL, Nunes MO, Paula GS, Cordeiro A, Penha-Pinto V, Neto JF, *et al.* Effects of dietary fish oil on thyroid hormone signaling in the liver. J Nutr Biochem 2010;21:935-40.
87. Mirazi N, Abdolmaleki N, Mahmoodi M. Study of *Salvia officinalis* hydroethanolic extract on serum thyroid hormone levels in hypothyroid male rat. J Hamadan Univ Med Sci 2013;19:27-35.
88. Zarei A, Taheri S, Changizi Ashtiyani S, Rezaei A. The study of the effect of the extract *Berberis vulgaris* root on serum levels of thyroid hormones in hypercholesterolemia rats. ISMJ 2015;18:270-9.
89. Subhan N, Alam A, Ahmed F, Shahid IZ. Antinociceptive and gastroprotective effect of the crude ethanolic extracts of *Excoecaria agallocha* Linn. Turk J Pharm Sci 2008;5:143-54.
90. Ganong W. Review of Medical Physiology. 17th ed. Connecticut: Appleton and Lange; 1995.
91. Monsef HR, Ghobadi A, Iranshahi M, Abdollahi M. Antinociceptive effects of *Peganum harmala* L. alkaloid extract on mouse formalin test. J Pharm Pharm Sci 2004;7:65-9.