REVIEW ARTICLE

Thyroid diseases: Pathophysiology and new hopes in treatment with medicinal plants and natural antioxidants

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Abstract

The thyroid gland regulates a wide range of physiological activities such as growth, metabolism, homeostasis, and cell proliferation and differentiation through the secretion of thyroid hormones (THs). Thyroid diseases are among the most common endocrine disorders, hypothyroidism is the most common clinical thyroid dysfunction. Hyperthyroidism means increased thyroid function and refers to excess metabolic state due to excessive synthesis and secretion of TH. Medicinal plants have been identified and used by humans throughout history. To name the herbs and natural antioxidants used to treat thyroid disorders including hypothyroidism and hyperthyroidism. Related articles were obtained using the Google Scholar, PubMed, and ScienceDirect databases. The results of this study indicate that medicinal plants include *Fucus vesiculosus, Aegle marmelos, Coleus forskohlii, Linum usitatissimum, Withania somnifera, Commiphora mukul, Nigella sativa,* and *Bacopa monnieri*. They can improve the hyperthyroidism in improving hyperthyroidism and herbal remedies, *Melissa officinalis A. marmelos*, *Lycopus europaeus, Leonurus cardiaca,* and *Aloe barbadensis* be effective. Herbal drugs cause comparatively fewer side effects. It is believed that the drugs derived from the plants are very safe and produce significant effects in the treatment of various diseases. Today, traditional medicine is being widely used and plants are still considered a major source of natural antioxidants that can serve as a clue for the development of new drugs.

Key words: Antioxidant role, hyperthyroidism, hypothyroidism, medicinal plants

INTRODUCTION

Function of the Thyroid Gland

The thyroid gland regulates a wide range of physiological activities such as growth, metabolism, homeostasis, and cell proliferation and differentiation by secretion of thyroid hormones (THs).[1] The main product of the thyroid gland is mainly T4 prohormone (3,5,3,5-tetraiodothyronin), also known as thyroxine, and in less amounts, T3 active hormone (3,5,3′-triiodo-L-thyronine).[2] The major part of T3 is produced by 5-deiodination of T4 by iodothyronine deiodinase Type 1 and Type 2, and T3 is converted to inactive rT3 by iodothyronine deiodinase Type 3. THs exert their biological activities through binding to the TH receptor (TR) and transcribing specific genes. TRs, along with the receptors for steroids, retinoids, and Vitamin D, belong to the large family of nuclear receptors. The two main isoforms of TR are TRα and TRβ that are coded on distinct genes. TRs bind to the TH response elements (TREs) in the promoter of target genes to regulate their transcription. Plasma levels of T3 and T4 are controlled by negative feedback through the hypothalamic-pituitary-thyroid axis by the secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus and the secretion of the thyroid-stimulating hormone (TSH)

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from the pituitary.[3] Thyroid diseases are among the most common endocrine disorders[4] whose incidence increases with increasing age.[5] Subclinical thyroid disease is defined by abnormal serum TSH, but normal T3 and T4 levels and the patients do not always need treatment, while people with clinical thyroid disease have abnormal serum TSH, T3, and T4 levels and need treatment.[6] 5–9% of adults suffer from subclinical thyroid disease and 7.5–8% of the general population develop clinical thyroid disease.[7] Early diagnosis and management of thyroid disease is very important as it is associated with increased pathogenicity and mortality, especially in the elderly.[5]

Hypothyroidism

Hypothyroidism is the most common clinical thyroid dysfunction[5] and is more prevalent in women and the elderly.[8] Its prevalence is approximately 2% in adult women and 0.2% in adult men and increases to 0.5% at age 75 years.[9] Hypothyroidism can be divided into two categories: Primary hypothyroidism and secondary hypothyroidism.[9] Primary hypothyroidism refers to thyroid deficiency to produce sufficient amounts of TH. Secondary (central) hypothyroidism occurs much less frequently and is due to decreased thyroid stimulation by TSH due to hypopituitarism or hypothalamic disease. The main cause of hypothyroidism across the globe is iodine deficiency, and in regions, where sufficient amounts of iodine are available, Hashimoto's (autoimmune) thyroiditis is the most common cause of the disease.[10] Iodine is essential for the production of THs. In 2005, almost 2 billion (one-third of the world's population) suffered from iodine deficiency and were at risk of developing iodine deficiency disorders (IDDs).[11] Women of reproductive age are at the highest risk of IDD due to effects on ovulation, fertility, and pregnancy.[12] Hashimoto's thyroiditis is a type of autoimmune thyroiditis that involves lymphocytic infiltration into the gland and production of autoantibodies toward thyroglobulin and thyroid peroxidase. As a result, the structural unit and the enzyme responsible for the production of the hormone are blocked.[13] Congenital hypothyroidism (CH) is one of the most important and preventable causes of mental retardation, and one of the most common diseases related to psychiatric disorders and growth restriction in newborns.[14] Today, thyroid screening is being conducted at birth in many countries across the world due to the importance of CH.[15] Subclinical hypothyroidism is a more moderate type of thyroid disease associated with high serum TSH levels (above the reference range) when serum FT4 concentrations are within the normal reference range.[16,17] The signs and symptoms of hypothyroidism are non-specific and delicate. The disease is often difficult to diagnose and may be misdiagnosed as other diseases, especially in postnatal women and the elderly.[18] Signs and symptoms of hypothyroidism include fatigue, lethargy, concentration difficulty, depression, weight gain, dryness, skin roughness and itching, hair thinning, cold intolerance, sweating, constipation, menstrual disorders, muscle cramps, infertility and abortion, bradycardia, and hypotension. Laboratory findings include decreased T4, increased TSH, specific antithyroid antibodies, increased low-density lipoprotein (LDL), increased LFTs, increased creatine and myoglobin, and anemia.[5,19-21] Irrespective of age, levothyroxine is the first drug of choice for hypothyroidism due to its long half-life. The average replacement dose is 16 μg/kg for each individual.[17] Children may need higher doses of levothyroxine, while the elderly may need lower doses. In some patients, a sudden increase in levothyroxine may increase myocardial oxygen demand and cause heart failure.[13] Thyroid function tests are performed 6 weeks after starting treatment and the effectiveness of the treatment is measured by TSH sensitivity testing.[13]

Hyperthyroidism

Hyperthyroidism means increased thyroid function and refers to excess metabolic state due to excessive synthesis and secretion of TH.[22] The prevalence of hyperthyroidism is 0.2–0.5% in women that is approximately 10 times higher than in men. The most common cause of hyperthyroidism in iodine-rich regions is Graves' disease, which results in the production of antibody against the TSH receptor that stimulates the thyroid gland and leads to overproduction of TH.[23] In areas where iodine insufficiency is common, production of excess TH due to toxic adenoma and toxic goiter is an important cause of hyperthyroidism.[24,25] Subclinical hyperthyroidism is a mild type of hyperthyroidism. It is associated with low levels of TSH (lower than the reference range) when the concentration of FT4 is within the reference range.[26,27] Diagnosis of hyperthyroidism is based on serum TSH levels. If T4 is measured at the same time, the accuracy of the diagnosis increases. Free T3 levels may be useful for confirmation of diagnosis, especially if T3 toxicity diagnosis is suspected.[24,28] The presence of antibodies against the TR shows the diagnosis of Graves' disease. The symptoms and signs of the disease include fatigue, irritability, anxiety and anger, insomnia, palpitations, weight loss, increased appetite, heat intolerance, sweating, menstrual dysfunction, tachycardia, anemia, osteoporosis, and eye problems.[5,28]

Treatment

Treatments of choice for hyperthyroidism are more than those for hypothyroidism and include antithyroid drugs to reduce the synthesis and secretion of TH, radioiodine for the gland, and thyroidectomy to remove the thyroid gland.[7] The use of antithyroid drugs is a short-term treatment and is conducted before radioiodine and surgery. This method is low cost and noninvasive, and the risk of developing hypothyroidism due to it is low.[28,29] Metimazol is the only antithyroid drug approved for the treatment of hyperthyroidism in children and adolescents in the United States, after the US Food and Drug Administration issued an immunological warning against the use of propylthiouracil due to an increased risk of drug-induced hepatic necrosis in children and adolescents.

The most common side effect of metimazol is skin rash, which is found in about 20% of patients, and the most severe side effects are bone marrow suppression and hepatotoxicity, occurring in <1% of patients.[30]

Treatments of Choice for Hypothyroidism

Instead of long-term antithyroid drug treatment, radioiodine is the preferred treatment of choice in most cases of Graves' disease and toxic goiter in the elderly. This is an effective or definitive treatment. A return to normal thyroid function occurs slowly. There is more than 60% chance of developing hypothyroidism. Pregnancy should be delayed by 6 months.[17] β-blockers are used in combination with antithyroid drugs and after radioiodine to reduce the risk of tachycardia. After treatment with radioiodine, patients should undergo follow-up examinations at frequent intervals because most patients develop hypothyroidism and require TH replacement therapy.[17] Thyroidectomy (the removal of a part of the thyroid gland) is used less frequently due to the effectiveness of radiotherapy, but radiotherapy is a treatment of choice in young patients resistant to drug therapy and in some people who have thyroid neoplasms. Surgery is invasive and costly. The development of permanent hypothyroidism and laryngeal nerve injury is also likely.[13]

MATERIALS AND METHODS

We retrieved relevant publications using the keywords medicinal plants, hypothyroidism, and hyperthyroidism, and antioxidant role from the databases Google Scholar, PubMed, and ScienceDirect. After conducting the initial search and retrieving obtaining numerous articles on this subject, we found the results below by limiting our analysis to the most relevant articles.

RESULTS

Medicinal plants have been identified and used by humans throughout history. The effects of plants on human's body are due to their chemical compounds. Herbal drugs cause comparatively fewer side effects. It is believed that the herbal drugs are very safe and lead to significant effects in treating various diseases.[31] Today, traditional medicine is being widely used and plants are still considered a major source of natural antioxidants that can serve as a clue for the development of new drugs.[32] Medicinal plants are rich in secondary metabolites that have an important role in the function of mammalian tissues in both health conditions and diseases.[33] Numerous antithyroid drugs are available, but they lead to adverse effects during long-term treatment. Therefore, medicinal plants can be used in the treatment of thyroid diseases. Many plants are used to treat thyroid diseases. Many of the plants act as an antithyroid agent in both hypothyroidism and hyperthyroidism.[34]

Antithyroid activity of certain plants has been demonstrated. Some of the important plants used to treat thyroid diseases are as follows:[35-40]

Bugleweed is used as a thyroid suppressor that stops thyroid function and is one of the most effective plants on thyroid disease.

Bugleweed and its extract have several beneficial effects including preventing the binding of thyroid-stimulating antibodies for Graves' disease to thyroid disease, prevent the production of TSH, reduce the peripheral T4 deiodination, and inhibit iodine metabolism.[34]

Avena sativa Linn.

A. sativa Linn. is a plant of the Poaceae family and is locally called *Jai* or *Javi*. Green meal that is also used as food contains minerals and Vitamin B that is effective on health and improves thyroid function.[41]

Plants Used to Treat Hypothyroidism

Gotu kola leaves are useful for treating hypothyroidism. The leaves contain asiatic, asiaticoside, brahmoside, and brahmic acid. It has been suggested that it stimulates the synthesis of T4.[34]

Ashwagandha

Ashwagandha is a plant of the Solanaceae family. *Withania somnifera* is one of the few iodine free medicinal plants that are known to stimulate TH function. Some studies have shown that Ashwagandha only increases T4, but some studies have indicated that it increases both T3 and T4.

In another recent study, Ashwagandha was found to increase TSH and T4 levels in TH status, and in people who did not receive Ashwagandha, thyroid function decreased.

In a study in 50 patients with hypothyroidism (increased TSH by 4.5–10 fold), 600 mg of Ashwagandha root extract and starch, a placebo, were administered for 8 weeks.

Ashwagandha, compared to the placebo, led to normal function of TSH, T3 (18.6% in week 4 and 41.5% in week 8) and T4 (9.3% in week 4 and 19.6% in week 8) levels increased.

Botanists have reported that the plant is more effective on borderline underactive thyroid than on advanced hypothyroidism. However, it can play a supportive role in conventional drug therapies.[42]

Ashwagandha contains steroidal alkaloids and saponin. These chemicals are involved in increasing the production of T4 hormone through converting T4 to T3.[34]

Previous studies have shown that Ashwagandha is a good treatment for hypothyroidism. Significant increases in serum T4 levels indicate stimulatory effects at the glandular level.

It also affects cellular antioxidant system. Withania can also indirectly stimulate thyroid activity by acting on the cellular antioxidant system.[43,44]

Guggul, known as *Commiphora mukul*, supports thyroid function. It is a member of the Burseraceae family and contains aromatic sticky resins with pharmaceutical properties.[45]

Guggul has been reported to be beneficial for increasing iodine absorption by the thyroid gland and also for enhancing the activity of peroxidase.[46] Guggul can also decrease lipid profile by supporting the basic function of the thyroid metabolism.[47]

Guggul contains a sterol called guggulsterones, which acts on the bile acid receptor and processes lipids and also is involved in its hyperlipidemic effects.[48] Guggul inhibits LDL oxidation, which is a part of the mechanism of atherosclerosis.[49]

LDL levels can be changed using guggul supplements. It can also reduce lipid profile through thyroid function, which has been demonstrated in animal studies.

A compound of *Commiphora*, oleoresin, increases iodine reabsorption by the thyroid gland and also increases the activity of thyroxidase. The guggul extract contains oleoresin. It has a strong thyroid-stimulating activity. It also increases the production of T3 by increasing the conversion of T4 to T3.

It increases lipid peroxidation and also increases serum T3 level. Recent studies have shown that certain compounds of guggul resin have anti-inflammatory properties, lower cholesterol, and other blood lipids and support thyroid function in different ways.[50] Preliminary studies have shown that guggul improves the thyroid function and increases the conversion of T4 to T3 and T3.[42]

Zingiber officinale (Rosc.) is a plant of the Zingiberaceae family. Ginger is an important domestic remedy for thyroid function.

Ginger is rich in zinc, potassium, and magnesium. Ginger is a suitable herbal remedy because of its anti-inflammatory properties. Ginger can be used in different ways to treat thyroid diseases.[51]

Other Effective Medicinal Plants on Hypothyroidism

Bacopa monnieri from the scrophulariaceae family Function: *B. monnieri* stimulates thyroid activity by increasing the amount of T4 and is used to treat hypothyroidism.[52]

Since T4 (but not T3) levels are increased by *B. monnieri*, it can be concluded that the plant extract stimulates or releases T4 directly at the glandular level, but not through peripheral conversion of T4 to T3.[53]

Two other herbs, *Aegle marmelos* and *Aloe vera,* reduce either one or both THs. Among these two plants, marmelos have a better potential to reduce T3 by 62%, which is comparable to the reduction by the standard drug propylthiouracil.

Although *A. vera* extract decreases serum T3 and T4 concentrations, its inhibition rates for the two hormones are 25% and 13%, respectively, which indicates that the extract may not be adequately effective in reducing the concentration of THs. However, *A. vera* extract can be a better choice for mild hyperthyroidism cases because it does not produce a toxic effect on the liver. It seems that *A. marmelos* is relatively more effective than *A. vera* to reduce thyroid function and can, therefore, be considered for the regulation of hyperthyroidism.[53]

Coleus forskohlii (Lamiaceae family)

C. forskohlii increases the production and secretion of the hormone. It can also help keep the hormone level. *C. forskohlii* leaves are recommended for hypothyroidism in some cases. *C. forskohlii* stimulates adenylate cyclase and, therefore, has been recommended to reduce the effect of TSH because the activated adenylate cyclase binds to the TSH receptor. The compound forskolin (obtained from *C. forskohlii* leaves) increases the synthesis of T4 through thyroid follicles.[54]

Linum usitatissimum is a member of the Linaceae family and is locally called *Alsi/Bijari*. *L. usitatissimum* seeds are important for thyroid health and help promote TH production, which reduces predisposition to hypothyroidism.[41]

Nigella (black cumin) seed

A study in 40 patients with Hashimoto's thyroiditis showed that *Nigella sativa* powder reduced TSH level and increased T3 and T4 levels.[42]

Coconut oil

Preliminary studies have shown that coconut oil and other fats, such as avocado oil, support thyroid function probably in a way in which the body activates the TH. Some reports have shown the improvement and reduction of goiter.[38] *Bacopa monnieri* (L.) Pennell: *B. monnieri* is a member of the Scrophulariaceae family and is locally called *Chhoti brahmi/Jal-Neem*. *B. monnieri* has been reported to treat hypothyroidism if used in half a glass twice a day for 7–10 days. This tonic medicinal plant is used for underactive thyroid. Preliminary studies have shown that *B. monnieri* increases T4 but is not effective on T3.[42]

Bladder wracks

Bladder wracks are a member of the Fucaceae family and the *Phaeophyceae* genus and are found in the Pacific Ocean. *Fucus vesiculosus* contains flavonoids and fluconazole

and has been reported to have high antioxidant activity. *F. vesiculosus*[55] is a rich source of iodine and bioavailable.

It is also rich in minerals such as calcium, potassium, comparatively lower amount of phosphorus, selenium, and magnesium. It also contains adequate amounts of Vitamins A, D, E, K, B2, B3, and B6. *F. vesiculosus*, which contains all of these minerals and vitamins, has a beneficial effect on thyroid function,[56] and also helps reduce the activity of trans-sialidase in the blood. Trans-sialidase is an enzyme associated with cholesterol accumulation.

This can be helpful for patients with hypothyroidism as reduced metabolism is associated with hyperlipidemia.[57]

Versicolor

Versicolor is also called blue flag. Versicolor is a small wild plant found in the marshlands of North America. Versicolor enhances the function of the thyroid gland by increasing the production of T3. It is a detoxifying agent and is specifically used to treat thyroid enlargement. It is also useful for the treatment of hepatosplenomegaly. It contains volatile oils, resins, alkaloids, and oleoresin.[49]

Plants Used to Treat Hyperthyroidism

Melissa officinalis (Lamiaceae family)

As noted in previous studies, the lemon balm affects the blocking of TSH binding to the receptor by influencing the hormone and the receptor itself. It also prevents the production of cyclic AMP stimulated by TSH receptor antibodies.

Conventionally, lemon balm is used to treat hyperthyroidism symptoms such as tachycardia, insomnia, and hyperactivity. The *M. officinalis* extract increases the secretion of TRH and TSH levels and subsequently increases T3 and T4 levels. The increase in T3 and T4 can ultimately lead to a decrease in TSH levels through negative feedback.[58] *A. marmelos* (L. Corr.) is a member of the Rutaceae family and is locally called *Bael/Shriphal*. Its pharmaceutical use is such that its leaves are sliced in half a glass and used 3 times a day for 7–10 days to treat hyperthyroidism.[41]

Aloe barbadensis (mill) is a member of the Liliaceae family and is locally called *Ghee kwar/Gwarpatha*. Its pharmaceutical use is such that its brewed leaf is used twice a day to treat hyperthyroidism.[41]

Lemon balm, motherwort, bugleweed, and self-heal: Lemon balm, motherwort, bugleweed, and self-heal are four medicinal plants that can be used, either in combination or separately to treat hyperthyroidism. Preliminary studies have shown that lemon balm (*M. officinalis*), motherwort (*Leonurus cardiaca*), and bugleweed (*Lycopus europaeus*) inhibit TSH through binding to receptor sites and reduce the excess production of TH.

These plants are rich in rosmarinic acid that is beneficial for various thyroid conditions. These plants also block the antithyroid effects of immunoglobulins and reduce conversion of T4 to T3.[42]

Lemon balm is used as a thyroid suppressant for the treatment of hyperthyroidism. The plant is effective on the hormone and the receptor by preventing the binding of TSH to the receptor.

It can also prevent the production of cyclic AMP to stimulate TSH receptor as an antibody. Lemon balm also contains a large amount of rosmarinic acid.

Motherwort mainly has anti-inflammatory activity, because it contains a flavonoid called quercetin. It is important to reduce inflammation or swelling to treat autoimmune diseases, and therefore, motherwort is a good choice to treat hyperthyroidism. In this case, the action of the 5-deiodinase is prevented.[34]

In a study in 400 hyperthyroid patients, bugleweed was found to significantly reduce the symptoms.[59] Cardiovascular stress that is common in hyperthyroidism has also been observed to reduce by motherwort and Bugleweed, and less markedly, by lemon balm.

Self-heal contains rosmarinic acid in abundance and has been found in a study to be able to goiter in both hyperthyroidism and hypothyroidism in combination with drug therapy.[42]

The gromwell belongs to the Boraginaceae family and contains rosmarinic acid. The most important action of this plant in hyperthyroidism is to prevent TSH from binding to thyroid follicles. It also reduces the peripheral deiodination of T4 and also reduces the secretion of the TH.[34]

Rose marry is a plant of the Lamiaceae family. It has a high amount of rosmarinic acid and is used to treat hyperthyroidism.

This acid influences the effect of TSH on the receptor site and also prevents the effect of immunoglobulin on TSH receptor. In addition, it reduces the peripheral change in T3.

Sage, the other members of this plant family, exerts the same effect.[34]

Some of the plant drugs which are used in the treatment of thyroid dysfunction in conditions of hypothyroidism and hyperthyroidism are given in Table 1.

Antioxidant Role and Thyroid Diseases

THs regulate oxidative metabolism and thus play an important role in the production of free radicals. In addition, they regulate synthesis and destruction of proteins and vitamins as well as synthesis of enzymes.[60] It is known that the TH biosynthesis is an oxidative biochemical reaction that

Table1: Plants act on hypothyroidism and hyperthyroidism

Plant	Family	Antithyroid effect
Fucus vesiculosus	*Fucaceae*	Treatment for thyroid disorders, a supplement for weight loss and iodine, especially for hypothyroidism [61]
Fucus and Laminaria	*Laminariaceae*	Seaweed contains iodine and polysaccharide that affects the production of TH. It has long been used to treat thyroid diseases [51]
Bauhinia purpurea	*Caesalpiniaceae*	It is known to have antibacterial, antidiabetic, anti-inflammatory, and anticancer properties and regulates TH [62]
Ficus carica	*Moraceae*	Only one TH, either T3 or T4, was altered by the plant extract [63]
Mangifera indica	*Anacardiaceae*	It plays thyroid-stimulating and antiperoxidase roles [64]
Lithospermum officinale	*Boraginaceae*	The club moss affects the hypothalamus-pituitary axis in the thyroid gland. It can prevent the peripheral deiodination of T4, and therefore, T3 is activated. The old studies on the composition of plants show that club moss can block TSH receptor [51]
Convolvulus pluricaulis choisy	*Convolvulaceae*	Convolvulus strongly affects some of the liver enzymes and helps improve the symptoms of hyperthyroidism. It has anti-inflammatory properties and plays a role in reducing the symptoms of hyperthyroidism. Studies have also shown that it is beneficial for the treatment of hypothyroidism [65]
Leonurus cardiac	*Lamiaceae*	Motherwort is very important in autoimmune diseases and inflammation and therefore is a good choice to treat hyperthyroidism. In addition to reducing inflammation, it also inhibits 5-deiodinase [51]
Annona squamosal	*Annonaceae*	The aqueous extract of *Annona squamosa* leaf can be useful to improve hyperthyroidism, which is an important causative factor for diabetes mellitus [66]
Rauvolfia serpentine	*Apocynaceae*	The injection of *Rauvolfia serpentina* root extract significantly reduced the serum concentrations of T3 and T4 in mice with T4-induced hyperthyroidism [67]

TSH: Thyroid-stimulating hormone, TH: Thyroid hormones

depends on peroxide formation.[68] Changes in THs levels can be one of the main physiological mediators for the regulation of oxidative stress *in vivo*, which depends on their known role in influencing the mitochondrial respiratory chain.[69] One of the main effects of THs is increasing mitochondrial respiratory chain that increases the production of reactive oxygen species (ROS), leading ultimately to oxidative damage to membrane lipids.[70] The thyroid gland is an organ where oxidative processes are essential for the production of TH. It is estimated that a large amount of ROS, especially H_2O_2, is produced in the thyroid under physiological conditions. Hydrogen peroxide is an essential factor for TH biosynthesis. This compound is produced in the thyroid gland.[71] The reactive nature of oxygen and its mediators seem to be involved in endocrine autoimmune diseases such as certain thyroid disorders.[72] The most common autoimmune disease is Graves' disease that is associated with excessive production of THs due to continuous stimulation of the TSH receptor by thyroid-stimulating antibodies.[73,74] Although the causes of autoimmune events have not yet been determined, evidence suggests the role of oxidative stress in the pathogenesis of the disease.[75] Experimental studies have confirmed that changes in thyroid function have a significant impact on the activity of the compounds of mitochondrial respiratory chain in mouse liver.[75,76] It has been suggested that mitochondrial respiratory chain dysfunction due to hyperthyroidism accelerates the formation of ROS[76,77] and may also cause changes in the potential of antioxidant systems. Hydrogen peroxide acts as an electron receptor at all steps of the TH synthesis, i.e., it is essential for activity of thyroperoxidase, the key enzyme for thyroid synthesis, in iodide oxidation and then its organization, as well as in the iodotyrosine binding reactions.[78] An increase in H2O2 production, alongside subsequent increase in free radicals (especially OH), occurs under all conditions associated with increased blood TSH levels. Therefore, stimulating TSH leads to goiter development, and under certain conditions, triggers the onset of thyroid cancer through the oxidative stress mechanism. Oxidative stress provides the conditions for cell proliferation.[79,80]

The natural antioxidants present in plants remove harmful free radicals from the body. Antioxidants exert effect by suppressing the formation of ROS by inhibiting enzymes or chelating rare elements. Antioxidants are vital elements that protect the body against oxidative stress damage that is induced by free radicals.[81] Clinical and experimental studies have shown increased free radical levels in hyperthyroidism. Hyperthyroidism is a Hyper meth asic state that increases with total oxygen consumption, causing the formation of ROS and other free radicals or the occurrence of oxidative stress.[82] Vitamin A increases the conversion of T4 to T3. Vitamin E is an important factor for suppressing free radicals and increasing immune system capacity.[83] The reduction of Vitamin E in thyroid disorders leads to the conclusion that high rates of free radical metabolism are ongoing.[84] Active oxygen radicals prevent the activity of the enzyme involved in conversion of T4 to active T3, which can be mitigated by

sufficient amounts of Vitamin E.[85] Vitamin E as an antioxidant can indirectly damage the H2O2 needed for iodine oxidation and thus reduces the TH biosynthesis.[86] Decreased Vitamin C levels in hyperthyroidism and a simultaneous increase in oxidative stress show that the antioxidant vitamin is oxidized, and therefore, antioxidant effect decreases. Hyperthyroidism is associated with an increase in the production of free radicals,[87] while in the hypothyroidism, the production of free radicals decreases. In fact, both hypothyroidism and hyperthyroidism are associated with an increase in oxidative stress and entail enzymatic and non-enzymatic antioxidants. In addition, some complaints due to hyperthyroidism are due to oxidative stress in target tissues. THs, unlike catalase (CAT), can act as oxidants and cause DNA damage, which occurs probably through the phenolic group. Other methods could include increased nitric oxide gene expression and excessive NO production, activation of hepatic Nf-Kb and subsequent increase in stimulating cytokines, ROS production, coupling mechanisms including uncoupling protein (UCP)-2 and UCP-3 regulated by THs in which increased turnover of mitochondrial proteins regulated by peroxisome proliferator-activated receptor-γ, whose expression is increased by administration of T3.[87] Hyperthyroidism is exacerbated by oxidative metabolism and decreased plasma levels of lipid and lipoprotein. In the hypermetabolic state that occurs due to hyperthyroidism, the production of free radicals and lipid peroxidation in the mitochondria is accelerated, and the antioxidant defense system is altered.[77,88] The amount of arachidonic acid, a saturated fatty acid, increases in hyperthyroidism due to increased lipid peroxidation. Tissue changes that are related to hyperthyroidism are associated with the effects of the two THs on antioxidant enzymes (Mn, superoxide dismutase [SOD] or Cu, Zn, CAT, and glutathione peroxidase [GPX]).

In humans, hyperthyroidism is associated with a decrease in circulating alpha-tocopherol levels, and coenzyme Q10 increases in hypothyroidism, and has been shown to be a sensitive indicator of the THs effect. Or, it can express TH in systemic disease conditions when T3 declines,[87] CAT activity increases in hyperthyroid patients and decreases in hypothyroid patients.[89-91] In another study, CAT was reduced in both hyperthyroidism and hypothyroidism. SOD activity increased in both hypothyroidism and hyperthyroidism, as well.[92] Regarding hypothyroidism, some have suggested that tissues may be protected against oxidative damage due to hypometabolic state.[66] However, recent studies have shown that oxidative stress increases in hypothyroidism.[93] In a study on 33 patients, it was argued that increased level of ROS in hypothyroidism may be associated with an oxidative environment, which results in a decrease in the antioxidant activity of PON1 and an increase in MDA and NO.[94] In a number of hypothyroid patients, the increase in MDA and NO levels was associated with a decrease in paraoxonase (PoN1), while the SOD level was not significantly different compared to the control group. Increased levels of MDA have also been reported in hypothyroid patients.[86] Chronic hypothyroidism manifests a defect in redox potential, leading to a free radical chain reaction, as well as metabolic suppression in antioxidant capacity. The use of antioxidants in hypothyroidism may be due to an increase in the production of free radicals in the respiratory chain in the mitochondrial inside layer.[89] Hypothyroidism is defined as decreased oxidative metabolism and elevated lipid and lipoprotein levels that occur due to metabolic suppression induced by low TSH levels.[95-97] In hypothyroidism, the amount of Vitamin E significantly decreases and β-carotene levels significantly increase, which can be attributed to the suppression of β-carotene to Vitamin E conversion due to TH deficiency.[98] Recently, it has been argued that active free radicals play an important role in the development of goiter in hypothyroidism.[99] T4 reduces H2O2 production by decreasing TSH secretion in hypothyroid patients, which results in an increase in GPX scavenging activity, and therefore, the destruction extent of thyrocytes is further limited.[100]

Lipid peroxidation and oxidative stress induced by hypothyroidism occur as a result of an increase in the production of free radicals as well as a decrease in the antioxidant defense capacity.[68] The metabolic disorder that occurs due to autoimmune hypothyroidism can also increase oxidative stress.[92] Previous studies have shown that both hypothyroidism and hyperthyroidism are associated with increased oxidative stress including enzymatic and non-enzymatic antioxidants.[68]

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