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Medicinal Plants Modulating Thyroid Hormone Regulation and Therapeutic Management of Thyroid Disorders

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ABSTRACT

The mortality rate of patients with thyroid cancer is not decreasing significantly in spite of earlier diagnosis and treatment. Risk factors for thyroid cancer are medical radiations and environmental carcinogens. There are several drugs that are used in the treatment of hypothyroidism and hyperthyroidism and improve symptoms in hypo and hyperthyroid patients. The present work constitutes a review of the therapeutic strategies as well as biosynthesis of thyroid hormones, causes, symptoms, and treatment of hypothyroidism and hyperthyroidism. We have discussed thyroid hormones and its analogues, radioactive iodides and medicinal plants which are used to treat thyroid related disorders. Drugs listed have potential activity and may aid the physician in the treatment of thyroid hormone problems.

Keywords: Thyroid diseases, medicinal plants, efficacy, therapeutic strategies, thyroxin, literature review

Introduction

The thyroid gland is formed by a midline out pouching of ectoderm of the primitive oral cavity (Fagman and Nilsson 2011). It consists of pockets of colloid surrounded by follicular cells and basement membrane. The thyroid gland is a U-shaped organ that weighs an average of 30 grammes. It is made up of two lobes that are lateral and inferior to the front portion of the larynx. These lobes are joined across the larynx

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by an isthmus (Policeni, Smoker et al. 2012). Galen vaguely described the thyroid in the second century (Toni 2000), but its identity as a ductless gland was first described by Holler in 1776 (Ajdukovi$\acute{c}$ 2017). Interestingly, Roger of Polermo used sponges and seaweed high in iodine content, in the treatment of goiter in the 12th century. Thyroid hormones are synthesized at the cellular level and stored in thyroglobulin. Thyroglobulin is a glycoprotein that is the main component of colloid (Di Jeso and Arvan 2015). Between the follicular cells are parafollicular cells, which are of neurogenic origin and secrete calcitonin. Thyroid hormones are synthesized in the thyroid gland from iodide, which is taken from the blood. The thyroid gland concentrates iodine from the blood and returns to the peripheral tissue in the form of thyroid hormone. Hormones are linked with carrier proteins known as thyroxin binding globulin and prealbumin. T4 is metabolized in the periphery to T3. Thyroid hormone has multiple physiological effects (Hameed, Patterson et al. 2017). It is essential for physical and neural development. There are treatment options to treat thyroid related disorders. Emphasis has been given to drugs that are known to inhibit thyroid hormone synthesis and/or secretion. In the gland, iodide is converted into iodine in the presence of peroxidase enzyme. Iodine thus formed causes the formation of monoiodotyrosine and diiodotyrosine by combining with tyrosine residues of the thyroglobulin molecule (a protein present in the thyroid gland). Two molecules of diiodotyrosine combines together to form one molecule of tetraiodothyroxine while one molecule of diiodotyrosine combine with monoiodotyrosine to form one molecule of triiodotyrosine. Both T3 and T4 are broken away from the thyroglobulin molecule by proteolytic enzymes and are released into the systemic circulation. Prevalence of thyroid cancer is also increasing Worldwide.

The Mortality rate of patients with thyroid cancer is not decreasing significantly in spite of earlier diagnosis and treatment. Risk factors for thyroid cancer are medical radiations and environmental carcinogens (Pellegriti, Frasca et al. 2013). There are various plants whose activity in hypo and hyperthyroidism has been investigated (Table 1). (Panda and Kar 1999) reported that Gugulu (*Commiphora mukul*) induces tri-iodothyronine production. The aim of present paper is interesting and is of much interest to the community working with natural

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materials characterized from wild plants.

Thyrotropin

Thyrotropin is a glycoprotein hormone which is synthesized and stored in particular basophilic cells of the adenohypophysis. Its primary action is to stimulate the thyroid (MONTOYA, SEIBEL et al. 1975; Tun, Beckett et al. 2016)

Effects of Thyroid Hormone on Protein, Carbohydrate, Lipid and Vitamin Metabolism

At normal plasma level, thyroxin has a protein anabolic effect. In hyperthyroidism, the high plasma thyroxin levels produce increased protein catabolism (Bates and Holder 1988). Carbohydrate metabolism is accelerated by an increase in the level of thyroxin. Increase level of thyroxin decreases cholesterol in the blood but mobilizes free fatty acids for the adipose tissues. Thyroxin enhances body demand of all the vitamins and coenzymes derived from them.

Biosynthesis of Thyroid Hormones

Iodides are first peroxidised to active iodine in the biosynthesis process. This iodine then combines with tyrosine to generate 3 monoiodotyrosine and then 3-5 diiodotyrosine. Thyroxin is created when the latter compound's two molecules combine. As an alternative, a diiodotyrosine molecule may combine with a monoiodotyrosine molecule to generate triiodotyrosine, which is subsequently iodinated to produce thyroxin. There is evidence that thyrotropin influences the condensation of two iodoamino acid molecules to produce either thyroxin or triiodothyronine, and the biosynthetic conversion of triiodothyronine to thyroxin has been found to be somewhat reversible (Brix, Führer et al. 2011). Triiodothyronine is the most active of the known thyroid metabolites but the significance of its metabolic relationship with thyroxin relative to biological control processes is unclear (Degroot and Niepomniszcze 1977; Mondal, Raja et al. 2016)

Regulation

Thyroid hormone release is regulated by thyroid-stimulating hormone and iodine (Mullur, Liu et al. 2014). TSH has both immediate and delayed action on the secretion of thyroid hormones (Glinoer 2004).

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Assessment of Thyroid Function

The concentration of thyroid hormone is measured in blood. Thyroid hormone level will be low in case of underactive thyroid gland and in contrast thyroid stimulating hormone level will be high. High concentration of thyroid hormone will show that thyroid gland is hyperactive and at the same time, thyroid stimulating hormone will be low than normal level. Measurement of serum thyroxin (T4): free T4 level is most useful. T3 level is measured when there is clinical suspicion of hyperthyroidism. TRF-stimulation test is performed for monitoring the release of TSH from the pituitary. Serum level of thyroxin-binding globulin is measured by radioimmunoassay (Stockigt 2003); (Blumenthal, Byth et al. 2016); (Ghirri, Lunardi et al. 2014); (Panicker 2011); (McAninch and Bianco 2016).

An Antibody Test

Increased generation of aberrant antibodies may cause goitre. An evaluation of blood antibodies may aid in the detection of thyroid gland abnormalities.

Types of Hypothyroidism

Primary hypothyroidism

Secondary hypothyroidism

Tertiary hypothyroidism

Risk Factors

Persons of all age group are at risk of developing goiter. People living in regions where iodine supplements are not available or iodine is short. Prevalence of goiter is more in female as compared to male. Prevalence of goiter is more after 40 years of age. Prevalence is more common in pregnancy. Radiation therapy to chest or neck increases possibility of goiter.

Causes of Hypothyroidism

A. Congenital

Congenital causes of hypothyroidism includes aplasia, hypoplasia of thyroid, iodide transport defect, thyroid peroxidase defect, thyroglobulin synthesis defect, deiodination defect, TSH unresponsiveness, idiopathic, congenital deficiency of TSH, congenital deficiency of TRH, maternal intake of drugs during pregnancy e.g. radioiodine and antithyroid drugs and iodides, iodine deficiency (endemic goiter) and maternal antibodies (thyrotropin receptor blocking antibody) (Abduljabbar and Afifi

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2012).

B. Acquired (Juvenile and adult hypothyroidism)

Acquired causes of hypothyroidism include thyroidectomy or radioiodine therapy, thyrotropin or TRH deficiency, acquired diseases, autoimmune thyroiditis (Hashimoto's thyroiditis), drugs (iodides, cobalt, antithyroid drugs) and infiltrative diseases (histiocytosis, cystinosis) (Lafranchi, 1992).

Cretinism

Hypothyroidism in children is called cretinism (Chen and Hetzel 2010). This is due to a relative deficiency of thyroid hormone and is often caused by lack of iodine (Singh, Purani et al. 2016). In contrast to growth modulation produced by growth hormone, thyroxin seems to be absolutely necessary for growth. In the total absence of thyroid hormones, linear growth ceases almost completely. The requirement of thyroxin for growth starts in the antenatal period and continues throughout childhood (Salisbury 2003). The study included 141 participants with hypothyroidism who were diagnosed within the first two years. When treatment was initiated during the first three months of life, the greatest mental development was attained. At this stage, the main physical symptoms of hypothyroidism are less common than later, and they typically include constipation, tiredness, and trouble feeding (Raiti and Newns 1971)

Symptoms

Symptoms do not appear until six months because enough thyroid hormone is present (Gadve, Sarma et al. 2012). Symptoms include stunted growth, deformed bones and teeth, dry skin, wrinkled hair, protruded tongue, broad nose and mental retardation etc (Fig. 1)

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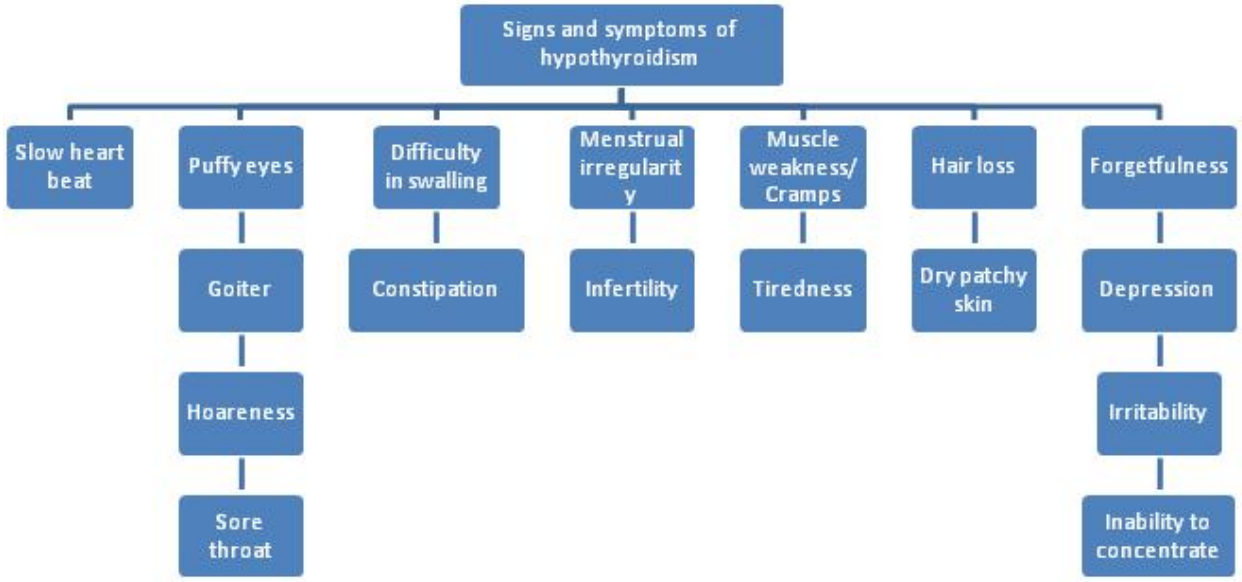


Fig. 1: Signs and sym ptom s of hypothyroidism

Hypothyroidism developing in older children and adults is known as myxedema. The most common cause is Hashimoto's thyroiditis (Zaletel and Gaberscek 2011). Other causes are the antithyroid drug, surgical removal, dietary iodine deficiency, and pituitary failure (Thompson and Henry 2017).

Manifestation

The manifestation of hypothyroidism includes generalized apathy, mental sluggishness, loss of hair, cold intolerance, obesity, constipation, non-pitting edema, hoarseness, cardiac enlargement, pericardial effusion, and enlargement of the tongue (Keen, Hassan et al. 2013).

Investigations

1. T4 level is decreased
2. Serum TSH

    TSH: elevated in primary hypothyroidism

    TSH: not elevated in secondary hypothyroidism

3. Serum T3 level is of little value because it only falls in extreme hypothyroidism

Treatment

Thyroxin replacement (Tebain 2017).

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Myxedema Coma

This is the end stage of untreated hypothyroidism. Myxedema coma is a serious and crisis staging of hypothyroidism. Though, the clinical characteristics and consequences of this state have been inadequately defined due to its infrequency. Its pathophysiology involves carbon dioxide retention and hypoxia, hypothermia, fluid retention and hyponatremia (Nabhan, Kreher et al. 2005).

Goiter

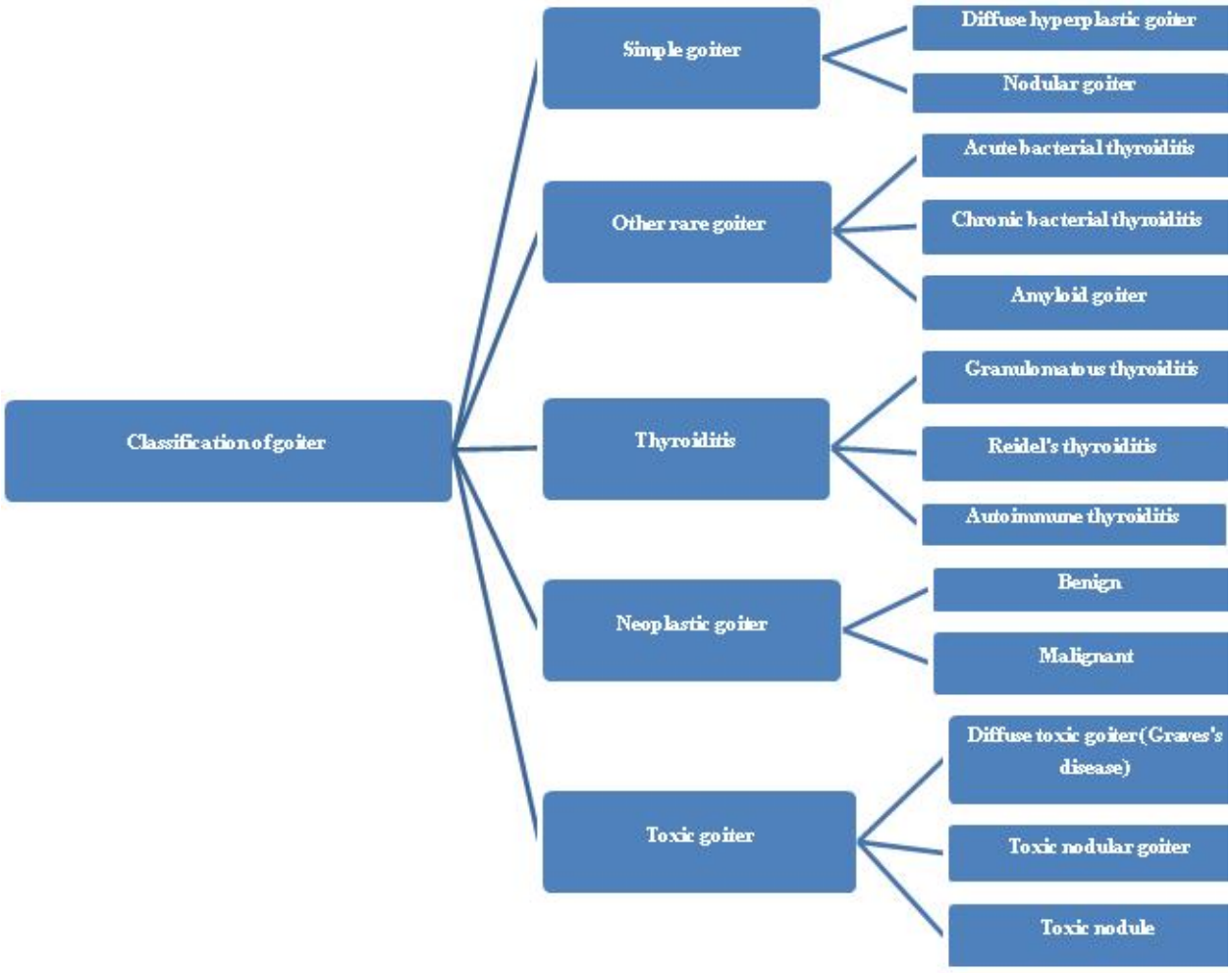
Goiter is classified in various types (Fig. 2). This health event can happen when there's an underproduction (hypothyroidism), overproduction (hyperthyroidism) or the correct production of the hormone (euthyroidism). The occurrence of a goiter at all times means that there's some state present leading to abnormal swelling of the thyroid gland. Usually, goiter occurs due to iodine deficiency in the diet. Thyroid gland uses iodine for formation of hormones that regulate the body growth and function. Due to dietary deficiency of iodine, thyroid gland becomes enlarged and it results in swelling in the neck and the condition is known as goiter (Kim, Lee et al. 2016). Dietary deficiency of iodine reduces the quantity of thyroxin and therefore reduces the circulating concentration of this hormone. In turn, this stimulates the secretion of TSH by the anterior pituitary. High concentrations of circulating TSH cause hypertrophy of the thyroid gland, increasing the mass of thyroid tissue, so the gland can extract more iodine from the plasma. Generally, the result is that sufficient thyroxin is produced but the gland is markedly enlarged (West, Tauer et al. 1987). (Abuye, Berhane et al. 2007) performed a cross-sectional study to evaluate the prevalence of goiter in Ethiopia in 2005. The total number of children was 10, 965. Age of children was between 6 to 12 years. Prevalence of goiter in children was 39.9%. This study indicated that severe iodine deficiency is found in Ethiopia. (Szybiński and Zarnecki 1993) conducted an epidemiological study to evaluate the prevalence of goiter in school children in Poland. The total number of children was 19, 300. Goiter is endemic in Poland. Prevalence of goiter was higher in northeastern parts, Carpathian and Sudeten of Poland. Less prevalence of goiter was observed in Northeastern areas of Poland. Percentage of people using iodized salt was about 20% only.

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Fig. 2: Classification of goiter



Hyperthyroidism

It is also called toxic goiter, thyrotoxicosis or Graves' disease (Negro and Greco 2016). In this disease, a long-acting stimulator (LATS), an antibody binds to the same receptors in thyroid cells. As a result of this binding, there is increased production of T3 and T4 (Collet, Gussekloo et al. 2012).

Subclinical Hyperthyroidism

In subclinical hyperthyroidism, the thyroid stimulating hormone is decreased however the levels of free thyroid hormone are normal. Endocrinologists consider this state as a predecessor of obvious or medical hyperthyroidism but there is a little question over whether this mild form of hyperthyroidism should be managed. Additional study is being continued in this vicinity. Recently, management is a topic for personal medical assessment and conversation among patient and clinician, while

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there is an agreement that management might be valuable in the old, predominantly if the cardiac beat turns into atypical or there is the weakening of the bones (Gharib, Tuttle et al. 2005).

Causes of Hyperthyroidism

Thyroiditis, autonomously functioning solitary thyroid nodule, multinodular goiter and Graves' disease are causes of hyperthyroidism (Léger and Carel 2013).

Symptoms

Exophthalmos (protrusion of the eyeballs) occurs due to edematous swelling of retrobulbar tissues and degenerative changes in extra ocular muscles (Ogun and Adeleye 2016). Vision is damaged due to the stretch of the optic nerve. Ulceration of the cornea occurs due to incomplete closure of the eyelids. Other symptoms of hyperthyroidism include insomnia, nervousness, mental disorders, tachycardia and palpitations, hypertension, increased. cardiac output, increased rate and depth of breathing, increased appetite, increased GIT mobility, increased body wt, increased sweating especially on hands and feet (Trivalle, Doucet et al. 1996).

Thyroid Hormone and Analogues

Endogenous: Thyroxin and triiodothyronine

Animal origin: Desiccated thyroid

Synthetic: Levothyroxine, levothyronine, liotrix

Clinical uses of Thyroxin

It is used in hypothyroidism and myxedema coma. Thyroxin is prescribed to treat infertility in hypothyroid women. It is used to prevent cretinism in hypothyroid infants (Joffe, Brimacombe et al. 2007).

Adverse Effects of Thyroxin

Adverse effects of thyroxin include restlessness, insomnia, nervousness, heat intolerance, palpitation, tachycardia, unexplained weight loss, accelerated bone maturation, and growth (Bartalena, Bogazzi et al. 1996).

Graves' Disease

In patients with Graves' disease, the thyroid gland becomes enlarged and massive overproduction of thyroid hormone occurs (Bartalena, Baldeschi et al. 2016). These patients have a circulating immunoglobulin linked to the TSH receptor on cells of

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the thyroid gland so that these receptors are activated continuously. This breaks the usual negative feedback and overproduction of thyroid hormones continues (Bahn 2012).

Treatment

Following are the three methods of treatment of hyperthyroidism

Anti-thyroid drugs

Subtotal thyroidectomy

Radioactive Iodine

Anti-thyroid drugs are carbimazole, propylthiouracil, beta blockers, radioactive iodine, and surgery (Haugen, Alexander et al. 2016). Anti-thyroid drugs are first tried for patients less than 40 years of age, if there is relapse then consider surgery. Radioactive iodine is administered in patients more than 40 years of age and those who develop recurrence after surgery (Brierley, Tsang et al. 2005). Thiourea drugs are propylthiouracil and carbimazole. Thiourea drugs decrease the synthesis of new thyroid hormone by inhibiting the iodination of tyrosine.

Beta-Blockers

Doctor may recommend a group of medicines recognized as beta-blockers that inhibit the activity of thyroid hormone on body. They generally make patient feel improved within few days, yet though they do not alter the increased concentration of thyroid hormone in blood. These medicines might be tremendously supportive in reducing heart rate and decreasing the manifestations of palpitations, nervousness and shakes until one of the other kinds of management has a possibility to exert effect. Propranolol was the first of this medicine to be introduced. Various doctors now favor other medicines such as Inderal, nadolol, metoprolol and atenolol.

Thyroid Surgery

Surgical procedure to excise whole or part of thyroid gland is definitively managing over activity of thyroid. This is an easy procedure when carried out by a skilled person, with a little possibility of complications. Hypothyroidism is a familiar adverse effect of surgery for which levothyroxine substitute will be required, lifetime. Thyroidectomy is a superior management choice for patients with a bulky goiter and for people with thyroid ophthalmic disorders. Earlier to thyroid surgery, over activity of thyroid requires to be restricted, typically with antithyroid medicines

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Drugs Interfering with the Synthesis of Thyroid Hormones

Propylthiouracil, methimazole, carbizole, thiouracil, thiourea, perchlorate, pertechnetate, and thiocyanate are among the medications that prevent the production of thyroid hormones (Surks and Sievert 1995).

Drugs Preventing the Release of Thyroid Hormones

These include potassium iodides, sodium iodide, diatrizoate, and lohexol.

Drugs Producing Thyroid Gland Destruction

Adjunctive Drugs

These include propranolol, guanethidine, reserpine, diltiazem, aspirin, and corticosteroids

Thioamides

Thioamides are used in thyrotoxicosis, thyrotoxic crisis and toxic multinodular goiter (Boelaert, Maisonneuve et al. 2013).

Adverse effects of thioamides

Adverse effects of thioamides include vasculitis, cholestatic jaundice, hepatitis, agranulocytosis, hypoprothrombinemia, lymphadenopathy, polyserositis, arthralgia, fever, lupus-like reaction, urticarial rash, and maculopapular pruritic rash (Lipsky and Gallego 1988).

Subtotal thyroidectomy

It is indicated in recurrent hyperthyroidism after the course of anti-thyroid drugs in patients of less than 40 years of age It can be an option in patients with severe hyperthyroidism and in those with large goiter (Liu, Liu et al. 2017).

Radioactive iodine

It is indicated in patients more than 40 years. It is also indicated in recurrence following surgery (Deandreis, Rubino et al. 2017).

Radioactive iodides

It is the preferred treatment for hyperthyroidism in patients over 21 years of age (Hesselink, Brouwers et al. 2016). It is sued as sodium iodide solution by the oral route. It is concentrated in the thyroid gland and emits beta rays, which penetrates about 0.5 mm and thus cause the destruction of a gland. In simple cases of hyperthyroidism radioactive iodine is used while the patient is treated with

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propranolol. In patients suffering from severe hyperthyroidism, coronary heart disease, or in elderly persons, treatment with thionamides is required to make the patient euthyroid. Thionamides should be stopped 5-7 days before the administration of radioactive iodine. Radioactive iodine will produce its effects in about 3 months. The drug is not given during pregnancy, as it crosses the placenta and can cause damage to the fetal thyroid gland (Villadsen, Sørensen et al. 2011).

Adverse effects of radioactive iodine

Adverse effects of radioactive iodine include delayed hypothyroidism and delayed onset in control of hyperthyroidism (Lu, Shan et al. 2016).

Treatment of thyroiditis

Numerous kinds of thyroiditis are self-limiting and over activity recovers unexpectedly and no management may be needed. If the individual has rigorous manifestations of thyrotoxicosis, beta blockers are useful. Though, in a number of cases, thyroiditis can be hurting or protracted and anti-inflammatory agents or steroids might be useful. Moreover, in a few cases, an episode of thyroid under activity might pursue the thyrotoxicosis, and this might need levothyroxine management if causing rigorous manifestations (Hueston 2001).

Thyroid surgery

A surgical procedure to excise mainly or the entire of the thyroid gland is one more method of effectively managing over-activity of the thyroid gland. This is a simple process as carried out via a skilled thyroid surgeon, with a little threat of complexities. Hypothyroidism is a documented adverse reaction of surgical procedure in favor of which levothyroxine substitute will be required, all-time. Thyroidectomy is a fine management opportunity for an individual with a bulky goiter and for persons with thyroid eye illness. Earlier in thyroid operation, over activity of thyroid requires being regulated, frequently with antithyroid medicines to build an anesthetic harmless. This is as an anesthetic in a hyperthyroid individual has an elevated threat of enhancing hazardous hyperthyroid disaster or "thyrotoxic storm (Rosato, Avenia et al. 2004)"

Medicinal plants used to treat thyroid related disorders

Raphanus sativus

It belongs to family Brassicaceae. Flowers of this plant are used for therapeutic

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purposes. Its chemical constituents are glucosinolates, isothiocyanates, phenolics, anthocyanin, anthocyanidins, pelargonidin, delphinidin, anthocyanidin, cyaniding. (Chandra, Mukhopadhyay et al. 2006) reported the efficacy of radish (*Raphanus sativus* Linn.) on thyroid status under conditions of varying iodine intake in rats. A study was conducted to investigate the effect of this plant under varying state of iodine intake. Albino rats were used for the study. Morphological and functional status of thyroid was evaluated in albino rats. Parameters for assessment were thyroid peroxidase activity, T3, T4, and thyrotropin levels. By chronic consumption of radish feeding, hypertrophy of thyroid gland was observed. Thyroid peroxidase activity was reduced. The thyroid hormone profile was also decreased. Thyrotropin levels were elevated. This condition caused a relative state of the hypoactive thyroid gland in comparison to control even after adequate iodine supplementations.

Moringa oleifera

Moringa oleifera belongs to family Moringaceae. *Moringa oleifera* is used to treat thyroid hormone problems and esophageal cancer (Tiloke, Phulukdaree et al. 2013). A study was conducted to investigate the efficacy of aqueous leaf extract of *Moringa oleifera* in the regulation of thyroid hormone. For this purpose, adult Swiss rats were selected. Leaf extract was administered at a dose of 175 mg/kg body wt. for 10 days). There was a significant decrease in the level of serum triiodothyronine (T (3) concentration in the males. Mechanism of this plant was to inhibit the conversion of T4 to T3. T3 level was decreased and T4 was increased suggesting its mechanism of action. This study suggests that intake of this plant extract is useful in regulation of thyroid hormones (Tahiliani and Kar 2000).

Lycopus virginicus

Lycopus virginicus belongs to family Labiatae. Luteolin, acacetin and apigenin has been isolated form aerial parts (Bucar and Kartnig 1995). It is sedative and astringent. It is used in hemorrhages, pericarditis, endocarditis, chronic inflammation, cough, and chest congestion. (Auf'mkolk, Köhrle et al. 1984) reported that *Lycopus virginicus* inhibits iodothyronine deiodinase of rat liver and is, therefore, useful in the treatment of hyperthyroidism.

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***Lycopus europaeus* L.**

Lycopus europaeus L. belongs to family Lamiaceae. This plant is used in the mild type of hyperthyroidism. TSH or thyroid hormone levels were reduced by use of a higher dose of this plant in animal experiments. The low dose of this plant improved the cardiac symptoms in patients with hyperthyroidism and there was no significant effect on thyroid hormone and TSH level. Lycopus extract was given i.p. to thyroxin-treated hyperthyroid rats. The hydroalcoholic extract of this plant was given one week later than T4-application and lasted 5.5 weeks. Atenolol was used as a reference drug. The low dose of extract reduced body temperature. There were no significant changes in the level of thyroid hormones. Blood pressure and heart rate were reduced by use of extract and reference drug atenolol. This study indicated that plant is useful in lowering blood pressure in patients with hyperthyroidism (Vonhoff, Baumgartner et al. 2006).

Kalanchoe brasiliensis

It belongs to family Crassulaceae. A study was conducted to investigate the efficacy of this plant to inhibit thyroid peroxidase activity. Aqueous extract of this plant inhibited thyroid peroxidase iodide-oxidation activity. This study indicated that plant has antithyroid effects (Ferreira, Rosenthal et al. 2000).

Conclusion

This review shows that there are various drugs in the modern and traditional system of medicine that are effective in the treatment of thyroid disorders. Isolated anti-thyroid compounds from the leaf, root and seed of different plants have positive effects on hypo & hyperthyroid patients. Alternative treatments for thyroid have more impact on lifestyle improvement and nutritional diet, providing spiritual support along with natural thyroid medication and also place a priority on improving functions of other organs that increase thyroid performance. Several drugs have shown in laboratory animals treated with thyroid hormones or in human subjects with hyperthyroidism, to lower the level of thyroid hormones or to otherwise lead to improvement in symptoms. A surgical procedure to excise mainly or the entire of the thyroid gland is one more method of effectively managing over-activity of the thyroid gland. Different herbal plants still need to be studied further.

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Ethical approval

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Table 1: Anti-hyperthyroid effect of plants

Plant name	Family	Part used	Dosage form design	Model	References
Aegle marmelos	Rutaceae	Leaves	Scopoletin (1.00 mg/kg, p.o.)	Rats	(Panda and Kar 2006)
Annona squamosa	Annonaceae	Seeds	Seed extract (200 mg/kg)	Mice	(Panda and Kar 2007)
Ecklonia kurome	Lessoniaceae	Whole plant	Aqueous extract (80, 160 and 320 mg/kg)	Rats	(Zhang, Li et al. 2017)
Emblica officinalis Gaertn	Euphorbiaceae	Fruit	Ethanolic extract (250 mg/kg/d (p.o.)	Mice	(Panda and Kar 2003)
Lagenaria siceraria	Cucurbitaceae	Peel	Peel extract (50, 100, 200 mg/kg)	Mice	(Dixit, Panda et al. 2008)
Hyperthyroid effects of plants					
Commiphora mukul	Burseraceae	Gum resins	Guggulu (200 mg/kg)	Mice	(Panda and Kar 2005)

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Costus pictus	Costaceae	Leaves	Methanolic extract (150 mg/kg)	Rats	(Ashwini, Bobby et al. 2017)
Withania somnifera	Solanaceae	Root	Root extract (1.4 g kg−1)	Mice	(Panda and Kar 1998)
Citrullus vulgaris	Cucurbitaceae	Fruit peel	Extract (100 mg/kg)	Rats	(Parmar and Kar 2009)

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