A REVIEW ON APPLICATION OF MEDICINAL PLANTS IN HYPOTHYROIDISM

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B.Sc. in Pharmacy

School of Pharmacy
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It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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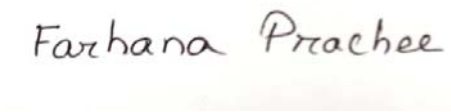

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Approval

The thesis/project titled "A Review on Application of Medicinal Plants in Hypothyroidism" submitted by Farhana Prachee (18146100) of Summer, 2021 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on March 6,2022.

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Ethics Statement

No human or animal tests are involved in this study.

Abstract

Hypothyroidism is one of the most common endocrine disorders globally where there is an elevated thyroid-stimulating hormone (TSH) in the setting of normal free thyroid hormone levels, both thyroxine and triiodothyronine. In the recent past, the detection of hypothyroidism has been increasing with evolving diagnostic tests and it shows that the prevalence of SCH is greater than that of type 2 diabetes mellitus. However, the influence of thyroid hormones action on lipid metabolism as well as on the heart is well known, so any disturbances of thyroid gland function could be followed by changed serum lipid levels associated with risk factors for cardiovascular disease. For treatment purpose, application of medicinal plants has proven to be effective with less adverse effect. It improves hypothyroid status and decrease serum TSH concentrations along with improvement of cholesterol profile. This review will summarize the potential role of the medicinal plants in treatment of hypothyroidism and improvement of thyroid status.

Keywords: Hypothyroidism, medicinal plants, thyroid-stimulating hormone (TSH).
thyroxine, triiodothyronine

Dedication

Dedicated to my family who has been a constant support and provided the best for me.

Acknowledgement

First of all, all the praises to Allah for His blessings toward me.

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List of Acronyms

TSH	Thyroid stimulating hormone
FT4	Free thyroxine
SCH	Subclinical hypothyroidism
LDL-C.	Low-density lipoprotein- cholesterol
T3	Triiodothyronine
T4	Thyroxine
CHD	Coronary heart disease
TH	Thyroid hormone
TRH	Thyrotropin releasing hormone
TSHR	Thyroid stimulating hormone receptor
LT-4	Levothyroxine
HPA	Hypothalamus-pituitary axis
COX-2	Cyclooxygenase
IL	Interleukin
VEGF	Vascular endothelial growth factor
HDL-C	High density lipoprotein- cholesterol

Chapter 1: Introduction

1.1 Hypothyroidism

Hypothyroidism is a condition where thyroid gland acts as an underactive gland which doesn't produce enough of crucial hormones. It's a very frequent condition that affects mostly the elderly, the women and particular ethnic groups. However, hypothyroidism can be of primary or secondary stage, also it can be either overt, with a raised TSH and low FT4 (free thyroxine) levels, or subclinical, with normal FT4 levels but an increased serum TSH.

Subclinical hypothyroidism (SCH) is one type of hypothyroidism which is defined by raised serum TSH or thyrotropin levels along with normal levels of thyroxine (T4) and triiodothyronine (T3) hormone. It's considerably more common when TSH is above 4.5 mcU/mL and FT4 is normal. TSH levels between 4.5 and 10 mcU/mL are used to diagnose it (Barbesino, 2019). However, SCH is usually thyroiditis with autoimmune complications, but it may also be caused by different factors (Sue & Leung, 2020a). Although this issue is not unique to the elderly, data suggests that TSH levels rise with age. When there is elevated serum TSH and low circulating THs, overt hypothyroidism is diagnosed, which affects 0.2 percent to 2% adults who are non-pregnant. A decrease in cardiac output, heart rate, and an increased peripheral vascular resistance with diastolic dysfunction, all are symptoms of overt hypothyroidism. Along with overt hypothyroidism, there are considerable changes in modifiable atherosclerotic risk factors, such as diastolic hypertension, hypercholesterolemia, raised carotid intimal-media thickness, and diminished endothelial nitric oxide. Both of the Overt and SCH are associated with impaired vascular function, increased carotid intima hyperplasia and diastolic hypertension (Razvi et al., 2018a).

1.1.1 Complications

As the receptors of thyroid hormone are found in almost all the organs and tissues of our body, the clinical indications of this insufficiency can be quite varied. The skin, kidneys and connective tissues, as well as the pulmonary, gastrointestinal, cardiovascular, musculoskeletal, and neurological systems, all may get affected. Moreover, hypothyroidism symptoms can range from mild to severe, depending on the severity of the condition (Aziz et al., 2017). Fatigue, weight gain, cold sensitivity and constipation are also symptoms of SCH, as are decreased quality of life, cognitive function, mood and memory. However, Individuals with SCH usually have milder clinical symptoms compared to those have overt hypothyroidism. They may not be present in people having grade 1 of SCH, but they may become more common and severe as TSH levels rise. Although it varies by age, gender, race/ethnicity, and location (Sue & Leung, 2020b). Furthermore, risk of cardiovascular diseases including coronary artery disease, liver disease, dyslipidemia and neuropsychiatric symptoms increases, as well as subfertility, low birth weight, and miscarriages, are all side effects of SCH. Also, hypothyroidism is linked to ovulatory dysfunction, menstrual abnormalities, infertility, and a higher likelihood of recurrent miscarriage. It should be noted that TSH levels were found considerably higher in individuals who generated oocytes which were not fertilized in women planning an in vitro fertilization cycle (Khan et al., 2017a).

1.1.2 Current Treatment Options

Underactive thyroid gland must be treated with replacement medication of thyroid hormone for body to function properly. While treatment with levothyroxine, a synthetic thyroxine, is the standard method for hypothyroidism, also combining T4 with T3, another thyroid hormone, can be a better option for some people (Shomon, 2021).

The standard of care suggested that treatment with thyroid hormone replacement with a once-daily dose of synthetic thyroxine, L-thyroxine or L-T4, is the treatment which is guidelines-approved for hypothyroidism. Hyperthyroidism can develop if too much levothyroxine is given (a condition known as T4 over-replacement). However, this is a rare adverse effect which can be corrected with a dose change. For the treatment of hypothyroidism, some of the doctor's recommendation is taking T3 (triiodothyronine) along with T4 (that is, two separate pills). The synthetic version of T3 is liothyronine. The issue with T3 is that it has a very short half-life, necessitating many doses throughout the day. Also, T3 levels fluctuate in the body as a result of the several daily doses required. If T3 levels are high, signs of hyperthyroidism are common. Hyperthyroidism is characterized by a rapid heart rate, sleeplessness, and anxiety. Atrial fibrillation, a kind of cardiac arrhythmia, and bone loss (osteoporosis) are both possible side effects. For the treatment of hypothyroidism, majority of the endocrinologists recommend taking levothyroxine over the T4/T3 combination therapy, mostly to avoid hyperthyroid impact. It's impossible to ignore "T3 spikes" when taking T3, which might cause hyperthyroid symptoms like high heart rate or anxiety. All of this being said, if there are hypothyroid symptoms still remain despite levothyroxine, then a three-to-six-month combination T4/T3 trial may be recommended by healthcare professional. Although there is normalization of their TSH and levels of thyroid hormone, research suggestion is that some of the people with hypothyroidism taking levothyroxine still have symptoms of fatigue, trouble losing weight, etc. Of course, before prescribing T4/T3 combination therapy, healthcare professional will check to see if the symptoms are caused by something other than hypothyroidism, such as anemia, depression, or fibromyalgia. Furthermore, regardless of whether there are chronic symptoms, only levothyroxine but not combined T4/T3 medication, is the recommended treatment for a pregnant woman who is hypothyroid (Shomon, 2021).

In addition, it's been claimed that levothyroxine replacement medication in individuals with SCH was linked to a lower incidence of CHD (Congenital heart defects). Levothyroxine therapy has been shown to have a wide range of effects on lipid profiles in patients with SCH in clinical trials. Although the effects are more obvious in people having TSH which is greater than 10mIU/l, a few studies have shown that levothyroxine medication improves the lipid profile in patients who has a TSH of less than 10mIU/l (Khan et al., 2017b).

However, precordialgia or palpitations may emerge in the initial hours following LT4 treatment, indicating sympathetic hyperactivity. This situation necessitates starting with very low dosages of LT4 and progressively increasing them, with normalizing TSH taking several months. The sympathetic hyperactivity could be caused by untreated iron deficiency anemia, which is exacerbated by thyroid hormone use. Thyroid hormone therapy should be temporarily stopped and then reintroduced at low levels to rectify anemia. Beta blockers may be used to control symptoms during the first few weeks of thyroid replacement treatment in certain circumstances (Abassi et al., n.d.). Studies on medicinal plants give important therapeutic data as their applications are directly strongly bound to the presence of an active chemicals along with healing capabilities (Taïbi et al., 2021)**.**

Thyroid gland dysfunction is a very prevalent medical problem. Patients are increasingly turning to medicinal herbs as a supplement to or replacement for traditional pharmacological therapies. Thyroid dysfunction treatment using medicinal plant preparations may be beneficial for these people. While the toxicity of these formulations has been reported to be minimal (Krepkova et al., 2021).

Some thyroid problems require lifetime care, and medication therapies frequently result in relapses and side effects. As a result of these obstacles, many have turned to alternative or supplementary

medicine to treat their problems. As a result, herbal therapies for thyroid issues have grown in popularity since they can be safe and effective, and have fewer adverse effects. Many plant species are taken for consumption around the world for normalizing thyroid hormones, supporting thyroid function as an iodine source or a thyroid suppressor because they have shown substantial improvements in thyroid function and a reduction in the rate of relapse and side effects comparing to drug therapy given alone (Taïbi et al., 2021).

1.2 Medicinal Plants in Hypothyroidism

Thyroid problem is common among endocrine disorders globally which are linked to a variety of factors like genetic and environmental, however dietary intake of iodine consumption is still a big factor. The thyroid gland's hyperfunction reduces TSH production, whereas hypofunction induces the pituitary to create more TSH. Both hyperthyroidism and hypothyroidism can be caused by a dysfunction of the pituitary gland, thyroid gland or hypothalamus. Both of them are common in women mostly than in males, though causes remain unknown. Furthermore, some thyroid problems require lifetime treatment, and pharmacological therapies frequently result in relapses and negative effects. As a result of these obstacles, many have turned to alternative or supplementary medicine to treat their problems. As a result, herbal therapies for thyroid issues have grown in popularity since they are thought to be safe and effective and have fewer adverse effects. Several plant species are ingested around the world to help balancing thyroid hormones, supporting thyroid function as a iodine source, or decreased function of thyroid. An ethnopharmacological investigation found probabilities of triiodothyronine which is T3 and thyroxin which is T4 analogs, that includes antagonists, agonists, along with a variety of substances capable of modulating thyroid receptors. As a result, ethnopharmacological research which is about herbal and traditional medicines could be a useful alternative technique for finding analogs

of natural hormone for replacement treatment of hormone. Thus, significant number of therapeutic evidences are provided on medicinal plants by various studies as because their uses have been linked directly to the active compound's presence along with healing properties (Taïbi et al., 2021).

The medicinal plants have bioactive ingredients which possess antioxidant and anti-inflammatory properties. Several plant compounds can disrupt thyroid function by competing with thyroid hormonogenesis enzymes like thyroid peroxidase (TPO) or suppressing the production of gene which is thyroid-specific involving in glandular function. Thyroid hormonogenesis deficiency leads to a decrease in T3 and T4 production and, as a result, an increase in TSH secretion. The latter promotes the formation and activity of thyrocytes, which may lead to thyroid hypertrophy. This occurs most frequently when many goitrogenic variables are present, such as the consumption of foods high in anti-thyroid phytochemicals combined with a low iodine intake. Some of the plant compounds, like alkaloids and polyphenols, have antiproliferative impact on thyroid cancer cells and can react with thyroid hormone metabolism or production. These findings are prompting research into the uses of the chemicals as therapeutic agents in patients with poorly identified thyroid carcinoma. Additionally, several chemicals may be useful in the therapy of thyroid autoimmunity (di Dalmazi & Giuliani, 2021).

And for treatment purpose of hypothyroidism the herbal plants which are available such as: Gotu Kola (*Centella asiatica*), Ashwagandha *(Withania Somnifera*) , Guggul (*Commiphora mukul*) , and Coleus or forskohlii *(Plectranthus barbatus*). These are the important plants which are used for treatment purpose of thyroid disease (Gupta et al., 2016a).

1.3 Purpose of the Study

The purpose of this review paper is to summarize the application of various medicinal plants in treatment of hypothyroidism. Such medicinal plants show less toxicity due to the presence of active constituents. Also, they are effective, safe, and have fewer adverse effects. Thus, application of hypothyroidism for treatment purpose can be an alternative thyroid treatment option which place more importance on improving lifestyles and nutritional diet along with natural thyroid medication that enhance human health. In this review paper, it has been tried to present all the activities of the medicinal plants which are carried out by different researchers.

Chapter 2: Methodology

This review paper is conducted based on relevant and recent research articles and papers from the journals that have high-impact factors. A thorough search of peer-reviewed journals, official papers, and articles was conducted. Basic and extra material was gathered from many books to enrich the review paper. The following search engines have been used to collect data for this paper- which are Science Direct, ResearchGate, Google Scholar, Elsevier, PubMed, Cell Press, etc. in which the major publications like ACS (American Chemistry Society), Nature, AACR (American Association for Cancer Research), Journal of Medicine, Molecular Cell, Cancer Cell, Journal of Molecular Biology, Science, etc. are available. To develop an optimal quality review on the application of medicinal plants for hypothyroidism, a comprehensive screening of journals was conducted, followed by a narrowing down to the most recent and relevant ones.

Chapter 3: Hypothyroidism and Pathophysiology of the Disease

3.1 Thyroid Hormone Production

The thyroid hormone production involves the hypothalamus, pituitary which has given rise to the term hypothalamus–pituitary–thyroid axis. It is tightly regulated process that is controlled by classic negative feedback loop. In our body, hypothalamus produces thyrotropin-releasing hormone (TRH). After reaching the pituitary gland, the released TRH binds to the TRH receptor, resulting in production of thyroid-stimulating hormone (TSH), also known as thyrotropin, and later on it is secreted. When the thyroid stimulating hormone binds to the TSH receptor (TSHR) in the thyroid, it causes in thyroid hormone (TH) production. The hormones, Triiodothyronine and tetraiodothyronine/ thyroxine, are secreted into the bloodstream when they are needed. THs block TSH and TRH production along with secretion in the hypothalamus and pituitary by the TH receptor β (THR β). Thus, a negative feedback loop is completed which keeps TSH, THs and TRH at physiological levels (Gauthier et al., 2020).

Thyroid releasing hormone (TRH) is metabolized by a specific set of neurons in the hypothalamus's paraventricular nucleus. TRH binds to the receptor, TRH, which is expressed in thyrotrophs as it reaches the pituitary gland, causing TSH to be produced and secrete in the circulation. The TSH after entering the thyroid gland, it binds to the receptor, TSHR (TSH receptor), which is found in the cell membrane of thyroid follicles, triggering the creation of TH and inducing iodine uptake by the NIS. Pendrin action mobilizes iodide to the colloid, which is oxidized by the thyroid peroxidase by utilizing H_2O_2. When tyrosine residues are iodinated, monoiodotyrosines and diiodotyrosines are formed, which are then linked to produce T3 and T4. In the follicle's colloid, these hormones bound with TG are secreted. The thyroid follicular

epithelial cells catabolize iodinated TG in creating T3(triiodothyronine) and T4(thyroxine), that are subsequently passed into the circulation when needed (Gauthier et al., 2020).

3.2 Thyroid Hormone Signaling Pathway

Classically, thyroid hormone in the form of T3 or triiodothyronine was intended to function to bind to cytosolic thyroid hormone (TH) receptors, which binding to TH response elements on DNA and influence expression of TH target genes. However, different types of THR/DNA association methods of TH action have lately been discovered, and four kinds of TH signaling have been identified (Jonklaas et al., 2021).

Thyroid hormone action is divided into four categories (Figure 1). Binding of THRs to DNA as a monomer, heterodimer or homodimer, generally in conjunction with RXR. The N-terminal DNA-binding domain (D) is required for this category. The protein's structure and interactions with transcription cofactors are altered when TH binds to the C-terminal ligand-binding region (L). THRs that are anchored to DNA by other proteins or multiprotein complexes are classified as type 2. THR's ability to bind DNA isn't required. THRs of type 3 don't need to be recruited to chromatin to function. Localization might take either in the cytoplasm or in the nucleus. Type 4: TH binds to proteins other than THRs, acting independently of THRs (Flamant et al., 2017).

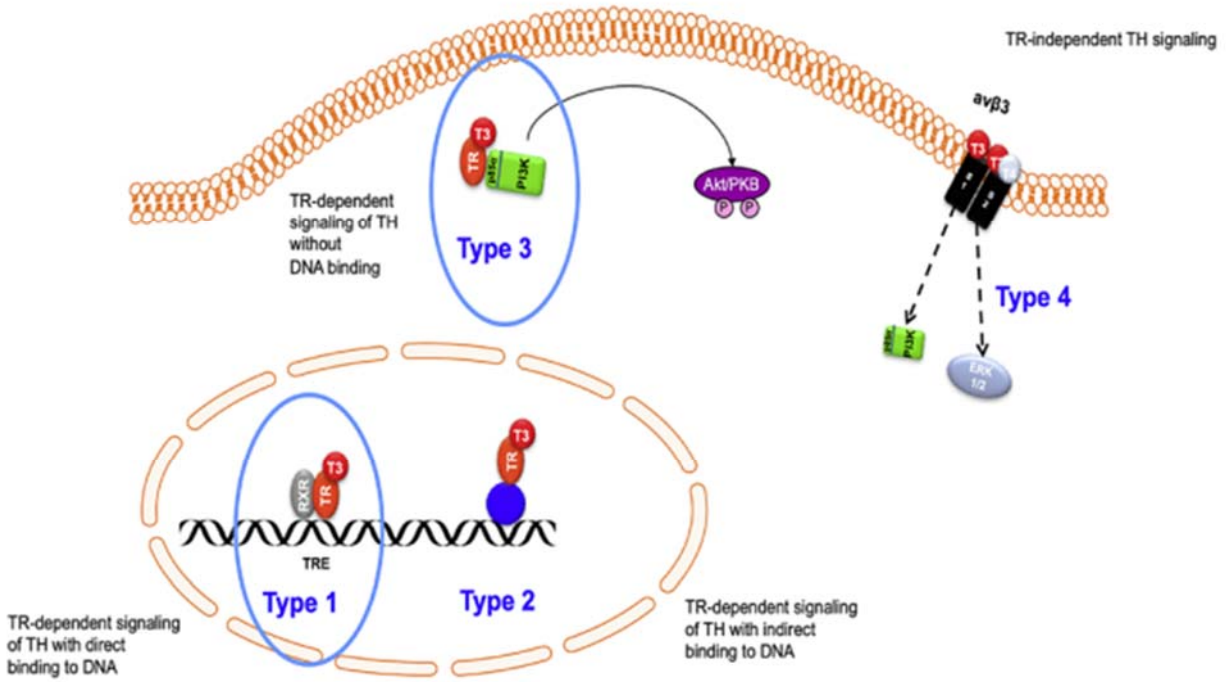


Figure 1: Four types signaling of thyroid hormone (Jonklaas et al., 2021).

3.3 Pathophysiology of the Disease

The most common cause of hypothyroidism is the thyroid gland's inability to produce adequate thyroid hormone; however, thyroid impairment can also be induced by the pituitary and hypothalamus. The brain produces thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to make thyroid-stimulating hormone (TSH). Thyroid-stimulating hormone (TSH) causes the thyroid gland to produce and secrete predominantly T4 (100-125 nmol daily) and less T3. T4 has a half-life of 7-10 days and is peripherally converted to T3 by 5'-deiodination. Levels of triiodothyronine which is T3 primarily and T4, thyroxine to some extent, in turn, exert negative feedback on the production of the TSH and TRH. Changes in the structure and function of any of these organs or pathways can induce hypothyroidism (Hypothyroidism - StatPearls - NCBI Bookshelf, n.d.)

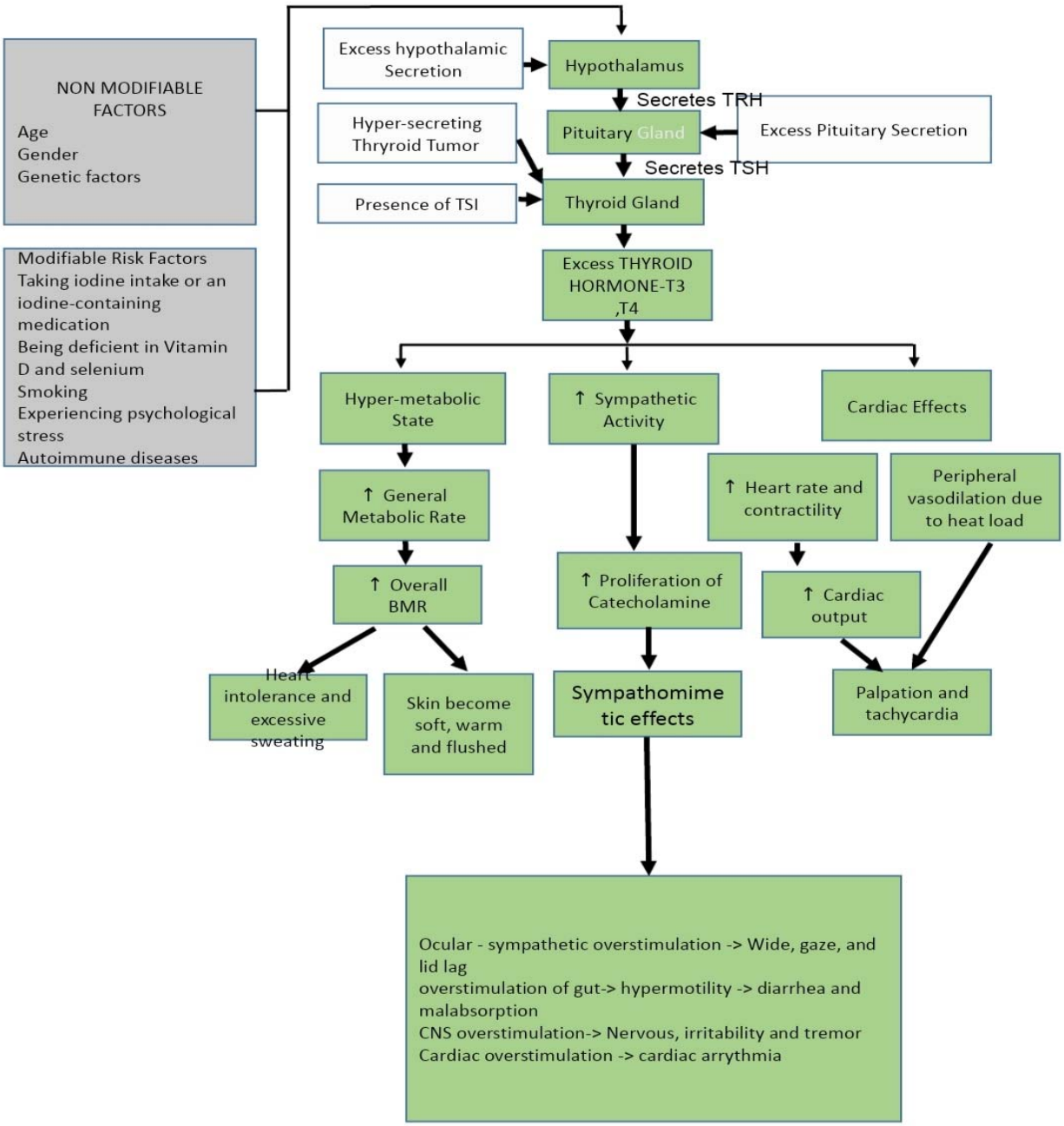


Figure 2: Pathophysiology of hypothyroidism

3.3.1 Causes and Symptoms

Deficiency od iodine is one of the common causes of hypothyroidism in the world. Autoimmune thyroiditis is another cause of hypothyroidism in iodine-deficient regions. Thyroid peroxidase

antibodies are also found in high proportions in the general population. TSH levels are somewhat higher, most likely due to diminished bioactivity. Pituitary adenomas are responsible for more than half of hypothyroidism cases. Pituitary or hypothalamic dysfunction caused by head trauma, pituitary surgery, radiotherapy, hereditary, and infiltrative illness, central hypothyroidism, post-surgical or post-ablative hypothyroidism and medication-induced hypothyroidism are some of the additional causes of hypothyroidism (Chaker et al., 2017).

It is important to evaluate symptoms of hypothyroid because they impact whether the replacement therapy of thyroid should be started. In adults, the most prevalent symptoms of hypothyroidism include fatigue, lethargy, cold intolerance, weight gain, constipation, voice changes, and dry skin, but the clinical presentation might vary depending on age, sex, and time between onset and diagnosis. The signs and symptoms of hypothyroidism are non-specific, especially in older patients who have fewer and less characteristic signs and symptoms than younger people. Dry skin, hair loss, loss of the brows, face puffiness, cholelithiasis, Diastolic hypertension, bradycardia, decreased attention span, muscular weakness, stiffness, irregular periods, and so on are some of the other symptoms (Hypothyroidism - StatPearls - NCBI Bookshelf, n.d.)

3.3.2 Effects of Hypothyroidism and Risk Factors

Hypothyroidism is associated with a higher prevalence of cardiovascular risk factors, as well as metabolic syndrome symptoms such as hypertension, increased waist circumference, and dyslipidemia. Total cholesterol, low-density lipoprotein, and homocysteine levels all rise with hypothyroidism. Nonalcoholic fatty liver disease, cancer mortality, arthritis, kidney failure, and diabetes have all been linked to hypothyroidism.

Furthermore, it is linked to a minor but considerable rise in lipid parameters, most notably an increase in low-density lipoproteins (LDLs). Also, it is linked to an increase in LDL oxidation, which promotes atherosclerosis and can be reversed with medication. Lipoprotein, a more powerful marker of atherogenesis, rises in overt hypothyroidism and falls with thyroid hormone replacement. Hyperlipidemia is caused by a decrease in LDL receptors in hypothyroidism, which results in decreased cholesterol elimination from the liver and decreased cholesterol activity (which is stimulated by TH) in breaking down cholesterol. Diastolic hypertension, decreased vascular function, and increased carotid intima hyperplasia are all linked to overt and SCH. Hyperlipidemia and a proinflammatory state are two variables that may have a role in arterial stiffness and endothelial dysfunction in SCH and hypothyroidism (Razvi et al., 2018b).

3.3.3 Hypothyroidisms and Lipid Metabolism

The number of LDL receptors is lowered in hypothyroidism because the expression of LDL mRNA is diminished. This results in decreased LDL binding to LDL receptors, which leads to an increase in LDL half-life, lower LDL breakdown in fibroblasts, increased serum residence time, and sensitivity to oxidation (Figure 3).

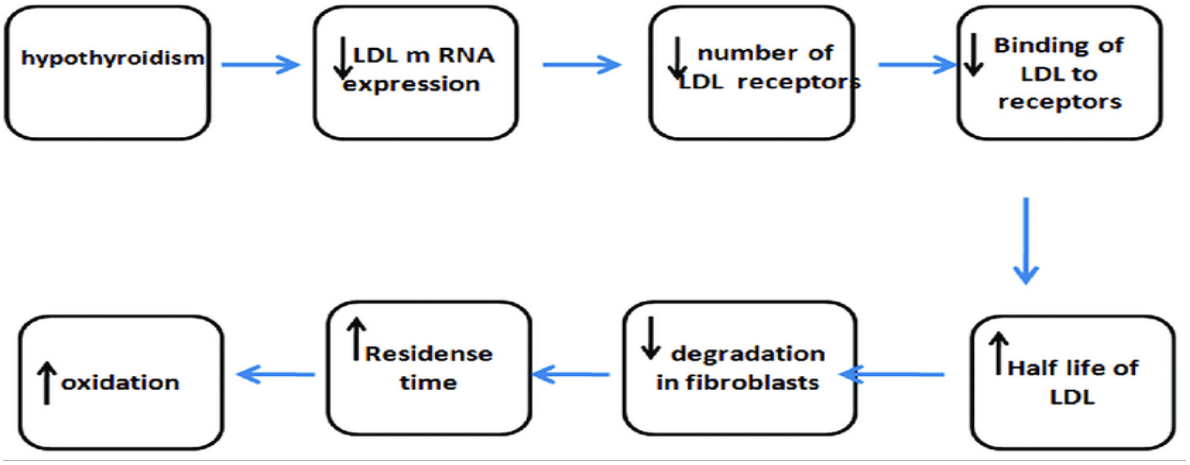


Figure 3: Effect of hypothyroidism on lipid profile (Krishna Veni et al., 2018).

3.3.4 Cardiac Changes Due to Hypothyroidism

Thyroid hormones (TH) have a number of cardiovascular actions which have a significant impact on the function of heart. Hypothyroidism is linked to a reduction in cardiac actions due to reduction of vascular smooth muscle relaxation and reduced availability of endothelial nitric oxide. Rise of arterial stiffness has a series of effect, leading to rise of systemic vascular resistance. Increased expression of phospholamban, which inhibits ATPase, and decreased expression of sarcoplasmic reticulum Ca2+-ATPase cause these changes at the molecular level. Thyroid hormones have an effect on the renin-angiotensin-aldosterone pathway. Renin substrates are produced in the liver when T3 is present. As a result, with hypothyroidism, pulse pressure falls, diastolic blood pressure rises and renin levels reduces (Figure 4).

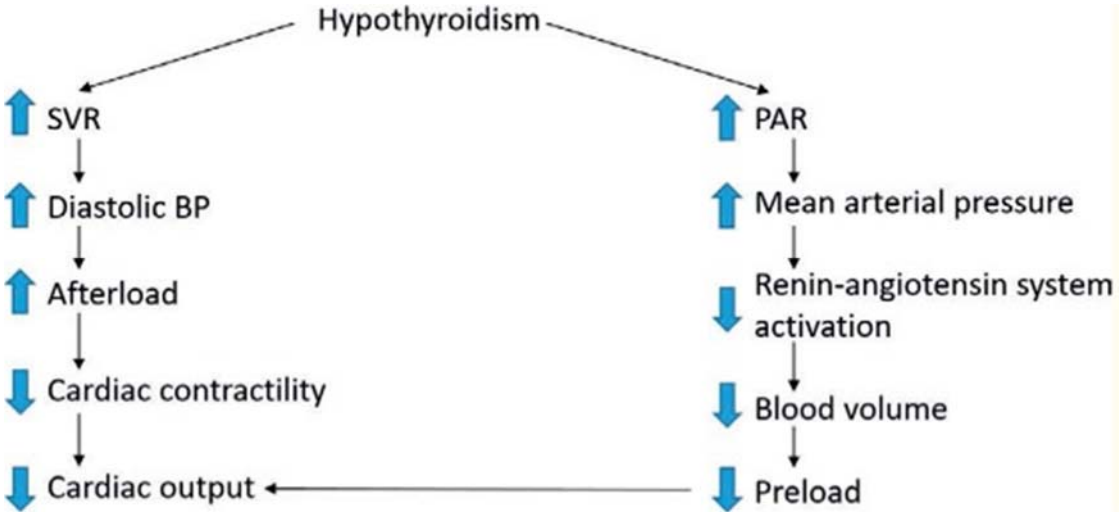


Figure 4:Effect of hypothyroidism on cardiac function; SVR stands for systemic vascular resistance and PAR stands peripheral arterial resistance (Maja Udovcic, 2017).

As a result, diastolic hypertension develops, which is frequently salt sensitive. T3 increases erythropoietin secretion, which may explain the normochromic, normocytic anemia seen in hypothyroidism. Thyroid hormones influence the beta-adrenergic system in cardiomyocytes as well as pacemaker-related genes through transcription. Heart rate rises in the presence of thyroid hormones and falls in hypothyroidism as a result of these mechanisms (Maja Udovcic, 2017).

Chapter 4: Medicinal Plants Used for Hypothyroidism

4.1 Medicinal Plants in the Treatment of Hypothyroidism

Herbal medicines for thyroid diseases have grown in popularity because of its effectiveness and safety, and have fewer adverse result. Several plant species are ingested around the world to help balancing thyroid hormones, supporting thyroid function as an iodine source, or decrease thyroid function. When compared to medication therapy the usage of a variety of medicinal herbs with potential for the treating thyroid issues has also been reported to be effective.

In an Ethnopharmacological study by Taïbi et al., 2021 revealed the use of medicinal plants for hypothyroidism treatment. Among them the mostly represented families were Lamiaceae, Apiaceae, Fabaceae Amaranthaceae and Asteraceae. The medicinal plants which were found to be effective for the treatment of hypothyroidism with their detail description is given below:

Table 1: Medicinal plants used for hypothyroidism (Mujammami, 2020),(Gupta et al., 2016b) &(Salehi et al., 2021).

Family name	**Species name**	**Common name**	**Availability (Country)**	**Active constituents**	**Uses**
Apiaceae	*Centella asiatica*	Gotu kola	Southeast Asian countries.	Madecassic acid	Enhance synthesis of T4 (Gupta et al., 2016b).

Solanaceae	*Withania Somnifera*	Ashwagandha	South Asia, Central Asia, and Africa	Withaferin	Improve Thyroid Activity, Enhance Antiperoxidation, production of T4 hormone with the help of conversion of T4 to T3 (Gupta et al., 2016b).
Ranunculaceae	*Nigella sativa L.*	black seed or black cumin	southwestern Asia and parts of the Mediterranean and African countries	Thymoquinone	it raises T3 and reduces the anti-TPO synthesis and decreases VEGF level (Salehi et al., 2021).
Asteraceae	*Saussurea Costus*	Costus root	Western Himalayan region of Pakistan and India	Sesquiterpene terpenes (ST)	Alleviation of hypothyroidism induced hepatic enzyme derangement.
Burseraceae	*Commiphora mukul*	Guggul	Areas of India, Bangladesh, and Pakistan	Guggulsterone	increases T3 synthesis by boosting T4 to T3 conversion and

					hepatic lipid peroxidation (Gupta et al., 2016b).
Lamiaceae	*Plectranthus barbatus*	Coleus or forskohlii	Brazil, tropical Africa and China	forskolin	Thyroid hormone production and synthesis are typically boosted (Gupta et al., 2016b)0

4.2 Selective Parts of Plants

Plant medicinal properties can be derived from various parts of the plant, like the leaves, flowers, fruit, bark, seeds, and roots. Within a same plant, different portions can contain distinct active chemicals. As a result, one section of a plant may be poisonous, while other part of the same plant could be safe (Medicinal Botany - Plant Parts Used, n.d.). Most selective parts of the plant for medicinal purpose is demonstrated below:

Seed: Seeds are used for their medicinal properties which maybe contained within a fruit or can be used on their own.

Root: For medicinal purpose the fleshy and woody roots are used which can be solid or fibrous.

Bark: Bark is the protective outer layer of a tree where most of the active constituents are found.

Flower: It has always been popular in traditional medicine like saffron

Leaf: For medicinal properties, leaf of plants, shrubs and trees are used. However, it can be used alone or with other parts also.

Tuber: It is the swollen and fleshy structure below the ground which can be of stem origin or partly root and stem origin.

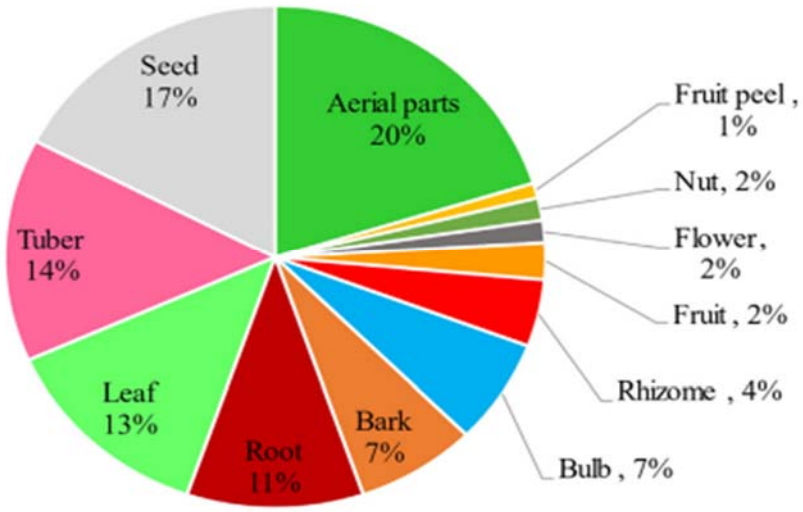


Figure 5: Parts of plant used in traditional medicines(Taïbi et al., 2021).

Most usually used plant parts are aerial portions, then by seeds, tubers, leaves, and roots as the next most useful plant parts. Bark and bulb are also consumed by people and use of rhizome is also found. The other areas highlighted here, on the other hand, are the least used according to an ethnopharmacological study (Taïbi et al., 2021).

4.3 Dosage and Application

As dosage varies so much among individuals, establishing standards and guidelines for use is difficult. Tablespoon, teaspoon, hand palm, little finger index, cup or glass measures are commonly used to carry out the specified prescriptions. A glass cup measure is used for decoction

and infusion, and tablespoon of honey can be used to blend with it, but sugar must not be added. Herbs are typically grinded and powdered, then additives like honey, milk, butter, water, olive oil or alcohol are mixed to make a paste which is taken orally or applicable. It is recommended that some mixes be made one or two hours before ingestion. Other preparations, on the other hand, should be ready and stored for a week before use. One to three teaspoons are usually taken one to three times per day by patients. A pie chart is given below showing different mode of application.

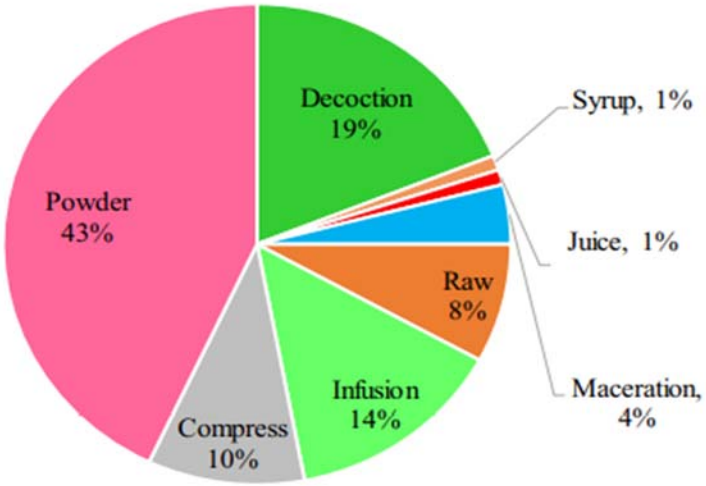


Figure 6:Different Mode of medicinal plants parts uses (Taïbi et al., 2021).

In terms of preparation, the mentioned medicinal plant is usually crushed or grinded. However, few are made as a decoction by boiling to make the volume by half, then the filterate is administered orally. Nonetheless, herbal infusions were utilized to make the medicinal herbs used in thyroid care, which were then taken orally Furthermore, some of the plants are used as compresses for outer application. Other uses, such as transformation to juice or syrup, have been documented in a few cases. Moreover, honey has been mentioned frequently. It was employed as an addition in the preparation of mixes containing multiple ingredients. Honey was given as a

single dose or as an infusion, in conjunction with other ingredients of various sources. Additionally, using goat's milk and butter, olive oil, and yoghurt etc are also mentionable. These ingredients, can increase healing, taste improvement, and lessen the adverse effects of plants medication.

4.4 Effect of Plant Constituent

Indeed, some plant ingredients can disrupt thyroid function by competing with thyroid hormonogenesis enzymes like TPO or suppressing the production of gene which is thyroid-specific. Thyroid hormonogenesis deficiency leads to a decrease in T3 and T4 production and, as a result, an increase in TSH secretion. Hypothyroidism can develop in extreme cases. Several investigations have discovered the main plant elements with anti-thyroid effects, as well as their modes of action, throughout the last few decades. Some of the compounds are described below:

One of them is alkaloid. They are secondary plant metabolites having biological properties and medicinal potential, for which they have been widely studied. Harmine, piperine, arecoline, and mitragynine are the alkaloids which interfere with the function of thyroid. Harmine can be used to inhibit TPO, implying that it could be used as an anti-thyroid medication. Piperine can be used to reduce serum T3 and T4 levels. Arecoline exposure results in an increase in blood T3 and T4 levels along with decrease in serum TSH. Another constituent is millet glycosyl flavones, that show the inhibition of the TPO activity. Also, it improves thyrotoxicosis, decrease of serum T4 and T3. Resveratrol, a well-known Stilbenes, administration improved animal behavior and reduced TSH and TRH secretion. It acts on the hypothalamus-pituitary axis, without increasing thyroid hormone plasma. There are some hydroxycinnammic substances which have the ability to block the activity of TPO or TSH binding on the thyroid plasma membrane in vitro studies. TPO activity and TSH binding to thyroid plasma membranes.

Chapter 5: Medicinal Plants for Treatment of Hypothyroidism

5.1 Gotu Kola (*Centella asiatica*)

The traditional Chinese medicinal plant, *Centella asiatica*, commonly known as *Centella asiatica (L.)* or Gotu kola, is used to cure a range of diseases in China and Southeast Asia. The active components of the plant have been the subject of several animal and cell investigations. It includes a number of pentacyclic triterpenoids, such as asiaticoside, brahmoside, and madecassic acid, as well as additional compounds including centellose, centelloside, and madecassoside. Triterpenes, primarily asiatic acid, asiaticoside, madecassoside, and madecassic acid, are the major chemical components which gives pharmacological effect (Sun et al., 2020).

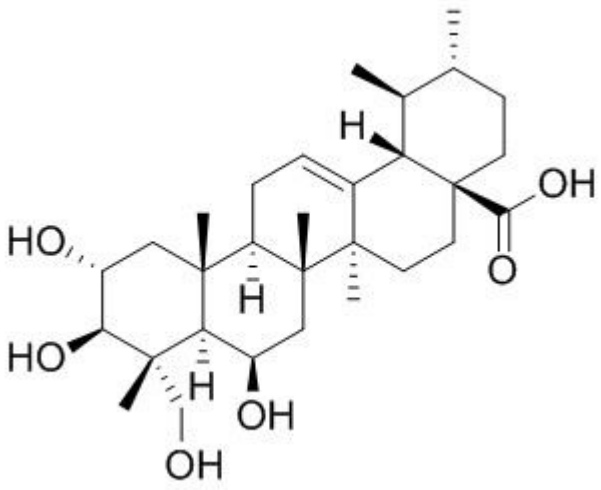


Figure 7: Structure of Madecassic acid (Gupta et al., 2016b).

The gotu kola leaf is widely used to treat hypothyroidism. Asiaticoside, asiatic acid, brahmoside, and brahmic acid, sometimes known as madecassic acid (Figure 7), are all found in it. It's more likely that the plant has the ability in increasing synthesis of T4. Also, it is utilized to boost energy and stamina by regulating the neurological system. As a result of the herbs' energizing action, T4

synthesis is enhanced or stimulated. The tincture of gotu leaf is commonly used to treat hypothyroidism (Gupta et al., 2016b).

5.2 Ashwagandha (*Withania Somnifera*)

Ashwagandha, often known as Indian ginseng or winter cherry, is a saponin glycoside found in the Solanaceae family of plants. Pharmacological research has shown that ashwagandha's plant preparation possesses anti-inflammatory, antioxidant, anticancer, anxiolytic, and immunomodulatory properties. It contains alkaloids, saponin and steroidal compounds, all of those are necessary for different pathways of hormone to function properly. These chemical components aid in the conversion of T4 to T3 and hence promote T4 hormone synthesis. According to a study, Ashwagandha extract has the ability to increase thyroid activity as well as tissue antiperoxidation activity (Gupta et al., 2016b). Also, it has an attenuating effect on the activity of hypothalamic-pituitary-adrenal (HPA) axis, as well as neurological, endocrine, and cardiovascular function. The HPA which is hypothalamic-pituitary-adrenal (HPA) axis, is linked to a cascade of responses in response to a stressor, all of which contribute to increased cortisol levels (Lopresti et al., 2019). Ashwagandha reduces cortisol levels, subjective stress, anxiety, and blood pressure in persons who are under chronic stress, according to research. Reduced cognitive function, negative moods such as anxiety and sadness, and exacerbating variables for chronic health diseases such as cardiovascular disease, obesity, and diabetes have all been linked to stress. Ashwagandha (*Withania somnifera*) is an adaptogen plant that is said to help prevent and treat stress-related symptoms. Adults with mild cognitive impairment benefit from the use of ashwagandha. Supplementing with Ashwagandha has been demonstrated to be safe and beneficial to cortisol levels, cognitive abilities, and self-reported stress, anxiety, sadness, and food cravings (Remenapp et al., 2022).

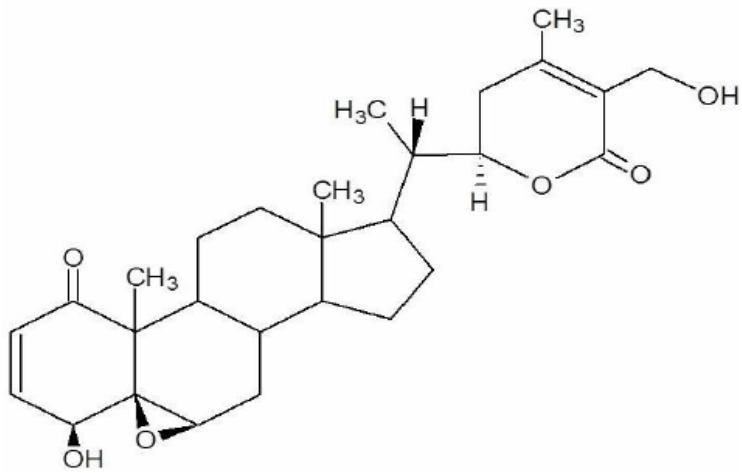


Figure 8: Chemical structure of Withaferin (Gupta et al., 2016b).

Hypothalamic Pituitary Dysfunction is a condition in which the pituitary gland in the hypothalamus malfunctions. The development of major depression and bipolar illnesses has been linked to the thyroid neuroendocrine axis. Furthermore, both overt hypothyroidism and unipolar depressive along with bipolar disorders share common symptoms like fatigue, mental slowness, both memory and attention difficulties, weight gain, exhaustion and depression. Given this, and given the well-established link between lithium and hypothyroidism, thyroid function is frequently tested and monitored in mood disorders. For ages, *Withania somnifera* extracts have been used in Ayurvedic medicine to reduce and relieve mental and physical stress. However, this plant causes rise in thyroid hormones, elevating T4, as well as its neuroprotective, anti-oxidant, anti-inflammatory and anti-depressant properties, suggests that this can be used to treat subclinical hypothyroidism in mood disorders (Gannon et al., 2014).

5.3 Black Cumin (*Nigella sativa L*)

Nigella sativa also known as black cumin is from family of Ranunculacea, is an annual herb with a variety of medicinal qualities. The constituent of this plant which is most prevalent is the volatile

oil of *Nigella sativa* (N. sativa) seeds is thymoquinone (TQ), that is also the constituent to which most of the herb's characteristics are attributed. Black seed and TQ have been found to have a variety of beneficial effects in the treatment of various metabolic syndrome, inflammatory and auto-immune disorders in patients. Because of the many benefits of this herbal medicine, its negative effects appear to be minor. As a result, it can be used in clinical trials. Some other effects like its hypolipidemic and hypoglycemic effects, is studied and are understood to allow for clinical trials in case of drug developments (Tavakkoli et al., 2017).

In case of thyroid disorder, the impact of NS in a recent study stated that black seeds oil was found to have antioxidant properties, reducing oxidative stress and thyroid follicular damage induced by medications like propylthiouracil (PTU). Another study found that NS oil raises T3, T4, LH, and estrogen levels (Pakdel et al., 2017).

It has been well established that oxidative damage to brain tissues is a key factor in memory loss, and antioxidative substances have the potential to aid learning and memory. Hypothyroidism has also been linked to negative effects on learning and memory, most likely due to oxidative damage in brain structures. As a result, the effect of hydroalcoholic extract on hypothyroidism-related oxidative stress would be effective (Beheshti et al., 2017).

5.3.1 Chemical Structure of Main Bioactive Compounds

The contents of black cumin seed include fixed oil, saponins, proteins, alkaloid and essential oil, according to extensive research. The volatile oil comprises of fatty acids which are saturated such as nigellone. It is the only carbonyl compound of the oil, thymohydroquinone (THQ), thymoquinone (TQ), dithymoquinone and p-cymene, t-anethole, carvacrol, 4-terpineol, and longifoline are also found in the seed's volatile oil. Vitamins, mineral elements, carbohydrates,

proteins and lipid, which contain important amino acids, make up the nutritional contents of N. sativa. It also includes a variety of vitamins and minerals like Fe, Ca, K, Zn, P, and Cu.

The quinine ingredient, of which TQ is the most common, is responsible for the majority of the pharmacological actions. Anticonvulsant, anti-inflammatory, antioxidant, anti-cancer, antifungal and antibacterial properties are all found in TQ (Forouzanfar et al., n.d.).

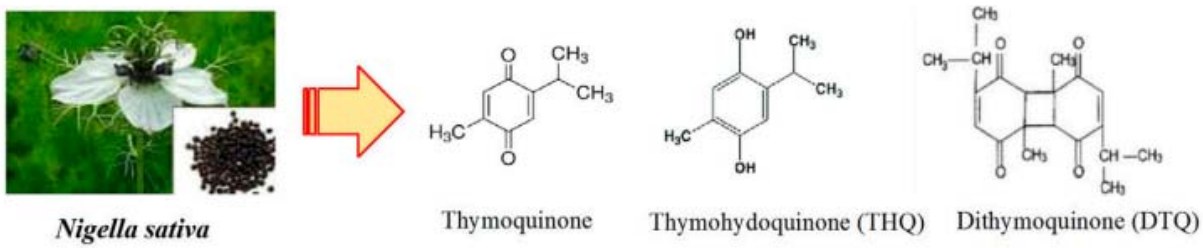


Figure 9: Main bioactive compounds with chemical structure (Anaeigoudari et al., 2021).

The primary components in the N. sativa extract include thymoquinone (TQ), thymohydroquinone (THQ), dithymoquinone (DTQ), and thymol (THY). The thymoquinone play a key role in the plant's medicinal properties. Furthermore, the oils of this plant contain carotenoids, sterols, tocols, and phenolics. *N. sativa* and its components have been linked to a variety of pharmacological activities, including immune system modulation, inflammatory response suppression, oxidative stress inhibition, cancer cell proliferation prevention, and germ death. This plant is effective effective in treating diseases like diabetes, dyslipidemia, and asthma (Anaeigoudari et al., 2021).

5.3.2 Pharmacological Effect:

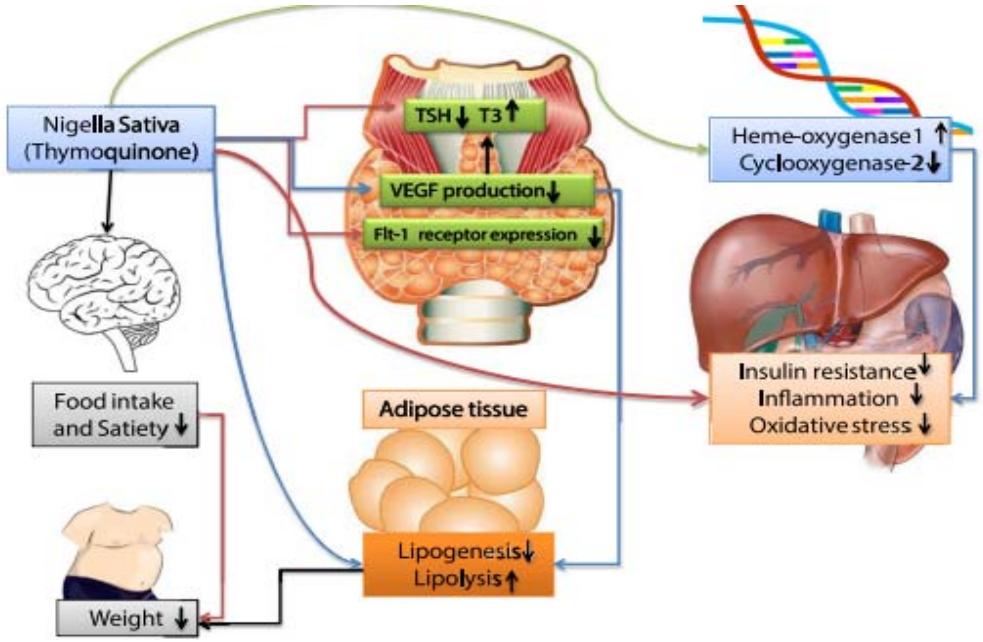


Figure 10: Effects of Thymoquione on thyroid status (Farhangi et al., 2016).

Thymoquinone, one of the active ingredients in N. sativa L, reduces thyroid inflammation by upregulating heme-oxygenase-1 expression and suppressing cyclooxygenase-2 (COX-2) production. It also increases the level of T3 while decreasing anti-TPO antibody production, as well as TGF-b and interleukin (IL) levels Furthermore, a study of vascular endothelial growth factor (VEGF) and its receptors (Flt-1), which play a role in the formation of thyroid epithelial cells, found that thymoquinone reduces VEGF levels, which are known to rise in response to high TSH levels (Taïbi et al., 2021).

5.3.3 Effect on Dyslipidemia and Thyroid Hormone

Dyslipidemia can be defined as abnormalities in lipoproteins of blood, such as high LDL-C, TG and/or TG levels, or low HDL-C levels alone. Hyperlipidemic patients who consumed NS seeds

had lower LDL-C and higher HDL-C, according to a study. Another RCT found that giving NS oil to volunteers who are healthy for few weeks caused substantial reductions in fasting blood cholesterol, glucose, LDL, TG, and HbA1C levels when compared to mineral oil. Male and female hyperlipidemic patients who were given NS seeds had higher HDL-C and lost weight. The administration of powdered NS seeds throughout a two-month intervention was reported to lower TG, LDL-C, and TC levels while increasing HDL-C levels in research. The lipid profiles in the NS-treated group, on the other hand, tended to return to pretreatment values one month after treatment ended. A supplement of powdered NS seeds improved various biochemical indicators, that includes the blood glucose and lipid profile, in another clinical experiment that lasted a similar amount of time.

Coronary heart disease is a leading cause of death worldwide, according to a World Health Organization (WHO) report. According to the findings of a study that looked at the impact of NS on lipid profiles in patients with stable coronary artery disease, taking NS powder for 6 months along with a statin reduced serum levels of LDL, TC, VLDL, and TG while also increasing HDL levels, whereas statin alone had no effect on TG, LDL, or TC levels (Tavakkoli et al., 2017).

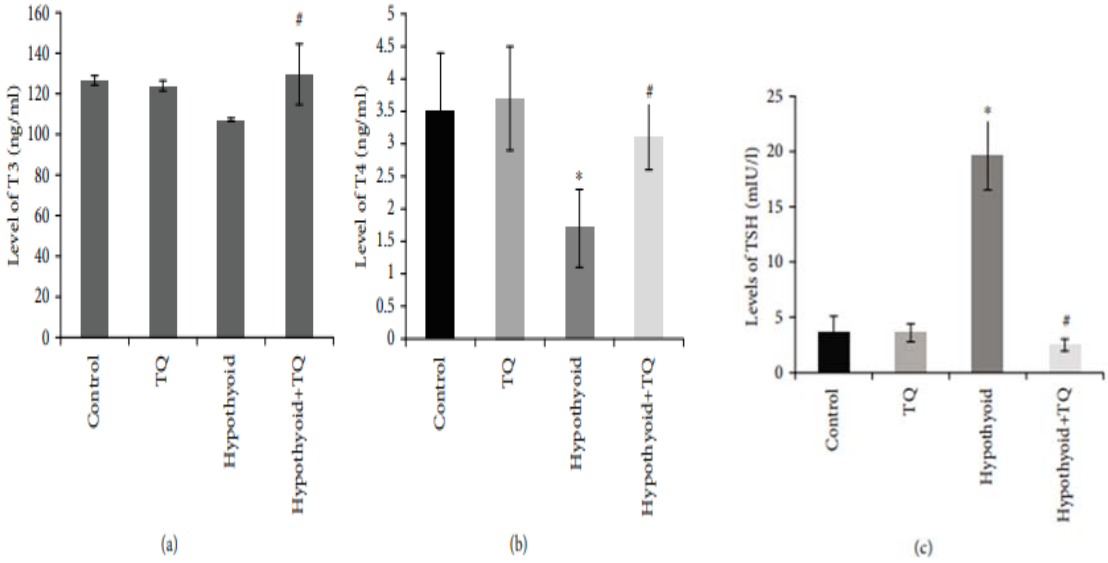


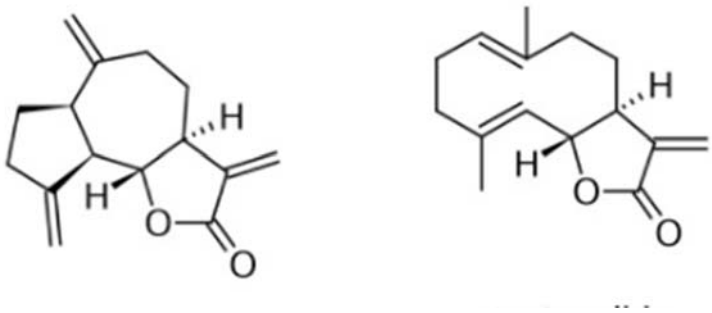
Figure 11:Effect of TQ on serum level of thyroid hormones (a, b), TSH (c) (Ayuob et al., 2020).

The following bar graph (Figure 11) shows *N. sativa* effect on thyroid hormone. TQ given to adult male Wister mice. The hypothyroid mice were treated with TQ for 4 weeks. TQ treatment resulted in a considerable increase in T3 and T4 levels, as well as a large drop in TSH, when compared to the hypothyroid group (Ayuob et al., 2020).

Nigella sativa treatment resulted in considerable weight loss and a lower BMI (Body Mass Index). The TSH and anti-thyroid peroxidase antibodies reduced in the treated group after 8 weeks, but the serum T3 levels increased. In the intervention group, serum VEGF concentrations were significantly lower.

5.4. Costus Root (*Saussurea Costus*)

Saussurea costus (S. costus) is a therapeutic plant that is widely used in Saudi Arabia. It is a member of the Asteraceae family. This plant's constituents have the potential to be turned into bioactive compounds. The flavonoids and antioxidant activities of *S. costus* could be a key factor in the plant's medicinal application. *Saussurea costus* is a medicinal plant with a high concentration of bioactive phytoconstituents. Many chemicals from S. costus have been isolated up to this point, which includes sesquiterpene terpenes (ST), alkaloids, and flavanoids. Dehydrocostus lactone (DCL), costunolide (CS), and -curcumene are the primary sesquiterpene terpenes found in *S. costus root*.



(a) (b)

Figure 12: Chemical structure of (a) dehydrocostus lactone DCL & (b)costunolide.

S. costus root extract is used in relieving hypothyroidism caused hepatic enzyme derangements in mice when compared to non-treated mice, according to a study. In the same study, Costus extract improved TSH, T4, potassium, sodium chloride, creatinine, albumin, urea, calcium ions, cholesterol, and triglycerides levels. Cholesterol and low-density lipoprotein levels are higher in hypothyroidism, possibly due to impaired metabolic clearance. S. costus oral therapy improved the lipid dysfunction in mice by lowering plasma LDL cholesterol, perhaps due to enhanced LDL

receptor function. Flavonoids including dillapiole, costunolide, and caffeic acid may have generated these beneficial effects on the thyroid gland by lowering thyroid peroxidase activity. When iodine levels are low, these effects can be more evident. Because hypothyroidism can cause hyperlipidemia, the extract of *S. costus* was found to have a hypolipidemic effect, which could be linked to its thyroid hormone regulating properties. *S. costus roots* have been proposed as an adjuvant co-therapy to thyroxine treatment in hypothyroidism, based on these findings (Mujammami, 2020).

5.5 Guggul (*Commiphora mukul*)

Ayurveda places a high importance on *Commiphora mukul* of family Burseraceae, often known as gum guggulu. For more than 2000 years, Ayurvedic medicine has employed the extract of this tree to treat a number of diseases including obesity, lipid abnormalities, rheumatoid arthritis, bone fractures, cardiovascular disease, and antihyperglycemic and antioxidant activity. This plant's oleoresin, also known as guggul, is a whitish compound with a balsamic odor. *C. mukul* (CM) has anti-inflammatory, hypoglycemia, antiseptic, and astringent qualities, as well as thyroid stimulant and antihyperlipidemic properties, according to traditional Indian applications. Gum guggul was one of the herbal constituents in every formulation used for ancient Ayurvedic obesity therapies. Guggulipid, an ethyl acetate extract of *C. mukul* resin, is a well-known hypolilpidemic drug. Using synthesized E and Z isomers, many investigations are undertaken for better understanding and explaination of the mechanism of action and therapeutic potential. The inhibition of the forsenoid X receptor and the bile acid receptor by guggulsterones decreased cholesterol production in the liver. Guggulsterone was utilized as a positive control to examine the hypolipidemic activity of other chemical compounds because of its demonstrated hypolipidemic efficiency in rats.

Guggulsterone and *C. mukul* were excellent antioxidants against LDL oxidation. Guggulipid significantly reduced hepatic microsomal lipid peroxidation (Bellamkonda et al., 2018a).

Also, the oleo-resin in guggul extract comes from the Commiphora mukul tree. Guggul's oleo-resin contains Z- guggulsterone, which has a powerful thyroid-stimulating effect. Guggulsterone also increases T3 synthesis by boosting T4 to T3 conversion and hepatic lipid peroxidation, as well as T3 levels. Increased T3 levels can help patients with hypothyroidism lower their LDL cholesterol levels. It is possible to stimulate weight loss. Guggul is utilized as a thyroid stimulant in traditional Ayurvedic medicine in India. As a result, it acts directly on the thyroid gland, stimulating thyroid hormones (Gupta et al., 2016b).

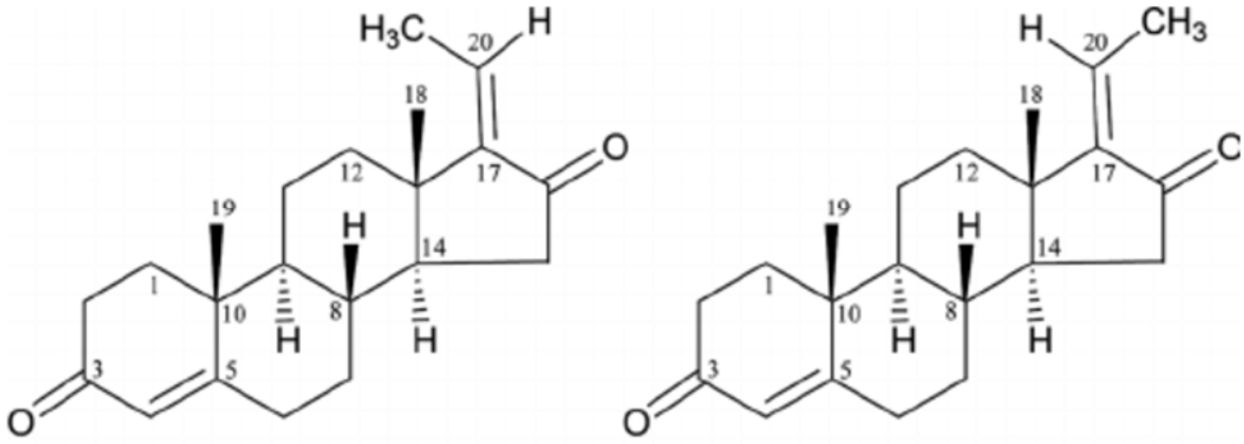


Figure 13: chemical structure of E- Guggulsterone and Z- Guggulsterone (Bellamkonda et al., 2018b).

5.6 Coleus or Forskohlii (*Plectranthus barbatus*)

Plectranthus barbatus is a most important plant in the Lamiaceae family, with a wide range of traditional medicinal applications. Its traditional applications could be explained by forskolin, a significant component with an adenylyl cyclase activation that is unique and underpins a variety of medicinal properties. It is present in various patented medicinal preparations that are sold over-

the-counter to treat a variety of diseases for anti-inflammatory, antibacterial, oxidative, cytotoxic, hypotensive, spasmolytic, hepatoprotective, and antifeedant properties which have been described for organic extracts, according to studies on numerous extracts with varied polarity derived from different parts of *P. barbatus* (Alasbahi & Melzig, 2010).

Because it contains essential oils and terpenes, Forskolin is commonly used to treat hypothyroidism. Thyroid hormone production and synthesis are typically boosted by this plant. It stimulates the cyclic AMP synthesis. Also, it used to boost thyroid gland output in patients who haven't been on medication for a long time (Gupta et al., 2016b).

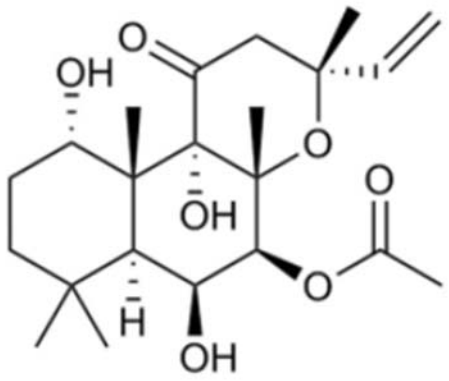


Figure 14: Chemical structure of Forskolin.

Furthermore, On the isolated guinea pig heart, isolated rabbit heart, and the dog and cat heart in situ, forskolin was found to have beneficial inotropic effects. In the isolated guinea pig heart, forskolin also increased coronary blood flow. In dogs, cats, rats, and rabbits, as well as spontaneously hypertensive and renal hypertensive rodents, forskolin raised heart rate and decreased blood pressure The cardiovascular impacts of forskolin, such as the pharmacologic effect, could be described mainly by a rise in cAMP in heart muscle, which is found to improve contractility by opening slow Ca2+-channels, leading to an increase in intracellular calcium, and

the hypotensive influence by an increase in cAMP in vascular smooth muscle, which creates relaxation by lowering the calcium sensitivity of the muscle contraction system of smooth muscle cells (Alasbahi & Melzig, 2010).

Chapter 6: Conclusion and Future Prospect

The subject of how crucial it is to treat subclinical hypothyroidism has set off a series of endless discussions**.** It is evident that hypothyroidism has influenced various key cardiovascular risk variables as high blood pressure, cholesterol, and coagulability along with various health problems. It is central of controlling the physiological and pathophysiological processes of our body. Therefore, treatment of hypothyroidism is essential for improving thyroid function in human. For treatment purpose, application of medicinal plants has proven to be effective with less adverse effect. It improves hypothyroid status and decrease serum TSH concentrations along with improvement of cholesterol profile. Moreover, there are other plants with medicinal properties which can also be used in case of hypothyroidism. However, treatment with thyroxin replacement therapy with levothyroxine is the first choice for treatment. But this is a lifelong process with limitations. So, application of medicinal plants can be in addition to disease-specific drugs, a useful herbal supplement. Therefore, for its popular usage, it's high time to step up scientific research into the mechanisms of action of these medicinal plants evidently.

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