In India 108 million people suffer from endocrine and metabolic disorders. Several of these diseases are caused by environmental factors. They are preventable and can be effectively treated at affordable cost. A unique feature of endocrine disorders is that early and reliable diagnosis is possible only by sensitive and specific hormone measurements. Endocrine disorders are most often present with imprecise symptoms early in their diagnosis. The full blown syndrome emerges late, and by then several systemic complications would have set in as a result of damage to vital organs. Recent estimates indicate that 800 million to one billion people are exposed to insufficient supply of iodine. At least 200 million have goiter. These conservative figures include large industrialized countries also (Shilotri, 2008).

Thyroid disorders are the most common among all the endocrine diseases in India. About 42 million people in India suffer from thyroid diseases (Abraham et al., 2009). The thyroid gland is a very important part of the human body that controls many functions including the growth and metabolism of the body. Thyroid disease occurs when the thyroid gland doesn't supply the proper amount of hormones needed by the body. Thyroid disorders often go undiagnosed. That’s because symptoms like fatigue, exhaustion and weight gain or loss are ascribed to a person’s lifestyle without considering a medical root. Thyroid gland is also unique among other endocrine glands in being influenced by environmental factors because of its dependence on adequate supply of iodine and its vulnerability to goitrogens. The spectrum of thyroid disorders encountered through infancy, childhood and adolescence in India is similar to that seen in most parts of the world (Unnikrishnan and Menon, 2011).
The review of literature pertaining to the study, “Influence of drug therapy in thyroid disorder patients and the effect of Sargassum wightii Greville and Maydis stigma on experimentally induced hypo and hyperthyroidism in Swiss albino rats” has been discussed under the following headings.

2.1 A Brief Overview of the Thyroid Gland
   2.1.1 Histology of the Thyroid Gland
   2.1.2 Thyroid Hormones
   2.1.3 Synthesis, Storage and Secretion of Thyroid Hormones

2.2 Effect of Thyroid Hormones

2.3 Thyroid and Lipid Metabolism

2.4 Thyroid Antibodies

2.5 Thyroid Dysfunction

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2.10 Medicinal Plants and Their Importance
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2.12 Sargassum wightii Greville and Maydis stigma

2.1 A Brief Overview of the Thyroid Gland

Thyroid is an endocrine gland which is derived from the Greek word ‘thyreoeides’, meaning shield shaped, situated at the root of the neck on either
side of the trachea. Thyroid gland is butterfly shaped and composed of two cone-like lobes or wings, which are connected in the middle by an isthmus. Normally the weight of thyroid is about 20 to 40 g in adults but it is subjected to variations under physiological conditions. It is brownish red in colour (Dowshen, 2009). It starts functioning even before birth. Thyroid gland is larger in females than males. The structure and the function of the thyroid gland changes in different stages of the sexual cycle in females. Its function increases slightly during pregnancy and lactation and decreases during menopause (Sembulingam and Sembulingam, 2010).

Figure 1

a) Thyroid gland   b) Section of thyroid gland
2.1.1 Histology of the Thyroid Gland

The major thyroid secretory cells, known as follicular cells are arranged into hollow spheres each of which forms a functional unit called a follicle. On a microscopic section, the follicles appear as rings of follicular cells enclosing an inner lumen filled with colloid which serves as an extracellular storage site for thyroid hormones and are proteinaceous in nature. The colloid within the follicular lumen is extracellular (that is, outside the thyroid cells) even though it is located within the extracellular fluid that surrounds the follicle (Sherwood, 2008). The chief constituent of the colloid is a large protein molecule known as thyroglobulin, within which are incorporated the thyroid hormones in their various stages of synthesis. The follicular cells produce two iodine containing hormones derived from the amino acid tyrosine: tetraiodothyronine (T4 or thyroxine) and triiodothyronine (T3). These two hormones collectively referred to as thyroid hormones are important regulators of overall basal metabolic rate. Thyroid receives very rich supply of blood. The amount of blood received by thyroid gland per minute is five times more than its weight (Khurana, 2006; Pal, 2007).

2.1.2 Thyroid Hormones

Hormones of the endocrine system are chemical messengers that are secreted by body tissues and blood and serves to regulate the activities of other tissue (Devi, 2010). Thyroid gland secretes three hormones namely: 3,5,3', 5'-tetraiodothyronine (T4), 3,5,3'-triiodothyronine (T3) and calcitonin. Among these T4 and T3 are the principal hormones responsible for proper functioning of the thyroid gland while calcitonin is responsible for calcium homeostasis (James and Kumar, 2012).

3,5,3',5'-tetraiodothyronine (T4) otherwise known as thyroxine is the major form of thyroid hormone in the blood. T4 forms about 90% of the total secretion, whereas, 3,5,3'-triiodothyronine (T3) is only 9 to 10%. The potency of T3 is four times more than that of T4. However, the duration of action is four times more for T4 than T3. This is because of the difference in the affinity of
these hormones to plasma proteins. T3 has less affinity for plasma proteins and combines loosely with them so that it is released quickly. T4 has more affinity and strongly binds with plasma proteins so that it is released slowly. Therefore, T3 acts on the target cells immediately and T4 acts slowly (Sembulingam and Sembulingam, 2010). Most of the daily T4 released from the thyroid gland undergoes deiodination, with subsequent deamination and decarboxylation. Some of the hormone molecules are coupled to sulphate and glucuronic acid in the liver and are excreted in the bile. In the intestine most of the coupled molecules are hydrolyzed and the hormones are resorbed by the blood, whereby they reach hepar again (the enterohepatic circuit).

Thyroxine’s principal function is to stimulate the consumption of oxygen and thus control the metabolism of all cells and tissues in the body. Excessive secretion of thyroxine in the body is known as hyperthyroidism and the deficient secretion of it is called hypothyroidism. T3 regulates almost every physiological process in the body, including growth and development, metabolism, body temperature and heart rate (Idris et al., 2012). The chemical structure of thyroxine and triiodothyronine are given below (http://www.biopsychiatry.com).

2.1.3 Synthesis, Storage and Secretion of Thyroid Hormones

The synthesis and storage of thyroid hormone occurs between the follicular cells and the colloid. Iodine and tyrosine are essential for the formation of thyroid hormone. Iodine is consumed through diet. It is converted into iodide and absorbed from gastro-intestinal tract (GI tract). Tyrosine is also consumed
through diet and is absorbed from GI tract. For the synthesis of normal quantities of thyroid hormone, approximately 1mg of iodine is required per week. To prevent iodine deficiency, common table salt is iodized with one part of sodium iodide to every 100,000 parts of sodium chloride (Sembulingam and Sembulingam, 2010).

Thyroid hormone synthesis and secretion is regulated by a negative feedback system that involves hypothalamus, pituitary and the thyroid gland (Chiamolera and Wondisford, 2009). The thyroid gland is the only endocrine gland that stores its secretory product in large quantities, normally about a 100 day supply. Synthesis and secretion of T₃ and T₄ occurs as follows (Tortora and Derrickson, 2009):

I) Iodide trapping: Thyroid follicular cells trap iodide ions (I⁻) by actively transporting them from the blood into the cytosol. As a result, the thyroid gland normally contains most of the iodide in the body.

II) Synthesis of thyroglobulin: While the follicular cells are trapping I⁻, they are also synthesizing thyroglobulin (Tg), a large glycoprotein that is produced in the rough endoplasmic reticulum, modified in the golgi complex and packaged into secretory vesicles. The vesicles then undergo exocytosis, which releases Tg into the lumen of the follicle.

III) Oxidation of iodide: Some of the amino acids in Tg are tyrosines which would be iodinated. However, negatively charged iodide ions cannot bind to tyrosine until they undergo oxidation to iodine: 2 I⁻ → I₂. As the iodide ions are being oxidized, they pass through the membrane into the lumen of the follicle.

IV) Iodination of tyrosine: As iodine molecules (I₂) form, they react with tyrosines that are part of thyroglobulin molecules. Binding of one iodine atom yields monoiiodotyrosine (T₁) and a second iodination produces diiodotyrosine (T₂). The Tg with attached iodine atoms, a sticky material that accumulates and is stored in the lumen of the thyroid follicles, is termed colloid.
V) Coupling of $T_1$ and $T_2$: During the last step in the synthesis of thyroid hormone, two $T_2$ molecules join to form $T_4$ or one $T_1$ and one $T_2$ join to form $T_3$.

VI) Pinocytosis and digestion of colloid: Droplets of colloid re-enter follicular cells by pinocytosis and merge with lysosomes. Digestive enzymes in the lysosomes break down Tg, cleaving off molecules of $T_3$ and $T_4$.

VII) Secretion of thyroid hormone: As $T_3$ and $T_4$ are lipid soluble, they diffuse through the plasma membrane into the interstitial fluid and then into the blood. $T_4$ normally is secreted in greater quantity than $T_3$, but $T_3$ is several times more potent. Moreover, after $T_4$ enters a body cell, most of it is converted to $T_3$ by removal of one iodine.

VIII) Transport in the blood: More than 99% of both $T_3$ and $T_4$ combine with transport proteins in the blood mainly thyroxine binding globulin (TGB) rendering them metabolically inactive. The remaining “free” thyroid hormone, the majority of which is $T_3$ binds to and activates thyroid hormone receptors exerting biological activity. Very small changes in the amount of carrier proteins will affect the percentage of unbound hormones. Oral contraceptives, pregnancy and conventional female hormone replacement therapy may increase thyroid carrier protein levels and thereby lower the amount of free thyroid hormone available.

Thyroid hormones are stored extracellularly in the colloid inside the follicle in the form of iodinated thyroglobulin. Each thyroglobulin molecule contains one to four $T_4$ molecules. An average of one $T_3$ molecule is present for fourteen $T_4$ molecules. The colloid of thyroid follicles has thyroid hormones sufficient for 2-3 month’s requirements. When there is requirement for the hormones to be released, they must be separated from the thyroglobulin molecules (Pal, 2007). Thyroglobulin is first absorbed by the cell from the colloid in the follicles, where it is acted upon by enzymes called proteinases that digest the large glycoprotein molecule freeing $T_3$ and $T_4$. These are then absorbed into
capillaries surrounding the follicles. Some of the iodinated tyrosine that may not be converted into thyroid hormone is also freed from thyroglobulin during this process. Instead of being released into circulation, these molecules are stripped of their iodine content which is then reused for further hormone production. This process requires an enzyme called deiodinase (Guyton and Hall, 2006).

2.2 Effect of Thyroid Hormones

Thyroid hormones have wide range of action. The response to an increase in thyroid hormone is detectable only after a delay of several hours and the maximal response is not evident for several days. The duration of the response is also quite long, partially because thyroid hormone is not rapidly degraded but also because the response to an increase in secretion continues to be expressed for days or even weeks after the plasma thyroid hormone concentration have returned to normal. Virtually every tissue in the body is affected either directly or indirectly by thyroid hormone. The effects of T$_3$ and T$_4$ can be grouped into several overlapping categories (Sherwood, 2011).

**Effect on metabolic rate and heat production**

Thyroid hormone increases body’s overall basal metabolic rate. It is the most important regulator of the body’s rate of oxygen consumption and energy expenditure under resting conditions. Thyroid hormone’s overall metabolic effect is calorigenic (“heat-producing”) effect. Increased metabolic activity results in increased heat production.

**Effect on intermediary metabolism**

Thyroid hormone modulates the rates of many specific reactions involved in fuel metabolism, and these are multifaceted: not only can it influence both the synthesis and degradation of carbohydrate, fat and protein. Small or large amounts of the hormone may also induce opposite effects. The conversion of glucose to glycogen is facilitated by small amounts of thyroid hormone, but the breakdown of glycogen into glucose occurs with large amounts of the hormone.
Adequate amounts of thyroid hormones are essential for the protein synthesis needed for normal bodily growth. Hyper secretion of thyroid hormone favours protein degradation. The overall metabolic effect of thyroid hormone at normal physiologic level is to favour the consumption rather than storage of body fuels (Moreno et al., 2008).

**Sympathomimetic effect**

Any action similar to one produced by the sympathetic nervous system is known as sympathomimetic effect. Thyroid hormone increases target cell responsiveness to catecholamines (epinephrine and norepinephrine). Thyroid hormone accomplishes this permissive action by causing a proliferation of specific catecholamine target cell receptors.

**Effect on heart**

Thyroid hormones increase heart rate and force of contraction thus increasing cardiac output.

**Effect on growth and the nervous system**

Thyroid hormone is essential for normal growth because of its effect on growth hormone (GH). Thyroid hormone not only stimulates GH secretion but also promotes the effect of GH (or somatomedins) on the synthesis of new structural proteins and on skeletal growth. Thyroid hormone plays a crucial role in the normal development of the nervous system especially the CNS, an effect impeded in children who have thyroid deficiency leading to cretinism.

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development (Araki et al., 2009).
2.3 Thyroid and Lipid Metabolism

Thyroid hormones influence all major metabolic pathways. Their most obvious and well-known action is an increase in basal energy expenditure through actions on protein, carbohydrate and lipid metabolism. With specific regard to liver lipid metabolism, thyroid hormones stimulate fatty acid and cholesterol synthesis, increase mobilization of plasma cholesterol and triglycerides (TGs) and stimulate fatty acid and cholesterol degradation (Shekhar et al., 2011). The effect of thyroid hormone on lipid metabolism is shown in Figure 2.

**Figure 2**

Effects of Thyroid hormone on lipid metabolism

Thyroid hormones induce 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Moreover, triiodothyronine ($T_3$) regulates LDL receptors by controlling the LDL receptor gene activation. This $T_3$-mediated gene activation is done by direct binding of $T_3$ to specific thyroid hormone responsive elements (TREs) (Rizos et al., 2011).
Furthermore, \( T_3 \) controls the sterol regulatory element-binding protein-2 (SREBP-2) which in turn regulates LDL receptor’s gene expression (Shin and Osborne, 2003). \( T_3 \) has also been associated with protecting LDL from oxidation (Faure et al., 2004).

Thyroid hormones can influence HDL metabolism by increasing cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL2 to the very low density lipoproteins (VLDL) and TG to the opposite direction. In addition, thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the TG-rich lipoproteins and the hepatic lipase (HL) which hydrolyzes HDL2 to HDL3 and contributes to the conversion of intermediate-density lipoproteins (IDL) to LDL and in turn LDL to small dense LDL (sdLDL) (Rizos et al., 2011). Another effect of \( T_3 \) is the up-regulation of apolipoprotein AV (ApoAV), which plays a major role in TG regulation (Prieur et al., 2005). Indeed, increased levels of ApoAV have been associated with decreased levels of TG. Proposed mechanisms for this effect include the decrease of hepatic VLDL-TG production and the increase of plasma LPL levels and activity, resulting in increase of lipoprotein remnant generation due to enhanced LPL-mediated lipolysis of VLDL-TG. Moreover, a greater clearance of lipoprotein core remnants, caused by increased hepatic uptake due to an enhanced affinity for the LDL receptor, has also been ascribed to ApoAV (Rensen et al., 2005).

### 2.4 Thyroid Antibodies

Historically, the first thyroid autoantibody discovered was antithyroglobulin antibody in 1956. Antibodies to other antigens present in the cytoplasm of thyroid follicular cells (first termed “antimicrosomal antibodies”) were detected in 1976. These “cytoplasmic” antigens were later found to be the enzyme thyroid peroxidase; hence today, these antibodies are more often called “thyroid peroxidase antibodies.” Thyroid peroxidase antibodies appeared to be much more prevalent than antithyroglobulin antibodies. These antibodies...
can even lyse the thyroid cells. B cells present the thyroid antigen to T cells. T cells secrete cytokines that activate a variety of other immune cells and has a role in antibody production (Th2 cells) and apoptotic destruction of thyroid cells by activating cytotoxic T cells (Th1 cells) (Shinto et al., 2010).

Thyroid autoantibodies appear mostly with the presence of lymphocytes in the targeted organ. There are three types of antibodies: thyroid peroxidase antibodies (TPO Ab/Anti-TPO), thyroglobulin antibodies (Tg Ab/Anti-Tg) and thyroid stimulating hormone receptor antibodies (TR Ab). These antibodies affect different targets in the thyroid gland. The three main targets are as follows: thyroglobulin, a protein specified in housing the thyroid hormones $T_3$, $T_4$ and TSH; the thyroid microsomal antigen also known as thyroid peroxidase, an enzyme in charge of regulating how much hormone the gland should produce and the thyrotropin receptors. A certain percentage of patients who are healthy may be positive for one or more thyroid antibodies (American Association for Clinical Chemistry, 2012).

Anti-thyroid peroxidase antibodies (anti-TPO antibodies) are most commonly associated with Hashimoto’s thyroiditis. Thus, an antibody titer can be used to assess disease activity in patients. TSH receptor antibodies are present in two forms: an activating antibody (associated with hyperthyroidism) and a blocking antibody (associated with thyroiditis). TSH receptor activating antibodies (TSHRAb) are characteristic of Graves’ disease (autoimmune hyperthyroidism). Thyroid peroxidase (TPO) antibody is measured more easily than the TSH receptor antibody and so is often used as a surrogate in the diagnosis of Graves’ disease. Thyroglobulin antibodies are sometimes used in the diagnosis of hyperthyroidism and are commonly used to monitor the thyroid cancer following removal of the organ (thyroidectomy) (Chardes et al., 2002).

Measurement of anti-thyroid peroxidase (anti-TPO) autoantibodies has higher sensitivity and equal specificity to anti-thyroglobulin (anti-Tg)
autoantibody measurements in the diagnosis of autoimmune thyroid disease. Anti-Tg autoantibody levels should therefore only be measured if anti-TPO autoantibody measurements are negative with clinical suspicion of autoimmune thyroid disease (Spencer et al., 2011).

2.5 Thyroid Dysfunction

Thyroid dysfunction is defined as the altered serum thyroid stimulating hormone (TSH) level with normal or altered thyroid hormone (T₃ and T₄) levels. Thyroid dysfunction is a common endocrine disorder affecting about 300 million people worldwide and over half are presumed to be unaware of their condition and frequently has significant clinical consequences (Aryal et al., 2010). Thyroid diseases are most common among women. Disorders of the thyroid include both overt and mild/subclinical hypothyroidism and hyperthyroidism, goiter and thyroid cancer.

Hypothyroidism is the clinical syndrome resulting from deficiency of thyroid hormones. It mainly affects women and is more prevalent in the middle-aged and elderly. Hypothyroidism is usually primary resulting from malfunction of the thyroid gland. Hypothyroidism results in decreased production of T₄ by the thyroid gland and consequently an abnormally low circulating T₄ concentration in blood. Subclinical hypothyroidism is a condition in which there are normal concentrations of thyroid hormones, raised concentrations of TSH, but no clinical symptoms (Shilotri, 2008). It is estimated that there are at least forty two million individuals with thyroid disease in India. Most of them are women and most hypothyroidism occurs after the birth of a baby called postpartum hypothyroidism. While thyroid diseases are increasing, there is a notion that it is prevalent in certain areas than others (James and Kumar, 2012).

The causes of hypothyroidism include the following:

1. **Loss of thyroid tissue**: Treatment of hyperthyroidism by radioactive destruction of thyroid tissue or surgical removal of thyroid tissue can result in hypothyroidism.
2. **Antithyroid antibodies:** These may be present in people who have diabetes, lupus, rheumatoid arthritis, chronic hepatitis, or Sjogren’s syndrome. These antibodies may cause decreased production of thyroid hormones.

3. **Congenital:** Hypothyroidism can be present from birth. This is commonly discovered early with nationwide newborn screening for this disease.

4. **Defects in the production of thyroid hormone:** Hashimoto's thyroiditis occurs when there are defects in the production of thyroid hormone, resulting in an increased amount of TSH. The increased TSH results in goiter (enlargement of thyroid gland itself that can be seen as an obvious swelling in front of the neck).

5. **Medications:** Some medications particularly lithium (Eskalith, Lithobid) may cause a drug-induced hypothyroidism.

Hyperthyroidism is a pathological syndrome in which tissue is exposed to excessive amounts of circulating thyroid hormone. The condition is often referred to as an "overactive thyroid." Clinical hyperthyroidism, also called thyrotoxicosis can be triggered by different disorders. Subclinical hyperthyroidism is a condition in which there are normal concentrations of thyroid hormones, lower concentrations of TSH, but no clinical symptoms. The diagnosis of hyperthyroidism is generally straight forward, with raised serum thyroid hormones and suppressed serum thyrotropin in almost all cases (Winter *et al.*, 2012).

Etiologic diagnosis influences prognosis and therapy. The proper treatment of hyperthyroidism depends on recognition of the signs and symptoms of the disease and determination of the etiology (Reid and Wheeler, 2005).
Review of Literature

The causes of hyperthyroidism include the following:

1. **Graves’ disease**: This thyroid condition results from abnormal stimulation of the thyroid gland by a material in the blood termed as thyroid stimulating immunoglobulin (TSI). TSI overstimulates the thyroid causing goiter. It also causes Graves’ eye disease, including a "bug-eyed" look and "frightened stare." This can progress to severe eye pain or eye muscle weakness causing tearing and double vision. It also causes raised, thickened skin over the shins (legs) or tops of the feet.

2. **Toxic multinodular goiter**: This occurs when part of the thyroid gland produces thyroid hormones all by itself, without regard to TSH stimulation. It usually occurs in people with a long-standing goiter, usually in elderly. Toxic multinodular goiter is different from Graves’ disease because of the general lack of eye complications and less severe signs of hyperthyroidism.

3. **Thyroiditis**: This inflammatory disorder of the thyroid gland includes such conditions as de Quervain's thyroiditis or Hashimoto's thyroiditis. In these conditions, periods of increased thyroid hormone release may occur due to inflammation, causing a hyperthyroid state. As thyroid failure occurs due to the inflammatory response, hypothyroidism may result.

4. **Pituitary adenoma**: This tumor of the pituitary gland causes independent TSH production leading to overstimulation of the thyroid gland.

5. **Drug-induced hyperthyroidism**: This is most commonly caused by the medication amiodarone (Cordarone) in heart patients.

Goiter refers to an enlarged thyroid gland. Biosynthetic defects, iodine deficiency, autoimmune disease and nodular diseases can each lead to goiter, though by different mechanisms. In a vast country like ours, goiter is endemic.
and health surgery facilities are stretched to the very maximum. A population of 9 million people are estimated to be affected by goiter (Shilotri, 2008).

Thyroid carcinoma is the most common malignancy of the endocrine system. It is subdivided into follicular and papillary. Secondary growths are rare. Blood borne metastases occur from primary carcinomas of breast, colon and kidney. Differentiated tumors, such as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC) are often curable and the prognosis is good for patients identified with early-stage disease. However, anaplastic thyroid cancer (ATC) is aggressive, responds poorly to treatment, and is associated with a poor prognosis (Faquin, 2008; Pallante et al., 2010).

2.6 Disorders due to Thyroid Dysfunction

Thyroid disorders can have a major impact on glucose control, and untreated thyroid disorders can affect management of diabetes. Hypothyroidism can decrease the insulin requirement in patients with diabetes and hyperthyroidism may worsen glucose tolerance or control. Underlying thyroid disorders may go undiagnosed because the common signs and symptoms of thyroid disorders are similar to those for diabetes and can be overlooked or attributed to other medical disorders. Symptoms of hypothyroidism are common in patients with type 2 diabetes and symptoms of hyperthyroidism may be attributed to poor diabetic control in patients with type 1 diabetes (http://www.thyroidtoday.com).

Hypothyroidism is believed to play an important role in the development of atherosclerosis, which is enhanced by the presence of hypercholesterolemia, which is the consequence of thyroid hormone deficiency with ultimate reduction in the activity of lipoprotein lipase (Mansourian, 2010). Long-standing hypothyroidism can cause significant reversible changes in renal function such as decrease in sodium resorption in the proximal tubules, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in urinary
urate excretion, a decrease in renal blood flow and glomerular filtration rate (GFR) (Tayal et al., 2009).

Thyroid hormone excess in hyperthyroidism causes a wide spectrum of cardiovascular changes, which arise from both direct and indirect effects on the cardiovascular system, and effects mediated by neurohormonal activation. The cardiovascular risk of subclinical hyperthyroidism is related to short-term effects due to electrophysiological effects of thyroid hormones and to long-term effects resulting from increased left ventricular mass and increased cardiac workload (Aly, 2007).

Overt hyperthyroidism is an important risk factor for osteoporosis and fractures. Thyroid hormones accelerate the rate of bone remodeling, leading to a negative calcium balance and a net bone loss that accelerates the development of osteoporosis and hence increases bone vulnerability to trauma (Reddy et al., 2012).

Thyroid hormones are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. Kidney is involved in the metabolism and elimination of thyroid hormone. From a clinical practice viewpoint it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte as well as in cardiovascular function (Iglesias and Diez, 2009). Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism and elimination of thyroid hormone. Thyroid dysfunction acquires special characteristics in those patients with advanced kidney diseases. Thyroid dysfunction causes significant changes in kidney function. Both hypothyroidism and hyperthyroidism affect renal blood flow, GFR, tubular function, electrolyte homeostasis, electrolyte pump functions and kidney structure. Thyroid disease may be linked to different forms of glomerulonephritis (Gurkan et al., 2009). Both hypothyroidism and hyperthyroidism can coincide with different forms of glomerular disease. The
more frequent form is membranous glomerulopathy and is associated with nephrotic syndrome. Although less frequent than glomerular disease, tubular or tubulointerstitial damage has also been reported to be associated with thyroid dysfunction. Isolated cases of hyperthyroidism have been reported in association with tubulointerstitial nephritis and uveitis, a self-limited syndrome of unknown etiology that responds to glucocorticoids (Ebihara et al., 2006; Hudde et al., 2007).

2.7 Thyroid Function Tests

Current laboratory techniques make the diagnosis and follow-up of thyroid disorders straightforward in the large majority of patients. Laboratory assessment of thyroid function is now often initiated with a low pre-test probability by clinicians who may not have a detailed knowledge of current methodology or testing strategies. Application of diagnostic strategy will differ depending on the test group, i.e. testing of untreated subjects in whom clinical features suggest thyroid dysfunction. Screening or case finding in risk groups, evaluation of the response to treatment or assessment with associated illness or drug therapy are likely to complicate both clinical and laboratory assessment (Haarburger, 2012).

Measurement of the serum thyroid stimulating hormone (TSH) concentration with an assay of adequate sensitivity is now the cornerstone of thyroid function testing. For untreated populations at risk of primary thyroid dysfunction, a normal TSH concentration rules out an abnormality with a high degree of certainty (Stockigt, 2003). The total T₄ test measures the concentration of thyroxine in serum, including both the protein bound and free hormone. The total (but not the free) hormone concentration is dependent on the concentration of thyroid transport proteins, specifically thyroid binding globulin (TBG), albumin and thyroid binding prealbumin (transthyretin). Thus any condition that affects levels of thyroid binding proteins will affect the total (but not the free) T₄ hormone levels. The total T₃ test measures the concentration of triiodothyronine in serum. The T₃ is increased in almost all
cases of hyperthyroidism and usually goes up before increasing the T₄ level. Thus T₃ levels are a more sensitive indicator of hyperthyroidism than T₄ levels (http://www.auburn.edu). The serum TT₄ measurement has evolved by the development of a variety of technologies over the past four decades. More commonly, TT₄ and TT₃ concentrations are measured by competitive non-isotopic immunoassay methods performed on automated platforms that use enzymes, fluorescence or chemiluminescent molecules as signals (Dufour, 2007). Total hormone methods require the inclusion of inhibitors, such as 8-anilino-1-napthalene-sulphonic acid to block hormone binding to serum proteins and to facilitate hormone binding to the antibody reagent (Spencer, 2010).

2.8 Medication for Hypo and Hyperthyroidism

Hypothyroidism is treated by thyroid hormone replacement therapy. Hyperthyroidism is treated using antithyroid drugs or beta-blockers or radio-iodine or surgical removal of thyroid gland.

2.8.1 Medication for Hypothyroidism

Commercially available hormones for thyroid hormone replacement therapy to treat hypothyroid subjects are:

1. **L-thyroxine (Synthroid, Levoxyl, Levothroid and Unithroid):** This medication is the mainstay of thyroid hormone replacement therapy in hypothyroidism. This is a synthetic form of thyroxine. This is exactly the same hormone that the thyroid makes. The body tissues convert it to the active product L-triiodothyronine. Side effects are rare and it has an excellent safety record.

2. **L-triiodothyronine:** This is rarely used alone as thyroid hormone replacement, because it has a much shorter persistence in the blood than L-thyroxine. Its use can cause rapid increase in L-triiodothyronine concentration which can be dangerous in the elderly and in people with cardiac disease.
3. **Thyroid extract or "natural" thyroid hormone:** This is dried and powdered pig thyroid gland. The hormone is not purified and the exact amount of $T_4$ and $T_3$ varies.

### 2.8.2 Medication for Hyperthyroidism

Hyperthyroidism can be treated using one of the following:

1. **Beta-blockers:** This class of medication works by blocking many of the body's responses to hyperthyroidism. It decreases tremor, nervousness and agitation. It also reduces the fast heart rate. Beta blocker tablets are prescribed to a patient with mild to moderate symptoms of hyperthyroidism.

2. **Propylthiouracil:** This antithyroid drug works by blocking thyroid hormone synthesis. It takes several months after starting the medication for the full therapeutic effect to be achieved.

3. **Methimazole (Tapazole):** This antithyroid drug works by blocking thyroid hormone synthesis. It may take slightly longer than propylthiouracil to achieve its full effect.

4. **Iodide (Lugol's solution, Strong iodine):** This medication works by inhibiting the release of thyroid hormone from the over functioning thyroid gland. It must be used in conjunction with an antithyroid drug because the iodine can be used to increase the amount of thyroid hormone produced and worsens hyperthyroidism.

5. **Radioactive iodine therapy:** An endocrinologist or nuclear medicine specialist can treat overactive thyroid conditions with radioactive iodine. This treatment takes several months by scarring down the thyroid gland, resulting in a smaller-sized gland, often accompanied by hypothyroidism.
2.9 Adverse Effects of Thyroid Medications

Patients prescribed too high a dose of levothyroxine may experience effects that mimic hyperthyroidism. Overdose could result in heart palpitations, abdominal pain, nausea, anxiousness, confusion, agitation, insomnia, weight loss and increased appetite (Lisandro, 2010). Allergic reactions to the drug are characterized by symptoms such as difficulty in breathing, shortness of breath, or swelling of the face and tongue. Acute overdose may cause fever, hypoglycemia, heart failure, coma and unrecognized adrenal insufficiency. Acute massive overdose may be life-threatening; treatment should be symptomatic and supportive. Massive overdose may require beta-blockers for increased parasympathetic activity. The effects of overdosing appear 6 hours to 11 days after ingestion (http://www.rxlist.com/synthroid-drug.htm).

According to Statathos and Wartofsky (2004) women treated with levothyroxine (L-T₄) had a 12.8% lower bone density at the femoral neck and a 10.1% lower bone density at the femoral trochanter compared to matched control. In very rare instances, both drugs can cause liver damage. In most severe cases, this can result in death. Regular follow-up visits with doctor will greatly reduce the risk of this severe complication (Heijckmann et al., 2005).

The most dangerous side-effect is agranulocytosis, this is an idiosyncratic reaction which generally resolves on cessation of drug. It occurs in about 0.2 to 0.3% of cases treated with antithyroid drugs. Others include granulocytopenia (dose dependent, which improves on cessation of the drug), aplastic anemia and fulminant liver failure. Patients on these medications should see a doctor if they develop sore throat or fever. The most common side effects are rashes and peripheral neuritis (Chitturi and Farrell, 2007).

Common mild side effects of propylthiouracil and methimazole includes itchy rashes. More rare, serious side effects include a decrease in white blood cell count, which can decrease the ability to fight off infection. This medication
can rarely cause liver dysfunction. Side effects of methimazole include cholestatic jaundice. Common side effects of iodide treatment include nausea and a metallic taste in the mouth (Brunton et al., 2006).

2.10 Medicinal Plants and Their Importance

India is the second largest exporter of medicinal plants. Plants and plant products have been a major source of medicine to cure human diseases since time immemorial because of their therapeutic value (Natarajan et al., 2011). Herbs produce and contain a variety of chemical compounds that act upon the body and are used to prevent or treat disease or promote health and well-being (Sharma et al., 2012). Herbal drugs have been used worldwide during the last few decades as evidenced by rapidly growing global and national markets of herbal drug. Today people rely more on herbal drugs because of high prices and harmful side effects of synthetic drugs and this trend is growing not only in developing countries but in developed countries too. Isolated active constituents from medicinal plants are used for applied research. For the last few decades, phytochemistry (study of plants) has been making rapid progress and herbal products are becoming popular (Bhowmik et al., 2009).

Plants are now occupying important position in allopathic medicine, herbal medicine, homeopathy and aromatherapy. Medicinal plants are the sources of many important drugs of the modern world (Lamaeswari and Ananthi, 2012). In recent years, secondary plant metabolites (phytochemicals) previously with unknown pharmacological activities have been extensively investigated as a source of medicinal agents (Kavitha et al., 2012).

2.10.1 Phytochemicals

The word “phyto” is the Greek word which means plant therefore phytochemicals means plant chemicals. Phytochemicals are the bioactive non-nutrient plant compounds in fruits, vegetables, grains and other plant foods that have health related effects (Nivya et al., 2012). They are naturally occurring biochemicals in plants that give plants their colour, flavour, smell and texture.
The medicinal values of the plant lie in their bioactive phytochemical constituents that produce definite physiological effects on human body. These natural compounds form the base of modern drugs we use today (Santhi et al., 2011). Some of the plants have pharmacological properties while others are used as indigenous medicine. There are many families of phytochemicals and they help the human body in a variety of ways. An estimation of more than 5000 phytochemicals have been identified in fruits, vegetables and grains. They are otherwise called as secondary metabolites. The phytochemicals vary in distribution within plant parts as well as in their occurrence within the plant species (Yadav et al., 2012).

As mentioned earlier phytochemicals can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulfur compounds. Among these phenolics and carotenoids are the most studied phytochemicals.

**Phenolics**

Phenolics are compounds possessing one or more aromatic rings with one or more hydroxyl groups and generally are categorized as phenolic acids, flavonoids, stilbenes, coumarins and tannins. Phenolics are the products of secondary metabolism in plants providing essential functions in the reproduction and the growth of the plants acting as defense mechanisms against pathogens, parasites and predators as well as contributing to the colour of plants. In addition to their roles in plants, phenolic compounds in our diet may provide health benefits associated with reduced risk of chronic diseases (Doughari et al., 2009).

**Flavonoids**

Flavonoids are a group of polyphenolic compounds with diverse chemical structure and characteristics. They are widely distributed in foods of plant origin such as vegetables, fruits, tea and wine. More than 4000 distinct flavonoids have been identified. Scavenging of free radicals seems to play a considerable
part in antioxidant activity of flavonoid compounds (Sava and Sirbu, 2010; Amudha and Pari, 2011).

**Phenolic acids**

Phenolic acids can be subdivided into two major groups, hydroxybenzoic acids and hydroxycinnamic acids. Hydroxybenzoic acid derivatives include \(\rho\)-hydroxybenzoic, protocatechuic, vannilic, syringic and gallic acids. They are commonly present in bound form and are typically a component of a complex structure like lignin and hydrolyzable tannin. They can also be found in the form of sugar derivatives and organic acids in plant foods (Godevac *et al*., 2010).

Polyphenols especially phenolic acids and flavonols have been considered as active components in prevention of cardiovascular diseases, cancers, neurodegenerative diseases and diabetes (Vauzour *et al*., 2010).

**Carotenoids**

Carotenoids are nature’s most widespread pigments and have also received substantial attention because of their provitamin and antioxidant roles. More than 600 different carotenoids have been identified in nature. They occur widely in plants, microorganisms and animals. Carotenoids at sufficient concentrations can prevent lipid oxidation and related oxidative stress. Phytochemicals such as carotenoids, tocopherols, ascorbates and phenols present in plants are natural antioxidants have an important role in health care systems (Mahajan and Gajare, 2012).

**2.10.2 Free Radicals and Antioxidants**

Free radicals are unstable chemical species that cause damage to lipid cells, proteins and DNA as a result of imbalance between the generation of reactive oxygen species (ROS) and the antioxidant enzyme. They are extremely reactive and are known to be the underlying cause of oxidative stress which is grossly implicated for more than 80 diseases including cancer, diabetes, cardiovascular diseases, liver damage, aging, cataract, rheumatism, metabolic
syndrome and other auto immune diseases (Subhashini et al., 2011; Doss et al., 2011). Examples of these radicals include superoxide anions, hydroxyl, nitric oxide and hydrogen peroxide radicals. Free radicals, especially the oxygen radical and superoxide, when formed could lead to the formation of other radicals (Ogunlana and Ogunlana, 2008). These free radicals may oxidize nucleic acids, proteins, lipids and DNA and can initiate degenerative diseases (Desai et al., 2011).

Antioxidants are compounds capable of either delaying or inhibiting the oxidation process which occurs under the influence of atmospheric oxygen or reactive oxygen species. They are used for the stabilization of polymeric products, petrochemicals, foodstuffs, cosmetics and pharmaceuticals. Antioxidants are involved in the defense mechanism of the organism against the pathologies associated with the attack of free radicals (Pisoschi and Negulescu, 2011). The potential of the antioxidant constituents of plant materials for the maintenance of health and protection from chronic diseases have also raised interest among scientists and food manufacturers as consumers move towards functional foods with specific health effects (Mandal and Ghosal, 2012). Meanwhile the ingestion of several synthetic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) has been reported toxic to man. The use of natural antioxidant has gained much attention from consumers because they are considered safer than synthetic antioxidants. Recently, there has been a worldwide trend towards the use and ingestion of natural antioxidants present in different parts of plants due to their phytochemical constituents (Mbaebie et al., 2012).

Specifically many researchers reported the presence of various antioxidants in seaweeds for example polysaccharides, dietary fibers, minerals, proteins, amino acids, vitamins, polyphenols and carotenoids. Seaweed produces various types of antioxidants to counteract environmental stresses. Therefore, seaweed is a potential source of novel antioxidant (Boonchum et al.,
Among the seaweed *Sargassum* sp. had the strongest antioxidant activity (Yangthong *et al.*, 2009). In contrast to terrestrial plant materials less research has been conducted on the antioxidant potential of marine seaweeds. Further, reports on the antioxidant properties of seaweed extracts from India are limited (Duan *et al.*, 2006). Currently there has been an increased interest globally to identify the antioxidant compounds that are pharmacologically potent and have low or no side effects for use in preventive medicine and food industry (Singh *et al.*, 2009).

**2.11 Herbal Remedies for Hypo and Hyperthyroidism**

It is well documented in archeological records that plants and plant products have been used for centuries for medicinal or health beneficial purposes. However many developing and under developed countries in the East still rely on ethanobotanical remedies for the treatment of many illness (Luthria, 2006).

There are several herbs that can be used for curing hypothyroidism. Bladderwack, also known as Kelp, contain iodine for maximum thyroid hormone stimulation. Ashwagandha root can be taken once daily in 1000 mg dosage. Sage is amongst one of the most popular herbs and can be taken daily in 300 mg dosage. Makandi is the rarest form of herb used for hypothyroidism (Yarnell and Abascal, 2006). A recent Japanese publication reports the detection of physiologically significant amounts of thyroxine (T$_4$) and Lithyroxine (T$_3$) as well as DIT and MIT in Laminaria species (Kombu) and *Sargassum* species (Sargasso weed) (Schaeffer and Krylov, 2000).

*Lycopus europea*, also called bugleweed is one of the main herbal remedies for treating hyperthyroidism. It reduces thyroid hormone production. It is especially effective in the early phase of hyperthyroidism. *Melissa officinalis*, also called Lemon balm is also one of the better known herbs for hyperthyroidism. It too reduces thyroid hormone. Lemon balm has been studied for its ability to successfully block the action of thyroid-stimulating
antibodies found in Graves’ disease (Hughes, 2011). *Leonurus cardiac,* familiarly known as Motherwort, was used by the ancient Greeks and Romans to treat heart palpitations as well as depression. Recently, Germany’s Commission E (the herbal regulating body in Germany) has approved the use of motherwort as part of an overall treatment plan for an overactive thyroid (http://www.herbalremediesworld.com).

2.12 *Sargassum wightii* Greville (Brown algae) and *Maydis stigma* (Sweet Corn Silk)

Seaweeds are one of the commercially important living marine resources that belong to the primitive groups of non-flowering plants. These marine algae grow abundantly along the coast of Tamil Nadu. About 700 species of marine algae have been reported from different parts of Indian coast (Elsie and Dhanarajan, 2010). Marine macro algae are mainly used for the production of agar, alginate, carrageenan (sulfated polysaccharides), liquid fertilizers and manures. Marine species have been used in a wide array of traditional remedies. There is an increasing demand for biodiversity in screening programmes for selecting therapeutic drugs from natural products, the marine organisms; especially seaweeds are of immense interest, since they are having a broad range of biological activities such as antiviral, antibiotic, anti-neoplastic, antifouling, anti-inflammatory, cytotoxic and antimitotic (Arunkumar and Sivakumar, 2012).

For several centuries there has been a traditional use of seaweeds as food in China, Japan and Republic of Korea (Iyapparaj et al., 2012). Both micro- and macro-algae have long been used to augment plant productivity and food production in various regions of the world through their beneficial effects when applied to soils. Seaweeds likewise have been used for millennia as fodder supplements to improve animal nutrition and productivity. Improved analytical techniques and instrumentation coupled with the use of molecular genetic tools are establishing that seaweed extracts can modify plant and animal responses at a fundamental level (Craigie, 2011).
Sargassum wightii Greville:

*Sargassum wightii* Greville is one of the marine brown algal species widely found in India. When dry, it is dark brown to blackish in colour. The alga is with well-marked discoidal holdfast. Upper portion is richly branched and radially organized. Axes are cylindrical and glabrous. Leaves are broad or narrow, oblong or linear measuring 5-8 cm in length and 2-9 mm in breadth, margins a little sinuate, dentate or more or less entire; tapering at base and apex; midrib inconspicuous, with few cryptostomata occurring on either sides of it. Vesicles are large, spherical or ellipsoidal, being 5-8 mm long and 3-4 mm broad, stipe of the vesicles is 5-7 mm long, seldom ending into a long tip. In Tamil, it is known as Kattaikkorai.

**Taxonomy of Sargassum wightii Greville**

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Chromista</th>
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<tbody>
<tr>
<td>Phylum</td>
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<td>Sargassum</td>
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<tr>
<td>Species</td>
<td>wightii</td>
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Binomial name: *Sargassum wightii* Greville

**BSI/SRC/5/23/2010-11/1715**

Marine seaweeds draw an extraordinary wealth of mineral elements from the sea that can account for up to 36% of its dry mass. The mineral nutrients present in seaweeds are diverse and the main elements being iodine and calcium (Varghese *et al.*, 2010). Brown algae are very important members of many marine communities ranging from the tropics to Polar Regions (Amsler and Fairhead, 2006). In India brown algae Sargassum are potential source of
Compatibility of Pongamia pinnata biofuel / diesel blends with few industrial metals

alginate. Species of *Sargassum* were used for cooling and blood cleaning effect. *Sargassum wightii* Greville has tremendous biological applications and are known to be rich in sulphated polysaccharide content (Josephine *et al.*, 2008). *Sargassum* has been used for curing scrofula, goiter, tumor, edema, testicular pain and swelling (Kandale *et al.*, 2011).

**Maydis stigma**

*Maydis stigma* which is also known as *Zea mays* hair or corn silks are yellowish thread-like strands or tassels called stigmas that are found inside the husks of corn. Stigmas are found on the female flower of corn, a grain that is also known as maize and is a member of the grass family (Gramineae or Poaceae). Fresh corn silk resembles soft silk threads 10-20 cm long that are either light green or yellow-brown in colour. They are mild sweetish in taste. Corn is known as solam in Tamil and corn silk as makasolampattu (Solam hair).

**Taxonomy of Maize**

- **Kingdom**: Plantae
- **Phylum**: Magnoliophyta
- **Class**: Liliopsida
- **Order**: Poales
- **Family**: Poaceae
- **Genus**: Zea
- **Species**: mays
- **Binomial name**: *Zea mays* L.

**BSI/SRC/5/23/2010-11/1614**

Based on folk remedies, corn silk has been used as an oral antidiabetic agent in China for decades. Corn silk has the potential to reduce hyperglycemia in alloxan-induced diabetic mice (Guo *et al.*, 2009). Corn silk has detoxifying, relaxing and diuretic activity. Corn silk is used to treat infections of the urinary and genital system. Corn silk helps to reduce frequent urination caused by
irritation of the bladder and is used to treat bed wetting problems (Rosli et al., 2010). It has been used to lessen the effects of premenstrual syndrome and promote relaxation. Studies indicate that corn silk can reduce blood clotting time and reduce high blood pressure. Corn silk also serves as a remedy for heart trouble, jaundice, malaria and obesity. Corn silk is rich in vitamin K, making it useful for controlling bleeding during childbirth. It has also been used to treat gonorrhea. In addition, corn silk has some nonmedical uses. Corn silk is an ingredient in cosmetic face powder (http://www.knowledgebase-script.com).