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## World Journal of Science and Research

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### Research Article

### Siddha Medicine

#### THYROID HORMONES AND HISTOPATHOLOGICAL STUDIES ON THE THERAPEUTIC EFFICIACY OF ARUMUGA CHENDOORAM IN EXPERIMENTAL HYPOTHYROIDISM

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#### ABSTRACT

#### Article Info:

The aim of the study was to investigate the hormones status and examine histopathological changes in thyroid on the therapeutic efficacy of Arumuga chendooram in experimental hypothyroidism. In the present study, methimazole treated rats decreased T<sub>3</sub>, T<sub>4</sub> and increased TSH level. This indicates that a state of severe hypothyroidism was successfully induced in the experimental animals. Hypothyroid rats treated with Arumuga chendooram (Hypothyroid + Arumuga chendooram group) exhibited a remarkable improvement in thyroid profile. These results clearly demonstrate that Arumuga chendooram has therapeutic potential to restore thyroid hormone levels in experimental hypothyroidism. Histopathological studies of thyroid gland further supported the biochemical changes.

Received on 15<sup>th</sup> Sep. 2016

Accepted on 09<sup>th</sup> Sep. 2016

Online September 2016

**Keywords:**  
Methimazole,  
Thyroid hormones,  
Arumuga  
chendooram,  
Histopathology,  
Hypothyroid

**Citation:** Albert Santharaj Deepak R and V. Elango (2016) Thyroid Hormones and Histopathological studies on the therapeutic efficacy of Arumuga Chendooram in Experimental Hypothyroidism *World Journal of Science and Research*. 1(3): 71-83.

### INTRODUCTION

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 (T<sub>4</sub>), 3,5,3'-triiodothyronine (T<sub>3</sub>) and calcitonin. Among these T<sub>4</sub> and T<sub>3</sub> 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 (T<sub>4</sub>) otherwise known as thyroxine is the major form of thyroid hormone in the blood. T<sub>4</sub> forms about 90% of the total secretion, whereas, 3,5,3'-triiodothyronine (T<sub>3</sub>) is only 9 to 10%. The potency of T<sub>3</sub> is four times more than that of T<sub>4</sub>. However, the duration of action is four times more for T<sub>4</sub> than T<sub>3</sub>. This is because of the difference in the affinity of these hormones to plasma proteins. T<sub>3</sub> has less affinity for plasma proteins and combines loosely with them so that it is released quickly. T<sub>4</sub> has more

affinity and strongly binds with plasma proteins so that it is released slowly.

Therefore,  $T_3$  acts on the target cells immediately and  $T_4$  acts slowly (Sembulingam and Sembulingam, 2010). Most of the daily  $T_4$  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 hepatic 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.  $T_3$  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>).

## MATERIALS AND METHODS

### Animals

Male albino rats of Wistar strain approximately weighing 180-190g were used in this study. They were healthy animals purchased from the Indian Institute of Science, Bangalore. The animals were housed in spacious polypropylene cages bedded with rice husk. The animal room was well ventilated and maintained under standard experimental conditions (Temperature  $27 \pm 2^\circ$  C and 12 hour light/dark cycle) throughout the experimental period. All the animals were fed with standard pellet diet and water were provided *ad libitum*. They were acclimatized to the environment for one week prior to experimental use. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

### Chemicals

Nitroblue tetrazolium (NBT), ethylenediaminetetra acetic acid (EDTA), Trichloro acetic acid (TCA), Thiobarbituric acid (TBA), 5,5'-dithio-bis (2-nitrobenzoic acid), glutathione (reduced), glutathione (oxidized) and Nicotinamide adenine dinucleotide phosphate ( $NADP^+/NADPH$ ) were purchased from Sigma Chemical Company (St. Louis, MO, USA). All other chemicals used were of analytical grade and were obtained from Glaxo

Laboratories, Mumbai, India, and Sisco Research Laboratories, Mumbai, India.

### Preparation of Arumuga chendooram

The Siddha medicine Arumuga chendooram was prepared at its different stages of preparation in departmental laboratory with the help of a traditional siddha medical practitioners as per the IMCOPS method.

In the first stage of the preparation of Arumuga chendooram. Five parts of purified mercury (Suththi seitha rasam), nine parts of purified sulphur (Suththi seitha kanthakam), seven parts of purified lode stone (Suththi seitha kantham), twelve parts of purified iron filing (Suththi seitha ayapodi), four parts of rock salt (Induppu) and eight parts of desiccated borax (Poriththa venkaram) were ground with sufficient quantity of aloe juice (Kumari charu for five days continuously. This was then made into small cakes and dried. It was then sealed in discs and burnt for 24 hours. If the colour of the chendooram does not appear as dark purple the grinding and burning are usually repeated equal to pH and then attractive particle interactions predominate which may influence the drug delivery.

### Experimental design

Body weights of the animals were recorded and they were divided into 4 groups of 6 animals each as follows. First group was normal rats fed with standard diet and served as a control which received saline. Second group was negative control administered Methimazole (40mg/kg) induced experimental hypothyroidism for 40 consecutive days. Third group was treatment group treated with Methimazole (40mg/kg) along with Arumuga chendooram (10mg/kg) for 40 days. Fourth group was positive control treated with Methimazole (40mg/kg) along with standard throxine sodium (20 $\mu$ g/kg) for 40 days.

### Collection of samples

On completion of the experimental period, animals were anaesthetized with thiopentone sodium (50mg/kg). The blood was collected with or without EDTA as anticoagulant. Blood, plasma and serum were separated for the estimation of various biochemical parameters. The Liver, heart and adipose tissues were dissected out, washed in ice-cold saline, and weighed. A known weight of them was used for homogenate preparation and used for various biochemical analyses. The thyroid gland fixed in 10% phosphate buffered formalin for histopathological studies.

**Thyroid Stimulating Hormone analysis:** The quantitative determination of thyroid stimulating hormone (TSH) in serum of the thyroid patients and

euthyroid controls was done by enzyme immunoassay test kit (Bio check, Inc. California).

**Triiodothyronine:** The estimation of serum triiodothyronine (T3) was done by enzyme immunoassay (EIA) test kit (Diagnostic automation, Inc. California) by the method of Klee (1996).

**Thyroxine:** The determination of serum thyroxine (T4) concentration was done by Microwell enzyme immunoassay test kit (Bio check, Inc. California) according to the method of Chopra *et al.* (1971).

**RESULTS AND DISCUSSION**

Hormones are chemical messengers secreted by glands. A number of hormones of the endocrine system serve to regulate the activities of other tissue. The hormones produced by thyroid gland enhance protein synthesis and oxygen utilization and these physiologic activities, in turn, influence the basal metabolic rate (BMR) (Boelaert and Franklyn, 2005). The activity of the thyroid gland is predominantly regulated by the concentration of the pituitary glycoprotein hormone, thyroid stimulating hormone (TSH). (Mariotti, 2011). TSH levels are further regulated by the hypothalamus, and also by other regulatory mechanisms, producing a feedback loop so that TSH increases as thyroid hormones decrease and TSH decreases when thyroid hormones increase. Measures of the amount of the thyroid hormones T3 (triiodothyronine) and T4 (thyroxine) in the blood plasma are considered a substantive evaluation of thyroid function (Mariotti, 2011).

In the present study, methimazole treated rats decreased T3, T4 and increased TSH level. This indicates that a state of severe hypothyroidism was successfully induced in the experimental animals (Table 1 and Fig.1). Hypothyroid rats treated with Arumuga chendooram (Hypothyroid + Arumuga chendooram group) exhibited a remarkable improvement in thyroid profile. These results clearly demonstrate that Arumuga chendooram has therapeutic potential to restore thyroid hormone levels in experimental hypothyroidism. Histopathological studies of thyroid gland further supported the biochemical changes.

**Table 1 Effect of Arumuga chendooram on Thyroid hormones in experimental rats**

Parameters	Group I	Group II	Group III	Group IV
T3 (ng/ml)	132 ±3.10 <sup>a</sup>	92.12±1.60 <sup>b</sup>	128.41±3.80 <sup>a</sup>	134.32±4.90 <sup>a</sup>
T4 (µg/dl)	7.12 ±0.4	5.14±0.35 <sup>b</sup>	6.95±0.48 <sup>a</sup>	6.87±0.48 <sup>a</sup>

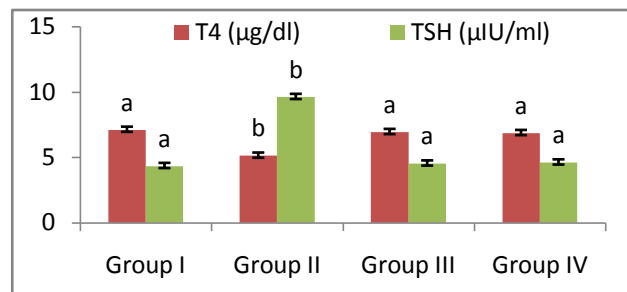
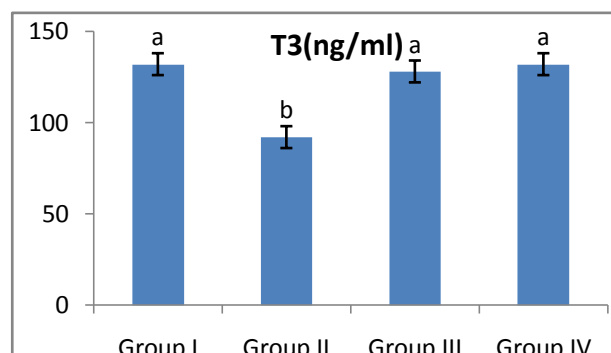
	9 <sup>a</sup>			
TSH (µIU/ml)	4.35 ±0.30 <sup>a</sup>	9.63±0.67 <sup>b</sup>	4.54±0.31 <sup>a</sup>	4.62±0.32 <sup>a</sup>

Values were expressed as mean ± SD for six rats in each group.

<sup>a</sup> Significantly different from Group II (p< 0.05)

<sup>b</sup> Significantly different from Group I, III and IV (p< 0.05)

**Figure 1 Effect of Arumuga chendooram on Thyroid hormones in experimental rats**



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The therapeutic effects of the antithyroid drug, methimazole (MMI) have been ascribed to its ability to decrease thyroid hormone production (Cooper, 1984). Antithyroid drugs are taken up by the thyroid gland as other anions similar to iodide (perchlorate, thiocyanate, and pertechnetate) (Cooper, 1984). Their target is the thyroid peroxidase. They block the iodination of tyrosine residues and the coupling of iodotyrosines into iodothyronines (Cooper, 1984).

Thyroid disease affects about most of the Indian population, but because the disease

predominantly strikes middle-aged women, the incidence within this group is rather high. Women are about four times more likely than men to suffer hyperthyroid disorders, eight times more likely to suffer hypothyroidism, and about twice as likely as men to suffer thyroid tumors. Approximately half the cases of thyroid disease involve hyperthyroidism and the other half involves hypothyroidism (Dharmananda, 2012; Saxena *et al.*, 2012). The current medical therapies for thyroid disorders other than iodine-deficiency goiter are often deemed inadequate because of difficulties in regulating the level of thyroid hormones through use of drugs or an exogenous source of thyroid hormone. Herbo-mineral-based drugs owe the advantage of being simple, effective and exhibit broad spectrum activity and also have continued to play a dominant role in the maintenance of human health since ancient times. In the present study to investigate the effect of Arumuga chendooram on Thyroid hormones in experimental rats.

Thyroid hormones influence nearly all major metabolic pathways. Their most obvious and well-known action is the increase in basal energy expenditure obtained acting on protein, carbohydrate and lipid metabolism. They do not intervene in the minute-to minute regulation of metabolism, but rather they modulate the activities of metabolic pathways on a medium-or long-term basis, either by a direct action or by modifying the activity of other regulatory hormones such as insulin, glucagon and catecholamines. The effect of thyroid hormones on protein metabolism is characterized by a profound stimulatory effect on the synthesis of numerous cytosolic and mitochondrial proteins as well as of secretory proteins such as albumin and hormones (Pucci *et al.*, 2000).

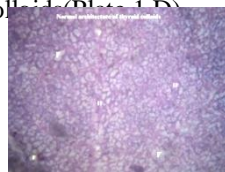
All aspects of lipid metabolism including synthesis, mobilization and degradation are influenced by thyroid hormones, but degradation is affected more than synthesis. Thyrotoxicosis is associated with a depletion in the stores of most lipids and with a decrease of their concentration in plasma. This is true for triglycerides, phospholipids and cholesterol. Opposite changes occur in conditions of thyroid hormone deficiency. The metabolism different apolipoproteins is also affected (Huang *et al.*, 2008). So, with an increase in thyroid activity, marked changes in thyroid hormone production, metabolism and action occur. This may result in an increased prevalence of sub-clinical thyroid disease that is associated with thyroid dysfunction (Peeters, 2008). Similar results have been observed in different plant extracts such as Caraway (Dehghani, 2010); Evelyouth and Dreamshape (Ohye *et al.*, 2005).

### Histological observation of thyroid gland

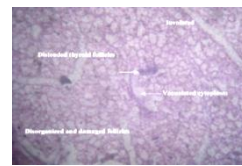
Effects of the Arumuga chendooram on histology of thyroid gland in control and experimental rats were examined. The photomicrograph of a section in the thyroid gland of a control rat (Group I - Plate 1 A) showing normal architecture of thyroid with thyroid follicles (F) of various sizes lined mainly with simple cuboidal cells (arrows) surrounding central lumen filled with homogenous acidophilic colloid (Co). Notice the interfollicular tissue (IF) can also be seen.

A photomicrograph of a section of the thyroid gland of a Methimazole treated group II (Plate 1 B) showing markedly distended thyroid follicles. They are lined mainly by flat cells with flat nuclei (arrow) and few low cuboidal cells with apparently rounded nuclei. Notice the detached follicular cells in the colloid of some follicles. Showing thyroid follicles of variable activity as some follicles are markedly distended and other follicles appear involuted. These follicles have minimal amount of colloid. The thyrocytes of most of the follicles have vacuolated cytoplasm, disorganized and damaged follicles with a wide interfollicular space. Most of follicles are destroyed with the epithelial lining of vacuolated cytoplasm and most follicles with no colloid.

Photomicrograph of a section in the thyroid gland of rat treated with Methimazole concomitantly with Arumuga chendooram showing most thyroid follicles appeared similar to those of the control (Plate.1 C), while thyroxine treated group IV with few follicles appeared with vacuolar cytoplasm otherwise normal architecture of thyroid colloid (Plate 1 D).



I)



I)

Plate 1 C (Group III)

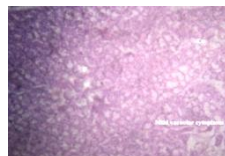


Plate 1 D (Group IV)

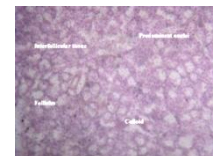


Plate 1 Photomicrograph of a section in the thyroid gland of control and experimental rats

The result of the study conclude that Hypothyroid rats treated with Arumuga chendooram (Hypothyroid + Arumuga chendooram group) exhibited a remarkable improvement in thyroid profile and histological changes. These results clearly demonstrate that Arumuga chendooram has therapeutic potential to restore thyroid hormone levels in experimental hypothyroidism. Histopathological studies of thyroid gland further supported the biochemical changes.

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