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Anti oxidant and hepatic enzyme changes in *Kanakalinga karpoorati mezhugu,* treated Experimental hypothyroid disorder

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ABSTRACT

Many metal and mineral raw drugs are prepared in Siddha medicine as Mezhugu, Pathangam, Parpam, Chenduram, Kalangu, Kattu, Urukku and Chunnams and need global standards. A detailed in-vivo and in-vitro studies of KLK mezhugu for its quality, efficacy other indications should be ascertained using modern parameters. Chemical nature of the KLK mezhugu depends upon the purification methods, materials mixed, quantity, quality of heat and flame, type of fuel, duration of heat, periodicity of grinding, size of the particle and solubility, assimilation and absorption in the alimentary tract are some of important factors to be studied. Male albino rats were used for this present thyro-toxicity study. Animals were provided with normal rats feed and normal water *ad libitum*. Methimazole was given to induce hypothyroidism and *KLK mezhugu* in water suspension was used a test drug. Animals were fasted overnight, anaesthetized with ether and sacrificed by cervical decapitation, blood was drawn and the serum was separated for biochemical analysis. Thyroid protective activity was done by assessing the significant changes in body weight, Serum T_3 triiodothyronine, T_4 thyroxine, TSH, Albumin, Cholesterol, Triglycerides, Lipid peroxide, Transaminases, Acid phosphotases were estimated and the Mean values standard were calculated for all the values carried out. The result of this study shows the significant protect activity in thyroid necrosis against methimazole induced thyroid-toxicity.

Keywords: KLK mezhugu, lipid profile, transaminases, thyroid toxicity, methimazole, herbomineral drug

INTRODUCTION

Many metal and mineral raw drugs are prepared both as mezhugu, pathangam, parpam, chenduram, kalangu, kattu, urukku and chunnams. A detailed in-vivo and in-vitro studies of mezhugu for their quality, efficacy other indications should be ascertained using modern parameters. The sequential processes from stage I to Stage III were responsible for numerous changes which translate the toxic materials to medicines. Chemical nature of the mezhugu depends upon the purification methods, materials mixed, quantity, quality of heat and flame, type of fuel, duration of heat, periodicity of grinding, size of the particle and solubility, assimilation and absorption in the alimentary tract are some of important factors to be studied.

The remarkable features in the preparation of mezhugu are the fine grinding in a stone mortar using a stone pestle. The production of heat during purification and strong force during grinding plays

significant role to transfer the toxic solid materials into gaseous state.

Literature survey revealed that the herbo mineral drug selected offers scope for systemic biochemical, phytochemical, pharmacological screening and clinical trial for ascertaining the efficacy of them. They have not yet been undertaken for scientific proof.

Kanakalinga karpoorathi mezhugu is a herbomineral drug preparatiom used in siddha system of medicine used to cure many diseases like,Type of kapha disorder, Abdominal pain, Epilepsy of mental disorders, Urethral discharge, Jaundice, Syphilitic disorder, Burning micturition, 64 varieties of fever, neuralgia with rheumatism, Abdominal swelling, Chronic and severe vatha disorders,, Bronchial asthma, Nenjadaippudan Marpil Kuthu, Kuthirai Valippu (a type of epilepsy). The drug is used in clinical studies for the treatment of thyroid disorders especially hypothyroidism. Thyroid disease is common, and disease is more prevalent with increasing age. 5%–9% of adults have subclinical thyroid disease and 0.8%–7.5% have clinical thyroid disease 1–3 in the general population [1] .The thyroid gland secretes 3 hormones- thyroxin (T4), triiodothyronine (T3) and calcitonin. Subclinical thyroid disease is defined by abnormal serum thyroid-stimulating hormone (TSH) but normal T4 and T3 levels and does not always require treatment, whereas persons with clinical thyroid disease have abnormal serum TSH, T4, and T3 levels and require treatment. Known risk factors for thyroid disease include autoimmunity, external irradiation of the head and neck, a biosynthetic defect in iodine organification, replacement of the thyroid gland by tumour, and use of certain drugs [13]. Other factors associated with an increased risk of thyroid disease include female sex, increasing age, and iodine deficiency [2,3]. Despite of tremendous advancement in Allopathic system of medicines, there are many areas in which allopathic medicines have failed to prove its effectiveness. Main drawback of allopathic system is its side effects, high cost of drugs, and lack of curative treatment for chronic diseases and reoccurrence of disease after stoppage of medication. People are losing their faith towards allopathic medicines and going towards the use of traditional medicines such as Ayurveda, Unani, Siddha and Naturopathy. As per the WHO, about three-quarters of the world's population currently use herbs and other forms of traditional medicines to treat their diseases. Herbo-mineral formulation uses the metals and minerals for chronic disorders in different combinations, dosage forms and at various levels of purities. Hence it is very essential to prepare it in a proper way. As per the reported data, there are so many herbo mineral formulations available in market which is useful in anemia, diabetes, cancer, liver diseases, skin diseases etc. Keeping in view, in the present study the chosen herbo-mineral drug as *KLM mezhugu* and evaluated the therapeutic efficacy in Methimazole induced experimental hypothyroidism.

Animals and Treatment

Male albino rats of 8 – 10 weeks of age weighing between 100 and 120g were used for this present thyro-toxicity study. The animals were purchased from Sri Venkateswara Enterprises (Ltd), Bangalore and housed in polypropylene cages. Animals were provided with normal rats feed and normal water *ad libitum*. Animals were divided into three groups of 4 animals. Group I: normal animals provided with usual rat feed and water. Group II: as control animals provided with rat feed and water along with 40mg/kg methimazole in 100ml distilled water and the Group III as Drug treated animals provided with rat feed and water along with methimazole and *KLK mezhugu*in water suspension andthe drug followed by it.

Collection of Blood Samples

At the end of treatment, animals were fasted overnight, anaesthetized with ether and sacrificed by cervical decapitation. Blood was drawn and the serum was separated for biochemical analysis.

Biochemical Studies

Thyroid protective activity was done by assessing the significant changes in body weight, Serum T_3 triiodothyronine, T_4 thyroxine, TSH was determined using ELISA kit method. Albumin level was measured spectrometrically at 600nm and total protein by biuret method a blue purple coloured complex with absorbance at 550nm. Cholesterol and Triglycerides were estimated Friedman and Young method by calorimetric kit method [4]. Lipid peroxide content was assayed by thio-barbituric acid method, catalase estimated calorimetrically. Transaminases activities were

estimated by Reitman and Frankel method and which was measured spectrometrically [5]. The acid phosphotases was estimated and the absorbance was read at 405nm. Mean values standard were calculated for all the values carried out [6].

RESULTS AND DISCUSSION

Methimazole (1-methyl-3H-imidazole 2-thione) is an antithyroid drug, methimazole also known as Tapazole or Thiamazole or MMI, and part of the thioamide group. Like its counterpart propylthiouracil, a major side effect of treatment is agranulocytosis.Methimazole molecular formula is $C_4H_6N_2S$. Methimazole inhibits the enzyme thyroperoxidase, which normally acts in thyroid hormone synthesis by oxidizing the anion iodine (I^-) to iodine (I_0), facilitating iodine's addition to tyrosine residues on the hormone precursor thyroglobulin, a necessary step in the synthesis of triiodothyronine (T_3) and thyroxine (T_4). [7]

The result of this study shows the significant thyrotoxicity induced by methimazole was evidenced by increase in serum T_3 Triiodothyronine, T_4 Thyroxine, TSH secretion due to thyroid cellular necrosis. The administration of crude powder of KLK mezhugufor 30 days was found able to treat and protect thyroid necrosis against methimazole induced thyroid-toxicity.

In the present experimental study shows that treatment with KLK mezhugucrude powder at the dose of 100mg/100g.b.wt, the serum T3 and T_4 was increased from the untreated control animal (methimazole induced). The active thyroid hormone, T3, is one of the most powerful molecules in the human body, affecting every system, every tissue of the body and every aspect of our well-being and health. It increases the mitochondrial energy production. [8]

Thyroid hormones, thyroxine (T_4), and triiodothyronine (T_3) play an important role in all major metabolic pathways. They regulate the basal energy expenditure through their effect on protein, carbohydrate, and lipid metabolism. This might be a direct effect or an indirect effect by modification of other regulatory hormones such as insulin or catecholamines [8].

The result of this study shows the significant hypothyrodism induced by methimazole was evidenced by increase in serum T3 and T4 and secretion due to thyro-necrosis. The administration of crude powder of KLK mezhugu for 30 days was found able to treat and protect thyroid cell or follicles damage against methimazole induced hypothyroidism.

The TSH level is not a measure of thyroid hormone sufficiency in any given patient, either untreated or treated; reliance on the TSH produces both under and over-diagnosis and under treatment. Dysfunctional central hypothyroidism with a normal TSH may be more common than primary hypothyroidism, and TSH-normalizing T4 therapy neither normalizes T3 levels nor restores euthyroidism. The TSH test is useful only for investigating the cause of clinically-diagnosed hypothyroidism. TSH test as the best screening test for the diagnosis of primary hypothyroidism and the best guide for its treatment. If the TSH is elevated, it is a compensatory mechanism, the increased stimulation of the dysfunctional thyroid gland may indeed work to maintain thyroid levels and effects. The TSH response to response to low FT4 levels declines by 80% between ages of 20 and 80 [22].Thus the result shows the increased level of Thyroid Stimulating Hormone (TSH) after the induction of KLK mezhugu in hypothyroidism induced rats.

Concentrations below the reference range usually reflect low albumin concentration, for instance in liver disease or acute infection. Rarely, low total protein may be a sign of immuno deficiency. Normally T3 is bound loosely by serum proteins and hence diffuse much more rapidly into the tissues. Thus the result shows the increased level of albumin and total protein due to the action of *KLK Mezhugu* the methimazole.

Hypothyroidism is one of the most common causes of hyperlipidemia in humans and animals and it is characterized by excessive cholesterol and TGL levels. There are various factors of increased oxidative stress in hypothyroidism, such as hyperlipidemia, deficient or imbalanced antioxidant system and excessive TSH. Excess TSH levels can cause over-production of oxidants in body and enhanced oxidative stress parameters were found in hypothyroidism [9].

Levels of cholesterol and triglycerides will be elevated [10] the impact of subclinical hypothyroidism on lipid parameters is less well-defined. After the 30 days of the treatment with KLK mezhugu against the methimazole the

cholesterol and triglycerides shows the normal level.

Thyroid hormones are associated with the oxidative and anti-oxidative status of the organism. Depression of metabolism due to hypothyroidism has been reported to decrease oxidant production and thus protects tissues against oxidant damage. The biological oxidative effects of free radicals on lipids, proteins, and DNA are controlled by a spectrum of antioxidants.

Enzymatic protection against reactive oxygen species (ROS) and the breakdown products of peroxidized lipids and oxidized protein and DNA are provided by several enzyme systems LPO and catalase (CAT) [10]. SOD catalyzes the dismutation of the superoxide anion into hydrogen peroxide (H_2O_2), which is then deactivated to water (H_2O) by catalase or glutathione peroxidase (GPx) [11].

Table: Anti-thyroid effect of KLK mezhugu on LPO, Catalase, AST, ALT

Group	Dose	LPO nMDA/ml	Catalase H_2O_2 decompose/mg protein	ALP U/l	AST U/l	ALT U/l
Normal	Saline	1.50±0.090	58.0±4.46	165.0±12.87	133.32±8.65	233.3±17.94
Control	40mg/kg	1.81±0.079	41.9±1.84	193.48±10.80	166.65±7.03	199.98±9.99
Methimazole treated KLK mezhugu	100mg/kg	1.43±0.07	32.2±1.77	138.2±4.41	99.99±4.49	166.65±9.26

Each values is the Mean ± SEM of three animals statistically significant from control

Thyroid hormones regulate Basal Metabolic Rate (BMR) and calorigenesis in tissues, including hepatocytes and thereby modulate hepatic function. The liver in turn metabolizes the thyroid hormones and regulates their systemic endocrine effect. Raised serum transaminase and phosphatase activities in absence of any overt liver dysfunction can therefore be attributed to primary thyroid dysfunction. The aim of this study is to assess the impairment in liver function by estimating serum Aspartate Transaminase (AST) and Alanine Transaminase (ALT) in experimental rats with hypothyroidism.

A complex relationship exists between the thyroid gland and the liver in both health and disease. The thyroid status depends not only on thyroxine secretion but also on normal thyroid hormone metabolism. Normal thyroid function, which is essential for normal growth, development and regulation of energy metabolism within the cells, is dependent on a normal functioning thyroid and liver axis. After the treatment of KLK mezhugu against the methimazole induced hypothyroidism after 30 days, it shows significant activity in the level of transaminase and phosphatase.

CONCLUSION

The crude powder of the plant KLK mezhugu has hypo thyroid protective activity against the methimazole induced thyrotoxic rats. Further studies, are needed to identify the chemical constituents of the plant *KLK mezhugu* that may be responsible for the Thyroid protective activity.

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