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Antioxidant and Protective Effects of *Chloroxylon Swietenia* in L-Thyroxine Induced Hyperthyroidism in Rats

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Research Article

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ABSTRACT

This study was performed to evaluate the anti-hyperthyroid effects and action mechanism of *Chloroxylon Swietenia*, a medicinal herb, on levothyroxine (LT_4)-induced hyperthyroidal rats. Wistar rats were divided into five groups, namely, thyroidal normal group (normal), hyperthyroidism control group (disease control), hyperthyroidism plus Propylthiouracil treated group (PTU) as a standard, hyperthyroidism plus 200 mg/kgm ethanolic extract of *Chloroxylon Swietenia* (MECS) treated group, and hyperthyroidism plus 400 mg/kg MECS-treated group. The rats in groups other than normal were injected with LT_4 for 12 days to induce hyperthyroidism and then were administrated each treatment for 17 days. Biochemical parameters related to hyperthyroidism were examined. Compared with the disease control group, serum T_3 and T_4 levels were significantly reduced in the test and PTU treated groups where as serum TSH levels and body weight were significantly increased in the test and PTU treated groups. These results suggest that *Chloroxylon Swietenia* has the potential to decrease T_3, T_4 levels and enhance the levels of Thyroid Stimulating Hormone (TSH) and body weight of the animals and therefore, *Chloroxylon Swietenia* could be an alternative therapy for hyperthyroidism. Phytoconstituents like flavonoids, alkaloids, phenols and terpenoids present in the *Chloroxylon Swietenia* leaf extract might be responsible for the beneficial effect in hyperthyroidism.

INTRODUCTION

A medical condition known as hyperthyroidism occurs when the thyroid gland produces and secretes an excessive amount of thyroid hormone. Normal or high thyroid radioactive iodine uptake is a defining feature (thyrotoxicosis with hyperthyroidism or true hyperthyroidism). The release of preformed thyroid hormones into the bloodstream along with poor thyroid radioactive iodine absorption is the two main causes of thyrotoxicosis without hyperthyroidism.

Hyperthyroidism can be overt or subclinical. Low serum levels of the Thyroid Stimulating Hormone (TSH) and elevated levels of the thyroid hormones Thyroxine (T_4), Triiodothyronine (T_3), or both, are characteristics of overt hyperthyroidism. Low serum TSH levels are indicative of subclinical hyperthyroidism, although serum T_4 and T_3 concentrations are normal. Graves' disease is the most typical cause of hyperthyroidism in regions with adequate iodine levels. Solitary toxic adenoma and toxic multinodular goiter are two more prevalent causes of hyperthyroidism. Although in iodine sufficient areas about 80% of patients with hyperthyroidism have Graves' disease, toxic multinodular goiter and toxic adenoma account for 50% of all cases of hyperthyroidism in iodine deficient areas, and are more predominant in elderly people. Thyroid nodules develop a sense of autonomy and start producing thyroid hormones without the help of TSH or TSH receptor antibodies. Less common causes of hyperthyroidism include thyrotropin induced thyrotoxicosis and trophoblastic tumours, in which TSH receptors are stimulated by excess TSH and human chorionic gonadotropin, respectively. Antihyperthyroid drugs available in the market cannot completely cure the root cause and in addition produce adverse effects which decrease the quality of life. Hence there is a need

to find alternative remedy with more efficacy and less side effects [1].
Chloroxylon Swietenia is a medium sized deciduous tree with height up to 9 m-15 m and 1 m-1.2 m girth having a spreading crown. The tree, also known as Ceylon Satinwood or East Indian Satinwood, is a native of Sri Lanka and India. *C.swietenia* is considered as a folklore medicinal plant having several medicinal uses in the folklore remedies. It is scientifically evaluated for, antidiabetic, anti-inflammatory, antihyperlipidemic, larvicidal activities [2].
Despite the fact that *Chloroxylon Swietenia* is well known to possess interesting properties in traditional medicine it has not been studied for its anti-hyperthyroidism activity. This study was aimed at providing experimental support for the traditional medicinal use of the methanolic leaf extract of *Chloroxylon Swietenia* in the management of hyperthyroidism [3].

MATERIALS AND METHODS

Plant collection and drying
Leaves of *Chloroxylon Swietenia* were distinguished, gathered, and confirmed by botanist, Government degree school, Kukatpally, Medchal locale. *Chloroxylon Swietenia* leaves were cleaned and dried under shade for around 15 days and powdered. The powdered material was stored [4-8].

Preparation of methanolic leaf extract of *Chloroxylon Swietenia* (Soxhlet)
The powdered material of *Chloroxylon Swietenia* leaves were dried and extracted with ethanol by soxhlation strategy [9].

Preliminary phytochemical analysis of the extract
The extract was exposed to fundamental phytochemical examinations to recognize different phytoconstituents present in the methanolic extract of *Chloroxylon Swietenia* leaves [10].

Acute toxicity testing
The acute toxicity study was conducted as per OECD 425 guidelines. Present study was done in CPCSEA endorsed lab of Gokaraju Rangaraju college of pharmacy, Bachupally, Hyderabad, India.

Animal housing
The rodents were housed in poly acrylic cages with not in excess of six animals for each enclosure; with 12 h light/12 h dark cycle. Animals have free access to standard rodent diet and drinking water ad libitum. The animals were acclimatized to the lab climate for seven days before the beginning of the experimentation. The animals were cared for and maintained in accordance with the authorised standards of the committee for the control and supervision of experiments on animals [11-18].

In vitro antioxidant activity
Hydrogen peroxide scavenging activity: A few enzymes are directly inactivated by hydrogen peroxide, a weak oxidizing agent, mainly by oxidizing vital thiol (-SH) groups. It can cross cell membranes rapidly; once inside the cell, it can probably react with Fe^{2+} and possibly Cu^{2+} ions to form hydroxyl radicals and this may be the origin of many of its toxic effects. It is therefore biologically advantageous for cells to control the amount of hydrogen peroxide that is allowed to accumulate [19].

Procedure: The ability of the *C. Swietenia* extracts to scavenge hydrogen peroxide was determined according to the method of Ruch, et al., In phosphate buffer, a solution of hydrogen peroxide (40 mM) was prepared (pH 7.4). Extracts were added to a hydrogen peroxide solution at a concentration of 100 g/mL in distilled water (0.6 mL, 40 mM). Ten minutes later, the hydrogen peroxide absorbance at 230 nm was measured in comparison to a blank solution made of phosphate buffer without hydrogen peroxide. The percentage of hydrogen peroxide scavenging of both *C. Swietenia* extracts and standard compounds were calculated.
percentage scavenged (H_2O_2)=((AC-AS)/AC) x 100

Superoxide radical scavenging activity: The scavenging ability of the crude extracts and flavonoids against chemically produced superoxide radicals was assessed by spectrophotometric analysis of the product on reduction of Nitro Blue Tetrazolium (NBT). Test samples were dissolved in DMSO and diluted in water to give a final concentration of 12% (v/v) for DMSO. Superoxide anions were generated in a nonenzymatic (Phenazinemethosulfate (PMS)/NADH) system. The reaction mixture contained 1 ml of test solution, 1.9 ml 0.1 M phosphate buffer, pH 7.4, 1 ml of 20 mM PMS, 156 mM NADH, and 25 mM of NBT in phosphate buffer, pH 7.4. After 2 min of incubation at 25°C, the colour was read on a Hitachi U-2000 spectrophotometer at 560 nm against blank samples, which contained no PMS. The percentage of scavenging activities (%) was calculated as follows:

Scavenging activities % (capacity to scavenge the superoxide radical)=(1-(absorbance of sample at 560 nm)/(absorbance of control at 560 nm)) ¥ 100

In vivo anti hyperthyroidism activity

In vivo evaluation of anti hyperthyroidism activity of the methanolic leaves extract of *Chloroxylon Swietenia* was carried out using the following model [22].

L-thyroxine induced hyperthyroidism

A total of five groups, control, disease control, test (2 groups), and standard will be selected for the study. Each group contains six wistar albino rats (thus a total of 30 animals) weighing 150 g-200 g. Group I animals received 0.1 mL saline every day for the entire study period and served as the normal control group. Rats in groups II were administered L-Thyroxine (L-T_4: 500 mg/kg per day, p.o) for 12 consecutive days to render them hyperthyroidic. Animals in group III and IV were treated with two doses of extract (200 mg/kg and 400 mg/kg per day, p.o.). The animals in group V received Propylthiouracil (PTU) as standard drug (10 mg/kg per day i.p) for duration of 17 days. After 17 days of treatment, the experiment was terminated. On the last day, the body weight of each animal was recorded. Blood was collected on 12th and 17th days and serum levels of T_3, T_4, and TSH were determined (Table 1) [23].

Table 1. Experimental study design of L-Thyroxine induced hyperthyroidism model.

S.No.	Groups	Treatment
1	Group-1	Normal control (saline)
2	Group-2	Disease control (L-Thyroxine–500 mg/kg, b.w, p.o) for 12 days
3	Group-3	L-Thyroxine-500 mg/kg, b.w, p.o for 12 days+MECS (200 mg/kg, p.o) for 17 days
4	Group-4	L-Thyroxine-500 mg/kg, b.w, p.o for 12 days+MECS (400 mg/kg, p.o) for 17 days
5	Group-5	L-Thyroxine–500 mg/kg, b.w, p.o for 12 days+Propylthiouracil (10 mg/kg, i.p) for 17 days

Statistical analysis

Results were expressed as mean ± SEM and analysed by one-way Analysis of Variance (ANOVA), followed by Dunnett's multiple comparison test. $p<0.05$ was the criterion for statistical significance.

RESULTS

Preliminary phytochemical analysis

The preliminary phytochemical investigation of methanolic leaf extract of *Chloroxylon Swietenia* showed presence of alkaloids, flavonoids, phenols, terpenoids.

Acute toxicity studies

Methanolic leaf extract of *Chloroxylon Swietenia* was tested on Swiss Albino mice up to a dose of 2000 mg/kg bd. wt. The animals didn't show any indications of toxicity or mortality up to 2000 mg/kg bd. wt. various morphological and behavioral characters were found to be normal. Thus, the extract was found to be safe up to 2000 mg/kg bd. wt.

Dose selection

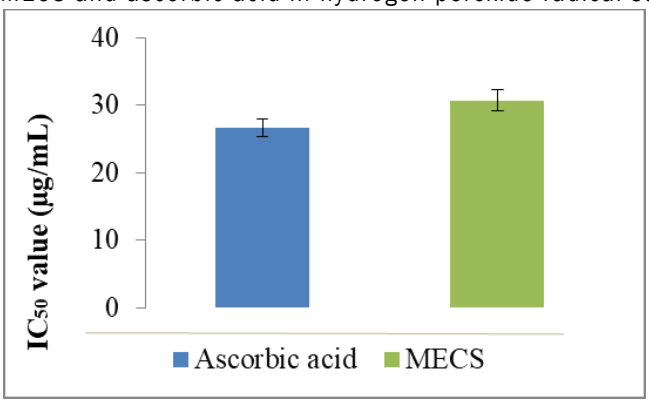
According to studies on toxicity, a dose of 2000 mg/kg bd. wt. was found to be safe, and the working doses were chosen as 200 and 400 mg/kg bd. wt.

The anti-oxidant activity of methanolic leaf extract of *Chloroxylon Swietenia* was carried out by hydrogen peroxide radical scavenging assay. MECS has shown increase in percentage inhibition of hydrogen peroxide radicals with increase in dose and its IC_{50} value was found to be 30.7 µg/ml (Table 2). The potential of the extract was comparable to that standard Ascorbic acid and its IC_{50} value was found to be 26.6 µg/ml (Figure 1).

Table 2. Hydrogen peroxide radical scavenging activity of MECS.

S.No	Compound	Concentration (µg/ml)	% Inhibition (MEAN±SEM)	IC_{50} (µg/ml)
1	MECS	10 20 30 40 50	16.6 ± 0.23 31.3 ± 0.35 48.7 ± 0.37 64.0 ± 0.54 71.0 ± 0.43	30.7
2	Ascorbic acid	10 20 30 40 50	18.6 ± 0.43 34.3 ± 0.34 56.2 ± 0.52 68.3 ± 0.40 74.8 ± 0.69	26.6

Figure 1. IC_{50} of MECS and ascorbic acid in hydrogen peroxide radical scavenging assay.

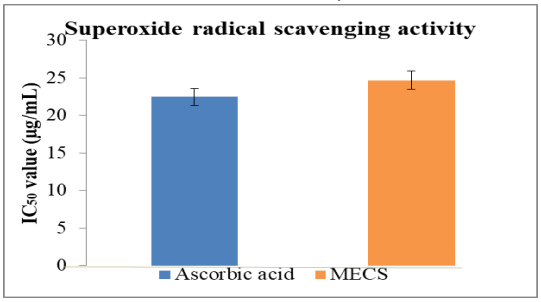


The anti-oxidant activity of methanolic leaf extract of *Chloroxylon Swietenia* was carried out by superoxide radical scavenging assay. MECS has shown increase in percentage inhibition of superoxide radicals with increase in dose and its IC_{50} value was found to be 24.7 µg/ml (Table 3). The potential of the extract was comparable to that of standard Ascorbic acid and its IC_{50} value was found to be 22.5 µg/ml (Figure 2).

Table 3. Superoxide radical scavenging activity of MECS.

S.No	Compound	Concentration	% inhibition	IC_{50}
1	MECS	10 20 30 40 50	17.9 ± 0.37 32.1 ± 0.40 60.7 ± 0.72 72.5 ± 0.83 77.0 ± 0.54	24.7
2	Ascorbic acid	10 20 30 40 50	20.2 ± 0.73 44.2 ± 0.39 65.5 ± 0.68 77.6 ± 0.38 83.7 ± 0.52	22.5

Figure 2. IC_{50} of MECS and ascorbic acid in superoxide radical scavenging assay.



L-Thyroxine induced hyperthyroidism

There was significant ($p<0.05$) decrease in the serum T_3, T_4 levels and increase in the TSH levels after administration of MECS (200 mg/kg and 400 mg/kg) compared to control group and was shown in Tables 4 and 5. Propylthiouracil at a dose of 10 mg/kg protected the rats against L-Thyroxine induced hyperthyroidism. Body weight of animals in the disease control group was found to decrease when compared to normal control indicating the induction of hyperthyroidism. Treatment with extract significantly increased the body weights of animal and the effect of 400 mg/kg extract was found to be comparable to that of standard propylthiouracil. Restoration of body weights with the treatment of the extract depicts its protective effect against hyperthyroidism (Figures 3-6).

Table 4. Effect of methanolic leaf extract of *Chloroxylon Swieteniaon* serum T_3 and T_4 levels.

Treatment groups	T_3 levels (µg /mL)		T_4 levels (µg/mL)	
	12th day	30th day	12th day	30th day
Normal control	1.06 ± 0.009	1.17 ± 0.033	9.65 ± 0.013	9.63 ± 0.011
Disease control	3.69 ± 0.011*	3.72 ± 0.101*	28.35 ± 0.011*	30.29 ± 0.201*
MECS (200 mg/kg)	3.33 ± 0.012*aA	2.80 ± 0.089*aA	26.14 ± 0.024*aA	20.5 ± 0.164*aA
MECS (400 mg/kg)	3.84 ± 0.014*aA	1.60 ± 0.149*a,ns	27.64 ± 0.109*aA	15.57 ± 0.156*aA
PTU (10 mg/kg)	3.56 ± 0.017*a	1.27 ±0.118ns,a	29.56 ± 0.017*a	11.71 ± 0.12*a
Values were expressed as mean ± SEM (n=6). One way ANOVA was used for the statistical analysis, followed by the Dunnett's multiple comparison test. Results were compared with control group (*=p<0.05); disease control (a=p<0.05) and standard (A=p<0.05); ns: non-significant.				

Figure 3. Effect of MECS on serum T_3 levels.

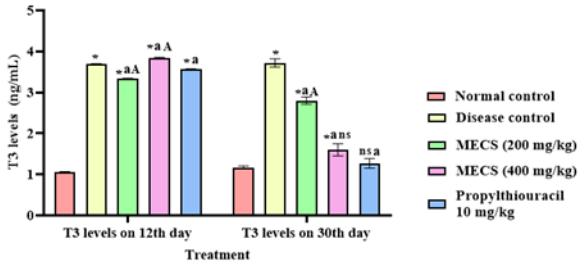


Figure 4. Effect of MECS on serum T_4 levels.

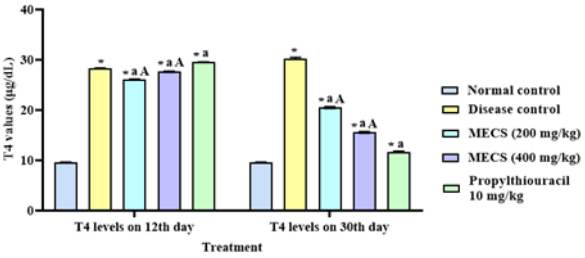


Table 5. Effect of MECS on serum TSH levels and body weight.

Treatment groups	TSH levels (µIU/mL)		Body weight (g)	
	12th day	30th day	12th day	30th day
Normal control	4.08 ± 0.135	4.15 ± 0.102	230.5 ± 0.096	234.4 ± 0.096
Disease control	1.36 ± 0.49*	0.91 ± 0.019*	152.3 ±0.105*	118.5 ± 0.076*
MECS (200 mg/kg)	1.62 ± 0.099*ns,A	2.46 ± 0.066*aA	124.4 ± 0.132*aA	173.4 ±0.132*aA
MECS (400 mg/kg)	1.91 ± 0.023*aA	2.60 ± 0.084*aA	118.2 ± 0.080*aA	203.5 ±0.116*aA
PTU (10 mg/kg)	2.41 ± 0.096*a	3.45 ± 0.1178*a	131.6 ± 0.096*a	220.6 ± 0.093*a
Values were expressed as mean ± SEM (n=6). One way ANOVA was used for the statistical analysis, followed by the Dunnett's multiple comparison test. Results were compared with control group				

(*=p<0.05); disease control ([a]=p<0.05) and standard ([A]=p<0.05); ns: non-significant.

Figure 5. Effect of MECS on serum TSH levels.

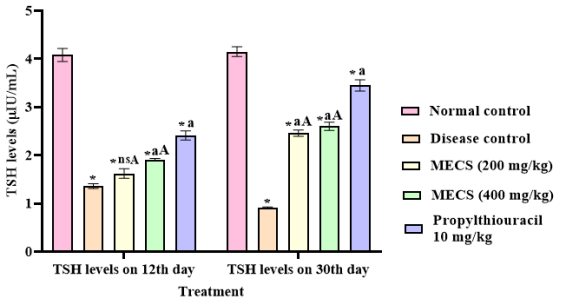
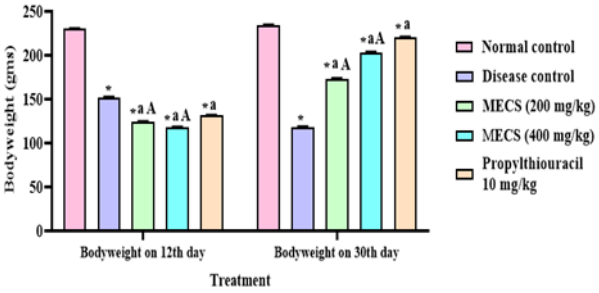


Figure 6. Effect of MECS on bodyweight.



DISCUSSION

Reactive Oxygen Species (ROS) generated endogenously or exogenously are associated with the pathogenesis of various diseases such as atherosclerosis, diabetes, cancer, arthritis, hyperthyroidism and ageing process. Normally the cellular antioxidant enzymes and free radical scavengers protect a cell from toxic effects of ROS. However, oxidative damage of cellular macromolecules occurs when generation of ROS overtakes the antioxidant defense and results in oxidative stress, which may be very damaging. ROS can attack lipids in cell membranes inducing oxidations that cause membrane damage such as membrane lipid peroxidation and a decrease in membrane fluidity. Free radicals readily combine and oxidize biomolecules such as carbohydrates, proteins and lipids making them inactive with subsequent damage to cells, tissues and organs. They also exert toxic effects including inactivation of enzymes and alteration of intracellular oxidation-reduction states. But DNA is probably the most biologically significant target of oxidative attack, and it is widely thought that continuous oxidative damage to DNA is a significant contributor to the age related development of major cancers.

ROS play a crucial role in normal thyroid function. Thyroid cells release oxidases, which catalyse ROS production. The generation of H_2O_2, which is required for iodination and the coupling of Iodotyrosine and Iodothyronine, as well as the synthesis of thyroid hormones are all regulated by inositols, which also play a role in normal thyroid function. Hypothyroidism may develop from inadequate thyroid hormone synthesis caused by an inositol deficit or impairment of the inositol cascades, which may be made worse by an increased requirement for inositols in response to high TSH levels. Treatment of hypothyroidism with myoinositol substantially reduces TSH levels. When used in combination with metformin and selenium, it has been shown to be more effective than inositol only therapy.

The synthesis of Thyroxine (T_4) and Triiodothyronine (T_3) catalyzed by Thyroid Peroxidase (TPO) in thyroid follicles is a very complex process involving ROS, notably, H_2O_2. In the first phase of thyroid hormone production, during iodide oxidation, ROS are already crucial. Additionally, thyroid hormones regulate metabolism by influencing mitochondrial activity. Because of the reliance on ROS in its function, the thyroid is particularly exposed to oxidative damage. Therefore, the antioxidant defense system of the thyroid must effectively regulate ROS production and scavenging.

Signalling functions in immune responses are initiated when molecular oxygen is oxidized to the reactive superoxide anion radical by the NADPH Oxidase (NOX) complex, itself an additional source of ROS. Subsequently, the superoxide is converted by Super Oxide Dismutase (SOD) to H_2O_2. Hydrogen peroxide is associated with a signalling function regulating cellular processes, due to its capacity to reversibly modify cysteine residues. The process alters redox signalling. Accumulation of excessive concentrations of H_2O_2 activates thiolate anion (Cys-S-) oxidation pathways. This is an irreversible process, resulting in permanent protein damage. Antioxidant systems serve a protective function, preventing intracellular accumulation of ROS by reversing the modification of cysteine residues.

In this study also, the methanolic leaf extract of *Chloroxylon Swietenia* exhibited a dose dependent inhibition of oxidation. Hence it may also be inferred that the methanolic leaf extract of *Chloroxylon Swietenia* possess scavenging activity against oxidizing agents like hydrogen peroxide and superoxide ions. In this context, *Chloroxylon Swietenia* can prove to be effective as a potent antioxidant agent since it is found to exhibit considerable *in vitro* antioxidant activity.

In present study the methanolic leaf extract of *Chloroxylon Swietenia* was studied for anti-hyperthyroidism activity by using L-Thyroxine induced hyperthyroidism. LT_4 stimulates thyroid activity and exerts its primary effect on the synthesis of the thyroid hormones, Thyroxin and Triidothyronine by blocking oxidative iodination within the thyroid gland itself. In addition, L-Thyroxine triggers the metabolism of thyroid hormones outside of the thyroid gland by interfering with the peripheral deiodination of LT_4.

The beneficial effect of MECS might be due to its inhibitory effect on the synthesis of thyroid hormones by favouring oxidative iodination in the thyroid gland. Phytoconstituents like flavonoids, alkaloids, phenols and terpenoids present in the extract might be responsible for the beneficial effect in hyperthyroidism.

CONCLUSION

The present study concludes that the methanolic leaf extract of *Chloroxylon Swietenia* possess significant anti-hyperthyroidism activity. The antioxidant potential of the active phytoconstituents might be responsible for the beneficial role of the extract in hyperthyroidism. Further study is required for isolation and identification of active constituents and to confirm exact mechanism.

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Conflict of interest

All authors have no conflicts of interest to declare.

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