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Potential Thyrotropic and Antihypercholesteronemic Activity Exhibited by Ethanolic Extract of *Crataeva nurvala* Bark

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ABSTRACT

Charaka, supports that the imbalance (*Ojus*) between the three bodily humours (doshas), along with the fat (*Meda*) leads to enlargement of the thyroid gland (*Galaganda*) and metabolic syndrome. This study aims to evaluate the effect of the ethanolic extract of *Crataeva nurvala* (CNet) bark, on free thyroxine (FT_4), thyroid stimulating hormone (TSH) and serum cholesterol (CHO) in Swiss albino female adult mice over conventional therapy. In this study, the animals were divided into four groups who were made hypothyroid using 6-propyl-2-thiouracil (PTU) for first 15 days and then Group I, treated with vehicle, Group II, treated with LT_4 (14.56 µg/kg), Group III, treated with CNet 400 mg/kg and Group IV treated with CNet 600 mg/kg (p.o.) for another 15 days. The variation in the biochemical parameters was recorded on Day 15th and Day 30th. The results were expressed as mean ± SEM, using two-way ANOVA followed by Bonferroni posttests. In comparison with the standard i.e. LT_4, significant (***P<0.001) thyroid stimulant activity was shown by CNet 600 mg/kg, with significant reduction in cholesterol levels whereas, less marked and erratic response with CNet 400 mg/kg was received. *Crataeva nurvala* was found effective at higher dose, that suggest its beneficial role in treating hypothyroidism and associated hypercholesteronemia.

INTRODUCTION

Levothyroxine (LT_4) is the standard replacement therapy in hypothyroidism, clinically that offers a similar life quality, whereas the psychological well being is compromised (Garber *et al.*, 2012; Petersen *et al.*, 1990; Jonklaas *et al.*, 2008; Saravanan *et al.*, 2002). Also, many physiological and pathological conditions can impair LT_4 absorption such as patient factors (compliance), certain foods (e.g. Grapes, coffee, soyabean, papaya etc.), age factor, drugs (e.g. Antacids containing aluminium, sucralfate, proton pump inhibitors, rifampicin, antiepileptics, etc.) gastrointestinal diseases (e.g. *Helicobacter pylori* infection, celiac disease). The principal adverse consequences of overtreatment are TSH suppression cardiovascular risk, skeletal or high risk of fracture, especially postmenopausal women, however, bone density does not reduce on short term administration and possible affective disturbances (Rees-Jones and Larsen, 1977; Razvi *et al.*, 2012; Schneider *et al.*, 2012; Ross, 1993; Biondi *et al.*, 1994; Botella-Carretero *et al.*, 2003).

Crataeva nurvala Buch-Ham, belonging to the family, Capparidaceae, synonymously called as C. *magna* (Lour.) DC., *C. religiosa* Hook. F and Varuna (Khare, 2007; Daniel, 2006). It is reported to possess analgesic, neuroprotective, antiarthiritic, anticancer, antidiabetic, cardioprotective, anti-inflammatory, antioxidant, hepatoprotective, nephroprotective activities (Khattar and Wal, 2012).

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In Ayurveda, thyroid disorders are discussed under the term *"Galaganda"* (enlarged thyroid gland). Ayurveda supports use of Varuna leaves, stem bark and root bark in regulating equilibrium among three doshas (bodily humours) *Vata* (air), *Pitta* (earth) and *Kapha* (mucous or water), whose imbalance leads to hormonal imbalance (*Ojus*), most commonly thyroid disorders (Kaur *et al.,* 2016). Traditionally it is also believed to be used for treating cancer, paralysis, thyroid problems etc. (Narayana and Subhose, 2005). So, it was hypothesized that this plant can have beneficial effects in hypothyroidism.

To the best of our knowledge, no scientific data regarding the thyrotropic activity of ethanolic extract of *C. nurvala* bark (CNet) in preclinical studies in hypothyroid mice is published. This study aimed to evaluate the thyrotropic and antihypercholesterolemic effect of the CNet in mice, whose thyroid status was disrupted by using (6-propyl-2-thiouracil) PTU, an antithyroid drug, that inhibit the thyroid gland and decline the thyroid hormone synthesis via inhibiting thyroid peroxidase (TPO), iodothyronine deiodinases type I (DIO1) and inhibiting thyroid receptor (TR) mediated transcriptional activities by dissociating the nuclear coactivators and by recruitment of corepressors present at the glandular levels thus causing primary hypothyroidism i.e. reducing the levels of FT_4 with concomitant increase in TSH (Moriyama *et al.,* 2007).

MATERIAL AND METHODS

Chemicals

6-Propyl-2-thiouracil (PTU), was supplied by Sigma-Aldrich Chemeie GmbH, Levothyroxine Sodium Tablets (Eltroxin-GSK) and all the other chemicals used in extraction and phytochemical screening were of reagent grade.

Animals

Swiss Albino female mice, aged between 3-5 months weighing 25-35 g, procured from Panacea Biotec Ltd, Lalru (140501), India and were housed in polypropylene cage, kept standard laboratory conditions (temperature 25±2º C, relative humidity 30-70% with 12/12h night/dark cycle), were fed with standard pellet diet procured from Shree Jagdambey Feed Industries, Moga, Punjab and water *ad libitum* for acclimatization period of one week before study.

Ethical approval

The study protocol was duly approved by the Institutional Animal Ethics Committee (IAEC) [Protocol no.: **IAEC-CTIPS/2015/VII/0042 (PCL-M)**] of the Institute under the guideline of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment & Forests, New Delhi.

Procurement and preparation of the CNet

The dried stem bark of *C. nurvala* (3.5 kg) was procured from Herbal Health Research Consortium Pvt. Ltd. Amritsar (Lot No. VRN-024, Certificate of Analysis A. R. No. 06/2015/IH/086, in compliance with Q.S.I.M.P. Volume 10, Page no. 106-108). A voucher (HHRC/RT/0416/15-16) and plant specimen has been submitted to the department of Pharmacology, of our college for future reference.

The bark extract was prepared using a repeated maceration technique (Hussain *et al.,* 2013). The shade dried bark of *C. nurvala* (3.5 kg) was rendered dust free and the size was reduced. The coarse powdered material (mesh #16) was macerated with 95% ethanol (1 kg in 3 l), the soaked material was strained through a double layered muslin cloth and the marc was pressed. The two filtrates were then combined and then clarified by filtering through Whatman No. 1 filter paper. This process was repeated every third day for 12 days. The filtrates from the four macerations were then combined and the solvent was recovered under vacuum at 37^{o}C and the extract was concentrated to obtain brown pasty mass. The percentage yield was found to be 1.37 %. The suspension (20 mg/ml) is prepared with 1 % of Gum Acacia solution and stored at 2-8^{o}C in amber colored bottle.

Phytochemical screening

The phytochemical identification of CNet was carried out using qualitative test like Keller-Killiani test, lead acetate test, sodium hydroxide test, silver nitrate test, Salkowski test, Lieberman's test, froathing test etc.

Evaluation of thyrotropic activity of *C.nurvala* in PTU induced hypothyroidism

Mice of 25-35 g were divided into four groups, administered PTU (10 mg/kg orally) for 15 days and then treated with vehicle, standard and test drug for next 15 days (Panda and Kar, 2005).

Group I, PTU (10 mg/kg) + VEH (Negative control)

Group II, PTU (10 mg/kg) + LT_4 (14.56 µg/kg) (Standard)

Group III, PTU (10 mg/kg) + CNet 400 mg/kg

Group IV, PTU (10 mg/kg) + CNet 600 mg/kg

C. nurvala has shown promising hypocholesteronemic activity in other animal model, moreover, literature sources support its neuroprotective, hepatoprotective and nephroprotective activities at different doses. However, two dose levels i.e. 400 and 600 mg/kg were evaluated in this study (Sikarwar and Patil, 2012; Bhattacharjee *et al.*, 2014; Panda *et al.*, 2014; Shelkea *et al.*, 2011).

The variation in the FT_4, TSH and CHO were analyzed via comparing Day 15th with Day 30th results in individual groups. Dosage administration was done every day between 9.00 am to 10.00 AM to avoid circadian variation.

Serum preparation

Blood sampling was done after 24 hours of the last dose on Day 15th and Day 30th via retro-orbital method. The samples were allowed to clot at room temperature and then centrifuged for

20 min to separate the serum. The serum samples were stored at -20°C to -80°C until assayed for biochemical investigations.

Biochemical estimation in serum

Serum FT_4, TSH was determined by ELISA as per the provided protocol by ERBA Lachema s.r.o., Czech Republic and Calbiotech Inc., Austin, CA on Day 15th and Day 30th. Serum CHO levels were determined using ERBA Mannheim GmbH, Germany autoanalyser kit.

Statistical analysis

The results are expressed as mean ± SEM, (n=6), Where ***P<0.001, **P<0.01 and *P<0.05 (PTU+VEH as control at Day 30th) and $^{###}P$<0.001, $^{##}P$<0.01 and $^{#}P$<0.05 (PTU+LT4 as control at Day 30th) for serum biochemical estimation, using Two-way RM ANOVA followed by a Bonferroni post test to compare replicated means by row in each column representing different points of time.

RESULTS

Phytochemical analysis

The CNet was screened for preliminary phytochemical identification tests which revealed the presence of mainly cardiac glycosides, flavonoids, alkaloids, terpenoids and saponins.

Effect on FT_4

The administration of PTU, an antithyroid drug for 15 days in all groups, was associated with low serum FT_4 levels, that significantly rose with the administration of standard drug, LT_4 i.e. 2.343 ng/dl (**P<0.01), test drugs CNet 400 and CNet 600 i.e. 3.258 ng/dl and 3.709 ng/dl (***P<0.001) at day 30th in comparison with PTU+VEH. Rise in FT_4 in PTU+CNet 600 was even considerably higher than standard, i.e.PTU+LT_4 ($^{#}P$<0.05) (Table 1, Figure 1).

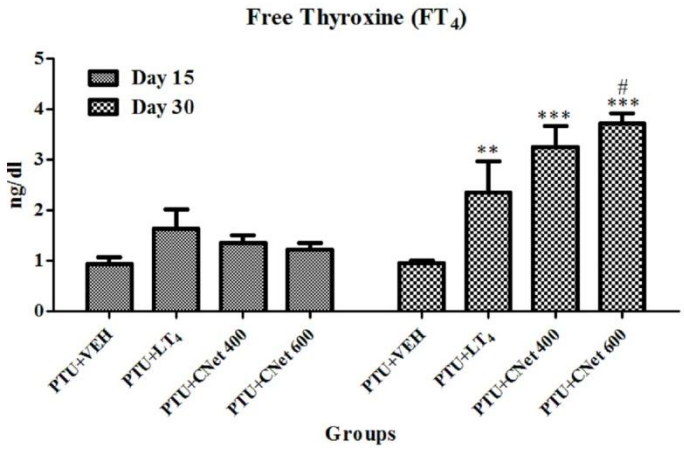

Fig. 1: Effect of *C.nurvala* on free thyroxine
The results are expressed as mean ± SEM, (n=6), Where ***P<0.001 and **P<0.01 (PTU+VEH as control at Day 30th) and $^{#}P$<0.05 (PTU+LT_4 as control at Day 30th), using Two-way RM ANOVA followed by a Bonferroni post test.

Effect on TSH

The administration of PTU for 15 days led to increase in TSH levels in PTU+VEH and PTU+CNet 600, whereas less rise was observed in other two groups. The administration of CNet 600 declined significantly the levels of TSH in PTU+CNet 600 (*P<0.05) i.e. 0.209 µIU/ml w.r.t PTU+VEH, but the levels were found to be raised in an erratic pattern in PTU+CNet 400 ($^{#}P$<0.05) in comparison with standard group (Table 1, Figure 2). However, the administration of vehicle and LT_4 showed no significant change in levels of TSH in PTU+VEH and PTU+LT_4 at day 30th.

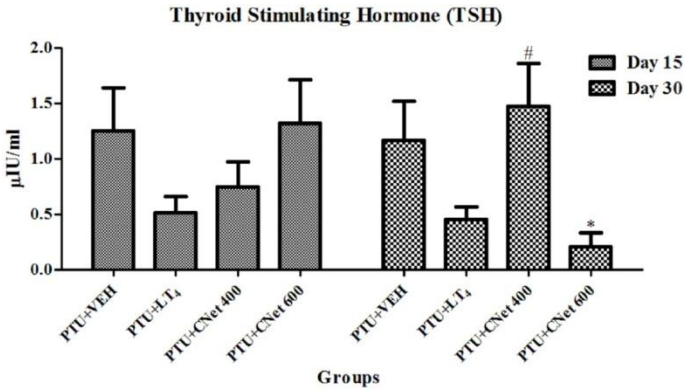

Fig 2: Effect of *C.nurvala* on thyroid stimulating hormone
The results are expressed as mean ± SEM, (n=6), Where *P<0.05 (PTU+VEH as control at Day 30th) and $^{#}P$<0.05 (PTU+LT_4 as control at Day 30th), using Two-way RM ANOVA followed by a Bonferroni post test.

Effect on CHO

The administration of PTU elevated the levels of cholesterol, that found to be less in PTU+CNet 400 and PTU+CNet 600, w.r.t. negative control (***P<0.001) and standard group i.e. 36.578 mg/dl ($^{##}P$<0.01) and 29.585 mg/dl ($^{###}P$<0.001) at Day 30th (Table 1, Figure 3). However, the levels elevated in PTU+VEH and PTU+LT_4.

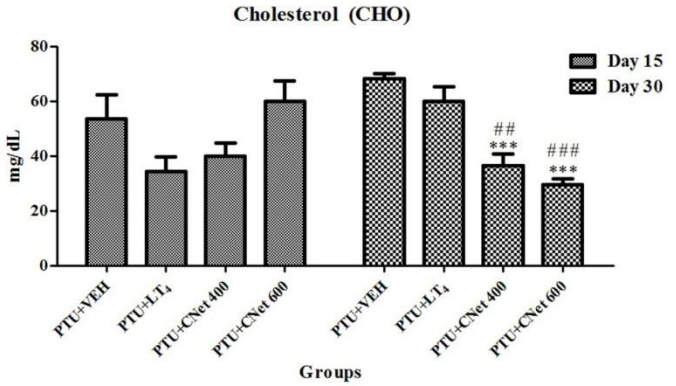

Fig 3: Effect of *C.nurvala* on cholesterol
The results are expressed as mean ± SEM, (n=6), Where ***P<0.001 (PTU+VEH as control at Day 30th) and $^{###}P$<0.001 and $^{##}P$<0.01 (PTU+LT_4 as control at Day 30th), using Two-way RM ANOVA followed by a Bonferroni post test.

Table 1: Effect of *C. nurvala* on thyroid parameters and cholesterol in hypothyroid mice at day 15th and 30th.

Groups		PTU+VEH	PTU+LT_4	PTU+CNet 400	PTU+CNet 600
Parameter	**Day**				
FT_4 (ng/dl)	15	0.941±0.119	1.630±0.379	1.354±0.142	1.221±0.136
	30	0.946±0.055	2.343±0.626**	3.258±0.411***	3.709±0.204***#
TSH (µIU/ml)	15	1.256±0.387	0.512±0.145	0.747±0.230	1.319±0.392
	30	1.168±0.353	0.451±0.113	1.340±0.368#	0.209±0.124*
CHO (mg/dl)	15	53.677±8.658	34.340±5.435	40.132±4.763	60.038±7.556
	30	68.169±2.066	60.110±5.177	36.578±4.116***##	29.585±2.251*** ###

The results are expressed as mean ± SEM, (n=6), Where ***P<0.001, **P<0.01 and *P<0.05 (PTU+VEH as control at Day 30th) and ###P<0.001, ##P<0.01 and #P<0.05 (PTU+LT_4 as control at Day 30th), using Two-way RM ANOVA followed by a Bonferroni post test.

DISCUSSION

Various studies supported the presence of cardiac glycosides (Sinha *et al.* 2013), flavonoids, alkaloids (Ahmad *et al.* 1987, Sinha *et al.* 2013, Bhattacharjee *et al.* 2014), terpenoids and saponins (Rao *et al.* 2011) in stem bark of *C. nurvala*.

In this study, the ethanolic extract of *C. nurvala* was evaluated for it thyrotropic effect in PTU induced hypothyroidism, that is an antithyroid drug, that decline the thyroid hormone synthesis via inhibiting thyroid peroxidase (TPO), iodothyronine deiodinases type I (DIO1) that peripherally convert T_4 to T_3 (Bianco *et al.,* 2002), in thyroid gland, liver etc. and inhibiting thyroid receptor (TR) mediated transcriptional activities at the glandular levels thus causing primary hypothyroidism i.e. reduced FT_4 levels with concomitant increase in TSH (Moriyama *et al.,* 2007; Geffner *et al.,* 1975).

Out of the two selected doses, CNet 600 had shown significant thyrotropic activity via raising FT_4 levels and reducing TSH levels. From previous studies, it was concluded that stimulation of Deiodonases (DIOs) reduces secretion of TSH (Baur *et al.* 2000). However, administration of CNet 400 raised the FT_4, with concomitant increase in TSH, which indicate that the lower dose, i.e. CNet 400 lack the stimulatory effect on DIO1 mediated T_4 to T_3 conversion inhibited by PTU. Similar study on *Moringa oleifera* and *Aegle marmelos*, also showed the extract raised the T_4 levels but decreased T_3 levels in female mice suggesting the inhibitory effect of extract on peripheral conversion of T_4 to T_3 (Tahiliani and Kar, 1999). However, not determining the T_3 levels was limitation of our study.

An earlier study on lupeol and its ester lupeol linoleate, pentacyclic triterpenes derived from *C. nurvala* bark reduced the lipid abnormalities and hypercholesterolemia in rats fed with high cholesterol diet (Sudhahar *et al.* 2006). On the similar grounds in our study, both CNet 400 and CNet 600 containing triterpenes, shown reduction in cholesterol levels in comparison with LT_4 treated group which can control CHO levels on long term therapy, along with dietary restriction and with use of hypolipidemic agents only (O'Brein *et al.,* 1993; Tanis *et al.,* 1996) and vehicle treated hypothyroid group. Mechanistically also, TH have been found to have crosstalk with other nuclear receptors including farnesoid X receptor (FXR), liver X receptor (LXR), peroxisome proliferator-activated receptor (PPAR), and PPARγ coactivator (PGC-1α) that regulate cholesterol levels indirectly (Oppenheimer *et al.,* 1991; Liu and Brent, 2010).

CONCLUSION

The results of the present study indicates that in comparison with the standard treatment, i.e. levothyroxine, CNet 600 mg/kg, showed stimulatory effects on the thyroid gland as evident from raised FT_4 levels and decreased TSH levels alongwith significant reduction in cholesterol levels, suggesting its beneficial role in treating hypothyroidism, whereas, less marked and erratic response was shown by CNet 400 mg/kg.

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