



IN- VIVO ANTIHYPERLIPIDEMIC ACTIVITY OF ETHANOLIC FRUIT EXTRACT OF *COCCINIA GRANDIS* LINN. AGAINST DEXAMETHASONE INDUCED HYPERLIPIDEMIA

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ABSTRACT

Key Words

Hyperlipidemia, *Coccinia grandis* Linn., Atorvastatin, Dexamethasone

Objectives: Herbal medicines are found to be effective in the treatment of various ailments but the major lacuna is lack of proper scientific validation. The present study is aimed at investigating *Coccinia grandis* Linn., fruit extract for the antihyperlipidemic activity in dexamethasone induced hyperlipidemia. **Materials and Methods:** Ethanolic extracts of *Coccinia grandis* Linn., fruits were evaluated for antihyperlipidemic activity in dexamethasone induced hyperlipidemia. Results were compared between the effects of *Coccinia grandis* Linn. fruit extract and a known anti-hyperlipidemic drug Atorvastatin (2mg/kg b.w). The results of the study were expressed as mean± S.E.M. and data was analyzed by using one way analysis of variance test (ANOVA) followed by Dunnett's t-test for multiple comparisons. Values with $P < 0.05$ were considered to be significant. **Results:** Oral administration of 400 mg/kg body wt. of the ethanolic extract of *Coccinia grandis* Linn. fruit exhibited a significant reduction ($P < 0.01$) in serum lipid parameters like total cholesterol (CH), triglycerides (TGs), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and increase in high density lipoprotein (HDL) when compared to hyperlipidemic control statistically. This plant extract was found to possess better antihyperlipidemic potential as compared to the standard control. **Conclusion:** Our results demonstrated that ethanolic extract of *Coccinia grandis* Linn. fruits possessed significant antihyperlipidemic activity, and hence it could be a potential herbal medicine as adjuvant with existing therapy for the treatment of hyperlipidemia.

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INTRODUCTION

Hyperlipidemia is a secondary metabolic dysregulation associated with diabetes. Besides the cause effect relationship with diabetes, elevated serum levels of triglycerides (TGs), cholesterol (CH) and low density lipoproteins (LDL) are major risk factors for the premature development of cardiovascular diseases like atherosclerosis, hypertension, coronary heart disease, etc [1]. Atherosclerosis is one of the leading causes of death in the world both in developed countries and as well as developing countries like India [2]. The elevated levels of LDL and very LDLs (VLDLs) associated with

CH and TGs is one of the primary risk factors for atherosclerosis [3]. Elevated lipid levels result from increased absorption through the gut or enhanced endogenous synthesis and therefore two ways are feasible to reduce hyperlipidemia; to block endogenous synthesis or to decrease absorption. The two factors can be assessed in normal rats without artificial diets. Anti-hyperlipidemic agents having various pharmacological actions are being tested clinically [4]. One of the best approaches for treating hyperlipidemia is by targeting the

atherogenic process [5]. A wide number of allopathic antihyperlipidemics are available in the market, but they were not popularized due to their side effects and contraindications. To overcome that recently herbal hypolipidemics have gained importance to fill the voids [6]. *Coccinia grandis* Linn. Voigt is one such medicinal plant explained in Indian materia medica (*Dravyaguna* Sastra.) The fruit of *Coccinia grandis* Linn. voigt is used as vegetable when green and eaten fresh. Each part of the plant is having considerable medicinal value and therefore used in indigenous system of medicine for treating various disorders. In Ayurveda *Cocciniagrandis* L. Voigt has been well documented for its therapeutic potentials and described in *Vamanopagadashemaniand urdhvabhagaharavarga* [7]. It is an edible perennial climber distributed in tropical Asia, commonly found in Sri Lanka, India and Pakistan [8]. The chemical composition of plant is carbohydrates, total protein, lipids, total phenol, vitamin C, β -carotene and minerals (like sodium, potassium, phosphorous, iron and calcium). The fruit of this plant contains β - Amyrin acetate, β - Sitosterol, β - Carotene, Cucurbitacin B, Lycopene, Lupeol, Taraxerol, and Taraxerone [9]. The pharmacological actions of this plant is hypoglycemic [8], Cure sores on tongue, analgesic and antipyretic [10], hepatoprotective, tuberculosis, eczema and anti-inflammatory. The complete research works done on this plant are medicinal & nutritive value [11], anti-bacterial [12], antioxidant, cell proliferative properties [13], and *in vivo* antitussive activity [14].

MATERIALS AND METHODS

Collection and Preparation of plant material

Coccinia grandis Linn. fruits were collected in the month of December 2019 from Tirupati market, Tirupati, in chittoor district, A.P, India. The fruits were washed with tap water, shade dried at room temperature and then subjected to size reduction to a coarse powder by using wiley mill. The powdered fruit material was packed in a Soxhlet apparatus and extracted with ethanol. The extraction was continued until the color of the solvent in the siphon tube became colorless. The ethanolic extract was concentrated in a rotary evaporator and this concentrated ethanolic extract of fruits of *Coccinia grandis* Linn., (EECG) was used for the *in vivo* studies [15].

Experimental animals: Male Wister rats (150-180 gm) were used and they were purchased from Invivo biosciences, Bangalore. They were kept in polypropylene animal cages and fed with normal rodent pellet diet and water ad libitum. All the animals were exposed to an alternate cycle of 12 h of darkness and 12 h of light. The experimental protocols were designed as per the guidelines of the Institutional Animal Ethic Committee (IAEC) which is certified by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India (1995/PO/Re/S/17/CPCSEA dt: 14.12.2019).

Acute toxicity studies

Acute toxicity study was performed for the EECG according to OECD guidelines [16]. EECG were administered orally as a single dose to mice at different dose levels of 5, 50, 300, 1000 and 2000mg/kg BW. Animals were observed periodically for the assessment of toxicity and death within 24h and then daily for 14 days. Fruits of *Coccinia grandis* Linn., produced no mortality at 2000mg/kg. Hence 1/10th (200mg/kg) and 1/5th (400mg/kg) of this dose were chosen for the antihyperlipidemic study.

Pharmacological evaluation

Dexamethasone-induced hyperlipidemia in rats [3]: Hyperlipidemia will be induced using dexamethasone; a glucocorticoid is known to evoke plasma lipid elevation. Dexamethasone (10 mg/kg/day, subcutaneous) was administered to rats for 8 days to induce hyperlipidemia.

Procedure: Experimental animals were divided into five groups each group contains five rats and the treatment schedule for 8 days as follows, **Group I:** Control (Vehicle, normal normal saline 1ml/kg *p.o.*), **Group II:** Hyperlipidemic (Disease) control (Dexamethasone 10 mg/kg/day, *s.c.*), **Group III:** Standard control (Dexamethasone + Atorvastatin 2mg/kg *i.p.*), **Group IV:** Low dose EECG (Dexamethasone + EECG 200mg/kg *p.o.*), and **Group V:** High dose EECG (Dexamethasone + EECG 400mg/kg *p.o.*). After the experimental period, the overnight fasted experimental rats were sacrificed by decapitation under light ether anesthesia and blood was collected. Serum was separated, and lipid profiles (biochemical parameters) like total cholesterol (TC), triglycerides (TGs), high density lipoprotein (HDL), very low density

lipoprotein (VLDL) and low density lipoprotein (LDL) were analyzed.

Statistical evaluation: All the values were expressed as Mean \pm S.E.M (n=5 in each group). The data were statistically analyzed by one-way ANOVA followed by Dennett's t-test, and value $P < 0.05$ was considered to be significant.

RESULTS

On acute toxicity studies: The EECG was found to be safe since no animal was died even at the dose of 2000mg/kg when administered orally and the animals did not show any gross behavioral effects.

On hyperlipidemic parameters: The present study was carried out to assess the antihyperlipidemic effect of EECG against dexamethasone induced hyperlipidemia in male Wister rats. After 8 days treatment of dexamethasone, a significant ($P < 0.05$) rise in lipid and lipoprotein levels were observed in dexamethasone induced group when compared to the normal group. When EECG was evaluated for its activity, it showed a statistically significant activity ($P < 0.01$) in reduced hyperlipid parameters at doses of 200 and 400 mg/kg by oral administration.

Effect of ethanolic extract of fruits of *Coccinia grandis* Linn. on TC and TGs level in hyperlipidemicrats: Hyperlipidemic rats showed an increase in total cholesterol and triglycerides, whereas the control rats TC and TGs remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Coccinia grandis* Linn., for 8days significantly ($P < 0.01$) reduced the levels and brought back total cholesterol and triglycerides towards normal. The results were tabulated in Table 1.

Effect of ethanolic extract of fruits of *Coccinia grandis* Linn., on HDL level in hyperlipidemicrats: Oral administration of dexamethasone significantly ($P < 0.05$) decreased HDL whereas in control rats HDL was remained same. Atrovastatin and ethanolic extract of fruit of *Coccinia grandis*Linn., administered for 8 days significantly ($P < 0.01$) increase the levels of HDL and brought back HDL towards normal (table 2).

Effect of ethanolic extract of fruits of *Coccinia grandis* Linn, on VLDL level in hyperlipidemic rats: Animals treated with dexamethasone showed a significantly ($P < 0.05$) elevated levels of LDL and VLDL when compared to control group. EECG 200 and 400 mg/kg showed a significant ($P < 0.01$) decreased LDL and VLDL when compared to Group II and Group III. The results were depicted in table 3.

DISCUSSION

Objective of the present study was to screen the antihyperlipidemic activity of *Coccinia grandis* Linn. fruit extract. Hyperlipidemia characterized by abnormally elevated serum triglycerides, total cholesterol, LDL and VLDL, is an established risk factor for the development of coronary artery disease (CAD). Hyperlipidemia will be induced using dexamethasone; a glucocorticoid is known to evoke plasma lipid elevation. Glucocorticoid hormonal level elevation induces the plasma lipid concentration but varies from species to species. Few synthesis of triacylglycerol in the liver is stimulated by the injection of glucocorticoid in rats and consequently may lead to the accumulation of fatty liver. The stimulation of the TG production could lead to increased secretion of VLDL. Increasing VLDL secretion has been reported when dexamethasone is injected for several days in rats. The increase in TG level induces imbalance in lipid metabolism leads to hyperlipidemia [17, 18]. In the present study, Dexamethasone induced model shows asignificant increase in TC and TGs levels in rats treated with Dexamethasone group as compared to normal control group. Ethanolic extracts of *Coccinia grandis* Linn was evaluated followed by s.c. administration of dexamethasone significantly reduces TC, TGs, LDL, VLDL and significantly shows improvement in HDL. Cholesterol is synthesized in all animal tissue. Its important relates to its role in the stabilization of membrane structures because of its rigid planar structure. Increased amount of cholesterol leads to cardiovascular diseases (CVD) [19]. The plasma cholesterol was reduced remarkably on treating the dexamethasone rats with EECG. The lipid lowering effects may be due to the presence of plant sterol. Plant sterol reduces the absorption of cholesterol and thus increases the fecal excretion of steroids that results in decrease of body lipids reduction 1% cholesterol produces a 2-3% reduction in CVD risk [20].

Table 1: Effect of ethanolic extract of *Coccinia grandis* Linn. on TC and TGs level in hyperlipidemic rats

S.No	Parameters	Group I	Group II	Group III	Group IV	Group V
1	TC	90±3.09	232±2.35 ^a	102±2.37 ^b	117±2.61 ^b	102±2.16 ^b
2	TGs	65.8±2.95	210±5.10 ^a	75±2.72 ^b	98±3.27 ^b	82±2.32 ^b

Values are as expressed as mean ± SEM (n=5); a. *P*<0.05 compared with control; b. *P*<0.01 compared with disease control.

Table 2: Effect of ethanolic extract of *Coccinia grandis* Linn. on HDL level in hyperlipidemic rats

S.No	Parameter	Group I	Group II	Group III	Group IV	Group V
1	HDL	23.4±0.97	13.6±1.29 ^a	26.18±1.75 ^b	20±1.19 ^b	22.63±1.34 ^b

Values are as expressed as mean ± SEM (n=5); a. *P*<0.05 compared with control; b. *P*<0.01 compared with disease control.

Table 3: Effect of ethanolic extract of *Coccinia grandis* Linn. on LDL and VLDL level in hyperlipidemic rats

S.No	Parameters	Group I	Group II	Group III	Group IV	Group V
1	LDL	50.5±3.80	183.7±2.67 ^a	58.36±3.42 ^b	82±2.25 ^b	62.1±2.29 ^b
2	VLDL	13.6±0.51	41.26±0.41 ^a	14.8±0.28 ^b	20.13±0.47 ^b	15.6±0.34 ^b

Values are as expressed as mean ± SEM (n=5); a. *P*<0.05 compared with control; b. *P*<0.01 compared with disease control.

The excess of fat diet elevated the TGs level which is one of the known causes of hardening of arteries. HDL is known as the good cholesterol it has reversed the transport function. It carries cholesterol away from the coronary categories and drops it off at the liver. HDL is directly anti-androgenic, and it is believed to remove cholesterol from the developing lesions. LDL is a risk factor and plays a role at several steps of atherosclerosis. A decrease in oxidative stress and protection of LDL from oxidation might, therefore, be a strategy with great promise for prevention of atherosclerosis associated CVD. VLDL production is directly related to the body fat. Severe elevation in the VLDL cholesterol leads to hypercholesterolemia. TGs are mainly stored in the adipose tissue. The plasma lipoproteins are major sources of fatty acid to synthesis triacylglycerol. The excess of fat diet increased the TG level which is one of the causes of hardening of arteries [21]. Atorvastatin is a HMG Co A reductase inhibitor which is used as standard drug. The elevation of serum cholesterol

levels following *s.c.* injection of dexamethasone solution to rats was due to stimulation of 3-hydroxy-3-methylglutaryl-Co-enzyme A (HMG-Co A) reductase activity in the liver by the dexamethasone. Ethanolic extract of *Coccinia grandis* Linn. shows lowering of TG levels by increasing the lipoprotein lipase activities. The cholesterol lowering effect of *Coccinia grandis* extract were observed in rats treated with the dexamethasone by the inhibition of HMG Co A reductase inhibition. The results were shown that ethanolic extracts of *Coccinia grandis* Linn of the plant have ability to reduce the risk of hyperlipidemia. The chemical constituent of *Coccinia grandis* Linn plant contains carbohydrates, total protein, lipids, total phenol, vitamin C, β-carotene and minerals (like sodium, potassium, phosphorous, iron and calcium). The fruit of this plant contains β- Amyrin acetate, β-Sitosterol, β- Carotene, Cucurbitacin B, Lycopene, Lupeol, Taraxerol, and Taraxerone. From the proof scientific evidence it reveals that the presence of above phytoconstituents in the

fruit has excellent antioxidant, anti-inflammatory, anti-atherogenic property which may be responsible for lowering of TC, TG, LDL and VLDL levels and reduces the cardiovascular disease by increasing HDL levels. *Coccinia grandis* Linn. fruit extract (200mg/kg) were shows less potent but at the dose of 400 mg/kg shows more potent antihyperlipidemic activity.

CONCLUSION

The results obtained from the pharmacological screening have led to the conclusions that, ethanolic extract of *Coccinia grandis* Linn. Have significant antihyperlipidemic activity. Hence it can be referred as antihyperlipidemic therapeutic agent or adjuvant therapy for the treatment of hyperlipidemia.

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