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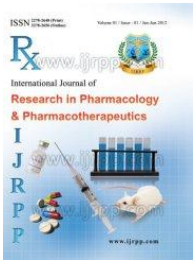

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Anti-hyperlipidemic effect of *Caralluma lasiantha* extract on hyperlipidemia induced by cafeteria-diet in *In vivo* model

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ABSTRACT

Hyperlipidemia is the greatest risk factor of coronary heart disease. Currently available anti-hyperlipidemic drugs have been associated with side effects. Herbal treatment for hyperlipidemia has less/no side effects and is relatively cheap and locally available. In the growing burden of atherosclerosis, the present study was designed to evaluate and to compare the anti-hyperlipidemic effect of *Caralluma lasiantha* extract with Chromium Picolinate on hyperlipidemia induced by Cafeteria-Diet in *Wistar albino* rats. Hyperlipidemia was induced by giving Cafeteria-Diet for three months, simultaneously *Caralluma lasiantha* (10, 20, and 40 mg/kg b.w.) & Chromium Picolinate (10 mg/kg b.w.) were administered for each group respectively once every day by oral route throughout the experimental period and serum lipid levels were estimated once every month. There was a marked decrease in total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels. Also there was a significant increase in high density lipoprotein (HDL) levels after the treatment with *Caralluma lasiantha* extract compared to untreated experimental rats and the lipid profile was comparable with Chromium Piclinate treared rats. The present work indicated that *Caralluma lasiantha* extract significantly suppressed the Cafeteria-Diet induced hyperlipidemia in *Wistar albino* rats, suggesting the anti-hyperlipidemic activity of the *Caralluma lasiantha*.

Keywords: *Caralluma lasiantha*, Anti-hyperlipidemic, Chromium Picolinate, Cafeteria-Diet.

INTRODUCTION

Hyperlipidemia is characterized by an elevation of the plasma lipids, including total cholesterol, low density, and very low-density lipoprotein and decreased high-density lipoprotein levels. An elevation of plasma lipids may be caused by a primary genetic defect or secondary to diet, drugs or diseases. Hyperlipidemia associated lipid disorders are considered to cause atherosclerotic cardiovascular disease. [1] Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions, such as Coronary Heart Disease (CHD), ischemic cerebrovascular disease and peripheral vascular disease. [2] Despite differences in

lipoprotein distribution and metabolism between humans and rats, hyper-lipidemic rat models are extensively used in lipid research**.** [3]

Hyperlipidemia can be produced in experimental animals like rats by offering them diet that is high in fat, sugar, or both. The most pronounced effects are obtained when the animals are offered an assortment of tasty fat and sugar-rich foods marketed for human consumption, which is referred to as cafeteria diet (CD). Hence cafeteria diet fed rat model is used to emulate hyperlipidemia-like condition in humans, in order to evaluate and to compare the effects of *Caralluma lasiantha* (CL) with Chromium Picolinate (Cr.Pic) in hyperlipidemia.

Chromium is an essential trace mineral that occurs naturally in small amounts in some foods, including brewer's yeast, lean meat, cheese, pork kidney and whole grain bread and cereals. It is poorly absorbed by the human body but is known to play an important role in the metabolism of carbohydrate, fat and protein. [4] Inadequate amounts of Chromium may result in improper functioning of the metabolic process and lead to a number of physiological disorders that increase risk for diabetes and cardiovascular diseases including elevated circulating insulin, glucose, triglycerides, total cholesterol, reduced HDL-cholesterol and impaired immune function. [5] Chromium Picolinate effectively improves the altered lipid profile in experimental diabetes. [6] Chromium Picolinate (Cr.Pic) is a stable compound for better absorption and it contains trivalent chromium which is chelated to three picolinic acid molecules. [7] Considering this background, Chromium Picolinate (Cr.Pic) has been used in our study to evaluate and to compare anti-hyperlipidemic effect of *Caralluma lasiantha* (CL) by animal model.

Caralluma is a genus in the *Asclepiadaceous* family. There are approximately 100 variable species in the genus. The plant *Caralluma adscendens* (Roxb) ver. *fimbriata* (*Ascalpedaceae*) is a tender succulent. *Caralluma adscendens* is reported for its hypolipidemic activity on Triton and Methimazole induced hyperlipidemic rats. [8] *Caralluma lasiantha* is also a succulent plant belongs to the same family and geuns of *Caralluma adscendens*. There are no reports on the Antihyperlipidemic or hypolipidemic activity of this plant; hence the present study was undertaken to evaluate the effect of methanolic extract of *Caralluma lasiantha* (CL) on hyperlipidemia induced by Cafeteria-Diet in experimental rats.

MATERIALS AND METHODS

Alcohol extract preparation

The shade dried aerial part of the plant material was coarsely powdered. The powdered plant material was taken in a round bottomed flask to which the Soxhlet apparatus was attached. Extraction was made with Methanol for 14 Cycles at boiling point of (65ºC) temperature. The Methanol extract was concentrated in a rotary evaporator and stored at 4°C. [9]

Clearance from the institutional animal ethical committee (IAEC)

All procedures were conducted in accordance with IAEC. The study was performed after obtaining clearance from IAEC.

Chromium picolinate

(Batch no- CP/OL/12/01)**:** Purchased from Oceanic Laboratories (P) LTD., L-91, MIDC, Tarapur, 401506.

Other requirements

Ether, Heparinized Micro capillary tubes, Centrifuge, Lipid profile reagents kit, Auto analyzer, etc.

Animals

Inbred strains of *Wistar albino rats* (n=36) weighing 180-200g of either sex were taken from the Central animal house, S.S. Institute of Medical Sciences & Research Center, Davangere. Rats were housed in polypropylene cages and maintained under standard conditions (12 h light and dark cycles, at 23±4◦ C and 40-60% humidity) and provided with standard rat pellet chow feed and water *ad libitum*. The animals were acclimatized to the Central animal house conditions before experimentation.

Grouping of the animals for treatment (*wistar albino rats*)

The rats were divided into six groups of six animals each for 90 days study and they were placed individually in different cages, one rat each in one

cage. After 1 week of adaptation period, treatment is started.

Group 1: Rats were fed Normal-Diet (ND) and treated with distilled water (DW).
Group 2: Rats were fed Cafeteria-Diet (CD) + ND and treated with DW.
Group 3: Rats were fed the CD + ND and treated with Cr.Pic 10 mg/kg/day
Group 4: Rats were fed the CD + ND and treated with CL 10 mg/kg/day
Group 5: Rats were fed the CD + ND and treated with CL 20 mg/kg/day.
Group 6: Rats were fed the CD + ND and treated with CL 40 mg/kg/day.
Test solutions were prepared fresh daily and the dose volume was adjusted to 1 ml/day.

All the rats were treated orally once daily with their respective drugs (Group 3 to 6) and they received fixed quantity of Cafeteria-diet (table-1) and pellet-chow (ND) & water *ad libitum* for 90 consecutive days except group 1, which was fed only with pellet-chow & water *ad libitum.*

Composition of cafeteria-diet (CD)

The CD consisted of 3 diets: (a) Condensed Milk (8g) + Bread (8g); (b) Chocolate (3g) + Biscuit (6g) + Dried coconut (6g); (c) Cheese (8g) + Boiled Potato (10g). The three diets were presented to the individual rats on days one, two & three, respectively, & then repeated in the same succession [9]. The caloric value of CD given in Table 1.

Table 1: Caloric value of Cafeteria Diet

INGREDIENTS	CALORIC VALUE (kcal/100g)
Condensed Milk	335
Bread	230
Chocolate	550
Biscuit	360
Dried Coconut	660
Cheese	320
Boiled potato	80

SAMPLE COLLECTION

During the treatment period, the animals were observed daily for toxic manifestations. Blood serum lipid parameters were assessed on 0^{th}, 30^{th}, 60^{th} and 90^{th} day of treatment. Blood samples were collected from the retro-orbital plexus of each rat after induction of mild anesthesia with ether using micro capillary tubes [10] for serum lipid parameters.

STATISTICAL ANALYSIS

The results obtained were expressed as mean ± S.D and subjected to Analysis of Variance (ANOVA) and Multiple Comparison Test using SPSS statistical package (Version: 17.5). The difference between the means with p values < 0.05 were considered statistically significant.

Within the group comparison was made between initial (Day '0') reading and readings recorded at different intervals (durations) of their respective groups to overcome the disparity in initial values between the different groups. In between group comparison was made, group 2 was compared with group 1 to assess the CD induced hyperlipidemia and all the groups were compared with group 2 & 3 on their respective days.

RESULTS

Serum Total Cholesterol (Table 2 & Fig. 1)

There was no significant change in the serum total cholesterol during various durations of the experiment in the rats of Group 1 which were fed with normal diet. Whereas cafeteria diet fed rats, Group 2, 3, 4, 5 & 6 produced a significant increase in the serum levels of Cholesterol compared to the level seen initially on day '0' of their respective groups.

Compared to Group 2 there was significant decrease in serum levels of Cholesterol observed in Group 1 & 3 on day 90 and Group 5 & 6 on day 30. Compared to Group 3 there was no significant change in the serum total cholesterol seen in Group 2, 4, 5 & 6, whereas significant decrease in serum total cholesterol was seen in Group1 on day 30.

Table 2: Effect of *CL* on Serum Total cholesterol (mg/dl) in *Wistar albino* rats fed with CD

	Group 1 Normal Diet (ND)	**Group 2** Cafeteria Diet (CD) + ND	**Group 3** CD + ND + CrPic. 10mg/Kg	**Group 4** CD + ND + CL 10mg/Kg	**Group 5** CD + ND + CL 20mg/Kg	**Group 6** CD + ND + CL 40mg/Kg
Day '0'	74.38 ± 3.05	74.28 ± 4.26	73.32 ± 2.36	72.84 ± 2.95	73.65 ± 3.06	74.22 ± 2.13
Day '30'	75.17 ± 5.57 b*** c*	89.38 ± 9.06 a*	84.29 ± 3.47 a**	81.75 ± 3.29	77.91 ± 4.91 b**	76.00 ± 1.90 b**
Day '60'	79.68 ± 15.60	93.53 ± 12.32 a*	86.09 ± 4.55 a***	84.70 ± 8.19 a*	84.29 ± 9.31	78.51 ± 1.93
Day '90'	86.81 ± 15.75 b*	105.97 ± 11.76 a***	89.60 ± 5.92 a*** b**	93.06 ± 7.16 a***	91.65 ± 9.30 a**	84.29 ± 4.06 a***

n=6. Mean ± S.D. a - Compared with day '0', b - Compared with group '2', c - Compared with group '3'. Values of respective group * P < 0.05, ** P < 0.01, *** P < 0.001.

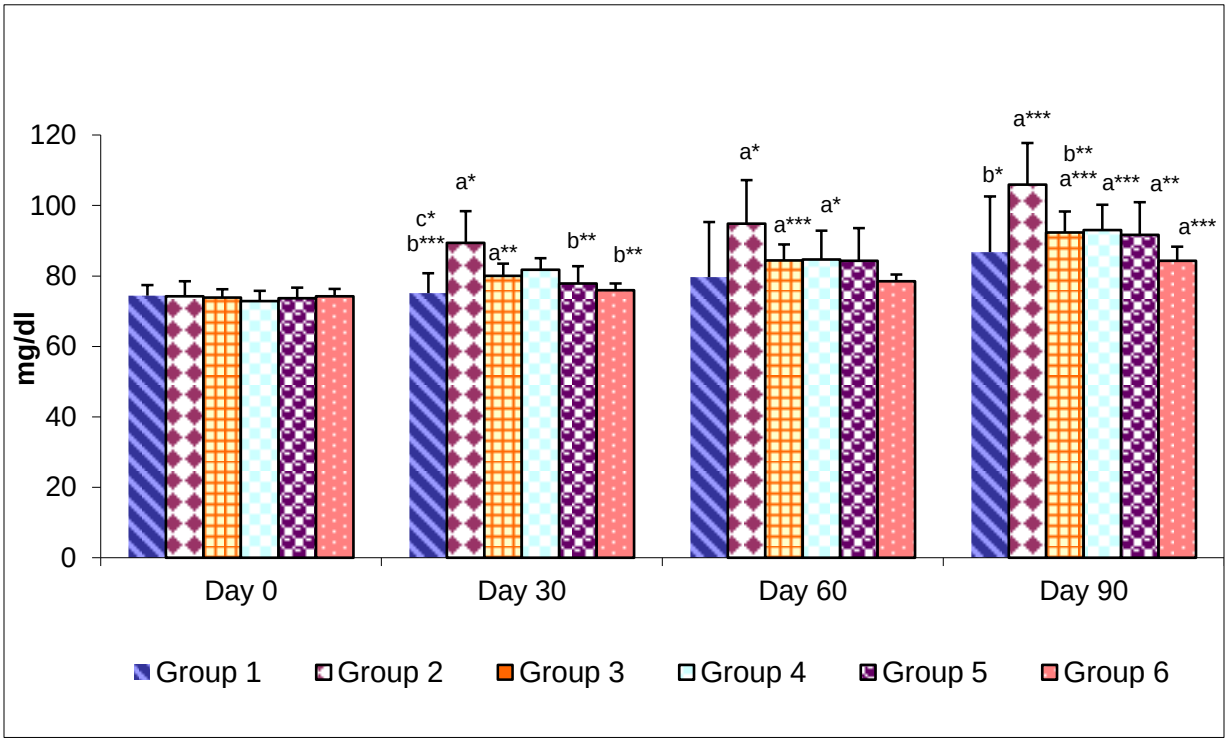

Fig. 1: Effect of *CL* on Serum Total cholesterol (mg/dl) in *Wistar albino* rats fed with CD

Table 3: Effect of *CL* on Serum Triglycerides (mg/dl) in *Wistar albino* rats fed with CD

	Group 1 Normal Diet (ND)	**Group 2** Cafeteria Diet (CD) + ND	**Group 3** CD + ND + CrPic. 10mg/Kg	**Group 4** CD + ND + CL 10mg/Kg	**Group 5** CD + ND + CL 20mg/Kg	**Group 6** CD + ND + CL 40mg/Kg
Day '0'	98.50 ± 1.47	97.12 ± 2.07	96.67 ± 2.85	97.42 2.07	97.64 ± 1.09	98.41 ± 0.59
Day '30'	101.46 ± 7.23	140.91 ± 18.11 a*	122.84 ± 4.29 a***	122.84 ± 55.37	103.37 ± 21.04	100.91 ± 1.45
Day '60'	109.05 ± 8.36 b**	175.27 ± 39.62 a*** c**	116.34 ± 5.12 a*** b**	115.44 ± 51.48 b**	100.63 ± 10.50 b***	99.35 ± 0.39 b***
Day '90'	110.35 ± 10.30 b***	184.12 ± 26.70 ac***	114.74 ± 11.26 a** b***	129.26 ± 34.99 b***	108.77 ± 9.09 b***	103.76 ± 5.21 a* b***

n=6. Mean ± S.D. a - Compared with day '0', b - Compared with group '2', c - Compared with group '3'. Values of respective group * P < 0.05, ** P < 0.01, *** P < 0.001.

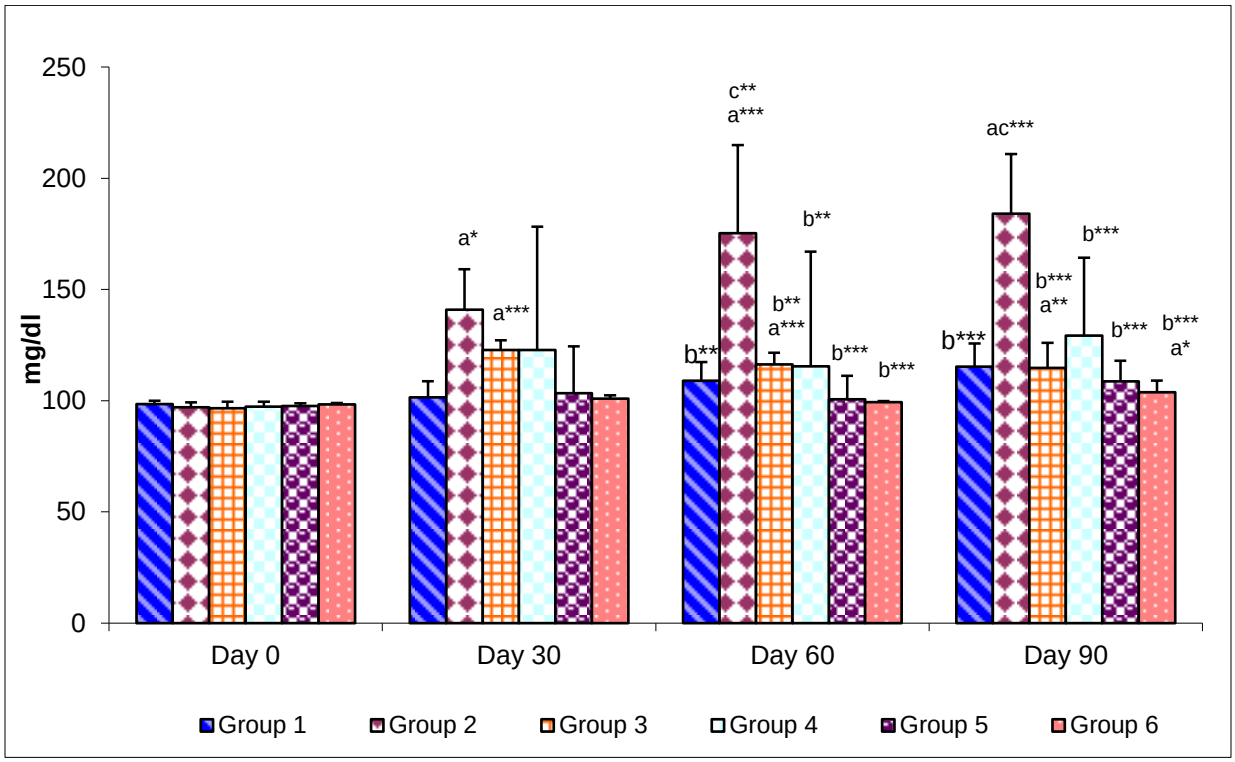

Fig. 2 Effect of *CL* on Serum Triglycerides (mg/dl) in *Wistar albino* rats fed with CD

Table 4: Effect of *CL* on Serum HDL (mg/dl) in *Wistar albino* rats fed with CD

	Group 1 Normal Diet (ND)	**Group 2** Cafeteria Diet (CD) + ND	**Group 3** CD + ND + CrPic. 10mg/Kg	**Group 4** CD + ND + CL 10mg/Kg	**Group 5** CD + ND + CL 20mg/Kg	**Group 6** CD + ND + CL 40mg/Kg
Day '0'	50.26 ± 1.57	51.58 ± 1.51	51.56 ± 2.42	49.96 ± 1.08	50.45 ± 1.37	50.48 ± 1.75
Day '30'	49.71 ± 2.62 b*** c*	30.74 ± 1.49 ac***	54.13 ± 3.48 b***	37.39 ± 1.56 abc***	49.35 ± 1.34 b***c**	53.45 ± 1.96 b***
Day '60'	46.91 ± 2.25 bc***	27.99 ± 2.11 ac***	56.09 ± 4.06 b***	40.78 ± 2.19 abc***	53.07 ± 2.13 b***	56.44 ± 2.03 a**b***
Day '90'	45.72 ± 2.09 bc***	23.60 ± 2.53 ac***	55.67 ± 3.78 b***	44.50 ± 2.15 abc***	48.13 ± 2.83 b***c*	51.75 ± 4.46 b***

n=6. Mean ± S.D. a - Compared with day '0', b - Compared with group '2', c - Compared with group '3'. Values of respective group * P < 0.05, ** P < 0.01, *** P < 0.001.

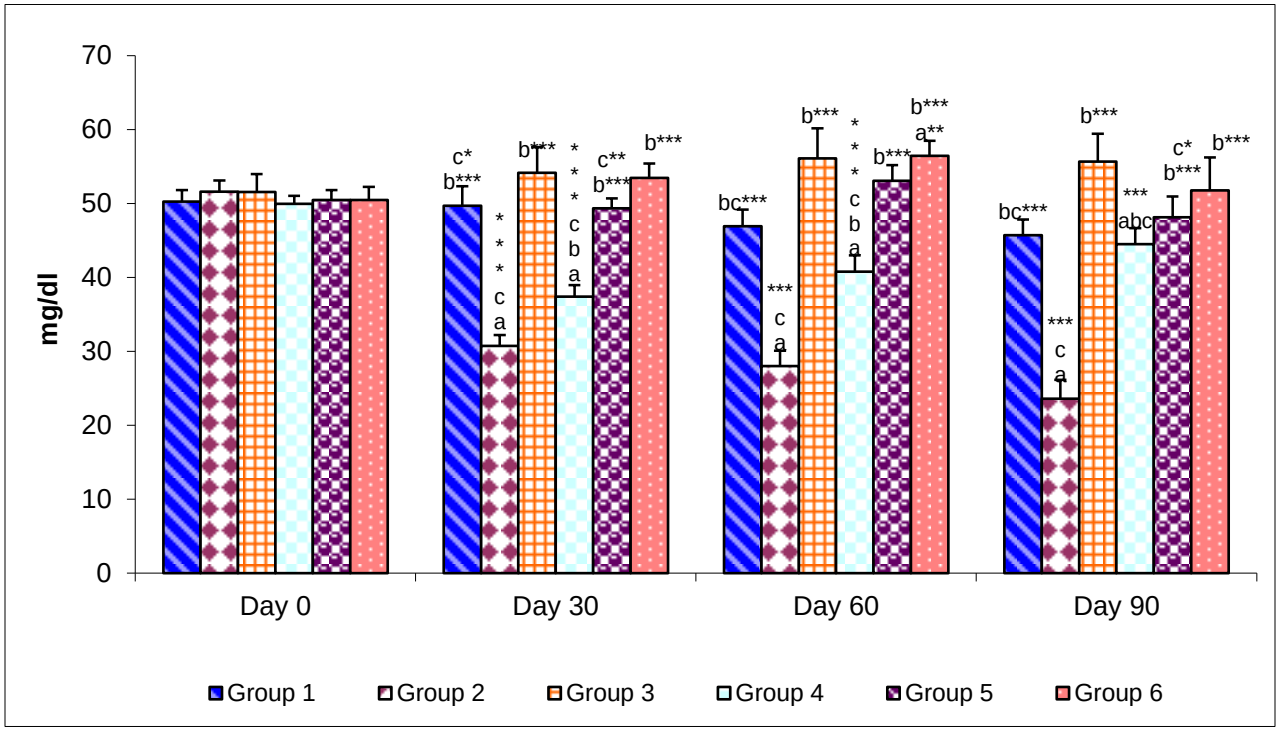

Fig. 3: Effect of *CL* on Serum HDL (mg/dl) in *Wistar albino* rats fed with CD

Table 5: Effect of *CL* on Serum LDL (mg/dl) in *Wistar albino* rats fed with CD

	Group 1 Normal Diet (ND)	**Group 2** Cafeteria Diet (CD) + ND	**Group 3** CD + ND + CrPic. 10mg/Kg	**Group 4** CD + ND + CL 10mg/Kg	**Group 5** CD + ND + CL 20mg/Kg	**Group 6** CD + ND + CL 40mg/Kg
Day '0'	4.42 ± 2.41	3.27 ± 4.09	2.43 ± 1.12	3.39 ± 3.04	3.67 ± 2.75	4.05 ± 1.78
Day '30'	5.16 ± 4.22 b***	30.46 ± 10.64 a** c***	5.59 ± 1.29 b***	19.79 ± 10.87 ac**	7.89 ± 0.15 b***	3.37 ± 1.92 b***
Day '60'	10.96 ± 15.15 b*	30.48 ± 14.02 ac**	6.74 ± 1.83 a*b**	20.83 ± 9.00 a** c*	11.09 ± 10.27 b*	2.20 ± 2.13 b***
Day '90'	18.02 ± 14.90 b***	45.54 ± 11.17 ac***	10.99 ± 3.92 ab***	22.70 ± 4.29 ab**	21.77 ± 9.96 ab**	11.78 ± 6.93 a*b***

n=6. Mean ± S.D. a - Compared with day '0', b - Compared with group '2', c - Compared with group '3'. Values of respective group * P < 0.05, ** P < 0.01, *** P < 0.001.

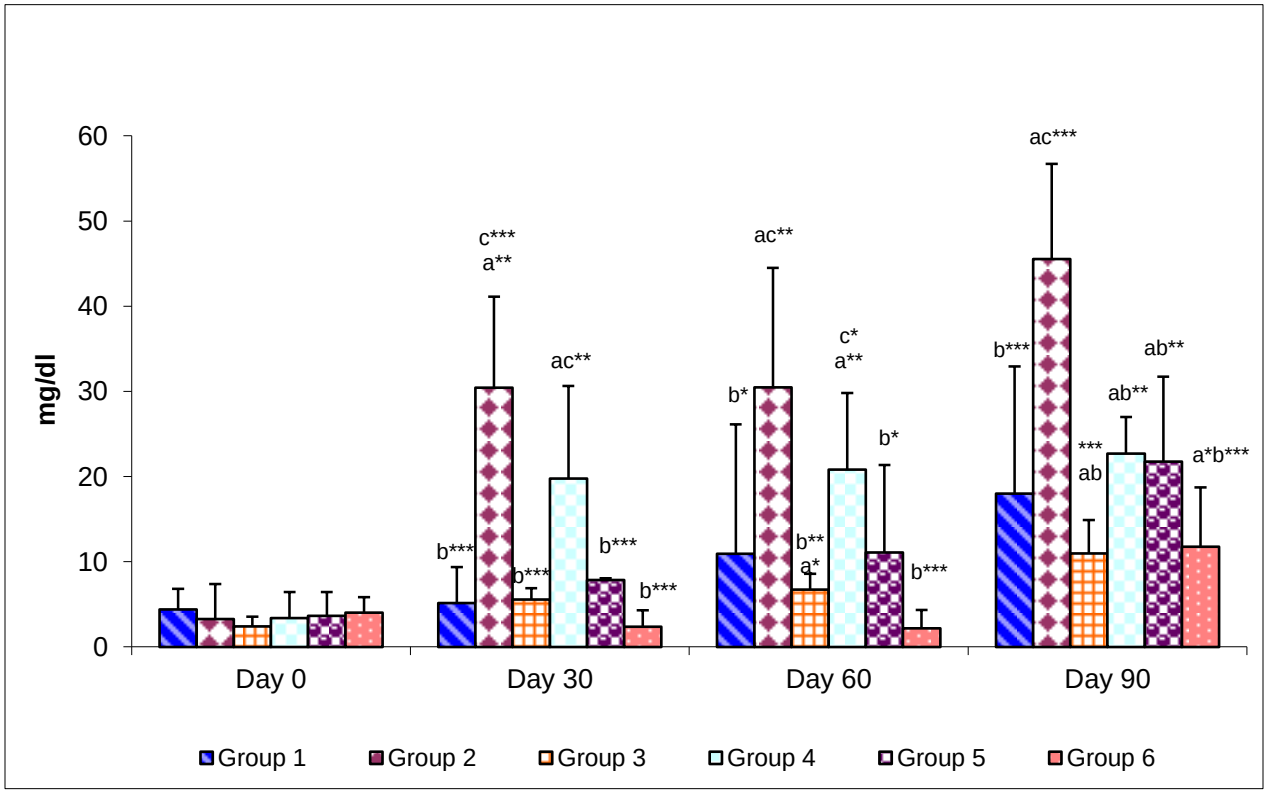

Fig. 4 Effect of *CL* on Serum LDL (mg/dl) in *Wistar albino* rats fed with CD

Table 6: Effect of *CL* on Serum VLDL (mg/dl) in *Wistar albino* rats fed with CD

	Group 1 Normal Diet (ND)	**Group 2** Cafeteria Diet (CD) + ND	**Group 3** CD + ND + CrPic. 10mg/Kg	**Group 4** CD + ND + CL 10mg/Kg	**Group 5** CD + ND + CL 20mg/Kg	**Group 6** CD + ND + CL 40mg/Kg
Day '0'	19.70 ± 0.29	19.42 ± 0.41	19.33 ± 0.57	19.48 ± 0.41	19.53 ± 0.22	19.68 ± 0.12
Day '30'	20.29 ± 1.45	28.18 ± 3.62	24.57 ± 0.86 a***	24.57 ± 11.07	20.67 ± 3.31	20.18 ± 0.29
Day '60'	21.81 ± 1.67 b**	35.05 ± 7.92 a***c**	23.27 ± 1.02 ab***	23.09 ± 10.30 b***	20.13 ± 2.10 b***	19.87 ± 0.08 b***
Day '90'	21.74 ± 2.06 b***	36.82 ± 5.34 ac***	22.95 ± 2.25 a**b***	25.85 ± 7.00 b***	21.75 ± 1.82 b***	20.75 ± 1.04 a*b***

n=6. Mean ± S.D. a - Compared with day '0', b - Compared with group '2', c - Compared with group '3'. Values of respective group * P < 0.05, ** P < 0.01, *** P < 0.001.

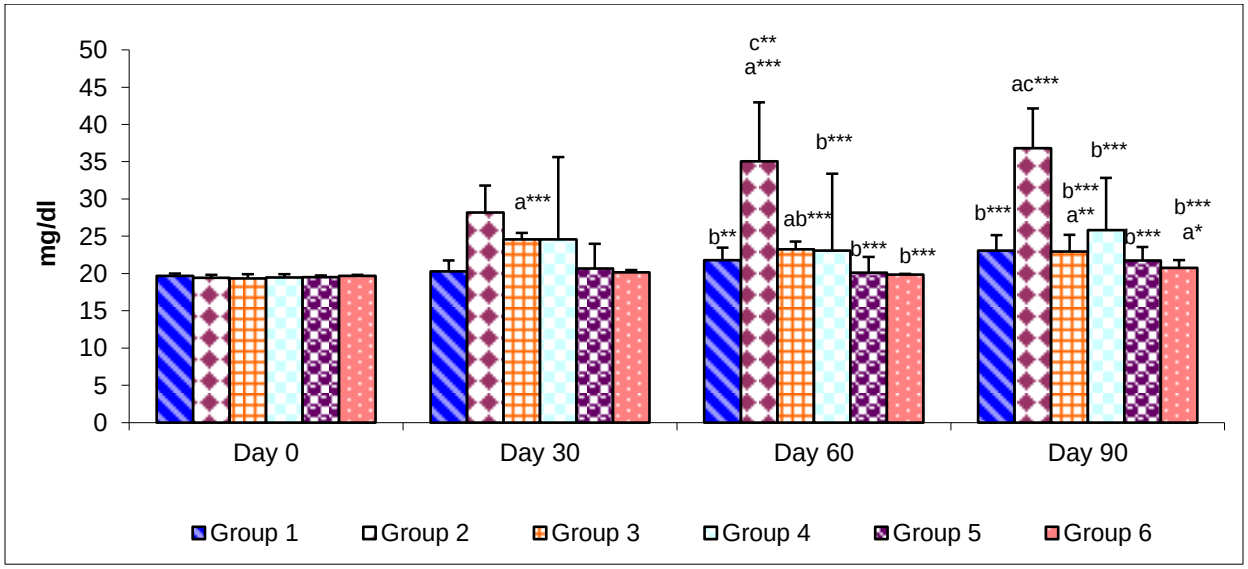

Fig. 5 Effect of *CL* on Serum VLDL (mg/dl) in *Wistar albino* rats fed with CD

Serum triglycerides (table 3 & fig. 2)

There was significant increase in the serum Triglycerides in Group 2 on day 30, 60, 90, Group 3 on day 30, 60, 90 & Group 6 on day 90, whereas no significant change was seen in Group1, 4 and 5 compared to the level observed initially on day '0' of their respective groups.

Compared to Group 2 there was significant decrease in serum Triglycerides levels observed in Group 1, 3, 4, 5 & 6 on day 60 and day 90 respectively. Compared to Group 3 there was significant increase in the serum Triglycerides seen in Group 2 on day 60 & 90, whereas no significant change in serum Triglycerides was noticed in Group1, 4, 5 and 6 throughout the experimental period.

Serum HDL - cholesterol (table 4 & fig. 3)

Significant decrease in the serum HDL was seen in Group 2 on day 30, 60, 90 and Group 4 on day 30, 60, 90, whereas significant increase in HDL was observed in Group 6 on day 60 compared to their respective groups initial HDL level observed on day '0'.

There was significant increase in serum HDL level in Group 1, 3, 4, 5 & 6 compared to Group 2 on day 30, 60 and day 90 respectively. Significant decrease in serum HDL level in Group 1, 2, 4 & 5 compared to Group 3. Whereas no significant change in serum HDL level in Group 6 compared to Group 3.

Serum LDL - cholesterol (table 5 & fig. 4)

Significant increase in the serum LDL – Cholesterol was observed in Group 2, 4 on day 30, 60, 90, Group 3 on day 60, 90 and Group 5 & 6 on day 90 compared to the level observed initially on day '0' of their respective groups.

Compared to Group 2 there was significant decrease in serum LDL – Cholesterol levels seen in Group 1, 3, 4, 5 & 6 throughout the study. There was no significant change observed in Group 1, 5 & 6 compared to Group 3. Significant increase in the serum LDL – Cholesterol was noticed in Group 2 on day 30, 60 & 90 and in Group 4 on day 30 & 60 compared to Group 3.

Serum VLDL - cholesterol (table 6 & fig. 5)

There was significant increase in the serum VLDL seen in Group 2 on day 60, 90, Group 3 on day 30, 60, 90 and Group 6 on day 90 compared to their respective groups initial VLDL level observed on day '0'.

There was significant decrease in serum VLDL level in Group 1, 3, 4, 5 & 6 compared to Group 2 on day 60 and day 90 respectively. No significant change in serum VLDL level in Group 1, 4, 5 & 6 compared to Group 3. Significant increase in serum VLDL level in Group 2 was observed on day 60 & 90 compared to Group 3.

DISCUSSION

In the present study rats were fed with a cafeteria diet (CD) or high fat diet (table 1) for 90 days, which inevitably caused hyperlipidemia compared to pellet chow or normal diet fed rats of Group 1. Feeding CD has successfully produced a significant increase in the serum levels of Total Cholesterol, Triglycerides, LDL, VLDL and also significant decrease in serum HDL level of Group 2 rats. Treatment with *Caralluma lasiantha* extract 10, 20 & 40 mg/kg/day; significantly reduced the serum total cholesterol, triglycerides, LDL, VLDL and significant increase in HDL level compared to Group 2 rats in dose-dependent manner was observed and these levels were comparable to Group 3 rats (Cr.Pic treated), which reveals that the *Caralluma lasiantha* extract has anti-hyperlipidemic effect.

Methanolic extract of *Caralluma lasiantha* at a dose of 20 and 40 mg/kg/day significantly lowered serum cholesterol and *CL* extract at a dose of 10, 20 and 40 mg/kg/day significantly lowered triglycerides levels when compared to Group 2. The large increase in serum triglycerides and cholesterol due to cafeteria diet administration results mostly from an increase of VLDL secretion by the liver accompanied by a strong reduction of VLDL and LDL catabolism. [11] The reduction of total cholesterol by the *Caralluma lasiantha* extract was associated with a decrease of its LDL fraction, which is the target of several hypolipidemic drugs. This result suggests that cholesterol-lowering activity of the herb extract can be result from the rapid catabolism of LDL cholesterol through its hepatic receptors for final elimination in the form of bile acids as demonstrated. [12] It is well known that HDL-Cholesterol levels have a protective role in Coronary artery disease. [13] Similarly increased level of serum LDL-cholesterol results in increased risk for the development of atherosclerosis. [14] The increased level of HDL-cholesterol and decreased cholesterol level along with its LDL fraction which is evident from the results could be due to an increased cholesterol excretion and decreased cholesterol absorption through gastro intestinal tract. Thus the decreasing cholesterol levels in the body under the influence of *Caralluma lasiantha* could have enhanced the enzymatic action by a positive feed back mechanism.

Qiu *et al*., has reported phytochemistry of the *Caralluma lasiantha*, two new bisdesmosidic C-21 steroidal (pregnane) glycosides, named as lasianthoside-A and -B, were isolated. In addition, a known flavonoid glycoside, luteolin neohesperidoside, was also isolated. [15] There are reports that the pregnane glycosides act directly on adipose tissue, by inhibiting adipocyte proliferation

and differentiation. [16, 17, 18] The adipogenesis process includes adipocyte proliferation and differentiation, alteration of cell shape, growth arrest and clonal expansion, which leads to a complex sequence of changes in gene expression and lipid storage. [19] Differentiation of fibroblastic preadipocytes into mature adipocytes involves differential regulation of adipogenic genes as well as lipid accumulation, [21] thus the presence of pregnane glycosides in *Caralluma lasiantha* may have a positive role in hyperlipidemia. Flavonoids have exhibited a variety of pharmacological activites, including the antiatherogenisis and antioxidant effect. [21] The result of our study suggests that the antihyperlipidemic activity of this *Caralluma lasiantha* could be attributed to the presence of the valuable glycosides and flavonoids in the extract.

The antihyperlipidemic activity of *Caralluma lasiantha* (10, 20 and 40 mg/kg/day) on cafeteria diet induced hyperlipidemia showed significant activity when compared to untreated CL groups in a dose dependent manner. Thus, our study showed that administration of Methanolic extract of *Caralluma lasiantha* was more effective to manage hyperlipidemia. The active ingredients present here may recover the disorders in lipid metabolism noted in hyperlipidemic state.

CONCLUSION

By this *in vivo* study, oral administration of *Caralluma lasiantha* extract has shown Anti-hyperlipidemic effect in Cafeteria-Diet induced hyperlipidemia in *wistar albino* rats. Further extensive clinical studies are required to confirm the prophylactic and therapeutic usefulness of *Caralluma lasiantha* on hyperlipidemia in humans.

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