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RESEARCH ARTICLE

Evaluation of Hypolipidemic Activity of *Ceiba pentandra* (L.) Gaertn. Leaves Extract in Experimental Rat Model

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Abstract

Background: Hyperlipidemia is a major risk factor for atherosclerosis and coronary artery diseases, significantly contributing to cardiovascular disease-related deaths. Plant-based treatments, particularly those rich in flavonoids, are recognized for their safety and efficacy in managing hyperlipidemia. *Ceiba pentandra* Gaertn. (Silk Cotton tree), a tropical plant from the *Malvaceae* family, is of particular interest for its potential hypolipidemic properties. **Aim:** To evaluate the hypolipidemic activity of 80 % hydroalcoholic extract of *C. pentandra* leaves (CPHAE) in high-fat diet-induced hyperlipidemia in Sprague-Dawley rats. **Methods:** Hyperlipidemia was induced in Sprague-Dawley rats by administering a high-fat diet (Indian vanaspati ghee: coconut oil, 3:1 v/v) for 21 days. CPHAE (250 mg/kg and 500 mg/kg) was administered from day 21 to day 42. Atorvastatin served as the standard drug. Lipid parameters, including Triglycerides (TG), Total Cholesterol (TC), Low-Density Lipoprotein (LDL), Very Low-Density Lipoprotein (VLDL), and the Atherogenic Index, were assessed and compared between groups. **Results:** The high-fat diet significantly ($p<0.05$) elevated lipid parameters, including TG, TC, LDL, and VLDL levels, and increased the Atherogenic Index. Treatment with CPHAE at both doses significantly ($p<0.05$) reduced lipid parameters. Notably, the higher dose (500 mg/kg) of CPHAE exhibited a significant hypolipidemic effect comparable to the standard drug, Atorvastatin. The Atherogenic Index also decreased significantly in the treatment groups. **Conclusion:** The results demonstrate the potential of *C. pentandra* leaf extract, particularly at higher doses, as a promising agent for the management of diet-induced hyperlipidemia. Further studies may confirm its clinical efficacy and safety.

Major Findings: Pre-clinical evaluation of 80% hydro-alcoholic extract of *Ceiba pentandra* Gaertn. (Silk Cotton tree) leaves which contains high flavonoid exhibit its hypolipidemic effect and diminish atherogenic index at higher dose. These effects were evaluated in Rat model of high-fat diet (Indian vanaspati ghee: coconut oil, 3:1 v/v) induced hyperlipidemia.

Keywords: *Ceiba pentandra* Gaertn, High-fat-diet, Hyperlipidemia, Hypolipidemic Effect, Silk Cotton Tree

1. Introduction

Hyperlipidemia is a condition of an elevation in one or more cholesterol carrying lipoprotein levels. Usually, it involves an increased in Low-Density Lipoprotein (LDL), Very Low-Density Lipoprotein (VLDL) and decreased in High Density Lipoprotein (HDL). It increases the risk of atherosclerosis (deposition of cholesterol in blood vessels) and coronary artery diseases and contributes to cardiovascular disease related death[1]. Lipid-lowering agents such as HMG-CoA reductase inhibitors, bile acid sequestrants, and

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fibric acid derivatives are widely used. These agents have several limitations due to their adverse effects such as elevated hepatic transaminase, GI disturbances, headache, myalgias, and rash[2]. Hence, new safer and more effective medicine development is crucial, and plants are considered a goldmine in drug research with safety and efficacy.

Ceiba pentandra Gaertn. commonly known as White Silk Cotton tree, a tropical tree from the *Malvaceae* family and the Malvales order, is native to regions such as Mexico, Central America, the Caribbean, parts of North and South America and tropical West Africa[3,4]. It is a large, elegant tree, found throughout hotter parts of India, especially in southern and western India and the Andaman Islands.

In *Ayurveda*, leaves of *C. pentandra* are used to balance *kapha* and *vata* doshas due to its bitter taste. It is also used in ailments related to the liver, spleen and blood, as well as in reducing tumours, fat and pain[5-7].

Medicinally, *C. pentandra* has been traditionally used to address various ailments, such as fever, respiratory issues like asthma, inflammation, and skin conditions including scabies. It has also been utilized for treating gonorrhea and as an expectorant, providing relief from respiratory congestion. Additionally, the plant is reported to help with digestive issues like gastritis and is sometimes used to treat scars. Extracts of *C. pentandra* have detoxifying (alexiteric) properties and are used in some cultures as a mouthwash for oral health[8]. Several pharmacological research highlight diverse therapeutic effects of leaves, including antipyretic, hypoglycemic, anti-obesity, diuretic, anti-convulsant, antioxidant, antibacterial, antivenom, anthelmintic, anti-diarrhoeal and anti-ulcer properties[7-17].

The plant's phytochemical profile includes a range of beneficial compounds, such as polyphenols, saponins, bitter resins, carbohydrates and flavonoids found in the leaves, while its seeds contain fixed oils[8]. Pre-liminary Phytochemical screening of *C. pentandra* leaves showed alkaloids, flavonoids, tannins, steroids, terpenoids, saponins, phenol and resin[18]. Plants having high flavonoid content possess hypolipidemic effect, is attributed by several researches[19]. 80% hydroalcoholic extract of *C. pentandra* leaves shows significantly higher number of flavonoids, which can have hypolipidemic effects. Literature research revealed that, 80% hydroalcoholic extract of *C. pentandra* leaves has not been evaluated for hypolipidemic activity. Therefore, the objective of this study was to investigate the hypolipidemic effects of an 80% hydroalcoholic extract derived from *Ceiba pentandra* leaves using a murine model of hyperlipidemia induced by a high-fat diet.

2. Materials and Methods

2.1 Animal Experimentation

Study approval (CCSEA/IAEC/ARCP/2023-24/12) was obtained from the IAEC (Institutional Animal Ethics Committee) and animal experiments were conducted. Female Sprague Dawley rats were procured from Torrent Pharmaceuticals, Ahmedabad and housed in accordance with CCSEA (Committee for Control and Supervision of Experiments on Animals) guidelines. The animals were provided with a standard laboratory diet and given free access to water *ad libitum*. Acute toxicity of the hydroalcoholic extract of *C. pentandra* leaves was conducted according to OECD Guideline 423 up to the dose of 2000mg/kg and appropriate dosages were selected. The animals were divided into five groups (n=6) Group I (Vehicle control), Group II (Model group), Group III (Atorvastatin-treated group), Group IV (CPHAE - High dose group) and Group V (CPHAE – Low dose group).

2.2 Preparation of High-fat Diet and Drugs

2.2.1 Preparation of High-fat Diet

High-Fat Diet (HFD) used to induce hyperlipidemia was prepared by mixing of an Indian Vanaspati ghee and Coconut oil in a 3:1 (v/v) ratio[20].

2.2.2 Preparation of Study Drug Extract

Fresh twigs of *C. pentandra* were collected from the botanical garden of A R College of Pharmacy, Vallabh Vidyanagar and authenticated by taxonomist of Department of Biosciences, Sardar Patel University, Vallabh Vidyanagar. Cleaned and shade dried leaves were powdered to mesh size 60 and stored in an airtight container. A 250 g sample of the powdered leaves was subjected to extraction using an 80% hydroalcoholic solvent (1:1 ethanol-water mixture) at room temperature for 24 hrs using the cold maceration method. The extract was filtered using Whatman filter paper No. 1 and concentrated in a water bath

until a residue was obtained. A stock solution (200 mg/ml) of the hydroalcoholic extract of *C. pentandra* leaves (CPHAE) was prepared by dissolving 2 gm of the extract in 10 ml of 0.5% carboxymethyl cellulose (CMC) solution.

2.2.3 Disease Induction and Drug Treatment

Group-I served as a vehicle control group and received 0.5% CMC daily for 6 weeks. Hyperlipidemia was induced in Groups II, III, IV and V by administering the prepared HFD (3 ml/kg/day, p.o.) daily for 6 weeks. During the last 3 weeks, animals of Group III, IV and V were additionally administered with Atorvastatin (10 mg/kg/day p.o.), CPHAE (500 mg/kg/day p.o.) and CPHAE (250 mg/kg/day p.o.) respectively.

2.2.4 Evaluation Parameters

The body weight of all animals was recorded daily using a weighing balance and changes in body weight calculated for Day 0, Day 21, and Day 42. For lipid profile analysis, blood samples were collected from the saphenous vein on Day 0, Day 21, and Day 42 using clot activator tubes. Collected blood samples were centrifuged, and lipid profile was analyzed in the serum using a blood analyzer. Based on the total cholesterol and HDL levels measured on Day 42, the Atherogenic Index (AI) was calculated using the formula: (Total Cholesterol – HDL level) ÷ HDL level.

2.3 Result Analysis

The results are expressed as Mean ± Standard Deviation (SD). Statistical analysis was performed using one-way ANOVA, followed by Tukey's post hoc test for comparisons. Data analysis was conducted using GraphPad Prism 9.0 software, and a p-value of <0.05 was considered statistical significance.

3. Results

3.1 Acute Toxicity Study

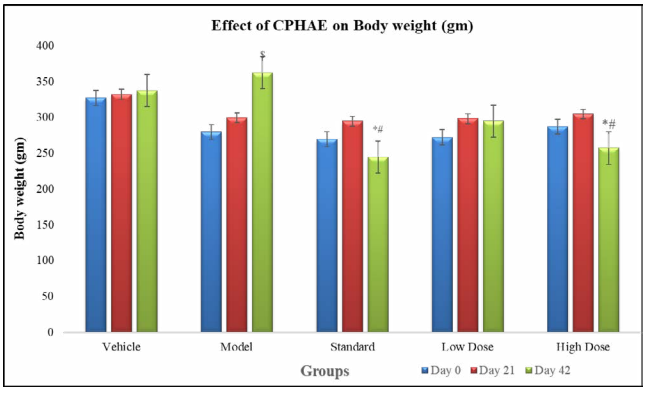
An acute toxicity study as per OECD guidelines 423 was performed and reported that 80% Hydroalcoholic extract of leaf of *C. pentandra* is non-toxic up to the dose of 2000 mg/kg body weight p.o., since no lethality or adverse toxic signs were observed during the 14 days observation period. As NOAEL was observed up to the dose of 2000mg/kg of CPHAE, so as per the literature 500mg/kg was selected as a high dose and 250mg/kg was selected as a low dose of CPHAE.

3.2 Change in Body Weight

The body weight of all animals of all groups was recorded daily and change in body weight was calculated for Day 0, Day 21, and Day 42. In the vehicle group, a slight increase in body weight was observed during the study. In all other groups, increased body weight was found on Day 21 as compared to Day 0. Continuous weight gain was observed in model group which received HFD only. Treatment with Atorvastatin and hydroalcoholic extract prevents HFD-induced body weight gain. Hydroalcoholic extract in high doses was found more effective as compared to low doses (Figure 1).

3.3 Effect of CPHAE on Lipid Profile

The effect of a high-fat diet, standard drug treatment and herbal extract on lipid level is depicted in Table 1. Hyperlipidemia induced by the High-Fat Diet (HFD) was confirmed by comparing lipid profiles from Day 0 to Day 21. A significant increase ($p<0.05$) in total cholesterol, triglycerides, LDL, and VLDL levels was observed across all groups, indicating successful induction of hyperlipidemia by Day 21. The effectiveness of the treatments was assessed on day 42. Atorvastatin, a hypolipidemic agent, significantly reduced ($p<0.05$) hyperlipidemia by a decrease in TC, TG, LDL and VLDL level in rats compared to the model group on Day 42. Similarly, treatment with the hydroalcoholic



$P<0.05 compared Day 42 with Day 0,
*P<0.05 compared with Vehicle group,
#P<0.05 compared with Model group.

Figure 1. Effect of CPHAE on Body Weight (gm).

Table 1. Effect of CPHAE on lipid profile

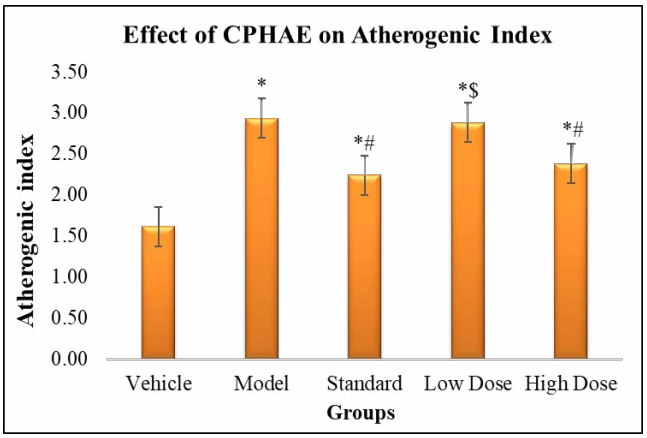
Parameters	Groups	Vehicle Group	Model Group	Standard group (Atorvastatin)	Low Dose CPHAE group (250mg/kg)	High Dose CPHAE group (500mg/kg)
Total Cholesterol	Day 0	104.67 ± 4.93	103 ± 2.61	107.83 ± 4.17	104 ± 2.9	105 ± 3.10
	Day 21	115.33 ± 4.76	136 ± 4.0*	138.83 ± 2.93*	136.17 ± 3.71*	137.83 ± 3.31*
	Day 42	123 ± 5.02	173.17 ± 3.66$^{\#\$}$	148.83 ± 2.86$^{\#@}$	163 ± 3.74$^{\#@}$	159 ± 3.03$^{\#@}$
TG	Day 0	170.67 ± 6.83	171.67 ± 3.72	170 ± 2.19	171 ± 2.37	172 ± 2.90
	Day 21	201 ± 4.94	245 ± 3.52*	246.17 ± 3.66*	241 ± 2.37*	239.33 ± 4.27*
	Day 42	208.83 ± 5.91	251 ± 4.0$^{\#\$}$	166.83 ± 2.93$^{\#@}$	201.33 ± 3.50$^{\#@}$	180.83 ± 2.93$^{\#@}$
HDL level	Day 0	45.00 ± 3.10	45.83 ± 3.54	46.83 ± 3.60	44.67 ± 3.44	46.17 ± 2.32
	Day 21	47.00 ± 3.85	44.67 ± 3.83	42.83 ± 3.60	45.67 ± 3.50	44.67 ± 3.78
	Day 42	47.00 ± 3.90	44.17 ± 3.37	45.67 ± 3.33	42.00 ± 2.90	47.00 ± 1.79
LDL level	Day 0	24.75 ± 1.20	25.2 ± 0.37	24.13 ± 0.33	24.37 ± 0.52	23.87 ± 0.40
	Day 21	26.72 ± 1.13	77.67 ± 4.63*	79.6 ± 1.39*	79.82 ± 1.13*	77.75 ± 0.71*
	Day 42	27.13 ± 1.15	89.67 ± 3.93$^{\#\$}$	28.2 ± 0.34$^{\#@}$	53.43 ± 0.85$^{\#@}$	48.2 ± 0.49$^{\#@}$
VLDL level	Day 0	34.17 ± 2.35	34.2 ± 0.38	34.23 ± 0.34	34.22 ± 0.67	34.22 ± 0.49
	Day 21	40.2 ± 1.67	45 ± 3.80*	44.6 ± 0.64*	44.8 ± 0.53*	45.75 ± 0.72*
	Day 42	42.27 ± 2.08	50.2 ± 0.62$^{\#\$}$	33.42 ± 0.56$^{\#@}$	40.23 ± 0.52$^{\#@}$	36.2 ± 0.38$^{\#@}$

Data are presented as Mean±SD (Standard deviation). *P<0.05 for comparison between Day 21 and Day 0; $^{\#}$P<0.05 for comparison between Day 42 and Day 21; $^{\$}$P<0.05 for comparison with Vehicle group; $^{@}$P<0.05 for comparison with Model group.

extract of *C. pentandra* (CPHAE) significantly reduced (p<0.05) HFD-induced hyperlipidemia by decrease in TC, TG, LDL and VLDL level in both the high-dose and low-dose groups when compared to the model group. However, compared to the standard treatment group receiving Atorvastatin, the extract exhibited a lower degree of protective effect. The high-dose group of CPHAE showed greater efficacy than the low-dose group. Furthermore, neither the high-fat diet nor the extract and drug treatments caused significant changes in HDL cholesterol levels across any of the groups during the 6-week study period. (Table 1)

3.4 Atherogenic Index

Atherogenic Index (AI) was found significantly (p<0.05) higher in all groups as compared to vehicle group. Highest AI was observed in the model group, whereas in treatment groups significantly (p<0.05) reduced Atherogenic index was observed. However, a high dose of hydroalcoholic extract was found significantly (p<0.05) more effective as compared to low dose (Figure 2).



*P<0.05 compared with the Vehicle group,
$^{\#}$P<0.05 compared with the Model group,
$^{\$}$P<0.05 compared with the Standard group.

Figure 2. Effect of CPHAE on Atherogenic Index.

4. Discussion

Hyperlipidemia, characterized by elevated lipid levels in blood, is considered as a major risk factor for atherosclerosis (Deposition of cholesterol and lipids in blood vessels) and Coronary Artery Diseases

(CAD). These conditions significantly contribute to Cardiovascular Disease (CVD) related mortality worldwide[21]. Effective management of hyperlipidemia is critical to reduce the burden of cardiovascular diseases. Anti-hyperlipidemic medications cause adverse effects like muscle pain, liver toxicity and gastrointestinal disturbances, which limits their long-term use[1]. Plants are considered a goldmine in disease management due to the presence of bioactive compounds like flavonoids, which could provide safe, cost-effective alternatives with potent antioxidant and anti-inflammatory effects in the management of hyperlipidemia and to reduce associated cardiovascular risks.

Several plants such as, *Phyllanthus embelica*[22], *Punica granatum*[23], *Citrus medica*[24], *Melissa officinalis*[25], *Tamarindus indica*[26] already been proven for their significant hypolipidemic effect due to presence of high flavonoid content. Flavonoids, a group of polyphenolic compounds are well-known for their antioxidant, anti-inflammatory, and lipid-lowering effects, which help in the prevention and management of hyperlipidemia and related cardiovascular risks. Similarly, 80% hydroalcoholic extract of *C. pentandra* leaves shows a significantly higher concentration of flavonoids, which can contribute to hypolipidemic effects. This study investigates the effect of 80% hydroalcoholic extract of *C. pentandra* leaves (CPHAE) on hyperlipidemia induced by a HFD in female Sprague-Dawley rats.

The acute toxicity study demonstrated that the CPHAE was non-toxic up to a dose of 2000 mg/kg, which justified the selection of 500 mg/kg as the high dose and 250 mg/kg as the low dose for further evaluation. Successful induction of hyperlipidemia in animals by high-fat diet is evident by a significant increase in levels of Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein (LDL) and Very Low-Density Lipoprotein (VLDL) in the model group and all treatment groups by Day 21. Elevated lipid levels, particularly LDL, are susceptible to oxidative modification, forming oxidized LDL (ox-LDL). Ox-LDL is a crucial factor in the initiation and progression of atherosclerosis as it promotes endothelial dysfunction, inflammation, and foam cell formation within blood vessels[27,28]. High-fat diets, as used in this study, are known to exacerbate oxidative stress and lipid peroxidation, which aggravates hyperlipidemia and cardiovascular risk. Study findings of change in lipid profile are align with similar other studies[29-33] and confirm the role of high-fat diet promotes lipid abnormalities, which function as a major risk factor for cardiovascular diseases. Treatment with Atorvastatin, a hypolipidemic agent, significantly reduced lipid levels by Day 42, confirms its efficacy in this experimental model.

Treatment with CPHAE at both High dose (500 mg/kg) and Low dose (250 mg/kg) significantly reduce in lipid levels; however, higher dose exhibited greater efficacy. These findings suggest that the presence of high flavonoid content with other phytochemicals such as alkaloids and terpenoids in hydroalcoholic extract of *C. pentandra*, exerts potent hypolipidemic effect. High flavonoid content scavenges free radicals and inhibits lipid peroxidation, thereby reducing oxidative stress. This antioxidant activity[33] plays a crucial role in mitigating High-Fat Diet (HFD) induced hyperlipidemia. This study results are aligned with similar research studies[34-43]. Interestingly, HFD and CPHAE both had no significant effect on HDL levels. This study shows that certain treatments can reduce harmful lipids without affecting HDL levels, which are considered protective against atherosclerosis.

Atherogenic Index (AI), a crucial indicator of cardiovascular risk, was found significantly elevated in all experimental groups as compared to the vehicle group, with the highest AI observed in the model group. Treatment with CPHAE significantly reduced the AI, with the high dose (500 mg/kg) demonstrating more significant effect than low-dose (250 mg/kg). The reduction in the Atherogenic Index (AI) suggests a potential anti-atherogenic effect of CPHAE, is possibly due to reduction of lipid peroxidation and oxidative stress[44,45]. It also helps to maintain the integrity of blood vessels, prevents the progression of atherosclerosis, and contributes to the management of hyperlipidemia, reduces cardiovascular disease risks. This reduction in AI suggests a potential anti-atherogenic effect of CPHAE by reducing lipid peroxidation and oxidative stress and maintaining the integrity of blood vessels and reduces the progression of cardiovascular disease and the management of hyperlipidemia. Study results for diminished Atherogenic index are aligned with other studies[35,43,46,47]. Several limitations of this study include its focus primarily on lipid levels without evaluating oxidative stress and lipid peroxidation, which are critical

aspects of flavonoid-mediated effects. Flavonoids exert their therapeutic actions largely through antioxidant and anti-inflammatory mechanisms. Therefore, further investigations are necessary to explore the molecular relationships and potential mechanisms of action underlying these effects.

5. Conclusion

The 80% hydroalcoholic extract of *C. pentandra* leaves (CPHAE), rich in flavonoids and other bioactive phytochemicals, demonstrated significant hypolipidemic activity in a high-fat diet-induced hyperlipidemia model. CPHAE treatment resulted in a dose-dependent reduction in lipid levels and atherogenic index, with the high dose showing superior efficacy. Therefore, *C. pentandra* extract has the potential to serve as a natural therapeutic agent for the management of hyperlipidemia and the prevention of cardiovascular diseases. Further research is needed to explore the underlying mechanisms of action and to evaluate the long-term safety and efficacy of this extract in larger animal models and clinical settings.

Authors' Contribution: Dhruti Nagda contributed to conceptualization, methodology, investigation, experimentation, visualization, writing-original draft, writing-review and editing and statistical analysis. Anandkumari Captain was involved in conceptualization, writing-review and editing, and supervision. Musaratafrin Saiyed was involved in methodology, investigation, experimentation, visualization and statistical analysis. Payal Panchal contributed to conceptualization, methodology, investigation, experimentation, visualization, writing-review and editing. All authors have read and agreed to the published version of the manuscript.

6. Author Contribution

Dhruti Nagda contributed to conceptualization, methodology, investigation, experimentation, visualization, writing-original draft, writing-review and editing and statistical analysis. Anandkumari Captain was involved in conceptualization, writing-review and editing, and supervision. Musaratafrin Saiyed was involved in methodology, investigation, experimentation, visualization and statistical analysis. Payal Panchal contributed to conceptualization, methodology, investigation, experimentation, visualization, writing-review and editing. All authors have read and agreed to the published version of the manuscript.

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