

Therapeutic Potential of *Clerodendrum Paniculatum* Against Hyperlipidaemia and Oxidative Damage: Mechanistic Insights from Experimental Models

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Abstract:

Objective: Hyperlipidaemia, a metabolic disorder characterized by elevated blood lipid levels due to impaired lipid metabolism, significantly contributes to diabetes, hepatic steatosis, and cardiovascular diseases. This study investigated the antihyperlipidemic and antioxidant effects of *Clerodendrum paniculatum* leaf ethanolic extract in high-fat diet (HFD)-induced hyperlipidaemic Wistar rats.

Material and Methods: Over an 8-week period, hyperlipidaemic rats were orally administered the extract at 200 and 400 mg/kg doses. The research assessed the extract's potential to modulate lipid profiles and enhance antioxidant defences, providing insights into its therapeutic role in metabolic disorders associated with dyslipidaemia. The study looked at the blood lipid profile, weight gain or loss, relative organ weight, 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition, liver histology, and antioxidant enzymes in blood and liver tissues.

Results: The blood lipid profile in rats given HFD was dose-dependently improved by administering the extract. Histopathological analysis revealed that *C. paniculatum* extract (400 mg/kg) effectively restored the hepatic architecture in hyperlipidaemic rats. Treatment significantly reduced body weight, relative liver weight (p-value<0.05), serum total cholesterol (p-value<0.05), and triglycerides (p-value<0.05), while elevating HDL-cholesterol (p-value<0.05). The

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extract demonstrated dose-dependent HMG-CoA reductase inhibition (12.8 and 9.8 U/mg protein at 200 and 400 mg/kg, respectively), indicating potent suppression of cholesterol biosynthesis. These findings suggest the extract's dual mechanism of action, improving lipid metabolism while protecting against hepatic damage in hyperlipidaemia.

Conclusion: The study suggests that *C. paniculatum* leaf extract may boost antioxidant defences, helping combat oxidative stress-related disorders. Findings indicate its potential to reduce hyperlipidaemia in HFD-fed rats by inhibiting HMG-CoA reductase and improving liver histopathology.

Keywords: anti-hyperlipidaemic activity, antioxidant activity, *Clerodendrum paniculatum*, high-fat diet, HMG-CoA reductase, serum cholesterol

Introduction

Cholesterol levels can contribute to health issues, even though cholesterol is an essential component of the human body. This reveals that recently, there has been an upsurge in cholesterol information and dietary advice being passed out to people. Cardiovascular diseases (CVDs) are a substantial worldwide health issue, contributing significantly to the disease burden¹. They are the primary reasons for death, illness, and healthcare costs in both industrialized and developing nations, making up around 30% of the yearly worldwide death rate and 10% of the global health burden^{2,3}. Hyperlipidaemia is the major risk factor for atherosclerotic heart disease, resulting in ischemic heart attacks, infarctions, and cerebrovascular incidents, hence necessitating the development of preventive strategies⁴⁻⁷.

Hypolipidemic medications can cause negative effects like hyperuricemia, impotence, gynecomastia, memory loss, muscle damage, and skin rashes⁸. Combining these medications increases myopathy and rhabdomyolysis risk. Long-term administration may worsen liver damage, making it more dangerous^{9,10}. Studying plant medications could uncover new compounds for enhancing lipid metabolism and treating hyperlipidaemia. Ayurveda, Unani, and Chinese traditional medicine offer herbal remedies for CVDs, addressing gaps in conventional allopathic medications¹¹⁻¹³.

Hyperlipidaemia increases oxidative stress by enhancing the production of reactive oxygen species (ROS), thereby promoting lipid peroxidation and leading to vascular dysfunction.¹⁴ Antioxidant enzymes function as the body's main defence against oxidative damage: superoxide dismutase (SOD) neutralizes superoxide radicals, catalase (CT) decomposes hydrogen peroxide, and glutathione scavenges free radicals while regenerating other antioxidants¹⁵.

Clerodendrum paniculatum Linn. (*Lamiaceae*), commonly known as Rathapushpa, is a medicinal plant valued for its pharmacological properties and striking orange-red inflorescences. Indigenous to tropical Asia, including India, Sri Lanka, and Southeast Asia, this species features prominently in traditional medicine systems. Its distinctive paniculate flower clusters make it a horticulturally significant species. Current research focuses on validating its ethnomedicinal uses through phytochemical and pharmacological investigations, particularly for metabolic disorders¹⁶⁻¹⁸. From a historical viewpoint, its antioxidant, anti-inflammatory, anti-cancerous, antiaging, and antibacterial properties have been evaluated⁹⁻¹². This study systematically evaluated the hypolipidemic and antioxidant potential of *C. paniculatum* ethanolic leaf extracts in a high-fat diet (HFD) induced hyperlipidaemic Wistar rat model. Specifically, the investigation focused on the extract's capacity to modulate

HMG-CoA reductase activity, the rate-limiting enzyme in cholesterol biosynthesis, while concurrently assessing its effects on oxidative stress markers. This dual approach provides mechanistic insights into the plant's therapeutic potential for managing dyslipidaemia and its associated metabolic complications.

Material and Methods

Plant collection and authentication

C. paniculatum fresh leaves were gathered from Malappuram, Kerala, in March 2013. They were then identified and verified by scientists at the Department of Botany at St. Thomas College, Pala. The voucher specimen was kept in the library under the reference number, USP/MGU/RIMSR/2013/HERB 8, for future use.

Plant extract preparation

C. paniculatum leaves were cleaned, dried, crushed, and extracted with ethanol (250 g) using a Soxhlet apparatus. Multiple iterations of siphoning were conducted at 55°C until all the oil components were removed. The ethanol was removed using a rotary evaporator (Rotary Flash Evaporator-Superfit 60 °C at 50 rpm). The percentage yield of the extract was found to be 18.34%. The sample was kept in a desiccator (100mm Borosil Flange 4082142) for future use.

Experimental protocol

Female Wistar rats (8 weeks old), weighing 150–200g, were sourced from the institutional breeding facility at Kerala Agricultural University's College of Veterinary Science. The rodents were maintained at 22±1 °C with 55±5% relative humidity under controlled 12-hour light/dark cycles. Animals received sterilized pellet feed (Sai Durga Feeds, Batch No. SDF/RD/0822) and UV-treated water *ad libitum* throughout the study duration. Hyperlipidaemia was induced through an 8-week HFD regimen containing

20% palm oil, 1.5% cholesterol, and 0.25% cholic acid, while control groups received normal chow¹⁹. There was a total of 30 rats used in the experiments, distributed evenly among 5 groups of 6. At the start of the research (day 1), the first group received a normal diet, while the second to fifth groups followed HFD. The third group got 60 mg/kg of orlistat (standard drug), while the fourth and fifth groups were given 200 and 400 mg/kg of ethanolic extracts of *C. paniculatum* leaves (EECPL) for 56 days^{11–13}.

Body weight estimation

The body weight in grams was measured using a digital weighing scale (Scaletec SAB 200E) on day 1 and then weekly for 56 days. Furthermore, weekly food intake measures were taken for each group over a period of 56 days.

Evaluation of biochemical parameters

On the 56th day of the study, the animals were euthanised using the CO₂ chamber procedure. After being collected by cardiac puncture, the blood samples were allowed to cool for half an hour at a temperature ranging from 20 to 25 °C. Isolating the clear liquid required 10 minutes of centrifugation at 2,500 rpm. Using a fully automated analyser (FUJI DRI-CHEM NX500i), the following biomarkers were measured: glucose in the blood, total cholesterol (TC), high density lipoprotein- cholesterol (HDL-C), triglyceride (TG), low density lipoprotein- cholesterol (LDL-C), aspartate transaminase (AST) and alanine transaminase (ALT).

Cholesterol biosynthesis regulation

Hepatic HMG-CoA reductase activity was quantified spectrophotometrically using a standardized commercial assay kit (Sigma-Aldrich, USA). The enzymatic reaction, performed at a physiological temperature (37±0.5 °C), monitored NADPH oxidation at 340 nm following incubation with the substrate HMG-CoA. Pravastatin (10 µM) was

employed as the positive control to validate assay sensitivity. Enzyme activity was expressed as units per milligram of microsomal protein (U/mg), with 1 unit defined as 1 μmol NADPH oxidized per minute under optimized reaction conditions²³.

Preparation of tissue homogenate

For tissue homogenate preparation, liver samples were homogenized in an appropriate cold buffer (1:9 or 1:3 w/v ratio), followed by centrifugation at 12,000 \times g for 20 minutes (4 °C). The resulting supernatant was carefully collected and used for subsequent biochemical analyses.

SOD assay

The SOD activity was assessed using the modified method of McCord and Fridovich (1969). Heparinized blood was subjected to centrifugation at 2,500 \times g to isolate packed red blood cells (RBCs), which were subsequently lysed in a 1:9 ratio with cold water and dehemoglobinized using a chloroform: ethanol mixture at a 1:2 volume ratio. Following centrifugation at 15,000 \times g for 60 minutes at 4 °C, the clear supernatant (100 μL) was combined with EDTA-NaCN (200 μL), NBT (100 μL), and phosphate buffer (67 mM, pH 7.8) to achieve a final volume of 2.95 mL. Riboflavin (0.05 mL) was introduced, and the reaction commenced following 15 minutes of photo-illumination. Absorbance at 560 nm was quantified prior to and following illumination. A single SOD unit is defined as the quantity of enzyme necessary to inhibit 50% of NBT reduction to formazan by superoxide radicals produced through a riboflavin/EDTA photoreaction. Results were presented as U per gram of hemoglobin²⁴.

CT assay

Catalase activity was determined spectrophotometrically by monitoring hydrogen peroxide (H_2O_2) decomposition at 240 nm. Packed erythrocytes were lysed in ice-cold water to obtain a hemoglobin concentration of ~5 g/dL, then

diluted 1:500 in 0.05 M phosphate buffer (pH 7.0). The reaction mixture contained 2 mL diluted hemolysate and 1 mL freshly prepared 30 mM H_2O_2 in the test cuvette, with a reference cuvette containing buffer and hemolysate without H_2O_2 . Absorbance changes were recorded every 15 seconds for 1 minute following thorough mixing. Enzyme activity, expressed as K/g hemoglobin, was calculated from the first-order rate constant of H_2O_2 degradation based on the absorbance decrease. Blood and tissue CT were analyzed using the modified Aebi (1974) and Beer & Sizer (1952) methods, respectively, with tissue homogenates processed equivalently to blood samples²⁵.

Reduced glutathione (GSH) quantification

Glutathione levels in blood and tissues were quantified utilizing the DTNB-based spectrophotometric technique. In summary, 500 μL of hemolysate (or tissue homogenate) was combined with 125 μL of 25% trichloroacetic acid (TCA), incubated on ice for 5 minutes, and subsequently diluted with 600 μL of 5% TCA. Following centrifugation at 3,000 \times g for 5 minutes, 150 μL of the supernatant was combined with 350 μL of phosphate buffer (0.2 M, pH 8.0) and 1 mL of DTNB reagent (0.6 mM). The yellow chromophore produced was quantified at 412 nm using a TCA blank as a reference. The concentration of GSH was determined via a standard curve ranging from 10 to 50 nmol GSH and is reported as nmol/mL for blood or nmol/mg protein for tissues. The method utilizes the reaction of GSH's sulfhydryl group with DTNB to produce the quantifiable 2-nitro-5-thiobenzoate anion²⁶.

Histopathological analysis

After 56 days, liver tissue was excised from the rats and placed in 10% formalin. After the liver tissue had been dehydrated, the small sections of the tissue that had been immersed in paraffin were obtained. Next, the sections deprived of paraffin were washed and fixed in water carefully.

Subsequently, they were processed through a series of H&E staining. The slides were examined using light microscopes with magnifications of 10x and 40x. For the purpose of recording the structural architecture, a photomicrograph was acquired using a Motic camera–MOTICAM–BTU10, and the Moti–connect Image Plus–2.0 software was used for the analysis.

Statistical evaluation

The data presented represent the average value along with the corresponding measure of variability. All the data were expressed as mean±S.D. The statistical significance was determined using IBM–Statistical Package for the Social Sciences (SPSS) (version 21.0) with a significance threshold of p -value<0.05 and p -value<0.001.

Results

Body weight analysis

The rats' starting weight ranged from 156.24 to 160.63 g. Their weight ranged from 157.66 to 326.48 g at day 56 after therapy. Using a paired t -test, the weight of

the rats in each group was compared to their initial weight after 45 days of treatment. The results (Figure 1) indicate a significant increase (p -value<0.001) in all the experimental groups.

Serum biochemical parameters estimation

Table 1 presents an overview of the TC, TG, LDL-C, and HDL-C levels found in the blood of the rats tested. Following a period of 8 weeks, the EECPL groups exhibited a significant increase in TC, TG, and LDL-C levels when compared to the normal control group (p -value<0.05). This was seen in rats fed a diet containing 1% cholesterol. In comparison to the control groups, the EECPL groups exhibited a significant rise in the HDL-C levels (p -value<0.05). Additionally, the findings demonstrated that there was a significant decrease in the elevated levels of both AST and ALT components in the extract-treated groups. Figure 2 displays the organ weight after 56 days of the treatment. This result showed that there was an increase in organ weight (HFD group), but after treatment with EECPL, it became normal.

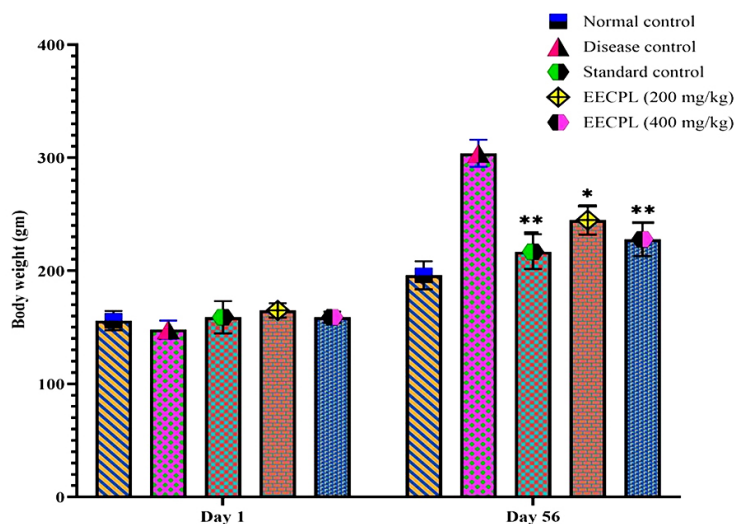


Figure 1 Effect of EECPL on the body weight of HFD-induced hyperlipidaemic rats. The data are expressed as mean±S.D. * p -value<0.001.

Table 1 Impact of EECPL on biochemical markers in a HFD rat model. All data are shown as mean±S.D. (n= 6).
Statistical significance, # p-value<0.05 and *p-value<0.001.

Biochemical Parameters (mg/dL)	Normal Control	Disease Control	Standard Control	EECPL (200mg/kg)	EECPL (400mg/kg)
TC	68.19±0.37	116.4 ±1.03	97.8±0.66	101.7±1.22	100.1±1.29*
TG	71.1±0.86	150.62±1.46	70.1±0.58 [#]	72.43±1.18	75.5±1.20*
HDL-C	35.1± 0.74	32.5±0.72	37.55±0.65	43.61±1.40	41.25±1.50*
LDL-C	21.32 ±0.35	74.24±2.11	43.62±0.61 [#]	49.13±1.22	52.16±1.20*
Glucose	126.22±1.57	148.1±0.48	127.34±1.25	130.24±0.80	132.68±0.90
AST	55.16±1.06	100.1±1.08	62.5±1.34	64.5±0.98	62.56±1.80*
ALT	27.23±1.64	76.18±1.50	33.2±0.88 [#]	36.5±0.44	34.4±0.68

*p-value<0.05 compared to the standard control, #p-value<0.001 compared to the normal control. EECPL=C. paniculatum leaves, HFD=high-fructose diet, TC=total cholesterol, HDL-C=high density lipoprotein- cholesterol, TG=triglyceride, LDL-C=low density lipoprotein- cholesterol, AST=aspartate transaminase, ALT=alanine transaminase

Cholesterol biosynthesis regulation

The antihyperlipidemic mechanism of EECPL was investigated through HMG-CoA reductase inhibition assays. Results demonstrated significant ($p<0.01$) dose-dependent suppression of enzymatic activity, with 200 mg/kg and 400 mg/kg EECPL treatments yielding 12.8±0.7 U/mg and 9.8±0.5 U/mg protein, respectively, compared to hyperlipidaemic controls. Pravastatin (10 mg/kg) exhibited superior inhibition (4.6±0.3 U/mg), establishing the assay's validity. These findings confirm EECPL's capacity to modulate the mevalonate pathway's rate-limiting step, substantiating its therapeutic potential for dietary hyperlipidaemia management (Figure 3).

Antioxidant enzyme levels

The study evaluated the effects of EECPL (200 and 400 mg/kg) on antioxidant enzyme levels in blood and liver tissue (Table 1, Table 2). In blood, EECPL 400 mg/kg significantly increased CT (133.33±15.29 K/g Hb), superoxide dismutase (SOD) (1229.66±61.04 U/g Hb), and glutathione (42.65±7.1 nmol/ml) compared to normal controls (77.63±11.76, 820.23 ±44.29, 22.75±4.3, respectively). EECPL 200 mg/kg also elevated these markers (108.09±12.01, 1119.42±61.03, 37.41±4.9). In liver

tissue, EECPL 400 mg/kg enhanced SOD (26.66±3.01 U/g Hb) and glutathione (10.5±2.3 nmol/ml), while CT (14.33±2.9 K/g Hb) was comparable to vitamin C (16.19 ±2.5). EECPL 200 mg/kg showed similar improvements (15.09±2.01, 22.52±2.03, 9.1±1.9). The results suggest EECPL dose-dependently boosts antioxidant activity, with 400 mg/kg exhibiting superior efficacy.

Prevention of histopathological alterations

Hepatic histopathology revealed cholestasis, lobular inflammation, macrovesicular steatosis, and fibrosis in rats fed with HFD. Liver tissues are shown in Figure 4 with their microscopic features. The hepatic anatomy of the control group was normal, with central veins, sinusoidal gaps, and well-defined liver cells. Some hepatocytes looked like polygons, with their cytoplasm still intact and their nuclei featuring clear nucleoli. The control group, which was considered normal, did not show any signs of cholestasis, lobular inflammation, fibrosis, or macrovesicular steatosis.

Discussion

Coronary artery disease risk factors include hyperlipidaemia. Consequently, it has become one of the leading public health concerns. Plants are being used

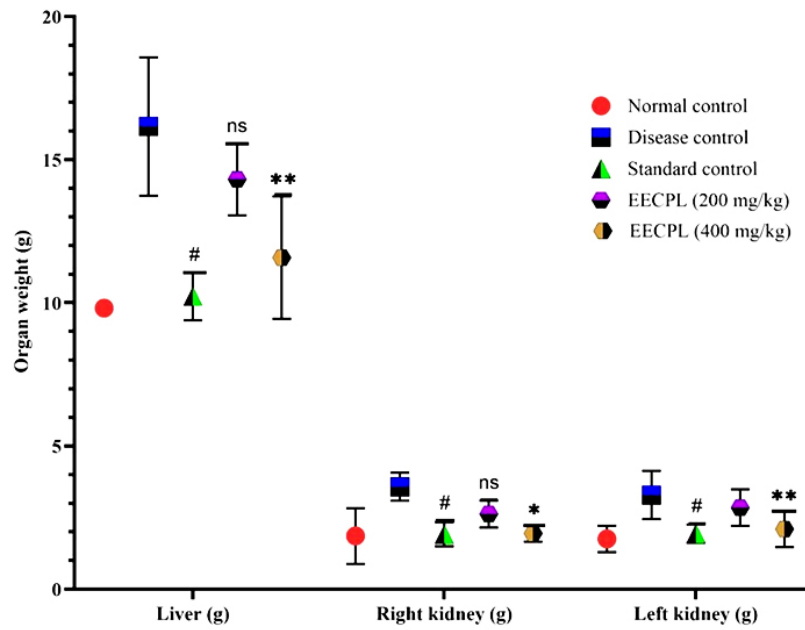


Figure 2 Organ weight of animals after 56 days of the treatment. All data are shown as mean±S.D. (n=6), *p-value<0.05 compared to the standard control, #p-value<0.001 compared to the normal control

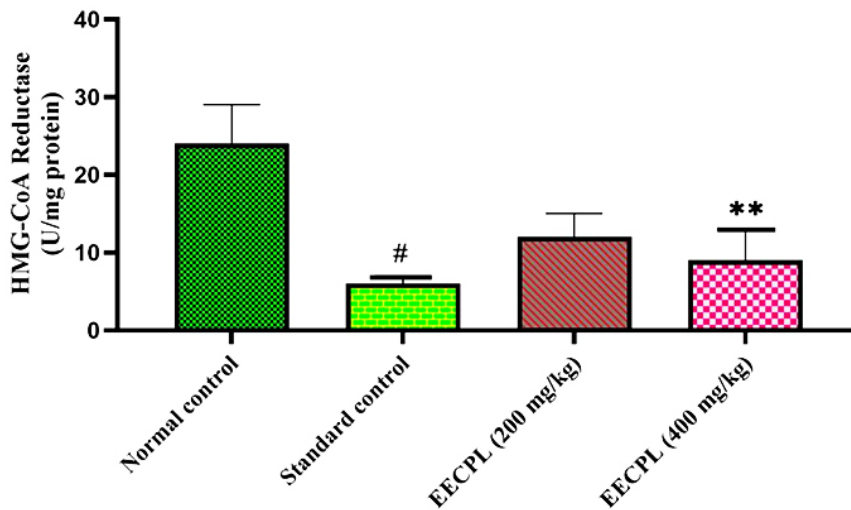


Figure 3 The *C. paniculatum* leaves (EECPL) inhibitory activity on 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme. The values are expressed as mean±S.D. Significance denoted by #p-value<0.001, *p-value<0.01

Table 2 Effect of EECPL on levels of glutathione (GSH) and other antioxidant enzyme activities in blood. The values are expressed as mean±S.D.

Group	Catalase (k/g Hb)	Superoxide dismutase (U/g Hb)	Glutathione (nmol/ml)
Normal	11.3±1.06	15.14±2.9	7.1±2.13
Vitamin C (µl/kg)	16.19±2.5 [#]	22.88±4.2 [#]	8.2±1.9
EECPL 200 mg/kg	15.09±2.01	22.52±2.03*	9.1±1.9
EECPL 400 mg/kg	14.33±2.9*	26.66±3.01	10.5±2.3*

*p-value<0.05 compared to standard control, [#]p-value<0.001 compared to normal control, S.D.=standard deviation, EECPL=ethanolic extracts of *C. paniculatum* leaves, K/g Hb=rate constant per gram of haemoglobin, U/g Hb=units per gram of haemoglobin, µl=microlitter, mg=milligram, kg=kilogram

Table 3 Effect of EECPL on levels of glutathione (GSH) and other antioxidant enzyme activities in liver tissues. The data expressed as mean±S.D.

Group	Catalase (k/g Hb)	Superoxide dismutase (U/g Hb)	Glutathione (nmol/ml)
Normal	11.3±1.06	15.14±2.9	7.1±2.13
Vitamin C (µl/kg)	16.19±2.5 [#]	22.88±4.2 [#]	8.2±1.9
EECPL 200 mg/kg	15.09±2.01	22.52±2.03	9.1±1.9
EECPL 400 mg/kg	14.33±2.9	26.66±3.01*	10.5±2.3*

*p-value<0.05 compared to standard control, [#]p-value<0.001 compared to normal control, S.D.=standard deviation, EECPL=ethanolic extracts of *C. paniculatum* leaves, K/g Hb=rate constant per gram of haemoglobin, U/g Hb=units per gram of haemoglobin, µl=microlitter, mg=milligram, kg=kilogram

globally for treating dyslipidaemia due to their vast range of pharmacological effects, achieved via different methods^{20,21}. The first step in harnessing the power of plant compounds for the development of nutritional supplements, medicines, cosmetics, and food additives is the extraction of bioactive components from plant materials^{21,22}.

The study found that an HFD led to increased triglycerides in animals. After EECPL treatment, lipid levels decreased and HDL-C levels increased, reaching normal levels. EECPL significantly impacted cholesterol levels at doses of 200 and 400 mg/kg²³. TG plays a critical role in controlling the interactions between lipoproteins to ensure proper lipid metabolism. There was a correlation between higher levels of triglycerides in the blood and an increased risk of CHD.²⁷ Oxygen free radicals oxidize LDL-C in artery

walls, attracting immune system scavengers, leading to atherosclerotic plaques and increased macrophages. TC TG levels and LDL-C risk of atherosclerosis are significant, while HDL-C levels have an inverse relationship. These processes can lead to heart disease, stroke, and occlusive artery disease in the legs. There is a correlation between atherosclerotic plaques and macrophages.²⁸⁻³¹ Research shows that EECPL's antihyperlipidemic properties are influenced by HMG-CoA reductase, an enzyme responsible for cholesterol production and breakdown, which can be effectively managed by inhibiting its activity²³.

Elevated antioxidant enzymes (CT, SOD, glutathione) play a crucial role in mitigating oxidative stress in hyperlipidaemia. Increased lipid peroxidation due to high cholesterol and triglycerides generates excess

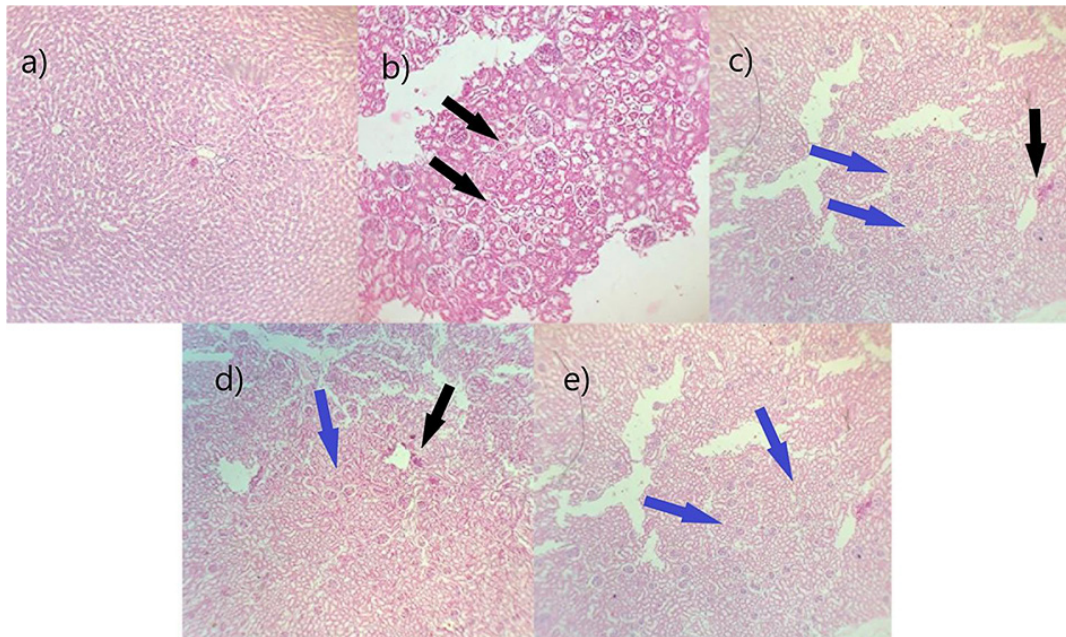


Figure 4 Impact of *C. paniculatum* leaves (EECPL) (200 mg/kg, 400 mg/kg) on the overall appearance and microscopic structure of a rat liver in rats with High-Fructose Diet (HFD)-induced hyperlipidaemia, evaluated using haematoxylin and eosin (H&E) staining. Liver samples (a)–normal control, from rats given HFD (b), and rats treated with orlistat at dosages of 60 mg/kg (c), EECPL 200 mg/kg (d), and 400 mg/kg (e), were examined under a microscope. The control group subjected to HFD exhibited significant coagulation necrosis of hepatocytes, macrovesicular steatosis, and cholestasis. Conversely, the rats treated with the EECPL had necrosis of hepatocytes, lobular inflammation with many tiny foci, and mild cholestasis, which was 100 times less severe. Hepatocyte coagulation necrosis and macrovascular steatosis are shown by the black arrow, whereas the blue arrow indicates normal hepatic cell

ROS, depleting endogenous antioxidants³². EECPL's enhancement of these enzymes suggests its potential in countering hyperlipidaemia-induced oxidative damage. SOD neutralizes superoxide radicals, CT decomposes hydrogen peroxide, and glutathione directly scavenges free radicals, collectively reducing lipid peroxidation and endothelial dysfunction³³. Thus, boosting these enzymes may improve lipid metabolism and prevent atherosclerosis. EECPL significantly enhances antioxidant enzyme activity in blood and liver tissue, demonstrating potent free radical-scavenging properties and mitigating oxidative stress by boosting endogenous defences.

The study found that EECPL significantly reduced lipid levels in rats given a High-Fructose Diet (HFD) at varying doses, indicating its effectiveness in lowering high lipid levels. The effects of EECPL on livers were dose-dependent, as observed in the histopathology, indicating its effectiveness in reducing lipid levels. The antihyperlipidemic effects of EECPL were demonstrated through the reduction of histological liver changes caused by HFD in the experimental rats, as observed in both the macroscopic and microscopic analyses. Figure 5 demonstrates the postulated mechanism of action for the anti-hyperlipidaemic activity of *C. paniculatum* leaf extract.

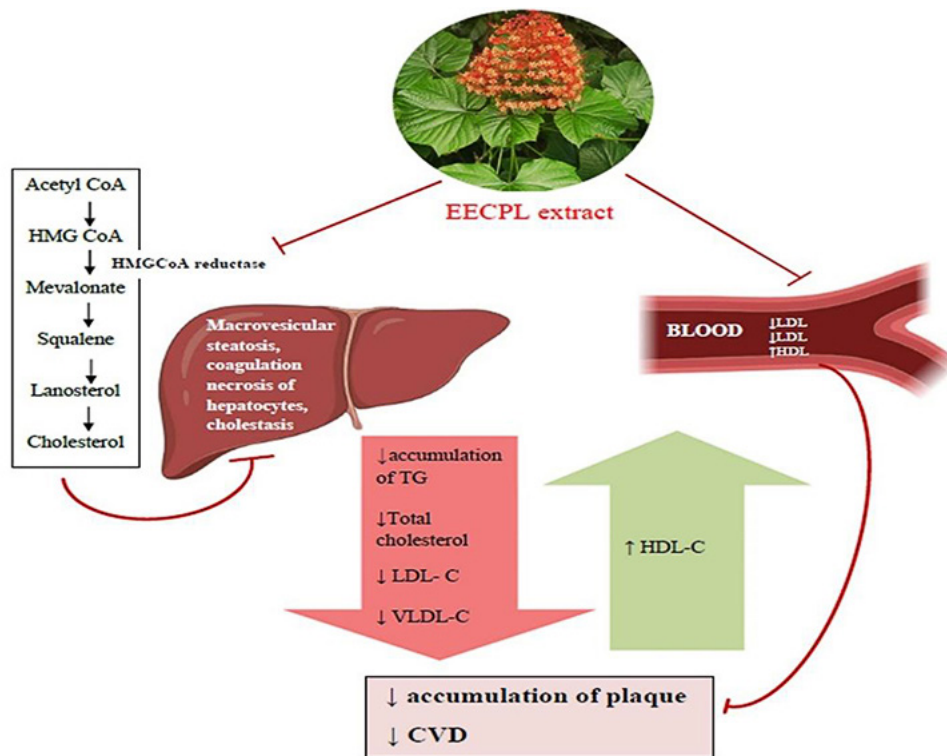


Figure 5 The postulated mechanism of action for the anti-hyperlipidaemic activity of *C. paniculatum* leaf extract: it reduces cholesterol synthesis by inhibiting 3-Hydroxy-3-methylglutaryl-coenzyme A reductase, which in turn inhibits blood and improves liver cell functions

Conclusion

The research findings indicate that the effectiveness of the extract in reducing blood and tissue lipids in rats on a high-cholesterol diet was directly proportional to the dosage administered. The highest dosage demonstrated the most significant antihyperlipidemic effect. The positive effects of the extract on hyperlipidaemia are likely due to multiple mechanisms, including inhibiting HMG-CoA reductase and decreasing the liver’s production of TC and TG. The findings demonstrate that the extract, particularly at 400 mg/kg, significantly enhances antioxidant enzyme levels in blood and liver tissue, surpassing normal controls and showing dose-dependent efficacy. This suggests its potential as a therapeutic agent in oxidative stress-related

conditions by strengthening the endogenous antioxidant defence system. The research indicates that EECPL has a strong antihyperlipidemic impact and could be advanced as a lipid-lowering treatment.

Conflict of interest

It has been declared by the authors that there are no conflicts of interest for this paper.

Ethical approval

With CPCSEA approval (Registration No-1195/PO/Re/S/08/CPCSEA), all relevant animal studies are conducted at Al Shifa College of Pharmacy.

Data availability

The principal investigators and corresponding author have made this original paper and all of the data accessible only for study purposes.

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