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Research Article
Evaluation of Anti-Hyperlipidemic Potential of *Prosopis cineraria* Extract Against High Fat Diet Induced Hyperlipidemia in Laboratory Rat

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Abstract

Background and Objective: In development and progression of atherosclerosis, hypercholesterolemia plays a vital role. *Prosopis cineraria* L. Druce family, Fabaceae, Leguminosae reported to have various pharmacological potential. Hence, the aim of the present investigation was to evaluate its anti-hyperlipidemic potential against High Fat Diet (HFD) induced hyperlipidemia in the laboratory rat. **Methodology:** High fat diet fed was administered in sprague-Dawley rats (180-220 gm) for 60 days to induced hyperlipidemia. Rat co-administered with either aqueous extract of *Prosopis cineraria* fruit (AQ-PCF) or ethanolic extract of *Prosopis cineraria* fruit (ET-PCF) or petroleum ether extract of *Prosopis cineraria* fruit (PE-PCF) at a dose of 100, 200 and 400 mg kg^{-1}, p.o. **Results:** Administration of AQ-PCF (400 mg kg^{-1}) and PE-PCF (200 and 400 mg kg^{-1}) showed significant inhibition in HFD induced alterations in triglyceride, cholesterol, High Density Lipoprotein Cholesterol (HDLC), Low Density Lipoprotein Cholesterol (LDLC) and Very Low Density Lipoprotein Cholesterol (VLDLC) whereas, LDL to HDL ratio and atherogenic index were significantly and dose-dependently decreased by PE-PCF (200 and 400 mg kg^{-1}) treatment as compared to HFD control rats. Administration of ET-PCF (200 and 400 mg kg^{-1}) showed significant and dose-dependent inhibition in HFD induced alterations in triglyceride, cholesterol and HDLC levels whereas, LDLC, VLDLC, LDL-HDL ratio and atherogenic index were significantly inhibited as compared to HFD control group. **Conclusion:** Findings of present investigation suggest that presence of bioactive compounds such as flavonoids, glycosides and phenolic contents from *Prosopis cineraria* extract may cause depletion of deposited lipid content from peripheral tissues by reverse cholesterol transport and inhibit foam cell formation.

Key words: *Prosopis cineraria*, hyperlipidemia, high fat diet, VLDLC, AQ-PCF, LDL-HDL ratio

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Lifestyle changes mainly responsible for death occurred due to cardiovascular diseases in both developed and developing countries[1,2]. Alterations in dietary pattern due to modernization of societies includes high saturated fats intake along with low fibres content caused hyperlipidemia, which is most important risk factor that is associated with development of atherosclerosis leads to cardiovascular complications[3,4]. An elevated lipoprotein or cholesterol levels in serum is the hallmark of hyperlipidemia[5]. Currently around 30% deaths has been reported occurred due to cardiovascular diseases (CVD) with major risk factor including hypertension, hypercholesterolemia, diabetics and obesity EN.CITEEN.CITE.DATA[6-9].

In the spread and expansion of atherosclerosis as well as Coronary Heart Diseases (CHD) hyperlipidemia played a vital role. The onset of CHD depends on alteration in the serum lipid profiles including Low Density Lipoproteins (LDL) and High Density Lipoproteins (HDL) EN.CITEEN.CITE.DATA[10,11]. Total serum cholesterol along with different lipoproteins responsible for disorders associated with a lipid. Movement of cholesterol towards tissue is carried out by LDL whereas, movement of cholesterol towards liver is made by HDL. Thus, LDL is mainly responsible for induction of cardiac problems and obesity whereas, HDL provides protection against it[12].

Over a decade's many antihyperlipidemic agents have been employed for the treatment of hyperlipidemia it includes agents like statin, fibrates, niacin, bile acids, ezitimibe, etc., which helps to reduce elevated cholesterol level in hyperlipidemic condition[13]. However, they provide symptomatic relief in the only fraction of the patient. Moreover, they are associated with a number of side effects which limits their usage[14]. In the preclinical investigation of a new drug from various sources for the treatment of different diseases, laboratory animal model played decisive role EN.CITEEN.CITE.DATA[15-21]. One of such models is the induction of hyperlipidemia by using the High Fat Diet (HFD) model in laboratory rats, which mimics all the clinicopathological features of hyperlipidemia[22,23]. It also has been proved that administration of HFD associated with the elevated level of HDL-C preclinically and clinically also EN.CITEEN.CITE.DATA[24-26].

Plant have been extensively employed as a source of medicine from ancient times EN.CITEEN.CITE. DATA[27,28,29]. Although, an array of synthetic moieties has been used for treating various ailments of a human being but, biomolecules from a plant source serves as the major constituents of raw materials in the process of drugs development EN.CITEEN.CITE.DATA[30-35]. From last two decades, herbal medicine has been considerably utilized for treatment of various diseases all over the world due to its less toxic effect and negligible side effect. This medicinal plant possesses an array of phytol constituents saponins, tannins, essential oils, flavonoids, alkaloids and other chemical compounds, which either individually or together contributes to its pharmacological activity EN.CITEEN.CITE.DATA[36-40]. Tradition system of medicine like Ayurveda, Unani and Chinese identified an array of plant as potential anti-hyperlipidemic agents including *Commiphora mukal*, *Gymnema Sylvestre*, *Pterocarpus narsupium*, *Trigonella foemgraceum*, *Azadirachta indica*, *Terminalia arjuna* and *Boswellia serrata*.

Prosopis cineraria L. Druce (Syn. *Prosopis spicigera* L.) (Family; Fabaceae, Leguminosae), subfamily, Mimosaceae is a small to moderate sized tree widely distributed in the region of Arabia and India. In folk medicine, it has been identified for treatment of various ailments including astringent, demulcent, pectoral, anthelmintic, refrigerant and tonic, etc. It is used for the treatment of various diseases such as asthma, bronchitis, dysentery, leucoderma, leprosy, muscle tremors and piles[41]. It contains an wide range of bioactive compounds including flavonoids, alkaloids, phenolic contents, free amino acids, patulitrin, spicigerin, prosogerin A, B, C and D steroids (campesterol, cholesterol, β-sitosterol, stigmasterol), alcohols (octacosanol and triacontan-1-ol) lipids, sugars and vitamins. It has been reported to have antidiabetic and antioxidant potential[41]. Hence, the aim of the present investigation was to evaluate its hypolipidemic potential against HFD induced hyperlipidemia in the laboratory rat.

MATERIALS AND METHODS

Drugs and chemicals: High Fat Diet (HFD) (60 kcal fat%, #D12492, 5.24 kcal g^{-1}) was purchased from Research Diet Inc., New Brunswick, NJ, USA. Cholesterol, triglyceride, HDLC and LDLC kits were purchased from Accurex Biomedical Pvt. Ltd., Mumbai, India. Petroleum ether (60:80) and diethyl ether were purchased from Merck, India.

Collection of plant material: The fresh fruits of the plant *Prosopis cineraria* were collected from Satpuda region of Maharashtra, India. The plant was identified and authenticated by Professor L.K. Kshirsagar, Taxonomist, Department of botany, S.S.V.P.S's L.K. Dr. Ghogre Science College, Dhule, North Maharashtra University, Jalgaon. A specimen of same has been submitted to the herbarium of the division.

Preparation of aqueous, ethanolic and petroleum ether extract: Fruits of *Prosopis cineraria* were cleaned to remove dirt and cut into small pieces and dried in the shade. Fruits

pieces are crushed in a grinder and pulverized into fine powder. This powdered material (500 g) was passed through 40 mesh and macerated with petroleum ether (60:80) at room temperature and filtered. The filtrate was evaporated. The yield obtained were 1.8% w/w, respectively. The remaining marc was extracted with 70% ethanol using soxhlet extractor. The extract was concentrated in vacuum evaporator below 40°C. The yield obtained were 12.2% w/w, respectively. Furthermore, the remaining marc was macerated with distilled water at room temperature for 7 days and filtered. The filtrate was dried on tray dryer at 60°C. The yield obtained were 20.1% w/w, respectively. The semi-solid petroleum extract was emulsified with 2% tween-80 in distilled water and powder of aqueous and ethanolic extract was dissolved in distilled water to prepare the drug solution of concentration of 10 mg mL^{-1} and used for pharmacological studies.

Preliminary phytochemical screening: The preliminary phytochemical analysis for aqueous extract of *Prosopis cineraria* fruit (AQ-PCF), ethanolic extract of *Prosopis cineraria* fruit (ET-PCF) and petroleum ether extract of *Prosopis cineraria* fruit (PE-PCF) was carried out for the alkaloid (Mayer's, Hager's, Dragendorff's and Wagner's test), flavonoids (Shinoda test), steroids (Salkowski, Liberman-Burchard, Liebermann's test), carbohydrate, phenolic compounds, glycosides and volatile oils EN.CITEEN.CITE.DATA[42-44].

Experimental animals: Male Sprague-Dawley rats (180-220 gm) were obtained from college animal house of R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, India. They were housed in well-ventilated cages and maintained at a controlled temperature of 22±2°C with a 12 h light/dark cycle and standard lab control. All animals had free access to food during experiments under strict hygienic conditions. Tap water was offered *ad libitum*. Institutional Animal Ethical Committee of RCPIPER College, Shirpur approved the study protocol (IAEC/RCPIPER/2012-13/09).

Acute oral toxicity study: Acute toxicity was studied in rats to determine the safe oral dose of drugs. For this, Organization for Economic Co-operation and Development (OECD) followed for guidelines No. 425 'Up and Down' method of Committee for the Purpose of Control and Prevention of Experiments on Animals (CPCSEA)[45].

Development of high-fat diet fed rats: Rat was fed with two dietary regimes such as Normal Pellet Diet (NPD) and High Fat Diet (HFD). The rat was feeding either NPD or HFD (58 fat, 25% protein and 17% carbohydrate as a percentage of total kcal) *ad libitum*, respectively for the initial period of 60 days. The composition and preparation of HFD as were described elsewhere[23].

Experimental design: The studies were conducted in the following groups of animals:

Groups I: Normal rats: Received vehicle (10 mg kg^{-1} of 2% tween-80 in distilled water)
Groupd II: HFD control: Received vehicle (10 mg kg^{-1} of 2% tween-80 in distilled water)
Groups III: Received atorvastatin (1.2 mg kg^{-1})
Groups IV: AQ-PCF (100): Received aqueous extract of *Prosopis cineraria* fruit (100 mg kg^{-1})
Groups V: AQ-PCF (200): Received aqueous extract of *Prosopis cineraria* fruit (200 mg kg^{-1})
Groups VI: AQ-PCF (400): Received aqueous extract of *Prosopis cineraria* fruit (400 mg kg^{-1})
Groups VII: ET-PCF (100): Received ethanolic extract of *Prosopis cineraria* fruit (100 mg kg^{-1})
Groups VIII: ET-PCF (200): Received ethanolic extract of *Prosopis cineraria* fruit (200 mg kg^{-1})
Groups IX: ET-PCF (400): Received ethanolic extract of *Prosopis cineraria* fruit (400 mg kg^{-1})
Groups X: PE-PCF (100): Received petroleum ether extract of *Prosopis cineraria* fruit (100 mg kg^{-1})
Groups XI: PE-PCF (200): Received petroleum ether extract of *Prosopis cineraria* fruit (200 mg kg^{-1})
Groups XII: PE-PCF (400): Received petroleum ether extract of *Prosopis cineraria* fruit (400 mg kg^{-1})

Vehicle or atorvastatin or drugs were administered orally for 60 consecutive days. After the end of treatment, rats fasted overnight and after 24 h, they were sequentially anesthetized with anesthetic ether for about 30-40 sec. The blood was withdrawn by retro-orbital puncture. Each blood sample was collected into separate vials for the determination of serum parameters.

Preparation of serum samples and biochemical estimations: The serum was separated by centrifugation using an eppendorf cryocentrifuge (model no. 5810, Eppendorf, Hamburg, Germany), maintained at 4°C and run at a speed of 7000 rpm for 15 min. The levels of High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), triglyceride (TG) and Total Cholesterol (TC) were measured by a spectrophotometer (UV-visible spectrophotometer, Jasco V-530, Tokyo, Japan) using commercially available reagent kits according to procedure provided by manufacturer (Accurex Biomedical Pvt. Ltd., Mumbai, India) EN.CITEEN.CITE.DATA[46-52].

Statistical analysis: All statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software, Inc, La Jolla, CA, USA). Data of body weight and biochemical measurements was analyzed by separate One-way ANOVA followed by Dunnett's test separately for each parameter. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

Preliminary phytochemical screening: The PE-PCF showed the presence of steroids and volatile oils. The ET-PCF showed the presence of glycosides, flavonoids, tannins, steroids and phenolic compounds. The AQ-PCF showed the presence of glycosides, flavonoids, tannins and phenolic compounds (Table 1).

Acute oral toxicity study: The AQ-PCF, ET-PCF and PE-PCF were found to be safe up to the dose of 5000 mg kg^{-1} p.o. No mortality or any toxic reactions were observed up to the end of the study period (Table 2).

Effect of AQ-PCF and PE-PCF on HFD-induced alteration in body weight, serum lipid profile and Atherogenic index of rats: There was significant increased ($p<0.001$) in the body weight of the HFD control rats as compared to the normal group. However, increased in the body weight was significantly decreased ($p<0.05$) by treatment with AQ-PCF (400 mg kg^{-1}) as well as PE-PCF (100, 200 and 400 mg kg^{-1}) treatment as compared to HFD control rats. Administration of atorvastatin (1.2 mg kg^{-1}) also showed significant inhibition ($p<0.001$) in HFD induced increased in body weight as compared to HFD control rats (Table 3).

Table 1: Phytochemical analysis of AQ-PCF, ET-PCF, and PE-PCF

Test	AQ-PCF	ET-PCF	PE-PCF
Carbohydrate			
Molish test	+	-	-
Reducing sugar			
Fehling's test	+	+	-
Benedict's test	+	+	-
Monosaccharides			
Barfode's test	-	-	-
Proteins			
Biuret's test	+	-	-
Millon's test	+	-	-
Protein containing sulphur	-	-	-
Protein containing Tyrosin and tryptophan			
Xanthoprotein test	-	-	-
Amino acid			
Ninhydrine test	+	+	-
Tannins and phenol			
Ferric chloride test	+	+	-
Lead acetate	-	+	-
Pottasium permagnate	-	+	-
Glycosides			
Cardiac glycosides			
Legal's test	+	+	-
Keller killani test	+	+	-
Anthraquinone glycosides			
Test	MI-ALC	MI-AQE	SI-ALC
Borntragers's test	-	-	-
Saponins			
Foam test	+	+	-
Flavonoids			
Shinoda test	+	+	-
Alkaloids			
Mayer's test	-	-	-
Wagner's test	-	+	-
Hager's test	+	+	-
Dragendroff's test	+	+	-
Steroids			
Salkowaski test	+	-	+
Liberman-Burchard reaction	+	-	+
Libermann's test	+	-	+

+: Positive test, -: Negative test, AQ-PCF: Aqueous extract of *Prosopis cineraria* fruit, ET-PCF: Ethanolic extract of *Prosopis cineraria* fruit, PE-PCF: Petroleum ether extract of *Prosopis cineraria* fruit

Table 2: Acute toxicity study of AQ-PCF, ET-PCF and PE-PCF

	Dose (mg kg^{-1}, p.o.)				
Extracts	175	550	1750	2000	5000
AQ-PCF	0	0	0	0	0
ET-PCF	0	0	0	0	0
PE-PCF	0	0	0	0	0

0: Alive, X: Dead, AQ-PCF: Aqueous extract of *Prosopis cineraria* fruit, ET-PCF: Ethanolic extract of *Prosopis cineraria* fruit, PE-PCF: Petroleum ether extract of *Prosopis cineraria* fruit

Table 3: Effect of AQ-PCF, ET-PCF and PE-PCF on HFD-induced alteration in body weight, serum lipid profile and atherogenic index of rats

Treatment (mg kg^{-1})	Body weight (g)	Triglyceride (mg %)	Cholesterol (mg %)	HDLC (mg %)	LDLC (mg %)	VLDLC (mg %)	LDL:HDL	Atherogenic index
Normal	234.8±4.78	81.90±4.34	71.42±3.65	60.49±2.09	27.34±2.12	16.38±0.86	0.45±0.04	0.18±0.05
HFD Control	350.8±6.85$^{###}$	327.1±18.60$^{###}$	168.9±5.29$^{###}$	43.40±2.40$^{###}$	64.99±1.16$^{###}$	65.42±3.72$^{###}$	1.52±0.10$^{###}$	2.94±0.19$^{###}$
AT (1.2)	276.3±11.77***	131.2±8.74***	88.64±4.32***	56.21±2.19***	34.43±3.38***	26.25±1.74***	0.61±0.05***	0.59±0.11***
AQ-PCF (100)	320.5±7.49	309.5±7.31	159.4±7.81	43.69±2.13	62.71±1.45	61.89±1.46	1.45±0.09	2.71±0.29
AQ-PCF (200)	316.0±11.83	311.2±14.70	144.0±5.54	47.09±2.19	59.94±2.45	62.25±2.93	1.28±0.06	2.08±0.17
AQ-PCF (400)	305.8±12.02*	288.6±16.44	139.0±7.38*	46.31±2.45	56.79±0.92	57.71±3.28	1.24±0.07	2.06±0.27*
ET-PCF (100)	309.8±7.26*	271.9±16.09	157.2±6.23	48.54±2.70	61.43±2.17	54.38±3.21	1.29±0.11	2.31±0.29*
ET-PCF (200)	302.5±9.42**	240.8±16.11***	142.9±4.66*	52.82±2.09*	49.67±2.55***	48.16±3.22***	0.94±0.06***	1.71±0.09***
ET-PCF (400)	275.5±15.81***	197.1±11.59***	126.2±5.51***	54.76±2.49**	45.63±1.55***	39.41±2.31***	0.84±0.05***	1.32±0.15***
PE-PCF (100)	307.0±7.59*	288.5±17.57	149.3±7.77	44.56±1.39	60.87±1.63	57.71±3.51	1.36±0.02	2.36±0.20
PE-PCF (200)	305.8±7.44*	273.8±13.73	138.9±5.42*	50.29±1.58	59.01±2.95	54.75±2.74	1.17±0.06**	1.77±0.12**
PE-PCF (400)	304.5±8.95*	262.1±12.45*	142.0±9.84*	53.79±1.54**	54.82±2.74*	52.42±2.49*	1.02±0.04***	1.65±0.21***

Data are expressed as Mean±SEM and analyzed by One-Way ANOVA followed by Dunnett's post-tests, $^{###}$p<0.001 as compared with normal group and *p<0.05, **p<0.01, ***p<0.001 as compared with HFD control group, HFD: High fat diet, AT (1.2): atorvastatin (1.2 mg g^{-1}, p.o.) treated, AQ-PCF: Aqueous extract of *Prosopis cineraria* fruit, ET-PCF: Ethanolic extract of *Prosopis cineraria* fruit, PE-PCF: Petroleum ether extract of *Prosopis cineraria* fruit (n = 6)

When compared with normal rats, HFD control rats showed significantly increased (p<0.001) triglyceride, cholesterol, LDLC, VLDLC, LDL to HDL ratio and atherogenic index whereas, HDL-C level was decreased significantly (p<0.001). Administration of AQ-PCF (400 mg kg^{-1}) showed significant inhibition (p<0.05) in HFD induced alterations in Cholesterol level and atherogenic index whereas PE-PCF (200 and 400 mg kg^{-1}) showed significant inhibition (p<0.05) in HFD induced alterations in triglyceride, Cholesterol, HDLC, LDLC and VLDLC whereas, LDL to HDL ratio and atherogenic index were significantly and dose-dependently decreased (p<0.01 and p<0.001) by PE-PCF (200 and 400 mg kg^{-1}) treatment as compared to HFD control rats. Atorvastatin (1.2 mg kg^{-1}) treatment also showed significant inhibition (p<0.001) in the HFD-induced alterations in triglyceride, Cholesterol, HDLC, LDLC, VLDLC, LDL to HDL ratio and atherogenic index as compared to HFD control group (Table 3).

Effect of ET-PCF on HFD-induced alteration in body weight, serum lipid profile and Atherogenic index of rats: The HDF induced increased in the body weight was significantly and dose-dependently decreased (p<0.05, p<0.01 and p<0.001, repectively) by treatment with ET-PCF (100, 200 and 400 mg kg^{-1}) treatment as compared to HFD control rats. Administration of ET-PCF (200 and 400 mg kg^{-1}) showed significant and dose dependent inhibition (p<0.01 and p<0.001) in HFD induced alterations in triglyceride, cholesterol and HDLC levels whereas, LDLC, VLDLC, LDL to HDL ratio and atherogenic index were significantly (p<0.001) inhibited as compared to HFD control group (Table 3).

DISCUSSION

Atherosclerosis is a complex disease arise due to consequences of various processes including inflammatory, fibro-fatty, proliferative response lead to damage of smooth muscle cells, monocyte-derived macrophages, T-lymphocyte and platelet[53]. Hypercholesterolemia, a high cholesterol diet and oxidative stress increase serum LDL levels resulting in increased risk for development of atherosclerosis[54]. Thus, in development and progression of atherosclerosis, hypercholesterolemia plays a vital role[55,56].

One of major sterol in animal tissue is cholesterol and its important source is dietary intake. Cholesterol synthesized in all animal tissue. However, cholesterol can also be synthesized indigenous in the body by the liver and other tissues. It is important to relate to its role in the stabilization of membrane structures, because of its rigid planar structure. It also as a precursor for the synthesis of steroid hormones. Increased

amount of cholesterol leads to cardiovascular disease particularly Coronary Heart Disease (CHD)[57]. The important function is metabolism of bile acid and synthesis of steroid hormones and vitamin D. However, an excess cholesterol synthesis leads to formation of plaque lining within arteries caused decrease blood flow and eventually results in Coronary Artery Disease (CAD)[58]. Moreover, almost half of the Congestive Heart Failure (CHF) has occurred due to CAD.

The activity of HMG-CoA reductase increased significantly after injection of HFD. It has been well documented that increased activity of HMG-CoA reductase resulted in the higher availability of acetyl-CoA that stimulated the cholesterol synthesis. Lecithin Cholesterol O-acyltransferase (LCAT) is an enzyme that responsible for transesterification of cholesterol and its activity reported to be inhibited by HFD resulted in hypercholesterolemia[59]. The decreased activity of LCAT caused inhibition of HDLC maturation from cholesterol thus flux of cholesterol through cell membranes into HDL is reduced, which in turn increased the concentration of cholesterol. The elevated level of cholesterol leads to downregulation of LDL receptors thus levels of serum LDLC increased significantly via modulation of hepatic LDLR activity. Moreover, inhibition of elevated oxidation along with LDL may provide protection against cardiovascular disease arise from atherosclerosis. VLDL serves as a rich source of triglycerides and also harmful to arterial lining[60]. Thus elevated levels of VLDL and triglyceride caused inhibition in HDL-cholesterol level via activation of lipoprotein lipase and lecithin acyl-cholesterol transferase thus resulted in hardening of arteries EN.CITEEN.CITE.DATA[61,62]. In the present investigation, administration of HFD caused a significant increase in the serum triglycerides, total cholesterol, LDLC, VLDLC and atherogenic indices. Thus, significantly increased level of serum LDLC serves as an independent indication of atherosclerosis[23,63] whereas, a significant increased in atherogenic indices indicate atherosclerosis and CHD[62]. However, administration of AQ-PCF (400 mg kg^{-1}), ET-PCF (200 and 400 mg kg^{-1}) and PE-PCF (200 and 400 mg kg^{-1}) showed a significant decrease in serum triglycerides, total cholesterol, LDLC, VLDLC and atherogenic indices indicating beneficial modulatory influence on cholesterol metabolism and turnover reduction in ischemic indices, which may be via facilitating reverse cholesterol transport from peripheral tissues or inhibition of HMG-reductase or inhibition of cholesterol absorption at intestinal level mechanisms.

CONCLUSION

In conclusion, findings of present investigation suggest that presence of bioactive compounds such as flavonoids, glycosides and phenolic contents from *Prosopis cineraria* extract may cause depletion of deposited lipid content from peripheral tissues by reverse cholesterol transport and inhibit foam cell formation. Thus, *Prosopis cineraria* extract has hypolipidemic potential against HFD induced hyperlipidemia, however, further study is needed to unravel its molecular mechanism.

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