

Assessment of the antihyperlipidemic activity of *Capparis divaricata* Lam. in a rat experimental model

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Abstract

Hyperlipidemia, a condition marked by high lipid levels, is major risk factor for cardiovascular diseases although synthetic hypolipidemic agents are available; their prolonged use can lead to negative side effects. Therefore, there is an increasing interest in investigating plant-based alternatives that have low toxicity current aim examine the Antihyperlipidemic effects of *Capparis divaricata* Lam. EECD in Wistar rats with D-fructose-induced hyperlipidaemia Hyperlipidaemia was triggered in rats by administering 25% D-fructose in their drinking water for a period of 21 days. The subjects were categorized into five groups Each group contain 6 animals normal control group, a negative control group (D-fructose), a standard group receiving Fenofibrate at 250 mg/kg and along with two experimental groups that received EECD at dose 250 and 500 mg/kg orally. According to LC-MS analysis flavonoids such as quercetin, kaempferol, rutin, isoquercitrin these major chemical constituents which are responsible for Antihyperlipidemic activity. Characteristics of the lipid profile In addition to a histological analysis of liver samples, factors such as cholesterol, TG, LDL, VLDL, HDL and creatinine were assessed. Administration of EECD produced marked decreases in cholesterol, triglycerides, LDL and VLDL, while progressively recovering HDL concentrations in a dose-dependent manner similar to fenofibrate. Additionally, extract demonstrated enhancements in liver histopathology, characterized by reducing hepatocyte ballooning, reduced steatosis and less leucocyte infiltration. The presence of flavonoids, phenolic compounds, tannins, alkaloids and glycosides was shown by preliminary phytochemical investigation these substances are major responsible the pharmacological effects that were noted. *Capparis divaricata* Lam. demonstrates significant antihyperlipidemic effects in rats with D-fructose-induced hyperlipidemia Its effectiveness is on par with the standard medication fenofibrate highlighting its promise as a natural treatment option for controlling hyperlipidemia.

Keywords:

Hyperlipidemia, *Capparis divaricata* Lam, Ethanolic extract of *Capparis divaricata*, D-fructose, Lipid profile.

Introduction

The most prevalent kind of hyperlipidemia is characterised by aberrant lipid characteristics, including raised levels of low-density lipoprotein (LDL) and unusually high blood levels of one or more lipids or lipoproteins. The condition is caused by intricate interplay between genetic predispositions and environmental circumstances which are important in the development of coronary artery disease and atherosclerosis. Treatment for hyperlipidemia may involve dietary changes and medications that influence lipid metabolism through various mechanisms. It is spotted worldwide, although it is common in the western hemisphere^{1,2}. One important risk factor for the onset of cardiovascular disorders, especially atherosclerotic coronary heart disease (CHD) is hyperlipidemia^{3,4}. For coronary artery disease, hypercholesterolemia and hypertriglyceridemia can hasten atherosclerosis. Increased levels of bad cholesterol build up in the artery's subendothelial region, where they are very toxic to vascular cells and atherogenic, encouraging the development of plaque and vascular injury⁵. Low HDL-C and high TG, LDL-C and VLDL-C values are important markers of hyperlipidemia⁶. A sedentary lifestyle, genetic susceptibility, obesity, diabetes, kidney disease can all contribute to the illness⁷. Members of the genus *Capparis*, specifically the *Capparidaceae* family, include *Capparis divaricata* Lam. With over 80 species, the genus *Capparis* is widely distributed throughout India, particularly in the Deccan Peninsula, which runs from Tamil Nadu to Maharashtra. Glycosides, alkaloids, flavonoids, tannins, and phenolic chemicals are all present in the plant, according to the first phytochemical analyses⁸. *Capparis divaricata* Lam. is a member of the *Capparaceae* family. It is also referred to as *Capparis caerulea* Heyne ex Wall, *Capparis horrida* Banks ex Wight & Arn, and *Capparis reticulata* Klein ex Wall. Commonly known as the spreading caper, *Capparis divaricata* has the vernacular name Pachunda⁹. *Capparis divaricata* has been reported to have various pharmacological activities including Analgesic, Antipyretic, Antioxidant, Anticancer¹⁰⁻¹³, antitubercular¹⁴, locomotor and diuretic properties¹⁵. Based on the literature, the presence of these bioactive phytoconstituents suggests the potential antihyperlipidemic activity of *Capparis divaricata*. Limited evidence exists on the antihyperlipidemic activity of *C. divaricata*. Hence, this plant was selected for the current investigation to explore its therapeutic potential against hyperlipidemia.

Materials and Methods

The plant *Capparis divaricata* Lam. was gathered from the local regions of Aundh Ghatmatha in the Satara district of Maharashtra. Plant specimens were recognized and verified at the Raja Shripatrao Bhagwantrao Mahavidyalaya, Aundh, and an (Accession No. 1123) was submitted for future reference.

Preparation of ethanolic extract of plant *Capparis divaricata* Lam.

Capparis divaricata Lam. leaves were allowed to dry in the shade for eight to ten days at room temperature. The leaves were dried, then cut and processed in a mixer grinder to a fine powder. Following the powdered plant material, the maceration procedure was used to extract it. A drug-to-solvent ratio of 1:5 was employed with ethanol serving as the solvent. In particular, 100 grams of the ground leaves were macerated for 72 hours while being shaken occasionally after being immersed in 500 milliliters of ethanol. After macerating the mixture,

Whatman filter paper was used to filter it and create the ethanolic extract. A water bath was then used to dry the filtrate^{16,17}.

Drugs and chemicals

D-Fructose was procured from Cynor Laboratories Surat and Fenofibrate was obtained from Angle Biopharma Pvt. Ltd. Ahmedabad (Batch No: ACHF240003) Ethanol is purchased from Loba chemie Pvt Ltd Mumbai.

Animals

Healthy Wistar rats, either of sex with weights ranging from 150 to 180 grams, were obtained from the Laboratory Animal House at YSPM's Yashoda Technical Campus, Faculty of M. Pharm, located at Wadhe Phata, NH-4, Satara – 415011 Maharashtra. The animals had access to regular laboratory feed and water at all times while being housed in a climate-controlled environment at (25 ± 1) °C with a 12-hour light/dark cycle. At YSPM's Yashoda Technical Campus in Satara, the Institutional Animal Ethics Committee (IAEC) gave its approval to the experimental protocol number(YSPM/YTC/PHARMAIAEC/2022025/(ResearchProposalNo-23067572821003)

D-Fructose induced hyperlipidemia

The primary cause of hyperlipidemia is the rapid and uncontrolled metabolism of D-fructose by the liver which encourages excessive triglyceride production through de novo lipogenesis. In contrast to glucose fructose avoids important glycolysis regulatory processes, which causes an excess of acetyl-CoA and glycerol-3-phosphate the building blocks of triglycerides. Plasma triglyceride levels increase as a result of their release into the circulation as very low-density lipoproteins Chronic use also increases the risk of hepatic insulin resistance and liver fat buildup, which exacerbates lipid imbalance and leads to the development of hyperlipidemia¹⁸.

According to research on animals drinking drinks with 25% fructose for 21 days dramatically raised the risk of hyperlipidemia. In order to cause hyperlipidemia, female Wistar rats were provided with drinking water that contained 25% fructose over a period of 21 days¹⁹

Role of fenofibrate in hyperlipidemia

The primary mechanism of action of the lipid-lowering medication fenofibrate is the activation of a nuclear receptor known as When PPAR- α is activated, it decreases the synthesis of apolipoprotein C-III (ApoC-III), an inhibitor of LPL while increasing the expression of genes related to fatty acid oxidation lipoprotein lipase (LPL) activity and HDL formation. Triglyceride-rich lipoproteins are broken down more effectively blood triglycerides are decreased, HDL cholesterol is raised and the lipid profile is improved overall²⁰.

Experimental protocol

Healthy wistar rats having weight 150-180 gm were used for study total 30 number of animal taken each group contain (n= 6) animals

Group I: Normal control: Administered distilled water only.

Group II: D- fructose induced group: Administered 25% D-fructose solution without treatment.

Group III: Fenofibrate treated group: Administered 25% D-fructose + Fenofibrate (250 mg/kg, p.o.)

Group IV: Low dose of extract EECD :Administered 25% D-fructose + Ethanolic Extract of *Capparis divaricata* (EECD) at 250 mg/kg(p.o.)

Group V: High dose of extract EECD : EECD treated group administrated D- Fructose (25% Drinking water+EECD 500mg/kg (p.o)

To induce hyperlipidaemia rats were provided with drinking water that contained 25% D-fructose for duration of 21 days. Fenofibrate (250 mg/kg) was administered orally as the standard reference treatment²¹.

Animals fasted for a whole night at the conclusion of the treatment session. After administering ketamine anaesthesia and collecting blood samples using the retro-orbital technique, serum was separated for the measurement of lipid markers, including creatinine, HDL, LDL, VLDL, triglycerides, cholesterol, and triglycerides. Using Merrill Biochemistry Kits and the Merrill Biochemistry Analyser to assess histopathological changes made this process easier.

Histopathological examination

Six rats from each group were taken for liver histology. After sacrifice, the livers were fixed in 10% formalin, embedded in paraffin, and cut into thin sections. The slides were stained with H&E and observed under a microscope.

Statistical analysis

In GraphPad InStat 3.10.5 for Windows, the mean ± Standard Error of the Mean (SEM) was used to represent the data. The Tukey-Kramer Multiple Comparisons Test and one- and two-way analysis of variance (ANOVA) were part of the statistical evaluation. Statistical significance was defined as a P-value of less than 0.05.

Result

Initial chemical test showed EECD contain alkaloid, flavonoids ,tannin, glycoside, carbohydrate , phenolic compound but does not contain steroids and proteins

Table 1. Phytochemical Tests

Sr. no	Phytochemical Tests	Results
1	Test for Alkaloids	+ve
2	Test flavonoids	+ ve
3	Test for Carbohydrate	+ ve
4	Test for Glycosides	+ ve
5	Test for Tannin	+ve
5	Test for Phenolic compound	+ ve
6	Test for Steroids	-ve
7	Test for Proteins	-ve
8	Test for Saponin	+ve

The LC-MS analysis of *Capparis divaricata* Lam. revealed the presence of several bioactive flavonoids, including quercetin, kaempferol, isoquercetin and rutin (Table 2, Fig.1).

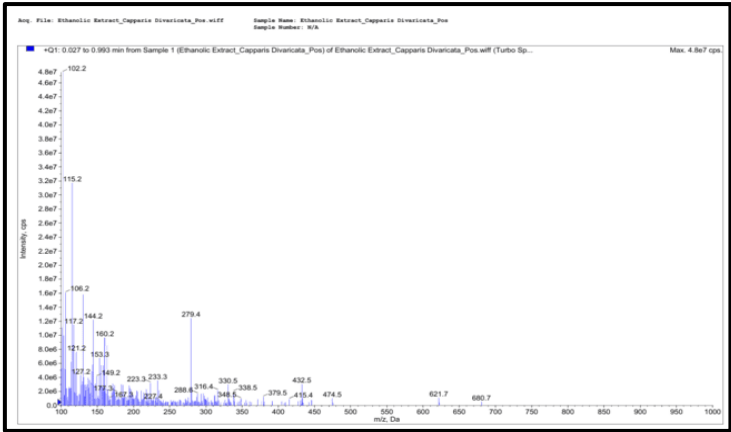


Fig 1. LC MS of EECD

Table 2. LC-MS of plant Capparis divaricata Lam

Observed m/z (Da)	Possible Phytochemical	Chemical Formula	MolecularWeight (Da)	Compound Class
102.2	Acetaminophen (fragment)	C8H9NO2	151.16	Phenolic compound
115.2	Valine (fragment)	C5H11NO2	117.15	Amino acid
144.2	Caffeic acid (fragment)	C9H8O4	180.16	Phenolic acid
160.2	Quercetin (fragment)	C15H10O7	302.24	Flavonoid
223.3	Rutin (fragment)	C27H30O16	610.52	Flavonoid glycoside
279.4	Kaempferol	C15H10O6	286.24	Flavonoid
330.5	Sinapic acid derivative	C11H12O5	224.21	Phenolic acid
432.5	Isoquercitrin	C21H20O12	464.38	Flavonoid glycoside
621.7	Tannic acid (fragment)	C76H52O46	~1700	Hydrolyzable tannin
680.7	Possibly ellagitannin	Variable	~680	Tannin (polyphenol)

Lipid profile

25% D-fructose was administered for 21 days, the fructose-induced group their blood cholesterol, triglycerides, LDL, VLDL, and creatinine levels increased compared with normal control group (table 3-4).

Treatment with fenofibrate (250 mg/kg) and ethanolic extract of *C. divaricata* (250 and 500 mg/kg) produced significant (P<0.001) reductions in cholesterol, triglycerides, LDL, VLDL, and creatinine, accompanied by marked improvement in HDL levels compared with the diseased control. The effects were dose-dependent and comparable to those of the standard drug fenofibrate (Table 3-4).

Table 3. Effect of Capparis divaricata Lam. extract on the serum lipid profile in rats with fructose-induced hyperlipidemia

Groups	Cholesterol(mg/dl)	TG(mg/dl)	LDL(mg/dl)
Normal control	49± 1.20	105.00±2.00	11±0.50
Negative control	130± 1.50 r	280±2.50 r	54± 1.00 r
Positive control	58±1.00 c	130±1.80 c	17±0.70 c
Test group 1	73±1.20 c, r	160± 2.00 c,r	32± 1.00 c,r
Test group 2	66±1.10 c, r	140±1.80 c,r	25± 0.60 c,r

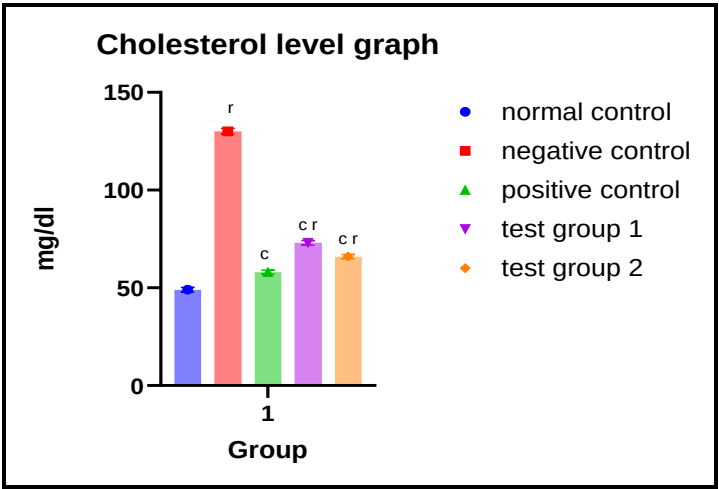
Values are mean ± SEM (n=6) Statistical significance determined by ANOVA followed by Tukey-Kramer test, $p < 0.05$ considered significant. $a < 0.05, b < 0.01, c < 0.001$ negative control group , $p < 0.05, q < 0.01, r < 0.001$ positive control group

Table 4. . Effect of Capparis divaricata Lam. extract on the serum lipid profile in rats with fructose-induced hyperlipidemia

Groups	VLDL(mg/dl)	HDL(mg/dl)	Creatinine(mg/dl)
Normal control	15±1.00	35 ±1.00	0.95±0.0057
Negative control	54± 1.00 r	22±1.00 r	2.045±0.0147 r
Positive control	17± 0.70 c	41±1.00 c	1.735±0.0076 c
Test group 1	32± 1.00 c,r	36±1.10 c,r	1.625±0.007 c,r
Test group 2	25± 0.60 c,r	38± 1.00 c,r	1.55±0.014 c,r

Values are mean ± SEM (n=6) Statistical significance determined by ANOVA followed by Tukey-Kramer test, $p < 0.05$ considered significant. $a < 0.05, b < 0.01, c < 0.001$ negative control group , $p < 0.05, q < 0.01, r < 0.001$ positive control group

Fig. No. 02: Effect of Capparis divaricata Lam. ethanolic extract on serum cholesterol levels in normal control, D- fructose induced group, Fenofibrate treated group , ethanolic extract–treated groups.

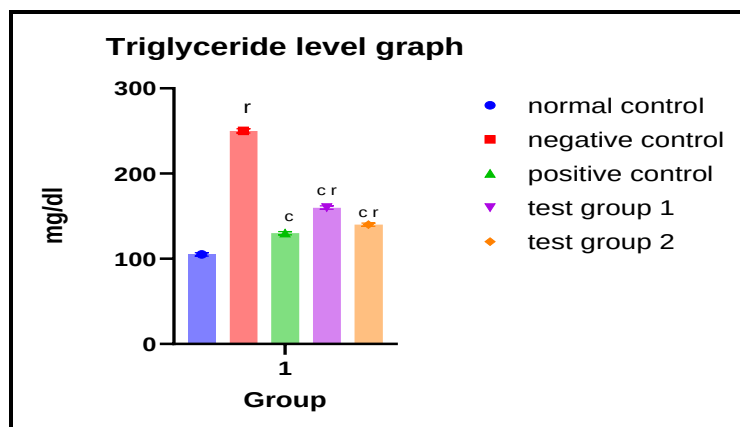


Result are expressed as mean $\pm$ SEM (n=6) comparison between the group was made by one way analysis of variance (ANOVA) followed by Turkey multiple comparison test. p values less than 0.05 was considered as statically significant a, b, c = $a < 0.05$, $b < 0.01$, $c < 0.001$. negative control compared with all group p, q, r = $p < 0.05$, $p < 0.01$, $p < 0.001$ positive control compared with all group

Significance

1. The positive control group cholesterol levels were significantly lower ($P < 0.001$) than those of the negative control group
2. The cholesterol levels of the group treated with ethanolic extract were significantly ($P < 0.001$) lower than those of the negative control group.

Fig No 03. Effect of Plant *Capparis divaricata* Lam. ethanolic extract on serumTriglyceride levels in normal control, 25% D-fructose (negative control), Fenofibrate (positive control), and ethanolic extract–treated groups.

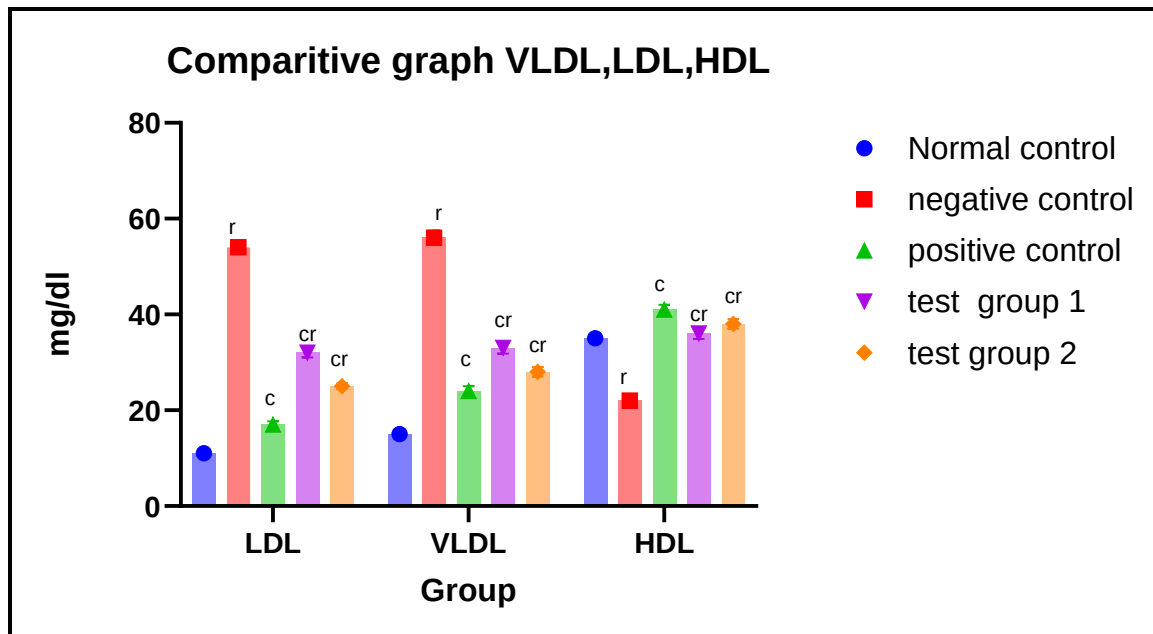


Result are expressed as mean $\pm$ SEM (n=6) comparison between the group was made by one way analysis of variance (ANOVA) followed by Turkey multiple comparison test. p values less than 0.05 was considered as statically significant a < 0.05 , $b < 0.01$, $c < 0.001$ compared with positive control group $p < 0.05$, $q < 0.01$, $r < 0.001$ show significant values

Significance

1. The positive control group triglyceride levels were significantly lower ($P < 0.001$) than those of the negative control group.
2. The Triglyceride levels of the group treated with ethanolic extract were significantly ($P < 0.001$) lower than those of the negative control group

Fig No 04. Effect of Plant *Capparis divaricata* Lam. ethanolic extract on serum LDL, VLDL, HDL in 25 % Fructose group(negative control), fenofibrate (standard group) and ethanolic extract treated group

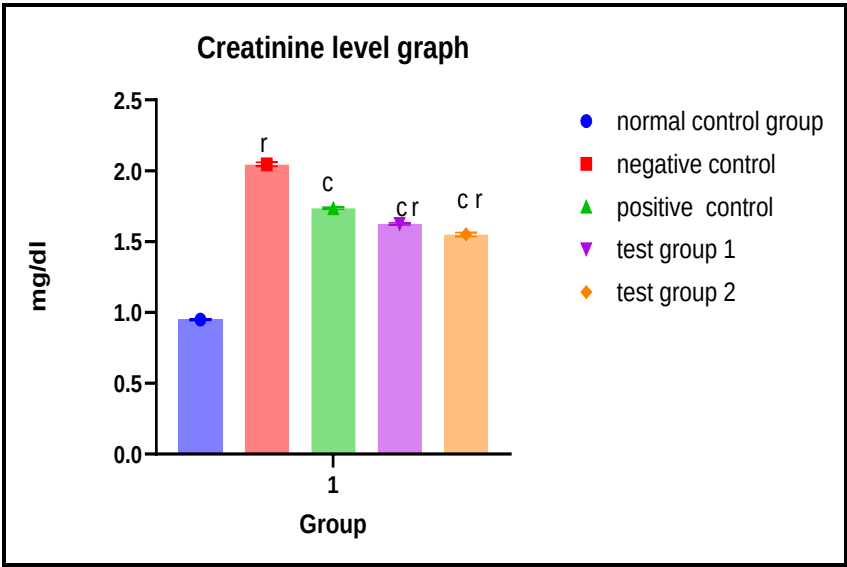


Result are expressed as mean $\pm$ SEM (n=6) comparison between the group was made by Two way analysis of variance (ANOVA) followed by Tukey multiple comparison test p values less than 0.05 was considered as stastically significant a < 0.05, b < 0.01, c < 0.001 negative control compared with all group p, q, r = $p < 0.05$, $p < 0.01$, $p < 0.001$ positive control compared with all group

Significance

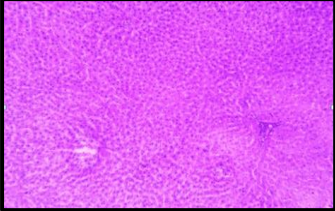
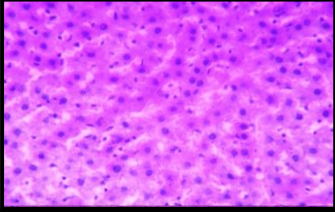
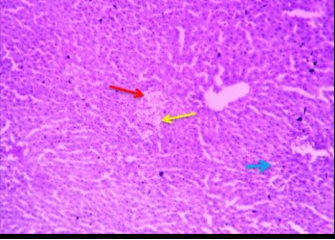
1. The positive control group LDL and VLDL values were significantly lower ($P < 0.001$) than those of the negative control group.
2. The LDL and VLDL levels in the group treated with ethanolic extract were significantly ($P < 0.001$) lower compared to those in the negative control group.
3. A notable increase ($P < 0.001$) in HDL levels was noted in both the positive control and the groups treated with ethanolic extract, in comparison to the negative control group.

Fig No 05. Effect of Plant *Capparis divaricata* Lam. ethanolic extract on Creatinine in 25 % Fructose group, fenofibrate treated group and EECD 250, 500 treated



Result are expressed as mean± SEM (n=6) comparison between the group was made by Two way analysis of variance (ANOVA)followed by Tukey multiple comparison test p values less than 0.05 was considered as stastically significant a < 0.05,b<0.01,c<0.001 negative control compared with all group p, q, r = $p < 0.05$, $p < 0.01$, $p < 0.001$ positive control compared with all group

Histopathology of liver

Photograph	Description
	Group – Normal control : normal structure of liver histopathology H&E stain 100X
	Group – Normal control : normal structure of liver histoH&E stain 400X
	Group Diseased control: ballooning of hepatocytes(red arrow), steatosis (yellow arrow), Leucocyte infiltration (indicated by the blue arrow), stained with H & E at 100X magnification.

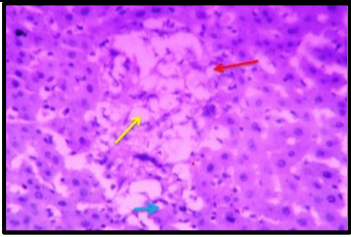
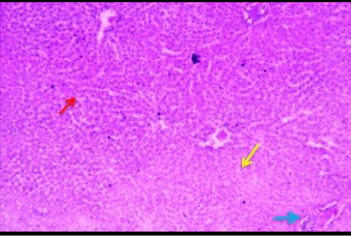
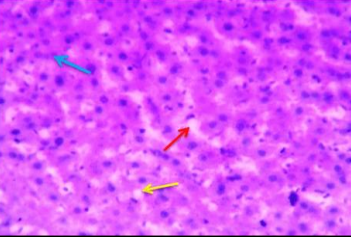
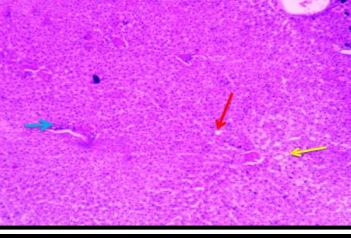
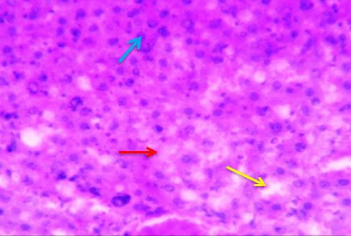
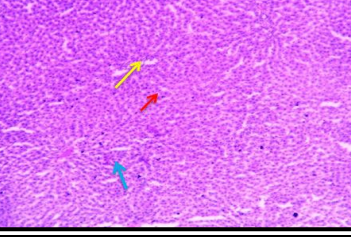
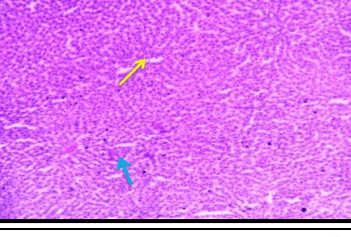
	Group: Disease control: ballooning of hepatocytes(red arrow), steatosis (yellow arrow)leucocyte infiltration(blue arrow),H & E stain 400X
	Group – Standard : -ballooning of hepatocytes (red arrow), steatosis (yellow arrow), leucocytic infiltration (blue arrow) ,H&E stain 100 X
	Group – Standard : ballooning of hepatocytes (red arrow), steatosis (yellow arrow), Leucocyte infiltration (indicated by the blue arrow), stained with H & E at 100X magnification.
	Group - Test I : ballooning of hepatocytes (red arrow), steatosis (yellow arrow), leucocyte infiltration stained with H & E at 100X magnification
	Group - Test I : ballooning of hepatocytes (red arrow), steatosis (yellow arrow), leucocytic infiltration (blue arrow) H&E stain 400 X
	Group – Test II : ballooning of hepatocytes (red arrow), steatosis (yellow arrow), leucocytic infiltration (blue arrow) H&E stain 100 X
	Group – Test II : ballooning of hepatocytes (red arrow), steatosis (yellow arrow), leucocytic infiltration (blue arrow) H&E stain 400 X

Fig 6. Histopathology of liver in D- Fructose induced model in rats

In an experimental study conducted over a period of 21 days, the liver histology of rats was examined Rats in the hyperlipidemic group were fed a diet consisting of 25% fructose, and their liver histology revealed

Table 5 . Histopathology of rat in D- Fructose induced model

Group	Ballooning of hepatocytes- Fatty changes	Steatosis	Leucocytic infiltration
Group Normal control	+	+	+
Group negative control	+++	+++	+++
Group Standard	++	+	+
Group Test I	++	++	+
Group Test II	++	+	+

Where += mild Changes, ++ = moderate changes, +++ = severe change

Discussion

The current investigation has demonstrated that the ethanolic extract of *Capparis divaricata* Lam. significantly improved the lipid profile in hyperlipidemic rats. The treatment resulted in decreased levels of serum cholesterol, triglycerides, LDL, and VLDL, while increasing HDL levels, which indicates its substantial antihyperlipidemic potential. Furthermore, the extract also lowered creatinine levels, suggesting an additional nephroprotective effect in lipid-stressed animals.

Reports of similar lipid-lowering effects have emerged from other *Capparis* species, such as *Capparis spinosa* and *Capparis decidua*, highlighting the genus's broad antihyperlipidemic potential. Improvements in lipid profiles have also been noted with fenofibrate, the standard pharmaceutical, although plant extracts offer the additional advantage of antioxidant support. Thus, the outcomes of this study are consistent with prior reports and extend the pharmacological relevance to *Capparis divaricata*, which has been less frequently studied.

D-fructose induces hyperlipidemia by promoting excessive fat production in the liver. It bypasses normal metabolic regulation, leading to increased formation of acetyl-CoA, which enhances de novo lipogenesis and triglyceride synthesis. These triglycerides are released into the blood as VLDL, raising serum lipid levels. Fructose also reduces fat oxidation and causes insulin resistance, further worsening lipid imbalance. This results in elevated triglycerides, increased LDL, and decreased HDL, contributing to a hyperlipidemic state²³.

The observed effects can be attributed to the phytochemical constituents present in *Capparis divaricata*, such as flavonoids, alkaloids, glycosides, Tanin , phenolic compounds which are well known for their antioxidant and antihyperlipidemic activity majorly flavonoids

Similar lipid-lowering effects have been observed in other *Capparis* species, such as *Capparis spinosa* and *Capparis decidua*, emphasizing the genus's overall antihyperlipidemic potential. Similar enhancements in lipid profiles have also been recorded with fenofibrate, the

conventional medication, although extracts from plants offer the extra advantage of antioxidant support. Therefore, the findings from this study align with earlier reports and broaden the pharmacological significance to *Capparis divaricata*, which has received less attention in research.

Flavonoids lower cholesterol by inhibiting HMG-CoA reductase, activating AMPK, and regulating SREBP and PPAR pathways, which reduce lipid synthesis and enhance fatty acid oxidation. Their antioxidant and anti-inflammatory actions prevent lipid peroxidation and improve vascular health, resulting in decreased TC, TG, LDL, VLDL and increased HDL²⁴ creatinine primarily serves as a sign of renal function. The kidneys may be stressed by excessive triglycerides and cholesterol, which raises creatinine levels. The observed drop in creatinine following ethanolic extract administration implies that the extract may possibly aid in kidney protection in addition to decreasing This effect is probably brought about by an increase in metabolism overall and a decrease in stress connected to fats.

Future Scope

The upcoming research will encompass collective impact of different phytoconstituents. Future investigations should prioritize the isolation of particular active constituents and assess their separate and combined effects on lipid regulation.

Conclusion

With potential to lower cholesterol, triglycerides, LDL, VLDL, and creatinine levels while raising HDL levels, the study demonstrated how the EECD improves lipid profiles. Since it works similarly to the common medication fenofibrate, its promise as a natural medicinal agent for the treatment of hyperlipidaemia is confirmed.

Acknowledgement

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Conflict of interest

According to the writers, they have no conflicts of interest.

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