ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 7, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

EVALUATION OF HYPOLIPIDEMIC ACTIVITY OF OPUNTIA ELATIOR FRUIT JUICE IN HIGH-FAT DIET-INDUCED HYPERLIPIDEMIA IN WISTAR ALBINO RATS

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Received: 10 April 2025, Revised and Accepted: 26 May 2025

ABSTRACT

Objectives: Evaluate the hypolipidemic activity of *Opuntia elatior* fruit juice (OFJ) in normal diet and high-fat diet-fed *Wistar* albino rats by plasma lipid profiles and compare it with atorvastatin. Assess the effect of *O. elatior* (OE) and atorvastatin on lipid accumulation in the liver by histopathological examination.

Methods: Hyperlipidemia was produced in rats by feeding them with cholesterol powder (2%) mixed with butter (10%). A total of six groups, six rats per group, divided into normal control (NC), disease control (DC), active control (AC), extract control, test group 1 (low-dose [LD] herb 5 mL/kg), and test group 2 (high-dose [HD] herb 10 mL/kg). Estimation of lipid profile levels, serum urea, and serum creatinine was done at different time intervals. OFJ was used at two different doses of 5 ml/kg (LD) and 10 ml/kg (HD) in test groups. At the conclusion of the experiment, the animals were euthanized in accordance with ethical guidelines, and liver tissues were collected for histopathological analysis.

Results: At both 5 mL/kg and 10 mL/kg doses, OFJ showed a significant reduction ($p<0.05$) of total cholesterol, triglycerides (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein and an increase in high-density lipoprotein when compared with DC group at the end of 8th week. The HD group showed more reduction in VLDL and TG than the AC group.

Conclusion: OE showed hypolipidemic activity.

Keywords: Hypolipidemic, *Opuntia elatior*, Cholesterol, Lipid profile.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i7.54619. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

India has experienced a significant change in its epidemiology during the past few decades. The prevalence of cardiovascular disease (CVD) is highest in India [1]. Data from the World Health Organization's Global Health Observatory indicate that elevated cholesterol is a contributing factor in nearly one-third of ischemic heart disease cases. Globally, it is associated with 4.5% of total deaths, approximately 2.6 million, and accounts for 2.0% of disability-adjusted life years, representing around 29.7 million years lost to ill-health, disability, or early death [2]. High blood pressure, high cholesterol, tobacco use, diabetes mellitus, and obesity are the five main modifiable risk factors that are prevalent in developed countries and account for around one-third of all CVD cases [3]. Hyperlipidemia is defined as low-density lipoprotein (LDL), total cholesterol (TC), triglyceride (TG), or lipoprotein (a) level >90th percentile, or a high-density lipoprotein (HDL) level <10th percentile compared to the general population [4]. Due to the strong association between lipid abnormalities and cardiovascular disorders, hyperlipidemia poses a significant challenge for health-care providers [5,6]. The development of cardiovascular disease is significantly influenced by increased levels of LDL cholesterol, as is widely acknowledged [7].

Statins and fibrates are the most commonly prescribed drugs for treating hyperlipidemia. Statins are lipid-lowering agents that block cholesterol production by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase [8]. The fibrates area class of peroxisome proliferator-activated receptor alpha agonists predominantly promotes fatty acid oxidation [9]. The most severe side effect of all statins, whether used alone or in combination, is myopathy that progresses to rhabdomyolysis and renal failure, and it appears to be dose-related. Since statin is intended to be used for a long period, there may be a risk of long-term harmful consequences such as cancer, teratogenicity, and mutagenicity [10]. Therefore, the use of traditional medicines – and especially the use of phytochemical compounds – is significantly increasing globally. Herbal medicines have better compatibility and allow greater tolerance even with prolonged use, it is also more economical, safe, and therapeutically effective [11].

The plant *Opuntia elatior* (OE) belongs to the Cactaceae family, which is thought to include about 1500 species and 130 genera spread out across the world. OE, commonly known as "Hathlo Thor," bears edible fruits traditionally consumed by tribal communities in the Saurashtra region of Gujarat, India. These fruits are valued for their hematinic, anti-asthmatic, and spasmolytic properties. Due to their edible nature, they are also referred to as prickly pears [12]. According to studies, OE contains the flavonoid quercetin, which exhibits potent antioxidant properties [13]. The hypolipidemic, hepatoprotective effect of flavonoid quercetin has already been shown in various studies [13-15]. Therefore, the purpose of the current study was to assess the hypolipidemic activity of OE fruit juice (OFJ) and to compare it with atorvastatin in rats by utilizing a high-fat, high-cholesterol diet model.

METHODS

(a) Experimental animals: 36 *Wistar* Albino rats were used for the experiment. Inclusion criteria: Sex (three males and three females/group), weight 150–200 g, and age 8–12 weeks were included in

the study. Exclusion criteria: Pregnant females, any visible signs of injury or illness or any congenital abnormalities, previously exposed to any pharmacological agents or experimental procedures were excluded from the study. Wistar rats were selected for this study due to their established responsiveness to high-fat–high-cholesterol diets, which induce significant alterations in lipid profiles and liver histopathology, as demonstrated in previous research [16]. The animals used in this study were sourced from the Central Animal House at Government Medical College, Bhavnagar, Gujarat, India. Animals were maintained in clear polycarbonate enclosures under standardized conditions, including a 12-h light/dark cycle, ambient temperature of 25±2°C, and relative humidity of 50±10%.

(b) Chemicals: Cholesterol powder was procured from High Purity Laboratory Chemicals Pvt. Ltd., Mumbai, India. Atorvastatin Calcium powder: Gift sample from Torrent Pharmaceuticals Ltd., Torrent Research Center, Ahmedabad, Gujarat, India. OFJ: Obtained locally and certified by the botany department, Sir P.P. Institute of Science, Bhavnagar, Gujarat, India.

(c) Dose selection**:** According to previous acute toxicity studies with OFJ on female albino rats (in accordance with OECD guideline 423), no mortality was recorded until 48 h in the animals treated with OFJ up to 20 mL/kg oral dose [17,18]. Based on that, we selected two different doses for the study: Low dose (5 mL/kg) and high dose (10 mL/kg).

(d) Methodology: The study was carried out in the animal room at the Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India. Each group consisted of six rats (n=6) [19]. Animals were categorized into the following groups: Group 1 normal control (NC): Normal diet (ND)+no treatment, Group 2 disease control (DC): High-fat diet (HFD)+no treatment, Group 3 active control (AC): HFD+atorvastatin (1.2 mg/kg), Group 4 extract control (EC): ND+OFJ (5 mL/kg), Group 5 test group 1 (low dose [LD] herb): HFD+OFJ (5 mL/kg), Group 6 test group 2 (high dose [HD] herb): HFD+OFJ (10 mL/kg). The animals were housed in the animal room for a 15-day acclimatization period. After 15 days, a baseline blood sample (1 mL) was obtained for lipid profile, urea, and creatinine after an overnight fast (from retro-orbital vein under ketamine+xylazine anesthesia 75+10 mg/kg i/p), and the weight of each animal was recorded [20]. ND (contained pellets of cereals and pulses [60% wheat and 35% Bengal gram)]) was administered to groups 1 and 4, and HFD (contained Cholesterol powder [2%] mixed with butter [10%]) was administered to groups 2, 3, 5, and 6 from 1st week to 8th week. Treatment (atorvastatin/HD herb/LD herb) began at the end of the 4th week and continued till the 8th week. Blood samples (1 mL) were collected for lipid profile from the retro-orbital vein at the end of the 4th, 6th, and 8th week, and weight of each animal was recorded. The weight of each animal was measured both before and after the study to assess any potential impact of OE on body weight. At the conclusion of the 8-week period, urea and creatinine levels were quantified. Subsequently, the rats were euthanized through the administration of higher doses of ketamine and xylazine. After scarification, a midline incision was made, and the liver was exposed. The liver from each animal was sent for histopathological analysis to a private pathology laboratory. Outcome measures: Serum lipid profile: Serum samples were analyzed for TC (enzymatic-colorimetric [CHOD-PAP method]) [21], HDL-C (direct enzymatic [PVS/PEGME two-point]), and TG (enzymatic [GPO-PAP]-colorimetric) [22], endpoint method, LDL-C (direct enzymatic [PVS/PEGME two-point]) and very LDL (VLDL)-C (calculation). Histopathological analysis: Specimens from the liver were fixed in 10% neutral buffered formalin. Sections were fixed with formalin, and unwanted alcohol was removed by xylene, which allowed infiltration with paraffin wax, stained with hematoxylin-eosin dye [23]. All sections were coded and analyzed by the pathologist (blinded) from a private laboratory without knowledge of diet or treatment plan.

Ethical approval

Approval was taken from the Institutional Animal Ethics Committee (IAEC) of Government Medical College, Bhavnagar, Gujarat, India (IAEC No. 76/2021). All experiments were conducted in compliance with the guidelines set by the Committee for the Control and Supervision of Experiments on Animals.

Statistical analysis

All parameters were expressed as mean±standard deviation (SD). Increases in the mean of weight from baseline to 4th, 6th, and 8th week in each group of animals were compared by Repeated measure analysis of variance (ANOVA) followed by the Tukey Multiple Comparison test. Percentage reduction of various lipid parameters at various study time points was calculated using the following formula: Percentage reduction = $(T_0–T_i)/T_0$ *100 Where, T_0 = Baseline lipid level, T_i = lipid level of respective time point. Percentage reduction was compared between the groups using one-way ANOVA followed by Tukey-Kramer multiple comparison test for parametric data and Kruskal–Wallis test followed by Dunn's multiple comparison test for non-parametric data. Statistical significance was defined as a p-value below 0.05. Statistical analyses were performed using GraphPad InStat, Demo version 3.06.

RESULTS

Lipid parameters

There were no statistically significant differences in lipid parameters between the groups at the start of the study. Group 1 and 4 were fed ND and Group 2,3,5 and 6 were fed HFD for first 4 weeks. At the end of 4th week, groups that were fed HFD showed statistically significant high TC, TG, VLDL, LDL and low HDL compared to groups that were fed with ND. There was no statistically significant difference in any lipid parameter between Group 1 and Group 4 (received ND) and between Group 2, Group 3, Group 5, and Group 6 (received HFD). We took the end of the 4th week as a baseline, as drugs were started at the end of the 4th week for further study to see the effect of OE on lipid parameters at the end of the 6th and 8th weeks.

(Table 1) shows a percentage change of all the lipid parameters at the end of the 6th and 8th weeks compared to the 4th week (baseline). In DC group, a significant increase in the TC, TG, VLDL, and LDL ($p<0.05$) and a significant decrease in the HDL ($p<0.05$) as compared to NC group at the end of the 8th week is seen. In AC group, a significant decrease in the TC, TG, VLDL, and LDL ($p<0.05$) and a significant increase in the HDL ($p<0.05$) as compared to DC group at the end of the 8th week is seen. In LD (5 mL/kg) group, significant changes were observed in TC, TG, VLDL, and HDL ($p<0.05$) when compared with DC group at the end of the 8th week. In HD (10 mL/kg) group, a significant decrease in the TC, TG, VLDL, and LDL ($p<0.05$) and a significant increase in the HDL ($p<0.05$) as compared to DC group at the end of the 8th week is seen. AC group showed more effect on TC, HDL, and LDL compared to the high-dose group, whereas on VLDL and TG, the high-dose treatment group showed more reduction compared to AC.

An intragroup comparison of weight change at the end of the 8th week showed a significant increase ($p<0.05$) in the weight of DC group animals compared to their baseline weight. In the remaining groups, there was no significant weight change at the end of the 8th week compared to the 4th week (Table 2).

When urea and creatinine were compared at the end of the 8th week with baseline levels, none of the groups had any significant change in their levels of laboratory-measured value (Table 3).

Histopathological analysis of liver samples revealed structural changes across groups (Figures 1-6).

DISCUSSION

The "high-fat–high-cholesterol diet-induced hyperlipidemia" model was used in this study. In comparison to other animal models, this model is affordable and simpler to develop [24]. The effect of OE stem extract on lipid modulation was evaluated in Swiss albino mice with gamma radiation-induced hyperlipidemia, comparing the presence (experimental) and absence (control) of *O. elatior* extract (OEE) at a

Table 1: Effect of *Opuntia elatior* and atorvastatin on lipid parameters in rats

Treatment groups (n=6)	Time period	Total cholesterol	High-density lipoprotein	Triglycerides	Very low-density lipoprotein	low-density lipoprotein
Normal control (group 1)	6th week	1.12±4.35	−2.37±19.07	0.06±5.67	−6.85±8.81	1.59±4.17
	8th week	1.89±3.87	−5.598±14.53	3.03±4.66	−5.18±11.03	1.59±4.17
Disease control (group 2)	6th week	12.335±7.67*$	−22.69±12.93	19.78±8.19$	35.89±35.51	34.044±25.61$
	8th week	34.24±13.26$	−43.74±6.84*$	33.66±12.99$	71.36±43.93$	54.83±32.46$
Active control HFD+Atorvastatin	6th week	−6.31±3.41*#	15.57±5.006*#	−5.94±4.16*#	−10.27±0.56*#	−7.12±4.26*#
(1.2 mg/kg) (group 3)	8th week	−22.48±4.01*	32.46±22.35*#	−13.52±6.72*#	−19.13±6.27*#	−15.65±6.56*#
Extract control normal diet+OFJ	6th week	1.61±4.06	6.99±18.71	−3.55±5.45	0.117±13.21	−1.302±9.23
(5 mL/kg) (group 4)	8th week	2.61±3.01@	5.50±16.77	−2.27±8.63	−9.82±19.08	−6.82±7.69
Test group 1 (LD) HFD+OFJ	6th week	1.07±0.44*#	3.99±18.79	−−5.28±7.35#	−11.35±0.05*#	−3.26±8.36#
(5 mL/kg) (group 5)	8th week	−3.65±0.24*@#	10.03±23.60*#	−10.92±13.73#	−11.31±11.21#	0.76±10.08#
Test group 2 (HD) HFD+OFJ	6th week	−4.26±5.44#	3.87±13.73	−7.405±2.33*#	−11.55±2.68*	−12.31±9.33*#
(10 mL/kg) (group 6)	8th week	−9.34±14.79*#	−1.62±28.35#	−19.96±10.97*#	−33.79±10.29*#	−15.89±12.28*#

Values expressed in mean±SD;*: p<0.05 as compared to baseline readings within the groups (repeated measure ANOVA followed by Tukey Multiple Comparison Test) @: p<0.05 active control group versus other groups, #: p<0.05 as compared to disease control group versus other groups, $: p<0.05 as compared to normal control group versus other groups (One way ANOVA followed by Tukey multiple comparison test [parametric data] and by Kruskal–Wallis test followed by Dunn's multiple comparison test [non-parametric data]), HFD: high-fat diet, OFJ: *Opuntia elatior fruit juice*, LD: low dose, HD: high dose, ANOVA: analysis of variance

Table 2: Effect of *Opuntia elatior* and atorvastatin on weight of rats

Treatment group	Weight of animal in grams			
	Baseline	At 4th week	At 6th week	At 8th week
Normal control	285.16±36.34	293.5±37.6	291.66±30.65	293±33.84
Disease control	293.16±24.6	342.6±38.2	368.5±30.78*	371±27.7*
Active control HFD+Atorvastatin (1.2 mg/kg)	311.83±16.26	352.33±22.8*	339.66±20.09	322.83±10.77
Extract Control normal diet+OFJ (5 mL/kg)	294.16±22.2	294.83±22.7	295±19.8	291±28.18
Test group 1 (LD) HFD+OFJ (5 mL/kg)	278.5±32.5	300.66±49.6	310.83±44.92	314.16±37.15

Values expressed in mean±SD. *: p<0.05 compared to baseline within the groups (repeated measure analysis of variance followed by Tukey Multiple Comparison Test). HFD: high-fat diet, OFJ: opuntia elatior fruit juice, LD: low dose, HD: high dose

Table 3: Effect of *Opuntia elatior* and atorvastatin on urea and creatinine

Treatment groups (n=6)	Time period	Urea (mg/dL)	Creatinine (mg/dL)
Normal control (group 1)	Baseline	39±2.19	0.56±0.096
	8th week	39.5±3	0.593±0.104
Disease control (group 2)	Baseline	37.5±1.87	0.681±0.124
	8th week	38.33±2.4	0.691±0.10
Active control HFD+atorvastatin (1.2 mg/kg) (group 3)	Baseline	39±2.36	0.6±0.16
	8th week	41±1.4	0.61±0.155
Extract control normal diet+OFJ (5 mL/kg) (group 4)	Baseline	37.33±1.63	0.58±0.15
	8th week	39.83±1.72	0.58±0.16
Test group 1 (LD) HFD+OFJ (5 mL/kg) (group 5)	Baseline	38.66±5.88	0.58±0.1
	8th week	42±4.81	0.581±0.07
Test group 2 (HD) HFD+OFJ (10 mL/kg) (group 6)	Baseline	39.33±6.7	0.66±0.066
	8th week	39.83±6.4	0.67±0.069

Values expressed in mean±SD. HFD: high-fat diet, OFJ: *Opuntia elatior* fruit juice, LD: low dose, HD: high dose

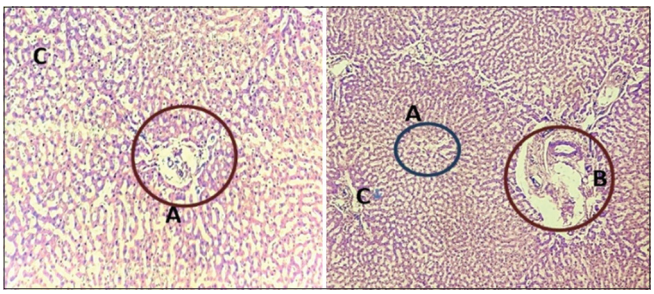

Figure 1: Liver histology (NC [group 1]) shows normal structures, A: Central vein, B: Portal triad: portal vein, hepatic artery, and bile duct, C: Hepatocytes with sinusoidal spaces between them

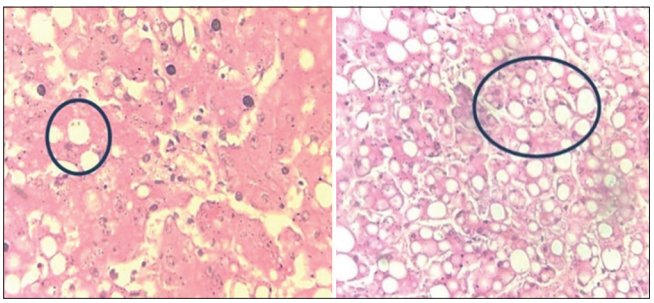

Figure 2: Liver histology (DC [group 2]) shows diffuse areas of ballooning degeneration of hepatocytes, macrovesicular fatty changes (grade-3), and congestion

dose of 10 mg/kg body weight to assess changes in blood cholesterol levels. OEE (acetone solvent) decreased cholesterol levels on day 15 and day 30 compared to day 1. In radiation-induced mice, it decreased cholesterol level on day 30 compared to day 15, but when OEE (ethanol

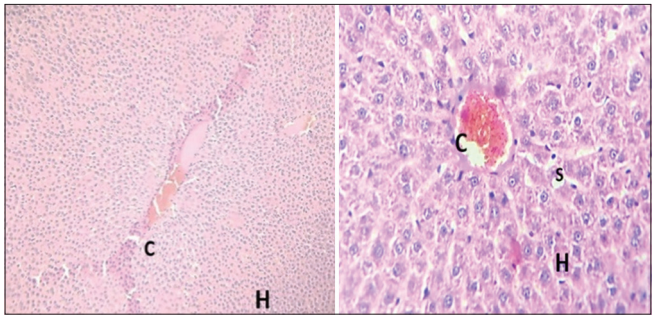

Figure 3: Liver histology (AC [group 3]). C: Central vein, H: Normal hepatocytes, S: Sinusoidal spaces

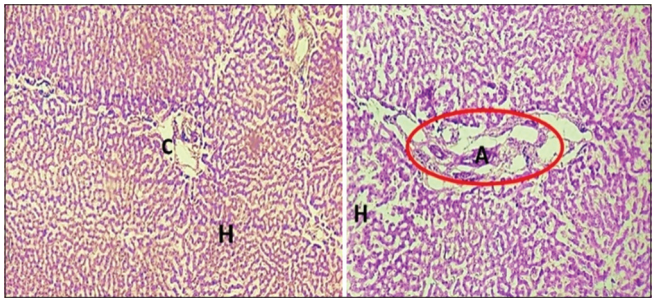

Figure 4: Liver histology (extract control [group 4]). C: Central vein, H: Normal hepatocytes, A: Portal triad: Portal vein, hepatic artery, and bile duct

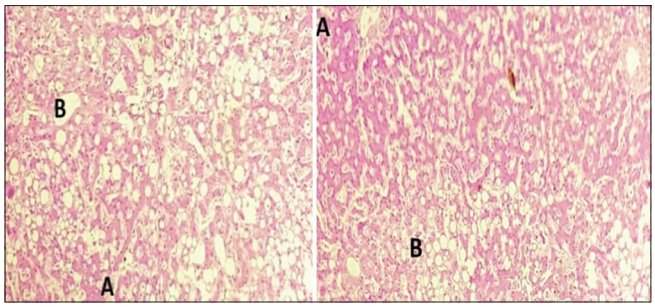

Figure 5: Liver histology ([LD] [group 5]). A: Normal hepatocytes, B: Hepatocytes show microvesicular fatty changes (grade-1)

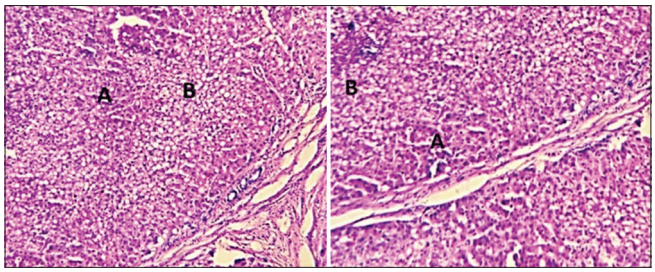

Figure 6: Liver histology ([HD] [group 6]). A: Normal hepatocytes, B: Hepatocytes show microvesicular fatty changes (grade-1)

solvent) was given, cholesterol was increased in herb only and herb plus radiation group on day 30 compared to day 1 and day 15 [25]. Studying the effect of OFJ and quercetin on the lipid profile of streptozotocin-induced diseased rats revealed that TC, TG, LDL, and HDL levels in herb treated group were comparable to DC, whereas TC, TG were significantly high and HDL, LDL were non-significantly high in disease group [26]. There are no other studies available that compare the hypolipidemic activity of OFJ, so we have compared the results of our study with similar studies on herb extracts of different species from the same family. In one study, the effect of three different doses of *Opuntia dillenii,* which is a species from the same family, was measured for the effect of the TC, LDL, HDL, VLDL, and TG on high-fat emulsion diet-induced hyperlipidemia in Sprague-Dawley rats. Herb showed a significant decrease in TC, LDL, HDL, and VLDL and a significant increase in HDL level compared to the normal model (HFD-induced hyperlipidemia) and positive control (high-fat plus zhibituo tablets) group [27]. In another study, the author evaluated different species of opuntia, one of which was opuntia robusta (OR). The impact of this herb on disrupted lipid metabolism was examined in rats. Intake of herbs (25 g/day) decreased TC (12%), LDL-cholesterol (15%), and TG (12%), whereas HDL-cholesterol remained unchanged [26]. In our study, an increase in HDL in low-dose and a reduction in VLDL in high-dose was also observed; other findings were similar. When the antihyperlipidemic effect of methanolic extract from *Opuntia joconostle* (OJ) seeds was checked in the hypercholesterolemic diet-fed mice, levels of TC and LDL were significantly decreased when compared to the hypercholesterolemic group, but change was not significant in HDL levels [28]. Results of the study on polysaccharides extraction from *Opuntia stricta* (OS) indicated that after the treatment with an HFD for 8 weeks, serum levels of TG, TC, and LDL significantly ($p<0.05$) increased in the group that received a high-fat diet. In contrast, serum level of HDL significantly ($p<0.05$) decreased in this group. Administration of OS restored normal levels of TC, TG, and LDL ($p<0.05$) and caused a significant increase in serum HDL levels ($p<0.05$) compared to the positive group. Results indicated that a diet with high cholesterol for 8 weeks has significantly increased the risk of atherosclerosis indicated by the atherogenic index of plasma and Castelli's risk index-I. The administration of POS for 8 weeks significantly ($p<0.05$) decreased the atherogenic risk compared to control rats [29].

CONCLUSION

The present study shows a significant lipid-lowering effect of OFJ that might be due to flavonoid-quercetin. Further studies can be planned to explore the exact mechanism of action for the hypolipidemic activity of OE.

AUTHOR'S CONTRIBUTION

Conception and design: Dr. Hemangi Virani, Dr. Mitul Upadhyay, Dr. Piyush pargi, and Dr. Ashish Anovadiya; acquisition, analysis, and interpretation of data: Dr. Hemangi Virani, Dr. Piyush pargi, and Dr. Ashish Anovadiya; manuscript preparation and editing: Dr. Hemangi Virani and Dr. Mitul Upadhyay; manuscript reviewing and final approval: Dr. Hemangi Virani, Dr. Mitul Upadhyay, Dr. Piyush pargi, and Dr. Ashish Anovadiya.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No external funding was received for this study.

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