Section: Pharmacology

Original Research Article

EFFECT OF EUGENIA JAMBOLANA EXTRACTS ON TRITON-INDUCED HYPERLIPIDEMIA AND ASSOCIATED CARDIAC RISKS IN WISTAR-ALBINO RATS

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Abstract

Background: Hyperlipidemia is implicated as major cause of atherosclerosis and coronary heart diseases. Long-term use of synthetic hypolipidemic agents have been associated with adverse effects, which limits their use. So, medicinal plants are being explored for their hypolipidemic potential with tolerable side effects, having efficacy comparable to statins. This study was attempted to validate the putative hypolipidemic effects of E. jambolana seed extracts (EJEE and EJAE) in Triton WR-1339 induced hyperlipidemic rats. **Materials and Methods:** A total of thirty male albino rats were allocated into five groups. Group I was treated as a normal control received vehicle. Group II was served as the positive control received triton (400 mg/kg, i.p) injection. Group III was treated with atorvastatin (40mg/kg, p.o). Group IV and V was treated with EJEE and EJAE (500mg/kg, p.o.), respectively for seven days. Blood samples were collected from the orbital plexus and the obtained serum was estimated for lipid profile and calculated various cardiovascular risk indices. **Result:** End of the study, triton induced hyperlipidemia, evident by significant ($P< 0.05$) raise in the TG, TC, LDL-C, VDL-C and with decreased HDL-C levels in normal rats. Further, hyperlipidemia is associated with significant increase in the cardiovascular risk in normal rats. While supplementation with EJEE and EJAE, significantly ($P<0.05$) attenuated the hyperlipidemia and cardiovascular risk indices, comparable to the atorvastatin in the hyperlipidemic rats. **Conclusion:** In this study, E. jambolana seed extracts showed potent hypolipidemic effects in triton induced hyperlipidemic rats. This inference may provide further insights into future drug research.

INTRODUCTION

Modern and sedentary lifestyle changes with high fat and or high carbohydrate diet intake significantly contribute to dyslipidemia and associated.[1] Dyslipidemia is an abnormal disorder of lipid metabolism with increased in one or more of the plasma lipids (triglycerides, cholesterol esters, phospholipids) and or lipoproteins (VLDL and LDL along with reduced HDL levels). Dyslipidemia is a major contributing factor of diabetes, obesity, fatty liver, and cardiovascular diseases (CVD) such as angina, atherosclerosis, ischemia, and stroke leading mortality.[2] Indian Council of Medical Research (ICMR) had conducted a survey in different parts of India and study results reveal that urban population has a greater prevalence of hypercholesterolemia than the rural population.[3] Clinical trials on hyperlipidemic subjects have shown that hypolipidemic agents decrease both morbidity and mortality also mitigating the cardiovascular complications as compared to those without receiving hypolipidemic agents.[1,2]

In fact, the exalted plasma lipid levels are a result of increased uptake of dietary lipids through the gut or through increased endogenous pathway of lipid synthesis. In addition, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is a rate controlling enzyme, which is involved in the conversion of HMG-CoA to mevalonate and finally

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synthesizes cholesterol.[4] So, any pharmacological agent that reduces the absorption of dietary lipids from gut and or inhibits the synthesis of endogenous lipids is beneficial in treatment and management of dyslipidemia. Presently, hypolipemic drugs including statins, bile acid binding resins, fibric acids are available to combat hyperlipidemia (Type I-V) and have possibility of causing several adverse effects like myopathy, hyperuricemia, flushing, hepatotoxicity, and gastric disturbances and interactions with other drugs limiting their usage for long-term needs.[5]

Therefore, it necessitates in search of medicinal plants or plant products beneficial in treating lipid disorders. Since ancient times, several medicinal plants have been discovered with a wide variety of pharmacological properties to treat and cure various diseases. Its strongly affirmed that plant and herbal medicines are safer, well tolerable and with fewer side effects as compared to synthetic drugs, because the bioactive principles of plants are of natural origin. Moreover, the World Health Organization (WHO) stated that most of the world's population trusts in the usage of medicinal plants or products for treatment.[2,6] Therefore, researchers have gained interest in identifying lipid lowering agents to treat lipid disorders and its complications with tolerable side effects.

Among medicinal plants, Eugenia jambolana (Myrtaceae) has gained importance in the treatment of various Meda Roga or Medo Dhatu (metabolic disorders), including diabetes and hyperlipidemia by traditional medicine practitioners. Its' popularly known as jamun and widely distributed in India and the Asian countries. Evidence from pre-clinical and clinical studies reveals that Jamun has various such as anti-inflammatory, antioxidant, antidiabetic, antisecretory, antibacterial, and neuro-psychopharmacological properties.[7-14]

Various hyperlipidemic models such as triton induced, high cholesterol diet, high fructose induced, drug induced hyperlipidemia, and transgenic animals are widely used for screening of hypolipidemic activity of any newer medicinal plants or synthetic molecules. Of these, triton- WR-1339 was selected due to its wide acceptance, reproducibility, and convenience to induce hyperlipidemia.[5,6] In present study, aim to investigate the hypolipidemic efficacy of E. jambolana seed extracts in triton WR-1339-induced hyperlipidemia in rats.

MATERIALS AND METHODS

Chemicals: Triton WR-1339 was procured from Sigma Aldrich. All other chemicals used were of analytical grade and obtained from Himedia and Loba chemie, diagnostic kits from Aspen diagnostics limited.

Plant Extracts: The ethanolic and aqueous extract of E. jambolana (EJEE and EJAE) of seeds were obtained as gift samples (Batch no: JFE/D26/STD03 and JFE/D26/STD04) from Greenchem, Bangalore.

Animals: Adult Wistar male albino healthy rats (200-250 g) were selected for this study. All the rats were housed in a room with 12 hour's light and dark cycles, humidity of 45±5%, and at a temperature of 22± 2 °C. The selected rats were allowed to acclimatize to the experimental room for seven days. Throughout the study, all the rats were fed with a pellet chow and water ad libitum. This protocol was approved by the Institutional Animal Ethics Committee (NGSMIPS/IAEC/December-2016/36) and study was conducted in accordance with the Committee for Control and Supervision of Experiments on Animals (CCSEA) guidelines.

Acute toxicity test: This study was carried out according to the Organization of Economic Cooperation and Development (OECD)-425 guidelines.[15] A single dose of 2000 mg/kg b. wt of E. jambolana (EJEE and EJAE) extract was given two groups of five rats in each. The treated groups were frequently monitored for 24 hours and thereafter periodically for the next 14 days, for changes in general behavior and any mortality. In this study, E. jambolana extracts were lack of toxicity in animals when administer at dose of 2000 mg/kg by oral. Hence, in this study, only one dose (500 mg/kg b. wt) was selected to screen for pharmacological activity in hyperlipidemia model.

Experimental study design[16]: A total of thirty rats were randomly allocated into five groups with six in each. Grouping of animals and dosage schedule was mentioned in Table-1. Group I was served as normal control received a vehicle (Carboxy methyl cellulose, CMC) alone. While Group-II to V were intoxicated with Triton to induce hyperlipidemia. Overnight fasted (16 hrs) were intoxicated with a freshly prepared triton (400mg/kg) solution, given intraperitoneally (i.p.) once to induce hyperlipidemia. After 72 hours of triton, standard drug (atorvastatin) and E. jambolana extracts were administered to the assigned groups continuously for the next seven days. Group II was served as the positive control received only triton without any treatment. Group III treated with single daily dose of atorvastatin (40mg/kg, p.o) orally. Similarly, Group IV and V were treated with single doses of plant extracts of EJEE and EJAE (500mg/kg b.wt. p.o.), respectively. All the animals had only access to water for the next two hours to avoid interaction with food and with supplements.

Sample Collection: On 8th day, the blood samples (3ml) were collected from the overnight fasted through retro-orbital puncture under mild ether anaesthesia. Serum thus was obtained by centrifuged (at 3,000 rpm) for 10-15 minutes to estimate the lipid profile and to calculate cardiovascular risk indices.[4,16]

Biochemical parameters estimation: Serum total cholesterol (TC), triglycerides (TG) were estimated by the method of CHOD-PAP and high-density lipoprotein-cholesterol (HDL-C) by the method of GPO-PAP by using Semi-autoanalyzer and with the help of diagnostic kits.[5,6] Low density lipoprotein cholesterol (LDL-C) and Very LDL-C (VLDL-C)

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levels were calculated by a standard formula from the TC and TG levels.[1,6] The atherogenic index (AI), anti-atherogenic index (AAI), coronary risk index (CRI) and cardiovascular risk index (CVRI), and percentage (%) of protection from hyperlipidemia were derived by mathematical calculation from the lipid profile values.[16]

Statistical Analysis: Data were expressed as Mean ± Standard error mean (SEM) and analyzed through One-way analysis of variance (ANOVA) followed by Tukey's test. A statistical software (A graph pad prism 5.0) was used for data interpretation and P<0.05 was set as the level of significance.[7]

RESULTS

Acute toxicity studies: E. jambolana extracts (EJEE and EJAE) didn't cause any behavioural changes among the treated rats. In addition, rats did not produce any sign of toxicity and lethality at a given higher dose (2000mg/kg, p.o), and hence the extracts were considered as a safe and non-toxic for further hypolipidemic screening.

Effect of E. jambolana extracts on TC: Positive control significantly (p<0.05) augmented the TC levels as compared to normal control. In comparison to normal control, a significant difference (p<0.05) existed among positive control, standard control, EJEE, and EJAE groups with respective to the TC levels. Also, a significant (p<0.05) difference was shown with respective to the TC, among the treatment groups (standard control, EJEE and EJAE), as compared to normal and positive control. Meanwhile, there was no significant difference in reducing TC by EJEE and EJAE with standard control. Results indicates that, both the EJEE and EJAE effectively reduced TC and produce comparable effects with atorvastatin [Figure 1].

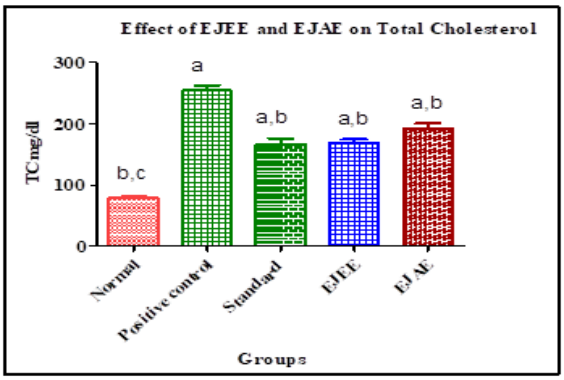

Figure 1: The effect of E. jambolana on TC in hyperlipidemic rats.

Data were expressed as Mean±SEM (n = 6)
a Statistically significant from the normal control.
b Statistically significant from the positive control.
c Statistically significant from standard control.

Effect of E. jambolana extracts on TG

A significant (p<0.05) rise in the TG's levels were observed in positive control, as compared to the normal control. Unlike the TC, standard, EJEE, and EJAE groups have not shown significant (p<0.05) difference with normal control. In contrast, normal control, standard control, EJEE, and EJAE groups shown a significant (p<0.05) difference with positive control. While compared to standard control, both EJEE and EJAE groups had shown no significant difference with respective to the TG levels. It indicates that both EJEE and EJAE treatment has effectively reduced the TG levels and produce comparable effects with atorvastatin [Figure 2].

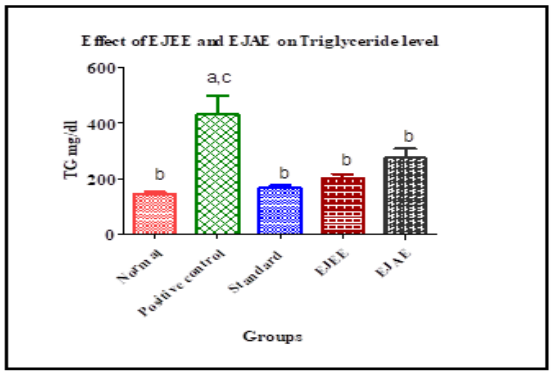

Figure 2: The effect of E. jambolana extracts on TG in hyperlipidemic rats.

Data were expressed as Mean±SEM (n = 6)
a Statistically significant from the normal control.
b Statistically significant from the positive control.
c Statistically significant from standard control.

Effect of E. jambolana extracts on HDL-C

Positive control exhibited a significant (p<0.05) decrease in the HDL-C levels, as compared to normal and standard control. Supplementation with EJEE and EJAE, a significant (p<0.05) difference was noted as compared to HDL-C levels of normal control. Simultaneously, both EJEE and EJAE groups demonstrated significant (p<0.05) difference with standard control, whereas no such difference with the positive control. Thus, it indicates that EJEE and EJAE was unable to elevate the HDL-C levels significantly as compared to atorvastatin [Figure 3].

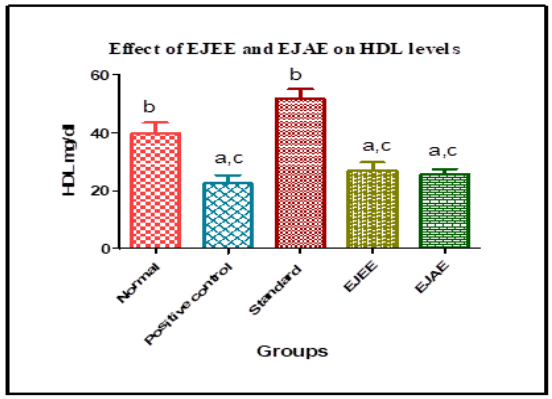

Figure 3: The effect of E. jambolana extracts on HDL in hyperlipidemic rats.

a Statistically significant from the normal control.

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b Statistically significant from the positive control.
c Statistically significant from standard control.

Effect of E. jambolana extracts on VLDL: Positive control exhibited a significant ($p<0.05$) increase in VLDL-C levels, as compared to normal control. Normal control, standard control, EJEE, and EJAE groups shown a significant ($p<0.05$) difference as compared to positive control. In comparison to the normal control, standard control, EJEE, and EJAE groups showed no significant difference in VLDL-C levels. Moreover, EJEE and EJAE supplementation produce similar effects like atorvastatin in significantly ($p<0.05$) lowering the VLDL-C levels [Figure 4].

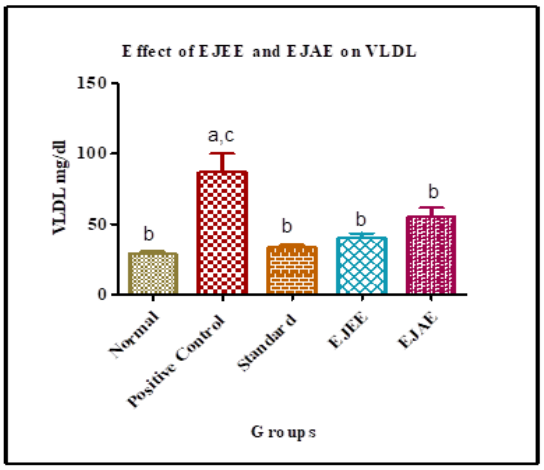

Figure 4: The Effect of E. jambolana extracts on VLDL in hyperlipidemic rats.

Data were expressed as Mean±SEM (n = 6)
a Statistically significant from the normal control.
b Statistically significant from the positive control.
c Statistically significant from standard control.

Effect of E. jambolana extracts on LDL: LDL levels significantly ($p<0.05$) increased in positive control as compared with normal control. While, standard control, EJEE, and EJAE groups significantly ($p<0.05$) decreased the LDL levels, as compared with positive control. Meanwhile, both EJEE and EJAE significantly ($p<0.05$) reduced LDL levels, similarly to the atorvastatin [Figure 5].

Effect of E. jambolana extracts on AI: All the groups showed significant ($p<0.05$) difference with respective to the AI, as compared to the positive control. In comparison to the normal control, positive control, EJEE, and EJAE groups shown significant ($p<0.05$) difference in AI values. While comparison with standard control, EJEE and normal control shown no significant difference, but existed with EJAE group. Results indicates that EJEE had significantly ($p<0.05$) reduced AI vales than EJAE and shown comparable effects with atorvastatin [Table 2].

Effect of E. jambolana extracts on CRI: All the groups shown significant ($p<0.05$) difference with respective to the CRI values as compared to the positive control. Except standard control, all groups showed a significant ($P<0.05$) difference in CRI values, as compared with normal control. While comparison with standard control, both EJEE and normal control showed no significant difference. It indicates that EJEE had significantly ($p<0.05$) reduced CRI values than EJAE, like the atorvastatin [Table 2].

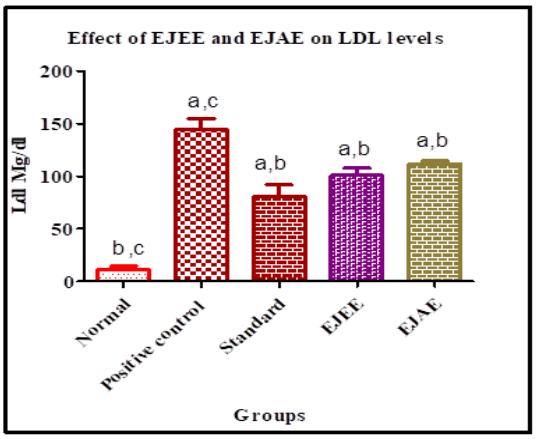

Figure 5: The Effect of E. jambolana extracts on LDL in hyperlipidemic rats.

Data were expressed as Mean±SEM (n = 6)
a Statistically significant from the normal control.
b Statistically significant from the positive control.
c Statistically significant from standard control.

Effect of E. jambolana extracts on AAI

Positive control shown significant ($p<0.05$) reduction in AAI values, as compared with normal control. Similarly, all groups showed significant ($p<0.05$) difference with respective to the AAI values, as compared to normal control. Supplementation with EJEE and EJAE has shown no significant difference and was ineffective to elevate AAI values, similarly to the atorvastatin [Table 2].

Effect of E. jambolana extracts on Cardiovascular risk index (CVRI): It was observed that CVRI values were significantly ($P<0.05$) greater in the positive control as compared to normal control. Except atorvastatin, all groups shown significant ($P<0.05$) difference with the normal control. Supplementation with atorvastatin and EJEE significantly decreased CVRI values in comparison with positive control. So, EJEE effectively reduced the CVRI, similarly to atorvastatin [Table 2].

Effect of E. jambolana extracts on percentage (%) of protection: End of the study, atorvastatin, EJEE, and EJAE have shown 80.38%, 53.93%, and 41.85% extended protection from the development of hyperlipidemia and its associated cardiovascular risks in hyperlipidemic rats.

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Table 1: Animal grouping and dosage schedule of standard drug and extracts in hyperlipidemic rats.

Groups (n=6)	Dosage schedule
I: Normal control	Received 5% vehicle (CMC) solution orally
II: Positive control	Normal rats received Triton (400mg/kg, i.p) to induce hyperlipidemia and 5% CMC solution orally for next 7 days
III: Standard control	Hyperlipidemic rats received Atorvastatin (40mg/kg, p.o) with 5% CMC solution once daily orally for next 7 days
IV: EJEE	Hyperlipidemic rats received Ethanolic extract of E. jambolana (500mg/kg, p.o) with 5% CMC solution once daily orally for next 7 days
V: EJAE	Hyperlipidemic rats received Aqueous extract of E. jambolana (500mg/kg, p.o) with 5% CMC solution once daily orally for next 7 days

Table 2: The effect of E. jambolana extracts on various risk indices in hyperlipidemic rats

Group	AI	CRI	AAI	CVRI
Normal	1.03±0.2[b]	2.03±0.2[b]	116.46±20.96[b]	0.31±0.12[b]
Positive control	11.55±2[a,c]	12.55±2[a,c]	10.04±1.69 [a]	7.18±1.40[a]
Standard control	2.27±0.29[b]	3.27±0.29[b]	46.93±4.57 [a]	1.61±0.28[b]
EJEE	5.32±0.31[a,b]	6.32±0.3[a,b]	19.11±1.08 [a]	3.78±0.23[a,b]
EJAE	6.72±0.36[a,b,c]	7.72±0.3[a,b,c]	15.11±0.81 [a]	4.48±0.25 [a,c]

a Statistically significant from the normal control.
b Statistically significant from the positive control.
c Statistically significant from standard control.

DISCUSSION

Liver plays a crucial role in the lipid homeostasis and is more susceptible to oxidative stress due to hyperlipidemia. Cholesterol is a primary constituent of various biological membranes and acts as a precursor molecule for the vitamins, hormones and bile acid synthesis. Hyperlipidemia is a predominant factor of CVD and fatty liver.[3,17] Present study, Triton WR-1339 was selected to induce hyperlipidemia in normal rats. This study demonstrated that, triton significantly elevated TC, TG-C, VLDL-C, and LDL-C levels with concurrent decrease in HDL-C levels in normal rats. End of the study, triton effectively induced hypercholesteremia and hypertriglyceridemia with altered lipoprotein levels. The findings of this study were in accordance with previous reports of Girija K et al., and Saravanan M et al., with respective to the triton induced hyperlipidemia.[18,19] Pre-clinical studies have documented that, triton induces hyperlipidemia by inhibiting lipoprotein lipase activity and thereby inhibiting the lipoproteins utilization from blood by the extra-hepatic tissues and accompanied by a reduction of VLDL and LDL catabolism, results in hypertriglyceridemia.[20,21] Experimental evidence that, triton augments the HMG-CoA reductase activity which results in the deposition of cholesterol in both the circulation and hepatocytes.[22,23] Furthermore, studies noted that triton may alter the structure of VLDL and showing resistance to the lipolytic enzymatic actions in the blood and tissues. Thus, it prevents or delays VLDL and its intermediates excretion and simultaneously enhances the hepatic cholesterol biosynthesis leading to hyperlipidemia.[21,23,24]

In this study, E. jambolana seed extracts (EJEE and EJAE, 500mg/kg of each) was evaluated for the hypolipidemic activity. Results shows that, EJEE and EJAE effectively decreased the TC, TG, VLDL-C and LDL-C levels in hyperlipidemic rats, which was almost comparable with atorvastatin, a standard drug. Contrastingly, EJEE and EJAE could not effectively augmented the HDL-C levels in hyperlipidemic rats, like atorvastatin. Furthermore, its clearly reported that EJEE is more effective than EJAE in exerting hypolipidemic effects. Thus, E. jambolana extracts significantly lowered the TGs, TC and LDL-C levels, which is a major target of hypolipidemic drugs. It's assumed that hypolipidemic activity of E. jambolana extracts could be due to inhibition of cholesterol and TG synthesis through HMG-CoA reductase activity and or increased catabolism of LDL-C through its hepatic receptors for excretion in the form of bile acids.[25] Previous studies involving hypolipidemic profile of E. jambolana extracts have been investigated in various models. Shankar M et al., and Tanwar RS et al., demonstrated that treatment with E. jambolana extract (25 mg/kg) in rats was effective in decreased TC, TG's, free fatty acids (FFA), LDL-C, and VLDL-C and increased HDL-C levels in a hyperlipidemic model.[26,27]

Hyperlipidemia aggravates the development of atherosclerosis and CVD. Further, increased structural configuration of LDL by glycosylation, oxidation, and both may trigger the endothelial injury may increase the foam cell formation and thickening the arterial intima. AI is an important risk indicator to measure the extent of atherosclerotic lesions. AI indicates the deposition of foam cells or fatty infiltration in heart, aorta, coronaries, liver, and kidney. In present, triton markedly increased the AI, CRI, and CVRI values with concurrent decrease in AAI values in normal rats.[7,28,29] Supplementation of E. jambolana extracts (EJEE and EJAE) effectively reduced the AI, CRI, and CVRI values along with improvement in AAI values similarly to atorvastatin. In agreement with the present study, Shankar M., et al. also documented that methanolic bark extract of E. jambolana (100, 200 and 400 mg/kg) effectively

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reduced AI values in a dose-dependent manner and comparable to atorvastatin in hyperlipidemic rats.[26] Tanwar RS et al., identified the active principle (FIIc) from aqueous extract of E. jambolana pulp (10, 15, and 20 mg/kg) which effectively reversed the abnormal lipid and lipoprotein levels with decreased in HDL-C to normal levels along with substantial improvement in oxidized LDL and apoproteins in diabetic and hyperlipidemic rats.[27]

CONCLUSION

This short-term study putative effects of hypolipidemic activity of E. jambolana seed extracts evidenced by the mitigation of hyperlipidemia and its associated complications in hyperlipidemic rats, similar to the atorvastatin. It's concluded that it may be used as an adjuvant for both the treatment and prevention of hyperlipidemia.

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