Evaluation of Hypolipidaemic Activity of Ethanolic Extract of Aegle marmelos Fruit on Albino Wistar Rat

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Abstrat:

Aegle marmelos (L), (Rutaceae) fruit is ascribed with many therapeutic effects. The present study was undertaken to explore the antihyperlipidemic effect of ethanol extract of the fruit of *A.marmelos* in Triton induced hyperlipidemic rats. The oral administration of the extracts, at dose of 200 mg/kg & 400 mg/kg per oral in hyperlipidemic rats, dose dependently reduced the cholesterol, triglycerides, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and significantly increased the high density lipoproteins (HDL) level. The standard drug Rosuvastatin at dose of 1.5 mg/kg per oral showed better effect. Phytochemical screening revealed the presence of flavonoids, tannins, terpenoids, coumarin glycoside, alkaloids, carbohydrates and proteins in the *A.marmelos* fruits. The results obtained suggest marked hypolipidaemic activity of the ethanol extracts of *A.marmelos* fruit.

Keywords: Antihyperlipidemic; fruit extract; *Aegle marmelos*; Triton WR-1339.

INTRODUCTION:

India has the unique advantage of having traditional, nature-derived medical systems that have been in existence for an elongated period of time. Plant based compounds have been used since ancient times for medicinal, therapeutic, or other applications. The traditional medicine system demonstrates that plants have generated a diverse range of prescription medications to alleviate human suffering from diseases[1]. All medications utilized in traditional medical systems are either synthetic drugs in their original form or preparations. Until the 19th century, even Western medicine (also known as allopathic medicine) relied heavily on primitive remedies. Despite the presence of several regulatory systems in the human body to limit their excessive activity, these substances have a singular method of action and may lead to numerous negative responses when administered in high quantities or for an extended duration. Conversely, the outcome may vary among people[2]. Synthetic medications may exhibit encouraging life-saving outcomes in acute illnesses but are often unsuitable for managing chronic conditions

Hyperlipidemia can be defined as the condition in which the level of lipids or lipoproteins in blood is raised to a more than demonstrated normal level owing to abnormal lipid metabolism or inappropriate biological processes. Such condition may develop due to different causes: poor diet, increased weight, genetic conditions such as familial hypercholesterolemia (FH) or other illnesses including diabetes[3]. Hyperlipidemia is the result of the buildup of lipids, or fatty substances, in the blood, and it constitutes a major risk factor for the development of atherosclerosis and cardiovascular diseases. The lipid elements present in the blood include cholesterol, triglycerides, and lipoproteins, which are complexes formed by fats and cholesterols combined with proteins. There are a multitude of types of lipoproteins such as Very low-density lipoproteins (VLDL), Low-density lipoproteins (LDL), Intermediate-density lipoproteins (IDL), and others. In addition lipoproteins, chylomicrons that are made up of triglycerides, cholesterol, and proteins[4]. High-density lipoproteins (HDL) are also worth mentioning in that they are considered the heart disease 'antirisk' factors because as their prevalence in the body increases, the chances of heart disease decrease[18] There are six distinct classifications of hyperlipidemias, which are identified based on the specific types of lipids that exhibit elevated levels in the bloodstream[5].

The current hypolipidemic drugs pose challenges due to adverse effects and rebound phenomena upon withdrawal. There are five major classes of antihyperlipidemic drugs, each with its drawbacks. HMGCoA Reductase Inhibitors (Statins) reduce cholesterol synthesis but may lead to gastrointestinal symptoms, myopathy, kidney damage, and an increased risk of type 2 diabetes. Bile Acid Sequestrants (cholestyramine), while increasing HDL and decreasing LDL, have poor patient tolerance and may cause gastrointestinal disturbances, osteoporosis, and hypertriglyceridemia[6]. Fibric Acid Derivatives (Fibrates) effectively reduce triglycerides and LDL while increasing HDL but may result in myopathy, arrhythmia, skin rashes, gallstones, and eosinophilia, necessitating caution in patients with liver and renal dysfunction. Nicotinic Acid Derivatives (Niacin) inhibits lipolysis, decreasing triglycerides and LDL levels but causes cutaneous flush, itching, heat, headache, nausea, and abdominal discomfort. Ezetimibe inhibits the absorption of phytosterols and cholesterol in the small intestine, reducing cholesterol delivery to the liver and increasing blood cholesterol clearance but results in headache, abdominal pain, and diarrhea[7].

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intestine, reducing cholesterol delivery to the liver and increasing blood cholesterol clearance but results in headache, abdominal pain, and diarrhea[9].

Hence keeping this fact in view the present study was planned to evaluate the hypolipidaemic activity of Aegle marmelos fruit on experimental animal.

MATERIALS AND METHOD

Animals

Wistar male and female rats weighing between 150 and 200 g were used in the studies. After a vet checked on them, the rats were housed in their cages under the standard laboratory conditions (22–23°C, relative humidity 50–60%) for five days before being dosed in the experimental room. Pelletized meal and ad libitum water were provided for the animals[10]. The Research Centre's Institutional Animal Ethical Committee gave their stamp of approval to the project.

Chemical and Instrument

Collection and Identification of plant material

The matured bael fruits were collected from the local area of Varanasi district in the month of their natural habitat of UP East region and authenticated from a botanist The Botanical Survey of India, Pune, verified the positive identification of each of these plant parts.

Extraction of plant material

The powder (500g) was extracted sequentially with 2.5 litres of 70% ethanol in a soxhlet apparatus at 65°C until the powder became exhausted totally. The resulting extracts were filtered, concentrated and dried in vaccum[11]. The extracts were stored in desiccators for use in subsequent experiments.

Preliminary Phytochemical Screening of Extracts

Extracts was subjected to phytochemical analysis to identify the different phytoconstituent found in the plant were put through a standard qualitative chemical examination to determine the type of phytochemical components they contained. The existence and nonexistence of various phytochemical constituents, like Alkaloids, Carbohydrates, Glycosides, Saponins, Amino acids and Proteins, Flavones and Flavonones, Tannins and Phenolics, Steroids, Fixed oils were determined using standard established techniques[12].

Drugs and standards

Tyloxapol (Triton WR-1339, Sigma Aldrich, USA), Rosuvastatin (Zydus Research Centre, Ahmedabad), enzyme kits (Lab care diagnostic Pvt.Ltd., India), and remaining compounds were of superior quality.

Acute toxicity studies

Rendering to OECD guidelines 425 wistar rats were used in acute toxicity tests on the ethanol extract of the fruit of Aegle marmelos. The ethanol extract of the fruit of Aegle marmelos was orally fed to each animal. Upto 48 hours, the animals were monitored for signs of mortality[13]. Up to 2000 mg/kg body weight, ethanol extract of the fruit of Aegle marmelos was deemed safe.

Experimental Protocol

Triton-induced hyperlipidemia

Five sets of six animals were put into distinct groups. There were five different groups: Triton was administered to group 2, a control group. AMFE (200 mg/kg body weight) to Group 3 for Triton-induced hyperlipidemia, AMFE (400 mg/kg body weight) to Group 4 and gold standard drug atrovastatin (1.5 mg/kg body weight) to group 5.

All the animals were kept in a controlled laboratory environment with a constant temperature of 25 to 26℃, humidity of 60 to 80%, and 12-hour light/12-hour dark cycle. Fresh water and a standard pellet meal (from NutrivaIndia Ltd) were given. A single intraperitoneal dose of tritonWR-1339 (400 mg/kg b. w.) caused hyperlipidemia in rats. After the rats were given their treatment, we made them fast for 18 hours before drawing blood under light ether anesthesia from their retro-orbital sinuses. The serum was separated from the other samples by centrifuging them at 2500 rpm for 10 minutes. Just prior to the sacrifice, blood work and biochemistry analyses were performed[14]. Tissues from the primary organs (liver) were stored in 10% formalin and histopathology was done on them (Figure 1a-c).

Evaluation Parameters

Blood glucose test

An electronic glucometer determined glucose concentration in blood.

Estimation of lipid profile

Triglyceride, cholesterol, high-density lipoprotein and low density lipoprotein levels in the serum were measured per established protocols.

Histopathology

Histological examinations were performed on liver tissue that had been fixed in 10% buffered neutral formalin. Tissues were fixed, then paraffin embedded, and slices were cut at a 4 to 5 mm thickness before being stained with eosin and hematoxylin; sections were photographed and analyzed using a light microscope[15].

Statistical Analysis

Statistics was analyzed by One-way ANOVA (Graph Pad Prism 5.0) and a comparison test and the findings were provided as Mean + SEM.

RESULTS

Collection and Identification

The fruits of *Aegle marmelos* were collected from East region of Uttar Pradesh. The initial identification was based on its organoleptic and morphological characteristics, and the verification was conducted by Botanical Survey of India, Pune.

Phytochemical screening

The ethanol extract of *Aegle marmelos* fruits showed positive detection to all phytochemical classes tested such as flavonoids, tannins, terpenoids, coumarin glycoside, alkaloids, carbohydrates and proteins was detected respectively. The findings are summarized in Table 1.

Table 1: Phytochemical analysis of *A. marmelos* fruit extract

Sr. No.	Phytochemical Compounds	Method	Observation	Inference
1.	Alkaloid	Mayer's test	Cream color precipitate at bottom	Present
2.	Terpenoids test	Salkowski test	Reddish brown coloration at interface	Present
3.	Proteins	Biuret test	Violet color	Present
4.	Carbohydrates	Molish test	Violet ring at junction	Present
5.	Tannins test	Ferric chloride	Dark green coloration	Present
6.	Flavonoid	Sulphuric acid test	yellow colored precipitate.	Present
7.	Coumarin glycoside	Alkali test	Blue-green fluorescence	Present

Changes in Serum Lipid Profile Caused by Ethanolic Extract of A. fruit in Triton-Induced Hyperlipidemic Rats

Serum levels of cholesterol, triglycerides, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol were dramatically reduced in Triton-induced hyperlipidemic rats following oral treatment with AMFE (200 and 400 mg/kg, p.o.). Serum HDL-cholesterol levels were increased in the AMFE compared to the Triton-treated rats (Tables 2 and 3).

Table 2: The effect of Aegle marmelos ethanolic extract of fruit on cholesterol, triglycerides, and overall glucose levels in hyperlipidemia induced by Triton.

Group	Cholesterol	Triglycerides	Glucose
Normal Control	72.26±2.26	67.56±2.12	80.4±4.85
Hyperlipidemic Control	156.72±2.66**	136.7±2.25**	273.2±9.88***
Triton+AMFE(200mg/kg, p.o.)	106.71±2.28	113.02±2.84	209.7±7.97**
Triton+AMFE(400mg/kg, p.o.)	92.14±2.02	90.45±2.05	173.8±6.73***
Triton+Rosuvastatin (1.5mg/kg, p.o.)	82.43±2.04	85.87±1.76	152.08±7.44***

Table 3: Impact of Aegle marmelos fruit ethanolic extract of fruit on high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) in hyperlipidemia induced by Triton.

Group	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal Control	22.64±1.50	35.44±3.16	13.10±0.44
Hyperlipidemic Control	15.33±1.04*	110.2±2.70**	31.12±0.57*
Triton+AMEE(200mg/kg, p.o.)	22.86±0.7	60.42±2.62	22.04±0.56
Triton+AMEE(400mg/kg, p.o.)	24.4±1.14	50.2±2.50	18.47±0.45
Triton+Rosuvastatin (1.5mg/kg, p.o.)	26.06±1.54	40.24±2.44	17.95±0.44

p-value: ***p < 0.001, **p < 0.01 & *p < 0.05 compared with normal group. Values are as mean ± SEM (n=6)

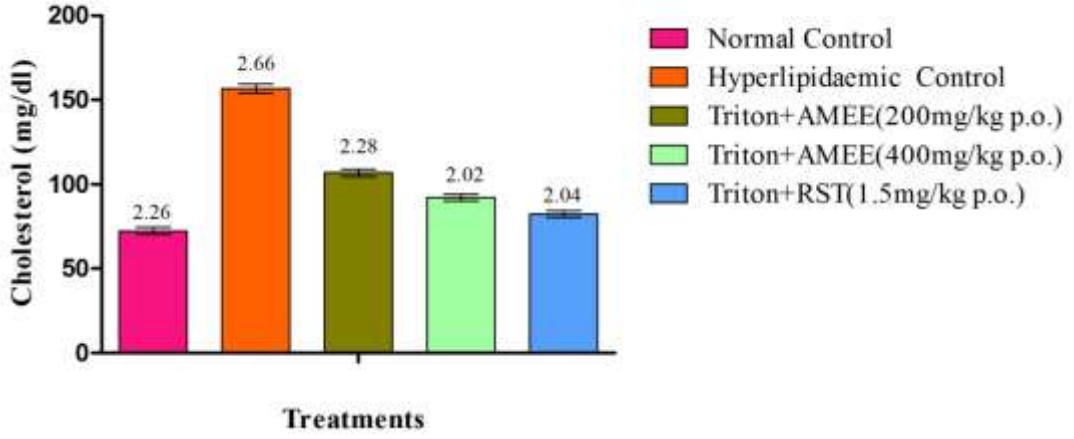


Figure 1(a): Effect of AMFE on Cholesterol level

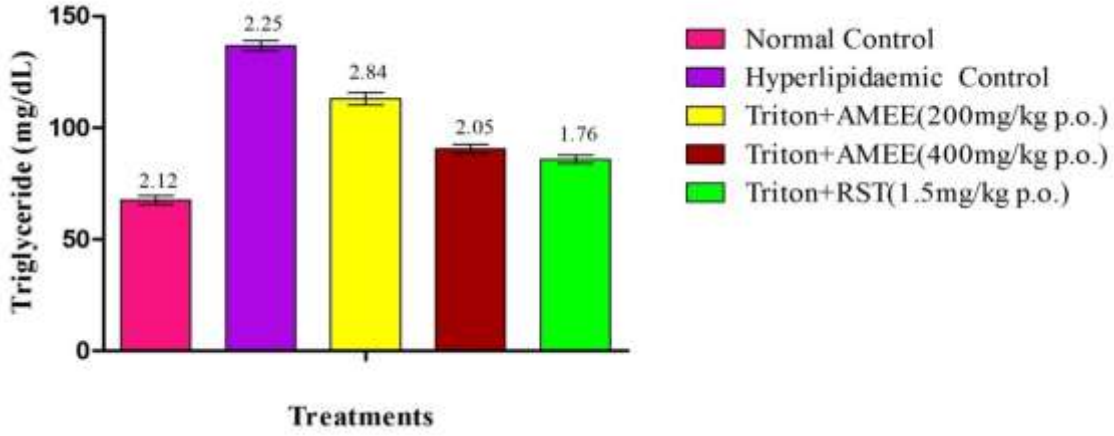


Figure 1 (b): Effect of AMFE on Triglyceride level

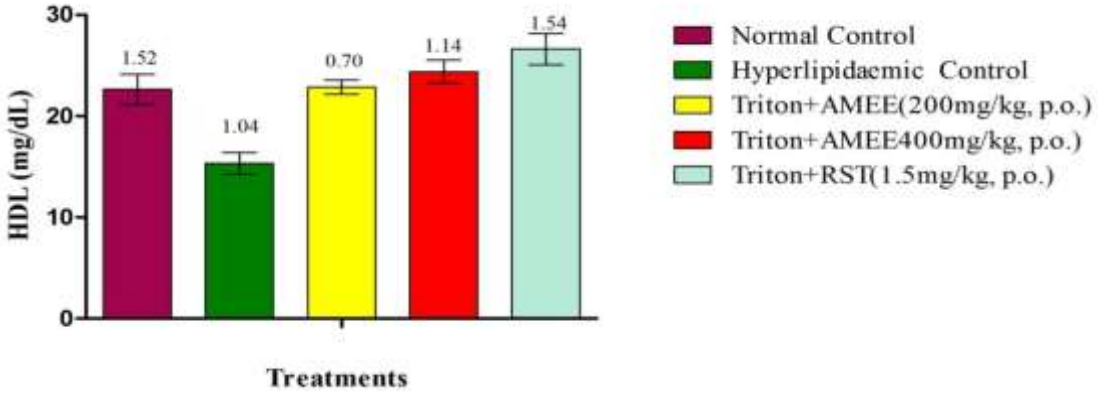


Figure 1(c): Effect of AMFE on HDL level

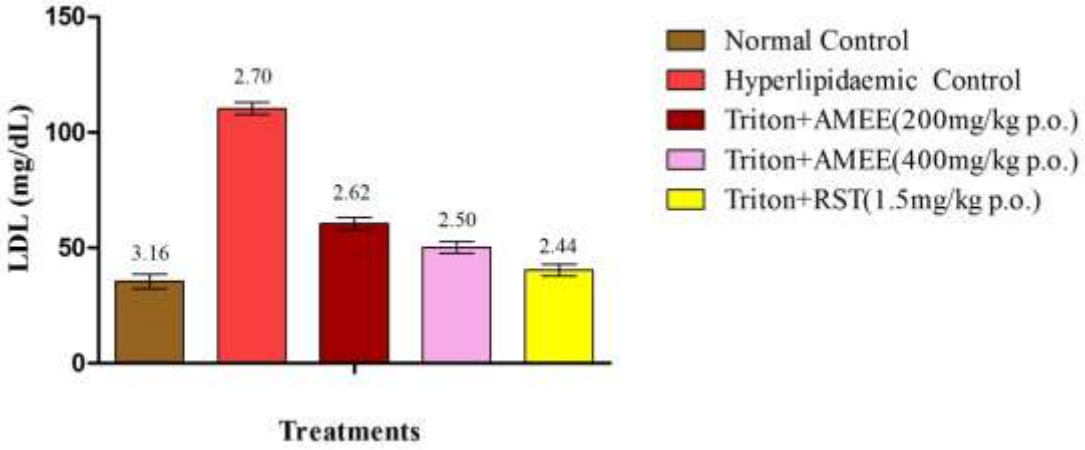
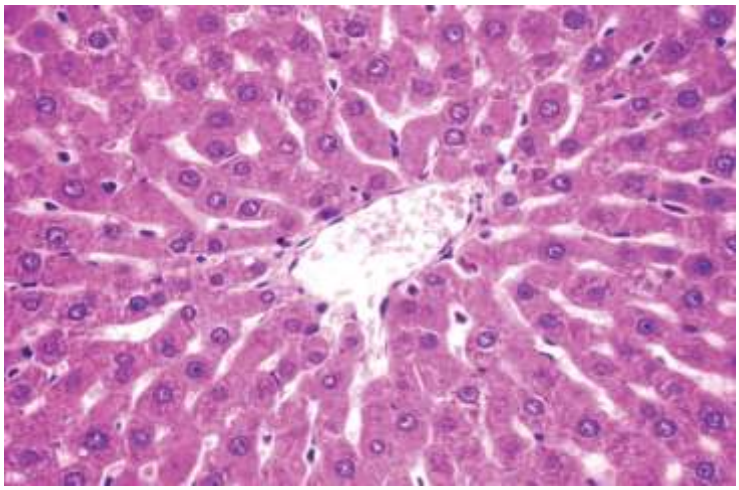


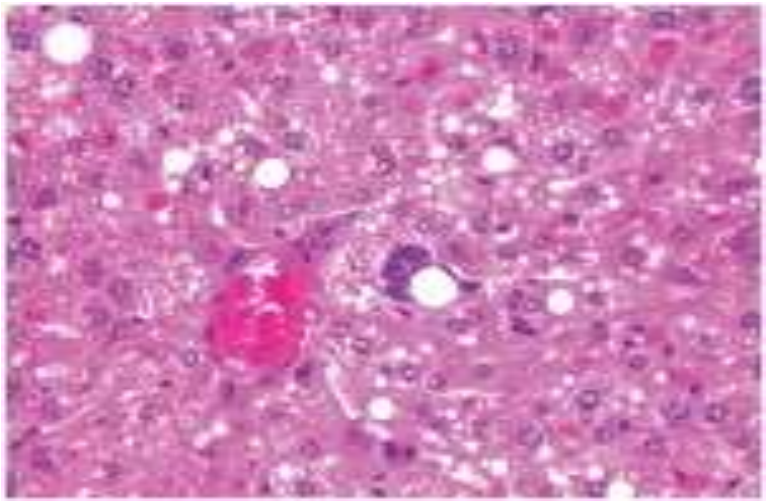
Figure 1(d): Effect of AMFE on LDL level

Effects of AMFE on liver histopathology

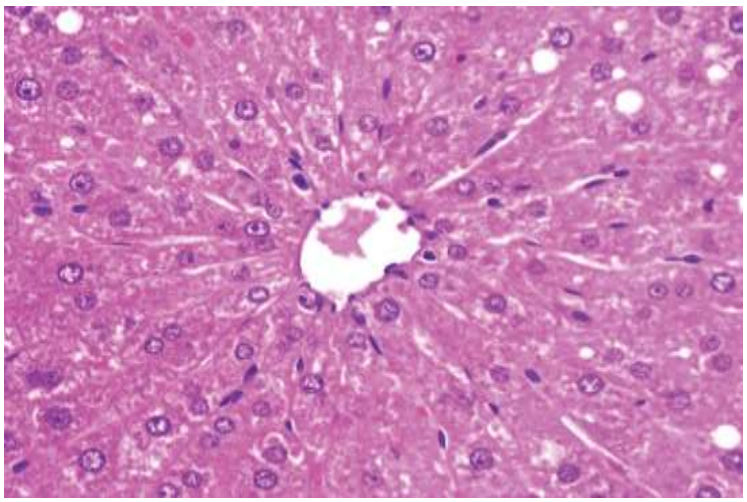
From histopathological analysis, the normal hepatocytes had centrally round nucleus and homogeneous cytoplasm (Figure 2(a)). There were flat endothelial cells around the central vein and sinusoid. Hepatocytes of hyperlipidaemic rats showed severe degeneration with diffuse vacuolar degeneration and necrosis (Figure 2(b)). The endothelial lining of the central vein exhibited more cell injury with increased accumulation of fat vacuoles in the hepatocytes. Hepatic cells of hyperlipidaemic rats treated with A. marmelos fruit extracts were improved with fewer endothelium injuries and less fat vacuoles (Figure 2(c)).



2 (a)



2 (b)



2 (c)

Figure 2: Histopathological appearance of liver (H&E×400).

DISCUSSION

For many reasons, including testing natural or chemical hypolipidemic medicines, the non-ionic detergent Triton WR-1339 is utilized extensively to inhibit peripheral tissue uptake of triacyl glycerol-rich lipoproteins from plasma. To achieve this goal, the hypolipidemic effects of many medicinal plants were evaluated against Triton WR-1339-induced hyperlipidemia. Examples of such herbs are *Camellia sinensis, Cassia tora Linn, and Sapindus emarginatus*[16]. After 24 hours of parenteral therapy with triton in adult rats, blood cholesterol and triglyceride levels peaked and returned to normal values.

Our results reveal that Triton WR-1339 injection significantly elevates serum cholesterol and triglyceride levels. This increase is due primarily to a decrease in VLDL and LDL catabolism, and an increase in VLDL production by the liver[17].

Success in decreasing cholesterol with extract leads to decline in the LDL component of blood and liver cholesterol, the target of many hypolipidemic drugs. Fast LDL cholesterol breakdown via its hepatic receptors for eventual elimination via bile acids is hypothesized to be responsible for the polyherbal formulation's cholesterol-lowering impact When LDL-cholesterol levels in the blood are high, atherosclerosis is more likely to develop,13 High levels of healthy cholesterol (HDL-Cholesterol) have been shown to reduce the risk of developing coronary heart disease[18]. Some research suggests that high-density lipoprotein (HDL) cholesterol may have a preventive effect against atherogenesis by lowering the risk of cardiovascular disease. Our polyherbal blend was also shown to have anti-hyperlipidemic efficacy by increasing HDL-cholesterol levels.

By increasing hepatic absorption, plasma LDL levels are lowered and the risk of cardiovascular diseases is lowered[19]. In our trials, we employed a statin, a medicine often used in clinical practise to reduce cholesterol levels, as a positive control to more accurately evaluate the anti-hyperlipemic impact.

The hypolipidemic effect of Aegle marmelos fruit extract is primarily attributed to the presence of aegeline, an alkaloid-amide. Aegeline has been shown to significantly lower plasma total cholesterol (TC), triglycerides (TG), and free fatty acids (FFA), while increasing high-density lipoprotein cholesterol (HDL-C)[20]. In addition to aegeline, other potential contributors to the hypolipidemic effect include Coumarins. Aegle marmelos contains various coumarins, such as marmin, marmelide, psoralen, and imperatorin, which have been linked to various biological activities, including antioxidant and anti-inflammatory effects[22]. Therefore, it is possible that the hypolipidemic activity of our extract is due to all of these constituents.

CONCLUSION

The current research revealed that *Aegle marmelos* ethanolic fruit extract at dose (200 and 400mg/kg, p.o.) possessed significant ($P<0.05$) hypolipidaemic activity in a dose-dependent manner. Furthermore *Aegle marmelos* ethanolic fruit extract (200 and 400mg/kg p.o) were effective as standard drug (Rosuvastatin 1.5 mg/kg, p.o). No major adverse effects were discovered during the evaluation of the formulation's acute toxicity. Fruit extract of *Aegle marmelos* possess hypolipidaemic effect which could be due to the presence of phytochemicals such as Alkaloid and Coumarins. The extract may work by blocking the HMG-CoA reductase enzyme pathway.

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