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Original Article

Hypolipidemic activity of friedelin isolated from *Azima tetracantha* in hyperlipidemic rats

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ABSTRACT

The hypolipidemic activity of friedelin isolated from *Azima tetracantha* Lam., Salvadoraceae, was studied in Triton WR-1339 and high-fat diet-induced hyperlipidemic rats. In Triton WR-1339 induced hyperlipidemic rats, treatment with friedelin (50 and 70 mg/kg) showed a significant ($p < 0.01$) lipid-lowering effect as assessed by reversal of plasma levels of total cholesterol (TC), triacylglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). In high-fat diet fed hyperlipidemic rats, treatment with friedelin (50 and 70 mg/kg) caused lowering of lipid levels in plasma and liver. The hypolipidemic activity of friedelin was compared with fenofibrate, a known lipid-lowering drug, in both models.

Introduction

Hyperlipidemia is a disorder characterized by increase in blood lipoprotein or cholesterol levels. It is the major cause of cardiovascular diseases, such as coronary heart disease, ischemic cerebrovascular disease, and peripheral vascular disease (Baby and Anuradha, 2013; Li et al., 2010). These diseases are the major causes of mortality and morbidity worldwide. Approximately 12 million people reportedly die of cardiovascular disease each year worldwide (Sunil et al., 2012). Experimental and epidemiological studies have demonstrated that excess low-density lipoprotein (LDL) deposited in the artery wall is an important risk factor in the initiation and progression of atherosclerotic impasse (Basuny et al., 2012). The known lipid-lowering drugs (fibrates, statins, bile acid sequestrants, etc.) regulate the lipid metabolism by different mechanisms, but they also have many side effects like hyperuricemia, diarrhea, nausea, severe muscle damage (myopathy), gastric irritation, flushing, dry skin and abnormal liver function (Sagar et al., 2012). Therefore, the development of lipid-lowering drugs from natural sources is the best option and is in great demand. A number of plants have been used traditionally for the treatment of various cardiovascular diseases. World ethanobotanical information reported that a number of herbal medicines from plants and vegetables are used for controlling hyperlipidemia (Stephen Irudayaraj et al., 2013). Therefore, efforts to develop effective hypolipidaemic drugs have led to discovery of natural products for the regulation of altered lipids.

Azima tetracantha Lam., Salvadoraceae, is known as 'Mulsangu' in Tamil and 'Kundali' in Sanskrit. Its root, root bark and leaves are used with food as a remedy for rheumatism (Kirtikar et al., 1984; Duraipandiyan et al., 2010). It is a powerful diuretic; it is used to treat dropsy, dyspepsia, chronic diarrhea, cough, phthisis, asthma, and small pox (Nargis Begum et al., 2009). The leaf extracts of *A. tetracantha* showed *in vitro* antioxidant and free radical scavenging activities (Thendral Hepsibha et al., 2011). Azimine, azecarpin, carpine, narcissoside, friedelin, lupeol, glutinol and β-sitosterol (Natarajan et al., 2014) are the isolated compounds from the leaves. It showed good anti-inflammatory, analgesic and antipyretic properties on various animal models (Antonisamy et al., 2011). Jiao et al. (2007) reported the antihyperlipidemic effect of friedelin from bamboo shavings. This study aimed to investigate the hypolipidemic activity of friedelin isolated from the leaves of *A. tetracantha* in Triton WR-1339 and high-fat diet-induced hyperlipidemic rats.

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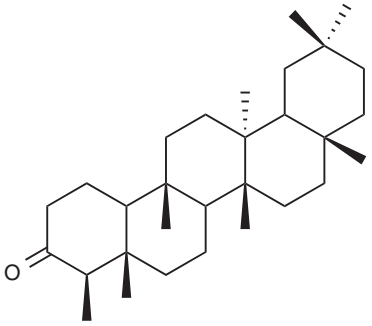
Materials and methods

Drugs and chemicals

Triton WR-1339 was obtained from Sigma Chemical Co. (St Louis, MO, USA). Fenofibrate was purchased from Ranbaxy, India. Biochemical kits and all other chemicals were of analytical grade.

Friedelin identification and characterization

Isolation and characterization of friedelin (**1**) from the leaves of *Azima tetracantha* has been previously reported (Antonisamy et al., 2011).



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Animals

Male Wistar rats (180–200 g) were reared at Entomology Research Institute. The animals were kept in polypropylene cages, under controlled temperature, humidity and 12/12 light/dark cycles. The animals were fed pellet diet (Pranav Agro Industries Ltd., Maharashtra) and water *ad libitum*. This study was carried out with prior approval from Institutional Animal Ethical Committee (IAEC-ERI-LC-28).

Acute toxicity study

The doses for the study were fixed based on Irwin test (Roux et al., 2004). Five groups of fasted healthy rats (six per group) were orally administered friedelin at a dose of 300, 400, 500, 600 and 700 mg/kg; the control group was given distilled water. The rats were observed for 1 h continuously and then hourly for 4 h and finally after every 24 h up to 14 days for any physical signs of toxicity, such as writhing, gasping, palpitation and decreased respiratory rate or mortality. On the 15^{th} day the animals were sacrificed and all the organs were observed for gross pathological lesions. Friedelin at these doses did not show any abnormal behavior. No treatment related gross pathological lesions were observed (data not shown). $1/10^{th}$–$1/20^{th}$ of the dose, in which no behavioral alterations were observed, was considered safe for further assays. Hence, doses of 30, 50 and 70 mg/kg b wt. were preferred for subsequent experiments based on Oliveira et al. (2008).

Effect of friedelin on Triton WR-1339-induced hyperlipidemic rats

Induction of hyperlipidemia

To investigate the short-term effects of friedelin (**1**) on triton-induced hyperlipidemic rats, male Wistar rats weighing 160–180 g were used in the study. The hyperlipidemia was induced by intraperitoneal injection of Triton WR-1339 (200 mg/kg) dissolved in phosphate buffered saline (pH 7.4) (Levine and Saltzman, 2007).

Overnight fasted rats were divided into six groups of six each. Group I served as normal control rats treated with vehicle; Groups II–VI were given intraperitoneal injection of Triton WR 1339. Group II hyperlipidemic rats were treated with vehicle alone; Group III–V hyperlipidemic rats were treated with friedelin 30, 50 and 70 mg/kg, respectively; Group VI hyperlipidemic rats were treated with fenofibrate (65 mg/kg) (Harnafi et al., 2007). Friedelin (dissolved in 1% tween 80) and fenofibrate were given orally, immediately after triton injection. In the following period of study (18 h), rats had access only to water. After 18 h from treatment, rats were euthanized and blood was collected. The blood samples were immediately centrifuged (2500 rpm/10 min) and plasma was used for lipid analysis.

Biochemical analysis of plasma

The plasma total cholesterol, triacylglycerides and HDL-C were quantified using enzymatic kits. LDL-C level was calculated using the formula of Friedewald et al. (1972): LDL-C = TC – (HDL-C – TG/5).

Effect of friedelin on high-fat diet-induced hyperlipidemic rats

Induction of hyperlipidemia

The hypolipidemic effect of friedelin was studied in high-fat diet-induced hyperlipidemic rats. Male Wistar rats weighing 180–200 g were used in this study. The rats were fed with a high-fat diet composed of standard rat chow-68%, dalda (saturated fat)-30% and cholesterol-2% for 15 days (Guido and Joseph, 1992).

The rats were divided into five groups of six rats. Group I and Groups II–V were fed continuously with normal pellet and high-fat diet, respectively for 28 days.

Group I normal control rats were treated with vehicle alone;

Group II hyperlipidemic control rats were treated with vehicle alone;

Group III and IV hyperlipidemic rats were treated with friedelin at 50 and 70 mg/kg, respectively.

Group V hyperlipidemic rats were treated with fenofibrate (65 mg/kg).

Friedelin (**1**) and fenofibrate were given once daily continuously for 28 days, orally. On days 0, 7, 14, 21 and 28, the blood samples were collected by retro-orbital sinus and the TC, TG, HDL-C and LDL-C levels were measured.

At the end of the study the rats were sacrificed, and blood and liver samples were collected. The liver samples were stored at −70° C for the analysis of TC and TG levels.

Biochemical analysis on serum and liver

The TC, TG and HDL-C were quantified using enzymatic kits. LDL-C level was calculated using the formula of Friedewald et al. (1972): LDL-C = TC – (HDL-C – TG/5).

Statistical analysis

The results were presented as mean ± SEM. Statistical analysis of all the data obtained was evaluated using one-way ANOVA followed by Dunnett's test (Graph Pad Instat; Version 3.10). The differences were considered significant at $p \leq 0.05$.

Results

Acute toxicity study

Acute toxicity study revealed the non-toxic nature of friedelin at the doses of 300–700 mg/kg. No mortality and behavioral alternations were observed in friedelin treated rats. There was no lethality