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RESEARCH ARTICLE

# The acute toxicity, antioxidant and antihyperlipidemic activity of flavonoid glycosides from *Ruta montana* in female rats with hyperlipidemia induced by Triton WR-1339

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## Abstract

This work aimed to evaluate the antihyperlipidemic activity of the aerial part of *Ruta montana* flavonoid- glycosides enriched extract (RMFEE) in Triton WR1339-induced hyperlipidemia in female rats, along with its antioxidant properties and acute toxicity. Female Wistar rats with Triton WR-1339-induced hyperlipidemia were used to assess RMFEE's antihyperlipidemic effects. The DPPH assay was used to determine antioxidant activity and acute toxicity was assessed via a single oral gavage of RMFEE at 600 and 2000 mg/kg body weight, following OECD 423 guidelines. Pretreatment with RMFEE at 150 and 400 mg/kg significantly reduced elevations in plasma levels of total cholesterol, triglycerides and non-HDL-C, while also significantly decreasing the atherogenic TG/HDL-C ratio in the hyperlipidemic rats. RMFEE also exhibited notable antioxidant activity in the DPPH assay. No mortality or signs of toxicity were observed within two weeks following a single oral administration of RMFEE at either 600 or 2000 mg/kg. Oral administration of RMFEE (150 and 400 mg/kg) prior to induction of hyperlipidemia by Triton WR-1339 demonstrated antihyperlipidemic activity in female rats. Specifically, the 400 mg/kg dose significantly prevented the increase in the TG/HDL ratio caused by Triton WR-1339. RMFEE also showed antioxidant activity with IC50=88.27 ± 3.12 µg/mL. The acute toxicity of the oral dose for RMFEE indicates very low toxicity, with an LD50 exceeding 2000 mg/kg.

**Keywords:** acute toxicity; antihyperlipidemic; antioxidant; flavonoid- glycosides; *Ruta montana*; triton WR1339

## Introduction

High cholesterol is a major risk factor for cardiovascular disease and death worldwide, as evidenced by numerous studies (1, 2). Indeed, several factors have been implicated in the development of this condition, including hereditary lipid metabolism disorders, excessive consumption of cholesterol-saturated fats, certain medications and various diseases (3, 4). Although effective against hyperlipidemia, many synthetic drugs, including fibrates, statins and niacin, are implicated in the development of numerous side effects ranging from hyperuricemia and gastric irritation to myopathy and hepatic dysfunction (5, 6).

Due to their generally milder side effects compared to synthetic drugs, herbal medicines often demonstrate better patient tolerance, even with long-term use (1, 7). Consequently, there is a growing emphasis on natural alternatives for managing hyperlipidemia (8). Numerous studies have highlighted the potential antihyperlipidemic properties of natural antioxidants (9-11). This approach may lead to new lipid-lowering drugs (12). Plant-derived antioxidants have garnered a great interest due to their ability to neutralize free radicals (13).

*Ruta montana* L., belonging to Rutaceae Family (a 20-60 cm tall), is an evergreen shrub widely distributed within the Mediterranean region. Notably, the plant is known for their various natural products, including flavonoids (14). These compounds are involved in various biological processes, such as antifungal and antioxidant activity and therapeutic effects like abortion treatment, depression relief, antidotes and reducing inflammation (15-17). Traditionally, the plant is used in southeastern Morocco (Tafilalet) to manage hypertension and cardiac diseases (17, 18). Our own research has confirmed the antidiabetic and antihypertensive properties of aqueous extracts from *Ruta montana* in STZ-induced diabetic rats (17) and hypertensive rats, induced by L-NAME (19). Despite the potential of RMFEE, it's in vivo antihyperlipidemic properties and in vitro antioxidant activity have not been previously reported. Therefore, this work aimed to study the effects of RMFEE on WR-1339-induced hyperlipidemia in female rats, as well as its radical scavenging activity.

## Materials and Methods

### Plant material

*Ruta montana* (RM) specimens (1 Kg), sourced from a local market in Errachidia province, Morocco, was taxonomically identified and authenticated by Dr. Abdelmonaim Homrani Bakali, from Regional Center of Agricultural Research of Tanger, National Institute of Agricultural Research. Rabat, Morocco. A voucher specimen (RM Sep-23) was deposited at the herbarium of the Faculty of Sciences and Techniques, Errachidia. The aerial parts of the plant were extracted as follows: 20 g of the powder obtained, was extracted in a Soxhlet apparatus during 12 hrs, using 200 ml of 80 % methanol. Thereafter, the methanolic extract was allowed to cool to room temperature (15 min) and then filtered using a Millipore filter (Millipore 0.2 mm, St Quentin en Yvelines, France) to remove particulate matter. The filtrate obtained undergone successive fractionations to extract flavonoid glycosides. Finally, the obtained extract was filtered and lyophilized (LABCONCO, G. BOYER, Casablanca) and was served for the preparation of the selected doses (150 and 400 mg/kg body weight) (20, 21).

### Chemical reagents

Triton WR-1339 (Sigma-Aldrich), DPPH (Sigma Chemical Co) and BHT, Folin-Ciocalteu reagent and methanol (Merck Co. Germany) were used in this study.

### The flavonoid-glycosides enriched extract preparation

The plant fractionation was conducted according to Ajebli and Eddouks, 2019 method (21), with slight modification. Briefly, the aerial parts of the plant were extracted sequentially using petroleum ether solvent to remove some organic compounds like chlorophyll and lipids. Afterwards, aqueous phase was recovered and subjected to a second fractionation using chloroform, to extract aglycone flavonoids. Then, the ethyl acetate was used to extract flavonoid glycosides. Finally, only the fraction of ethyl acetate was recovered and the organic solvents were removed by rotary evaporation (EYELA-N-1200A, China). Following extraction, the sample was lyophilized using a LABCONCO freeze-dryer (G. BOYER, Casablanca, Morocco) and refrigerated at 4 °C. Also, the Shinoda's test (22),was performed for the detection of flavonoids. Additionally, the extract yield of total flavonoid was performed using $FeCl_3$ method (23).

### Animal groups and experiments

Adult female Wistar rats (120-220 g), in good health, were assembled in polyethylene cages under standard laboratory conditions. Before experimental examination, the rats were kept for a few weeks to ensure their acclimatization. Following a 12 hrs fast, the rats were assigned to five groups as follows:

**Group 1**

The control rats (n = 5) were given 10 mL/kg of distilled water orally 30 min before being injected intraperitoneally with 1 mL/ kg of saline.

**Group 2**

Hyperlipidemic rats (n = 5) were given 10 mL/kg of distilled water orally 30 min prior to receiving an intraperitoneal injection of 200 mg/kg of Triton WR-1339 (1 mL/kg).

**Group 3 and Group 4**

The rats were given RMFEE (150 and 400 mg/kg orally, respectively) 30 min before being injected intraperitoneally with 200 mg/kg of Triton WR-1339 (1 mL/kg).

**Group 5**

The rats were given simvastatin (10 mg/kg; 10 mL/kg orally) 30 min before being injected intraperitoneally with 200 mg/kg of Triton WR-1339 (1 mL/kg).

All rats in the study were fasted for 36 hrs (24). After 24 hrs post-injection, blood samples were collected from the retro -orbital sinus of anesthetized rats treated with Triton WR-1339; heparin was used as an anticoagulant. Centrifugation (HUMAX-K, HUMAN-Germany) at 3000 rpm for 10 min yielded plasma for lipid analysis.

### Dosage of plasma lipid levels

The determination of triglycerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) was carried out using a kit supplied by DiaSys Diagnostic Systems GmbH (Germany) and by auto-analyzer Erba XL 600 (Mannheim, Germany). Plasma lipid levels were expressed as mmol/L. Non-HDL-C was calculated by subtracting the HDL-C value from the TC value. The ratio of TG to HDL-C was used as an atherogenic biomarker to assess cardiometabolic risk, insulin resistance and prediabetes (25).

### Acute toxicity analysis

The acute toxicity of RMFEE was assessed in rats according to OECD guidelines 423 (26). Briefly, adult female rats, under standard laboratory conditions, were administered a single dose of RMFEE and observed for two weeks of experiments. The study was stepwise with the use of 3 adult female rats (120 - 220 g) per step. Thus, three groups of rats were deprived of food overnight. Two of these groups were given oral doses of RMFEE (600 and 2000 mg/kg of B.W, respectively). Whereas the remaining group served as a control and received 10 mL/ Kg B.W of distilled water. The rats in the experiment were observed periodically, 30 min after administration, every hour for 4 hrs and once daily for 14 days to detect late clinical signs of toxicity and mortality (27, 28). Notably, during a 14-day observation period, we carefully assessed the toxicity of RMFEE by monitoring for signs of toxicity (convulsions, tremors, lethargy and salivation), observing morphological changes (particularly in skin, fur, nose and eyes) and measuring body weight on days 0, 7 and 14.

### Free radical scavenging activity

The DPPH assay was used to determine antioxidant activity of RMFEE (29). Briefly, DPPH solution was prepared, in test tubes, using methanol solution (4 mg/100 mL) and was kept for 3 hrs away from the light. Serial dilution of the extract (prepared from the stock solution 5 mg/10 mL) and the positive control [butylated hydroxytoluene (BHT) prepared from the stock solution 0.0625 mg/mL] were carried out with the final concentrations of 1.96, 3.91, 7.81, 15.63, 31.25 and 62.5 µg/mL. The mixture containing test tubes were mixed properly after adding 5 mL DPPH solution. The samples were placed at room temperature for 30 min in dark. The mixture containing DPPH and methanol (V/V) solvents was considered as negative control. Absorbance of all the samples were measured at 515

nm using UV/Vis spectrophotometer (DLAB SP-UV1100) and antioxidant activity of the sample was calculated (29-30).

### Statistical analysis

All data were presented as mean ± SEM. One-way ANOVA was used to assess the parameters. Mean body weight of experimental animals was assessed using two-way ANOVA. Statistical analysis was performed using GraphPad Prism 8. The values with $p < 0.05$, $p<0.01$, $p<0.001$, $p<0.0001$ were considered as statistically significant.

## Results

### Effect of RMFEE and simvastatin on plasma lipid parameters in female rats with hyperlipidemia induced by Triton WR-1339

The enriched extract was prepared from the aerial parts of *Ruta montana*, yielding 24.326 g of extract per 100 g of powdered plant material. This enriched extract was orally administered to female rats to assess its acute toxicity and antihyperlipidemic activity in Triton WR-1339-induced hyperlipidemia.

Lipid parameter results showed that Triton WR-1339 (200 mg/kg) administration in female rats significantly increased plasma TC, TG and non-HDL cholesterol levels (Fig. 1). However, pretreatment with RMFEE (150 and 400 mg/kg BW) significantly attenuated this increase in TC ($p < 0.001$ and $p < 0.0001$, respectively), TG ($p < 0.01$ and $p < 0.001$, respectively) and non-HDL cholesterol ($p < 0.01$ and $p < 0.05$, respectively) levels. Pretreatment with simvastatin (10 mg/kg body weight) also significantly prevented the Triton WR-1339-induced increase in TC and TG levels ($p < 0.001$, $p < 0.01$). However, it did not affect non-HDL cholesterol levels.

The results of the atherogenic marker, TG/HDL ratio, showed that Triton WR-1339 administered to female rats induced a significant increase in TG/HDL-C ratio (Fig. 2). However, pretreatment with RMFEE (400 mg/kg BW) significantly ($p<0.05$) attenuated this increase.

### Acute toxicity analysis

The acute toxicity results of RMFEE are shown in Table 1. Thus, during 14 days of the experiment, single oral administration of RMFEE at doses of 600 or 2000 mg/kg did not produce any signs of toxicity or mortality in female rats. The rats remained healthy throughout the study period. Thus, the acute toxicity of the oral dose for RMFEE indicates very low toxicity, with an LD50 exceeding 2000 mg/kg.

### Body weight

As illustrated in Fig. 3, following oral administration of a single dose of RMFEE (600 or 2000 mg/kg body weight), body weight of treated animals increased significantly ($p < 0.05$ and $p < 0.001$, respectively) on days 7 and 14 compared to baseline levels.

### Antioxidant property of RMFEE

The antioxidant capacity of RMFEE was evaluated using DPPH radical scavenging assay (Fig. 4). Indeed, increasing concentrations of RMFEE (1.96, 3.91, 7.81, 15.63, 31.25 and 62.5 µg/mL) resulted in increased free radical inhibition. The IC50 value of RMFEE was calculated from the linear regression and was found to be 88.27 ± 3.12 µg/mL with a correlation coefficient ($R^2$) of 0.9937. While BHT as a standard antioxidant, showed an IC50 of 66.92 ± 4.07 µg/mL and $R^2$ of 0.9407.

## Discussion

This work aimed to evaluate the antihyperlipidemic activity of RMFEE (150 and 400 mg/kg BW) in female rats with hyperlipidemia induced by Triton WR-1339 (31-33). The acute toxicity and antioxidant activities of the flavonoid enriched extract were, also, investigated. Indeed, hyperlipidemia or dyslipidemia contributes to cardiovascular diseases, highlighting their significant health implications (34).

Hyperlipidemia is characterized by disruptions in lipid metabolism which results in elevated blood levels of free fatty acids, triglycerides, total cholesterol and non-HDL cholesterol (1, 4). In the current study hyperlipidemia was induced, using the Triton WR-1339 (200 mg/kg). The latter has been widely reported to induce hypercholesterolemia in animal studies (31, 35, 36), making it a good tool in the search for antihyperlipidemic drugs (4). Interestingly, in this work, in female rats with Triton WR-1339-induced hyperlipidemia, pre-treatment with RMFEE (150 and 400 mg/kg BW) significantly attenuated TC (2,37±0,25$^{***}$ and 1,93±0,22$^{****}$,respectively), TG (2,20±0,57$^{**}$ and 0,73±0,09$^{***}$, respectively) and non-HDL cholesterol (0,83±0,28$^{**}$ and 1,07±0,24$^{*}$, respectively) levels. From the literature, flavonoids are reported for their hypolipidemic activity (37, 38) and may contribute to improving lipid metabolism through several mechanisms, including decreasing apo B secretion (39).

Additionally, taking into the account of some biological changes specific to women, including pregnancy and postmenopausal status, lipid profile parameters are affected because of insulin resistance (34, 40, 41). Accordingly, the ratio of triglycerides to HDL cholesterol (TG/HDL ratio) is a well-established link to insulin resistance and a predictor of cardiovascular disease risk (40). This ratio has also been identified as a marker for increased cardiometabolic risk, even in women who are insulin resistant and who go on to develop diabetes (25). In this work, pretreatment with 400 mg/kg of RMFEE significantly lessened the increased TG/HDL ratio ($p<0.05$) in female rats with hyperlipidemia induced by Triton WR-1339. Considering this result, the flavonoid-enriched extract could probably protect the changes in lipid metabolism associated with insulin resistance which may be supported by

**Table 1.** Toxicity and mortality during acute toxicity test of RMFEE in rats. n=3; none = no toxic symptoms during the observation period

| Groups | Dose (mg/kg BW) | Sex | Dead | Treated rats | Toxic symptoms |
|---|---|---|---|---|---|
| Control | 0 | Female | 0 | 3 | None |
| RMFEE | 600 | Female | 0 | 3 | None |
| RMFEE | 2000 | Female | 0 | 3 | None |

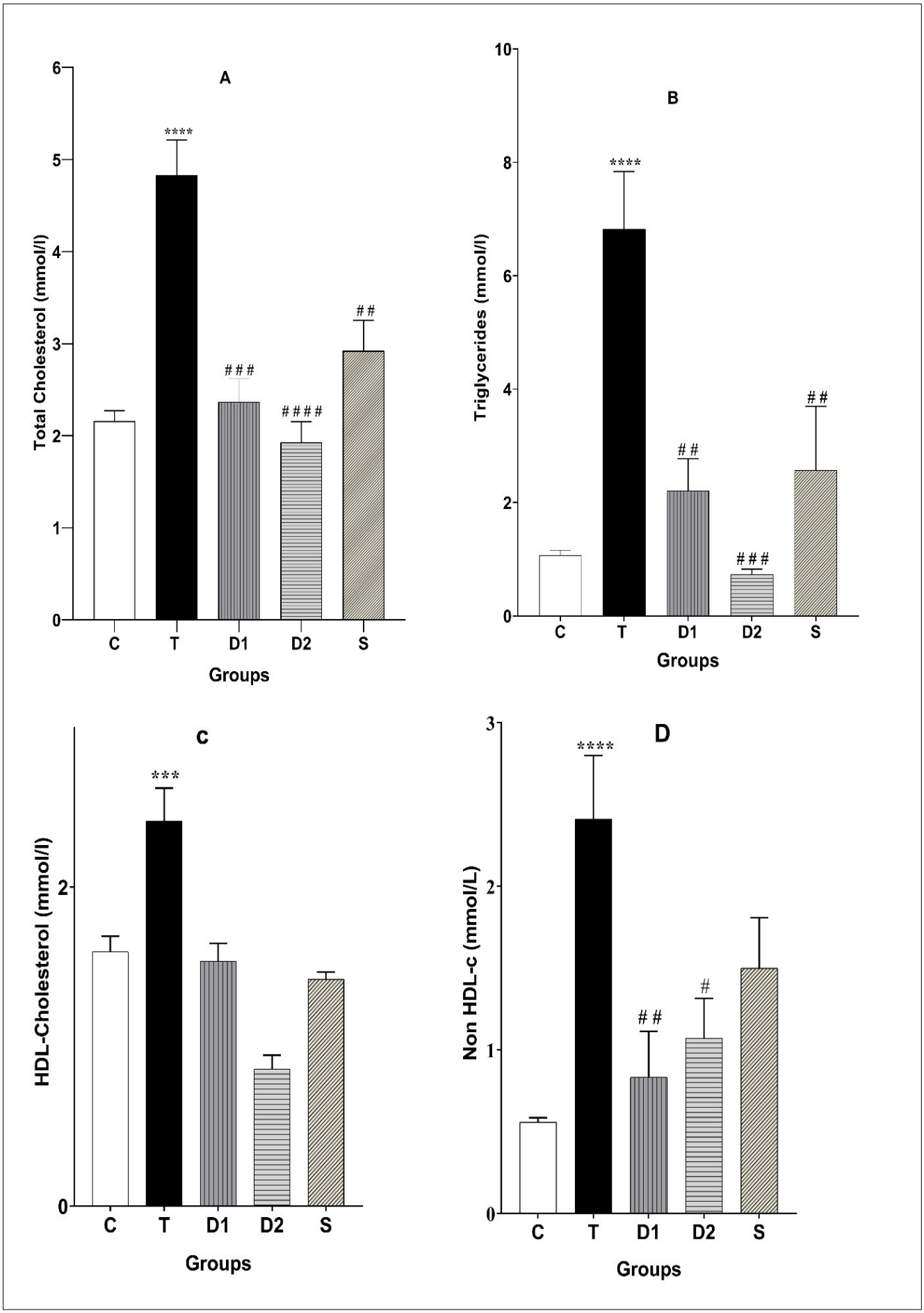


**Fig. 1.** Effect of RMFEE on total plasma cholesterol, triglyceride, HDL-C and non-HDL-C content in female rats with hyperlipidemia induced by Triton WR-1339. Values are expressed as mean ±SEM (n=5). ***P <0.001 and ****P <0.0001 (C vs. T); #P <0.05 and ##P <0.01 and ###P <0.001 and ####P <0.0001 (T vs. D1; T vs. D2; T vs S). C: normolipidemic control group; T: hyperlipidemic control group; D1: RMFEE (150 mg/kg)-treated group; D2: RMFEE (400 mg/kg); S: Simvastatin- treated group.

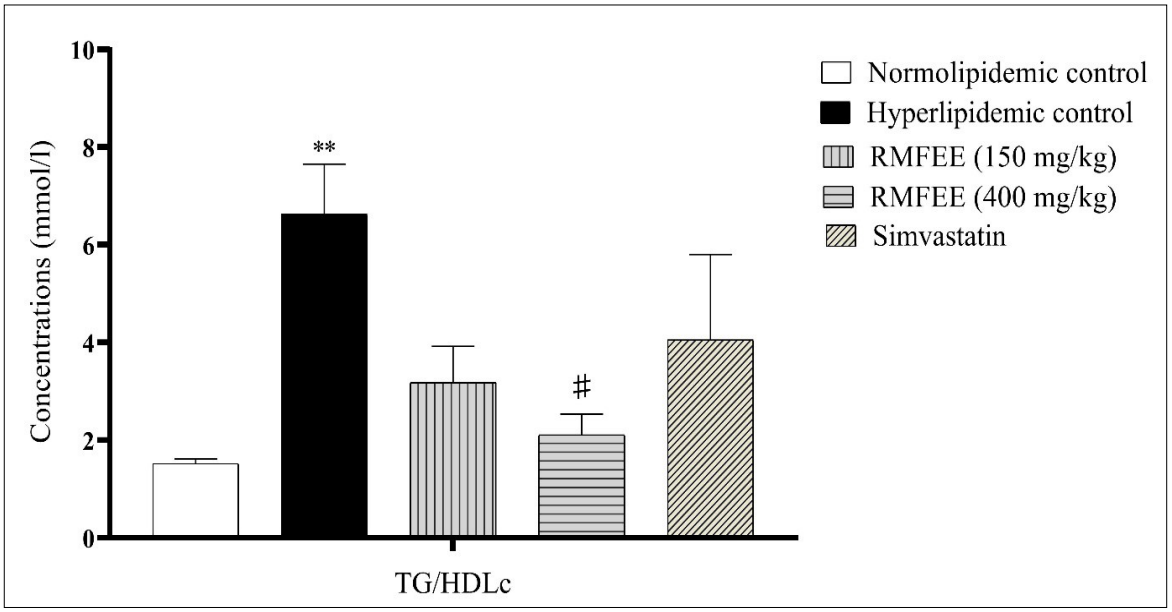


**Fig. 2.** Effect of RMFEE on TG/HDL-c ratio in female rats with hyperlipidemia induced by Triton WR-1339. Values are expressed as mean ±SEM (n=5). **P <0.01 (Normolipidemic control vs. Hyperlipidemic control); #P<0.05 (Hyperlipidemic control vs. RMFEE (150 mg/kg); Hyperlipidemic control vs RMFEE (400 mg/kg)).

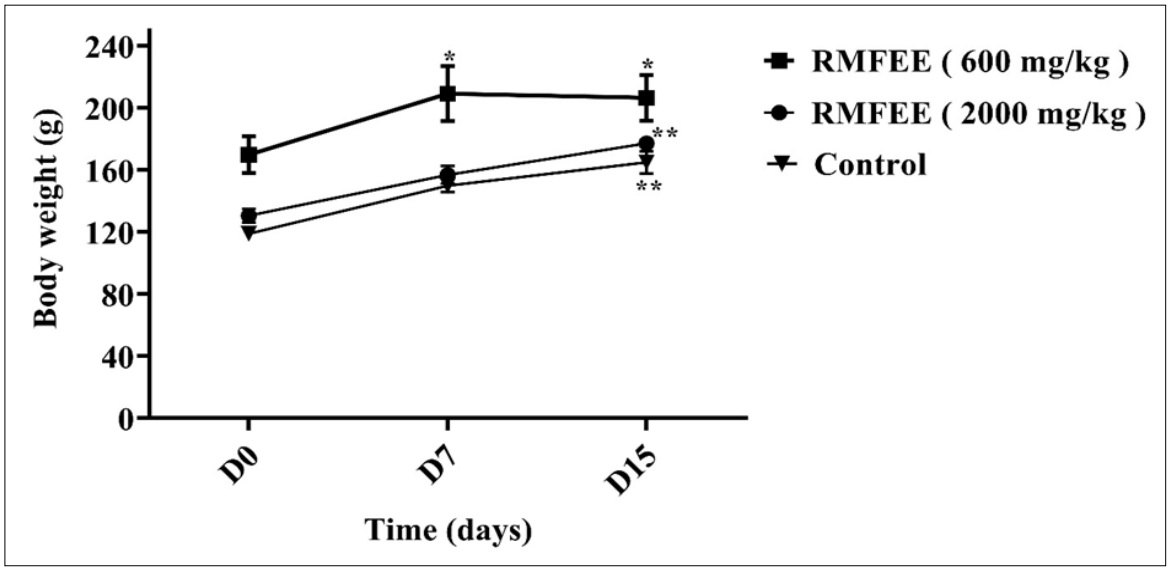


**Fig. 3.** The effect of orally administered of RMFEE (600 and 2000 mg/kg) on body weight in female rats. A single oral administration of RMFEE over 14 days. Data are expressed as mean ± S.E.M. (n= 5). *p<0.05 and **p<0.01 when compared to baseline values (the start oftreatment).

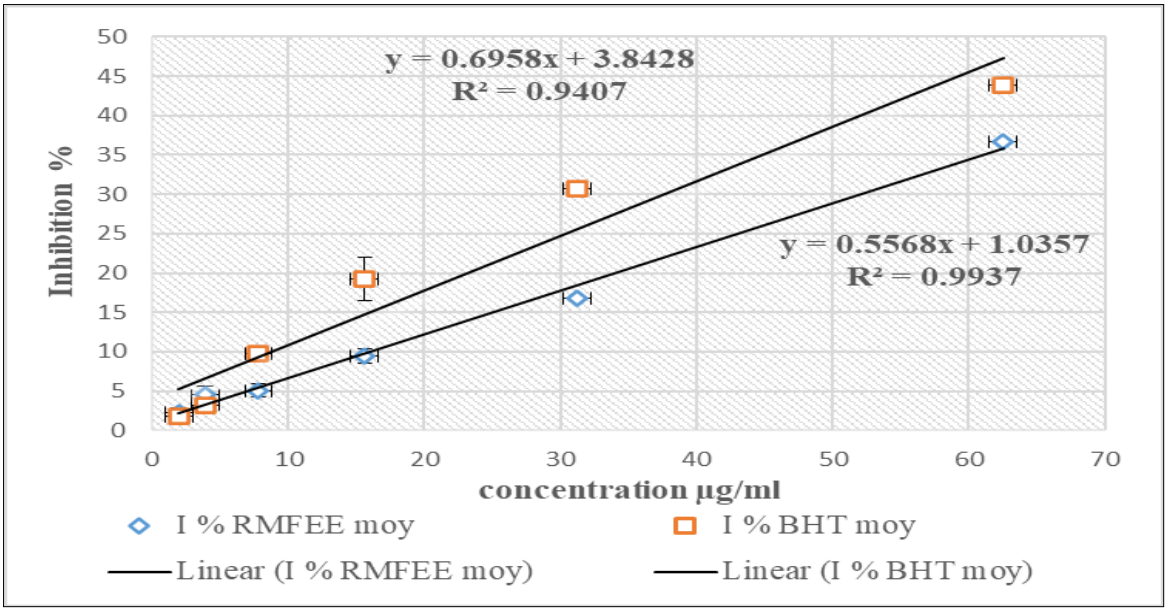


**Fig. 4.** DPPH radical scavenging activity of RMFEE (BHT: butylhydroxytoluene).

other findings (42).

Moreover, it is well known that the use of Triton WR-1339 for the induction of hyperlipidemia was accompanied by an increase in markers of oxidative stress (36). Thus, many research has linked the use of supplemental antioxidants to the prevention and treatment of dyslipidemia (43). Indeed, flavonoids are reported for their beneficial biological effects against various diseases through their antioxidant activity (13, 44). Therefore, the antioxidant activity of RMFEE demonstrated in this finding may suggest, at least in part, the antihyperlipidemic activity of RMFEE.

In the present work, the safety of RMFEE was evaluated to identify any signs of toxicity and the level of exposure inducing these signs (45). The acute toxicity study indicates that oral administration of RMFEE at doses of 600 and 2000 mg/kg body weight did not produce any signs of toxicity or death in female rats, with an LD50 greater than 2000 mg/kg. This suggests that RMFEE may be safe (46).

## Conclusion

We conclude that RMFEE, demonstrated antihyperli-pidemic activity in female rats with hyperlipidemia induced by Triton WR-1339. The protective effect of RMFEE against acute hyperlipidemia may suggest the implication of its antioxidant properties. Moreover, according to the acuate toxicity test, the safety of RMFEE has been demonstrated. Despite this finding, further research is still needed to understand the mechanisms underlying the lipid-lowering properties of RMFEE.

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## Authors' contributions

OF analyzed the data, performed the experiments, wrote the main manuscript. AA and IB conceived and designed research. SE analysis tools or data. AQ prepared figures and contributed the reagents. ME conceived and supervised research. All authors read and approved the manuscript.

## Compliance with ethical standards

**Conflict of interest:** Authors do not have any conflict of interest to declare.

**Ethical issues:** All applicable guidelines for the care and use of animals were followed according to the local ethical committee (FSTE/2015).

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