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Anti-Hyperlipidemic Effect of *Ruta chalepensis* Ethanolic Extract in Triton WR-1339-Induced Hyperlipidemia in Rats

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Abstract: High levels of fats like triglycerides and cholesterol in the blood can cause cardiovascular diseases, prompting the search for safer, natural treatments. This study investigates the efficacy of *Ruta chalepensis* ethanol extract in lowering cholesterol levels using a rat model of hyperlipidemia induced by Triton WR-1339. Leaves and flowers of *R. chalepensis* were extracted with ethanol, and LC-MS analysis revealed high levels of quercetin (9.5%), 2,2-Dimethyl-3-methylidenebicyclo [2.2.1] heptane (8.1%), and other compounds, with monoterpenes being the most common class. Male Wistar rats received doses of the extract at 20 and 40 mg/kg, while fenofibrate (100 mg/kg) was the positive control. After 20 h, plasma lipid levels were significantly affected, showing a 72.1% reduction in total cholesterol for the 40 mg/kg group ($p < 0.01$) and a 67.6% reduction for the 20 mg/kg group ($p < 0.01$). High-density lipoprotein cholesterol levels decreased by 68.8% in the 40 mg/kg group ($p < 0.01$) and 58.6% in the 20 mg/kg group ($p < 0.01$). Low-density lipoprotein cholesterol saw reductions of 67.3% ($p < 0.001$) in the 40 mg/kg group and 60.4% ($p < 0.01$) in the 20 mg/kg group. Triglycerides dropped by 90.6% in the 40 mg/kg group ($p < 0.001$) and 86.7% in the 20 mg/kg group ($p < 0.001$). Overall, the results highlighted a stronger anti-hyperlipidemic effect in the 40 mg/kg group across all lipid parameters measured. The extract outperformed fenofibrate, particularly at the higher dose. These results imply that *R. chalepensis* extract is a promising natural alternative for managing hyperlipidemia.

Keywords: *Ruta chalepensis*; anti-hyperlipidemic activity; hyperlipidemia; Triton WR-1339; lipid profiles; LC-MS

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1. Introduction

Elevated blood triglyceride, cholesterol, and other lipid levels are known as hyperlipidemia. This condition is linked to several cardiovascular illnesses, including atherosclerosis, coronary artery disease, and stroke [1,2]. Pharmaceutical treatments like statins are commonly used to treat such illnesses, which are frequently made worse by lifestyle choices, including poor diet and inactivity. However, because these drugs might have unfavorable side effects [3], people are looking for safer, more natural alternatives that can provide comparable results. Recent studies have highlighted the efficacy of various plant extracts, such as *Lavandula angustifolia*, which has shown promise in treating metabolic disorders [4].

The recent surge in interest in plant-based therapies is a beacon of hope, primarily due to the diverse bioactive compounds in medicinal plants. These natural compounds, including flavonoids, polyphenols, terpenoids, and alkaloids, have shown promise in modulating lipid metabolism, reducing cholesterol absorption, and improving overall lipid profiles [5]. For instance, polyphenols from Citrus Tacle® Extract have demonstrated HMGCR inhibitory activity, suggesting its potential as a natural remedy for anti-hypercholesterolemia [6]. The potential of plant extracts to combat hyperlipidemia is significant, as they can inhibit critical enzymes involved in lipid synthesis, enhance the excretion of bile acids [7,8], and improve antioxidant status, thereby protecting against oxidative stress-related lipid peroxidation.

Ruta chalepensis, commonly known as fringed rue, is a perennial herb traditionally used in various cultures for its medicinal properties [9]. This plant is rich in bioactive compounds, including flavonoids, alkaloids, coumarins, and essential oils, contributing to its diverse biological activities, such as antioxidant [10,11], cytotoxic [12], antihemolytic [12], and antibacterial activity [10,11]. Among these, its potential anti-hyperlipidemic effect has recently gained significant attention, sparking intrigue and interest in the research community.

Animal models of induced hyperlipidemia are commonly employed to assess the lipid-lowering potential of natural products, as they effectively mimic human hyperlipidemic conditions. This study utilized a rat model of Triton WR-1339-induced hyperlipidemia to evaluate the anti-hyperlipidemic effects of *Ruta chalepensis* ethanolic extracts. The model simulates the pathological elevation of plasma lipid levels observed in humans [13] providing a controlled environment for systematically investigating the extract's impact on lipid metabolism and cardiovascular health. The extract's efficacy was comprehensively evaluated by measuring key indicators such as blood total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) markers, offering insights into its potential for improving lipid profiles and overall cardiovascular health.

Besides pharmacological induction, dietary methods like the atherogenic diet in Wistar rats are commonly employed to mimic hyperlipidemic circumstances. These models offer insights into long-term lipid metabolism, liver histology, and cardiovascular health by feeding rats high-cholesterol or high-fat diets over extended periods. The model of atherogenic diet, as presented by Kelle et al. [14], is a proper adjunctive technique in the study of hyperlipidemia since it has been demonstrated to cause pathological alterations such as thickening of the abdominal aorta and hyperlipidemia. Based on the particular goals of the study, either of the two models can be chosen because they each have unique benefits.

Investigating the anti-hyperlipidemic potential of *R. chalepensis* ethanolic extracts is a significant contribution to the growing body of evidence supporting the use of plant-based therapies in managing hyperlipidemia. The findings of this study are not just valuable, but they are also crucial, providing insights into the development of safer and more effective natural alternatives to conventional lipid-lowering drugs. This research addresses the urgent need for treatments that lower lipid levels and improve overall cardiovascular health.

2. Materials and Methods

2.1. Collection of Plant Material and Preparation of Extract

In the spring of 2023, *Ruta chalepensis* leaves and flowers were collected from Amman, Jordan, with the plant's identity and authenticity confirmed by Prof. Sawsan Oran. A voucher specimen (No. RC/2021/20) was deposited at the herbarium of the Department of Biological Sciences in Amman. The plant parts were air-dried in the dark at room temperature (23–25 °C) for five weeks. Once dried, the material was finely ground using an electric blender. For extraction, 5 g of the powdered plant material was mixed with 50 mL of absolute ethanol, adhering strictly to the protocol outlined by Althaher et al. [11]. Afterward, the solvent was evaporated, and the extract was stored at 4 °C to maintain its properties.

2.2. LC-MS Analysis

The analysis utilized an LCMS-8030 Liquid Chromatograph–Mass Spectrometer (Triple Quad MS, Kyoto, Japan) connected to an LC-8030 MS/MS with electrospray ionization. The Shimadzu LC system (Tokyo, Japan) was outfitted with several components, including a CBM-20A Control Bus Module, a CTO-30A Column Oven, an LC-30AD Liquid Chromatograph, and an SIL-30AC Auto Sampler. Chromatographic separation was performed on a Primesil RP-C18 column (150 × 4.6 mm, 5 µm). Mobile phase A consisted of water/acetonitrile (80:20% v/v) with 0.01% formic acid (pH 3) from Merck (Merck KGaA, Darmstadt, Germany) while mobile phase B was acetonitrile containing 0.01% formic acid (Merck). The plant ethanolic extract was dissolved in 2 mL of methanol, and a 10 µL

sample was injected for LC-MS/MS analysis. The column temperature was 25 °C, with a 0.7 mL/min flow rate.

The gradient elution process was meticulously designed, starting with 20% of mobile phase B and gradually increasing to 50% B by 18 min, then reaching 100% B at 20 min and holding for 1 min. At 22 min, the gradient returned to 20% B, maintaining that level for an additional 2 min, resulting in a total run time of 31 min. Before injecting the sample, solvents and extracts used for the mobile phases were filtered using a 0.45 µm PTFE syringe filter, ensuring the purity of the sample. The obtained mass spectral data and retention indices were compared with the NIST (2016) mass spectral library to determine the extract's chemical composition [11], leaving no stone unturned in the analysis process.

2.3. Animal Experiment

The study was carried out at the Animal Care Center, Faculty of Pharmacy, Al-Zaytoonah University of Jordan, Amman. The subjects were male Wistar rats, two months old, weighing between 200 and 250 g. This age was chosen because it represents a developmental stage where the rats are sufficiently mature for metabolic studies while remaining responsive to experimental interventions. Moreover, the exclusive use of male rats helps to minimize variability caused by hormonal fluctuations present in females, leading to more consistent and reliable results. The rules of the Federation of European Laboratory Animal Science Associations and the general standards for the care and use of laboratory animals were adhered to in this work [13]. During the 24 h experiment, the rats had access only to tap water. They were housed under controlled conditions with a 12 h light/dark cycle, a temperature of 22 °C ± 2 °C, and regulated humidity. Approval for the experiment was granted by the local Ethics Committee of Animal Welfare on 3 September 2024, under reference number 2/5/2023-2024.

2.4. Induction of Hyperlipidemia Using the Triton WR-1339 Model

During the experiment, Triton WR-1339 (Sigma-Aldrich in St. Louis, MO, USA) was injected intraperitoneally into the rats at a high dose of 300 mg per kg of body weight. As a result, acute hyperlipidemia was induced, as reported by Hussein et al. [15].

2.5. Pharmacological Study Design

Twenty-five rats who had fasted the whole night were divided into five groups, each with five rats. The first group to receive an intraperitoneal (IP) injection of dimethyl sulfoxide (DMSO) was the normal control group (NCG). The hyperlipidemic control group (HCG) is the second group, and they were given an IP injection of Triton WR-1339 that had been dissolved in DMSO. Groups three and four of rats received intragastric injections of *R. chalepensis* ethanolic extract (derived from both leaves and flowers) at 20 and 40 mg per kg after receiving a Triton injection. A powerful anti-hypertriglyceridemic drug called fenofibrate (100 mg/kg body weight) was injected intragastrically into the fifth group [13] Blood samples were obtained after a 20 h treatment period, and they underwent a rigorous centrifugation procedure for 10 min at 3000 rpm. Lipid content in the collected serums was carefully assessed using an automated analyzer (Model Erba XL-300, Mannheim, Germany) and enzymatic techniques.

2.6. Statistical Analysis

The data were presented as mean ± standard deviation (SD). The statistical analysis was performed using GraphPad Prism 10. Student's *t*-test was used to compare two groups, while one-way ANOVA followed by Dunnett's multiple comparisons test was employed to compare multiple groups. Statistical significance was determined at $p < 0.05$.

3. Results

3.1. Phytochemical Analysis

Table 1 lists the chemical components of the *R. chalepensis* ethanolic extract, as well as their % content, elution sequence, and retention period. The chemical analysis revealed a total of thirty-four components (96.4%) in the extract. The LC/MS chromatogram in Figure 1 illustrates this. Notably, the extract contains high concentrations of quercetin (9.5%), 2,2-Dimethyl-3-methylidenebicyclo [2.2.1] heptane (8.1%), and myricetol (8.0%). Conversely, the least prevalent component in the extract was phellandrene (0.1%).

Table 1. Chemical profile of *R. chalepensis* ethanolic extract.

No.	Compound	Retention Time (min)	Percentage (%)
1	Phellandrene	1.5	0.1
2	2,2-Dimethyl-3-methylidenebicyclo [2.2.1] heptane	2.3	8.1
3	D-Limonene	3.4	4.9
4	Alpha-Pinene	5	6.1
5	Methyl heptyl ketone	6.1	2.2
6	2-Bornanone	7.9	6.4
7	Piperitone	8.3	1
8	P-Menth-4(8)-en-3-one	9.1	0.3
9	Eucalyptol	9.9	2.2
10	2-Bornanol	10.3	1.5
11	2-Isoborneol	10.9	3
12	3,7-Dimethylocta-1,6-dien-3-ol	11.1	6.9
13	γ-Terpinene	12.3	5.9
14	Methyl nonyl ketone	13.2	2.1
15	4-Hydroxycinnamic acid	13.9	3.8
16	4-Hydroxy-3-methoxybenzoic acid	14.3	0.3
17	3,4,5-Trihydroxybenzoic acid	15.1	4.1
18	Methyl undecyl ketone	16.1	0.9
19	3,4-Dihydroxycinnamic acid	16.6	1.8
20	Methyl decyl ketone	17.1	1.1
21	4-Hydroxy-3-methoxycinnamic acid	18.2	0.9
22	Linalool acetate, 3,7-Dimethylocta-1,6-dien-3-yl acetate	19.4	2.1
23	Alpha-Humulene	21.1	0.2
24	Unknown	21.9	0.2
25	(−)-β-Eudesmol	23	0.8
26	Elemane, Elemol alcohol	23.3	1.9
27	Viridifloral	23.6	1.4
28	Octadecanoic acid	24.3	2.4
29	Quercetin	25.9	9.5
30	3‘-Methylquercetin	26.4	1
31	Myricetol	27.7	8
32	5-Caffeoylquinic acid	28.4	0.3
33	Unknown	29.6	3.4
34	Rutin	31.1	5.2
Total identified compounds			
96.4%			

The identified compounds were meticulously categorized based on their chemical structure, providing a comprehensive understanding of the *R. chalepensis* ethanolic extract. Monoterpenes emerged as the most abundant, comprising 48.5% of the extract. Flavonoids (23.7%) and phenols (11.2%) were the most prevalent classes, while fatty acids represented the minor portion of the extract, making up just 2.4% (Table 2).

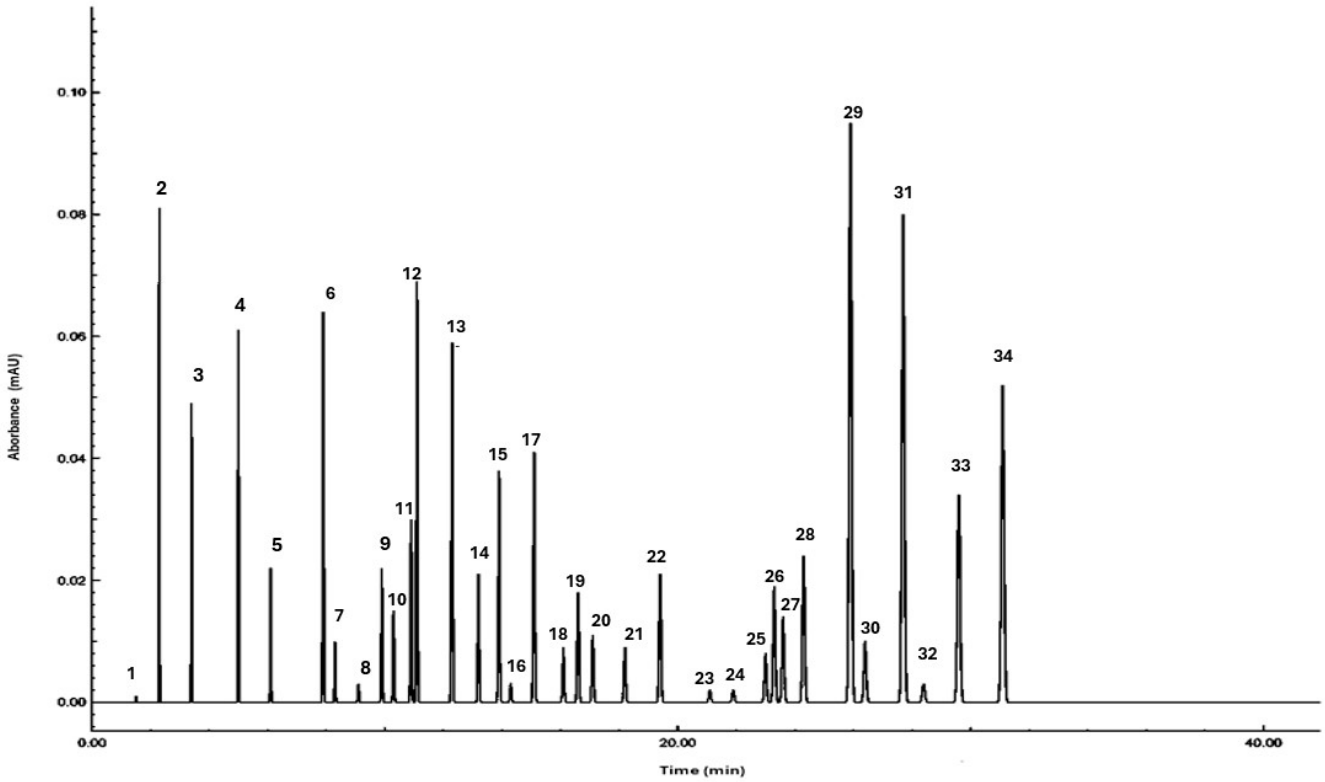


Figure 1. Chromatographic profile of *Ruta chalepensis* ethanolic extract.

Table 2. Chemical classes in *Ruta chalepensis* ethanolic extract.

Component	Percentage (%)
Fatty acid	2.4%
Flavonoid	23.7%
Phenol	11.2%
Ketone	6.3%
Monoterpene	48.5%
Sesquiterpene	4.3%

3.2. Hyperlipidemia Induction Using Triton WR-1339

Triton WR-1339 induces rapid hyperlipidemia in rats by inhibiting lipoprotein lipase (LPL) activity, thereby impeding the clearance of triglyceride-rich lipoproteins (TLRs). An individual intraperitoneal (IP) administration of 300 mg/kg is adequate for inducing acute hyperlipidemia, with peak plasma levels of triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) achieved within 20 h [16]; this approach is commonly employed to evaluate the effectiveness of anti-hyperlipidemic medications

A comparison of the lipid profiles between the hyperlipidemic control group (HCG) and the normal control group (NCG) reveals significant variations (refer to Table 3). In the HCG, total cholesterol (TC) is elevated by 340% compared to the NCG ($p < 0.01$). Additionally, there is a 25% reduction in HDL cholesterol in the HCG ($p < 0.05$), signifying a notable decrease. LDL cholesterol in the HCG exceeds normal levels by over 1.933% ($p < 0.01$), indicating a substantial increase. Furthermore, triglycerides (TGs) exhibit a significant elevation, with levels in the HCG being 5.146% higher than those in the NCG ($p < 0.01$). These findings demonstrate that Triton WR-1339 induces severe lipid disturbances, leading to elevated total cholesterol, LDL, and triglycerides, and a considerable reduction

in HDL. These statistically significant changes could contribute to the development of hyperlipidemia and associated cardiovascular complications.

Table 3. Plasma lipid levels after 20 h of Triton WR-1339 administration.

	(Mean ± SD)	
Lipid Parameter	**NCG (Control)**	**HCG (Triton)**
Total Cholesterol (TC) (mg/dL)	87.6 ± 13.3	385.25 ± 96.8 **
High-Density Lipoprotein (HDL-C) (mg/dL)	37.2 ± 7.0	28 ± 2.8 *
Low-Density Lipoprotein (LDL-C) (mg/dL)	9.0 ± 1.6	183 ± 51.3 **
Triglycerides (TGs) (mg/dL)	65.2 ± 9.4	3421 ± 1114.2 **

Values are presented as means ± SD from five animals per group. NCG: normal control group, HCG: hyperlipidemic control group. TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TGs: triglycerides (* $p < 0.05$, ** $p < 0.01$).

3.3. Effect of R. chalepensis Ethanolic Extract and Fenofibrate on Plasma Lipid Profile

In the current study, Figure 2A–D illustrate the effects of *R. chalepensis* ethanolic extract (RCEE) at different doses (20 mg/kg, 40 mg/kg) and fenofibrate (FF) on the plasma levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) in treated rats after 20 h.

Total Cholesterol (TC): The most significant reduction in TC levels was observed in the RCEE 40 mg/kg group, showing a remarkable 72.1% decrease compared to the high-cholesterol diet (HCG) control. This was followed by the RCEE 20 mg/kg group, which exhibited a substantial 67.6% reduction. The fenofibrate (FF) group demonstrated a 39.6% decrease. All changes were statistically significant, with the RCEE 40 mg/kg group showing the highest significance ($p < 0.001$), followed by the RCEE 20 mg/kg group ($p < 0.001$) and the FF group ($p < 0.01$) (Figure 2A).

High-density lipoprotein cholesterol (HDL-C): Regarding HDL-C levels, the RCEE 40 mg/kg group again showed the most pronounced effect, with a significant reduction of 68.8% compared to the HCG control. The RCEE 20 mg/kg and FF groups also demonstrated significant decreases of 58.6% and 58.1%, respectively. The differences for all treatment groups were statistically significant, with the RCEE 40 mg/kg group having the highest significance ($p < 0.01$) (Figure 2B).

Low-density lipoprotein cholesterol (LDL-C): The RCEE 40 mg/kg group also led to the most significant reduction in LDL levels, with a 67.3% decrease compared to the HCG control. The RCEE 20 mg/kg group showed a 60.4% reduction, while the FF group exhibited a 47.7% decrease. All reductions were statistically significant, with the RCEE 40 mg/kg group demonstrating the highest significance ($p < 0.001$), followed by the RCEE 20 mg/kg and FF groups at ($p < 0.01$) (Figure 2C).

Triglycerides (TGs): Lastly, for TG levels, the RCEE 40 mg/kg group had the most substantial impact, resulting in a 90.6% decrease compared to the HCG control. The RCEE 20 mg/kg group showed an 86.7% reduction, while the FF group exhibited an 84.6% decrease. All reductions were statistically significant, with the RCEE 40 mg/kg group again showing the most pronounced effect ($p < 0.001$), followed closely by the RCEE 20 mg/kg and FF groups ($p < 0.001$) (Figure 2D).

Notably, no adverse effects related to intraperitoneal injections of Triton WR-1339 or the administration of *R. chalepensis* ethanolic extract or fenofibrate were observed.

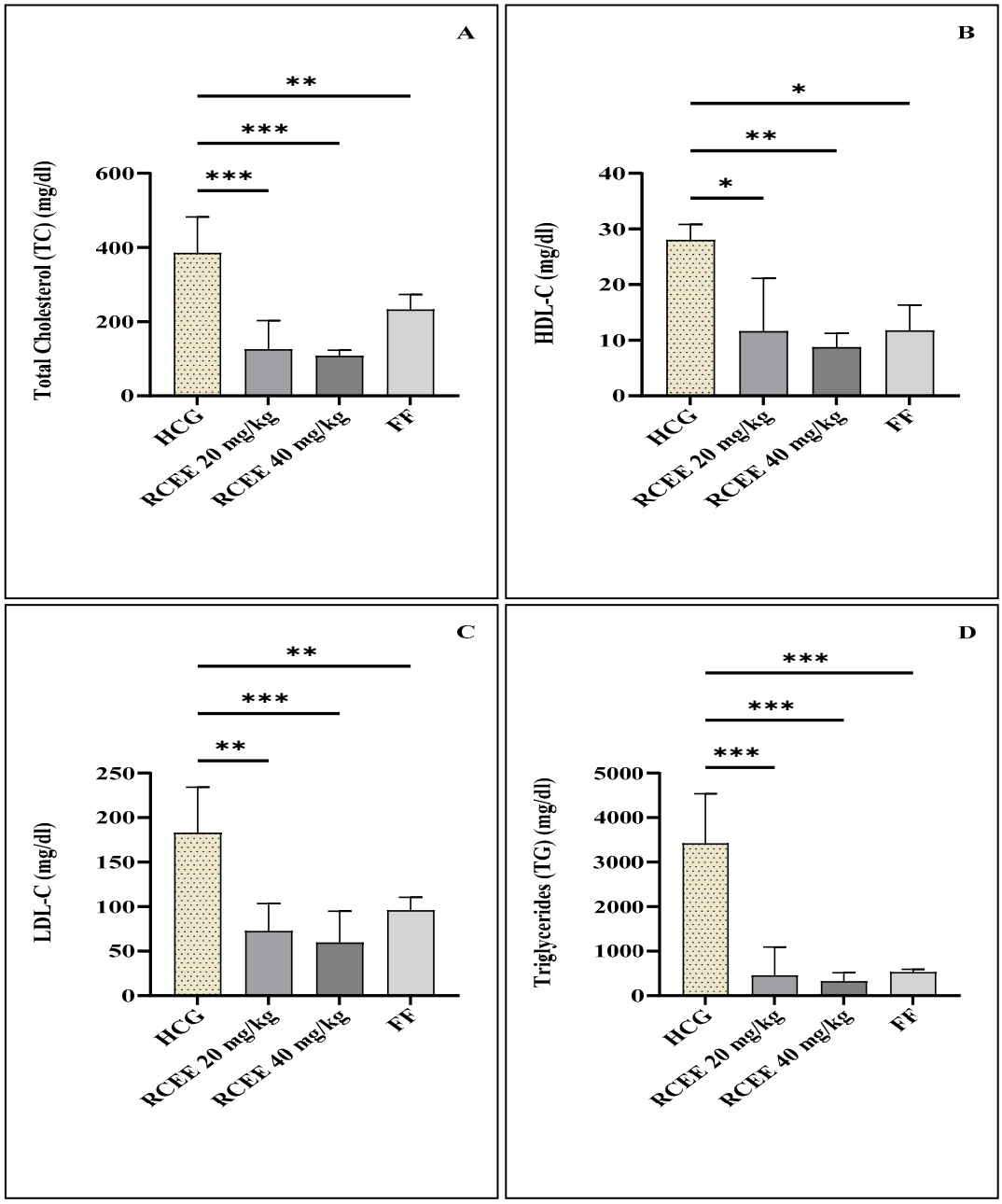


Figure 2. Effect of *R. chalepensis* ethanolic extract (RCEE) at 20 mg/kg and 40 mg/kg on lipid profiles after 20 h. Values are presented as means ± SD from five animals per group. HCG: hyperlipidemic control group; FF: fenofibrate. ns: non-significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. (**A**) Total cholesterol (TC) levels (mg/dL). (**B**) High-density lipoprotein cholesterol (HDL-C) levels (mg/dL). (**C**) Low-density lipoprotein cholesterol (LDL-C) levels (mg/dL). (**D**) Triglyceride (TG) levels (mg/dL).

4. Discussion

Secondary metabolites are the hidden gems of medicinal plants, driving their potential to heal, protect, and enhance human health. These potent compounds are responsible for crafting pharmaceutical medications, creating cutting-edge cosmetics, and combating diseases in plants and humans. What is truly fascinating is how the chemical composition of these plants can vary dramatically, even within the same species—especially those with anti-hyperlipidemic effects. This variability is not just random; it is a dynamic interplay of factors like climate, genotype, rainfall, geography, developmental stage, and

the precise moment of harvesting. Even the extraction techniques can sway these life-changing metabolites' concentration and potency [17]. Understanding these nuances is critical to unlocking the full therapeutic potential of plant-based treatments for conditions like hyperlipidemia.

Our meticulous analysis of the ethanolic extract of *R. chalepensis*, in contrast to the previous study conducted by Althaher et al. [11], revealed similarly high levels of quercetin (9.5%) and myricetin (8.0%). The primary compound in the previous study, camphene (8.0%), was not prominent in our extract. Furthermore, our research process identified phellandrene (0.1%) as the least abundant compound, in contrast to the previous study's α-humulene (0.1%), underscoring the thoroughness of our approach.

Both studies found monoterpenes to be the dominant class, with similar percentages (48.5% in our study vs. 45.7% in the previous study). Notably, flavonoids were also prominent in both studies, though phenols and organic acids showed some variation. Fatty acids were the category that represented the least in both studies.

These results highlight the importance of *R. chalepensis* extracts from several research studies, which have similarities and minor differences in chemical composition. These results highlight how important it is that *R. chalepensis* extracts from several studies have certain similarities and minor differences in their chemical composition. They also emphasize the crucial influence of factors such as extraction methods and other factors on the plant's phytochemical profile, thereby contributing to our understanding of this field.

Conversely, a Moroccan study identified 2-undecanone (64.35%) as the dominant compound in *R. chalepensis* essential oil, along with piperonyl piperazine (11.9%), 2-decanoate (5.12%), 2-dodecanone (4.52%), decipidone (3.9%), and 2-tridecanone (2.36%) [18].

In Iraq, the methanolic extract of *R. chalepensis* was found to contain a fascinating variety of metabolites, including alkaloids, coumarins, flavonoid glycosides, and a cinnamic acid derivative, three$''$,6$'$-disinapoylsucrose [19]. A Tunisian study added another layer of intrigue with LC-MS analysis, uncovering a wealth of coumarins and alkaloid compounds in *R. chalepensis* [20].

These studies underscore the diverse chemical compositions of *R. chalepensis* from different regions. The differences in metabolite profiles and prominent chemicals that result from extraction techniques and geographic origin improve our knowledge of this area.

This study is the first to investigate the lipid-lowering effects of *R. chalepensis* ethanolic extract (RCEE). The findings indicate significant anti-hyperlipidemic activity in a rat model of Triton WR-1339-induced hyperlipidemia, a commonly used model for evaluating lipid-lowering agents. Both doses of RCEE (20 mg/kg and 40 mg/kg) led to marked reductions in triglycerides, total cholesterol, LDL-C, and HDL-C levels, suggesting a potential to lower the risk of atherosclerosis and cardiovascular diseases.

The hyperlipidemic control group (HCG) exhibited substantial lipid abnormalities, with sharp increases in total cholesterol, LDL, and triglycerides, and decreased HDL, confirming the severity of hyperlipidemia induced by Triton WR-1339. Treatment with RCEE significantly lowered TC, LDL, and TG levels, with the 40 mg/kg dose showing the most pronounced effects. While RCEE also reduced HDL-C levels, this reduction was less significant than other lipid parameters. Fenofibrate (FF), a standard lipid-lowering drug, similarly reduced TC, LDL, and TG levels, though less effectively than RCEE, particularly at the higher dose.

These results affirm that RCEE, particularly at a 40 mg/kg dose, is highly effective in reducing lipid levels, offering a promising natural alternative or complement to conventional treatments like fenofibrate for managing hyperlipidemia. The significant reductions in harmful lipid levels and the potential cardiovascular benefits underscore the therapeutic potential of *R. chalepensis* in treating hyperlipidemic conditions.

Several notable findings emerge when comparing our study on *R. chalepensis* to other research. A study on *R. chalepensis* leaf extract from Tunisia demonstrated significant lipid-lowering effects, with obese rats showing a 44% reduction in serum total cholesterol and a 68% decrease in LDL-C levels. Additionally, the extract led to a remarkable 91% increase

in HDL-C levels in rats fed a high-fat, high-fructose diet [21]. These results align with our findings, affirming *R. chalepensis* as an effective agent for managing hyperlipidemia. However, differences in the extent of lipid modulation between studies may be attributed to variations in experimental models, extract preparation, dosage, and geographical origin of the plant material.

In contrast, the study on *R. tuberculata* revealed mild toxicity at higher doses, with an oral LD50 exceeding 5000 mg/kg. Paracetamol (PCM) administration significantly increased hepatic enzyme activities, cholesterol, triglycerides, and glycemic levels. These adverse effects were substantially reduced by co-treatment with vitamin C and *Ruta* methanolic extract (RME), with RME showing superior efficacy compared to the aqueous extract (RAE) in preventing PCM-induced histological changes and reducing hepatic damage [22].

Furthermore, *R. chalepensis* was found to restore zinc levels, improve lipid profiles—by reducing total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol—and enhance antioxidant defenses in diabetic rats on a zinc-deficient diet [23]. This comprehensive profile underscores the potential therapeutic benefits of different species of *Ruta* in managing hyperlipidemia and supporting overall health.

In Triton WR-1339-induced hyperlipidemic rats, *R. chalepensis* ethanolic extract (20 mg/kg, 40 mg/kg) reduced lipid levels, which can be attributed to the modulation of several key genes involved in lipid metabolism by modulating multiple essential genes related to cholesterol metabolism, including Peroxisome Proliferator-Activated Receptor Alpha (*Ppara)*, Liver X Receptor Alpha (*Lxra*), Sterol Regulatory Element-Binding Protein 1c (*Srebp-1c*), 3-Hydroxy-3-Methylglutaryl-CoA Reductase (*Hmgcr*), and Low-Density Lipoprotein Receptor (*Ldlr)*. PPAR-alpha plays a critical role by enhancing the expression of genes like Carnitine Palmitoyl transferase 1A (*Cpt1a*), Acyl-CoA Oxidase 1 (*Acox1*), and lipoprotein lipase (*Lpl)*, which are pivotal in promoting fatty acid oxidation and reducing triglyceride levels [24]. Additionally, LXR-alpha upregulates ATP-Binding Cassette Transporter A1 (*Abca1*) and ATP-Binding Cassette Transporter G1 (*Abcg1*), facilitating cholesterol efflux and increasing HDL-C levels while downregulating SREBP-1c to limit lipid synthesis [25]. The reduced total cholesterol and LDL-C levels are further supported by the downregulation of *Hmgcr*, the rate-limiting enzyme in cholesterol biosynthesis, and the upregulation of *Ldlr*, which enhances LDL clearance [26]. The ability of *R. chalepensis* to downregulate these pro-lipogenic genes and upregulate those involved in lipid catabolism underscores its potential as a therapeutic agent for managing hyperlipidemia and reducing the risk of atherosclerosis and cardiovascular diseases.

5. Conclusions

In conclusion, *R. chalepensis* ethanolic extract (RCEE), derived from both the leaves and flowers, demonstrates strong potential in managing hyperlipidemia by effectively reducing triglycerides, total cholesterol, and LDL-C in a rat model of hyperlipidemia, with the 40 mg/kg dose showing the most pronounced effects. While RCEE also lowers HDL-C, this reduction is less significant compared to other lipid parameters. Fenofibrate, a standard lipid-lowering drug, was less effective than RCEE. The extract is notably rich in quercetin, with monoterpenes, flavonoids, and phenols as the primary components. Future research should explore its specific mechanisms of action and optimize extraction methods and dosages to enhance its potential as a natural treatment for hyperlipidemia.

Author Contributions: M.A., A.R.A. and T.A.-Q. conceptualized the project and designed the experiments. A.R.A., M.A., A.H., D.A.-M. and M.W.A. conducted the laboratory experiments. A.R.A. and M.A. analyzed the data. A.R.A., M.A. and T.A.-Q. wrote the manuscript. All authors revised the manuscript and read and approved the final submission. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable.

Data Availability Statement: Data available on request from the authors.

Conflicts of Interest: The authors report there are no competing interests to declare.

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