Effect of introducing the Jordanian common rue (*Ruta chalepensis* L.) on blood lipid profile in adult male Sprague Dawley rats toxified with Paracetamol

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Abstract

This study aimed to determine the effect of *Ruta chalepensis* L. on blood lipid profile of rats**.** An animal experiment was conducted using five groups of Sprague Dawley rats, 9 rats in each group. The groups were fed: Normal diet, high cholesterol diet (HCD), HCD with or without the plant and with or without paracetamol. The experiment lasted six weeks; at the end of the sixth week; a single dose of 3g paracetamol /kg body weight was given to two groups, then blood samples were collected to evaluate blood lipid profile. There were no significant differences among groups in initial weight, final weight, weight gain, and feed efficiency ratio (FER). Furthermore, HCD significantly increased the accumulative feed intake, whereas the paracetamol (PCM) toxin dose significantly lowered the accumulative feed intake. The addition of the plant to the diet of rats on HCD significantly lowered the risk of hyperlipidemia, by increasing high-density lipoprotein (HDL) and lowering the triglycerides blood levels ($P<0.05$). However, the addition of the plant to the diet did not significantly affect HDL levels in rats toxified with paracetamol. It can be concluded that the addition of *Ruta chalepensis* L. plant to hypercholesterolemic rats would increase their HDL and lower their Triglyceride serum levels. Besides, the plant can beneficially affect the lipid profile in paracetamol-toxified rats.

Keywords: Lipid Profile*, Ruta chalepensis* L., Paracetamol, High cholesterol diet.

1. Introduction

Flora of Jordan is highly diversified in its number of vascular, flowering plants (Oran, 2015). It was reported that 2500 species exist in Jordan. Many of these plants are edible and grow as wild and are rich in nutrients including vitamins and minerals and trace elements; therefore, they complement staple foods towards a balanced diet (Dogan et al., 2013). Among the edible plants that are common in Jordan, is common rue (*Ruta chalepensis* L.) (Afifi and Abu-Irmaileh, 2000).

Common rue is an ornamental, aromatic, culinary and medicinal plant, grown in the wild and can be cultivated in gardens (Abbas, 2017). It belongs to the Rutaceae family. It is a hard, evergreen shrub of up to one-meter height with a characteristic grayish color and a sharp pleasant odor (Al-Shuneigat et al., 2015). It is endemic in the Mediterranean region and has been introduced to and cultivated in many parts of the world because of its medicinal properties. A total of 45 compounds were detected in its leaves. These include alkaloids, flavonoids, lignans, terpenes, and coumarins (Kong et al., 1989) which represent approximately 93% of the total quantity (Perera et al., 2017). The plant has been reported to have anti-inflammatory (Raghav et al., 2006), anti-tumor (Preethi et al., 2006), anti-nociceptive (Atta and Alkofahi, 1998), antirheumatic (Khouri and El-Akawi, 2005), antimicrobial (Ivanova et al., 2005), anti-carcinogenic, antimutagenic and cardioprotective effects (Volf et al., 2014).

Antioxidants are compounds that can delay or inhibit the oxidation of lipids or other molecules by inhibiting the initiation or propagation of oxidizing chain reactions (Volf et al., 2014). Another property that a compound should have to be considered as an antioxidant is the ability, after scavenging the radical, to form a new radical that is stable through intramolecular hydrogen bonding on further oxidation (Carocho and Ferreira, 2013).

Currently, enhancing the antioxidant capacity via medications have potential adverse effects despite its efficacy. Therefore, plant products are generally considered to be less toxic and less prone to side effects and have been receiving more and more attention in recent years (Blumberg et al., 2015). Nowadays, antioxidant agents of natural origin have attracted special interest because they can protect the human body from free radicals, due to its high content of polyphenolic compounds (Pandey and Rizvi, 2009). Accordingly, antioxidants can protect the body from reactive oxygen species (ROS) that damages cells and prevent carcinogenesis by scavenging them. They also protect people from developing many diseases (Terkmane et al., 2018).

Dyslipidemia refers to having abnormal levels of lipids and/or lipoproteins in the blood. It is characterized by an increase of low-density lipoprotein (LDL) and triglycerides (TG) concentrations in the blood, associated with a decrease in high-density lipoproteins (HDL) (Manjunath et al., 2013). Hyperlipidemia is an important risk factor for coronary artery disease and stroke (Kopin and Lowenstein, 2017). The Expert Panel of the National Cholesterol Education Program (NCEP) (2001) in their report on detection, evaluation and treatment of high blood cholesterol in adults defined hypercholesterolemia as ≥ 200 mg/dL (5.2 mmol/L), hypertriglyceridemia as ≥ 150 mg/dL (1.69 mmol/L), high LDL as ≥ 120 mg/dL (3.1 mmol/L) and low HDL as ≤ 40 mg/dL (1.04 mmol/L).

Lipid disorders seem to be common and highly prevalent in many countries of the world, including Jordan. The Jordanian Ministry of Health (MOH) (2007) reported that the prevalence of hypercholesterolemia among Jordanians aged 18 years and over was 36% and that 33.8% had a low level of HDL, 24.2% had elevated level of LDL and 48.8% had elevated TG blood levels. Khader *et al.* (2010) also assessed the prevalence of hyperlipidemia among Jordanian adults; they showed in their study that almost half of the study volunteers (48.8%) had elevated level of total cholesterol, (40.7%) had elevated LDL, (40.1%) had low HDL and (43.6%) had elevated TG concentrations. These authors reported that more than three quarters (75.7%) had at least one abnormal lipid measurement. The objective of this study was to determine the effect of *Ruta chalepensis* L. on blood lipid profile of rats toxified with paracetamol.

2. Materials and methods

2.1. Plant collection, drying, and grinding

The fresh common rue was collected from Ajloun Mountains (North Jordan) from March to April 2018 (the season of their growth). The leaves, flowers and the top 10-15 cm of the fresh stems aerial parts were used in the study. It was shade-dried at room temperature for approximately three weeks with occasional flipping. The dry plant was powdered mechanically to an average diameter of 0.4 mm using a high-efficiency food grinder (CHAORAN, 220V, 1700W, China) and sieved to remove the large particles. The powder was packed in glass containers and stored in a refrigerator at 4 C° for further investigations. Macronutrients were determined using standard proximate analysis procedures of the Official Methods of Analysis of AOAC International, 19th edition (Latimer, 2012). The determination of moisture, ash, protein, fat and fiber were performed in triplicate. Carbohydrate or the nitrogen-free extract (NFE) percent was calculated by subtracting the sum of percentages of (moisture, ash, protein, fat and fiber) from 100. Table (1) show the proximate analysis of the dry plant.

Table (1): Proximate analysis of the dried plant

Plant	Moisture %	Ash %	Protein %	Fat %	Fiber %	NFE%
Ruta chalepensis	**9.34**	**9.56**	**12.00**	**5.09**	**13.95**	**50.06**

2.2. Experimental animals

The use of animals in this study was approved by the school of graduate studies ethical committee at The University of Jordan. Forty-five adult male rats at eight weeks of age, weighing (200 - 250 g) were obtained from the Animal Unit at Jordan University of Science and Technology (Irbid, Jordan) and transferred to the Animal Unit at the

Department of Nutrition and Food Technology / Faculty of Agriculture / The University of Jordan. Rats were weighed and kept for a week for acclimatization before starting the experiment. The rats were fed standard diet served in glass jars with open access to tap water *ad libitum*. Then rats were housed individually in plastic cages under controlled conditions including temperature (23± 2° C), humidity (49± 5%), and hygienic conditions in a ventilated room that is maintained at 12-hr light/dark cycle. After acclimatization, rats were weighed and randomized into five groups, nine rats each, according to their initial body weight. The groups regarding dietary treatment were:

Group 1: Normal Diet
Group 2: High cholesterol diet (HCD)
Group 3: High cholesterol diet (HCD) with 2.5% plant
Group 4: High cholesterol diet (HCD) that received paracetamol dose without plant
Group 5: High cholesterol diet (HCD) that received paracetamol dose with 2.5% plant

Three types of experimental diet mixtures were prepared according to the guidelines of the American Institute of Nutrition 1993 for adult animals (AIN-93M) recommended by Reeves, (1997). The HCD was prepared by adding 10 mg cholesterol per one kg diet. The synthetic antioxidant tertiary butylhydroquinone (TBHQ) was added to prevent the oxidation of the highly polyunsaturated fatty acids in foods (10 mg for each 10 g fat). The amount of corn starch, egg white and soybean oil in the AIN-93M diet were modified based on the proximate analysis of the plant sample to establish approximately an isocaloric diet. A modification was done by using egg white as a source of protein instead of casein. Therefore, biotin premix was added (10g/kg Diet) (Reeves, 1997).

Also, feed intake was determined by weighing feed jars and estimating the amount of spilled feed once a week. Feed Efficiency Ratio (FER) was calculated to assess the utilization of feed consumed according to the following equation: (FER= Body weight gain (g) / Weight of feed eaten).

2.3. Preparation of paracetamol suspension and inducing liver toxicity

In this experiment, paracetamol (PCM) was used in a concentration of 3 g/ kg body weight (Janakat and Al-Amour, 2014; Shaban et al., 2015). A single dose of PCM in syrup suspension was given to all rats in groups 4 and 5 only. The rats in those two groups were weighed on the same day of the toxification process to calculate the accurate dose needed. The dose was introduced to the rats via oral gavage needle before 48 hours of dissection.

2.4. Animal dissection and blood samples collection

After six weeks of the experiment, the rats were fasted overnight. In the morning, rats were anesthetized by chloroform, and blood samples were collected from the right ventricle of the heart by a medical syringe and transferred into plain tubes with gel. The blood samples were left for 30 minutes to clot. After clotting, blood samples were centrifuged at 3500 rpm for 10 minutes (HERMLE Z200A, LaborTechnik, Wehingen, Germany). Finally, each serum sample was separated into three Eppendorf tubes and preserved at -18˚C until analyzed.

2.5. Blood lipid profile assay

The analyses of serum lipids were done in private Medical Laboratory (Amman, Jordan). An automated clinical analyzer (ARCHITECT plus, Serial number: i1SR56522, Abbott, Germany) was used for the analysis. The analyzer was calibrated before performing the analyses tests; calibration of the analyzer for triglyceride (TG), total cholesterol (TC), Low-density lipoprotein (LDL) and High-density lipoprotein (HDL) was done according to the manufacturer's instructions.

Statistical Analysis

Statistical analysis of the data was performed using the Statistical Package for Social Science (SPSS) software version 24. Data were expressed as mean± standard error of the mean (SEM) and the levels of significance were at ($P<0.05$). Analysis of variance (ANOVA) followed by the Least Significance Difference (LSD) test was used to determine any significant differences among the variable means of the study groups.

3. Results

3.1. Initial and final body weights, body weight gain, accumulative feed intake and feed efficiency ratio (FER)

Table (2) shows the mean and the standard error of the mean for initial and final body weight (g), total weight gain (g), accumulative feed Intake (g) and feed efficiency ratio for the studied groups. It is clear from the table that the values of initial and final body weight among the different experimental groups were close to each other with no significant differences (*P>0.05*). Total body weight gain values were also not significantly different among experimental groups (*P>0.05*). Regarding accumulative feed intake, there was a significant difference between group 1 and groups 2 and 3. Furthermore, the feed efficiency ratio (FER) (g/100g feed intake) values were not significantly different among different groups (*P>0.05*).

Table (2): Initial and final body weight, body weight gain, accumulative feed intake, and feed efficiency ratio

Group Description[1]	Initial Weight (g) [2]	Final Weight (g)	Total Weight Gain (g)	Accumulative Feed Intake (g)	Feed Efficiency Ratio [3]
1. Normal AIN Diet	189.7 ± 7.2 [a]	304.2 ± 10.9 [a]	114.5 ± 7.3 [a]	675.2 ± 6.8 [a]	16.4 ± 0.8 [a]
2. HCD w/o plant w/o PCM	191.3 ± 6.5 [a]	311.6 ± 7.6 [a]	120.3 ± 7.4 [a]	773.9 ± 17.3 [b]	15.5 ± 0.7 [a]
3. HCD w plant w/o PCM	191.7 ± 6.5 [a]	313.7 ± 9.2 [a]	121.9 ± 5.2 [a]	792.7 ± 17.2 [b]	15.4 ± 0.5 [a]
4. HCD w/o plant w PCM	192.0 ± 6.7 [a]	300.3 ± 12.2 [a]	108.3 ± 8.9 [a]	753.8 ± 31.4 [ab]	14.4 ± 1.0 [a]
5. HCD w plant w PCM	192.5 ± 6.7 [a]	294.3 ± 9.5 [a]	101.8 ± 6.51 [a]	742.3 ± 25.1 [ab]	13.7 ± 0.8 [a]

[1]HCD: High cholesterol diet, w: with, w/o: without, PCM: Paracetamol

[2] values are expressed as Mean ±SEM. Values with different superscription within the same column are significantly different at *P <0.05.* Different letters in the column indicate a significant difference.

[3] Feed efficiency ratio = body weight gain (g)/ 100 g feed intake

3.2. Serum lipid profile assay

Table (3) shows the means of serum levels of lipids and fasting glucose values in (mg/dl) for rats fed the different experimental diets for six weeks. The cholesterol level in group 4 (HCD without plant but with PCM) (147.3 ± 19.4 mg/dl) was significantly higher (*P <0.05*) than those of groups 1, 3 and 5 (67.6 ± 2.5, 102.6 ± 6.3 and 112.3 ± 7.1 mg/dl; respectively), but it was not significantly different from group 2 (HCD) (130.5 ± 5.2 mg/dl). The addition of the plant in both group 3 (102.6 ± 6.3 mg/dl) and group 5 (112.3 ± 7.1 mg/dl) decreased the cholesterol levels significantly (*P <0.05*) as compared with group 4, and increased cholesterol levels significantly (*P <0.05*) in comparison with group 1 (67.6 ± 2.5 mg/dl). While the cholesterol levels for both groups 4 and 5 were not significantly different (*P>0.05*) from each other. Also, the blood cholesterol levels in group 2 (the high cholesterol group) (130.5 ± 5.2 mg/dl) were only significantly (*P <0.05*) different from group 1. Finally, group 1 (Control group) had a significantly (*P <0.05*) lower value of cholesterol (67.6 ± 2.5 mg/dl) as compared with the other groups.

Regarding the triglycerides levels (TG), the addition of the plant to rats given PCM in group 5 significantly (*P <0.05*) decreased the TG levels (183.6 ± 3.7 mg/dl) as compared with group 4 (183.6 ± 3.7 mg/dl). The TG levels in the negative control group (group 1) (83.7 ± 3.9 mg/dl) and the positive control group (group 2) (88.4 ± 7.8 mg/dl) were significantly lower (*P <0.05*) than those for the other groups, but with no significant difference between them (*P>0.05*). The addition of PCM to both group 3 and group 5 resulted in significantly (*P <0.05*) higher levels of TG ((120.0 ± 8.3 mg/dl and 124.2 ± 14.6 mg/dl) respectively) in comparison with those for groups 1 and 2 (83.7 ± 3.9 and 88.4 ± 7.8 respectively), and significantly lower than those in group 4 (183.6 ± 3.7 mg/dl), but with no significant differences between them (*P>0.05*).

Low-density Lipoprotein (LDL) value for group 4 to which PCM was added with no addition of the plant (160.5 ± 32.1 mg/dl) was significantly (*P <0.05*) higher than those of all other groups. Ingestion of the plant as an addition to the HCD in group 3 lowered the LDL value (47.8 ± 3.0 mg/dl) to become with no significant difference from the negative control group (27.1 ± 1.9 mg/dl), but the negative control group had significantly (*P <0.05*) lower LDL than those of groups 2, 4 and 5.

Moreover, regarding HDL concentrations, the groups that had the addition of PCM (Group 4 and group 5 (5.3 ± 0.2 and 6.1 ± 0.9 mg/dl, respectively) had significantly *P <0.05*) lower HDL values (than groups 1 (negative control group; 22.8 ± 1.1 mg/dl), group 2 (HCD) (18.2 ± 1.2 mg/dl) and group 3 (HCD with plant without PCM) (25.4 ± 0.9 mg/dl); but there was no significant difference (*P>0.05*) between group 4 and group 5 (to which PCM was added).

Table (3): Blood Lipid profile (mg/ dl) among experimental groups

Group Description [1]	Blood Lipid Profile [2]			
	Cholesterol	TG	LDL	HDL
1. Normal AIN Diet	67.6 ± 2.5 [a]	83.7 ± 3.9 [a]	27.1 ± 1.9 [a]	22.8 ± 1.1 [c]
2. HCD w/o plant w/o PCM	130.5 ± 5.2 [bcd]	88.4 ± 7.8 [a]	84.5 ± 4.2 [b]	18.2 ± 1.2 [b]
3. HCD w plant w/o PCM	102.6 ± 6.3 [b]	120.0 ± 8.3 [b]	47.8 ± 3.0 [ab]	25.4 ± 0.9 [d]
4. HCD w/o plant w PCM	147.3 ± 19.4 [d]	183.6 ± 3.7 [c]	160.5 ± 32.1 [c]	5.3 ± 0.2 [a]
5. HCD w plant w PCM	112.3 ± 7.1 [bc]	124.2 ± 14.6 [b]	89.6 ± 7.2 [b]	6.1 ± 0.9 [a]

[1] AIN: American Institute of Nutrition, HCD: high cholesterol diet, PCM: Paracetamol, TG: triglyceride, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein.

[2] values are expressed as Mean ± SEM. Values with different superscripts within the same column are significantly different at *P <0.05.* Different letters in columns indicate a significant difference.

4. Discussion

Dietary fat and type of fat can affect health. Lipid oxidation occurs during the food processing, heat treatment of raw materials and storage of cooked and raw foods (Kacem et al., 2015). Antioxidants can delay or inhibit the oxidation of lipids or other molecules (Volf et al., 2014). The utilization of synthetic antioxidants is progressively restricted in the food industry because of their potential carcinogenicity (Volf et al., 2014).

Plants such as *Ruta chalepensis* L. are considered a valuable source of bioactive components such as natural antioxidants which possess defense mechanism against reactive oxygen species (ROS) (Ouerghemmi et al., 2017; Romojaro et al., 2013). Polyphenols constitute the main bioactive phytochemicals that have been proven effective in the prevention of certain chronic diseases such as coronary heart diseases, cancers, and diabetes because of their free radical-scavenging activities (Lamien-Meda et al., 2008).

4.1. Accumulative feed Intake, feed efficiency ratio (FER), absolute and relative liver weight

Accumulative feed intake, as shown in table (2), could be an indicator of the acceptability and palatability of feed. According to the results of this study, accumulative feed intake of high cholesterol diet groups was significantly higher than that of the normal diet group, but not significantly higher than that of HCD groups with PCM dose. The lack of impact of PCM on feed intake may be attributed to the fact that the toxification period is too short to show a significant difference in accumulative feed intake. It was reported by other researchers (Moraes et al., 2012; An et al., 2011) that accumulative feed intake of the group that received a standard normal diet was significantly higher than that of the group which received HCD. This result was not observed in this research.

Regarding FER, there were no significant differences among experimental groups in the present study. This result may be attributed to many reasons; diets of all of the groups had the same caloric density and the filling effect of the plant fibers. Also, the consumption of foods containing certain polyphenols or their corresponding supplements

changes lipid and energy metabolism and may facilitate weight loss and prevent weight gain (Meydani and Hasan, 2010).

4.2. Blood lipid profile assay

From this study, we can observe from table (3) that there was an increase in HDL and a decrease in TG and LDL in rats fed the plant. This effect on blood lipid profile may be explained by the ability of plant fibers to reduce the cholesterol absorption, increase the clearance of TG and LDL and increase the release of HDL. This finding agrees with the results of Makni *et al*. (2008) who found a significant inverse relationship between lipid parameters and the fiber content. Makni *et al*. (2008) also found that rats fed a rich-cholesterol diet had an increase in plasma TG, TC and LDL levels, with decreased circulating HDL, thus providing a model for dietary hyperlipidemia. This result was consistent with those of the present study.

5. Conclusion

Based on this study, it can be concluded that *Ruta chalepensis* L. plant would increase the HDL and lower the triglyceride serum levels when added to the high-cholesterol diet in the rat model. Besides, the plant may beneficially affect the lipid profile in paracetamol-toxified rats, since it lowered LDL, TG and TC serum levels when added to their high cholesterol diet.

6. Future recommendations

We look forward to trying several plant concentrations and comparing the effect of different plant parts. It is also intended to study the effect of other plants on preventing paracetamol toxified liver.

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