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Effects of *Ruta graveolens* total and flavonoids extracts on rat blood glucose, cholesterol, triglycerides and urea comparing synthetic drugs

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Abstract. *Noori M, Jafari M, Azimi H, Node-Farahani M. 2019. Effects of* Ruta graveolens *total and flavonoids extracts on rat blood glucose, cholesterol, triglycerides and urea comparing synthetic drugs. Nusantara Bioscience 11: 23-29.* Rue (*Ruta graveolens* L.: Rutaceae) is a medicinal plant that is used to treat many diseases in America, Asia and Europe due to its pharmaceutical properties. So far more than 120 different phytochemicals such as flavonoids have been extracted and identified from the species, which make it valuable in traditional medicine and manufacturing of synthetic drugs. Due to its endemic and high potential pharmacological effects, this study examined the oral effect of each of its total, flavonoids and non-flavonoids extracts on reducing blood glucose, cholesterol, triglycerides and urea in STZ-diabetic rats comparing to control and Atorvastatin, Allopurinol, Metformin as synthetic drugs. Aerial part of the plant was collected from around Yazd, Iran and dried in shade, crushed and extracted in 70% ethanol in three steps. Total and flavonoid extracts were prepared after rotary evaporation, then were used for making required doses after calculation. The plant flavonoids were identified using two-dimensional, thin-layer chromatography and TLC Scanner3 methods. Atorvastatin, Allopurinol and Metformin were obtained and also appropriate doses were prepared. Thirty-six adult male Wistar rats were divided in 12 groups (n=3): control, synthetic drugs control, total and flavonoids control, STZ-diabetic control, diabetic treated with synthetic drugs, total and flavonoids extracts, then weighed. All rats were treated orally at a specific time for 2 weeks. Subsequently, the secondary rat weights were determined and blood donation was performed after anesthesia. Then, blood serum glucose, cholesterol, triglycerides and urea were determined by spectrophotometry using commercial enzymatic chlorometric assay kits. All data were analyzed using EXCEL and SPSS software. Results showed aerial part of *R. graveolens* contains flavones *C* and *C-/O* glycosides, flavonoid sulphates and had no aglycones. Apigenin, chrycin, isorhamnetin, kaempferol, myricetin, quercetin, rutin and vitexin were found in the species aerial part. This plant had 329/99 gr/kgDW of effective material and 257.7 g/kgDW of flavonoids. The lowest blood glucose levels were observed in treated Metformin and flavonoids control rats respectively. Diabetic rats treated with *R. graveolens* total extract had the lowest blood cholesterol, urea and glucose levels. The highest renal damage was observed in control diabetic rats and the least renal damage was observed in the STZ-diabetic rats treated with the plant total extract. These results indicate that *R. graveolens* extract and its rutin contained antihyperglycemia, antihyperlipidemia, insulinity and protective properties.

Keywords: Blood glucose, cholesterol, flavonoids, medicinal plant, *Ruta graveolens*.

INTRODUCTION

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al. 2004). Diabetes mellitus (DM) is the world's largest growing metabolic disorder of the endocrine system, presently affecting about 5-10 percent people around the globe (Arif et al. 2014). Diabetes is characterized by hyperglycemia together with biochemical alterations of lipid metabolism (Jensen et al. 1988). Also El Agraa et al. (2002) reported correlation between clinical effects and pathological changes in various organs, alterations in serum constituents, hematological values and the concentrations of metal ions in the tissues (El Agraa et al. 2002).

Since ancient times, plants have been an exemplary source of medicine. Various medicinal plants are effective on treating diabetes (Grover et al. 2002; Arumugam et al. 2013). Several clinical trials have documented beneficial modifications of the LDL/HDL ratio after intake of flavonoid-containing food products (Weggemans and Trautwein 2003). Alarcon-Aguilara et al. (1998) examined anti-hyperglycemic effect of 28 medicinal plants for treatment of diabetes mellitus. Each plant was processed in traditional way and intragastrically administered to temporarily hyperglycemic rabbits (Alarcon-Aguilara et al. 1998). Numerous studies reported the clinical benefits of plants from family Rutaceae for diabetes treatment. *Citrus paradisi* Macfad (Rutaceae) seed methanolic extract is used for treatment of anemia, diabetes mellitus and obesity in human (Adeneye 2008). *Murraya koenigii* (Rutaceae) leaves are traditionally used to treat diabetes (Dineshkumar et al. 2010).

Ruta genus from Rutaceae includes 14 species in the world and 2 species (*R. graveolens* and *R. chalepensis*) in Iran and India. *R. chalepensis* can be found as wild plant in southern region of Iran (Mozaffarian 1996). *R. graveolens* has been used for reducing the oxidative severity of zinc deficiency in experimental diabetes through its hypoglycemic and antioxidant actions (Hamdiken et al.

2017). *R. graveolens* L. (Yuin Siang, Sodab, bitter herb or Rue) is a medicinal plant used since time immemorial in ethnobotany (Nazish et al. 2009). It is cultivated as a medicinal and ornamental herb in many countries including Iran and India (Kannan and Babu 2012). The species has been used in America, Asia, and Europe for the treatment of many diseases having various pharmacological activities (Diwan et al. 2012, Gentile et al. 2015, Amabye and Shalkh 2015, Malik et al. 2017). More than 100-120 compounds have been identified up to now from *R. graveolens* root and aerial part. These compounds belong to some major classes of substances: acridone alkaloids, coumarins, flavonoids, essential oil and fluoroquinolones. These phytochemical compounds may find potential applications in pharmaceutical and drug industry (EMEA 1999, Kannan and Baba 2012, Asgarpanah and Khoshkam 2012). *R. graveolens* essential oils detection was done by Dzhurmanski (2011). *R. montana* aerial part extract exhibits a potent hypoglycemic effect in normal rats and an antidiabetic effect in STZ-induced rats (Farid et al. 2017). Mahmoud et al. (2015) showed marked protective effect of *R. graveolens* extract against AC-induced hyper-ammonemia in rats through its antioxidant and anti-inflammatory efficacies. Toserkani et al. (2012) examined lipid profiles, glucose, and hemogram changes after administration of *R. graveolens* extract in diabetic rats. The rats showed a significant decrease in cholesterol and LDL-c levels, whereas no significant changes were seen in glucose, triglycerides, VLDL-c, and HDL-c values indicating that *R. graveolens* extract has significant effects on total cholesterol and LDL-c in diabetic rats (Toserkani et al. 2012). Also powerful hypolipidemic properties of *R. graveolens* flavonoids were reported by Koshy and Vijayalakshmi (2001). Decreasing lipid peroxidation product and increasing antioxidant enzymes activities by *R. graveolens* have been reported *(*Ratheesh et al. 2009). Also protective effects of isolated polyphenolic and alkaloid fractions of *Ruta graveolens* on acute and chronic models of inflammation was studied (Ratheesh et al. 2010).

Rutin, Quercetin, Kaempferol and Vitexin were found in *R. graveolens* aerial part (Figueroa-Valverde et al. 2009; Noori et al. 2015). Rutin is a flavonoid found in many plants having highly potent and shows a wide range of biological activities including anti-inflammatory, antioxidant, neuroprotective, nephroprotective, hepato-protective and antidiabetic effects (Ghorbani 2017) with increasing insulin receptor kinase activity on kidney (Hsu et al. 2014). Ahmad et al. (2010) studies showed antihyperglycemic and antihyperlipidemic efficacy of *R. graveolens* extract and Rutin in Nicotinamide Streptozotocin-induced diabetic rats which may be mediated *via* pancreatic and extrapancreatic effects (Ahmad et al. 2010). Antidiabetic and cytotoxicity of the species as a traditional treatment for diabetic cases were studied (Van Huyssteen et al. 2011). In this research isolation, purification and identification of *R. graveolens* aerial part flavonoid compounds were done. Flavonoids compounds and total extracts of the species effects on rat glucose, fat and urine in comparison with antihyperglycemia, antihyperlipidemia and anti-hyperuricemia synthetic drugs were simultaneously investigated.

MATERIALS AND METHODS

Extraction and identification of flavonoids from *Ruta graveolens* L. aerial part

Ruta graveolans L. (Rue) aerial part samples were collected from around Yazd villages, Iran. The plant species were identified and authenticated using valuable and available references (Ghahreman 1994, Rechinger 1966). The plant material was dried in the shade and prepared by grounding into fine powder (100 g). Extraction was done using perculation method with 70% ethanol in three steps for 72 h and all three extracts mixed together. This initial ethanolic extract was dried at 40°C and 40 m/sec using Heidolph Rotary evaporator Laborota 4000/G1 (Noori 2002). The effective amount of active ingredient per kilogram of dry matter was calculated by weight/volume after dissolving the dry extract in 70 % ethanol; henceforth referred to as crude extract. A portion of the crude extract is kept as is, while the rest of the extract was used to prepare the flavonoid extract.

Flavonoids extract preparation using acid hydrolysis method

To 200 mL of a total alcoholic extract was added 200 mL of Chloride acid 2 M hydrochloric acid and placed in water bath at 100°C for 30 minutes. After cooling, 200 mL ethyl acetate was added to separate and the flavonoid extract from the non-flavonoids extract. The flavonoid extract, soluble in ethyl acetate at 40°C and 40 m/sec, was distilled off in a vacuum. Flavonoids content (gram per kilogram of dry plant matter) was measured by weight/volume method after dissolving the dry extract in 70% ethanol. Then flavonoids in aqueous-ethanolic extract were isolated, detected and identified by two-dimensional paper and thin layer chromatography according to the methods described by Markham (1982). The flavonoids extracted from the plant aerial part were kept in dark vials and stored in cool conditions until further use.

Flavonoid identification by 2-dimensional paper and thin layer chromatography

After preparation spotted Whatman No 1 chromatogram with concentrated flavonoids extract and Rutin (=Quercetin 3-*O*-rutinoside) as a standard, the paper was developed in BAW (n-BuOH-HOAc-H_2O=4:1:5; V/V; upper layer), 1st direction, and HOAc (=15% aqueous acetic acid), 2nd direction. Then paper was studied in UV 366 nm and any dark absorbing and fluorescent spots were marked. R_f -values in BAW and 15% HOAc were calculated. Hydrolyzed flavonoids extract was applied as spot on thin layer chromatogram (cellulose). Co-chromatography with standards was also performed where possible. Flavonoid standards available for comparison during the study were apigenin, chrysin, genistein, hesperidin, isorhamnetin, kaempferol, luteolin, morin, myricetin, naringenin,

quercetin, rhamnetin, rutin, tricine and vitexin (all obtained commercially, Rutin from Merck, apigenin and luteolin from sigma and the rest from Fluka). TLC plate was viewed in UV245 nm each spot R_f -values and color comparing to standards helped flavonoids identification after running in solvents (Mabry et al. 1970; Markham 1982).

Experimental animals

Sixty adult male Wistar rats weighing 200±50g were selected from the Arak University animal house. They were kept in plastic cages at 22±2°C with 12 h light, 12 h dark cycle and free access to diet during experiments and without any noise and contamination. The animals were randomly divided into twelve groups based on Table 1 (n=5). To induce diabetes Streptozotocin (STZ) was injected intraperitoneally (50 mg kg^{-1} b. wt.) and rat with a blood sugar ≥200 $mgdl^{-1}$ was considered as diabetic rat. The rat blood sugar level was measured using glucometer at the beginning of the experiment to confirm the normal blood sugar and after 7 days to check the rise in blood sugar in diabetic rats. After the establishment of diabetes, all animals have treated treatments orally for two weeks based on Table 1. Allopurinol as antihyperuricemia, Atorvastatin as antihyperlipidemia and Metformin as antihyperglycemia synthetic drugs were used. The weight of experimental animals was measured before treatment (W1 and the weight after treatment (W2) using laboratory rat balance.

After two weeks of treatment, rats were anesthetized by chloroform, blood samples were taken by heart puncture, and heparinized plasmas were separated for determination of lipid profiles, glucose and blood urea.

Biochemical estimations

The plasma levels of blood cholesterol, glucose, triglycerides and urea were determined spectrophotometrically using enzymatic colorimetric assay kits (Cholesterol CHOD-PAP 95008, Glucose GOD-PAP 95012, Triglycerides GPO-PAP 95007 and Urea UV-TESE 95008) in Sina Medical Laboratory, Iran.

Table 1. Experimental groups, showing their codes and treatments

Code	Groups	Treatments
C	Control	0.5 ml distilled water
CS	Control Streptozotocin	0.5 ml distilled water
CAt	Control Atorvastatin	0.03 mg/kg Atorvastatin
SAt	STZ + Atorvastatin	0.03 mg/kg Atorvastatin
CMe	Control Metformin	1.25 mg/kg Metformin,
SMe	STZ + Metformin	1.25 mg/kg Metformin
CAl	Control Allopurinol	0.75 mg/kg
SAl	STZ + Allopurinol	0.75 mg/kg
CRF	Control *Ruta* flavonoids extract	0.25 mg/per kg flavonoids extract
SRF	STZ + *Ruta* flavonoids extract	0.25 mg/kg
CRT	Control *Ruta* total extract	0.33 mg/per kg total extract
SRT	STZ + *Ruta* total extract	0.33 mg/ kg

Statistical analysis

All of data were expressed as the mean ± SE and then analyzed using SPSS 16.0 software. These analyses were performed using Fisher's, Chi-square, simple linear regression, Spearman correlation coefficient and ANOVA ($P<0.05$, $P<0.01$).

RESULTS AND DISCUSSION

Phytochemical results

Results showed aerial part of *R. graveolen*s contains flavones *C* and *C-/O* glycosides, flavonoid sulfates and had no aglycones (Figure 1). Flavonoids including apigenin, chrysin, isorhamnetin, kaempferol, myricetin, quercetin, rutin, and vitexin were found in the species aerial part (Figure 2). Quantification of *R. graveolen*s showed 329/99 g active ingredient/ kg plant dry weight (g/kg DW) effective material and 257.7 g/kg DW of flavonoids.

Weight, blood serum glucose, cholesterol, triglycerides, and urea determination

Table 2 shows mean ± SE of weight, blood serum glucose, cholesterol, triglycerides and urea determination in treated rats in comparison with control. Also, Figure 3 shows comparison of weight changes and studied blood serum parameters in control and treated rats.

Data statistical analysis results

Table 3 shows simple linear regression with treatment type variant and studied parameters. Statistical analysis data results with 1-tailed (Spearman) method using SPSS for determination of correlation between blood serum glucose, cholesterol, triglycerides, urea and weight in experimental rats was done ($P\leq0.05$, $P\leq0.01$). Also, Data analysis using ANOVA method with treatments consideration as dependant variant has been done ($P\leq0.05$ that confirmed each other. So, Data analysis results using ANOVA method has been shown in Table 4.

Discussion

Ruta species are important because many active compounds and hitherto many different secondary metabolites such as flavonoids have been isolated and identified from them. Kannan and Baba (2012) recorded more than 120 different phytochemical compounds from *R. graveolens* root and aerial parts. Our study showed six flavone *C* and *C-/O* glycosides and flavonoid sulfates presence in the species aerial part. Also, apigenin, chrysin, isorhamnetin, kaempferol, myricetin, quercetin, rutin, and vitexin were identified using chromatographical methods. These results are similar to Figueroa-Valverde et al. 2009, Noori et al. (2015). Isolation and identification of rutin and quercetin from *R. graveolens* have been reported by some researchers (Ravindran and Divakaran 2012; Eldalawy 2017). As our results show, *R. graveolens* having 329/99 g/kgDW of effective material and 257 7 gr/kg DW of flavonoids, is a medicinal plant and good natural source of pharmaceutical properties.

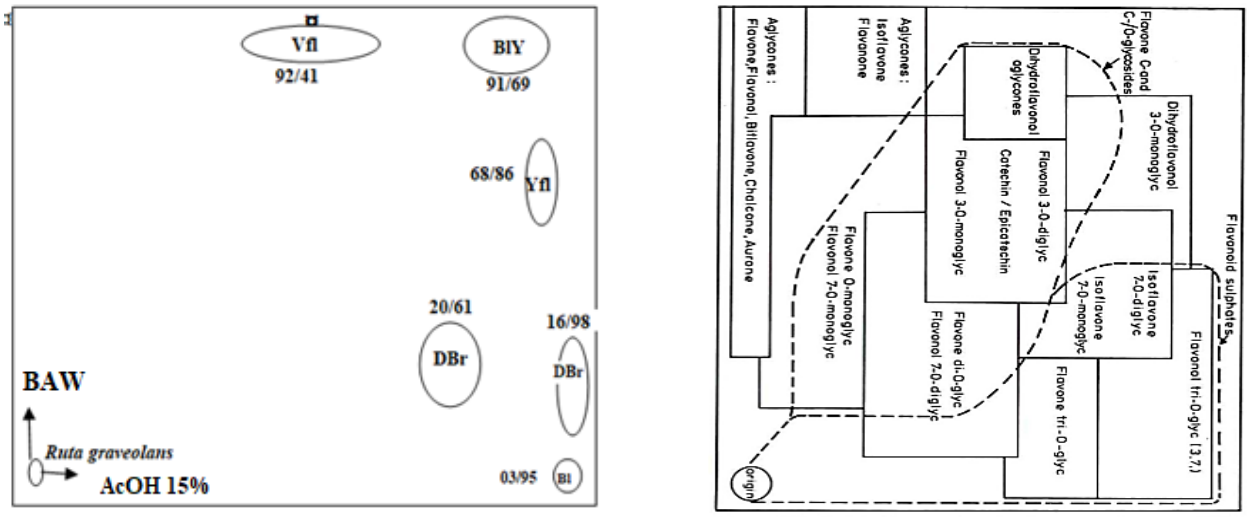

Figure 1. Two dimensional paper chromatography results of *Ruta graveolens* aerial part. Left numbers are spot *Rf* in BAW and right numbers are Spot *Rf* in AcOH 15 %. Note: Bl=blue, Br+brown, D=dark, fl=fluorescence, V=violet, Y=yellow (Based on Mabry et al. 1970; Markham 1988)

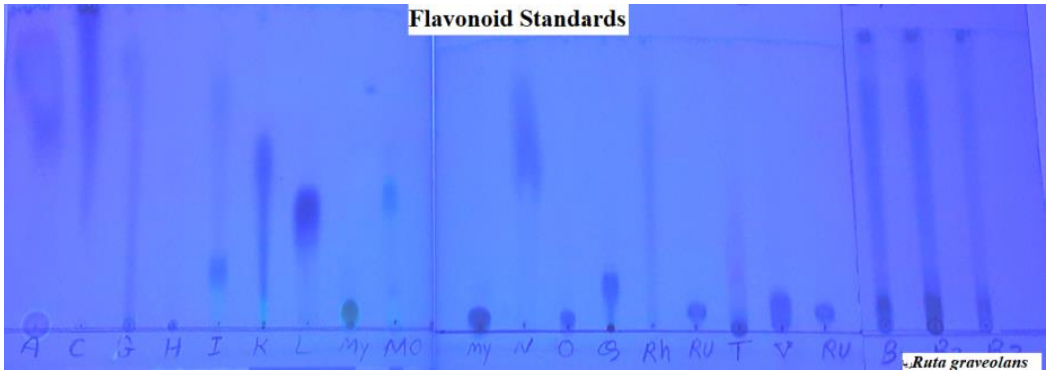

Figure 2. *Ruta graveolens* TLC chromatogram of used flavonoid standards in CAW; Abbreviations: A = Apigenin, C = Chrysin, G = Genistein, H = Hesperidin, I = Isorhamnetin, K = Kaempferol, L = Luteolin, Mo = Morin, My = Myricetin, N = Naringenin, Q = Quercetin, Rh = Rhamnetin, Ru = Rutin, T = Tricine and V = Vitexin (all obtained commercially from Merck, apigenin, luteolin and hesperidin from Sigma and the rest from Fluka)

Table 2. Weight and studied blood serum parameters determination in treated rats in comparison with control; for code explanations refer to Table 1.

Groups	M±SE							
	W1	W2	W2/W1	W2-W1	Gluc (mg/dL)	Urea (mg/dL)	Chol (mg/dL)	TG (mg/dL)
C	194.2(3.3)	237.4(4.9)	1.2	43.2	214(4.3)	61.3(3.6)	56.3(1.9)	118(12.7)
CS	239.7(14)	230.2(7.8)	1.0	-9.5	568(10.8)	70.8(2.4)	75(4.2)	151(21.2)
CAt	225(10.2)	254.3(12.3)	1.1	29.3	235.7(27.3)	52(8.0)	63(5.9)	62.3(0.5)
SAt	225(10.2)	247.8(4.8)	1.1	22.8	576.3(4.7)	71(20.1)	58.7(3.3)	67.7(8.0)
CMe	247.3(4.5)	276.2(36.9)	1.1	28.9	193.7(46.2)	50(3.5)	61.7(6.6)	120.3(5.9)
SMe	301.3(8.2)	276.2(36.9)	0.9	-25.3	580.7(22.2)	62.2(5.5)	62(5.7)	116.3(10.8)
CAl	266.7(11.8)	298.2(9.7)	1.1	31.5	567.3(47.6)	80.9(11.2)	60(2.8)	59.3(7.5)
SAl	248.3(1.9)	210.9(14.5)	0.8	-37.4	573.7(6.9)	77.2(7.8)	61.3(6.2)	50.7(10.5)
CRF	201 (9.2)	245.5(10.5)	1.2	44.5	243(36.8)	40.8(1.3)	50(2.8)	48.3(1.9)
SRF	259 (7.8)	244(18.3)	0.9	-15	569(34.7)	112.2(4.3)	46.3(3.3)	42.3(1.9)
CRT	205.5(4.3)	316.5(43.0)	1.5	111	611.3(21.2)	113(10.5)	58.7(6.6)	117(2.8)
SRT	231.5(19.4)	221.2(33.2)	0.9	-10.3	221(19.6)	55.1(4.4)	53.7(2.9)	220.7(12.3)

Note: W1 = the weight before treatment, W2 = the weight after treatment, Gl = glucose, Ur = Urea, Ch = Cholesterol, Tg = Triglycerides, C = Control, CS = STZ control, At = Atorvastatin, Me = Metformin, Al = Allopurinol, S = streptozotocin, R = *Ruta graveolans*, F = Flavonoids, T = total, M = mean, SD = standard

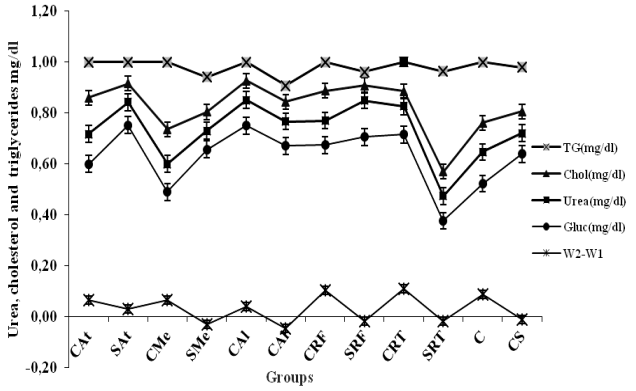

Figure 3. Comparison of mean weight variety and studied blood serum parameters in control and treated rats. Refer to Tables 1 and 2 for abbreviations explanation

Table 3. Simple linear regression with treatment type variant and studied parameters

Model Summary b

Model	R	R Square	Adjusted R Square	SE the Estimate
1	.924a	.853	.773	4.00484E-1

Note: a. Predictors: (Constant), Blood triglycerides, Second weight, Blood urea, W2/W1, Blood cholesterol, Blood glucose. b. Dependent Variable: Treatment

Table 4. Data analysis results of *Ruta graveolens* total, flavonoids and non-flavonoids extracts on weight, blood glucose, cholesterol, triglycerides and urea in experimental rats comparing used synthetic drugs using ANOVA method ($P \leq 0.05$)

Coefficients[a]

Model	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	SE	Beta		
(Constant)	1.984	.819	-	2.423	*.034
Second wiegth	-.010	.005	-.537	-2.090	.061
W2/W1	3.124	.651	.943	4.798	*.001
Blood glucose	.001	.001	.162	.738	.476
Blood urea	.006	.006	.227	1.013	.333
Blood cholesterol	-.047	.022	-.442	-2.164	.053
Blood triglycerids	.009	.002	.665	4.701	*.001

Note: *Bold numbers significant ($P \leq 0.05$). a. Dependent Variable: Treatment

Table 2 shows the lowest blood glucose levels in treated Metformin control (CMe 193.7 mg/dL) and control (C 214 mg/dL) rats respectively (Table 2, Figure 3). The highest blood glucose levels were observed in control treated Rue total extract (CRT 611.3 mg/dL) and diabetic treated Metformin rats (SMe 580.7 mg/dL), respectively (Table 2, Figure 3). Diabetic rats treated with *R. graveolens* total extract (SRT 221 mg/dL) had the lowest blood glucose levels nearly similar control (C 214 mg/dL) and CMe groups. These results show that Rue can be considered as antidiabetic plant because it has reduced blood glucose level in diabetic rats. Interestingly, rue treatment increase blood glucose level in control (Table 2, Figure3). It is seemed that using rue extract in health people is not only useful but also caused some disorder in the body by the reason toxicity and damaging the kidney or other entrails. Farid et al. (2017) showed useful effects of Rue aerial part for diabetic rat therapy. Also Eddouks et al. (2016) reported decreasing blood glucose level STZ-induced diabetic rats using Rue aerial part aquatic extract. Anti-diabetic effects of *R. graveolens* with three other plants have been reported for diabetic patient therapy in traditional prescription (Van Huyssteen et al. 2011). Ahmed et al. (2010) did not show qualified anti-diabetic effect for Rue but their results revealed that both *R. graveolens* and Rutin exhibit antihyperglycemic and anti-hyperlipidemic properties via their insulinogenic effects, decreasing intestinal glucose and cholesterol absorption, improving peripheral insulin action, affecting mediators of insulin resistance, enhancing peripheral glucose uptake and decreasing hepatic glucose output in addition to the ameliorating effect on the antioxidant status in this condition. Their results suggest that both Rue and Rutin improve glucose tolerance and this amelioration seemed to be mediated via alleviation of the islet architecture, enhancement of insulin release, insulin binding affinity, and peripheral glucose uptake and decreasing intestinal glucose absorption in addition to decreasing the activity of gluconeogenic and glycogenolytic enzymes (Ahmed et al. 2010).

The lowest blood urea level was observed in CRF group with 40.8 mg/dL, then CMe (50 mg/dL), CAt (52 mg/dL) and SRT (55.1 mg/dL) were respectively. CRT group (113 mg/dL) had the highest blood urea level (Table 2). These results show that Rue flavonoids extract, Metformin and Atorvastatin caused decreasing blood urea in control and health rats, but Rue total extract has decreased blood urea in STZ-induced diabetic rats. Both C and CRF groups showed lower blood urea than two Allopurinol treated groups (CAl and SAl). Mahmoud (2012), Mahmoud et al. (2014 and 2015) and also Ganeshpurkar and Saluja (2017) studies showed *R. graveolens* effects on blood serum urea, , and uric acid reduction. Blood urea nitrogen (BUN) test is done to see how well kidneys are working. If kidneys are not able to remove urea from the blood normally, BUN level rises. They believed that these properties and protective effects of the plant are by the reason rutin presence in the Rue. Our results confirmed Rutin in Rue flavonoids extract.

Both CRF and SRF groups showed the lowest cholesterol (46.3 and 50 mg/dL) respectively, and CS group had the highest level. These results show Rue flavonoids extract on cholesterol reduction in health and diabetic individuals. Toserkani et al. (2012) reported cholesterol and LDL reduction using the plant extract, although were not observed any qualified changes in glucose, triglycerides, VLDL and HDL levels. They showed cholesterol and LDL reduction levels in diabetic rats after Rue extracts medication. Our results showed that using both Rue total and flavonoids extracts caused cholesterol reduction in diabetic rats (SRF and SRT) in

comparison with control (C) and treated Atorvastatin diabetic rats (SAt) (Table 2). The cluster of lipid abnormalities associated with type 2 diabetes is defined by a high concentration of TG and small dense LDL and a low concentration of HDL cholesterol. Diabetes carries a high risk of atherosclerosis, and cardiovascular disease, especially coronary heart disease (CHD) and stroke, is by far the leading cause of death among patients with type 2 diabetes (Bitzur et al. 2009).

The lowest mean blood serum triglycerides were observed in SRF (42.3 mg/dL) and CRF (48.3 mg/dL) groups respectively. SRT group showed the highest level of triglycerides (220.7 mg/dL) comparing to C and CAt groups. These results confirmed that *R. graveolens* flavonoids extract has antitriglycerides effect in comparison with its total extract (Table 2). As Figure 1 shows SRT and CMe groups had respectively the most glucose, urea and cholesterol reductions levels. But total and flavonoids extracts and Metformin were not effective on triglycerides reduction. These results are similar Toserkani et al. (2012) studies. Malika et al. (2012) reported antilipidemic effects of Rue.

Histotechniques studies of experimental rat kidneys showed the highest renal damage in control diabetic rats (Noori et al. 2018). The least renal damage was observed in the STZ-diabetic rats treated with the plant total extract (SRT) comparing SMe group that we will separately report. These results show that using Rue as antidiabetic medicinal plant has protective effect comparing Metformin by the reason of having phenolic and alkaloids compounds (EMEA 1999; Kannan and Baba 2012; Asgarpanah and Khoshkam 2012).

As Table 4 shows, weight, blood triglycerides, and glucose levels were significant in treated rats. These results show that Rue and its chemical compounds are effective on weight, blood cholesterol and glucose (Starry numbers show significant correlation between the studied parameters). As Wang et al. (2009) showed that serum chemerin is correlated with insulin level, body fat disposition, and lipid metabolism which suggesting that it may play a role in the pathophysiology of obesity and metabolic syndrome. In Table 2 cholesterol reduction was observed in diabetic rats treated with Rue total and flavonoids extracts. Also, Toserkani et al. (2012) reported cholesterol and LDL reduction in treated Rue extract diabetic rats. Farid et al. (2017) studies also showed a beneficial effect on using Rue aerial parts for STZ-diabetic rats' treatment and blood glucose reduction in non-diabetic rats.

Observation of the least renal damage in the STZ-diabetic rats treated with the Rue total extract and the highest renal damage in control diabetic rats (Noori et al. 2018) indicate that *R. graveolens* extract and its Rutin contained anti-hyperglycemia and protective properties. Ratheesh et al. (2010) recorded protective effects of isolated polyphenolic and alkaloid fractions of *R. graveolens* on acute and chronic models of inflammation. Long et al. (2005) studied on *Drynaria fortune* flavonoids protection against acute renal failure. They found that flavonoid fraction prevents nephrotoxicity, improves kidney function and promotes kidney primary epithelial tubular cell regeneration (Long et al. 2005). Rutin as a water-soluble flavonoid glycoside has the most potent uterotonic (Salib et al. 2014, Ganeshpurkar and Saluja 2017), anti-diabetic (Hosseinzadeh and Nassiri-Asl 2014), anti-hyperglycemic, antioxidant effects (Kamalakkannan and Prince 2006) with increasing insulin receptor kinase activity on kidney (Hsu et al. 2014).

In conclusion, *R. graveolens* having effective phytochemical compounds especially flavonoids can be used as anti-hyperglycemia natural drug. Its flavonoids as antioxidant protect kidney against renal failure. Studying Rue chemical compounds effects on diabetic patients alone or with synthetic drugs can be useful. Then prescription Rue aerial part in human diet is suggested.

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