Effect of Rheum Ribes and Urtica Dioica on Type 2 Diabetic Rats

Zahra Sadat Hussaini[1], Hakima Askndari[1], Kawsar Alami[1], Sayed Yousof Mousavi[2]*

[1]Research and Technology Center, Khatam Al-Nabieen University, Kabul, Afghanistan.
[2]Department of Physiology, Khatam Al-Nabieen University, Kabul, Afghanistan.

ABSTRACT

The prevalence of type 2 diabetes is increasing and considered a major cause of mortality in the world. Medicinal plants are a part of complementary and alternative medicine, which have wide use in the treatment of diabetes. Besides, combination therapy as an effective therapeutic strategy is highly recommended for controlling hyperglycemia. The present study aimed to determine the hypoglycemic effect of Afghan Rheum Ribes L. and Urtica Dioica L. extracts either alone or in combination on blood glucose level in type 2 diabetic rats. Diabetes was induced by single-dose administration of Streptozotocin (50 mg/kg) in rats. Diabetic rats were received intraperitoneal administration of R. Ribes aqueous extract (40 and 60 mg/kg), U. Dioica aqueous-alcoholic extract (100 and 200 mg/kg), and their combination for 21 days. The fasting blood glucose and body weight of rats were determined on 0, 7th, 14th, and 21st days. The results showed that R. Ribes extract (40 and 60 mg/kg), U. Dioica extract (200 mg/kg), and their combination could significantly decrease the blood glucose level on 0, 7th, 14th, and 21st days ($P<0.0001$). Only 200 mg/kg of U. Dioica had a positive effect on the bodyweight loss of diabetic rats ($P<0.01$). It can be concluded that Afghan R. Ribes and U. Dioica extracts and their combination have a hypoglycemic effect. However, their combinations do not show any synergic or antagonistic effects.

Key Words: *Afghanistan, Rheum Ribes, Urtica Dioica, Combination, Blood glucose level*

eIJPPR 2021; 11(1):63-69

HOW TO CITE THIS ARTICLE: Hussaini ZS, Askndari H, Alami K, Mousavi SY. Effect of Rheum Ribes and Urtica Dioica on Type 2 Diabetic Rats. Int J Pharm Phytopharmacol Res. 2021;11(1):63-9. https://doi.org/10.51847/EZXsU4H

INTRODUCTION

Type 2 Diabetes mellitus is a serious, chronic metabolic disorder, which is characterized by hyperglycemia, insulin resistance, and a relative lack of insulin in the body [1, 2]. It is considered the most common type of diabetes and consists of 90 percent of diabetic patients cases [3, 4]. In most countries, the prevalence of type 2 diabetes is increasing and considered a major cause of mortality [5].

Hyperglycemia is the most common feature of diabetes, which can result in major, serious, and life-threatening complications [6-8]. Activation of oxidative stress pathways as a result of chronic hyperglycemia can lead to multiple diabetes complications [9]. Therefore, the main purpose of diabetes, especially types 2, is the control of hyperglycemia and prevention of its complications [10].

Nature gifts various plants and fruits to humans [11]. Medicinal plants are a part of complementary and alternative medicines that are widely used by many people, especially in developing countries. Researchers all over the world are also focused on the effect of medicinal plants and their constituents on diabetes, because of their fewer side effects than synthetic drugs [12-14]. In traditional medicine, it is recommended to use herbs combinations, because there are some reports that multiple herbs combinations have more effects than individual herbs [15]. Many researchers consider the combination therapy as a new and effective therapeutic strategy for controlling hyperglycemia [16].

Reum Ribes L. (R. Ribes) is one of the medicinal plants and belongs to the Polygonaceae family [17]. It is widely used as a food ingredient and herbal drug [18]. The root of R. Ribes has a potent antioxidant activity and contains phenolic compounds, tannins, and anthracene derivate. Anthraquinone and stilbene are considered as its main constituents [17, 19]. Multiple studies have shown that R. Ribes roots have antidiabetic activity, including

Corresponding author: Sayed Yousof Mousavi
Address: Department of Physiology, Khatam Al-Nabieen University, Kabul, Afghanistan.
E-mail: ✉ Mousavi.knurtc@knu.edu.af
Received: 15 November 2020; **Revised:** 21 January 2021; **Accepted:** 24 January 2021

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antihyperglycemic, insulin-releasing, and antiretinopathic activities [20-23].

Urtica Dioica (U. Dioica) is another medicinal plant, which belongs to the Urticaceae family. This plant is also famous for its use as a food ingredient and herbal drug [24]. The constituents of U. Dioica leaves are flavonoids, peptides, and amines. It also contains a peptide ring that has a potent antidiabetic activity [25, 26]. Various studies have reported the antidiabetic activities of its leaves, including hypoglycemic, antilipidemic, and insulin-enhancing activities [27-29].

However, because of the considerable impact of climate and geographical conditions on the biological activities of plants [30], and also the most effective of herbs combinations on the control of hyperglycemia [15, 16], this study investigates the hypoglycemic effect of Afghan R. ribes and U. dioica extracts, either alone or in combination on diabetic rats.

MATERIALS AND METHODS

Materials

The main equipment and plants used in this study are as follows: Streptozotocin (STZ) (Sigma Aldrich, USA), glucometer (On-call plus, Acon, USA), fresh R. Ribes roots, and U. Dioica leaves (Afghanistan).

Animals

Forty-eight adult Sprague-Dawley male rats weighing between 180 and 200 g, randomly selected from Khatam Al-Nabieen University Research and Technology Center (KNURTC), were housed in Plexiglass cages with free access to food and water. Animals were kept under stable room temperature (23±2°C) and a 12 hours light/dark cycle (the light period started at 7 a.m.). The experimental protocol related to animal's use has complied with all the relevant national regulations and institutional policies, so approved by the ethic research board of Khatam Al-Nabieen University (Approval No. AF. KNU.REB.1397.28) and were conducted following the ethical guidelines set by the 8th edition of National Institute of Health (NIH) guide for the care and use of laboratory animals. Rats were carefully handled to minimize unwanted stress during housing and experiments [31-35].

Plants collection and extraction

R. Ribes: Fresh roots of R. Ribes were collected from Qafqol mountains, the black valley of Yakawlang, Bamyan province of Afghanistan. Roots were washed with stilled water, dried in the shade, and then grinded. 50 g of its powder was soaked in 300 ml normal saline and kept at an ambient temperature for 12 hours. The mixture was then filtered and evaporated at 40°C [21].

U. Dioica: Fresh leaves of U. Dioica were collected from Jerf Valley, Sheikh Ali, Parwan province of Afghanistan. Leaves were washed with stilled water and dried in the shade. Dried leaves were then grinded. 200 g of grinded leaves were macerated in 70% ethanol (1:4), kept for 72 hours at ambient temperature, and shaken occasionally. Then, the mixture was filtered and evaporated at room temperature [8]. Both plants were identified in Kabul University, Faculty of Science, by Prof. Nasim Sediqi, Department of Pharmacognosy, Faculty of Pharmacy, Kabul University.

Induction of experimental diabetes

The experimental diabetes was induced by a single intraperitoneal (i.p.) administration of streptozotocin (STZ) (50 mg/kg) after 8 hours of fasting. The STZ was dissolved in 0.1 M citrate buffer. 72 hours later, the FBG level was determined and diabetes was confirmed. The rats with 200 mg/dl FBG levels were only considered for the experiment [36].

Experimental groups

Rats were divided into 8 groups (n=6):

Group I (Normal), Rats of this group received Normal saline (1 ml, i.p.) for 21 days;

Group II (Diabetic), Rats of this group became diabetic and received Normal saline (1 ml, i.p.) for 21 days;

Group III-V (R. Ribes 40, 60, 80 mg/kg), Diabetic rats received R. Ribes Aqueous extract (40, 60 and 80 mg/kg, respectively, i.p.) for 21 days;

Group VI-VII (U. Dioica 100, 200 mg/kg), Diabetic rats received U. Dioica Aqueous-alcoholic extract (100 and 200 mg/kg, respectively, i.p.) for 21 days;

Group VIII (combination): Diabetic rats received a combination of R. Ribes Aqueous extract and U. Dioica Aqueous-alcoholic extract effective doses for 21 days.

The dose of 80 mg/kg of R. Ribes was toxic and killed all rats of the group, within the first few days. Thus, the R. Ribes 80 mg/kg group was excluded from the continuation of the experiment.

FBG level measurement: After 8 hours fasting, the FBG levels of all rats were measured by blood withdrawn from the tail of rats using strips and glucometer on 0, 7th, 14th, and 21st days (considering after 3 days of STZ administration).

Body weight determination: The body weight of all rats was determined on 0, 7th, 14th, and 21st days.

Statistical analysis: The statistical analysis was done with Graph pad prism (6.07) software. The FBG levels were analyzed by Two-way ANOVA, followed by Dunnets test multiple comparisons. The difference between body weights of different groups was analyzed by the One-Way ANOVA test. The difference amongst means was

considered statistically significant if the P<0.05. The results are expressed as mean ± SEM.

RESULTS AND DISCUSSION

FBG level measurement

The FBG level of all groups was measured on 0, 7th, 14th, and 21st days. There was a significant difference in the level of FBG among normal and diabetic groups (P<0.0001). The FBG level was significantly decreased in R. Ribes 40 and 60 mg/kg groups as compared with the diabetic group on the 7th, 14th, and 21st days (P<0.0001) **(Figure 1)**. In addition, the effect of U. Dioica different doses was evaluated on the FBG level **(Figure 2)**. The difference in the level of FBG only between U. Dioica 200 mg/kg and the diabetic group was significant, on the 7th, 14th, and 21st days, and especially on the 21st day (P<0.0001). The FBG level was not significantly decreased in U. Dioica 100 mg/kg group. As a result, the 40 mg/kg of R. Ribes and 200 mg/kg of U. Dioica extracts were considered as effective doses, combined and their hypoglycemic effect was evaluated **(Figure 3)**. The FBG level was significantly decreased in the combination group, as compared with the diabetic group on days 7, 14, and 21 (P<0.0001).

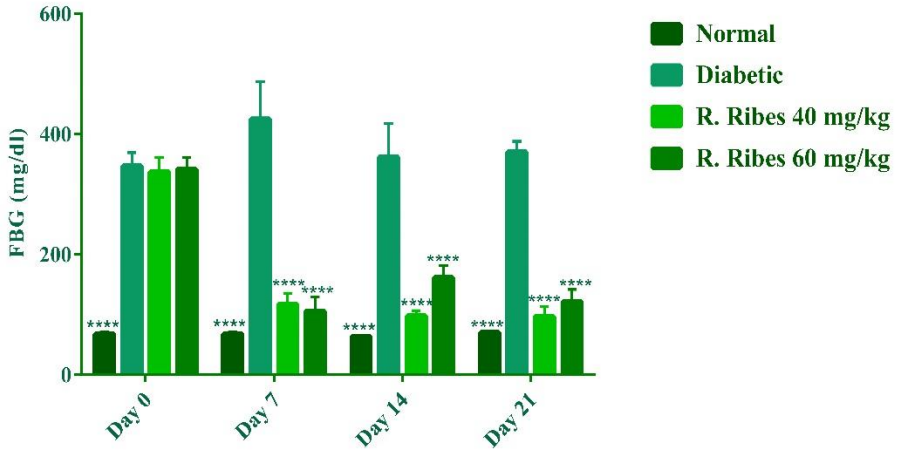

Figure 1. The Effect of R. Ribes (40 and 60 mg/kg) Extract on the FBG Level of Diabetic Rats
Data is shown as Mean±SEM. FBG, fasting blood glucose. ****: P<0.0001 as compared with the diabetic group.

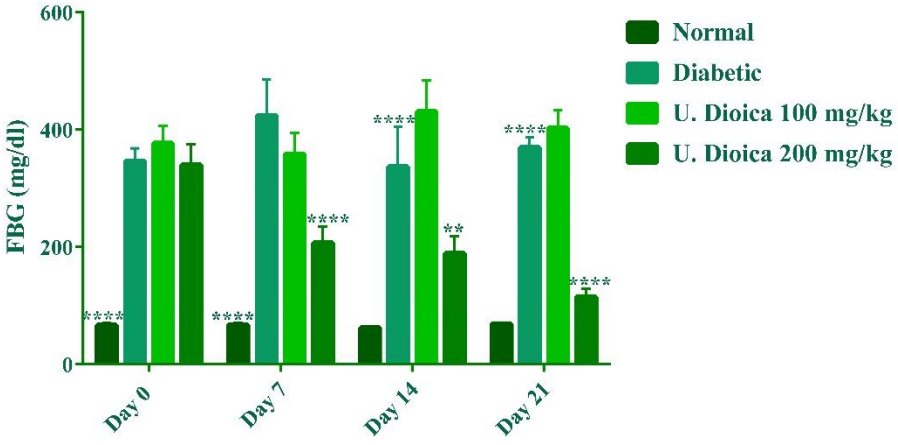

Figure 2. The Effect of U. Dioica (100 and 200 mg/kg) Extract on FBG Level of Diabetic Rats Data is shown as Mean±SEM. FBG, fasting blood glucose. **: P<0.01, ****: P<0.0001 as compared with the diabetic group.

ISSN (Online) 2249-6084 (Print) 2250-1029

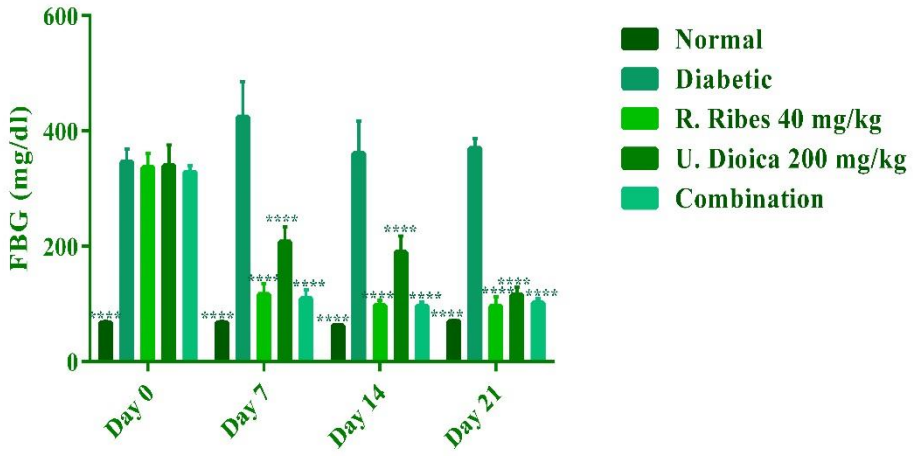

Figure 3. The Effect of R. Ribes and U. Dioica Extracts Combination on the FBG Level of Diabetic Rats
Data is shown as Mean±SEM. FBG, fasting blood glucose. ****: P<0.0001 as compared with the diabetic group.

Body weight determination

The bodyweight of all groups was determined on 0, 7th, 14th, and 21st days. There was a significant body weight loss in a diabetic group as compared with the normal group (P<0.001). The body weight was significantly increased only in U. Dioica 200 mg/kg group as compared with the diabetic group (P<0.01). However, there was not a significant difference in the body weight among R. Ribes 40 and 60 mg/kg, U. Dioica 100 mg/kg, and combination groups, and the diabetic group (P>0.05) **(Table 1)**.

Table 1. The Body Weight of Different Groups

Groups	Body Weight (g)				Weight Gain/Lost
	Day 0	Day 7	Day 14	Day 21	Day 0-21
Normal	184.67±1.52	185.83±1.35	196.17±1.81	205.00±2.28	20.33±3.02***
Diabetic	185.00±8.37	173.17±6.19	174.00±5.53	172.67±4.83	-12.33±4.72
R. Ribes 40 mg/kg	175.83±6.72	163.67±6.77	168.67±5.60	180.00±4.60	4.17±8.56
R. Ribes 60 mg/kg	176.67±3.89	170.17±3.61	169.50±5.14	171.83±6.20	-4.83±3.13
U. Dioica 100 mg/kg	173.50±3.70	162.67±3.96	157.17±6.00	153.50±7.10	-20.00±4.02
U. Dioica 200 mg/kg	186.17±5.29	184.00±5.58	189.50±4.94	201.67±7.52	15.50±3.87**
Combination	176.00±3.78	167.20±4.87	170.20±5.39	180.00±7.29	4.00±3.96

Data is shown as Mean±SEM. **: P<0.01, ***: P<0.001 as compared with the diabetic group.

In this study, the effect of R. Ribes and U. Dioica extracts either alone or in combination on the FBG level of STZ-induced diabetic rats was evaluated. STZ, a toxic compound, is used for the induction of diabetes in rodents. Administration of this compound leads to an increase in blood glucose level, decrease in insulin level and decrease in body weight, through activation of oxidative stress pathway [8].

Similarly, this study showed that a single i.p. administration of STZ increased the FBG level and decreased body weight in the diabetic group in comparison with the normal group. Therefore, we can conclude that STZ in this study could develop an experimental diabetes model.

Moreover, i.p. administration of R. Ribes aqueous extract (40 and 60 mg/kg) for 21 days could decrease the FBG level significantly. However, neither of R. Ribes aqueous extract doses could significantly increase the bodyweight of rats. This shows that Afghan R. Ribes aqueous extract has a hypoglycemic effect.

Similarly, previous studies showed that R. Ribes extract can decrease the FBG level in diabetic rats and confirm the results of this study. For instance, in one study, the effect of oral administration of R. Ribes root hydroalcoholic extract (75 and 150 mg/kg), for 28 days, was evaluated on FBG, body weight, lipid profile, urea, and creatinine in diabetic rats. Based on their results, the extract showed hypoglycemic and hypolipidemic effects and improved renal dysfunction in diabetic female rats [37]. Another study was evaluated the antioxidant effect of aqueous and ethanolic extracts of R. Ribes root on diabetic rats. Results showed that oral administration of 50 mg/kg R. Ribes both aqueous and ethanolic extracts for 15 days could significantly decrease the FBG and oxidative stress activity

and increase the levels of antioxidants [20]. Moreover, the effect of oral administration of R. ribes roots different extracts in 5 mg/kg doses on blood glucose level and insulin secretion rate of healthy mice was evaluated. The results have shown that only the aqueous extract of R. Ribes showed hypoglycemic activity and enhanced the secretion of insulin [22]. All in all, different studies have shown the antidiabetic effects of R. Ribes and its possible mechanisms. Thus, the hypoglycemic effect of R. Ribes extract may result from its insulin-enhancing effect and its potent antioxidant property [20, 22].

Besides, the present study has shown that the i.p. administration of U. Dioica aqueous-alcoholic extract for 21 days could decrease the FBG level significantly. However, only 200 mg/kg was significantly decreased by the FBG level. Furthermore, the 200 mg/kg dose of U. Dioica has significantly increased the bodyweight of rats, in comparison with the diabetic group. Thus, we can conclude that the Afghan U. Dioica has a potent anti-diabetic activity, especially at high-dose.

Previous studies have also confirmed the results of this study. In one study, the effect of U. Dioica leaves hydroalcoholic extract was evaluated on blood glucose and insulin levels, insulin resistance, and lipid profile of fructose-induced insulin resistance in rats. Results showed that 100 and 200 mg/kg doses of U. Dioica could significantly decrease the blood glucose level and 50, 100 and 200 mg/kg doses could decrease the insulin level and insulin resistance in rats. In addition, these doses of U. Dioica extract showed an antihyperlipidemic effect [27]. Moreover, another study showed the effect of oral administration of aqueous extract of U. Dioica leaves (1.25 g/10 ml/kg) on glucose level, lipidemic status, CRP, and serum insulin of type 1 diabetic rats for 21 days. The results showed that the extract exhibits anti-diabetic activity and decreased the blood glucose level, cholesterol and triglyceride, CRP inflammatory marker, and increased insulin level [29]. Furthermore, the effect of U. Dioica was evaluated on glycemia and insulin resistance in type 2 diabetic rats. They showed that U. Dioica over an 8-week administration period could significantly decrease the blood and urine glucose level [38]. In summary, one can conclude that U. Dioica has anti-diabetic properties. The possible mechanism for its effects may be its anti-inflammatory and insulin-enhancing properties and also decreasing insulin resistance [27, 39].

In addition, after the determination of effective doses of Afghan R. Ribes and U. Dioica extracts on the blood glucose level of type 2 diabetic rats, the effect of the combination of their effective doses on FBG level was evaluated. The results showed that the combination of R. Ribes and U. Dioica extracts also could decrease the FBG level in diabetic rats. However, there was no difference between the hypoglycemic effect of individual extract and their combination. Therefore, it can be concluded that they did not have any synergic or antagonistic effect on FBG level of diabetic rats. Their interaction may classify as an indifferent type of behavior. The possible explanation for this may be the same mechanism of action of R. Ribes and U. Dioica for lowering blood glucose level, including insulin-enhancing property because there are pieces of evidence that synergic effect is mostly resulted from different mechanisms of action of plants or drugs [16].

CONCLUSION

It can be concluded that Afghan R. Ribes and U. Dioica extracts and their combination have a hypoglycemic effect. However, they did not show any synergic or antagonistic effect.

Acknowledgments: This work is supported by the Research and Technology Center of Khatam Al-Nabieen University of Kabul, Afghanistan. We thank all officials for their valuable support in providing the equipment and facilities for this study.

Conflict of interest: None

Financial support: None

Ethics statement: None

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