

## *Rumex crispus* Extract Exerts Anti-Diabetic Properties in Streptozotocin-Induced Diabetes in Rats

Özgen ÇELİK<sup>1</sup>, Evren KOÇ<sup>1\*</sup>

**ABSTRACT:** *Rumex crispus* is a natural, wild plant that grows spontaneously on riverside and wet meadows, and has been used for centuries in alternative medicine. In the present study, the effects of *R. crispus* on body weights, fasting blood glucose levels, plasma lipid profile, liver enzyme activities and antioxidant system were investigated in streptozotocin (STZ) induced diabetic rats. The animals were divided into 4 groups. Group I: control; group II: 3 mg kg<sup>-1</sup> *R. crispus*; group III: 50 mg kg<sup>-1</sup> Streptozotocin (STZ)-induced diabetes; group IV: 50 mg kg<sup>-1</sup> STZ-induced diabetes + 3 mg kg<sup>-1</sup> *R. crispus*. It was found that *R. crispus* extract reduced diabetes-related weight loss and blood glucose levels 10 days after the formation of diabetes. At the end of 14-day treatment period, HDL cholesterol (HDL-C) levels significantly decreased (P<0.01) while triglyceride, LDL cholesterol (LDL-C) and VLDL cholesterol (VLDL-C) levels increased in *R. crispus* supplemented diabetic rats (P<0.001). The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly increased in response to *R. crispus* (P<0.001). Total antioxidant status (TAS) significantly decreased and total oxidant status (TOS) increased in diabetic group; however, in response to *R. crispus* treatment, TAS significantly increased and TOS decreased relative to control group (P<0.001, for both). Supplementation of *R. crispus* extract shows anti-diabetic properties in rats and might have a clinical potential for diabetic individuals.

**Keywords:** Diabetes, lipid profile, liver enzymes, oxidative status, *Rumex crispus*

### *Rumex crispus* Ekstraktı Sıçanlarda Streptozotosin ile Oluşturulan Diyabette Anti-Diyabetik Özellikler Gösterir

**ÖZET:** *Rumex crispus*, nehir kenarı ve ıslak çayırlarda kendiliğinden yetişen ve alternatif tıpta yüzyıllardır kullanılan doğal, yabani bir bitkidir. Bu çalışmada, streptozotosin (STZ) aracılığıyla diyabet oluşturulan sıçanlarda *R. crispus*'un canlı ağırlıkları, açlık kan glukoz seviyeleri, plazma lipid profili, karaciğer enzim aktiviteleri ve antioksidan sisteme etkileri araştırıldı. Hayvanlar 4 gruba ayrıldı. I. grup: kontrol; II. grup: 3 mg kg<sup>-1</sup> *R. crispus*; grup III: 50 mg kg<sup>-1</sup> Streptozotosin (STZ) ile diyabet oluşturulan grup; grup IV: 50 mg kg<sup>-1</sup> STZ ile diyabet oluşturulan + 3 mg kg<sup>-1</sup> *R. crispus* uygulanan grup şeklinde belirlendi. *R. crispus* ekstraktının, diyabet oluşumundan 10 gün sonra diyabete bağlı ağırlık kaybını ve kan glikoz seviyesini azalttığı tespit edildi. 14 günlük uygulama süresinin sonunda, *R. crispus* uygulanan diyabetik sıçanlarda trigliserit, LDL kolesterol (LDL-C) ve VLDL kolesterol (VLDL-C) düzeyleri artarken (P<0.001), HDL kolesterol (HDL-C) seviyeleri anlamlı derecede azaldı (P<0.01). Alanin aminotransferaz (ALT) ve aspartat aminotransferaz (AST) seviyeleri, *R. crispus*'a cevaben önemli ölçüde artmıştır (P<0.001). Diyabetik grupta total antioksidan seviye (TAS) anlamlı derecede azalırken, total oksidan seviyenin (TOS) artış gösterdiği belirlendi. Bununla birlikte, *R. crispus* tedavisine cevap olarak, TAS anlamlı şekilde artmış ve TOS kontrol grubuna göre azalmıştır (her ikisi için de P<0.001). *R. crispus* ekstraktının takviyesi, sıçanlarda anti-diyabetik özellikler gösterir ve diyabetik bireyler için klinik bir potansiyele sahip olabilir.

**Anahtar Kelimeler:** Diyabet, lipit profili, karaciğer enzimleri, oksidatif durum, *Rumex crispus*

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## INTRODUCTION

Diabetes mellitus is one of the common health problems associated with the development of disorders in the carbohydrate, lipid and protein metabolisms. Due to hyperglycemic condition in diabetes, glycation and lipid peroxidation may lead to diabetes associated complications (Nawale et al., 2006; Aouacheri et al., 2015). Oxidative stress is a condition developing from formation of free radicals which target to stay stable through matching the electrons with proteins, lipids and cellular DNA. Imbalance of oxidant/anti-oxidants in favor of free radicals leads to oxidative stress which is known as the major cause of oxidative damage of biological molecules (Shiwani et al., 2012). Increased oxidative stress results from increased free radicals and impaired anti-oxidant defense system (Aouacheri et al., 2015). Diabetes is the metabolic disorder-related oxidative stress. Increased metabolic stress leads to structural and functional damages through increasing oxidative stress. Diabetes is the oxidative stress in which free oxygen radicals and lipid peroxidation increase and anti-oxidant system becomes irregular (Caner et al., 2012). Many authors have reported that increased diabetes complications is directly related with oxidative stress (Caner et al., 2012; Aouacheri et al., 2015).

Humans have used various plants with traditional methods for treating or prevention of diseases (Xavier et al., 2012; Ha et al., 2014). Food obtained from eatable natural resources like plant extracts are known to be used for prevention and treatment of metabolic diseases like diabetes (Ha et al., 2014). *R. crispus* is one of these plants and traditionally consumed as raw or cooked due to its effects on kidney infection, gynecological diseases, internal diseases (Özgen et al., 2012). *R. crispus* is reported to have beneficial health effects due to its anti-oxidant, anti-fungal and anti-inflammatory effects (Kim et al., 2013). Shiwani et al. (2012) have reported that *R. crispus* is a quite important oxidant scavenger and prevent impairment of DNA and protein

structures through this effect (Shiwani et al., 2012). The antioxidant, antifungal and anti-inflammatory properties of *R. crispus* have been previously proposed; however, the antidiabetic quality of *R. crispus* has not been studied up-to-date. The present study aims at investigating the effects of *R. crispus* on weights of animals, fasting blood glucose levels, plasma lipid profile, liver enzyme activities and oxidant/anti-oxidant balance in rats with STZ-induced diabetes.

## MATERIALS AND METHODS

**Animal Material:** Four-five months of male *Sprague dawley* rats were used as animal material. Local ethics committee approval was obtained from Kafkas University Animal Tests Local Ethics Committee (2015/111). Animals were kept at  $25 \pm 2^\circ\text{C}$  temperature, 60-65% humidity and 12 hr of dark and light cycle before and fed as ad libitum.

Animals were divided into 4 groups with 10 animals in each.

**Group I** was control group and animals were administered physiological saline intraperitoneally (i.p).

**Group II**, 3 mg kg<sup>-1</sup> (b.w.) *R. crispus* (with oral gavage) was given for 14 days.

**Group III**, 50 mg kg<sup>-1</sup> (b.w.) Streptozotocin (STZ) was injected intraperitoneally (i.p.) for diabetes induction.

**Group IV**, 50 mg kg<sup>-1</sup> (b.w.) i.p. STZ and 3 mg kg<sup>-1</sup> (b.w.) *R. crispus* extract combination were given to this experimental group for 14 days. Streptozotocin (STZ, Sigma, St. Louis, MO, USA) freshly dissolved in 0.01 M citrate buffer (pH 4.5) was given as single dose 50 mg kg<sup>-1</sup> (b.w.) i.p. to rats.

Blood samples were taken into heparinized tubes with cardiac puncture under sevoflurane anesthesia for analyses at the end of 14 days and centrifuged at 3000 rpm, +4 °C for 10 min. Obtained plasma was stored at -20 °C until analyses.

**Preparation of plant extract:** Plant extract was prepared using soxhlet extraction method.

According to this method, 20 g plant sample was extracted three times with 500 ml methanol. Extract-containing methanol was evaporated at 40°C and diluted 4 folds with tween 80, stored at -25°C until used (Özkan et al., 2010).

### Diabetes Formation and Biochemical

**Analyses:** After 72 hr after STZ administration with glucometer and fasting blood glucose levels >200 mg/dl were accepted as diabetic (Alejandro et al., 2013).

Plasma lipid and liver enzyme analyses were detected using auto-analyzer. Plasma anti-oxidant and oxidant levels were measured using commercial kits (Total Antioxidant Status (TAS) and Total Oxidant Status (TOS) Assay kit (Rel Assay Diagnostics, Clinical Chemistry Solutions, Gaziantep, Turkey).

**Statistical Analyses:** Statistical analyses were done using SPSS 22 package program. In-group normality analysis was done using Shapiro Wilk-W test. Inter-group comparisons were done using one-way variance analysis (One-way ANOVA). Tukey test was used for defining inter-group differences. Results were given as mean  $\pm$  standard deviation (means  $\pm$  SD) and a p level of <0.05 was accepted as statistically significant.

## RESULTS AND DISCUSSION

In order to investigate if *R. crispus* had any weight loss preventative action which was seen in diabetic rats, the weights of the animals were measured. After 10 days of diabetes formation, the weights of the animals were significantly dropped. Daily *R. crispus* supplementation in these animals reversed weight loss significantly ( $P < 0.05$ ) starting 10-day regimen (Figure 1). Next, we evaluated whether this extract had an influence on fasting blood glucose levels. The blood glucose level reducing property of *R. crispus* was first detected after 10 days of supplementation, however it reached its maximum at 14 days of treatment. In diabetes induced animals, the blood glucose levels (about 242 mg dl<sup>-1</sup>) were significantly higher than the control (about 85 mg dl<sup>-1</sup>) on average ( $P < 0.001$ )

at the end of 14-day period. 14 days of daily *R. crispus* supplementation significantly dropped blood glucose levels in STZ-induced diabetes and brought back the level to about 120 mg dl<sup>-1</sup> ( $P < 0.001$ ) (Figure 2).

HDL-C levels significantly decreased ( $P < 0.01$ ) whereas triglyceride (TG), LDL-C and VLDL-C levels were detected to significantly increase in diabetes + *R. crispus* group ( $P < 0.001$ ) (Fig. 3). AST and ALT liver enzyme levels significantly increased upon *R. crispus* supplementation in diabetic rats as compared to only STZ-induced diabetes groups ( $P < 0.001$ ) (Table 1).

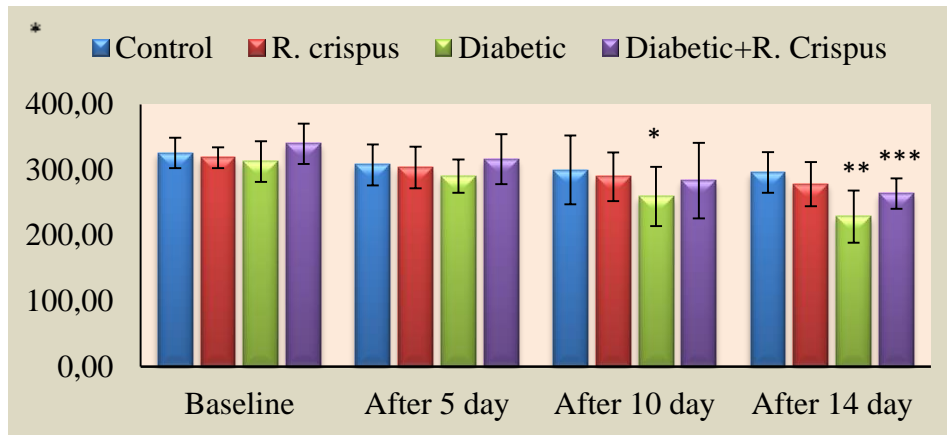
*R. crispus* decreased oxidative damage associated with STZ-induced diabetes by increasing Total Antioxidant Status (TAS) and decreasing the activity of oxidative stress causing compounds in STZ-induced diabetes ( $P < 0.001$ ) (Table 2).

In summary, *R. crispus* supplementation might have beneficial properties against diabetes by decreasing diabetic weight loss, decreasing hyperglycemia, and increasing antioxidant enzyme activity.

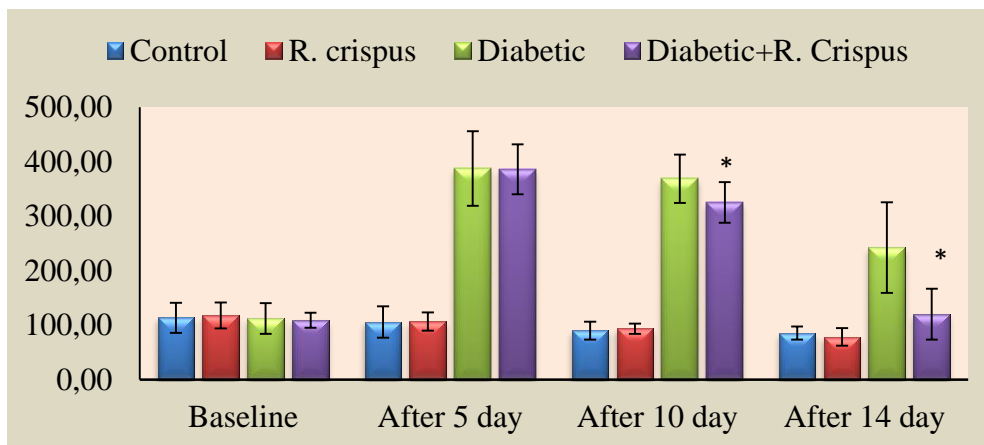
The imbalance between reactive oxygen species and anti-oxidant defense systems is an important condition in diabetes as in all metabolic disorders (Lupi et al., 2007). Oxidative stress is an important factor which plays a role in pathogenesis and complications of diabetes (Nogueira-Machado et al., 2006). Increased oxidant production increases the risk for diabetes development through leading to pancreas beta cell dysfunction (Aouacheri et al., 2015). An ample amount of diseases including diabetes cannot be treated today despite the developments in medicine. In developed and developing countries, people tend to use alternative medicine due to the side effects of chemicals (Hamdan and Afifi, 2004). Alternative medicine studies seem to become common for treatment of diabetes. Influences of acorn extract (*Quercus branti* Lindl.) have been investigated in rats with experimentally STZ-induced diabetes and it was

reported to have a protective effect on liver and pancreas (Yaman and Doğan, 2016). Another study has reported that *Momordica charantia* L. and *Prunus laurocerasus* L. could have an

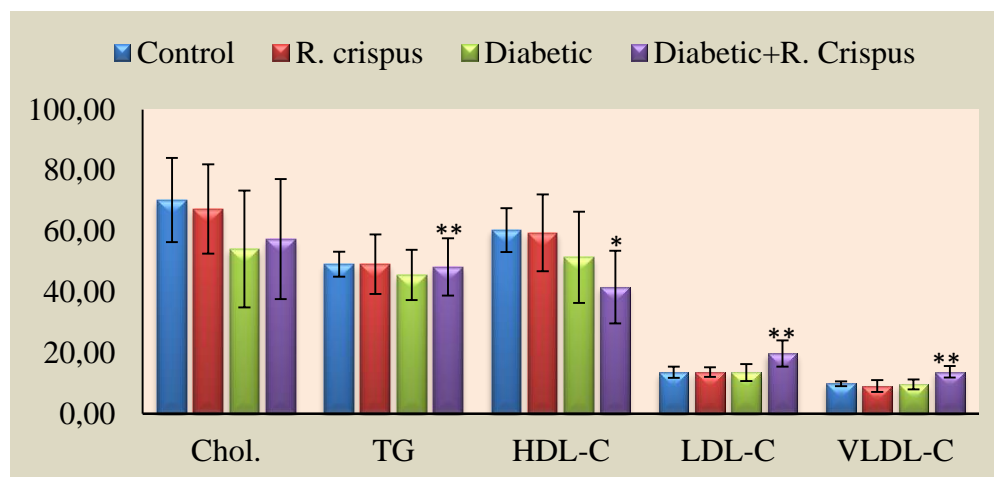
important effect in treatment of diabetes-related disorders in rats with STZ-induced diabetes (Atila et al., 2015; Uslu et al., 2018).



**Figure 1:** Weights of animals (g) in control and experimental groups (means ± SD). \* P < 0.05, \*\* P < 0.001 and \*\*\* P < 0.01 (as compared to control).



**Figure 2:** Fasting blood glucose levels (mg/dl) of animals in control and experimental groups (means ± SD). \* P < 0.001 (as compared to diabetic).



**Figure 3:** Plasma total Cholesterol (Chol.), tryglyceride (TG), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), VLDL cholesterol (VLDL-C) concentrations (mg/dl) in rats at control and experimental groups (means ± SD). \* P < 0.01, \*\* P < 0.001 (as compared to diabetic).

**Table 1:** Liver enzyme levels (ng ml<sup>-1</sup>) of animals in control and experimental groups (means ± SD).

|     | Groups  |                   |          |                              |
|-----|---------|-------------------|----------|------------------------------|
|     | Control | <i>R. crispus</i> | Diabetes | Diabetes + <i>R. crispus</i> |
| AST | 121 ± 7 | 133 ± 14          | 177 ± 21 | 200 ± 19 *                   |
| ALT | 49 ± 15 | 49 ± 11           | 71 ± 19  | 159 ± 33 *                   |

\* P<0.001 (as compared to diabetic).

**Table 2:** Oxidative stress enzyme activities of animals in control and experimental groups (means ± SD).

|   | Groups      |                   |               |                              |
|---|-------------|-------------------|---------------|------------------------------|
|   | Control     | <i>R. crispus</i> | Diabetes      | Diabetes + <i>R. crispus</i> |
| TAS (mmolTrolox Equiv./L)                         | 0.53 ± 0.15 | 0.68 ± 0.14       | 0.37 ± 0.13 * | 0.91 ± 0.09 *                |
| TOS (µmol H <sub>2</sub> O <sub>2</sub> Equiv./L) | 5.11 ± 1.89 | 8.38 ± 1.92       | 7.01 ± 2.53 * | 6.27 ± 1.99                  |

\* P<0.001 (as compared to control).

Different *Rumex* types are seen to be studied with regard to healing effects in diabetes which does not have treatment in modern medicine and about which alternative medicine studies are intensive. *Rumex* species are plants which are widely used in alternative medicine due to anti-diabetic, anti-oxidant, anti-microbial and anti-fungal properties (Ha et al., 2014; Muselin et al., 2015). Some researchers has reported that plasma and serum glucose levels was lower than in diabetes group when *Rumex patientia* was administered to the rats with STZ-induced diabetes (Degirmenci et al., 2005; Sedaghat et al., 2011). In the present study, *R. crispus* was detected to decrease fasting blood glucose levels after day 10 through showing anti-diabetic effect. Also weight of the animals was detected to decrease on days 10 and 14 after diabetes formation and this reduction in weight was detected to decrease with administration of *R. crispus* extract in diabetic animals.

Many studies have been conducted for reducing diabetes complications through *Rumex* species. In a study about lipid profile in rats with STZ-induced diabetes, *R. patientia* administration was detected not to lead to a significant alteration in serum total cholesterol and triglyceride levels, HDL cholesterol was detected to increase, LDL cholesterol was

detected to significantly decrease, *R. patientia* was concluded to improve lipid profile directly or indirectly by reducing plasma glucose (Sedaghat et al., 2011). While a significant alteration was not detected in cholesterol levels, TG, LDL and VLDL cholesterol levels were detected to significantly increase in STZ-induced diabetes + *R. crispus* group in the present study. We suggest that if this extract is used for the treatment of diabetes, blood lipid composition should be monitored and additional medicines for the treatment of bad cholesterol levels could be utilized. More comprehensive studies should be carried out for investigating the causes of unexpected elevation in these parameters.

Alanine amino-transferase (ALT) and aspartate amino-transferase (AST) are the liver enzymes which take part in gluconeogenesis and amino acid metabolism and catalyse the intermediate reactions of glucose and protein metabolisms (Zareei et al., 2017). Although AST is present in various tissues, it has the highest concentrations in skeletal muscle, myocardium, red blood cells and liver. ALT is primarily present in hepatocyte cytoplasm. These enzymes catalyze conversion of amino acids to each other through amino acid transfer (Mayer and Donnelly, 2013). The present study has revealed that AST level increased in all groups when compared with

control group, maximum elevation was found in STZ-induced diabetes + *R. crispus* group. Another liver enzyme, ALT level was detected to significantly increase in STZ-induced diabetes and STZ-induced diabetes + *R. crispus* group, maximum elevation was found in STZ-induced diabetes + *R. crispus* group. Elevated levels of liver enzymes due to *R. crispus* extract administration in diabetic rats were considered to result from increased gluconeogenesis. One may think that the elevation of AST and ALT levels might be associated with liver damage. We observed that the *R. crispus* didn't cause an increase in the levels of these enzymes in the control group. Therefore, it's possible that the increase in these enzymes might be related to a compensatory mechanism in glucose metabolism. Elzaawely and Tawata, (2012) have detected that *R. dentatus* had a high phenolic content and thereby high anti-oxidant activity (Elzaawely and Tawata, 2012). Similarly, Coruh *et al.* (2008) have reported that *R. crispus* had a high anti-oxidant activity (Coruh *et al.*, 2008). In a study investigating anti-oxidant properties of *R. crispus*, it was shown to have strong anti-oxidant effect, reduce lipid peroxidation, increase glutathione level in carbon-tetrachloride-induced oxidative stress (Maksimović *et al.*, 2011). *R. patientia* administration was reported to reduce MDA level and increase SOD activity in rats with STZ-induced rats (Sedaghat *et al.*, 2011). In the present study, TAS level of STZ-induced diabetes group was found lower in *R. crispus* group and significantly increased in STZ-induced diabetes + *R. crispus* group. While an increase was observed in all administration groups compared to control group, maximum elevation was seen to occur in only *R. crispus* group.

## CONCLUSION

*R. crispus* extract administration was detected to show protective effect against STZ-induced diabetes through preventing diabetes-related weight loss, lowering hyperglycemia, increasing anti-oxidant enzyme activity, reducing oxidant level in rats. Besides all its beneficial

actions, this extract might have some side effects especially on the lipid metabolism. This extract might have multiple active molecules for glucose metabolism. Therefore, further studies are needed to detect this molecules and their molecular mechanism of action. Its beneficial potential should be further evaluated in a clinic setting.

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