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The Effect of *Rosa Pisiformis* (Christ) D.Sosn on Some Metabolic Enzyme Activities in STZ Applied Diabetic Rats

Mahire Bayramoğlu AKKOYUN[1*], Aydın Şükrü BENGÜ[2], Yusuf TEMEL[3], Hurrem Turan AKKOYUN[1], Suat EKIN[4], Mehmet CIFTCI[5]

ABSTRACT: This study was aimed to study in vivo impacts of *Rosa pisiformis (Christ) D.Sosn.* (VANF F13827 END.) on some metabolic enzymes (G6PD, 6PGD, GR, TrxR and GST) in Streptozotocin (STZ) applied diabetic rats. 32 male Wistar albino rats divided four groups. Group I: Control, Group II:Streptozotocin, Group III: *Rosa pisiformis* and Group IV: Streptozotocin+*Rosa pisiformis*. Experimental study contunied for 30 days and enzyme activities were spectrophotometrically measured. *R.p.*fruit extract and STZ+*R.p.* fruit extract administrations increased Glucose 6-phosphate dehydrogenase (G6PD) activity meaningfully compared to control ($p<0.001$). 6-phosphogluconate dehydrogenase (6PGD) enzyme activity reduced in diabetes group compared to control, whereas it increased in *R.p.* fruit extract and STZ+*R.p.* fruit administered groups. Glutathione reductase (GR) activity raised in *R.p.* fruit administered group compared to control group meaningfully ($p<0.001$). Thioredoxin reductase (TrxR) activity decrease no statistical importance in diabetic rats compared control whereas this activity increased in *Rosa pisiformis* fruit extract group. Glutathione S-transferases (GST) enzyme activity reduction significantly in STZ group compared to control ($p<0.05$). As a result, It is thought that the fruits of *Rosa pisiformis*, which grows as an endemic species belonging to the Rosaceae family, may have a reducing or preventing effect on the 6PGD, TrxR and GST enzyme activities in rats by inhibiting caused by STZ.

Keywords: G6PD, GR, GST, 6PGD, *Rosa pisiformis*, TrxR

STZ İle Diyabet Oluşturulan Sıçanlarda Rosa Pisiformis(Christ) D.Sons'un Bazı Metabolik Enzim Aktiviteleri Üzerine Etkisi

ÖZET: Bu çalışmada Streptozotosin (STZ) ile diyabet oluşturulan sıçanlarda *Rosa pisiformis* (Christ) D.Sosn. (VANF F13827 END.) 'in bazı metabolik enzimler üzerine in vivo etkilerinin araştırılması amaçlandı. 32 adet wistar albino cinsi erkek sıçan dört gruba ayrıldı. Grup I:Kontrol, Grup II:Streptozotosin, Grup III: *Rosa pisiformis*, Grup IV: Streptozotosin + *Rosa pisiformis*. Deneysel çalışma 30 gün sürdürüldü ve enzim aktiviteleri spektrofotometrik olarak ölçüldü. Glukoz 6-fosfat dehidrogenaz (G6PD) aktivitesinde *R.p.*meyve ekstraktı ve STZ+*R.p* meyve ekstraktı uygulanan gruplarda kontrolle kıyaslandığında anlamlı düzeyde artış görüldü($p<0.001$). 6-fosfoglukonat dehidrogenaz (6PGD) enzim aktivitesi diyabet oluşturulan grupta kontrole oranla azaldı. Aksine *R.p* meyve ekstraktı ve STZ+*R.p* meyve ekstraktı uygulanan grupta arttı. Glutatyon reduktaz (GR) enzim aktivitesi *R.p* meyve ekstraktı uygulanan grupta kontrole oranla istatistiksel olarak anlamlı düzeyde yükseldi ($p<0.001$). Tioredoksin redüktaz (TrxR) aktivitesi diyabetik sıçanlarda kontrol ile karşılaştırıldığında istatistiksel olarak önemli bir azalma göstermezken, *Rosa pisiformis* meyve ekstraktı uygulanan grupta arttı. Glutatyon S-transferaz (GST) enzim aktivitesinin STZ uygulanan grupta kontrole oranla anlamlı şekilde azaldığı görüldü ($p<0.05$). Sonuç olarak; Rosaceae familyasına ait endemik bir tür olarak yetişen *Rosa pisiformis* meyvelerinin sıçanlarda 6PGD, TrxR ve GST enzim aktiviteleri üzerine STZ'nin neden olduğu inhibisyonu azaltıcı yada önleyici etkisinin olabileceği düşünülmektedir.

Anahtar Kelimeler: G6PD, GR, GST, 6PGD, *Rosa pisiformis*, TrxR

[1]Mahire BAYRAMOĞLU AKKOYUN(**Orcid ID:** 0000-0001-5150-5402), Department of Basic Sciences, Faculty of Veterinary Medicine, Siirt University, Siirt, Turkey. [2]Aydın Şükrü BENGÜ (**Orcid ID:** 0000-0002-7635-4885), Health Services Vocational School, Bingöl University, Bingöl, Turkey. [3]Yusuf TEMEL (**Orcid ID:** 0000-0001-8148-3718), Solhan Health Services Vocational School, Bingöl University, Bingöl, Turkey. [1]Hurrem Turan AKKOYUN(**Orcid ID:**0000-0002-4547-8003), Department of Basic Sciences, Faculty of Veterinary Medicine, Siirt University, Siirt, Turkey. [4]Suat EKİN (**Orcid ID:** 0000-0002-6502-5028), Department of Chemistry, Faculty of Sciences, YYU University, Van, Turkey. [5]Mehmet ÇİFTCİ(**Orcid ID:** 0000-0003-4971-4242), Department of Chemistry, Faculty of Arts and Sciences, Bingöl University, Bingöl, Turkey.

***Sorumlu Yazar/Corresponding Author:** Mahire Bayramoğlu Akkoyun, e-mail: mahireakkoyun@siirt.edu.tr

ETHICS COMMITTEE APPROVAL: For the animal experiment in this article, Ethics Committee Approval was obtained with the decision of the "Bingöl University Rectorate Animal Experiments Local Ethics Committee", with the decision dated 21.02.2018 Meeting No 2018/02, Decision No: 02/07.

INTRODUCTION

Diabetes is an important metabolic disease defined by an increasing degree of deterioration in carbohydrate, fat and protein metabolism, especially in developed countries in recent year (Sensoy and Gençoğlan, 2009; Yüzüak and Aybak, 2015). It includes many metabolic disorders such as hyperglycemia, dyslipidemia, glycosuria (Cilaker-Mıcılı et al., 2012). Diabetes can influence various organ-systems in the metabolism and can cause critical complications over time (Metelko et al., 2000). In general, complications are considered as microvascular or macrovascular. Microvascular complications contain harm to the nervous system, injury to the kidney system, and diabetic retinopathy. Macrovascular complications are considered as cardiovascular illness, stroke and peripheral vascular illness. Peripheral vascular illness can cause uncured tissue injuries, gangrene, and ultimately amputation (Deshpande et al., 2008). Streptozotocin is produced by *Streptomycetes achromogenes*. Streptozotocin (STZ) is an antineoplastic antibiotic (Szkudelski, 2001). It is known as a potential oxidative stress source and can cause DNA damage (Imaeda et al., 2002). Streptozotocin is a highly potent cytotoxic agent for pancreatic βcells (Junod et al., 1969). It have been used for the development of diabetes by intravenous injection in emprical animals due to their high toxicity to β cells (Rossini et al., 1977; Lezen, 2008). Plants are used in many fields such as medicine, nutrition, culinary, dyeing, odor thickening, cigarettes, cosmetics and other fields. The herbs are welds of compounds with antioxidant activity such as pharmacologically active components like phenolic acids, flavonoids, anthocyanins (Lopez et al., 2007). Since prehistoric times, plants have been the basis of nearly all drug treatment until the development of synthetic drugs (Djeridane et al., 2006). Concerns about the use of synthetic drugs and antioxidants for instance BHA, BHT and TBHQ have recently increased their relevance to plant-based compounds such as phenolic compounds, flavonoids, and hydroxamic acids on natural antioxidants (Balasundram et al., 2006). The previous studies have indicate that a diet wealthy in plants has protective effects against some diseases for example cancer, obesity, hypertension, diabetes, cataract and cardiovascular diseases (Halvorsen et al., 2002; Acosta-Montoya et al., 2010). *Rosa pisiformis* (Christ) D. Sosn. plant is an endemic plant species of the Rosaceae family that grows in our country to Turkey (Ercisli, 2005). The elements of the Rosaceae family are mostly used for nutrition and medical goals. This is explained by the phenolic compounds present in the family and it has been reported that the members have biochemical activity such as antioxidant, antimutagenic and anticarcinogenic (Ercisli, 2007). Glucose 6-phosphate dehydrogenase is an enzyme catalyzing transformation of glucose-6-phosphate to 6-phosphogluconolactone via reduction of $NADP^+$, firstly and speed-limiting step in pentose phosphate metabolic pathway (Au et al., 2000; Temel and Koçyiğit, 2017; Bayindir et al., 2018; Karaman et al., 2020). 6- phosphogluconate dehydrogenase is the third enzyme of the pentose phosphate metabolic pathway and catalyzes 6-PGA (6-phosphogluconate) to D-riboluse-5-phosphate in asset of $NADP^+$ (Beydemir et al., 2004; Bayindir et al., 2018; Bayramoğlu Akkoyun et al., 2018; Temel and Taysi, 2018). As a result of the reactions catalyzed by G6PD and 6PGD, NADPH is produced which protects cells against reactive molecules by producing decreased glutathione (GSH) (Nelson and Cox, 2000). Therefore, G6PD and 6PGD may be described as second-order antioxidant enzymes (Kozar et al., 2000; Çiftçi et al., 2001). Glutathione reductase catalyzes the reduction of reduced glutathione disulfide (GSSG) to decreased form (GSH) in the asset of NADPH (Akkemik et al., 2011; Tandoğan et al., 2011; Adem and Çiftçi, 2016; Temel et al., 2017; Aybek et al., 2020). Thioredoxin reductase are enzymes catalyzing the catalytic area with Cys-Val-Asn-Val-Gly-Cys amino acids and with the binding site nicotinamide adenine dinucleotide phosphate(NADPH) (Temel et al; 2017; Temel and Taysi, 2018). They also contain selenocysteine in

the C-terminal region required for redox activity. Thioredoxin has an effect on gene expression, signal transduction, regulation of redox activity and oxidative damage (Sen and Packer,1996). Glutathione S-transferases are generally cytosolic, mitochondrial and microsomal enzymes which are present in metabolism (Pljesa-Ercegovac et al., 2018; Temel et al., 2018; Zariç, 2018; Özaslan et al., 2019; Türkan et al., 2020).

In our study, it was aimed to study in vivo impacts of *Rosa pisiformis (Christ) D.Sosn.* (VANF F13827 END.) on some metabolic enzymes (G6PD, 6PGD, GR, TrxR and GST) in STZ applied diabetic rats.

MATERIALS AND METHODS

In vivo Effect of Streptozotocin and *Rosa pisiformis* (Christ) D. Sosn

32 male Wistar albino rats (250-300 gr weight) were acquired from the Experimental Research Center of Bingol University. Four groups of rats were formed: Group I: control (C: %0.9 NaCI), Group II: Streptozotocin (STZ:60 mg kg^{-1} single dose, i.p.) (Wang et al., 2000), Group III: *Rosa pisiformis* (*R.p.*:300 mg kg^{-1}, with gavage) (Bayramoglu et al., 2016) and Group IV: Streptozotocin+*Rosa pisiformis* (STZ 60 mg kg^{-1} single dose, i.p, *R.p.*:300 mg kg^{-1}**,** with gavage). Animals were kept in cages in a controlled room provided with a stable heat of 20-22 ºC and a 12 hour light-dark period. Water and food were given *ad libitum*. Following this adaptation period to their cages for a week, experimental procedures had started. Twelve hours prior to the experiment, feeding except water was stopped and blood samples were taken at the end of the 30^{th} day and prepared for experimental analyzes.

Obtainment of the Hemolysate

Blood samples were taken into EDTA inclusive and centrifuged at 2500 x g for 15 min. Plasma and leukocytes were then eliminated. The erythrocytes were washed 3 times with KCl (0.16 M) and the supernatant was removed by centrifugation of the samples each time (2,500 x g). Erythrocytes were hemolysed with 5 times the volume of erythrocyte volumes and then centrifuged at +4 °C and 10,000 x g for 30 min to eliminate cell membranes and insoluble parts. The supernatant was kept for analysis (Bayramoğlu Akkoyun et al., 2018; Temel and Bayindir, 2019).

Measurement of activity of the some metabolic enzymes

G6PD and 6PGD enzyme activities were measured according to the Beutler process (Beutler, 1971; Çiftçi et al., 2001), The enzyme activity of GR was evaluated spectrophotometrically at 340 nm according to the Carlberg and Mannervik process (Calberg and Mannervik, 1986; Tandoğan et al., 2011). The thioredoxin reductase (TrxR) enzyme activity assay was evaluated at 412 nm according to the Holmgren process (Holmgren 1977; Branco et al., 2014; Temel et al., 2017). GST enzyme activity was evaluated according to the proposed process defined by Habig et al (Habig et al., 1974).

Analysis of kinetic data

SPSS version 20 program was used for in vivo analyzes. Conclusions were statistically analyzed using one-way ANOVA with post hoc Least important difference (LSD) test.

RESULTS AND DISCUSSION

For the G6PD enzyme; Group II (STZ) ($p > 0.05$), Group III (*R.p.* fruit) and Group IV (Stz + *R.p.* fruit) were found to be $p < 0.001$ when compared with the control group. In group 2, the enzyme activity rise in no significant differences ($p > 0.05$) and in group 3 and 4 it was found that enzyme activities increased important ($p < 0.001$). For 6PGD enzyme; group II was determined to be ($p > 0.05$) Group III ($p > 0.05$) Group IV ($p > 0.05$) when compared with the control group. There was no important significance decrease in enzyme activity in the group II and insignificant rise in the group

III and group IV. For the GR enzyme; Group II ($p > 0.05$), Group III $p < 0.001$ compared to the control group. Group IV was found to be ($p > 0.05$). There was a no significant rise in GR enzyme activity in the second group ($p > 0.05$). There was a statistically important rise in the third group ($p < 0.001$). There was statistically unimportant change in the group IV and the enzyme activity values were near to the control group ($p > 0.05$). For the TrxR enzyme; When compared with the control group, Group II was determined to be ($p > 0.05$) Group III ($p > 0.05$), Group IV ($p > 0.05$). A statistically unimportant increase in enzyme activity in the *Rosa pisiformis* fruit extract group and no significant reduce in the STZ+*R.p.* fruit group were found ($p > 0.05$). In addition TrxR enzyme activity in diabetic rats decreased no significant ($p > 0.05$). For the GST enzyme; Group II was determined to be $p < 0.05$, Group III was found to be $p>0.05$ and Group IV was found to be $p>0.05$ in comparison with the control group. A statistically importance decline ($p<0.05$) in the diabetic group, no important decrease ($p > 0.05$) in the *Rosa pisiformis* fruit group and STZ+ *R.p.* fruit group was determined.

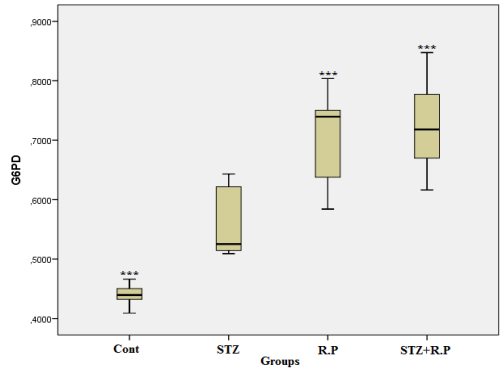

Figure 1. *In vivo* effect of STZ and *Rosa pisiformis* on rat erythrocyte G6PD enzyme activity of groups(***p<0,001).

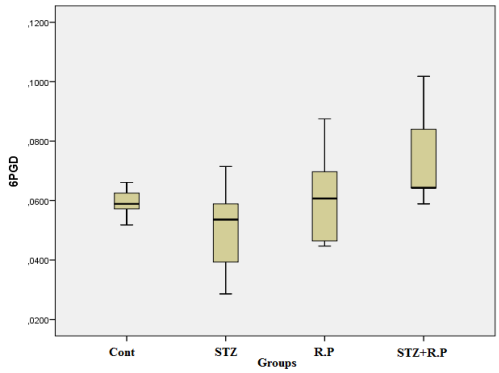

Figure 2. *In vivo* effect of STZ and *Rosa pisiformis* on rat erythrocyte 6PGD enzyme activity of groups

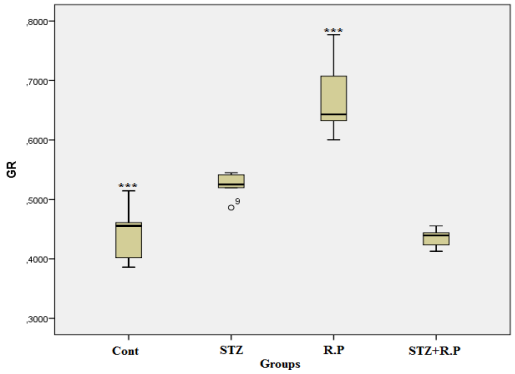

Figure 3. In vivo effect of STZ and *Rosa pisiformis* on rat erythrocyte GR enzyme activity of groups(***p<0.001)

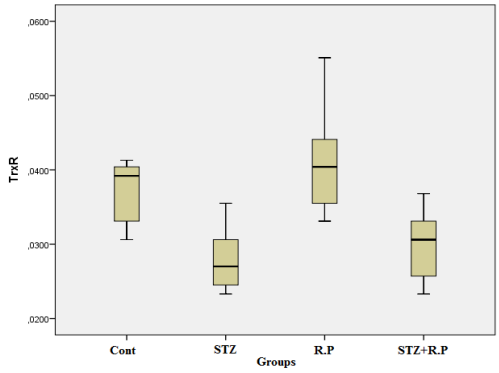

Figure 4. In vivo effect of STZ and *Rosa pisiformis* on rat erythrocyte TrxR enzyme activity of groups

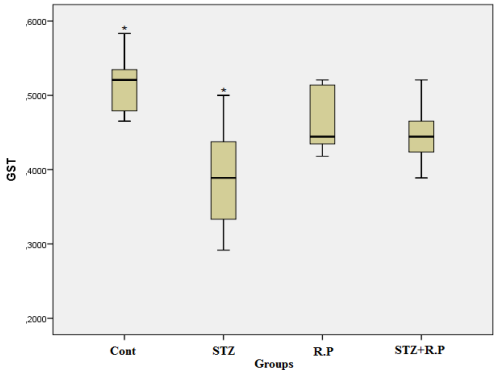

Figure 5. In vivo effect of STZ and *Rosa pisiformis* on rat erythrocyte GST enzyme activity of groups (*p < 0.05).

Diabetes is a serious problem worldwide, characterized by increased cardiovascular mortality associated with the development of nephropathy, neuropathy, retinopathy (Maritim et al., 2003). In accordance with, the World Health Organization, over 150 million human in the world have diabetes mellitus (Akbarzadeh et al., 2007). Today, the inadequacy of the antioxidant defense mechanism against the oxidative stress created by the increase of free radicals is one of the most important elements in the emergence of diabetes and its effects (Maritim et al., 2003). STZ has long been used to create diabetes mellitus (DM) in empirical animals (Federiuk et al., 2004). In rats, STZ administration causes a serious and stationary injury with a decrease in insulin levels. STZ damages the beta cells of the pancreatic Langerhans is lets and entail the development of a cytotoxic model of diabetes causing type I diabetes mellitus (Öztaşan et al., 2005).

In late years there has been in the world trend towards the use of spontaneous phytochemicals found in fruit plants, vegetables, oilseeds, beans, fruits (Lee et al., 2003). These plant-derived natural antioxidants are especially important due to their phenolic content. Epidemiologic research have demonstrated that consumption of herbal food containing antioxidants is helpful for health, and that cancer has many preventative effects, especially cardiovascular diseases(Sultana et al., 2009). In this study, the impact of *Rosa pisiformis* fruit extract grown as an endemic species on the activities of important metabolic enzymes for example G6PD, 6PGD, GR, TrxR, and GST in diabetic rats with STZ were investigated. When group enzyme activity levels were evaluated in the study; an increase in the STZ group was observed when the glucose-6-phosphate dehydrogenase (G6PD) enzyme activity was compared with the control group, but this increase was not statistically importance ($p > 0.05$). Enzyme activity in *R.p.* fruit administered and STZ+*R.p.* fruit application groups was found to be increased compared to control, and this rise was statistically significant ($p < 0.001$). When the 6-phosphogluconate dehydrogenase (6PGD) activity, which is one of the important enzymes of the pentose phosphate pathway, was evaluated, there was a decrease in the STZ administered group compared to the control group and no significant increase in the *R.p.* fruit administered group and similarly the STZ+*R.p.* fruit administered group compared to the control group. When the glutathione reductase activity level, which is very important in antioxidant defense system, is evaluated; there was a statistically insignificant increase in the diabetic group (STZ) when the enzyme activity was compared to the control ($p > 0.05$). A statistically significant increase was observed in the *R.p.* fruit application group compared to the control ($p < 0.001$). In the STZ+*R.p.* fruit group, the enzyme activity values were found to be close to the control group. When TrxR enzyme activity was evaluated; TrxR enzyme activity in diabetic rats decreased statistically insignificant ($p > 0.05$). There was a statistically insignificant increase in enzyme activity in the *Rosa pisiformis* fruit extract group and a statistically insignificant reduce in the STZ+*R.p.* fruit group ($p > 0.05$). STZ+*R.p.* fruit, when compared to STZ group, enzyme activities were increased and close to the control group. Its suggests that *Rosa pisiformis* plant extract may reduce the inhibitory impact of STZ on TrxR enzyme activity. When compared to the GST enzyme activity control group; the increase in activity in *R.p.* and STZ+*R.p.* fruit groups, in which the enzyme activity in the diabetes group decreases, suggesting that the *R.p.* fruit extract on GST enzyme activity may also inhibit the inhibitory effect of STZ. In a study using a different species of Rosa, *Rosa damascena* Mill showed that they have antidiabetic effect on diabetic rats (Gholamhoseinian et al., 2009). Orhan et al. have determined that Rosa canina fruit used in traditional medicine is used for diabetes mellitus and has antidiabetic effect (Orhan et al., 2009). Another line of the Rosaceae family has also been reported to have antidiabetic effect (Taghizadeh et al., 2016). A different study, the effects of *Rosa damascene* flowers on alpha-glucosidase enzyme activity in normal and diabetic rats have been evaluated (Gholamhoseinian et al., 2009). The results

obtained in the study we have presented are in accordance with the literature studies given. The results support each other. In another study, 30 different plants from 17 families were diagnosed for diabetes treatment. Roseceae family has an important place among these families and has antidiabetic effect (Taghizadeh et al., 2016). In a different study conducted by Vianna et al., ethanol extract of a different species belonging to the rosaceae family was used in rats with diabetes mellitus using STZ. At the end of the study, it was reported that the species belonging to the rosaceae family has an anti-diabetic effect (Vianna et al., 2011). Anti-hyperglycemic and anti-hyperlipidemic effects were investigated in streptomycin-induced diabetic mice in a study with a different species belonging to Rosaceae famila. It has been revealed that the species belonging to the Rosaceae family will support the traditional use (Kifle and Belayneh., 2020). In a review conducted by Rahimi et al., it was stated that oligosaccharide fractions isolated from Rosa canina may have positive effects on diabetes induced by using STZ in rats (Rahimi et al., 2020).Within the scope of the study, different metabolic enzyme activities with important relative in the antioxidant defense system were evaluated.

CONCLUSION

The conclusions of our study suggest that *Rosa pisiformis* fruits grown as an endemic strain of the Rosaceae family regulated of G6PD, 6PGD, GR, GST and TrxR enzyme activities in diabetic rats. The results of this research will be a guide for the studies investigating the medical use of the *Rosa pisiformis* family and its effect on biological systems and enzymes.

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Conflict of Interest

The authors declare no conflicts of interest regarding the present study.

Author's Contributions

The authors declare that they have contributed equally to the article.

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