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# Effects of Grape Seed and Soybean Extracts on Lipid Peroxidation in Streptozotocin Induced Rats

# Streptozotosin Uygulanan Sıçanlarda Lipit Peroksidasyonu Üzerine Üzüm Çekirdeği ve Soya Ekstraktlarının Etkileri

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**ÖZET**

**Amaç:** Son zamanlarda, yetersiz insülin sekresyonu ve etkileri ile karakterize olan diabetes mellitusta lipid peroksidasyonunun önemi bildirilmektedir. Bu hastalığı tedavi etmek için bitkisel tedaviler ve antioksidan ajanlar uygulanmış çalışmalar yapılmıştır. Bu çalışmanın amacı, streptozotosin ile indüklenen diyabetik sıçanlarda üzüm çekirdeği ve soya fasulyesi ekstraktlarının lipid peroksidasyonu üzerine olası etkilerini belirlemektir. **Gereç ve Yöntem:** Sıçanlar 8 gruba ayrıldı: kontrol, diyabetik kontrol ve 6 ekstrakt grubu [üzüm çekirdeği (100 mg/kg, 200 mg/kg ve 400 mg/kg dozları) ve soya fasulyesi (100 mg/kg, 200 mg/kg ve 400 mg/kg dozları)]. Birinci grup (kontrol grubu) normal bir diyetle beslendi. Diyabetik gruplar (grup 2, 3, 4, 5, 6, 7 ve 8) yüksek yağlı bir diyetle beslendi ve Diabetes Mellitus, tek bir intraperitoneal 35 mg/kg STZ enjeksiyonu ile indüklendi. Daha sonra ekstreler, bir gavaj kullanılarak 28 gün boyunca ilgili tedavi gruplarına belirtilen dozlarda oral yoldan verildi. Tedavi sonunda karaciğer ve pankreas dokuları toplandı ve lipit peroksidasyon parametreleri ile malondialdehit ve glutatyon seviyeleri spektrofotometrik yöntemle ölçüldü. **Bulgular:** Her iki doku için de diyabetik kontrol grubunda malondialdehit seviyeleri yüksek, glutatyon seviyeleri düşüktü. Tedavi gruplarında doza bağlı olarak malondialdehit seviyeleri azaldı ve glutatyon seviyeleri arttı ($p < 0.05$). **Sonuç:** Sonuçlara göre üzüm çekirdeği ve soya ekstraktları diyabette lipid peroksidasyonunun neden olduğu hasarı önleyebilir.

**Anahtar kelimeler:** Deneysel diabetes mellitus, üzüm çekirdeği ekstresi, lipid peroksidasyonu, soya fasulyesi, streptozotosin

**ABSTRACT**

**Objective:** Recently, the importance of lipid peroxidation in diabetes mellitus, which is characterized by insufficient insulin secretion and impacts, has been reported. To treat this disease, studies have applied herbal treatments and antioxidant agents. The aim of this study determine the possible effects of grape seed and soybean extracts on lipid peroxidation in streptozotocin-induced diabetic rats. **Materials and Methods:** The rats were divided into 8 groups: control, diabetic control, and 6 extract groups [grape seed (100 mg/kg, 200 mg/kg, and 400 mg/kg dosages) and soybean (100 mg/kg, 200 mg/kg, and 400 mg/kg dosages)]. The first group (control group) was fed a normal diet. The diabetic groups (groups 2, 3, 4, 5, 6, 7, and 8) were fed a high-fat diet, and Diabetes Mellitus was induced by a single intraperitoneal injection of 35 mg/kg streptozotocin. Afterward, extracts were given orally at the indicated dosages to the corresponding treatment groups for 28 days using a gastric tube. At the end of the treatment, liver and pancreatic tissues were collected, and lipid peroxidation parameters and malondialdehyde and glutathione levels were measured by a spectrophotometric method. **Results:** For both tissues, malondialdehyde levels in the diabetic control group were high, while glutathione levels were low. In the treatment groups, malondialdehyde levels decreased and glutathione levels increased dose-dependently ($p < 0.05$). **Conclusion:** According to our results, grape and soybean seed extracts can prevent damage caused by lipid peroxidation in diabetes.

**Keywords:** Experimental diabetes mellitus, grape seed extract, lipid peroxidation, soybean, streptozotocin

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## INTRODUCTION

Diabetes mellitus, which involves insufficiency or deficiency of the insulin hormone and is characterized by hyperglycemia, causes many metabolic disorders in the body (Eckel et al., 2011). Changes in antioxidant capacity and increased diabetes-mediated oxidative stress play a role in increasing disease symptoms. (Armagan et al., 2006). Malondialdehyde (MDA) directly deteriorates the structure of the cell membrane and, subsequently, the remaining components of the cell by producing reactive aldehydes. As a result of this effect, tissue damage and many diseases occur (Tsikas, 2017). The MDA method, which is highly applied due to its simple experimental procedure, uses one of the end products of lipid peroxidation to determine the level of lipid peroxidation (Al-Rawi, 2011). Antioxidants provide defense against oxidative stress by preventing, stopping, and repairing damage to structures such as DNA, lipids, and proteins due oxidation (Donma, 2012). Antioxidants are particularly effective at high concentrations (Al-Rawi, 2011). Repair enzymes play the primary role in repair and reconstruction. Various defense mechanisms such as glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), and chloramphenicol acetyltransferase enzymes remove free radicals such as superoxide, hydrogen peroxide, and hydroxyl radicals (Harman, 1995; Cadenzas and Packer, 1996; Sies, 1996). GSH is one of the most powerful antioxidants in the body and is soluble in water. It is synthesized from glycerin, cysteine, and glutamate in many tissues, primarily in the liver, and its effect is exerted by reaction with free radicals and peroxides (Forman et al., 2009).

Antioxidant defenses against free radicals produced during normal cell aerobic respiration can be endogenous (enzymatic and non-enzymatic) or dietary (vitamins, carotenoids, flavonoids, etc.) (Harman, 1995). Plants contain a wide variety of antioxidants, including flavonoids. Flavonoids have many physiological properties including antioxidant, antibacterial, antiviral, anti-inflammatory, antimutagenic and antitumoral activities (Chis et al., 2009). Grape seeds are a rich source of many biologically active compounds such as resveratrol, anthocyanins, proanthocyanidins, and polyphenolic flavonoids (Nassiri-Asl and Hosseinzadeh, 2009). These flavonoids have chemoprotective properties for oxidative stress (Mansouri et al., 2011). Soybeans contain high amounts of protein (38%–40%) and a variety of phenolic compounds, including saponins, tannins, phenolic acids, and phytoestrogens, which have significant antioxidant effects (Girard and Mazza, 1998; Liu, 2004).

In this research, impacts by grape seed and soybean extracts over lipid peroxidation parameters (MDA and GSH) in pancreatic and liver tissues in diabetic rats were investigated.

## MATERIALS AND METHODS

### Extraction

Grapes were separated from the cluster and their seeds were extracted. Both soybeans and grape seeds were washed and dried at room temperature. The seeds were powdered form and extracted using methanol by method suggested the Downey et al. (2007). The crude extracts obtained was weighed to calculate the extraction efficiency afterwhich it was then lyophilized. The lyophilized extract was later dissolved in distilled water at concentrations of 100 mg/kg, 200 mg/kg, and 400 mg/kg.

**Animals, Experimental Groups, and Diabetes Induction**

Liver and pancreatic tissues from 8–12-week-old female Wistar-Albino rats constituted the study materials. The experimental groups included a total of 40 female rats in the control, diabetic control, and treatment groups [grape seed (100, 200 and 400 mg / kg dosages) and soybean (100, 200 and 400 mg / kg dosages)]. In total, 8 groups were designated.

The diabetic control, and treatment groups were fed a high-fat diet from Bas et al. (2012), and diabetes was induced by a single intraperitoneal injection of STZ (35 mg / kg). Blood samples were taken from the tail veins of all non-fasting rats after STZ injection, and rats with blood glucose levels > 300 mg / dL were considered diabetic.

**Ethics Committee and Ethical Principles**

This study was approved by the KTO Karatay University Drug and Non-Medical Device Research Ethics Committee (2020/015).

**Extract Application**

Grape seed and soybean extracts were administered at the specified dosages by gavage once per day for 28 days to the animals considered diabetic in the extract groups. Finally, all rats have been euthanasia with cervical dislocation. MDA and GSH analyses were performed using liver and pancreatic tissues.

**Evaluation of Oxidative Stress**

**MDA Analysis**

Analysis of MDA levels in the tissues was performed using the Ohkawa et al. method (1979). The absorbance was determined using the Multiskan Sky Microplate Spectrophotometer (Thermo Fisher Scientific), and the results were expressed in nmol / g protein.

**GSH Analysis**

The values inside the tissues have been evaluated with Ellmann's technique (1959). The absorbance was measured by the Multiskan Sky Microplate Spectrophotometer (Thermo Fisher Scientific), and the results were expressed in nmol/g protein.

**Protein Determination:** The Biuret method (Tiftik, 1997) was used to measure protein. The absorbance was evaluated using the Multiskan Sky Microplate Spectrophotometer (Thermo Fisher Scientific).

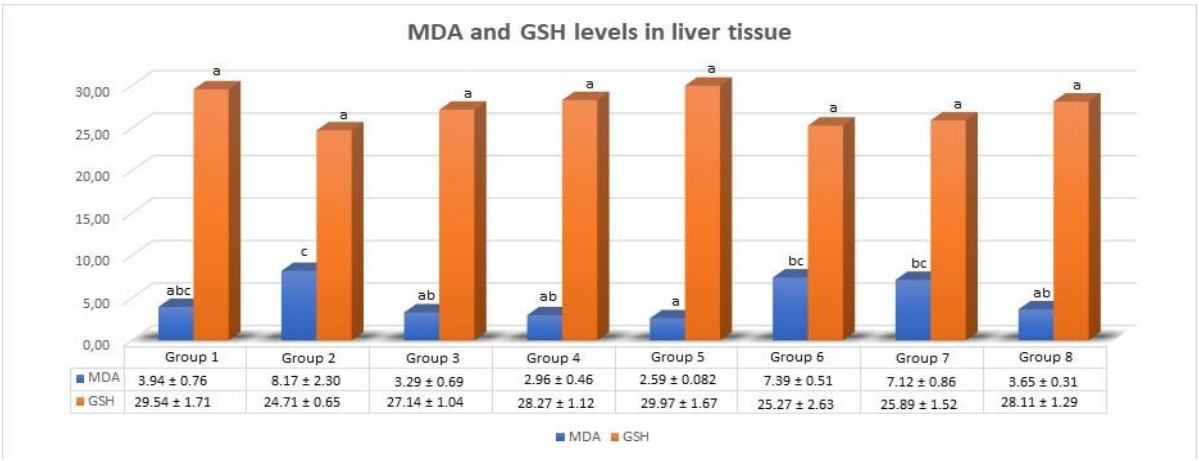
**Statistical Analysis**

The datum has been evaluated by the Statistical Package for the Social Sciences program. Average and ordinary deflection value on numeric data's have been evaluated. One-way analysis of variance (ANOVA) was used to determine the differences between groups, and Duncan's multiple comparison test was used to determine from which group the differences originated. Differences at $p < 0.05$ were thought meaningful. The Shapiro Wilk statical analyze have been by define datum's normality.

## RESULTS

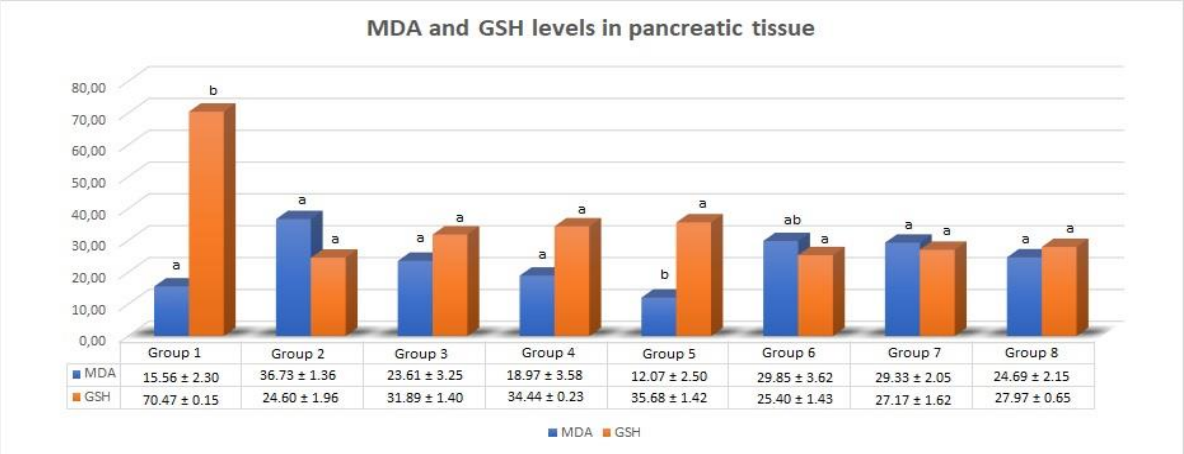
MDA and GSH levels of liver tissue that results, and comparisons were provided in Figure 1. Liver tissue MDA levels were highest in the diabetic control group (Group 2). It was determined that liver tissue MDA levels were recovered after grape seed application. Especially in the groups that received Group 4 and Group 5 doses at Figure 1, it was found to be at a higher level than the control group (Group 1). There was a decrease in MDA levels in the soybean group. At the soybean extract dosage of 400 mg / kg (Group 8), the MDA level was close to that of the control group (Group 1) ($p < 0.05$). GSH levels were lower in the diabetic control group (Group 2) compared to the control group (Group 1). Grape seed extract application increased GSH levels, and the GSH level of Group 5 have been upward of compare the control group (Group 1). GSH levels increased in the soybean groups, with the GSH level of the 400 mg / kg (Group 8) dosage group being the highest ($p < 0.05$).

The results and comparisons of pancreatic tissue MDA and GSH levels were given in Figure 2. The MDA level of the diabetic control group (Group 2) was higher than that of the control group (Group 1). It was determined that grape seed extract application lowers MDA levels. Particularly, the group (Group 5) administered 400 mg / kg dosage had a lower MDA level than that of the control group (Group 1). MDA levels also decreased in the soybean extract groups (Groups 6, 7, and 8) but were still higher than that of the control. Levels of GSH within all extract animals were significantly lower than that of the diabetic control group. It was determined that both grape seed and soybean extracts decreased GSH levels, but the levels remained upward of compare the Group 2 ($p < 0.05$).




| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 | Group 7 | Group 8 |
|---|---|---|---|---|---|---|---|---|
| MDA | 3.94 ± 0.76 | 8.17 ± 2.30 | 3.29 ± 0.69 | 2.96 ± 0.46 | 2.59 ± 0.082 | 7.39 ± 0.51 | 7.12 ± 0.86 | 3.65 ± 0.31 |
| GSH | 29.54 ± 1.71 | 24.71 ± 0.65 | 27.14 ± 1.04 | 28.27 ± 1.12 | 29.97 ± 1.67 | 25.27 ± 2.63 | 25.89 ± 1.52 | 28.11 ± 1.29 |

**Figure 1. MDA and GSH levels in liver tissue of the study groups [MDA; nmol/g protein (Mean ± SE), GSH; mg/g protein (Mean ± SE)]**




| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 | Group 7 | Group 8 |
|---|---|---|---|---|---|---|---|---|
| MDA | 15.56 ± 2.30 | 36.73 ± 1.36 | 23.61 ± 3.25 | 18.97 ± 3.58 | 12.07 ± 2.50 | 29.85 ± 3.62 | 29.33 ± 2.05 | 24.69 ± 2.15 |
| GSH | 70.47 ± 0.15 | 24.60 ± 1.96 | 31.89 ± 1.40 | 34.44 ± 0.23 | 35.68 ± 1.42 | 25.40 ± 1.43 | 27.17 ± 1.62 | 27.97 ± 0.65 |

**Figure 2. MDA and GSH levels in pancreatic tissue of the study groups [MDA; nmol/g protein (Mean ± SE), GSH; mg/g protein (Mean ± SE)]**

## DISCUSSION

Oxidative damage occurs due to disruption of the balance between free radicals and antioxidants in favor of free radicals, which occurs during physiological or pathological processes in organisms. Organisms protect themselves from this situation by enzymatic and nonenzymatic means (Savas et al., 2016). Various studies show that while free radical formation increases with increasing oxidative stress in diabetes, antioxidant production decreases (Gray and Jandeleit-Dahm, 2014; Hamamcioglu, 2017). STZ is a toxin capable of inducing selecting extermination β-cells in pancreas islets, ending among insulin lack and increased glycemia. (Zhang et al., 2003). Continuation of the hyperglycemic state leads to increasing production of reactive oxygen species (ROS), which causes protein glycosylation through autoxidation of glucose (Ugarte et al., 2012). In STZ-induced diabetic rats, glutathione homeostasis impairment and significant decreases in antioxidant defense elements have been reported (Yegin and Mert, 2013; Ergenc et al., 2017; Ozok and Gunes, 2019; Doganay et al., 2020).

In this study, which was compatible with previous studies, MDA levels in pancreatic and liver tissues increased in STZ-induced diabetic rats. GSH is an intracellular antioxidant produced by glutathione reductase that reduces free radical effects (Jayachandran et al., 2018). A decrease in the GSH level due to diabetic oxidative stress is considered an important indicator in the antioxidant defense system. In addition, endogenous GSH acts as a co-substrate of GPx in addition to its scavenging action against free radicals (Ozok and Gunes, 2019). Herbal treatments for hyperglycemia and liver toxicity have been used as effective and safe alternatives to traditional medicine. Interest in herbal treatments has increased due to their activity, minimal side effects, and relatively low cost. Herbal medicines and their extracts are widely recommended for use, even when the biological effects of their compositions are not well known (Gupta et al., 2005). Phenolic compounds are commonly found in plants (Naczk and Shahidi, 2004). Recent studies state that procyanidins, which are phenolic compounds, provide high antioxidant effects (Miller et al., 2006). Proanthocyanidin is a very powerful health-protective substance found in grape seed extract (Şendoğdu et al., 2006; Ganjali et al., 2012). Researchers examined the effect of ethanolic *Vitis vinifera* L. leaf extract by measuring GSH and MDA levels in liver, kidney, and heart tissues. They stated that the ethanolic *Vitis vinifera*

leaf extract showed antidiabetic and antioxidant impacts 250 mg / kg dose. Another group of researchers orally administered grape seed extract to diabetic rats 100 mg / kg / day dose, found that the antioxidant impacts on plasma and liver tissues through animals inside the treatment animals improved compared to the diabetic controls (Chis et al., 2009). In this study, in accordance with previous studies, all dosages of grape seed extract particularly, the 400 mg / kg dosage showed antioxidant activity in both liver and pancreatic tissues. Isoflavones are colorless, crystalline phenolic ketones isolated from plants and are among the most widely available flavonoids among phenolic substances (Nilüfer and Boyacıoğlu, 2008).
Soybeans are also a rich source of isoflavones and exhibit antioxidant properties (Mourad et al., 2017). No previous studies have investigated the effects of applying soybean extract on lipid peroxidation in rats with experimentally induced diabetes. However, Lee (2006) investigated the impacts on soybean protein, which is basic isoflavones, over hepatic SOD, catalase, and GPx antioxidant activities inside diabetic rats, found which activities were significantly reduced compared to control rats. In the present study, all doses of soybean extract showed antioxidant activity in both liver and pancreatic tissues. At the 400 mg/kg dosage, the MDA level decreased more than at the other dosages, but the GSH level was almost the same as that at the 200 mg / kg dosage.

## CONCLUSION

In conclusion, antioxidant activities of different dosages of grape seed and soybean extracts were investigated in this study, and the extracts had positive effects on MDA and GSH in liver and pancreatic tissue samples. This effect is thought to be due to the presence of phenolic compounds in the plants. The data obtained show that the identification and quantification of phenolic substances are necessary further analyze impacts through on antioxidant activity.

These data form an important basis for future studies. It is also thought that these plants may provide important clues for their use in the healthcare field.

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**Author contributions**

Contribute to the emergence and maintenance of the article: EA, HA
Plan, design: EA, HA, EGM
Financing: EA, EGM
Materiel: EGM, SV
Data collection / processing of collected data to prepare for analysis: EGM, SV
Data analysis: EGM
Literature review: SV, KZÇS
Writing and corrections: EGM, SV, KZÇS
Checking and reviewing: EA

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