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# Effects of Ferula Rigidula plant extract on hyperglycemia, hyperlipidemia and pancreatic tissue oxidative stress in rats with experimental diabetes

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**Abstract**

Ferula rigidula (FR) is one of the herbs used in traditional treatments. The aim of this study is to investigate the effects of this plant, which is used in traditional treatment, on insulin secretion, blood glucose level, lipid profile and some oxidative stress parameters in diabetes.In addition, studies on the total phenolic and flavonoid content of the plant extract, the determination of antioxidant activity by DPPH and CUPRAC method, and the lethal dose of FR were also performed. For the diabetes study, 49 male Wistar albino rats were used. Rats were divided into seven groups as control, diabetes, diabetes+ FR (250mg/kg), diabetes+ FR (500 mg/kg), diabetes+glibenclamide (5 mg/kg), FR (250 mg/kg), FR (500 mg/kg) group. According to the diabetes group, fasting blood glucose levels in the diabetes+FR 500 mg/kg group decreased. Cholesterol and HDL levels decreased in the diabetes+FR 250-500 mg/kg and diabetes+glibenclamide groups. MDA level decreased in diabetes+FR 250-500 mg/kg and diabetes+glibenclamide groups but it was determined that GSH level and CAT, GSH-Px, SOD enzyme activities increased. The positive effects of FR on some parameters that change in diabetes and examined in this study are explained.

**Keywords:** Antioxidant activity; Diabetes mellitus; Ferula rigidula; Oxidative stress; Rat

## 1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease caused by irregularities in carbohydrate, protein and fat metabolism. It is a disorder in the secretion, effect or combination of the insulin hormone (Bulduk et al., 2022; Meydan et al., 2022). The amount of free radicals increases as a result of hyperglycemia, nonenzymatic protein glucosylation and autooxidation of glucose during diabetes. Some molecules that act as antioxidants under normal conditions help prevent possible damage by acting on free radicals. It is known that phenolic and flavonoid compounds, which are mostly found in plants, have antioxidant effects (Gao et al., 2022; Bazencir and Meydan, 2022).Under normal conditions, there are enzymatic catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), glutathione reductase (GSHR) etc.) and nonenzymatic (glutathione etc.) antioxidant defense systems that act as protective and reparative in the organism. This system fights against free radicals and the oxidative destruction caused by these radicals.Oxidative stress is the deterioration of the balance between antioxidants and oxidants in favor of oxidants. Oxidative stress plays an important role in the etiology and progression of diabetes(Özdek et al., 2020; Doğan et al., 2022).

In our country, the plants from the Apiacea (Umbelliferae) family, which have antioxidant and antihyperglycemic properties, have used widely against the diabetes (Özdek et al., 2020). Ferula L. is the third largest genus of the Apiaceae family and has 180-185 species. The FR species, which grows in the mountains of eastern and central Anatolia, is popularly known as siyabo (Arıtuluk et al., 2016).Like

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other members of the Apiacea family, FR has been reported to be used in traditional treatments (Arıtuluk et al., 2016; Köse and Ocak, 2018). Bulut et al. (2014), in their interviews with the local people, reported that the above-ground part of the FR plant was used in the traditional treatment of diabetes and high cholesterol, and positive effects were obtained. However, no research has been found on the toxicity and antidiabetic effect of this plant.

Streptozotocin (STZ) is used to create a diabetes model in animal experiments. STZ causes the formation of reactive carbonium ions in pancreatic beta cells. These reactive carbonium ions, the poly (ADP-ribose) polymerase involved in DNA alkylation and subsequent DNA repair, consume nicotinamide adenine dinucleotide (NAD) in the cell, thereby blocking the ATP source. Necrosis occurs in beta cells, via the consumption of the energy source. In addition, the oxidant effect of STZ and the formation of nitric oxide (NO) are effective in DNA damage caused by STZ (Rais et al., 2021).

Therefore, in the presented study, it was aimed to determine the antioxidant activity, total phenolic and flavonoid quantitation, lethal dose (LD50) of FR ethanol extract and to investigate the effects on blood insulin and glucose levels, lipid profile and oxidative stress parameters in diabetes. The effects of FR extract, which is used in the traditional treatment of established experimental diabetes, on serum fasting blood glucose (FBG), insulin, cholesterol, triglyceride, HDL, LDL levels were investigated.

## 2. MATERIALS and METHODS

### 2.1. Animal material

Five adult female Albino mice (20-30 g) were used in acute toxicity study and 49 male Wistar albino rats (200-250 g) were used in the experimental diabetes study. These animals were obtained from Van Yüzüncü Yıl University Experimental Animals Unit. The experimental animals were housed in cages where they were fed *ad libitum* without restriction in terms of feed and water, in rooms with 12 hours of darkness/lighting during the experiment and the temperature set to 22 ± 2°C. This study was carried out by obtaining the research application approval document dated 25.06.2020 and decision number 2020/06-14 of the Animal Experiments Local Ethics Committee of Van Yüzüncü Yıl University.

### 2.2. Supplying of *Ferula rigidula* plant

The FR plant used in this study was collected from its natural environment on the rocks of Çavuştepe Castle in Gürpınar district of Van province in May-June. Herbarium registration number: VANF-164116.

### 2.3. Preparation of plant extract for analysis

The collected FR plant was dried in an environment without sunlight, with direct light air flow. The dried plant was pulverized with the help of a grinder. 100 grams of this powder was taken and kept in 1000 mL of 96% ethyl alcohol for 24 hours and then filtered. In the second step, the remaining filtrate was kept in 70% ethanol for 24 hours and filtered again. Then, both filtrates were combined and dried in the evaporator at 50 °C at 70 rpm. The remainder was kept at 40 °C until completely dry (Özdek et al., 2020).

### 2.4. In vitro analyzes of *Ferula rigidula* extract:

The Folin-Ciocalteus method (Singleton et al., 1999) was used to determine the total phenolic content of the FR extract. The aluminum nitrate method (Moreno et al., 2000) was used as the total amount of flavonoids equivalent to quercetin, and the CUPRAC method (Singleton et al., 1999) was used to determine the antioxidant capacity. The method based on reduction of neocuproin (Nc) complex

to colored Cu(I)-Nc chelate (Apak et al., 2004) and free radical scavenging activity were determined using DPPH free radical (Blois, 1958).

### 2.5. Acute toxicity study and dose determination

This test was carried out according to the Organization for Economic Corporation and Development (OECD) guideline 425 (Olela et al., 2020). For this, 5 female Albino mice, 8-12 weeks old, healthy, naive and non-pregnant at a dose of 2000 mg/kg body weight(BW) as specified in the test guideline were used. When performing the Limit Test according to the OECD 425 Test Guideline, mice deprived of feed and water 4 hours prior to dosing were weighed. After the dose of FR extract, calculated according to its weight, was dissolved in distilled water and administered by gavage, it was placed in a separate cage and followed for one day in terms of acute toxic symptoms (locomotor activity, strange behavior, abnormal sounding, sensitivity to pain, sensitivity to sound, tremor, etc.) No adverse symptoms were observed. Since death did not occur, the other 4 mice, which were deprived of 2000 mg/kg(BW) of feed and water beforehand, were administered the weight-calculated dose of FR extract by gavage. For 14 days, animals were monitored for delayed toxic effects, as no deaths occurred during this period, with an LD50 considered greater than 2000 mg/kg(BW). According to the results of this study, the dose of FR extract to be used was determined as 250 and 500 mg/kg(BW), taking into account the studies conducted with other plants from the Apiacea family (Yusufoglu et al., 2015; Özdek et al., 2020).

### 2.6. Establishment of working groups

In the study, 49 male Wistar albino rats were grouped as 7 in each after weighing. Groups, Group 1: Normal control, Group 2: Diabetes control, Group 3: Diabetes + FR (250 mg/kg), Group 4: Diabetes + FR (500 mg/kg), Group 5: Diabetes + glibenclamide (5 mg/kg), Group 6: FR control (250 mg/kg), Group 7: FR control (500 mg/kg). In order to induce diabetes, streptozotocin (STZ) dissolved in cold sodium citrate buffer (pH: 4.5) was administered intraperitoneally (*i.p.*) as a single dose of 45 mg/kg to rats that were fasted the night before. FBG levels were measured with the Accu-Check Active blood glucose monitor in blood samples taken from the tail vein of the rats 72 hours after the application. Those with blood sugar levels above 200 mg/dl were accepted as diabetes and included in the study (Kumar, Jain, Rathore, & Ahmed, 2016). FR extract was dissolved in distilled water and given as 250 mg/kg to groups 3 and 6, and 500 mg/kg to groups 4 and 7, as a single daily dose for 28 days, simultaneously via gastric gavage. Glibenclamide was dissolved in distilled water and given to Group 5 as 5 mg/kg, as a single daily dose for 28 days, simultaneously via gastric gavage (Andrade-Cetto, 2011).

### 2.7. Taking blood and pancreatic tissue samples

At the end of the 28-day trial, rats that were fasted for 12 hours were administered ketamine anesthesia (75 mg/kg ketamine + 10 mg/kg xylazine, ip) and intracardiac blood samples were taken into vacuum tubes with and without anticoagulant. After the blood samples were taken, the pancreas of the rats sacrificed by the bloodless method were removed and divided. One part was fixed with 10% formalin for histopathological evaluation. The other fragment was stored at -80 °C until analysis.

### 2.8. Analysis of blood

The blood taken into vacuum tubes without anticoagulant was centrifuged at 3000 rpm for 5 minutes. In the obtained serum samples, glucose, triglyceride, cholesterol and HDL measurements were made in an auto analyzer (ArchitecCi 1600) using a commercial kit. LDL amount was calculated according to the Fried ward formula (Giribabu et al., 2014).

LDL cholesterol = Cholesterol – (HDL cholesterol + TG/5).

Insulin level was measured in ELISA (Biotek ELx800) based on the double antibody sandwich method using commercial kit (BT-Lab, Cat. No E0707Ra.).

### 2.9. Preparation of tissue homogenate

The removed pancreatic tissue was weighed and 10 times the weight of phosphate buffer (pH: 7.2 – 7.4) was added to it and homogenized for 3 minutes at 16000 rpm with the help of a homogenizer. Homogenization was carried out in an ice bucket. The homogenates were centrifuged at 2000 – 3000 rpm, +4 ℃ for 20 minutes (Özdek et al., 2018). The obtained supernatants were used for biochemical analysis.

### 2.10. Analyzes in tissue homogenizer

Tissue molondialdehyde (MDA) level(Placer, Cushman, & Johnson, 1966), catalase enzyme (CAT) activity (Aebi, 1984), glutathione (GSH) and protein levels(Lowry, Rosebrough, Farr, & Randall, 1951) were determined using by spectrophotometric method. Glutathian peroxidase (GSH-Px, BT-Lab, Cat. No. E1759Ra) and superoxide dismutase (SOD, BT-Lab, Cat. No. E0168Ra) enzyme activities were determined by using an ELISA reader (Biotek ELx800) in accordance with the commercial ELISA kit insert used.

### 2.11. Histopathological analysis of pancreatic tissue

Pancreatic tissues taken for histopathological evaluation were fixed in 10% buffered formalin solution for 48-72 hours and then washed in running tap water for 12 hours. In routine tissue follow-up, after passing through alcohol (70°, 80°, 90°, 96° and 100°) and xylol series, they were blocked in paraffin, and 4 mμ thick sections were taken from each block and slides were prepared. Preparations prepared for histopathological examination were stained with Hematoxylin Eosin (HE) and examined with light microscopy. The required fields are illustrated (Altındağ et al., 2021).

### 2.12. Statistical Analysis

In the study, Duncan's test was used to compare group means in terms of characteristics (variables), one-way analysis of variance (ANOVA) and analysis of variance in the 'SPSS statistics 23' program to determine statistical significance between groups. The statistical significance level was taken as 0.05 in the calculations.

## 3. RESULTS and DISCUSSION

The total phenolic content of FR extract was determined as 22.37±0.60 μg GA/mg extract and the total flavonoid content was determined as 16.87±2.06 μg CE/mg extract (**Table 1**). According to the CUPRAC method, the antioxidant activity of FR extract increased depending on the concentration, it was higher than the standard α-TOC, but lower than BHT (excluding 10 μg/mL) and BHA (**Table 2**). It was observed that the DPPH free radical scavenging activity of FR extract increased depending on the concentration, it was higher than the standard α-TOC and BHT, and it was close to BHA (**Table 3**).

***Table 1:*** *Total phenolic and flavonoid content of Ferula rigidula extract*

| | **Total phenolic content (μg GA/mg extract)†** | **Total flovonoid content (μg QE/mg extract)‡** |
|---|---|---|
| ***Ferula rigidula*** | 22.37±0.60 | 16.87±2.06 |

Values were determined as mean±standard deviation after three parallel measurements. † GA, gallic acid equivalent, ‡ QE, quercetin equivalent

***Table 2:*** *Antioxidant activity results of Ferula rigidula extract, BHT, BHA and α-TOC by CUPRAC method*

| | ***Ferula rigidula*** | **BHT** | **BHA** | **α-TOC** |
|---|---|---|---|---|
| **10 µg/mL** | 0.17±0.02 | 0.17±0.01 | 0.24±0.02 | 0.16±0.03 |
| **25 µg/mL** | 0.31±0.01 | 0.33±0.01 | 0.48±0.06 | 0.18±0.01 |
| **50 µg/mL** | 0.55±0.04 | 0.62±0.01 | 0.89±0.01 | 0.24±0.05 |
| **100 µg/mL** | 1.03±0.04 | 1.24±0.05 | 1.63±0.03 | 0.31±0.01 |

Values were determined as mean±standard deviation after three parallel measurements.

***Table 3:*** *DPPH free radical scavenging activity % inhibition results of Ferula rigidula extract, BHT, BHA and α-TOC*

| | ***Ferula rigidula*** | **BHT** | **BHA** | **α-TOC** |
|---|---|---|---|---|
| **50 µg/mL** | 90.23±2.94 | 88.09±3.01 | 92.80±2.44 | 80.55±4.11 |
| **100 µg/mL** | 90.83±1.83 | 89.53±2.77 | 92.82±2.56 | 83.60±2.72 |
| **250 µg/mL** | 92.21±1.32 | 91.63±4.96 | 92.90±2.87 | 86.53±0.45 |
| **500 µg/mL** | 92.64±3.02 | 92.05±1.92 | 94.26±1.88 | 88.94±2.90 |

Values were determined as mean±standard deviation after three parallel measurements.

On the 1st and 28th days of the study, the mean rat weights and the percent change in the mean weight in the same group were calculated. In the control group, a 6.4% increase in group mean weight was noted at the end of the study. A decrease of 24.4% was found in the mean weight of rats in the diabetes group. It was determined that there was a decrease of 21.4%, 24.1% and 22.0%, respectively, at the end of the study in the groups to which FR extract (250, 500 mg/kg) and glibenclamide (5 mg/kg) were administered with diabetes. It was found that there was an increase of 6.5% and 6.9%, respectively, in Groups 6 and 7 to which FR extract was applied (**Table 4**).

***Table 4:*** *Live weight levels of the groups*

| **Groups (n =7)** | **Grup 1** | **Grup 2** | **Grup 3** | **Grup 4** | **Grup 5** | **Grup 6** | **Grup 7** |
|---|---|---|---|---|---|---|---|
| **A** | 235 | 242 | 238 | 245 | 236 | 248 | 245 |
| **B** | 250 | 183 | 187 | 186 | 184 | 264 | 262 |
| **%** | +6.4 | -24.4 | -21.4 | -24.1 | -22.0 | +6.4 | +6.9 |

A: Live weight averages (g) on the 1st day of the study, B; Average live weight (g) on the 28th day of the study, %; The rate of change in weight in the same group after the study (%). Group 1: Normal control, Group 2: Diabetes control, Group 3: Diabetes+FR (250 mg/kg), Group 4: Diabetes+ FR (500 mg/kg), Group 5: Diabetes+glibenclamide (5 mg/kg) kg), Group 6: FR control (250 mg/kg), Group 7: FR control (500 mg/kg).

When serum FBG levels were compared, it was determined that there was an increase in the groups 2, 3, 4 and 5 compared to the group 1. This increase was statistically significant. 1 ($P<0.05$). FBG level decreased in group 4 compared to group 2 ($P<0.05$). The decrease in groups 3 and 5 was not statistically significant when compared to group 2 ($P>0.05$). When it was compared in terms of serum insulin levels. It was determined that there was a statistically significant decrease in the groups 2, 3, 4 and 5 compared to the group 1 ($P<0.05$). It was determined that insulin levels in groups 4 and 5 increased compared to group 2 ($P<0.05$).

Cholesterol and HDL levels, it was determined that there was a significant increase in the diabetes group comparing to healthy rats ($P<0.05$). In Groups 3 and 4 treated with FR extract, increased cholesterol and HDL levels due to diabetes were found to be decreased, which was close to the control group. When it was compared in terms of triglyceride level, a statistically significant increase was found in the group 2 comparing to the group 1 ($P<0.05$). When the TG values in the groups 3, 4 and 5 were compared with both the group 1 and the group 2, it was determined that there was no statistical difference between them ($P>0.05$). LDL levels in groups 2 and 5 were statistically higher than Group 1 ($P<0.05$). It was determined that the LDL levels of the diabetic groups treated with FR extract were significantly lower than the diabetes group ($P<0.05$). When the control group and healthy groups (Group 6-7) given FR extract were compared in terms of the parameters which were examined, it was found that the differences were not statistically significant ($P>0.05$) (**Table 5**).

***Table 5:*** *Comparison of serum glucose, insulin and lipid profile parameters levels between study groups.*

| | FBG (mg/dl) | INS (mLU/L) | KOL (mg/dl) | TG (mg/dl) | HDL (mg/dl) | LDL (mg/dl) |
|---|---|---|---|---|---|---|
| **Grup 1** | 110.67±5.24$^{a}$ | 4.81±0.19$^{a}$ | 35.64±2.39$^{b}$ | 37.8±4.42$^{b}$ | 19.68±1.34$^{b}$ | 6.82±2.21$^{c,d}$ |
| **Grup 2** | 416.71±26.80$^{c}$ | 2.10±0.05$^{c}$ | 53.94±1.23$^{a}$ | 51.98±4.16$^{a}$ | 27.38±1.20$^{a}$ | 17.98±1.91$^{a}$ |
| **Grup 3** | 406.29±27.83$^{b,c}$ | 2.88±0.14$^{b,c}$ | 37.18±3.52$^{b}$ | 41.72±4.36$^{a,b}$ | 18.80±1.35$^{b}$ | 10.01±1.83$^{b,c,d}$ |
| **Grup 4** | 347.14±29.02$^{b}$ | 3.50±0.15$^{b}$ | 38.40±2.78$^{b}$ | 42.16±4.04$^{a,b}$ | 17.78±2.40$^{b}$ | 12.19±1.36$^{b,c}$ |
| **Grup 5** | 382.40±16.78$^{b,c}$ | 3.23±0.11$^{b}$ | 37.16±1.66$^{b}$ | 41.90±2.73$^{a,b}$ | 14.64±1.68$^{b}$ | 14.14±1.81$^{a,b}$ |
| **Grup 6** | 91.67±2.80$^{a}$ | 4.51±0.29$^{a}$ | 30.36±2.31$^{b}$ | 36.50±2.30$^{b}$ | 17.62±1.57$^{b}$ | 5.44±1.74$^{d}$ |
| **Grup 7** | 107.86±5.09$^{a}$ | 4.53±0.66$^{a}$ | 32.64±2.72$^{b}$ | 37.24±4.69$^{b}$ | 19.66±0.72$^{b}$ | 5.53±2.16$^{d}$ |

a,b,c: Different letters in each column represent the statistical difference between groups ($P<0.05$). FBG: Fasting blood glucose, INS: Insulin, COL: Cholesterol, TG: Triglyceride. Group 1: Normal control, Group 2: Diabetes control, Group 3: Diabetes+ FR (250 mg/kg), Group 4: Diabetes+ FR (500 mg/kg), Group 5: Diabetes+glibenclamide (5 mg/kg) kg), Group 6: FR control (250 mg/kg), Group 7: FR control (500 mg/kg).

### 3.1. Pancreatic tissue analysis results of experimental groups

There was a statistically significant increase in pancreatic tissue MDA level in all the diabetes groups compared to the control group ($P<0.05$). Compared to Group 2, the decrease in MDA levels in the diabetic groups (Group 3-4) given FR extract and glibenclamide group (Group 5) was found to be statistically significant. ($P<0.05$). When pancreatic tissue CAT, GSH-Px, SOD enzyme activities and

GSH levels were compared, it was determined that there was a significant decrease in all diabetes groups compared to the control group (P<0.05). It was found that the increase in the treated diabetic groups (groups 3, 4 and 5) was statistically significant (P<0.05), but the increase in Group 4 in terms of GSH-Px was not significant (P>0.05). When the control group and FR extract control groups were compared in terms of the parameters examined; It was found that the difference between group 1 and group 6 and 7 in pancreatic tissue was not statistically significant (P>0.05) (**Table 6**).

***Table 6:*** *Pancreatic tissue oxidative stress parameters analysis results of the experimental groups*

| | **MDA (nmol/g protein)** | **CAT (U/mg protein)** | **GSH-Px (U/mg protein)** | **SOD (ng/g protein)** | **GSH (µmol/g protein)** |
|---|---|---|---|---|---|
| **Grup 1** | 0.86±0.04d | 3.21±0.20a | 536.95±41.02a | 10.24±0.78a | 22.99±0.16a |
| **Grup 2** | 3.11±0.12a | 1.07±0.05c | 140.91±12.91c | 2.67±0.26c | 17.2±0.18c |
| **Grup 3** | 2.16±0.04b | 1.87±0.09b | 327.21±8.26b | 6.26±0.16b | 20.33±0.48b |
| **Grup 4** | 1.69±0.06c | 1.69±0.11b | 154.20±6.75c | 2.95±0.13b | 19.69±0.16b |
| **Grup 5** | 2.06±0.08b | 1.48±0.12b | 251.07±3.95b | 4.80±0.08b | 19.22±0.14b |
| **Grup 6** | 0.99±0.02d | 3.37±0.16a | 555.91±37.28a | 9.50±1.11a | 23.37±0.73a |
| **Grup 7** | 1.02±0.08d | 3.24±0.19a | 560.99±52.56a | 10.36±0.63a | 23.74±0.59a |

a,b,c: Different letters in each column represent the statistical difference between groups (P<0.05). MDA: Malondialdehyde, CAT: Catalase, GSH-Px: Glutathione peroxidase, SOD: Superoxide dismutase, GSH: Glutathione. Group 1: Normal control, Group 2: Diabetes control, Group 3: Diabetes+FR (250 mg/kg), Group 4: Diabetes+FR (500 mg/kg), Group 5: Diabetes+glibenclamide (5mg/kg) ), Group 6: FR control (250 mg/kg), Group 7: FR control (500 mg/kg).

### 3.2. Histopathological evaluations

It was observed that the pancreatic tissue of the rats in the groups formed from healthy rats (groups 1, 6 and 7) had normal histological architecture. It was observed that islet cells were polygonal in healthy groups. In these groups, blood vessels and pancreatic ducts were normal. It was determined that the pancreatic tissue and pancreatic islet of Langerhans in the rats in Group 2 and 3 had shrinkage and intensely necrotic cells. Moderately necrotic cells were detected in the pancreatic tissue and pancreatic islet of Langerhans in the rats in Groups 4 and 5 (**Figure 1**).

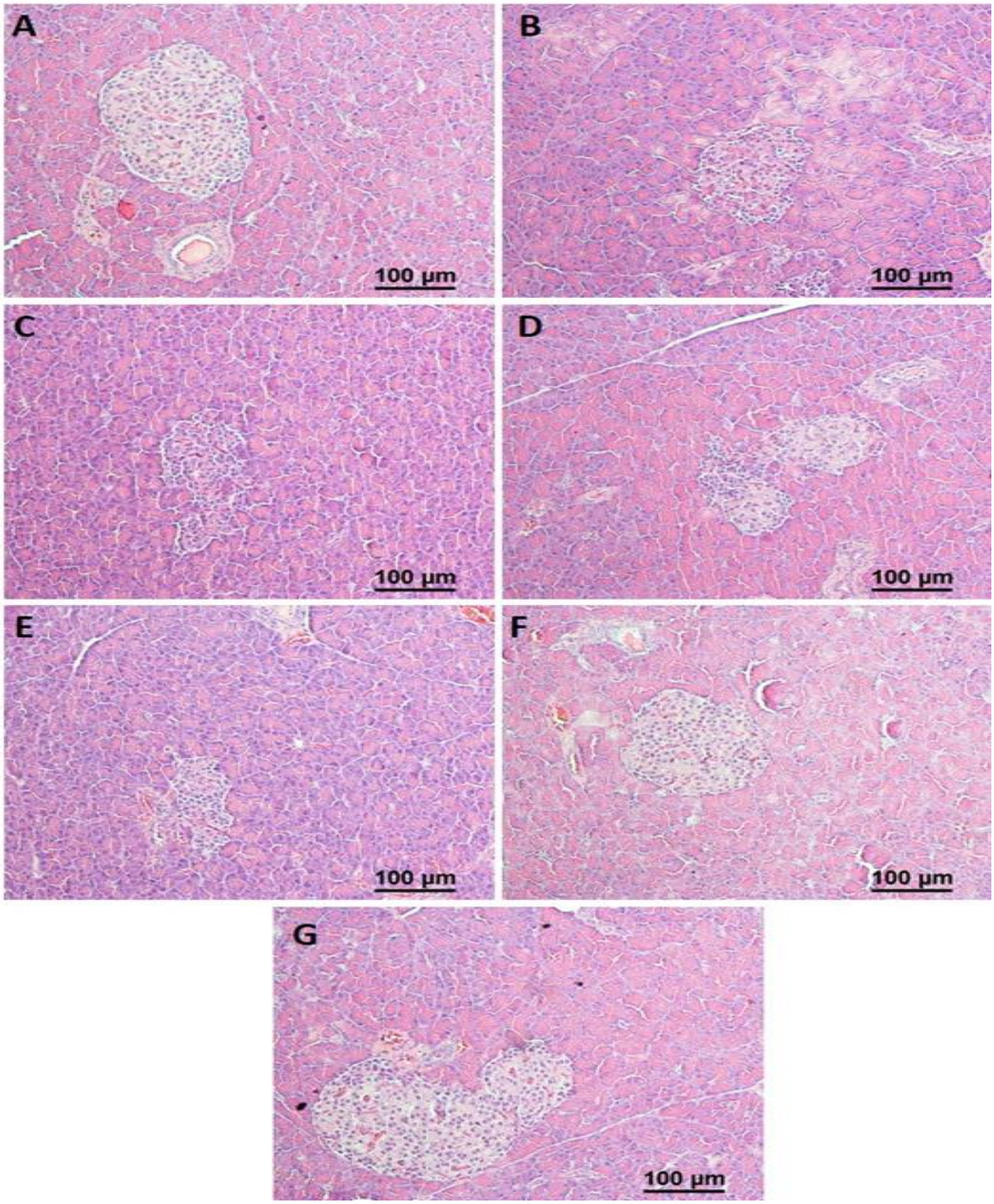


***Figure 1***. *Histological appearance of pancreatic tissue belonging to the experimental groups. Group 1 (A): Normal control, Group 2 (B): Diabetes control, Group 3 (C): Diabetes+FR (250 mg/kg), Group 4 (D): Diabetes+FR (500 mg/kg), Group 5 (E): Diabetes+glibenclamide (5mg/kg), Group 6 (F): FR control (250 mg/kg), Group 7 (G): FR control (500 mg/kg).*

From ancient times to the present, it is known that many plants are used in traditional treatment methods and alternative medicine in our country and in the world. There are many scientific studies conducted with different plants in the *Apiaceae* family (Abu-Zaiton, 2010). Different plants belonging to the *Apiaceae* family are traditionally used to relieve different complaints such as carminative, spasmodic gastrointestinal complaints, bloating, stomach complaints, indigestion, anorexia, diabetes, and blood pressure regulator (Arıtuluk et al., 2016; Özdek et al., 2020). In pharmacological and biological studies with these plants, antimicrobial (Şenol & Ocak, 2018), antiviral, antifungal (Kaval & Tonçer, 2020), cancer chemopreventive (Cinar et al., 2020), antidiabetic (Arıtuluk et al., 2016; Özdek et al., 2020) and blood pressure regulator (Esmaeili et al., 2020)properties were examined.

Oxidative stress, which occurs when the balance between oxidants and antioxidants is disturbed in favor of oxidants, plays an important role in the formation and course of diabetes. Free radicals that arise as a result of oxidative stress cause metabolic disorders and decrease insulin secretion in beta cells of the pancreas (Giribabu et al., 2014). After it was understood that free radicals are effective in the formation of diabetes, it has been suggested that plants with antioxidant properties can be used in the treatment or support of diabetes. It has been shown in different studies that antioxidants suppress oxidative stress and prevent possible cell damage (Yusufoglu et al., 2015). Another method to strengthen the antioxidant defense system is through dietary minerals, vitamins and natural antioxidant compounds. Examples of natural antioxidant compounds are isoflavones, flavonoids, flavones, coumarins, α-tocopherol, β-carotene, isocatechins, anthocyanins, catechins, vitamins C and E (Jain et al., 2008). In studies which were conducted, it has been determined that the molecules contained in plants are effective in antioxidant defense (Jalili-Nik et al., 2019; Özdek et al., 2020). Phenolic compounds and flavonoids from these molecules eliminate the negative effects of free radicals that occur naturally in metabolism (Gao et al., 2022). Therefore, in many studies with plants, the total phenolic and flavonoid content of the plant was investigated (Özdek et al., 2020). Different methods such as β-carotene color bleaching, DPPH free radical, ABTS cation radical and superoxide anion radical removal and CUPRAC methods are used to determine antioxidant capacity. Studies have shown that there is a parallelism between total phenolic and flavonoid content levels and antioxidant capacity (Kose & Ocak, 2018; Ozdek et al., 2020). Kose and Ocak (2018) investigated the total phenol content and DPPH free radical scavenging activity of methyl alcohol, ethyl alcohol and acetone extracts of FR plant. They stated that methyl alcohol extract has more phenolic content, while DPPH free radical scavenging activity is at the highest level in ethyl alcohol extract.In the present study, the total phenolic content of the FR ethyl alcohol extract was found to be 22.37±0.60 µg GA/mg and the total flavonoid content was 16.87±2.06 µg CE/mg. In order to determine the antioxidant activity, in the studied CUPRAC method, it was found that the antioxidant activity of FR extract increased depending on the concentration and was higher than the α-TOC used as the standard. DPPH free radical scavenging activity was found to be higher than the standard α-TOC and BHT. These results show that the total phenolic and flavonoid content of the plant is at a good level.

It should be ensured that the plant or different substances do not have a toxic effect in the use of living things. There are different toxicity tests used for this purpose. Most current toxicity testing methods involve the use of laboratory animals (eg, mice, rats, rabbits). In recent years, toxicity methods recommended by the Organization for Economic Cooperation and Development (OECD) have been used to spend less experimental animals (Krishnasamy et al., 2016; Bhandari et al., 2021). In the presented study, the lethal dose of FR extract was found to be more than 2000 mg/kg according to OECD Test Guideline 425 before the intended diabetes study was conducted. While determining the application dose for the treatment of diabetes, the doses of plants from the same family as FR used in scientific research were taken into account. These doses were determined as 250-500 mg/kg (Jagtap & Patil, 2010; Yusufoglu et al., 2015).

DM is one of the most common diseases seen in societies. The incidence of DM, which is also common in developed countries, is increasing by 50% every decade (Shaw et al., 2010). Due to hyperglycemia in DM, major damage may occur in different organs, especially kidney, heart, eyes, nervous system and blood vessels (Fadem, 2022). In the treatment of diabetes, in addition to exercise and nutrition methods, oral antidiabetic drugs and insulin are used to maintain metabolic balance. Glibenclamide belongs to the group of sulfonylureas among oral antidiabetics and is used as a reference drug in experimental diabetes studies. Drugs in this group have an antihyperglycemic effect by increasing the secretion and effect of insulin in the beta cells of the pancreas (Lazzaroni et al., 2021). Different *Ferula* species belonging to the Apiaceae family are used in the treatment of different diseases

in local treatments (Yusufoglu et al., 2015; Arıtuluk et al., 2016; Özdek et al., 2020). As a result of the examinations, no literature investigating the effect of FR on diabetes was found. In this study, an experimental diabetes model was created using streptozotocin (STZ) in Wistar rats. The effects of different doses of FR extract on serum biochemical parameters, pancreatic tissue oxidant and antioxidant parameters and histopathology were evaluated.

Due to the deterioration in metabolism in diabetes mellitus, the use of fat and protein increases, despite the high level of glucose in the blood. Therefore, a decrease in body weight is observed. In different studies, significant reductions in body weight were found in rats with experimental diabetes (Jagtap & Patil, 2010; Jalili-Nik et al., 2019; Özdek et al., 2020). In the presented study, it was determined that in all diabetes groups (groups 2, 3, 4 and 5), the mean body weight at the end of the study was significantly decreased compared to the mean body weight at baseline.

In diabetes mellitus, a hyperglycemic picture occurs due to damage to the beta cells that produce insulin in the pancreas (Noriega-Cisneros et al., 2012). It has been reported that as a result of STZ injection, serum insulin level decreased (Giribabu et al., 2014; Lazzaroni et al., 2021) and glucose level increased in blood samples of animals with diabetes mellitus, compared to the control group, due to beta cell destruction(Jagtap & Patil, 2010; Akhlaghi et al., 2012; Abou Khalil et al., 2016). In these studies, it was stated that Cuminum cyminum (Jagtap & Patil, 2010), *Ferula gummosa-oleo resin*(Jalili-Nik et al., 2019) and *Petroselinum sativum*(Abou Khalil et al., 2016) plants belonging to the *Apiacea* family increased the serum insulin level and decreased the glucose level in rats with diabetes. Unlike these literature results, it was found that plant extracts of *Petroselinum crispum*(Yanardağ et al., 2003), *Ferula assafoetida*(Akhlaghi et al., 2012) and *Eryngium carlinae*(Noriega-Cisneros et al., 2012) did not cause any change in serum glucose level with diabetes. In the presented study, it was determined that the diabetes group had low serum insulin levels and high glucose levels. This result that we obtained is in line with the literature. In the diabetic group, where 500 mg/kg of FR extract was administered, the decrease in the FBG level and the increase in the insulin level were significant compared to the diabetes group.The reason for this partial improvement may be the curative effect of FR on the pancreatic tissue due to its antioxidant properties. While the decrease in FBG level in the glibenclamide given group was not significant compared to the diabetic group, the increase in insulin level was found to be significant.

In the pathogenesis of diabetes mellitus, besides carbohydrate metabolism, lipid and lipoprotein metabolism are also impaired. Hypertriglyceridemia and hypercholesterolemia are very common conditions in diabetes patients. The main lipoprotein lipase and hepatic lipase enzymes, which are responsible for the level of blood lipids, are under the influence of the hormone insulin. It is observed that the blood lipid profile is also affected by the changes in the insulin level (Özdek et al., 2020). It was determined that serum triglyceride, cholesterol and LDL levels increased and HDL levels decreased in the studies investigating the effects of diabetes on blood lipid profile (Giribabu et al., 2014). There are studies showing different effects of other plants belonging to this plant family on serum lipid profile (Yusufoglu et al., 2015). It was determined that, with the administration of *Ferula durani* root extract in rats with experimental diabetes, the level of total cholesterol, triglyceride and LDL, which increased with diabetes, decreased, while there was an increase in the level of HDL, which decreased with diabetes. In another study, Jalili-Nik et al. (2019) found that the increased total cholesterol, triglyceride, LDL and HDL levels decreased with the administration of *Ferula gummosa-oleo resin* in rats with experimental diabetes. However, Akhlaghi et al. (2012) found that there was no significant change in triglyceride, cholesterol, HDL cholesterol and LDL cholesterol levels in diabetic rats in their study with *Ferula assafoetida* plant. In the presented study, cholesterol, triglyceride and HDL and LDL levels were found to be significantly increased in the diabetes group compared to the controls. Compared to the diabetes

group, it was determined that the cholesterol and HDL levels decreased in the diabetic groups treated with 250-500 mg/kg FR extract and glibenclamide, as well as having results close to the control group values.The decrease in the increased LDL level in diabetic groups treated with FR extract is an indication of the positive effect of this plant on the lipid profile.

Oxidative stress occurs as a result of free radicals formed in rats with STZ-induced diabetes. Malondialdehyde (MDA) is a product of lipid peroxidation. The amount of MDA gives important information about the level of oxidative stress (Abou Khalil et al., 2016). It has been determined that *Cuminum cyminum* plant extract from the *Apiacea* family significantly reduces the increased MDA level in the pancreas of diabetic rats, and there is no difference between the MDA level of the control group (Jagtap & Patil, 2010). Yusufoglu et al. (2015), found that the increased MDA level in the pancreas and liver tissue decreased with the administration of *Ferula duranii* root extract in rats with experimental diabetes. Özdek, (2017) determined that the increased MDA level in the pancreatic tissue of diabetic rats decreased with the administration of *Diplotaenia turcica* root extract. In this study, it was observed that the pancreatic tissue MDA level was significantly increased in the diabetes group compared to the control group, which supports the above literature results. According to the diabetes group, it was determined that the MDA level decreased significantly in the groups treated with 250-500 mg/kg of FR extract and glibenclamide with diabetes, and the decrease was the most in the group that was administered 500 mg/kg of FR extract. It is thought that this significant decrease in MDA level in pancreatic tissue may be related to the inhibition of lipid peroxidation due to antioxidant properties of FR extract in defense against oxidative damage due to diabetes.

Antioxidant enzymes are used to make free radicals more harmless or ineffective. Thus, they protect the metabolism against oxidative stres.GSH is an intracellular non-enzymatic antioxidant substance. By reacting directly with peroxides and free radicals, it prevents the formation of oxidative damage that will occur as a result of oxidative stres.While GSH resists radical-induced damage, it acts as a substrate for antioxidant enzymes and acts as a radical scavenger (Gomathi et al., 2013).

In the studies which were conducted, different results were found regarding the antioxidant substance level and enzyme activities in the pancreatic tissue. Yusufoglu et al. (2015) and Özdek (2017) reported that GSH-Px, CAT, SOD enzyme activities and GSH levels decreased in pancreatic tissue of STZ-induced rats when it was compared with the control group. On the other hand, Yang and Cherian (1994) only evaluated SOD activity and found that there was no change in the enzyme activity in the question. In another study, reported that SOD and CAT enzyme activities increased in pancreatic tissue of STZ-induced rats when compared with the control group (Shukla et al., 2007). And also, in these studies; Yusufoglu et al. (2015) found that *Ferula duranii* root extract, Özdek (2017) determined that the GSH level, which they stated decreased in liver and pancreas tissue, and SOD, CAT and GSH-Px enzyme activities increased significantly with the use of *Diplotaenia turcica* root extract. In this study, it was determined that CAT, GSH-Px, SOD, enzyme activities and GSH levels of pancreatic tissue in the diabetes group were significantly decreased,when it was compared to the control group. This result showed a parallelism with the data of the above studies, thus it was revealed that antioxidant levels and/or enzyme activities decreased in the pancreatic tissue of diabetic groups. In diabetic rats, the decreased CAT, GSH-Px (except 500 mg/kg), SOD enzyme activities and GSH levels were found to increase statistically in the groups treated with 250-500 mg/kg of FR extract and glibenclamide. On the other hand, 250 mg/kg of FR extract was found to be more effective in increasing CAT, GSH-Px and SOD enzyme activities. This increase in antioxidant parameters in pancreatic tissue may be due to the free radical scavenging and protective effect of FR extract against oxidative stress. It was found that there was no difference between the groups administered 250-500 mg/kg of FR extract and the control

group in terms of CAT, GSH-Px, SOD enzyme activities and GSH level. Significant pathological findings have been reported in histopathological and immunohistochemical studies in STZ-induced rats, and atrophy in pancreatic islets of Langerhans, degeneration and necrosis in beta cells were detected (Altındağ et al., 2021; Özdek et al., 2020). In the presented study when it was compared to the control group, pancreatic islets of Langerhans decreased in size and dense necrotic cells were observed in the diabetes group. In the group given 250 mg/kg FR extract, similar to the diabetes group, pancreatic islets of Langerhans decreased in size and had dense necrotic cells. It was observed that the groups given FR extract 500 mg/kg and glibenclamide had moderately necrotic cells in the pancreatic islet of Langerhans. It was determined that the pancreatic tissue of the groups given 250-500 mg/kg FR extract had a normal histopathological structure.

## 4. CONCLUSION

In experimental studies with plants, antihyperglycemic effects have been demonstrated in different ways. These plants can cause a decrease in blood glucose level by triggering events such as increasing insulin synthesis, reducing insulin resistance, absorbing glucose from the intestines, consuming more glucose in cells, and regeneration in pancreatic cells. The antihyperglycemic effect of *Ferula rigidula* extract may be associated with its curative effect on pancreatic islets of Langerhans. The effects of the antihyperglycemic property of *Ferula rigidula* extract on other possible pathways need to be clarified by different studies. Based on this information, it was concluded that 500 mg/kg administered dose of *Ferula rigidula* extract could be useful to investigate clinical use possibilities, since it reduces the oxidative stress in the pancreatic tissue in an experimental diabetes model and has a healing effect on beta cells in the pancreatic islets of Langerhans.

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## 6. AUTHOR CONTRIBUTIONS

The authors have contributed equally to this study.

## 7. CONFLICT of INTEREST

The authors declare there is no conflict of interest.

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