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Antioxidant and antidiabetic properties of *Capparis ovata var. canescens* plant extract

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ABSTRACT: Diabetes mellitus (DM) is a prevalent metabolic disorder that adversely affects multiple organ systems, including the heart, kidneys, brain, and eyes. Capparis ovata, a plant used in traditional medicine, has demonstrated various pharmacological properties, including antioxidant, anticholinesterase, anti-inflammatory, antitumor, antibacterial, and immunostimulatory effects. In this study, we investigated the potential antidiabetic properties of Capparis ovata var. canescens (CO) through in vivo experiments. The above-ground parts of the CO plant were extracted using the maceration method with methanol. Type 2 diabetes mellitus (T2DM) was induced in Sprague-Dawley rats via streptozotocin and nicotinamide administration, after which the rats were treated with CO at doses of 20 mg/kg and 40 mg/kg for 21 days. During this period, key diabetic parameters, including body weight, blood glucose levels, oral glucose tolerance test (OGTT), and insulin tolerance test (ITT), were assessed, along with biochemical analyses of pancreatic tissue. The results indicated that CO significantly improved blood glucose regulation at both doses, as evidenced by OGTT and ITT findings. Notably, the 40 mg/kg CO treatment enhanced insulin sensitivity in ITT, showing effects comparable to the positive control group treated with metformin (400 mg/kg). Furthermore, analysis of antioxidant parameters in pancreatic tissue suggested that CO may exhibit antioxidant activity and mitigate oxidative stress. These findings suggest that CO possesses potential therapeutic properties for the management and regulation of T2DM.

KEYWORDS: *Capparis ovata var. canescens*; Type 2 Diabetes Mellitus; oxidative stress; streptozotocin/nicotinamide.

1. INTRODUCTION

Diabetes Mellitus (DM) is a complicated, metabolic-related disease that causes numerous harmful complications in a patient, which could be acute or chronic [1]. A study report has shown that in 2021, 10.5% of the patients had DM globally. This number of patients has been increasing yearly, becoming a globally concerned issue for the healthcare system. According to the data analysis of the International Diabetes Federation (IDF), DM patients will be 700 million by 2045 [2]. DM is characterized by hyperglycemia because of inadequate insulin secretion or dysfunction of the pancreatic β-cells [3]. Prolonged high glucose levels (HGL) exacerbate the body's essential organs, such as the kidneys, eyes, heart, nerves, and blood vessels [4]. The researchers differentiate many types of diabetes and among them, type 2 diabetes mellitus (T2DM) is the most common form of diabetes in nearly 90% of DM cases [5].

Numerous research has demonstrated that oxidative stress (OS) plays a central role in the development of diabetic complications, especially affecting the vascular system and nervous tissue [6]. OS refers to the imbalance between reactive oxygen species (ROS), reactive nitrogen species (RNS), and antioxidant defense activity. The enhancement of free radicals such as nitric oxide (NO), superoxide, hydrogen peroxide (H_2O_2), and hydroxide promote lipid peroxidation and damages the antioxidant protective system [7]. OS plays a key role in diabetic pathogenesis by degrading lipids, DNA, and proteins and deteriorating insulin secretion and gene expression. Chronic hyperglycemia worsens oxidative stress and develops diabetic complications. High levels of OS biomarkers are found in people with DM, showing a link between OS and DM progression [8]. Glutathione (GSH) reduction is a prime antioxidant and secondary

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factor for the synthesis of NO, which yields from L-arginine. Hyperglycemia-induced free radicals cause a decrease in GSH levels and lower NADPH, especially in DM which can alter the endothelial cell function [9].

The management protocols of DM have significantly developed in the last few decades. Metformin (Met) is a promising medicine that belongs to the class of antidiabetic drugs, and it reduces the blood glucose level by inhibiting glycogenesis in the liver [10]. Met is used along with other medicine combinations to treat T2DM, and it is the first-line medicine selected to cure DM in most cases [11]. Nevertheless, antidiabetic medicines have noteworthy side effects such as diabetic nephropathy, hepatic problems, diabetic retinopathy, neurological disorders, hypertension, and hypoglycemia [12].The World Health Organization has recommended treating DM by using medicinal plants in foods and vitamins such as E, C, and D [13]. The biological products produced from plant sources have recently become well-known in the Western world and are used in conventional therapeutic medicine [14]. The phytochemical research has revealed that various phytochemical compounds have antidiabetic properties such as alkaloids, coumarins, aromatic acids, flavonoids, glycosides, terpenes, carotenoids, phenols, saponins, and essential oils [13, 15].

The genus *Capparis L.* (Capparaceae) contains approximately more than 350 species and is grown widely around the world, especially in the Mediterranean regions, and demonstrated numerous pharmacological and aromatic properties [16]. The *Capparis ovata* var. *canescens* (CO) has been enormously applied as a traditional medicine to treat several ailments including rheumatism, kidney diseases, liver diseases, stomach problems, and many types of aches such as toothache and headache [17]. Moreover, CO plant parts such as fruits and flower buds are used as food excipients, cosmetics for their extreme flavor and pungency, and pharmaceuticals in Turkey for their therapeutic properties [18]. One study has shown that the Soxhlet methanol extract of the caper plant was evaluated to have the medicinal properties of anti-urease, antioxidant, anti-inflammatory, and anticholinesterase [19]. The phytochemical studies have exhibited that active phenolic compounds such as gallic acid, syringic acid, 3,4-dihydroxybenzoic acid, 1,2-dihydroxybenzene, kaempferol-3-O-rutinoside, rutin, quercetin-3-O-hexoside, and quercetin-hexoxide-hexoxide were observed [19,20]. Numerous pharmacological and phytochemical studies have been conducted on this genus, particularly on the *Capparis ovata* (CO) plant, and a variety of medicinal properties and biological compounds have been identified that are beneficial for humankind to treat common diseases. However, this study mainly focuses on the antioxidant and potential antidiabetic properties of the CO plant, which is a gap in previous research. Therefore, in this study, the possible anti-diabetic effect of the CO plant were investigated by using the methanolic extract of the *Capparis ovata* plant in the Sprague Dawley rats by inducing diabetes with streptozotocin and nicotinamide.

2. RESULTS

2.1. Effect of *Capparis ovata var. canescens* plant extract on body weight and blood glucose levels

Figure 1a represents body weight measurement results. The body weights in the T2DM group decreased throughout the experimental period. In the last week of the experiment, the body weight of the T2DM group showed a significant decrease compared to the control group ($p<0.05$). The body weight of the CO treatment groups did not show any statistical difference compared to the control group. It can be observed that CO extract maintains a favorable body weight loss compared with the T2DM group, especially in week three. On the other hand, Figure 1b represents the blood glucose levels of all groups. The decrease in blood glucose levels in other groups was statistically significant compared to the T2DM group. It was demonstrated that the CO extract at different doses (20mg/kg, 40mg/kg) reduced blood glucose levels significantly ($p<0.001$), particularly in weeks two and three compared with the T2DM group.

2.2. Effect *of Capparis ovata var. canescens* plant extract on Oral Glucose Tolerance Test (OGTT)

The OGTT was conducted to evaluate the CO extract effect on T2DM-induced Sprague Dawley rats and the data gained from the experiments is exhibited in Figure 1c. The T2DM group showed the highest blood glucose levels compared with other groups during the 120 min. The T2DM+Met group and the other two treatments of CO extract (20 mg/kg, 40mg/kg) groups showed a significant reduction in blood glucose levels, in contrast to the untreated T2DM group. The measurements of the OGTT were taken by using a glucometer at different periods 30, 60, 90, and 120 after induction of T2DM in rats, and the highest 40 mg/kg dose of CO extract demonstrated a significant ($p<0.001$) effect similar to the T2DM+Met group. The lowest

dose (20 mg/kg) of CO extract also exhibited an effect of antidiabetic slightly less than metformin but significant ($p < 0.001$).

2.3. Effect of *Capparis ovata var. canescens* plant extract on Insulin Tolerance Test (ITT)

The ITT results are presented in the Figure 1d. In the ITT, the highest dose (40mg/kg) of CO extract illustrated the substantial insulin sensitivity property ($p < 0.01$) similar to standard metformin medicine, but a lower dose (20mg/kg) showed less effect compared with the dose (40mg/kg). The metformin-treated group showed noticeable insulin tolerance action compared with the disease group. The higher dose exhibited a more significant effect; consequently, we can say that the results obtained from the investigation of CO plant extracts demonstrated a dose-based considerable impact on T2DM in OGTT and ITT assessment. The observations show that the effective dose could significantly control DM and treat insulin resistance.

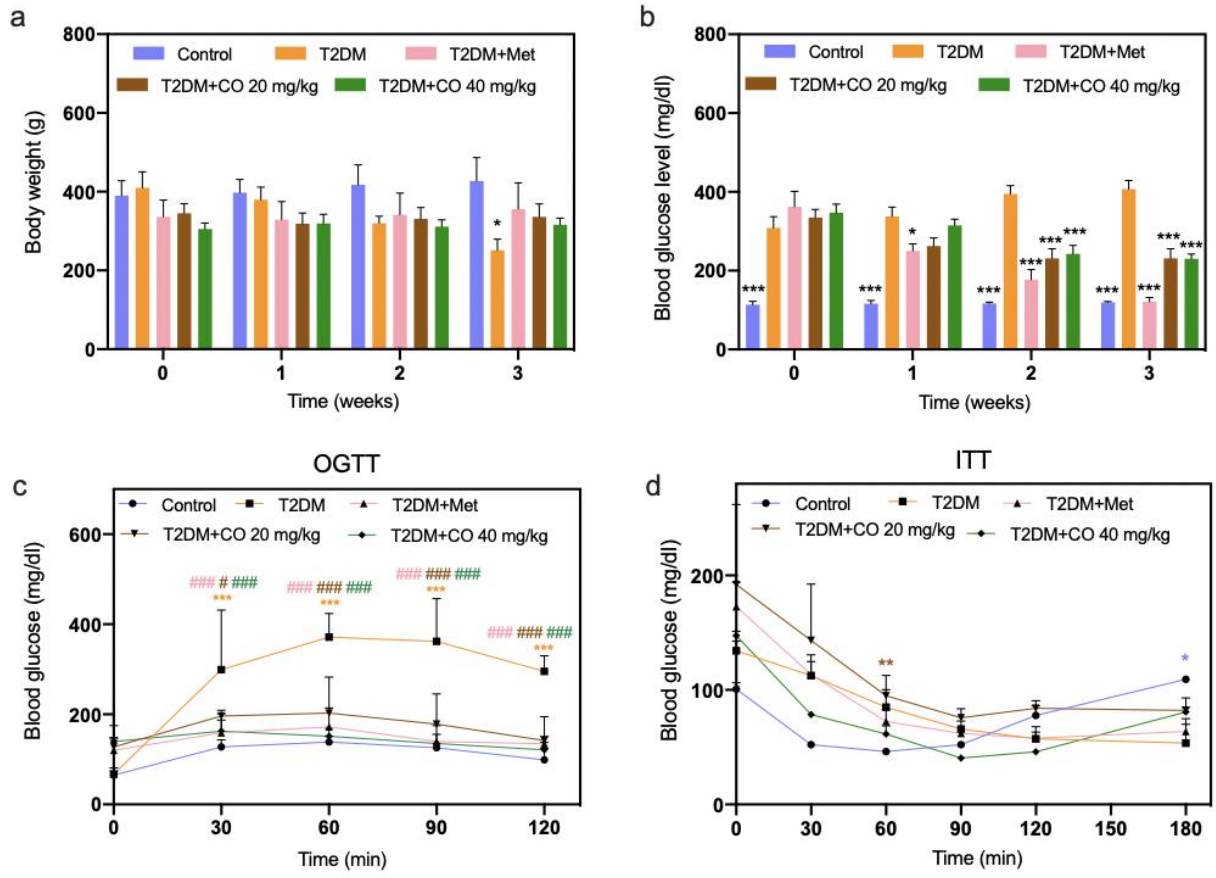


Figure 1. (a) Body weight (g) of rats for 3 weeks. *$p < 0.05$ in comparison to the control group, (b) blood glucose (mg/dl) of rats during 3 weeks (n=6). *$p < 0.05$, ***$p < 0.001$ in comparison to the T2DM group, (c) blood glucose levels of rats on 0, 30, 60, 90, and 120 min in OGTT (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ in comparison to the control group; #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ in comparison to the T2DM group. (b) Blood glucose (mg/dl) of rats on min 0, 30, 60, 90, 120, 150, and 180 in the ITT (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ in comparison to T2DM. Each group represents the mean ±standard error of the mean. T2DM: Type-2 Diabetes Mellitus, CO: *Capparis ovata var. canescens*, OGTT: Oral glucose tolerance test, ITT: Insulin tolerance test.

2.4. Effect of *Capparis ovata var. canescens* plant extract on oxidative processes

A Lipid Peroxidation test (LPO) was performed, and it was discovered that the oxidative stress was noticeably high in the T2DM groups compared with the control group. The T2DM+Met and CO extract treatments groups significantly reduced the LPO level. Moreover, the most significant dose (40mg/kg) of CO showed a noticeable reduction of LPO level more than (T2DM+Met), close to the control group, demonstrating a strong antioxidant effect. Glutathione (GSH) levels of pancreatic tissues were observed by applying the Beutler method. The GSH level was lower in the T2DM group compared with the control

(p<0.01). The highest dose (40mg/kg) of CO and metformin have approximately the same ability to restore GSH levels. It showed that the CO plant can maintain oxidative stress and control redox balance. and MPO was raised in the T2DM groups. The plant extracts significantly decrease the MPO level at different doses, nearly matching the metformin effect.

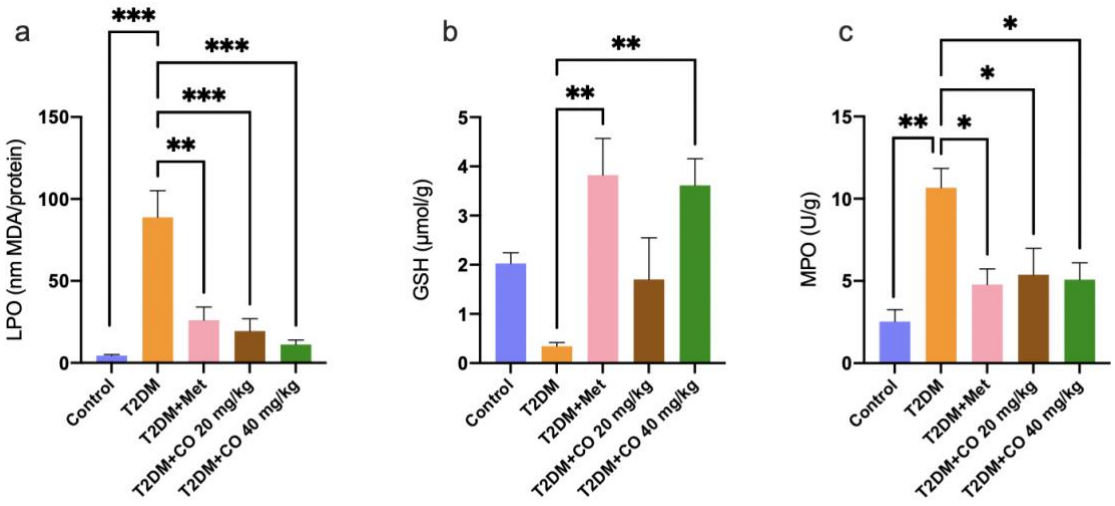


Figure 2. Lipid peroxidation (LPO) (a), glutathione (GSH) levels (b), and myeloperoxidase (MPO) activity (c) measurements in the pancreas tissue of rats, which were control, T2DM, T2DM+CO 20 mg/kg, and T2DM+CO 40 mg/kg groups. Each group (n = 6) represents the mean□standard error of the mean. Values are given statistically when *p < 0.05, **p < 0.01, ***p < 0.001 compared to the T2DM group. T2DM: Type-2 Diabetes Mellitus, CO: *Capparis ovata var. canescens*.

3. DISCUSSION

The primary focus of our study is to investigate the antidiabetic and antioxidant activities of *Capparis ovata var. canescens* (CO) extract in STZ/NA-induced T2DM Sprague-Dawley rats. Therefore, this is the first to examine the effect of CO extract on antioxidant effects in pancreatic tissue and antidiabetic capacity. Additionally, this study is the first to compare the effects of two different doses of CO extract in an animal model.

T2DM is a disease characterized by weight loss, high blood glucose and insulin resistance, and in experimental studies, the evaluation of these parameters to evaluate the effectiveness of a plant can give an idea about its antidiabetic activity [21]. In the study, body weight, blood glucose levels, OGTT and ITT analyses, which are among the diabetic parameters, were performed. As seen in the results of previous research, the body weights of the animals in the T2DM group decreased and showed a statistical difference compared to the control group in the last week of the experiment [22]. It was found that weight loss decreased in both groups where CO extract was applied, similar to the T2DM+Met group. In the weekly blood glucose levels results, it was found that CO extract reduced blood glucose at doses of 20 mg/kg and 40 mg/kg during the experiment. In fact, blood glucose decreased significantly in the CO-administered groups compared to the disease group. In addition, no statistical difference was observed with the T2DM+Met group, which may indicate that CO extract may have a regulatory role in the management of hyperglycemia. According to the OGTT and ITT results, it was found that CO extract tolerated blood glucose and reduced insulin resistance in both doses. In the OGTT analysis, while blood glucose was still not under control at the 120th minute in the disease group, blood glucose control was achieved in the CO extract-applied groups similar to the T2DM+Met group. This result obtained in the CO extract-applied groups compared to the disease and positive control groups can be associated with the CO extract increasing glucose tolerance [23]. In the ITT, the highest dose of CO extract illustrated the substantial insulin sensitivity property similar to standard metformin medicine, but a lower dose showed less effect compared with the high dose. The metformin-treated group showed noticeable insulin tolerance action compared with the T2DM group. The higher dose exhibited a more significant effect; consequently, we can say that the results obtained from the investigation of CO plant extracts demonstrated a dose-based considerable impact on T2DM in OGTT and ITT assessment. The observations suggest that CO extract may efficiently regulate insulin signals and how

bodies use glucose, possibly by adjusting pathways linked to insulin sensitivity, and may treat insulin resistance [24].

Changes in antioxidant enzymes and the formation of lipid peroxides, which increase free radicals, occur during chronic hyperglycemia in DM [21]. The enhancement of free radicals such as NO, superoxide, H_2O_2, and hydroxide promote lipid peroxidation and damages the antioxidant protective system [7].The overproduction of ROS has been shown to be a contributing factor to the destruction of pancreatic islets and the aggravation of β-cell damage [21]. This study also assessed the lipid peroxidation (LPO), GSH, and MPO levels in the pancreatic tissues. Aldehydes formed due to LPO production and the processes that occur afterwards cause damage to the pancreas. Increased LPO and decreased GSH in diabetic pancreatic tissues increase the severity of oxidative damage in DM [25]. GSH levels in diabetic rats decreased similar to those in the previous studies, indicating that antioxidant mechanisms were under threat. On the contrary, similar to the T2DM+Met group, LPO levels decreased and GSH levels increased occurred in the CO extract-treated groups. According to the results, CO extract may enhance antioxidant capacity and scavenge free oxidative radicals [25, 26]. MPO is the key neutrophilic inflammation indicator characterized by pancreatic inflammation. The decrease in MPO levels in the CO-treated groups and the similar profile to the positive control group are associated with the decrease in inflammation in the pancreatic tissues. This results showed that CO extract has a protective effect on the pancreas by reducing inflammation in addition to the antioxidant mechanism [27].

These results may indicate that the CO plant possesses an antioxidant and antidiabetic effect. Therefore, our findings reveal that the CO plant extract could be helpful as the potential therapeutic agent to treat hyperglycemia and insulin resistance in T2DM. Furthermore, it is indicated that the CO plant has a strong antioxidant effect and anti-inflammation properties dose dependent by reducing the level of LPO and MPO and increasing the level of GSH. Nevertheless, additional investigation should be required to understand the mechanism of action and optimize the effective dose, dosage form, and toxicity studies.

4. CONCLUSION and FUTURE DIRECTIONS

Our results indicate that *Capparis ovata var. canescens* extract may have both antidiabetic and antioxidant properties, potentially a candidate for managing hyperglycemia, insulin resistance, and oxidative stress associated with T2DM. Its dose-dependent effects in both regulating blood glucose and reducing pancreatic inflammation and oxidative damage highlight its therapeutic potential. This study could contribute significantly to the investigation of medicinal plants in diabetes management, offering a novel approach with potential applications.

5. MATERIALS AND METHODS

5.1. Drugs and chemicals

Streptozotocin, nicotinamide, and metformin were obtained from Sigma Aldrich. In addition, *Capparis ovata var. canescens* (CO) plant extract was prepared by Assoc. Prof. Turgut Taskin, faculty member of the Department of Pharmacognosy at Marmara University. All purchased materials are suitable for analytical procedures.

5.2. Plant material and preparation of plant extract

The CO plant was identified by Assoc. Prof. Gizem Bulut, a faculty member of the Department of Botany, Faculty of Pharmacy, Marmara University, is stored in the Herbarium of the Faculty of Pharmacy, Marmara University, with the code MARE=18469. The above-ground parts of the CO plant were dried at room temperature conditions. The dried plant was macerated using methanol solvent. The methanol extract was obtained at room temperature by maceration consumption method until a colorless solution was obtained and filtered through filter paper. The crude extracts were obtained by evaporation at a temperature not exceeding 50 °C in the rotary evaporator and the extracts were stored in the refrigerator at +4 °C until the day the study was started.

5.3. Experimental design

All *in vivo* studies were conducted with the approval (No: 68.2022mar) of the Marmara University, Animal Experiments Local Ethics Committee (MUHDEK). Adult male/female Sprague-Dawley (SD) rats (250-350 g) (n=6 in each group for the study) were provided by the Experimental Animals Research and

Implementation Center of Marmara University. The animals were placed in rooms with conditioned temperature (20-23 °C), humidity (40-60%), and brightness (12 h light/dark cycle) and fed freely with a standard rodent chow and water ad libitum. All necessary precautions were taken before the experiment and factors that could negatively affect the parameters during the study were minimized. The rats were randomly distributed into 5 groups with 6 animals in each group. The details of the experiment are mentioned below:

Group I (Control group): The control rats which STZ/NA were not and received saline.

Group II (Diabetic control group): The T2DM was induced with a single STZ/NA administration and no treatment was applied.

Group III (Positive control group): The T2DM was induced with a single STZ/NA administration and the metformin (400 mg/kg) (26) where solved in saline, was administered to rats intragastrically (i.g.).

Group IV (Treatment group): The T2DM was induced with a single STZ/NA administration and the CO extract where solved in saline, and administrated i.g. at 20 mg/kg doses.

Group V (Treatment group): The T2DM was induced with a single STZ/NA administration and the CO extract where solved in saline, and administrated i.g. at 40 mg/kg doses. All the animals were treated for 21 days.

5.4. Induction of type 2 diabetes mellitus (T2DM)

To induce T2DM, a single intraperitoneal (i.p.) injection of STZ and NA was administered to rats and the rats were fasted for 12 h before inducing T2DM. Then NA (100 mg/kg dissolved in saline) was injected once before STZ administration to minimize the cytotoxic effect of STZ and STZ-induced pancreatic β-cell damage. 15 min later, the rats were injected with STZ (55 mg/kg, 0.1 M citrate buffer, pH: 4.5) to induce T2DM [15, 28-30]. To prevent STZ-related hypoglycemic deaths, vials containing 5% (w/v) glucose solution were placed in the cages overnight after STZ/NA injection [28]. Blood samples were taken by intravenous blood sampling from the tail 72 hours after the injection and fasting blood glucose was measured with a glucometer (Contour Plus, Bayer Diagnostics). Rats with fasting blood glucose levels above 200 mg/dL (11.1 mmol/L) were classified as diabetic and used for experiments. Blood glucose levels were measured with a glucometer on days 0, 7, 14, and 21. Animals were euthanized on day 21 of the experiment and peripheral blood was taken from the animals [31, 32]. Pancreatic tissues were excised immediately and stored at -80 °C for use in biochemical analysis.

5.5. Measurement of body weights and blood glucose levels of animals

The body weights and blood glucose levels were measured weekly in all groups of rats. The blood glucose levels were measured by glucometer.

5.6. Oral glucose tolerance test (OGTT)

The OGTT was performed on the 17th day of the experiment. Before the OGTT, the animals were fasted for 12 hours and their water intake was free. After the 12-hour fast, the treatments were applied as usual and 30 minutes after the treatment, the rats were given glucose solution at a dose of 2 g/kg. The blood glucose levels of all animals in the groups were measured using a glucometer at 0, 30, 60, 90, and 120 minutes following glucose administration, with blood samples collected from the tail vein [30].

5.7. Insulin tolerance test (ITT)

ITT was performed 3 days after the OGTT. Before the test, animals were fasted for 12 hours, water intake was free. At the end of 12 hours of fasting, treatments were applied as usual and 30 minutes after the treatment application, rats were injected with intraperitoneal insulin (0.50 IU/kg). Blood glucose levels of all animals in the groups were measured with a glucometer in blood taken from the tail pricking method at 0, 30, 60, 90, 120, and 180 min after insulin application [33, 34].

5.8. Biochemical analyses

5.8.1. Determination of lipid peroxidation

Lipid peroxidation was measured using malondialdehyde (MDA) levels according to the procedure of Esterbauer et al. In the reaction, MDA and thiobarbituric acid (TBA) react to form thiobarbituric acid reactive substance (TBRAS). Pancreatic tissues were homogenized by adding 10 volumes of 10% cold trichloracetic acid. Then, the samples were centrifuged (3000 rpm) at 4°C for 15 minutes. After TBA and supernatant were boiled the pink TBRAS forms were measured spectrophotometrically at 532 nm and the results were expressed as nmol/g [35].

5.8.2. Determination of glutathione levels

GSH levels of pancreatic tissues were determined according to the Beutler method. Ellman reagent is degraded by sulfhydryl compounds present in GSH, producing the yellow decomposition 5,5′-dithiobis-2-nitrobenzoic acid (DTNB). The DTNB which is a reduction product is yellow and analyzed spectrophotometrically at 412 nm [36].

5.8.3. Determination of myeloperoxidase levels

Myeloperoxidase (MPO) is a heme protein expressed in phagocytes, and enzyme activation was assessed in pancreatic tissues using the spectrophotometric assay according to the procedures of Hillegas et al. Pancreatic tissues homogenized in cold potassium phosphate buffer (50 mM K_2HPO_4, pH 6.0) containing hexadecyltrimethylammonium bromide (HETAB; %0.5 w/v) were centrifuged (12.000 rpm) at 4°C for 10 min. The obtained pellet was then re-homogenised with an equivalent volume of 50 mM K_2HPO_4 containing HETAB 0.5% (w/v) and 10 mM ethylenediaminetetraacetic acid (EDTA). MPO activity was evaluated by measuring the oxidation of o-dianisidine by H_2O_2, the reaction initiated by H_2O_2 was stopped by Na-azide. The activity of the enzyme was defined as the amount of MPO present causing an absorbance change at 460 nm and 37°C and expressed as U/g tissue [37].

5.9. Statistical analysis

The statistical analysis of the data obtained from the tests was performed using the GraphPad Prism 8 statistical program. The analysis results were given as mean ± standard error. Analysis of variance (ANOVA) followed by Turkey post hoc test was used to compare between groups. Two-way ANOVA was used for weekly blood glucose and body weight measurements, OGTT, and ITT analyses, while One-way ANOVA was used in biochemical analyses. $p<0.05$ values were considered significant, $p>0.05$ values were not considered significant.

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