

The effects of *Origanum onites* in streptozotocin-induced diabetes mellitus in rats

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ABSTRACT: Diabetes mellitus is a chronic disease characterized by decreased insulin synthesis and/or increased blood glucose due to insulin resistance. In this study, streptozotocin (STZ)-induced diabetic rats were evaluated and it was aimed to investigate the protective effects of *Origanum onites* L. (OO) against possible changes in these parameters. Male Sprague-Dawley rats weighing 300-400g were divided into three groups control (C), diabetes mellitus (DM) and diabetes mellitus + OO (OO group). DM was induced by administration of STZ 60 mg/kg dose intraperitoneally (i.p.) after 48 hours, rats with blood glucose values higher than 200 mg/dL were considered DM. Origanum extract was administered i.p. to the OO group at 50 mg/kg per day for 6 weeks. Serum AST, ALT, creatinine, and inflammatory cytokine levels were measured. MDA and GSH levels were measured in liver tissues. AST, ALT, creatinine, and MDA levels were found to be increased in the DM group, while a significant decrease in these levels was observed in the treated group. While GSH values fell in the DM group, a significant increase occurred in the OO group (n=6, p<0.0001; two-way ANOVA). When the plasma levels of cytokines were examined, an increase was observed in the DM group and a significant decrease was observed in the OO group. When we evaluate our findings, we think that OO has a protective effect against complications that may occur in DM by preventing oxidant damage and inflammation. Further studies are needed on the protective effects of OO in DM.

KEYWORDS: Diabetes mellitus, oxidative stress, liver, *Origanum onites*, inflammatory cytokine

1. INTRODUCTION

Diabetes mellitus (DM) affects approximately 387 million people worldwide and its prevalence is estimated to double during the next 20 years involving more than half a billion people. The actual cost of DM is evaluated in terms of both a financial burden and human distress, with multiple complications of the disease rather than the daily care being associated with the actual cost related to DM (1). Both insulin deficiency resulting from autoimmune destruction of beta cells in the pancreas and insulin resistance resulting from metabolic disorders are important pathological processes that play a role in the development of DM (2). Chronic hyperglycemia, which is the main clinical and diagnostic feature of DM, causes complications related to loss of function and organ failure because of long-term damage to various organs, especially the nervous system, cardiovascular system, urinary system, and eyes (3). The progression of these complications in DM impairs the quality of life and increases the incidence of mortality and morbidity. Microvascular, macrovascular, and neurological complications that developed because of DM have different progression mechanisms (4).

The development of potent antidiabetic drugs such as insulin, oral antidiabetics (sulfonylureas, biguanides, thiazolidinediones, incretin mimetics, dipeptidyl peptidase-4 inhibitors, and sodium-dependent glucose transporter-2 inhibitors) and aldose reductase inhibitors together with controlling hyperglycemia has significantly reduced rates of mortality and acute complications related to the disease (5). However, since current drugs can not completely prevent chronic complications of DM, the reported toxic side effects found in some of these pharmaceutical treatments and considering the development of tolerance due to long-term

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use of these drugs leads to the need for further clinical studies. In addition, there is expanding argument on the effect of the use of medical herbal supplements for DM prevention and management (6).

Worldwide, between 50.000 and 80.000 flowering plants are used medicinally. The number of medical plants being grown in Türkiye is around 12.000. *Origanum* species are used in traditional medicine for the treatment of various diseases. The genus *Origanum* L. (Lamiaceae) consists of 43 species and 18 hybrids, most of which are distributed throughout the Eastern Mediterranean region. *Origanum* species growing in Türkiye have gained great commercial importance in the world markets in recent years. Especially, *Origanum onites* L. (OO) is preferred due to its high quality (7).

Natural antioxidants are thought to be beneficial agents in the prevention of different diseases. Many studies have shown that phenolic compounds in plant essential oils exhibit antioxidant activity due to their free radical scavenging capacity. Many types of *Origanum* species have shown a high phenolic content in their essential oils. The main compounds of the essential oil of OO, as seen in many plant oils, are carvacrol (71.22%) and thymol (5.97%). Carvacrol (2-methyl-5-(1-methylethyl) phenol), a cyclic monoterpene, is a component of thyme essential oil (8). Many studies have indicated the effect of oxidative processes in the development of DM complications. Therefore, the investigation of novel pathogenic factors and targetable signal transduction pathways that mediate secondary complications of DM is critical for the development of new therapies and the improvement of disease outcomes. In our study, we aimed to investigate the protective effects of endemic OO extracts in the damage caused by hyperglycemia-induced production of free oxygen radicals on liver and kidney tissues.

2. RESULTS

2.1. Effects of *Origanum onites* on body weight and blood glucose

The effects of OO on body weight and blood glucose are shown in figure 1. The animals of similar body weights were used for the experiment. While no weight loss was observed in the control and OO groups, significant weight loss was observed in the DM group (Fig. 1a). At the end of the study, diabetic rats lost 40% of their body weight, whereas diabetic rats treated with OO lost only 12%. At the end of the study, diabetic rats lost 40% of their body weight, whereas diabetic rats treated with OO lost only 12%. At the end of 3 weeks, there was a 6% decrease in blood glucose levels in the group treated with OO, while there was no change in blood glucose levels in the untreated group.

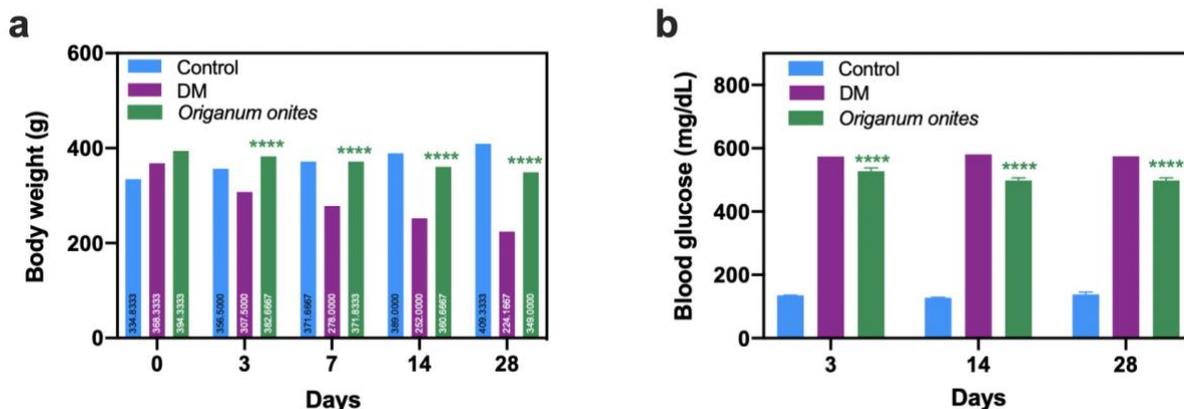


Figure 1. Effect of *Origanum onites* on (a) body weight (g) and (b) blood glucose levels of diabetic animals. The value of each group (n=6) was given as mean \pm standard error. Data analysis was performed using two-way ANOVA and Bonferroni test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to the control group.

2.2. Effect of *Origanum onites* on serum ALT, AST, and creatinine levels

While an increase was observed in ALT and AST levels in rats in the DM group, a significant decrease was observed in the OO group compared to the DM group (p<0.0001) (Fig. 2a and b). Plasma creatinine concentration is entirely stable and because of this, high creatinine levels are represented by problems in kidney function. There had an increase in creatinine levels in rats in the DM group, and a significant decrease was found in the OO group compared to the DM group (p<0.0001) (Fig. 2c).

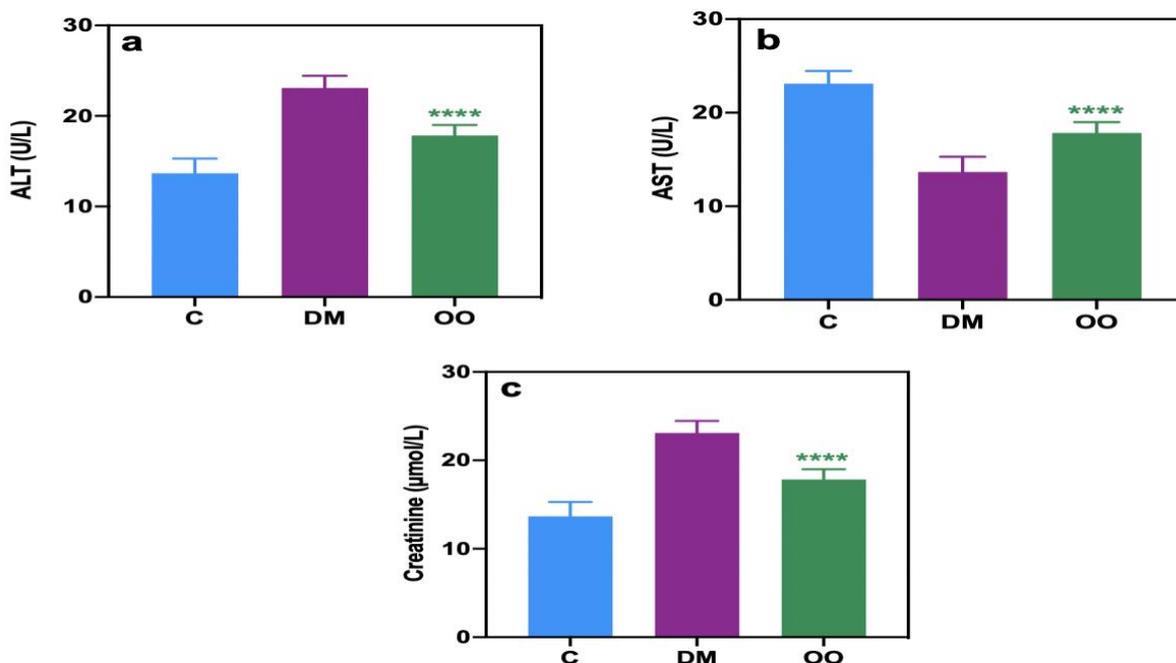


Figure 2. Effect of *Origanum onites* on serum (a) ALT, (b) AST, and (c) creatine levels of diabetic animals. The value of each group (n=6) was given as mean \pm standard error. Data analysis was performed using two-way ANOVA and Bonferroni test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to the control group.

2.3. Effect of *Origanum onites* on liver GSH and MDA levels

Oxidative damage can be measured by GSH and MDA experiments (Fig. 3). In this context, the levels of GSH and MDA in the liver were investigated. In the GSH measurements made in the liver, a significant increase was observed in the OO group compared to the DM group (p<0.0001). In MDA measurements, there was a significant decrease in liver tissue in the treatment group compared to the DM group (p<0.01).

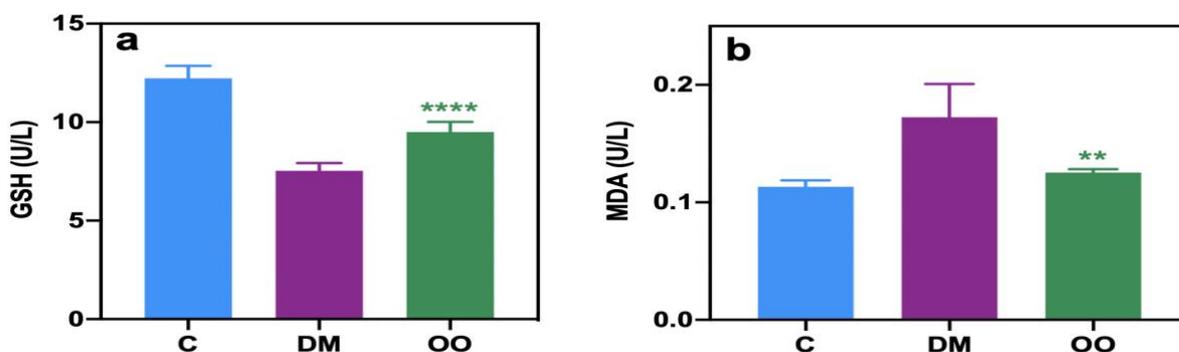


Figure 3. Effect of *Origanum onites* on liver (a) GSH and (b) MDA levels of diabetic animals. The value of each group (n=6) was given as mean \pm standard error. Data analysis was performed using two-way ANOVA and Bonferroni test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to the control group.

2.4. Effect of *Origanum onites* on serum IL-1 β , IL-10, IL-6, IL-17, IL-4, IL-12, and IFN- γ levels

Interleukin-1 β (IL-1 β) is a potent proinflammatory cytokine that is crucial for host defence responses in the event of infection and injury (9). A significant decrease was observed in the OO group compared to the DM group in IL-1 β measurements made in the plasma (p<0.0001) (Fig. 4a). On the other hand, interleukin-10 (IL-10), an anti-inflammatory cytokine, has been suggested to play a protective role in DM. IL-10 is a Th2-type cytokine produced by a wide variety of immunological cell types, including monocytes/macrophages, and is a potent inhibitor of proinflammatory cytokines and chemokines (10, 11). In our results, IL-10 measurements in plasma showed a significant increase in the OO group compared to those in the DM group (p<0.0001) (Fig.

4b). In the IL-6, IL-17, IL-4, and IL-12 measurements made in the plasma, a significant decrease was observed in the OO group compared to the DM group ($p < 0.0001$) (Fig. 4c, d, e, and f). The associated studies indicate that interferon- γ (IFN- γ) is a cytokine expressed by T lymphocytes (12). As well as, IFN- γ measurements in plasma showed a significant decrease in the OO group compared to those in the DM group ($p < 0.0001$) (Fig. 4g).

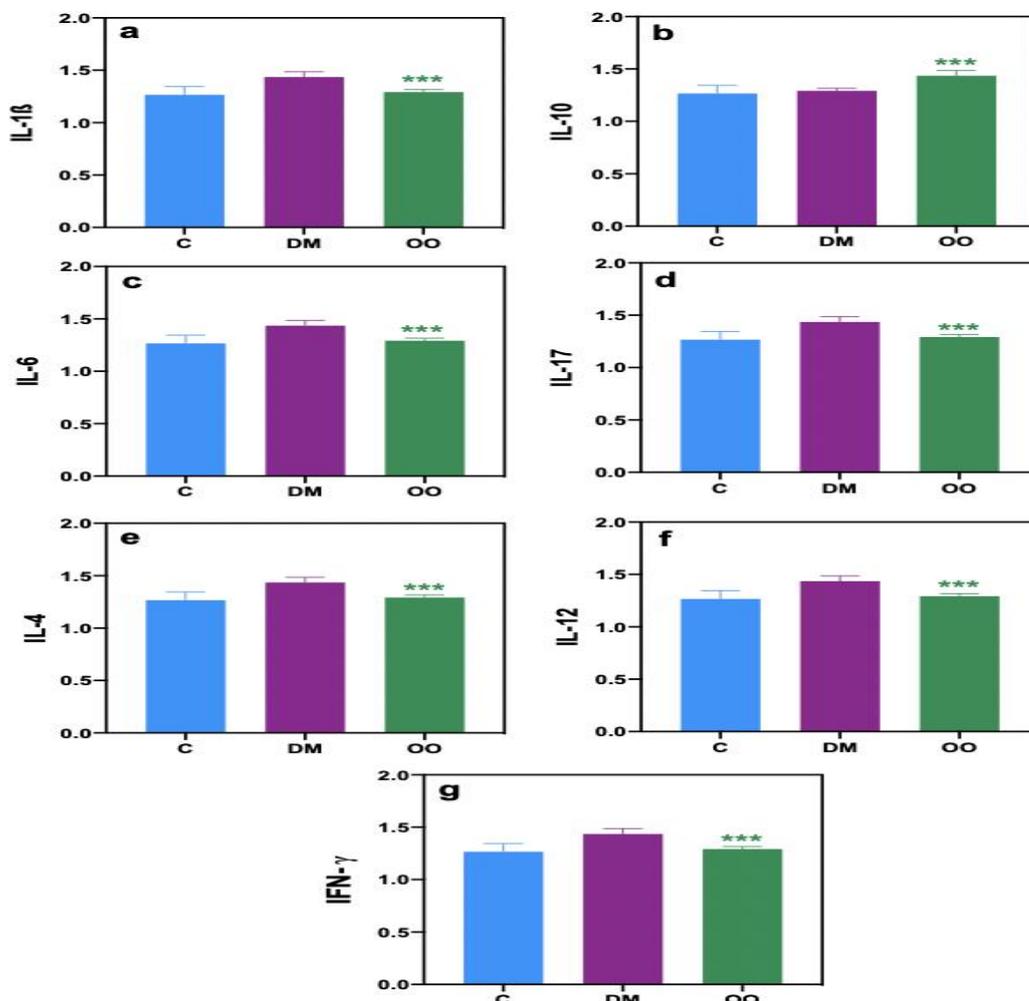


Figure 4. Effect of *Origanum onites* on serum IL-1 β , IL-10, IL-6, IL-17, IL-4, IL-12, and IFN- γ levels of diabetic animals. The value of each group (n=6) was given as mean \pm standard error. Data analysis was performed using two-way ANOVA and Bonferroni test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to the control group.

3. DISCUSSION

DM is a heterogeneous metabolic disorder characterized by hyperglycemia resulting from a complete or partial deficiency of insulin production (13). Chronic hyperglycemia due to DM is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (14).

Biochemical disorders developed as a result of chronic hyperglycemia and oxidative stress may play a role in the symptoms and progression of the disease. Oxidative stress in cells and tissues results from the increased generation of reactive oxygen species (ROS) and/or decreased antioxidant defence mechanisms. In particular, various hypotheses such as polyol pathway activation, the activation of DAG/PKC, the creation of advanced glycation end-product (AGE), and hexosamine pathway activation has been put forward to explain the increase in the formation of free radicals in DM (13, 15).

Endothelial dysfunction develops because of long-term exposure to oxidative stress in DM, and as a result, serious complications that affect different organ systems occur. DM-related complications, including cardiovascular diseases, kidney diseases, neuropathy, blindness, and lower extremity amputation, are a major

cause of increased morbidity and mortality among people with DM and place a heavy economic burden on the healthcare system (16).

Insulin resistance and β -cell dysfunction are two major components of type-2 DM pathology. β -cell dysfunction begins to occur even before impaired glucose tolerance appears. Histological characteristic changes of inflammation such as immune cell infiltration, amyloid deposition, cell death, and fibrosis which occur in the islets of Langerhans in type-2 DM patient subjects indicate the association of inflammation in β -cell dysfunction (17).

Cytokines have divided into two groups: pro-inflammatory (e. g. IL-1, IL-6, TNF- α , TGF- γ) and anti-inflammatory (e.g., IL-1Ra, IL-4, IL-10, IL-13) cytokines. Cytokine-mediated pro-inflammatory effects can be inhibited by anti-inflammatory cytokines or receptor-specific antagonists. A balance between pro- and anti-inflammatory cytokines observes in many diseases (18).

In type-1 DM, loss of β -cell mass in the pancreatic islets of Langerhans causes insufficient insulin secretion and hyperglycemia. Proinflammatory cytokines, especially IL-1 β , are believed to be an immune-mediated process that plays an important role in the pathogenesis of the disease. In addition, the association of IL-1 β in type-2 DM has also been determined. Under in vitro conditions, the increase of IL-1 β or interferon (IFN)- γ and/or TNF- α alone in insulin-secreting cells (pancreatic islets) leads to cell death by impairing β -cell function and inducing apoptosis. Similarly, it was reported that increased IL-1 impairs insulin secretion and triggers β -cell apoptosis as well. These results suggested the contribution of not only β cell dysfunction but also the decrease in β cell mass in the development of type-2 DM caused by increasing β cell apoptosis (19). Natural antioxidants are thought to be beneficial agents in the prevention of different diseases. Many studies have suggested antioxidant activity of phenolic compounds found in plant essential oils thanks to their free radical scavenging capacity (20). Many *Origanum* species have shown a high phenolic content in their essential oils. Essential oils, which are lipophilic, can exert their effects by crossing the plasma membrane and interacting with intracellular proteins and/or organellar. Monoterpenes, on the other hand, are highly hydrophobic substances found in plant essential oils (7).

The main compounds of the essential oil of OO include carvacrol (71.22%) and thymol (5.97%). Carvacrol (2-methyl-5-(1-methylethyl) phenol), a cyclic monoterpene, is a component of thyme essential oil. Its use in flavoring and as an antibacterial or antifungal agent in food preservation methods has attracted the attention of researchers. Thymol (5-methyl-2-(1-methylethyl) phenol) is an isomer of carvacrol having the hydroxyl group at a different position on the phenolic ring. The hydrophobic nature of carvacrol and thymol allows them to react with the lipids of the cell membrane and mitochondria, resulting in leakage of cell components (8).

Origanum species have a wide range of medical uses that include secretolytic, bronchospasmolytic, and antimicrobial effects, in addition to their stomachic, analgesic, and carminative effect due to the relaxing effect on smooth muscles. Essential oils of these species have also antiseptic, antimicrobial, antiviral, and insecticidal effects. There are many preparations containing essential oils of *Origanum majorana* applied as internal or external treatments for medical, cosmetics and aromatherapy purposes (21). Moreover, they have been known for their powerful antioxidant efficacy that attracted the attention of many researchers in recent years (22).

In this study, we aimed to investigate the effect of OO in the treatment of streptozotocin-induced diabetes in rats. 'Evaluating of changes in rats' weight after 6 weeks from the beginning of the study showed no change in the C group, a 12% reduction in body weight of the diabetic rats treated with OO and a 40% reduction of the body weight of DM group. Blood glucose levels were increased in diabetic rats and decreased in OO group.

In our study, serum levels of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Creatinine, IL-1 β , IL-10, IL-6, IL-17, IL-4, IL-12 and IFN- γ were measured. Malondialdehyde (MDA) and Glutathione (GSH) values were measured in liver tissues. AST, ALT, and creatinine levels were decreased in the OO group.

In order to examine the inflammatory response, cytokine amount analysis was performed in the serum, and the pro-inflammatory levels of IL-1 β , IL-6, IL-17, IL-12, and IFN- γ were decreased in the treated group. In addition, serum levels of IL-10 and IL-4, which are anti-inflammatory cytokines secreted in response to chronic inflammation, were examined. The results showed an increase in serum levels of IL-10 and a decrease in IL-4 levels in the OO group.

DM is often associated with liver dysfunction that leads to abnormal hepatic lipid accumulation, known as non-alcoholic fatty liver disease (NAFLD). Numerous clinical studies have shown that ROS may

contribute to the progression of liver fibrosis and cirrhosis after linking diabetes with NAFLD. Therefore, end-stage liver diseases represent an important cause of mortality in diabetic patients (23).

A study about the effect of OO oil on tissue damage, glycemia, and hematological changes in a streptozotocin-induced DM model showed that the application of essential oil did not cause any decrease in blood glucose level in streptozotocin-induced DM rats, while it caused significant reductions in AST, ALT, creatinine, urea, and cholesterol levels. As a result, it was suggested that long-term use of essential oils may be effective in preventing or at least delaying the development of some complications of DM (24, 25). Similarly, the application of essential oils, alcohol extract and aqueous extract of *Origanum majorana* significantly reduced AST, ALT, creatinine, and urea levels in acetate-induced liver damage in mice (26).

ALT and AST are markers of attack against hepatocytes and are crucial indicators of increased liver inflammation in the identification of liver disorders. In agreement with the results of many studies, our results showed that serum levels of ALT, AST and creatinine were increased in DM group, while a significant decrease of these levels was observed in the treated group. Our results indicate that OO by reducing inflammation may have a protective effect on tissue damage.

In our study, GSH and MDA measurements made in liver tissue showed a significant increase of GSH and a significant decrease in MDA levels in the OO group compared to the DM group. While MDA determination is an important indicator of lipid peroxidation, GSH levels are usually checked in response to oxidative stress in the body. In this context, changes in GSH and MDA levels in both liver tissue after treatment with OO indicate an antioxidant efficacy.

Inflammatory mechanisms have been suggested to play a critical role in the processes/ progression of type-1 DM and type-2 DM. Cytokines play an important role in the autoimmune factors involved in the onset and maintenance of type-1 DM. Even low levels of inflammation seen in beginnings during the development of type-2 DM tend to damage β cells in the pancreas in the long term. It was reported that treatment with origanum extract decreased the synthesis of the proinflammatory cytokines TNF- α , IL-1 β and IL-6 but increased the production of the anti-inflammatory cytokine IL-10. These results indicate the anti-inflammatory effect of thyme extracts and their compounds (22).

In a study on non-obese diabetic (NOD) mice whose T cells produce relatively low amounts of IL-4, administration of recombinant interleukin-4 (rIL-4) has shown to slow down the development of diabetes in this model.

IL-6 plays a role in acute and chronic inflammation by interacting with various inflammatory responses. Depending on the nature or site of inflammation, IL-6 increases the production of acute phase proteins in response to stimuli. Irregular production of IL-6 typically found in tissues leads to low-grade inflammation that is strongly associated with many types of inflammatory diseases. Some studies have shown that IL-6 inhibits glucose-stimulated insulin secretion from pancreatic islets in experimental animal models, while other studies have shown that acute exposure to IL-6 does not affect the normal function of pancreatic islets. Recent in vitro studies have shown that IL-6 potentiates IL-1-induced NO synthesis in rats. In addition, in NOD mice, overexpression of IL-6 in islets has also been associated with the destruction of β -cells in pancreatic islets (27).

In human DM studies, IL10 "low sensitivity" or "IL10 resistance" in immune cells and macrophages has been detected (28). Interleukin IL-12 is known to induce Th1-cell differentiation and cytokine production. A link between type-1 DM and IL-12 has been suggested in NOD mice, BB rats, and humans. In addition, a correlation between IL-12 expression and destruction of insulin-producing cells and disease progression has been reported in NOD mice. Administration of IL-12 to young NOD mice has been shown to accelerate the development of diabetes by decreasing IL-4 production while increasing interferon- γ (IFN- γ) production (29). In parallel with the studies performed, in our study, measuring of serum cytokine levels of the OO group indicated that pro-inflammatory levels of IL-1 β , IL-6, IL-17, IL-12 and IFN- γ were decreased. In addition, serum levels of IL-10 and IL-4, which are anti-inflammatory cytokines secreted in response to chronic inflammation, showed an increase in IL-10 and a decrease in IL-4 levels in the OO group. Positive effects of OO seen on pro-inflammatory and anti-inflammatory cytokines makes us think that it can prevent β -cell loss by reducing inflammation and thus, slowing the progression of DM. Findings obtained from our study together with the results from many previous literatures indicate that OO had a protective effect on oxidative stress-induced tissue damage thanks to its antioxidant effect. Thus, its use as a supportive treatment should be considered. More studies are needed for better understanding of the protective effects of *Origanum* species in diabetes and to prevent or reduce organ or tissue damage that may occur in long term treatment.

4. CONCLUSION

In this study, we aimed to investigate the effect of OO in the treatment of streptozotocin-induced diabetes in rats. We concluded that OO had a protective effect on oxidative stress-induced tissue damage due to its antioxidant effect. According to the findings obtained, the OO group decreased the levels of IL-1 β , IL-6, IL-17, IL-12 and IFN- γ . In addition, serum levels of IL-10 and IL-4, which are anti-inflammatory cytokines secreted in response to chronic inflammation, showed an increase in IL-10 and a decrease in IL-4 levels in the OO group. Positive effects of OO seen on pro-inflammatory and anti-inflammatory cytokines makes us think that it can prevent β -cell loss by reducing inflammation and thus, slowing the progression of DM.

5. MATERIALS AND METHODS

5.1. Preparation of plant material and extracts

The above-ground parts of the endemic OO, whose protective effects we have investigated in the tissue damage in DM, were dusted and 15 g was weighed on a precision balance and left to maceration with EtOH (ethyl alcohol) at room temperature, the process was continued until the solvent became colorless. The solvent was evaporated in a rotary evaporator at a temperature not exceeding 50°C, and the remaining volatile solvent was dried on the hot plate until it evaporated. The obtained extracts were stored in the refrigerator at +4°C to be used in the analysis.

5.2. Animals

Male Sprague-Dawley (SD) rats (300–400 g) were housed in a room at a constant temperature of (25 \pm 2°C), with 12-h light/dark cycles, and fed on standard pellet chow and water ad libitum. The study was approved by the Marmara University, School of Medicine, Animal Care and Use Committee (020.2016.mar).

5.3. Experimental groups

Origanum extract was administered to rats intraperitoneally (i.p.) was applied as 24 rats were divided into 3 groups (n=8 per group); saline (10 ml/kg i.p.) was given to healthy rats in the Control Group (C). In the second group, rats whose blood glucose level was above 200 mg/dl after 48 hours of STZ administration, were given 10 ml/kg saline i.p. daily for 6 weeks. In the third group, rats whose blood glucose level was above 200 mg/dl 48 hours after STZ administration, were given 50 mg/kg OO extract dissolved in water i.p. daily for 6 weeks. Hyperglycemia was confirmed by measuring blood glucose levels using a glucometer 48 h after streptozotocin administration. Rats with blood glucose levels of 200 mg/dl were considered diabetic. After six weeks, blood glucose values were measured using a glucometer.

5.4. Diabetes induction with STZ administration

Streptozotocin (STZ) i.p. at a dose of 60 mg/kg (dissolved in 0.1 M citrate buffer, pH adjusted to 4.5) was administered to rats to induce diabetes. Blood samples were taken by tail-cutting method after 48 hours of administering STZ injection. Fasting blood glucose was measured with a glucometer, and rats with fasting blood glucose values higher than 200 mg/dL (11.1 mmol/L) were considered as diabetic and included in the experiment.

5.5. Biochemical assays

Biochemical analyzes were performed from blood samples taken from the heart under light ether anesthesia and from liver tissues after decapitation. Part of the tissue was stored at -80°C for the measurement of glutathione activity and lipid peroxidation (malondialdehyde levels).

Blood samples were taken from the heart under light ether anesthesia before decapitation, then kidney and liver tissues were removed. Malondialdehyde (MDA) and glutathione (GSH) measurements were made in some of the tissue samples in order to examine the oxidant damage. MDA levels were measured by the Buege method, while GSH levels were determined by the Ellman method. In serum samples, creatinine was measured to examine kidney functions, while ALT and AST were measured to test liver functions.

Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured using ELISA (Enzyme-Linked Immunosorbent Assay) kits to examine the liver function and to identify liver tissue damage. And also, serum levels of IL-1 β , IL-10, IL-4, IL-4, and IL-12 were measured using ELISA kits to investigate the anti-oxidant effects of OO.

5.6. Statistical analysis

All data of this study are expressed as mean \pm S.E.M. P-value <0.05 is considered statistically significant. Values and calculations were performed using the computer statistical program Graphpad prism 6.0 (GraphPad Software, San Diego; CA; USA). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey and Bonferroni tests.

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