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# Antioxidant effects of rosemary oil in streptozotocin-induced diabetic rats

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**Abstract**: This study designed to investigate the potential effects of rosemary oil on oxidative stress markers in streptozotocin-induced diabetic rats. The rats divided into four groups such as control group, rosemary group, diabetes group and diabetes + rosemary group. Blood samples were analyzed to assess with enzyme-linked immunosorbent assay various parameters including malondialdehyde (MDA), glutathione (GSH), super oxide dismutase (SOD). Insulin and glucose levels were also determined through autoanalyzer. The results indicated significant increase in MDA levels and significant decrease in GSH and SOD levels in the diabetes group. Following the administration of rosemary oil to streptozotocin-induced diabetic rats, a significant decrease in MDA level and significant increase in GSH and SOD levels was observed in comparison to the diabetes group. In the research, rats induced with streptozotocin-induced diabetes were displayed notably lower insulin levels compared to the control group, accompanied by significantly higher glucose levels. Upon the administration of rosemary oil to these diabetic rats, there was marked amelioration in insulin and glucose levels compared to the untreated diabetic group. These findings collectively suggest that the utilization of rosemary oil in diabetic rats potentially have positive effects on oxidative stress markers, indicating its promising role as a therapeutic intervention in diabetic conditions.

**Keywords**: Diabetes, rosemary, antioxidant, rats.

## INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose levels and insufficient insulin secretion or action from the pancreas (Maritim *et al*., 2003; Fareed *et al*., 2023). There is a consensus in understanding that oxidative stress significantly contributes to the onset and progression of complications associated with diabetes (Pham-Huy *et al*., 2008; Hussein *et al*., 2022). The escalation in reactive oxygen species observed in diabetes may arise from heightened production and/or diminished breakdown by catalase, superoxide dismutase and glutathione peroxidase antioxidants. Variations in the levels of these enzymes render tissues more susceptible to oxidative stress, thereby fostering the development of diabetic complications (Lipinski, 2001; Asmat *et al*., 2016). The generation of free radicals in diabetes leads to detrimental effects on enzymes and cellular mechanisms, further exacerbating insulin resistance owing to the presence of oxidative stress (Maritim *et al*., 2003).

Given the high cost associated with insulin and other conventional medical interventions for managing diabetes and its complications, there is a need to explore alternative strategies as complement modern pharmacotherapy. The rosemary plant, belonging to the Lamiaceae family, is a vast botanical family comprising globally around 236 genera and 6900-7200 species (Raja, 2012). Within the Lamiaceae family, notably including rosmarinic acid, numerous compounds with significant antibacterial, antiviral and anti-inflammatory effects are found (Farzaneh *et al*., 2005). One of the prominent medicinal plants in the Lamiaceae family is Rosmarinus officinalis L., commonly known as rosemary. This plant species is rich in phytochemicals such as rosmarinic acid, carnosol, camphor, ursolic acid, caffeic acid, carnosic acid and betulinic acid (Ulbricht *et al*., 2010; Saied *et al*., 2023).

The Lamiaceae family has attracted considerable research attention owing to its high polyphenol content, making it a focal point in studies investigating antioxidant compounds (Botsoglou *et al*., 2010). Research involving supplementation with rosemary essential oil in Wistar rats has evaluated catalase, glutathione peroxidase, superoxide dismutase and nitric oxide synthase activities as well as lipid peroxidation and reactive oxygen species in brain and heart tissues. Studies utilizing essential oil and carnosic acid have indicated that rosemary exhibits a capacity to mitigate oxidative stress by eliminating free radicals, inhibiting lipid peroxidation and enhancing antioxidant status in rat tissues (Botsoglou *et al*., 2010; Andrade *et al*., 2018). Rosemary has been recognized for its diverse pharmacological functions, which encompass hypocholesterolemic, antiatherogenic, antihypertensive, antioxidant, antiproliferative, antifungal, antiviral, antitumoral, hypoglycemic, anti-inflammatory, antithrombotic, hepatoprotective, antidepressant, antinociceptive, antiulcerogenic and antibacterial properties (Andrade *et al*., 2018; Neves *et al*., 2018; Fareed *et al*., 2023). These total findings underscore the potential therapeutic benefits of rosemary in health

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conditions, reflecting its significance in pharmacological research and applications.

The aim of this investigation was to carry out the potential impact of applying rosemary on oxidative stress markers in diabetic rats induced by streptozotocin. We hope that rosemary application would be beneficial as an alternative strategy to complement modern pharmacotherapy in diabetes.

## MATERIALS AND METHODS

### *Animals*

The study was totally conducted on thirty-two adult male Wistar Albino rats were utilized, maintaining standardized living conditions throughout experimental period. Following randomization, the rats were divided into four groups. Throughout the study, the animals were provided ad libitum access to both water and standard feed.

### *Materials*

Rosemary oil (Softem, Aksu Vital, Turkey) were obtained from a local medicinal herb store and this natural oil commercially produced by distillation methods. It has been suggested that the active ingredient amount of plant extracts is determined by HPLC.

### *Experimental procedure*

The control group animals (C, n=6) did not undergo any specific treatment. Animals in the rosemary group (R, n=6) were administered orally with 200 mg/kg of rosemary oil daily for a duration of three weeks. Diabetes was induced by subcutaneous injections of streptozotocin (SigmaAldrich, St. Louis, MO, USA) at dosage of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) for two consecutive days as a single daily dose in diabetes group animals (STZ, n=10). In the diabetes+rosemary group (STZ+R, n=10), 200 mg/kg rosemary oil was orally applicated daily for three weeks following diabetes was similarly induced above procedure. Six hours subsequent to the administration of streptozotocin, the rats were orally given a 5% dextrose solution for duration of three days to prevent hypoglycemia.

### *Measurements*

Confirmation of diabetes was established by measuring blood glucose levels using glucometer strips (PlusMED Accuro, Taiwan) via the tail vein one week following the streptozotocin injections. The animals exhibiting blood glucose levels that exceeded 250 mg/dl were considered as diabetic and subsequently included in the experimental procedures. At the end of the study, blood samples were collected from all animals for the determination of MDA, GSH, SOD, insulin and glucose levels.

MDA, GSH and SOD levels were assessed with ELISA (Biotek ELx800, Biotek Instrumentations, Inc, Winooski, VT, USA) using sandwich enzyme-linked immunosorbent method via commercial kits (BT Lab [Bioassay Technology Laboratory] marka ELİSA kiti). Insulin and glucose levels were measured using Abbott kits through the Abbott-C8000 autoanalyzer.

### *Ethical approval*

The experimental procedures were conducted in accordance with the ethical standards and guidelines approved by the Ethics Committee of Selçuk University Experimental Medicine Research and Application Center (Report No.2021-61).

## STATISTICAL ANALYSIS

Statistical analysis of the collected data was performed by one-way analysis of variance (ANOVA) through SPSS 19.0 software. Differences among experimental groups were assessed using Duncan's multiple range tests at the $p<0.05$.

## RESULTS

In the study, the effects of 200 mg/kg rosemary oil administration on MDA, GSH, SOD, insulin and glucose levels in diabetic rats are shown in table 1.

## DISCUSSION

Diabetes mellitus, affecting carbohydrate, protein and fat metabolism, arises from either absolute or relative deficiency in insulin secretion, often insulin resistance accompanied by this chronic disorder (Barar, 2000). Elevated blood glucose levels that are characteristic of diabetes instigate the overproduction of free radicals and this is a process central to the formation of oxidative stress in diabetes. Glucose, in the presence of metal ions, undergoes autooxidation, resulting in the generation of oxygen-free radicals that compromise cell membrane integrity through oxidative damage (Bakırel *et al*., 2008; Khalil *et al*., 2012). Furthermore, hyperglycemia induces the generation of free radicals, which impair endogenous antioxidant defense mechanisms. This impairment involves the depletion of endogenous antioxidants like glutathione and vitamin E, along with reduction in the activities of pivotal antioxidant enzymes such as SOD, GPx and CAT (Matough *et al*., 2012).

Qu *et al*. (2018) observed evident oxidative stress characterized by elevated MDA levels in diabetic group, while they have noted a significant reduction in SOD activity and GSH levels in the heart, liver and kidneys of diabetic rats.

Additionally, El-Boshy *et al*. (2015) reported a notable decrease in GSH, CAT and SOD levels, which are antioxidant markers, alongside an important increase in MDA levels within the diabetic group to the control group. Glutathione, a critical non-protein thiol, assumes a

**Table 1**: Effects of rosemary oil on MDA, GSH, SOD, insulin and glucose levels in streptozotocin-induced diabetic rats (Mean±SE).

| | MDA (µmol/L) | GSH (µg/ml) | SOD (ng/ml) | Insulin (U/ml) | Glucose (mg/dl) |
|---|---|---|---|---|---|
| C | 5.32±0.75$^{b}$ | 23.29±1.34$^{a}$ | 13.56±1.09$^{ab}$ | 14.57±1.28$^{a}$ | 93.33±4.47$^{c}$ |
| R | 5.49±0.82$^{b}$ | 24.03±1.25$^{a}$ | 14.17±0.89$^{a}$ | 13.73±0.76$^{a}$ | 91.54±4.14$^{c}$ |
| STZ | 9.73±0.88$^{a}$ | 10.53±0.91$^{c}$ | 8.49±0.75$^{c}$ | 6.70±0.77$^{b}$ | 394.60±10.26$^{a}$ |
| STZ+R | 7.24±0.70$^{b}$ | 19.89±0.98$^{b}$ | 11.34±0.72$^{b}$ | 11.86±0.74$^{a}$ | 248.71±11.55$^{b}$ |

$^{a-c}$ Different superscripts in the same column indicate that the difference between the mean values is significant ($p<0.05$).

pivotal role in orchestrating the antioxidant defense mechanisms (Khalil *et al*., 2012). This reduced form of glutathione, primarily synthesized in the liver, serves as a crucial non-enzymatic antioxidant within the antioxidant defense system. Kaplowitz *et al*. (1985) suggested that the observed depletion of GSH in alloxan-induced diabetic rats might be attributed to its utilization as a substrate by two fundamental antioxidant enzymes, namely GPx (glutathione peroxidase) and GST (glutathione S-transferase).

There was (table 1, $p<0.05$) an important increase in the level of malondialdehyde (MDA) in the diabetic group to the control group, which serves as the end product of lipid peroxidation and as a crucial marker in assessing oxidative stress. The levels of glutathione (GSH), a pivotal component in detoxification reactions and the levels of superoxide dismutase (SOD), one of the antioxidant parameters that constitute the primary defense against free radicals, exhibited a significantly decrease (table 1, $p<0.05$) in diabetes compared to the control group. These observed alterations in the present study are compatible with the researches mentioned above.

In the current study, insulin level, which is one of the biomarkers used to determine the occurrence of diabetes, notably decreased and glucose level notably increased as a result of inducing diabetes with streptozotocin (table 1, $p<0.05$). Additionally, it has been stated that hyperglycemia enhances the formation of advanced glycation end products (AGE) and oxidative/ inflammatory events (Tang *et al*., 2007), which in turn further increases the production of AGEs, thus contribute to a detrimental loop amplifying the oxidative degradation of β-cells in diabetes (Kaneto *et al*., 2007; Lenzen, 2008). Moreover, owing to the diminished expression of antioxidant enzymes in pancreatic β-cells, these cells are notably susceptible to the deleterious effects induced by ROS, which suppress insulin biosynthesis and induce apoptosis (El-Alfy *et al*., 2005; Vijayakumar *et al*., 2006).

In a study conducted in rats in which diabetes was induced with streptozotocin, it was reported that erythrocyte MDA levels significantly increased and this was accompanied by increased plasma glucose concentration (Nazem *et al*., 2015). It has been suggested that it was exists a clear correlation between lipid peroxidation and glucose concentration, which potentially contributes to heightened lipid peroxidation in diabetes mellitus (Varashree and Gopalakrishna Bhat, 2011). Certain studies have demonstrated that glucose can undergo enolization and subsequently undergo reduction by giving molecular oxygen to alpha-keto aldehydes, hydrogen peroxide and reactive oxygen species (ROS) (Jain *et al*., 1989). These compounds have been caused in the peroxidative breakdown of phospholipid fatty acids, ultimately leading to the accumulation of malondialdehyde (MDA) (Varashree and Gopalakrishna Bhat, 2011). Additionally, it has been reported that hypoinsulinemia in diabetes contributes to lipid peroxidation by upregulating the activity of fatty acyl coenzyme A oxidase enzyme, which initiates the beta-oxidation of fatty acids (Moussa, 2008). Studies have consistently shown to decrease levels of antioxidant enzymes alongside increased lipid peroxidation in diabetic animals (Mohammadi *et al*., 2010; Oyedemi *et al*., 2011).

There has been increased interest in utilizing of natural antioxidants to alleviate oxidative damage in diabetes (Al-Azzawie and Alhamdani, 2006). It is known that numerous plant species are used in folk medicine practices of diverse cultures due to their hypoglycemic properties and are therefore also used in the treatment of diabetes (Bakırel *et al*., 2008). These plants include Rosmarinus Officinalis L., which is widely consumed for various medicinal practices. Rosmarinus officinalis finds widespread application in the food and cosmetic industries, in various medical applications such as respiratory and skin disorders, as well as in the treatment of disorders associated with the gastrointestinal, nervous, menstrual, cardiovascular, genitourinary, hepatic and reproductive systems (Stefanovits-Bányai *et al*., 2003; de Macedo *et al*., 2020). Analysis of diverse rosemary extracts has shown that the primary pharmacologically active components of the rosemary plant are phenolic acids, phenolic diterpenes and triterpenes (Tomi *et al*., 2016). It has been reported that carnosol, carnosic acid and rosmarinic acid, categorized among the phenolic compounds in rosemary plant, demonstrate diverse pharmacological effects, including anti-inflammatory, antioxidant, antiviral and antibacterial effects (Farkhondeh *et al*., 2019).

In our study, the application of rosemary oil to diabetic rats resulted in an important decrease (table 1, $p<0.05$) in

MDA levels when compared to the diabetic rats. The observed decrease in GSH and SOD levels of diabetic rats significantly increased with the application of rosemary oil to diabetic rats when compared to the diabetic group (table 1, $p<0.05$). When rosemary oil was administered to rats induced with diabetes via streptozotocin, there was (table 1, $p<0.05$) a significant increase in insulin levels and an important decrease in glucose levels compared to the diabetic group. These outcomes are consistent with previous observations by Krishnakumar *et al*. (1999) and Nazem *et al*. (2015), highlighting the hypoglycemic and antioxidant effects of rosemary extract in diabetic rats.

Khalil *et al*. (2012) has been shown that *Rosmarinus officinalis* corrected blood glucose and also increased antioxidant activity in experimental mice. In this study, it was reported that MDA level was increased in diabetic rats and this increase was corrected as a result of rosemary oil application. Furthermore, it was noted that a reduction in GST, CAT and GPx levels was observed in diabetic rats, but this decline was reversed with the administration of rosemary oil. Khalil *et al*. (2012) also stated that rosmarinus officinalis has hypoglycemic activity. It has been suggested that this hypoglycemic effect in diabetic rats may be possible through mechanisms such as insulinomimetic effect, inhibition of endogenous glucose production, stimulation of glucose uptake by peripheral tissue, activation of gluconeogenesis in liver and muscle (Khalil *et al*., 2012).

In another study, it was observed that MDA level in rabbits with diabetes induced by alloxan significantly increased when compared to the control group. It has been suggested that the application of 200 mg/kg Rosmarinus officinalis extract to diabetic rats inhibited this increase in MDA level on both the 5th and 8th days. It was stated that the decreased SOD and CAT activities in the diabetic group showed a significant increase on the 5th day with 200 mg/kg rosemary extract administration to diabetic rabbits (Bakirel *et al*., 2008). It has been reported that MDA level was increased and SOD activity and GSH levels was significantly reduced in the heart, liver and kidney of rats with streptozotocin-induced diabetes compared to the normal group. It was also indicated that the application of Rosmarinic acid and Carnosic acid resulted in a notable reduction of oxidative stress in diabetic rats (Qu *et al*., 2018). El-Boshy *et al*. (2015) showed that the depletion in the antioxidant system was corrected by the application of rosmarinus officinalis extract to diabetic rats. Cheung and Tai (2007) reported that there was increase in the antioxidant system and decrease in lipid peroxidation serum levels in diabetic rabbits administered Rosmarinus officinalis extract.

Hölihan *et al*. (1985) and Wu *et al*. (1982) emphasized that the rosemary plant's antioxidant characteristics are attributed to its abundance of isoprenoid quinones. These compounds function as chain terminators of free radicals and chelators for reactive oxygen species. Additionally, Gordon (1990) has indicated that the phenolic compounds in commercially available rosemary plant extracts serve as primary antioxidants to convert them into more stable products by reacting with lipid and hydroxyl radicals. Fang and Wada (1993) emphasized that these compounds can act as metal ions chelators, particularly Fe+2, thereby reducing the rate of formation of oxygen-derived reactive species.

Rosmarinic acid has been suggested to exhibit free radical scavenging activity in hepatic stellate cells by increasing the synthesis of glutathione and participating in NF-κB-dependent inhibition of MMP-2 activity (matrix metallopeptidase-2). It has also been suggested to have the ability to revert activated hepatic stellate cells to passif cells, ultimately to inhibit MMP-2 activity. Rosmarinic acid has been reported to suppress lipid peroxidation, reduce reactive oxygen species formation and increase cellular GSH in HSC-T6 cells (Adomako-Bonsu *et al*., 2017; Lu *et al*., 2017). Nuclear factor-like 2 (Nrf2) is responsible for the transcription of genes encoding antioxidant enzymes and it was reported that its expression increased after treatment with Rosmarinus officinalis (de Oliveira *et al*., 2019).

Elevated blood glucose levels (hyperglycemia) contribute to oxidative stress by inducing free radicals production. This process contributes to the onset and progression of diabetic complications, including atherosclerosis, hyperlipidemia, hypertension and damage to various tissues and cells, notably pancreatic β-cells. A study involving oral administration of ethanol rosemary extract has demonstrated a reduction in blood glucose levels in both normoglycemic and glucose-hyperglycemic rabbits (Bakırel *et al*., 2008). El-Boshy *et al*. (2015) reported a notable antihyperglycemic effect leading to an important reduce in fasting blood glucose in diabetes associated with *Rosmarinus officinalis* extract. It has been suggested that Rosemary may stimulates insulin secretion from remaining or renewed β-cells (Cheung and Tai, 2007) and that this may be due to the increase in the secretion of betatrophin hormone, which promotes the proliferation of insulin producing cells in pancreas (Yi *et al*., 2013). Ayaz (2012) suggested that the hypoglycemic effect of the aqueous extract of *Rosmarinus officinalis* could be attributed to its ability to stimulate insulin secretion from the pancreas β-cells in diabetic rats.

## CONCLUSION

Based on the results obtained in the study, it was concluded that rosemary oil could alleviate the negative effects of diabetes on these parameters due to the significant changes determined in MDA, GSH and SOD levels with the application of rosemary oil to rats with diabetes induced by streptozotocin. However, future researches on different doses and durations of *Rosmarinus*

*officinalis* are needed to elucidate the exact mechanism of its antioxidant effect in animal and humans.

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