NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2025;62:145–149
https://doi.org/10.29399/npa.28586

In Diabetic Aged Female Rats, Resveratrol Supplementation Prevents Retinal Tissue Damage By Increasing Antioxidant Activity Through SIRT1 Gene Expression

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ABSTRACT

Introduction: The present study was carried out to investigate how resveratrol administration affects retinal SIRT1 levels and retinal tissue damage in diabetic elderly female rats.

Methods: A total of 24 elderly female rats were divided equally into 4 groups (G): G1, Control; G2, Control + Resveratrol; G3, Diabetes; G4, Diabetes + Resveratrol. Experimental diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) in G3 and G4. The G2 and G4 were given intraperitoneal (ip) resveratrol (5 mg/kg/day) for 4 weeks in addition to the normal diet. After 4-weeks of resveratrol treatment, Sirtuin 1 (SIRT1) gene expression and malondialdehyde (MDA) ve glutathione (GSH) levels were determined by PCR and ELISA, respectively, in retinal tissue samples of the animals.

Results: The highest retinal MDA values were in the diabetes group (G3), the highest retinal GSH levels were in the Diabetes + Resveratrol group (G4). The retinal MDA and GSH levels of the other groups were not different from each other. The highest retinal SIRT1 expression values were in the Diabetes + Resveratrol (G4) group. The retinal SIRT1 expression values of the diabetes group (G3) were lower than G4, and higher than the G1 and G2. Retinal SIRT1 expression values of the G1 and G2 were not different from each other.

Conclusion: Resveratrol supplementation prevented retinal tissue damage that occurs in diabetic-aged female rats. This antidiabetic effect of resveratrol supplementation occurs by increasing both antioxidant activity and SIRT1 expression in diabetic-aged rats.

Keywords: Aged female rat, diabetes, resveratrol, retina, SIRT1, tissue damage.

Cite this article as: Atacak A, Gümüş H, Gülbahçe Mutlu E, Baltacı SB, Moğulkoç R, Baltacı AK. In Diabetic Aged Female Rats, Resveratrol Supplementation Prevents Retinal Tissue Damage By Increasing Antioxidant Activity Through SIRT1 Gene Expression. Arch Neuropsychiatry 2025;62:145–149.

INTRODUCTION

Diabetes mellitus (DM) is now recognized as a global public health problem. Diabetic retinopathy (DR), which is the leading cause of blindness in adult individuals, occurs as a result of a common complication of DM (1). Diabetic patients may have multiple symptoms of eye diseases, including keratitis and DR, which accelerate the formation of cataracts. Therefore, if diabetic retinopathy is not tightly controlled, it can lead to permanent loss of visual function (2).

It has been reported that oxidative stress caused by high glucose levels can damage human lens epithelial cells and trigger cataract formation (3). It is known that retinal tissue damage develops more rapidly in patients with DM (4). In recent years, many treatment options have been developed for the late stages of diabetic retinopathy. These treatment options often target vasculopathy of the retina (1). Treatment methods that can reduce the incidence and/or prevent the progression of DR, which is accepted as a common neurovascular complication of diabetes, are also very limited (1,5). In DR, dysfunctions in neuronal and glial functions are generally considered occuring before vascular abnormalities. This is because it has been demonstrated in the investigation of retinal functions in both diabetic humans and experimental diabetic animal models (1,5).

Highlights

- **Diabetes causes tissue damage to the retina in elderly female rats.**
- **Resveratrol can prevent retinal oxidant stress in diabetic aged female rats.**
- **Resveratrol is a powerful stimulant of SIRT1 that prevents retinal damage.**

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Received: 24.08.2023, **Accepted:** 24.01.2024, **Available Online Date:** 18.06.2025

Resveratrol (trans-3,4,5-trihydroxystylben), a polyphenol phytoalexin, is abundant in different plants such as grapes, peanuts and strawberries (6). Resveratrol has been reported to have numerous biological functions due to its cardioprotective, anticoagulant, therapeutic effects on tumoral events as well as its preventive effects on tissue damage (7). In recent years, the antidiabetic effect of resveratrol has been emphasized in the prevention or treatment of diabetes complications, including DR (8,9).

Sirtuin 1 (SIRT1) is the most important sirtuin family member, affects cell aging, differentiation, apoptosis, and lipid and glucose metabolism (10,11). SIRT1 can alleviate tissue damage in endothelial tissue as well as improve against vascular inflammation by preventing the decrease in vascular pressure. It may also protect against endothelial dysfunction (12). Therefore, previous relevant studies have suggested that SIRT1 may restrict retinal vascular endothelial cell dysfunction under hyperglycemic state (13). SIRT1 is also known to play a critical role in preventing DR (4). Although the mechanism of SIRT1 in inhibiting DR has not been defined, SIRT1 can prevent lipid peroxidation in retinal tissue cells and plays a critical protective role in the regulation of apoptosis (4).

Based on the fact that resveratrol is an activator of SIRT1, regulation of SIRT1 by resveratrol may be effective in preventing inflammation, lipid peroxidation, cell death and loss of endothelial function (14). However, there are conflicting data on the subject. Contrary to previously published data showing significant effects in retinopathy associated with SIRT1 deficiency (15). Michan et al. (16) has shown that increased SIRT1 gene expression does not alter pathological neovascularization or neuronal degeneration in mouse retinal neurons or vessels. In addition, it was reported that treatment with resveratrol, did not show a protective effect against the development of retinopathy (16). It has been previously reported that a 16-fold increase in SIRT1 in hippocampal mouse neurons has no effect on synaptic plasticity and learning and memory (17). It has been reported that increasing SIRT1 over 8 times in the heart may have a negative effect on cardiac functions (18). Studies in different mouse models of human diseases have shown that the high level of increase in SIRT1 gene activity does not cause protective effects, whereas moderate SIRT1 gene activation may be protective (17).

As a result, resveratrol was used as a preventive treatment against diabetic retinopathy. However, the mechanisms underlying this protective effect are not fully elucidated. The aim of this study was to investigate how resveratrol supplementation affects retinal SIRT-1 levels and tissue damage in diabetic elderly female rats.

METHODS

Animal Material and Groups

This study was carried out on 24 adult old female Wistar rats (16 months old) obtained from Selçuk University Experimental Medicine Research and Application Center. The rats were fed ad libitum and kept in 12-h light/dark cycle. The study protocol was approved by the ethics committee of the same center (2019-6). A total of 24 elderly female Wistar rats were divided into 4 equal groups as follows:

G1, Control Group (n=6): The group was fed with a standard diet in which no administration was applied.

G2, Resveratrol Group (n=6): The group was given intraperitoneal (ip) resveratrol (5 mg/kg/day) for 4 weeks in addition to the normal diet.

G3, Diabetes group (n=6): The group in which diabetes was induced by 40 mg/kg of ip Streptozotocin (STZ).

G4, Diabetic Resveratrol Group (n=6): The group in which diabetes was induced by ip STZ (40 mg/kg) and then resveratrol supplemented for 4 weeks (5 mg/kg/day).

Experimental Diabetes

In order to induce experimental diabetes, the rats in G3 and G4 were injected ip STZ (Sigma S-0130) of 40 mg/kg. 6 days after the injections, blood glucose levels in the tail vein of the animals were measured using a diagnostic glucose kit. Rats with a blood glucose of 300 mg/dL and above were postulated as diabetic (19).

Resveratrol Application

Resveratrol (R5010-Sigma) was applied intraperitoneally to the rats in G2 and G4 daily at 5 mg/kg for four weeks.

Taking Tissue Samples

After the end of the four-week applications, the animals were sacrificed under general anesthesia by intramuscular administration of the combination of Ketalar (60 mg/kg), Parke-Davis and xylazine (5 mg/kg) "Rompun, Bayer". Retinal tissue samples of sacrificed animals were taken. Retinal tissue samples taken were kept at -80 C° until analysis time.

Biochemical Analysis

Determination of Tissue Malondialdehyde (MDA): Retinal MDA levels were determined using the method of Mihara and Uchiyama (20). Results are given as nmol/g tissue.

Tissue Glutathione (GSH) Analysis: Retinal GSH levels were measured using Ellman's method (21). The data obtained were given as mg/gr tissue.

Real-Time PCR Analysis

Retinal mRNA levels were determined with a real-time PCR system. The change in SIRT1 expression due to diabetes and resveratrol treatment was measured using a real-time RT-PCR in eye tissue mRNA isolates.

RNA Isolation

Total RNA was isolated from retinal tissue (50 mg) using Nucleozol (Macherey-Nagel, Düren, Germany) RNA Isolation Kit according to the manufacturer's instructions. The purity and amount of RNA obtained was measured using a SMA1000 model spectrophotometer (Merinton, China) device. In addition, isolated RNA were run in 1% agarose gel to display specific 18S and 28S RNA bands.

Real-Time Quantitative PCR Analysis

The cDNA was obtained with the Bio-Rad (California, USA) cDNA synthesis kit using 1 µg of RNA of each sample. The cDNA mix, with a total volume of 20 µl, contained 1 µg of RNA, 4 µl of cDNA master buffer, and 1 µl of reverse transcriptase enzyme. The obtained cDNAs were used for quantitative real-time PCR amplification of the targeted genes and reference gene. The target and reference genes were synthesized by the manufacturer company SENTEGEN (Ankara, Türkiye). The bases belonging to these primers are given in Table 1.

Samples were amplified in a volume of 20 µl reaction mix, with a concentration of 1 µl of forward and reverse primers, 10 µl of Lightcycler SYBR Green (Roche Diagnostics, Germany), 5 µl cDNA, nuclease-free water to 20 µl.

For PCR, each sample was tested in triplicate and the results were normalized using the amplification of the same cDNAs using the reference genes-actin calculations with ΔΔCt.

Analysis of the results obtained

Reference and target CT values of each sample obtained using the quantification analysis program of the Biorad connect device were taken. Calculations were made on the Delta CT formula and the results were obtained for statistical analysis.

Statistical Evaluations

Statistical evaluation of the findings was made with the IBM Statistical Package for Social Sciences (SPSS) program version 22.0 computer package program, and the arithmetic means and standard deviations of all parameters were calculated. "Shapiro-Wilk" test to determine the homogeneity of the data was done and it was determined that the data showed normal distribution. The Kruskal-Wallis H test was used to detect differences between groups, and the Mann-Whitney U test was used to determine which group caused the difference. Differences at $p<0.05$ were considered significant.

RESULTS

The highest retinal MDA values were in the diabetes group (G3) ($p<0.05$). Retinal MDA levels of the general control (G1), Control + Resveratrol (G2) and Diabetes + Resveratrol (G4) groups were not different from each other (Figure 1). The highest retinal GSH values were in the Diabetes + Resveratrol group (G4) ($p<0.05$). Retinal GSH levels of the general control (G1), Control + Resveratrol (G2) and Diabetes (G3) groups were not different from each other (Figure 2).

The highest retinal SIRT1 expression values were in the Diabetes + resveratrol (G4) group ($p<0.05$). The retinal SIRT1 expression values of the diabetes group (G3) were lower than G4 ($p<0.05$), and higher than the General control (G1) and Control + Resveratrol (G2) groups ($p<0.05$). Retinal SIRT1 expression values of the general control (G1) and Control + Resveratrol (G2) groups were not different from each other (Figure 3).

DISCUSSION

Discussion of Retinal Lipid Peroxidation Parameters

In our study, the highest retinal tissue MDA values were in the diabetes group (G3). The retinal MDA levels of the other groups were not different from each other.

Although the pathogenesis of diabetic retinopathy is not certain, the oxidative stress caused by hyperglycemia plays an important role. The main pathology here is that excessively reactive oxygen species cannot be neutralized with antioxidants (22). There is increasing evidence that retinal tissue damage occurring in DR triggers events that lead

Tablo 1. Primers for real-time quantitative PCR

Gene	Forward primer	Reverse primer
SIRT-1	CATAGGTTAGGTGGCGAGTATG	GTTGGTGGCAACTCTGATAAATG
B-actin	TGTGACGTTGACATCCGTAAAG	GGCAGTAATCTCCTTCTGCATC

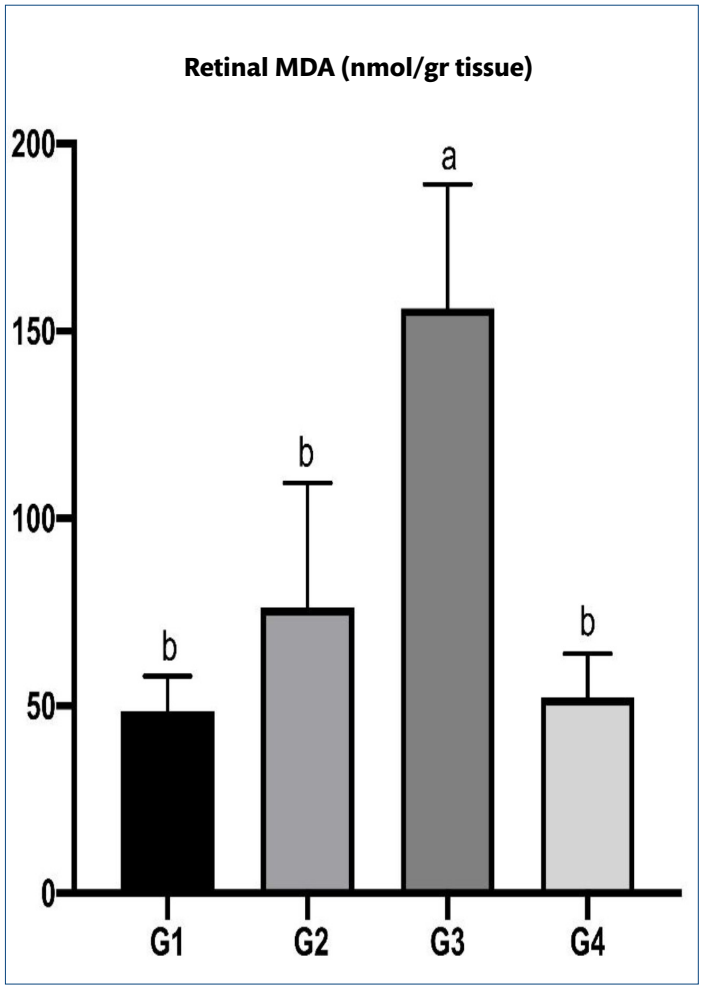

Figure 1. Retinal MDA levels of the study groups (differences between the means with different letters in the same column are significant [$p<0.05$], [a > b]).

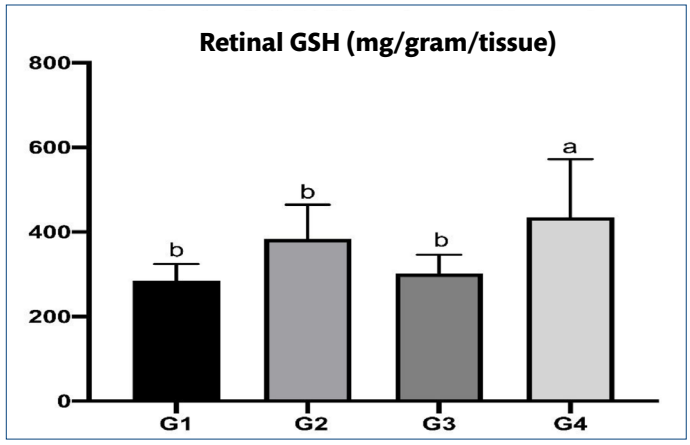

Figure 2. Retinal GSH levels of the study groups (differences between the means with different letters in the same column are significant [$p<0.05$], [a > b]).

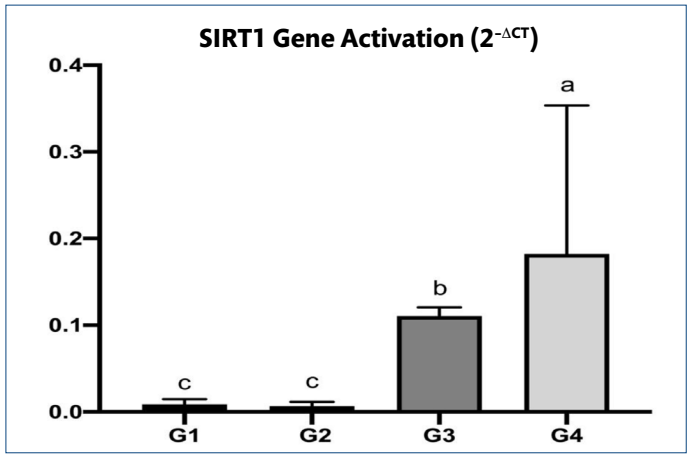

Figure 3. Retinal SIRT1 gene expression of the study groups ($2^{-\Delta CT}$) (differences between the means with different letters in the same column are significant [$p<0.05$], [a > b >c]).

to progressive blindness. It was suggested that resveratrol may have therapeutic potential in DR due to its antidiabetic and oxidant damage preventive effects (23).

Free radicals increase in ischemia-reperfusion injury due to hypoxic damage in tissues, and membrane-related polyunsaturated fatty acids cause tissue damage by binding to free radicals (24). Malondialdehyde levels, an indicator of lipid peroxidation, increase in ischemia-reperfusion injury (24). Resveratrol, on the other hand, prevents tissue damage in ischemia-reperfusion injury with its antioxidant properties (25,26). Based on this point, Deng et al. (27) reported that tissue damage in the ischemic rat retina can be prevented with resveratrol supplementation. This effect of resveratrol was associated with the decreased production of inflammatory mediators that cause tissue damage (27). Moine et al. (28) showed that retinal tissue damage caused by oxidation and photo-oxidation reactions can be prevented with resveratrol supplementation. Similarly, it has been reported that the survival of retinal ganglion cells associated with ischemia-reperfusion injury has increased with resveratrol administration (29). These results show that resveratrol can be used in the prevention of retinal tissue damage. In our study, we determined higher MDA levels in the retina of diabetic elderly rats compared to other groups, which reversed with resveratrol administration. This finding is consistent with the findings of the data above and emphasizes the antioxidant properties of resveratrol.

The highest retinal tissue GSH values were determined in the Diabetes + Resveratrol group (G4). The retinal GSH levels were not different among other groups. Glutathione is an important endogenous antioxidant and plays a critical role in protecting against oxidative stress. It has been reported that low doses of resveratrol have a therapeutic effect on the liver by increasing GSH levels in ischemic tissue damage (30,31). High blood sugar levels as a result of diabetes, diabetic retinopathy also increases retinal tissue damage and leads to fibrotic changes (32). Resveratrol prevents tissue damage that occurs in diabetic retinopathy (32). A growing body of evidence suggests the role of oxidative stress in age-related visual impairments. It is accepted that resveratrol can be a good candidate for the correction of age-related visual disorders, especially due to its antioxidant and anti-inflammatory activities (33).

In one study, four months of resveratrol administration (5 mg/kg/day) was shown to significantly reduce hyperglycemia in retinal tissue and improve the retinal apoptosis in diabetic rats (22). In the study we conducted, we found the highest retinal GSH values in the Diabetes + Resveratrol group. These results show that resveratrol increases antioxidant activity in diabetic rats

Discussion of Retinal SIRT1 Gene Expression

Diabetic retinopathy is the most important known microvascular complication of diabetes. Itcan cause eye impairment and even complete loss of visual function. Chronic subclinical retinal inflammation has been shown to be the main contributor of many vascular lesions in diabetic retinopathy. Although factors such as proinflammatory cytokines and/or oxidative stress associated with hyperglycemia have not been clearly defined yet, they play a critical role in the development of diabetic retinopathy (34). Sirtuin 1 is a long-lived gene that is thought to be critical in the development of advanced treatment methods due to its association with many events such as metabolism, aging, cancer and neurodegeneration (35). Endothelial dysfunction and vascular inflammation caused by hyperglycemia is a precursor and a powerful predictor of diabetic retinopathy (35). Sirtuin 1 may be effective in preventing inflammation, lipid peroxidation, cell death, and loss of endothelial function seen in diabetic retinopathy (12). Previous relevant studies hypothesized that SIRT 1 could limit these dysfunctions seen in diabetic retinopathy (13). Therefore, activation of SIRT1 gene expression by resveratrol is beneficial in preventing inflammation, lipid peroxidation, cell death, and loss of endothelial cell function, which are the common markers of diabetic retinopathy (14).

In our study, we obtained the highest retinal SIRT1 expression values in the diabetic (G4) group with resveratrol was applied. The retinal SIRT1 expression values of the diabetic group (G3) without resveratrol application were lower than G4, but higher than the control groups (G1) and resveratrol supplemented group (G2).

Kowluru et al. (11) reported that SIRT1 expression is suppressed in diabetic retinopathy and the most important event leading to suppression of SIRT1 is increased tissue damage in the retina [11]. In the same study, it was suggested that preventing retinal SIRT1 inhibition may also prevent the development of diabetic retinopathy (11). Besides being a powerful stimulant with antioxidant properties, resveratrol is an activator of SIRT1 (14). Activation of SIRT1 by resveratrol also reacts to prevent tissue damage by suppressing inflammation and increasing antioxidant activity in various pathological conditions, including DR (13). Mohammad et al. (34) showed that SIRT1 expression in vitreous samples of patients with diabetic retinopathy decreased compared to controls, and treatment with SIRT1 activators could protect retinal endothelial barrier dysfunction caused by diabetes. Resveratrol is thought to be useful in the treatment of diabetes mellitus and its complications (36). Activation of SIRT1 is thought to be critical in the antidiabetic effects of resveratrol. SIRT1 activation leads to a decrease in circulating levels of proinflammatory cytokines and proapoptotic cells by activating the antioxidant system. The result is the antidiabetic effects of resveratrol (36). In our study, we found the highest increase in SIRT1 gene expression in diabetic rats supplemented with resveratrol. However, SIRT1 expression was higher in diabetic rats that were not given resveratrol compared to control groups. This finding contrasts with the reports (11,34) where SIRT1 expression is reduced in diabetic retinopathy. In our study, the old female rats were used and a single dose STZ (40 mg/kg) was administered to animals to induce diabetes, which may be the reason for the increased SIRT1 expression in the diabetic group without resveratrol supplementation. In our study, it is certain that the increased SIRT1 expression in the diabetic elderly female rats compared to the control groups is not sufficient to prevent retinal tissue damage.

The findings of our study show that retinal oxidative stress can be prevented with resveratrol supplementation in diabetic elderly female rats. This protective effect of resveratrol administration in diabetic elderly female rats may occur by promoting retinal antioxidant activity through SIRT1 gene expression.

As a result resveratrol supplementation in diabetic elderly female rats prevented retinal tissue damage by increasing antioxidant activity through SIRT1 gene expression.

Ethics Committee Approval: The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University's Experimental Medicine Research and Application Center (2019–6).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- AKB, RM, HG; Design- AKB, RM, HG; Supervision- AKB; Resource- AKB, RM, HG; Materials- AA, EGM, SBB; Data Collection and/or Processing- AA, EGM, SBB; Analysis and/or Interpretation- AKB, RM, HG; Literature Search- AA, EGM, SBB; Writing- SBB, AKB; Critical Reviews- AKB, RM, HG.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: This study was supported by the Scientific Research Projects Coordinatorship of Selcuk University (SUBAPK; project no. 19202021).

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