ORIGINAL ARTICLE

Phnx Med J. July 2022, Volume 4 No 2
DOI: 10.38175/phnx.1103944

Effects of Cinnamon on VEGF and NF-κB Immunoreaction in the Lung Tissue of Diabetic Rats

Tarçının Diyabetik Sıçanların Akciğer Dokusunda VEGF ve NF-κB İmmünoreaksiyonu Üzerindeki Etkileri

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ABSTRACT

Objective: *Diabetes mellitus is a metabolic disorder described as hyperglycemia induced by insulin deficiency or resistance. Increasing evidence in studies has shown that the lung is the target of diabetic complications. According to traditional medicine theories, cinnamon is considered a supportive treatment method for diabetics. The aim of this study is to investigate the effect of cinnamon on the immunohistochemical expression of VEGF and NF-κB in lung tissue of streptozotocin-induced experimental diabetic rats.*

Material and Method: *Thirty-two male rats were randomly divided into four groups: Diabetes, Diabetes + cinnamon, Cinnamon, and Control. The immunohistochemical expression of VEGF and NF-κB in the lung tissue was determined by using the streptavidin-biotin complex method.*

Results: *It was determined that while cinnamon application alone did not change VEGF expression in lung tissue, the decreased VEGF expression in the diabetes group increased with the cinnamon application. There was no significant difference in the intensity of NF-κB expression between the control and cinnamon groups. As a remarkable finding, in the diabetic group's lung tissue, there were strong positive NF-κB reactions. In addition, a weak positive NF-κB reaction was detected in the diabetes+cinnamom group.*

Conclusion: *As a result, in our study cinnamon caused reduced the increase in NF-κB expression caused by diabetes and increased the decreased VEGF expression. In conclusion, we believe that this work will be valuable in understanding possible cytokine mechanism changes that may occur in lung tissue as a result of diabetes and the development of therapeutic techniques.*

ÖZET

Amaç: *Diabetes mellitus, insülin eksikliği veya direncinin neden olduğu hiperglisemi olarak tanımlanan metabolik bir hastalıktır. Çalışmalarda artan kanıtlar, akciğerin diyabetik komplikasyonların hedefi olduğunu göstermiştir. Geleneksel tıp teorilerine göre tarçın, şeker hastaları için destekleyici bir tedavi yöntemi olarak kabul edilmektedir. Bu çalışmanın amacı, tarçının streptozotosin ile indüklenen deneysel diyabetik sıçanların akciğer dokusunda VEGF ve NF-κB'nin immünohistokimyasal ekspresyonu üzerindeki etkisini araştırmaktır.*

Gereç ve Yöntem: *Otuz iki erkek sıçan rastgele dört gruba ayrıldı: Diyabet, Diyabet + tarçın, Tarçın ve Kontrol. VEGF ve NF-κB'nin akciğer dokusunda immünohistokimyasal ekspresyonu, streptavidin-biotin kompleksi kullanılarak belirlendi.*

Bulgular: *Tarçın uygulamasının tek başına akciğer dokusunda VEGF ekspresyonunu değiştirmezken, diyabet grubunda tarçın uygulaması ile azalmış VEGF ekspresyonunun arttığı belirlendi. Kontrol ve tarçın grupları arasında NF-κB ekspresyonunun yoğunluğunda anlamlı bir fark yoktu. Dikkat çekici bir bulgu olarak, diyabetik grubun akciğer dokusunda güçlü pozitif NF-κB reaksiyonları vardı. Ayrıca diyabet+cinnamom grubunda zayıf pozitif NF-κB reaksiyonu tespit edildi.*

Sonuç: *Sonuç olarak bialışmamızda tarçın diyabetin neden olduğu NF-κB ekspresyonundaki artışın azalmasına, azalmış VEGF ekspresyonunun ise artmasına neden olmuştur. Bu bakımdan, çalışmamızda elde edilen bulguların diyabet sonucu akciğer dokusunda meydana gelebilecek olası sitokin mekanizması değişikliklerinin anlaşılmasında ve terapötik tekniklerin geliştirilmesi açısından değerli olacağı kanaatindeyiz.*

Keywords:
Cinnamon
Diabetes
Lung
NF-κB
VEGF

Anahtar Kelimeler:
Tarçın
Diyabet
Akciğer
NF-κB
VEGF

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder described as hyperglycemia induced by insulin deficiency or resistance, with long-term consequences for several organs (1). DM is a health problem associated with many serious complications. Increasing evidence in studies has shown that the lung is the target of diabetic complications (2). Predisposition to infections, pneumonia, asthma, pulmonary fibrosis, and chronic obstructive pulmonary disease are disorders induced by diabetes in the lungs (3). Today, it has been shown that alternative treatments are needed to control diabetes and reduce its complications (4). According to traditional medicine theories, cinnamon is considered a supportive treatment method for diabetics (5). Cinnamon is a spice that contains a wide range of active phytochemical compounds that have antioxidant

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Cite as: Ertuğrul T, Sevilgen G. Effects of Cinnamon on VEGF and NF-κB Immunoreaction in the Lung Tissue of Diabetic Rats. Phnx Med J. 2022;4(2):72-77.
Received: 15.04.2022 **Accepted:** 13.05.2022

properties (6). It stimulates the production of insulin-sensitive glucose transporters, which leads to lower insulin resistance (7).

Nuclear factor-kappa B (NF-κB) is a transcription factor that regulates gene expression and codes for chemokines, immune response surface receptors, cytokines, cell adhesion molecules, and inflammation (8). It also affects the signaling onset for cell differentiation and apoptosis inhibition (9). NF-κB is well known for its ability to aggregate an inflammatory response by regulating the expression of numerous inflammatory factors (10). This is accomplished by positively and negatively controlling the expression of a large number of important genes involved in the process (11).

Vascular endothelial growth factor (VEGF) is a angiogenic factor that induces the proliferation and migration of vascular endothelial cells as well as the permeability of blood vessels (12). VEGF plays a crucial role in diabetic retinopathy, inflammatory diseases, and acute lung injury. Hypoxia, different growth factors, cytokines, and other extracellular substances can all affect VEGF expression (13). It is known that there is a significant expression of VEGF in the normal lung without significant mitogenesis or angiogenesis (14). Moreover, VEGF can act as a paracrine survival factor for lung epithelial cells and endothelial cells (15).

This study's main objective is to investigate the effect of cinnamon on the immunohistochemical expression of VEGF and NF-κB, which are also expressed by many tissues and cells in the lung tissue of experimental diabetic rats induced by streptozotocin (STZ).

MATERIAL AND METHOD

Animal material

This study was approved by the Ondokuz Mayis University Animal Experiments Local Ethics Committee (dated: 11.03.2020, approval number: 68489742-604.01.03-E.6122). In this study, 32 male rats weighing 250-300 g were used. The rats were housed in a standard cage with 12 hours of light and 12 hours of darkness in a 22°C ambient temperature environment, and they were given ad libitum food and tap water.

Experiment groups

450 mg of STZ (Sigma, S0130-1G) was prepared by dissolving in 10 ml of distilled water and administered to diabetic groups (16). Thirty two rats were randomly divided into four groups. No application was made in the control group (n=8). The cinnamon group (n=8) received cinnamon extract by oral gavage at a dose of 0.5 mg/kg for 14 days (17). In the diabetes group (n=8): a single intraperitoneal injection of STZ at a dose of 45 mg/kg was used to induce experimental diabetes. Diabetes + cinnamon group (n=8): experimental diabetes was induced by a single intraperitoneal injection of STZ (45 mg/kg) and the cinnamon extract was administered to the STZ-induced diabetic rats (0.5 mg/kg for 14 days by oral gavage). Then, the rats in all groups were sacrificed, and lung tissue samples were collected for immunohistochemistry. The lung tissue samples were fixed in 10% formaldehyde solution, and the tissue sections were taken with a thickness of 5 μm from the prepared paraffin blocks.

Determination of blood glucose levels

A glucometer (PlusMED Accuro) was used to take blood from the hungry animals' tail vein 8 hours before the start of the trial to determine their blood glucose level preprandial. Animals involved in the study with a glucose level of 300 mg/dL had their preprandial blood glucose level measured for 8 hours on the 3rd day of STZ practice. From day 3 of STZ practice, cinnamon extract was administered by oral gavage for 14 days.

Immunohistochemistry

Using the Streptavidin biotin complex method, five-micrometer lung sections were stained immunohistochemically using mouse monoclonal VEGF (1/500 dilution, Santa Cruz Biotechnology, sc7269) and mouse monoclonal NF-κB (1/500 dilution, Santa Cruz Biotechnology, sc8008) primary antibodies (18). The secondary antibody was Histostain Plus (Zymed kit: 85-6743, United States). Following deparaffinization, sections were heated in a microwave oven at 700 W for antigen retrieval in a citrate buffer (pH:6) solution. The tissues were incubated in a 3% hydrogen peroxide solution to block endogenous peroxidase activity. To prevent nonspecific protein binding in sections, serum from the kit was instilled after washing with phosphate buffer solution (PBS). The primary antibody was applied, and the samples were kept at +4 0C overnight. In the negative control group, only PBS solution was used. After washing, sections were instilled with biotinylated secondary antibody and incubated at streptavidin-horseradish peroxidase complex. The final stage involved using 3,3'-diaminobenzidine (DAP) as a chromogen and covering the slides with entellan after hematoxylin counterstaining.

Immunohistochemical examination

The intensity of positive staining in immunohistochemical examination was evaluated semiquantitatively using a standard four-point scoring scale for intensity being scored as negatively (-), weakly (+), moderately (++), strongly (+++) stained (19). A Nikon digital-sight imaging system was used with a Nikon Eclipse 50i microscope to take histological pictures.

RESULTS

VEGF Expression

In alveolar epithelial cells, bronchial and bronchiole epithelial cells, smooth muscle cells, and smooth muscle cells of the median layers of large vessels, various intense reactions were observed when the VEGF immunohistochemical expression results were evaluated in general. Also, VEGF immunopositive cells were observed in the connective tissue surrounding the bronchi and bronchioles, alveolar macrophages, as well as the interalveolar areas and bronchial-associated lymphoid tissue (BALT) (Figure 1A, 1B, 1C, 1D). It was determined that while cinnamon application alone did not change VEGF expression in lung tissue, the decreased VEGF expression in the diabetes group increased with cinnamon application. The semi-quantitative analysis between groups for VEGF immunohistochemical staining are summarized in Table 1.

NF-κB Expression

In lung tissues of all groups, there were positive immunoreactions were observed in the alveolar epithelial

Table 1: Results of semi-quantitative analysis of VEGF and NF-κB immunohistochemical reactions in lung tissue.

	VEGF	NF-κB
Control group	++	++
Diabetes group	+	+++
Diabetes + cinnamom group	++	+
Cinnamon group	++	++

Semiquantitative scoring of immunostaining intensities: -, negative; +, weak; ++, moderate; +++, strong.

cells, bronchial and bronchiolar epithelial cells, and smooth muscle cells. When the immunostaining in the groups was examined no difference was observed in NF-κB immunoreaction between the control and cinnamon groups. As a remarkable finding, in the diabetic group's lung tissue, there were strong positive NF-κB reactions. In addition, a weak positive NF-κB reaction was detected in diabetes + cinnamom group (Figure 2A, 2B, 2C, 2D). The immunohistochemistry reactions and group comparisons are shown in Table 1.

DISCUSSION

Increased production of reactive oxygen species causes oxidative stress, which plays a crucial role in the pathogenesis of diabetes' late complications. NF-κB regulates the expression of most of the genes of many growth factors, including VEGF (20). Also, a study investigating the relationship between VEGF and NF-κB reported that lncRNA ANRIL, which is overexpressed in diabetes complicated with cerebral infarction, activates the NF-κB signaling pathway by upregulating VEGF (21). Hyperglycemia activates the transcription factor NF-κB, which helps control the expression of many inflammation-related genes by causing free oxygen radicals to be produced (22). NF-κB proteins can be considered regulators of cellular homeostasis because their activity is spontaneously regulated by a variety of stimuli (23). Dysregulation of NF-κB has been linked to the pathology of a variety of diseases due to its central role

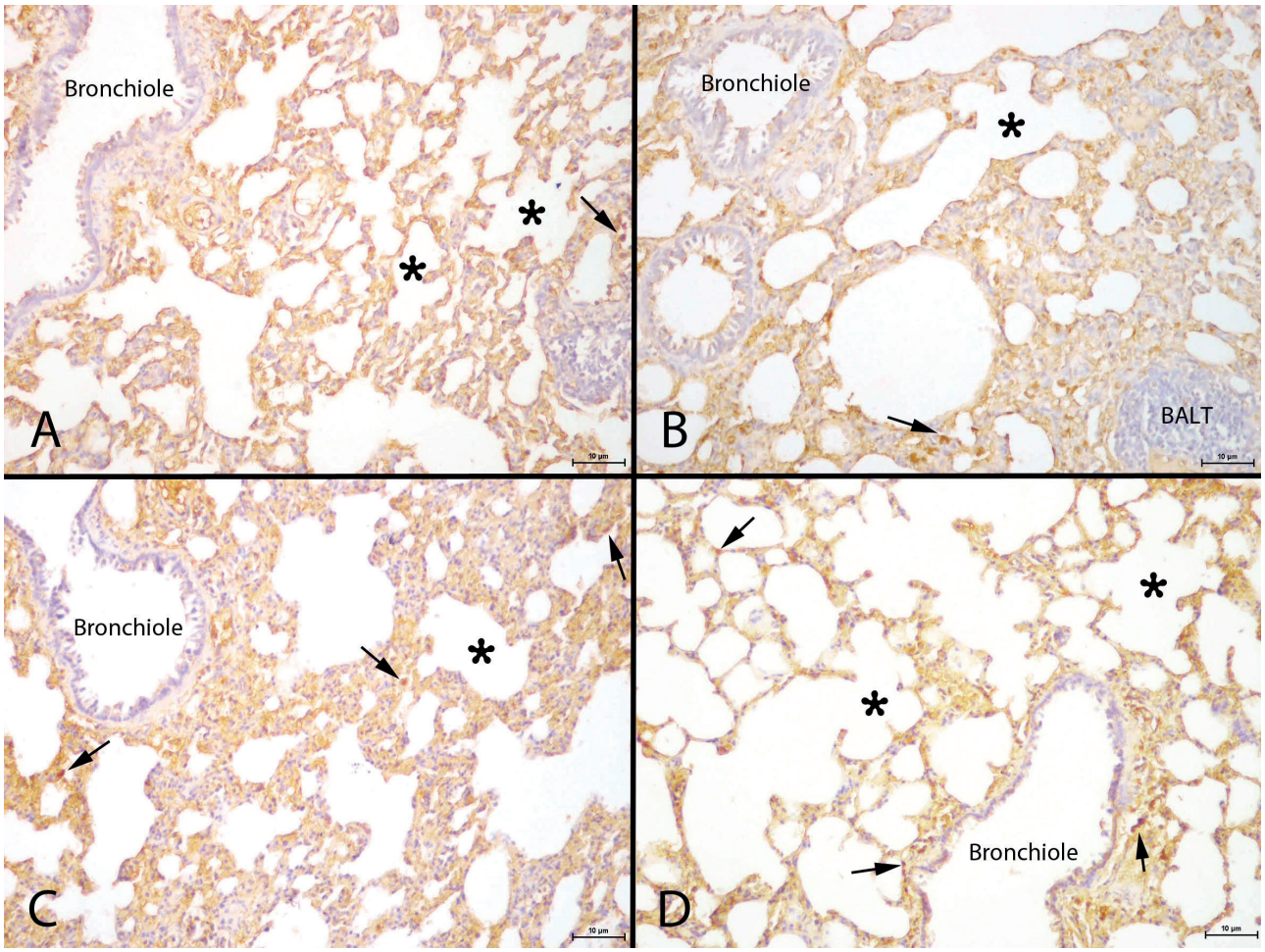

Figure 1: Representation of lung section imagings of VEGF immunohistochemical staining; A: Control group, (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris. B: Diabetes group (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris, (BALT): bronchus-associated lymphatic tissue. C: Diabetes + cinnamom group, (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris. D: Cinnamon group (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris, original magnification X20; range bar, 10 µm.

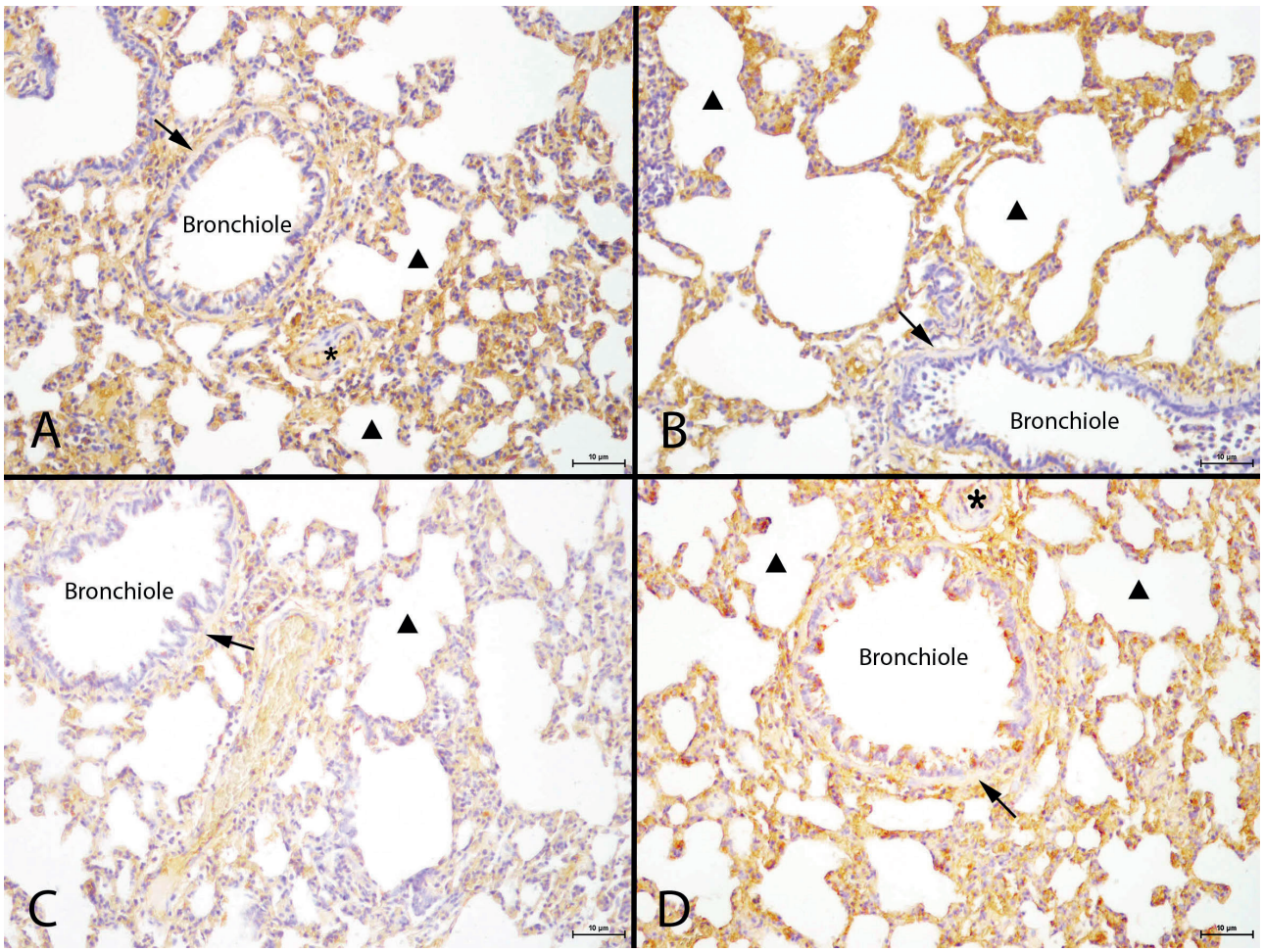

Figure 2: Representation of lung section imagings of NF-κB immunohistochemical staining; A: Control group, (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris, (asterix): blood vessel. B: Diabetes group (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris. C: Diabetes + cinnamom group (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris. D: Cinnamon group (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris, (asterix): blood vessel, original magnification X20; range bar, 10 µm.

in many cellular processes (24). It has been shown that various tissue damage pathways caused by high glucose concentration can change the expression of several genes important in the pathogenesis of diabetic complications by activating transcription factors such as NF-κB (25). According to a recent study, NF-κB can affect the insulin signaling pathway and subscribe to insulin resistance, suggesting that blocking NF-κB activity could be a novel treatment option for insulin resistance (26). A prior study has demonstrated that in the ovarian tissue of diabetic rats compared to the control group of normal rats, determined that NF-κB immunoexpression was significantly increased (27). According to a study conducted on rats, it was reported that diabetes increased the expression of NF-κB in liver tissue, and this increase decreased with ghrelin treatment (28). The study of Wang et al. indicated that dysbiosis of the gut-lung microbiota in STZ-induced diabetic mice increased the risk of pulmonary fibrotic changes by activating the NF-κB signaling pathway (29). A recent study observed that high blood sugar levels decreased after daily administration of cinnamon extract in diabetic female and male rats. In addition, the absence of any adverse effects on tissues such as kidneys and pancreas in the histochemical examination was acknowledged as positive effects of cinnamon (30). In this study, while increased NF-κB immunohistochemistry was observed in the diabetes group, it was noted that NF-κB expression decreased in the cinnamon + diabetes group. When compared to the control group, no difference was observed in the cinnamon-only group. This suggested that cinnamon may reduce the possible harmful effects that may develop due to diabetes by reducing the transmission of diabetes-related cytokines in the lung. Also, in our study, NF-κB increased immunohistochemically in rat lung tissue in the diabetes group, which may suggest that NF-κB plays an significant role in the pathogenesis of diabetes-induced lung.

The main sources of VEGF in the airways are alveolar epithelial cells, bronchial epithelial cells and smooth muscle cells, fibroblasts, and alveolar macrophages (31). Studies in animal models indicate that the absence of VEGF signaling may cause capillary and alveolar hypoplasia and decreased lung maturation and surfactant production (32, 33). Due to oxidative stress, the synthesis and secretion of VEGF in diabetic patients might deteriorate (34). According to a study on rats, it was determined that in testis tissue VEGF expression decreased in diabetic rats (35). A previous study specified that VEGF immunolocalization

was observed to decrease gradually in the lung tissue of diabetic rats 7 and 14 days after the development of diabetes, compared to the control group (36). It has also been specified that diabetes may be associated with impairments in VEGF expression and action (37). For instance, several studies suggested that both impaired angiogenesis and microcirculatory dysfunction in diabetics may be due in part to decreased expression of VEGF and its receptors (38, 39). Cinnamaldehyde, one of the cinnamon's components, has been shown to lower blood glucose levels in diabetic rats and increase plasma insulin levels. Furthermore, it has been reported that cinnamaldehyde regenerated pancreatic islets damaged by STZ through its antioxidant activity and stimulation of β-cells, which directly resembles the insulin secretagogue effect (40). Although diabetes decreased VEGF expression in our study, it was observed that cinnamon treatment reversed this effect and increased VEGF expression. However, there was no significant difference in VEGF expression between the cinnamon-treated and control groups. These data suggest that cinnamon may be contributing to the VEGF expression. Thus, it is thought that possible lung damage caused by diabetes can be prevented. But clearly, more investigations are needed to define the interaction between cinnamon and VEGF.

As a result, in our study cinnamon caused decreased the increase in NF-κB expression caused by diabetes and increased the decreased VEGF expression. In conclusion, we believe that this study will be useful in understanding possible cytokine mechanism changes that may occur in the lung tissue due to diabetes and in the development of treatment methods.

Conflict of Interest: No conflict of interest was declared by the authors
Ethics: Animal Experiments Local Ethics Committee of Ondokuz Mayıs University (Date: 11/03/2020 an Number: 68489742-604.01.03-E.6122).
Funding: There is no financial support of any person or institution in this research.
Approval of final manuscript: All authors

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