Effects of resveratrol on diabetes-induced vascular tissue damage and inflammation in male rats
Resveratrolün erkek sıçanlarda diyabetin oluşturduğu vasküler doku hasarı ve inflamasyonu üzerine etkileri

Abstract

Objective: The present study aims to investigate the short-term effects of resveratrol on histopathological characteristics and inflammatory cytokines of the heart and thoracic aorta tissues in animal models of streptozotocin (STZ)-induced diabetes.

Methods: Male Wistar rats were randomly divided into four groups; (1) control/vehicle, (2) control/20 mg/kg resveratrol, (3) diabetic/vehicle, (4) diabetic/20 mg/kg resveratrol. Heart and thoracic aorta were examined histopathologically and the levels of interleukin (IL)-1β, IL-18 and tissue necrosis factor (TNF)-α were analyzed by ELISA. Malondialdehyde (MDA) contents were determined with HPLC.

Results: Diabetes group had significantly higher vascular MDA content (p < 0.05) as compared with the control and resveratrol treated groups. Resveratrol significantly reduced vascular MDA level in diabetic animals (p < 0.05). Significant elevation in IL-1β and TNF-α contents in thoracic aorta and IL-18 contents in cardiac and arterial tissues with diabetes were almost normalized with resveratrol treatment. Additionally, diabetic animals demonstrated significant endothelial damage, irregularities in smooth muscle fibers and degeneration of elastic fibers in thoracic aortas together with significant irregularities and hypertrophy in cardiac muscle fibers. Resveratrol significantly improved most of these histopathological alterations.

Conclusion: Four-week-long intraperitoneal administration of resveratrol may restore the diabetes related inflammation and oxidative stress within the cardiovascular system.

Keywords: Diabetes; Heart; Artery; Inflammation; Oxidative stress; Resveratrol.

Özet

Amaç: Bu çalışma, streptozotocin (STZ) ile oluşturulmuş diyabetin hayvan modellerinde resveratrolun kalp ve damar dokularında histopatolojik özellikler ve inflamatuvar sitokinler üzerine kısa süreli etkilerini araştırmayı amaçlamıştır.

Metod: Erkek Wistar sıçanları (1) kontrol, (2) kontrol/20 mg/kg resveratrol, (3) diyabetik, (4) diyabetik/20 mg/kg resveratrol olmak üzere dört gruba ayrılmıştır. Kalp ve damar dokuları histopatolojik olarak incelenmiştir. Buna ilave olarak, interleukin (IL)-1β, IL-18 ve dokunekroz faktör (TNF)-α düzeyleri ELISA yöntemile, malondialdehit (MDA) miktarı ise HPLC ile belirlenmiştir.
Introduction

Diabetes mellitus is a multifactorial disease that has been associated with various pathological conditions including dyslipidemia, thrombosis, infarction, hypertension, endothelial dysfunction and coronary artery diseases [1]. Inflammation is a protective mechanism elicited by the host in response to infection, injury, and tissue damage. It is also closely associated with the development and progression of a variety of diseases including diabetes [2].

Vascular endothelium is considered to be an active participant of inflammation [3, 4]. Inflamed endothelium mediates diverse activities including the regulation of leukocyte recruitment and infiltration, cytokine production and vascular permeability [5]. Endothelium also exerts a potent inflammatory role by secreting certain cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) which up-regulates the intercellular adhesion molecule-1 (ICAM-1) and enhances leukocyte adherence to the activated endothelium [3, 4]. Interleukin-18 (IL-18) is a unique pro-inflammatory cytokine playing a role in many inflammatory diseases [6].

There is a growing body of evidence about the roles of both oxidative stress and inflammatory activity in the pathogenesis of diabetes mellitus [7, 8]. In our previous studies, we confirmed that diabetes leads to insulin resistance, increases hepatic oxidative stress and inflammation [9]. Malondialdehyde (MDA) which is one of the most important indicators of oxidative damage [10], and pro-inflammatory cytokines such as TNF-α and IL-1β were increased in different tissues of diabetic animals [11–13]. However, inflammatory effects of short-term diabetes on cardiac and vascular smooth muscle haven’t been clarified yet.

Resveratrol is a versatile phytochemical that shows high antioxidant and anti-inflammatory effects [14]. It is found that resveratrol reduces inflammation effectively in several disease conditions [15]. The extensively reported molecular target of resveratrol is the blockade of the activation of Nf-κB [16]; an inducible transcription factor for the genes involved in inflammation, such as TNF-α and IL-1β [17].

Recently, we have published that impaired glucose metabolism in the liver tissues leads to adverse effects on hepatic functions and inflammation that could be returned to the normal values with resveratrol [9]. To make track for the concrete molecular action mechanism of the resveratrol through the regulation of the cardiac and vascular dysfunction and inflammation, the present study was designed to investigate the effects of resveratrol on histopathological features and inflammatory components of the cardiac and thoracic arterial tissues in an animal model of streptozotocin (STZ)-induced diabetes.

Materials and methods

Animals and treatment procedure

The animal protocols were confirmed by the Ethical Animal Research Committee of Karamanoglu Mehmetbey University (K.M.U. ET-11/01-02) and carried out strictly according to rules of the Guide for the Care and Use of Laboratory Animals as published by the US National Institute of Health (NIH Publication No: 85/23, revised in 1986). Eight week old male Wistar rats were housed under temperature-controlled rooms (20–22°C) with a 12-h light-dark cycle. The animals were fed with standard rodent diet composed of 62% starch, 23% protein, 4% fat, 7% cellulose, standard vitamins and salt mixture (chow pellet). After acclimation for 1 week, animals were randomly assigned to four groups. The control group (n = 12) were injected only vehicle; 10% dimethylsulfoxide (DMSO) for 4-weeks. The resveratrol group (n = 12) were given a daily intraperitoneal dose of 20 mg/kg/day resveratrol in vehicle throughout the 4-week period. The diabetes group (n = 12) received a single dose of STZ
(55 mg/kg) dissolved in 0.05 M citrate buffer (pH: 4.5) and daily vehicle for 4-weeks. The diabetes + resveratrol group consisted of nine rats which received a daily intraperitoneal dose of 20 mg/kg/day resveratrol throughout the 4-week period, starting from 2 days after STZ administration. Blood glucose concentrations were determined by Accu-check-go (Roche, Germany) glucometer weekly from the blood of the tail veins. The criteria for the diabetes were the blood glucose concentration higher than 200 mg/dL. At the end of the study period, all rats were decapitated and the heart and thoracic aorta tissues were blotted dry, frozen in liquid nitrogen, and stored at −85°C for further use.

**Histopathological examinations**

Tissue samples obtained from the heart and thoracic aorta were fixed with 10% neutral formalin and embedded in paraffin blocks for 3 days. After five micron thick sections were obtained from these blocks, cardiac tissues were stained with Masson’s Trichrome dye, while aortas were stained with Verhoeff-van Gieson dye. They were evaluated with high magnification under light microscopy (NikonEclipse E-600). Slides were graded according to the degree of endothelial damage, inflammatory cell migration, hypertrophy, congestion and degeneration.

**Measurement of inflammation and oxidative stress markers**

Tissue samples obtained from the heart and thoracic aorta were homogenized in phosphate buffer 1:10 (w/v), 0.1 M, pH 7.4 and centrifuged at 10,000 g for 10 min and then supernatants were collected. Total protein contents were measured with the Lowry method [18]. The cardiac and vascular MDA contents were determined by HPLC chromatography with a fluorescent detector (Ex:515 Em:553 nm) using commercial kits (Chromsystems Diagnostics, Munich, Germany). Tissue levels of IL-1β, IL-18, and TNF-α were measured using commercially available rat specific ELISA kits (eBioscience, Bender Med. Systems GmbH, Vienna, Austria) according to the manufacturer’s protocols.

**Statistical analysis**

Collected data were analyzed by Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). The results were expressed as mean ± standard error of the mean (SEM) and Student’s t-test or one-way analysis of variance followed by the Tukey’s Honestly Significant Difference post-hoc analysis was used where appropriate. p-values < 0.05 were accepted to be statistically significant.

**Results**

**Effects of resveratrol on metabolic characteristics of the rats**

Table 1 compares the metabolic characteristics of the control, resveratrol, diabetes and diabetes + resveratrol groups. All four groups had statistically similar initial body weights and blood glucose levels. When compared with the control and resveratrol groups, the diabetes and diabetes + resveratrol groups had significantly lower final body weight and higher blood glucose concentrations (p < 0.05 for all). When compared with the control and resveratrol groups, the diabetes group had significantly higher vascular MDA content (p < 0.05). The

|                         | Control       | Res           | Diab          | Diab + Res    |
|-------------------------|---------------|---------------|---------------|---------------|
| Initial body weight (g) | 440.81 ± 21.03| 399.56 ± 6.96 | 393.74 ± 11.23| 392.61 ± 6.94 |
| Final body weight (g)   | 447.70 ± 16.93| 411.82 ± 14.41| 319.30 ± 16.86*| 309.43 ± 14.62*|
| Initial blood glucose (mg/dL) | 101.60 ± 3.40 | 96.90 ± 8.10  | 98.80 ± 7.90  | 103.90 ± 8.60 |
| Blood glucose (mg/dL) after STZ treatment | NA | NA | 401.70 ± 27.60 | 373.30 ± 34.20* |
| Vascular MDA (μmol/g protein) | 55.9 ± 8.7 | 68.6 ± 6.9 | 81.3 ± 16.4* | 52.5 ± 1.7* |
| Cardiac MDA (μmol/g protein) | 39.2 ± 2.5 | 44.5 ± 3.5 | 48.5 ± 5.5 | 45.3 ± 4.7 |

Data represents the means and the standard error of the mean (SEM) values of at least six rats. *Indicates that the means were significantly different (p < 0.05) compared with control groups, †indicates that the means were significantly different (p < 0.05) compared with diabetic groups. Diab, Diabetic; Res, resveratrol; NA, not applicable.
diabetes + resveratrol group had significantly lower vascular MDA level than that of the diabetes group (p < 0.05). All four groups were statistically similar with respect to cardiac MDA concentrations.

**Effects of resveratrol on histopathological characteristics**

Figure 1A–D demonstrate the histopathological characteristics of the vascular tissues obtained from control, resveratrol, diabetes and resveratrol + diabetes groups, respectively. The control group had a normal histological appearance indicating regular endothelial cell localization and elastic fibril distribution (Figure 1A). The resveratrol group had slight irregularity in elastic fibrils (black arrows), endothelial degeneration (blue dotted arrows) and also mild smooth muscle irregularity (asterisk) (Figure 1B). The diabetes group displayed significant endothelial damage, irregularity in smooth muscle fibers (asterisk) and degeneration in elastic fibers (black arrows) (Figure 1C). The resveratrol + diabetes group showed significant improvement in these histopathological alterations (Figure 1D).

Figure 2A–D demonstrate the histopathological characteristics of the cardiac tissues obtained from control, resveratrol, diabetes and resveratrol + diabetes groups, respectively. The control group had a normal histological appearance indicating regular cardiac muscle localization and distribution (Figure 2A). The resveratrol group also had a normal histological appearance (Figure 2B). The diabetes group showed significant irregularity and hypertrophy in cardiac muscle fibers (Figure 2C). The resveratrol + diabetes group displayed significant improvement in these histopathological alterations (Figure 2D).

![Figure 1](image.jpg)

*Figure 1: Images of Van-Gieson staining of control (A), resveratrol treated control (B), diabetic (C) and resveratrol treated diabetic (D) rat arterial sections. Black arrows indicate elastic fibrils’ irregularities while blue dotted arrows designate endothelial degeneration. Asterisks (*) specify the smooth muscle irregularities (VG, X 400, scale bar = 50 μm).*
Anti-inflammatory effects of resveratrol on cardiac and vascular tissues

A significant increase was detected in IL-1β and TNF-α levels of the thoracic aorta tissues belonging to the diabetic rats (Figure 3A and C). The IL-18 concentration was also significantly elevated in both the cardiac and arterial tissues of the diabetic rats (Figure 3B and E). However, there was no significant difference in cardiac IL-1β and TNF-α levels of the diabetic rats (Figure 3D and F). The IL-1β, IL-18 and TNF-α concentrations of thoracic aorta and the cardiac content of IL-18 decreased significantly in the diabetes + resveratrol group (Figure 3A, B, E and F).

Discussion

Diabetes mellitus causes hyperglycemia which induces non-enzymatic glycosylation of proteins and generation of advanced glycation end products via enhanced lipid peroxidation. Such alterations lead to the occurrence of inflammation within the cardiovascular system which subsequently results in long-term complications. These changes are associated with up-regulation of cytokines including TNF-α, IL-1β, IL-6 and NfkB [19–23]. Moreover, diabetes mellitus inhibits catalase and superoxide dismutase which causes an increase in the generation of free oxygen radicals and, thus, triggers oxidative stress within the cardiovascular system [24, 25].

Resveratrol is a potent anti-oxidant and anti-inflammatory molecule which can be used to prevent cardiovascular complications associated with diabetes mellitus [15, 19]. It has been shown that resveratrol supplementation has improving effects on numerous cytokines [20, 26]. On the other hand, there is not any sufficient data about the short-term effects of resveratrol supplementation on the cardiovascular system which is affected by diabetes mellitus. The present study aims to determine the short-term
effects of intraperitoneal resveratrol administration on cardiovascular system by evaluating the histopathological alterations and cytokine concentrations.

In this study, an animal model of diabetes mellitus was established by STZ administration. Although blood glucose concentrations increased significantly in diabetic rats, their weights were significantly lower than those of the control and resveratrol groups. Such discrepancy may be attributed to the possible shift in energy metabolism which favors the usage of lipids and proteins rather than glucose.

MDA is a stable end product of lipid peroxidation which arises from oxidative stress and thus it can be used as a marker for oxidative stress. Prior studies reported that resveratrol administration significantly reduces serum MDA levels in diabetic rats and in rats with cisplatin or doxorubicin induced cardiotoxicity [27–30]. This study showed that the MDA contents in thoracic aorta tissues of the diabetic rats were significantly higher but there was no significant change in the MDA content of their cardiac tissues. This finding may suggest that vascular tissues are more prone to oxidative damage than the cardiac tissues in diabetic animals. As for the diabetes + resveratrol group, the MDA content in thoracic aorta tissues was significantly lower. This may support the improving effects of resveratrol on diabetes related oxidative stress within the cardiovascular system. Moreover, significant endothelial damage, irregularity in smooth muscle fibers and degeneration in elastic fibers was observed in thoracic aorta of diabetic rats. Similarly, significant irregularity and hypertrophy was detected in cardiac muscle fibers of the diabetic rats. The resveratrol + diabetes group displayed significant improvement in these histopathological alterations.

The most common indicators of the tissue inflammation are the presence of free oxygen radicals, oxidized lipids and inflammatory cytokines such as IL-1β, IL-18 and TNF-α [31]. The IL-18 is a pro-inflammatory cytokine that belongs to IL-1β family. IL-18 stimulates natural killer cells and certain T cells to release another important cytokine called interferon-γ which plays an important role in activating the macrophages or other cells. In other words, IL-18 acts as a compensatory mechanism to suppress pro-inflammatory cytokines such as IL-1β and TNF-α [6]. It has been stated that serum IL-1β and TNF-α concentrations are increased in diabetes associated cardiovascular diseases [31–33]. Also plasma IL-18 levels are found to be elevated significantly in acute rheumatic fever and coronary artery diseases [6]. It has been reported that resveratrol decreases serum levels of IL-1β and TNF-α in cardiovascular diseases. This study confirms the presence of significant increase in IL-1β and TNF-α content of the thoracic aorta tissues of the diabetic rats. However, there was no significant difference
in cardiac tissue levels of IL-1β and TNF-α in diabetic rats. This finding implies that inflammation is more prominent in vascular smooth muscles than in cardiac tissues of diabetic rats. The IL-18 concentration was also significantly elevated in both the cardiac and arterial tissues of the diabetic rats. To the best of our knowledge, this is the first study to evaluate the tissue concentration of IL-18 in cardiovascular systems of diabetic rats.

Previously published animal studies have investigated the efficiency of resveratrol treatment in diabetes-induced disorders. In these studies, resveratrol was given to the experimental animals in their foods or drinking water ad libitum for at least 8 weeks [19, 34]. On the contrary, this research demonstrated that 4-week-long intraperitoneal administration of resveratrol may restore the diabetes related inflammation and oxidative stress within the cardiovascular system. This observation is based on the significant decrease in thoracic aorta concentrations of MDA, IL-1β, IL-18, and TNF-α as well as the significant improvement in histopathological alterations of the diabetes + resveratrol group.

The power of the present study is limited by relatively small cohort, relatively short study period and lack of data related with other oxidative stress markers. Further research is needed to clarify the effects of intraperitoneal resveratrol administration in diabetes related cardiovascular disorders.

Acknowledgments: This study was partially supported by grants from TUBITAK research fund (3501/112T159).

Conflict of interest statement: There is no conflict of interest to disclose for any of the authors.

References

1. Wang J, Song Y, Wang Q, Kralik PM, Epstein PN. Causes and characteristics of diabetic cardiomyopathy. Rev Diabet Stud 2006;3:108–17.
2. Csizsar A. Anti-inflammatory effects of resveratrol: possible role in prevention of age-related cardiovascular disease. Ann N Y Acad Sci 2012;1215:117–22.
3. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat Rev Immunol 2007;7:678–89.
4. Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. Nat Rev Immunol 2007;7:803–15.
5. Folkman J. Angiogenesis-dependent diseases. Semin Oncol 2001;28:536–42.
6. Dinarello CA. Interleukin-18 and the pathogenesis of inflammatory diseases. Semin Nephrol 2007;27:98–114.
7. Padiya R, Chowdhury D, Borkar R, Srinivas R, Pal Bhadra M, Banerjee SK. Garlic attenuates cardiac oxidative stress via activation of PI3K/AKT/Nrf2-Keap1 pathway in fructose-fed diabetic rat. PLoS One 2014;9:3–10.
8. Ceriello A, Quagliaro L, D’Amico M, Di Filippo C, Marfella R, Nappo F, et al. Acute hyperglycemia induces nitrotyrosine formation and apoptosis in perfused heart from rat. Diabetes 2002;51:1076–82.
9. Sadi G, Pektas MB, Koca HB, Tosun M, Koca T. Resveratrol improves hepatic insulin signaling and reduces the inflammatory response in streptozotocin-induced diabetes. Gene 2015;570:213–20.
10. Akhtar MS, Pillai KK, Hassan Q, Ansari SH, Ali J, Akhtar M, et al. Levosimendan suppresses oxidative injury, apoptotic signaling and mitochondrial degeneration in streptozotocin-induced diabetic cardiomyopathy. Clin Exp Hypertens 2016;38:10–22.
11. Cieslak M, Wojtczak A, Cieslak M. Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment. Acta Biochim Pol 2015;62:15–21.
12. Urate Y, Yamamoto H, Goto S, Tsushima H, Akazawa S, Yamashita S, et al. Long exposure to high glucose concentration impairs the responsive expression of gamma-glutamylcysteine synthetase by interleukin-1beta and tumor necrosis factor-alpha in mouse endothelial cells. J Biol Chem 1996;271:15146–52.
13. Lee B-H, Hsu W-H, Chang Y-Y, Kuo H-F, Hsu Y-W, Pan T-M. Ankaflavin: a natural novel PPARγ agonist upregulates Nrf2 to attenuate methylglyoxal-induced diabetes in vivo. Free Radic Biol Med 2012;53:2008–16.
14. Fu D. Regulation of redox signalling and autophagy during cardiovascular diseases-role of resveratrol 2015;19:1530–6.
15. Chen M-L, Yi L, Jin X, Liang X-Y, Zhou Y, Zhang T, et al. Resveratrol attenuates vascular endothelial inflammation by inducing autophagy through the cAMP signaling pathway. Autophagy 2013;9:2033–45.
16. Chiou Y-S, Tsai M-L, Nagabhushanam K, Wang Y-J, Wu C-H, Ho C-T, et al. Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. J Agric Food Chem 2011;59:2725–33.
17. Gilmore TD. Introduction to NF-kappaB: players, pathways, perspectives. Oncogene 2006;25:6680–4.
18. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265–75.
19. Akar F, Pektas MB, Tufan C, Soymezer S, Sepici A, Ulus AT, et al. Resveratrol shows vasoprotective effect reducing oxidative stress without affecting metabolic disturbances in insulin-dependent diabetes of rabbits. Cardiovasc Drugs Ther 2011;25:119–31.
20. Jiang H, Liu W, Liu Y, Cao F. High levels of HB-EGF and interleukin-18 are associated with a high risk of in-silent restenosis. Anatol J Cardiol 2015;15:907–12.
21. G RK, K MS, G KK, Kurapatil M, M S, T MA, et al. Evaluation of Hs-CRP levels and Interleukin 18 (-1376C) promoter polymorphism in risk prediction of coronary artery disease in first degree relatives. PLoS One 2015;10:e0120359.
22. Lozano I, Van der Werf R, Bietiger W, Seyfritz E, Peronet C, Pinget M, et al. High-fructose and high-fat diet-induced disorders in rats: impact on diabetes risk, hepatic and vascular complications. Nutr Metab (Lond) 2016;13:15.
23. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. Lancet (London, England) 1980;1:1373–6.

24. Ma H, Zhang S, Shi D, Mao Y, Cui J. MicroRNA-26a promotes regulatory T cells and suppresses autoimmune diabetes in mice. Inflammation 2016;39:1–9.

25. Tabei SM, Fakher S, Djalali M, Javanbakht MH, Zarei M, Derakhshanian H, et al. Effect of vitamins A, E, C and omega-3 fatty acids supplementation on the level of catalase and superoxide dismutase activities in streptozotocin-induced diabetic rats. Bratisl Lek Listy 2015;116:115–8.

26. Pektaş MB, Sadi G, Koca HB, Yuksel Y, Vurmaz A, Koca T, et al. Resveratrol Ameliorates the components of hepatic inflammation and apoptosis in a rat model of streptozotocin-induced diabetes. Drug Dev Res 2016;77:12–9.

27. Mozafari M, Nekooeian AA, Panjeshahin MR, Zare HR. The effects of resveratrol in rats with simultaneous type 2 diabetes and renal hypertension: a study of antihypertensive mechanisms. Iran J Med Sci 2015;40:152–60.

28. Elbe H, Esrefoglu M, Vardi N, Taslidere E, Ozerol E, Tanbek K. Melatonin, quercetin and resveratrol attenuates oxidative hepatic cellular injury in streptozotocin-induced diabetic rats. Hum Exp Toxicol 2015;34:859–68.

29. Al-Harthi SE, Alarabi OM, Ramadan WS, Alaama MN, Al-Kreathy HM, Damanhouri ZA, et al. Amelioration of doxorubicin-induced cardiotoxicity by resveratrol. Mol Med Rep 2014;10:1455–60.

30. Fang Q, Wang J, Wang L, Zhang Y, Yin H, Li Y, et al. Attenuation of inflammatory response by a novel chalcone protects kidney and heart from hyperglycemia-induced injuries in type 1 diabetic mice. Toxicol Appl Pharmacol 2015;288:179–91.

31. Zheng X, Zhu S, Chang S, Cao Y, Dong J, Li J, et al. Protective effects of chronic resveratrol treatment on vascular inflammatory injury in streptozotocin-induced type 2 diabetic rats: Role of NF-kappa B signaling. Eur J Pharmacol 2013;720:147–57.

32. Gao Y, Kang L, Li C, Wang X, Sun C, Li Q, et al. Resveratrol Ameliorates Diabetes-Induced Cardiac Dysfunction Through AT1R-ERK/p38 MAPK Signaling Pathway. Cardiovasc Toxicol 2016;16:130–7.

33. Lou X, Wang H, Xia S, Skog S, Sun J. Effects of resveratrol on the expression and DNA methylation of cytokine genes in diabetic rat aortas. Arch Immunol Ther Exp (Warsz) 2014;62:329–40.

34. Pektaş MB, Sadi G, Akar F. Long-term dietary fructose causes gender-different metabolic and vascular dysfunction in rats: modulatory effects of resveratrol. Cell Physiol Biochem 2015;37:1407–20.