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Resveratrol Reorganizes the Impaired Cellular Functions of ARPE-19 Cells Created in Diabetes Model

Resveratrol Diyabet Modeli Oluşturulmuş ARPE-19 Hücrelerinin Bozulmuş Hücre Fonksiyonlarini Yeniden Düzenler

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ABSTRACT

Objective: It is well known that high blood glucose levels can damage many visual functions. So, the study aimed to investigate the effects of resveratrol on cellular lipid peroxidation (MDA), cytokines, VEGF-A and apoptosis levels in vitro diabetes model-induced ARPE-19 cells.

Materials and Methods: Six experimental groups were conceptualized as follows. 1-Control group: Received no treatment (Standard Growth Medium), 2-Mannitol Group (M): Cells incubated in 19.5 mM Mannitol supplemented medium, 3-High Glucose Group (HG): Cells incubated in high glucose (25 mM Glucose), 4-Resveratrol Group (R): Cells incubated with 100 µM resveratrol Standard Growth Medium, 5-Mannitol + Resveratrol Group (M+R), 6-High Glucose + Resveratrol Group (HG+R). In All groups, cells were incubated for 48 hrs, and MDA, IL-1β, TNF-α, VEGF-A and Apoptosis levels were measured.

Results: High glucose medium increased the MDA, IL-1β, TNF-α and VEGF-A levels while resveratrol caused a significant decrement in MDA, IL-1β, TNF-α and VEGF-A levels in diabetes model-induced ARPE-19 cells. As a result, resveratrol prevented the ARPE-19 cells against diabetes related impaired conditions.

Conclusions: In conclusion, resveratrol can reverse disrupted cellular functions by reducing cellular oxidative stress and supporting cellular viability.

Keywords: Apoptosis, ARPE-19, diabetes, resveratrol, VEGF-A

ÖZ

in vitro diyabet modeli oluşturulan ARPE-19 hücrelerinin hücresel lipid peroksidasyonu (MDA), sitokinler, VEGF-A ve apoptoz seviyeleri üzerindeki etkileri amaçlanmıştır.

Materyal ve Metot: Altı deney grubu aşağıdaki şekilde oluşturulmuştur. 1-Kontrol grubu: Hiçbir tedavi uygulanmadı (Standart Büyütme Medyumu), 2-Mannitol Grubu (M): 19,5 mM mannitol takviyeli ortamda inkübe edilen hücreler, 3-Yüksek Glikoz Grubu (HG): Yüksek glikozda (25 mM Glikoz) inkübe edilen hücreler, 4-Resveratrol Grubu (R): Standart Büyütme Medyumunda ve 100 µM resveratrol ile inkübe edilen hücreler, 5-Mannitol + Resveratrol Grubu (M+R), 6-Yüksek Glikoz + Resveratrol Grubu (HG+R). Tüm gruplar 48 saat inkübasyon sonrasında MDA, IL-1β, TNF-α, VEGF-A ve Apoptozis düzeyleri ölçüldü.

Bulgular: Yüksek glikoz ortamı ARPE-19 hücrelerinde MDA, IL-1β, TNF-α ve VEGF-A seviyelerinde artışa neden olurken resveratrol, diyabet modeli oluşturulmuş hücrelerde MDA, IL-1β, TNF-α ve VEGF-A seviyelerinde önemli bir azalmaya neden olduğu görülmüştür. Sonuç olarak resveratrolün ARPE-19 hücrelerinin diyabet modeline bağlı olarak bozulmuş hücresel fonksiyonların düzeltilmesine yardımcı olduğu belirlenmiştir.

Sonuç: Resveratrol'ün hücresel oksidatif stresi azaltarak ve hücresel canlılığı destekleyerek bozulan hücresel fonksiyonları tersine çevirebileceği sonucuna varılmıştır.

Anahtar Kelimeler: Apoptoz, ARPE-19, diyabet, resveratrol, VEGF-A

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INTRODUCTION

Diabetes can significantly impact eye health, leading to conditions collectively known as diabetic eye disease. Diabetic retinopathy, the most prevalent condition, arises when increased blood sugar harms the retinal blood vessels, which can lead to vision impairment. Other related conditions include diabetic macular oedema, cataracts, and glaucoma.[1-3]

Oxidative stress is a condition that occurs because of an imbalance between the production of oxidizing compounds and detoxification by antioxidant defence systems, causing increased ROS production and resulting in cell damage. Oxidative stress can provoke many diseases, such as Alzheimer's, Parkinson's, diabetes, age-related macular degeneration, and atherosclerosis.[4-7]

Resveratrol, a type of stilbene phytophenol, is present in over 70 plant species and their derivatives, such as grape seeds, peanuts, blueberries, and cranberries.[8] Resveratrol has anti-inflammatory,[9]antioxidant,[9] and anti-angiogenic[10] properties. Resveratrol is used as a micronutrient in age-related macular degeneration.[11]

Thus, this study was undertaken to assess the effects of resveratrol on cellular lipid peroxidation, cytokines, VEGF-A and apoptosis levels of in vitro diabetes model-induced ARPE-19 cells.

MATERIALS AND METHODS

Ethics Committee Approval: Not applicable. Since ARPE-19 cells were commercially obtained from American Type Cell Culture (ATCC® CRL-2302™, Manassas, VA, USA), the study does not need ethical committee approval. It complies with the international standards of The Committee on Publication Ethics (COPE).

Cell Culture: ARPE-19 cells, purchased from American Type Cell Culture (ATCC, Manassas, VA, USA), harvested in a humidified %5 CO_2 incubator. A culture medium was formulated with 50% Ham's F12 medium and 50% Dulbecco's Modified Eagle Medium (DMEM), enhanced with 10% FBS and 1% Penicillin-Streptomycin mix. The passage number of cells was from 5 to 10 utilized in the study. Subculturing and treatments to the cells were performed as explained and elsewhere.[7,12]

Experimental Groups: The study groups and treatments were as follows:

1-Control Group: Cells were seeded in an incubator without treatment in a standard growth medium (5.5 mM Glucose) for 48 hrs.[12]

2- Mannitol Group (M): The standard growth medium supplemented with extra mannitol (19.5 mM) and cells were seeded for 48 hrs.[12]

3-High Glucose Group (HG): Cells were seeded in High Glucose Medium (25 mM Glucose) for 48 hrs.[12]

4-Resveratrol Group (R): Cells were seeded in standard growth medium (5.5 mM Glucose) supplemented with 100 µM resveratrol for 48 hrs.[10,12]

5- Mannitol + Resveratrol Group (M+R): The standard growth medium supplemented with extra mannitol (19.5 mM) + 100 µM resveratrol cells were seeded for 48 hrs.[10,12]

6-High Glucose + Resveratrol Group (HG+R): Cells were seeded in High Glucose Medium (25 mM Glucose) + 100 µM resveratrol for 48 hrs.[10,12]

Material Preparation: After trypsinization, the cells were collected in a collecting tube with all contents. One part of the content was separated for Apoptosis experiments before homogenization. The remaining contents were homogenized for 2 minutes by an ultrasonic homogenizer for Lipid peroxidation (MDA), cellular cytokines (IL-1β and TNF-α) and VEGF-A experiments.[13]

Lipid Peroxidation: The protein content of ARPE-19 cells was detected by Lowry's method.[14] As an indicator of lipid peroxidation levels of MDA has been assayed by a spectrophotometrically (Shimadzu, Kyoto, Japan) method, which was defined previously by Placer et al.[15] MDA levels of ARPE-19 cell homogenates were expressed as µmol/g protein.

Measurement of Cellular Cytokines (*IL-1β and TNF-α*), VEGF-A and Apoptosis: IL-1β, TNF-α and VEGF-A levels were quantified by using a multi-well reader (Infinite pro200) at 450 nm wavelength according to the ELISA kit Manufacturer's instructions. Levels of IL-1β, TNF-α and VEGF-A in groups were expressed in ng/ml, pg/ml and pg/ml, respectively, percentages of control after standard curves were calculated.[16]

Non-homogenized cells were used for the detection of apoptosis levels. The APO Percentage kit (Northern Ireland, UK), a commercial apoptosis detection assay, was utilized to measure the apoptosis rate. The dye inside the assay can only pass through the asymmetric cell membranes of apoptotic cells. Thus, only apoptotic cells stain in red, which was detected by spectrophotometrically at 550 nm wavelength. The level of apoptosis in groups was given as a percentage (%) of the control.[17]

Statistical Analysis: All data were presented as means ± standard deviations. Differences between recorded arithmetic mean values examined between groups were analysed by Prism 8 computer software (GraphPad Software, CA, USA). The significance of inter-groups was assessed using one-way ANOVA and Tukey's multiple comparison test. The p-value less than 0.05 was considered statistically significant for all groups.

RESULTS

The levels of lipid peroxidation were presented in Figure 1. MDA level was measured lowest (11.90±1.21) in the resveratrol group and highest (28.80±3.42) in the HG group. Except for the resveratrol group in all groups, malondialdehyde (MDA) levels were statistically higher ($^{a}p< 0.001$) versus the control group, while it was found to be significantly lower ($^{a}p< 0.001$) in the resveratrol group versus the control. High glucose medium or mannitol supplementation to medium led to a significant increase ($^{a}p< 0.001$) of the MDA level of M and HG groups. Resveratrol incubation succeeded in reversing the level of lipid peroxidation in M+R ($^{b}p< 0.001$) and HG+R ($^{c}p< 0.001$) groups. In the R group, MDA level was significantly lower ($^{a}p< 0.001$, $^{b}p< 0.001$, $^{c}p< 0.001$ and $^{d}p< 0.001$) than all groups, while there was no significance between M+R and HG+R groups.

Interleukin-1β (IL-1β) levels were presented in figure 2. IL-1β level was measured lowest (5.66±0.54) in the resveratrol group and highest (22.65±1.14) in the HG group. IL-1β level was meaningfully increased ($^{a}p< 0.001$) in M, HG, M+R, and HG+R groups compared to the control group, while it dramatically decreased ($^{a}p< 0.001$) in the R group versus the control group. There was no statistically considerable change between M, M+R and HG+R groups. It was shown that resveratrol supplementation alleviated the IL-1β formation in the HG+R group versus the HG group ($^{c}p< 0.001$). On the other hand, no alteration was determined between the M+R group versus the M group. In the R group level of IL-1β formation was significantly lower ($^{a}p< 0.001$, $^{b}p< 0.001$, $^{c}p< 0.001$ and $^{d}p< 0.001$) than all groups, while there was no considerable significance between M+R and HG+R groups.

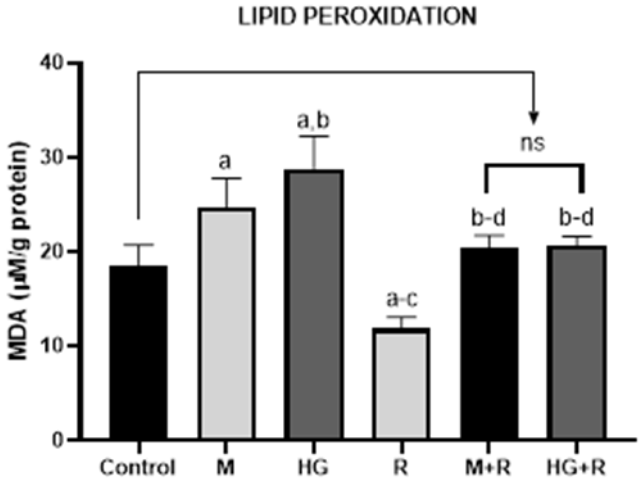

Figure 1. Levels of lipid peroxidation in ARPE-19 Cells. ^{a}: p<0.001 vs. Control; ^{b}: p<0.001 vs. Mannitol; ^{c}: p<0.001vs. High Glucose; ^{d}: p<0.001 vs. Resveratrol; ns: no significance.

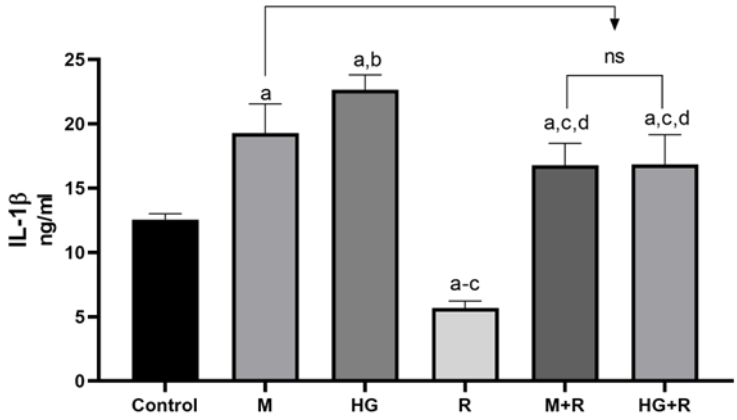

Figure 2. Levels of interleukin-1β in ARPE-19 Cells. ^{a}: p<0.001 vs. Control; ^{b}: p<0.001 vs. Mannitol; ^{c}: p<0.001vs. High Glucose; ^{d}: p<0.001 vs. Resveratrol; ns: no significance. R2 was calculated as 0.996.

TNF- α levels were presented in Figure 3. TNF- α level was measured lowest (22.23±2.00) in the resveratrol group and highest (70.10±4.54) in the HG group. TNF- α level was meaningfully increased in M, HG, M+R, and HG+R groups compared to the control group ($^{a}p< 0.001$), while it was meaningfully decreased ($^{a}p< 0.001$) in the R group versus the control group. No statistically significant difference has been determined between M versus HG and M+R and HG+R groups. Resveratrol supplementation to the medium led to a considerable reduction of the TNF- α levels in M+R and HG+R groups compared to M ($^{b}p< 0.001$) and HG ($^{c}p< 0.001$) groups, respectively. TNF- α production in the R group was significantly less than versus all other groups ($^{a}p< 0.001$, $^{b}p< 0.001$, $^{c}p< 0.001$ and $^{d}p< 0.001$).

VEGF-A levels were presented in figure 4. VEGF-A level was determined lowest (20.07±2.84) in the R group and highest (62.36±5.56) in the M and (60.93±4.32) HG groups. There was no significance between the control group compared to M+R and HG+R groups, albeit a statistical significance has been found between the control group compared to the M, HG and R groups ($^{a}p< 0.001$). It was found that production of VEGF-A decreased in the M+R group versus the M group ($^{b}p< 0.001$) and the HG+R group versus and HG group ($^{c}p< 0.001$) by resveratrol addition to medium. In M+R and HG+R groups, VEGF-A levels considerably raised compared to the R group ($^{d}p< 0.001$).

Apoptosis levels were presented as % change versus control in Figure 5. The highest apoptosis rate was measured in the HG group (182.60±10.72), and was lowest was in the R group (75.44±2.14). No statistical significance has been found between the control, M+R and HG+R groups, but there was a significant decrement in the R group and a significant increment in the HG group versus the control group ($^{a}p< 0.001$). Compared to the M ($^{b}p< 0.001$) and HG ($^{c}p< 0.001$) groups, apoptosis rates were considerably decreased in R, M+R and HG+R groups. The lowest apoptosis rate was measured in the R group compared to all other groups ($^{d}p< 0.001$).

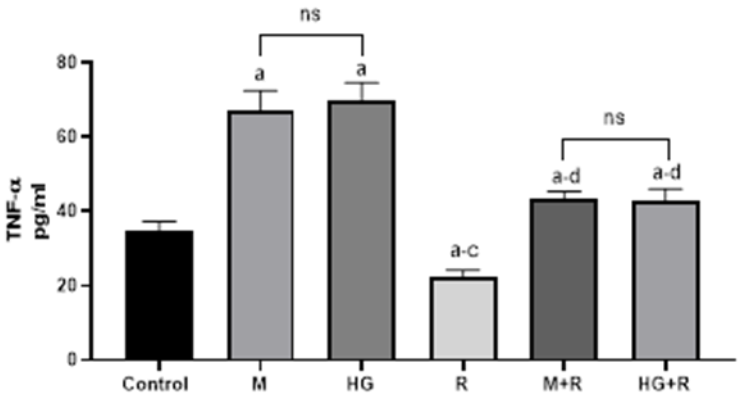

Figure 3. Levels of tumour necrosis factor-alpha (TNF- α) in ARPE-19 Cells. [a]: p<0.001 vs. Control; [b]: p<0.001 vs. Mannitol; [c]: p<0.001vs. High Glucose; [d]: p<0.001 vs. Resveratrol; ns: no significance. R2 was calculated as 0.992.

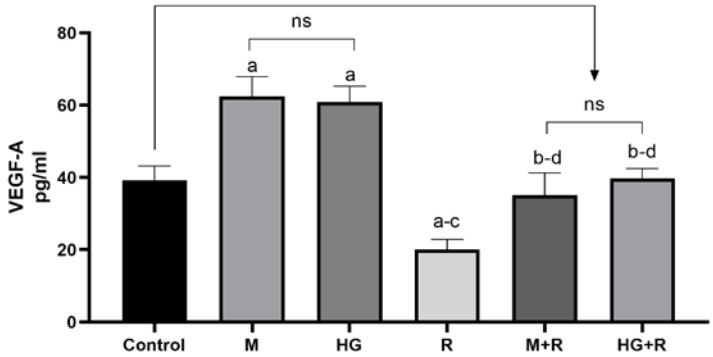

Figure 4. Levels of vascular endothelial growth factor A (VEGF-A) in ARPE-19 Cells. [a]: p<0.001 vs. Control; [b]: p<0.001 vs. Mannitol; [c]: p<0.001vs. High Glucose; [d]: p<0.001 vs. Resveratrol; ns: no significance. R2 was calculated as 0.990.

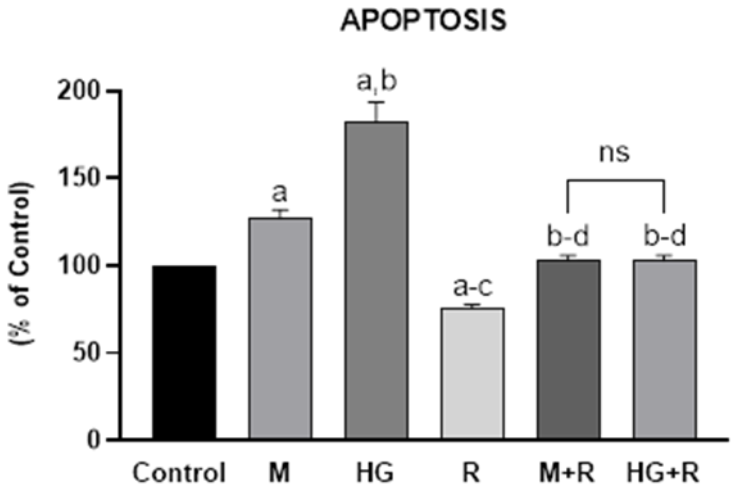

Figure 5. Apoptosis in ARPE-19 cells. [a]: p<0.001 vs. Control; [b]: p<0.001 vs. Mannitol; [c]: p<0.001vs. High Glucose; [d]: p<0.001 vs. Resveratrol; ns: no significance.

DISCUSSION AND CONCLUSION

It has been postulated that resveratrol may lead to reduced oxidation and proliferation of human retinal pigment epithelial cells by extracellular signal-regulated kinase inhibition. Additionally, it is proven that H_2O_2-induced ERK 1/2 activation could be diminished when cells were pre-treated with resveratrol. Similarly, these results showed that resveratrol may reduce the level of cellular lipid peroxidation.[18] Akbel et al. showed that resveratrol and Coenzyme-Q_{10} treatment together or alone may reduce the cyclophosphamide induced lipid peroxidation in rats.[19] It is found that ferroptosis-related lipid peroxidation levels may be attenuated by resveratrol in hepatocytes (HepG2) in cell culture.[20] It has been proven that glyoxal increases lipid peroxidation, ROS production and cell death in rat kidney cells.[21] In the same study, the use of resveratrol, curcumin and gallic acid were shown to reduce lipid peroxidation, ROS production and cell death.[21] The findings support that resveratrol may help to decrease the cellular lipid peroxidation elevated by high glucose in ARPE-19 cells in vitro, and it is consonant with similar studies in the literature.

Inflammation is the normal response of living organisms to injury caused by physical or harmful chemical stimuli or microbiological characteristics. Many proinflammatory mediators, such as IL-1β and TNF-α, play a role in the pathogenesis of inflammation.[22] Resveratrol has anti-inflammatory properties and provides a significant decrease in TNF-α levels.[23] In a study conducted on rat liver cells, Tanaoğlu et al.[24] demonstrated the protective effects of resveratrol use against cell damage by reducing IL-1β levels. In the study, a significant decrease in IL-1β and TNF-α levels was obtained in the resveratrol group.

Many factors, including hypoxia of retinal tissue, inflammatory cytokines, growth factors, and reactive oxygen species in diabetic patients, can cause overexpression of VEGF.[25] VEGF increases vascular permeability in the ischemic retina, stimulating the growth of endothelial cells, increasing angiogenesis and causing neovascularization.[26] In the study, an increase in VEGF levels was found in the control group at high glucose levels. In the resveratrol application, the VEGF level was found to be like the control group. The decrease in VEGF levels when resveratrol was applied supports the antiangiogenic properties of resveratrol.

Retinal pigment epithelium (RPE) cells play an important role in diabetic retinopathy, and hyperglycaemia-induced RPE cell apoptosis is thought to be associated with the progression of diabetic retinopathy. High glucose levels increase cell death by apoptosis in ARPE-19 cells.[27,28] Resveratrol use has been shown to increase nitric oxide levels, reduce oxidative stress and inhibit apoptosis in vascular endothelial cells.[29] Resveratrol inhibits apoptosis and autophagy in heart muscle cells and alleviates heart muscle damage in the experiment conducted on rats by Xiong et al.[30] In our study, it was shown that apoptosis, which increased at high glucose levels in ARPE-19 cells, was significantly reduced in the resveratrol group.

In conclusion, resveratrol can lead the ARPE-19 cell survival by reducing the level of lipid peroxidation and modulating the cellular cytokines such as (IL-1β, and TNF- α) and VEGF-A. Taking it together, it is concluded that resveratrol can reverse the disrupted cellular functions by supporting cellular viability. While cell culture studies provide valuable data, their lack of support from in-vivo studies is considered a limitation.

Ethics Committee Approval: This study doesn't need to have ethics committee approval.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept –MA, ÖÇ; Supervision – MA; Materials – MA, ÖÇ; Data Collection and/or Processing – MA, ÖÇ; Analysis and/or Interpretation – ÖÇ; Writing – MA, ÖÇ.

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