Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Original Article

Effect of Oleuropein Extract from Olive on Brain Oxidative Stress in Ovariectomized Diabetic Rats

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Received: 2020/12/02
Revised: 2021/05/02
Accepted: 2021/05/05

DOI: 10.29252/mlj.16.3.36

ABSTRACT

Background and objectives: Increased oxidative stress and altered antioxidant levels play an essential role in the pathogenesis of diabetes mellitus. Menopause is associated with increased food intake, weight gain, metabolic disorders, and increased level of inflammatory and oxidative stress factors. This study evaluated effects of oleuropein extract on brain tissue and serum oxidative status in ovariectomized diabetic rats.

Methods: In this study, 40 female Wistar rats weighing 250±20 grams were randomly divided into four groups: control, sham (surgery without ovariectomy), ovariectomy+diabetes, and ovariectomy+diabetes+oleuropein supplementation. Diabetes was induced by intraperitoneal injection of streptozotocin. The rats in the treatment group received 60 mg/kg of oleuropein for 30 days by oral gavage. Finally, blood glucose, superoxide dismutase, glutathione peroxidase, total antioxidant capacity, and malonaldehyde levels were evaluated in serum and brain tissue samples.

Results: Weight, blood glucose level, and antioxidant enzymes activity increased significantly in the ovariectomy+diabetes group compared to the control group.

Conclusion: This study suggested that the administration of oleuropein extract has beneficial effects on blood glucose level and antioxidant status in serum and brain tissue of ovariectomized diabetic rats.

Keywords: Oleuropein, Diabetes Mellitus, Antioxidants.

INTRODUCTION

Diabetes is an endocrine disorder associated with systemic and neurological complications. According to the World Health Organization's report, more than 420 million adults are living with diabetes worldwide. The exact causes of diabetes are still unknown, although genetics, obesity, and sedentary lifestyle play essential roles in the development of diabetes (1). Increased oxidative stress and change in antioxidants' levels also play a significant role in the pathogenesis of diabetes mellitus (2). It is well understood that menopause causes an increase in oxidative stress and inflammatory biomarkers (3). The complications of diabetes increase during menopause. Estrogen and its derivatives are potent antioxidants that reduce lipid peroxidation. These compounds exert protective effects by upregulation of glutathione peroxidase (GPX) and superoxide dismutase (SOD) in females (3). Mohammadi and Zare reported impaired spatial memory and motor index activities in diabetic and ovariectomized rats (4). However, the benefits of using estrogen in the treatment of diabetes complications during menopause are well-demonstrated. Oxidative stress can be increased during menopause, either due to the overproduction of free radicals or impaired antioxidant defense(5). Also, SOD activity is decreased in different tissues of diabetic and ovariectomized rats. A decrease in GPX and catalase activity was also observed in H_2O_2 detoxification (5).

Recently, the use of herbal drugs has increased due to their positive effects, few side effects, and relatively low cost. Therefore, seeking new, natural antidiabetic and antioxidants is of great importance. Dietary supplementation of antioxidants, such as vitamin E and flavonoids, can have beneficial effects on diabetic patients (6). A study by Nasirzadeh et al. reported increased serum MDA levels and reduced SOD and GPX activity in streptozotocin-induced diabetic rats (7). Another study showed that type 2 diabetes could affect learning and memory. On the other hand, metformin not only improves learning and memory but also reduces brain tissue MDA level (8).

Oleuropein is a phenolic compound present in olive oil (9). According to studies, oleuropein is an antioxidant that prevents lipid oxidation and removes free radicals in vitro (10). Nekooeian et al. reported that oleuropein has cardioprotective effect that partly results from its antioxidant activity (11). Given the antioxidant properties of oleuropein and its health benefits, this study investigated the effect of oleuropein extract on brain tissue and serum oxidative status in ovariectomized diabetic rats.

MATERIALS AND METHODS

In this study, 40 female, Wistar rats (weighing 200±20 g) were randomly divided into four groups (n=10). All rats were purchased from the Pasteur Institute of Iran (Tehran, Iran). The rats were kept under the same conditions (60% humidity, 23±2˚C, and 12:12 light–dark cycle) with free access to water and food. The study's protocol was approved by the Ethics Committee of the Islamic Azad University of Tabriz, Iran (ethical code: IR.IAU.TABRIZ.REC.1398.020). The animals were divided into four groups: control group (intact animals), sham (surgery without ovariectomy), ovariectomized rats with diabetes (Ovx+D), ovariectomized rats with diabetes, receiving oleuropein extract (Ovx+D+Ole).

Ovaries in the Ovx+D and Ovx+D+Ole groups were removed under anesthesia with 50 mg/kg ketamine chloride (Alfasan, Germany) and 5 mg/kg xylazine chloride (Alfasan, Germany) with minimum disruption to the surrounding soft tissues (12). Ten days after the ovariectomy and animals' recovery, the rats received a high-fat diet for eight weeks with free access to water. Type 2 diabetes was induced by intraperitoneal injection of streptozotocin (35 mg/kg) solubilized in 0.1 mM citrate buffer (13).

Oleuropein was prepared at Ardabil Azad University of Medical Sciences using the seeds of the *Marie canned* olive were harvested. Then, oleuropein was automatically separated and purified by using preparative high-performance liquid chromatography. Purity of the extracted oleuropein was measured with that of standard oleuropein (Sigma Aldrich, USA) (6).

At the end of the study, the rats were anesthetized by intraperitoneal injection of ketamine (50mg/kg) and xylazine (10mg/kg), and blood samples were taken from the heart. The samples were centrifuged at 3000 rpm for 10 minutes to separate serum. The serum samples were kept at -20 °C until used for

measurement of antioxidant enzyme activity and MDA level. Brain samples were taken and washed using phosphate buffer saline (pH=7.4). Then, one g of brain tissue was homogenized in five ml of cold buffer (Tris-HCl 50 mM, pH=7.5, ethylenediaminetetraacetic acid 5 mM, dithiothreitol 1 mM). The final solution was centrifuged at 10000 rpm for 15 minutes. The supernatant was used for evaluation of antioxidant enzyme activity and brain MDA level. Fasting blood glucose levels were measured at baseline and at the end of the study using a glucometer (AccuaChek, USA). Serum glucose levels were determined 72 hours after the streptozotocin injection, and a blood glucose level above 300 mg/dl confirmed induction of diabetes (14). Weight of the rats in each group was measured at baseline, after the streptozotocin injection, and after the high-fat diet. Next, SOD, GPX, and total antioxidant capacity (TAC) were measured using commercial kits (Randox, UK). We used a modified colorimetric method to measure plasma concentration of lipid peroxidation index (MDA) (15). This method was based on the MDA reaction with thiobarbituric acid (Cell Biolabs Inc., USA).

The obtained data were analyzed by one-way variance analysis (ANOVA) and Duncan test. All statistical analysis was carried out in SPSS software (version 22), with the statistical significance set at 0.05.

RESULTS

The weight of rats did not differ significantly at baseline. However, after diabetes induction, the weight increased significantly in the diabetic groups compared to the control group (p<0.05).

The final weight of animals was significantly lower in the Ovx+D+Ole group compared to the Ovx+D group (p<0.05) (Table 1). At baseline, blood glucose level did not differ significantly between the groups. However, blood glucose level was significantly higher in the diabetic groups than the control group (p<0.05).

At the end of the study period, blood glucose level was significantly lower in the Ovx+D+Ole group compared with the Ovx+D group (p<0.05), but there was no significant difference between the control and Ovx+D+Ole groups (Table 1).

Table 1- Mean body weight of rats and serum concentration of glucose in different study groups

Groups	Initial weight (g)	Diabetic weight (g)	Final weight (g)	Initial blood glucose (mg/dl)	Confirmatory blood glucose (mg/dl)	Final blood glucose (mg/dl)
Control	198.21±4.46 [a]	202.46±5.20 [b]	205.33±3.38 [b]	105.16±1.72 [a]	102.83±2.92 [c]	100.50±2.81 [c]
Sham	201.41±5.41 [a]	201.92±4.94 [b]	208.66±2.33 [b]	105.41±4.40 [a]	104.83±3.18 [c]	101.83±2.99 [c]
Ovx+D	199±5.95 [a]	233.62±5.37 [a]	224±3.63 [a]	107.83±3.18 [a]	314.08±3.52 [a]	368.16±2.13 [a]
Ovx+D+Ole	203±5.38 [a]	239.92±3.06 [a]	210.33±3.01 [b]	104.58±3.04 [a]	404±3.28 [b]	125.15±2.07 [b]
Groups	Initial weight (g)	Diabetic weight (g)	Final weight (g)	Initial blood glucose (mg/dl)	Confirmatory blood glucose (mg/dl)	Final blood glucose (mg/dl)
Control	198.21±4.46 a	202.46±5.20 b	205.33±3.38 b	105.16±1.72 a	102.83±2.92 c	100.50±2.81 c
Sham	201.41±5.41 a	201.92±4.94 b	208.66±2.33 b	105.41±4.40 a	104.83±3.18 c	101.83±2.99 c
Ovx+D	199±5.95 a	233.62±5.37 a	224±3.63 a	107.83±3.18 a	314.08±3.52 a	368.16±2.13 a
Ovx+D+Ole	203±5.38 a	239.92±3.06 a	210.33±3.01 b	104.58±3.04 a	404±3.28 b	125.15±2.07 b

Data are presented as mean±standard deviation.
abcde: Non-identical letters in each column indicate a statistically significant difference (p<0.05).
Ovx+D: ovariectomized rats with diabetes, Ovx+D+Ole: ovariectomized rats with diabetes, receiving oleuropein extract.

Based on the results, SOD activity in diabetic groups was significantly lower than in the control group (p<0.05). In addition, SOD activity was significantly lower in the Ovx+D group compared with other groups (p<0.05). Also, GPX activity was significantly lower in the Ovx+D group than in other groups (p<0.05). There was no significant difference between the control and Ovx+D+Ole groups in terms of GPX activity. The level of TAC was significantly lower in the Ovx+D group compared to the control group (p<0.05). Moreover, MDA level was significantly increased in the Ovx+D group compared to the control group (p<0.05). There was no significant difference between the Ovx+D and Ovx+D+Ole groups in terms of MDA level (Table 2).

According to the results, brain tissue SOD activity was significantly lower in the Ovx+D group than in other groups (p<0.05). However, GPX activity in the brain tissue was

significantly higher in the control group than in other groups (p<0.05). The level of brain tissue TAC did not differ significantly between the study groups. In addition, MDA level in brain tissue was significantly higher in the Ovx+D group compared to the control group (Table 2).

Table 2-Mean level of serum and brain antioxidant enzymes activity in rats in different study groups

Groups	Serum TAC (mmol/L)	Serum MDA (µmol/ml)	Serum GPX (U/gHb)	Serum SOD (U/ml)	Brain TAC (mmol/mg protein)	Brain MDA (nmol/mg protein)	Brain GPX (u/mg protein)
Control	6.40.±0.28 [b]	2.04±0.03 [b]	56.55±0.96 [c]	5.65±0.22 [c]	3.27±0.11 [a]	2.31±0.05 [c]	50.15±0.61 [a]
Sham	6.41±0.39 [b]	2.04±0.04 [b]	56.53±2.18 [c]	5.59±0.19 [c]	3.33±0.18 [a]	3.23±0.05 [c]	50.67±0.33 [a]
Ovx+D	4.25±0.02 [a]	3.56±0.01 [a]	41.81±2.57 [a]	3.41±0.23 [a]	3.15±0.05 [a]	3.49±0.02 [a]	31.22±0.43 [b]
Ovx+D+Ole	6.12±0.05 [b]	3.54±0.04 [a]	50.47±1.75 [b]	4.13±0.08 [b]	3.28±0.08 [a]	3.17±0.06 [b]	31.55±0.45 [b]

abcde: Non-identical letters in each column indicate a statistically significant difference (p<0.05).
Data are presented as mean±standard deviation.
Ovx+D: ovariectomized rats with diabetes, Ovx+D+Ole: ovariectomized rats with diabetes, receiving oleuropein extract.

DISCUSSION

In addition to hyperglycemia, the production of reactive oxygen species increases in diabetes. Therefore, managing antioxidant status and enzymes involved in glucose metabolism may be useful in controlling diabetes. In a study by Özkaya et al., similar to our study, diabetes was induced by using a high-fat diet and low-dose streptozotocin. Consistent with other studies, the present study showed that type 2 diabetes causes an increase in body weight and blood glucose levels of rats (16). In addition, oleuropein supplementation prevented weight gain in ovariectomized diabetic rats. The results also showed that the Ovx+D group blood glucose was significantly higher than other groups. However, there was no difference between the control group and the Ovx+D+Ole group. In line with previous studies This indicates that oleuropein extract can prevent hyperglycemia, which has been demonstrated in previous studies (7,14). The phenolic components of olive have high bioavailability. It has been shown that oleuropein is rapidly absorbed after oral administration and reaches maximum plasma concentration after two hours. Oleuropein has several pharmacologic properties, including antimicrobial (17), anti-inflammatory (18), anti-atherogenic (19), and antioxidant (20) effects. It inhibits low-density lipoprotein oxidation and can scavenge free radicals. Oleuropein has been shown to scavenge hypochlorous acid, an oxidative substance released from neutrophil myeloperoxidase at the site of inflammation. Mitochondrial phospholipids are predominantly susceptible to peroxidation and can be damaged by free radicals (9).

Studies have shown that oral oleuropein administration in alloxan- and streptozotocin-induced diabetic rats causes a significant reduction in blood sugar level (21). In this study, we measured MDA, SOD, GPX, and TAC in both brain tissue and serum samples of rats. Malondialdehyde is an essential indicator of oxidative stress and cell damage (22,23). In the present study, serum MDA level in the Ovx+D group was significantly increased compared to other groups, which is in agreement with results of a previous study (14). On the other hand, SOD and GPX levels in the Ovx+D group were significantly decreased. The decrease in SOD activity in the Ovx+D group may be caused by the inhibition of enzyme activity by glycation (16). Consistent with our findings, Altunkaynak et al. reported that menopause and diabetes may lower levels of lipid peroxidation, SOD, catalase, total glutathione, and myeloperoxidase, and cause destruction of hippocampal neurons in a rat model (24). In this study, TAC in the Ovx+D group was significantly lower than that of other groups. Similar to serum MDA, brain tissue MDA

level in the Ovx+D group was significantly increased compared to other groups. In another study, exercise increased catalase and GPx activity and decreased lipid peroxidation index in the brain tissue of diabetic rats. These findings are consistent with the results of our study (16). It has been also reported that diabetes could increase MDA and decrease antioxidant system activity (25).

CONCLUSION

In summary, the results of this research indicate the beneficial effects of oleuropein on hyperglycemia, lipid peroxidation index, and antioxidant enzymes activity in serum and brain of ovariectomized diabetic rats. Therefore, oleuropein can be used as an antioxidant to reduce the risk of oxidative stress-related diseases, such as diabetes. However, further studies are required to determine the molecular mechanisms involved in the neuroprotective effects of oleuropein.

ACKNOWLEDGEMENTS

The article had been derived from a research project approved by the Islamic Azad University, Tabriz Branch, Iran. The authors would like to express their gratitude to the university officials and laboratory experts at the faculty of veterinary medicine for their cooperation.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethics approvals and consent to participate

The study's protocol was approved by the Ethics Committee of the Islamic Azad University of Tabriz, Iran (ethical code: IR.IAU.TABRIZ.REC.1398.020).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article.

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How to Cite:
Athari SZ, Nourazar MA, Nasirzadeh R [Effect of Oleuropein Extract from Olive on Brain Oxidative Stress in Ovariectomized Diabetic Rats]. mljgoums. 2022; 16(3): 36-41 DOI: 10.29252/mlj.16.3.36