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Article

Long-term resveratrol administration improves diabetes- induced pancreatic oxidative stress, inflammatory status, and β cell function in male rats

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Diabetes is a metabolic disorder caused by insulin resistance or a defect in the pancreatic beta cells in insulin secretion. The aim of this study was to evaluate the possible effectiveness of long-term administration of resveratrol on inflammatory and oxidative stress markers in the pancreatic tissue of diabetic rats. Male Wistar rats (n = 24) were randomly divided into four groups of six animals, namely a healthy group, a healthy group receiving resveratrol, a diabetic control group, and a diabetic group receiving resveratrol. Diabetes was induced by single dose injection of streptozotocin (50 mg/kg; ip), 15 min after injection of nicotinamide (110 mg/kg; ip). Resveratrol was also administered by gavage (5 mg/kg/day) for 4 months. Administration of resveratrol alleviated hyperglycemia, weight loss and pancreatic β cell function measured by HOMA-β. Resveratrol improved oxidative stress (nitrate/nitrite, 8-isoprostane and glutathione) and proinflammatory markers (tumor necrosis factor α, cyclooxygenase 2, interleukin 6 and nuclear factor kappa B) in the pancreatic tissue of diabetic rats. Resveratrol administration had no significant effect on the activity of superoxide dismutase and catalase enzyme. These observations indicate that resveratrol administration may be effective as a beneficial factor in improving pancreatic function and reducing the complications of diabetes.

Keywords: Hyperglycemia. HOMA-β. IL-6. NF-κB. Resveratrol. TNF-α.

INTRODUCTION

Diabetes mellitus is a widespread metabolic disorder caused by the impaired secretion of insulin by the beta cells of the islets of Langerhans or insulin resistance (Dooley *et al*., 2016). In recent years, the prevalence of diabetes has sharply increased in almost all regions of the world, so that 425 million people worldwide are now suffering from diabetes (Herrera *et al*., 2021).

Hyperglycemia causes oxidative stress by increasing the production of reactive oxygen species (ROS) and impairment of antioxidant defenses through reducing antioxidants such as glutathione (GSH) and the activity of antioxidant enzymes (Robertson *et al*., 2004; Zhang *et al.* 2020). Documents indicate that oxidative stress plays a key role in the pathogenesis of diabetes (Zhang *et al.* 2020). Hyperglycemia along with oxidative stress promotes the production of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and activates the proinflammatory transcription factor nuclear factor kappa B, NF-κB which in turn increases the production of inflammatory cytokines. This process leads to inflammation, cell damages (including lipid peroxidation, protein oxidation, and DNA damage) and eventually cell death (Palsamy, Subramanian, 2010; Zephy, Ahmad, 2015). Oxidative stress and inflammation in the pancreatic tissue have also been shown to cause dysfunction and death of

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beta cells of the Langerhans islets (Palsamy, Subramanian, 2010; van der Spuy, Pretorius, 2009).

Resveratrol (trans-3, 5, 4'-trihydroxystilbene) is an Stilbene compound and a phytoalexin produced due to the reactions of plants to stressful stimuli. (Weiskirchen, Weiskirchen, 2016). The beneficial effects of this compound, including antioxidant, anti-cancer, anti-inflammatory, and anti-obesity roles, as well as protection of the heart and nerves, have been observed in both humans and laboratory animals. Previous studies have shown that short-term resveratrol administration can exert beneficial anti-diabetic effects such as lowering blood sugar in hyperglycemic animals, protection of pancreatic beta cells, improvement of insulin function, and reduction of insulin secretion in hyperinsulinemic animals (Ku *et al*., 2011; Szkudelski, Szkudelska, 2015).

Also, Palsamy and Subramanian (2010) reported that short- term administration of resveratrol (30 days) reduces oxidative stress in the pancreas of diabetic rats.

While short- term administration of resveratrol has been suggested to have a protective effect on pancreatic beta cells and improves pancreatic structure and function, there is insufficient information on the effect of long-term administration. The present study, therefore, aims to evaluate the effect of long-term (4 months) resveratrol administration at a dose of 5 mg/kg/day on inflammatory and oxidative stress markers in the pancreatic tissue of diabetic rats.

MATERIAL AND METHODS

Experimental animals and group design

A total of 24 male Wistar rats (Razi Institute, Tehran, Iran), weighing 320-350 g, in standard conditions (temperature 22-25 °C, 12 h dark-light condition, and free access to water and food) were selected randomly and divided into four groups of 6 animals as follows:

1. Healthy control group (NC): No intervention was performed on the rats of this group.
2. Healthy group receiving resveratrol (NTR): Rats in this group received resveratrol for 4 months.
3. Diabetic control group (DC): Diabetic animals were retained for 4 months.
4. Diabetic group receiving resveratrol (DTR): Rats in this group received resveratrol for 4 months after one week of diabetes induction.

The study approved by the Ethical Committee of Tabriz University of Medical Sciences (Code: IR.TBZMED.REC.1389.82), and adhered to the tenets of the Declaration of Helsinki (Arvin *et al*., 2017).

Induction of diabetes

To induce type 2 diabetes, was first 110 mg/kg of nicotinamide injected intrapritoneally and after 15 minutes, 50 mg/kg of streptozotocin (STZ) dissolved in 0.1 molar citrate buffer (pH = 4.5) was injected intraperitoneally. Nicotinamide protects pancreatic β cells (up to 40%) from STZ cytotoxicity, causing insulin-independent diabetes mellitus (type 2 diabetes) (Masiello *et al*., 1998). To prevent hypoglycemia due to insulin secretion from pancreatic cells degraded by STZ, 10% glucose solution was provided to diabetic rats for 24 h after 6 h of streptozotocin injection. After 48 h of injection, blood glucose of rats was measured by a glucometer (Arkray, Kyoto, Japan) and values above 250 mg/dl were considered as type 2 diabetes (Figure 1). Water-soluble resveratrol (Cayman chem., Ann Arbor, MI, USA) at a dose of 5 mg/kg was given as gavage daily for 4 months at noon times and the dose of resveratrol was monitored and adjusted weekly (Palsamy, Subramanian, 2008). At the end of the experimental period, rats were anesthetized with 80 mg/kg of ketamine and killed by beheading. Blood (5 ml) was collected from the retroorbital sinus of rats. Pancreatic tissues were removed by dissecting the abdomen of rats, immediately frozen in liquid nitrogen, and kept at −70 °C until homogenization. All interventions were performed from morning to noon and all measurements were done at noon interval.

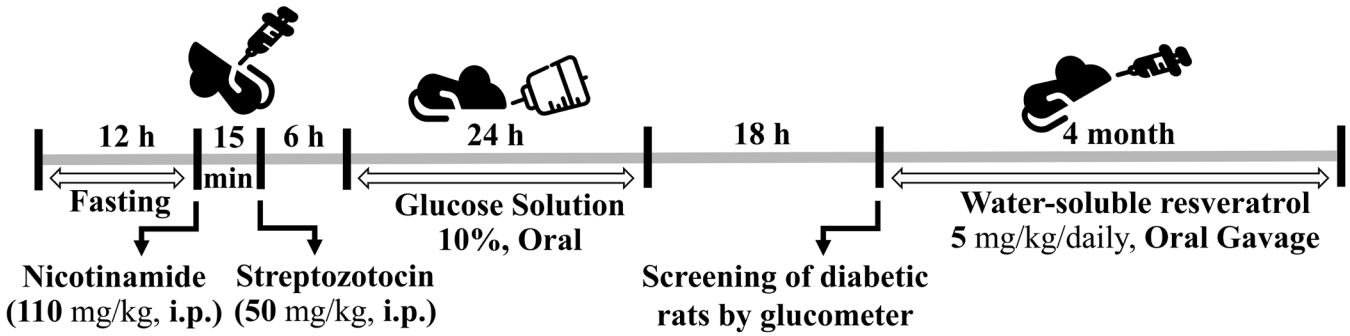

FIGURE 1 - The scheme of experimental procedures.

Tissue homogenization

According to the instructions of the Cayman commercial kit (Cayman chem., Ann Arbor, MI; Item No: 10409), 200 mg of fresh pancreatic tissue with 400 µl of cold hypotonic buffer (10 mM NaCl, 2 mM MgCl2, 10 mM HEPES, 20% glycerol 0.1% Triton X-100, 1 mM dithiothreitol, 3 µl of 1 M of 10% P-40, complete protease inhibitor cocktail, pH 7.4), were homogenized for 15 minutes and then for 10 minutes at 4 °C at 14,000 rpm were centrifuged. Supernatant containing cytoplasmic proteins was used to measure TNF-α, IL-6, 8-Isoprostane, SOD, GSH, CAT and COX-2. The precipitate residue was homogenized in 50 µl of cold extraction buffer (hypotonic buffer, 39.8 µl of 5 M NaCl and 5 µl of 10 mM dithiothreitol) and centrifuged for 10 minutes at 4 ° C at 14000 g, and the supernatant contained the nuclear proteins was used to measure NF-κB. Protein determination kit (Cayman chem., Ann Arbor, MI; Item No: 704002) was used to evaluate the cytoplasmic and nuclear protein concentrations of the pancreas.

Measurement of glucose and insulin

Blood glucose was measured by a glucometer (Arkray, Kyoto, Japan). Insulin was determined by a proprietary kit (Cayman Chem., Ann Arbor, MI, USA) according to the instructions by the ELISA method at 450 nm and then calculated by drawing a standard curve (Soufi, Mohammad Nejad, Ahmadieh, 2012).

Homeostasis Model of Assessment

The homeostasis model assessment for insulin resistance (HOMA-IR) and assessing pancreatic β – cell function (HOMA - β) was calculated via the following equations (Ghiasi *et al*., 2015):

HOMA-IR = Glucose (mg/dl) × Insulin (ng/ml)/405
HOMA-β = 360 × Insulin (ng/ml)/Glucose (mg/dl) - 63

Measurement of oxidative stress markers

SOD activity, GSH and 8-Isoprostane concentrations, and nitrate to nitrite ratio, were assessed by a proprietary kit (Cayman Chem., Ann Arbor, MI, USA) according to the instructions by the ELISA method and then calculated by drawing standard curves. CAT activity was also measured using the IBL kit (IBL, Hamburg Germany) according to the Abei method. Measurements were based on hydrogen peroxide decomposition rate at 240 nm at 20 °C and the enzyme activity (nmol/mg protein) was obtained through the following formula (Khameneh *et al*., 2013).

K=0.153 (log A240 at t=0/A240 at t=15)

Measurement of inflammatory markers

IL-6 and TNF-α levels were determined using IL-6 and TNF-α inflammatory factor kits (Invitrogen, USA) by the ELISA method based on the manufacturer's instructions at 450 nm. NF-κB activity was measured

using a NF-κB p65 transcription factor kit (Cayman chem., Ann Arbor, MI) according to the manufacturer's instructions and expressed as OD 450 nm/mg protein (Soufi *et al.*, 2012). COX-2 activity was assessed by a ELISA kit (Cayman Chem., Ann Arbor, MI, USA) according to the instructions and then calculated by drawing standard curves (Khameneh *et al.*, 2013).

Statistical analysis

The obtained data were expressed as mean ± standard error (SE) and p-values < 0.05 were considered statistically significant. Differences between different groups were compared by one way analysis of variance (ANOVA) and Tukey's test using SPSS software version 18.

RESULTS

Changes in body weight, blood sugar, and blood insulin

As shown in Table I, body weight and blood insulin concentrations decreased significantly in diabetic rats compared to the healthy control animals 4 months after the induction of diabetes ($p < 0.01$ for both factors), while blood sugar level was significantly higher in the diabetic group than the healthy control ($p < 0.01$). Administration of resveratrol in healthy rats changed none of these variables compared to the healthy control group. However resveratrol administration in diabetic rats increased body weight and decreased blood sugar compared to the diabetic group ($p < 0.05$ for both factors), it failed to reach similar levels in the healthy control group. Although long-term use of resveratrol increased insulin levels in diabetic rats, this increase was not at a significant level ($p = 0.059$).

TABLE I - Values for the measured factors of body weight, blood sugar, and blood insulin in the study groups

	Study groups			
Measured factors	**NC**	**DC**	**NTR**	**DTR**
Body weight (gr)	469.33 ±4.56	220.28±5.01**	443.71±3.88	281.99±5.11**
Blood glucose (mg/dL)	111.18±4.09	507.33±4.27**	101.62±5.31	388.73±7.03**
Blood insulin (ng/mL)	18.18±0.31	6.11±0.21**	21.61±0.49	7.91±0.83**

Values are expressed as mean ± SE for six rats in each group. **: indicates $p < 0.01$ relative to the healthy control group, and # indicates $p < 0.05$ relative to the diabetic control group. NTR and DTR represent resveratrol-administered healthy and diabetic groups, respectively.

Changes in insulin resistance and assessing pancreatic β – cell function:

Figure 2-A illustrates that 4 months after induction of diabetes, insulin resistance level increased significantly in both diabetic groups compared to healthy control rats ($p < 0.01$ for both) and resveratrol administration in both healthy and diabetic groups had no effect on insulin resistance. Figure 2-B also illustrates that pancreatic beta cell function was significantly lower in rats in both diabetic groups than that in control group rats ($p < 0.01$ for both) and long-term resveratrol administration improved pancreatic beta cell function in both healthy and diabetic rats ($p < 0.05$ for both).

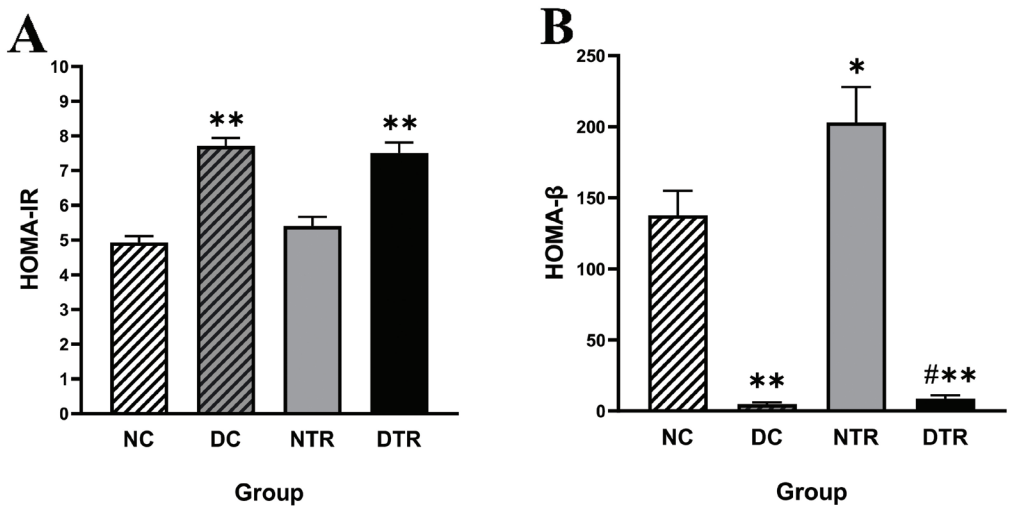

FIGURE 2 - The effect of long-term resveratrol administration on Insulin resistance index (HOMA- IR) and beta cell function index (HOMA-β) in pancreatic tissues of the studied groups during the experimental period. Values are expressed as mean ± SE for six rats in each group. The sign * indicates $p < 0.05$ and the sign ** indicates $p < 0.01$ relative to the healthy control group (NC); # indicate $p < 0.05$ relative to the diabetic control group (DC). NTR and DTR represent resveratrol-administered healthy and diabetic groups, respectively.

Changes in oxidative stress markers

Figure 3, shows that long-term diabetes has increased the concentration of 8-Isoprostane and the ratio of nitrate to nitrite ($p < 0.01$ for both factors) and decreased SOD activity ($p < 0.05$) and GSH concentrations ($p < 0.01$) in the pancreatic tissues of diabetic rats compared to those in healthy controls. Four months resveratrol administration prevented a significant decrease in SOD activity in resveratrol-treated diabetic rats compared to the healthy group. Resveratrol also reduced the concentration of 8-Isoprostane ($p < 0.01$) and the ratio of nitrate to nitrite ($p < 0.05$) and increased GSH content ($p < 0.05$) compared to the diabetic group, but it failed to reach similar levels in healthy control group. Administration of resveratrol in healthy rats was only led to a significant increase in CAT activity ($p < 0.05$).

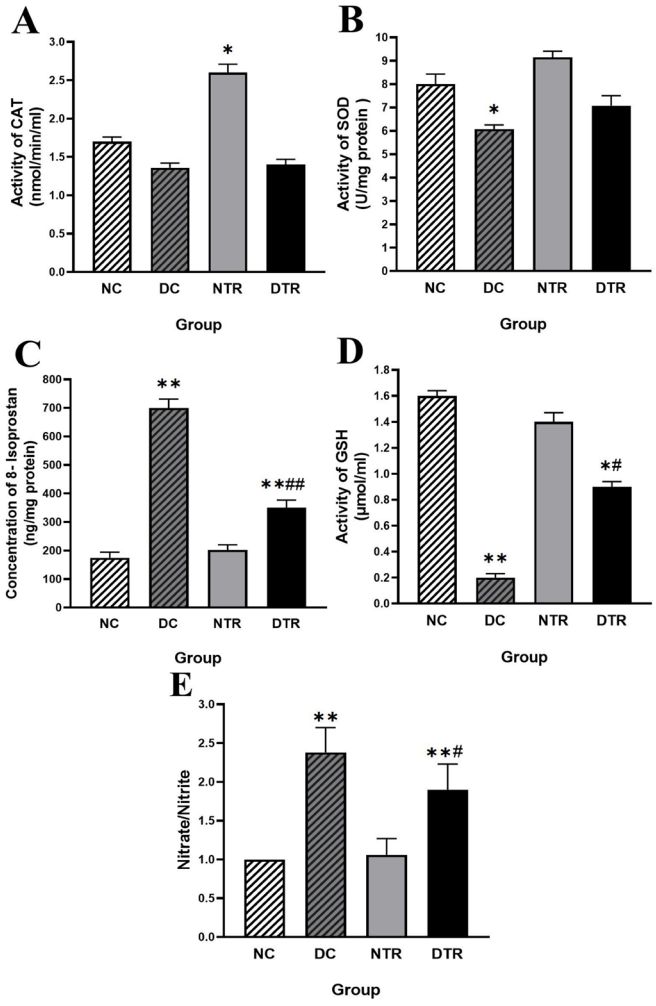

FIGURE 3 - The effect of long-term resveratrol administration on catalase activity (A) superoxide dismutase activity (B) 8-Isoprostane concentration (C) reductive glutathione activity (D) and nitrate to nitrite ratio (E) in pancreatic tissues of rats studied during the experimental period. Values are expressed as mean ± SE for six rats in each group. * and ** indicate $p < 0.05$ and $p < 0.01$ relative to the healthy control group (NC), respectively. # and ## indicate $p < 0.05$ and $p < 0.01$ relative to the diabetic control group (DC), respectively. NTR and DTR represent resveratrol-administered healthy and diabetic groups, respectively.

Changes in inflammatory markers

Figure 4 shows that COX-2 and NF-κB activities ($p < 0.05$) and TNF-α and IL-6 concentrations ($p < 0.01$) increased significantly in pancreatic tissues of diabetic rats in comparison to healthy control animals. These variables remained unchanged in healthy rats administered with resveratrol compared to the healthy group. In diabetic rats receiving resveratrol, however, it prevented significant increases in COX-2 activity and IL-6 concentrations in comparison to the healthy group and decreased NF-κB activity and TNF-α concentrations compared with the diabetic rats ($P < 0.05$ for both factors). Nonetheless, NF-κB activity ($p < 0.05$) and TNF-α concentrations ($p < 0.01$) were still significantly higher than healthy control group.

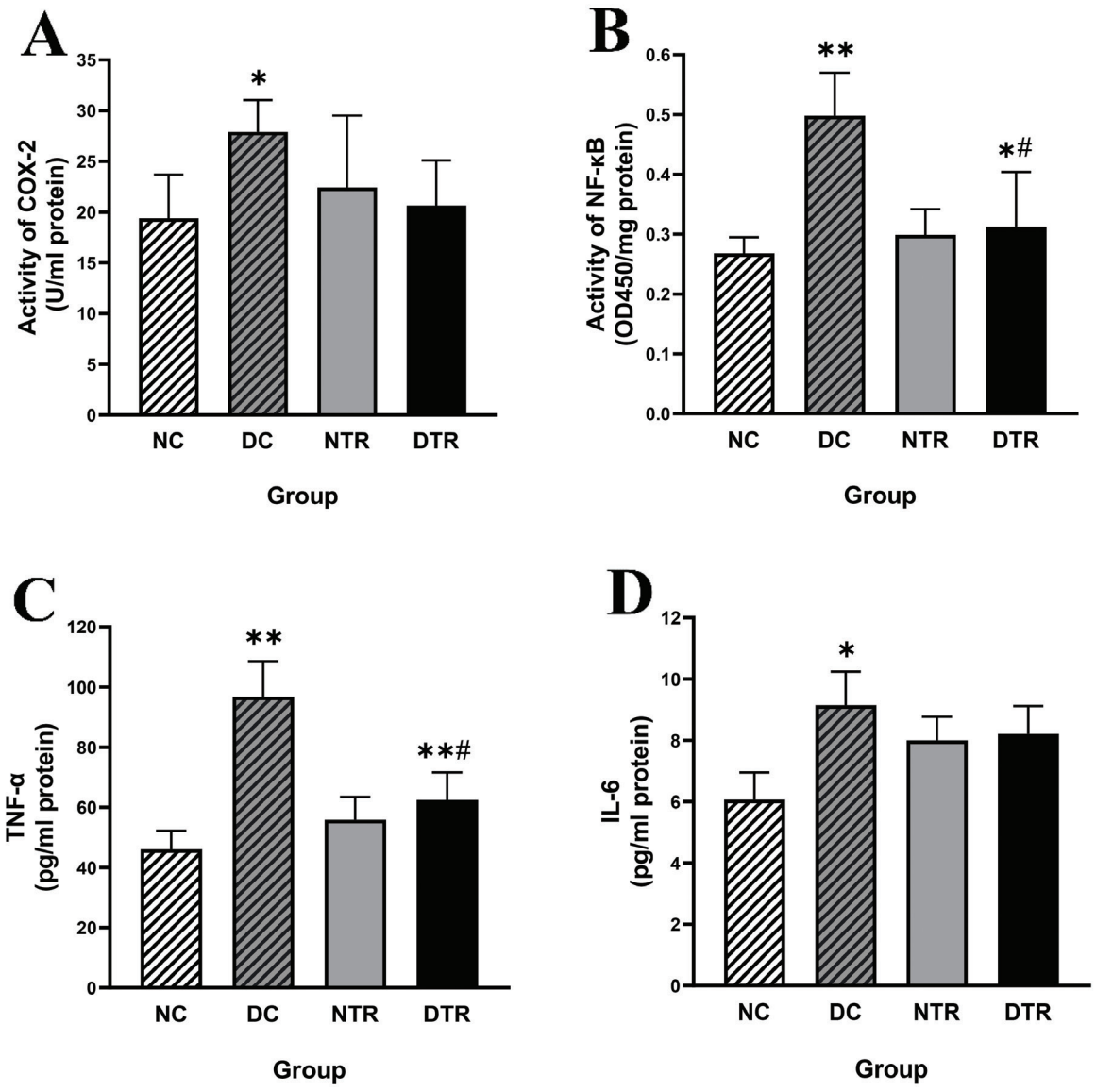

FIGURE 4 - The effect of long-term resveratrol administration on COX-2 (A) and NF-Kb (B) activities and concentrations of TNF-α (C) and IL-6 (D) in pancreatic tissues of the studied groups during the experimental period. Values are expressed as mean ± SE for six rats in each group. The sign * indicates $p < 0.05$ and the sign ** indicates $p < 0.01$ relative to the healthy control group (NC); # and ## indicate $p < 0.05$ and $p < 0.01$, respectively, relative to the diabetic control group (DC). NTR and DTR represent resveratrol-administered healthy and diabetic groups, respectively.

DISCUSSION

Oxidative stress has been shown to be one of the major causes of hyperglycemia. In other words, oxidative stress in the pancreatic beta cells reduces the activity and mRNA production of the insulin gene promoter, resulting in the inhibition of insulin gene expression. A reduction has also been reported in DNA binding capacity to PDX-1, an important transcription factor for the insulin gene (Evans *et al.*, 2002; O'Brien, Granner, 1996). In this condition, the body has to break down proteins and fats to provide the required energy from their storage sources, causing muscle atrophy and fat mass, and thus an evident weight loss (Palsamy, Sivakumar, Subramanian, 2010). In line with previous studies, our results revealed that diabetic rats developed hyperglycemia and gradual but noticeable

weight loss over a 4-month period (Soylemez *et al.*, 2008). However, the administration of resveratrol to diabetic rats for 4 months led to weakened hyperglycemia and the weight loss process, with a relative increasing trend in blood insulin levels (though this increase was not significant; $p = 0.059$), indicating a possible improvement in energy metabolism.

Resveratrol has been reported can protect the pancreas, improve the function of pancreatic β cells and reduce insulin secretion (Szkudelski, Szkudelska, 2015). This condition enables the pancreas to produce and secrete more insulin over a longer time period and therefore helps to improve metabolism and weight regulation in the long run (Soylemez *et al.*, 2008; Leonard *et al.*, 2003).

Results of the present study also suggest the effectiveness of resveratrol on pancreatic beta cell function, so that resveratrol administration increased the HOMA-β index in both healthy and diabetic rats, which are consistent with results of other studies (Movahed *et al.*, 2013).

Studies suggest that resveratrol leads to more efficient signaling for insulin through the Akt pathway by reducing oxidative stress, resulting in reduced insulin resistance (Brasnyó *et al.*, 2011). In a study conducted by Cheng *et al.* (2015) resveratrol could reduce the level of HOMA-IR index in the pancreatic tissue of diabetic rats. A similar result was observed in a human study conducted by Movahed *et al.* (2013). However, in some human studies (Goh *et al.*, 2014) and in the present study, resveratrol administration could not reduce this index. The reason for this difference in results may be due to differences in the methods (consumed dose, duration of resveratrol consumption) in various studies.

In normal conditions, mitochondria and the NADPH oxidase pathway produce moderate levels of reactive oxygen species (ROS), such as superoxide species ($\bullet O_2$), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH), which participate in some physiological processes. In the first step, ROS is detoxified by SOD, resulting in the dismutation of $\bullet O_2$ to H_2O_2, and the latter is then detoxified by catalase or glutathione peroxidase and converted to water and molecular oxygen (Su, Hung, Chen, 2006). Additionally, GSH, another intracellular antioxidant molecule, is an essential substrate for the activity of glutathione peroxidase and acts as a direct scavenger of ROS by being converted to GSSG.

Overproduction of ROS or declined ability of antioxidants in their detoxification causes oxidative stress, which can be traced by measuring lipid peroxidation, decreased activity of antioxidant enzymes, protein oxidation, and apoptosis (Soufi, Mohammad Nejad, Ahmadieh, 2012). Chronic hyperglycemia has been shown to induce oxidative stress by direct production of ROS or by alteration of the redox balance (van der Spuy, Pretorius, 2009).

Our results are in line with previous studies in this field, so that rats in diabetic groups developed chronic hyperglycemia with elevated 8-Isoprostane level, decreased SOD antioxidant activity, increased nitrate to nitrite ratio, and declined GSH concentration in pancreatic tissue ().

As a member of the eicosanoids family, 8-isoprostane is known as an indicator of lipid peroxidation during oxidative stress and antioxidant deficiency, and is produced by the oxidation of phospholipids by oxygen radicals (Morrow *et al.*, 1995). Nitric oxide (NO•) is another factor contributing to oxidative stress, which can react with superoxide to form a powerful oxidant, called peroxynitrite (•ONOO), causing more cell damage. NO has a short half-life that limits its direct measurement. Therefore, its metabolites, nitrite (NO_2^-) and nitrate (NO_3^-), are usually measured in studies (Pitocco *et al.*, 2010).

Palsamy and Subramanian (2010) reported that administration of resveratrol for 30 days resulted in significant reductions in lipid peroxidases, hydroperoxidases, and carbonyl proteins, as well as an enhancement in the activity of antioxidant enzymes in treated diabetic rats. Additionally, the antioxidant effects of resveratrol improved the structure and function of the pancreas The results of this study are in line with previous studies, so that 4-month administration of resveratrol prevented excessive increase in lipid peroxidation (8- isoprostane level), a decrease of SOD antioxidant enzyme activity, a significant increase in the ratio of nitrate to nitrite, and a significant decrease in GSH concentration in the pancreatic tissue.

Hyperglycemia increases the activity of NF-κB transcription factor in various ways. NF-κB is one of the most important proinflammatory transcription factors and plays a key role in the progression of diabetes-induced inflammations in different tissues (Clarkson, Thompson,

2000; Mantha *et al*., 1993). This factor increases collagen production, cell-binding molecules, mobilization and activation of leukocytes in tissues by activating proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, in addition to being in a positive feedback loop leading to greater NF-κB activity and the production of inflammatory agents, including cyclooxygenase-2 (COX-2). This inflammation-inducing process, along with tissue damage due to oxidative stress, leads to apoptosis in the tissue. Inflammatory cytokines are involved in increasing COX-2 expression in many tissues by the activation of NF-κB and MAPK (mitogen-activating protein kinase) (Paik *et al*., 2000; Palsamy, Subramanian, 2010).

In terms of tissue inflammation, the results of this study are also in agreement with those of other studies, so that the activities of NF-κB and COX-2 and the concentrations of TNFα and IL-6 were significantly higher in pancreatic tissues of diabetic rats than in healthy rats.

There are several studies on the anti-inflammatory effects of resveratrol. Kennedy *et al.* (2009), for instance, investigated the effects of resveratrol on the reduction of inflammation in human adipocytes, and observed that resveratrol administration blocked inflammatory responses and inhibited the induction of IL-6, IL-8, and IL-1β expression levels. Palsamy and Subramanian (2011) also studied the effects of resveratrol on kidneys of diabetic rats and reported that resveratrol administration for 30 days improved proinflammatory factors, such as NF-κB, COX-2, IL-6, and TNF-α, in a diabetic group compared to diabetic controls. In another study oral administration of resveratrol (5 mg/kg body weight) to diabetic rats for 30 days resulted in significant reductions in the levels of inflammatory markers, TNF-α, IL-1β, IL-6, and NF-κB, in the pancreatic tissue (Palsamy, Subramanian, 2010).The present results are consistent with those of other investigations, so that 4-month administration of resveratrol decreased NF-κB activity and TNF-α concentration, and prevented the increase of COX-2 activity and IL-6 concentrations in the pancreas of diabetic rats.

CONCLUSION

Diabetes has been shown to cause oxidative stress, an increase in proinflammatory mediators, and inflammation in the pancreas tissue. On the other hand, long-term administration of resveratrol attenuated blood sugar reduction and mitigated the adverse effects of diabetes on the pancreatic tissue. Therefore, given that previous studies are indicative of no significant side effects by resveratrol administration, it has a significant beneficial reducing effect on the complications of diabetes in the pancreatic tissue and can be useful as a supplement in the reduction of diabetes-induced problems. To confirm this hypothesis, however, further clinical trials are needed in humans.

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