Protective effects of resveratrol improve cardiovascular function in rats with diabetes

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Abstract. Resveratrol is a flavonoid with a stilbene structure that is able to suppress acute pulmonary thromboembolism-induced pulmonary artery hypertension. Furthermore, it possesses anti-cancer and antioxidant properties, is able to regulate blood lipids and increase life expectancy. In the present study, it was evaluated whether the protective effect of resveratrol was able to improve cardiovascular function in rats with diabetes. The effects of resveratrol on blood glucose, body weight, heart/body weight ratio, plasma triglyceride levels, heart rate, aspartate transaminase (AST)/alanine transaminase (ALT) ratio and total plasma insulin were evaluated. Levels of inflammation and oxidative stress were also evaluated using ELISA kits, and the expressions of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) and phosphorylated (p)-p38 protein were evaluated via western blot analysis. The results demonstrated that administration of resveratrol in rats with diabetes-related myocardial infarction (DRMI) significantly reduced blood glucose, body weight, plasma triglyceride levels, heart rate and AST/ALT ratio (all $P<0.01$) and significantly increased total plasma insulin ($P<0.01$). Furthermore, resveratrol significantly reduced levels of inflammation factors ($P<0.01$) and malondialdehyde, a marker for oxidative stress, in rats with DRMI ($P<0.01$). Resveratrol significantly increased the expression of eNOS ($P<0.01$) and suppressed the expression of VEGF and p-p38 (both $P<0.01$) in rats with DRMI. These results suggest that treatment with resveratrol is able to improve cardiovascular function via inhibition of eNOS and VEGF, and suppression of p38 phosphorylation in rats with DRMI.

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Introduction

Diabetes mellitus is a disease characterized by high morbidity, disability and fatality rates, which poses a notable threat to human health (1). Diabetes-associated cardiovascular complications are a leading cause of mortality (2). According to the 2007 European Society of Cardiology/European Association for the Study of Diabetes guidelines, the risk of cardiovascular complication is increased by 2-3 times for males with diabetes, and by 3-5 times for females, compared with non-diabetic people (3). A study reported that the occurrence rate of non-flow with revascularization treatment following acute myocardial infarction was four times higher in patients with diabetes compared with patients without diabetes (4). The occurrence rates of congestive heart failure following acute myocardial infarction are three times higher for patients with diabetes compared with those without (5). It would therefore be of great benefit to identify an effective intervention target to prevent cardiovascular complications in patients with diabetes.

Diabetic myocardial microvascular damage serves an important role in the occurrence and progression of cardiovascular complications in patients with diabetes (6). Myocardial perfusion levels are dependent on myocardial microvessel coronary flow reserve (6). Under diabetic conditions, myocardial microvascular damage occurs earlier than damage in the larger vessels and myocardial cells (7,8). A previous study demonstrated that the cell junctions of cardiac microvascular endothelial cells in patients with diabetes are not complete and have a lower barrier function (9). Furthermore, the density of microvessels in the myocardium and the microvessel/cardiac muscle fiber ratio is lowered (10). These changes lead to disturbances in microcirculation (11). Myocardial microcirculation is where the interchange of materials between the myocardial cells and blood occurs, and microcirculation disturbance may affect microcirculatory perfusion and induce an imbalance in oxygen supply and blood flow volume locally or to the whole myocardium (7), therefore contributing to structural changes in and dysfunction of the heart. Although no obvious hemadostenosis occurs in coronary vessels, microcirculation disturbance may lead to adverse clinical events (12). Therefore, to reduce the occurrence of diabetes-related microcirculation injuries, it is important to develop a preventative treatment for diabetic cardiovascular complications (13).

Resveratrol exerts its cardioprotective effect by reducing the extent of myocardial ischemia-reperfusion injury, vasodilation

and atherosclerosis (14). Physiological concentrations are able to induce vasodilation, therefore decreasing the risk of hypertension and cardiovascular diseases (15). Traditionally, Chinese medicines such as *Polygonum cuspidatum* and fleece-flower roots, which are rich in resveratrol, have been used to treat and prevent hyperlipidemia and arteriosclerosis (16). A recent study demonstrated that resveratrol is an effective molecule which may be able to prevent cardiac dysfunction (17). The present study aimed to investigate whether the protective effect of resveratrol was able to improve cardiovascular functions in rats with diabetes.

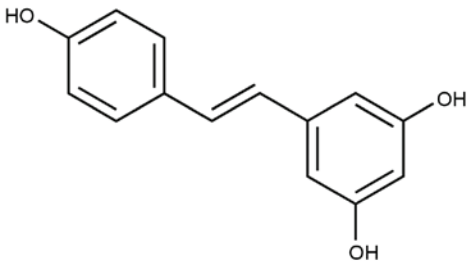

Figure 1. Chemical structure of resveratrol.

Materials and methods

Experimental animals and experimental grouping. A total of 46 male Sprague Dawley rats (weight, 280-320 g; age, 10-11 weeks) were purchased from Vital River Laboratories Co., Ltd. (Beijing, China) and housed in the Laboratory Animal Unit of China Armed Police General Hospital (Beijing, China) under standard conditions at 25±2˚C, 55-60% humidity with a 12 h light/dark cycle and had *ad libitum* access to food and water. Diabetes-related myocardial infarction (DRMI) was induced in 40 rats via administration of streptozocin (STZ) through the femoral vein (65 mg/kg; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany). A total of 6 normal rats were administered with an equivalent volume of saline as a control group. Blood samples (200 μl) were harvested via the tail vein one week post-infection. Plasma glucose levels were measured using plasma glucose test films and enzymatic diagnostic kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Plasma glucose levels ≥300 mg/dl, polyphagia, polyuria and polydipsia were observed in the experimental group, confirming the induction of diabetes. Rats with STZ-induced DRMI (STZ-DRMI) were randomly divided into two groups (n=20 each); DRMI model group and resveratrol group. Rats in the resveratrol group were administered with 0.75 mg/kg resveratrol (Sigma-Aldrich; Merck KGaA) three times per day at 8 h intervals for four weeks, and the DRMI model group was treated with an equivalent amount of normal saline. Plasma glucose (F006), triglyceride (F001-1) and insulin (H203) levels were measured using the appropriate enzymatic diagnostic kits (Nanjing Jiancheng Bioengineering Institute). The methodology of the present study was reviewed and approved by the Animal Ethics Committee of China Armed Police General Hospital.

Body weight, heart rate and heart/body weight ratio. Rats were weighed once a day throughout the experiment. The heart rate of each rat was measured using a CODA 8-channel tailcuff blood pressure system (Kent Scientific Corporation, Torrington, CT, USA). After treatment with resveratrol ended, rats were euthanized by decapitation under anesthesia and the heart was immediately harvested, washed with PBS, superficially blotted and weighed.

Biochemical measurements. Serum samples were collected after centrifugation at 1,000 x g for 10 min at 4˚C and used to analyze biochemical measurements. Aspartate transaminase (AST, C010-2), alanine transaminase (ALT, C009-2), nuclear factor (NF)-κB (H202), tumor necrosis factor (TNF)-α (R019), interleukin (IL)-1β (H002), IL-6 (H007), malondialdehyde (MDA, A003-1) and superoxide dismutase (SOD; A001-3) activities were evaluated using commercial kit reagents (Nanjing Jiancheng Bioengineering Institute) according to the manufacturers' protocol with a microplate reader (Multiskan EX Microplate Photometer; Thermo Fisher Scientific, Inc., Waltham, MA, USA).

Western blot analysis. Heart tissue samples were obtained and placed in ice-cold PBS. Heart samples were homogenized using radioimmunoprecipitation lysis buffer (Beyotime Institute of Biotechnology) and centrifugation at 12,000 x g for 10 min at 4˚C. The supernatant was collected and used to assess protein concentrations using a bicinchoninic acid protein assay kit (PerkinElmer, Inc., Waltham, MA, USA). Protein samples (50 μg) were loaded into each lane, separated by 8-12% SDS-PAGE and transferred onto polyvinylidene fluoride membranes. Membranes were subsequently blocked with 5% skimmed milk solution at 37˚C for 1 h, followed by overnight incubation at 4˚C with the following antibodies; anti-eNOS (sc-654, 1:300; Santa Cruz Biotechnology, Inc., Dallas, TX, USA), anti-VEGF (sc-13083, 1:300; Santa Cruz Biotechnology, Inc.), anti-phosphorylated (p)-p38 (sc-101759, 1:300; Santa Cruz Biotechnology, Inc.) and anti-β-actin (AA128, 1:1,000; Beyotime Institute of Biotechnology, Haimen, China). Membranes were subsequently incubated with anti-rabbit horseradish peroxidase-conjugated secondary antibodies (sc-2357, 1:2,000, Santa Cruz Biotechnology, Inc.) for 2 h at room temperature and developed with enhanced chemiluminescence reagent (Beyotime Institute of Biotechnology). Three replicates were performed. Results were quantified using ImageJ analysis software (National Institutes of Health, Bethesda, MD, USA).

Statistical analysis. Data were expressed as the mean ± standard error of the mean. Comparisons between groups were performed using one-way analysis of variance followed by Bonferroni's test as appropriate. P-values were calculated using Student's t-test and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Body weight and blood glucose. The chemical structure of resveratrol is displayed in Fig. 1. Blood glucose and body weight were recorded to evaluate whether resveratrol treatment had any effect. Blood glucose levels in rats with STZ-DRMI were demonstrated to be significantly higher compared with

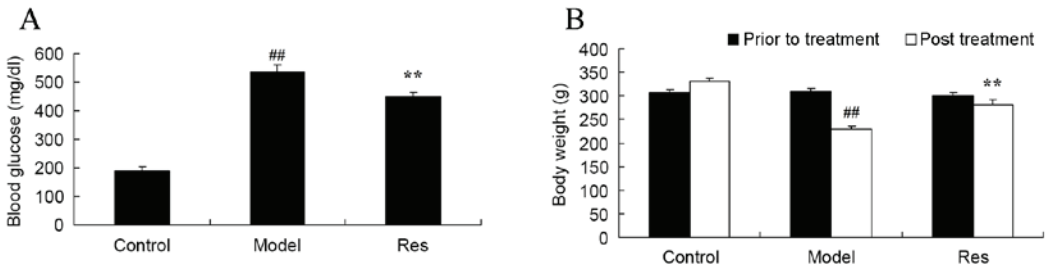

Figure 2. Blood glucose and body weight. (A) Blood glucose and (B) body weight. ##P<0.01 vs. control group, **P<0.01 vs. model group. Control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

the control group (P<0.01; Fig. 2) and the mean body weight of rats with STZ-DRMI decreased compared with the control group (P<0.01; Fig. 2B). However, treatment with resveratrol was able to significantly reverse the effects of STZ-DRMI on body weight and blood glucose in rats (P<0.01; Fig. 2A and B).

Heart/body weight ratio. As demonstrated in Fig. 3, resveratrol did not significantly affect heart/body weight ratio of STZ-DRMI rats and STZ-DRMI did also not significantly affect heart/body weight ratio in rats.

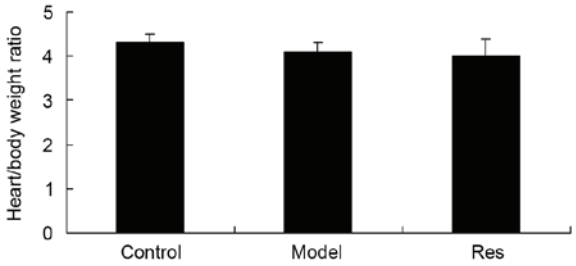

Figure 3. Heart/body weight ratio. Control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

Plasma triglyceride levels, heart rate, AST/ALT ratio and total plasma insulin. In the present study, the effects of resveratrol on plasma triglyceride levels, heart rate, AST/ALT ratio and total plasma insulin in rats with STZ-DRMI were evaluated. Significant increases in plasma triglyceride levels, heart rate and AST/ALT ratio were observed in rats with STZ-DRMI compared with the control group (P<0.01; Fig. 4A-C). Additionally, total plasma insulin was significantly lower in rats with STZ-DRMI compared with the control group (P<0.01; Fig. 4D). Overall, resveratrol treatment significantly suppressed the effects of STZ-DRMI on plasma triglyceride levels, heart rate and AST/ALT ratio and plasma insulin in rats (P<0.01; Fig. 4A-D).

Inflammation factors. To evaluate the effects of resveratrol on inflammation factors, NF-κB, TNF-α, IL-1β and IL-6 levels were evaluated. As expected, NF-κB, TNF-α, IL-1β and IL-6 levels were significantly elevated in rats with STZ-DRMI compared with the control group (P<0.01; Fig. 5A-D). Treatment with resveratrol significantly reduced the effects of STZ-DRMI on NF-κB, TNF-α, IL-1β and IL-6 levels in rats (P<0.01; Fig. 5A-D).

Oxidative stress. To evaluate the *in vivo* effects of resveratrol treatment on oxidative stress in rats with STZ-DRMI, the activity of MDA and SOD were measured in the present study. A significant increase in MDA activity and significant decrease in SOD activity were observed in rats with STZ-DRMI compared with control rats (P<0.01; Fig. 6A and B). Treatment of rats with STZ-DRMI with resveratrol was demonstrated to significantly reverse these effects (P<0.01; Fig. 6A and B).

eNOS protein expression. The effect of resveratrol on the expression of eNOS was investigated in the present study. As demonstrated in Fig. 7, eNOS protein expression was significantly suppressed in rats with STZ-DRMI compared with control rats (P<0.01). Resveratrol treatment, however, was able to significantly increase the expression of eNOS in rats with STZ-DRMI (P<0.01; Fig. 7B).

VEGF expression. The expression of VEGF was evaluated via western blotting (Fig. 8) demonstrated to be significantly higher in rats with STZ-DRMI compared with the control group (P<0.01; Fig. 8B) Treatment with resveratrol induced a significant decrease in the expression of VEGF in rats with STZ-DRMI (P<0.01; Fig. 8B).

p-p38 expression. The role of p-p38 expression in the modulation effects of resveratrol treatment in rats with STZ-DRMI was investigated via western blotting (Fig. 9). Rats with STZ-DRMI exhibited a significant increase in p-p38 expression compared with the control group (P<0.01; Fig. 9B). The results demonstrate that resveratrol treatment was able to significantly suppress the expression of p-p38 in rats with STZ-DRMI (P<0.01; Fig. 9B).

Discussion

Diabetes is a life-threatening disease, the severity and prevalence of which have captured attention worldwide (5). According to the 2010 International Diabetes Federation annual report, the number of patients with diabetes worldwide was close to 250 million (18). It has been predicted that this number will increase at a rate of 10% every year (19). In China, there are now ~90 million patients with diabetes, and almost 150 million people are presenting with the early signs of diabetes (7). Consequently, diabetes is currently listed as one of the three most dangerous diseases in China (20). Diabetes-related cardiovascular complications are a leading cause of mortality in patients with diabetes (10). It has

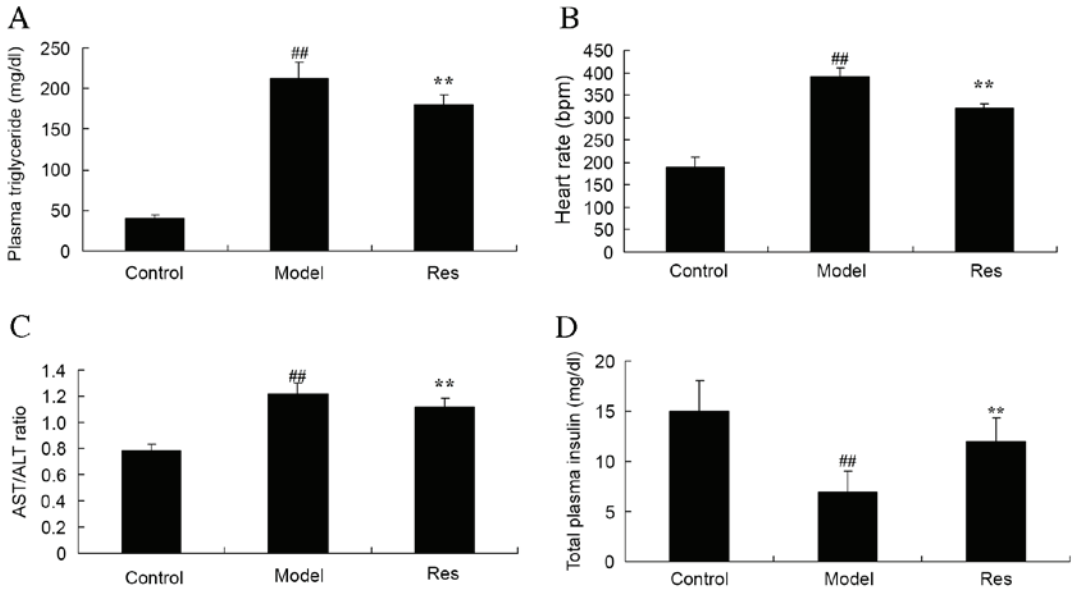

Figure 4. Plasma triglyceride, heart rate, AST/ALT ratio and total plasma insulin. (A) Plasma triglyceride levels. (B) Heart rate. (C) AST/ALT ratio. (D) Total plasma insulin levels. ##P<0.01 vs. control group, **P<0.01 vs. model group. AST, aspartate transaminase; ALT, alanine transaminase; control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

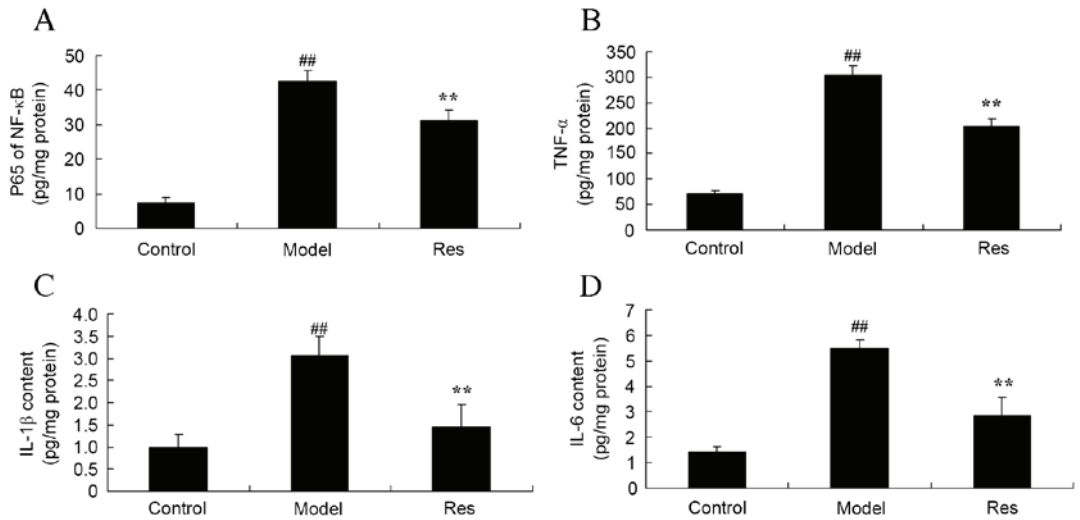

Figure 5. Inflammation factors. Levels of (A) NF-κB, (B) TNF-α, (C) IL-1β and (D) IL-6. ##P<0.01 vs. control group, **P<0.01 vs. model group. NF, nuclear factor; TNF, tumor necrosis factor; IL, interleukin; control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

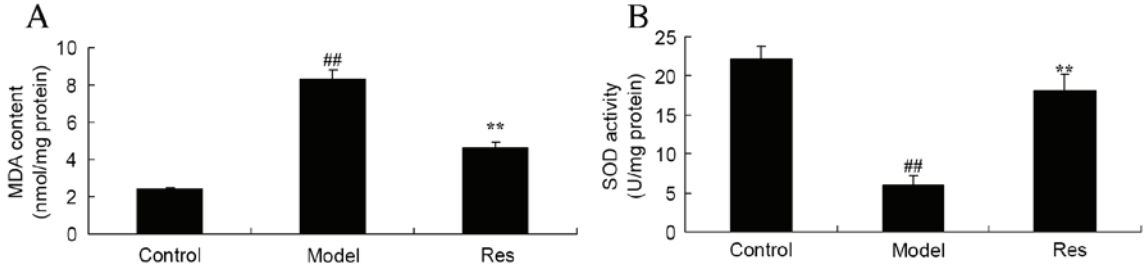

Figure 6. Oxidative stress. Activity of (A) MDA and (B) SOD. ##P<0.01 vs. control group, **P<0.01 vs. model group. MDA, malondialdehyde; SOD, superoxide dismutase; control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

previously been reported that the occurrence rates of myocardial infarction are six times higher in patients with diabetes that in non-diabetic populations (15). In order to reduce the prevalence of DRMI, it is vital to identify an effective novel intervention target. The results of the present study demonstrated that resveratrol treatment was able to effectively inhibit blood

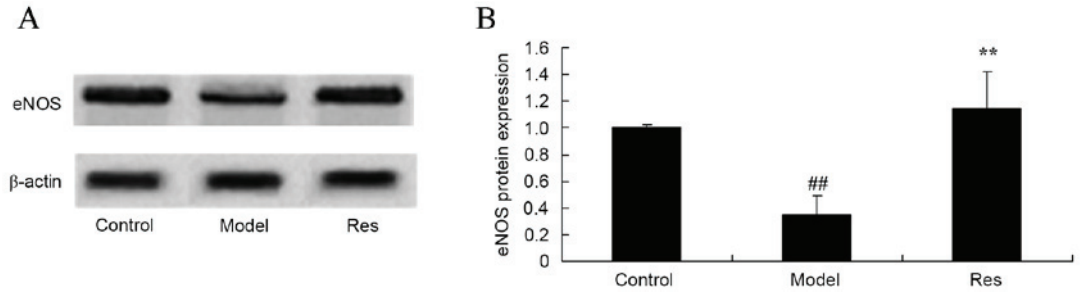

Figure 7. eNOS protein expression. (A) Evaluation of eNOS expression using western blotting and (B) statistical analysis of eNOS expression. ##P<0.01 vs. control group, **P<0.01 vs. model group. eNOS, endothelial nitric oxide synthase; control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

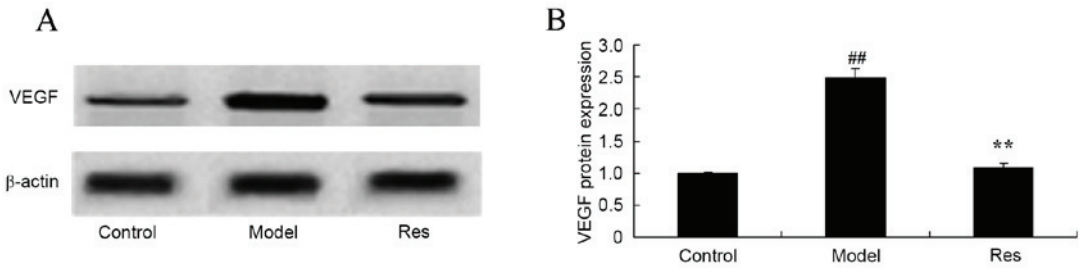

Figure 8. VEGF protein expression. (A) Evaluation of VEGF protein expression using western blotting and (B) statistical analysis of VEGF protein expression. ##P<0.01 vs. control group, **P<0.01 vs. model group. VEGF, vascular endothelial growth factor; control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

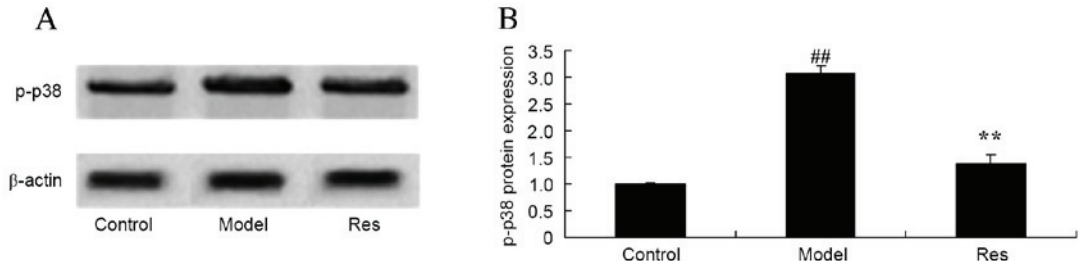

Figure 9. p-p38 protein expression. (A) Evaluation of p-p38 protein expression using western blotting and (B) statistical analysis of p-p38 protein expression. ##P<0.01 vs. control group, **P<0.01 vs. model group. p-p38, phosphorylated p38 protein; control, control group; model, diabetes-related myocardial infarction group; res, resveratrol group.

glucose levels and increase body weight without affecting the heart/body weight ratio, suppress plasma triglyceride levels, reduce heart and AST/ALT ratios and decrease total plasma insulin in rats with STZ-DRMI. Resveratrol treatment in rats with STZ-DRMI also suppressed elevated NF-κB, TNF-α, IL-1β and IL-6 content levels, inhibited MDA activity and advanced SOD. Yeh *et al* (21) reported that resveratrol is able to protect against lung ischemia and reperfusion-induced pulmonary capillary injury via reducing oxidative stress and inflammation. Tao *et al* (22) suggested that resveratrol may be able to alleviate the inflammatory response in severe burn injuries.

VEGF is able to promote the division of endothelial cells, enhance vascular permeability and induce neovascularization (23). Under normal conditions, the expression of VEGF is relatively low (24), and estrogen, protein kinase C and oxygen deficits are able to induce the expression of VEGF. Ischemic heart disease and arteriosclerosis obliterans are caused by atherosclerosis (25) and it has therefore been suggested that VEGF is associated with arteriosclerosis. Arteriosclerosis is able to enhance tissue ischemia and oxygen deficit, which in turn greatly increases the synthesis of VEGF (26), which then acts on endothelial cells and induces angiogenesis (26). The present study demonstrated that treatment with resveratrol is able to significantly inhibit VEGF expression in rats with STZ-DRMI. Seong *et al* (27) demonstrated that resveratrol was able to suppress VEGF secretion in ARPE-19 cells.

The synthesis and secretion of nitric oxide (NO) is one of the key functions of vascular endothelial cells. NO is catalyzed by eNOS from L-arginine (28) and functions by expanding blood vessels, lowering blood pressure and smoothing vascular muscles. NO is also able to transmit signals and regulate enzymatic activities and immunoregulation, inhibit vascular smooth muscle cell proliferation and platelet adhesion and accumulation, and induce resistance to oxidative damage (28). Capillary endothelial cell eNOS catalyzes the secretion of NO that enters

the surrounding cardiac and vascular smooth muscle cells, which protects granular leukocytes and blood platelets (29). In the present study, resveratrol treatment significantly increased the expression of eNOS expression in rats with STZ-DRMI. Chong *et al* (30) previously reported that resveratrol was able to reduce susceptibility to atrial fibrillation via activating the PI3K/AKT/eNOS signaling pathway.

Mitogen-activated protein kinase (MAPK) is able to promote the proliferation and transmission of stress signals (31). Its family includes extracellular signal-related kinases, c-Jun N-terminal kinases and p38 (32). A recent study demonstrated that high levels of glucose-protein kinase C pathways, glycation end products, oxidative stress, growth factor, osmotic pressure and stretches under diabetic conditions may activate MAPK families, increase the activity of transcription factors and lead to chronic diabetic complications (33). Blocking MAPK trans-pass may be an effective novel direction for the treatment of chronic diabetic complications (33). The present study illustrated that resveratrol administration is able to significantly suppress the expression of p-p38 in rats with STZ-DRMI. Chun *et al* (17) suggested that resveratrol was able to suppress acute pulmonary thromboembolism-induced pulmonary artery hypertension via p38 MAPK signaling in rats.

In conclusion, the present study demonstrated that early administration of resveratrol was able to improve cardiovascular function in rat with diabetes, exerting anti-inflammatory and anti-oxidative properties via modulation of eNOS, VEGF and p38 MAPK. This should be taken into consideration in future studies aimed at evaluating resveratrol as a potential novel drug for the treatment of diabetes-related cardiovascular disease.

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