

# Novel therapeutic effects of sesamin on diabetes-induced cardiac dysfunction

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**Abstract.** Diabetes is a risk factor that increases the occurrence and severity of cardiovascular events. Cardiovascular complications are the leading cause of mortality of 75% of patients with diabetes >40 years old. Sesamin, the bioactive compound extracted from *Sesamum indicum*, is a natural compound that has diverse beneficial effects on hypoglycemia and reducing cholesterol. The aim of this study is to investigate sesamin effects to diabetes-inducing cardiac hypertrophy. In the present study bioinformatics analysis demonstrated cardiac hypertrophy signaling may be the most important pathway for upregulating genes in sesamin-treated groups. To verify the bioinformatics prediction, sesamin was used as the main bioactive compound to attenuate the impact of diabetes induced by streptozotocin (STZ) on cardiac function in a rat model. The results revealed that oral administration of sesamin for 4 weeks (100 and 200 mg/kg body weight) marginally improved blood glucose levels, body weight and significantly ameliorated the effects on heart rate and blood pressure in rats with type 1 diabetes relative to control rats. The QT interval of sesamin was also reduced relative to the control group. The findings indicated that sesamin has potential cardioprotective effects in the STZ-induced diabetes model. This suggested that this can be used as a novel treatment for patients with diabetes with cardiac dysfunction complication.

## Introduction

Diabetes mellitus (DM) is a metabolic disease in patients with high blood glucose over prolonged period (1). It has been well documented as an urgent worldwide health issue present in a wide age range, from children to adults (2). Diabetes leads to numerous complications associated with the heart, including ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (3). Type 1 DM is caused by the autoimmune destruction of the pancreatic  $\beta$ -cells resulting in reduced insulin production (4). Chronically, microvascular and macrovascular complications are the major reasons for increasing morbidity and mortality in patients with diabetes. In developed countries, cardiovascular disease is the main complication causing death resulted from diabetes (5,6).

Patients with type 1 DM face a two to four times higher mortality rate than non-diabetic people (7-10). The main risk factor raising the mortality and morbidity of type 1 DM is cardiovascular complications. Their impact has become clearer and more pernicious to patients with DM (7,10). Coronary atherosclerosis appears in the majority of the diabetes population, with the mortality of up to 20% diabetic subjects caused by myocardial infarction (9). Normoglycemia is the key to attenuate the microvascular and neurological complications of type 1 diabetes. There are many methods of maintaining normal blood sugar levels, including treatment with insulin focus to a therapy area by external pumps, blood glucose monitoring and physical exercise. However, there is an increasing interest in using natural foods as herbal treatments, including as diabetes therapeutics (11-14). The pharmacological properties of herbal remedies, including the amelioration of insulin sensitivity, the promotion of insulin secretion, the increase of glucose uptake by adipose and muscle tissues, the inhibition of sugar absorption in intestines and the generation of sugar by hepatocytes, have been demonstrated in several studies (15,16). Herbal and traditional Chinese medicine have also exhibited a strong impact on treatment of cardiovascular complications in diabetes (17). *Sesamum indicum* has been

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used as a nutrient-rich food with medicinal functions for many years; it is also known as a precious herb. Sesamin is the bioactive compound that is extracted in high amounts from *Sesamum indicum*. Sesamin has been used in pharmaceuticals to perform various valuable functions (18). Numerous studies have demonstrated that sesamin provides considerable support to human health by improving fat metabolism, antioxidant activity, hypolipidemic activity, reducing cholesterol, preventing inflammation and enhancing the potency of vitamin E (18-21). However, whether sesamin can regulate diabetes or the cardiac disease network remains largely unknown.

High-throughput microarray technology is the most powerful tool to analyze gene expression on a global scale, offering measurement of the expression of a huge number of genes. With the rapid expansion of microarray datasets, high-throughput microarray technology has become more popular and more accessible from the Gene Expression Omnibus (GEO) (22), under the management of National Center for Biotechnology Information. Expression data from the GEO (series accession no. GSE42693) was selected (23) for analyzing the potential signal transduction pathways in sesamin-treated rats compared with a group treated with a controlled diet. Previous studies have also demonstrated that sesamin can regulate fatty acid oxidation in rats, while other studies have reported that sesamin can recover left ventricular remodeling in spontaneously hypertensive rats (24). However, the association between diabetes-induced cardiac hypertrophy and sesamin remains largely unknown.

Sesamin has been revealed to reduce the effects of oxidative stress and nitric oxide synthesis on  $\beta$ -cell destruction (25). However, to the best of our knowledge, there has been no previous research on the effect of sesamin on cardiac dysfunction in type 1 diabetes. Thus, the current study was a comparative analysis of how sesamin affected diabetes-induced cardiac dysfunction. Based on the bioinformatics analysis within the present study, the microarray network data demonstrated that the cardiac hypertrophy pathway was an important pathway in the sesamin-treated group. Therefore, the present study aimed to investigate the cardioprotective effect of sesamin in rats with type 1 diabetes induced by streptozotocin (STZ).

## Materials and methods

**Bioinformatics analysis.** Previous research reported that the decline in responsiveness of diabetes-associated heart disease induced by STZ is caused via  $\beta$ -adrenoreceptor (AR) agonists as a consequent of decrease of  $\beta$ 1-AR and the increase in  $\beta$ 3-AR expression (26). A report also demonstrated that the maximal left ventricular developed pressure (LVDP) is increased by the effect of  $\beta$ 3-AR agonists in STZ-induced diabetic rats (24). However, the details of the association between sesamin and diabetic-induced cardiac hypertrophy remain. Thus, the GEO database (<http://www.ncbi.nlm.nih.gov/geo/>; series accession no. GSE42693) was used to analyze the potential pathways that are stimulated in sesamin-treated rats (23).

From the GSE42693 dataset, male Sprague Dawley (SD) rats with type 1 DM were treated with 0.2% sesamin in their diet, whereas the control rats were provided with diet free of sesamin for a period of 15 days. RNA extracted from the rats was

subjected to microarray analysis. A robust multichip average algorithm was applied to analyze the raw data correction and normalization, and its signal was calculated for gene-level probe set summaries with the Affymetrix Expression Console Version 1.3.1.187 (<http://www.affymetrix.com/>). Then the fold change and expression level between the sesamin-treated group and the control group were also calculated. MetaCore (GeneGo, Inc., St. Joseph, MI, USA) was employed to investigate the signal transduction pathways regulating the sesamin-treated group by analyzing gene ontology molecular functions and GeneGo pathways. MetaCore received the data input and created biological links with associated processes. In order to compare the average expression level of rats treated with sesamin (n=5) and the control (n=5), the upper quartile of highest expressed genes (7,774 genes) with significant expression differences was uploaded to the MetaCore software. From the analysis, the cardiac hypertrophy pathway was considered to be a crucial pathway in the sesamin-treated group.  $P < 0.05$  was considered to indicate a statistically significant difference.

**Sesamin preparation and reagents.** Pure sesamin compound was purchased from ChemBio Co. (Taipei, Taiwan), a glucose kit was purchased from Randox Laboratories Ltd. (County Antrim, UK) and STZ was purchased from Sigma-Aldrich (Merck Millipore, Darmstadt, Germany).

**STZ-induced type 1 diabetes rat model.** A total of 30 male, pathogen and disease-free Sprague-Dawley rats (4-week-old; weight, 100-120 g) from the National Laboratory Animal Center (Taipei, Taiwan), were used in the current study. The rats were raised under standard experimental conditions with a 12 h light/12 h dark cycle at 23-25°C. Animals were fed *ad libitum* with free access to water. All animal experiments were approved by the Institutional Animal Care and Use Committee or Panel (IACUC/IACUP) of Chinese Culture University (Taipei, Taiwan). The diabetes rat model was created in 10 rats by STZ injection following a standard protocol of the Animal Models of Diabetic Complications Consortium (27). STZ was diluted in sodium citrate buffer solution (pH 4.5). The rats were fasted for 4 h before the STZ injection and then were anesthetized using 2% isoflurane mixed with 2l/min compressed oxygen (KYS Technology, Taipei, Taiwan). An appropriate amount of the STZ solution (50 mg/kg) was injected subcutaneously in the abdomen area, repeating one injection each day for five consecutive days. Each rat was supplied with 10% sucrose water following each injection, was allowed to awaken and was placed back in the cage. The rats were tested for sufficient levels of hyperglycemia and only rats with blood glucose level  $> 200$  mg/dl (5 rats) were selected for further experimentation.

**Sesamin treatment in STZ-induced diabetic rats.** A total of 5 groups of experiments with 5 rats of each were used in this study (control, model diabetes, and sesamin treatment (3 groups). Sesamin (dissolved in olive oil) oral administration was performed after the STZ-treated rats were randomly divided into three groups that received different sesamin concentrations as follows: Low concentration (50 mg/kg body weight), medium concentration (100 mg/kg body weight), and high concentration (200 mg/kg body weight). The experimental

process was performed for 4 weeks (oral administration of sesamin to rats was performed once per day), and after each 7-day period of treatment with sesamin, blood samples were collected in order to determine the blood glucose levels. Body weight, heart rate (HR) and blood pressure (BP) were also measured, and echocardiogram was performed.

**Blood glucose measurement.** The rats were fasted for 4 h before the blood sample collections on day 0, 7, 14, 21 and 28 of the sesamin administration process. Serum was separated for the measurement of the blood glucose, using commercial kits according to the manufacturer's protocols (Randox Laboratories, Ltd., County Antrim, UK).

**Blood pressure and electrocardiogram measurements.** BP was measured by inserting two catheters into the femoral artery. For BP, the custom catheter (polyurethane; 1 French size) was inserted to the femoral artery. The waveforms delivering information about LVDP were visualized on a computer monitor.

The electrocardiogram was measured by using three lead vectors, one connected to the chest, one connected to the armpit, and the third connected to the femoral part of the rat. All results were recorded and analyzed by the LabChart 7 software (ADInstruments, Ltd., Dunedin, New Zealand).

**Histopathological assay.** Rats were scarified by anesthetizing with 2% isoflurane (KYS Technology, Taipei, Taiwan) mixed with 2l/min of compressed oxygen and followed by decapitalization. The hearts were collected and stored in 10% formalin at 4°C for subsequent paraffin embedding. Sections (5  $\mu$ m) of each tissue were stained with hematoxylin and eosin (H&E) staining and were observed for histopathological alterations under a light microscope.

**Data collection and analysis.** Heart rate measurements, electrocardiography performance and blood pressure recording was performed using cardiovascular continuous monitoring software (PowerLab/4SP; ADInstruments, Ltd.). Values for hemodynamic measures were derived by a 1 KHz sampling rate.

**Statistical analysis.** All results are presented as the mean  $\pm$  standard deviation. Statistical analysis was evaluated by one-way analysis of variance followed by the Student-Newman-Keuls test with SPSS software (version 16.0; SPSS, Inc., Chicago, IL, USA).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Cardiac hypertrophy pathways are modulated by sesamin treatment.** MetaCore GeneGo software was used to identify genes with different expression levels in sesamin-treated and control samples. MetaCore software employs an exclusive, manually selected and organized database comprising of protein-protein, protein-DNA, protein compound interactions, and their metabolic and signaling pathways. There were 7,774 genes with significant expression differences between the sesamin-treated ( $n=5$ ) and the control diet-treated rats ( $n=5$ ).

MetaCore pathway analysis of these two groups indicated that most significant signaling pathway for upregulated genes in sesamin-treated rats was cardiac hypertrophy signaling ( $P=1.148E-10$  and  $FDR=9.945E-8$ ).

Cardiac hypertrophy is a compensatory mechanism of the heart to maintain stable cardiac output throughout different medical states. The outcome of this chronic process results in pathological cardiac growth and is correlated with increased morbidity and mortality. Myocyte enhancer factor 2 (MEF2) family proteins (MEF2A, MEF2C, MEF2D) are involved as intermediate signal responses of the cardiac transcriptional program (26,28,29). Numerous genes serve roles in the cardiac hypertrophy process, including  $\alpha$ -myosin ( $\alpha$ -MHC) and  $\beta$ -MHC, troponin I cardiac and troponin T cardiac, via a system of transcription factors and co-factors (GATA binding protein 4, NK2 homeobox 5, calmodulin binding transcription activator 2, MEF2, heart and neural crest derivatives expressed 1 (HAND1), HAND2, CREB binding protein and E1A binding protein p300) incorporating with nuclear factor of activated T-cells (NF-AT) signaling (30-32). The bioinformatics results suggest that sesamin may participate in the cardiac hypertrophy pathway via NF-AT signaling (Fig. 1). However, currently, the detailed mechanism of how sesamin affects cardiac hypertrophy is still obscured and demands more investigation in animal model.

**Histology of the cardiac tissue.** Results from H&E staining demonstrated that the nuclei in the control group were oval, single and observed at the center of the cardiomyocytes (Fig. 2). However, deformation in the shapes and sizes of nuclei was observed in the diabetes group. In addition, the cardiac myofiber pattern in this group spread irregularly relative to the control group. An increase in protein degradation may lead to this observation. Compared with the diabetic group, serious histological changes in the sesamin oral administration group were reduced. Among the treatment groups, the medium-dose group improved features compared with the diabetes group. Massive fibroblast infiltration in the left ventricle was observed in the diabetes group. Treatment with different doses of sesamin induced different changes in the diabetes rats. In the low-dose group, the cardiomyocytes degenerated, and segmentation was observed after 4 weeks of sesamin administration. Even mature fibrocyte infiltration was observed in this group. In the high-dose group, the staining indicated degenerated, vacuolated and dissociated myocardial fibers in the focal region of the left ventricle. By contrast, the heart tissue improved greatly after 4 weeks of oral treatment with the medium sesamin dose.

**Effect of sesamin on blood glucose and body weight.** Following STZ injection, SD rats exhibited high glucose blood level ( $>200$  mg/dl). At day 28th of the treatment, The STZ-treated rats exhibited a reduction in body weight ( $160.2 \pm 6.49$  g,  $n=5$ ) and an increase in blood glucose ( $220.47 \pm 6.19$  mg/dl,  $n=5$ ) compared with the age-matched controls, with  $200.4 \pm 6.34$  g and  $107.81 \pm 6.69$  mg/dl, respectively (Fig. 3A). However, following oral sesamin administration, there was significant glycemic amelioration compared with the diabetes group by 17% in the low dose group, by 30% in the medium dose group and by 26% in the high dose group. Body weight was

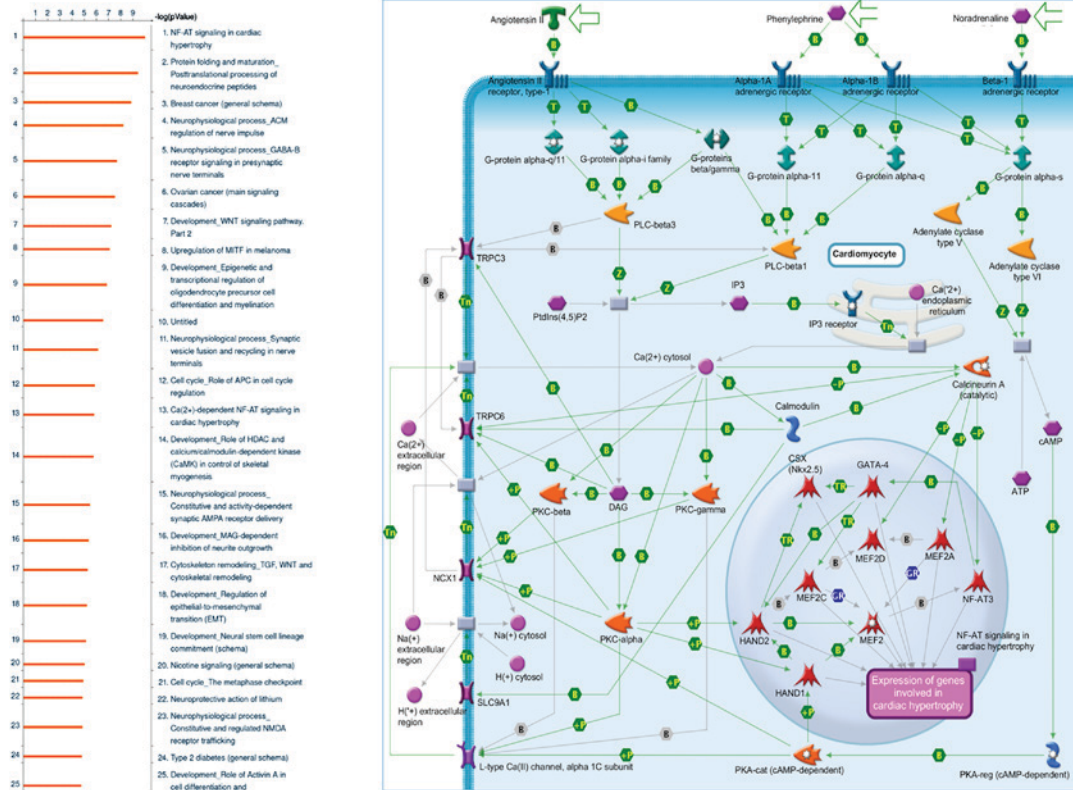


Figure 1. Meta Core pathway analysis indicated that cardiac hypertrophy signaling was significantly associated with sesamin-treated samples ( $P=1.148E-10$ ). Green arrows indicate activation.

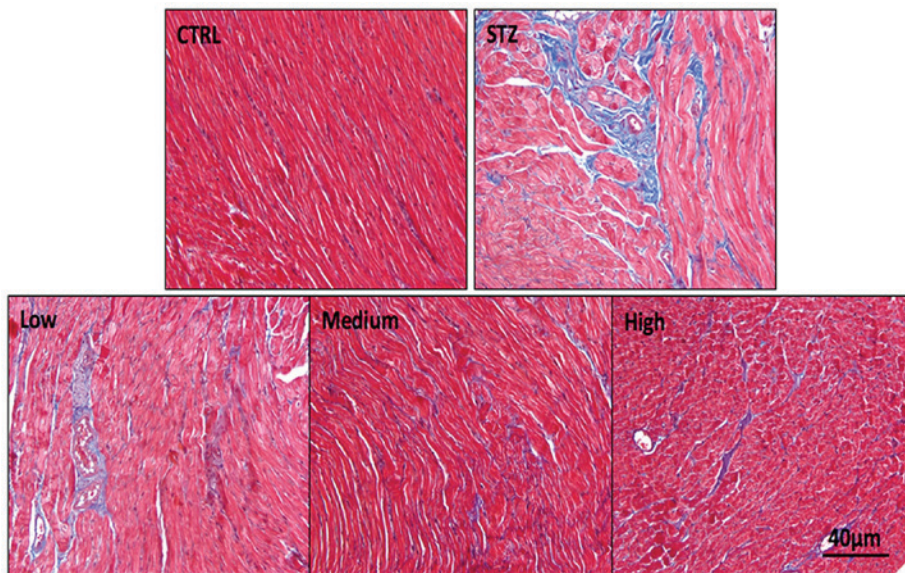


Figure 2. Histological examination of cardiac tissue from the control group, diabetes group (STZ), low-dose sesamin oral administration group, medium-dose sesamin oral administration group and high-dose sesamin oral administration group. CTRL, control; STZ, streptozotocin.

increased compared with the diabetes group by 17% in the low dose group, 18% in the medium dose group, and 20% in the high dose group at 4 weeks (Fig. 3B). The body weight was increased in the sesamin-treated groups compared with the diabetes group, however, for the groups administered medium and high doses of sesamin, blood glucose levels were reduced further than in the low dose group.

*Effect of sesamin on blood pressure.* After STZ-induction, at day 28th of the treatment, the systolic and diastolic blood pressure in the diabetic subjects ( $85.46 \pm 0.92$  and  $55.59 \pm 1.06$  mmHg) was markedly reduced compared with the control subjects ( $123.12 \pm 1.54$  and  $81.90 \pm 1.09$  mmHg,  $n=5$ ) (Fig. 3C). Following sesamin consumption, blood pressure was significantly increased in STZ-induced rats, particularly

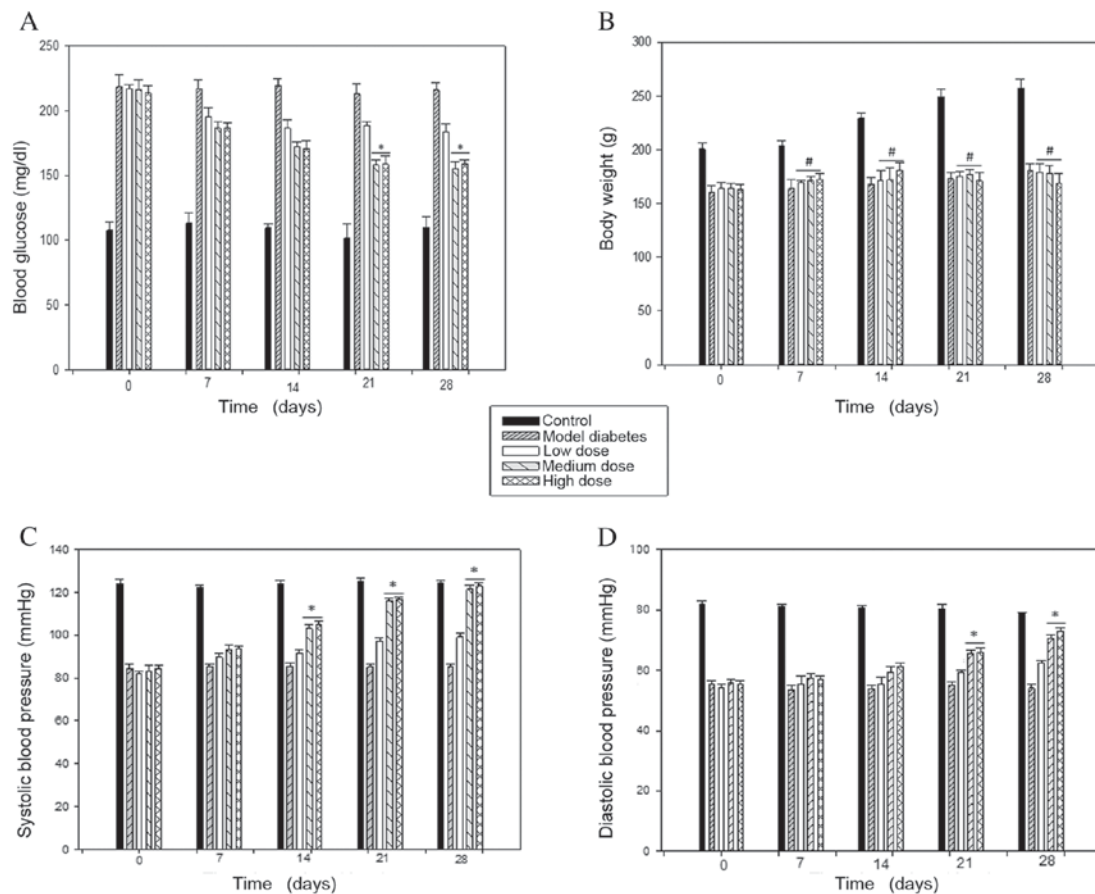


Figure 3. Effect of sesamin on (A) fasting plasma glucose, (B) body weight, (C) systolic bold pressure and (D) diastolic blood pressure of streptozotocin-treated Sprague-Dawley rats. Data are presented as the mean  $\pm$  standard deviation (n=5; \*P<0.05 vs. low-dose group; #P<0.05 vs. model diabetes).

in the groups administered medium and high doses of sesamin, with the low-dose group from  $82.28 \pm 0.98 / 54.34 \pm 0.99$  mmHg to  $99.15 \pm 1.59 / 62.49 \pm 0.82$  mmHg, the medium-dose group from  $83.74 \pm 0.87$  to  $121.47 \pm 1.09 / 55.96 \pm 1.67 / 70.67 \pm 1.05$ , and the high-dose group from  $84.53 \pm 1.19 / 55.48 \pm 1.16$  mmHg to  $123.14 \pm 1.21 / 72.99 \pm 1.14$  mmHg (Fig. 3D).

**Effect of sesamin on heart rate.** The heart rate in rats injected with STZ declined by  $\sim 1.33$ -fold compared with the healthy subjects ( $333.6 \pm 10.21$  vs.  $249.4 \pm 12.17$  BPM). The heart rate was significantly increased following treatment with sesamin compared with the diabetes group, particularly in the high-dose sesamin group at day 28th of the treatment ( $255 \pm 9.61$  vs.  $308 \pm 5.65$  BPM; Fig. 4A).

**The effect of sesamin on QT interval.** The uncorrected QT interval was prolonged in STZ-treated rats compared with the control group at day 28th of the treatment ( $73.29 \pm 3.31$  vs.  $54.71 \pm 2.18$  msec). Following sesamin treatment, the QT interval dramatically recovered by 7.4, 11.5 and 15.2% at day 28th of the treatment with the low-dose, medium-dose and high-dose group, respectively, compared with the STZ-treated rats (Fig. 4B). Fridericia's formula was used to correct the QT interval by adjusting to an R-R interval. Corrected QT intervals were  $82.67 \pm 3.99$  and  $63.28 \pm 1.77$  msec in STZ-treated rats and control rats at day 28th of the treatment, respectively. There was a corrected QT interval of 8, 12 and 14% in the

low-dose, medium-dose and high-dose groups at day 28th of the treatment, respectively (Fig. 4C).

## Discussion

Cardiac fibrosis and pressure dysfunction in patients with diabetes were reported in a previous study (33). Diabetic cardiomyopathy in rats with type 2 diabetes causes an increase in heart weight and in the nuclei size in cardiomyocytes. However, in rats with type 1 diabetes, studies by Cosyns *et al* (34) and Thent *et al* (35) demonstrated the same result, where the disarray in cardiac myofibers and changes in nuclei size led to a decrease in the cardiomyocytes, which caused cardiac atrophy (34,35). Cardiac atrophy may be due to an insulin deficiency, leading to a decline in protein synthesis and serious protein degradation, which affects the function of the mitochondria and leads to the damage of myocardial myofibers (36). Other causes that can lead to atrophy of the heart include an increase in hyperosmolarity in hyperglycemic conditions, an increase of collagen bundles, and a rise in the left ventricle contraction; all of these may lead to the changing of nuclei sizes and the shapes of cardiomyocytes (37). Sesame contains large amounts of antioxidants such as flavonoids and vitamin C and E. Sesamin extracted from *Sesamum indicum* has anti-inflammatory effects, supports vitamin E absorption, and reduces  $\beta$  cell-destroying factors, therefore, increasing the amount of insulin, ameliorating hyperglycemia, and increasing

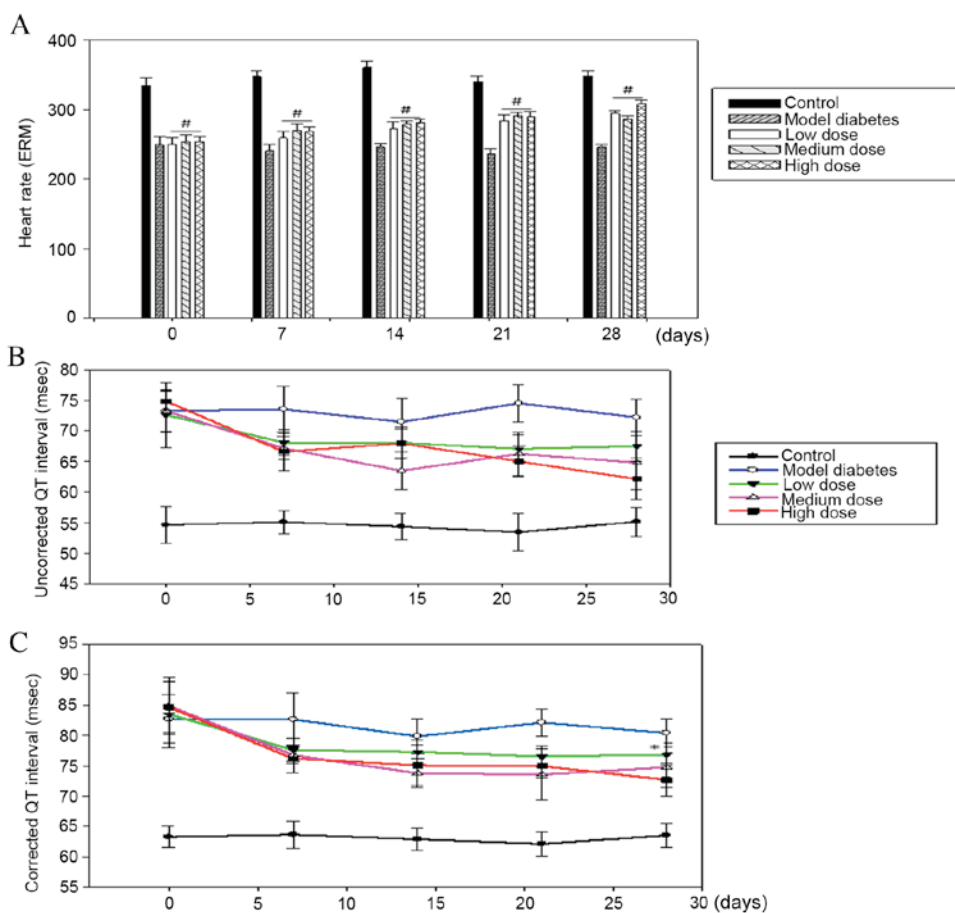


Figure 4. Effect of sesamin on (A) heart rate, (B) QT interval and (C) corrected QTcF (msec) interval (using the Fridericia formula) following oral sesamin administration. \* $P < 0.05$  vs. controls; # $P < 0.05$  vs. model diabetes.

protein synthesis (38). Through the anti-inflammatory effects of sesamin, the myocardial injury also somewhat improved. It reduced the contraction of the left ventricle, decreasing the size and changing the shape of the nuclei of myocardial cells, thus, improving the disorder in the myofiber arrangement (39). In the current study, the results of H&E staining demonstrated that structural cardiomyocytes in rats with diabetes induced by STZ were damaged. The order links among the myofibers were broken, and the nuclei of cardiac muscle cells were deformed and fragmented in the diabetic group. However, in the treatment groups, the disordered associations were markedly minimized, particularly in the medium-dose group. Findings of myocardial injury were also reduced. But these injuries were still visible in the low and high sesamin concentration groups.

The combined consumption of sesame oil and glibenclamide reduces blood glucose levels significantly (36% with treatment compared with no treatment), and it also decreases total plasma cholesterol; this significantly improves the condition of patients with diabetic disease (40). An STZ-induced diabetic heart has been revealed exhibit decreased responsiveness via  $\beta$ -AR agonists, in which reduced  $\beta_1$ -AR and increased  $\beta_3$ -AR expression are important factors (26). In addition, a  $\beta_3$ -AR agonist also raised the maximal LVDP responses in rats with STZ-induced diabetes (41). The data of the current study demonstrated that following STZ injection, the body weight and blood glucose level of rats declined rapidly and markedly,

which has also been described in a previous study (42). This is explained by the destruction of  $\beta$  cells induced by STZ (43). In a previous study, significant improvements in the blood sugar levels and body weight of rats were observed (44). However, there was no marked change in the body weight of diabetes rats treated with sesamin relative to model diabetes rat in the current study.

Following oral administration of sesamin, the blood glucose level of rats was significantly reduced compared with STZ-induced rats, particularly at the medium and high sesamin concentrations. This demonstrates that sesamin has a marked hypoglycemic effect; the previous studies also reported a similar outcome (45,46). However, the results in Fig. 1 indicate that using the correct sesamin concentration is critical because the reduction in blood glucose levels is not significant at the low sesamin concentration.

The data of the present study demonstrated that STZ-induced diabetes results in a decrease in blood pressure and that sesamin treatment can restore blood pressure in diabetic rats. Following oral sesamin administration, the blood pressure was restored significantly. This is reflected in the recovery of the diastolic and systolic blood pressure. Previous studies reported a significant attenuation of vascular dysfunction following treatment with sesamin (44). Possibly the recovery of the blood vessels in mice with sesamin treatment led to the recovery of the blood pressure. Endothelial cells are involved in the restoration of blood vessel walls. Due

to these cells, the improvement of the blood vessels via the sesamin treatment was considerably increased (44).

Another study demonstrated that sesamin had an effect on the protection of  $\beta$  cells following STZ-induction. The administration of sesamin reversed the STZ-induced cells viability reduction. Increasing the oxidative stressors and nitride oxide synthesis by sesamin led to reduced  $\beta$  cells destruction (41). In rats with STZ-induced diabetes, the heart rate was decreased in the present study, which is consistent with what has been revealed in previous studies (47,48). Hyperglycemia appears to be the predominant cause of this clinical abnormality (slow heart rate) (48). Also, the effect of STZ on repolarization and the action potential may have led to heart rate reduction (44). An increased heart rate in patients with type 1 diabetes is closely associated with cardiac autonomic neuropathy, thus, leading to many abnormal problems, including high blood pressure and poor blood supply (47). Due to the effect of sesamin treatment, the  $\beta$  cells were significantly restored, causing reduced glycemia and leading to a recovered heart rate in a previous report (38). Improving blood pressure is involved in the effect of sesamin that led to the heart rate recovery in STZ-treated animals (44).

QT interval measurement can predict sudden cardiac death in certain diseases, including hypertension (49), chronic heart failure (50,51) and peripheral vascular disease (52). QT interval is a good factor to predict cardiac malfunction and state in patients with diabetes (53,54). A previous study reported a significant reduction of the QT interval in subjects with type 1 diabetes; however, when adjusted by RR intervals, the difference was abolished (55). The previous study also reported a prolonged QT interval (by ~35%) (56). The correction of the QT interval was computed by Fridericia's formulation:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

The formulation used the cube root of RR (53). This difference was maintained in QTcF (prolonged~30%). This may explain by the decline in heart rate affected by high blood sugar and high blood pressure. This difference was maintained in the corrected QT interval in the current study.

Following oral administration of sesamin, the QT interval and QTcF were markedly improved, by 15.2 and 14% at day 28th of treatment, respectively, in the high-dose group. This suggests that sesamin has a positive effect in restoring the QT interval in an STZ-induced type 1 diabetes rat. The restoration of blood pressure and  $\beta$  cells (38,44) reduced the blood glucose levels, leading to a reduction in the heart rate and substantial improvement of the QT interval. The beneficial effects of sesamin have been demonstrated through various previous studies (57-62). The data of the current revealed that sesamin has a positive role in improving cardiovascular dysfunction in rats with STZ-induced type 1 diabetes.

In conclusion, cardiovascular dysfunction has caused more mortality among patients than any other complications of type 1 diabetes. The oral administration of sesamin for 4 weeks significantly ameliorated the changes to heart rate, blood pressure and QT interval in STZ-induced type 1 diabetes. This indicates that sesamin has a potential therapeutic effect in reducing cardiovascular complications in diabetic subjects.

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