Indian Journal of Biochemistry & Biophysics
Vol. 63, January 2026, pp. 86-93
DOI: 10.56042/ijbb.v63i1.18901

Hesperidin alleviates streptozotocin-induced cardiac damage in rats through modulation oxidative stress, inflammation and apoptosis

Kenan Yildizhan[1]*, Mehmet Hafit Bayir[2], Zübeyir Huyut[3] & Fikret Altindağ[2]

[1]Department of Biophysics, Faculty of Medicine; [2]Department of Histology and Embryology, Faculty of Medicine; [3]Department of Biochemistry, Faculty of Medicine, Van Yuzuncu Yil University, Van, Turkey

Received 18 April 2025; *revised 18 November 2025*

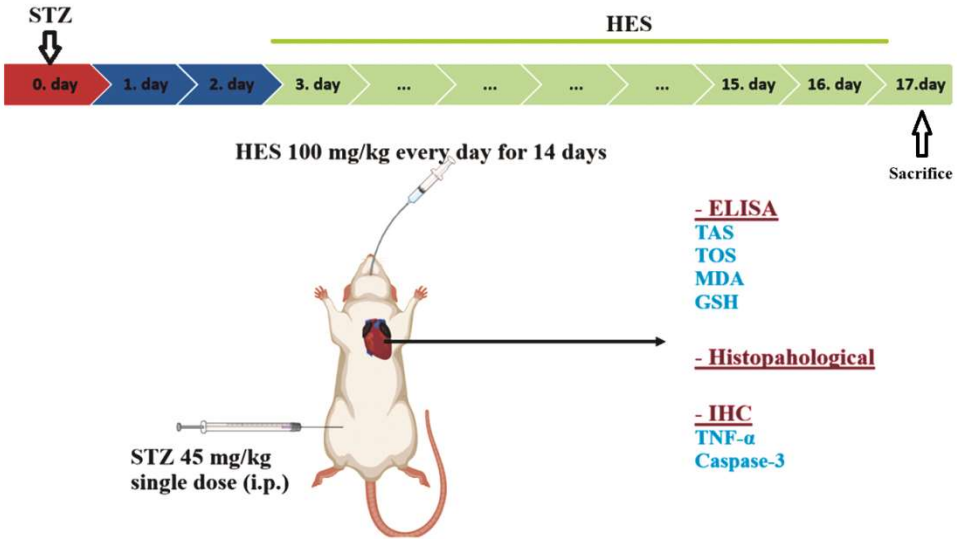
This study investigated the potential cardioprotective effects of hesperidin (HES) against cardiac damage induced by streptozotocin (STZ)-mediated diabetes in rats. Diabetes was induced by a single intraperitoneal injection of STZ (45 mg/kg) and HES (100 mg/kg/day) were administered intragastrically to treatment groups for 14 days. Cardiac tissue samples were analyzed using the ELISA method for Total Antioxidant Status (TAS) Total Oxidant Status (TOS) malondialdehyde (MDA) and glutathione (GSH) levels, while inflammatory (TNF-α) and apoptotic (Caspase-3) markers were assessed immunohistochemically. STZ administration resulted in significantly increased TNF-α expression, TOS and MDA levels, and reduced TAS and GSH levels, accompanied by severe myocardial degeneration, necrosis, and vascular congestion. HES treatment markedly improved antioxidant status, decreased oxidative and inflammatory markers, and reduced apoptosis. Histopathological evaluations demonstrated substantial preservation of cardiac morphology in the STZ+HES group. Overall, these findings suggest that HES has a protective effect against diabetes-induced cardiac injury, likely through the modulation of oxidative stress, inflammation, and apoptosis.

Keywords: Apoptosis, Cardiac damage, Diabetes, Hesperidin, Oxidative stress, Streptozotocin

Diabetes mellitus (DM) is a chronic metabolic disorder that has become one of the most significant global health challenges due to its rapidly increasing prevalence and its broad spectrum of systemic complications. Beyond its classical metabolic manifestations, diabetes exerts profound deleterious effects on the cardiovascular system, where sustained hyperglycemia, mitochondrial dysfunction, and enhanced generation of reactive oxygen species collectively contribute to myocardial structural and functional alterations[1-3]. High blood sugar levels in DM increase the production of reactive oxygen species (ROS). ROS causes oxidative damage to lipids, proteins and DNA in cells. Cardiac tissue is particularly sensitive to oxidative stress due to its high metabolic activity[4]. Abukhalil *et al*. reported that there was a significant increase in malondialdehyde (MDA) protein carbonyl, nuclear factor kappa B (NF-κB) p65, tumour necrosis factor-alpha (TNF-α) interleukin 1-beta (IL-1β) inducible nitric oxide synthase (iNOS) IL-6, Bax, caspase-3 (Casp/3) and 8-Oxo-7'8-dihydro-2'-deoxyguanosine (8-Oxo-dG) parameters and a decrease in superoxide dismutase (SOD) catalase (CAT) glutathione (GSH) and Bcl-2 levels in heart tissue samples of rats in which they created an experimental diabetes model[5]. Liang *et al*. observed a significant decrease in antioxidant parameters GSH, SOD and CAT levels, and an increase in cardiac fibrosis and proinflammatory cytokine levels in streptozotocin-induced diabetic rats compared to the control group[6]. Since oxidative stress plays a crucial role in all damage mechanisms, approaches that reduce oxidative stress have gained importance among the treatment methods considered for DM.

Hesperidin (HES) is a compound belonging to the flavonoid group and is especially prevalent in citrus fruits (such as orange, lemon, and grapefruit)[7]. HES can potentially prevent and treat various diseases associated with oxidative stress, due to its potent antioxidant properties. HES protects cellular health by neutralizing free radicals, metal chelating, anti-inflammatory effects, and activating enzymatic antioxidant systems[8-10]. Kakadiya *et al*. reported that HES was effective in reducing cardiovascular complications and controlling blood glucose levels

*Correspondence:
Phone: + 90-4322150471
Fax: + 90-04322168519
E-mail: kenanyldzhan@gmail.com



Graphical abstract

and cardiac complications in diabetes-induced rat myocardial infarction[11]. Agrawal *et al*. reported that in streptozotocin-isoproterenol-induced myocardial toxicity in rats, HES reduced oxidative stress and apoptosis and improved cardiac function *via* the PPAR-γ pathway[12].

This study investigated the protective effect of HES on cardiac injury in a streptozotocin-induced diabetes model. For this purpose, the levels of TAS, TOS, MDA, and GSH, as well as the immunohistochemical expressions of TNF-α and Caspase-3, were investigated in the heart tissue of the STZ-induced DM model. The effects of HES on tissue injury were determined by histopathological examination and other measured parameters.

Materials and Methods

Materials

The following materials were used for the experiments: hesperidin (Sigma-Aldrich, MO, USA); streptozotocin (Santa Cruz Biotec., USA); TNF-α (Santa Cruz Biotechnology, sc-52746, 1/200); Casp/3 (Biorbyt Explore Bioreagents, orb500787, 1:100); and TAS, TOS, MDA and GSH ELISA kits ((Reed Biotech, Wuhan, China).

Animals and experimental design

Wistar Albino rats, weighing between 200 and 250 grams, were maintained under specific pathogen-free conditions with a controlled 12-hour light/dark cycle and provided with food and water ad libitum. The experimental protocol prioritised the minimisation of animal distress and aimed to reduce the total number of subjects utilised. A cohort of twenty-eight rats was randomly assigned to one of four experimental groups (control, STZ, HES, and STZ+HES) with each group comprising seven animals. For the induction of diabetes in the STZ groups, a single intraperitoneal (i.p.) injection of streptozotocin (STZ) at a dosage of 45 mg/kg was administered[13]. Seventy-two hours post-STZ administration, blood samples were obtained from the caudal veins of all rats, and glucose concentrations were determined using a glucometer. Rats exhibiting a fasting blood glucose level of 250 mg/dL or higher were classified as diabetic, and this day was designated as the commencement of the 14-day experimental period. Throughout this 14-day duration, the HES group received a daily intragastric (i.g.) administration of hydroxyethyl starch (HES) at a dosage of 100 mg/kg, dissolved in a saline solution[14]. The experimental period concluded on the fourteenth day. Subsequently, all rats were subjected to deep sedation via intraperitoneal injection of a ketamine (50 mg/kg) and xylazine (20 mg/kg) combination within the facilities of the same research center. Following euthanasia, cardiac tissue samples were harvested. A subset of these samples was immediately cryopreserved at -80°C for subsequent biochemical analyses. The remaining portions of the heart tissue were immersed in a 10% formaldehyde solution for downstream histopathological and immunohistochemical evaluations.

Biochemical analysis

TAS, TOS, MDA, and GSH levels in heart tissue homogenates were determined using an ELISA device

(BioTEK ELx80) at 450 nm with commercial ELISA kits (Reed Biotech, Wuhan, China). The Bradford method was measured for protein amounts in the heart tissue homogenates[15]. Protein concentrations were quantitatively determined from the generated standard curve equation using the acquired absorbance values.

Histological analysis

Following formalin fixation, the tissues of the hearts were embedded in paraffin blocks and dissected into 4 μm-thick sections. Then, sections were stained using H&E for examination of histopathological changes by using a light microscope (Olympus_Bx53, Tokyo, Japan).

Immunohistochemical analysis for TNF-α and Casp/3expressions

Immunohistochemical analysis for the assessment of TNF-α and Casp/3 expression was conducted utilising the avidin-biotin complex (ABC) method, employing a commercially available streptavidin/biotin immunoperoxidase kit (Histostain-Plus Bulk Kit; Zymed, South San Francisco, CA, USA). Briefly, prepared tissue sections were mounted on adhesive slides and sequentially dehydrated through a series of xylene and graded ethanol solutions. Following rehydration in phosphate-buffered saline (PBS) endogenous peroxidase activity was quenched by incubation in a 3% hydrogen peroxide (H_2O_2) solution for 20 min. Antigen retrieval was then performed by immersing the sections in a citrate buffer solution and subjecting them to two 20 min heat treatments. Subsequently, the samples were allowed to cool to ambient temperature. Following a further wash with PBS, non-specific binding was blocked by incubating the samples with a protein blocking solution for 20 min. Subsequently, the sections were incubated overnight at 4°C with primary polyclonal antibodies specific for Casp/3 and TNF-α. After rinsing with PBS, the sections were incubated with a biotinylated secondary antibody for 20 min at room temperature. This was followed by another PBS washing step and incubation with streptavidin-peroxidase for an additional 20 min. After a final wash with PBS, the chromogenic substrate diaminobenzidine was applied for 1-2 min to visualize the immunoreactivity. All tissue sections were then counterstained with Mayer's hematoxylin for 1-2 min and rinsed under tap water. Dehydration was achieved by sequential passage through a graded series of ethanol and xylene solutions, and the slides were finally mounted with Entellan. To confirm the specificity of the staining, negative control sections were processed identically but with PBS substituted for the primary antibodies. Microscopic examination and photomicrography were performed using a light microscope. Immunohistochemical staining intensity within the tissue was subjectively assessed and categorized as negative (−) mild (+) moderate (++) or intense (+++)[16].

Statistical analysis

To ascertain the magnitude of the experimental intervention's effect on differentiating parameter and biomarker values, the effect size was quantified using Eta-squared (η^2). An a priori statistical power analysis was conducted, setting the effect size at 0.8 (based on η^2) alpha level (α) at 0.05, and desired power at 0.90. This analysis determined a minimum total sample size of 28 subjects, distributed across the four experimental groups. The normality of the data distribution for each parameter was assessed using the Shapiro-Wilk test, while the homogeneity of population variances across the groups was evaluated with Levene's test. The results of these tests indicated that all parameters within the groups conformed to the assumption of normality. Descriptive statistics for the parameters are presented as means and standard deviations. To compare the parameter measurements between the control and experimental groups, a bootstrap one-way ANOVA linear contrast analysis was employed. This bootstrap ANOVA, utilizing a simple sampling method, was performed based on 1000 resampled datasets. Following the ANOVA, post-hoc analyses were conducted using either Tukey's Honestly Significant Difference (HSD) test (in cases of homogeneous variances) or the Games-Howell test (when variances were unequal) to identify specific group differences that reached statistical significance. Histopathological findings were analysed by transforming theminto semi-quantitative data. Where the assumptions of parametric tests concerning the inter-group differences in histopathology results were satisfied, a one-way ANOVA was performed. Conversely, the Kruskal-Wallis test was employed when these assumptions were not met. Subsequently, post-hoc multiple comparisons were conducted using either the Bonferroni-corrected Mann-Whitney U test or the Games-Howell test, as appropriate. Histograms were generated to visually represent the distribution of parameters within the experimental groups and to

illustrate the outcomes of the post-hoc analyses. Statistical analyses of the collected data were performed using the SPSS software package (version 26.0, SPSS Inc., Chicago). Significance levels were determined using asymptotic two-sided tests, with a p-value of less than 0.05 considered statistically significant.

Results

Effects of HES on TAS, TOS, GSH and MDA levels

The levels of TAS, TOS, GSH and MDA in the heart tissues of STZ-induced diabetic ratsare shown in (Fig. 1). When compared to the control and HES groups, the TAS and GSH levels of the STZ groups (STZ and STZ+HES) were the lowest, while the TOS and MDA levels were the highest ($P< 0.05$). In the STZ+HES group, in which HES treatment was applied to diabetic rats, the levels of TAS and GSH were higher compared to the STZ group, while the levels of TOS and MDA were lower ($P< 0.05$).

Histopathological results

Normal histologic structure of the heart was observed in the control (a) and HES (b) groups. In the STZ group (c) the most prominent morphologic changes in myocytes were severe degeneration and necrosis (*). Vascular congestion was also observed. In addition, it was noted that the heart tissues of the rats in the STZ+HES group (d) had almost normal histologic structures (Fig. 2).

Immunohistochemical results

TNF-α Figure 3, and Casp/3 Figure 4, Expressions: These two marker antigens applied to the heart tissues of all the rats produced negative reactions in the control and HES groups, a high positive expression in the STZ group, a low positive expression in the STZ+HES group (Table 1).

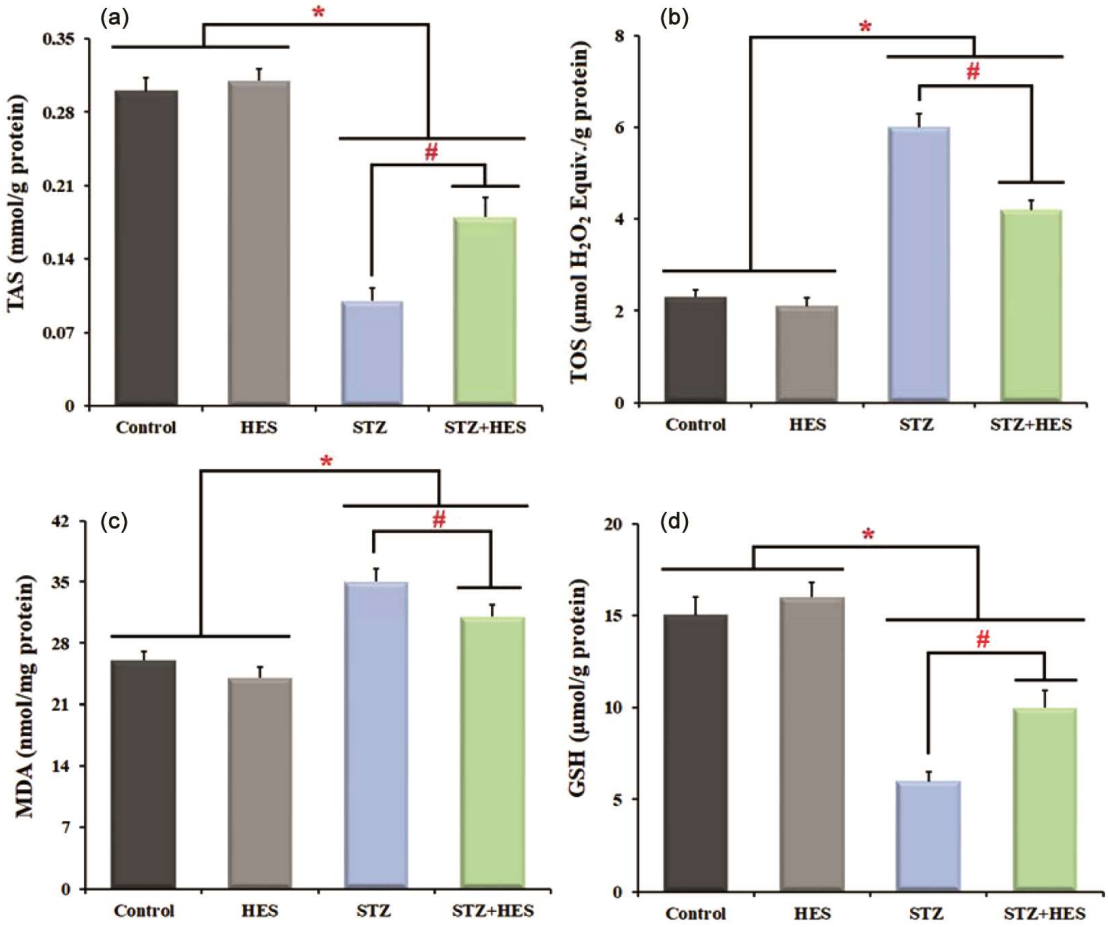


Fig. 1 — Effect of HES on TAS (a) TOS (b) MDA (c) and GSH (d) levels in STZ-induced cardiac damage. (Data are shown as mean ± SD). ($^{*}p< 0.01$ compared with control and HES groups, $^{\#}p<0.05$; compared with STZ group, Significance levels were obtained according to the Post Hoc HSD test)

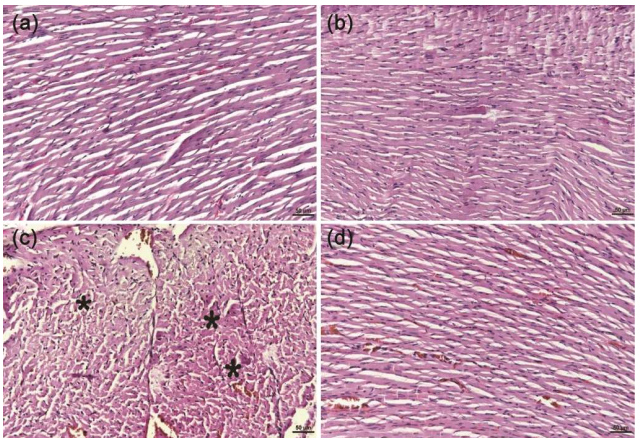


Fig. 2 — Light microscopic images of heart tissue stained with hematoxylin and eosin (H&E). Control group (a) and HES group; (b) The histological structure of the heart appears normal. STZ group; (c) Coagulation necrosis and degeneration in the myocytes (*) and vascular congestion. STZ+HES group; and (d) Almost normal histologic structure was observed (Bar: 50 µm)

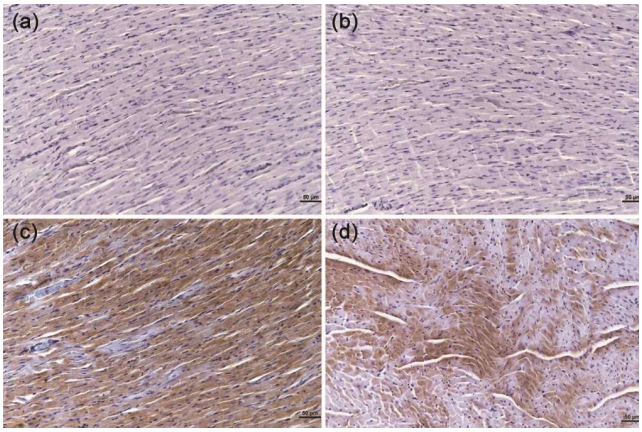


Fig. 3 — Effect of HES on immune expression of TNF-α in heart tissue of rats: TNF-α expression was detected by immunohistochemical staining. (a) Control; (b) HES; (c) STZ, and (d) STZ+HES (Bar: 50 µm)

Discussion

HES has been reported to have anti-inflammatory, antioxidant, and anticancer activities, and can regulate cholesterol levels and blood pressure, playing a therapeutic role in diseases such as diabetes and obesity[17-19]. In this study, the effect of HES on heart tissue damage in the STZ-induced diabetes model was examined histopathologically, and the TAS, TOS, MDA, and GSH levels, as well as the expression levels of Cas/3 and TNF-α, were also determined.

Diabetes, which is thought to be of hereditary origin and whose incidence is increasing due to many reasons such as nutritional deficiencies and inactivity, and which has a chronic course, is thought to be one of the most basic health problems encountered

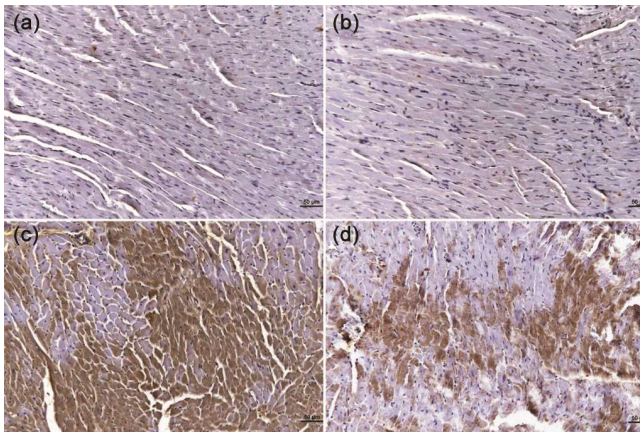


Fig. 4 — Effect of HES on immune expression of Casp/3 in heart tissue of rats: Casp/3 expression was detected by immunohistochemical staining. (a) Control; (b) HES; (c) STZ, and (d) STZ+HES (Bar: 50 µm)

Table 1 —The intensity of the TNF-α and Casp/3 immunoreactivity in the rat heart tissues

	Groups			
	Control	HES	STZ	STZ+HES
TNF-α	-	-	+++	++
Casp/3	-	-	+++	+

Negative (-) mild (+) moderate (++) and intense (+++)

globally in the future[1,2,20]. Factors such as diabetes, high blood sugar, insulin resistance, hypertension, cholesterol disorders, oxidative stress, inflammation and obesity pose serious threats to cardiovascular health[21]. Heart tissue is extremely sensitive to oxidative stress due to its high content of mitochondria. In the heart, oxidative stress due to transient or persistent increases in steady-state reactive oxygen species levels leads to impaired signalling pathways and oxidative modification of cellular components, which can then lead to cell dysfunction or even cell death through necrosis or apoptosis[3,22]. Yıldırım *et al*. investigated the effects of ethanol extract of the rhubarb (*Rheum ribes* L.) plant on oxidative stress parameters in heart tissue in experimentally diabetic rats, and they reported that MDA levels increased, while SOD, catalase and GSH levels decreased in the diabetic group[23]. Naghdi *et al.* investigated the effects of type 1 diabetic rats on oxidative stress and apoptosis in the heart tissue and showed that increased TOS, OSI and MDA levels and decreased CAT, SOD and GSH-Px activities were in the diabetic group compared to the control group[24].In the present study, the decreased TAS and GSH levels and increased TOS and MDA levels were observed in

the heart tissues of rats induced with STZ diabetes. On the other hand, in the STZ+HES group, it was shown that received HES treatment, TAS and GSH levels increased, and TOS and MDA levels decreased compared to the STZ group (Fig. 1).

Wardani *et al*., in STZ-induced diabetic rats, histological examination showed that STZ administration caused necrosis in cardiac cells[25]. Another study reported an increasing histopathological scoring and inflammatory cell infiltration as indicators of histopathological anomalies in rats due to diabetes[26]. Laddha *et al*. reported in their experimental model of diabetic cardiomyopathy in rats that various lesions, such as focal minimal to multifocal moderate lymphocytic infiltration and focal minimal to multifocal mild degeneration and angiogenesis, were observed in the heart tissue of diabetic animals[27]. Raish *et al*. reported that histological examination of heart tissues from STZ-induced diabetic rats revealed deformed nuclei, interstitial oedema, and focal cytoplasmic vacuolization in addition to irregular cardiac myofibril spreading when compared with the control group[28]. In this study, where the effect of HES on heart tissue damage was investigated in the STZ-induced diabetes model, normal histological appearance was observed in the heart tissues of the control and HES groups, while the most obvious morphological changes in myocytes in the STZ group were severe degeneration and necrosis. Vascular congestion was also observed in the STZ group. In addition, it was noted that the heart tissues of rats in the STZ+HES group had almost normal histological structures (Fig. 2).

TNF-α, as a potent pro-inflammatory cytokine, is considered an important mediator in diabetic cardiomyopathy. Increased glucose levels and other metabolic abnormalities may trigger TNF-α production in cardiac tissue[29,30]. TNF-α, in turn, may have direct toxic effects on cardiomyocytes, impair contractile function and induce apoptosis. The increased TNF-α expression in our study suggestedthat inflammatory processes were activated in diabetic cardiac tissue and contributed to tissue damage[31,32]. In their studies on the heart and pancreas during the early development of diabetic cardiomyopathy and pancreatic damage, Abdulwahab *et al*. noted an increase in proinflammatory cytokines (TNF-α, IL-6 and IL-1β) and Bax, Casp/3 and P53 expressions in diabetic rats[33]. Zhong *et al*., in their study on rodents with streptozotocin-induced type 1 diabetes, showed that the mRNA levels of inflammatory markers such as TNF-α, IL-1β and IL-6 were reported to be significantly higher in heart tissues of the DM group compared to the control group. They also showed that the TNF-α level in heart tissues increased due to diabetes using immunohistochemical methods[34]. Apoptosis is an important mechanism of cardiomyocyte loss in diabetic cardiomyopathy[35]. Casp/3 is a central effect or protein in the apoptosis pathway, and its activation leads to cell death. In our study,an increase in the number of Casp/3 positive cells in the heart tissue of diabetic rats indicates increased cardiomyocyte apoptosis. It is known that excessive increases in OS and inflammation levels can trigger apoptosis by activating the caspase cascade[36,37]. Shafey *et al*., in a model of diabetes-induced cardiomyopathy in rats, determined that TNF-α and Casp/3 levels were significantly increased in the heart tissues of diabetic rats compared to the control group[38]. In their study on experimental type 2 diabetes-induced cardiac damage. Huo *et al*. immunofluorescence results showed higher Casp/3 and caspase-9 expression in the heart tissue of diabetic mice compared with the control group[39]. In parallel with the literature, our study results exhibited that there was an increase in Cas/3 and TNF-α levels in the heart tissue of diabetic rats compared to the control and HES groups (Figs. 3 & 4).

Conclusion

The findings of this study provided essential information about the molecular mechanisms underlying the damage caused by diabetes in cardiac tissue. In particular, this study highlighted the critical roles of increased oxidative stress, inflammatory processes, and apoptosis in diabetic-induced cardiac damage. The study's findings revealed that HES may have a protective effect against the STZ-induced diabetic cardiac damage by reducing oxidative stress, pro-inflammatory cytokine, and apoptosis marker levels. HES may be a potential target for the development of new treatment strategies in the STZ-induced diabetes model.

Conflict of interest

All authors declare no conflicts of interest.

References

1 Kumar A, Aswal S, Semwal RB, Chauhan A, Joshi SK & Semwal DK, Role of plant-derived alkaloids against diabetes and diabetes-related complications: a mechanism-based approach. *Phytochem Rev* 18 (2019) 1277.

2 Chawla A, Chawla R & Jaggi S, Microvasular and macrovascular complications in diabetes mellitus: distinct or continuum? *Indian J Endocrinol Metab,* 20 (2016) 546.

3 De Geest B & Mishra M, Role of oxidative stress in diabetic cardiomyopathy. *Antioxidants,* 11 (2022) 784.

4 Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V & Kovacic JC, Oxidative stress and cardiovascular risk: obesity, diabetes, smoking, and pollution: part 3 of a 3-part series. *J Am Coll Cardiol,* 70 (2017) 230.

5 Abukhalil MH, Althunibat OY, Aladaileh SH, Al-Amarat W, Obeidat HM, Alayn'Al-marddyah A, Hussein OE, Alfwuaires MA, Algefare AI & Alanazi KM, Galangin attenuates diabetic cardiomyopathy through modulating oxidative stress, inflammation and apoptosis in rats. *Biomed Pharmacother,* 138 (2021) 111410.

6 Liang RK, Zhao YY, Shi ML, Zhang G, Zhao YJ, Zhang BG & Liang RJ, Skimmin protects diabetic cardiomyopathy in streptozotocin-induced diabetic rats. *Kaohsiung J Med Sci,* 37 (2021) 136.

7 ur Rehman MF, Batool AI, Qadir R & Aslam M, Hesperidin and naringenin. *A centum of valuable plant bioactives*. Elsevier; 2021:403.

8 Abdelgawad AA, El Bassossy TA & Ahmed FA, Synthesis, chemical characterization, and biological investigation of naturally isolated hesperidin and its metal complexes. *Bull. Chem Soc Ethiop,* 38 (2024) 385.

9 Famurewa AC, Renu K, Eladl MA, Chakraborty R, Myakala H, El-Sherbiny M, Elsherbini DMA, Vellingiri B, Madhyastha H & Wanjari UR, Hesperidin and hesperetin against heavy metal toxicity: Insight on the molecular mechanism of mitigation. *Biomed Pharmacother,* 149 (2022) 112914.

10 Bayir MH, Yıldızhan K & Altındağ F, Effect of hesperidin on sciatic nerve damage in STZ-induced diabetic neuropathy: modulation of TRPM2 channel. *Neurotox Res,* 41 (2023) 638.

11 Kakadiya J, Mulani H & Shah N, Protective effect of hesperidin on cardiovascular complication in experimentally induced myocardial infarction in diabetes in rats. *J Basic Clin Pharm,* 1 (2010) 85.

12 Agrawal YO, Sharma PK, Shrivastava B, Arya DS & Goyal SN, Hesperidin blunts streptozotocin-isoproternol induced myocardial toxicity in rats by altering of PPAR-γ receptor. *Chem Biol Interact,* 219 (2014) 211.

13 Kundu A, Dey P, Sarkar P, Karmakar S, Tae IH, Kim KS, Park JH, Lee SH, Lee BM & Renthlei L, Protective effects of Croton hookeri on streptozotocin-induced diabetic nephropathy. *Food Chem Toxicol,* 135 (2020) 110873.

14 Agrawal YO, Sharma PK, Shrivastava B, Ojha S, Upadhya HM, Arya DS & Goyal SN, Hesperidin produces cardioprotective activity via PPAR-γ pathway in ischemic heart disease model in diabetic rats. *PLoS One,* 9 (2014) e111212.

15 Yıldızhan K, Huyut Z & Altındağ F, Involvement of TRPM2 channel on doxorubicin-induced experimental cardiotoxicity model: protective role of selenium. *Biol Trace Elem Res,* 201 (2023) 2458.

16 Huyut Z, Yildizhan K & Altındağ F, The effects of berberine and curcumin on cardiac, lipid profile and fibrosis markers in cyclophosphamide-induced cardiac damage: The role of the TRPM2 channel. *J Biochem Mol Toxicol,* 38 (2024) e23783.

17 Dunnigan SK, Ebadi H, Breiner A, Katzberg HD, Lovblom LE, Perkins BA & Bril V, Conduction slowing in diabetic sensorimotor polyneuropathy. *Diab Care,* 36 (2013) 3684.

18 Callaghan BC, Price RS, Chen KS & Feldman EL, The importance of rare subtypes in diagnosis and treatment of peripheral neuropathy: a review. *JAMA Neurol,* 72 (2015) 1510.

19 Xiong H, Wang J, Ran Q, Lou G, Peng C, Gan Q, Hu J, Sun J, Yao R & Huang Q, Hesperidin: A therapeutic agent for obesity. *Drug Des Devel Ther,* (2019) 3855.

20 Alam S, Hasan MK, Neaz S, Hussain N, Hossain MF & Rahman T, Diabetes Mellitus: insights from epidemiology, biochemistry, risk factors, diagnosis, complications and comprehensive management. *Diabetology,* 2 (2021) 36.

21 Ciumărnean L, Milaciu MV, Negrean V, Orăşan OH, Vesa SC, Sălăgean O, Iluţ S & Vlaicu SI, Cardiovascular risk factors and physical activity for the prevention of cardiovascular diseases in the elderly. *Int J Environ Res Public Health,* 19 (2021) 207.

22 De Geest B & Mishra M, Role of oxidative stress in heart failure: insights from gene transfer studies. *Biomedicines,* 9 (2021) 1645.

23 Yıldırım M, Değirmenci U, Akkapulu M, Berköz M, Yalın AE, Çömelekoğlu Ü & Yalın S, Rheum Ribes L. Ekstraktının Diyabetik Sıçanların Kalp Dokusundaki Oksidatif Stres Üzerine Etkisi. *Van Sağlık Bilimleri Dergisi,* 13 (2020) 20.

24 Naghdi A, Goodarzi MT, Karimi J, Hashemnia M & Khodadadi I, Effects of curcumin and metformin on oxidative stress and apoptosis in heart tissue of type 1 diabetic rats. *J Cardiovasc Thorac Res,* 14 (2022) 128.

25 Wardani G, Nugraha J, Mustafa MR, Kurnijasanti R & Sudjarwo SA, Antioxidative Stress and Antiapoptosis Effect of Chitosan Nanoparticles to Protect Cardiac Cell Damage on Streptozotocin-Induced Diabetic Rat. *Oxid Med Cell Longev,* 2022 (2022) 3081397.

26 Youssef ME, El-Azab MF, Abdel-Dayem MA, Yahya G, Alanazi IS & Saber S, Electrocardiographic and histopathological characterizations of diabetic cardiomyopathy in rats. *Environ Sci Pollut Res Int,* 29 (2022) 25723.

27 Laddha AP & Kulkarni YA, Daidzein mitigates myocardial injury in streptozotocin-induced diabetes in rats. *Life Sci,* 284 (2021) 119664.

28 Raish M, Ahmad A, Jardan YAB, Shahid M, Alkharfy KM, Ahad A, Ansari MA, Abdelrahman IA & Al-Jenoobi FI, Sinapic acid ameliorates cardiac dysfunction and cardiomyopathy by modulating NF-κB and Nrf2/HO-1 signaling pathways in streptozocin induced diabetic rats. *Biomed Pharmacother,* 145 (2022) 112412.

29 Westermann D, Van Linthout S, Dhayat S, Dhayat N, Schmidt A, Noutsias M, Song X-Y, Spillmann F, Riad A & Schultheiss HP, Tumor necrosis factor-alpha antagonism protects from myocardial inflammation and fibrosis in experimental diabetic cardiomyopathy. *Basic Res Cardiol,* 102 (2007) 500.

30 Popa C, Netea MG, Van Riel PL, Van Der Meer JW & Stalenhoef AF, The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res,* 48 (2007) 751.

31 Dhingra S, Sharma AK, Arora RC, Slezak J & Singal PK, IL-10 attenuates TNF-α-induced NFκB pathway activation and cardiomyocyte apoptosis. *Cardiovasc Res,* 2 (2009) 59.

32 Pedersen BK, Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur J Clin Invest,* 47 (2017) 600.
33 Abdulwahab DA, El-Missiry MA, Shabana S, Othman AI & Amer ME, Melatonin protects the heart and pancreas by improving glucose homeostasis, oxidative stress, inflammation and apoptosis in T2DM-induced rats. *Heliyon,* 7 (2021)
34 Zhong P, Peng J, Liu T & Ding H-s, AAV9-mediated cardiac CNTF overexpression exacerbated adverse cardiac remodeling in streptozotocin-induced type 1 diabetic models. *Cardiovasc Toxicol,* (2022) 1.
35 Guo R, Liu W, Liu B, Zhang B, Li W & Xu Y, SIRT1 suppresses cardiomyocyte apoptosis in diabetic cardiomyopathy: an insight into endoplasmic reticulum stress response mechanism. *Int J Cardiol,* 191 (2015) 36.
36 Yang B, Ye D & Wang Y, Caspase-3 as a therapeutic target for heart failure. *Expert Opin Ther Targets,* 17 (2013) 255.
37 Kesavardhana S, Malireddi RS & Kanneganti TD, Caspases in cell death, inflammation, and pyroptosis. *Annu Rev Immunol,* 38 (2020) 567.
38 El-Shafey M, El-Agawy MSE-d, Eldosoky M, Ebrahim HA, Elsherbini DMA, El-Sherbiny M, Asseri SM & Elsherbiny NM, Role of dapagliflozin and liraglutide on diabetes-induced cardiomyopathy in rats: implication of oxidative stress, inflammation, and apoptosis. *Front Endocrinol,* 13 (2022) 862394.
39 Huo Y, Mijiti A, Cai R, Gao Z, Aini M, Mijiti A, Wang Z & Qie R, Scutellarin alleviates type 2 diabetes (HFD/low dose STZ)-induced cardiac injury through modulation of oxidative stress, inflammation, apoptosis and fibrosis in mice. *Hum Exp Toxicol,* 40 (2021) S460.