

Research Article

The synergistic effect of interval exercise and thyme honey on inflammatory gene downregulation and insulin sensitivity in diabetic nephropathy

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Abstract

This study investigated the combined efficacy of interval training and thyme honey in attenuating the expression of inflammatory genes (TNF- α and TGF- β) in renal tissue and improving insulin resistance in diabetic rats. In this experimental study, 32 young male Wistar rats were divided into 4 groups: diabetes mellitus control (DM), diabetes and interval training (DM+HIIT), diabetes and thyme honey (DM+TH), and diabetes and interval training-thyme honey (DM+HIIT+TH). Animals in the training group underwent 40 sessions of training over two months with a gradual increase in the number of intense intervals from 2 to 8 intervals and an intensity of 80 to 95% of maximum running speed. At the same time, the samples in the TH groups received thyme honey at a rate of g/kg 3 and 5 days per week. Insulin resistance index (HOMA-IR) was performed using the formula. TNF- α and TGF- β gene expression in kidney tissue was evaluated using Real-Time PCR. Based on the results of the present study, DM+HIIT significantly reduced HOMA-IR compared to the diabetes group ($p < 0.05$). However, the DM+HIIT+TH group did not yield a greater improvement in HOMA-IR than the DM+HIIT group alone. Also, TNF- α and TGF- β genes in the DM+HIIT, DM+TH and DM+HIIT+TH groups showed a significant decrease compared to the diabetes group ($p < 0.05$). In conclusion, our findings provide strong evidence that both interval training and thyme honey supplementation independently ameliorate diabetic nephropathy by downregulating key pro-fibrotic and inflammatory mediators. While the combination therapy was highly effective at suppressing inflammatory genes, it did not provide a synergistic benefit for insulin sensitivity compared to exercise alone. These results suggest that interval exercise is the primary driver of improved insulin sensitivity in this model.

Key Words: Interval training, Thyme honey, Kidney, Inflammation, Insulin resistance

Introduction

Diabetic nephropathy (DN) remains one of the leading causes of end-stage renal disease worldwide, significantly contributing to morbidity and mortality among diabetic patients (Cheng et al., 2021). Characterized by persistent albuminuria, glomerulosclerosis, and progressive decline in renal function, DN results from complex pathophysiological mechanisms involving hyperglycemia-induced oxidative stress, inflammatory responses, and fibrotic processes in the kidney (Dwivedi & Sikarwar, 2024). Central to these mechanisms is the heightened expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and transforming growth factor-beta (TGF- β), which promote renal inflammation and fibrosis, exacerbating tissue damage and functional impairment (Wang et al., 2021). Despite advances in pharmacological treatments, the prevalence of DN underscores the urgent need for complementary non-pharmacological interventions that target inflammation and metabolic dysregulation in diabetic kidney disease (Habib et al., 2021).

Physical exercise, particularly high-intensity interval training (HIIT), has emerged as a potent therapeutic strategy to improve metabolic health and reduce inflammation in various chronic conditions, including diabetes (Khalafi & Symonds, 2020). HIIT involves repeated bouts of intense exercise interspersed with recovery periods, leading to superior improvements in insulin sensitivity, cardiovascular fitness, and anti-inflammatory effects compared to traditional moderate-intensity exercise (Leiva-Valderrama et al., 2021). Recent studies have demonstrated that HIIT mitigates systemic inflammation and oxidative stress, reducing the expression of cytokines such as TNF- α and TGF- β in experimental models of diabetes and renal disease (Baranchi & Agha-Alinejad, 2021; Shahouzehi et al., 2021). These beneficial adaptations likely stem from enhanced mitochondrial function, improved glucose metabolism, and modulation of signaling pathways involved in inflammatory and fibrotic responses, suggesting that HIIT could be a promising adjunct therapy for ameliorating DN progression.

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In parallel, natural products with antioxidant and anti-inflammatory properties have garnered attention as complementary agents in managing diabetic complications. Thyme honey, renowned for its rich polyphenolic content and bioactive compounds, exhibits potent antimicrobial, antioxidative, and anti-inflammatory effects (Ghalwash et al., 2025; Lazaridis et al., 2024). Numerous experimental and clinical studies have reported that honey supplementation can alleviate hyperglycemia-induced oxidative damage, suppress pro-inflammatory cytokine production, and promote tissue repair (Ranneh et al., 2019). Specifically, thyme honey has been shown to modulate immune responses and reduce renal inflammation in diabetic animal models, making it a valuable candidate for integrative therapies aimed at protecting renal function (Masad et al., 2022). Its natural origin, safety profile, and multifaceted biological activities position thyme honey as a favorable nutritional supplement in diabetes management strategies.

Despite the individual benefits of HIIT and thyme honey, their combined effects on diabetic nephropathy have not been thoroughly investigated. Considering that both interventions target overlapping yet distinct molecular pathways implicated in renal inflammation and insulin resistance, their synergistic use may potentiate therapeutic outcomes. This study was designed to evaluate the combined impact of interval exercise and thyme honey on inflammatory gene expression (TNF- α and TGF- β) and insulin resistance in diabetic rats. By exploring this interaction, we aim to provide evidence supporting a novel, non-pharmacological approach to attenuate diabetes-induced renal damage and improve metabolic control, thereby advancing the development of integrated therapeutic regimens for diabetic nephropathy.

Materials and methods

Animals

The present research method was experimental and was conducted using 32 young male Wistar rats as a statistical sample. The sample size (n=8 per group) was determined based on a power analysis (G*Power software, version 3.1.9.7) using an effect size of 1.4 (derived from similar studies), an alpha of 0.05, and a power of 0.80. Their average weight was 110 \pm 10 grams. The rats were purchased from Royan Institute (Tehran, Iran) and after receiving the ethics code IR.SSRC.REC.1404.034 and observing the ethical principles of working with laboratory animals based on the Declaration of Helsinki, they were transferred to the Razi Laboratory Animal House, Islamic Azad University, Tehran Science and Research Branch. These animals were kept in transparent polycarbonate chambers with autoclaving capability, under controlled conditions including temperature of 20 to 24 degrees Celsius, relative humidity of about 30 to 60 percent, and a light cycle of 12 hours light-12 hours dark, for two weeks to adapt to the environment, and with unlimi-

-ted access to water and food. After familiarization and diabetes induction the rats were divided into 4 groups (n=8 per group) of diabetes mellitus control (DM), diabetes and interval training (DM+HIIT), diabetes and thyme honey (DM+TH), and diabetes and interval training-thyme honey (DM+HIIT+TH).

High fat diet and STZ

After the rats reached an average weight of 197.70 \pm 19.46 g, a high-fat diet (HFD) was applied to induce obesity, which consisted of 12 weeks of a 45% fat diet and 8 weeks of a 60% fat diet (Srinivasan et al., 2005). After reaching a weight of 402.75 \pm 51.69 g, intraperitoneal injection of streptozotocin (STZ) at a dose of 25 mg/kg was used to induce diabetes (Zou et al., 2009). One week after the injection, fasting blood sugar (FBS) was measured by glucometer and fasting insulin (FI) by ELISA using a rat insulin kit manufactured by Pars Azmoun (Iran). Then the insulin resistance index (HOMA-IR) was calculated using the following formula:

$$\text{Fasting glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{IU/mL}) / 405 = \text{Insulin resistance (HOMA-IR)}$$

Interval training

The training groups (DM+HIIT and DM+HIIT+TH, n=8 per group) underwent 8 weeks of HIIT training, 5 sessions per week, with a gradual increase in speed every two weeks from 32 to 38 meters per minute with high-intensity intervals (80 to 95% of maximum speed) and 16 to 22 meters per minute in rest intervals (50 to 56% of maximum speed) for 16 to 34 minutes per session according to the protocol.

To familiarize the rats with the rodent treadmill, one week before the start of the training protocol, they walked on the treadmill three times a week for 10, 12, and 15 minutes at a speed of 5 meters per minute and a zero incline. Also, during the protocol, the control group also performed the same treadmill program (Akbarzadeh, 2018; Rezaei et al., 2015).

Given the lack of access to instruments such as respiratory gas analyzers to directly measure VO_2max , and based on the high correlation between treadmill running speed and VO_2max in rats ($r = 0.94-0.98$; $P < 0.05$), aerobic exercise intensity was estimated using the maximal exercise treadmill test (MERT) (Høydal et al., 2007). For this test, rats performed a training session every two weeks consisting of a 5-min warm-up at 10 m/min and a 2-min run at 15 m/min. Then, the speed was increased by 3 m/min every 3 min until the animal could not continue running and remained on the shocker; the speed recorded at that moment was considered the maximal speed.

Thyme honey

Simultaneously with the training intervention, the groups fed with thyme honey (DM+TH and DM+HIIT+TH, n=8 per group) received Shirazi thyme honey extract daily (5 days per week) at a fixed dose of 3 g per kg of body weight per day by gavage. This extract was diluted with distilled water to a standard volume (e.g., 1-2 mL) to ensure consistent administration. To prepare this extract, 3 kg of thyme plants were collected from Shiraz farms and placed in a shaker with a solution of distilled water and alcohol in a ratio of 30:70 for 48 hours. The resulting mixture was filtered twice and, after evaporation at 35°C, turned into a thick paste. Then, this paste was dissolved in water and provided as food for honeybees to produce pure thyme honey (Erejuwa et al., 2011).

Laboratory measurement and gene expression

At the conclusion of the experiment, all animals were euthanized. The method of euthanasia was deep anesthesia induced by inhaled diethyl ether, followed by decapitation to ensure death. Blood was collected from the heart tissue to measure HOMA-IR using formula. Kidney tissue was removed to study gene expression and after leaving the rat body, it was placed in a nitrogen tank and after separation from liquid nitrogen and stored in a freezer at -80 °C.

Relative gene expression was calculated using the $\Delta\Delta Ct$ method with the formula:

$$\text{Fold Change} = 2^{(-\Delta\Delta Ct)}$$

$$\Delta Ct = Ct_{\text{Target gene}} - Ct_{\text{Housekeeping gene}}$$

$$\Delta\Delta Ct = \Delta Ct_{\text{Sample}} - \Delta Ct_{\text{Reference sample (control)}}$$

Primer design was performed using Primer express version 3 software (Table 1).

Statistical analysis

For statistical analysis of the findings, descriptive statistics (mean and standard deviation) and drawing tables and graphs were used to describe the data. For inferential analysis of the data, one-way analysis of variance and Bonferroni post hoc test were

used to compare the mean changes between groups. Statistical analysis was performed using SPSS-22 software and the significance level in all measurements was considered $P \geq 0.05$.

Results

HOMA-IR

Insulin resistance was assessed in the present study using the HOMA-IR formula, which is also shown in Figure 1. As can be seen, the HOMA-IR index values in the DM+HIIT group showed a significant decrease compared to the DM group ($p=0.0014$). However, the DM+TH and DM+HIIT+TH groups showed a significant increase in the HOMA-IR index compared to the DM+HIIT group ($p<0.0001$ for both).

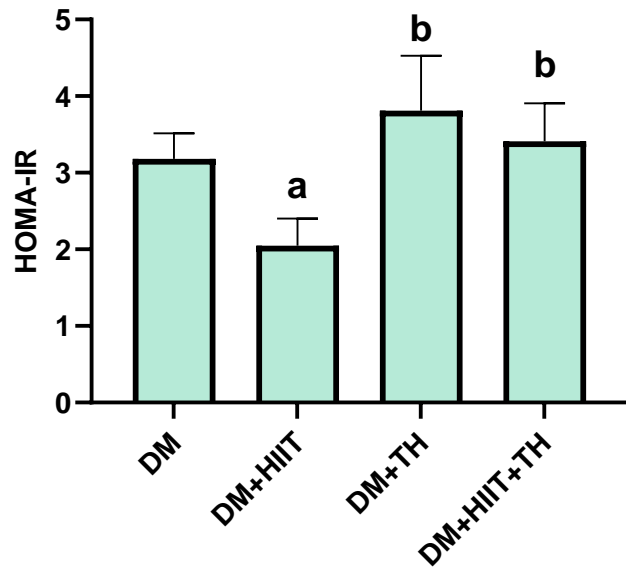


Figure 2. Expression of TNF-a gene at kidney tissue in different research groups. Data are shown as mean \pm standard deviation. Data were analyzed with one way ANOVA and Tukey post hoc test. a: Significant sign compared to DM group ($p<0.05$), b: Significant sign compared to DM+HIIT group ($p<0.05$), c: Significant sign compared to DM+TH group ($p<0.05$). DM: Diabetes mellitus, HIIT: High-intensity interval training, TH: Thyme honey

Table 1. Information on primers used in the study

Gene	sequence	Product length	Accession number
Rattus norvegicus glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	Forward: CAAGTCAACGGCACAGTCA Reverse: CCCATTGATGTTAGCGGG	102 nt	NM_017008.4
transforming growth factor, beta 1 (TGF- β)	Forward: CGCCTGCAGAGATTCAAGTC Reverse: GCCCTGTATTCCGCTCCTT	183nt	
Rattus norvegicus tumor necrosis factor (TNF- α)	Forward: ATGGGCTCCCTCTCATCAGT Reverse: GCTTGGTGGTTTGCTACGAC	106 nt	NM_012675.3

Kidney TNF- α gene expression

Real time PCR was used to examine the renal TNF- α gene, and its expression changes are shown in Figure 2. As can be seen, compared to the DM group, the DM+HIIT, DM+TH, and DM+HIIT+TH groups showed a significant decrease in renal TNF- α ($p < 0.0001$). However, the DM+TH group showed a significant increase in renal TNF- α gene expression compared to the DM+HIIT group ($p = 0.0005$). The DM+HIIT+TH group showed a significant decrease in renal TNF- α compared to the DM+TH group ($p < 0.0001$).

Kidney TGF- β gene expression

Real time PCR was used to examine the renal TGF- β gene, and its expression changes are shown in Figure 3. As can be seen, the DM+HIIT, DM+TH, and DM+HIIT+TH groups showed a significant decrease in renal TGF- β compared to the DM group ($p < 0.0001$). However, the DM+TH group showed a significant increase in renal TGF- β gene expression compared to the DM+HIIT group ($p = 0.0002$). The DM+HIIT+TH group showed a significant decrease in renal TGF- β compared to the DM+TH group ($p = 0.0202$).

Discussion

The present study demonstrated a significant reduction in insulin resistance, as measured by the HOMA-IR index, in the diabetic group subjected to high-intensity interval training (DM+HIIT) com-

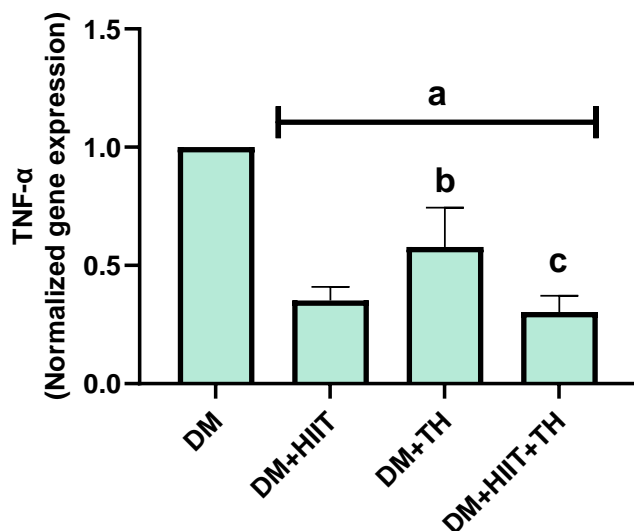


Figure 2. Expression of TNF- α gene at kidney tissue in different research groups. Data are shown as mean \pm standard deviation. Data were analyzed with one way ANOVA and Tukey post hoc test. a: Significant sign compared to DM group ($p < 0.05$), b: Significant sign compared to DM+HIIT group ($p < 0.05$), c: Significant sign compared to DM+TH group ($p < 0.05$). DM: Diabetes mellitus, HIIT: High-intensity interval training, TH: Thyme honey

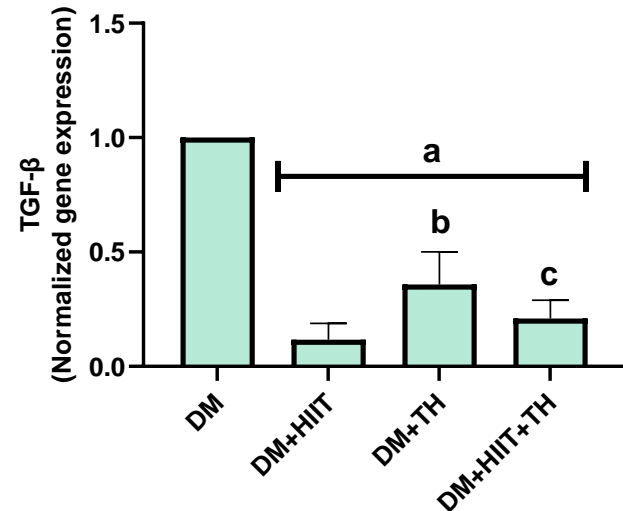


Figure 3. Expression of TGF- β gene at kidney tissue in different research groups. Data are shown as mean \pm standard deviation. Data were analyzed with one way ANOVA and Tukey post hoc test. a: Significant sign compared to DM group ($p < 0.05$), b: Significant sign compared to DM+HIIT group ($p < 0.05$), c: Significant sign compared to DM+TH group ($p < 0.05$). DM: Diabetes mellitus, HIIT: High-intensity interval training, TH: Thyme honey

-pared to the untreated diabetic group (DM). This finding aligns with numerous studies documenting HIIT's efficacy in improving insulin sensitivity in diabetic populations. The primary mechanism underlying this effect involves an increase in skeletal muscle glucose uptake owing to enhanced GLUT4 translocation to the plasma membrane during and after HIIT sessions, driven by AMP-activated protein kinase (AMPK) activation and increased insulin signaling throughput. Moreover, HIIT induces mitochondrial biogenesis through upregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), improving oxidative capacity and thereby enhancing glucose oxidation and reducing circulating glucose and insulin levels—culminating in a decreased HOMA-IR (de Souza et al., 2017). The repeated bursts of intense exercise also mitigate chronic low-grade inflammation, reducing cytokines that impair insulin action. However, in this study, groups supplemented with thyme honey (TH) alone or combined with HIIT (DM+TH and DM+HIIT+TH) showed increased HOMA-IR compared to HIIT alone, suggesting that thyme honey's impact on insulin sensitivity may be complex, potentially mediated by its fructose content or dose-dependent metabolic effects that could transiently impair insulin signaling if not synergistic with exercise (Khoramipour et al., 2025; Kosha et al., 2023).

Regarding renal inflammation, all experimental interventions (DM+HIIT, DM+TH, and DM+HIIT+TH) induced significant downregulation TNF- α gene expression compared to untreated

diabetes. TNF- α is a critical proinflammatory cytokine promoting diabetic nephropathy by activating nuclear factor-kappa B (NF- κ B) pathways in renal cells, which elevates oxidative stress, chemokine production, and leukocyte infiltration, exacerbating glomerular and tubular injury. HIIT likely reduces systemic and renal-specific TNF- α through anti-inflammatory effects, partly by promoting myokine secretion such as IL-6 that has an anti-inflammatory role in this context, lowering macrophage activation and cytokine release (Sen et al., 2023). Thyme honey's phenolic components, including gallic acid and caffeic acid, possess antioxidant and anti-inflammatory properties that inhibit TNF- α expression via modulation of redox-sensitive transcription factors (Tananaki et al., 2024). Notably, the DM+TH group showed higher TNF- α expression than DM+HIIT, which might reflect a less potent or slower anti-inflammatory action of TH alone on renal inflammation, while the combined intervention (DM+HIIT+TH) synergistically reduced TNF- α beyond TH alone, supporting a complementary anti-inflammatory mechanism (Lafraxo et al., 2021).

The observed reduction in renal TGF- β gene expression across all treatment groups also highlights critical antifibrotic and anti-inflammatory benefits. TGF- β is a key mediator of kidney fibrosis in diabetes, promoting extracellular matrix production by activating Smad3-dependent signaling that leads to glomerulosclerosis and tubulointerstitial fibrosis (Gu et al., 2020). Its paradoxical role includes some immunosuppressive functions, but pathological overexpression accelerates progressive renal damage. HIIT's inhibitory effect on TGF- β may derive from attenuation of hyperglycemia and oxidative stress, reducing the stimulus for TGF- β upregulation. Additionally, thyme honey's antioxidant polyphenols can block TGF- β signaling pathways, likely through reactive oxygen species (ROS) scavenging and downregulation of Smad3 activity. The higher expression of TGF- β in the DM+TH group compared to DM+HIIT suggests exercise may exert stronger regulatory control on fibrotic signaling than honey alone. The combined treatment's ability to further suppress TGF- β relative to TH alone indicates a synergistic mechanistic interplay between improved metabolic regulation by exercise and antioxidant flavonoids in thyme honey (Rani et al., 2025; Wang et al., 2021).

In summary, the HIIT protocol effectively improved insulin resistance through enhancement of skeletal muscle glucose metabolism and systemic anti-inflammatory effects, which in turn attenuated renal TNF- α and TGF- β expression—key mediators in diabetic renal inflammation and fibrosis. Thyme honey demonstrated antioxidant and anti-inflammatory effects but appeared less effective alone in improving insulin resistance and

mitigating proinflammatory and profibrotic gene expression compared to HIIT. Critically, the combination treatment revealed a dissociation between metabolic and inflammatory outcomes: while HIIT+TH showed partial synergism in reducing renal TNF- α and TGF- β , it blunted the superior improvement in insulin sensitivity achieved by HIIT alone. This suggests that the integration of exercise with natural antioxidant-rich supplements might offer additive renal protective benefits in diabetes, but that the formulation and timing of such supplements are crucial to avoid negating the critical metabolic benefits of exercise. Future studies should explore molecular pathways linking honey bioactive compounds and exercise-induced myokines and specifically investigate the timing and dosage of supplementation to optimize both metabolic and anti-inflammatory outcomes.

Conclusion

The findings of this study highlight that HIIT significantly improves insulin resistance in diabetic subjects, primarily through enhanced glucose uptake and metabolic adaptations at the cellular level. Thyme honey, while possessing notable antioxidant and anti-inflammatory properties, showed a more complex influence on insulin sensitivity. Most notably, our results indicate that co-administration of thyme honey attenuated the positive effects of HIIT on insulin sensitivity, suggesting a potential metabolic interference that requires further investigation. Nevertheless, thyme honey demonstrated beneficial effects in reducing renal inflammatory and fibrotic gene expressions, particularly TNF- α and TGF- β . Importantly, the combined intervention of HIIT and thyme honey produced synergistic effects in further suppressing these deleterious renal markers, indicating a tissue-specific effect where renal anti-inflammatory benefits can be achieved even when systemic metabolic improvements are blunted. These results strongly support the use of HIIT as an effective therapeutic strategy for metabolic and renal improvements in diabetes. They also suggest that natural supplements like thyme honey may best be used to target specific pathologies like inflammation and fibrosis, but their use must be carefully optimized to avoid unintended consequences on glucose metabolism. Future research should focus on elucidating the precise molecular interactions underlying this dissociation and optimizing treatment protocols including dose, timing, and formulation to maximize clinical outcomes in diabetic kidney disease.

What is already known on this subject?

Diabetic nephropathy (DN) remains one of the leading causes of end-stage renal disease worldwide, significantly contributing to morbidity and mortality among diabetic patients.

What this study adds?

Thyme honey demonstrated beneficial effects in reducing renal inflammatory and fibrotic gene expressions, particularly TNF- α and TGF- β . Importantly, the combined intervention of HIIT and thyme honey produced synergistic effects in further suppressing these deleterious renal markers, indicating a tissue-specific effect where renal anti-inflammatory benefits can be achieved even when systemic metabolic improvements are blunted.

Organ Cross-Talk Tips:

- Interval training (HIIT) improved whole-body pancreas-liver crosstalk (by reducing insulin resistance/HOMA-IR), which was associated with reduced inflammatory gene expression in the kidney, demonstrating a systemic metabolic benefit protecting a specific organ.
- While both thyme honey and exercise reduced kidney inflammation (a local effect), only exercise improved systemic insulin sensitivity. This shows that an intervention can have powerful organ-specific anti-inflammatory effects without necessarily altering the broader metabolic crosstalk.

Acknowledgements

None

Funding

No sources of funding were sought or awarded for this study.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The rats were purchased from Royan Institute (Tehran, Iran) and after receiving the ethics code IR.SSRC.REC.1404.034 and observing the ethical principles of working with laboratory animals based on the Declaration of Helsinki, they were transferred to the Razi Laboratory Animal House, Islamic Azad University, Tehran Science and Research Branch.

Informed consent Animal study.

Author contributions

Conceptualization: M.R, F.Gh.; Methodology: M.Gh, F.Gh.; Software: H.A.; Validation: M.Gh.; Formal analysis: M.R, F.Gh.; Investigation: H.A.; Resources: M.Gh, H.A.; Data curation: H.A.; Writing - original draft: M.R, F.Gh.; Writing - review & editing: H.A

M.R, F.Gh.; Visualization: M.Gh, H.A.; Supervision: H.A.; Project administration: M.R, F.Gh.; Funding acquisition: H.A.

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