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# The effect of eight weeks of continuous and interval training combined with crocin on BDNF and NGF gene expression in the gastrocnemius muscle of diabetic rats

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## Abstract

**Background:** Diabetes mellitus (DM) is a chronic metabolic disorder associated with reduced neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) in peripheral tissues. This study aimed to investigate the effects of eight weeks of Low-Intensity Continuous Training (LICT) and High-Intensity Interval Training (HIIT) combined with crocin administration on BDNF and NGF gene expression in the gastrocnemius muscle of diabetic rats induced by a High-Fat Diet (HFD).

**Methods:** In this experimental study, 42 male Sprague-Dawley rats (Mean weight 229 ± 8.9 g) were fed a high-fat diet for 8 weeks, followed by a single intraperitoneal injection of streptozotocin (STZ, 30 mg/kg) to induce type 2 diabetes. The rats were randomly divided into six groups (n=7): (1) Diabetic Control, (2) Crocin (25 mg/kg daily), (3) LICT, (4) HIIT, (5) LICT + Crocin, and (6) HIIT + Crocin. Crocin (Or saline) was injected 2 hours prior to each training session. The training protocols were performed on a rodent treadmill in five sessions per week for eight weeks. Forty-eight hours after the final session, gastrocnemius muscle tissue was extracted, and BDNF and NGF gene expression levels were measured using Real-Time PCR. The sample size was calculated using G-Power (Power = 0.80, $\alpha = 0.05$), and blinding was applied during injections and PCR analyses. Data were analyzed using one-way ANOVA and Bonferroni post-hoc tests. The level of statistical significance was set at 0.05.

**Results:** One way ANOVA revealed significant effects of interventions on BDNF ($F_{5,36} = 7.480$, P-Value < 0.001) and NGF ($F_{5,36} = 10.291$, P-Value < 0.001) gene expression. Although the study was not designed to formally test interaction effects, the combination groups (LICT+Crocin and HIIT+Crocin) consistently showed higher mean values compared to single intervention groups, suggesting an additive or potentiating effect. Post-hoc analysis indicated that the HIIT + Crocin group exhibited significantly higher BDNF and NGF gene expression compared to all other groups (P-Value < 0.05). The LICT + Crocin group also showed significant increases compared to the control and single intervention groups. A comparison between LICT+Crocin and HIIT-only showed a trend toward significance but did not reach statistical significance (P-Value = 0.065).

**Conclusion**: The combination of exercise training and crocin, particularly the combined effect of High-Intensity Interval Training with crocin, significantly upregulates BDNF and NGF gene expression in the skeletal muscle of diabetic rats. This combined strategy may serve as a potential adjunctive approach for improving the muscular neurotrophic environment in diabetes. Future studies with factorial designs are needed to confirm synergistic interactions.

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Gene expression



## Highlights

**What is current knowledge?**

- Diabetes mellitus reduces BDNF and NGF expression in skeletal muscle, contributing to impaired insulin signaling, mitochondrial dysfunction, and metabolic disturbance.
- Both continuous training and HIIT upregulate BDNF and NGF in peripheral tissues; HIIT may be more potent.
- Crocin has antioxidant, anti-inflammatory, antihyperglycemic, and neuroprotective effects.
- The combined effect of exercise (Especially HIIT) and Crocin on muscle neurotrophic gene expression in diabetic models has not been investigated.

**What is new here?**

- First study to examine eight weeks of HIIT and low-intensity continuous training combined with Crocin on gastrocnemius BDNF and NGF in diabetic rats.
- HIIT + Crocin significantly upregulated BDNF and NGF compared with single interventions, indicating an additive or potentiating effect.
- LICT + Crocin also produced significant increases versus control and single interventions; the difference from HIIT alone approached significance.
- HIIT combined with Crocin serves as an adjunctive strategy to improve the muscular neurotrophic environment in diabetes, supporting future factorial-design studies.

## Introduction

Diabetes mellitus (DM) is a chronic disease that affects millions of people worldwide and has severe consequences for health and quality of life (1). Diabetes is a complex, multisystem metabolic disorder characterized by hyperglycemia, which leads to complications that diminish quality of life and increase mortality. Its pathophysiology involves dysfunction of beta cells, adipose tissue, skeletal muscle, and the liver (2). Skeletal muscle plays a pivotal role in glucose homeostasis, and diabetic conditions are associated with reduced expression of neurotrophic factors, such as Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF), within this tissue (3). Reduced levels of these factors in muscle are linked to impaired insulin signaling, decreased mitochondrial function, and aggravated metabolic disturbances (4).

In recent years, regular physical activity has been recognized as an effective means of improving neurotrophic indices in peripheral tissues. Research indicates that continuous and interval training may exert distinct and potentially complementary effects on neurotrophic factor production in skeletal muscle (5). Continuous training (CT), which involves sustained, steady-state activity, provides notable metabolic health benefits, whereas interval training, characterized by alternating periods of work and rest, may exert distinct and sometimes more potent stimulatory effects on neurotrophic pathways in muscle (6).

Alongside exercise, the use of natural and herbal compounds has attracted considerable attention. Crocin, a colored active constituent of saffron, has demonstrated potent anti-inflammatory and antioxidant properties (7). Furthermore, studies indicate that crocin may exert protective effects on peripheral tissues, improve neurotrophic indices, and mitigate the adverse effects of diabetes on muscle metabolism by reducing oxidative stress and advanced glycation end-products (AGEs) (8). Numerous animal studies indicate that combining regular exercise training with natural supplementation can produce additive effects and, in some instances, ameliorate diabetes-induced abnormalities (9).

Moghadasi et al. (2024) investigated the combined effects of aerobic exercise and crocin on memory, learning, and the expression of hippocampal tau and neurotrophin genes in a rat model resembling Alzheimer's disease. Forty male Sprague-Dawley rats were randomly assigned to five groups: (1) Healthy Control, (2) Alzheimer's Control, (3) Endurance Training, (4) Crocin, and (5) Endurance Training + Crocin. Alzheimer's disease was induced in groups 2-5 through an intraperitoneal injection of 8 mg/kg TMT. Rats in groups 3 and 5 performed treadmill running three sessions per week, 15-30 minutes per session, at 15-20 m/min for eight weeks, whereas groups 4 and 5 received 25 mg/kg crocin daily. The authors concluded that endurance training, particularly when combined with crocin, may improve memory, learning, and neurotrophin gene expression while reducing tau gene expression in rats with an Alzheimer's disease model. These findings suggest the potential of combined interventions to enhance therapeutic outcomes (10).

In this context, the present study aims to evaluate the effects of eight weeks of continuous and interval training combined with crocin administration on neurotrophic indices in rats rendered diabetic via a high-fat diet, thereby assessing the role of these interventions in protecting brain function and improving neurotrophic factors. Type 2 diabetes, as a condition linked to insulin resistance and weight gain, exerts specific impacts on the nervous system. Reduced expression of genes associated with neurotrophic factor production in the brain, including BDNF and Nerve Growth Factor (NGF), is linked to an increased risk of cognitive decline and neurological disorders (11). This highlights the importance of research into effective strategies for enhancing these factors in diabetic patients. Therefore, studying the effects of regular exercise training and natural supplements on neurotrophic indices may contribute to developing effective therapeutic strategies. Previous research indicates that regular exercise training, particularly interval training, can increase BDNF and NGF levels in the brain and promote neurogenesis and neuroprotection (12). Additionally, crocin administration has been effective in increasing neurotrophic factor levels and reducing oxidative stress in the brains of diabetic rats (13).

Consequently, understanding the integrative and synergistic effects of these two interventions is fundamental for designing novel therapeutic programs. Regarding planning for the treatment and prevention of cerebral complications of diabetes, considerable evidence suggests that combining regular exercise with natural compounds as low-risk, easily applicable options alongside pharmacotherapy can play a crucial role. Studies indicate that these strategies, besides enhancing brain function, are effective in controlling insulin resistance and reducing systemic inflammation (14). Therefore, the ultimate objective of this study is to evaluate the effects of eight weeks of continuous and interval training combined with crocin on neurotrophic factors in diabetic rats. The conclusions of this research may provide novel and practical approaches for improving brain health in diabetic patients and mitigating the negative impacts of this disease on neural structure and function. Overall, combining regular exercise with natural compounds represents a reliable and cost-effective strategy to counteract the adverse effects of diabetes on the brain, potentially holding a significant place in future preventive and rehabilitative programs. In this context, the present study aims to evaluate the effects of eight weeks of continuous and interval training combined with crocin administration on BDNF and NGF gene expression in the gastrocnemius muscle of rats rendered diabetic via a high-fat diet. Understanding the integrative effects of these two interventions is fundamental for designing novel therapeutic programs to counteract the adverse effects of diabetes on skeletal muscle structure and function.

## Methods

### Experimental animals and study design

This experimental study was conducted on 42 male Sprague-Dawley rats, 8 weeks of age, with a mean weight of 229 ± 8.9 g, obtained from the breeding and animal facility center of Islamic Azad University, Marvdasht Branch. The animals were housed in a room maintained at 22 ± 2°C under a 12-hour light/dark cycle, with ad libitum access to water and food. Type 2 Diabetes (T2D) was induced using a combination of a High-Fat Diet (HFD) and Streptozotocin (STZ) injection.

For this purpose, all rats were placed on an ad libitum HFD (Providing 45% of total energy from fat (Derived from animal oil), containing 24 g fat, 24 g protein, and 41 g carbohydrate per 100 g) for 8 weeks (15). After 8 weeks, diabetes was induced via a single intraperitoneal injection of Streptozotocin (STZ) dissolved in sodium citrate buffer (pH = 4.5) at a dose of 30 mg/kg body weight. To confirm diabetes induction, 96 hours post-STZ injection, a small tail incision was made, and a drop of blood was placed on a glucometer test strip. Rats with fasting blood glucose levels exceeding 300 mg/dL were selected as diabetic subjects (15). Subsequently, rats were stratified based on fasting glucose into 6 groups (n=7 per group): (1) Diabetic Control, (2) Crocin, (3) Low-Intensity Continuous Training (LICT), (4) High-Intensity Interval Training (HIIT), (5) LICT + Crocin, and (6) HIIT + Crocin. Randomization was performed using block randomization with random number generation. Sample size was calculated using G-Power software (Effect size = 0.40, $\alpha = 0.05$, power = 0.80), resulting in n=7 per group. Groups 3, 4, 5, and 6 ran on a treadmill for eight weeks, five sessions per week. Groups 2, 5, and 6 received daily intraperitoneal injections of crocin at a dose of 25 mg/kg for eight weeks (16). Crocin (Or saline vehicle) was injected 2 hours prior to each exercise session. To prepare the crocin solution, pre-purchased crocin powder (495 mg) was dissolved daily in 18 mL of physiological saline and injected intraperitoneally at the specified volume using an insulin syringe. To control for the effects of injection, the control group received daily intraperitoneal injections of the solvent (Saline) vehicle. Blinding was ensured by having a separate technician (Unaware of group assignments) perform the injections, and RTPCR analyses were conducted by an operator blinded to group codes.

Forty-eight hours after the final training session, rats were anesthetized with ketamine 10% (50 mg/kg body weight) and xylazine 2% (10 mg/kg body weight) and sacrificed. Gastrocnemius muscle tissue was rapidly excised without prior perfusion to avoid washout effects on gene expression, snap-frozen in liquid nitrogen, and transferred to the laboratory for analysis.

### High-Intensity Interval Training (HIIT) and Low-Intensity Continuous Training (LICT) protocols

To familiarize the animals with the treadmill protocol, they were initially placed on the treadmill and allowed to run at a speed of 8 m/min with a 0° incline for 10 minutes. A very mild electrical stimulus was applied at the rear of the treadmill to encourage continuous movement. To minimize potential harm from the electrical stimulus, the animals were initially conditioned using gentle tapping on the treadmill, relatively soft sounds, or contact with the animal's tail.

To estimate maximum running speed, a graded exercise performance test with a 0° incline was performed. Starting at a speed of 10 m/min, the treadmill speed was increased by 1 m/min every minute until the rat reached exhaustion (Unable to continue running). The HIIT protocol consisted of exercise bouts performed at 80-85% of maximum speed for 2 minutes, interspersed with 1-minute active rest periods. The number of intervals progressed from 6 bouts in the first week to 12 bouts in the final week. The total exercise volume (Intensity, duration, and repetitions) was matched between training groups. For the LICT group, exercise intensity was set at 50-55% of maximum running speed. Accordingly, the duration of LICT sessions progressed from 25 minutes in the first week to 50 minutes in the final week (15).

**Table 1.** Primer sequences used for real-time PCR

| Gene | Forward primer (5'- 3') | \| ('5-3') Reverse primer | (bp) |
|---|---|---|---|
| B2m | CGTGCTTGCCATTCAGAAA | ATATACATCGGTCTCGGTGG | **244** |
| BDNF | CTGCAGAGGATGATTGCTGA | GATCAGCTCGGGCACTTTAG | **174** |
| NGF | ATCGCTCTGTGGATGACTGAGTAC | AGAGACAGCCAGGAGAAATCAAAC | **134** |

### RNA extraction and real-time PCR analysis

RNA extraction was performed according to the manufacturer's instructions using an RNA extraction kit (Yekta Tajhiz, Iran). Briefly, 30 mg of gastrocnemius muscle tissue was homogenized in a sterile mortar. Lysis Buffer (Buffer RB) containing β-mercaptoethanol was added to the sample. The lysate was transferred to a Filter Column and centrifuged. The clear flow-through was mixed with 70% ethanol and transferred to an RB Mini Column. After centrifugation and washing steps with Wash Buffer 1 and Wash Buffer 2, total RNA was eluted using RNase-free dd$H_2O$. RNA concentration and purity were assessed via spectrophotometry. Complementary DNA (cDNA) was synthesized using a Revert-Aid™ First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, K1622) with Revert-Aid™ M-MuLV Reverse Transcriptase, following the manufacturer's protocol using random hexamer and oligo(dT) primers.

Following optimization, cDNA from experimental groups was subjected to Real-Time PCR using SYBR Green Master Mix (Takara). The annealing temperature for all primers was 60°C. Primer sequences are presented in Table 1. After amplification, the relative change in gene expression of target genes compared to the reference gene (B2m) and relative to the control group was calculated using the 2^(-ΔΔCt) method.

### Statistical analysis

Descriptive statistics are presented as the mean ± standard deviation. The normality of the data distribution was assessed using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used for group comparisons, followed by Bonferroni post-hoc tests for pairwise comparisons. This approach was selected because the study design involved six independent groups, and the primary objective was to compare group means rather than to test factorial interactions. The level of statistical significance was set at 0.05.

## Results

The body weights of the rats at different stages of the study are presented in Table 2. The results of the one-way ANOVA indicated that continuous or interval training combined with crocin had no significant effect on body weight (P-Value > 0.05).

One-way ANOVA showed no significant effect of the interventions on body weight (P-Value > 0.05). Furthermore, one-way ANOVA revealed a significant effect of continuous and interval training combined with crocin on BDNF levels in the gastrocnemius muscle of the rats ($F_{5,36} = 7.480$, P-Value <0.001) (Figure 1).

Specifically, between-group comparisons using the Bonferroni test demonstrated that mean BDNF levels in the LICT + Crocin group were significantly higher than those in the Control (P-Value = 0.009), Crocin-only (P-Value = 0.022), LICT-only (P-Value = 0.050), and HIIT-only (P-Value = 0.065) groups. The comparison with the HIIT-only group indicated a trend but did not reach statistical significance (P-Value = 0.065). Similarly, mean BDNF levels in the HIIT + Crocin group were significantly elevated relative to those in the Control (P-Value = 0.001), Crocin-only (P-Value = 0.003), LICT-only (P-Value = 0.008), and HIIT-only (P-Value = 0.010) groups.

**Table 2.** Body weight (g) of rats at different stages of the study (Mean ± SD)

| Group | Initial weight | Post-diabetes induction | Post-intervention |
|---|---|---|---|
| Control | 229.4 ± 9.1 | 312.5 ± 11.2 | 318.7 ± 12.4 |
| Crocin | 228.7 ± 8.5 | 315.3 ± 10.8 | 316.2 ± 11.9 |
| LICT | 230.1 ± 9.3 | 314.8 ± 12.1 | 310.5 ± 13.2 |
| HIIT | 229.9 ± 8.7 | 316.2 ± 11.5 | 312.8 ± 12.7 |
| LICT+Crocin | 228.2 ± 8.2 | 313.9 ± 10.2 | 309.4 ± 11.8 |
| HIIT+Crocin | 229.6 ± 9.0 | 315.7 ± 11.9 | 311.3 ± 12.5 |

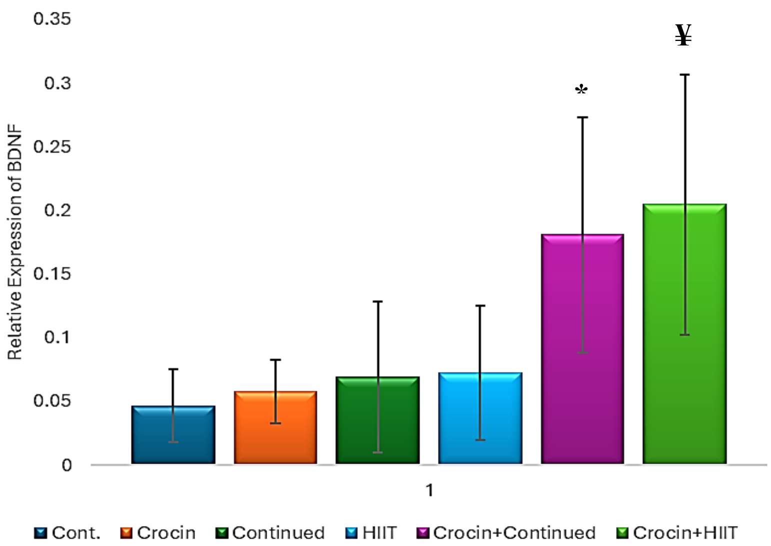


**Figure 1.** Mean BDNF expression levels in the gastrocnemius muscle across different experimental groups. Values are presented as mean ± SD. Symbols (* and ¥) Indicate significant differences between groups based on Bonferroni post hoc test.

One-way ANOVA also showed a significant effect of continuous and interval training combined with crocin on NGF levels ($F_{5,36}$ = 10.291, P-Value < 0.001) (Figure 2). Post-hoc comparisons indicated that mean NGF levels in the LICT + Crocin group were significantly higher than those in the Control (P-Value = 0.003), Crocin-only (P-Value = 0.006), LICT-only (P-Value = 0.017), and HIIT-only (P-Value = 0.012) groups. Similarly, mean NGF levels in the HIIT + Crocin group were significantly higher than those in the Control (P-Value < 0.001), Crocin-only (P-Value < 0.001), LICT-only (P-Value < 0.001), and HIIT-only (P-Value < 0.001) groups.

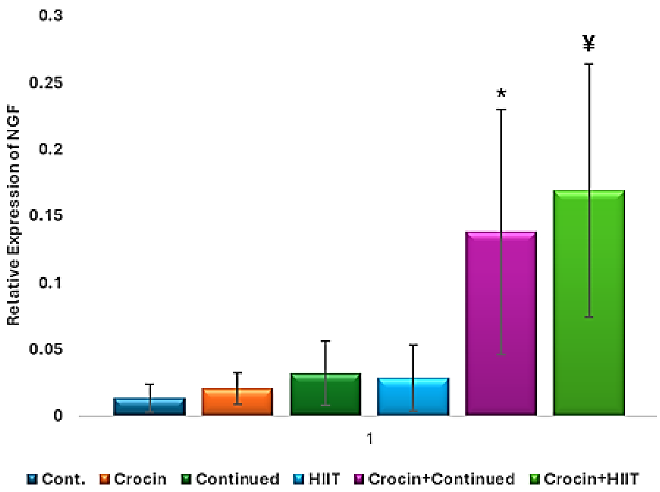


**Figure 2.** Mean NGF expression levels in the gastrocnemius muscle across different experimental groups. Values are presented as mean ± SD.

Symbols (*and ¥) indicate significant differences between groups based on Bonferroni post hoc test.

## Discussion

Diabetes mellitus is associated with numerous complications, including peripheral neuropathy and reduced levels of neurotrophic factors such as BDNF and NGF in skeletal muscle (17). These factors play a crucial role in muscle metabolism, regeneration, and insulin sensitivity; their reduction in diabetes leads to impaired metabolic signaling and exacerbation of myopathy. Exercise training, possesses the potential to upregulate BDNF, TrkB, and dopamin gene expression through mechanisms such as increased muscle blood flow, reduced oxidative stress, and improved insulin signaling (18).

Simultaneously, crocin, the active constituent of saffron, may provide a favorable environment for tissue regeneration through its potent antioxidant, anti-inflammatory, and antihyperglycemic properties, including the inhibition of inflammatory pathways (e.g., NF-κB) and the reduction of Advanced Glycation End-products (AGEs) (10).

The present findings suggest the superior efficacy of High-Intensity Interval Training combined with crocin. Unlike previous studies focused on brain tissue (e.g., hippocampal BDNF), our results in skeletal muscle are consistent with the muscle-specific actions of exercise. For instance, Marquez Saucedo et al. (2015) demonstrated that HIIT evokes larger serum BDNF responses compared to continuous exercise, which may originate from peripheral tissues such as muscle (19). Furthermore, research by Vosadi et al. (2020) indicated that HIIT significantly affects BDNF expression in rat hippocampus, but more importantly, these adaptations are mirrored in metabolic tissues (20). Taheri et al. (2021) showed that HIIT modulates antioxidant enzyme activity in the rat brain, suggesting systemic effects that likely extend to skeletal muscle (21).

The combined effect observed in this study, particularly the significant differences between combination groups and single-intervention groups, supports the presence of an additive or potentiating effect between HIIT and crocin. This combined effect is likely attributable to crocin's ability to enhance neurotrophic signaling (Via TrkB/PI3K and MAPK/Erk pathways) and neutralize oxidative stress induced by intense exercise. However, we acknowledge that the term synergistic is used specifically in the context of gene expression, and functional outcomes require further investigation. Research suggests that both HIIT and MICT can elevate BDNF gene expression, but the magnitude of this increase may be greater with HIIT (19).

Studies have shown that High-Intensity Interval Training (HIIT) can produce greater increases in BDNF expression than Moderate-Intensity Continuous Training (MICT), both acutely and potentially over the long term. HIIT appears to be more effective than MICT in acutely increasing BDNF expression. It also shows promise for producing long-term elevations in BDNF and may therefore be a preferred training modality for promoting peripheral neurotrophic health. Although both HIIT and MICT can increase BDNF expression relative to rest, HIIT may induce larger increases (20).

This study has several limitations. First, we measured only gene expression (mRNA) levels; protein levels and biological activity of BDNF and NGF were not assessed. Second, a healthy nondiabetic control group was not included, which limits the ability to determine whether the interventions normalized or exceeded physiological levels. Third, only male rats were used, and no behavioral or functional nerve conduction studies were performed.

Fourth, the absence of inflammatory marker measurement (e.g., TNFα, IL6) limits the mechanistic interpretation of crocin's anti-inflammatory role in muscle. Fifth, the study design (Six independent groups) did not include a full factorial arrangement to formally test the interaction between exercise and crocin. Therefore, while the combination groups showed superior outcomes, the term synergy should be interpreted with caution, and future studies with larger sample sizes and 2×3 factorial designs are needed to confirm additive or synergistic effects. Future studies should address these gaps by incorporating protein analysis, female subjects, functional assessments, and factorial designs.

## Conclusion

The results of this study demonstrate that combining High-Intensity Interval Training (HIIT) with crocin (25 mg/kg) significantly increases BDNF and NGF gene expression in the gastrocnemius muscle of diabetic rats, with the combined effect surpassing that of continuous training or crocin administration alone. This effect is likely attributable to crocin's ability to enhance neurotrophic signaling and neutralize oxidative stress induced by intense exercise. The findings indicate the therapeutic potential of this combination for improving the muscular neurotrophic environment in diabetes. Future studies should investigate changes in protein levels, functional outcomes, and peripheral neuropathy using higher doses of crocin, longer intervention periods, and factorial designs to confirm interaction effects.

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## Ethical Statement

All experimental procedures on animals were conducted in accordance with institutional guidelines and approved by the Animal Ethics Committee of Islamic Azad University, Marvdasht Branch, Marvdasht, Iran (Ethics Code: IR.MIAU.REC.1396.143).

## Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this manuscript.

## Author Contributions

Conceptualization: Someyyh Nowroozi, Seyed Ali Hosseini. Data curation: Someyyh Nowroozi. Formal analysis: Someyyh Nowroozi, Seyed Ali Hosseini. Writing - Original draft: Iman Fathi. Writing - Review and Editing: Iman Fathi. Literature review: Someyyh Nowroozi, Seyed Ali Hosseini. Project administration: Seyed Ali Hosseini. Other contributions: None.

## Data Availability Statement

The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon reasonable request.

## Use of Artificial Intelligence

No artificial intelligence (AI) tools were used in the writing of this manuscript, data analysis, or the creation of any part of this work.

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