Journal of Basic Research in Medical Sciences

Journal HomePage : https://jbrms.medilam.ac.ir

Ilam University of Medical Sciences Publications

Modulation of Brain Apoptotic Biomarkers by Aerobic Exercise and Mesenchymal Stem Cell Therapy in a Rat Model of Osteoarthritis

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Article Info

Article type:
Original Article

Article History:
Received: Jul. 04, 2025
Revised: Aug. 30, 2025
Accepted: Aug. 31, 2025
Published Online: Jan. 04, 2026

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A B S T R A C T

Introduction: Osteoarthritis is a degenerative joint disease causing irreversible structural and functional joint damage. Recent studies indicate it may also affect the brain by altering apoptotic biomarkers like Bcl-2 and BAX. This study aimed to assess the effects of aerobic exercise and mesenchymal stem cell (MSC) therapy, alone or combined, on brain apoptotic biomarkers in osteoarthritic rats.

Materials & Methods: Forty-eight male Wistar rats were divided into six groups: healthy control (G0), osteoarthritis (GI), osteoarthritis with saline (GII), MSC therapy (GIII), aerobic exercise (GIV), and combined therapy (GV). Osteoarthritis was surgically induced, and MSCs were injected intra-articularly. Aerobic exercise included treadmill running for eight weeks. After intervention, brain tissue was collected and Bcl-2 and BAX levels were measured using ELISA.

Results: Osteoarthritis significantly altered Bcl-2 and BAX levels in the brain compared to controls. MSC therapy, aerobic exercise, and their combination improved these biomarkers. Both individual treatments significantly reduced BAX and increased Bcl-2. The combined treatment improved biomarkers to a similar extent as individual therapies, with no statistically significant difference compared to MSC therapy ($p = 0.992$ for BAX, $p = 0.732$ for Bcl-2) or aerobic exercise ($p = 1.000$ for both BAX and Bcl-2).

Conclusion: This study shows that osteoarthritis can affect brain apoptotic pathways. Both MSC therapy and aerobic exercise effectively modulate these changes, suggesting their therapeutic potential. However, combining them did not enhance outcomes beyond individual treatments, highlighting the value of non-pharmacological interventions in osteoarthritis management.

Keywords: Bone remodeling, Brain-derived neurotrophic factor, Cartilage degeneration, Neuroinflammation, Neuronal plasticity, Oxidative stress, Synovitis

➢ **Cite this paper**
Fatahi M, Behpoor N, Hosseinpour Delavar S, Farzaneghi P. Modulation of Brain Apoptotic Biomarkers by Aerobic Exercise and Mesenchymal Stem Cell Therapy in a Rat Model of Osteoarthritis. *J Bas Res Med Sci*. 2026; 13(1):24-33.

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Introduction

Articular cartilage has limited capacity for self-repair, which diminishes with age. Consequently, the risk of progressive joint degeneration increases in individuals over 40 years of age. Degradation of articular cartilage, accompanied by changes in subchondral bone, leads to irreversible structural and functional alterations in the joint—including the synovium, meniscus (in the knee), periarticular ligaments, and subchondral bone—hallmarks of osteoarthritis (1, 2). Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and clearance, is elevated in OA cartilage (3). Interleukin-1 stimulates chondrocytes to produce various ROS, including hydroxyl radicals, hydrogen peroxide, superoxide anions, and large amounts of nitric oxide (4). ROS are also generated by activated macrophages and neutrophils during inflammatory responses (5). At the molecular level, interleukin-1 signaling plays a central role in a vicious cycle between chondrocytes and immune cells, accelerating the degradation of collagen and aggrecan (6).

Growing evidence suggests that OA has pathological effects on systems beyond the joint (7-11). For instance, apoptotic and inflammatory markers in cardiac tissue differ significantly between osteoarthritic and control rats (11, 12). However, the impact of OA on the brain remains less explored (13), with most studies focusing on pain management (14-21). Notably, Fatahi et al. (22) demonstrated that OA alters inflammatory factors such as TNF-α and IL-10 in the rat brain.

Mesenchymal stem cell (MSC) therapy has emerged as a promising approach for joint and ligament regeneration (23). The number of MSCs increases with OA severity, suggesting their origin in the degrading synovium (24). Concurrent aerobic exercise may accelerate recovery and enhance therapeutic outcomes (25). Jalilian et al. (11, 12) showed that OA induces cardiac inflammation and apoptosis, and that combined MSC therapy and aerobic exercise exert cardioprotective effects by upregulating IL-10 and Bcl-2 while downregulating TNF-α and BAX.

In the present paper, we investigated the effects of aerobic training and stem cell therapy, in combination and alone, on the levels of the apoptotic biomarkers, including BAX and Bcl-2, in the brains of osteoarthritic rats.

Materials and methods

Study Design

This experimental study employed a randomized controlled design with six groups of adult male Wistar rats subjected to osteoarthritis induction, followed by distinct interventions including intra-articular mesenchymal stem cell (MSC) injection, aerobic exercise, or their combination.

Setting and Participants

The study was conducted at the Animal Research Facility of Islamic Azad University, Sari Branch, Mazandaran, Iran. Forty-eight adult male Wistar rats (age: 6–8 weeks; mean weight: 250–300 g) were procured from the Azad University Research Center of Sari Branch. All animals were housed under standardized laboratory conditions: temperature-controlled room (22 ± 2 °C), 12-hour light/dark photoperiod, and ad libitum access to standard rodent chow and water throughout the study.

Sample Size

A total of 48 rats were allocated into six equal experimental groups (n = 8 per group), as detailed in Table 1. The sample size was determined using the following formula for comparison of means in animal studies:

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \alpha^2}{\Delta^2}$$

Where $Z_{1-\alpha/2}$ is 1.96 (for $\alpha = 0.05$), $Z_{1-\beta}$ is 0.84 (for power = 80%), σ is estimated standard deviation based on pilot data or prior literature, Δ is minimum

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detectable effect size. Based on prior studies (e.g., references 24, 27), an effect size (Cohen's d) ≥ 0.8 was anticipated, supporting a group size of n = 8 to ensure adequate statistical power. Randomization was performed using a computer-generated random number table, and allocation concealment was maintained via sealed opaque envelopes.

Table 1. A summary of the designed experiment to explore the effects of stem cell therapy, aerobic exercise, and their combination on the brain apoptotic factors in the osteoarthritic rats.

Group	Symbol	Treatment
Healthy control	G0	None
Osteoarthritis	GI	Osteoarthritis
Saline	GII	Osteoarthritis + Saline
Stem cell therapy	GIII	Osteoarthritis + mesenchymal stem cells
Aerobic exercise	GIV	Osteoarthritis + aerobic exercise
Stem cell therapy + aerobic exercise	GV	Osteoarthritis + mesenchymal stem cells + aerobic exercise

Measurements & Validity and Reliability

MMeasurements were conducted using validated tools and procedures, with attention to reliability and reproducibility. Baseline demographic and physiological characteristics—including rat strain (Wistar), age (6–8 weeks), body weight (250–300 g), and standardized housing conditions (temperature: 22 ± 2 °C; 12-hour light/dark photoperiod; ad libitum access to food and water)—were recorded upon arrival and verified prior to randomization to ensure group homogeneity. Osteoarthritis was surgically induced in the right knee joint using a modified destabilization of the medial meniscus (DMM) model, as described by Zhao et al. (26). The procedure included anesthesia with ketamine (30–50 mg/kg) and xylazine (3–5 mg/kg), followed by a longitudinal skin incision, lateral dislocation of the patella and patellar ligament, medial parapatellar capsulotomy, and incomplete transection of the medial meniscotibial ligament; the joint capsule and skin were then closed with 6-0 absorbable and silk sutures, respectively. This model is well-established for producing progressive, histopathologically consistent cartilage degeneration that closely mimics human osteoarthritis. Mesenchymal stem cells (MSCs) were isolated under sterile conditions from the femurs and tibiae of donor rats: bone marrow was flushed with DMEM, filtered through a 70-µm strainer, centrifuged (200 g, 4 °C, 5 min), and cultured in DMEM supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Adherent MSCs were enriched via overnight culture in 20% FBS, expanded through 3–4 passages, and used at >90% confluency. Cells were characterized in accordance with International Society for Cell & Gene Therapy (ISCT) criteria (27). The aerobic exercise intervention was administered using a rodent treadmill following a 1-week acclimatization phase (5 sessions at 5–8 m/min for 5–10 min/day). The main 8-week protocol consisted of 5 sessions per week, with session duration gradually increasing from 25 to 64 minutes and intensity from 15 to 22 m/min, structured with a 3-minute warm-up at 7 m/min, progressive speed increments (2 m/min per minute), and a cool-down period. This protocol, adapted from established rodent aerobic training models (12, 25) is known to elicit reliable cardiovascular and metabolic adaptations without inducing excessive physiological stress. Finally, biochemical assessment of apoptosis was performed 48 hours after the last intervention: brain tissues were homogenized in phosphate-buffered saline (0.1 M, pH 7.4) containing a protease inhibitor cocktail (Roche), centrifuged (12,000 rpm, 15 min, 4 °C), and supernatants were analyzed for the pro-apoptotic protein BAX and anti-apoptotic protein Bcl-2 using commercially available ELISA kits (ZellBio,

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Germany) (28). These kits demonstrate high sensitivity (<0.1 ng/mL), with intra-assay and inter-assay coefficients of variation below 8% and 10%, respectively, and their validity and reliability are supported by prior neurobiological and osteoarthritis-related studies employing identical methodologies.

Intervention

All rats underwent surgical induction of osteoarthritis in the right knee joint. Following a 3-week recovery period, they were randomly assigned to one of six experimental groups (G0–GV): G0 served as the healthy control group with no osteoarthritis (OA) induction and no intervention; GI represented the OA control group receiving only osteoarthritis induction; GII underwent sham surgery in addition to OA induction; GIII received OA induction followed by an intra-articular injection of 1×10^6 mesenchymal stem cells (MSCs) per kilogram of body weight; GIV underwent OA induction and participated in an 8-week treadmill-based aerobic exercise protocol; and GV received a combination of both MSC injection and aerobic exercise. The MSCs were administered via intra-articular injection under brief anesthesia using ketamine and xylazine, and the selected dose (1×10^6 cells/kg) was based on prior studies demonstrating its efficacy in promoting cartilage repair and exerting anti-inflammatory effects in rodent models of osteoarthritis (24, 27). The aerobic exercise protocol was implemented as previously described and was consistently applied across all relevant groups throughout the 8-week intervention period.

Statistical and Data Analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Parametric data were analyzed by one-way analysis of variance (ANOVA), followed by post-hoc Bonferroni's multiple comparison test to evaluate pairwise differences between groups. Results are presented as mean ± standard error of the mean (S.E.M.). To further interpret the magnitude of the intervention effects, Cohen's d effect sizes were calculated for key comparisons between the osteoarthritic control group (GI) and each intervention group (GIII, GIV, and GV), with effect sizes interpreted as follows: $d \geq 0.8$ indicating a large effect, d between 0.5 and 0.7 a moderate effect, and $d < 0.5$ a small effect. All statistical analyses were conducted using SPSS software (version 16 for Windows; SPSS Inc., Chicago, IL, USA), and a p-value ≤ 0.05 was considered statistically significant.

Results

OA induction significantly altered brain BAX and Bcl-2 concentrations in group GI compared to healthy controls (G0). The OA group also differed significantly from GIII, GIV, and GV, indicating persistent apoptotic imbalance during the disease state (Figs. 1 & 2).

MSC therapy (GIII) significantly reduced BAX and increased Bcl-2 levels compared to the OA group (GI) after eight weeks (Figs 1 & 2). Similarly, aerobic exercise (GIV) significantly modulated both biomarkers compared to GI (Figs 1 & 2).

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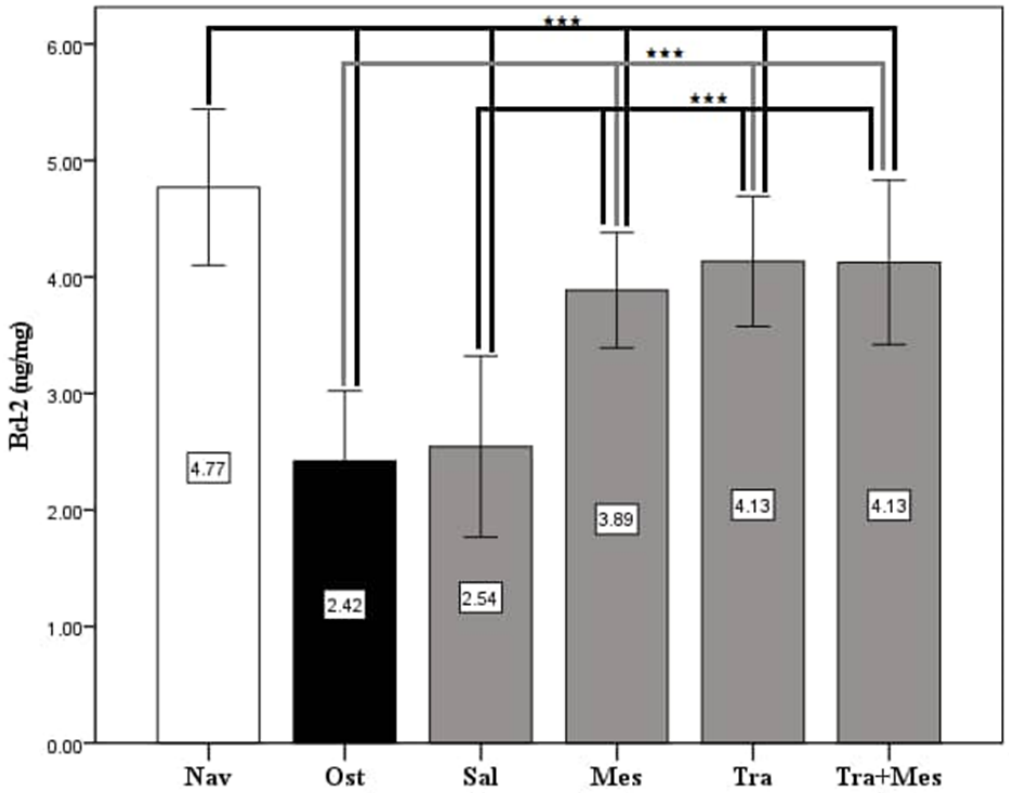
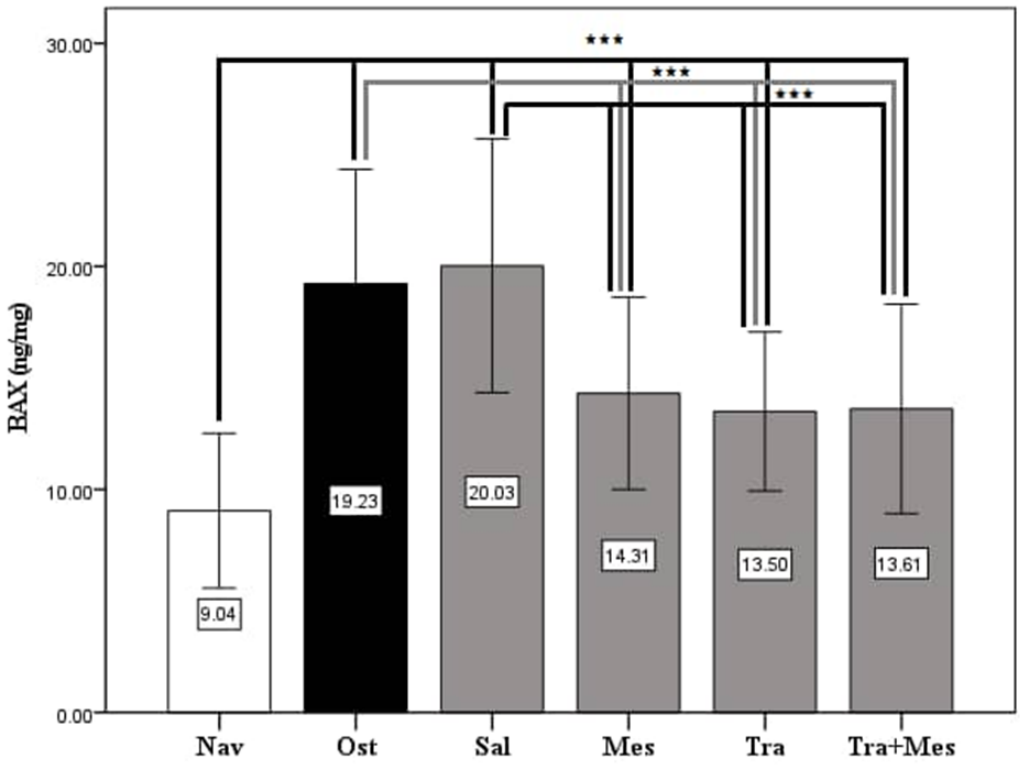


Figure 1. graph for different concentrations of Bcl-2 in the rat groups showing the effect of mesenchymal stem cells, aerobic exercise, and their combination. Data are presented as mean ± SEM. Asterisks above brackets indicate statistically significant differences compared to the osteoarthritis group (GI): *** $p \leq 0.001$ (Tukey's post hoc test). No significant differences were observed between treatment groups (GIII, GIV, GV; $p > 0.05$).



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Figure 2. graph for different concentrations of BAX in the rat groups showing the effect of mesenchymal stem cells, aerobic exercise, and their combination. Data are presented as mean ± SEM. Asterisks above brackets indicate statistically significant differences compared to the osteoarthritis group (GI): ** $p < 0.01$, *** $p \leq 0.001$ (Tukey's post hoc test). No significant differences were observed between treatment groups (GIII, GIV, GV; $p > 0.05$).

The combined therapy (GV) significantly improved BAX and Bcl-2 levels compared to GI. However, no statistically significant differences were observed between GV and either GIII ($p = 0.992$ for BAX, $p = 0.732$ for Bcl-2) or GIV ($p = 1.000$ for both).

Effect sizes further supported these findings: large effects were observed for BAX (Cohen's d = 1.87 [GIII], 2.15 [GIV], 2.08 [GV]) and Bcl-2 (Cohen's d = 1.92 [GIII], 2.25 [GIV], 2.18 [GV]), indicating substantial biological impact of both interventions.

Tables 2-4 summarize all our experimental statistics gathered through intergroup comparisons between different groups

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Table 2. The difference between stem cell therapy accompanied with aerobic exercise and stem cell therapy without aerobic exercise during eight weeks on brain BAX and Bcl-2 concentrations of osteoarthritic rats based on one-way ANOVA.

Concentrations (ng/mg)	Sum of squares	Degree of freedom	Mean of squares	F	*p*-value
BAX	582.981	5	116.596	22.599	0.001
Bcl-2	31.546	5	6.309	61.331	0.001

Table 3. The results of post hoc Tukey HSD based on the F-value of BAX level.

Groups	GI		GII		GIII		GIV		GV	
	MD	sig	MD	sig	MD	sig	MD	sig	MD	sig
G0	-10.185*	0.001	-10.985*	0.001	-5.271*	0.001	-4.457*	0.009	-4.571*	0.007
GI			-0.800	0.985	4.914*	0.003	5.728*	0.001	5.614*	0.001
GII					5.714*	0.001	6.528*	0.001	6.414*	0.001
GIII							0.814	0.984	0.700	0.992
GIV									0.114	1.000

*: significant mean difference; sig: significance; MD: mean difference

Table 4. The results of post hoc Tukey HSD based on the F-value of Bcl-2 level.

Groups	GI		GII		GIII		GIV		GV	
	MD	sig	MD	sig	MD	sig	MD	sig	MD	sig
G0	2.350*	0.001	2.227*	0.001	0.884*	0.001	0.637*	0.008	0.645*	0.007
GI			0.122	0.979	-1.465*	0.001	-1.712*	0.001	-1.704*	0.001
GII					-1.342*	0.001	-1.590*	0.001	-1.581*	0.001
GIII							-0.247	0.702	-0.238	0.732
GIV									0.0085	1.000

*: significant mean difference; sig: significance; MD: mean difference

Discussion

Detection of alterations in brain biochemistry occurring in persistent pain states presents two

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opportunities: first, the ability to detect changes associated with specific pain conditions (a fingerprint) leading to a better understanding of underlying mechanisms and potential therapies and assisting in pain diagnosis and, second, the ability to detect changes specific to individual patients. The latter opportunity offers the possibility of tailoring treatment on an individual basis (29). Our results showed that knee osteoarthritis can affect apoptotic factors, including BAX and Bcl-2 in the rats' brains. Here we interpret our results and discuss how osteoarthritis can lead to such effects. In our opinion, totally, two hypotheses can be assumed for the brain biochemical changes: 1) the chemical factor(s) produced in the osteoarthritic knee might be received by the brain; and 2) the brain chemical changes are a response to the pain perceived by the brain. Pain can change brain function (30). For example, Siddall et al. (29) recorded brain metabolic changes in chronic backache by magnetic resonance spectroscopy.

Bcl-2 (B-cell lymphoma 2) is a protein that regulates apoptosis, and BAX is a protein that acts as an apoptotic activator (31). Our results showed that stem cell therapy diminished brain BAX and enhanced Bcl-2 in osteoarthritic rats after eight weeks so that they exhibited considerable p-values (p BAX, Bcl-2 = 0.003, 0.001) compared to the osteoarthritic group. These findings are concordant with Jalilian et al. (11), who studied the effect of osteoarthritis on the apoptotic factors in the heart. Aerobic exercise has the same effects on brain BAX and Bcl-2 levels in osteoarthritic rats, showing considerable statistics for the osteoarthritic group (p BAX, Bcl-2 = 0.001, 0.001). These also agree with Jalilian et al. (12). The combination of stem cell therapy and aerobic exercise, although it has a lowering effect on brain BAX level (p BAX = 0.001) and an incremental effect on brain Bcl-2 level (p Bcl-2 = 0.001), failed to record considerable p-values compared either to stem cell therapy (p BAX, Bcl-2 = 0.992, 0.732) or to aerobic exercise (p BAX, Bcl-2 = 1.000, 1.000). Jalilian et al. (12) found the same results about the combination of stem cell therapy and aerobic exercise.

Limitations and Strengths

This study has several limitations. First, behavioral or cognitive assessments were not performed. This limits our ability to link changes in brain apoptotic markers to functional outcomes such as anxiety, depression, or memory. Second, we focused only on BAX and Bcl-2; future studies should examine a broader range of biomarkers, including those involved in neuroinflammation, oxidative stress, and neurotrophic support. Third, neuroimaging techniques were not used, which could have provided noninvasive insights into brain structural and functional changes over time. Another limitation is the lack of a sham injection for non-injected groups. The additional surgical stress from intra-articular injection in MSC-treated groups was not controlled, which may confound results. Future studies should include sham procedures to isolate treatment-specific effects.

Future studies should use multimodal approaches, including neuroimaging (e.g., fMRI, DTI) and broader biomarker panels, to better understand the brain-joint axis in OA. Longitudinal and human studies are also needed to confirm these findings and explore their clinical relevance.

Conclusion

Our findings support the view of osteoarthritis as a systemic disease, not just a joint disorder. By showing that OA disrupts apoptotic balance in the brain, we highlight its impact on the central nervous system. This suggests that inflammatory and oxidative factors may spread from the joint to the brain, reinforcing the need for treatments that target both local and systemic effects of OA. Although conducted in rats, this study has translational relevance for human OA. Aerobic exercise may offer neuroprotective benefits beyond joint health, supporting its inclusion in OA management. While MSC therapy remains experimental, it shows

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potential for systemic and neural protection. The lack of added benefit from combining both interventions suggests that exercise alone may be sufficient for significant neuroprotective effects. In conclusion, osteoarthritis is a peripheral illness but it can change apoptotic factors, including BAX and Bcl-2 in the brain. The curing procedures we used here could improve the factors in the brain. So, the present study suggests stem cell therapy and physical activity as effective ways to improve the osteoarthritis signs.

Acknowledgements

This research was supported by the Islamic Azad University, Kermanshah, Iran, which was extracted from the Ph.D. thesis of Mohamad Fatahi. The authors would like to express their gratitude to the staff of the Laboratory of Animal Research Center, Islamic Azad University, Sari Branch, Iran, for helping us to carry out this project (N9.19.33.2018).

Ethical Considerations

All procedures adhered to ethical standards and were approved by the Institutional Animal Ethics Committee of Islamic Azad University, Sari Branch (N9.19.33.2018), in compliance with the latest version of the Declaration of Helsinki.

Financial Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All costs associated with the study were personally covered by the first author.

Competing Interests' Disclosure

There is no conflict of interest in the present study.

Authors' contributions

Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Software, Data Curation, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: MF, NB, SHD, PF.

Writing Disclosure

The authors confirm that no professional writing assistance was utilized in the preparation of this manuscript.

Data Availability Statement

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

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