Research in Pharmaceutical Sciences, October 2024; 19(5): 509-519
Received: 17-06-2023
Peer Reviewed: 01-08-2023
Revised: 13-12-2023
Accepted: 07-09-2024
Published: 22-10-2024

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Curcumin and exercise prevent depression *via* alleviating hippocampus injury and improve depressive-like behaviors in chronically stressed depression rats

Elaheh Ahmadi[1], Ali Pourmotabbed[1], Nilofar Aghaz[1], Seyed Ershad Nedaei[1], Mojgan Veisi[1], Zahra Salimi[2], Fatemeh Zarei[3], Cyrus Jalili[4], Farshad Moradpour[1], and Motahareh Zeinivand[1,*]

[1]*Department of Physiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, I.R. Iran.*
[2]*Department of Biology, Faculty of Science, University of Qom, Qom, I.R. Iran.*
[3]*Department of Biology, Faculty of Science, Razi University, Kermanshah, I.R. Iran.*
[4]*Department of Anatomical Sciences, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, I.R. Iran.*

Abstract

Background and purpose: Depression is a growing public health concern worldwide, characterized by cognitive impairment and structural abnormalities of the hippocampus. Current antidepressant treatment sometimes causes the late onset of results and the much faster occurrence of side effects. For this reason, the interest in new treatment strategies including exercise and natural products such as curcumin has increased to treat depression. The present study investigated the role of curcumin and exercise in improving depressive-like behavior and hippocampal damage induced by mild unpredictable chronic stress in male rats.
Experimental approach: This study analyzed the effects of curcumin (100 mg/kg/day, P.O for 14 days) and exercise (treadmill running, 45 min/day for 14 days) on immobility behavior (forced swimming test), locomotor activity (open field test), anhedonia (sucrose preference test) and cell survival (Nissl staining) of the hippocampal CA3 region in chronically stressed depression rats.
Findings/Results: In the current study, curcumin treatment combined with exercise effectively improved immobility behavior, locomotor activity, and increased hippocampal cell survival resulted in preventing the development of hippocampus dysfunction and depressive-like behaviors.
Conclusion and implications: This study demonstrated a new prospect for treating depression. The current findings give researchers the confidence to continue the investigations on the effects of curcumin accompanied with exercise as a novel therapy for the treatment of depression.

Keywords: Chronic stress; Curcumin; Depressive behaviors; Exercise; Hippocampus injury.

INTRODUCTION

Despite intensive research worldwide, there is a constant increase in the number of patients suffering from depression (1,2). Depression is related to a higher risk of mortality (3). The cause of depression is complex and results from both genetic and environmental factors (4). As yet, there are a few antidepressant drugs including selective serotonin reuptake inhibitors which are generally first-line choices (5). However, almost one-half of patients with depression display treatment resistance (6). Moreover, all available antidepressant drugs have a delayed onset of effect in the treatment, which usually takes as long as 2 to 8 weeks to arrive at their therapeutic effects (7). Despite depression being successfully treated, the elimination of symptoms is often only short-term or petty (7).

*Corresponding author: M. Zeinivand
Tel: +98-8334274622, Fax: +98-8334274677
Email: m_zeinivand2000@yahoo.com

Access this article online	
	Website: http://rps.mui.ac.ir
	DOI: 10.4103/RPS.RPS_94_23

Regrettably, the current definition of recovery from depressive disorder does not fully take into account all aspects of patient recovery, and the remission amount for depression is only 20%-40% (6). Furthermore, antidepressant drugs have significant harmful effects including sedation, constipation, dry mouth, urinary retention, orthostatic hypotension, glaucoma, and cardiac arrhythmias (8). Recent evidence suggests that about 50% of depressed patients have to lower the dose of the anti-depressant drugs or even stop taking them because of the side effects of the drugs (9). For this reason, discovering effective and safe pharmacotherapy with downside effects is still in great demand. As mentioned above, the development of promising new antidepressant drugs with decreased side effects and fully novel actions is necessary. Fortunately, with the progress of modern medicine, traditional medicine has achieved much attention as a promising drug candidate for new medication in recent years. Specifically, quite a lot of herbal medicinal products with high side safety have been developed to be useful in treating depression, such as the *Curcuma longa* (9). *Curcuma longa* chiefly has three active agents including curcumin, demethoxycurcumin, and bisdemethoxycurcumin (10). Among them, the main active healing compound is curcumin (11). Curcumin has both medical and nutritional properties and is utilized as a non-toxic flavoring, additive, and coloring ingredient worldwide (9). In addition to food supplements, curcumin has also displayed extensive biological and pharmacological features, such as anti-inflammatory action (12), anti-carcinogenic, antimicrobial, antioxidant (13), and neuroprotective effects (14). Interestingly, curcumin possesses significant antidepressant effects as well (9).

Recent studies reported the approving effects of exercise on the treatment and rehabilitation of mental and brain diseases (15), considering exercise as a nonpharmacological and potent approach to the prevention and management of depression (16). Recently, a study showed the effect of regular walking on reducing women's depression symptoms (17). Also, the effect of 3-week aerobic exercise on reducing depression has been reported (18), and the effect of 4-week moderate-intensity swimming in improving the behavior of depressed people was stated (19). Another study found curcumin supplementation effective in reducing depression (20). The relationship between depression and inflammatory factors has been mentioned in basic research (21), therefore, it was important to design the current research because the effect of aerobic exercise and curcumin supplementation on behavior like depression had not been reported in any applied research. In addition, hippocampal atrophy has been widely reported which is associated with cognitive deficits as well as depressive symptoms (19). Considering the important role of the hippocampus in the occurrence of depression symptoms, one study performed on hippocampal neurons has provided more knowledge about depression (22). The hippocampus consists of 3 closely related regions including the hippocampus proper (Cornu Ammonis, CA), the dentate gyrus, and the subiculum. In depression, the changes in hippocampal synaptic plasticity are also reflected in the hippocampal subregions, especially the CA3 (20). Accordingly, the present study investigated the effect of exercise and co-administration of curcumin on the prevention of hippocampal damage and depression-like behaviors in rats with chronic depression.

MATERIALS AND METHODS

Animals and housing

The study was performed on adult male Wistar rats weighing 180-200 g. Animals were purchased from the Experimental Animal Center, Kermanshah University of Medical Sciences, and housed under standard laboratory conditions including a temperature of 21 ± 2 °C, 12-h light/dark cycle, a humidity of 45 ± 5%, and free access to food and water. All animal experiments were carried out according to the guidelines approved by the Animal Ethics of Kermanshah University of Medical Sciences, Kermanshah, Iran (Ethical No. IR. KUMS. MED.REC.1400.026).

Study design

Thirty-five male rats were divided into 5 groups (7 rats in each group) as follows: 1. rats receiving curcumin solvent as the placebo

for 2 weeks without exposing any stress (control group), 2. rats subjected to chronic unpredictable mild stress (CUMS) for 4 weeks (stress group) according to the CUMS approved protocol (23) to develop the depression model, 3. stress + curcumin (stress + Cur), 4. stress + curcumin solvent + exercise (stress + Ex), and 5. stress + exercise + curcumin (stress + Ex + Cur). Curcumin was administered at a dose of 100 mg/kg for 2 weeks, and the respective groups subjected to exercise were also forced to do aerobic exercise (running on a treadmill) for 2 weeks. The respective groups received curcumin and exercise either alone or in combination in the 2nd and 3rd weeks of CUMS period. Powder curcumin (Sigma-Aldrich Company, China, product No. 458-37-7) was dissolved in propylene glycol (Sigma-Aldrich, USA) and administered orally through gavage at the dose of 100 mg/kg/day. The selected dose of curcumin showed neuroprotective effects against neurotoxicity and depression in the previous study (24). Two days after the interventions behavioral tests including a forced swimming test (FST), open field test (OFT), and sucrose preference test (SPT) were performed. In addition, the structural changes in the hippocampus were examined using Nissl staining. A schematic of the study procedure is presented in Fig. 1.

Protocol of CUMS

Animals subjected to the stress groups were exposed to CUMS procedure for 4 weeks according to the protocol used previously with a little modification (25). Rats (2 animals in each cage) were put under stress containing overnight illumination, and water deprivation for 18 h immediately followed by 1 h exposure to an empty bottle, food deprivation for 18 h, tilted cage at a slop 45° for 8 h, restrained stress for 1 h, bare cage for 8 h, grouped housing for 4 h, white noise for 8 h, flashing light during the night for 8 h, and wet bedding for 8 h. Two stressors were applied daily in a random manner. Rats in the control group were housed in separate cages in the room with no manipulation.

Protocol of aerobic exercise

The exercise protocol was the performance on the treadmill (26). Each animal was placed on a treadmill belt with a speed of 0.78 Km/h for the first 5 min, which increased to 1.02 Km/h for 45 min. The exercise protocol was running at 8:30-11:30 a.m. for 2 weeks. Rats were forced to maintain running in the course of the exercise period by the electric shock stimulus (0.0-5.0 mA) implemented at the end of the belt.

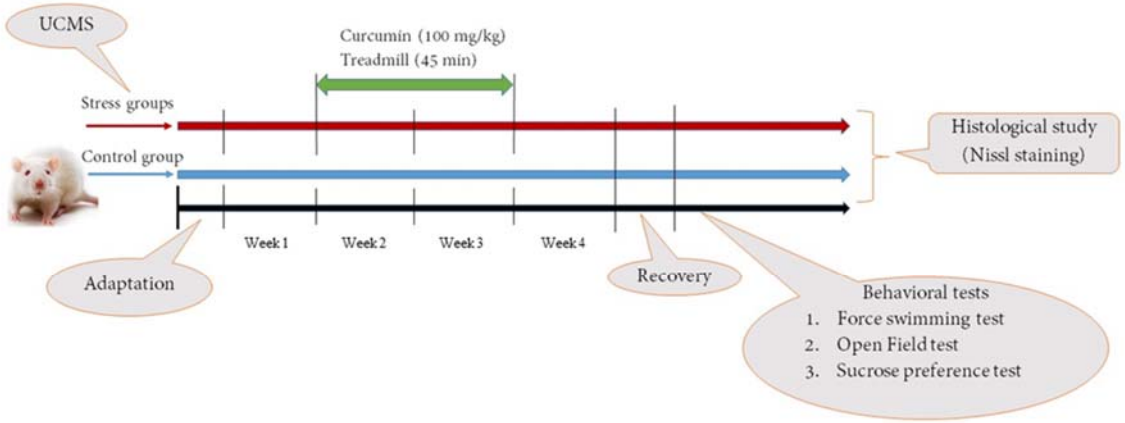

Fig. 1. Graphic representation of the current study. Control group received curcumin solvent as a placebo, but was not exposed to CUMS. Groups under stress were included stress, stress + Ex, stress + Cur, and stress + Ex + Cur groups. Stress and stress + Ex groups received curcumin solvent as a placebo. CUMS, Chronic unpredictable mild stress; Ex, exercise; Cur, curcumin.

Behavioral assessment

The behavioral tests were carried out 2 days (27) after completing the course of the 4-week CUMS in order of FST, OFT, and SPT to investigate the effects of curcumin and exercise on the depressive-like behaviors of animals.

FST

The FST considered immobility to assay psychomotor retardation as an indicator of the depression-like status. The test was conducted in a plexiglass cylinder (height = 45 cm and diameter = 20 cm) filled with water with a temperature of 25 °C and a depth of 30 cm (27). The FST was performed based on the method described in the literature with few modifications (28). On the first day, each rat was individually placed in water to swim for 15 min. After 24 h rats were forced to swim for 6 min. The first 1 min was considered habituation, and the animal behaviors were recorded on videotape over the next 5 min. Immobility was the index of depressive-like behavior, in which the rat made no escape-oriented movements, for example jumping, exploring, climbing, and swimming.

OFT

Changes in locomotion can be indicative of altered neurological processes and may therefore reflect abnormal brain function (29). The OFT is a useful experiment to assay general locomotor activity levels, anxiety, and willingness to explore in rodents (30). The test used to assess anxiety and exploratory behaviors is based on the natural tendency of an animal to explore and protect itself using avoidance which is spending more time in the periphery of the open field arena than in the center (the most anxiogenic area) compared with a normal animal. Briefly, the apparatus consisted of a gray square with 100 cm × 100 cm × 20 cm was divided into 25 equal squares. The squares connected to the walls were outer, and the other squares were central. The box was maintained dark-light. Each animal was placed on central squares and observed the running square numbers for 10 min and upright numbers for 10 min in each rat. All behaviors were recorded using a video camera located above the arena. After each test, the arena was cleaned with a 90% alcohol solution. After completing the test, computer tracking programs analyzed the movements of animals over time. This assay can measure horizontal activity, time spent in the various regions of the open field apparatus, and the total distance traveled (31).

SPT

The SPT was performed to assess anhedonia in rats as described previously with minor modifications (32). In the initial adaption phase, rats were placed individually in cages with 2 bottles containing sucrose solution (1%, w/v) for a 24-h period; one bottle was then replaced with tap water for the second 24-h period. In the test phase, rats were deprived of water and food for 24 h and then permitted for 3 h to freely access the two bottles, one filled with 100 mL of 1% sucrose solution and the other 100 mL of tap water (32,33).

Nissl staining

Following the behavioral experiments, the rats were deeply anesthetized with intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and perfused through the left ventricle with 50 mL of 0.9% saline followed by 100-150 mL of fixative solution containing 4% paraformaldehyde in 0.1 M phosphate buffer (PB, pH 7.4) followed by 100 mL of 0.1 M PB containing 10% sucrose. After that, the brains were removed from the skull, and the tissue blocks were prepared and then processed and sectioned in 7 µm thickness slices by microtome (Leica, Germany). The sections were collected in PB (0.1 M) and stained with 0.1% cresyl violet (Sigma, USA). Three continuous slices from the hippocampus CA3 region were selected for counting cells. Cell counting was performed twice for each slice. The slices were observed by an Olympus microscope (CX31, Tokyo, Japan) with a 40× objective lens. Images were captured using a digital camera (Olympus, Japan) and displayed on a computer monitor. In Nissl stained sections, the number of dark neurons counted was used as an index of cell death (34,35). In this study, the number of healthy neurons was counted to investigate the protective effects of curcumin and exercise.

Statistical analysis

All data were expressed as mean ± SEM. Prisma 9 software was used for statistical analysis. To compare the experimental groups one-way ANOVA followed by Tukey post-hoc test was applied. In all statistical analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Immobility behavior assay

Immobility time as an index of behavioral depression is shown in Fig. 2. The analysis of data showed that there was a significant difference in immobility time among different groups (F 4, 30 = 9.87). Tukey's post-hoc test revealed a significant increase in immobility time in the stress group compared to the control group. The immobility time was significantly reduced in the stress + Cur and stress + Ex + Cur groups compared to the stress group. Also, the immobility time in the stress + Ex + Cur group was significantly reduced compared to the stress + Ex group.

Locomotor activity assay

The OFT often is used to investigate the level of locomotor activity in rodents. The results of the time spent in the center in different groups were shown in Fig. 3A. The analysis of data showed that there was a significant difference in the time spent in the center among different groups (F 4, 30 = 3.71, Fig. 3A). Tukey's post-hoc test revealed a significant decrease in the time spent in the center in the stress group compared to the control group. The findings showed a significant increase in the time spent in the center in the stress + Ex + Cur group compared to the stress group (Fig. 3A). In addition, the total distance traveled in the entire area in different groups was shown in Fig. 3B. The total distance traveled in the entire area did not show a significant difference among different groups (F 4, 30 = 0.89, Fig. 3B).

Anhedonia assay

The assessment of anhedonia in the SPT (sucrose reduction) was shown in Fig. 4. The analysis of data showed that there was a significant difference among different groups (F 4, 30 = 9.28, Fig. 4). Tukey's post-hoc test revealed a significant decrease in the sucrose preference in stress, stress + Ex, and stress + Ex + Cur groups compared to the control group. On the other hand, the sucrose preference in the stress + Cur group effectively increased compared to the stress + Ex group.

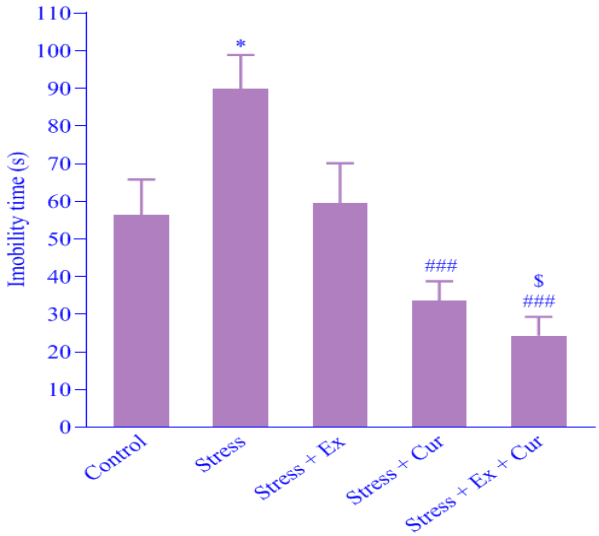

Fig. 2. Forced swimming test as immobility behavior time in the experimental groups. The data were presented as mean ± SEM, n = 7. Control, stress, and stress + Ex groups received curcumin solvent as a placebo. $^{*}P < 0.05$ demonstrates significant difference compared to control group; $^{###}P < 0.001$ versus stress group; $^{\$}P < 0.05$ versus stress + Ex group. Ex, exercise; Cur, curcumin.

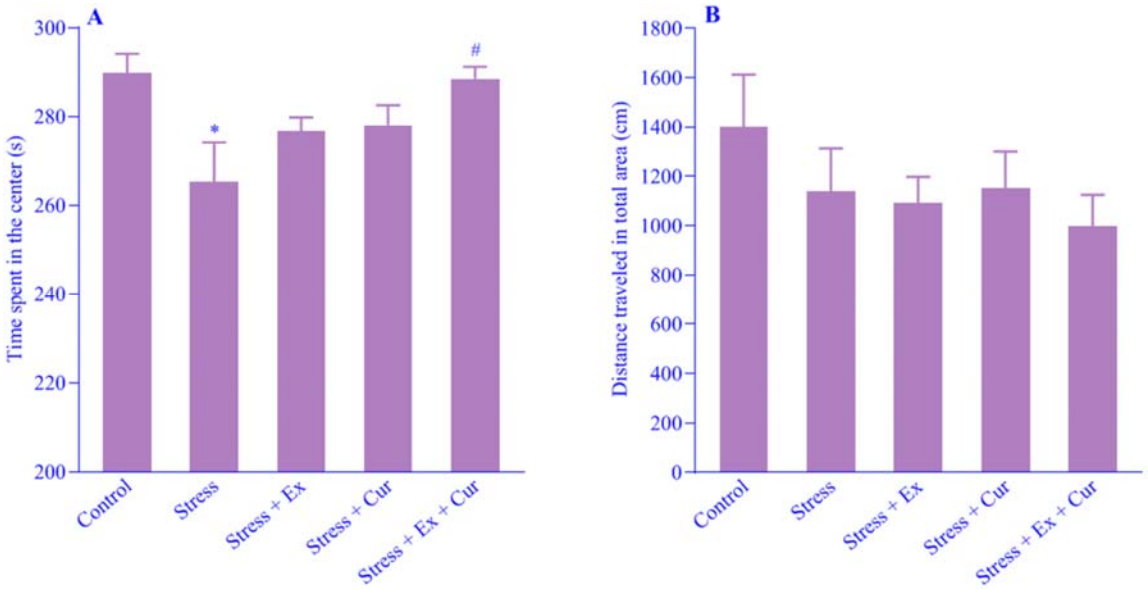

Fig. 3. Open field test as locomotor activity in the experimental groups. (A) Time spent in the center and (B) distance traveled in total area. The data were presented as means ± SEM, n = 7. Control, stress, and stress + Ex groups received curcumin solvent as a placebo. $^{*}P < 0.05$ demonstrates significant difference compared to control group; $^{\#}P < 0.05$ versus stress group. Ex, exercise; Cur, curcumin.

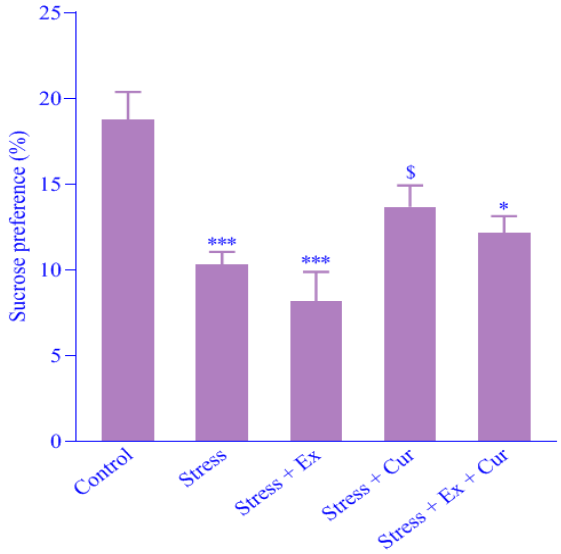

Fig. 4. Sucrose preference test as anhedonia in the experimental groups. The data were presented as mean ± SEM, n = 7. Control, stress, and stress + Ex groups received curcumin solvent as a placebo. $^{*}P < 0.05$ and $^{***}P < 0.001$ demonstrate significant differences compared to control group; $^{\$}P < 0.05$ versus stress + Ex group. Ex, exercise; Cur, curcumin.

Hippocampal CA3 neurons count

The current study investigated the effect of curcumin and exercise following CUMS on the number of neurons in the hippocampal CA3 region by using Nissl staining (Fig. 5A). The analysis of data showed that there were significant differences among different groups ($F_{4, 30} = 14.06$, Fig. 5B). Tukey's post-hoc test revealed that the number of neurons in the CA3 region of the hippocampus after stress was significantly reduced compared to the control group, while the number of neurons after the treatment of groups under stress treated by curcumin alone, exercise alone, or curcumin + exercise showed a significant increase compared to the stress group.

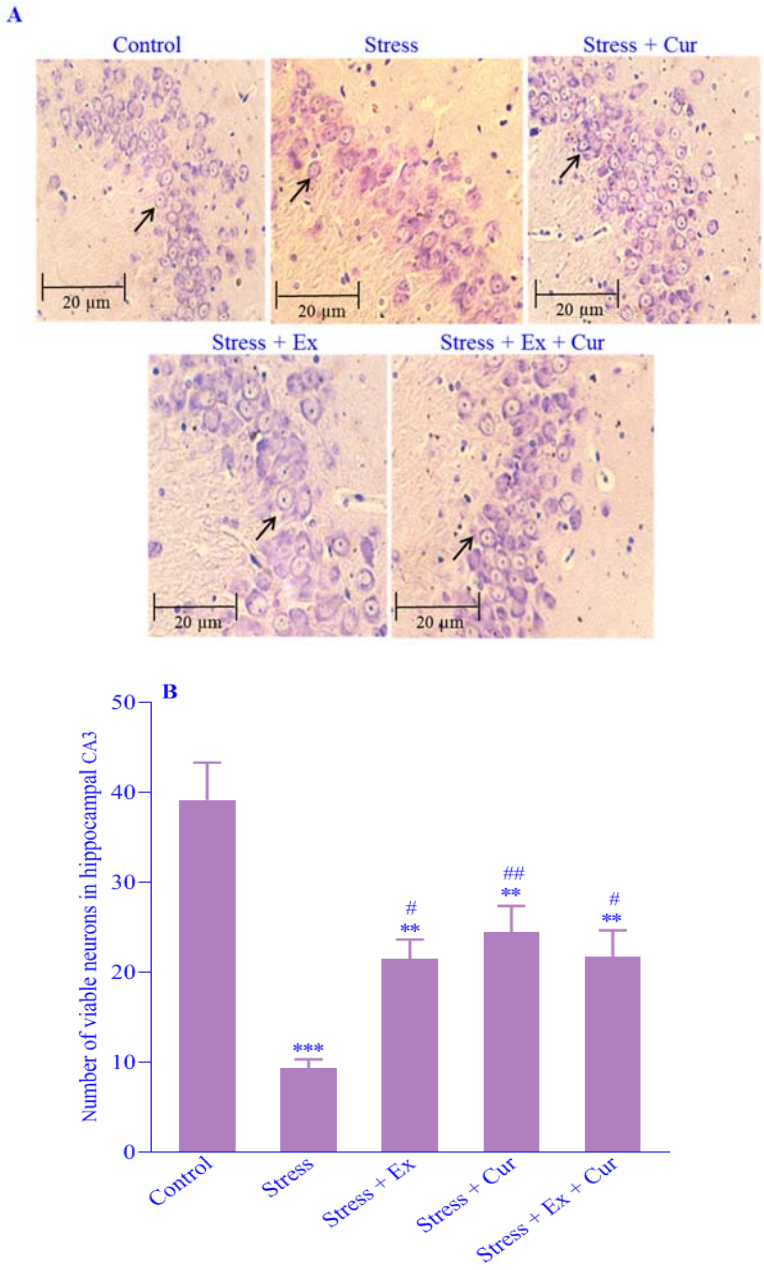

Fig. 5. Count of hippocampal CA3 viable neurons by Nissl staining in experimental groups. (A) Photomicrograph of the hippocampus CA3 region (magnification 400×) and (B) quantitative amount of viable neurons in hippocampal CA3. The data were presented as mean ± SEM. Control, stress, and stress + Ex groups received curcumin solvent as a placebo. $^{**}P < 0.01$ and $^{***}P < 0.001$ demonstrate significant differences compared to control group; $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ versus stress group. Ex, exercise; Cur, curcumin.

DISCUSSION

The results of the present study showed that curcumin treatment with exercise for 2 weeks significantly improved depressive behavior and prevented the significant decrease in the number of neurons in the CA3 region of the hippocampus after depression caused by CUMS. Depression is associated with plasticity impairment at different degrees that eventually translates into a cognitive deficiency (36). The hippocampus plays an important role in cognition, a function that declines with CUMS-induced depression (37). It has been

reported that exposure to stress decreases the number of hippocampal neurons, reduces neurogenesis, and results in depression-like behavior (38). Recent evidence has indicated that depression is associated with structural and functional injury within specific brain regions (23). The present study focused on the CA3 region of the hippocampus, a critical brain region involved in depression. Studies have revealed that the number of neurons in the CA3 region of the hippocampus decreases in depression (39,40). Moreover, structural and functional alterations were also found within the CA3 in response to chronic stress in animal models (41). The present results indicated that CUMS exposure induced neuronal degeneration in the CA3 indicated by significant increases in the number of neuronal dead in this area. Based on the present findings, the combination of curcumin treatment with exercise prevented the death of nerve cells in rats under stress. This finding may be associated with improved neurogenesis in the CA3 region of the hippocampus due to curcumin and exercise. However, further study is required to determine the effects of curcumin on neurogenesis in the depression model. In confirmation of our findings, curcumin administration (42) and aerobic exercise (43) have been found to provide neuroprotective effects by reducing hippocampal neuron apoptosis (44). Therefore, the effects could lead to ameliorating cognitive deficits in CUMS-induced depression, as measured by behavioral assessment. There is a marked correlation between CUMS-induced depression and behavioral alteration. According to current results, CUMS-induced depression led to the poor performance of depressed rats in the behavioral tests including FST, OFT, and SPT. Interestingly, the behavioral results of the current study showed that curcumin treatment with exercise for 2 weeks increased the time spent in the center in the OFT, enhanced sucrose consumption, and decreased immobility time.

Traditionally, FST is defined as behavioral despair. This behavior has been implicated in the literature as an index of behavioral depression (45). FST has high predictive validity, and if a treatment could reduce immobility, FST could suggest its antidepressant effect (46). It has been documented that the second most important behavior for assessing the level of depression is the consumption of sucrose (47). This is consistent with the fact that the animals consuming more sucrose were those that showed lower levels of immobility (48). The lower levels of sucrose consumption and SPT in rats under stress have been interpreted as an anhedonia marker (47). Similarly, the results of this study showed that the consumption of sucrose decreased in all groups under stress compared to the control group. Still, curcumin and exercise either alone or in combination could not significantly alter the consumption of sucrose. In contrast, the stress + Cur group had a significant increment of sucrose consumption in comparison to the stress + Ex group.

In literature, the anxiety measures of OFT have been suggested to be sensitive to antidepressant treatment (45). In rodents, anxiety and behavioral habituation are often examined in terms of exploratory behavior, especially during exposure to an open field. This causes pronounced behavioral activity in a novel environment and reduced behavioral activity when they are familiar (49,50). Here, we observed that rats under CUMS receiving curcumin in combination with exercise showed increases in the time spent in the center.

The current study had several limitations. This research did not focus on changes in stress-induced markers in the rat hippocampus, which suggests that exercise improves the reduction of depression-induced disorders.

CONCLUSION

The present study showed that the administration of curcumin together with exercise could reduce the symptoms of depression. The observed results including the prevention of depressive-like behaviors along with the improvement of hippocampal cell viability emphasized the neuroprotective effects of curcumin and exercise in a stress-induced depression model. The findings showed that the use of curcumin with exercise could be considered a new treatment, especially for treatment-resistant depression.

Acknowledgements

This research was supported by the Department of Physiology of Kermanshah University of Medical Sciences (Grant No. 4000786).

Conflict of interest statement

All authors declared no conflict of interest in this study.

Authors' contributions

A. Pourmotabbed, M. Zeinivand, C. Jalili, M. Veisi, and S.E. Nedaei conducted the study, contributed to data collection, and data analysis; S.E. Nedaei contributed to data collection, data analysis, and manuscript preparation; F. Moradpour helped design the study and manuscript preparation; F. Zarei, Z. Salimi, E. Ahmadi, and N. Aghaz assisted with manuscript drafting and revision.

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