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Original Research Article

# Curcumin Increases BDNF and VEGF Levels in the Prefrontal Cortex but not in the Hippocampus in Adolescent Rats Undergoing Exhausting Swimming Exercise

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**ABSTRACT**

Physical exercise during adolescence affects brain functions for a long time, extending into adulthood. This study was aimed to examine the effect of curcumin supplementation on Brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) levels in the brain in adolescent rats subjected to weight-loaded forced swimming exercise. Female Sprague-Dawley rats at 6 weeks of age were randomly assigned to four groups: control, swimming exercised (SE), curcumin (CCM) and swimming exercised+curcumin (SE+CCM). After 1 week of adaptation training, SE and SE+CCM groups were given weight-loaded swimming exercise 5 days a week for 4 weeks. Curcumin was administered to rats in CCM SE+CCM groups via intragastric gavage at a dose of 50 mg/kg/d for 5 weeks. Prefrontal cortex and hippocampus BDNF and VEGF levels, and immunoreactivities were evaluated. BDNF levels of the SE group were significantly lower than the control and SE+CCM groups in the prefrontal cortex. VEGF levels of the SE group were significantly lower than the CCM and SE+CCM groups in the prefrontal cortex. VEGF values of the control group was increased compared to the SE and SE+CCM groups in the hippocampus. BDNF and VEGF immunoreactivities of the SE group were significantly lower than the control, CCM and SE+CCM groups. Our study show that curcumin supplementation reduces the inhibitory effect of exhaustive swimming exercise on the neurotrophic factors in the brain. The underlining mechanism of the effect of curcumin is related to BDNF and VEGF levels.



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## 1. Introduction

Physical exercise contributes markedly to physical and mental health and reduces the risk of cardiovascular and metabolic diseases. However, long-term and intense exercise can cause fatigue through different mechanisms such as depletion of energy resources, oxidative stress or changes in cytokine balance. Fatigue can cause changes that limit motor skill performance and lead to a decrease in physical and mental functions (Liu et al., 2017, Chang et al., 2013). In studies examining the effects of exhausting swimming exercise on the brain, rodent models were used with loads varying between 2-10% of the body and applied for variable periods of time. It has been found that exercise-induced fatigue may cause inflammation (Li et al., 2019) besides the damages such as apoptosis and impairment of synaptic plasticity in the hippocampus (Ding et al., 2015). It has also been shown that exhaustive swimming exercise may cause brain damage due to mitochondrial functions, neuroinflammation, apoptosis, and disruption of neurotransmitter balance and, accordingly, neurobehavioral impairment (Peng et al., 2021).

Although the cognitive effects of fatigue due to excessive exercise depend on multiple factors, changes in the levels of neurotransmitters and neurotrophic factors may be involved in the etiology (Kim et al., 2022). Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in processes such as neuroplasticity, learning and memory. Regular exercise mediates the positive effects of exercise on cognitive functions by increasing BDNF levels in the brain. BDNF levels decrease in processes such as neurodegenerative diseases and aging (Leger et al.2024, Bathina & Das, 2015). Additionally, high corticosterone reduces BDNF expression in the frontal cortex and hippocampus (HP). Forced exercise can cause stress, increasing corticosterone levels and causing a decrease in BDNF levels (Rostami, Haghparast, & Fayazmilani, 2021). Vascular endothelial growth factor (VEGF) is a cytokine that provides angiogenesis and also functions as a neurotrophic factor. VEGF facilitates neurogenesis in the brain and has a neuroprotective effect by inhibiting apoptosis. It also plays a role in the learning and memory process by contributing to synaptic plasticity. In cases of increased stress, VEGF expression, like BDNF, also decreases (Nowacka & Obuchowicz, 2012; Sun & Guo, 2005). In a study examining the effects of regular swimming exercise depending on the duration-intensity, a cerebral infarction rat model was used. The study showed that the moderate duration of swimming exercise, rather than short or long duration, can improve neurocognitive function by increasing hippocampal BNDF and VEGF levels (Song et al.2019). It has been shown that cognitive impairment seen in a rat model of vascular dementia can be ameliorated by increased BDNF expression levels in the cerebral cortex and hippocampus due to high-intensity interval training (Guo et al.2023). A similar study has found that aerobic exercise at different intensities may improve cognitive functions by increasing BDNF expression levels in the brain in an Alzheimer's disease-induced rat model, and high-intensity aerobic exercise was the most effective method (Lee et al., 2023).

Curcuma longa (turmeric) is a plant native to India and widely grown in Southeast Asia. Curcumin is the active component of turmeric. It is responsible for the plant's yellow color and many of turmeric's therapeutic effects. Curcumin has antioxidant, anti-inflammatory and anti-proliferative activities. It also has neuroprotectant and tumor-preventing effects (Assi et al., 2023; Yildiran, Macit, & Özata 2020; Wilken et al., 2011). Since BDNF is associated

with energy homeostasis, exercise and nutritional supplement use may have a positive effect on cognitive functions by regulating BDNF levels (Gomez-Pinilla & Gomez, 2011). Physical exercise performed during adolescence has positive effects on brain functions until adulthood. Changes in brain development continue throughout adolescence. Forced exercise during this period may cause stress, change the levels of neurotrophic factors, and brain development may be negatively affected (Rostami, Haghparast, & Fayazmilani, 2021). There are limited studies showing that curcumin, together with treadmill exercise, has a positive effect on cognitive functions and regulates BDNF levels in neurotoxicity models (Sokouti, Mohajeri, & Nourazar, 2022; Hosseinzadeh, Roshan, & Mahjoub, 2013). It has been shown that 8 weeks of curcumin administration in aged rats increased BDNF and VEGF levels in the brain (Cheriki, Habibian, & Moosavi, 2024). The effect of curcumin administration in combination with forced swimming exercise on BDNF and VEGF levels in the brain is unclear. This study was aimed to examine the effect of curcumin supplementation on BDNF and VEGF levels in the brain in adolescent rats subjected to weight-loaded forced swimming exercise.

## 2. Material and Method

*2.1. Animals*

This study was approved by the Ethics Committee of Dokuz Eylul University Faculty of Medicine (approval number: 39/2021). All experiments were performed in accordance with the rules provided by the Experimental Animals Laboratory. Rats were maintained on a 12-hour light/dark cycle under temperature- and humidity-controlled conditions. In the study of Cheriki et al. (2024) considering the effect of curcumin on BDNF and VEGF levels in the brain in rats, the sample size of animals in the groups was determined based on a power of 85% and a p value of 0.05 using the G* power program (3.1.9.4). Female Sprague-Dawley rats at 6 weeks of age were randomly assigned to four groups:

Group I: Control (C, n=7); sedentary group with no swimming exercise.

Group II: Swimming Exercised (SE, n=7); after 1 week of adaptation training, rats were given swimming exercise 5 days a week for 4 weeks.

Group III: Curcumin (CCM, n=8); rats were given curcumin 5 days a week for 5 weeks and did not exercise.

Group IV: Swimming Exercised and CCM group (SE+CCM n=8); rats were given swimming exercise and curcumin 5 days a week for 5 weeks.

Curcumin (C1386-10G, Sigma) was administered to rats in CCM group and SE+CCM group via intragastric gavage at a dose of 50 mg/kg/d for 5 weeks (Shirpoor et al.2021). Curcumin was dissolved in dimethyl sulfoxide (DMSO). Curcumin was applied to the rats in SE+CCM group one hour before exercise. An equal volume of DMSO was administered to the rats in the groups control and SE via intragastric gavage.

Adaptation training was applied to rats in groups SE and SE+CCM in the first week. Adaptation exercises consisting of 10-minute sessions of swimming without weights for 3 days, and treadmill application at a speed of 10 m/min for 2 days without incline. In the $2^{nd}$, $3^{rd}$ and $4^{th}$ weeks, the rats were subjected to 10-minute swimming exercises with a

load of 2%, 4% and 6% of their body weight, respectively (Petiz et al., 2017). In the last week, the rats were made to swim with an additional load of 10% of their body weight until they were exhausted.

The swimming exercise was performed in a cylindrical tank filled with water with a diameter of 30 cm. The water level in the tank was adjusted so that the rats could not jump out and had to swim (40 cm). The temperature of the water was kept at 25±2°C. Rats were monitored with the Noldus Ethovision XT video-tracking system during exercise. The total climbing and swimming behavior times until the rats were exhausted were recorded. It was accepted as exhaustion if the rats submerge into water due to fatigue and remained under water for 10 seconds (Shin et al. 2019). Control and CCM rats were kept in the exercise area without being placed in the water tank. All rats were sacrificed after the final exhaustive swimming exercise. Brain tissue samples were taken quickly (Fig.1. Experimental study design).

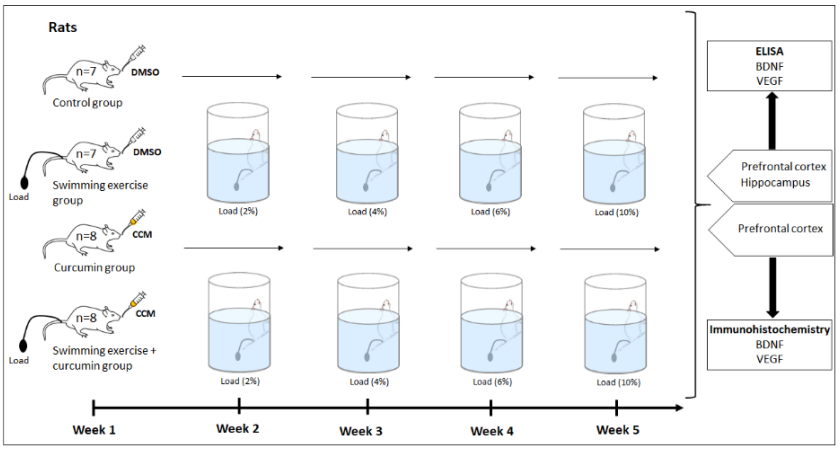


**Figure 1.** Experimental study design

*2.2. Biochemical Estimations*

After all rats were sacrificed under light ether anesthesia, brain tissues were taken. Half of the brain tissues of all rats were used for enzyme-linked immunosorbent assay (ELISA) measurements and the other part for light microscopic examination. Prefrontal cortex (PFC) and HP tissues, which are brain regions associated with cognitive functions, were dissected on a cold surface, and kept at -80°C until ELISA measurements were made.

Tissue BDNF and VEGF levels were determined using a plate reader (BioTek ELx800, Vermont, USA) according to the kit instructions (E0476Ra (BDNF), BT Lab, China and E0940Ra (VEGF), BT Lab, China, respectively). The test principle applied in the kits is Sandwich enzyme immunoassay. For the measurement of tissue protein levels, Pierce BCA Protein Assay Kit (23227, Thermo Scientific, Illinois, USA) was used. PFC and HP tissues were homogenized in buffer (1:9) and supernatant was obtained by centrifugation for 20 min at 5000xg at 4 ºC. To determine BDNF and VEGF levels, 40 µl sample was added to an antibody-coated 96-well plate and then 10 µl biotinylated antibody were added. Streptavidin-HRP of 50 µl was added into wells and kept at 37°C for 60 minutes. Then, chromogen A and B (50 µl each) were applied and incubated for 10 min at 37°C in the dark. The optical density was measured at 450 nm and the concentrations of BDNF and VEGF were calculated using standard curve regression method.

*2.3. Immunohistochemistry*

The brain tissues were kept in 10% formalin in phosphate buffer for 24 h. After the routine histological processions, paraffin blocks were prepared. 5 µm thick sections were taken from paraffin blocks using a microtome (Finesse ME+, Thermo Scientific). The coronal sections were obtained from the PFC corresponding approximately to plates 9 and 11, in the rat atlas of Paxinos and Watson. The sections were kept at 60°C overnight and then deparaffinized in xylene and rehydrated. Tissue endogenous peroxidase activity was inhibited by applying the hydrogen peroxide block for 10 minutes. The sections were then incubated with a protein block (IHC Detection Kit ab64259, Abcam, USA) for 10 minutes at room temperature. After overnight incubation of the primary antibody at 4°C (1:200, bs-4989R (BDNF) and bs-0279R (VEGF), Bioss Antibodies, USA), the sections were kept in biotin for 10 minutes. Negative controls were obtained by omitting the primary antibody. The secondary antibody was bound with streptavidin peroxidase. Then, the antibody-biotin-streptavidin peroxidase complex was visualized with Diaminobenzidine (DAB) chromogen. To counterstain the sections, Hematoxylin was used. Antibody reactivity levels were evaluated utilizing a light microscopic image analysis system comprising a microscope (Olympus CX-41) and a video camera (Olympus DP25), operated with CellSens Entry 1.7 software (Olympus, Pennsylvania, USA). Immunoreactivity for BDNF and VEGF was evaluated semi-quantitatively in three sections from each sample and graded from 0 to 4; 0; no obvious staining, 1; low, 2; moderate, 3; high and 4; severe staining (Uysal et al.2015). Immunohistochemical scoring was performed by a blinded investigator.

*2.4. Statistics*

The results were expressed as mean ± standard error of the mean (SEM). Statistics were performed utilizing SPSS 27.0 (IBM Inc., IL, USA). Group differences in normally distributed values were assessed using the one-way analysis of variance (ANOVA) followed by the post-hoc LSD test. The Kruskal-Wallis test was employed for non-normally distributed data. Significance values were adjusted for multiple comparisons with Bonferroni correction. Statistically significance was defined as $p<0.05$.

## 3. Results and Discussions

*3.1. Results*

The mean BDNF levels of all groups are shown in Fig. 2. When the BDNF levels of the groups were compared in the PFC, a significant difference was observed between groups ($F(3,26)=4.00$, $p=0.018$). There is a significant difference between the control and the SE rats ($p=0.015$). BDNF levels of the control are significantly higher than the SE rats. There is a significant difference between the SE and the SE+CCM rats ($p=0.006$). BDNF values of the SE rats were significantly decreased compared to the SE+CCM rats. There is no significant difference between groups in BDNF levels in the HP ($p>0.05$).

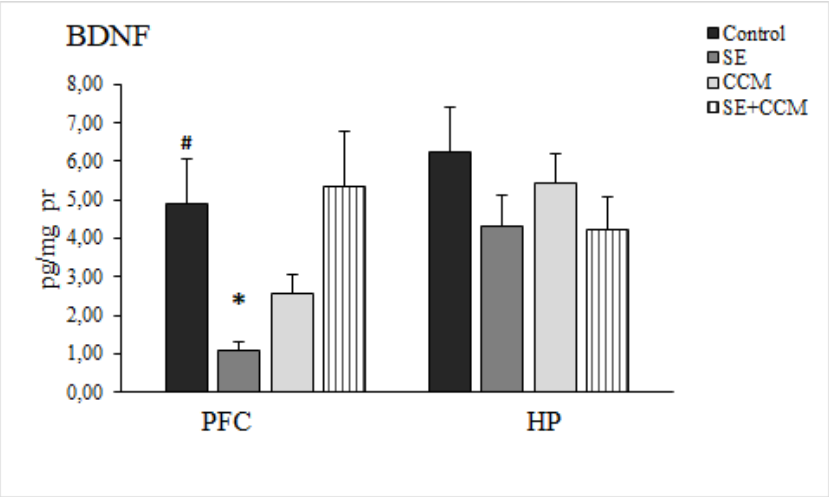


**Figure 2.** BDNF levels of rats. *Significantly different from SE+CCM group. #Significantly different from SE group.

The mean VEGF levels of all groups are shown in Fig. 3. When the VEGF levels of the groups were compared in the PFC, a significant difference was observed between groups ($F(3,26)=4.95$, $p=0.004$). There is a significant difference between the control and the SE rats ($p = 0.003$). VEGF levels of the control group are significantly higher than the SE group. There is a significant difference between the SE rats and the CCM and SE+CCM groups ($p=0.011$ and $p<0.001$, respectively). VEGF values of the SE rats were significantly lower than the CCM and SE+CCM rats. There is a significant difference between groups in VEGF levels in the HP ($F(3,26)=4.35$, $p=0.013$). VEGF levels of the control group are significantly higher than the SE and SE+CCM groups ($p=0.005$ and $p= 0.004$, respectively). There is no significant difference between VEGF levels of the SE and SE+CCM groups ($p>0.005$).

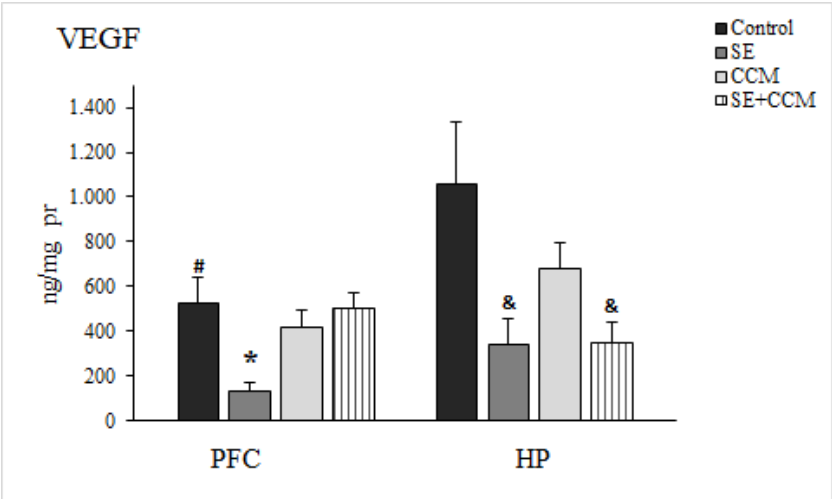


**Figure 3.** VEGF levels of rats. *Significantly different from CCM and SE+CCM group. #Significantly different from SE group. &Significantly different from control group.

Comparing the BDNF and VEGF immunoreactivity in the PFC region showed a significant difference between groups (Fig.4, $F(3,16)=3.90$, $p=0.029$ and $F(3,16)=4.63$, $p=0.016$, respectively). Significant difference was found between the SE rats and the control, CCM and SE+CCM groups ($p=0.008$, $p=0.019$ and $p=0.019$, respectively). BDNF immunoreactivity of the SE rats was significantly lower than the other groups. VEGF immunoreactivity of the SE group was significantly lower than the control, CCM and SE+CCM groups ($p=0.040$, $p=0.003$ and $p=0.016$,

respectively). Light microscopic images of BDNF and VEGF immunohistochemistry are presented in Fig.5 and Fig.6. In the SE group, the expression of BDNF and VEGF was observed to be decreased compared to other groups.

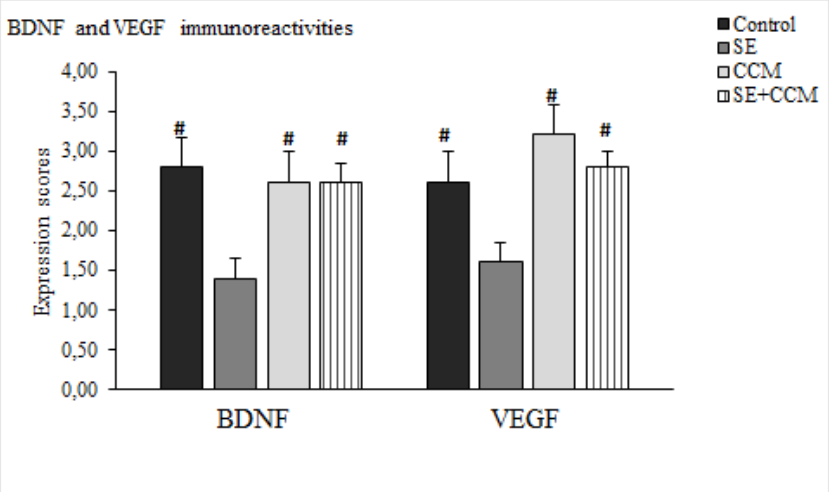


**Figure 4.** BDNF and VEGF immunoreactivities of rats. #Significantly different from SE group.

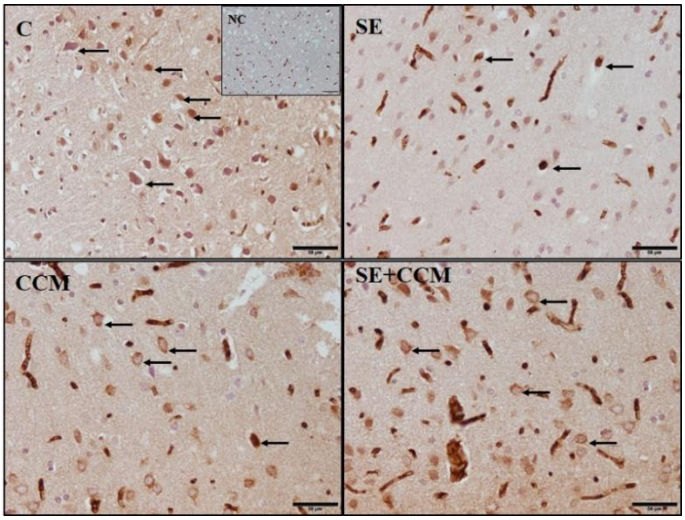


**Figure 5.** Immunostaining of rat brains with BDNF antibody. Black arrows: immunopositive cells (inset: NC; negative control). C: Control, SE: Swimming Exercised, CCM: Curcumin, SE+CCM: Swimming Exercised + Curcumin.

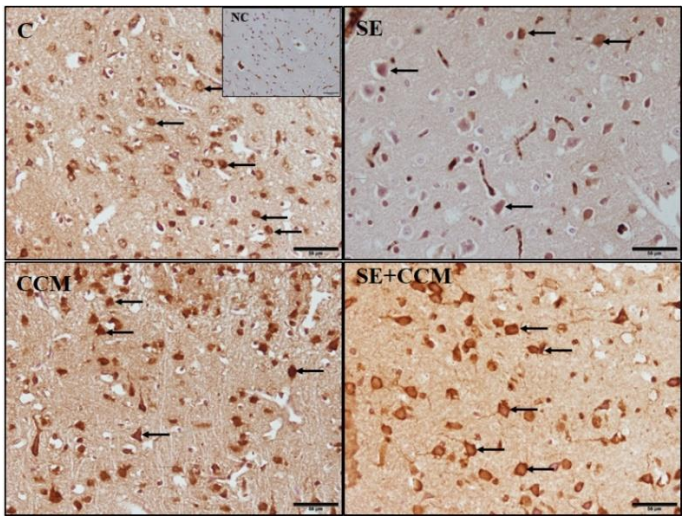


**Figure 6.** Immunostaining of rat brains with VEGF antibody. Black arrows: immunopositive cells (inset: NC; negative control). C: Control, SE: Swimming Exercised, CCM: Curcumin, SE+CCM: Swimming Exercised + Curcumin.

### *3.2. Discussion*

In this study, we examined the effects of curcumin on adolescent rat brain BDNF and VEGF levels that underwent exhaustive swimming exercise. The results of the study show that weight-loaded forced swimming exercise reduces BDNF and VEGF levels in the PFC and VEGF levels in the HP. Results showed that curcumin with exhaustive exercise significantly increased PFC BDNF and VEGF levels and no increased in HP. Previous studies have shown that curcumin has a neuroprotective effect and protects cognitive functions, but there is not any information about its modulating actions on exhaustive exercise-dependent change in BDNF and VEGF levels.

In our study, neurotrophic factor BDNF in the PFC, but not in the HP, were found to be significantly lower in the SE group than in the other groups. Lou et al. showed that there is a change in BDNF expression depending on exercise intensity. It has been shown that after 1 week of treadmill exercise in juvenile rats, BDNF expression in the HP increased in the low intensity exercise group and decreased in the high intensity exercise group (Lou et al., 2008). BDNF levels in the brain decrease in situations that cause stress, such as exhaustive forced exercise. It has been reported that BDNF immunoexpression was reduced in the PFC and dentate gyrus in rats developed as a depression model (Algaidi et al., 2019). Serum BDNF levels in trained men who exercise regularly were found to be significantly lower than in sedentary subjects (Nofuji et al., 2008). According to our study, exhaustive exercise-induced decrease in BDNF levels can be rescued by curcumin. In ovariectomized adult rats, curcumin supplementation has been shown to increase BDNF expression in the limbic system (Abd-Rabo et al., 2019). Curcumin supplementation along with treadmill exercise or swimming exercise improved BDNF levels in the HP in rats with neurotoxicity (Feizolahi et al., 2019; Dabidi et al., 2013). In our study, the results suggest that curcumin combined with exercise may have a neuroprotective effect on the PFC tissue by increasing the neurotrophic protein BDNF. Failure to change BDNF protein levels in HP with curcumin treatment may be related to treatment duration or dose.

VEGF is among the growth factors and is a regulator in many signaling pathways such as angiogenesis and neurogenesis. In our study, VEGF levels were significantly lower in the PFC and the HP of rats subjected to exhaustive swimming exercise compared to the control group. VEGF levels have contradictory results in studies involving exercise. It has been shown that 8 weeks of treadmill exercise in ovariectomized female rats increases VEGF expression in the brain (Yoon et al., 2023). Zadeh et al. (2023) showed that while BDNF levels were not affected in the HP of rats that underwent treadmill exercise for two weeks, VEGF levels increased. On the other hand, it was observed that VEGF levels in the HP did not change in adult rats that underwent swimming exercise for 4 weeks (Jiang et al., 2014). Our data demonstrated that curcumin with exercise increased VEGF levels in the PFC, but not in the HP. Previous studies have reported the antidepressant effect of curcumin and its relationship with BDNF, but the relationship of curcumin administration with exhaustive exercise to VEGF is unclear (Abd-Rabo et al., 2019). Krupa et al. showed that nanocurcumin treatment did not have a significant effect on VEGF expression in rats with spinal cord injury (Krupa et al., 2019). It has been shown that two-week curcumin treatment in mice modeled with vascular dementia increases VEGF expression in the cerebral cortex (Zhang et al., 2021).

## 4. Conclusions

We showed that curcumin supplementation reduces the inhibitory effect of exhaustive swimming exercise on the neurotrophic factors in the prefrontal cortex and hippocampus regions in this study. The mechanism underlying the effect of curcumin in this study can be explained, at least partially, regarding the levels of BDNF and VEGF. Further studies will be revealing to demonstrate the effects of curcumin supplementation combined with exercise during adolescence.

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## Declaration of Competing Interest and Ethics

The authors declare no conflict of interest. This research study complies with research publishing ethics. The scientific and legal responsibility for manuscripts published in OPS Journal belongs to the authors.

## References

Abd-Rabo, M. M., Georgy, G. S., Saied, N. M., & Hassan, W. A. (2019). Involvement of the serotonergic system and neuroplasticity in the antidepressant effect of curcumin in ovariectomized rats: Comparison with oestradiol and fluoxetine. *Phytotherapy Research*, *33*(2), 387–396. https://doi.org/10.1002/ptr.6232

Algaidi, S. A., Eldomiaty, M. A., Elbastwisy, Y. M., Almasry, S. M., Desouky, M. K., & Elnaggar, A. M. (2019). Effect of voluntary running on expression of myokines in brains of rats with depression. *International Journal of Immunopathology and Pharmacology*, *33*,2058738419833533. https://doi.org/10.1177/2058738419833533

Assi, A. A., Farrag, M. M. Y., Badary, D. M., Allam, E. A. H., & Nicola, M. A. (2023). Protective effects of curcumin and Ginkgo biloba extract combination on a new model of Alzheimer's disease. *Inflammopharmacology*, *31*(3), 1449-1464. https://doi.org/10.1007/s10787-023-01164-6

Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of Medical Science*, *11*(6), 1164-1178. https://doi.org/10.5114/aoms.2015.56342

Chang, Q., Miao, X., Ju, X., Zhu, L., Huang, C., Huang, T., Zuo, X., & Gao, C. (2013). Effects of pulse current on endurance exercise and its anti-fatigue properties in the hepatic tissue of trained rats. *PloS ONE*, *8*(10), e75093. https://doi.org/10.1371/journal.pone.0075093

Cheriki, M., Habibian, M., & Moosavi, S. J. (2024). Curcumin attenuates brain aging by reducing apoptosis and oxidative stress. *Metabolic Brain Disease*, https://doi.org/10.1007/s11011-023-01326-z

Dabidi, R. V., Hosseinzadeh, S., Mahjoub, S., Hosseinzadeh, M., & Myers, J. (2013). Endurance exercise training and diferuloyl methane supplement: changes in neurotrophic factor and oxidative stress induced by lead in rat brain. *Biology of Sport*, *30*(1), 41-46. https://doi.org/10.5604/20831862.1029820

Ding, Y., Xie, L., Chang, C. Q., Chen, Z. M., & Ai, H. (2015). Activation of γ-aminobutyric Acid (A) Receptor Protects Hippocampus from Intense Exercise-induced Synapses Damage and Apoptosis in Rats. *Chinese Medical Journal*, *128*(17), 2330-2339. https://doi.org/10.4103/0366-6999.163392

Feizolahi, F., Azarbayjani, M. A., Nasehi, M., Peeri, M., & Zarrindast, M. R. (2019). The combination of swimming and curcumin consumption may improve spatial memory recovery after binge ethanol drinking. *Physiology & Behavior*, *207*, 139–150. https://doi.org/10.1016/j.physbeh.2019.03.018

Gomez-Pinilla, F., & Gomez, A. G. (2011). The influence of dietary factors in central nervous system plasticity and injury recovery. *PM&R*, *3*, S111–S116. https://doi.org/10.1016/j.pmrj.2011.03.001

Guo, C., Yao, Y., Ma, C., Wang, Z. (2023). High-intensity interval training improves cognitive impairment of vascular dementia rats by up-regulating expression of brain-derived neurotrophic factor in the hippocampus. *NeuroReport., 34(8)*, 411-418. https://doi.org/10.1097/WNR.0000000000001903

Hosseinzadeh, S., Roshan, V. D., & Mahjoub, S. (2013). Continuous exercise training and curcumin attenuate changes in brain-derived neurotrophic factor and oxidative stress induced by lead acetate in the hippocampus of male rats. *Pharmaceutical Biology*, *51*(2), 240–245. https://doi.org/10.3109/13880209.2012.717230

Jiang, P., Dang, R. L., Li, H. D., Zhang, L. H., Zhu, W. Y., Xue, Y., & Tang, M. M. (2014). The impacts of swimming exercise on hippocampal expression of neurotrophic factors in rats exposed to chronic unpredictable mild stress. *Evidence-Based Complementary and Alternative Medicine*, Article ID 729827. https://doi.org/10.1155/2014/729827

Kim, M. J., Zhang, T., Kim, K. N., Bae, G. W., Yoon, S. M., Yue, Y., Wu, X., & Park, S. (2022). Alleviation of cognitive and physical fatigue with enzymatic porcine placenta hydrolysate intake through reducing oxidative stress and inflammation in intensely exercised rats. *Biology*, *11*(12), 1739. https://doi.org/10.3390/biology11121739

Krupa, P., Svobodova, B., Dubisova, J., Kubinova, S., Jendelova, P., & Machova Urdzikova, L. (2019). Nano-formulated curcumin (Lipodisq™) modulates the local inflammatory response, reduces glial scar and preserves the white matter after spinal cord injury in rats. *Neuropharmacology*, *155*, 54–64. https://doi.org/10.1016/j.neuropharm.2019.05.018

Lee, D. Y., Im, S. C., Kang, N. Y., & Kim, K. (2023). Analysis of effect of intensity of aerobic exercise on cognitive and motor functions and neurotrophic factor expression patterns in an Alzheimer's disease rat model. *Journal of Personalized Medicine*, *13*(11), 1622. https://doi.org/10.3390/jpm13111622

Leger, C., Quirié, A., Méloux, A., Fontanier, E., Chaney, R., Basset, C., Lemaire, S., Garnier, P., & Prigent-Tessier, A. (2024). Impact of exercise intensity on cerebral BDNF levels: Role of FNDC5/Irisin. *International Journal of Molecular Sciences*, *25*(2), 1213. https://doi.org/10.3390/ijms25021213

Li, T. G., Shui, L., Ge, D. Y., Pu, R., Bai, S. M., Lu, J., & Chen, Y. S. (2019). Moxibustion reduces inflammatory response in the hippocampus of a chronic exercise-induced fatigue rat. *Frontiers in Integrative Neuroscience*, *13*, 48. https://doi.org/10.3389/fnint.2019.00048

Liu, L., Wu, X., Zhang, B., Yang, W., Li, D., Dong, Y., Yin, Y., & Chen, Q. (2017). Protective effects of tea polyphenols on exhaustive exercise-induced fatigue, inflammation and tissue damage. *Food & Nutrition Research*, *61*(1), 1333390. https://doi.org/10.1080/16546628.2017.1333390

Lou, S. J., Liu, J. Y., Chang, H., & Chen, P. J. (2008). Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. *Brain Research*, *1210*, 48-55. https://doi.org/10.1016/j.brainres.2008.02.080

Nofuji, Y., Suwa, M., Moriyama, Y., Nakano, H., Ichimiya, A., Nishichi, R., Sasaki, H., Radak, Z., & Kumagai, S. (2008). Decreased serum brain-derived neurotrophic factor in trained men. *Neuroscience Letters*, *437*(1), 29-32. https://doi.org/10.1016/j.neulet.2008.03.057

Nowacka, M. M., & Obuchowicz, E. (2012). Vascular endothelial growth factor (VEGF) and its role in the central nervous system: a new element in the neurotrophic hypothesis of antidepressant drug action. *Neuropeptides*, *46*(1), 1–10. https://doi.org/10.1016/j.npep.2011.05.005

Peng, G., Zheng, H., Wu, C., Wu, C., Ma, X., Xiong, J., Hou, J., Zhang, L., Yang, L., & Pan, H. (2021). Intranasal administration of DHED protects against exhaustive exercise-induced brain injury in rats. *Brain Research*, *1772*, 147665. https://doi.org/10.1016/j.brainres.2021.147665

Petiz, L. L., Girardi, C. S., Bortolin, R. C., Kunzler, A., Gasparotto, J., Rabelo, T. K., Matté, C., Moreira, J. C., & Gelain, D. P. (2017). Vitamin a oral supplementation induces oxidative stress and suppresses IL-10 and HSP70 in skeletal muscle of trained rats. *Nutrients*, *9*(4), 353. https://doi.org/10.3390/nu9040353

Rostami, S., Haghparast, A., & Fayazmilani, R. (2021). The downstream effects of forced exercise training and voluntary physical activity in an enriched environment on hippocampal plasticity in preadolescent rats. *Brain Research*, *1759*, 147373. https://doi.org/10.1016/j.brainres.2021.147373

Shin, I. S., Kim, D. H., Jang, E. Y., Kim, H. Y., & Yoo, H. S. (2019). Anti-fatigue properties of cultivated wild ginseng distilled extract and its active component panaxydol in rats. *Journal of Pharmacopuncture*, *22*(2), 68-74. https://doi.org/10.3831/KPI.2019.22.008

Shirpoor, M., Tofighi, A., Shirpoor, A., Pourjabali, M., & Chodari, L. (2021). Effect of moderate exercises and curcumin on hepatic transcriptional factors associated with lipid metabolism and steatosis in elderly male rat. *Research in Pharmaceutical Sciences*, *16*(3), 294–304. https://doi.org/10.4103/1735-5362.314828

Sokouti, H., Mohajeri, D., & Nourazar, M. A. (2022). 6-Hydroxydopamine-induced neurotoxicity in rat model of Parkinson's disease: Is reversed via anti-oxidative activities of curcumin and aerobic exercise therapy. *Physiological Research*, *71*(4), 551–560. https://doi.org/10.33549/physiolres.934929

Song, M. K., Kim, E. J., Kim, J. K., Park, H. K., & Lee, S. G. (2019). Effect of regular swimming exercise to duration-intensity on neurocognitive function in cerebral infarction rat model. *Neurological Research, 41*(1), 37-44. https://doi.org/10.1080/01616412.2018.1524087

Sun, F. Y., & Guo, X. (2005). Molecular and cellular mechanisms of neuroprotection by vascular endothelial growth factor. *Journal of Neuroscience Research*, *79*(1-2), 180–184. https://doi.org/10.1002/jnr.20321

Uysal, N., Kiray, M., Sisman, A. R., Camsari, U. M., Gencoglu, C., Baykara, B., Cetinkaya, C., & Aksu, I. (2015). Effects of voluntary and involuntary exercise on cognitive functions, and VEGF and BDNF levels in adolescent rats. *Biotechnic & Histochemistry*, *90*(1), 55–68. https://doi.org/10.3109/10520295.2014.946968

Wilken, R., Veena, M. S., Wang, M. B., & Srivatsan, E. S. (2011). Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. *Molecular Cancer*, *10*, 12. https://doi.org/10.1186/1476-4598-10-12

Yildiran, H., Macit, M. S., & Özata Uyar, G. (2020). New approach to peripheral nerve injury: Nutritional therapy. *Nutritional Neuroscience, 23*(10), 744-755. https://doi.org/10.1080/1028415X.2018.1554322

Yoon, E. J., Jeong, J., Yoon, E., & Park, D. (2023). The effects of treadmill exercise on brain angiogenesis in ovariectomized rats. *Physiological Reports*, *11*(21), 1-9. https://doi.org/10.14814/phy2.15864

Zadeh, H. J., Roholamini, Z., Aminizadeh, S., & Deh-Ahmadi, M. A. (2023). Endurance training and MitoQ supplementation improve spatial memory, VEGF expression, and neurogenic factors in hippocampal tissue of rats. *Journal of Clinical and Translational Research*, *9*(1), 1–7. http://dx.doi.org/10.18053/jctres.09.202301.001

Zhang, R., Zhao, T., Zheng, B., Zhang, Y., Li, X., Zhang, F., Cen, J., & Duan, S. (2021). Curcumin derivative Cur20 attenuated cerebral ischemic injury by antioxidant effect and HIF-1α/VEGF/TFEB-activated angiogenesis. *Frontiers in Pharmacology*, *12*, 648107. https://doi.org/10.3389/fphar.2021.648107