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ORIGINAL ARTICLE

Curcumin attenuates brain aging by reducing apoptosis and oxidative stress

Mehran Cheriki[1] · **Masoumeh Habibian**[1] · **Seyyed Jafar Moosavi**[1]

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Abstract

Brain aging is a physiological event, and oxidative stress and apoptosis are involved in the natural aging process of the brain. Curcumin is a natural antioxidant with potent anti-aging and neuroprotective properties. Therefore, we investigated the protective effects of curcumin on brain apoptosis and oxidative stress, brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF) in aged rats. Old female Wistar rats were randomly divided into three groups (n = 7); as follows: (1) control; (2); saline and (3) curcumin (received 30 mg/kg of curcumin, 5 days/week for 8 weeks, intraperitoneally). Our results indicated that treatment with curcumin in aged rats attenuates brain lipid peroxidation, which was accompanied by a significant increase in the BDNF, VEGF, superoxide dismutase (SOD) activity, and anti-apoptotic protein BCl-2. No significant change in brain anti-apoptotic Bax protein levels was observed after curcumin treatment. The study indicates that curcumin could alleviate brain aging which may be due to attenuating oxidative stress, inhibiting apoptosis, and up-regulating SOD activity, which in turn enhances VEGF and BDNF. Therefore, curcumin has potential therapeutic value in the treatment of neurological apoptosis, neurogenesis, and angiogenesis changes caused by brain aging.

Highlights

- Brain aging plays a key role in the development of neurodegenerative diseases.
- Oxidative stress is considered one of the main mechanisms of cellular aging.
- Brain tissue has relatively low levels of antioxidant enzymes and is more vulnerable to oxidative stress.
- During the aging process, apoptosis and susceptibility to apoptosis enhance in several types of intact cells.
- Age-related decline in vascular structural integrity and neovascularization capacity occurs throughout the aged brain.
- Curcumin, exerts its neuroprotective and anti-aging effects in the aged brain.

Keywords Aged rats · Brain-derived neurotrophic factor · Vascular endothelial growth factor · Superoxide dismutase

Abbreviations

BDNF	Brain-derived neurotrophic factor
Bax	BCL-2 associated x protein
Bcl-2	B cell leukemia/lymphoma 2
DNA	Deoxyribonucleic acid
H2O2	Hydrogen Peroxide
Flk-1	Fetal liver kinase-1
i.p.	Intraperitoneal
NRF2	*NF-E2 p45-related factor 2*
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
VEGF	Vascular endothelial growth factor
TGF-β1	Transforming growth factor β1

✉ Masoumeh Habibian
masoumeh.Habibian@iau.ac.ir

Mehran Cheriki
m.hab@qaemiau.ac.ir

Seyyed Jafar Moosavi
Seyyed.Moosavi@iau.ac.ir

[1] Department of Physical Education and Sports Sciences, Qaemshahar Branch, Islamic Azad University, Qaemshahar, Iran

TrkB Tropomyosin receptor kinase B

Introduction

Aging is a multifactorial and natural process that is associated with many physiological changes, functional disorders, and behavioral capacity. Brain aging is considered an important aspect of the aging process because it plays a key role in the development of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (Wu et al. 2014). Aging induces several physiological phenomena in the brain such as a reduction of the number of cerebral nerve cells, deterioration of tissue proteins, tissue atrophy, a slight decrease in the brain size, and reduction of cerebral blood flow (Park and Yeo 2013). Several pathways cause brain aging, but the exact responsible molecular mechanisms are still unknown.

It has been widely found that aging affects both angiogenesis and vascularization (Pineda et al. 2013). Moreover, cerebral neurogenesis decreases with aging, causing a progressive cognitive decline (Gao et al. 2009). Vascular endothelial growth factor (VEGF) exerts both neurogenic and angiogenic functions (Greenberg and Jin 2005). Studies indicate that VEGF-positive cells and microvessel density are decreased in the different brain regions of old rats, and exogenous VEGF may lead to an increase in vascular formation as well as a delay in the aging of the nervous system (Wang et al. 2014). Age-related decline in vascular structural integrity and neovascularization capacity occurs throughout the aged brain, and decreased responsiveness to VEGF is one of the involved mechanisms, possibly due to decreased expression levels of VEGF itself (Watanabe et al. 2020). Oxidative stress is considered one of the main mechanisms of cellular aging. Due to the high concentration of polyunsaturated fatty acids and transition metals in brain tissue, it is very susceptible to oxidative damage (Ionescu-Tucker and Cotman 2021). Reactive oxygen species (ROS) are metabolic byproducts that levels of these oxidative stressors increase gradually with aging, and can lead to irreversible damage to the cytoskeleton and the microtubular network, impairing mitochondrial function and damaging the central nervous system (Molinari et al. 2020; Sechi al. 2015). Additionally, increasing cellular senescence and oxidative stress can cause inflammation, cell membrane damage, and consequently neuronal death (Toricelli et al. 2021). Age-related oxidative brain impairment occurs due to lipid peroxidation products, protein oxidation, and alterations in nuclear and mitochondrial DNA (Castelli et al. 2019). Brain tissue has relatively low levels of antioxidant enzymes and is more vulnerable to ROS compared with other organs (Lee et al. 2020a). The imbalance between pro-oxidant species and antioxidant systems leads to the accumulation of neurotoxic proteins in the brain (Balendra and Singh 2021). Superoxide dismutase (SOD) is an enzymatic endogenous antioxidant, which is made by the body and catalyzes the dismutation of superoxide radicals into hydrogen peroxide (H2O2) and ordinary molecular oxygen (Lee et al. 2020a). It has been reported that SOD deficiency is involved in several neurological diseases such as Alzheimer's disease, Parkinson's disease, and stroke (Zhang et al. 2022) and SOD expression exerts an essential role in maintaining cellular redox balance and brain function during aging (Watanabe et al. 2014). Studies have found that normal brain aging was associated with a decreased tendency of SOD in the brain, and the level of lipid peroxidation in the brain was significantly higher in older than that in young rats. The age-related increase in brain lipid peroxidation suggests a role of ROS in the pathogenesis of aging (Haider et al. 2014).

During the aging process, apoptosis and susceptibility to apoptosis are enhanced in several types of intact cells (Higami and Shimokawa 2000). Apoptosis is programmed cell death that in two major regulatory intrinsic and extrinsic pathways induces neuronal death (Toricelli et al. 2021). The B cell leukemia/lymphoma 2(Bcl-2) family can regulate cell death in the central nervous system, and is related to the apoptotic intrinsic pathway (Andreotti et al. 2020). The anti-apoptotic protein Bcl-2 and pro-apoptotic Bcl2 associated X protein (Bax) belong to the Bcl-2 family, which have two distinct functional roles in cell death (Toricelli et al. 2021; Andreotti et al. 2020). The loss of neuronal and glial cell populations is closely associated with dysfunction of the central nervous system (Toricelli et al. 2021) and motor neuron disability in neurodegenerative diseases (Lin and Beal 2006). Apoptosis is traditionally considered an index of brain injury and contributes to various pathological conditions resulting in aging (Wu et al. 2014).

Brain-derived neurotrophic factor (BDNF) is the most important neurotrophin in the brain that performs a neurotrophic function. BDNF exerts its biological actions through tyrosine receptor kinase B and plays a key role in regulating neuronal development, maintenance, survival, and plasticity throughout life (Wu et al. 2014; Waterhouse and Xu 2009). This neurotrophin influences the process of neurogenesis and participates in both structural and functional neuroplasticity (Toricelli et al. 2021). Also, BDNF possesses other neuroprotective effects including anti-apoptosis, anti-oxidation, and suppression of autophagy (Chen et al. 2017). In the brain, BDNF is mainly synthesized in different types of cells and has a crucial role in learning and memory mechanisms (Molinari et al. 2020). Studies have shown that BDNF decreases with normal brain aging and multiple brain disorders, indicating that a disorder of regulation of BDNF signaling is involved BDNF plays a crucial role in

mental illness and neurodegenerative diseases including Alzheimer's disease (Molinari et al. 2020; Hock et al. 2000; Oh et al. 2016). Thus, drugs targeting BDNF signaling may be an effective neuroprotective agent for brain aging as well as neurodegenerative disorders.

It has already been demonstrated in the literature that curcumin, a lipophilic polyphenol compound derived from the rhizome of the plant *Curcuma longa* can enhance neuroprotection and is one of the most promising anti-aging natural compounds (Vaiserman et al. 2020; Benameur et al. 2021). A previous study has shown that curcumin exerts its neuroprotective and anti-aging effects in aged rat brain regions (Bala et al. 2006) and can cross the blood–brain barrier (Mythri and Bharath 2012). Curcumin has many pharmacological activities, including anti-inflammatory, anti-oxidant, anti-proliferative, and nontoxic (Benameur et al. 2021). Moreover, it has been shown that curcumin, may attenuate D galactose-induced brain aging via regulation of antioxidant enzymes and apoptosis (Lee et al. 2020b). However, the ability of curcumin to improve normal brain aging by mediator factors in angiogenesis and neurogenesis has not been elucidated.

While life expectancy is increasing nowadays, aging is associated with a gradual decline of systemic functioning, especially brain aging is very common among neurodegenerative disorders and dementia (Kandlur et al. 2020). It seems important to increase the focus on understanding the effective mechanisms of compounds with anti-aging properties on brain aging. Therefore, the present study aimed to investigate the protective effect of curcumin on brain apoptosis and oxidative stress, BDNF, and VEGF in aged rats.

Materials and methods

Solvents and drugs

Curcumin, all chemicals, and reagents for biochemical assays were purchased from Sigma Aldrich (USA). Superoxide dismutase (SOD) and TBARS (thiobarbituric acid reactive substances) test kits were purchased from Cayman Chemical Company (Ann Arbor, MI, USA). Assay kits for the measurements of BDNF, VEGF, BCl-2, and Bax were obtained from Cusabio Biotech Co., Ltd., (Wuhan, China).

Animals and administration

Twenty-one healthy female Wistar rats that were 24 months old (body weight: 250–300 g) were purchased from the animal experiment center of Pasteur Institute of Iran and were kept on a 12-hour light-dark cycle at a constant temperature (22 ± 2 °C) and 50% humidity with food and water ad libitum.

After one week of adaptation, the rats were randomly and equally assigned to three groups: (1) the control group received no treatment; (2) the saline group: rats received an intraperitoneal injection (i.p.) of saline (0.9% NaCl) diluted dimethyl sulfoxide (DMSO) and (3) the Curcumin group: rats received 30 mg/kg curcumin (i.p.) dissolved in DMSO for five days per week over eight weeks (Habibian et al. 2016; Ahmadabady et al. 2021). All the animal experimental protocols were approved by the Institutional Animal Ethics Committee of Qaemshahar Branch, Islamic Azad University (IAU. 11,768) and were performed according to the guidelines set out in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. $85-23$, revised 1985).

Preparation for brain samples

The rats were sacrificed after being anesthetized with a mixture of ketamine (60 mg/kg) and xylazine (5 mg/kg). The brains of the rats were carefully and quickly removed. Samples were homogenized in 0.05 M Tris-HCl buffer with protease inhibitors and then centrifuged at 4000 g for 10 min. The supernatant was conserved at -80 °C for subsequent experiments.

Biochemical analysis

TBARS, as a marker of lipid peroxidation index, in the brain was measured using a colorimetric assay by thiobarbituric acid (TBA) reagent. Briefly, brain homogenates were incubated with equal volumes of TBA at 90 °C for 10 min. Finally, the mixture was cooled and quantification of the TBARS was determined at 532 nm by comparing the absorption to the standard curve of MDA equivalents generated by acid-catalyzed hydrolysis of 1,1,3,3-tetramethoxypropane and is expressed as nmol/mg protein (El-Sayed et al. 2022).

The activity of SOD was assessed spectrophotometrically through measuring its ability to inhibit the photochemical reduction of nitrobluetetrazolium (NBT) according to the method described by Sun et al. (1988). Enzyme activity is expressed as unit /mg protein, and one unit SOD is defined as the amount of enzyme required to inhibit the reduction of NBT by 50%.

Statistical analyses

Data were expressed as mean ± standard deviation and analyzed by one-way analysis of variance (ANOVA) followed by the Tukey test post hoc test for multiple comparisons

Table 1 Influence of curcumin treatment on BCl-2 and Bax levels in the brains of aged rats

Indices	Control	Saline	curcumin
BCl-2 (ng/mg protein)	20.36 ± 2.09	20.00 ± 1.98	24.96 ± 3.04[b]
Bax(ng/mg protein)	10.09 ± 1.67	10.06 ± 1.92	8.08 ± 1.40
Bax/Bcl-2 ratio	0.49 ± 0.03	0.50 ± 0.05	0.32 ± 0.02[a]

Data are presented as means ± standard deviations. [a] $P < 0.001$ versus control and saline; [b] $P < 0.05$ versus control and saline

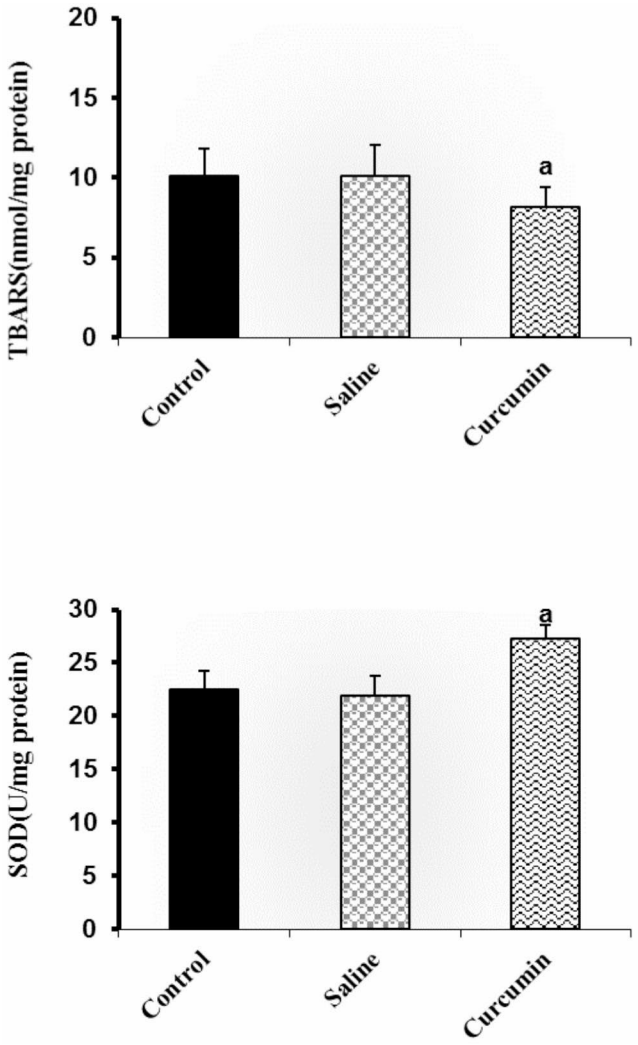

Fig. 1 Impact of Curcumin treatments on the levels of TBARS and SOD activity in the brain tissue of aged rats. Data are presented as means ± standard deviations. [a] $P < 0.001$ versus control and saline

among the groups. Data were analyzed using SPSS software v. 20.0. (IBM, Armonk, NY, USA), and differences were taken to be statistically significant at $P < 0.05$.

Results

Impact on pro and anti-apoptosis factors

As shown in Table 1, curcumin treatment up-regulated the level of anti-apoptotic protein Bcl-2 and reduced the Bax/Bcl-2 ratio in the brains of aged rats, as compared to the control (22.59%, $P = 0.022$; 34.69%, $P < 0.001$, respectively) and saline (24.80%, $P = 0.012$; 36.00%, $P < 0.001$, respectively) groups, but had no significant effect on Bax protein.

Impact on lipid peroxidation and SOD activity

Chronic treatment of the curcumin resulted in a significant attenuation in the lipid peroxidation as evidenced by the decreased level of TBARS compared with the control (19.16%, $P < 0.001$) and saline (19.40%, $P < 0.001$) groups, whereas; brain SOD activity significantly elevated in the curcumin group compared to the control 20.91%, $P < 0.001$) and saline (24.84%, $P < 0.001$) groups (Fig. 1).

Impact on BDNF and VEGF levels

Furthermore, eight weeks of curcumin intervention significantly increased the levels of BDNF and VEGF proteins compared with the respective values in the control (31.70%, $P < 0.001$; 25.13%, $P < 0.001$, respectively), saline (29.22%, $P < 0.001$; 12.34%, $P < 0.001$, respectively) groups (Fig. 2).

Discussion

The complex structural and molecular processes contribute to brain aging that leads to a balance between protective and degenerative factors. This study examined the neuroprotective effects of curcumin in aged rats, and our results indicated that curcumin administration significantly decreased lipid peroxidation and improved SOD activity in the brain tissue of aged rats, suggesting that curcumin can alleviate oxidative damage in cellular senescence by enhancing the antioxidant capacity in the aging brain process (Habibian et al. 2016; Banji et al. 2014). Oxidative stress is known as one of the most important processes of the aging brain. The brain is an aerobic organ with the highest oxygen consumption rates based on weight and is more susceptible to free radical damage (Haider et al. 2014). Previous studies have

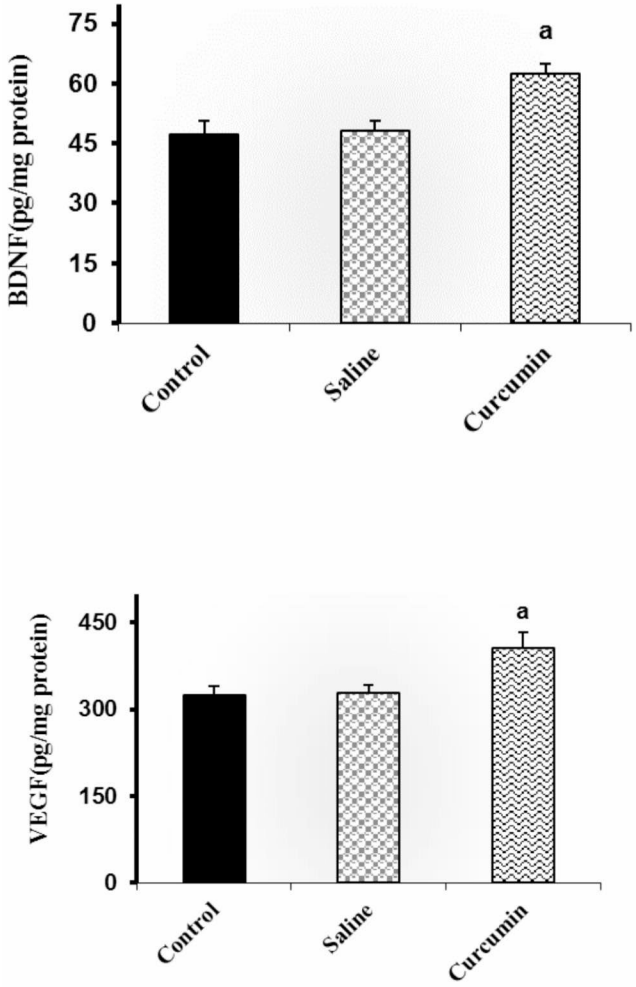

Fig. 2 Impact of Curcumin treatments on the levels of BDNF and VEGF in the brain tissue of aged rats. Data are presented as means ± standard deviations. [a] $P < 0.001$ versus control and saline

shown an elevation in the level of lipid peroxidation in the hippocampus, midbrain, cortex, and cerebellum in rat brains with a reduction in the SOD activity during aging (Samarghandian et al. 2015), and the presence of oxidative stress in aged cells (Kandlur et al. 2020). Curcumin can attenuate brain tissue damage induced by oxidative stress by activating the antioxidant enzymes such as SOD (Habibian et al. 2016; Namgyal et al. 2021). Another study was showed that intraperitoneal administration of curcumin significantly attenuated restraint stress-induced oxidative damage and increased antioxidant defense mechanisms in the rat brain (Samarghandian et al. 2017). Curcumin is one of the potent antioxidants with powerful hydrogen-donating antioxidant activity and triggers the NF-E2 p45-related factor 2(Nrf2) pathway which has a pivotal role in activating antioxidative enzymes. Curcumin is a bioactive polyphenol with anti-aging properties that attenuates age-related cellular damage via a decrease in oxidative stress (Zia et al. 2021).

Our results revealed that chronic curcumin administration in old rats significantly increased the level of BCl-2 protein and decreased the Bax/Bcl-2 ratio in the brain, but was not accompanied by significant changes in the brain Bax protein level. These results suggest that curcumin can have a neuroprotective effect against neuronal apoptosis in old brain tissue by increasing the Bcl-2 anti-apoptotic protein, and failure to change protein Bax pro-apoptotic protein with curcumin treatment may be related to short treatment duration and/or dosage. Animal studies have demonstrated that pro- and anti-apoptosis factors were altered in the aged brain, with increased expression of Bax protein and a decrease in the Bcl-2 protein (Wu et al. 2014; Lee et al. 2020b; Banji et al. 2014; Mao et al. 2007). Moreover, the ratio of Bax to/ Bcl-2 is a crucial factor that determines the cellular response to death stimuli and the progress of cell apoptosis (Wu et al. 2014; Mao et al. 2007) that decreases with the aging brain. It is well established that during aging, increased levels of mitochondrial ROS in aged animals and humans can activate the apoptosis pathway, which is associated with a decrease in the number of functioning cells (Isaev et al. 2018). Similarly, recent studies have also shown that administration of curcumin tended to regulate neuronal loss and suppress apoptosis in the cerebral cortex (Lee et al. 2020b) and brain (El-Far et al. 2021) by down-regulating Bax and increasing Bcl-2 expression through increasing antioxidant enzyme expression (Lee et al. 2020b).

Moreover, our findings also demonstrated that curcumin administration caused an increase in BDNF and VEGF levels in the brains of aged rats. These data provide further insights into the mechanisms underlying the improvement in brain health in normal aging. The up-regulation of VEGF and BDNF which are two key angiogenic and neurogenesis proteins may play a role in healthy brain aging. This is in line with an earlier report showing that oral treatment with curcumin (300 mg/, daily for 3 weeks), increased the levels of BDNF in the hippocampus of D-galactose-induced aged mice (Nam et al. 2014). Franco-Robles et al. (2014) found that curcumin supplementation (50 mg/kg, daily for 8 weeks) improved or restored BDNF levels to normal levels in diabetic db/db mice. Another study has shown that treatment with curcumin significantly reversed the chronic unpredictable stress-induced decreased hippocampal BDNF levels in stressed rats (Liu et al. 2014). These observations confirm that the protective effect of curcumin on the aging brain occurs in part through enhancing the BDNF level, while the effect of curcumin on VEGF levels in the aging brain remains unclear, and it can be considered one of the limitations of this study. Due to the involvement of the VEGF gene family in neuroprotection through multiple biological pathways, conflicting results have been reported for changes in VEGF during brain aging and brain disease. (Mahoney

et al. 2021; Shim and Madsen 2018). Accumulated evidence has indicated that the mRNA and protein expression of VEGF is reduced in the hippocampus and cortex of the amyloid beta-injected rats (Guo et al. 2019; Zarezadehmehrizi et al. 2021), and normal aging of the healthy brain is associated whit a decrease in VEGF levels (Shim and Madsen 2018; Villar-Cheda et al. 2009). Curcumin prevents amyloid-β aggregation, and after crossing the blood-brain barrier exerts its protective effect on neurons against toxic insults of aging and amyloid-β (Reddy et al. 2018). It seems that this curcumin's functional properties are in part related to the up-regulation of VEGF, which counteracts amyloid-β-induced morphological alteration synaptic dysfunction (Martin et al. 2021). It has been reported an age-related decline of VEGF in the brain and cerebral angiogenesis (Viboolvorakul and Patumraj 2014; Rivard et al. 2000) may lead to the inhibition of apoptosis following brain injury (Nag et al. 2019). In addition, elevated cerebrospinal fluid VEGF can improve normal brain aging (Hohman et al. 2015). Both BDNF and VEGF exert angiogenic and neurotrophic effects via binding to their tyrosine kinase receptors such as tropomyosin receptor kinase B (TrkB) and fetal liver kinase-1(Flk-1), respectively. BDNF can stimulate the formation of new vessels by releasing VEGF-mediated angiogenesis (Deyama et al. 2019; Afarid et al. 2020). Furthermore, neurogenesis occurs in proximity to blood vessels with high VEGF expression, and the production and release of BDNF enhance the new vasculature (Chen et al. 2005).

Conclusion

According to the results, it can be delineated that curcumin was effective in ameliorating brain aging. These protective effects may be mediated, at least partly, through reducing oxidative damage, enhancing the Bcl-2 protein, and up-regulating SOD activity, which in turn enhances VEGF and BDNF. These results imply that curcumin could improve age-induced apoptosis, neurogenesis, and angiogenesis changes, and suggest that curcumin has the potential to be used as a potent nutrient for preventing brain aging and age-related diseases. The limitations of this study are the absence of a histological examination of the brain, as well as the evaluation of other indicators of oxidative stress and apoptosis, which can provide more insight into curcumin. Further studies are needed to explore the neuroprotective effect of curcumin for healthy brain aging and to determine the safe dose of curcumin and its optimal administration, especially during aging.

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Data Availability Not applicable.

Declarations

Ethics approval All the animal experimental protocols were approved by the Institutional Animal Ethics Committee of Qaemshahar Branch, Islamic Azad University (IAU. 11768) and were performed in accordance with the guidelines set out in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85 – 23, revised 1985).

Consent to participate All participants signed a written informed consent before enrolment after explaining the importance of this study.

Consent for publication Not applicable.

Competing interests The authors have no relevant financial or nonfinancial interests to disclose.

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