Original Article

Nano-curcumin Attenuates Brain Oxidative Stress and Cognitive Deficit in Ketamine-induced Anesthesia in Adolescent Rats

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ABSTRACT

Background: Anesthetics play a crucial role in medical procedures; however, some may have neurotoxic effects, particularly through oxidative stress mechanisms. Ketamine, a widely used anesthetic, has been associated with neurotoxicity characterized by an imbalance in reactive oxygen species (ROS) production and antioxidant defenses.

Objectives: This study aimed to investigate the effects of nano-curcumin on ketamine-induced alterations in the hippocampal antioxidant components and cognitive function in adolescent rats.

Methods: Sixty male Wistar rats were used for two experiments. experiment 1 assessed the biochemical effects of nano-curcumin on ketamine anesthesia, while experiment 2 evaluated its impact on spatial learning and memory. At the end of the experiment, oxidative stress parameters, such as malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT), were measured. The Morris water maze (MWM) test was used to assess cognitive function.

Results: Biochemical assays revealed that ketamine anesthesia reduced antioxidant enzyme activity and total antioxidant capacity (TAC) in the hippocampus (HP) while increasing lipid peroxidation. Nano-curcumin treatment alleviated these effects, restoring antioxidant enzyme activity by significantly increasing SOD and CAT levels and reducing lipid peroxidation ($P \leq 0.05$). In the MWM test, ketamine anesthesia impaired spatial learning and memory, which was attenuated by nano-curcumin pretreatment.

Conclusion: Nano-curcumin effectively prevented ketamine-induced neurotoxicity by restoring the antioxidant balance and ameliorating cognitive deficits. These results highlight the potential therapeutic utility of nano-curcumin in mitigating anesthesia-induced neurotoxicity and emphasize the importance of oxidative stress in anesthesia-related neurological complications.

Keywords: Anesthesia, Brain, Ketamine, Nano-curcumin, Oxidative stress

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Introduction

Anesthetics are employed in medical procedures to induce anesthesia. While most anesthetics are considered safe, some may have neurotoxic effects, even at standard doses. Incompatible results exist regarding the impact of anesthetics on neuronal function and development. Different anesthetics and anticonvulsant medications cause neuronal injury, dysfunction and apoptosis, both in laboratory settings and in living organisms (Alam et al., 2017; Quiroz-Padilla et al., 2018; Clausen et al., 2019; Hajizadeh et al., 2018). However, the mechanisms by which anesthesia induces these changes are poorly understood. One prominent theory is that the onset of oxidative stress may trigger neuroapoptosis (Stevens et al., 2019; Resae et al., 2022), initiating a chain reaction with adverse neurological consequences. Under such circumstances, t the generation of reactive oxygen species (ROS) is escalated. Oxidative stress is triggered by an imbalance between free radical generation, mainly ROS and nitrogen reactive species (Barfourooshi et al., 2023; Chukwu et al., 2023; Shahsavari et al., 2023). Ordinarily, ROS is a routine outcome of brain cell metabolism. However, their buildup during oxidative stress can overpower the brain's innate protective antioxidant mechanisms, resulting in cellular impairment and demise (Gascoigne et al., 2022). Extensive research indicates that ROS play a significant role in developing various diseases, particularly neurological and psychiatric disorders, given the brain's heightened susceptibility to oxidative harm (Singh et al., 2019; Ng et al., 2008). Moreover, oxidative stress has been implicated in aging, inflammation, cancer, degenerative conditions (Hussain AlDulaimi, 2024; Liguori et al., 2018), as well as in exposure to xenobiotics and medications, including anesthetics (Lee et al., 2015). Anaesthetic-induced oxidative stress can affect lipids, proteins, and DNA (Alavuk Kundović et al., 2020). Therefore, Select anesthetics that minimize oxidative stress is crucial to prevent tissue damage.

Ketamine, a short-acting blocker of N-methyl-D-aspartate (NMDA) receptors, has been widely utilized as an anesthetic since the 1960s. Chemically, it is identified as (2-O-chlorophenyl-2-[methylamino] cyclohexanone) (Moghaddam, 2021), belonging to the phencyclidine derivative class. Initially hailed as an ideal anesthetic due to its ability to fulfill all the essential components of surgical anesthesia (such as pain relief, immobility, amnesia, and loss of consciousness) (Annetta et al., 2005). Ketamine exerts its pharmacological effects by modulating neurotransmission at postsynaptic receptors, including NMDA glutamate and gamma-aminobutyric acid receptors. Functioning as an uncompetitive antagonist, ketamine blocks NMDA receptors, leading to dissociative anesthesia (Zhou & Duan, 2023). Studies in humans have indicated that ketamine can induce neurotoxicity via oxidative stress mechanisms (Reus et al., 2017). In rodent models, ketamine prompts a compensatory overexpression of NMDA receptors. It elevates Ca^{2+} levels (Li et al., 2018), resulting in Ca^{2+} accumulation, leading to mitochondrial excitotoxic injury and the generation of ROS (Li et al., 2018, Liu et al., 2013). Oliveira et al. demonstrated that various sub-anesthetic doses of ketamine affect lipid peroxidation and tissue protein oxidation in multiple cerebral structures (de Oliveira et al., 2009).

Turmeric *(curcuma longa*), a member of the Zingiberaceae family, has been used for centuries throughout Asia as a food additive and traditional herbal medicine. Epidemiological evidence supports a link between better cognitive function in elderly Asians and curry consumption with turmeric (Assi et al., 2023). Curcumin is the major yellow polyphenol present in the rhizomes of turmeric (Khayatan et al., 2022; Banji et al., 2021, Kaboutari et al., 2023; Tamadonfard et al., 2010). Studies indicate that curcumin has several properties, including antioxidant, anti-infection, anti-tumor characteristics and neuroprotective potential (Khayatan et al., 2022; Godse et al., 2023; Gholipour-Shoshod et al., 2023). Curcumin exhibits potent anti-inflammatory properties by reducing the production of inflammatory cytokines, such as interferon-γ, tumor necrosis factor (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), as well as inhibiting cyclooxygenase-2 activity (Kahkhaie et al., 2019). However, its health benefits are limited due to its low water solubility, rapid metabolism and quick elimination from the body (Hewlings & Kalman, 2017). Curcumin, a hydrophobic natural polyphenol, has low solubility in aqueous solvents but high solubility in organic solvents (Maiti & Dunbar, 2018). Additionally, curcumin readily transforms into hydrophilic metabolites that can impede its absorption (Jäger et al., 2014). Consequently, curcumin is poorly absorbed from the gut, resulting in low bioavailability and negligible serum levels when administered alone. To address this issue, various delivery systems, such as nanoparticles (e.g. poly lactic-co-glycolic acid [PLGA] nanoparticles, lipid-based nanoparticles, nanosuspensions, lipid-PLGA nanobubbles, and nanoemulsions), ultrasound-targeted microbubbles, micelles, dendrimers and exosomes have been developed to enhance curcumin's physicochemical properties, bioavailability and pharmacokinetics (Panzarini et al., 2020, Mohammed et al., 2021, Ashjazadeh et al., 2019). Nanoparticles of curcumin protect it from metabolism and enhance its stability, prolonging its time

Table 1. Experimental design in experiment 1

Groups		Time of Sample Collection After Anesthesia (h)
Curcumin treated	T1	0
	T2	4
	T3	12
	T4	Without anesthesia
Normal saline	S1	0
	S2	4
	S3	12
	S4	Without anesthesia

in the bloodstream (Moballegh Nasery et al., 2020). In light of this evidence, the current study aimed to assess the effects of nano-curcumin on ketamine-induced alterations in hippocampal antioxidant components and cognitive function.

Materials and Methods

Animals

Sixty male Wistar rats (200-220 g) obtained from the Laboratory Animal Center (Lorestan University of Medical Sciences and Health Services) were used in this study. Rats were kept under controlled conditions of 23±2 ˚C and light conditions for 12 h of light and 12 h of darkness in the animal house of the Faculty of Veterinary Medicine affiliated with Lorestan University. All animals were allowed free access to a standard chow diet and tap water ad libitum.

Experimental design

Experiment 1 was conducted to assess the effects of nano-curcumin on biochemical alterations following ketamine anesthesia. Forty rats were divided into curcumin-treated (T) and normal saline-treated (S). Each group had four subgroups: T1-T4 and S1-S4 (n=5 per subgroup) (Table 1). The animals in groups T1-T4 were subjected to daily gavage of nano-curcumin 20.00 mg kg-1 (Sina curcumin capsule, each capsule contains 80.00 mg curcumin as nano micelle, these spherical nanomicelles have a particle size of about 10 nm) for 2 weeks and groups S1-S4 were received normal saline for the same duration. On the last day of administration, all groups, except T4 and S4, were anesthetized with ketamine. Rats in groups T1, T2 and T3 were euthanized immediately, 4 and 12 h after anesthesia, respectively, and their hippocampi were collected for biochemical examinations. A similar protocol was performed for anesthesia and brain tissue collection in groups S1, S2 and S3. Groups T4 and S4 were not anesthetized but were also sampled following cervical dislocation without ketamine injection. The dose of nano-curcumin (20 mg/kg) was determined based on the results of our pilot study. All treatments were applied intraperitoneal injection. Experiment 2 was designed to investigate the effects of nano-curcumin on spatial learning and memory after ketamine anesthesia. Twenty rats were divided into four groups (n=5 per group) as follows:

Group I-received normal saline without anesthesia (control); group II-received normal saline with anesthesia (ketamine); group III-received nano-curcumin without anesthesia (curcumin); group IV-received nano-curcumin with anesthesia (curcumin+ketamin)

All injections were administered IP once daily for two weeks. The dose of curcumin used was 20 mg/kg. On the last day of injection, rats in groups II and IV were anesthetized with ketamine. After recovering from anesthesia, all rats were subjected to the Morris water maze (MWM) test to evaluate spatial learning and memory.

Biochemical estimations

The rats were sacrificed by cervical dislocation under ether anesthesia at the time of sample collection and the hippocampi were dissected on an ice-cold surface. Tissue homogenates were prepared as previously described by Carrillo et al. (1991). Supernatants were recovered and stored at -70 ˚C until malondialdehyde (MDA) levels (an indicator of lipid peroxidation), superoxide

dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) enzyme activities and total antioxidant capacity (TAC) were determined.

Measurement of lipid peroxidation

The level of lipid peroxidation was determined by the MDA content in the hippocampus (HP) using commercial biochemical kits (Asan, Khorramabad, Iran).

Determination of GPx and SOD activities

SOD and GPx activities were measured in the supernatant using Asan kits (Khorramabad, Iran), according to the manufacturer's instructions. GPx and SOD activities were expressed as milliunits per milligram of tissue protein (mU/mg protein).

Determination of CAT activities

The CAT concentrations were measured using Asan commercial kits (Khorramabad, Iran).

Protein measurement

The protein content of the tissue homogenates was determined using the Lowry colorimetric method with bovine serum albumin as the standard (Lowry et al., 1951).

MWM testing

Hipocampal-dependent spatial learning and memory were evaluated using the standard MWM task (Morris et al., 1982). The one-day water maze test was performed as described previously (Frick et al., 2000) with minor modifications. This version of the water maze test was chosen for practical reasons because it can rapidly evaluate learning and memory in rodents. The water maze consisted of a circular tank (190 cm in diameter) filled with water (up to 30 cm deep; temperature, 22±2 °C). The tank was divided into four zones and a platform (18×18 cm) was submerged 2 cm below the water surface in one of these zones. Any spatial learning and memory improvements were confirmed using the spatial acquisition and probe trials, respectively. In the first test (spatial acquisition), each rat underwent three blocks of four swims separated by 30 minute interval. Each rat was gently released into water in a randomly chosen quadrant in the swimming trials. The rat swam and learned to find the hidden platform within 60 s. After reaching, the rat was allowed to stay on the platform for 10 s and return to the cage. Rats were placed on the platform by hand for 10 s if they could not escape to the platform within 60 s, and their escape latency was accepted as 60 s. The time to reach the platform (latency), the length of the swim path, and the swim speed were recorded using a video tracking system. In the second test (probe trial), which was conducted after a 30 minute break, the platform was removed, and the rats underwent a single trial of 60 s. The percentage of time spent in each zone, including the correct quadrant was recorded. At the end of each block, all animals were return to their cages for rest.

Statistics

All data were analyzed using SPSS software, version 24. To compare the data on SOD, CAT and GPx enzyme activities and TAC and MDA levels, one-way analysis of variance (ANOVA) and post-hoc Tukey's tests were used. The escape latencies, path length and swimming speed in the water maze were analyzed by two-way ANOVA for between-subjects differences between nano-curcumin and normal saline ("curcumin" effect) and repeated measures (within subjects) effects across block interval 1 to 3 ("block" effect). The probe trial data for the percentage of time spent in each of the four zones were analyzed using a multivariate ANOVA. The results of the experiments are expressed as the Mean±SEM. A $P \leq 0.05$ value was considered to be statistically significant.

Results

As shown in Figure 1, ketamine anesthesia significantly reduced the levels of GPx compared to the non-anesthetized group ($P \leq 0.05$). Treatment with curcumin increased GPx levels, but no significant difference was observed ($P \leq 0.05$).

Anesthesia significantly reduced levels of CAT compared to the non-anesthetized group ($P \leq 0.05$) (Figure 2A). Curcumin increased the amount of CAT in the treatment groups; however, a significant increment was observed only in the T3 group ($P \leq 0.05$) (Figure 2B).

As shown in Figure 3A, In the T group, no significant difference was observed between the anesthetized and non-anesthetized groups with ketamine. While in the saline-treated groups, ketamine anesthesia significantly decreased levels of SOD ($P \leq 0.05$). As shown in Figure 3B, the T3 group showed significantly higher SOD levels than the S3 group ($P \leq 0.05$).

Anesthesia significantly reduced TAC levels when compared to the T4 and S4 groups in, which did not receive anesthesia ($P \leq 0.05$) (Figure 4). No significant difference in TAC was observed between the curcumin and saline-treated groups (Figure 4B).

Following ketamine anesthesia, MDA significantly reduced (P≤0.05) (Figure 5A). MDA levels decreased in the curcumin-treated groups, but the difference was not statistically significant (P>0.05) (Figure 5B).

Figure 6 shows the latency time results. Based on the graph, anesthesia with ketamine significantly increased the latency time compared to the control group without anesthesia (P≤0.05). The curcumin-treated group showed a significantly reduced latency time compared to the control group (P≤0.05). In the ketamine+curcumin-treated group, latency time was significantly lower than that of the ketamine group (P≤0.05).

Figure 7 shows the results of the time spent in the target zone (%). Based on the graph, anesthesia by ketamine significantly reduced the time spent in the target zone compared to the control group (P≤0.05). Although the ketamine and ketamine+curcumin groups showed increased time spent in the target zone, it was insignificant compared to the ketamine group (P>0.05).

Discussion

The current study demonstrated that administering curcumin (20 mg/kg, for 14 days), an active compound found in turmeric (*curcuma longa*), to rats before exposure to ketamine effectively prevented the behavioral and pro-oxidant effects induced by ketamine in adolescent rats. The behavioral and biochemical impacts of ketamine appear to be contingent upon its dosage. Studies have revealed that low doses of ketamine (5–10 mg/kg) have antidepressant properties (Katalinic et al., 2013). Conversely, moderate doses (10–50 mg/kg) of ketamine can lead to hyperlocomotion and cellular dysfunction (Sedky & Magdy, 2021), while higher doses result in anesthetic and dissociative effects. Gazal et al. (2014) demonstrated that administering ketamine (25 mg/kg) for 8 days induces hyperlocomotion in the open-field test and oxidative damage in the prefrontal cortex and HP.

Furthermore, another study found that administering a sub-anesthetic dose of ketamine altered the oxidative stress parameters in the rat brain. Da Silva et al. demonstrated increased lipid peroxidation and nitrite content in the cortex of mice following a single dose of ketamine. In preclinical models, non-anesthetic doses of ketamine can induce hyperlocomotion, stereotypy, impaired cognitive function, and social interaction (Gazal et al., 2014). It is worth noting that, in the current study, the anesthetic dose of ketamine (75 mg/kg, intraperitoneal) and its acute effects on behavioral and neurochemical changes were assessed.

An imbalance in oxidation-reduction processes within living organisms leads to the accumulation of ROS, resulting in oxidative stress (Costantini, 2019). To counteract this, organisms employ various antioxidant defense mechanisms. Enzymatic antioxidants included SOD, CAT, GPx and glutathione reductase. SOD, a key player in ROS defense, facilitates the conversion of superoxide anions (O_2^-) into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) (Carmo de Carvalho e Martins et al., 2022). Subsequently, H_2O_2 reacts with iron to generate highly reactive hydroxyl radicals (Halliwell & Gutteridge, 2015). CAT converts H_2O_2 into water and O_2, thereby completing the detoxification process. (Cecerska-Heryć et al., 2022). Neuronal cells are particularly susceptible to oxidative damage due to their heightened oxygen consumption, relatively weak antioxidant defenses (Cobley et al., 2018) and abundant polyunsaturated fatty acids in their membranes. Specifically, the lipid composition of neuronal membranes is rich in polyunsaturated fatty acids, rendering them more vulnerable to oxidative stress.

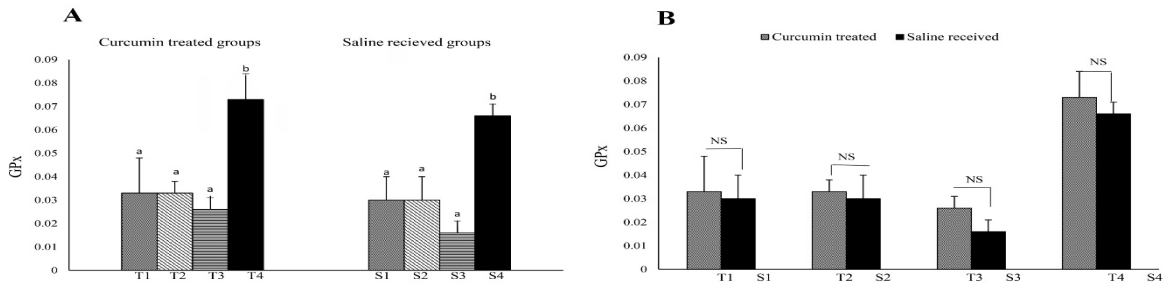

Figure 1. Evaluation of GPx in experimental groups of the study

A) Comparison between anesthetized and non-anesthetized groups of curcumin and saline treated, B) Comparison between curcumin and saline treatment groups of the same time frame

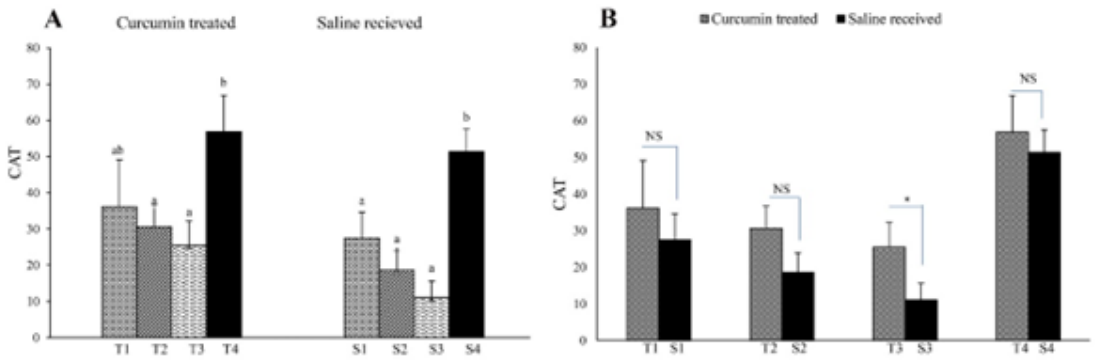

Figure 2. Evaluation of CAT in experimental groups of the study

A) Comparison between anesthetized and non-anesthetized groups of curcumin and saline treated, B) Comparison between curcumin and saline treatment groups of the same time frame

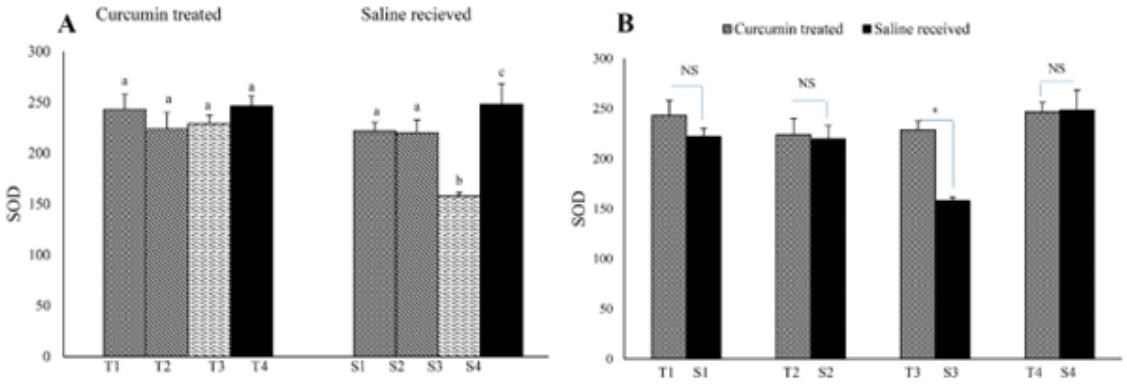

Figure 3. Evaluation of SOD in experimental groups of the study

A) Comparison between anesthetized and non-anesthetized groups of curcumin and saline treated, B) Comparison between curcumin and saline treatment groups of the same time frame

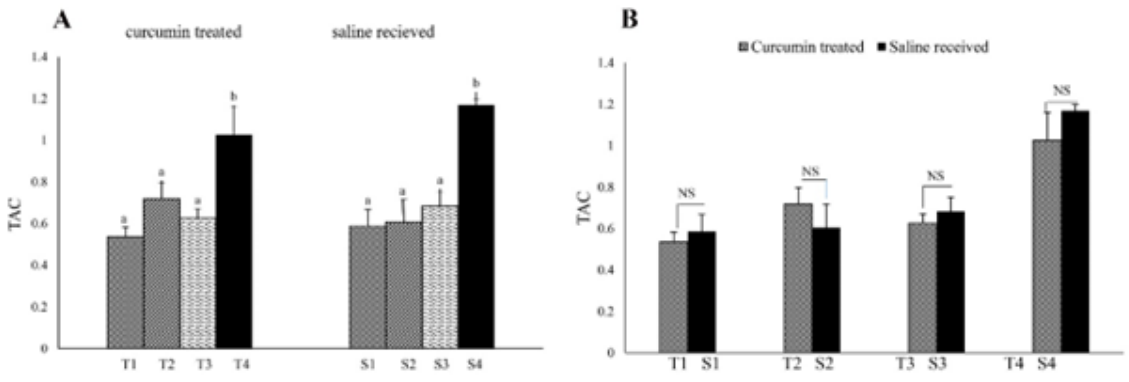

Figure 4. Evaluation of TAC in experimental groups of the study

A) Comparison between anesthetized and non-anesthetized groups of curcumin and saline treated, B) Comparison between curcumin and saline treatment groups of the same time frame

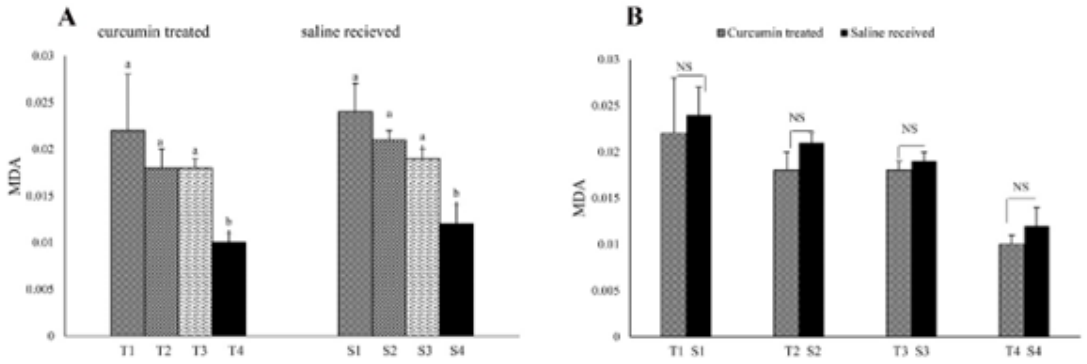

Figure 5. Evaluation of MDA in experimental groups of the study

A: Comparison between anesthetized and non-anesthetized groups of curcumin and saline treated, B: Comparison between curcumin and saline treatment groups of the same time frame.

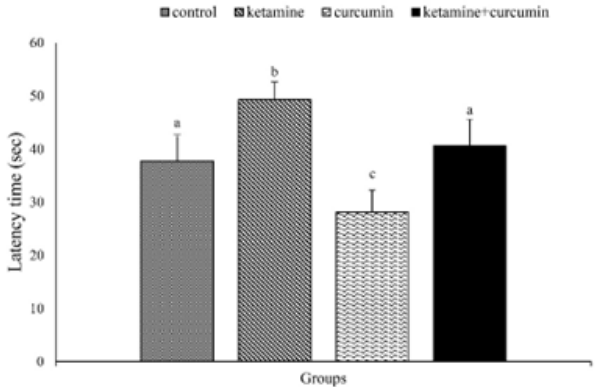

Figure 6. Effect of ketamine and nano-curcumin treatment on spatial learning as measured by the MWM task

Note: Escape latency to reach the hidden platform in rats received ketamine enhanced compared to the control group. Nano-curcumin administration significantly reversed ketamine-induced impairment. Significant differences are observed between groups with different superscripts in the columns (a, b and c; P≤0.05). Each point represents the Mean±SEM.

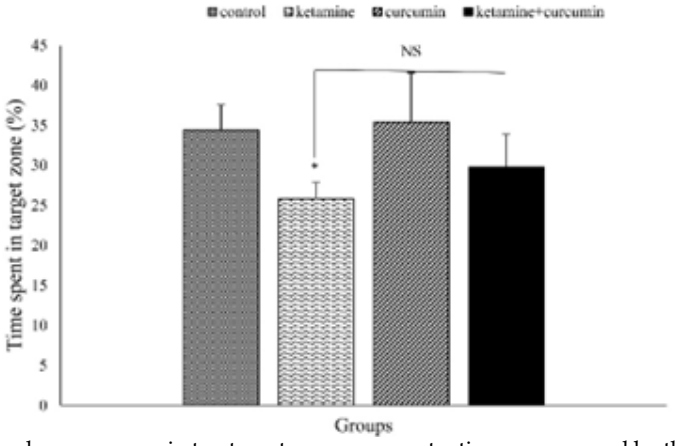

Figure 7. Effect of ketamine and nano-curcumin treatment on memory retention, as measured by the MWM task

NS: Non-significant.

*Significant difference between the ketamine and control groups (P≤0.05).

Note: The mean time spent by the rats in the target zone was significantly lower in the ketamine group than in the control group. Administration of nano-curcumin improved the memory impairment caused by ketamine.

Elevated ROS levels harm various cellular processes, such as signal transduction, structural plasticity, and cellular resilience, primarily by inducing lipid peroxidation in membranes and damaging proteins and nucleic acids (Mahadik et al., 2001). Moreover, mitochondria in presynaptic terminals are exposed to elevated calcium levels from voltage-gated calcium channels, accelerating oxidative damage at synaptic sites (Grimm & Eckert, 2017). Our study revealed that ketamine-induced changes in certain oxidative stress parameters, such as increased MDA levels and decreased TAC in rats' HP. In our experiment, ketamine administration reduced activity of antioxidant enzymes such as GPx, SOD and CAT in the HP. Previous studies have documented the effects of ketamine on lipid peroxidation in various brain regions (Brocardo et al., 2010).

The HP, a critical structure within the limbic system, plays a pivotal role in cognitive functions, such as learning, memory consolidation, and recall of declarative memories (Eichenbaum, 2001). It is vital for spatial memory map formation (Papp et al., 2007). Research has shown that decreased hippocampal lipid peroxidation enhances spatial cognition and learning memory (Gamoh et al., 2001), while increased antioxidative activity in the HP prevents (Hashimoto et al., 2002) or mitigates (Hashimoto et al., 2005) impairments in learning ability in rats. Furthermore, preclinical evidence suggests that ketamine exerts rapid effects on synaptogenesis in the HP, a brain region strongly implicated in memory consolidation (Kandlur et al., 2020).

Consistent with a study conducted by Gazal et al. (2014) our results suggest that curcumin effectively prevented cognitive deficits and alterations in oxidative stress parameters induced by ketamine in rats. Numerous studies have highlighted curcumin's anti-inflammatory and antioxidant properties (Peng et al., 2021; Vaiserman et al., 2020). It has been demonstrated that curcumin can normalize levels of cellular antioxidant enzymes, including SOD and CAT and reduce oxidative stress in cellular models of Alzheimer's disease (Huang et al., 2012).

Due to its antioxidative properties, curcumin has shown promise in preclinical models of various conditions, including neurodegenerative disorders, depression and aging (Menon & Sudheer, 2007). Consistent with these results, our study showed that curcumin improves learning impairments in ketamine-treated rats. Abundant evidence indicated that curcumin administration can enhance memory function and cerebral blood flow (Rajasekar et al., 2013) and elevate levels of brain-derived neurotrophic factor and hippocampal neurogenesis (Xu et al., 2007).

Researchers have explored the relationship between curry consumption, curcumin, and cognitive function. Individuals who consumed curry occasionally (less than once a month) or often (more than once a month) performed better on cognitive function tests than those who rarely or never consumed curry (Mishra & Palanivelu, 2008). In a previous study, we demonstrated that an herbal extract with antioxidant properties improved ethanol-induced spatial memory impairment (Taati et al., 2011). Considering the HP's role in spatial learning and its susceptibility to oxidative damage induced by ketamine (Gazal et al., 2014), it is evident that oxidative stress plays a role in ketamine-induced cognitive impairment in spatial water maze performance.

To our knowledge, no reports are found on the effects of curcumin on spatial learning and memory in ketamine-treated adolescent rats. In this study, pretreatment with curcumin significantly reduced latency time and mitigated ketamine's effects on learning performance compared to the ketamine-only group. These results suggest that co-treatment with curcumin ameliorates ketamine-induced memory deficits during rat acquisition process. However, this did not significantly affect the retrieval process of spatial memory performance. Previous studies have shown that antioxidant components in plants can enhance cognitive function (Renis et al., 1996; Bisson et al., 2008; Kumar et al., 2009; Khalili et al., 2009, Farshchi et al., 2010; Juyal et al., 2010).

Conclusion

In conclusion, our results suggest that the improvement in spatial memory deficits induced by ketamine can be attributed to the antioxidant properties of curcumin.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Lorestan University, Khorramabad, Iran (Code: LU. ECRA.2023.22).

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This paper was extracted form the DVM thesis of Reza Tahmaseby, approved by the Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran.

Authors' contributions

Methodology, and writing the original draft: Reza Tahmaseby; Conceptualization, supervision, and validation: Abbas Raisi; Investigation: Reza Tahmaseby, Majid Taati and Soroush Afshar Ghahramani; Data curation, and resources: Majid Taati and Soroush Afshar Ghahramani; Review and editing: Abbas Raisi, Majid Taati, and Soroush Afshar Ghahramani.

Conflict of interest

The authors declared no conflict of interest.

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