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# Possible Protective Effects Of Cerium Oxide Nanoparticles ($Ceo_2Nps$) On Aluminum Chloride ($Alcl_3$)-Induced Neurotoxicity In Male Albino Rats

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***Abstract***
*Aluminum chloride ($AlCl_3$) is recognized as neurotoxin that causes oxidative stress (OS), inflammation, and structural damage to the brain, potentially resulting in neurodegenerative conditions. Cerium oxide nanoparticles ($CeO_2NPs$) exhibited important antioxidant and anti-inflammatory capabilities that may mitigate these effects. The present study is aimed at assessing the histopathological alterations caused by $AlCl_3$ in brain tissue and the possible protective effects of $CeO_2NPs$ in male albino rats. The rats were randomly dividing into six groups: a control group and five experimental groups, in which two groups receiving $CeO_2NPs$ at two doses of 10 and 100 mg/kg body weight, as well as the other group receiving $AlCl_3$ (1000 mg/L), and two combined treatment groups receiving $AlCl_3$ alongside $CeO_2NPs$ at 10 and 100 mg/kg, respectively.*
*Histological sections of brain tissues have been taken and stained with Hematoxylin and Eosin (H&E) to examine histoarchitecture. Furthermore, Masson's Trichrome (MT) is used to examine fibrosis. Sections stained with H&E revealed that $AlCl_3$ caused substantial neuronal degeneration, gliosis, and inflammatory infiltration, whereas both dose (10 and 100 mg/kg) with $CeO_2NPs$, maintained brain architecture and mitigated damage but the effect of the higher dose was greater than the lower one. Sections stained with MT showed more collagen deposition in the $AlCl_3$ treated group, however those alterations were diminished in nanoparticles treated groups. In conclusion the present study indicated that $CeO_2NPs$ mitigate $AlCl_3$-induced neurotoxicity and fibrosis in brain tissue, with an increased dosages providing enhanced protection.*
***Keywords:*** *Cerium Oxide Nanoparticles, Aluminum Chloride, Neurodegeneration, Fibrosis.*

## INTRODUCTION

Aluminum (Al) is the third most abundant element and the most frequent metal in the Earth's crust, constituting almost 8% of its mass [1]. The extensive application of Al in sectors like transportation , construction, electronics, and packaging has led to the release of its compounds into the water, soil ,and air. Moreover, Al-based items such as cookware, drinking containers, and antacids boost our regular exposure to this element [2]. It has been linked to the alteration of many biomolecules related to neurotoxicity and the onset of several disorders of neurodegenerations [3-7], inducing OS, inflammatory processes, and neuronal damage. Nonetheless, it isn't crucial for human metabolism. [8, 9],and conversely, it may be harmful to the human body, especially the brain [10, 11].

OS generated by Reactive oxygen species (ROS) have been associated with numerous brain conditions [12].ROS, including superoxide radicals, hydrogen peroxide ($H_2O_2$), and hydroxyl radicals, are produced under physiological circumstances and can inflict damage on lipids and nucleic acids and proteins [13, 14]. Al affects approximately 200 critical biological responses and negatively influences the central nervous system, along with several processes associated with brain development, such as gene expression, protein degradation, synaptic transmission, neurotransmitter synthesis, axonal transport, protein phosphorylation and dephosphorylation, lipid peroxidation, and inflammatory responses [15]. It is widely recognized as a neurotoxic which has the ability to cause neuronal damage [16].

Literature indicates that chronic intoxication of Al leads to observed inflammation of the neuron in the spinal cord, brainstem , cerebral cortex, and hippocampus, accompanied by symptoms akin to late-stage neurodegeneration [17-19].Substantial evidence suggests that it can penetrate the blood-brain barrier (BBB) and accumulate in several brain regions, including the cerebral cortex and hippocampus, which are associated with learning and memory functions. Additionally, the infiltration of inflammatory cells and neuronal degeneration is observed in the brains of rats administered $AlCl_3$ [20].

.The exact methods via penetrating BBB are not completely understood; nonetheless, it is belived that it transports through transferrin and settles in cortical areas rich in transferrin receptors [21, 22].Studies

demonstrate that the settling of this metal in the brain contributes to neurodegenerative illnesses, including Parkinson's and Alzheimer's Disease (AD) [23].

Nanoceria, or cerium oxide nanoparticles ($CeO_2$NPs), are widely employed in the materials industry [24] and have garnered interest for their potential biomedical applications in addressing diseases related with OS especially in the of neurodegenerative conditions, [12, 25-34] owing to their strong ability to remove free radicals which derived from their surface $Ce^{3+}/Ce^{4+}$ redox stoichiometry [35]. They replicate the scavenging functions of peroxidase, catalase (CAT), superoxide dismutase (SOD), hydroxyl radicals, and nitric oxide (NO) [36].This study aims to evaluate the histopathological changes induced by $AlCl_3$ in brain tissue and the possible protective benefits of $CeO_2$NPs in male albino rats.

## METHODOLOGY

### Chemicals

### Cerium oxide nanoparticles ($CeO_2$ NPs)

$CeO_2$ NPs was made by US research nanomaterials CAS #:1306-383, their sizes less than 50 nm , they were prepared at doses of 10 and 100 mg/kg (B.W), administrated by oral gavage 5 days /week for a month.

### Aluminum chloride ($AlCl_3$)

Anhydrous aluminum chloride ($AlCl_3$) powder, CAS No. 7446-70-0, was procured from Sigma-Aldrich Chemical Co. Dissolved $AlCl_3$ is provided via the drinking bottle in the cage, at a concentration 1000 mg/L, daily for the span of 30 days.

### Animals and Grouping

The experiment was conducted at the animal care facility of Cihan University-Erbil, using thirty healthy adult male albino rats, their age were 10 to 12 weeks with the weight around 190 to 240 grams. The rats were housed in clean polypropylene cages within a well-ventilated environment subjected to a 12-hour light/dark cycle. Environmental conditions were controlled, with temperatures maintained between 24°C and 30°C. Body weights were recorded weekly to adjust treatment doses accordingly and to track any changes throughout the experiment.

The animals were split into six groups (G) at random, five individual per group (n=5).

**G1** (Control): Received standard chow and tap water freely for a month.

**G2**: Treated with only $CeO_2$NPs (10 mg/kg B.W) via oral gavage, 5 days/week for 30 days.

**G3**: Administered $CeO_2$NPs (10 mg/kg B.W) through oral gavage for the same duration.

**G4**: Given only $AlCl_3$ (1000 mg/L) in drinking water bottle daily for a month.

**G5**: Received a combination of $AlCl_3$ (1000 mg/L in drinking water, daily) and $CeO_2$NPs (10 mg/kg B.W via oral gavage, 5 days/week week) for four weeks.

**G6**: Treated with $AlCl_3$ (1000 mg/L in drinking water, daily) alongside $CeO_2$NPs (100 mg/kg B.W via oral gavage, 5 days / week) for duration of four weeks.

### Animal sacrifice & Tissue collection

Upon completion of the experiment the rats were euthanized by decapitation after a single intramuscular injection of both ketamine and xylazine. Brain tissues were carefully removed and promptly fixed in 10% neutral buffered formalin for 24 hours. Following fixation, the tissue samples went through dehydration using a sequential series of ethanol concentrations (50%, 70%, 90%, and three changes of 100% alcohol), and were subsequently cleared with xylene. The tissues were later infiltrated and embedded in paraffin wax at temperatures between 55°C and 60°C to create solid blocks. Thin serial sections, 5-10 µm in thickness, were produced with the aid of a rotary microtome [37].

### Tissue Staining Protocol

### Hematoxylin and Eosin staining

The sections were deparaffinized using xylene, immersed in hematoxylin stain for 7 minutes, thoroughly rinsed with running tap water, then re-immersed in hematoxylin for 3 minutes, and excess stain was removed with water. Subsequently, the slices were dried in alcohol, cleaned with xylene, and then mounted with Dibutyl-phthalate Polystyrene Xylene (DPX) and over slip for comprehensive histological investigation [37].

### Masson's Trichrome Staining

Tissue pieces were initially deparaffinized and rehydrated through a graded series of alcohols to water. The mercury pigment was then eliminated using an iodine–sodium thiosulfate sequence, followed by thorough

rinsing with tap water. Subsequently, nuclear staining was performed using the celestine blue–hematoxylin technique, after which the sections were differentiated in 1% acid alcohol and rinsed again with tap water. Thereafter, the sections were stained with acid fuchsin solution for 5 minutes, washed with distilled water, and treated with phosphomolybdic acid solution for an additional 5 minutes. Following drainage, counterstaining was carried out with methyl blue solution for 2–5 minutes, and the sections were rinsed once more with distilled water. A final treatment with 1% acetic acid was applied for 2 minutes, after which the sections were dehydrated in ascending grades of alcohol, cleared in xylene, and mounted in DPX for microscopic examination [38].

## RESULTS

Histopathological examination of brain tissues was performed to assess the effects of $AlCl_3$ exposure and the potential neuroprotective role of $CeO_2$NPs. Representative photomicrographs of all experimental groups, stained with H&E and MT, are presented in Figures 1,2,3 and 4 respectively.

### Histopathological Findings

Brain tissue sections from the control and $CeO_2$NPs (10 and 100 mg/kg) groups showed normal glial architecture, which included various types of glial cells and neurons, without any pathological alterations (Figure.1). In contrast, exposure to $AlCl_3$ induced distinct neuropathological changes characterized by moderate mixed inflammatory cell infiltration, moderate neuronal degeneration, and moderate diffuse gliosis. Multifocal positivity with MT's stain further supported these findings, confirming the presence of moderate fibrosis (Figure.2). While co-treatment with nanoceria showed a dose-dependent neuroprotective effect.

In the group of $AlCl_3$ + $CeO_2$ (10 mg/kg), brain sections exhibited mild multifocal mixed inflammatory cell infiltration, mild neuronal degeneration, and mild focal gliosis, which were accompanied by focal positivity with MT, indicating reduced fibrotic deposition (Figure. 3). Furthermore, in the $AlCl_3$ + $CeO_2$ (100 mg/kg), sections demonstrated only focal mild mixed inflammatory cell infiltration, mild neuronal degeneration, and mild focal gliosis. Importantly, no fibrotic changes were detected in glial tissue, as confirmed by a negative MT (Figure. 4).

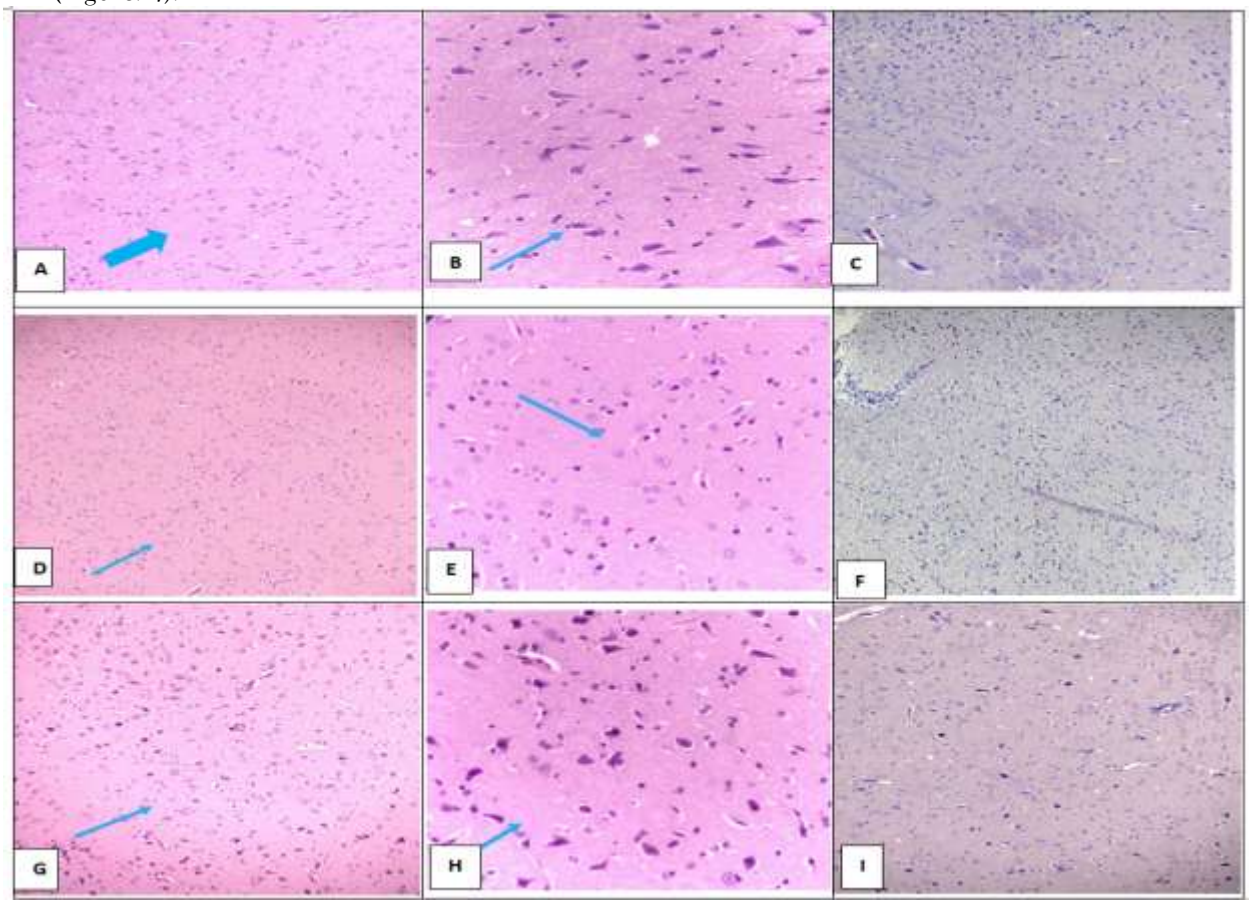

Figure 1. Photomicrographs of rat brain tissue sections of the control groups. (A, B) Control group showing normal glial tissue (blue arrows) with H&E at 100× and 400×. (C) Control group with normal glial tissue under negative MT at 100×. (D, E) $CeO_2$NPs (10 mg/kg) control group showing normal glial tissue (blue arrows) with H&E at 100× and 400×. (F) $CeO_2$NPs (10 mg/kg) control group with normal glial tissue under negative MT at 100×. (G, H) $CeO_2$NPs (100 mg/kg) control group displaying normal glial tissue (blue arrows) with H&E at 100× and 400×. (I) $CeO_2$NPs (100 mg/kg) control group with normal glial tissue under negative MT at 100×.

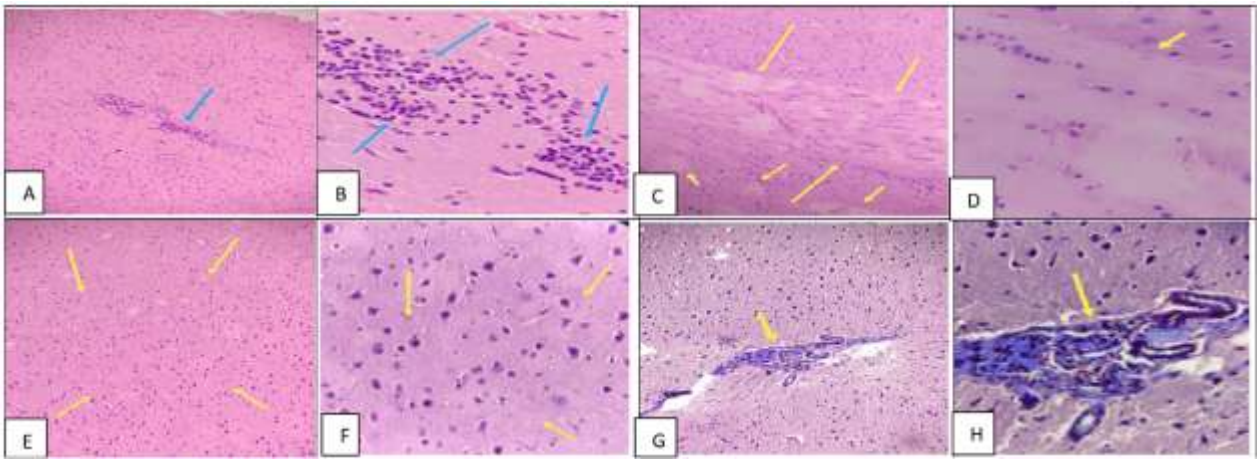


Figure 2. Photomicrographs of rat brain tissue sections from the ($AlCl_3$, 1000 mg/L)-induced group. (A, B) Moderate infiltration of mixed inflammatory cells (blue arrows) observed with H&E at 100× and 400× (C, D) Moderate neuronal degeneration (yellow arrows) with H&E at 100× and 400×. (E, F) Moderate gliosis (yellow arrows) evident with H&E at 100× and 400×. (G, H) Moderate fibrosis (yellow arrows) demonstrated by positive MT at 100× and 400×, respectively.

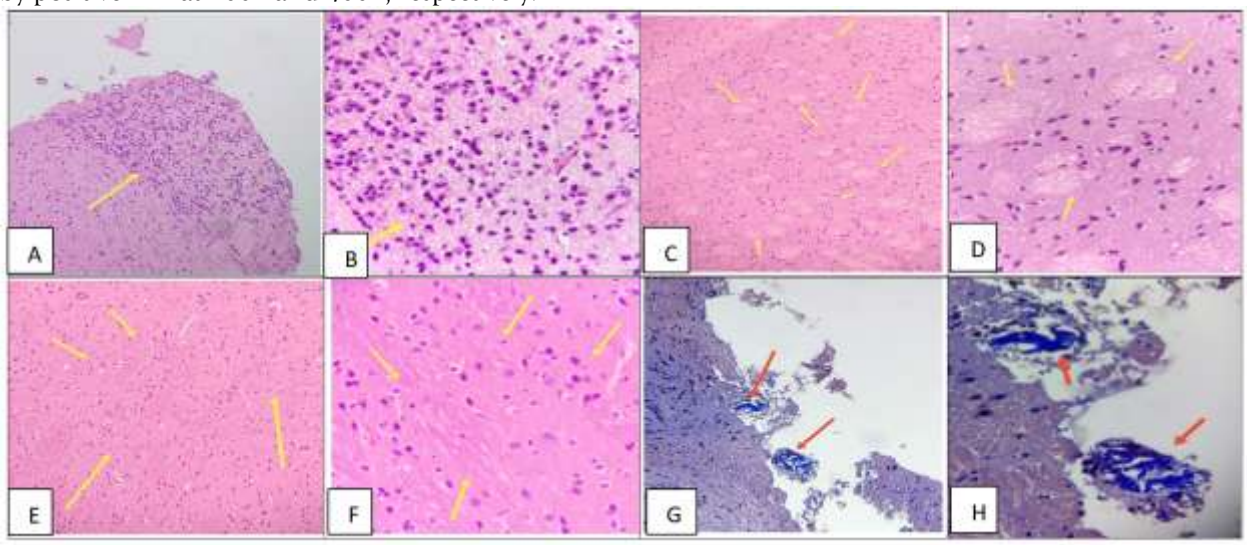


Figure 3. Photomicrographs of rat brain tissue sections from the combined $AlCl_3$ + $CeO_2$NPs (10 mg/kg) treated group. (A, B) Mild infiltration of mixed inflammatory cells (yellow arrows) observed with H&E at 100× and 400×. (C, D) Mild neuronal degeneration (yellow arrows) with H&E at 100× and 400×. (E, F) Mild gliosis (yellow arrows) evident with H&E at 100× and 400×. (G, H) Mild fibrosis (red arrows) demonstrated by positive MT at 100× and 400×, respectively.

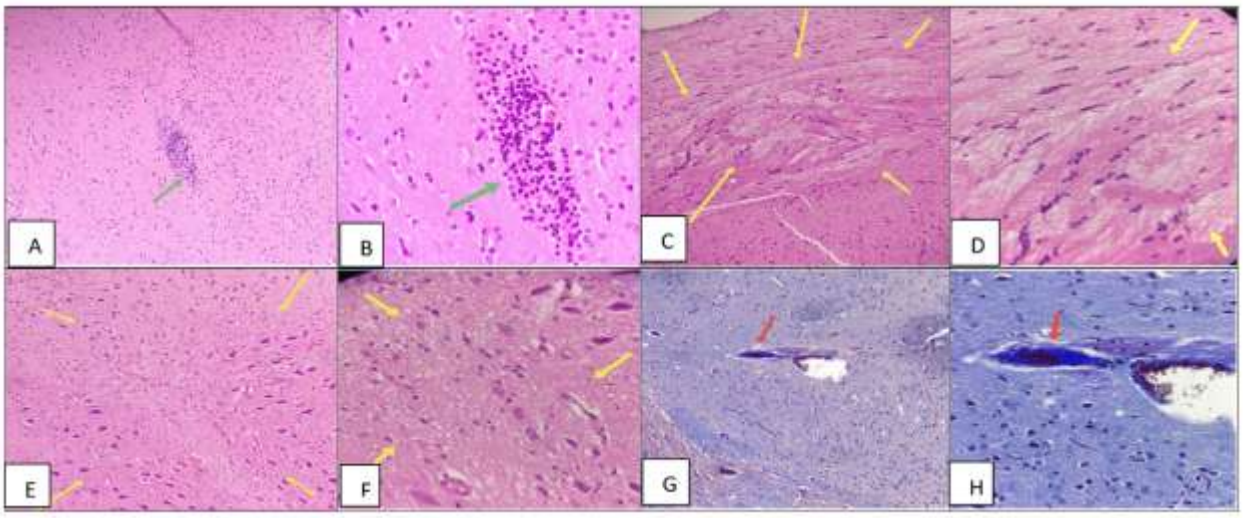


Figure 4. Photomicrographs of rat brain tissue sections from the combined $AlCl_3$ + $CeO_2$NPs (100 mg/kg) treated group. (A, B) Mild infiltration of mixed inflammatory cells (green arrows) observed with H&E at 100× and 400× . (C, D) Mild neuronal degeneration (yellow arrows) with H&E at 100× and 400×. (E, F) Mild gliosis (yellow arrows) evident with H&E at 100× and 400×. (G, H) Absence of fibrosis indicated by negative MT ; however, positive MT staining around blood vessels (red arrows) demonstrates collagen fibers within the vascular wall (positive control) at 100× and 400×, respectively.

**DISCUSSION**

The findings of the present study clearly revealed that neurotoxic potential of $AlCl_3$ and the significant neuroprotective efficacy of $CeO_2$NPs against $AlCl_3$-induced brain injury in a rat model. The results of the present study are consistent with a large body of existing literature that establishes Al as a potent neurotoxin. It is an accumulative toxic heavy metal known to cause injurious effects to organs like the brain, liver and spleen [39]. The ability of Al to cross the BBB [40] and persist in the tissue of brain for extended periods underpins its detrimental effect on the central nervous system (CNS), leading to neuroinflammation and cognitive deficits, as confirmed in both in vitro and in vivo studies [10].

The histopathological alterations observed in the $AlCl_3$-induced group, provide clear visual evidence of this neurotoxicity particularly the presence of fibrosis. In which, identified by an increase in interstitial fibrous tissue, is a critical indicator of uncontrolled inflammatory reactions and aberrant tissue repair following injury [41] These findings align with previous research showing that $AlCl_3$ causes destructive effects on brain hippocampal tissue, including cellular degeneration, congestion and vacuolation [42]. The oral administration of $AlCl_3$ has been previously linked to neurobehavioral changes, increased OS and decreased neurotransmitter levels [43].

In striking contrast, co-treatment with $CeO_2$NPs, particularly at the higher dose of 100 mg/kg, markedly attenuated these pathological changes. The groups receiving $AlCl_3$ alongside $CeO_2$NPs showed only mild inflammatory infiltration, mild neuronal degeneration, and mild gliosis. Most significantly, the group treated with the higher dose of $CeO_2$NPs (100 mg/kg) exhibited a complete absence of fibrosis, as indicated by negative MT staining. This powerful anti-fibrotic effect is a pivotal finding of this study.

The mechanism behind this profound neuroprotection is undoubtedly linked to the unique regenerative antioxidant properties of $CeO_2$NPs as established in the literature, they can continuously switch between $Ce^{3+}$ and $Ce^{4+}$ oxidation states, endowing them with catalase- and superoxide dismutase-mimicking capabilities that allow them to scavenge free radicals in a regenerative manner without needing repetitive injection [44, 45] ,Their effectiveness via potent antioxidant and anti-inflammatory properties has been confirmed in several studies [46, 47] , showing promise for treating conditions associated with oxidative stress and neurodegeneration. By effectively eliminating ROS [48] , $CeO_2$NPs likely disrupt the OS cascade initiated by Al toxicity.

This reduction in free radicals consequently suppresses the activation of glial cells and the ensuing inflammatory and fibrotic pathways [49], thereby preserving neuronal integrity and function. This aligns with

studies where nanoceria extended the lifespan of neurons in culture, reduced apoptosis, and elevated genes associated with neuroprotection [50, 51]. The prevention of fibrosis, as seen in our results, directly supports their noted anti-fibrotic potential [52].The dose-dependent efficacy, with the 100 mg/kg dose proving more effective than the 10 mg/kg dose in preventing fibrosis, underscores the therapeutic potential of $CeO_2$NPs, this progression to utilizing them for neurodegenerative diseases is logical given their superior role as regenerative antioxidants [53].

Our results are consistent with other in vivo models, such as the study by [54] , which concluded that nanoceria strongly reduce neuronal death and inflammatory response in a rat model of retinal neurodegeneration. The results strongly support the hypothesis that the regenerative free-radical scavenging activity of $CeO_2$NPs mitigates OS, thereby breaking the cycle of inflammation and tissue damage that leads to fibrosis and degeneration of the neurons.

## CONCLUSION

This study demonstrates that aluminum induces pronounced neurotoxicity, evidenced by neuronal degeneration, gliosis, fibrosis, and inflammatory cell infiltration in rat brain tissue. Co-administration of cerium NPs markedly attenuated these pathological alterations, alleviating inflammation and preventing fibrosis. The observed neuroprotection is attributed to the unique antioxidant and anti-inflammatory properties of the nanoparticles, which counteract OS and interrupt neuroinflammatory cascades. Overall, these findings showed the potential for these nanoparticles as a promising therapeutic strategy for heavy metal–induced neurotoxicity and related neurodegenerative disorders.

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