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Original Research

Indole-3-Carbinol Confers Neuroprotection Against $AlCl_3$-Induced Alzheimer's Disease-Like Pathology by Attenuating Amyloidogenesis, Oxidative Stress, and Neuroinflammation

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Abstract

Background: Indole-3-carbinol (I3C) has been reported to possess neuroprotective effects on cognitive and memory functions. However, its protective effects against Alzheimer's disease (AD)-like pathology *in vivo* have not been explored. The current study evaluated the cognitive-enhancing and neuroprotective actions of I3C, as well as its ability to attenuate amyloid-beta (Aβ) formation following aluminum chloride ($AlCl_3$) treatment in rats. **Methods:** Male Wistar rats were allocated to the following experimental groups: control, $AlCl_3$, $AlCl_3$+I3C 50 mg/kg, $AlCl_3$+I3C 100 mg/kg, and $AlCl_3$+donepezil (DPZ) 5 mg/kg. Morris water maze was used to assess memory function. Amyloidogenesis, oxidative stress, neuroinflammation, apoptosis, and brain-derived neurotrophic factor (BDNF) levels were measured. Thioflavin S and Nissl staining were performed to study Aβ deposition and neurodegeneration. **Results:** I3C treatment improved memory in $AlCl_3$-treated rats, accompanied by diminished acetylcholinesterase (AChE) activity and elevated acetylcholine (ACh) levels. I3C also reduced Aβ deposition and levels of $A\beta_{1-42}$, amyloid precursor protein (APP), and β-site APP-cleaving enzyme 1 (BACE1), suggesting attenuation of amyloidogenic processes. In addition, I3C lowered reactive oxygen species (ROS) and malondialdehyde (MDA) levels and enhanced nuclear factor erythroid 2-related factor 2 (NRF2), heme oxygenase-1 (HO-1), catalase, and superoxide dismutase (SOD), indicating improved antioxidant defenses. I3C treatment also reduced the toll-like receptor 4 (TLR4), nuclear factor-kappa B (NF-κB), and NLRP3 levels, while increasing IL-10, suggesting attenuation of neuroinflammation. The treatment further reduced Bax, cytochrome c, and caspase-3 levels and increased Bcl2 levels, indicating attenuation of mitochondria-mediated apoptosis. Histological findings showed improved neuronal architecture in the CA1 region and cortex, along with increased BDNF levels. Across the parameters examined, the effects of I3C 50 mg/kg were similar to the actions of DPZ, however, I3C 100 mg/kg treatment showed better neuroprotective outcomes than DPZ. **Conclusion:** Overall, these findings indicate that I3C can counteract several features of $AlCl_3$-induced AD-like pathology, including amyloidogenesis, oxidative stress, neuroinflammation, apoptosis, and neuronal loss. Further studies are needed to elucidate the underlying mechanism of I3C in AD.

Keywords: Alzheimer's disease; aluminum trichloride; amyloid beta-peptides; indole 3 carbinol; oxidative damage; neuroinflammatory diseases; neuroprotection; memory

1. Introduction

Alzheimer's disease (AD) is the predominant form of neurodegenerative disease with dementia, and its prevalence continues to increase owing to population ageing [1]. AD is characterised by extracellular accumulation of amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles containing hyperphosphorylated tau, synaptic dysfunction, and progressive neuronal loss, eventually causing cognitive and memory impairment [2]. Although Aβ accumulation is considered a central hallmark of AD, increasing evidence suggests that oxidative stress and neuroinflammation are involved in AD progression and promote neurodegeneration [3].

AD is accompanied by excessive production of reactive oxygen species (ROS) with a diminished endogenous antioxidant defense system, keeping the brain in an oxidative stress environment [4]. The nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (NRF2/HO-1) signalling pathway represents one of the principal endogenous antioxidant mechanisms protecting neurons against oxidative damage. However, suppression of NRF2/HO-1 signalling results in redox imbalance, lipid peroxidation, mitochondrial dysfunction, and neuronal injury [5]. Moreover, oxidative stress has been shown to promote the formation of amyloid precursor protein (APP), thereby increasing Aβ production and accelerating AD pathology.

Neuroinflammation is another critical contributor to AD progression. Aβ and hyperphosphorylated tau activate

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toll-like receptor 4 (TLR4), leading to activation of the nuclear factor-kappa B (NF-κB) signalling pathway and subsequent upregulation of NLRP3 [6,7]. Persistent stimulation of the TLR4/NF-κB/NLRP3 inflammatory pathway amplifies neuroinflammation and contributes to the progression of AD [6]. Therefore, therapeutic approaches capable of simultaneously suppressing oxidative stress and neuroinflammation may provide greater neuroprotection than targeting a single pathological pathway [3].

In addition to oxidative stress and neuroinflammation, cholinergic dysfunction is a well-established pathological event of AD and its associated cognitive impairment [8]. Reduced acetylcholine (ACh) levels resulting from increased acetylcholinesterase (AChE) activity impair synaptic transmission and memory formation. Consequently, AChE inhibitors remain the primary pharmacological treatment for symptomatic management of AD, although they do not halt disease progression [9]. Another factor, brain-derived neurotrophic factor (BDNF), an important regulator of synaptic plasticity, neuronal survival, and memory, is markedly reduced in experimental models of AD [10]. Therefore, therapeutic agents that improve cholinergic neurotransmission and restore BDNF levels may offer additional neuroprotective benefits.

Naturally occurring phytochemicals from cruciferous vegetables have attracted considerable attention because of their antioxidant, anti-inflammatory, and neuroprotective properties [11]. One of them is indole-3-carbinol (I3C), which has demonstrated neuroprotective efficacy in several neurological disorders, including ischemic stroke, Parkinson's disease, and depression [12]. In our previous studies, I3C has been shown to significantly inhibit AChE activity, increase ACh levels, and improve cognitive function in models of global cerebral hypoperfusion [13] and scopolamine-induced amnesia [14], and inhibit AChE-mediated and self-induced Aβ aggregation [15]. These findings suggest that I3C possesses both cholinergic-enhancing and anti-amyloidogenic properties. Additionally, I3C has been shown to exhibit neuroprotective effects due to its ability to alleviate neuroinflammation and oxidative stress [12]. Despite these promising observations, whether I3C modifies the formation of Aβ and its associated oxidative stress and neuroinflammation has not been studied.

Therefore, this study examined the neuroprotective effects of I3C in an aluminum chloride ($AlCl_3$)-induced rat model of AD-like pathology. We hypothesised that I3C can ameliorate cognitive impairment by improving cholinergic neurotransmission, attenuating amyloidogenesis, triggering the NRF2/HO-1 antioxidant pathway, suppressing the TLR4/NF-κB/NLRP3 inflammatory pathway, inhibiting mitochondria-mediated apoptosis, and improving neuronal integrity through restoration of BDNF expression. Correspondingly, we have observed significant improvements in cognition and memory, enhancement of cholinergic function and BDNF, and suppression of amyloidogenesis, oxidative stress, neuroinflammation, and mitochondria-mediated apoptosis.

2. Materials and Methods

2.1 Chemicals

Indole-3-carbinol (CAS No. 700-06-1), $AlCl_3$ (CAS No. 7446-70-0), and Thioflavin S (CAS No. 1326-12-1), DCFDA (CAS No. 4091-99-0), and Cresyl violet (CAS No. 10510-54-0) were procured from Merck, India. ELISA kits were purchased from Krishgen Biosystems Pvt. Ltd., India. The biochemical reagents were obtained from the local distributor of analytical-grade reagents.

2.2 Experimental Animals

Adult male Wistar rats (240–260 g, 12–14 weeks old) were procured from Vyas Labs, Hyderabad, India (Committee for Control and Supervision of Experiments on Animals (CCSEA) registered No-2085/PO/RcBiBt/S/19/CPCSEA). The animals were housed (n = 4–5 per cage) under a standard laboratory environment (temperature of 25 ± 1 °C and relative humidity of 45–55%) with free access to water and a normal pellet diet. The experimental study was approved by the institutional animal ethics committee, SIMS College of Pharmacy, Guntur, India (protocol no 07/IAEC/SIMS/2025) and strictly adhered to the guidelines provided by CCSEA, India, in compliance with ARRIVE guidelines. Following a two-week adaptation period, rats were divided randomly using computer based = RAND() function, into five experimental groups (total 50 animals, n = 10 per group): control, $AlCl_3$ monotherapy (100 mg/kg), two combination groups receiving $AlCl_3$ (100 mg/kg) with either 50 mg/kg or 100 mg/kg of I3C, orally, and a positive control group receiving $AlCl_3$ (100 mg/kg) + donepezil (DPZ, 5 mg/kg, oral). The sample size for the present study was determined using G*Power software to achieve a statistical power of at least 80%. I3C and DPZ doses were selected based on their neuroprotective and memory-enhancing properties [14]. A fresh solution of $AlCl_3$ was prepared and orally administered for 42 days [16]. I3C was suspended in 0.5% carboxymethyl cellulose (CMC) and orally administered from day 29 to day 42. Similarly, DPZ was also administered. The control group of rats was given 0.5% CMC continuously for 42 days. Y-maze analysis was performed to confirm that memory was impaired and no animal was excluded from the study. Following that, I3C treatment was initiated from day 28 and continued to day 42. Morris water maze (MWM) was employed to study the learning and memory improvement following I3C treatment. Blinding was employed for behavioral experiments and their subsequent analysis. After the MWM experiment, all the animals were euthanised using isoflurane (3%) anaesthesia, followed by cervical dislocation, and brains were quickly isolated. For histopathological studies, under isoflurane anaesthesia, cardiac perfusion

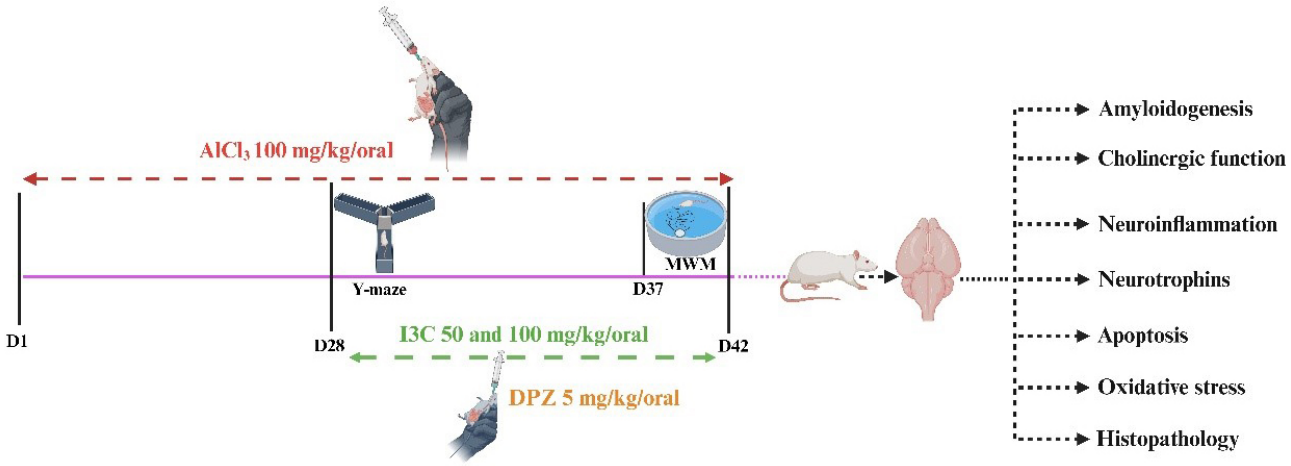


Fig. 1. Study design. DPZ, donepezil; $AlCl_3$, aluminum chloride; D, day; I3C, indole-3-carbinol; MWM, Morris water maze. Created in BioRender.com. Ramakrishna, K. (2026). https://BioRender.com/15etdm5.

was performed with phosphate buffer saline (PBS, pH 7.4), and then with 4% paraformaldehyde solution (PFA), and Nissl staining and thioflavin S staining were performed (n = 4). For biochemical and ELISA studies, animals under isoflurane anaesthesia were decapitated, and brains were collected and homogenised at 10,000 rpm for 10 min at 4 ºC (n = 6). The complete study design is represented in Fig. 1.

2.3 Y-maze and Morris Water Maze Test

The Y-maze procedures were applied to study the $AlCl_3$-induced memory impairment. Y-maze arms were marked as A, B, and C. Briefly, animals were placed in the centre of the Y-maze and allowed for 5 minutes to freely explore the arms of the Y-maze. An arm entry was recorded when both hind paws were inside the arm, and a correct alternation was defined as consecutive entries into all three different arms (e.g., ABC, BCA, or CAB). Then, spontaneous alternation (%) was calculated as per earlier reports [14]. Learning and memory were studied using the Morris water maze (MWM) test. Briefly, in a circular pool, animals were individually placed to find the hidden platform in one of the four zones. Animals were allowed 120 seconds to find the platform. Four trials with four different quadrants were performed per day, with at least a 10-minute interval between each trial for five days. On day 6, a probe trial was performed by removing the hidden platform and allowing animals to swim for 90 seconds. The animal's swimming was recorded and analyzed using ANY-maze video tracking software. Escape latency, time spent in the target quadrant, and number of entries to the target quadrant were counted to assess memory [13].

2.4 Thioflavin S Staining

After completion of behavioral studies, animals were anesthetised (isoflurane, 3%), and cardiac perfusion was performed with PBS and chilled 4% PFA solution, respectively. Then, brains were processed and embedded in paraffin, and 5 µm-thick sections were made using a microtome (Leica Histocore Autocut, Germany). Then, the brain sections were mounted on glass slides and dried overnight at room temperature. After drying, slides were prewashed with xylene for 5 minutes; thereafter, sections were gradually rehydrated by sequential immersion in different concentrations such as 100%, 90%, and 70% ethanol for 5 minutes each, followed by a water wash before staining. Subsequently, slides were incubated with 1% thioflavin S solution for 10 min at room temperature in a dark environment. Excess stain on the slides was cleared by a water wash followed by gradual dehydration for 3 minutes for each step. After that, the slides were air-dried for 5 to 10 min. The slides were mounted with DPX and observed under a fluorescence microscope (Leica microscope, Germany).

2.5 Nissl Staining

Brain tissue sections were deparaffinized in xylene for 5 minutes and rehydrated with absolute ethanol followed by 100%, 95%, 70%, and 50% ethanol. The sections were then stained with 0.5% filtered cresyl violet solution for 2–3 minutes and rinsed thoroughly with distilled water. Further, slides were dipped (2–3 times) in acid alcohol (0.25% glacial acetic acid + alcohol) to remove the excess stain. Subsequently, the sections were dehydrated through ethanol, and sections were mounted with DPX mounting medium and then allowed to air-dry and examined under a microscope [17]. Images were captured at 20× (CA1 hippocampus) and 40× (cortex) using a microscope (Leica microscope, Germany). The total cell count was measured in a blinded fashion.

2.6 Oxidative Stress Markers

Rat brains were quickly removed under deep anaesthesia and then homogenised in phosphate-buffered saline (PBS) to prepare a 10% (w/v) tissue homogenate. The homogenised solution was then centrifuged (Eppendorf 5425 R) at 10,000 rpm for 10 min at 4 °C. The obtained supernatant was collected for biochemical analysis to estimate oxidative stress parameters such as ROS [16], MDA [18], CAT [19], and SOD [20] activities as per earlier reports.

2.7 ELISA

$A\beta_{1-42}$ (KLR2456), APP (KLR3514), BACE1 (KLR1225), NRF2 (KLR1083), HO-1 (KLR4658), NF-κB (KLR0287), IL-10 (KLR0108), NLRP3 (KLM1627), TLR4 (KLR0080), Bax (KLR0034), Bcl2 (KLR0037), cytochrome c (KLR2901), and caspase-3 (KLR1648) ELISA kits were procured from Krishgen Biosystems Pvt. Ltd., India, and ELISA was performed as per the manufacturer's recommended guidelines using an antibody dilution factor of 1:100.

2.8 Statistical Analysis

The data obtained in this study are expressed as the mean ± standard deviation (SD). One-way ANOVA followed by Tukey's post hoc test was employed for identifying the statistical differences among the groups. Two-way ANOVA followed by Bonferroni's post hoc test was used to measure the escape latency in MWM. *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1 I3C Enhances Memory Through Cholinergic Improvement

Fig. 2 demonstrates the memory improvement following I3C treatment. $AlCl_3$-treated rats were observed to have increased AChE activity and lower ACh levels, which are associated with a memory decline (increased escape latency, decreased number of entries, and time spent in the target quadrant) compared to control group rats. I3C dose-dependently reduced the escape latency, enhanced the number of entries and the time spent in the target quadrant, and elevated the ACh levels by reducing AChE enzyme activity. No substantial differences between the I3C 100 mg/kg, DPZ, and control groups of rats. Among I3C doses, 100 mg/kg treated rats showed better cognitive and memory improvement. These findings suggest that I3C improves cholinergic neurotransmission, at least in part, through inhibition of AChE and restoration of ACh levels.

3.2 I3C Prevented Aβ Formation

The inhibition of Aβ formation in cortex and CA1 hippocampal neurons after I3C treatment is shown in Fig. 3. The thioflavin S staining qualitative analysis shows clear formation of Aβ in the cortex and hippocampal CA1 regions. I3C 100 mg/kg treatment shows lower Aβ in the cortex and CA1 neurons than in $AlCl_3$ group and DPZ-treated rats. Correspondingly, ELISA analysis showed that cortex and CA1 $A\beta_{1-42}$ levels were significantly higher in $AlCl_3$-treated rats than in control groups and I3C dose-dependently reduced $A\beta_{1-42}$ in $AlCl_3$-treated rats (Fig. 3C). Significant differences were observed between DPZ- and I3C-treated (50 and 100 mg/kg) $AlCl_3$-exposed rats, with I3C (100 mg/kg) exhibiting a higher reduction in $A\beta_{1-42}$ levels than DPZ, but not I3C 50 mg/kg treatment. Further, when compared to control groups, $AlCl_3$-treated rats showed elevated levels of APP (Fig. 3A) and BACE1 (Fig. 3B) compared to control groups of rats. I3C treatment substantially reduced the APP and BACE1 levels compared to $AlCl_3$- and DPZ-treated rats, in a dose-dependent manner. Overall, I3C 100 mg/kg treatment lowered the APP, BACE1, and $A\beta_{1-42}$ levels more than DPZ treatment, but the I3C 50 mg/kg treatment showed higher levels of these markers than DPZ treatment. These results suggest that I3C reduced Aβ formation by lowering BACE1 levels.

3.3 I3C Mitigated $AlCl_3$-Induced Oxidative Stress

Fig. 4 represents the antioxidant potential of I3C against $AlCl_3$-induced oxidative stress. Statistical analysis showed significant differences across the groups. $AlCl_3$-treated rats had substantially elevated ROS and MDA and reduced CAT and SOD enzyme activities and NRF2 and HO-1 protein levels compared with the control group. I3C treatment substantially lowered the ROS and MDA levels and elevated the NRF2 and HO-1 protein levels, along with increased CAT and SOD enzyme activities. The observed effects of I3C are dose-dependent. When compared with DPZ treatment, I3C 100 mg/kg shows superior antioxidant potential. These findings suggest that I3C mitigated $AlCl_3$-induced oxidative stress through its antioxidant effects.

3.4 I3C Suppressed the $AlCl_3$-Induced Neuroinflammation

Fig. 5 represents the anti-neuroinflammatory effects of I3C against $AlCl_3$-induced neuroinflammation. The inflammatory markers such as NF-κB, TLR4, and NLRP3 were significantly elevated in $AlCl_3$-treated rats compared to control rats, while IL-10 was reduced in $AlCl_3$-treated rats compared to the control group. I3C treatment substantially reduced the NF-κB, TLR4, and NLRP3 levels and elevated IL-10 in $AlCl_3$-intoxicated rats. Treatment with I3C at 100 mg/kg exhibited superior anti-neuroinflammatory effects when compared to DPZ-treated rats. These results indicate the anti-inflammatory effects of I3C leading to neuroprotection.

3.5 I3C Mitigated $AlCl_3$-Induced Mitochondrial-Mediated Apoptosis

The I3C's antiapoptotic properties against $AlCl_3$-induced apoptosis are shown in Fig. 6. The statistical data show that $AlCl_3$-intoxicated rats were identified with

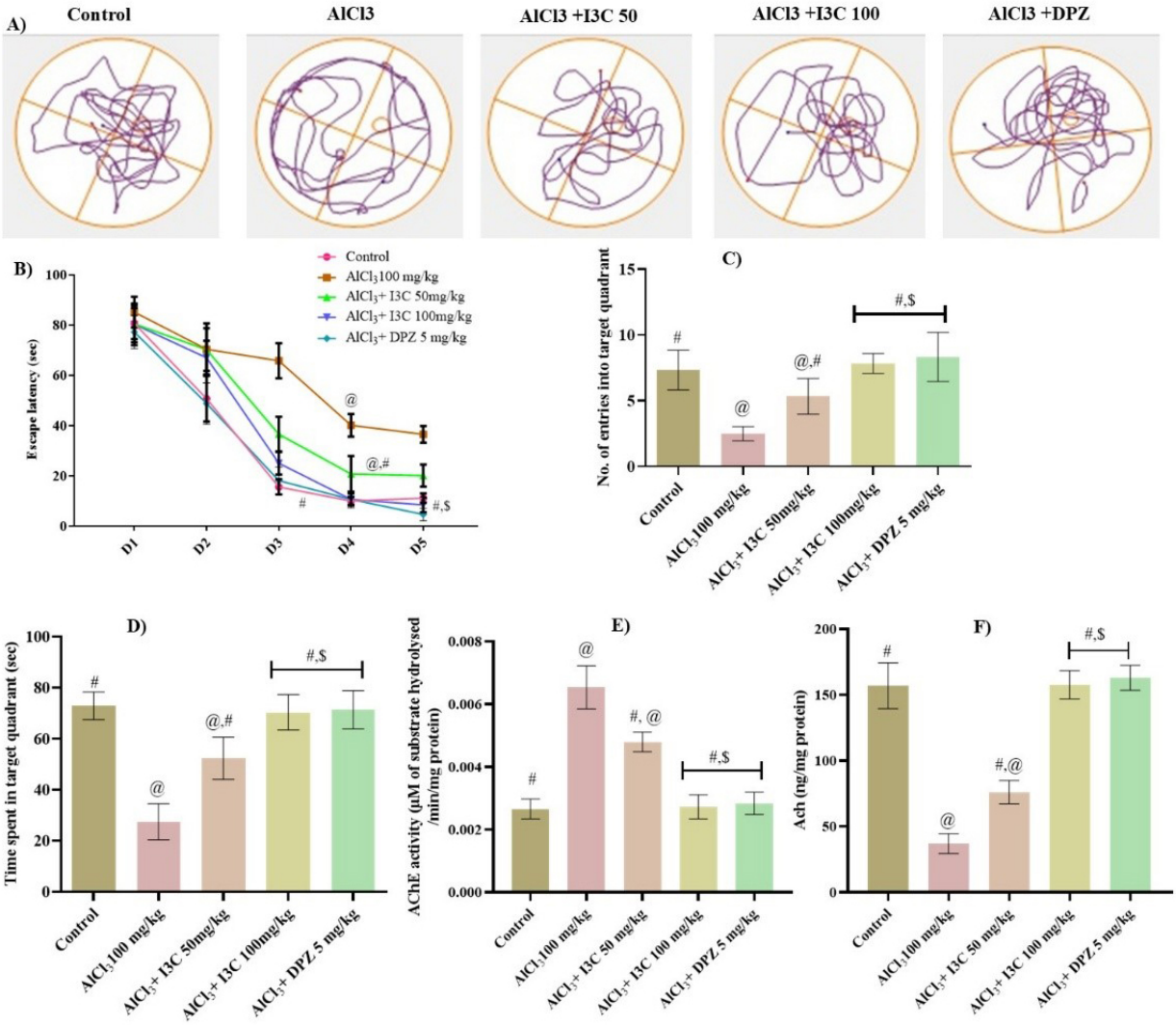


Fig. 2. I3C-mediated cholinergic and memory improvement. (A) indicates the selective trajectory plots of the probe trial in MWM. Escape latency, number of entries, and time spent in the target quadrant zone, AChE, and ACh levels are indicated in (B–F), respectively. $^{\#}p < 0.05$ vs $AlCl_3$, $^{@}p < 0.05$ vs control, $^{\$}p < 0.05$ vs $AlCl_3$+I3C 50 mg/kg. Two-way ANOVA followed by Bonferroni's post hoc test was applied for escape latency. The remaining data were calculated with one-way ANOVA using Tukey's post hoc analysis (n = 10 for behavioral analysis and n = 6 for acetylcholinesterase (AChE) and acetylcholine (ACh)).

significant elevation of Bax, cytochrome c, and caspase-3 levels, while Bcl2 protein levels decreased as compared to control group rats. I3C treatment in $AlCl_3$-intoxicated rats showed reduced Bax, cytochrome c, and caspase-3 levels and increased Bcl2 protein levels dose-dependently. Further, I3C 100 mg/kg treated rats exhibited substantial differences when compared with DPZ-treated rats. Collectively, the above observations indicate I3C as an antiapoptotic agent.

3.6 I3C Prevented Neuronal Loss by Increasing BDNF

The prevention of neuronal loss by I3C in $AlCl_3$-induced neurodegeneration or alterations in neuronal structure is depicted in Fig. 7. The Nissl staining images of the cortex and CA1 neurons show loss of neurons, their architecture, and alignment in $AlCl_3$-treated rats. Whereas I3C treatment improved the neurons number, architecture, and their alignment. Quantitatively, $AlCl_3$-intoxicated rats exhibited a substantial decline in cortical and CA1 neurons count than control rats. I3C treatment in $AlCl_3$-intoxicated rats showed greater improvement in cortical and CA1 neuronal number than in $AlCl_3$- and DPZ-treated rats. Similarly, $AlCl_3$-intoxicated rats exhibited lower BDNF levels compared to control animals. Whereas I3C treatment increased BDNF levels in $AlCl_3$-intoxicated rats. Further, I3C 100 mg/kg significantly elevated BDNF levels compared to DPZ- and untreated ($AlCl_3$) rats. Together, I3C prevented neuronal loss by enhancing the neurotrophin BDNF.

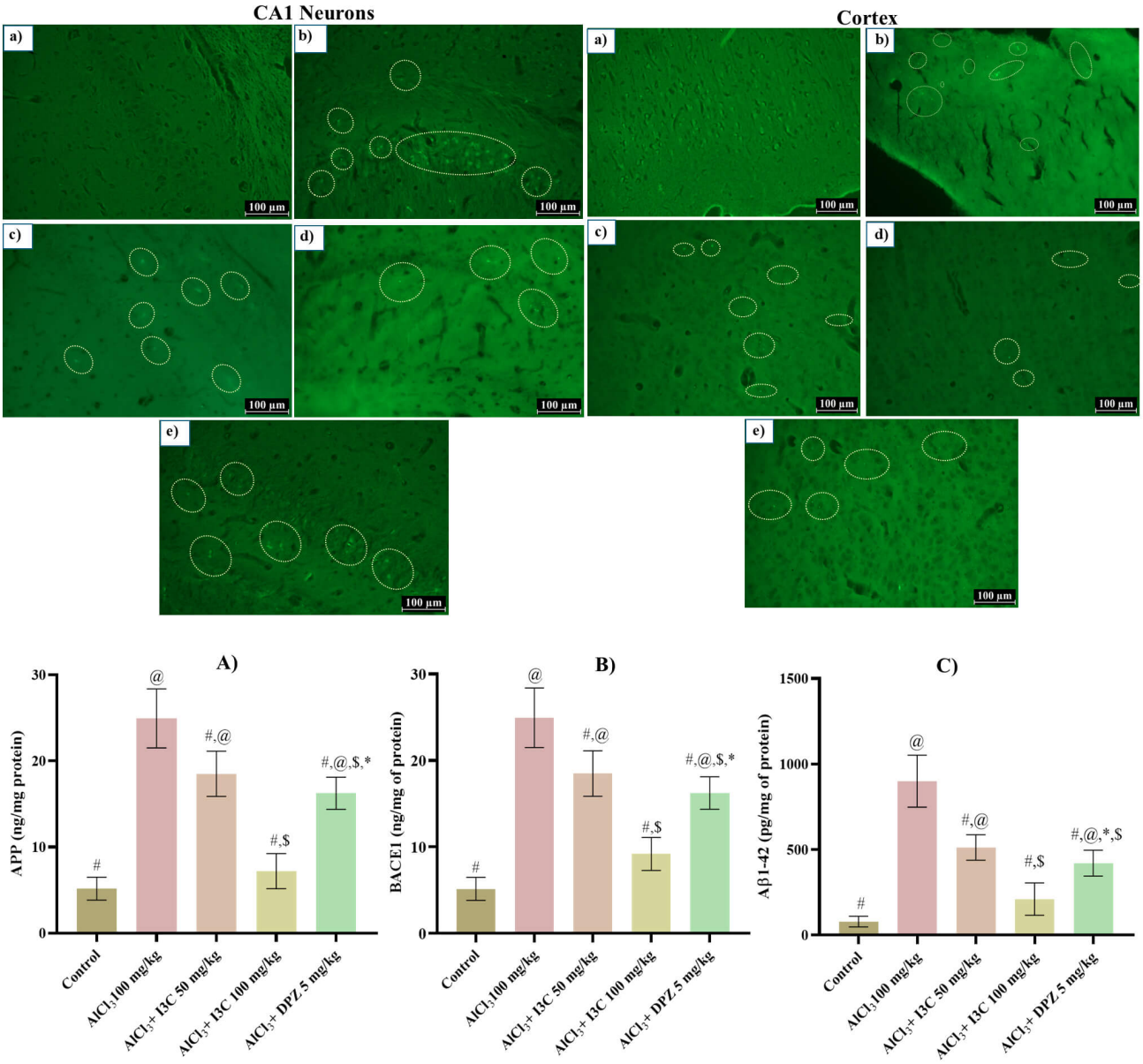


Fig. 3. The inhibition of Aβ$_{1–42}$ formation by I3C. The left and right panel images show Aβ formation for CA1 and cortical neurons, respectively. The figures labeled (a–e) represent their respective treatment groups for CA1 and cortical neurons; (a) control, (b) $AlCl_3$ 100 mg/kg, (c) $AlCl_3$+I3C 50 mg/kg, (d) $AlCl_3$+I3C 100 mg/kg, (e) $AlCl_3$+DPZ 5 mg/kg. The APP, BACE1, and Aβ$_{1–42}$ levels are represented in (A–C), respectively. The circles in the image represent the presence of amyloid beta-peptides. Scale bar = 100 µm. $^{\#}p <$ 0.05 vs $AlCl_3$, $^{@}p < 0.05$ vs control, $^{\$}p < 0.05$ vs $AlCl_3$+I3C 50 mg/kg, and $^{*}p < 0.05$ vs $AlCl_3$+I3C 100 mg/kg (n = 4 for thioflavin S staining and n = 6 for Aβ$_{1–42}$, APP, and BACE1).

4. Discussion

The current study demonstrates the memory-improving and neuroprotective roles of indole-3-carbinol (I3C) against an $AlCl_3$-induced experimental model of AD-like pathology. I3C improved cholinergic neurotransmission and attenuated Aβ formation and neuroinflammation by reversing the overactivation of the TLR4/NF-κB/NLRP3 pathway and mitochondrial-mediated apoptosis, and activated NRF2/HO-1 signalling. Further, I3C enhanced BDNF levels and improved the neuronal architecture of the CA1 region and cortex. Collectively, these findings suggest that I3C protects against neurodegeneration via modulating multiple pathological events associated with AD.

Aluminum chloride ($AlCl_3$) induces experimental AD-like pathology in preclinical models and is widely practised due to AD similarities, such as inducing cholinergic dysfunction, oxidative stress, neuroinflammation, and tau and amyloidogenesis [21]. In the present study, we have used an $AlCl_3$ dose (100 mg/kg) that was administered

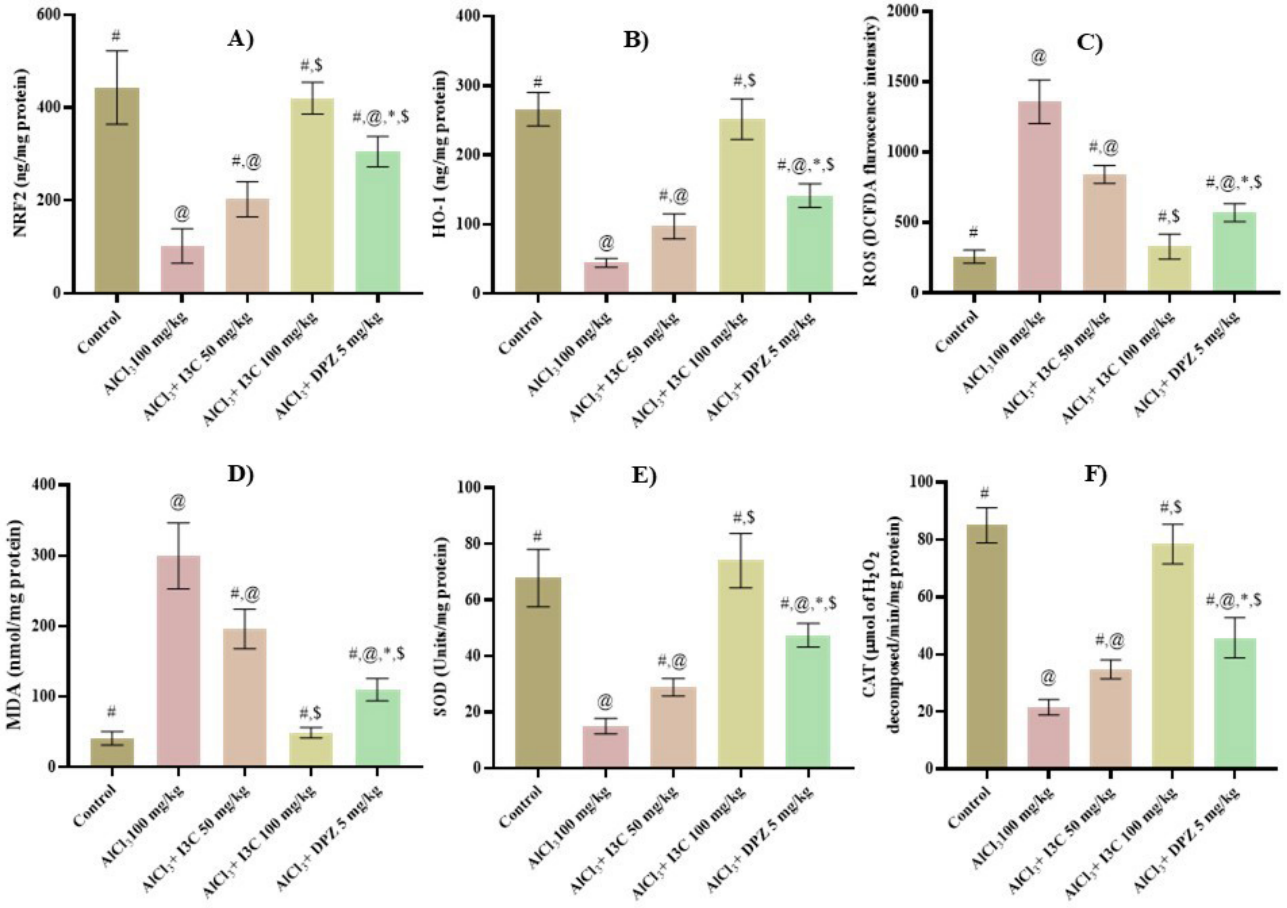


Fig. 4. The antioxidant effects of I3C against $AlCl_3$-mediated oxidative stress. (A–F) represent NRF2 and HO-1 protein levels, ROS fluorescence intensity, MDA levels, SOD activity, and CAT activity, respectively. $^{\#}p < 0.05$ vs $AlCl_3$, $^{@}p < 0.05$ vs control, $^{\$}p < 0.05$ vs $AlCl_3$+I3C 50 mg/kg, $^{*}p < 0.05$ vs $AlCl_3$+I3C 100 mg/kg (n = 6).

chronically to steadily induce moderate AD-like pathology. Consistent with previous reports [16,22] our study observed the above-mentioned pathophysiological events, which are seen in AD pathology, suggesting the establishment of AD-like pathology.

Aβ plaque deposition is widely used to assess AD progression and the therapeutic efficacy of anti-AD interventions [23,24]. $AlCl_3$-treated rats exhibited a marked increase in Aβ plaque deposition in CA1 neurons and cortex, as evidenced by thioflavin S staining. Consistently, quantitative ELISA analysis demonstrated a significant elevation in $A\beta_{1–42}$ levels, confirming enhanced amyloidogenesis following $AlCl_3$ administration. In contrast, I3C treatment significantly reduced both Aβ plaque deposition and $A\beta_{1–42}$ levels, indicating its potent anti-amyloidogenic activity. These findings suggest that I3C mitigates Aβ formation and accumulation, thereby potentially slowing the progression of AD pathology. In our previous study, we found that I3C inhibits the self-aggregation of Aβ peptides *in vitro* [15]. Consistent with those findings, the present study adds that I3C not only inhibits Aβ aggregation but also inhibits its formation. Since I3C markedly reduced Aβ deposition and $A\beta_{1–42}$ levels, we further investigated whether this effect was associated with modulation of BACE1. Our results demonstrated that I3C significantly reduced BACE1 levels, accompanied by decreased APP and $A\beta_{1–42}$ levels, suggesting that inhibition of BACE1-mediated amyloidogenic processing contributes, at least in part, to the anti-amyloidogenic effects of I3C. Given that γ-secretase also participates in Aβ generation [25], further studies are warranted to determine whether I3C additionally modulates other enzymes involved in APP processing. Collectively, these findings indicate that I3C possesses the potential to inhibit both Aβ formation and aggregation, thereby hindering amyloid pathology in AD partly through inhibiting BACE1.

Numerous studies have reported that aluminum induces oxidative stress by disrupting cellular redox homeostasis. Both postmortem studies of AD brains and preclinical models have demonstrated that oxidative stress is a key pathological feature of AD [26]. The NRF2/HO-1 pathway is a major endogenous antioxidant defense mechanism that protects against oxidative damage. However, aluminum suppresses NRF2/HO-1 signalling, thereby exacerbating oxidative stress [27], a phenomenon that is also

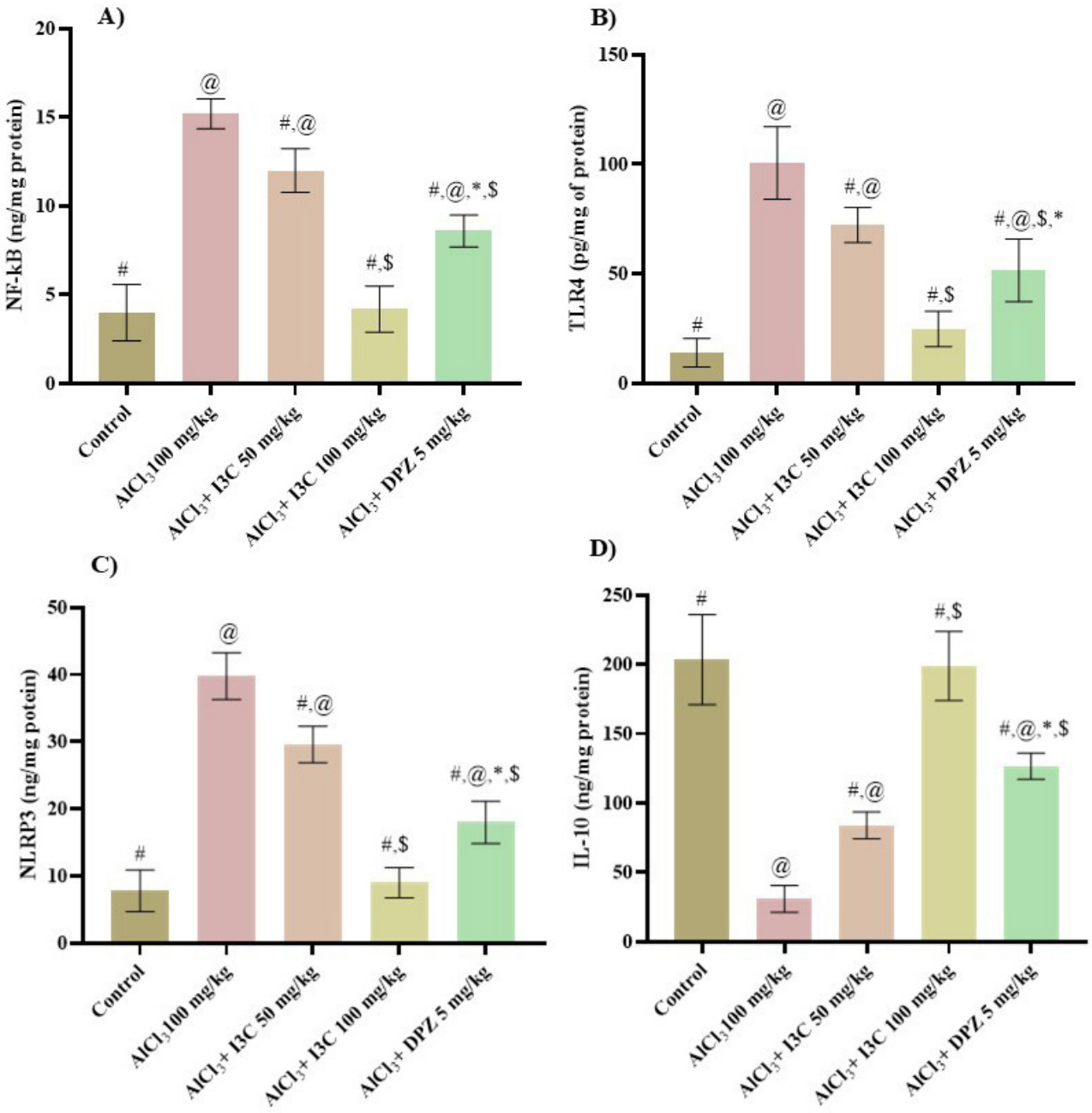


Fig. 5. The anti-inflammatory effects of I3C against neuroinflammation induced by $AlCl_3$. (A–D) indicate the NF-κB, TLR4, NLRP3, and IL-10 protein levels, respectively. $^{\#}p < 0.05$ vs $AlCl_3$, $^{@}p < 0.05$ vs control, $^{\$}p < 0.05$ vs $AlCl_3$+I3C 50 mg/kg, $^{*}p < 0.05$ vs $AlCl_3$+I3C 100 mg/kg (n = 6).

observed in human AD. In agreement with these observations, we observed increased ROS and MDA levels, accompanied by reduced SOD and CAT activities and decreased NRF2 and HO-1 expression in $AlCl_3$-treated rats, indicating severe redox imbalance. I3C treatment markedly reversed these alterations by reducing oxidative stress and restoring NRF2/HO-1 signalling, along with the activities of endogenous antioxidant enzymes. Previous studies have demonstrated that I3C exerts neuroprotective effects through its antioxidant properties [28,29,30]. Likewise, our earlier findings also showed that I3C possesses potent antioxidant activity [13,14,15]. Collectively, our findings imply that I3C's neuroprotective effects against AD are mediated through triggering the NRF2/HO-1 pathway, thereby restoring redox homeostasis.

Neuroinflammation represents a crucial pathological feature of AD, contributing to disease progression [6]. Aβ and tau proteins activate innate immune responses through pattern-recognition receptors, including TLR4, thereby activating NF-κB signalling and subsequent upregulation of

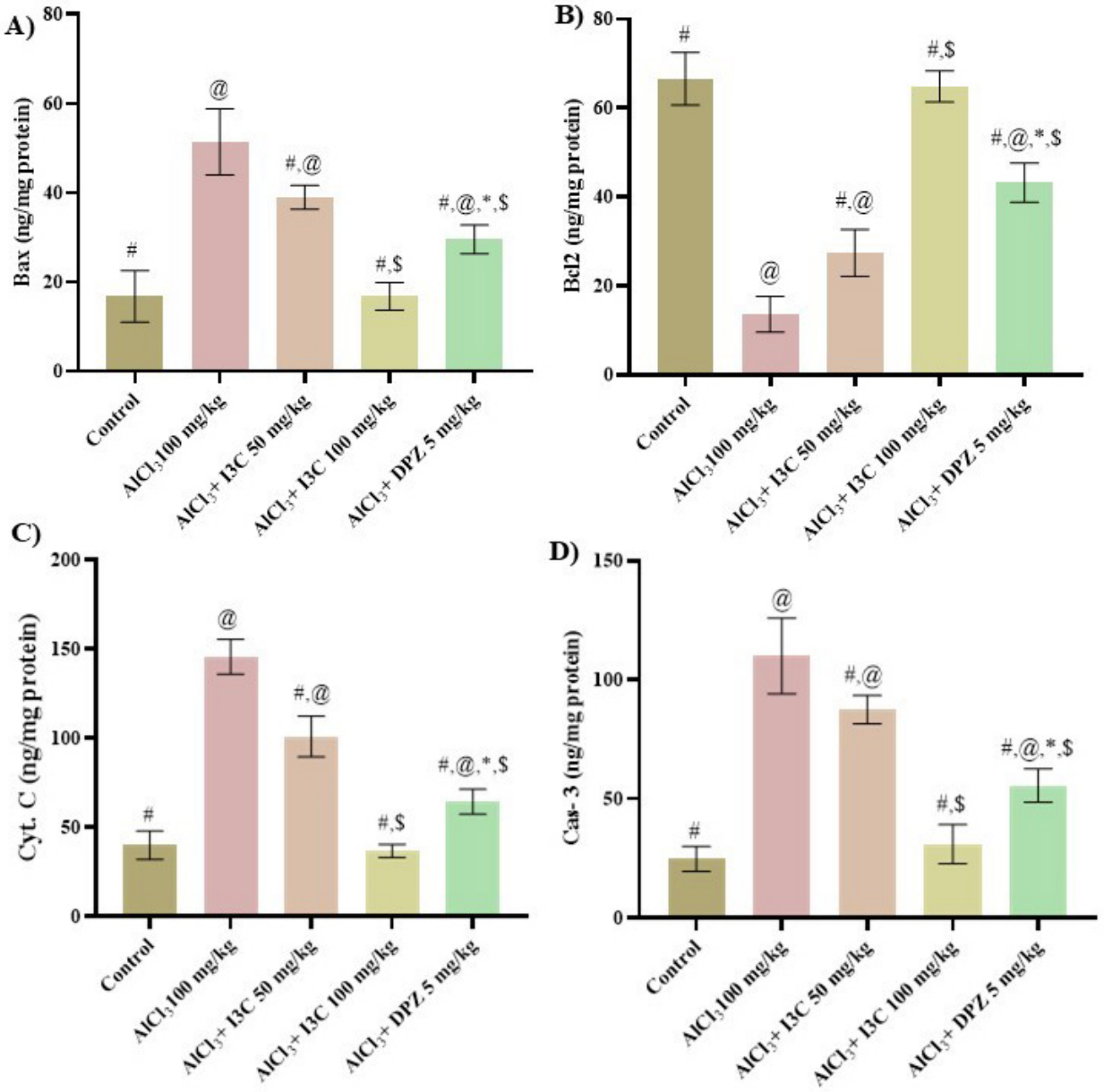


Fig. 6. The antiapoptotic effects of I3C. (A–D) represent Bax, Bcl2, cytochrome c and caspase-3 levels, respectively. $^{\#}p < 0.05$ vs $AlCl_3$, $^{@}p < 0.05$ vs control, $^{\$}p < 0.05$ vs $AlCl_3$+I3C 50 mg/kg, $^{*}p < 0.05$ vs $AlCl_3$+I3C 100 mg/kg (n = 6).

NLRP3 and pro-inflammatory cytokines [31,32]. Previous studies have reported that $AlCl_3$ activates the TLR4/NF-κB/NLRP3 signalling pathway, which contributes to the amplification of neuroinflammatory responses [6]. Furthermore, Aβ accumulation is associated with activation of TLR4 signalling, leading to NF-κB activation and increased NLRP3 expression [32]. Consistent with these reports, $AlCl_3$ administration significantly elevated TLR4, NF-κB, and NLRP3 levels, indicating activation of the TLR4/NF-κB/NLRP3 inflammatory signalling pathway. I3C treatment markedly attenuated these inflammatory responses by reducing TLR4, NF-κB, and NLRP3 levels and elevating the anti-inflammatory cytokine IL-10, suggesting the attenuation of neuroinflammation. Moreover, I3C simultaneously reduced Aβ accumulation along with the increased levels of TLR4, NF-κB, and NLRP3, suggesting that the anti-inflammatory effects of I3C contribute to the suppression of Aβ formation and Aβ-mediated stimulation of the TLR4/NF-κB/NLRP3 pathway or vice versa. Although we show a reduction in NLRP3 levels, the association and activation of the NLRP3 inflammasome were not directly evaluated in the present study; further investigations are required to determine whether I3C modulates inflammasome activation in addition to suppressing upstream inflammatory signalling.

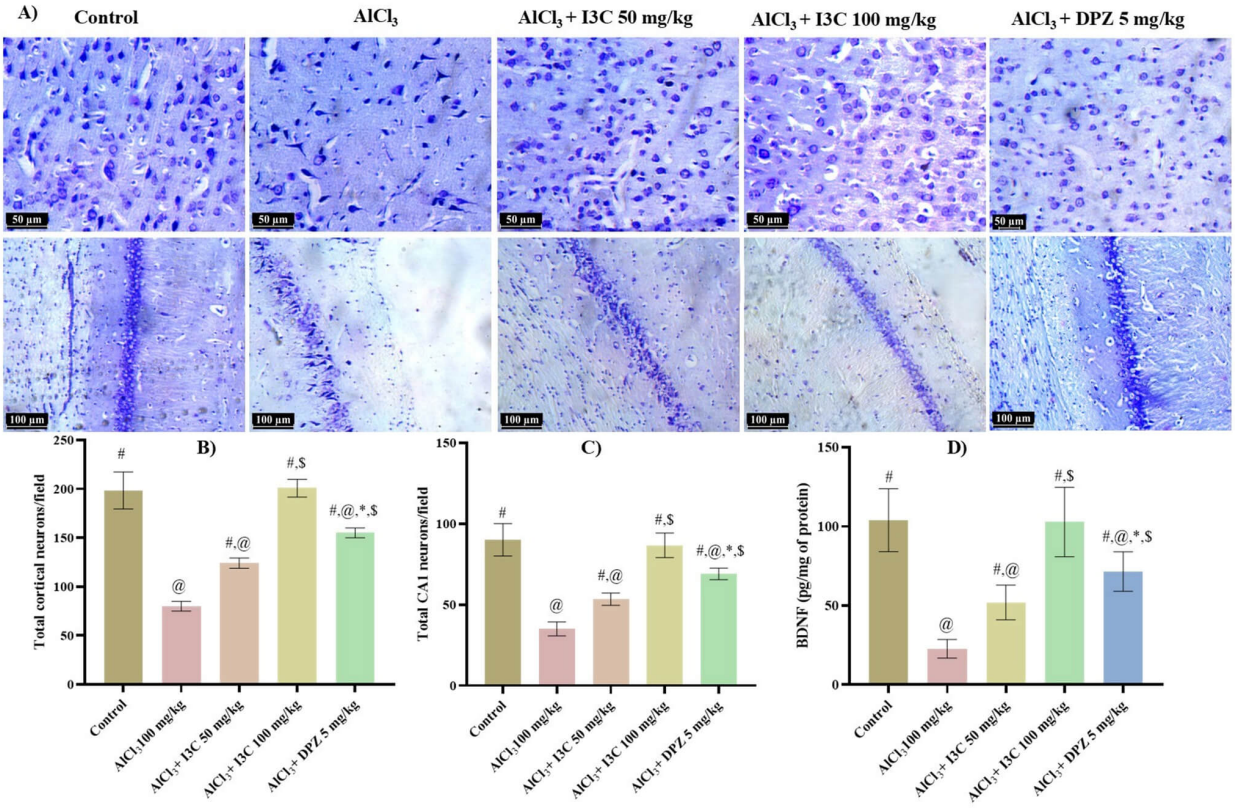


Fig. 7. I3C attenuates $AlCl_3$-induced neurodegeneration. (A) represents the Nissl staining images of the cortex (top row) and CA1 neurons (bottom row). Total cortical and CA1 neurons/field and BDNF levels are represented in (B–D), respectively. $^{\#}p < 0.05$ vs $AlCl_3$, $^{@}p < 0.05$ vs control, $^{\$}p < 0.05$ vs $AlCl_3$+I3C 50 mg/kg, $^{*}p < 0.05$ vs $AlCl_3$+I3C 100 mg/kg (n = 4 for Nissl staining and n = 6 for BDNF). The cortical images are captured at 40×, and CA1 images are captured at 20× magnification. Scale bars = 50 µm and 100 µm for cortex and CA1 neurons, respectively.

Apoptosis is a major pathological event contributing to neurodegeneration in AD [33,34]. In accord with previous findings [35], our study demonstrated that $AlCl_3$-intoxication markedly elevated the proapoptotic markers such as Bax, cytochrome c, and caspase-3, while reducing the antiapoptotic protein Bcl2, indicating mitochondria-mediated apoptotic pathway activation. I3C treatment significantly attenuated these apoptotic changes by reducing Bax, cytochrome c, and caspase-3 levels while restoring Bcl2 levels, suggesting inhibition of mitochondria-mediated neuronal apoptosis. These reductions in apoptotic markers were further supported by improvement in neuronal integrity and neuronal count. Further, $AlCl_3$-induced neurotoxicity was associated with decreased Nissl-positive cells in the cortex and CA1 of the hippocampus, suggesting neurodegeneration. I3C enhanced the Nissl-positive cells in these regions, emphasising that it prevented the $AlCl_3$-induced neurodegeneration. Therefore, our results allow us to conclude that the improved neuronal number in $AlCl_3$-intoxicated rats might be partly due to preventing mitochondrial-mediated apoptosis.

To further ascertain the reasons for the prevention of neuronal loss, we evaluated BDNF, a key regulator of neuronal survival, synaptic plasticity, and cognitive function, widely implicated in neurodegeneration of central nervous system diseases, including AD [36]. Several studies reported that $AlCl_3$-treated rats exhibited a significant reduction in BDNF levels [37]. Correspondingly, we have observed low levels of BDNF in $AlCl_3$-treated rats, whereas I3C treatment markedly enhanced BDNF levels in the brain. Previous studies have also demonstrated the upregulation of BDNF expression following I3C treatment, which supports its neuroprotective potential [38]. Similarly, we have observed increased BDNF levels following I3C treatment against AD-like pathology, suggesting that I3C enhanced neurotrophin levels. Indeed, BDNF is a neurotrophin, often promoting neuronal regeneration [39]. In support of the elevation of BDNF levels, we have observed a substantial increase in Nissl-positive cells in the brain, which is positively associated with BDNF levels, indicating that I3C partly or fully prevents neuronal loss by enhancing BDNF levels in AD. Taken together, these findings suggest that I3C mitigates neurodegeneration by inhibiting apoptosis while promoting neuronal survival and neurotrophic support.

Cholinergic dysfunction is a commonly observed underlying cause of cognitive and memory impairment in AD [8]. Currently, no disease-modifying therapy is available for managing AD, and the existing pharmacological interventions primarily support symptomatic relief by inhibiting AChE, thereby enhancing cholinergic neurotransmission [40]. In our previous studies, I3C was found to significantly inhibit AChE activity and reduce AChE-mediated Aβ aggregation [15] and improve cholinergic function in experimental models of chronic cerebral hypoperfusion [13] and scopolamine-induced memory impairment through AChE inhibition [14]. Aligned with the above memory-enhancing properties, I3C demonstrated significant improvement in memory by inhibiting AChE activity while simultaneously increasing ACh levels in $AlCl_3$-treated rats, representing improvement in cholinergic neurotransmission. Collectively, these findings suggest that I3C improves cognitive function, at least in part, by restoring cholinergic neurotransmission.

Further, we have assessed the I3C's nootropic and neuroprotective potential with donepezil (DPZ), a clinically approved AChE inhibitor used for the symptomatic management of AD. I3C-mediated (100 mg/kg) memory improvement and modulation of several pathological mechanisms associated with AD, including oxidative stress, neuroinflammation, amyloidogenesis, apoptosis, and neurodegeneration, showing superior effects compared with DPZ-treated rats, but not with I3C 50 mg/kg-treated rats. Similar observations were also reported in our previous study using a scopolamine-induced model of cognitive impairment, in which I3C demonstrated neuroprotective effects similar to or superior to DPZ intervention [14]. Collectively, these findings suggest that, in addition to improving memory, I3C exerts neuroprotection by targeting multiple pathological pathways involved in AD. Overall, the present study demonstrates that I3C ameliorates $AlCl_3$-induced AD-like pathology by attenuating amyloidogenesis, oxidative stress, neuroinflammation, apoptosis, and neurodegeneration while improving cognitive function.

5. Limitations

Although we reported anti-AD effects of I3C against $AlCl_3$-induced AD-like pathology, the present study has some limitations. For example, (i) the present study shows inhibition of Aβ formation through inhibiting BACE1; however, whether I3C also prevents tau hyperphosphorylation has not been evaluated, (ii) choline acetyltransferase (ChAT) enzyme is responsible for the biosynthesis of ACh and its activity is reported to be suppressed in AD, and our results concluded that the increased ACh levels are primarily attributed to inhibition of AChE enzyme activity [41]; however, whether I3C stimulates ChAT activity has not been determined, (iii) we have identified the reduced BDNF levels in AD and increased following I3C treatment; however, the downstream BDNF pathways have not been evaluated, and (iv) the detailed mechanism pertaining to NLRP3-mediated inflammasome inhibition by I3C has to be further studied.

6. Conclusion

In conclusion, I3C exhibited cognitive and memory-enhancing effects by improving cholinergic neurotransmission. I3C attenuated amyloidogenesis, as evidenced by reduced BACE1 and Aβ levels. Furthermore, I3C exerted neuroprotective effects by NRF2/HO-1 pathway activation, suppressing the TLR4/NF-κB/NLRP3 inflammatory signalling pathway, and inhibiting mitochondria-mediated apoptosis. In addition, I3C improved hippocampal neuronal architecture and increased BDNF levels, indicating protection against neurodegeneration. Collectively, these findings demonstrate that I3C ameliorates $AlCl_3$-induced AD-like pathology by targeting multiple interconnected pathological mechanisms while improving cognitive function. Further studies are required to underscore the detailed molecular mechanisms of the neuroprotective effects of I3C and to evaluate its translational potential for the treatment of AD.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LAV performed experiments, curated the data, analyzed it, and wrote the original draft. HKRD performed the research, collected the data, helped in the experimental process, and edited the manuscript. SY collected the data, investigated and analyzed the data. VPN was involved in investigation, formal analysis, and review and editing. Conceptualization, data curation, study design, supervision, and review and editing of the original draft by RK. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The experimental study was approved by the institutional animal ethics committee, SIMS College of Pharmacy, Guntur, India (protocol no 07/IAEC/SIMS/2025) and strictly followed the guidelines provided by CCSEA, in compliance with ARRIVE guidelines. The study strictly adhered to the 3Rs principles to avoid animal suffering during the experiments.

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Conflicts of Interest

The authors declare no competing interests. Lakshmi Anusha Vinjavarapu, Hari Krishna Reddy Dontiboina, Srikanth Yadava, and Ramakrishna Kakarla are affiliated with Koneru Lakshmaiah Education Foundation, the judgments in data interpretation and writing were not influenced by this relationship.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL57221.

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