Ind. J. Pharm. Edu. Res., 2026; 60(1):258-269.
https://www.ijper.org

Original Article

Neuroprotective Effect of *Inula racemosa* on Chronic Stress-Aluminum Chloride Induced Memory Deficits

Bhagya Venkanna Rao*, Kanimozhi Loganathan, Sushma Raju, Ramya Vasudev

Department of Pharmacology, KLE College of Pharmacy (KLE Academy of Higher Education and Research -Belagavi (Deemed to be University), Bengaluru, Karnataka, INDIA.

ABSTRACT

Introduction: Alzheimer's Disease (AD) is characterized by cognitive impairment resulting from the accumulation of amyloid beta and tau plaques, reduced Brain-Derived Neurotrophic Factor (BDNF) expression, neuronal death, and brain inflammation. Chronic stress accelerates aging, while aluminum, a neurotoxin, is implicated in AD pathology. **Objectives:** This study aimed to assess the potential beneficial effects of *Inula racemosa* on cognitive deficits induced by chronic stress and aluminum chloride exposure. **Materials and Methods:** Rats were subjected to restraint stress (3 hr per day) and aluminum chloride (100 mg/kg) for 21 days. Following this, *Inula racemosa* (200 and 400 mg/kg) was administered for 14 days. Cognitive function was assessed through the sucrose preference test, forced swim test, Novel Object Recognition Test (NORT), and T-maze task. Biomarkers such as amyloid beta, Brain Derived Neurotrophic Factor (BDNF), and antioxidants Superoxide Dismutase (SOD), Malondialdehyde (MDA), Glutathione (GSH), and Catalase (CAT) were measured in the hippocampus and prefrontal cortex. **Results:** Chronic stress and aluminum chloride exposure led to decreased antioxidant levels, reduced BDNF expression, cognitive decline, increased amyloid beta plaques, and depressive-like behavior. Treatment with *Inula racemosa* mitigated these effects, improving cognition by restoring recognition memory in the NORT and spatial working memory in the T-maze task while also alleviating depressive behavior. Furthermore, it reduced oxidative stress, increased antioxidant levels in the hippocampus and prefrontal cortex, decreased amyloid beta plaque formation, and restored BDNF expression. **Conclusion:** *Inula racemosa* exhibited antioxidant and neuroprotective properties, offering protection against neurodegeneration. These findings underscore the potential of phytochemicals as neuroprotective agents.

Keywords: Aluminum Chloride, chronic Stress, Cognitive Impairment, Amyloid Beta, BDNF, *Inula racemosa*.

Correspondence:
Dr. Bhagya Venkanna Rao
Professor, Department of Pharmacology, KLE College of Pharmacy (KLE Academy of Higher Education and Research -Belagavi (Deemed to be University), Belagavi-590010, Karnataka, INDIA.
Email: bhagyavrao.klecop@gmail.com/bhagyapkumar@gmail.com

Received: 14-04-2025;
Revised: 09-06-2025;
Accepted: 30-07-2025.

INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders affecting older individuals, marked by cognitive decline and memory loss. It is characterized by the formation of amyloid plaques and neurofibrillary tangles, primarily in the brain's cerebral gyri.[1] These plaques and tangles cause brain damage and result in widening of the sulci. The main contributor to cognitive impairment in AD is synaptic loss, which can be detected even in the early stages of Mild Cognitive Impairment. These pathological alterations disrupt neuronal function and drive the progression of AD.[2]

Chronic stress plays a key role in the advancement of AD, affecting both physical and mental health.[3] Stress activates physiological responses, including the stimulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and an increase in Glucocorticoid (GC) levels, such as cortisol.[4,5] These changes adversely affect the hippocampus, a region essential for memory and cognitive functions.[6,7] In AD patients, elevated cortisol levels worsen synaptic loss, impair memory, and accelerate disease progression by increasing amyloid beta production.[8]The link between chronic stress, elevated GC levels, and AD highlights the importance of managing stress to protect cognitive health.[9]

Exposure to Aluminum (Al) is a significant factor in the development of Alzheimer's disease (AD). Aluminum accumulates in brain tissue, contributing to the formation of Neurofibrillary Tangles and amyloid plaques, which are key characteristics of AD.[10] Elevated aluminum levels interfere with neuronal function and promote the accumulation of amyloid Beta-Protein Precursor (APP), leading to neurodegeneration and cognitive decline.[11] Chronic aluminum exposure is linked to neurotoxic effects, such as oxidative stress and neuronal apoptosis,

DOI: 10.5530/ijper.20261730

which intensify memory impairments and other symptoms associated with neurodegenerative diseases like AD.[12,13]

Inula racemosa, a medicinal plant from the Inula genus, offers promising therapeutic potential for neurodegenerative diseases like AD.[14] The root of *Inula racemosa* contains sesquiterpenes and eudesmalolide esters, which exhibit various biological activities, including anti-inflammatory and antioxidant properties.[15] Alantolactone, a sesquiterpene lactone found in this herb, has shown promise in reducing oxidative stress and protecting neurons.[16] This study investigated whether Inula racemosa could improve cognitive impairment caused by chronic stress and aluminum chloride exposure.

MATERIALS AND METHODS

Experimental Animals

Male Wistar rats (180-200 g) of similar age (1.5-2 months) were procured from *In vivo* Biosciences (1165/PO/RcBiBt-S/NRC-L/08/CPCSEA). The animals were kept in polypropylene cages under the conditions of a 12-hr light-dark cycle, with the temperature maintained at 22±3ºC and a relative humidity ranging from 50-70%. They were allowed to have access to rodent food and drink water ad libitum. Before studies, animals were sheltered in an animal care facility for a week to allow them to adjust to their surroundings. Animals were monitored for any illnesses, infections, or toxicological symptoms. The Institutional Animal Ethics Committee (IAEC) of KLE College of Pharmacy, Bengaluru, approved the study.

Drugs

- Aluminum chloride hexahydrate was procured from Yarrow Chem Products, Maharashtra.
- *Inula racemosa* rhizomes were collected from Manipur, Mao Trip, and their extracts were given by Green Chem in Bengaluru, India, for use as test substances in the study. Dr. N. Dhatchanamoorthy, Assistant Professor, Plant Systematic and Nomenclature, Foundation for Revitalization of Local Health Traditions, Bengaluru 560064, verified the authenticity of the rhizomes.
- The standard drug, piracetam (injection), was purchased from a pharmacy. The drugs used for the study were in analytical grade, $AlCl_3$ and *Inula racemosa* Hook. f. were dissolved in distilled water for oral administration. The standard drug piracetam were available as injection liquid and were given by Intra-Peritoneal (i.p) administration.

Chronic Restraint Stress (CRS)

Animals were exposed to chronic restraint stress for 3 hr daily over a period of 21 days.[17]

Group of animals

Animals were segregated in to five groups each group containing 8 animals.

Group I: Normal control, no induction of stress and were given saline administration for 21 days. Group II: Animals were exposed to restraint stress (3hr/day) and $AlCl_3$ (100 mg/kg, orally) for 21 days. Group III, Group IV and Group V: Animals were exposed to restraint stress (3h/day) along with $AlCl_3$ (100 mg/kg, orally) for 21 days and were given *Inula racemosa* Hook. f. (200 mg/kg, orally), (400 mg/kg, orally) and Piracetam (200 mg/kg, i.p), as treatment for 14 days.

Behavioral tests

Sucrose Preference Test

The Sucrose Preference Test (SPT) is used to assess behavioral depression, particularly anhedonia. The test was conducted over a 3-day period. During the 48-hr habituation phase (spanning 2 days), each animal had access to two bottles in their cage: one containing drinking water and the other with a 1% w/v sucrose solution. The animals' intake of sucrose solution and water was measured every 24 hr, and the positions of the bottles (right and left) were alternated to prevent position bias. After the habituation period, the animals underwent an 18-hr fast without food or water, followed by a 2-hr testing phase. At the end of the test, the remaining liquid in each bottle was measured to determine the total fluid consumption. The sucrose preference score was calculated as a percentage of the total fluid intake.[18,19]

$$\% \text{ Sucrose preference} = \frac{\text{Sucrose water consumed}}{\text{Total liquid consumed}} \times 100$$

Forced Swim Test

The Forced Swim Test (FST) was used to assess behavioral despair in rats over a two-day period. On the first day, a familiarization session was conducted. Rats were placed in a water-filled plastic container (maintained at 23-25ºC) with a depth of 35 cm, ensuring they could not touch the bottom with their feet, and allowed to swim for 15 min. Afterward, they were removed from the water, thoroughly dried, warmed under a lamp, and returned to their home cages. The test session took place the following day. Rats were again placed in the water-filled container and allowed to swim for 5 min. Their behavior during this period was recorded on video for later analysis. Immobility was defined as passive floating in the water, with the rats only moving to keep their nose or head above the surface. Active climbing or swimming along the container walls was not considered immobility. The data from this test were presented as the percentage of time spent immobile.[18,19]

Novel object recognition test

The study involved several phases conducted in an open arena with rats. The first phase was a 5-min acclimatization session,

allowing the animals to familiarize themselves with the arena. Following day, the rats were placed in the arena with two objects for a 10-min habituation phase, during which they had the opportunity to explore both objects equally. After the habituation period, the rats were tested 24 hr later by returning them to the arena, where one of the objects was replaced with a new one. This test lasted 10 min, and the rats' behavior was recorded on video for later analysis. The key parameters assessed included the time spent interacting with the novel object (Tn, in seconds), the time spent with the familiar objects (Tf, in seconds), and the calculation of a discrimination index, which indicated the rats' preference for the novel object compared to the familiar ones.[20-22]

$$\text{Discrimination Index (DI)} = \frac{\text{Tn} - \text{Tf}}{\text{Total time with both objects}}$$

T-maze test

Spatial memory was evaluated using the T-maze rewarded alternation task. The maze consists of a start arm (45 cm x 10 cm x 10 cm) and two target arms (30 cm x 10 cm x 10 cm). The testing procedure involved three phases:

1. **Acclimatization Phase:** Rats were partially food-deprived for 24 hr before being placed in the T-maze for a 15-min session. After spending 30 sec in the start box, the door was opened, allowing the rats to explore the goal arms and eat food pellets placed in each arm.
2. **Acquisition Phase:** During this phase, rats explored the T-maze for 15 min, similar to the acclimatization phase. However, food pellets were only placed in one of the goal arms, and the rats were required to alternate between the arms to receive the reward. Each rat completed 10 trials, and the number of days needed to achieve an 80% success rate in obtaining the reward was recorded. There was a 30-sec interval between trials, and the maze was cleaned with 70% alcohol between each trial.
3. **Retention Test:** After the final training session, a retention test was conducted following a two-day interval. The rats underwent 10 consecutive trials with a 30-sec inter-trial interval. The focus was on counting the number of errors, which were defined as instances when the rat entered a non-rewarded arm.[17]

Biochemical estimation

a. **Tissue Preparation:** After the behavioral tests, the rats were euthanized, and their brains were quickly dissected to isolate the hippocampus and prefrontal cortex. The tissue samples were homogenized by blending with ice-cold phosphate buffer (pH 7.4). Following centrifugation at 5,000 g for 5 min at 4°C, the resulting homogenates were stored at -80°C for further analysis. The hippocampal and prefrontal cortex homogenates were analyzed for oxidative stress and antioxidant markers using ELISA assay kits. Malondialdehyde (Cat. No.: ER1878Ra) was used as the oxidative stress marker, while the antioxidant markers measured included superoxide dismutase (Cat. No.: E0290MO), catalase (Cat. No.: E0076MO), and GSH (Cat. No.: EA0104MO).

b. **Biomarker Estimation:** Enzyme-linked immunosorbent assay (ELISA) kits were used to measure the levels of BDNF (Cat. No.: E0476Ra) and amyloid beta-peptide 1-40 (Aβ1-40, Cat. No.: E0092Ra) in the prefrontal cortex and hippocampus. All assays were performed according to the manufacturer's instructions.

Statistical Analysis

Data were analyzed using GraphPad Prism 5.0 software. Significant differences between groups were determined using one-way ANOVA followed by Tukey's *post hoc* test, as well as two-way ANOVA with Bonferroni post hoc test for subsequent group comparisons. Data are presented as Mean ± SEM.

RESULTS

Effect of *Inula racemosa* treatment on different behavioral parameters in chronic restraint stress and aluminum chloride-induced Alzheimer's disease

Effect of Inula racemosa on chronic restraint stress and aluminum chloride-induced anhedonia

The sucrose preference test, which measures anhedonia (a depressive-like behavior) in rats, revealed the following findings: On Day 1, rats in the CRS +$AlCl_3$ group (Figure 1A: $F_{4,35}$=42.56, p<0.001) consumed significantly less sucrose water compared to the normal control group. However, treatment with *Inula racemosa* at doses of 200 mg/kg and 400 mg/kg significantly increased (p<0.001) sucrose water intake in this group. On Day 2, when compared to the normal control group, the CRS+$AlCl_3$ rats showed a reduced preference for sucrose water (Figure 1B: $F_{4,35}$=78.80, p<0.001). Treatment with the standard drug and *Inula racemosa* (200 mg/kg and 400 mg/kg) led to a significant increase in sucrose water consumption (p<0.001). On the final testing day, the CRS+$AlCl_3$ rats (Figure 1C: $F_{4,35}$=12.47, p<0.001) again consumed significantly less sucrose water than the normal control group. In contrast, *Inula racemosa* treatment at both 200 mg/kg and 400 mg/kg doses significantly enhanced the preference for sucrose water (p<0.001).

Effect of *Inula racemosa* on chronic restraint stress and aluminum chloride-induced bhavioral despair in the Forced Swim Test (FST)

The forced swim test was utilized to assess behavioral despair, measured by the duration of immobility. The CRS+$AlCl_3$ group displayed a significant increase in immobility time (Figure 2:

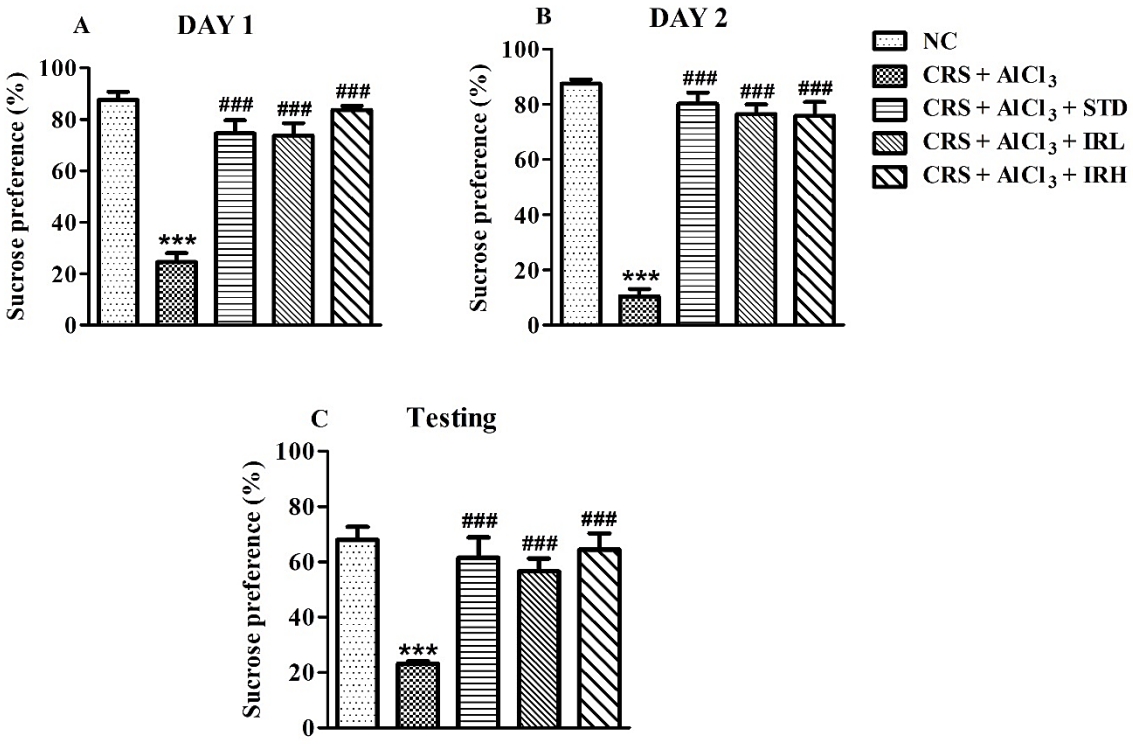

Figure 1: Effect of *Inula racemosa* on chronic restraint stress and aluminum chloride-induced anhedonia. (A) Day 1 ($F_{4,35}$=42.56, p<0.001); (B) Day 2 ($F_{4,35}$=78.80, p<0.001); (C) Testing Day($F_{4,35}$=12.47, p<0.001). NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as mean±SEM. Statistical analysis was done using a one-way ANOVA with *post hoc* test (Tukey's). ***p<0.001 as compared to the normal control; ###p<0.001 as compared to the disease control group.

$F_{4,35}$=12.14, p<0.001) compared to the normal control group. However, treatment with high doses of *Inula racemosa* and the standard drug led to a significant reduction in immobility time (p<0.001). In contrast, animals treated with a low dose of Inula racemosa did not show any improvement in their depressive-like behavior.

Effect of *Inula racemosa* treatment on chronic restraint stress and aluminum chloride-induced cognitive deficits in Novel Object Recognition Test (NORT)

In comparison to the normal control group, the CRS+$AlCl_3$ group spent less time with novel objects (Figure 3B: $F_{4,35}$=28.59, p<0.001) and more time exploring familiar objects (Figure 3A: $F_{4,35}$=35.99, p<0.001), indicating an inability to differentiate between the two. However, rats treated with *Inula racemosa* (400 mg/kg) and the standard drug were able to distinguish between familiar and novel objects, with their recognition memory restored (p<0.001). These groups spent more time exploring the novel objects than the familiar ones. In contrast, rats treated with the lower dose of *Inula racemosa* (200 mg/kg) showed no improvement.

The CRS+$AlCl_3$ group exhibited a reduced recognition index (Figure 3C: $F_{4,35}$=94.55, p<0.001), failing to distinguish between novel and familiar objects when compared to the normal control. Treatment with a high dose of *Inula racemosa* (400 mg/kg) and the standard drug resulted in a significant increase in the recognition index (p<0.001) compared to the disease control group. In contrast, the low dose of *Inula racemosa* (200 mg/kg) slightly improved the recognition index, partially restoring memory (p<0.05). Rats in the CRS+$AlCl_3$ group showed a significantly lower discrimination ratio compared to the control group (Figure 3D: $F_{4,35}$=83.77, p<0.001). However, treatment with *Inula racemosa* at both 200 mg/kg and 400 mg/kg doses, along with the standard drug, significantly enhanced the discrimination ratio compared to the $AlCl_3$ group (p<0.001).

Effect of *Inula racemosa* treatment on chronic restraint stress and aluminum chloride-induced altered spatial working memory in the T-maze task

The rewarded alternation task, which assesses spatial learning and working memory, is a key parameter measured in the T-maze. During the training phase, the CRS+$AlCl_3$ group, showing both an interaction effect (Figure 4A: $F_{20,175}$=1.298, p<0.001) and a time effect ($F_{4,175}$=13.83, p<0.001), made more errors in selecting the correct options compared to the normal control group. In

contrast, the *Inula racemosa* treated groups (200 mg/kg and 400 mg/kg) demonstrated an increase in correct choices (p<0.001) compared to the disease control group, indicating a significant improvement in spatial learning and memory during the training sessions.

In the retention test, the CRS+$AlCl_3$ group (Figure 4B: $F_{4,35}$=14.98, p<0.001) made significantly fewer correct choices relative to the normal control group. Meanwhile, *Inula racemsa* (200 mg/kg and 400 mg/kg) has restored their spatial learning and working memory by increasing correct choices (p<0.001) compared to the disease control group.

Effect of *Inula racemosa* treatment on biomarker expression in chronic restraint stress and aluminum chloride-induced Alzheimer's disease

Effect of Inula racemosa treatment on chronic restraint stress and aluminum chloride-induced altered BDNF levels in the hippocampus

BDNF levels in the hippocampus were measured using the ELISA method to investigate the mechanism behind *Inula racemosa*'s memory-enhancing and neuroprotective effects. Analysis of variance revealed that the CRS+$AlCl_3$ group had significantly lower BDNF levels in the hippocampus compared to the normal control group (Figure 5: $F_{4,25}$=176.4, p<0.001). However, rats treated with 200 mg/kg and 400 mg/kg of *Inula racemosa* showed a significant increase in BDNF levels (Figure 5: $F_{4,25}$=176.4, p<0.001), indicating neurotrophic support.

Effect of *Inula racemosa* treatment on chronic restraint stress and aluminumchloride-induced altered amyloid beta ($A\beta_{1-40}$) levels in the hippocampus and prefrontal cortex

The results showed that the CRS+$AlCl_3$ group had higher levels of amyloid beta deposition in the hippocampal regions (Figure 6A: $F_{4,25}$=55.22, p<0.001) and prefrontal cortex (Figure 6B: $F_{4,25}$=76.12, p<0.001) than the normal control group. On the other hand, administration of two doses of *Inula racemosa* resulted in a partial reduction of amyloid beta buildup in the hippocampus (Figure 6A: $F_{4,25}$=55.22, p<0.01). Amyloid beta levels were shown to be significantly reduced in the prefrontal cortex by a high dose of *Inula racemosa* (Figure 6B: $F_{4,25}$=76.12, p<0.001) and, partially, by a low dose (Figure 6B: $F_{4,25}$=76.12, p<0.01).

Effect of *Inula racemosa* treatment on chronic restraint stress and aluminum chloride exposure activated oxidative stress and anti-oxidant markers in the brain

The effect of oral administration of *Inula racemosa* on oxidative stress was assessed by measuring MDA (Malondialdehyde, a marker of lipid peroxidation) levels and antioxidant enzymes (CAT, GSH, and SOD) in the hippocampus and prefrontal cortex. In the CRS+$AlCl_3$ group, MDA levels were significantly higher (Figure 7D: $F_{4,25}$=239.9, p<0.001) in the hippocampus compared to the normal control. However, treatment with *Inula racemosa* (200 mg/kg and 400 mg/kg) significantly reduced MDA levels compared to the CRS+$AlCl_3$ group (Figure7D: $F_{4,25}$=239.9, p<0.001). Additionally, SOD (Figure 7B: $F_{4,25}$=135.5, p<0.001), CAT (Figure 7C: $F_{4,25}$=63.65, p<0.001), and GSH levels (Figure

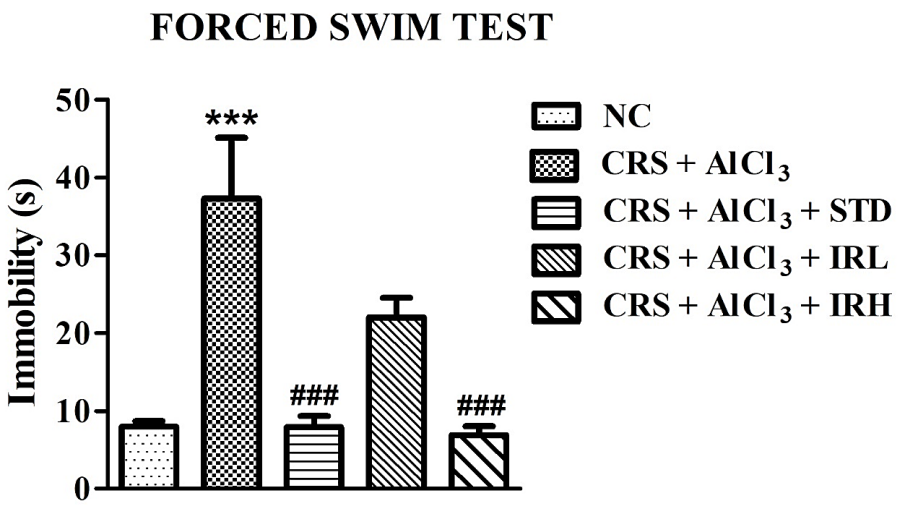

Figure 2: Effect of *Inula racemosa* on chronic restraint stress and aluminum chloride-induced depressive-like behavior in the forced swim test. NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as mean±SEM. Statistical analysis was done using a one-way ANOVA followed by a *post hoc* test (Tukey's). ***p<0.001 ($F_{4,35}$=12.14, p<0.001) as compared to normal control;###p<0.001 as compared to disease control group.

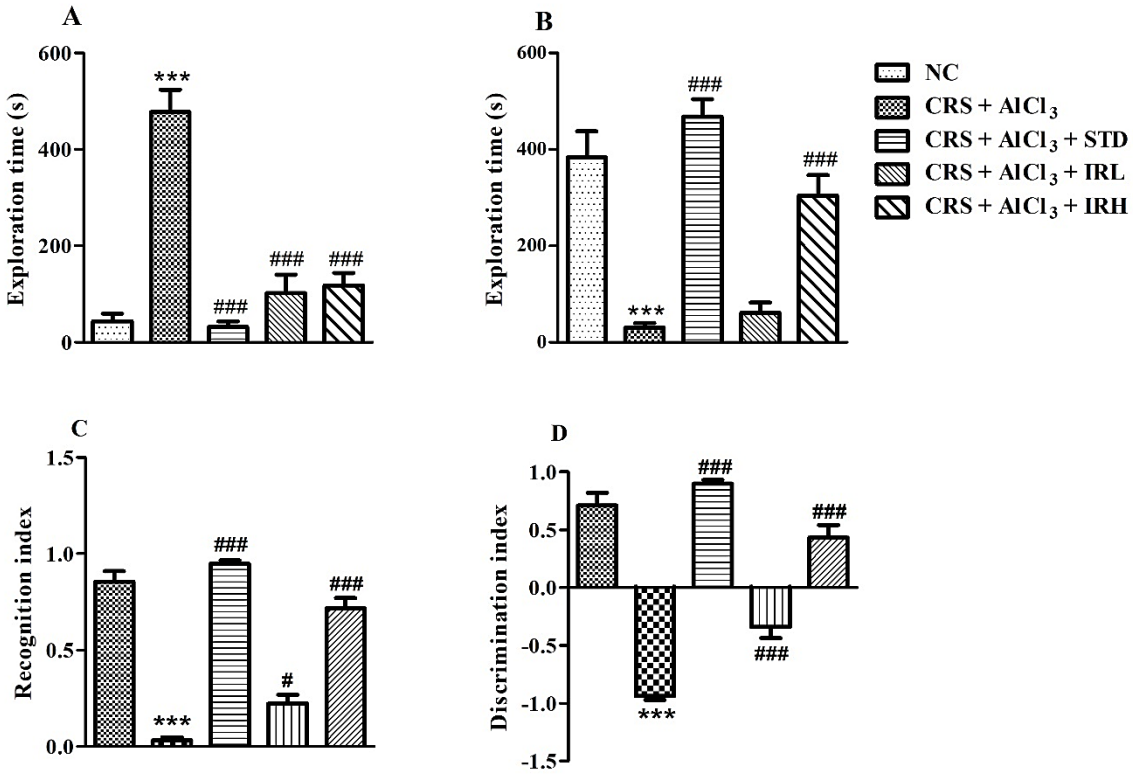

Figure 3: Effect of *Inula racemosa* on chronic restraint stress and aluminum chloride- induced impairment of recognition memory in the novel object recognition test (NORT). (A) Exploration time with the familiar object ($F_{4,35}$=35.99, p<0.001); (B) Exploration time with the novel object ($F_{4,35}$=28.59, p<0.001); (C) Recognition index ($F_{4,35}$=94.55, p< 0.001); (D) Discrimination index ($F_{4,35}$=83.77, p<0.001). NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as Mean±SEM. Statistical analysis was done using a one-way ANOVA followed by *post hoc* test (Tukey's). ***p<0.001 as compared to the normal control; ###p<0.001 as compared to the disease control group.

7A: $F_{4,25}$=95.49, p<0.001) were significantly lower (p<0.001) in the CRS+$AlCl_3$ group than in the normal control group. *Inula racemosa* treatment (200 mg/kg and 400 mg/kg) significantly increased SOD (Figure 7B: $F_{4,25}$=135.5, p<0.001), CAT (Figure 7C: $F_{4,25}$=63.65, p<0.001) and GSH (Figure 7A: $F_{4,25}$=95.49, p<0.001) levels compared to the CRS+$AlCl_3$ group (p<0.001).

In the prefrontal cortex, MDA levels were significantly elevated in the CRS+$AlCl_3$ group compared to the normal control group (Figure 8D: $F_{4,25}$=109.0, p<0.001). However, treatment with *Inula racemosa* at 400 mg/kg significantly reduced MDA levels compared to the CRS+$AlCl_3$ group (p<0.001), while the lower dose of 200 mg/kg partially decreased MDA levels (p<0.01). GSH levels were lower in the CRS+$AlCl_3$ group compared to the normal control, but treatment with both 200 mg/kg and 400 mg/kg of *Inula racemosa* significantly increased GSH levels (Figure 8A: $F_{4,25}$=96.91, p<0.001). Superoxide Dismutase (SOD) levels were reduced in the CRS+$AlCl_3$ group compared to the normal control; however, high-dose *Inula racemosa* restored SOD levels to normal (Figure 8B: $F_{4,25}$=144.3, p<0.001), while the 200 mg/kg dose only partially increased SOD levels (p<0.01). Additionally, *Inula racemosa* treatment fully restored the reduced catalase levels in the CRS+$AlCl_3$ group (Figure 8C: $F_{4,25}$=29.67, p<0.001). These findings support the antioxidant properties of *Inula racemosa*.

DISCUSSION

In this study, we used chronic restraint stress combined with aluminum chloride for 21 days to develop an animal model of Alzheimer's disease. The animals showed reduced sucrose water preference in the sucrose preference test, increased immobility in the forced swim test, and poorer performance in the novel object recognition and T-maze tasks, which were linked to higher amyloid beta accumulation, decreased BDNF expression, and increased oxidative stress. Treatment with *Inula racemosa* at doses of 200 mg/kg and 400 mg/kg alleviated these symptoms, improving sucrose preference, reducing immobility, and enhancing object recognition and spatial learning. It also reduced amyloid beta plaques, restored BDNF levels, and lowered MDA levels in the hippocampus and prefrontal cortex. These results suggest that *Inula racemosa* has neuroprotective effects, likely through its antioxidant activity and regulation of neurotrophic factors, making it a promising candidate for treating Alzheimer's disease.

Memory impairment in common neurodegenerative disorders significantly impacts cognitive functions. This impairment is marked by the accumulation of amyloid-β plaques, tau proteins, and neurofibrillary tangles, particularly in the hippocampus and frontal cortex, which disrupt memory.[23] These proteins play a crucial role in the progression of Alzheimer's disease by hindering neurotransmission between nerve cells, leading to neuronal cell death and subsequent loss of brain tissue in specific regions.[24] The plaques are considered toxic as they activate microglia and cytokines, triggering an immune response and inflammation that contributes to cell death and neuronal loss.[25]

Psychosocial stress is a key bio-behavioral factor linked to accelerated aging. In addition to its role in mental disorders such as major depressive disorder and Post-Traumatic Stress Disorder, prolonged psychological stress has been shown in numerous studies to promote aging. This suggests that

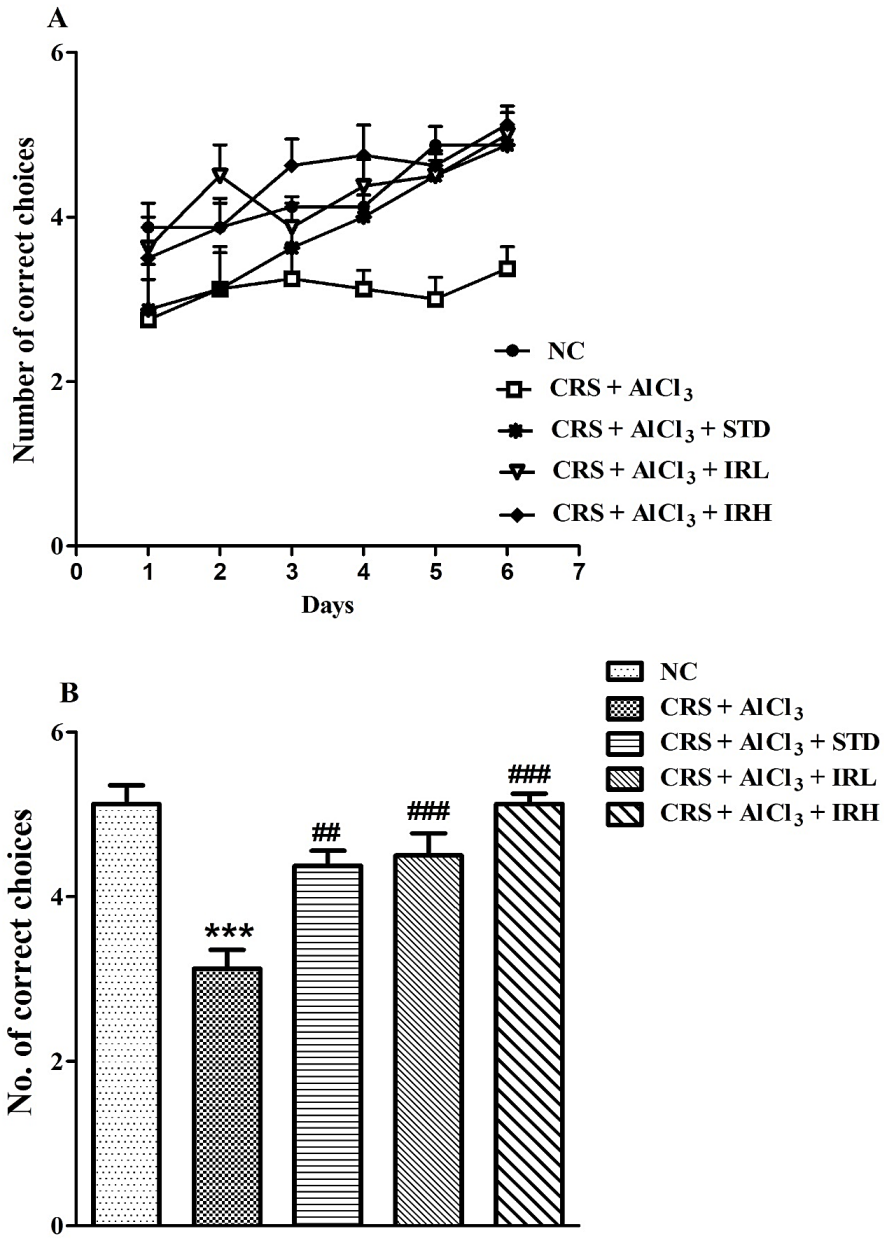

Figure 4: Effect of *Inula racemosa* on chronic restraint stress and aluminum chloride-induced altered spatial working memory impairment in the T-maze alteration task (A) Acquisition ($F_{4,175}$=13.83, p<0.001); (B) Retention test ($F_{4,35}$=14.98, p<0.001). NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as Mean±SEM. Statistical analysis was done using atwo-way ANOVA, followed by a *post hoc* test (Bonferroni) and one-way ANOVA followed by Tukey's *post hoc* test***p<0.001 as compared to the normal control; ###p<0.001 as compared to the disease control group; ##p<0.01 as compared to the disease control group.

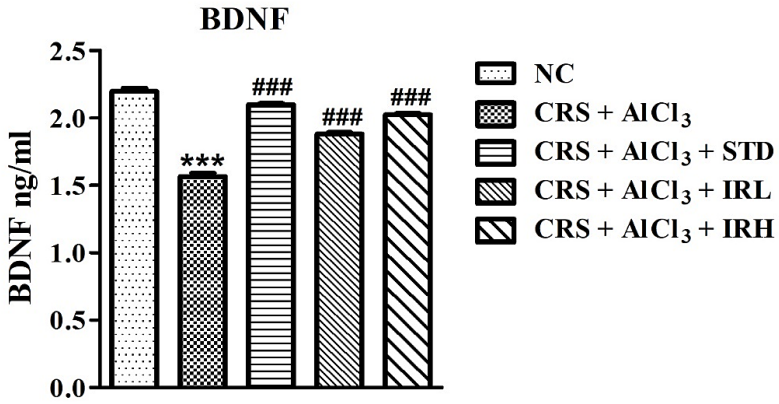

Figure 5: Effect of *Inula racemosa* on BDNF levels in the hippocampus of chronic restraint stress and aluminum chloride-induced disease control rats. NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as Mean±SEM. Statistical analysis was done using a one-way ANOVA followed by a *post hoc* test (Tukey's). ***p<0.001 ($F_{4,25}$=176.4, p<0.001) as compared to the normal control; ###p<0.001 as compared to the disease control group.

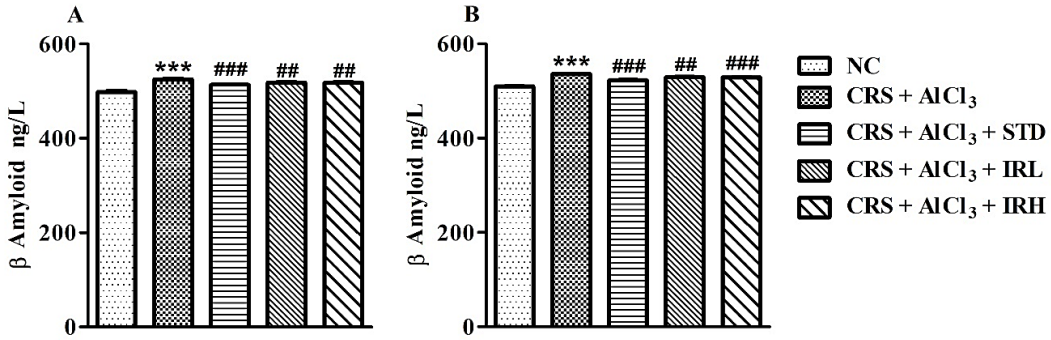

Figure 6: Effect of *Inula racemosa* on (A) amyloid beta (H) ($F_{4,25}$=55.22, p<0.001); (B) amyloid beta (PFC) ($F_{4,25}$=76.12, p<0.001) levels in the hippocampus and prefrontal cortex of chronic restraint stress and aluminum chloride-induced disease control rats. NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as mean±SEM. Statistical analysis was done using a one-way ANOVA followed by a *post hoc* test (Tukey's). ***p<0.001 as compared to the normal control; ###p<0.001, ##p<0.01 as compared to the disease control group.

molecular, physiological, neurological, and genetic pathways are involved. Moreover, extended psychological stress is believed to trigger the release of pro-inflammatory cytokines, leading to inflammation.[26,27] Chronic stress alters the body's response systems, prompting the release of neuroendocrine mediators that accelerate aging.[28] Intense stress stimulates catecholamine release, activates the sympathetic nervous system and HPA axis, and alters the immune system. It also increases glucocorticoid levels, affecting these molecules and influencing the biological aging process.[29]

Several neurotoxicants are implicated in dementia, either directly or indirectly, and have been linked to the development of Alzheimer's disease (AD).[30,31] One such neurotoxin is aluminum chloride, which can disrupt the Blood-Brain Barrier and accumulate in the brain, leading to aluminum-induced brain toxicity. Previous studies have shown that prolonged exposure to aluminum chloride causes memory impairment, disorientation, dementia, and other neurodegenerative changes.[32] Additionally, alterations in neurofilament structures have been observed in the cerebral cortex, spinal cord, and hippocampus of animals exposed to $AlCl_3$. Long-term exposure to aluminum chloride also stimulates Acetylcholinesterase (AChE), reduces acetylcholine levels, promotes tau protein accumulation, enhances amyloid β plaque formation, increases oxidative stress, and raises Brain-Derived Neurotrophic Factor (BDNF) levels.[33] The harmful effects of amyloid β over expression include a reduction in BDNF expression. BDNF is a crucial neurotrophin that plays a key role in cognition, neurogenesis, synaptic plasticity, and dendritic growth in neurons. In Alzheimer's disease, BDNF levels are decreased, leading to deficits in learning and memory. Consequently, restoring BDNF levels is essential for improving memory and cognitive functions.[20]

Chronic restraint stress causes both psychological and physiological changes simultaneously. A key mechanism behind the cognitive impairment observed in CRS is the reduction of BDNF levels, with prolonged stress triggering hyperactivity of the HPA axis and elevated corticosterone levels.[34] Increased glucocorticoids inhibit BDNF-mediated neuroplasticity in the hippocampus and prefrontal cortex while simultaneously increasing BDNF levels in the amygdala.[35] Additionally, glucocorticoids worsen tau hyperphosphorylation and Amyloid Beta (Aβ) accumulation.[36] CRS also induces excessive Reactive Oxygen Species (ROS) production, leading to irreversible damage to proteins, lipids, and DNA, and promoting Aβ aggregation. This damage further stimulates the production of pro-inflammatory cytokines, which accelerates Aβ accumulation and contributes to neurodegeneration.[37,38] Ultimately, this cascade of events can result in apoptosis, or cell death, which is closely associated with impaired cognitive function.[39]

Previous research has shown that chronic restraint stress impairs cognitive functions dependent on the hippocampus, particularly learning and memory. It also alters neuronal morphology and causes synaptic loss, resulting in depressive-like behavior. Animals exposed to CRS have demonstrated a decrease in their preference for sucrose water[40-42] and an increase in immobility time.[43,44] Animals exposed to CRS and aluminum chloride exhibited reduced ability to recognize and discriminate between novel and familiar objects[45-48] and diminished spatial working memory in the T-maze.[17,49] Prolonged stress and exposure to aluminum chloride alter the HPA axis and increase the production of reactive oxygen species. Increased ROS production contributes to amyloid-β aggregation in various areas of the brain[48,50-54] This results in diminished synaptic vesicles, reduced axonal mitochondria turnover, or disruption of the Golgi apparatus.[55]

Inula racemosa is recognized for its anti-inflammatory, antioxidant, antimicrobial, and anthelmintic properties. The root extract of *Inula racemosa* contains compounds such as sesquiterpene lactones, alantolactones, and isoalantolactones.[56] Its alkaloids, flavonoids, and phenols play a significant role in alleviating the effects of chronic restraint stress and aluminum chloride exposure.[57] In a traumatic brain injury model, alantolactone affects the production of free radicals and influences apoptotic and inflammatory pathways.[58] Both Alantolactone (ALT) and Isoalantolactone (IALT) offer protection against brain damage induced by scopolamine by enhancing Nrf2 signaling and boosting antioxidant enzymes. Certain sesquiterpenoids also effectively inhibit Acetylcholinesterase (AChE) activity.[59] Mice deficient in Nrf2 consistently exhibit lower cognitive abilities

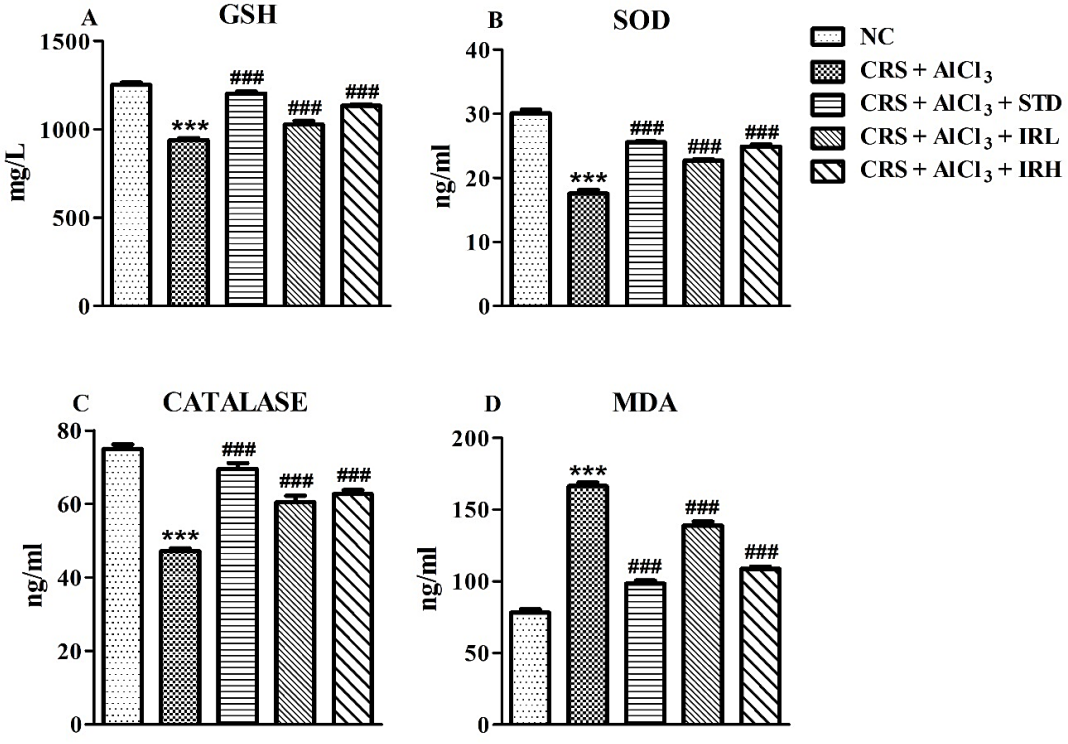

Figure 7: Effect of *Inula racemosa* on the oxidative stress markers of chronic restraint stress and the aluminum chloride-induced disease model in rats. (A) GSH activity ($F_{4,25}$=95.49); (B) SOD activity ($F_{4,25}$=135.5); (C) catalase content ($F_{4,25}$=63.65); (D) MDA activity ($F_{4,25}$=239.9) in the hippocampus. NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as mean±SEM. Statistical analysis was done using a one-way ANOVA followed by a *post hoc* test (Tukey's). ***p<0.001 as compared to the normal control; ###p<0.001 as compared to the disease control group.

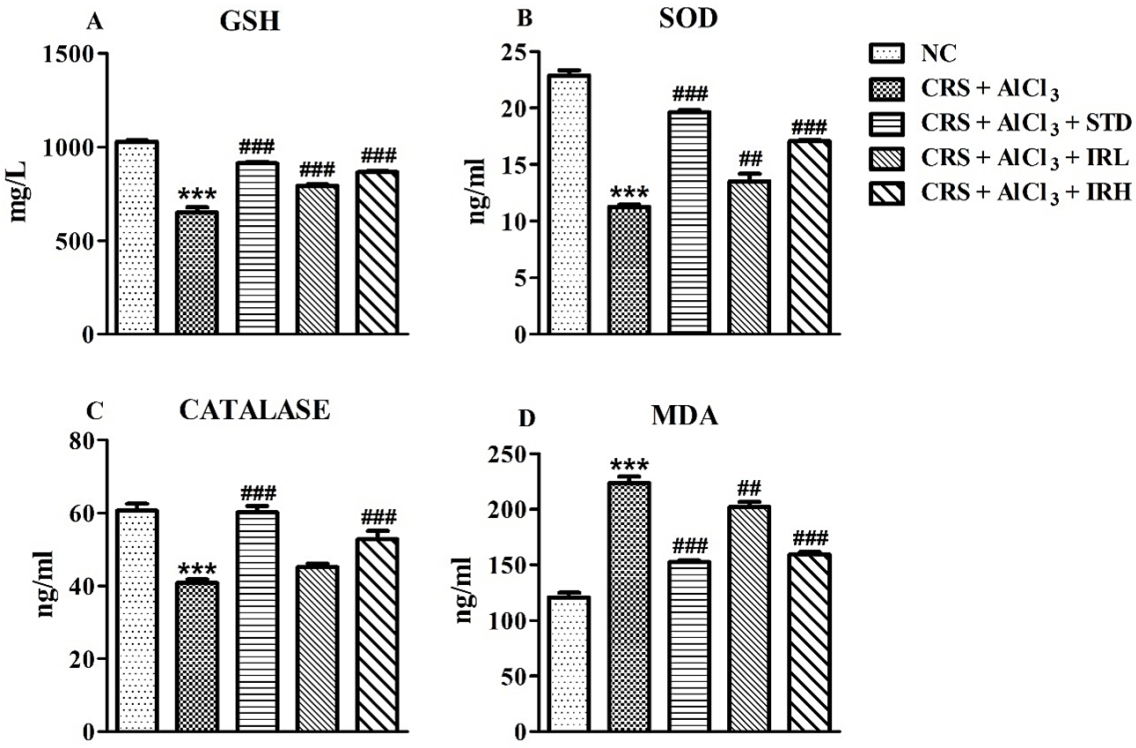

Figure 8: Effect of *Inula racemosa* on the oxidative stress markers of chronic restraint stress and the aluminum chloride-induced disease model in rats. (A) GSH activity ($F_{4,25}$=96.91); (B) SOD activity ($F_{4,25}$=144.3); (C) catalase content ($F_{4,25}$=29.67); (D) MDA activity ($F_{4,25}$=109.0) in prefrontal cortex. NC: normal control; CRS: chronic restraint stress; $AlCl_3$: aluminum chloride; STD: standard; IRL: *Inula racemosa* low dose; IRH: *Inula racemosa* high dose. Data are expressed as mean±SEM. Statistical analysis was done using a one-way ANOVA followed by a *post hoc* test (Tukey's). ***p<0.001 as compared to the normal control; $^{###}p$<0.001 as compared to the disease control group.

compared to wild-type mice, underscoring the critical role of antioxidant enzymes in supporting cognitive function and memory.[60]

Previous research on ALT's neuromodulatory effects found that it reduced the size of infarcts and the amount of water in brain tissue, prevented neuronal apoptosis and necrosis, and conserved brain structure. The potential therapeutic benefit of ALT for cerebral ischemia-reperfusion injury is its inhibitory effect on neuroinflammation.[61] Furthermore, ALT reduced inflammatory reactions, oxidative stress, and cell death induced by cigarette smoke. Treatment with ALT had an impact on inflammatory cytokines, including interleukin derivatives and TNF-α. It showed an antioxidant effect, reduced oxidative stress, and prevented cell damage.[62]

The differential effects observed between the two doses of *Inula racemosa*, 200 mg/kg and 400 mg/kg on depressive-like behaviour suggests a potential dose-dependent pharmacological action. In the present study, the lower dose (200 mg/kg) did not produce significant improvements in behavioural parameters associated with depression, whereas the higher dose (400 mg/kg) showed more pronounced antidepressant-like effects. There are several possible explanations for this observation. First, it is likely that the active phytoconstituents responsible for the neuroprotective and antidepressant effects, such as sesquiterpene lactones, flavonoids, and alkaloids, are not present in sufficient concentrations at the lower dose to elicit a therapeutic response. Many herbal compounds exhibit a threshold effect, wherein a minimum concentration is required to activate specific biochemical pathways, including those involved in neurogenesis, modulation of neurotransmitters, or reduction of oxidative stress and inflammation.

While the current study provides valuable insights into Alzheimer's disease (AD) pathology using the Chronic Restraint Stress (CRS) combined with Aluminium Chloride ($AlCl_3$) model, several limitations should be acknowledged. Firstly, the CRS+$AlCl_3$ model, although widely used, does not fully replicate the complex aetiology and progressive nature of human AD. This model primarily mimics certain behavioural and biochemical features of the disease, but lacks the hallmark amyloid plaques and neurofibrillary tangles observed in human patients. Moreover, the use of $AlCl_3$ as a neurotoxic agent remains controversial, as its role in the pathogenesis of AD in humans is not conclusively established.

Secondly, translating findings from rodent models to human AD poses inherent challenges due to fundamental differences in brain structure, lifespan, and disease progression. The response

to interventions in animal models may not accurately predict clinical efficacy in humans. Therefore, while the findings of this study contribute to the growing understanding of stress and neurotoxicity in AD, further validation in alternative models and clinical studies is necessary to confirm their relevance to human disease.

Lastly, potential sex differences, genetic variability, and environmental factors, key contributors to AD in humans were not addressed in this study and may further limit the generalizability of the findings. Future studies employing more sophisticated or genetically engineered models, along with longitudinal designs and human data comparisons, are warranted to enhance the translational relevance of preclinical AD research.

Although the current study highlights the neuroprotective effects of *Inula racemosa*, the precise molecular mechanisms remain to be fully elucidated. Future investigations should focus on dissecting key intracellular signaling pathways, such as MAPK and PI3K-AKT, to better understand the compound's mode of action and its therapeutic potential in neurodegenerative conditions.

CONCLUSION

Our current study demonstrated that persistent restraint stress combined with aluminum chloride impaired memory and cognitive functions. Chronic stress exposure led to depression, as well as impairments in recognition and spatial memory. Furthermore, there was a decrease in Brain-Derived Neurotrophic Factor (BDNF) expression, an increase in free radicals, a reduction in antioxidant levels, and an accumulation of amyloid beta plaques. Aluminum, a neurotoxin that disrupts the blood-brain barrier, accumulates in the brain and is difficult to eliminate. It also exacerbates oxidative stress, promotes amyloid beta plaque formation, accelerates tau protein buildup, reduces acetylcholine levels, and lowers BDNF expression. Treatment with *Inula racemosa* improved sucrose water preference, reduced immobility, enhanced recognition memory, and restored spatial learning in the T-maze task. In the prefrontal cortex and hippocampus, *Inula racemosa* decreased amyloid beta plaque accumulation and oxidative stress while increasing BDNF and antioxidant levels. The neuroprotective effects of *Inula racemosa* are likely due to its antioxidant properties, which help reduce neuronal damage, protect the brain from inflammation and free radicals, and offer potential for the development of herbal treatments for neurodegenerative conditions.

ACKNOWLEDGEMENT

The authors are thankful to KLE College of Pharmacy, Bengaluru for providing infrastructure for the current study.

ABBREVIATIONS

AChE: Acetylcholinesterase; **ALT:** Alantolactone; **AlCl3:** Aluminum chloride; **AD:** Alzheimer's disease; **ANOVA:** Analysis of variance; **BDNF:** Brain-Derived Neurotrophic Factor; **CAT:** Catalase; **CRS:** Chronic Restraint Stress; **ELISA:** Enzyme-Linked Immunosorbent Assay; **FST:** Forced Swim Test; **GC:** Glucocorticoid; **GSH:** Glutathione; **HPA:** Hypothalamic-Pituitary-Adrenal; **IALT:** Isoalantolactone; **MDA:** Malondialdehyde; **NORT:** Novel Object Recognition Test; **SEM:** Standard Error Mean; **SOD:** Superoxide Dismutase; **SPT:** Sucrose Preference Test; **ROS:** Reactive Oxygen Species.

CONFLICT OF INEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study investigated the neuroprotective effects of *Inula racemosa* in a rat model of Alzheimer's-like cognitive impairment induced by chronic stress and aluminum chloride. Exposure led to oxidative stress, reduced BDNF levels, amyloid beta accumulation, and memory deficits. Treatment with *Inula racemosa* significantly improved cognitive function, reduced depressive behavior, restored antioxidant and BDNF levels, and decreased amyloid beta deposition. These findings suggest that *Inula racemosa* has promising antioxidant and neuroprotective potential against neurodegenerative conditions.

REFERENCES

1. Blazquez-Llorca L, Valero-Freitag S, Rodrigues EF, Merchán-Pérez Á, Rodríguez JR, Dorostkar MM, *et al.* High plasticity of axonal pathology in Alzheimer's disease mouse models. ActaNeuropatholCommun. 2017; 5: 14.
2. Arendt T. Synaptic degeneration in Alzheimer's disease. ActaNeuropathol. 2009; 118: 167-79.
3. Jauregui-Huerta F, Ruvalcaba-Delgadillo Y, Gonzalez-Perez O, Gonzalez- Castaneda R, Garcia-Estrada J, Luquin S. Responses of glial cells to stress and glucocorticoids. CurrImmunol Rev. 2010; 6: 195-204.
4. Vyas S, Rodrigues AJ, Silva JM, Tronche F, Almeida OF, Sousa N, Sotiropoulos I. Chronic stress and glucocorticoids: From neuronal plasticity to neurodegeneration. Neural Plast. 2016; 2016: 6391686.
5. Simard M, Hudon C, van Reekum R. Psychological distress and risk for dementia. Curr Psychiatry Rep. 2009; 11: 41-7.
6. Hoogendijk WJG, Meynen G, Endert E, Hofman MA, Swaab DF. Increased cerebrospinal fluid cortisol level in Alzheimer's disease is not related to depression. Neurobiol Aging. 2006; 27: 780.e1-780.e2.
7. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, Morris JC. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry. 2006; 163: 2164-9.
8. Lucassen PJ, Pruessner J, Sousa N, Almeida OF, Van Dam AM, Rajkowska G, *et al.* Neuropathology of stress. ActaNeuropathol. 2014; 127: 109-35.
9. Jeong YH, Park CH, Yoo J, Shin KY, Ahn SM, Kim HS, *et al.* Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPV717I-CT100 transgenic mice, an Alzheimer's disease model. FASEB J. 2006; 20: 729-31.
10. Exley C, Clarkson E. Aluminium in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism. Sci Rep. 2020; 10: 7770.
11. Tomljenovic L. Aluminum and Alzheimer's disease: After a century of controversy, is there a plausible link? Journal of Alzheimer's Disease. 2011; 23: 567-98.
12. Exley C. What is the risk of aluminium as a neurotoxin? Expert Rev Neurother. 2014; 14: 589-91.

13. Walton JR, Wang MX. APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. J InorgBiochem. 2009; 103: 1548-54.
14. Mohan S, Gupta D. Phytochemical analysis and differential *in vitro* cytotoxicity assessment of root extracts of *Inula racemosa*. Biomedicine and Pharmacotherapy. 2017; 89: 781-95.
15. Wang Z, Geng L, Chen Z, Lin B, Zhang M, Zheng S. *In vivo* therapeutic potential of *Inula racemosa* in hepatic ischemia reperfusion injury following orthotopic liver transplantation in male albino rats. AMB Express. 2017; 7: 211.
16. Wang X, Lan YL, Xing JS, Lan XQ, Wang LT, Zhang B. Alantolactone plays neuroprotective roles in traumatic brain injury in rats via anti-inflammatory, anti-oxidative and anti-apoptosis pathways. Am J Transl Res. 2018; 10: 368-80.
17. Bhagya V, Christofer T, Shankaranarayana Rao B. Neuroprotective effect of *Celastrus paniculatus* on chronic stress induced cognitive impairment. Indian J Pharmacol. 2016; 48: 687-93.
18. Bhagya V, Srikumar BN, Raju TR, Shankaranarayana Rao BS. Neonatal clomipramine induced endogenous depression in rats is associated with learning impairment in adulthood. Behavioural Brain Research. 2008; 187: 190-4.
19. Mahati K, Bhagya V, Christofer T, Sneha A, Shankaranarayana Rao BS. Enriched environment ameliorates depression-induced cognitive deficits and restores abnormal hippocampal synaptic plasticity. Neurobiol Learn Mem. 2016; 134: 379-91.
20. Lueptow LM. Novel object recognition test for the investigation of learning and memory in mice. Journal of Visualized Experiments. 2017; 126: 55718.
21. Moretti RL, Dias EN, Kiel SG, Augusto MCM, Rodrigues PS, Sampaio ACS, *et al.* Behavioral and morphological effects of resveratrol and curcumin in rats submitted to doxorubicin induced cognitive impairment. Res Vet Sci. 2021; 140: 242-50.
22. Okuda S, Roozendaal B, McGaugh JL. Glucocorticoid effects on object recognition memory require training-associated emotional arousal. Proceedings of the National Academy of Sciences. 2004; 101: 853-8.
23. Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, *et al.* Alzheimer's disease. The Lancet. 2016; 388: 505-17.
24. Khan S, Barve KH, Kumar MS. Recent advancements in pathogenesis, diagnostics and treatment of Alzheimer's disease. CurrNeuropharmacol. 2020; 18: 1106-25.
25. Barage SH, Sonawane KD. Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides. 2015; 52: 1-18.
26. O'Donovan A, Tomiyama AJ, Lin J, Puterman E, Adler NE, Kemeny M, *et al.* Stress appraisals and cellular aging: A key role for anticipatory threat in the relationship between psychological stress and telomere length. Brain Behav Immun. 2012; 26: 573-9.
27. Toft H, Bramness JG, Lien L, Abebe DS, Wampold BE, Tilden T, *et al.* PTSD patients show increasing cytokine levels during treatment despite reduced psychological distress. Neuropsychiatr Dis Treat. 2018; 14: 2367-78.
28. Polsky LR, Rentscher KE, Carroll JE. Stress-induced biological aging: A review and guide for research priorities. Brain Behav Immun. 2022; 104: 97-109.
29. Sloan EK, Capitanio JP, Cole SW. Stress-induced remodeling of lymphoid innervation. Brain Behav Immun. 2008; 22: 15-21.
30. Justin Thenmozhi A, William Raja TR, Manivasagam T, Janakiraman U, Essa MM. Hesperidin ameliorates cognitive dysfunction, oxidative stress and apoptosis against aluminium chloride induced rat model of Alzheimer's disease. NutrNeurosci. 2017; 20: 360-8.
31. Yaseen. Potential protection from Alzheimer's disease by wheat germ and rice bran nano-form in rat model. J Appl Pharm Sci. 2019; 9: 67-76.
32. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: An overview of environmental risk factors. Environ Health Perspect. 2005; 113: 1250-6.
33. Ogunlade B, Adelakun SA, Agie JA. Nutritional supplementation of gallic acid ameliorates Alzheimer-type hippocampal neurodegeneration and cognitive impairment induced by aluminum chloride exposure in adult Wistar rats. Drug ChemToxicol. 2022; 45: 651-62.
34. Gallo-Payet N, Battista MC. Steroidogenesis-adrenal cell signal transduction. Compr Physiol. 2014; 4: 889-964.
35. Mohammadi S, Zandi M, DoustiKataj P, KarimiZandi L. Chronic stress and Alzheimer's disease. BiotechnolApplBiochem. 2022; 69: 1451-8.
36. Sotiropoulos I, Catania C, Pinto LG, Silva R, Pollerberg GE, Takashima A, *et al.* Stress acts cumulatively to precipitate Alzheimer's disease-like tau pathology and cognitive deficits. J Neurosci. 2011; 31: 7840-7.
37. John J, Nampoothiri M, Kumar N, Mudgal J, Nampurath GK, Chamallamudi MR. Sesamol, a lipid lowering agent, ameliorates aluminium chloride induced behavioral and biochemical alterations in rats. Pharmacogn Mag. 2015; 11: 327-36.
38. Mohamed EA, Ahmed HI, Zaky HS, Badr AM. Boswellic acids ameliorate neurodegeneration induced by AlCl3: the implication of Wnt/β-catenin pathway. Environ SciPollut Res Int. 2022; 29: 76135-43.
39. Jiang N, Wang K, Zhang Y, Huang H, Lv JW, Wang Q, *et al.* Protective effect of ginsenoside Rb1 against Chronic Restraint Stress (CRS)-induced memory impairments in rats. Behav Brain Res. 2021; 405: 113146.
40. Ma J, Wang R, Chen Y, Wang Z, Dong Y. 5-HT attenuates chronic stress-induced cognitive impairment in mice through intestinal flora disruption. J Neuroinflammation. 2023; 20: 23.
41. Ning JI, Jing-Wei LV, Hai-Xia WA, Hong HU, Qiong WA, Shan-Guang CH, *et al.* Antidepressant-like effects of ginsenoside Rg1 in the chronic restraint stress-induced rat model. Digital Chinese Medicine. 2019; 2: 207-18.
42. Olave FA, Aguayo FI, Román-Albasini L, Corrales WA, Silva JP, González PI, *et al.* Chronic restraint stress produces sex-specific behavioral and molecular outcomes in the dorsal and ventral rat hippocampus. Neurobiol Stress. 2022; 17: 100440.
43. García-Rojo G, Fresno C, Vilches N, Díaz-Véliz G, Mora S, Aguayo F, *et al.* The ROCK inhibitor fasudil prevents chronic restraint stress-induced depressive-like behaviors and dendritic spine loss in rat hippocampus. Int J Neuropsychopharmacol. 2017; 20: 336-45.
44. Peng G, Yang L, Wu CY, Zhang LL, Wu CY, Li F, *et al.* Whole body vibration training improves depression-like behaviors in a rat chronic restraint stress model. Neurochem Int. 2021; 142: 104926.
45. Chiroma SM, HidayatBaharuldin MT, Mat Taib CN, Amom Z, Jagadeesan S, Adenan MI, *et al.* Protective effect of *Centellaasiatica* against D-galactose and aluminium chloride induced rats: Behavioral and ultrastructural approaches. Biomed Pharmacother. 2019; 109: 853-64.
46. Elmorsy E, Elsharkawy E, Alhumaydhi FA, Salama M. The protective effect of *Indian catechu* methanolic extract against aluminum chloride-induced neurotoxicity, A rodent model of Alzheimer's disease. Heliyon. 2021; 7: e06269.
47. Justin-Thenmozhi A, DhivyaBharathi M, Kiruthika R, Manivasagam T, Borah A, Essa MM. Attenuation of aluminum chloride-induced neuroinflammation and caspase activation through the AKT/GSK-3β pathway by hesperidin in Wistar rats. Neurotox Res. 2018; 34: 463-76.
48. Wu J, Liu C, Zhang L, He B, Shi WP, Shi HL, *et al.* Chronic restraint stress impairs cognition via modulating HDAC2 expression. TranslNeurosci. 2021; 12: 154-63.
49. Rafi H, Rafiq H, Khan R, Ahmad F, Anis J, Farhan M. Neuroethological study of AlCl3 and chronic forced swim stress induced memory and cognitive deficits in albino rats. The Journal of Neurobehavioral Sciences. 2019; 6: 149-58.
50. Lu C, Lv J, Dong L, Jiang N, Wang Y, Fan B, *et al.* The protective effect of 20 (S)-protopanaxadiol (PPD) against Chronic Sleep Deprivation (CSD)-induced memory impairments in mice. Brain Res Bull. 2018; 137: 249-56.
51. Choudhury Barua C, Buragohain L, Rahman F, Elancheran R, Rizavi H. *Zanthoxylum alatum* attenuates chronic restraint stress adverse behavioral effects via the mitigation of oxidative stress and modulating the expression of genes involved in endoplasmic reticulum stress in mice. Basic ClinNeurosci. 2022; 13: 647-60.
52. Samarghandian S, Azimi-Nezhad M, Farkhondeh T, Samini F. Anti-oxidative effects of curcumin on immobilization-induced oxidative stress in rat brain, liver and kidney. Biomed Pharmacother. 2017; 87: 223-9.
53. Ramadan LA, Daidamoony MA, Elgindy AM, Mustafa AM, Hassan E, Abdel-Rahman HM, *et al.* Mitigation of aluminum chloride-induced Alzheimer's disease by blueberry in rat model. ERU Research Journal. 2023; 2: 682-98.
54. Zhang Z, Wu H, Qi S, Tang Y, Qin C, Liu R, *et al.* 5-Methyltetrahydrofolate alleviates memory impairment in a rat model of Alzheimer's disease induced by D-galactose and aluminum chloride. Int J Environ Res Public Health. 2022; 19: 16426.
55. Kumar A, Prakash A, Dogra S. Neuroprotective effect of carvedilol against aluminium induced toxicity: possible behavioral and biochemical alterations in rats. Pharmacol Rep. 2011; 63: 915-23.
56. Seth R, Devi A, Sharma B, Masand M, Singh G, Pal P, *et al.* An integrative transcriptional network revealed spatial molecular interplay underlying alantolactone and inulin biosynthesis in *Inula racemosa* Hook f. Int J Mol Sci. 2022; 23: 11213.
57. Dinkova-Kostova AT. Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Med. 2008; 74: 1548-59.
58. Wang X, Lan YL, Xing JS, Lan XQ, Wang LT, Zhang B. Alantolactone plays neuroprotective roles in traumatic brain injury in rats via anti-inflammatory, anti-oxidative and anti-apoptosis pathways. Am J Transl Res. 2018; 10: 368-80.
59. Hajimehdipoor H, Mosaddegh M, Naghibi F, Haeri A, Hamzeloo-Moghadam M. Natural sesquiterpen lactones as acetylcholinesterase inhibitors. An Acad Bras Cienc. 2014; 86: 801-6.
60. Seo JY, Lim SS, Kim J, Lee KW, Kim JS. Alantolactone and Isoalantolactone Prevent Amyloid β25-35 -induced Toxicity in Mouse Cortical Neurons and Scopolamine-induced Cognitive Impairment in Mice. Phytother Res. 2017; 31: 801-11.
61. Tan L, Li J, Wang Y, Tan R. Anti-Neuroinflammatory effect of alantolactone through the suppression of the NF-κB and MAPK signaling pathways. Cells. 2019; 8: 739.
62. Dang X, He B, Ning Q, Liu Y, Guo J, Niu G, *et al.* Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of Nrf2/HO-1 and inhibition of the NF-κB pathways. Respir Res. 2020; 21: 95.

Cite this article: Rao BV, Loganathan K, Raju S, Vasudev R. Neuroprotective Effect of *Inula racemosa* on Chronic Stress-Aluminum Chloride Induced Memory Deficits. Indian J of Pharmaceutical Education and Research. 2026;60(1):258-69.