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Protective Role of Launaea taraxacifolia Against Cadmium Chloride-Induced Hippocampal and Cortical Damage: A Study of Nitric Oxide Dysregulation and Bax Immunoreactivity in Male Wistar Rats

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ABSTRACT

Background: Cadmium chloride ($CdCl_2$) is a pervasive environmental neurotoxin known to induce nitrosative stress, disrupt neuronal signaling, and trigger apoptotic pathways in the brain.

Objective: This study explored the neuroprotective potential of *Launaea taraxacifolia* aqueous extract against $CdCl_2$-induced hippocampal and cortical injury, emphasizing nitric oxide (NO) dysregulation and Bax-mediated apoptosis in Wistar rats.

Methods: 32 male Wistar rats were randomly divided into four groups, each consisting of eight animals. For 21 consecutive days, Group I received distilled water orally; Group II received cadmium chloride ($CdCl_2$) at a dose of 5 mg/kg orally; Group III received *Launaea taraxacifolia* aqueous extract (LTAE) at 400 mg/kg orally; while Group IV received 5 mg/kg of $CdCl_2$ followed by 400 mg/kg of LTAE orally. Biochemical analysis (NO) and Bax immunostaining were performed to assess $CdCl_2$-induced hippocampal and cortical damage.

Results: There was a significant increase ($p<0.05$) in NO activity and overexpression of Bax in the cerebral cortex and hippocampus of Wistar rats that received $CdCl_2$. However, these changes were significantly ($p<0.05$) reversed by reduced NO activity and Bax expression in rats that received LTAE as a co-treatment with $CdCl_2$ when compared with the $CdCl_2$-treated rats.

Conclusion: These findings suggest that L. taraxacifolia provides neuroprotection by mitigating nitrosative stress and apoptosis through modulation of NO signaling and Bax-mediated pathways. Keywords: Cadmium Chloride, Launaea taraxacifolia, Cerebral cortex, Hippocampus

INTRODUCTION

Heavy metal pollution remains one of the most persistent environmental challenges of the global health, with cadmium ranking among the most hazardous [17]. This metal is introduced into the ecosystem through industrial emissions, mining, fertilizers, and contaminated food and water sources [7]. Once cadmium chloride is absorbed into the body, it accumulates slowly within tissues and exerts long-lasting toxic effects [7]. Prolonged exposure to cadmium, even at low concentrations, can result in bioaccumulation within the body and lead to multi-organ toxicity [7]. One of the targets of cadmium-induced injury is the brain, as the metal readily enters the blood– brain barrier and interferes with delicate neurochemical balance required for normal brain function [22].

In neural tissues, cadmium promotes the generation of reactive oxygen and nitrogen species, triggering oxidative and nitrosative stress [19]. These events disrupt mitochondrial function, impair neurotransmission, and alter signaling pathways involved in neuronal survival. The hippocampus and cerebral cortex, key regions involved in memory, learning, and higher cognitive processing, are particularly susceptible to such insults [23]. One of the molecular mechanisms of cadmium toxicity is the abnormal regulation of nitric oxide (NO), a

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signaling molecule that normally supports synaptic activity [3]. When its production becomes excessive, NO contributes to neuronal damage through inflammatory and apoptotic cascades [6]. Cadmium exposure has also been linked to increased expression of Bax, a pivotal pro-apoptotic protein that promotes cell death and structural deterioration within vulnerable brain regions [8].

The search for natural remedies against cadmium-induced neurotoxicity has drawn attention to the use of medicinal plants with antioxidant and anti-apoptotic properties. *Launaea taraxacifolia*, commonly referred to as wild lettuce, is one such plant, widely consumed as a leafy vegetable across Africa [2], [12], [14]. Beyond its nutritional value, it is traditionally used to manage inflammation and oxidative disorders [12]. Rich in phytochemical compounds such as flavonoids and phenolic acids, *L. taraxacifolia* may offer neuroprotective potential, though evidence remains limited. This study therefore investigates the ability of *Launaea taraxacifolia* aqueous extract to attenuate cadmium chloride–induced hippocampal and cortical damage in male Wistar rats. By focusing on nitric oxide dysregulation and Bax immunoreactivity, the research aims to elucidate how this plant extract may modulate key neurotoxic pathways and preserve neuronal integrity under heavy metal stress.

MATERIALS AND METHODS

A. Preparation of Launaea taraxacifolia Aqueous Extract

Launaea taraxacifolia leaves were harvested and air-dried for four days and pulverized into a fine powder. After soaking 300g of the powdered leaves in 4 liters of distilled water that had been continuously heated to 60^{o}C for 24 hours, the leaves were filtered through filter paper. A rotary evaporator was used to concentrate the filtrate, and the yield (Y) was computed using the following formula:

Y (%) = (Mass of extract) / (Mass of plant material used)×100

The stock solution, which was made by diluting 6 g of extract with 48 ml of distilled water at 3-day intervals, was used to determine the dosage of the dried extract that was given.

B. Experimental Animals

Thirty-two (32) healthy adult male rats weighing between 200g -250g were used. The animals were housed in standard laboratory cages under normal light and dark cycles. They were provided with clean drinking water and fed a standard laboratory diet throughout the experiment. Before the commencement of administration, the animals were acclimatized for fourteen days. All animals used for the experiment were handled in accordance with the guidelines for animal research as detailed in the National Institute of Health Guidelines for the Care and Use of Laboratory Animals, 2008 [10].

C. Experimental Design

The animals were assigned into four groups (n=8) and treated as follows;

Group I: Received distilled water orally for 21 days.

Group II: Received 5 mg/kg $CdCl_2$ orally for 21 days.

Group III: Received 400 mg/kg LTAE orally for 21 days.
Group IV: Received 5 mg/kg $CdCl_2$, followed by 400 mg/kg LTAE orally for 21 days.

The dosage of $CdCl_2$ was chosen based on previous studies that reported a significant increase in $CdCl_2$ accumulation in brain tissues [18].

Aqueous extract was dissolved in distilled water at the dose of 400 mg/kg and were administered using oral cannula.

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D. Nitric Oxide Assay

Nitric oxide (NO) activity was quantified using the Griess assay, following the procedure described by [8]. About 100 µL of the tissue supernatant was reacted sequentially with sulfanilic acid and N-(1-naphthyl) ethylenediamine dihydrochloride to form a chromophoric azo compound, and the absorbance was measured at 540 nm. A sodium nitrite standard curve was used to determine the concentrations of nitrite. For nitrate estimation, samples were first reduced to nitrite using nitrate reductase before undergoing the same assay procedure. Total nitrite and nitrate levels were normalized to tissue protein content and expressed as micromoles per gram of tissue.

E. Bax Immunohistochemistry

Bax immunohistochemistry was performed as described by [11]. Briefly, paraffin-embedded brain sections (5 µm) were deparaffinized and subjected to antigen retrieval in citrate buffer (pH 6.0) for 20 minutes, followed by cooling at room temperature. Endogenous peroxidase activity was quenched with 0.3% hydrogen peroxide in Tris-buffered saline, and nonspecific binding was blocked with 2.5% normal horse serum. Sections were then incubated with the primary Bax antibody (1:200) for one hour at room temperature, followed by ImmPRESS™ Polymer Anti-Rabbit IgG reagent. Immunoreactivity was visualized using a DAB peroxidase substrate kit and counterstained with Harris hematoxylin. Representative photomicrographs were obtained using Toupview software.

F. Photomicrography and Image Analysis

Photomicrography and image analysis were conducted as previously described [1]. The cerebral cortex and hippocampus were photographed at 400x magnification using a light microscope. A light microscope using the 'OMAX Toup View' eyepiece connected to a computer was used to capture the images of stained tissues. Cell counting was performed using Image Analysis and Processing for Java (ImageJ) software. Photomicrographs were uploaded into the software. Pyramidal cells were identified and marked using the marker tool, and the software automatically displayed the total count in the statistics window.

G. Statistical Analysis

GraphPad Prism version 8.0 was used to analyze the data using one-way ANOVA and Tukey's post hoc test. The findings were presented as mean ± standard error of the mean (SEM). Statistical significance was defined as $p < 0.05$.

RESULTS

A. Effect of LTAE on Nitric Oxide in $CdCl_2$-induced Brain Damage

Figure 1-2 shows the nitrate and nitrite levels (metabolites of nitric oxide) in the brain homogenates of Wistar rats across groups. There was a significant increase ($p < 0.05$) in the nitrate and nitrite levels in $CdCl_2$-treated group compared with the control group. In addition, rats that received LTAE as a co-treatment with $CdCl_2$ ($CdCl_2$+LTAE) showed a significant decrease ($p < 0.05$) in the nitrate and nitrite levels as compared with $CdCl_2$ group.

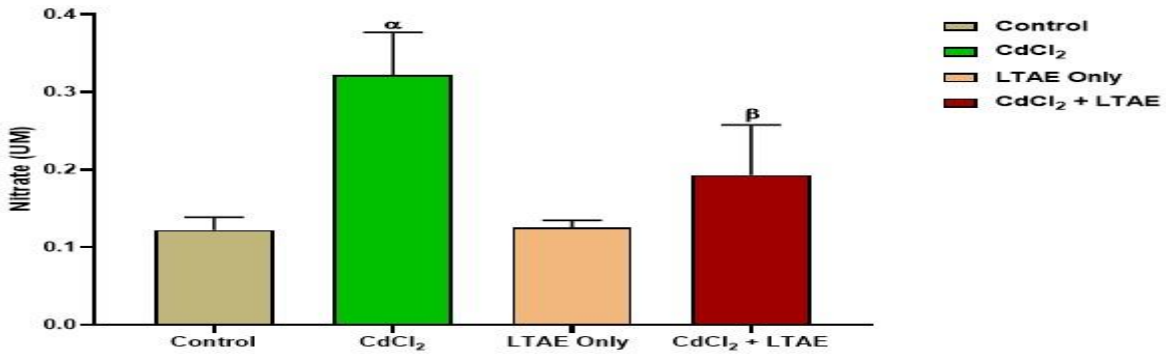

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Fig. 1 Effect of LTAE on nitrate level in $CdCl_2$-induced Wistar rats. All data were estimated with the help of one-way ANOVA trailed by Tukey's multiple comparisons tests. Data were expressed as mean ± S.E.M (n =5). α: significant change with respect to control; β: significant change with respect to $CdCl_2$. Value of $p < 0.05$ was considered significant. ($CdCl_2$=Cadmium chloride; LTAE= *Launaea taraxacifolia* aqueous extract).

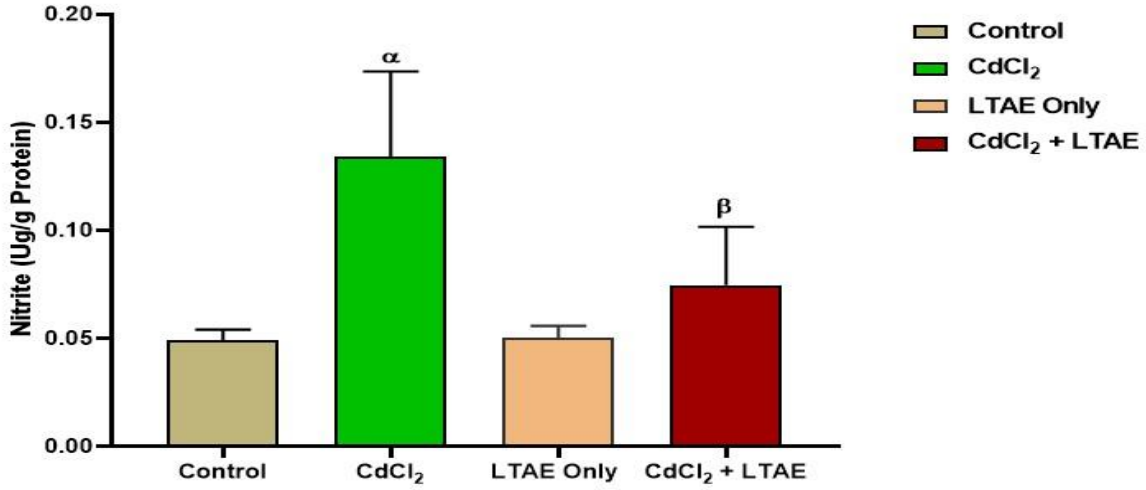

Fig. 2 Effect of LTAE on nitrite level in $CdCl_2$-induced Wistar rats. All data were estimated with the help of one-way ANOVA trailed by Tukey's multiple comparisons tests. Data were expressed as mean ± S.E.M (n =5). α: significant change with respect to control; β: significant change with respect to $CdCl_2$. Value of $p < 0.05$ was considered significant. ($CdCl_2$=Cadmium chloride; LTAE= Launaea taraxacifolia aqueous extract).

B. Effects of LTAE on the Expression of Bax in the Brains of Wistar Rats

Plate 1 – 2 represent the photomicrographs of bax immunostaining of the cerebral cortex and hippocampus of Wistar rats across groups. Microscopic examination of the control and the LTAE-alone treated group shows normal bax immunoactivity in the cerebral cortex and hippocampus. In the $CdCl_2$-treated group, Bax expression was significantly increased ($p < 0.05$) within the cortex and hippocampus compared to the control group. In the ameliorative group ($CdCl_2$ + LTAE), there was a significant decrease ($p < 0.05$) in Bax expression within the cortex and hippocampal layers compared to the $CdCl_2$-treated group.

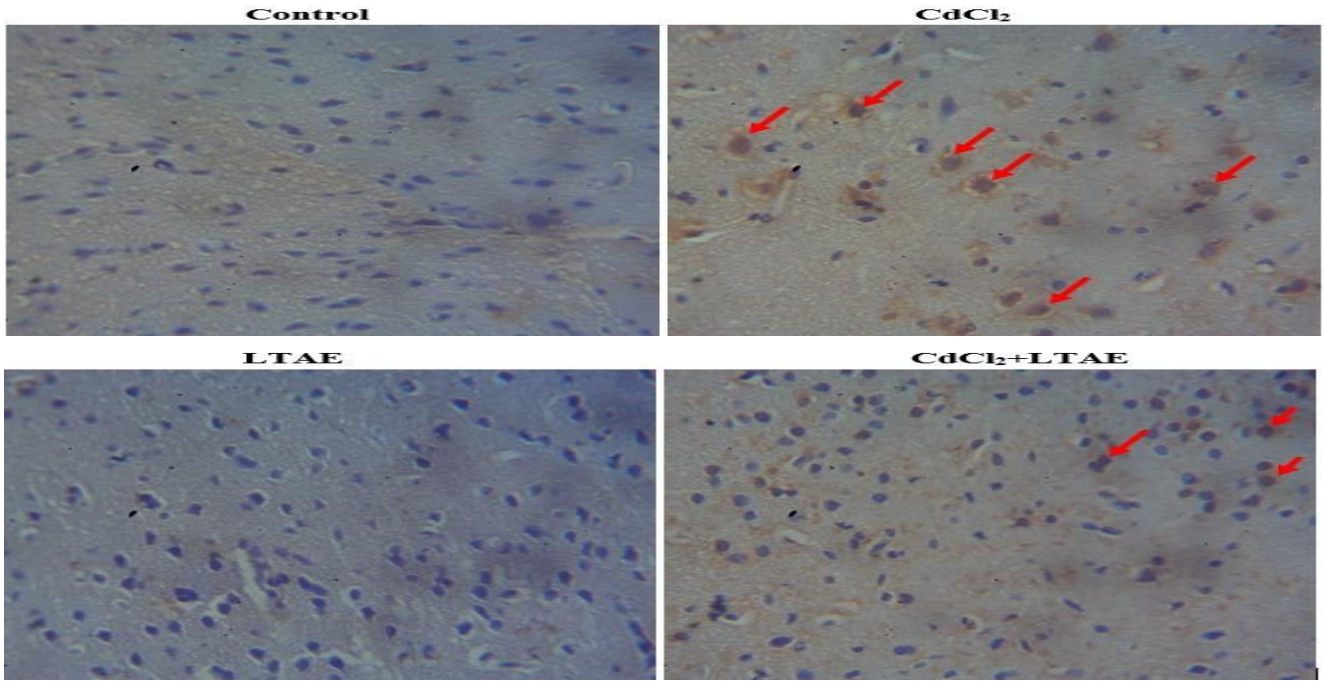

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Plate 1 Effects of LTAE on $CdCl_2$-induced immunohistochemical changes in the pyramidal layer of the cerebral cortex of Wistar rats (Bax, 400X). The cerebral cortex of the control group presents minimal Bax expression. The $CdCl_2$ group was characterised with strong Bax immunostaining (red arrows). LTAE treated group with a weak Bax expression. Treatment of $CdCl_2$ rats with LTAE shows a decrease in Bax expression (red arrows). ($CdCl_2$=Cadmium chloride; LTAE= Launaea taraxacifolia aqueous extract).

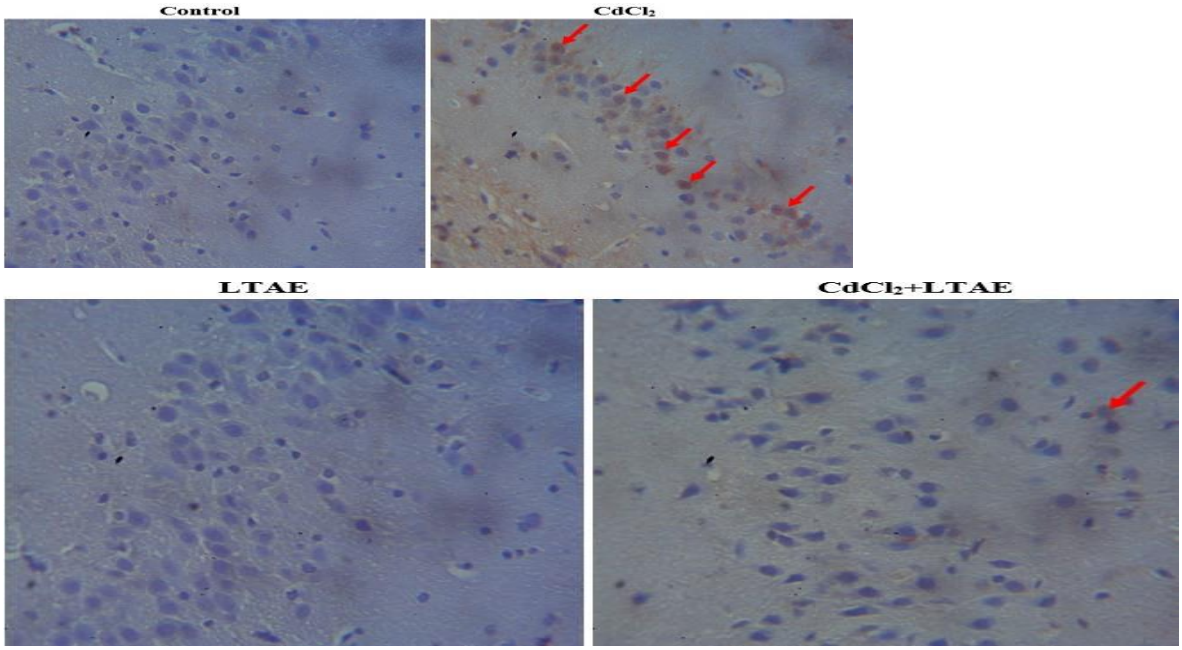

Plate 2 Effects of LTAE on $CdCl_2$-induced immunohistochemical changes in the CA1 region of the hippocampus of Wistar rats (Bax, 400X). The CA1 region of the control group presents minimal Bax expression. The $CdCl_2$ group was characterised with strong Bax immunostaining (red arrows). LTAE treated group with a weak Bax expression. Treatment of $CdCl_2$ rats with LTAE shows a decrease in Bax expression (red arrow). ($CdCl_2$=Cadmium chloride; LTAE= *Launaea taraxacifolia* aqueous extract).

C. Effects of LTAE on the Stereological Assessment of Bax +ve cells in the Brain of Wistar Rats

Figure 3-4 shows the stereological assessment of Bax +ve cells in the cerebral cortex and hippocampus of rat brain across groups. A significant increase ($p < 0.05$) in the number of Bax +ve cells was seen in the cerebral cortex and hippocampus of rats that received $CdCl_2$ compared to control group. There was a significant decrease ($p < 0.05$) in the number of Bax +ve cells in the $CdCl_2$ + LTAE and LTAE only groups compared to the $CdCl_2$ group.

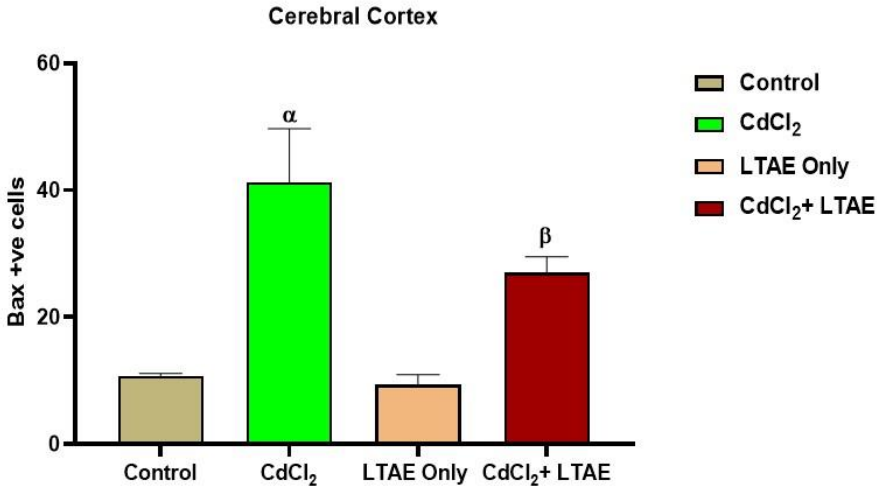

Fig. 3 Effects of LTAE on the stereological assessment of Bax +ve cells in the cerebral cortex of rat brain across groups. All data were estimated with the help of one-way ANOVA trailed by Tukey's multiple

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comparisons tests. Data were expressed as Mean ± S.E.M (n =7). α: significant change with respect to control; β: significant change with respect to $CdCl_2$. Value of $p < 0.05$ was considered significant.
($CdCl_2$=Cadmium chloride; LTAE= Launaea taraxacifolia aqueous extract).

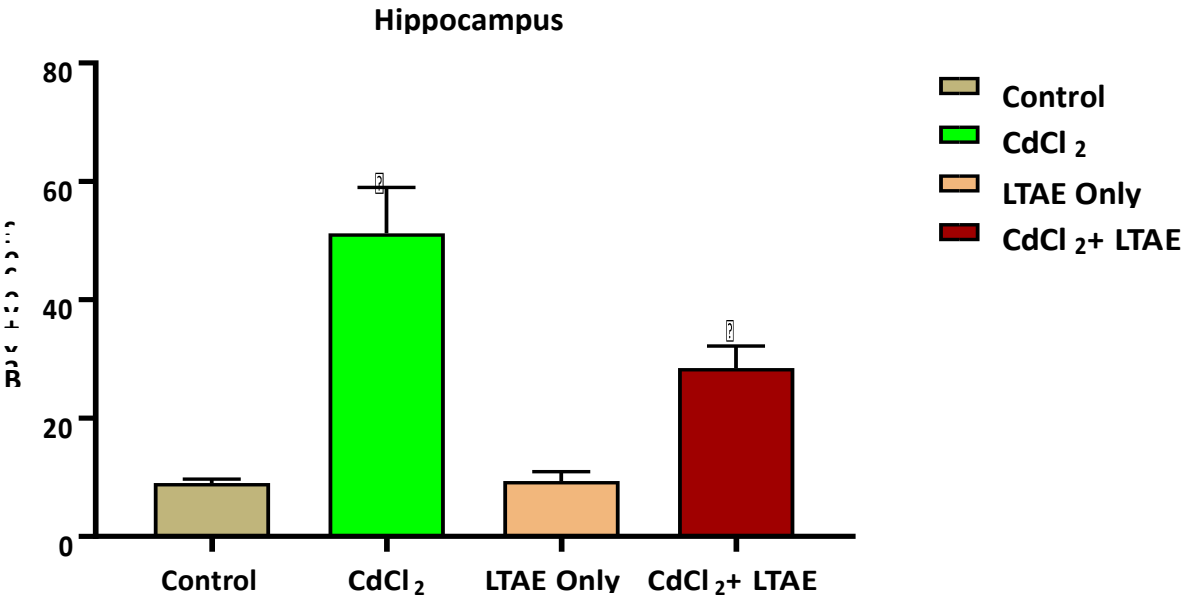

Fig. 4 Effects of LTAE on the stereological assessment of Bax +ve cells in the CA1 region of the hippocampus of rat brain across groups. All data were estimated with the help of one-way ANOVA trailed by Tukey's multiple comparisons tests. Data were expressed as Mean ± S.E.M (n =7). α: significant change with respect to control; β: significant change with respect to $CdCl_2$. Value of $p < 0.05$ was considered significant. ($CdCl_2$=Cadmium chloride; LTAE= Launaea taraxacifolia aqueous extract).

DISCUSSION

The present study provides evidence that *Launaea taraxacifolia* aqueous extract offers neuroprotection against cadmium chloride–induced neuronal damage, likely through mechanisms involving oxidative stress attenuation and apoptosis regulation. According to the Oxidative Stress Theory, an imbalance between reactive oxygen/nitrogen species and the body's antioxidant defense system plays a central role in the initiation and progression of neurodegenerative processes [23]. Cadmium is known to generate excessive free radicals that impair mitochondrial function, damage cellular macromolecules, and disrupt neural homeostasis [23]. In this study, cadmium exposure led to elevated levels of nitrite and nitrate, stable end-products of NO, indicating increased NO production and subsequent oxidative damage. This is in line with the study of [13] who reported an increase in the level of nitric oxide in the brain of rats exposed to cadmium. The increased levels of nitrite and nitrate are likely a result of cadmium-induced inflammation. Neuroinflammation is a result of the upregulation of nitric oxide synthase (NOS), the enzyme that produces NO, during inflammatory reactions [15]. Cadmium exposure is thought to cause inflammatory reactions in the brain, which is supported by the high nitrite and nitrate levels seen in the cadmium-treated group. Treatment with *Launaea taraxacifolia* aqueous extract significantly reduced the levels of nitrite and nitrate. This decrease implies that the plant extract might have antiinflammatory properties, either by reducing NOS activity or by altering the inflammatory pathways that cadmium triggers. Launaea taraxacifolia's bioactive components, such as flavonoids and terpenoids, which are known to prevent neuroinflammation and suppress the synthesis of pro-inflammatory mediators, may be responsible for its anti-inflammatory qualities. Launaea taraxacifolia may lessen neuroinflammation and its related neurotoxic effects by lowering NO overproduction. The observed reduction in nitric oxide activity in *L. taraxacifolia*–treated rats indicate that the extract may have mitigated nitrosative and oxidative stress by enhancing endogenous antioxidant defenses or directly scavenging reactive species.

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Bax immunostaining was used to identify apoptotic cell death as Bax is a key pro-apoptotic protein that promotes mitochondrial outer membrane permeabilization, leading to cytochrome c release and activation of downstream caspases responsible for programmed cell death [20]. In the brain tissue of cadmium-exposed rats, a significant increase in Bax expression was observed, indicating the activation of apoptotic pathways and neuronal cell death. This is similar to the study of Manal et al. whereby up-regulation of Bax expression in cadmium-treated rats was reported [8]. Neuronal apoptosis is known to result from the activation of proapoptotic proteins like Bax, which is brought on by cadmium-induced oxidative stress and mitochondrial dysfunction [21]. However, in rats treated with *Launaea taraxacifolia* aqueous extract, a significant reduction in Bax expression was observed, indicating a decrease in apoptotic cell death. The observations in this study suggests that the plant extract may inhibit cadmium-induced apoptosis by modulating the apoptotic signaling pathways. The suppression of Bax expression implies that the extract may stabilize mitochondrial integrity and inhibit the intrinsic apoptotic cascade, thereby preserving neuronal viability. *Launaea taraxacifolia* may have neuroprotective effects by promoting neuronal survival and preventing apoptotic cell death, as evidenced by the decrease in Bax expression. This might be accomplished by the plant's antioxidant properties, which preserve mitochondrial function and lessen oxidative stress, as well as its possible capacity to control apoptotic proteins.

Collectively, these findings suggest that the neuroprotective action of *L. taraxacifolia* involves a dual mechanism, attenuation of oxidative/nitrosative stress and inhibition of apoptotic pathways. Such multimodal protection is particularly valuable in combating complex neurotoxic insults, where oxidative damage and apoptosis act synergistically to exacerbate neuronal degeneration.

CONCLUSION

In conclusion, *Launaea taraxacifolia* aqueous extract demonstrates significant neuroprotective potential against cadmium chloride–induced hippocampal and cortical injury, mediated through suppression of nitric oxide dysregulation and downregulation of Bax-dependent apoptosis. The plant’s antioxidative and antiapoptotic properties underscore its therapeutic promise as a natural neuroprotective agent. Future studies should aim to conduct dose–response assessments to identify the most effective and safe concentration range for neuroprotection. Additionally, bioassay-guided fractionation and isolation of active phytoconstituents are essential to determine the specific compounds responsible for the observed effects. Molecular investigations should also focus on elucidating how *L. taraxacifolia* modulates intracellular signaling pathways involved in oxidative stress, mitochondrial function, and apoptosis regulation. Long-term behavioral and cognitive assessments in animal models, coupled with translational studies, would further validate its potential as a candidate for therapeutic development in heavy metal–induced neurotoxicity and possibly other neurodegenerative disorders.

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EOA: Conducted experiments, data collection, data analysis, and writing- original draft. **TSO**: Conceptualization, supervision, project administration, proofreading and final manuscript editing. **GTA**: Conceptualization, supervision, methodology, project administration.

Ethical Approval

All procedures were in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and approved by the ethical standards of the institution (FUTA/ETH/25/235).

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