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Original Research

Diacerein attenuates cisplatin-induced cerebellar neurotoxicity in rats: modulation of PI3K/AKT signaling and inhibition of NLRP3-mediated pyroptosis

Diacerein protects against cisplatin neurotoxicity

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Abstract

Aim: This study investigated Diacerein's capacity to protect the cerebellum from cisplatin-driven neurotoxicity characterized by oxidative stress, inflammation, and apoptosis and clarified the associated molecular pathways.

Methods: Forty adult male Wistar rats were assigned to four groups: control, Diacerein (100 mg/kg), cisplatin (10 mg/kg), and cisplatin plus Diacerein. After seven days of treatment, cerebellar tissues were assessed for oxidative, inflammatory, apoptotic, and pyroptotic alterations using biochemical assays, ELISA, and qRT-PCR.

Results: Cisplatin exposure caused profound cerebellar degeneration, evidenced by heightened lipid peroxidation, depletion of endogenous antioxidant defenses, and marked suppression of the PI3K/AKT survival pathway. These disturbances were accompanied by robust activation of the NF-κB/NLRP3 inflammasome axis, resulting in elevated pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and increased pyroptotic mediators (caspase-1, IL-18, GSDMD). Apoptotic imbalance was also apparent, with upregulation of Bax and caspase-3 and reduced Bcl-2 expression. Histopathological examination corroborated these biochemical disruptions. Co-administration of Diacerein significantly mitigated cisplatin-induced cerebellar toxicity by restoring redox homeostasis, reactivating PI3K/AKT signaling, and suppressing NF-κB-driven inflammatory and pyroptotic cascades. Diacerein also normalized apoptotic markers and preserved cerebellar architecture.

Conclusion: Collectively, these findings indicate that Diacerein affords substantial neuroprotection against cisplatin-induced cerebellar degeneration through coordinated modulation of oxidative stress, inflammation, and programmed cell death pathways, highlighting its promise as an adjuvant strategy to reduce chemotherapy-associated neurotoxicity.

Keywords

cisplatin, diacerein, cerebellar degeneration, neuroprotection, oxidative stress

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Introduction

Cisplatin (CS) remains a first-line chemotherapeutic drug for various cancers, including those of the esophagus, testes, cervix, bladder, ovaries, head, and neck.[1] Nevertheless, its therapeutic benefit is restricted by considerable harm to non-cancerous tissues.[2] Common neurological complications include impaired cognition, shortened attention span, and loss of executive function.[3] Healthy cells tend to take up more cisplatin than malignant cells, increasing their vulnerability to injury.[4] Severe peripheral neuropathy often necessitates lowering the dose or stopping treatment early.[5] Additional reported adverse effects involve hearing loss, kidney damage, cardiovascular issues, gonadal dysfunction, liver injury, and toxicity to both central and peripheral nerves.[6]

Oxidative stress is a major contributor to cisplatin-induced tissue damage. Physiologically, cells manage reactive oxygen species (ROS) through antioxidant defenses. Cisplatin disrupts this equilibrium by attacking mitochondrial sulfhydryl groups, interfering with calcium uptake, collapsing the mitochondrial membrane potential,[7] lowering glutathione (GSH) levels, and weakening antioxidant capacity.[8] These events cause widespread harm to proteins, lipids, and DNA. In neural tissue, excessive ROS generation, DNA injury, inflammatory responses, mitochondrial failure, and regulated cell death are key drivers of cisplatin-evoked neurotoxicity.[9] Despite previous research, the exact apoptotic pathways triggered by cisplatin in the brain remain incompletely understood.

Diacerein (DIA), an anthraquinone compound originally developed for osteoarthritis, blocks IL-1β-converting enzyme and antagonizes IL-1β receptor binding.[10] Evidence from animal models and human trials indicates that DIA offers substantial protection against inflammatory damage [11] by reducing nitric oxide, TNF-α, and IL-1β, as well as downregulating the IL-1β receptor.[12] DIA also suppresses TLR4/NF-κB signaling, thereby decreasing inflammatory mediator production.[13] Based on these properties, this study examined whether DIA could protect against cisplatin-induced cerebellar injury in male rats, with emphasis on the PI3K/AKT signaling pathway.

Materials and Methods

Experimental Animals

Adult male Wistar albino rats (*n* = 40, 160–200 g) were kept in polypropylene cages under controlled conditions (23 ± 2°C, 45–50% humidity, natural light/dark cycle) with unlimited food and water throughout the study.

Experimental Design

For this study, forty adult male rats were randomly assigned to four groups (*n* = 10 per group) using a computer-generated random number table. The control group received 1 mL of oral saline daily for seven days. The DIA group was given diacerein orally at 100 mg/kg body weight each day for seven consecutive days; this dose was chosen based on our preliminary experiments and prior reports.[11] The CS group received a single intraperitoneal injection of cisplatin (10 mg/kg) on experiment day four,[14] without any diacerein treatment. The CS+DIA group received the same cisplatin injection (10 mg/kg i.p. on day four) plus oral diacerein (100 mg/kg/day) for the full seven days. Sample size (*n* = 10 per group) was determined based on a power analysis with 80% power and α = 0.05, calculated using G*Power software. About 24 hours after the last treatment, final body weights were recorded. Rats were then deeply anesthetized with an intraperitoneal ketamine/xylazine mixture and euthanized by decapitation.

Brains were quickly and carefully removed. Small pieces of cerebellar tissue were immediately cut out, frozen in liquid nitrogen, and kept at -80°C for later qPCR analysis. The remaining cerebellar tissue was rinsed with cold phosphate-buffered saline (PBS, pH 7.4), then homogenized in fresh cold PBS. The homogenate was spun at 3000 × g for 10 minutes at 4°C to pellet debris. The resulting supernatant was collected, aliquoted, and stored at -20°C for biochemical measurements. Additional cerebellar samples were placed in 10% neutral buffered formalin for histological examination.

Biochemical Assay

Thawed cerebellar samples were weighed and homogenized (10% w/v) in cold phosphate buffer at 12,000 rpm for 2 minutes. MDA was measured at 532 nm. GSH was read at 410 nm. SOD activity was assessed at 560 nm. CAT activity was tracked by H_2O_2 degradation at 240 nm over one minute. Protein was quantified via the Lowry method for normalization.

Histological Analysis of Cerebellar Tissue

Cerebellar samples were fixed for 6–8 hours in 4% paraformaldehyde (0.1 M phosphate buffer, pH 7.4), then dehydrated in graded ethanol, cleared with xylene, and embedded in paraffin. Sections (4 µm) were cut, deparaffinized, rehydrated, stained with H&E, and examined by light microscopy.

ELISA Assay

The concentrations of inflammatory, apoptotic, and signaling biomarkers were quantified using commercially available ELISA kits following the manufacturers' instructions. The following kits and detection ranges were used in this study: p-AKT (MyBioSource, San Diego, CA, USA; Cat# MBS8821006, 15.63–1000 pg/mL), PI3K (MyBioSource, San Diego, CA, USA; Cat# MBS702819, 15.6–1000 pg/mL), caspase-1 (Novus Biologicals, Centennial, CO, USA; Cat# NBP2-75015, 62.50–4000 pg/mL), GSDMD (LifeSpan BioSciences, Seattle, WA, USA; Cat# LS-F39621-1, 0.156–10 ng/mL), IL-1β (Thermo Fisher Scientific, Waltham, MA, USA; Cat# BMS630, 31.3–2000 pg/mL), IL-6 (Thermo Fisher Scientific, Waltham, MA, USA; Cat# ERA31RB, 30–10,000 pg/mL), TNF-α (ELK Biotechnology, Wuhan, China; Cat# ELK1396, 15.63–1000 pg/mL), NF-κB (MyBioSource, San Diego, CA, USA; Cat# MBS453975, 0.312–20 ng/mL), IL-18 (Elabscience, Houston, TX, USA; Cat# E-EL-R0567, 15.63–1000 pg/mL), Bax (ELK Biotechnology, Wuhan, China; Cat# ELK5698, 12.5–800 pg/mL), caspase-3 (BioAssay Systems, Hayward, CA, USA; Cat# E1648Ra, 0.05–10 ng/mL), and Bcl-2 (Novus Biologicals, Centennial, CO, USA; Cat# NBP2-69947, 0.16–10 ng/mL).

Quantitative Real-Time PCR (qRT-PCR) Analysis

Total cerebellar RNA was extracted with TRIzol per the manufacturer's protocol. RNA purity and concentration were checked. One microgram of RNA was reverse-transcribed to cDNA using a commercial kit. qRT-PCR was run on a CFX96 system with SYBR Green mix. Cycling conditions: 95°C for 15 minutes, then 40 cycles of 95°C for 30 seconds, 60°C for 60 seconds, and 72°C for 60 seconds. NLRP3 primers (forward: TGCATGCCGTATCTGGTTGT, reverse: ACCTCTTGCGAGGGTCTTTG) and GAPDH primers (forward: AACTCCCATTCCTCCACCTT, reverse: GAGGGCCTCTCTCTTGCTCT) were used. Gene expression was calculated by the $2^{-}\Delta\Delta CT$ method and normalized to GAPDH.

Ethical Approval

The study was approved by the Ethics Committee of Umm Al-Qura University, Makkah, Saudi Arabia (Date: 05.02.2026, Decision No: HAPO-02-K-012-2026-05-3445).

Statistical Analysis

All data were first tested for normality using the Shapiro–Wilk test. Data were analyzed by one-way and two-way ANOVA, followed by Tukey's post hoc test for group comparisons. GraphPad Prism 8.02 (GraphPad Software, San Diego, CA, USA) was used for all analyses. Results are expressed as mean ± SD. Statistical significance was set at $P < .05$.

Reporting Guidelines

The study was designed, conducted, and reported in accordance with the ARRIVE 2.0 guidelines.

Results

Protective Effect of Diacerein on Cerebellar Histology

Histological examination of cerebellar sections from the control group and the diacerein-only negative control group revealed normal grey matter histology, with well-defined molecular, Purkinje, and granular layers. In contrast, sections from the CS-treated group showed marked degeneration of the Purkinje layer, characterized by neuronal damage and loss. However, the group co-treated with diacerein and CS exhibited significant improvement in Purkinje neuronal histology, with only a few damaged neurons remaining (Figure 1A–D). These findings indicate a protective effect of diacerein on cerebellar histology in the CS-induced cerebellar toxicity.

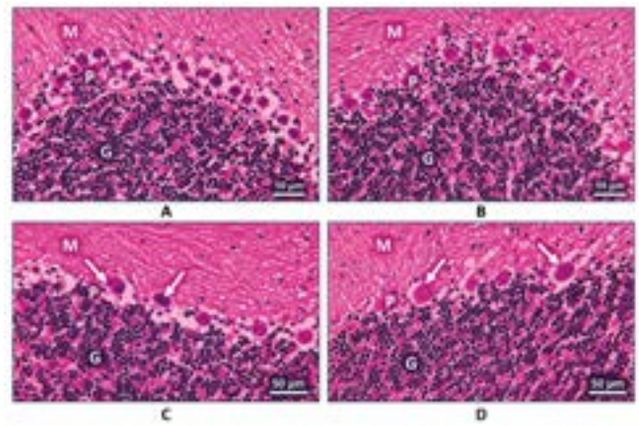


Figure 1. *Histological Changes in the Cerebellar Cortex Across Experimental Groups*

(A, B) Normal cerebellar folia are seen in the control and DIA groups, consisting of gray matter and white matter (W). The gray matter consists of the molecular layer (ML), Purkinje cell layer (PL), and granule cell layer (GL). (C) Cerebellar gray matter in the CS group shows degeneration (arrowheads) and loss of many neurons (black arrows) in the Purkinje cell layer (PL). (D) Cerebellar gray matter in the CS+DIA group shows mild degeneration (arrowheads) and loss of a few neurons (black arrows) in the Purkinje cell layer (PL). H&E, ×400; scale bar = 50 μm.

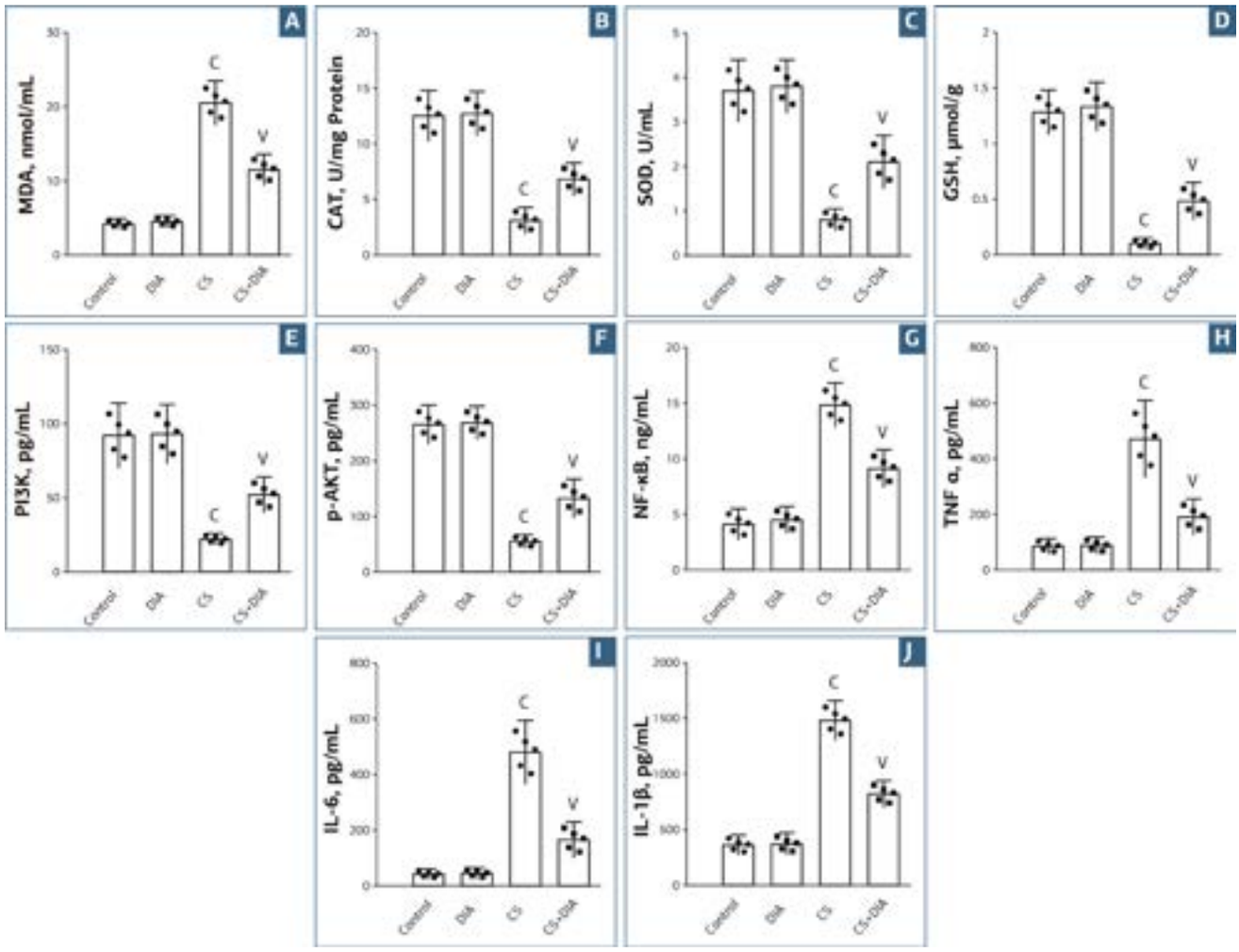


Figure 2. *Cerebellar Oxidative Stress, PI3K/AKT Signaling, and Inflammatory Markers in Experimental Groups*

Cerebellar supernatant levels of (A) MDA, (B) CAT, (C) SOD, (D) GSH, (E) PI3K, (F) phosphorylated AKT, (G) NF-κB, (H) TNF-α, (I) IL-6, and (J) IL-1β in the different experimental groups. Data are presented as mean ± SD. C indicates a significant difference compared with the control group; V indicates a significant difference compared with CS-treated animals.

Antioxidant Effect of DIA Against CS-induced Cerebellar Oxidation

As demonstrated in Figure 2A–D, a single intraperitoneal dose of CS induced severe oxidative stress in cerebellar tissue, evidenced by a marked elevation in MDA levels accompanied by a significant ($P < .05$) reduction in cerebellar SOD, GSH, and CAT activities compared with normal rats. In Group IV, which received 100 mg/kg DIA along with a single dose of CS, a clear attenuation of CS-induced cerebellar oxidative stress was observed. This was reflected by the reversal of the previously altered oxidant and antioxidant parameters. Overall, DIA exerted a strong antioxidant effect, ameliorating the pathological changes associated with CS-induced cerebellar oxidative degeneration in this rat model.

Impact of CS and DIA on the PI3K/AKT Pathway

ELISA quantification of cerebellar PI3K and p-AKT levels (Figure 2E, F) revealed a marked reduction in Group III (CS-treated rats) compared with the control group. In contrast, the combined treatment group that received DIA alongside CS showed significantly elevated levels of both PI3K and p-AKT in cerebellar homogenates relative to the CS group. These findings indicate that DIA exerts a positive modulatory effect on the PI3K/AKT pathway, counteracting the inhibitory impact induced by CS.

Effects of DIA and CS on the NF-κB/NLRP3 Inflammatory and Pyroptotic Pathway

Figure 2G–J demonstrates the pronounced inflammatory response induced by CS in cerebellar tissue. CS exposure markedly increased cerebellar NF-κB levels, indicating activation of this key inflammatory transcription factor. Consequently, ELISA measurements showed significant elevations in pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β.

NF-κB activation further triggered pyroptotic signaling by stimulating the NLRP3 inflammasome, which in turn activated caspase-1. Caspase-1 activation enhanced the maturation and secretion of IL-1β and promoted increased production of the inflammatory cytokine IL-18. In addition, the upregulated pathway activated GSDMD, leading to pore formation in the cellular membrane and subsequent membrane rupture—hallmark features of pyroptotic cell death (Figure 3A–D).

All these inflammatory and pyroptotic markers were markedly elevated in the CS-treated group compared with normal animals. Interestingly, co-treatment with DIA (CS + DIA group) significantly reduced all inflammatory parameters and key components of the pyroptotic pathway relative to the CS group.

Collectively, these findings confirm the potent anti-inflammatory and anti-pyroptotic effects of DIA, highlighting its central mechanistic role in mitigating CS-induced cerebellar degeneration in this animal model.

Amelioration of CS-induced Cerebellar Apoptosis by DIA Administration

Figure 3E–G illustrates the cerebellar apoptotic profile, showing significant elevations in the pro-apoptotic markers caspase-3 and Bax, accompanied by a marked reduction in the anti-apoptotic protein Bcl-2 in the CS-treated group compared with normal rats. In contrast, co-administration of CS with oral DIA produced a clear protective effect, characterized by a notable increase in Bcl-2 levels alongside a significant reduction in caspase-3 and Bax protein expression. These findings strongly support the anti-apoptotic action of DIA in counteracting CS-induced cerebellar apoptotic changes, further corroborated by the accompanying histological observations.

Discussion

Cisplatin's cancer-killing power is limited by toxicity to healthy tissues via oxidative stress and cell death, but our findings show that diacerein co-administration protects cerebellar tissue from this damage.

Oxidative stress plays a central role in CS-related injury to both neural and non-neural tissues.[15] Our data show that a single CS injection on day four raised MDA levels and lowered both enzyme-based and non-enzyme antioxidants in the cerebellum compared to healthy controls. Treating with diacerein alongside CS significantly reduced this oxidative burden. Similar protective effects were reported by Abd Elrazik and Abd El Salam,[16] who found that diacerein lowered MDA and raised GSH in a model of liver-related

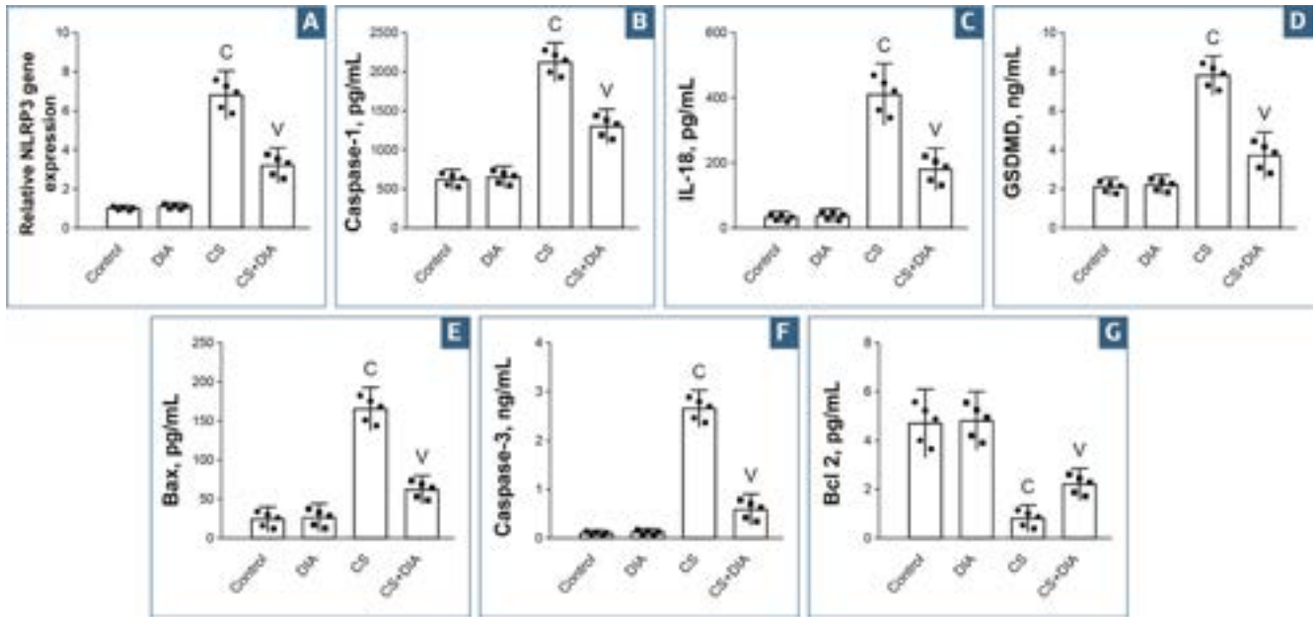


Figure 3. *Cerebellar Pyroptotic and Apoptotic Markers Across Experimental Groups*

(A) Gene expression of NLRP3; (B–D) ELISA levels of caspase-1, IL-18, and GSDMD; and (E–G) caspase-3, Bax, and Bcl-2 levels in cerebellar tissue across the experimental groups. Data are presented as mean ± SD. C indicates a significant difference compared with the control group; V indicates a significant difference compared with the CS group.

brain damage. Likewise, El-Sherbiny et al. [17] showed that diacerein reduced MDA while increasing SOD, CAT, and GSH in prostate tissue.

Earlier work has shown that cisplatin exposure provokes an inflammatory reaction in the mouse cerebellar cortex.[18] In line with this, we saw marked rises in pro-inflammatory markers in CS-treated animals. Such cytokines are key players in neuroinflammation.[19] In cultured cerebellar cells, these inflammatory signals can cause myelin loss and damage to nerve fibers. Furthermore, neuroinflammation and the resulting cytokine release have been linked to cognitive and memory impairment, including those observed in Alzheimer's disease.

Our results agree with these earlier reports. We found that CS greatly increased NF-κB and several pro-inflammatory cytokines in the cerebellum. Giving diacerein orally reversed this neuroinflammatory state, lowering NF-κB, TNF-α, IL-6, and IL-1β. This matches previous studies showing that diacerein blocks NF-κB activation in models of urethritis.[20]

The NLRP3 inflammasome is an important part of the body's innate immune defense and has been linked to disease progression, especially in kidney and brain tissues.[21] Our work showed strong activation of inflammasome components, including NLRP3, IL-1β, caspase-1, IL-18, and GSDMD, pointing to pyroptosis in cerebellar neurons. When CS was given with diacerein, this pyroptotic pathway was suppressed by inhibiting inflammasome formation, consistent with earlier findings.[22]

CS caused clear structural damage in the cerebellum, including loss of Purkinje cells. It is believed that CS attaches to acetylcholine receptors on these cells, setting off cell death pathways. Similar observations were made by Mohiuddin and Kasahara,[23] who found that activating cisplatin receptors led to programmed cell death in brain progenitor cells. Our data confirm that CS raised pro-apoptotic markers (Bax, caspase-3) and lowered the protective marker Bcl-2 in the cerebellum. Giving diacerein along with CS reversed these changes and preserved tissue structure, consistent with the work of Rasheed et al. [24] who reported that diacerein helps maintain normal cerebellar architecture.

Limitations

This study has limitations (short duration, single dose, male-only, no pathway inhibitors, cerebellar focus only). Nevertheless, diacerein consistently protected against cisplatin-induced cerebellar injury across multiple molecular pathways, providing a strong foundation for future animal studies.

Conclusion

In summary, diacerein protects against cisplatin-induced cerebellar damage by lowering oxidative stress, reactivating PI3K/AKT, suppressing NF-κB/NLRP3-driven pyroptosis, and restoring apoptotic balance (increased Bcl-2, decreased Bax and caspase-3).

Declarations

Animal and Human Rights Statement

All animal experiments were conducted in accordance with institutional and national guidelines for the care and use of laboratory animals.

Informed Consent

Not applicable.

Data Availability

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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None.

Author Contributions (CRediT Taxonomy)

Conceptualization: A.F.
Methodology: A.F.
Validation: A.F.
Formal Analysis: A.F.
Investigation: A.F.
Resources: A.F.
Data Curation: A.F.
Writing – Original Draft: A.F.
Writing – Review & Editing: A.F.
Visualization: A.F.
Supervision: A.F.
Project Administration: A.F.
Funding Acquisition: A.F.

AI Usage Disclosure

The authors declare that no generative artificial intelligence or large language models were used to write, generate content, perform data analysis, interpret results, or create figures for this study. AI tools were not used in the conceptualization, design, execution, or interpretation of the research. All content is the original work of the authors.

Abbreviations

AKT: Protein kinase b
ANOVA: Analysis of variance
Bax: Bcl-2–associated x protein
Bcl-2: B-cell lymphoma 2
CAT: Catalase
CS: Cisplatin
DIA: Diacerein
ELISA: Enzyme-linked immunosorbent assay
GAPDH: Glyceraldehyde-3-phosphate dehydrogenase
GSDMD: Gasdermin d
GSH: Glutathione
H&E: Hematoxylin and eosin
IL: Interleukin
MDA: Malondialdehyde
NF-κB: Nuclear factor kappa b
NLRP3: Nod-like receptor family pyrin domain containing 3
PBS: Phosphate-buffered saline
PI3K: Phosphoinositide 3-kinase
qRT-PCR: Quantitative real-time polymerase chain reaction
ROS: Reactive oxygen species
SOD: Superoxide dismutase
TLR4: Toll-like receptor 4
TNF-α: Tumor necrosis factor alpha

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