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Ellagic acid mitigates cyclophosphamide-induced cerebellar damage through its inhibitory effect on oxidative damage, TLR4/Myd88/ NF-κB signaling pathway, and neuronal apoptosis in experimental rats

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Abstract

Cyclophosphamide (CYP), a widely used chemotherapeutic agent, is known to induce neurotoxicity primarily through oxidative stress, inflammation, and apoptosis. This research aimed to evaluate the neuroprotective potential of ellagic acid (EA), against CYP-induced cerebellar injury in rats. Thirty-two male rats were grouped into: Control, EA, CYP, and EA + CYP. EA was administered intraperitoneally at 10 mg/kg for five consecutive days, while CYP take a single intraperitoneal dose of 200 mg/kg on day five. Biochemical, histopathological, and immunological assessments were conducted on cerebellar tissues. CYP administration significantly elevated malondialdehyde (MDA) levels and reduced antioxidant enzyme activities (SOD and CAT), indicating oxidative stress. It also upregulated the TLR4/MyD88/NF-κB pathway and increased (TNF-α, IL-6, IL-1β), along with apoptotic markers (caspase-3, Bax) and reduced anti-apoptotic Bcl-2 expression. In contrast, EA pretreatment markedly attenuated these effects by restoring antioxidant defenses, suppressing inflammatory signaling, and reducing apoptotic activity. Histological analysis further confirmed the protective role of EA in preserving cerebellar architecture and Purkinje cell integrity. These findings suggest that EA offers significant protection against CYP-induced cerebellar damage, supporting its potential as a neuroprotective agent in chemotherapy-associated neurotoxicity.

Keywords: Cyclophosphamide, ellagic acid, cerebellum, oxidative stress, inflammation, apoptosis

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1. INTRODUCTION

Cyclophosphamide (CYP), first synthesized in 1958, is an oxazaphosphorine alkylating agent widely employed in cancer therapy (Dabbish et al., 2023). It has demonstrated efficacy against a broad spectrum of malignancies, including leukemia, lymphoma, and cancers of the breast, lung, prostate, and ovary (Olayinka et al., 2015). The therapeutic and toxic effects of CYP are largely dependent on its metabolic activation by hepatic cytochrome P450 enzymes. This biotransformation yields phosphoramide mustard, the active metabolite responsible for CYP's antineoplastic and immunosuppressive properties, and acrolein, a byproduct associated with its toxic side effects (Alam et al., 2023). CYP's cytotoxicity is non-selective,

affecting both malignant and healthy proliferating cells (Olowe et al., 2024). This systemic toxicity can impact multiple organs, including the brain, liver, testes, bladder, heart, kidneys, and immune system (Famurewa et al., 2023). Emerging evidence highlights CYP's neurotoxic potential, manifesting as peripheral neuropathy, central nervous system disturbances (such as cognitive impairment or "chemo-brain"), enteric neuropathy, nausea, and emesis (Was et al., 2022). CYP induces neurotoxicity through mechanisms involving oxidative stress, inflammation, and apoptosis. Studies in animal models have shown that CPA impairs antioxidant defenses in the brain and cerebellum, leading to increased ROS production and oxidative insult (Singh and Kumar, 2019). This oxidative stress acts as a precursor to neuroinflammation and apoptotic signaling, contributing to neuronal damage (Fesharaki-Zadeh, 2022; Hassan et al., 2022).

Ellagic acid (EA) is a naturally occurring polyphenolic compound abundantly found in berries such as raspberries, blueberries, blackberries, and strawberries as well as in walnuts and other nuts. Many researches explored EA biological activities, including antioxidant, anti-inflammatory, antidepressant, (Aslan, 2015; Aslan et al., 2016; Dhingra and Jangra, 2014; Firdaus et al., 2018). EA has shown protective effects against cognitive impairments induced by agents such as scopolamine and diazepam, and it may also offer neuroprotection in stroke-related brain injury (Baluchnejadmojarad et al., 2017; Mansouri et al., 2016). Given the well-established neurotoxic potential of cyclophosphamide (CYP) and the documented neuroprotective and antioxidant properties of EA, this study aims to examine the potential shielding effects of EA against CYP-induced cerebellar degeneration in rats and to elucidate the underlying mechanisms involved.

2. MATERIALS AND METHODS

2.1. Animals and study design

A total of thirty-two (n = 32) 8-week-old male Wistar albino rats were used in this study. The animals were housed under standard laboratory conditions (temperature: 20–25°C; relative humidity: 50–60%) with a 12-hour light/dark cycle and had ad libitum access to food and water. After a one-week acclimatization period, the rats were randomly divided into four experimental groups (n = 8 per group). The Control Group received normal saline (2 mL/kg body weight) for five consecutive days. The EA Group received i.p. injections of ellagic acid (EA; 10 mg/kg body weight) for five consecutive days (Aslan et al., 2020). The CYP Group received a single i.p. injection of cyclophosphamide (CYP; 200 mg/kg body weight) on day 5 only (Temel et al., 2020). The EA + CYP Group received i.p. injections of EA (10 mg/kg body weight) for five consecutive days, along with a single i.p. injection of CYP (200 mg/kg body weight) on day 5. On day 6, all rats were anesthetized using diethyl ether and sacrificed via decapitation. The skulls were carefully opened, and the cerebellum, the target organ for injury assessment, was rapidly excised. Each cerebellar sample was divided for biochemical and histopathological analysis. For biochemical analysis, samples were homogenized in ice-cold 0.1 M phosphate-buffered saline (PBS, pH 7.4) at a 1:10 (w/v) ratio. The homogenates were centrifuged at 3500 × g for 20 minutes at 4°C, and the resulting supernatant was aliquoted into clean tubes and stored at -20°C until analysis. For histopathological analysis, samples were immediately fixed in 10% neutral buffered formalin solution for at least 24 hours. The study was conducted in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals (NIH Publication No. 8023, revised 1996).

2.2. Biochemical Examinations

Oxidative stress was evaluated by measuring malondialdehyde (MDA) levels and the activities of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT). MDA concentrations were expressed in nanomoles per milliliter (nmol/mL), while SOD and CAT activities were reported as units per milligram of protein (U/mg protein).

Additionally, levels of Toll-like receptor 4 (TLR4), myeloid differentiation primary response 88 (MyD88), nuclear factor kappa B (NF-κB), and the inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), as well as apoptotic markers caspase-3, Bax, and Bcl-2, were quantified using enzyme-linked immunosorbent assay (ELISA) kits (Cat# E-EL-R0990, EKN47172-96T, MBS453975, KRC3011, BMS625, BMS630, ELK1528, OKCD07340, MBS2515143, respectively).

2.3. Histopathological examination

Following sacrifice, cerebellar tissues were excised, rinsed with ice-cold saline, and fixed in 10% neutral buffered formalin for at least 24 hours. The samples were then dehydrated through a graded series of

alcohols, cleared in xylene, and embedded in paraffin wax. Tissue sections of 5 µm thickness were prepared using a rotary microtome and stained with hematoxylin and eosin (H&E) for microscopic evaluation. The stained slides were examined under a light microscope by an observer blinded to the treatment groups. Histopathological changes in the cerebellum were assessed semi-quantitatively using a grading scale from 0 to 3, where 0 indicated no damage, 1 indicated mild damage, 2 indicated moderate damage, and 3 indicated severe damage (Aslankoc et al., 2022).

2.4. Statistical analysis

All data were expressed as mean ± standard deviation (SD) for each group (n = 8). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. Analyses were conducted using GraphPad Prism software (version 8.2; San Diego, CA, USA). A p-value less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Protective Effect of EA against CYP-Induced Cerebellar Injury

As shown in Figure 1, the control group displayed normal cerebellar architecture with well-organized layers and intact, healthy Purkinje cells (Fig. 1A, B). In contrast, administration of a single dose of cyclophosphamide (CYP) at 200 mg/kg body weight induced significant degeneration of Purkinje cells, evident by cellular shrinkage and disrupted morphology (Fig. 1C). Remarkably, pretreatment with ellagic acid (EA) markedly improved the histological appearance of Purkinje cells in CYP-treated rats (Fig. 1D). These observations, supported by histopathological scoring, highlight the neuroprotective effect of EA against CYP-induced cerebellar damage.

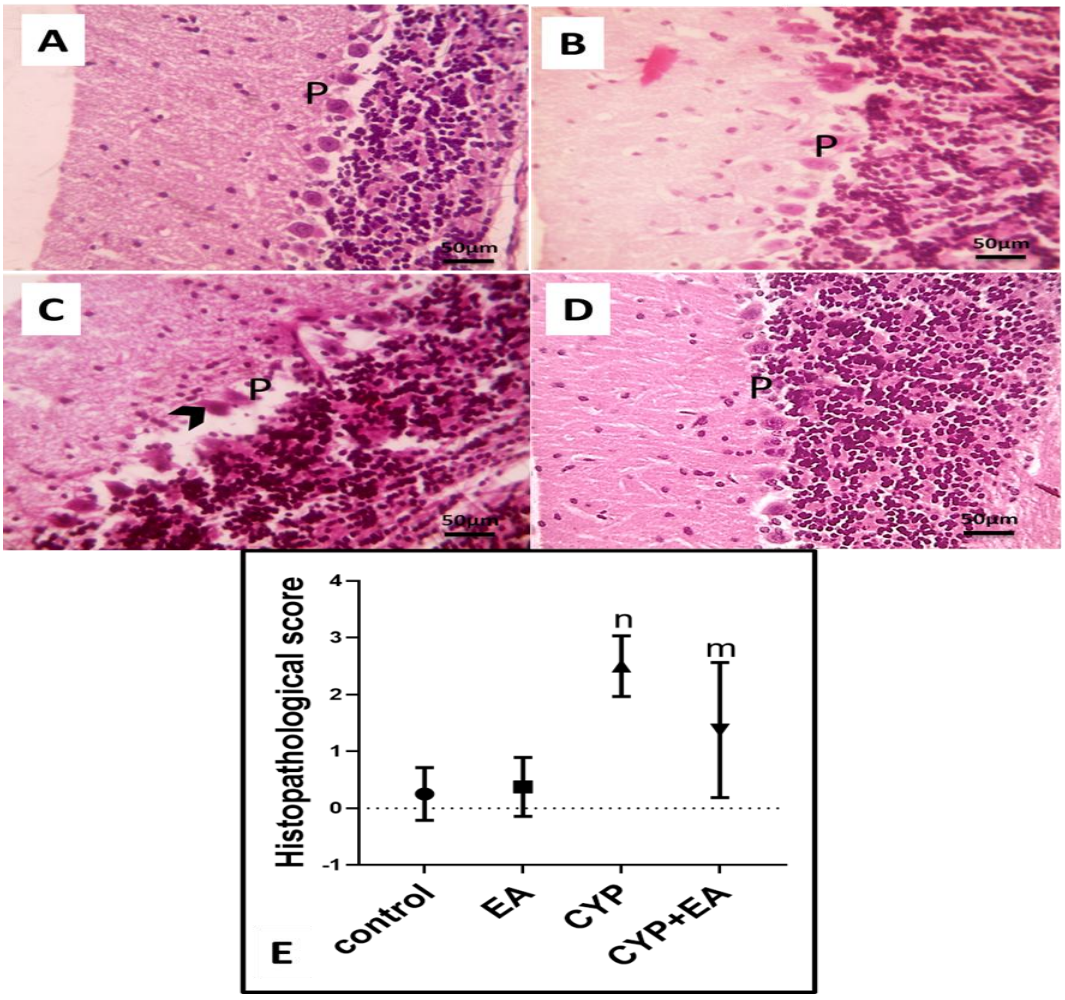

Fig. 1. Microscopic pictures of H&E-stained cerebellar sections showing normal flask shaped Purkinje neurons (P) in grey matter of control and EA groups (A, B). Cerebellar sections from CYP group show

marked shrinkage &apoptosis of Purkinje neurons (arrowheads) with more eosinophilia (C). Cerebellar sections from CYP+EA group showing retained normal appearance of flask shaped Purkinje neurons (P) (D). Histopathological scoring (E). X: 400 bar 50.

3.2. Antioxidant Effect of EA against CYP-Induced Cerebellar Oxidative Stress

As illustrated in Figure 2, cyclophosphamide (CYP) administration significantly ($p < 0.05$) induced oxidative stress in the cerebellum, evidenced by a marked increase in the lipid peroxidation marker malondialdehyde (MDA), along with a significant reduction in SOD and CAT, compared to the control group. Conversely, the group pretreated with ellagic acid (EA) demonstrated a notable antioxidant response, as indicated by a significant decrease in MDA levels and a restoration of SOD and CAT activities relative to the CYP-treated group. These results highlight the antioxidant potential of EA in mitigating CYP-induced oxidative damage in cerebellar tissue.

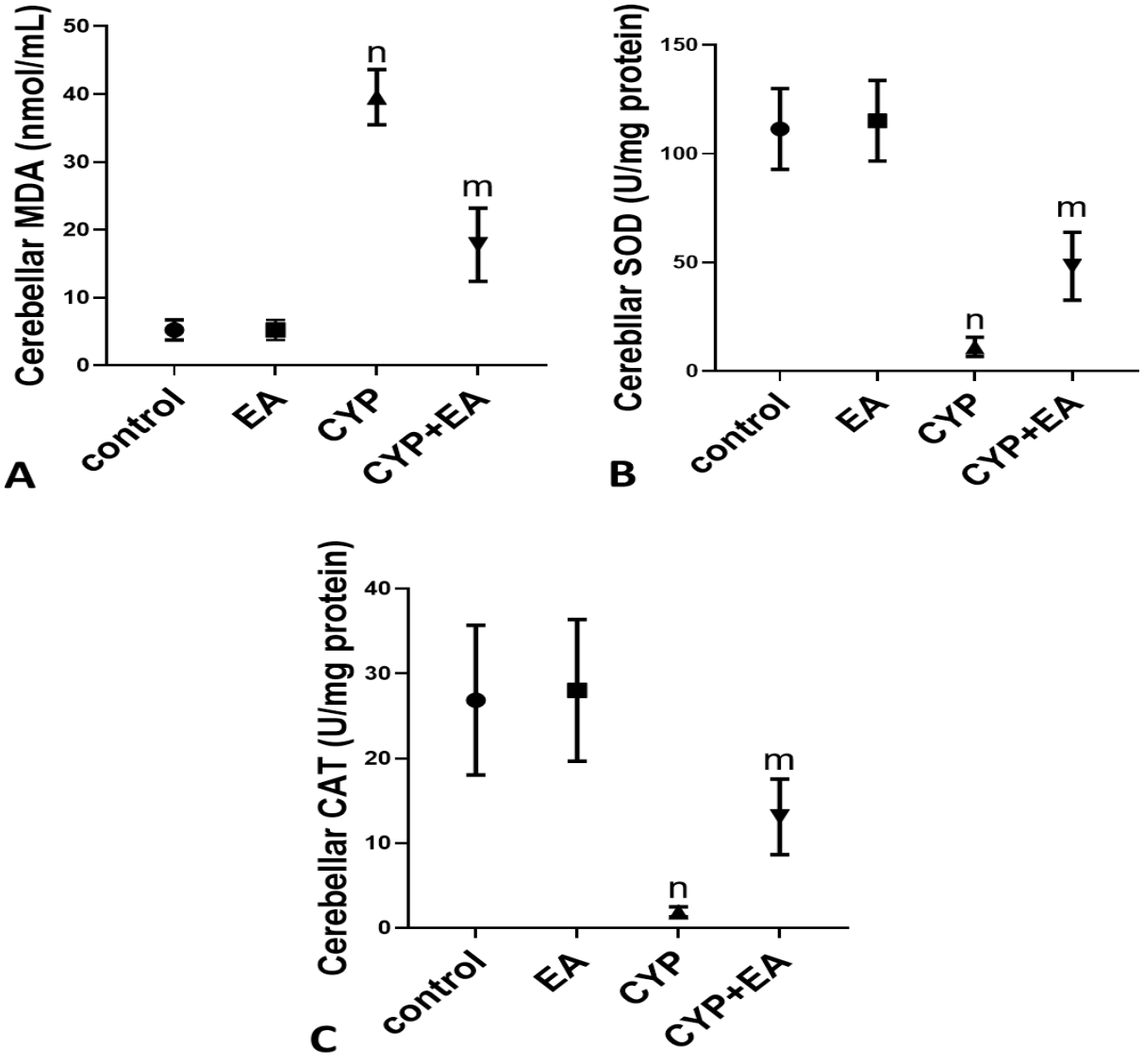

Fig. 2. Effect of CYP and EA on (A) MDA, (B) SOD, and (C) CAT in different groups. n $p < 0.05$ against control animals; m $p < 0.05$ against CYP treated animals.

3.3. Impact of EA on the TLR4/MyD88/NF-κB Inflammatory Pathway

As shown in Figure 3, a single dose of cyclophosphamide (CYP) significantly ($p < 0.05$) upregulated the TLR4/NF-κB pathway, as proved by uprise in the levels of TLR4, MyD88, and NF-κB in the cerebellar

supernatant. This activation was accompanied by elevated concentrations of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. However, pretreatment with ellagic acid (EA) demonstrated a potent anti-inflammatory effect against CYP-induced neuroinflammation. EA effectively downregulated the expression of TLR4, MyD88, and NF-κB, inhibited pathway activation, and reduced the release of inflammatory mediators.

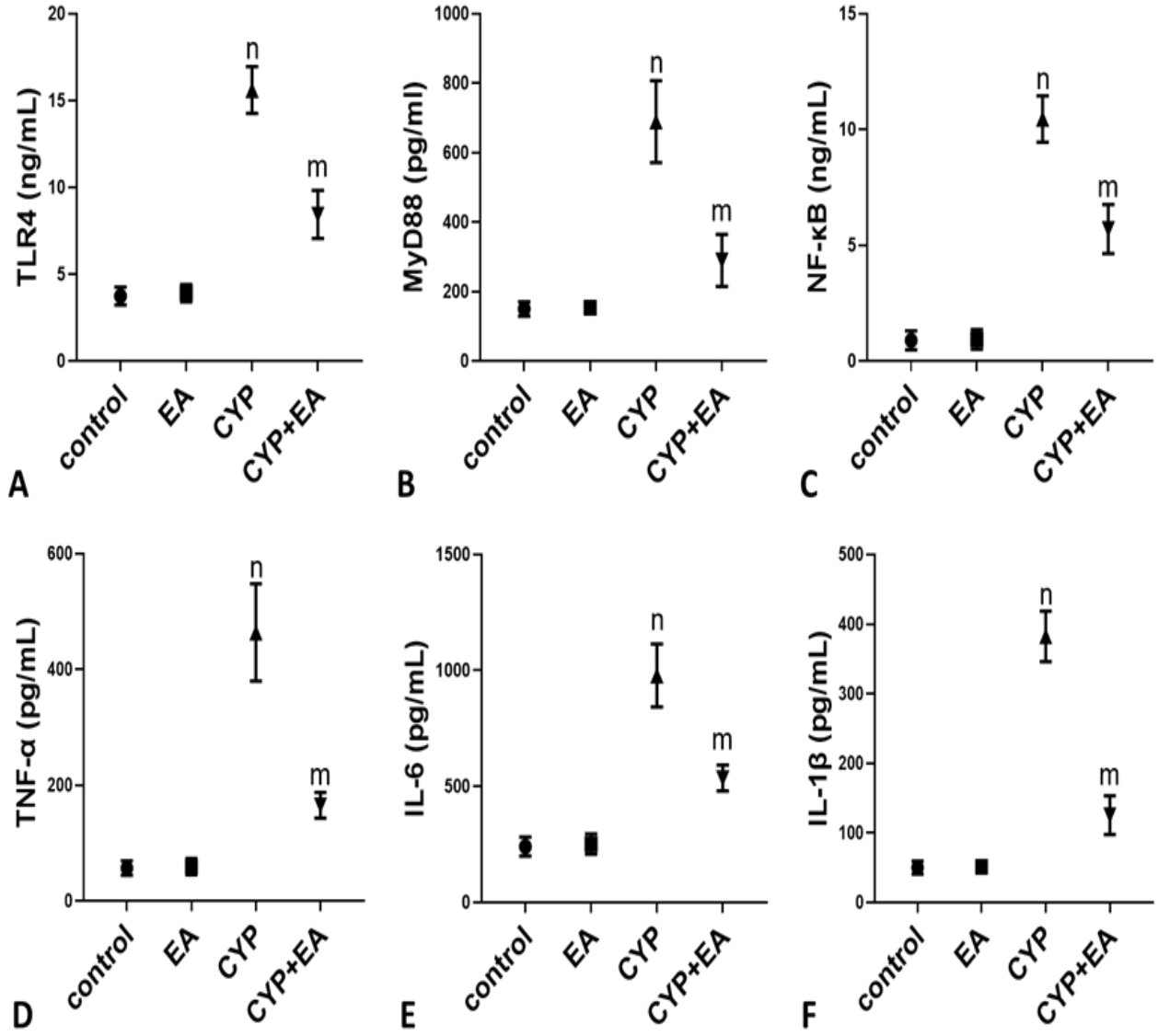

Fig. 3. Impact of CYP and EA on cerebellar supernatants of (A) TLR4, (B) MyD88, (C) NF-κB, (D) TNF-α, (E) Il-6, and (F) IL-1β. n $p < 0.05$ vs control groups; m $p < 0.05$ vs CYP group.

3.4. Anti-apoptotic effect of EA against CYP-induced neuronal apoptosis

As shown in Figure 4, CYP administration resulted in a significant increase in cerebellar protein levels of the caspase-3 and Bax, along with a marked decline in the anti-apoptotic protein Bcl-2. Notably, co-administration of ellagic acid (EA) with CYP significantly reduced caspase-3 and Bax, while markedly elevating Bcl-2 levels relative to the CYP group. These findings suggest that EA mitigates CYP-induced apoptosis and supports the preservation of Purkinje cell integrity, as evidenced by improved histological features and reduced apoptotic cell death.

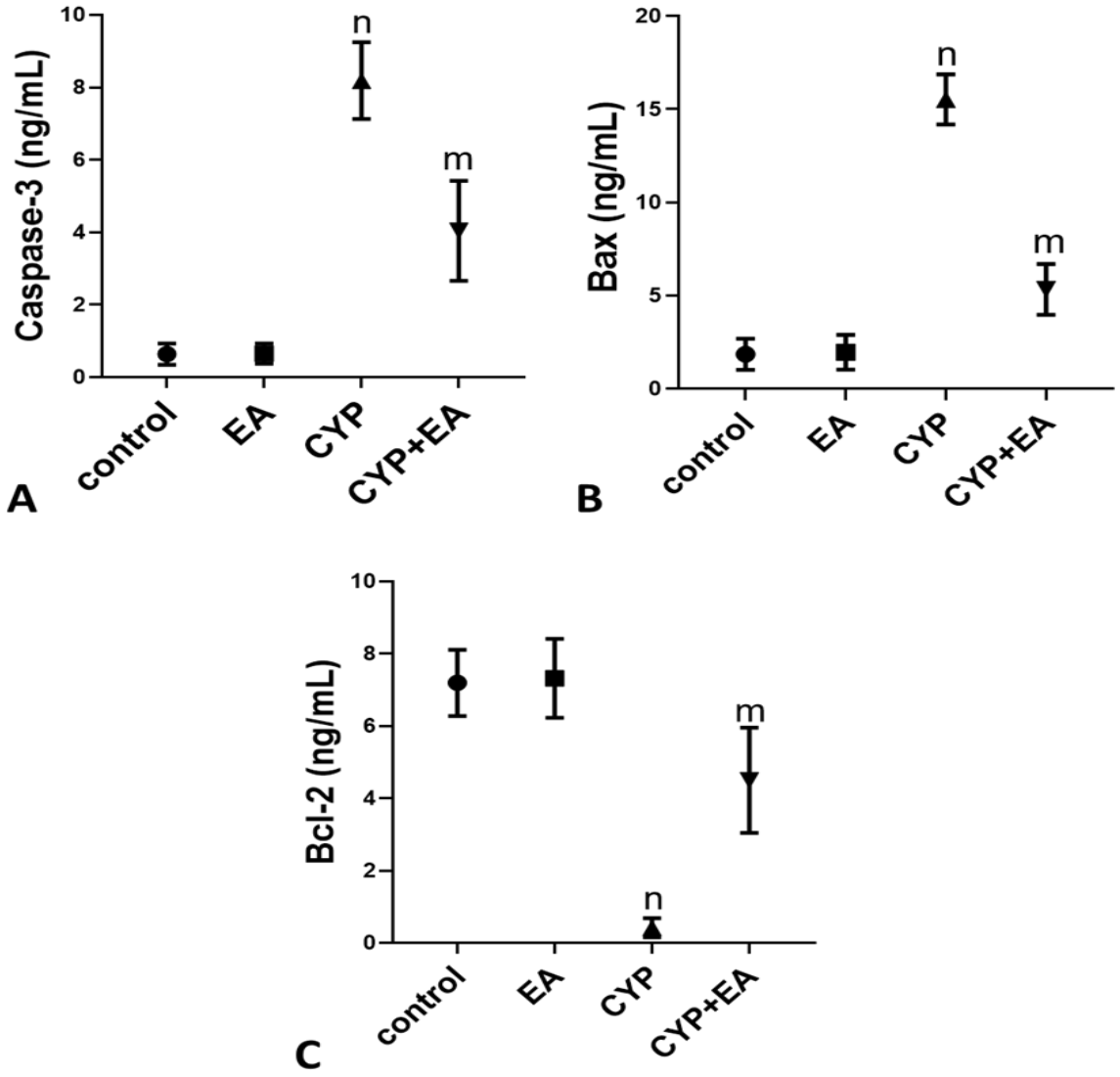

Fig. 4. ELISA level of (A) caspase-3, (B) Bax, and (C) Bcl-2 in different groups. n $p < 0.05$ means significant to normal groups; m $p < 0.05$ means significant to CYP group.

4. DISCUSSION

The repurposing of non-cancer clinical drugs for treating toxicity and various pathologies is an expanding area of global research (Famurewa et al., 2022). This study highlights the neuroprotective effects of ellagic acid (EA) against cyclophosphamide (CYP)-induced neurotoxicity, demonstrating its ability to mitigate cerebellar oxidative stress, neuroinflammation, and neuronal apoptosis through its antioxidant properties.

Research consistently identifies redox imbalance as a key mechanism underlying cyclophosphamide (CYP) toxicity, primarily through the induction of oxidative stress (Al-Amarat et al., 2022). When oxidants overwhelm antioxidant defenses, this stress leads to the oxidation of cellular components DNA, proteins, and lipids and activates metabolic pathways that generate excessive reactive oxygen species (ROS). In line with this, our study revealed that a single intraperitoneal injection of CYP significantly increased malondialdehyde (MDA) levels and reduced antioxidant defenses in cerebellar supernatant compared to the control group. Conversely, co-administration of ellagic acid (EA) with CYP markedly attenuated oxidative stress by reducing lipid peroxidation and enhancing antioxidant enzyme activity. These findings align with previous research by Goudarzi et al. (2018), who reported the protective effect of EA against

sodium arsenate-induced cerebral toxicity. Their study demonstrated that EA reduced oxidative stress by lowering MDA and nitric oxide (NO) levels while increasing GSH, GPx, and TAC in cerebral tissues. The antioxidant effect of EA can be attributed to its potent ability to directly scavenge ROS, inhibit lipid peroxidation, and enhance the endogenous antioxidant defense system.

The inflammatory response is regulated by multiple interconnected signaling pathways. Among them, Toll-like receptors (TLRs) serve as critical sensors of inflammation and innate immunity (Zhou et al., 2009). Upon activation, TLR4 stimulates the NF-κB pathway (Kawasaki and Kawai, 2014), leading to its nuclear translocation and the subsequent upregulation of proinflammatory cytokines. In the present study, a single dose of cyclophosphamide (CYP) markedly activated the inflammatory pathway, as evidenced by elevated protein levels of key components in the TLR4/NF-κB signaling cascade and increased levels of cytokines. These findings are consistent with those of Akram et al. (2024), who reported that CYP stimulates the TLR4/NF-κB/NLRP3 signaling in the pathogenesis of cardiotoxicity in an experimental model, as shown by increased immunoexpression of NF-κB and inflammatory mediators in cardiac tissues. Similarly, Famurewa et al. (2023) demonstrated that CYP upregulates the inflammatory pathway in a neurotoxicity model, with elevated protein levels of NF-κB, IL-6 and TNF-α in cerebral tissues compared to control animals.

Notably, administration of ellagic acid (EA) prior to CYP exposure significantly downregulated the inflammatory signaling cascade, resulting in the inhibition of neuroinflammation. This is in line with findings by Wang et al. (2020), who reported the ameliorative effects of EA against sleep deprivation-induced anxiety through suppression of neuroinflammation and inhibition of TLR4 signaling. Their study showed decreased protein levels of TLR4, NF-κB, MyD88, and phosphorylated IκBα (p-IκBα) in cerebellar tissue. Similarly, Zhao et al. (2021) documented the hepatoprotective effects of EA against alcohol-induced liver inflammation in a mouse model, noting reduced gene expression of TLR4, MyD88, and NF-κB, along with decreased protein levels of inflammatory markers. In a diabetic nephropathy model, EA treatment also downregulated the level of TLR4 in renal tissues, further confirming its anti-inflammatory potential (Zhou et al., 2019). The inhibitory effect of EA on inflammatory pathways may be attributed to its ability to upregulate IκB levels and reduce phosphorylated IκB (p-IκB), thereby preventing NF-κB activation and nuclear translocation (Yumubek et al., 2024).

The pathophysiology of CYP toxicity is predominantly driven by oxidative stress (Singh et al., 2019). Literature indicates that anticancer drug toxicities often induce oxidative apoptosis in cerebral tissues (Famurewa et al., 2021), and a growing body of evidence implicates the interplay between oxidative stress and apoptosis in CYP-mediated organ injury (Was et al., 2022). However, the specific contribution of apoptosis to CYP-induced neurotoxicity remains to be fully elucidated. Our findings revealed that CYP induces neuronal apoptosis, as indicated by elevated levels of caspase-3 and Bax, along with a reduction in the anti-apoptotic marker Bcl-2. These molecular changes were corroborated by histopathological scoring, which showed significant neuronal damage. In contrast, EA exhibited a protective effect against CYP-induced Purkinje cell shrinkage by attenuating cellular apoptosis. This was evidenced by reduced expression of apoptotic markers and increased expression of anti-apoptotic indicators. These results are consistent with those of Liu et al. (2024), who reported that EA exerts anti-apoptotic effects against cadmium-induced apoptosis in HT22 cells by downregulating apoptotic marker expression.

5. CONCLUSIONS AND RECOMMENDATIONS

This study demonstrates that ellagic acid (EA) exerts significant neuroprotective effects against cyclophosphamide (CYP)-induced cerebellar toxicity in rats. EA effectively mitigated oxidative stress, suppressed TLR4/MyD88/NF-κB-mediated neuroinflammation, and reduced neuronal apoptosis. These

findings highlight EA's therapeutic potential as a protective agent against chemotherapy-induced neurotoxicity.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. Akram, W.; Najmi, A. K.; Alam, M. M.; Haque, S. E. Levocabastine ameliorates cyclophosphamide-induced cardiotoxicity in Swiss albino mice: Targeting TLR4/NF-κB/NLRP3 signaling pathway. Toxicol. Appl. Pharmacol., 483, 116838, 2024.
2. Alam, M. F.; Ajeibi, A. O.; Safhi, M. H.; Alabdly, A. J. A.; Alshahrani, S.; Rashid, H.; Qadri, M.; Jali, A. M.; Alqahtani, S.; Nomier, Y.; Moni, S. S.; Khalid, M.; Anwer, T. Therapeutic potential of capsaicin against cyclophosphamide-induced liver damage. J. Clin. Med., 12(3), 911, 2023.
3. Al-Amarat, W.; Abukhalil, M. H.; Alruhaimi, R. S.; Alqhtani, H. A.; Aldawood, N.; Alfwuaires, M. A.; Althunibat, O. Y.; Aladaileh, S. H.; Algefare, A. I.; Alanezi, A. A.; AbouEl-Ezz, A. M.; Ahmeda, A. F.; Mahmoud, A. M. Upregulation of Nrf2/HO-1 signaling and attenuation of oxidative stress, inflammation, and cell death mediate the protective effect of apigenin against cyclophosphamide hepatotoxicity. Metabolites, 12(7), 648, 2022.
4. Aslan, A.; Gok, O.; Beyaz, S.; Arslan, E.; Erman, O.; Ağca, C. A. The preventive effect of ellagic acid on brain damage in rats via regulating of Nrf-2, NF-κB and apoptotic pathway. J. Food Biochem., 44(6), e13217, 2020.
5. Aslan, A. The effects of different essential fruit juice and their combination on Saccharomyces cerevisiae cell growth. Prog. Nutr., 17, 36–40, 2015.
6. Aslan, A.; Boydak, D.; Can, M. I.; Kuloglu, T.; Baspinar, S. Black cumin may be a potential drug for development of carbon-tetrachloride-induced lung damage in rats. Prog. Nutr., 18, 56–62, 2016.
7. Aslankoc, R.; Ozmen, O.; Yalçın, A. Astaxanthin ameliorates damage to the cerebral cortex, hippocampus and cerebellar cortex caused by methotrexate. Biotech. Histochem., 97(5), 382–393, 2022.
8. Baluchnejadmojarad, T.; Rabiee, N.; Zabihnejad, S.; Roghani, M. Ellagic acid exerts protective effect in intrastriatal 6-hydroxydopamine rat model of Parkinson's disease: Possible involvement of ERβ/Nrf2/HO-1 signaling. Brain Res., 1662, 23–30, 2017.
9. Dabbish, E.; Scoditti, S.; Shehata, M. N. I.; Ritacco, I.; Ibrahim, M. A. A.; Shoeib, T.; Sicilia, E. Insights on cyclophosphamide metabolism and anticancer mechanism of action: A computational study. J. Comput. Chem., 2023.
10. Dhingra, D.; Jangra, A. Antiepileptic activity of ellagic acid, a naturally occurring polyphenolic compound, in mice. J. Funct. Foods, 10, 364–369, 2014.
11. Famurewa, A. C.; Asogwa, N. T.; Ezea, S. C. Antidiabetic drug sitagliptin blocks cyclophosphamide cerebral neurotoxicity by activating Nrf2 and suppressing redox cycle imbalance, inflammatory iNOS/NO/NF-κB response and caspase-3/Bax activation in rats. Int. Immunopharmacol., 116, 109816, 2023.
12. Famurewa, A. C.; Edeogu, C. O.; Offor, F. I.; Besong, E. E.; Akunna, G. G.; Maduagwuna, E. K. Downregulation of redox imbalance and iNOS/NF-κB/caspase-3 signalling with zinc supplementation prevents urotoxicity of cyclophosphamide-induced hemorrhagic cystitis in rats. Life Sci., 266, 118913, 2021.
13. Famurewa, A. C.; Mukherjee, A. G.; Wanjari, U. R.; Sukumar, A.; Murali, R.; Renu, K.; Vellingiri, B.; Dey, A.; Valsala Gopalakrishnan, A. Repurposing FDA-approved drugs against the toxicity of platinum-based anticancer drugs. Life Sci., 305, 120789, 2022.
14. Fesharaki-Zadeh, A. Oxidative stress in traumatic brain injury. Int. J. Mol. Sci., 23(21), 13000, 2022.

15. Firdaus, F.; Zafeer, M. F.; Anis, E.; Ahmed, M.; Afza, M. Ellagic acid attenuates arsenic-induced neuroinflammation and mitochondrial dysfunction-associated apoptosis. Toxicol. Rep., 5, 411–417, 2018.
16. Goudarzi, M.; Amiri, S.; Nesari, A.; Hosseinzadeh, A.; Mansouri, E.; Mehrzadi, S. The possible neuroprotective effect of ellagic acid on sodium arsenate-induced neurotoxicity in rats. Life Sci., 198, 38–45, 2018.
17. Hassan, S. S. U.; Samanta, S.; Dash, R.; Karpiński, T. M.; Habibi, E.; Sadiq, A.; Ahmadi, A.; Bunagu, S. The neuroprotective effects of fisetin, a natural flavonoid in neurodegenerative diseases: Focus on the role of oxidative stress. Front. Pharmacol., 13, 1015835, 2022.
18. Kawasaki, T.; Kawai, T. Toll-like receptor signaling pathways. Front. Immunol., 5, 461, 2014.
19. Liu, Y.; Chen, C.; Hao, Z.; Shen, J.; Tang, S.; Dai, C. Ellagic acid reduces cadmium exposure-induced apoptosis in HT22 cells via inhibiting oxidative stress and mitochondrial dysfunction and activating Nrf2/HO-1 pathway. Antioxidants (Basel), 13(11), 1296, 2024.
20. Mansouri, M. T.; Farbood, Y.; Naghizadeh, B.; Shabani, S.; Mirshekar, M. A.; Sarkaki, A. Beneficial effects of ellagic acid against animal models of scopolamine- and diazepam-induced cognitive impairments. Pharm. Biol., 54, 1947–1953, 2016.
21. Olayinka, E. T.; Ore, A.; Ola, O. S.; Adeyemo, O. A. Ameliorative effect of gallic acid on cyclophosphamide-induced oxidative injury and hepatic dysfunction in rats. Med. Sci., 3, 78–92, 2015.
22. Olowe, T. G.; Oyovwi, M. O.; Nwangwa, K. E.; Ohwin, E. P.; Oghenetega, O. B. Cytotoxic properties of cyclophosphamide: A focus on its mechanistic impacts on male gonadal functions. J. Explor. Res. Pharmacol., 9(2), 106–115, 2024.
23. Singh, S.; Kumar, A. Protective effect of edaravone on cyclophosphamide-induced oxidative stress and neurotoxicity in rats. Curr. Drug Saf., 14(3), 209–216, 2019.
24. Temel, Y.; Kucukler, S.; Yıldırım, S.; Caglayan, C.; Kandemir, F. M. Protective effect of chrysin on cyclophosphamide-induced hepatotoxicity and nephrotoxicity via the inhibition of oxidative stress, inflammation, and apoptosis. Naunyn Schmiedebergs Arch. Pharmacol., 393(3), 325–337, 2020.
25. Wang, W.; Yang, L.; Liu, T.; Wang, J.; Wen, A.; Ding, Y. Ellagic acid protects mice against sleep deprivation-induced memory impairment and anxiety by inhibiting TLR4 and activating Nrf2. Aging (Albany NY), 12(11), 10457–10472, 2020.
26. Was, H.; Borkowska, A.; Bagues, A.; Tu, L.; Liu, J. Y. H.; Lu, Z.; Rudd, J. A.; Nurgali, K.; Abalo, R. Mechanisms of chemotherapy-induced neurotoxicity. Front. Pharmacol., 13, 750507, 2022.
27. Yumubek, A.; Kahar, T.; Awuti, G. Research progress of ellagic acid in systemic and oral diseases. Acad. J. Med. Health Sci., 5(2), 46–49, 2024.
28. Zhao, L.; Mehmood, A.; Soliman, M. M.; Iftikhar, A.; Iftikhar, M.; Aboelenin, S. M.; Wang, C. Protective effects of ellagic acid against alcoholic liver disease in mice. Front. Nutr., 8, 744520, 2021.
29. Zhou, H.; Andonegui, G.; Wong, C. H.; Kubes, P. Role of endothelial TLR4 for neutrophil recruitment into central nervous system microvessels in systemic inflammation. J. Immunol., 183(8), 5244–5250, 2009.
30. Zhou, B.; Li, Q.; Wang, J.; Chen, P.; Jiang, S. Ellagic acid attenuates streptozocin-induced diabetic nephropathy via the regulation of oxidative stress and inflammatory signaling. Food Chem. Toxicol., 123, 16–27, 2019.

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