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Original Article

Quercetin 100 mg/kg fails to mitigate cisplatin-induced neurotoxicity in adult Wistar rats

[1,2]Edagha, I.A; [1]Aquaisua, A.N.; [3]Akpan, B.C.; [1]Sunday-Jimmy, P.B.; [1]Ataben, M.A.; [1]Katumu, A.U.; [1]Okokon, G.

Abstract

OBJECTIVE: The survival rate of cancer patients has improved with cisplatin, a platinum-based chemotherapy. However, neurological deficits are prevalent in cancer patients administered with cisplatin. Interestingly, quercetin is reported to possess neuroprotective and antioxidant properties. We hypothesized that quercetin 100 mg/kg may offer ameliorative potential against cisplatin-induced neurotoxicity.

MATERIALS AND METHODS: Twenty (20) male adult Wistar rats (150 to 180 g) were allotted into four groups (n = 5), namely groups I (placebo distilled water 10 mL kg^{-1} body weight), II (cisplatin 5 mg kg^{-1} body weight), III (cisplatin/quercetin 5/100 $mgkg^{-1}$ body weights,) and IV (quercetin 100 mg kg^{-1} body weight, respectively). Cisplatin was administered intraperitoneally, once a week, and twice in 14 days, while quercetin was administered orally once daily for 14 days. Animals were deeply anesthetized with ketamine (100 mg/kg body weight, intraperitoneally). Then transcardially perfused with phosphate buffer saline (PBS) followed by perfusion in 4% paraformaldehyde in PBS (pH 7.4) for fixation. Each brain was harvested and postfixed overnight in the same fixation solution and prepared for tissue processing. Biochemical assays for brain antioxidant level were performed.

RESULTS: No significant change in the levels of antioxidant assays (SOD, CAT, GPx), but we did observe a significant increase in GSH and the levels of MDA ($p < 0.005$) in all administered groups compared to the control group. Neurodegenerations with pyknotic neurons and vacuolations were demonstrated in administered groups of the cerebellum, prefrontal cortex and hippocampus, with neuronal cell shrinkages and hyperchromatic cells

CONCLUSION: The results suggest that 100 mg/kg bw of quercetin cannot not ameliorate cisplatin-induced neurotoxicity in rats thus more of quercetin may not always be better. It is necessary to determine the dose beneficial threshold of quercetin.

Keywords:
Cisplatin; Quercetin; Brain; Neurotoxicity; Antioxidants

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INTRODUCTION

Chemotherapy is one of the most widely used methods for treating cancer. It involves using drugs to target rapidly dividing cancer cells, often combined with surgery and radiation therapy for enhanced effectiveness (Anand *et al.,* 2022; Amjad *et al.,* 2023). However, chemotherapy also affects healthy cells, leading to significant side effects, including neurotoxicity. Cisplatin, a standard chemotherapy drug, presents neurotoxic challenges due to its limited penetration into the brain- less than 5% of the dose crosses the blood-brain barrier (BBB), restricting its effectiveness in treating brain-involved cancers (Cetinkaya-Fisgin *et al.,* 2020). Techniques like ultrasound (US) combined with microbubbles (MBs) have been explored to temporarily open the BBB, allowing higher concentrations of cisplatin in the brain, particularly in targeted areas like glioblastoma sites (Enríquez Pérez *et al.,* 2019; Hagiwara *et al.,*concentrations of cisplatin in the brain, particularly in targeted areas like glioblastoma sites (Enríquez Pérez *et al.,* 2019; Hagiwara *et al.,* 2023). Despite such advances, cisplatin-based therapies are associated with neurological side effects, both peripheral and central neurotoxicity, that impair cognitive and motor functions (Staff *et al.,* 2019). Cisplatin affects vital brain regions, especially the hippocampus and cerebellum. The hippocampus, located in the temporal lobe, plays essential roles in memory and emotion. Cisplatin has been shown to reduce dendritic branching and spine density in its cells, affecting cognitive functions (Kiernan *et al.,* 2014; Naomi *et al.,* 2017). The cerebellum, responsible for motor coordination and balance, is also vulnerable, with cisplatin-induced neurotoxicity impairing motor skills,

[1]*Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Uyo, Nigeria;*
[2]*Department of Human Anatomy, School of Medicine, Moi University, Eldoret, Kenya;*
[3]*Department of Chemical Pathology, Federal Neuropsychiatric Hospital, Calabar, Nigeria.*

Address for Correspondence:
Edagha, I.A.
Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Uyo, Nigeria.
innocentedagha@mu.ac.ke

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posture, and learning (Kiernan *et al.,* 2014; Jimsheleishvili and Dididze, 2021).

To address chemotherapy-induced neurotoxicity, natural antioxidant flavonoid found in fruits, vegetables, and grains (David *et al.,* 2016; Xu *et al.,* 2019), has garnered significant interest for its potential anticancer properties with excellent antioxidant properties. (Xu *et al.,* 2019; Lotfi *et al.,* 2023). Typical dietary intake of quercetin ranges from 25 to 50 mg (Edagha *et al.,* 2024). However, supplements are available at higher doses, raising questions about whether increased amounts could provide additional protective effects.

Studies by Aghababaei *et al*. (2023) and Salehi *et al*. (2020) demonstrate quercetin's potential to reduce inflammation and protect neurons from oxidative stress. Therefore, we hypothesized that perhaps more is better, wherein quercetin (100 mg) could mitigate cisplatin-induced oxidative stress and neuronal death in male rats. We employed morphological analysis and brain antioxidant assays to test this while focusing on the prefrontal cortex, hippocampus and cerebellum microanatomical alterations. These regions are critical for memory, executive functions, and motor control, making them essential in studying neurodegeneration and neurotoxicity in vivo in experimental models.

MATERIALS AND METHODS

Animals

Twenty (20) adult male albino Wistar rats (150 – 220 g) aged 12 weeks were used for this study. They were obtained from the Department of Pharmacology and Toxicology Animal House, University of Uyo (UNIUYO). The protocols for this study were approved by the Department of Human Anatomy, University of Uyo, Nigeria, which in accordance with the National Institutes of Health guidelines for the care and use of experimental animals, with ethical approval obtained from the Health Research Ethics Committee of the Akwa Ibom State Ministry of Health (Ref: MH/PRS/99/Vol.IV/699). All animals were weighed, marked for identification, and placed in standard plastic cages for one week acclimatization under optimum pathogen-free environment and maintained in a 12 h light/dark cycles of 25–27 ^{o}C at relative humidity of 40 – 60% measured using the CEM hydrometer (DT 615, Shenzhen China). All animals were fed with pelletized growers mash (Grand Cereal Vital® Feed Ltd. Jos) and provided with drinking water *ad libitum*.

Acquisition of Drugs

Cisplatin was obtained from the Celon Laboratories PVT. Ltd, India (Lot no.14/RR/AP/2008/F/CC), and quercetin was sourced from Squared Brands LLC, Miami, Florida (Lot no. 30012). These drugs were chosen for their established effects and safety profiles in similar studies.

Experimental Design

The animals were weighed, marked and distributed into 4 groups (labelled I to IV) of five rats per group. The experimental drugs were administered orally according to the body weight of animal. The dosage was calculated from their normal dose for a 70 kg man. The dosage of drugs administered was calculated using the formula: weight of animal/ 1000 x dosage/stock (Edagha *et al.,* 2022).

In this study, animals were allocated randomly into four experimental groups. Normal control group (group I) received distilled water 10 mL/kg; the anti-cancer drug group (group II) was administered cisplatin at 5 mg kg^{-1} body weight once weekly for 14 days; the combined anti-cancer and antioxidant group (group III) received both cisplatin (5 mg kg^{-1}) and quercetin (100 mg kg^{-1}), respectively; and the antioxidant supplement group (group IV) was treated with quercetin alone at 100 mg kg^{-1} daily for 14 days.

Determination of Body Weight

Animal body weights were taken before administration and before sacrifice. Percentage change in body weights was calculated as (Final weight – Initial weight)/Final weight x 100.

Termination of Experimental and Sample Collection

After 14 days of administration, on day 15 of the research, the rats were anaesthetized and euthanized with ketamine (100 mg/kg, i.p). Whole brain perfusion was performed with phosphate buffered saline for 2 mins and thereafter with 4% paraformaldehyde until tail stiffness in approx. The brains were then dissected out, and then processed for light microscopy within 72 h. The paraffin wax blocked tissues were sectioned at 5 µm sampling 5 ribbons sections per tissue blocks using the rotary microtome (Microtome Thermo Scientific – Microm HM 325, England) and stained with haematoxylin and eosin

Determination of Organo-Somatic Indices

The organo-somatic index can be described as the ratio of organ weight to total body weight, wherein the measured organ in relation to body mass can be directly linked to the toxic effects of chemicals on target organs. Organo-somatic index = Organ weight/ Final body weight × 100.

Histopathological Assessment

The H&E staining process for 5 µm paraffin-embedded tissue sections begins with deparaffinization in two xylene changes for 5 minutes each. Rehydration follows through descending ethanol grades (100%, 95%, 70%) for 5 minutes each. Sections are rinsed in running tap water for 15 minutes. Staining involves immersion in hematoxylin for 30 seconds, followed by a tap water rinse, then eosin for 1 minute. After rinsing, dehydration occurs through ascending ethanol grades (50%, 60%, 70%, 80%, 95%, 100%). Sections are cleared in xylene, mounted with DPX, cover-slipped, and blot-dried. Photomicrographs are captured using a light microscope (Olympus CX31) with an attached AmScope digital camera (MU 1000) and blindly assessed by at least three independent histopathologists.

Biochemical Assessment

The biochemical assessment of oxidative stress markers involves a series of sophisticated assays to measure antioxidant enzyme activities and oxidative damage products in brain homogenates.

Superoxide dismutase (SOD) activity is determined by its ability to inhibit epinephrine auto-oxidation as described by Mishra and Fridovich (1972). The reaction is monitored spectrophotometrically at 480 nm for 5 minutes, using a sodium carbonate buffer (pH 10.2) and epinephrine in HCl as the substrate. The enzyme activity is calculated based on the change in absorbance, with a molar extinction coefficient of 4020 M^{-1} cm^{-1}.

Catalase activity is assessed by monitoring the decomposition of H_2O_2 at 620 nm over 5 minutes as described by Singha (1972). The assay uses a phosphate buffer (pH 7.0) and H_2O_2 as the substrate. The reaction is stopped with a dichromate-acetic acid reagent, and the results are expressed as µmoles of H_2O_2 consumed/min/mg protein, using a molar extinction coefficient of 40 M^{-1} cm^{-1}.

Glutathione peroxidase (GPx) activity is analyzed using a modified Rotruck *et al*. (1973). The assay involves incubating the brain homogenate with phosphate buffer, sodium azide, reduced glutathione (GSH), and H_2O_2. The reaction is stopped with trichloroacetic acid (TCA), and the remaining GSH is measured using DTNB (Ellman's reagent) at 412 nm.

Lipid peroxidation is evaluated by measuring malondialdehyde (MDA) levels. Brain supernatant is mixed with Tris-KCl buffer, TCA, and thiobarbituric acid, then boiled and cooled. The resulting chromogen is measured spectrophotometrically at 532 nm. Reduced glutathione (GSH) was estimated using Ellman's reagent (DTNB) as described by Moron *et al*. (1979). Brain homogenates are treated with TCA, and the supernatant is reacted with DTNB in phosphate buffer. The resulting color is measured at 412 nm and compared to GSH standards.

Statistical Analysis

Data was expressed as Means ± Standard Error of Mean (SEM) performed with the IBM Statistical Package for Social Science (SPSS) version 25 software. The one-way analysis of variance (ANOVA) was used to establish the level of comparison among groups, with Tukey multiple-comparison as *post-hoc* test analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Antioxidant and oxidative stress assays

The effects of cisplatin and quercetin on antioxidant assays and oxidative stress markers are shown in Table 2. The SOD and GPx levels were not significantly different in the administered groups compared to the control. CAT level was increase in C + Q group only compared to control. However, the level of MDA, a maker for oxidative stress was significantly increased ($p < 0.005$) in all the administered groups compared to the control. Reduced glutathione level (GSH) was also significantly increased ($p < 0.005$) in administered groups III and IV compared to normal control.

Histopathological Assessment

The histoarchitecture of the hippocampus in the control group demonstrated normal cellular arrangement in the cornus ammonis regions (CA 1-3). Administered group II (cisplatin 5 mg/kg bw) showed degenerated and pyknosis pyramidal neurons, vacuolation and atrophy of pyramidal cells. Administered group III (cisplatin 5 mg/kg + quercetin 100 mg/kg bw) had few degenerated pyramidal neurons, some vacuolations of the pyramidal cells, few pyknotic appearances of pyramidal cell and few astrocytes. Administered group IV (quercetin 100 mg/kg bw) exhibited numerous vacuolations of pyramidal cells, astrocytes, some pyknotic pyramidal cells and an irregular/ hyperchromatic pyramidal cell as seen in Figures 1 - 3.

The photomicrograph sections of the prefrontal cortex in normal control group with pyramidal cells, Cajal and fusiform cells. Administered group II (cisplatin only) showed vacuolation, shrinkage of pyramidal cells and hyperchromatic cells. Administered group IV (quercetin only) had vacuolation, degeneration of pyramidal cells and hypertrophied cells. Administered group III (cisplatin + quercetin: 5 mg/kg + 100 mg/kg bw) exhibited vacuolations, shrinkage of pyramidal cells and hypertrophied cells as shown in Figure 4.

The photomicrographs of the cerebellum in the normal control group, a molecular layer (ML) with superficial stellate cells (SC) and basal basket cells (BC), the Purkinje cell layer with single layer of large Purkinje cells and the granular layer with granule cells and cerebellar islands. Administered group II (cisplatin only indicated dark stained BC and degenerated Purkinje cells, with some hyperchromatic Purkinje cells and necrotic Purkinje. Administered group III animals (on combined C+Q 5 mg/kg + 100 mg/kg bw) demonstrated Purkinje cell heterotopias, pyknosis of the Purkinje cells and a scanty granular cell layer with degenerated granule cells. Administered group IV rats (given quercetin only) had mild to moderately atrophied cells in the Purkinje cell layer with vacuolations and a less dense granular layer as shown in Figure 5.

Table 1: Effects of Cisplatin and Quercetin on Antioxidant Status of Rats

Group	GPx (µmol/mL)	SOD (µmol/mL)	CAT (µmol/mL)	MDA (µmol/mL)	GSH (µmol/mL)
NC	5.93±0.23	19.72 ± 1.79	46.42 ± 2.01	2.49 ± 0.13	18.26 ± 0.83
C	5.89 ± 0.15	21.14 ± 0.65	49.55 ± 2.73	4.64 ± 0.63***	19.48 ± 1.43
C+Q	6.10 ± 0.03	20.27 ± 0.94	53.81 ± 0.48#	7.04 ± 0.05***	23.15 ± 0.52a
Q	5.91 ± 0.08	21.38 ± 0.52	46.19 ± 1.30#	4.95 ± 0.72***	22.17 ± 0.27a
P value	0.733	0.792	0.032	0.001	0.004

Values are presented as Mean ± Standard error of mean for 5 rats per group. Legend: Glutathione peroxidase (GPx), Superoxide dismutase (SOD), Catalase (CAT), Malondialdehyde (MDA), Glutathione (GSH), Normal control (NC), Cisplatin (C), Cisplatin+Quercetin C+Q) and Quercetin (Q).

- indicates significant increase as compared to NC and Q groups respectively.

*** - Significant increased compared to the NC group.

a - Significant increased compared to the NC group.

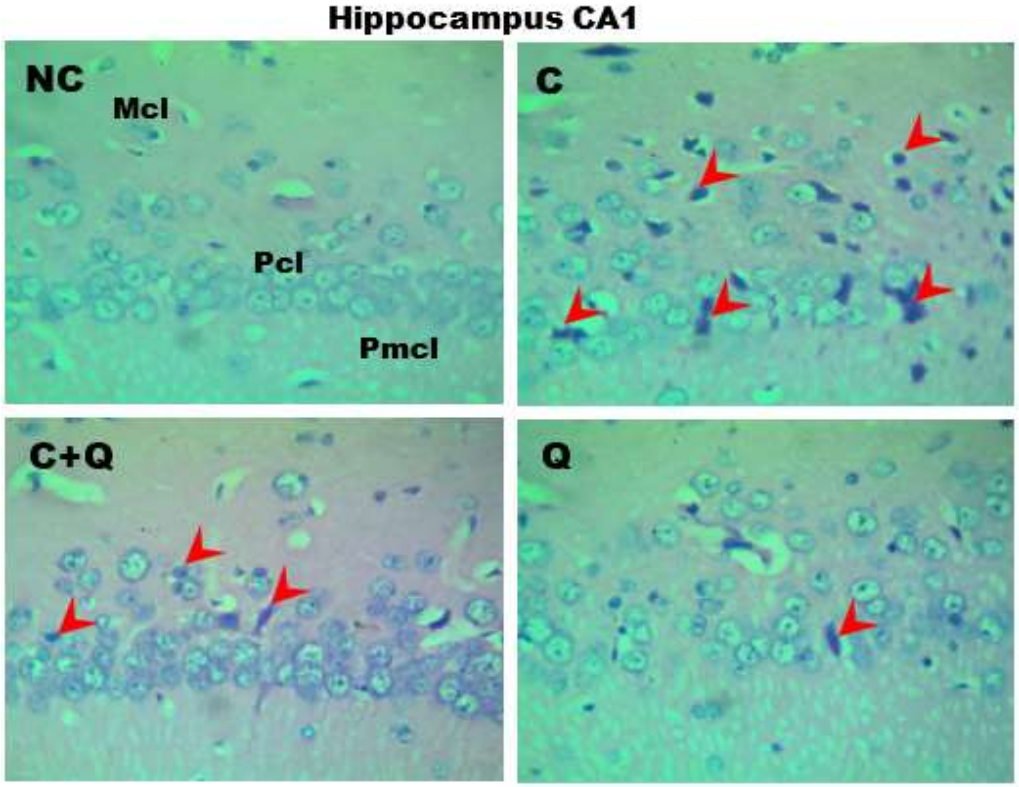

Figure 1. Photomicrographs of the transverse section of the hippocampus (CA1). Legend: Normal control group (NC), Cisplatin (C), Cisplatin and Quercetin (C+Q), and Quercetin (Q). Molecular cell layer (Mcl), Pyramidal cell layer (Pcl), and Polymorphic cell layer (Pmcl). Evidence of neuronal atrophy with intense basophilic expression (red arrowheads) (H & E; 400x).

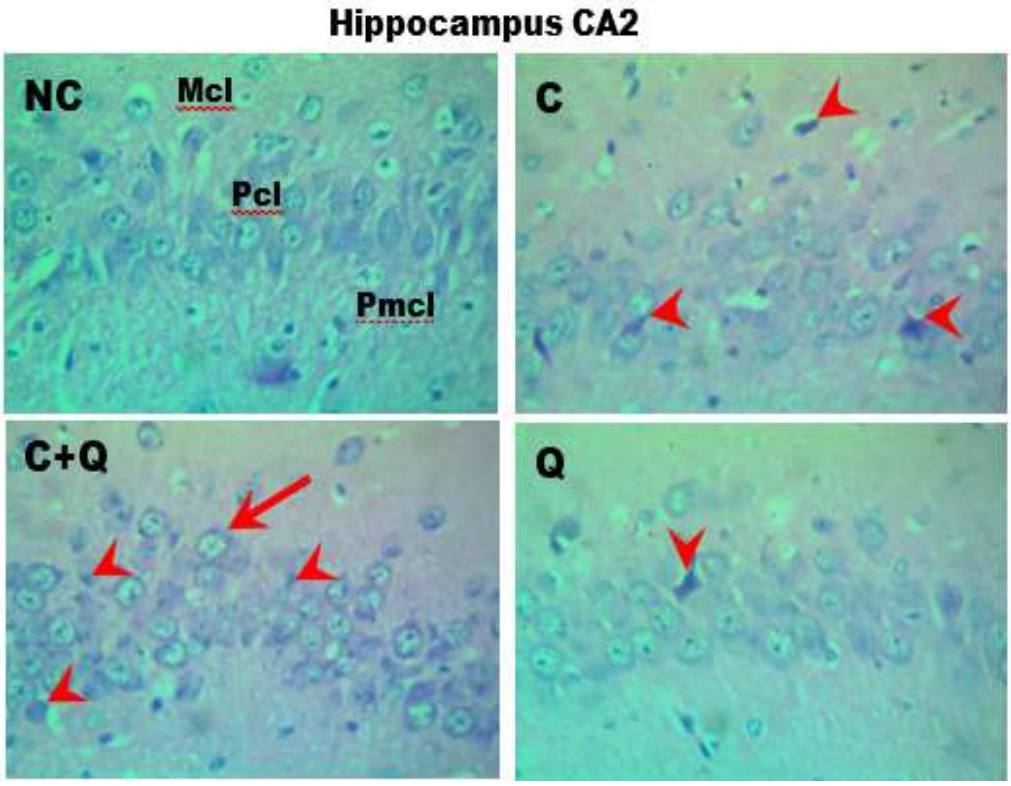

Figure 2. Photomicrographs of the transverse section of the hippocampus (CA2). Legend: Normal control group (NC), Cisplatin (C), Cisplatin and Quercetin (C+Q), and Quercetin (Q). Molecular cell layer (Mcl), Pyramidal cell layer (Pcl), and Polymorphic cell layer (Pmcl). Evidence of neuronal atrophy with intense basophilic expression (red arrowheads) and hypertrophy (red arrow) (H & E; 400x).

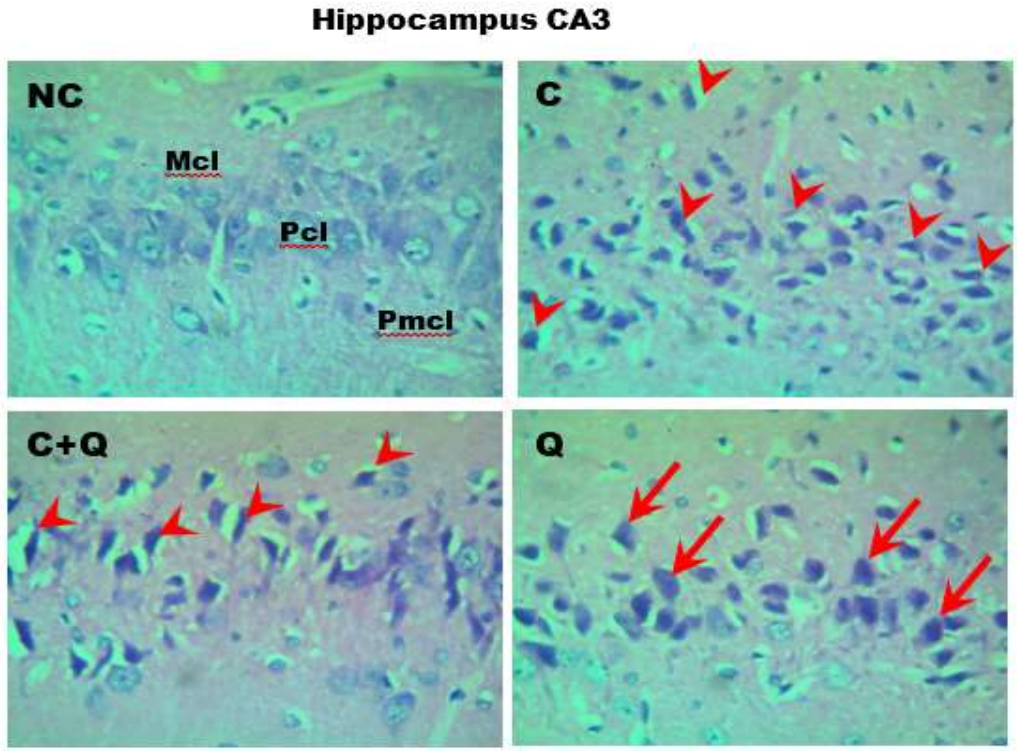

Figure 3. Photomicrographs of the transverse section of the hippocampus (CA3). Legend: Normal control group (NC), Cisplatin (C), Cisplatin and Quercetin (C+Q), and Quercetin (Q). Molecular cell layer (Mcl), Pyramidal cell layer (Pcl), and Polymorphic cell layer (Pmcl). Evidence of neuronal atrophy with intense basophilic expression (red arrowheads) and hypertrophy (red arrows) (H & E; 400x).

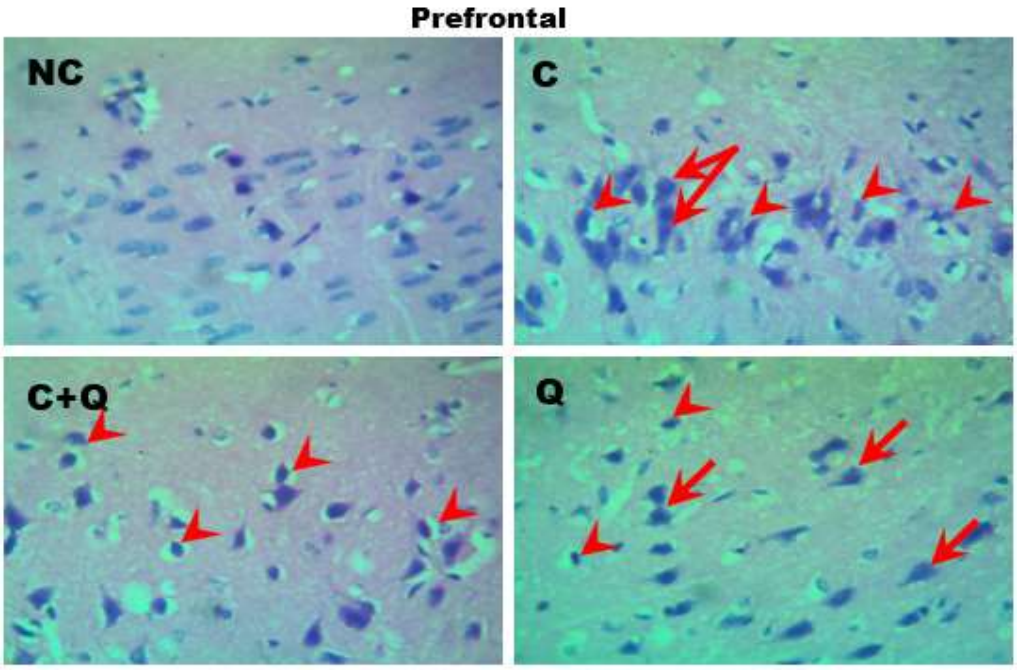

Figure 4. Photomicrographs of the transverse section of the Prefrontal cortex. Legend: Normal control group (NC), Cisplatin (C), Cisplatin and Quercetin (C+Q), and Quercetin (Q). Evidence of neuronal atrophy with intense basophilic expression (red arrowheads) with hollow spaces (vacuolations) and hypertrophy (red arrowhead). (H & E; 400x).

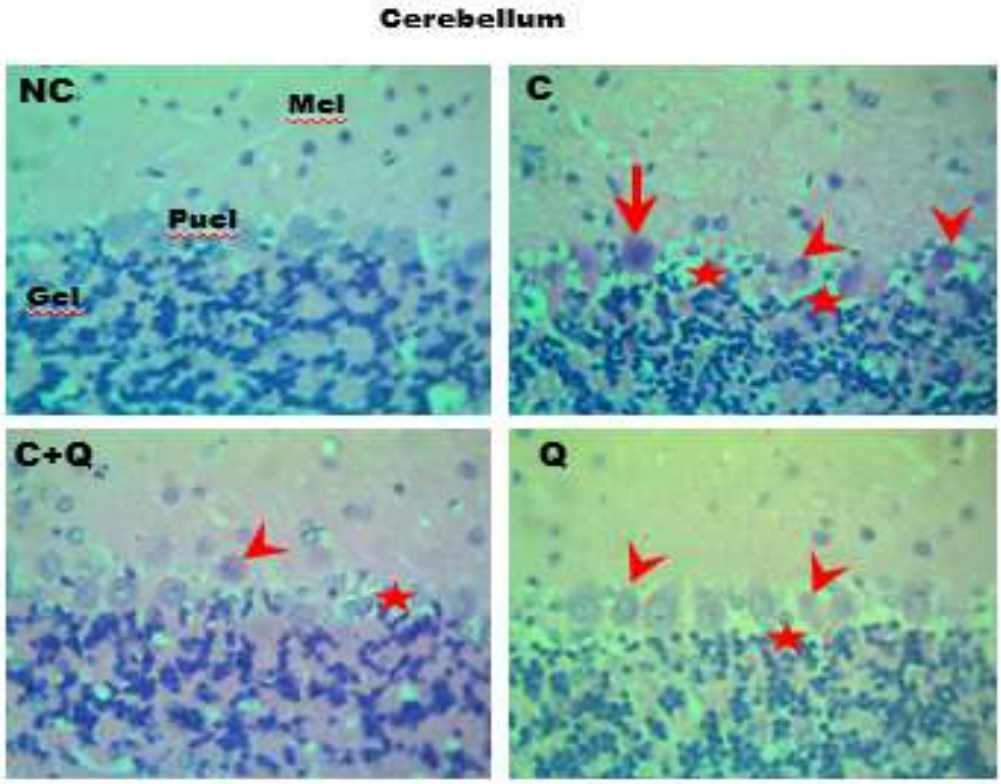

Figure 5. Photomicrographs of the transverse section of the cerebellum. Legend: Normal control group (NC), Cisplatin (C), Cisplatin and Quercetin (C+Q), and Quercetin (Q). Molecular cell layer, Purkinje cell layer (Pucl), and Granule cell layer (Gcl). Evidence of neuronal atrophy with intense basophilic expression (red arrowhead), hypertrophy (red arrow) and lesions (red asterisk) (H & E; 400x).

DISCUSSION

Cisplatin remains a cornerstone of cancer chemotherapy due to its ability to enter cancer cells and bind to deoxyribonucleic acid (DNA), forming crosslinks between purine bases. This binding disrupts DNA replication and transcription, leading to DNA damage and apoptosis in cancer cells (Brown *et al.,* 2019). Treatment for cancers has improved due to the significant impact of cisplatin, an anti-neoplastic drug (World Health Organization, 2022; American Cancer Society, 2024). Nevertheless, a high prevalence of neurotoxicity has been associated with cisplatin therapy (Noha *et al.,* 2017; Neife *et al.,* 2020), while quercetin has been reported as an ameliorative agent of protection against neurotoxicity and cadio-hepato-renal toxicity (Sánchez-González *et al.,* 2017; Edagha *et al.,* 2024).

Quercetin exerts anticancer effects by inducing apoptosis and autophagy in cancer cells. It also inhibits cancer cell proliferation and angiogenesis, which tumors need for growth (Salehi *et al.,* 2020; Lotfi *et al.,* 2023). Quercetin can cross the blood-brain barrier (BBB) because of its lipophilic nature, which allows it to diffuse through the BBB's lipid bilayer. Studies have shown that quercetin may also help protect the BBB by modulating the PI3K/Akt/Erk signaling pathways, which help keep the tight junctions between endothelial cells. Quercetin exhibits strong antioxidant properties by scavenging free radicals and chelating metal ions, which helps protect neurons against oxidative stress, neurotoxicity, and reduces neuroinflammation in animal models of neurological disorders (Salehi *et al.,* 2020; Sun *et al.,* 2024).

In this present study, it was found that cisplatin-administered groups showed a significant decrease in body weight (not reported), overwhelming levels of antioxidant assays (SOD, CAT and GPx), and an increase in oxidative stress marker (GSH, and MDA). Cisplatin-induced weight loss is often associated with cachexia, a complex syndrome characterized by severe muscle wasting and weight loss despite adequate caloric intake. It is a common effect of chemotherapy and significantly impacts the quality of life and treatment outcomes (Murphy *et al.,* 2021; Kim *et al.,* 2022). Studies in animal models have shown that cisplatin treatment leads to anorexia and muscle wasting, which contributes to the overall reduction in body weight (Conte *et al.,* 2020; Kim *et al.,* 2022), and these may have contributed to the weight loss we observed in this study.

Oxidative stress results from an imbalance between the production of reactive species and the body's ability to detoxify them or repair the resulting damage (Chaudhary *et al.,* 2023). Antioxidants are molecules that neutralize free radicals and oxidants, thereby preventing cellular damage (Zhou *et al.,* 2022). Increased oxidative stress in disease states can deplete antioxidant levels. This depletion exacerbates cellular damage and contributes to the progression of diseases like cancer. Cisplatin is known to induce oxidative stress by generating reactive oxygen species (ROS) and depleting the body's endogenous antioxidants (Katanić Stanković *et al.,* 2023). We observed no significant change in the levels of antioxidant assays (SOD, CAT, GPx), but we did observe a significant increase in GSH and the levels of MDA, a marker for oxidative stress, in the cisplatin-administered groups, which suggests an increase in ROS, which are early signaling molecules that trigger a cascade of pathological reactions such as apoptosis and necrosis, which is evident in our microanatomical examination in Figure 1 and supports other studies (Zhou *et al.,* 2022; Katanić Stanković *et al.,* 2023).

Antioxidant supplementation is often explored as a therapeutic strategy to restore balance and mitigate oxidative damage (Sánchez-González *et al.,* 2017; Zhou *et al.,* 2022). Quercetin's ability to mitigate oxidative stress in cisplatin-induced toxicity is well-supported by animal studies at 50 mg/kg body weight for 14 consecutive days (Mahmoud *et al.,* 2023). It boosts antioxidant defenses, lowers oxidative damage, and shields tissues from the harmful effects of cisplatin, though study had reported any possible higher dose in the brain. This was evident with mild improvement in the quercetin + cisplatin group compared to the cisplatin-only group in this study with alterations in microanatomical examination in Figure 1 to 5. This finding is dissimilar to various studies showing the antioxidant properties of quercetin at lower doses and how it upregulates the expression of genes associated with antioxidant defense, further enhancing its protective effects against oxidative stress (Sánchez-González *et al.,* 2017; Edagha *et al.,* 2024).

Contrary to the common belief that consuming more good stuff is synonymous with improved benefits, our neuro-microanatomical examination in the hippocampus, and cerebellum, as shown in Figure 1 to 5, demonstrated that quercetin at 100 mg/kg bw may exhibit pro-oxidant effects thus eliciting mild toxicity, which is observed with increased hyperchromasia, slightly edematous cells, and petit vacuolations in the quercetin-administered group. These findings suggest that quercetin may act as a pro-oxidant at a certain dose threshold rather than an antioxidant across dose ranges, potentially leading to an increased trend of oxidative stress and cellular damage, as shown in Table 1 in the level of antioxidant assays and oxidative stress markers, which support the findings in other studies (Vieira-Frez *et al.,* 2020). It may become pivotal therefore to ascertain the beneficial dose limits of quercetin. We suggest conducting detailed dose-response studies in animal models to determine the threshold at which quercetin shifts from being protective to toxic and explore the molecular mechanisms underlying the pro-oxidant effects of high-dose quercetin, such as its impact on mitochondrial function and oxidative stress pathways.

To summarize, quercetin may possibly be effective in mitigating cisplatin-induced neurotoxicity by improving antioxidant assay levels and reducing oxidative stress and inflammation, but better understanding of the dual role of quercetin as both an antioxidant and a pro-oxidant is needed, particularly at higher doses of 100

mg/kg as demonstrated in this present study and providing a clearer safety profile for its use.

Conclusion: In this study, we investigated the potential ameliorative effects of quercetin at 100 mg/kg on cisplatin-induced neurotoxicity in the prefrontal cortex, hippocampus, and cerebellum as well as on brain antioxidant levels in adult male Wistar rats. Our findings revealed significant microanatomical alterations in the brain regions of the cisplatin-administered group, which were not remarkably ameliorated in cisplatin plus quercetin group, suggesting there is a dose-dependent threshold for the benefit of the supplement. Thus, quercetin at higher doses may potentially be more neurotoxic.

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