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Research Article

Morin Reduces Ciprofloxacin-Induced Brain Damage by Regulating Oxidative Stress, Inflammation, and Histopathological Changes

Morin, Oksidatif Stresi, İnflamasyonu ve Histopatolojik Değişiklikleri Düzenleyerek Siprofloksasin Kaynaklı Beyin Hasarını Azaltır

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Abstract
Ciprofloxacin (CPFX), one of the fluoroquinones, is an antibacterial antibiotic that is used in the treatment of urinary tract, respiratory, abdominal and gastrointestinal infections as well as having negative side effects on the central nervous system. Morin, a bioactive flavonoid, is an antioxidant with neuroprotective properties thanks to its many pharmacological properties. This study aimed to investigate the protective effect of morin against brain damage caused by the broad-spectrum antibiotic CPFX. Twentyeight female rats were divided into four groups as control, Morin, CPFX, CPFX+Morin. CPFX, and Morin was administered once a day for seven days. Oxidative stress and inflammation parameters were analyzed to determine brain tissue damage and histopathological analysis was performed to determine tissue damage and structural changes. According to the findings obtained as a result of the analyses, CPFX increased nuclear factor kappa B (NF-κB), malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α), and interleukin 1β (IL-1β) and decreased glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) in brain. Co-administration of CPFX with morin increased GSH and GPx, SOD, CAT and decreased NF-κB, MDA, TNF-α, IL-1β levels. According to findings, when evaluated together, it was found that CPFX caused damage in brain tissue by causing oxidative stress and inflammation and morin as a supportive treatment reduced the damage in brain tissue by bringing these markers closer to normal.
Key Words: Brain, Ciprofloxacin, Inflammation, Morin, Oxidative stress

Öz
Florokinonlardan olan siprofloksasin (CPFX), idrar yolu, solunum, abdominal ve gastrointestinal enfeksiyonların tedavisinde kullanılmasının yanı sıra merkezi sinir sistemi üzerinde olumsuz yan etkileri bulunan antibakteriyel antibiyotiktir. Biyoaktif flavonoid olan morin, birçok farmakolojik özellikleri sayesinde nöroprotektif özelliğe sahip antioksidandır. Bu çalışmada, geniş spektrumlu antibiyotik olan CPFX'in neden olduğu beyin hasarına karşı morinin koruyucu etkisinin araştırılması amaçlandı. Bu amaçla yapılan çalışmada yirmi sekiz adet dişi sıçan kontrol, Morin, CPFX, CPFX+Morin olarak dört gruba ayrıldı. CPFX ve Morin yedi gün boyunca günde bir defa uygulandı. Beyin dokusunda hasarı belirlemek amacıyla oksidatif stres ve inflamasyon parametreleri ve doku hasarını ve yapısal değişiklikleri belirlemek için histopatolojik analiz yapıldı. Analizler sonucunda elde edilen bulgulara göre CPFX, beyinde nuclear factor kappa B (NF-κB), malondialdehit (MDA), tumor necrozis factor-alfa (TNF-α) ve interleukin 1β (IL-1β)'i artırdığı, glutatyon peroksidaz (GPx), süperoksit dismutaz (SOD), katalaz (CAT) ile glutatyonu (GSH) azalttığı bulundu. CPFX'in Morin ile birlikte uygulanmasının GSH ile GPx, SOD, CAT'i artırdığı, NF-κB, MDA, TNF-α, IL-1β düzeylerini azalttığı tespit edildi. Elde edilen bulgulara göre birlikte değerlendirildiğinde, CPFX'in oksidatif stres ve inflamasyona neden olarak beyin dokusunda hasara neden olduğu ve destekleyici tedavi olarak morinin bu belirteçleri normale yaklaştırarak beyin dokusunda hasarı azalttığı bulundu.
Anahtar Kelimer: Beyin, İnflamasyon, Morin, Oksidatif stres, Siprofloksasin

Introduction

Fluoroquinolones are broad-spectrum antibacterial antibiotics used to treat diseases such as respiratory tract, skin, intra-abdominal, joint, and bone infections (Al-Naely et al. 2022). Ciprofloxacin (CPFX), which is effective against gram negative-positive bacteria, is a fluoroquinolone group antibiotic (Ibitoye et al. 2020; Ibrahim et al. 2025). It has been reported to easily pass into tissues following oral administration (Ubaid et al. 2022). However, it causes side effects such as dizziness, seizures, abnormal vision, drowsiness, encephalopathy, anxiety, and neurological disorders (Ibitoye et al. 2020; Al-Naely et al. 2022). In addition to these side effects, drug toxicity has been reported to cause adverse effects on the central nervous system, especially through inhibition of deoxyribose nucleic acid (DNA) gyrase, the type II topoisomerase of CPFX (Al-Naely et al. 2022; Hassan et al. 2023). Increased microbial resistance to CPFX and drug abuse have been reported to cause tissue damage (Adedara et al. 2021). Even if the exact mechanism of tissue damage has not been elucidated, it is thought that CPFX causes an increase in reactive oxygen species (ROS), and increased ROS causes oxidative stress, and inflammation, triggering tissue apoptosis, which in turn increases brain damage (Hassan et al. 2023; Ibrahim et al. 2025). It has been reported that ROS produced in excessive amounts cause oxidative damage by damaging membrane lipids, proteins, DNA (Mojoyinola et al. 2023). It has also been reported to trigger neurodegenerative diseases by damaging brain tissue as a result of changes in molecules such as increased ROS, superoxide radical anion (O_2^-), hydroxyl radicals (HO^-), and hydrogen peroxide (H_2O_2) (Salama et al. 2021; Khalaf et al. 2024). Natural compounds, which are widely used in the treatment of many diseases, have recently been the focus of intense interest of researchers (Ishola et al. 2022).

Flavonoids, which are natural polyphenolic compound found in plants, have many pharmacological properties such as antiinflammatory, antioxidant and tissue integrity protection (Cakmak et al. 2023; Kızıl et al. 2023). Morin, which belongs to the *Moraceae* family, is a flavonoid obtained from compounds such as almonds, coffee, white mulberry, tea and onion, which has neuroprotective properties against various neurological diseases (Alla et al. 2024). This neuroprotective activity is thought to be due to its antiinflammatory, antioxidant properties (Khamchai et al. 2022; Alla et al. 2024). In addition to all these positive effects of Morin, it has been reported to have limited toxic effects and to be easily tolerated in long-term use (Varışlı et al. 2022). In different studies, it has been reported that Morin, which is used in supportive treatment, is effective in reducing or preventing tissue damage by suppressing ROS production, reducing oxidative stress, regulating many pathways such as inflammation, and showing neuroprotective activity thanks to these properties (Thangarajan et al. 2018; Banaeeyeh et al. 2024).

In the present study, we aimed to investigate the effects of Morin on oxidative stress, inflammation and histopathological changes on brain damage induced by CPFX that a fluoroquinolone.

Materials and Methods

Groups and Experimental Procedures

28 *Sprague Dawley* female rats (220-250 g) were used. Ethical approval was obtained from Atatürk University Animal Experiments Local Ethics Committee (Approval No: 2025/01/23). The rats were housed in cages in an environment with a twelve h dark-light cycle and a temperature of 24-25 °C. The rats were divided into four groups, with seven animals in each group.

1.Control: Saline was administered orally for seven days.

2.Morin: Morin 100 mg/kg was administered orally for seven days (Gür et al. 2021).

3.Ciprofloxacin (CPFX): CPFX 100 mg/kg was administered orally for seven days (Ibitoye et al. 2020).

4.Ciprofloxacin+Morin (CPFX+Morin): Animals were given CPFX orally, followed by Morin half an hour later. Treatment continued for seven days.

One day after the last CPFX, and Morin administration, rats were decapitated under mild sevoflurane (Sevorane®; Queenborough, UK) anesthesia and brain tissue was removed. A portion of the brain tissue was stored at -80 °C for biochemical examinations, while the other portion was stored in 10% formaldehyde solution for histological analysis.

Oxidative Stress Analyses

Brain tissue was homogenized with 1.15% potassium chloride (KCl) for malondialdehyde (MDA), and glutathione (GSH) and catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) activities and the supernatant was obtained by centrifugation (Gür et al. 2021). To determine the level of lipid peroxidation in brain tissue, the absorbance at 532 nm of the color formed by thiobarbituric acid reaction was measured (Placer et al. 1966). SOD, GPx, CAT activities and GSH level were analyzed to determine the antioxidant status. GSH level according to Sedlak and Lindsay (1968), SOD activity according to Sun et al. (1988), CAT activity was analyzed according to Aebi (1984), GPx activity according to Lawrence and Burk (1976). Total protein content of brain tissue was determined according to the method of Lowry et al. (1951).

RNA extraction and real-time polymerase chain reaction (RT-PCR) analysis

According to the manufacturer's guidelines, total RNA was extracted from brain tissue using QIAzol Lysis Reagent (Qiagen, Germany). The concentration and purity of the RNA samples were evaluated using a NanoDrop® spectrophotometer (BioTek Epoch). cDNA was synthesized from 2 μg of total RNA using the Qiagen High-Capacity cDNA Kit (Thermoscientific, Lithuania). RT-PCR was conducted using the Power SYBR Green Master Mix PCR kit (Qiagen, Germany) on the Rotor-Gene Q 5plex HRM platform (Qiagen, Germany). The mRNA levels of NF-κB, IL-1β, TNF-α, in the brain tissues were analyzed in triplicate using gene-specific primers (Table 1). *β-actin* was used as reference gene. The relative gene expression levels were determined from the Ct value and calculated using the $2^{-\Delta\Delta Ct}$ method Livak and Schmittgen (2001).

Table 1. Primer sequences of genes analyzed in RT-PCR. (RT-PCR: Real-time polymerase chain reaction, NF-κB: Nuclear factor kappa B, TNF-α: Tumor necrosis factor-alpha, IL-1β: Interleukin 1β).

Gene	Accession Number	Primers	Product Size (bp)
β-actin	NM_031144.3	**F:** GGAGATTACTGCCCTGGCTCCTAGC	
		R: GGCCGGACTCATCGTACTCCTGCTT	155
NF-κB	NM_001415012.1	**F:** CAGCACTCCTTATCAACCACC	
		R: CTCCTGAGCGTTGACTTCTG	125
TNF-α	NM_012675.3	**F:** ATGGGCTCCCTCTCATCAGT	106
		R: GCTTGGTGGTTTGCTACGAC	
IL-1β	NM_031512.2	**F:** AGCTCTCCACCTCAATGGAC	
		R: TTGTTTGGGATCCACACTCTCC	187

H&E Staining

At the end of the experiment, the brain tissues obtained from the rats were identified with reference to the Paxinos and Watson (2007) rat brain atlas, and the cerebral cortex region was defined. The cerebral cortex

samples were taken from the anterior part of the frontal cortex. Tissue samples were collected using the microscopic dissection method. The obtained tissues were kept in 10% neutral formalin solution for 48 hours for fixation.

After the routine processing procedure, 5-micrometer sections were obtained using a microtome and stained with hematoxylin and eosin. The stained preparations were evaluated, and images were obtained using a binocular Olympus Cx43 light microscope (Olympus Inc., Tokyo, Japan) equipped with an EP50 camera (Olympus Inc., Tokyo, Japan).

Statistical Analysis

Power analysis was performed for sample size, and when the number of animals for each group was set at seven, the alpha value was determined as 0.05 and the power value as 0.86. The study by Dhouibi et al. (2021) was taken as reference for the power analysis. The data obtained at the end of the study were statistically evaluated using the SPSS 26.0 package program. Data are expressed as mean ± standard error (SEM). Before applying parametric tests, normality of data distribution was assessed with the Shapiro-Wilk test, and homogeneity of variance was assessed with the Levene test.

In cases where both assumptions were met, one-way analysis of variance (One-Way ANOVA) was used to determine differences between groups, and Tukey post hoc test was applied for pairwise comparisons between groups. Statistical significance was determined at the $p < 0.05$ level.

Results

Effects of CPFX and Morin on Oxidative Stress Levels in Brain Tissue

MDA (Figure 1A), GSH (Figure 1B) levels and SOD (Figure 1C), CAT (Figure 1D), and GPx (Figure 1E) activities were evaluated to determine oxidative stress in brain tissue. It was found that MDA level increased in CPFX group compared to control, and Morin groups, while GSH level and SOD, CAT, and GPx activities decreased. Morin+CPFX treatment decreased MDA level and increased CAT, SOD, GPx, activities GSH level and strengthened the antioxidant defense system.

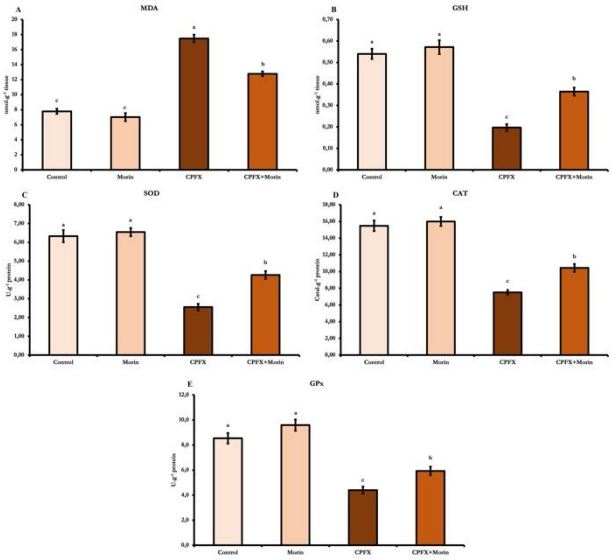

Figure 1. Effect of CPFX and Morin administration on MDA and GSH levels and SOD, CAT, GPx activities in brain tissue. Each group values are given as mean ± SEM. Different letters in the columns (a-b-c) indicate the difference in the groups ($p < 0.05$). (CPFX: Ciprofloxacin, MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase, GSH: Glutathione).

Effects of CPFX and Morin on IL-1β, NF-κB, and TNF-α Levels in Brain Tissue

The effects of CPFX on brain tissue of rats were examined and the findings are given in Figure 2. IL-1β (Figure 2A), TNF-α (Figure 2B), and NF-κB (Figure 2C) levels were evaluated to determine the level of inflammation in brain tissue. According to the data obtained, IL-1β, NF-κB, and TNF-α increased in the CPFX group compared to the control and Morin groups, and CPFX+Morin treatment was found to be effective in bringing these markers to levels close to those in the control group.

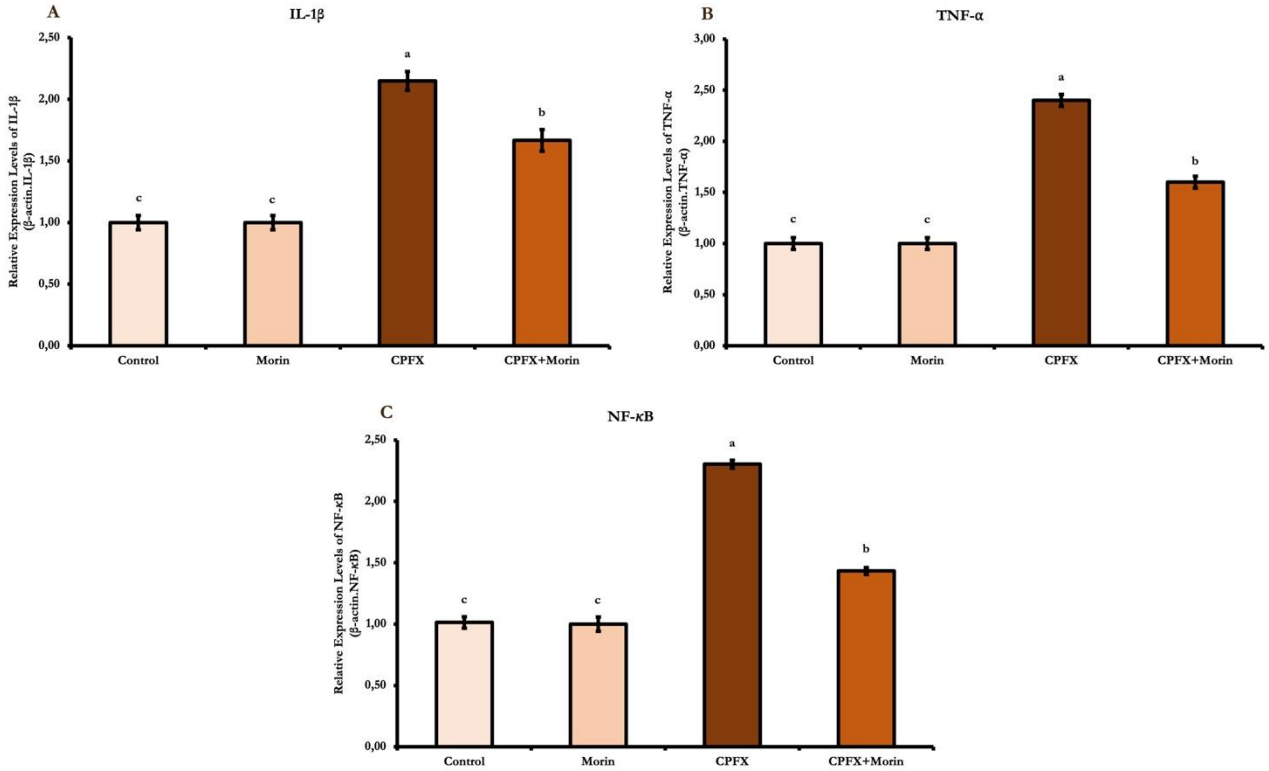

Figure 2. Effect of CPFX and Morin administration on NF-κB, TNF-α and IL-1β levels in brain tissue. Each group values are given as mean ± SEM. Different letters in the columns (a-b-c) indicate the difference in the groups ($p < 0.05$). (CPFX: Ciprofloxacin, TNF-α: Tumor necrosis factor-alpha, IL-1β: Interleukin 1β, NF-κB: Nuclear factor kappa B).

Histopathologic Results

Hematoxylin-eosin staining results of the cerebral cortex obtained from the experimental groups are given in Figure 3. When the brain tissues of the control group were examined, normal histologic structure was observed (Figure 3A). Similarly, no pathologic findings were observed in the Morin group (Figure 3B). In the sections of the CPFX-treated group, diffusely degenerated neurons were observed. The nuclei of neurons and glial cells became very small and pyknotic due to the effect of CPFX. In addition, meningeal vessels were extremely hyperemic (Figure 3C). In the CPFX+Morin group, degeneration in neurons and hyperemia in vessels decreased (Figure 3D).

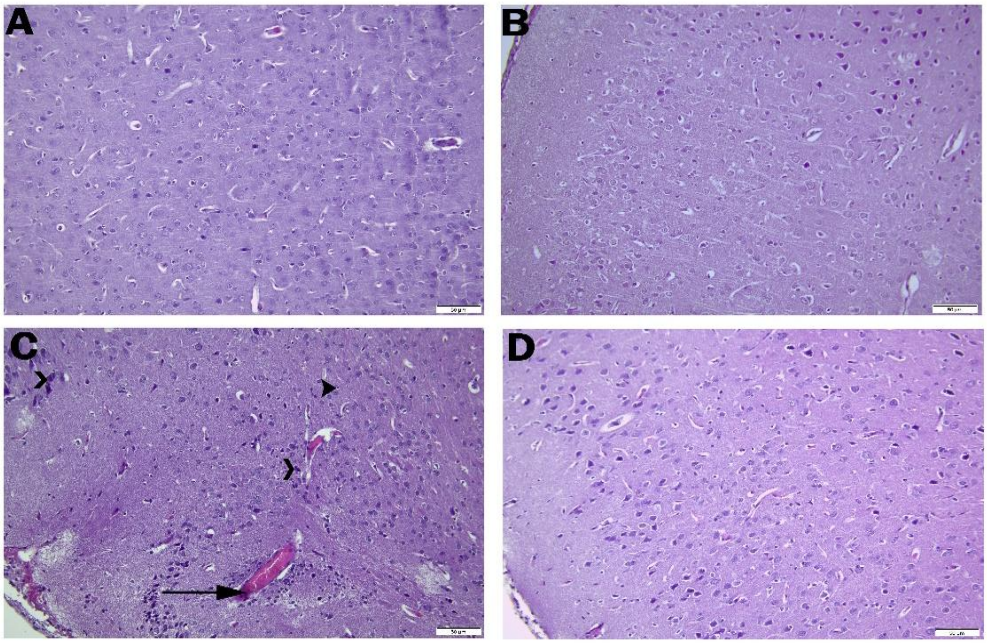

Figure 3. Photomicrographs (x200) of H&E stained cerebral cortex region of control and different experimental groups. Cerebral cortices of control and Morin groups showed normal structure. CPFX group showed an increase in degenerative cells (arrowhead), hyperemia (arrow) and cells with deep dark pyknotic nuclei (arrowhead). CPFX+Morin group showed improvement similar to the control group.

Discussion

CPFX, a broad-spectrum antibiotic that inhibits bacterial DNA replication, is known to cross the blood brain barrier and cause damage to brain tissue. This damage in brain tissue is associated with increased ROS production triggering oxidative stress and activation of damage pathways such as inflammation by oxidative stress. Therefore, in this study, the effects of Morin, which has even minimal toxic effects, on CPFX-induced brain damage were investigated.

It has been stated that oxidative stress, which consists of an imbalance between reactive nitrogen species and ROS, is a condition that causes damage at the cellular and molecular level (Badawy et al. 2021; Gür and Kandemir 2022). Increased ROS release as a result of drug exposure causes protein and DNA modifications and lipid peroxidation, resulting in the formation of free hydroxyl radical (Aksu et al. 2018; Ibrahim et al. 2025). MDA, the strongest marker of oxidative stress, increases ROS production by damaging the lipid layer in the cell by causing lipid peroxidation as a result of excessive free radicals (Kandemir et al. 2018; Aktas Senocak et al. 2024). As s result of increased ROS production, mitochondrial activity is affected, causing damage in the cell as a result of negatively affected adenosine triphosphate (ATP) synthesis (Aksu et al. 2021). SOD, one of the antioxidant enzymes that form the antioxidant defense line at the cellular level, is responsible for scavenging free radical. CAT is responsible for converting H_2O_2 into molecular oxygen and water, and GPx, another antioxidant enzyme, is responsible for the neutralization of H_2O_2. GSH in cells has been reported to be a non-enzymatic antioxidant that helps to maintain redox status by removing toxic substances (Genc et al. 2019; Varışlı et al. 2023). Oxidative stress damages cells by decreasing antioxidant activities and increasing oxidants (Ileriturk et al. 2022; Küçükler et al. 2024). Non-enzymatic and enzymatic antioxidants have been reported to reduce oxidant balance in cells by removing ROS (Aktas et al. 2017; Tuncer et al. 2023). In the present study, it was determined that CPFX administration increased the MDA level in the brain tissue of rats, decreased CAT, GPx, and SOD enzyme activities and GSH level, as a result, oxidative stress developed,

oxidative stress caused damage in brain tissue. In different studies on the subject, it has been stated that CPFX application increases ROS production in brain tissue and oxidative stress develops due to ROS production and oxidative stress develops damage in brain tissue (Al-Naely et al. 2022; Khalaf et al. 2024). In the present study, it was found that administration of Morin, a potent antioxidant, together with CPFX to rats decreased the increased MDA level in brain tissue, increased GPx, CAT, and SOD enzyme activities and GSH level, and as a result, improved oxidative stress by reducing the increased ROS levels. In the studies, it has been stated that Morin is a strong antioxidant and has a healing effect against damage by suppressing ROS production in different tissues in different toxication studies and strengthening the antioxidant defense system as a result of reducing oxidative stress (Cakmak et al. 2023; Kızıl et al. 2023).

Inflammation, an important pathway in the development of peripheral neuropathy, is activated by increased ROS (Küçükler et al. 2021; Yardim et al. 2022; Yakut et al. 2024). NF-κB, the first transcription factor in the inflammatory pathway activated by increased ROS, triggers tissue damage by causing the release of proinflammatory cytokines such as IL-1β, and TNF-α, which play an important role in inflammation (Caglayan et al. 2022; Yılmaz et al. 2024; Tuncer et al. 2024). This situation has been reported to affect gene activities via disrupting the antioxidant balance in the organism and disrupting protein activities after increased ROS (Hanedan et al. 2018; Şimşek et al. 2023; Ekinci Akdemir et al. 2025). It has been stated that antioxidants found naturally in plants may show anti-neuroinflammatory properties by inhibiting the NF-κB pathway and may be important in reducing or alleviating neurodegenerative disorders (Çelik et al. 2020). In the present study, it was found that CPFX administration increased the mRNA expression levels of NF-κB, IL-1β, and TNF-α cytokines, which play an active role in the inflammation pathway in brain tissue of rats, and as a result, caused damage to the brain tissue. This increase was supported by histopathologic examinations in brain tissue. Salama et al. (2021) reported that cytokine levels increased in brain tissue of rats administered CPFX and therefore caused inflammatory damage. In different studies, it was determined that CPFX caused damage and the mechanism of this damage was stated to be oxidative stress due to ROS production and oxidative stress triggering inflammatory damage (Hassan et al. 2023). In this study, it was determined that the co-administration of Morin, a natural flavonoid, with CPFX decreased the mRNA expression levels of increased inflammation parameters in the brain tissue. This decrease was supported by histopathological examinations in brain tissue. In studies on the subject, they expressed the therapeutic potential of Morin in reducing and alleviating inflammation by significantly regulating the inflammation pathway of Morin against different toxic agents (Cakmak et al. 2023; Aygörmez et al. 2025).

Histopathological evaluation revealed that neurons exhibiting widespread degeneration, and the nuclei of neurons and glial cells became very small and pyknotic due to CPFX, and meningeal vessels were extremely hyperemic, supporting the biochemical changes observed in CPFX-induced brain damage. CPFX+Morin treatment reduced neuronal degeneration and vascular hyperemia, demonstrating that Morin may protect brain structure and integrity. Morin has been reported to reduce neuronal degeneration, pyknotic changes, and vascular hyperemia in response to various toxic agents in brain tissue (Aygörmez et al. 2025).

CONCLUSION

In conclusion, CPFX induced tissue structural and functional changes in brain tissue by interfering with damage pathways such as oxidative stress and inflammation. Morin, which has no toxic effect, showed ameliorative effect against CPFX-induced brain damage. These effects suggest that Morin will guide clinical trials.

Conflict of interest: The authors declare no conflict of interest.

Authors' Contributions: S. A., N. A., E. D., Ş. M.; Methodology, S. A., N. A., E. D., Ş. M.; Investigation, S. A., N. A., E. D., Ş. M.; Resources, S. A., N. A., E. D., Ş. M.; Data curation, S. A., N. A., E. D., Ş. M.; Writing-original draft, S. A., N. A., E. D., Ş. M.; Writing-review & editing, S. A., N. A., E. D., Ş. M.; Visualization, S. A., N. A., E.

D., Ş. M.; Supervision, S. A., N. A., E. D., Ş. M.; All authors have read and agreed to the published version of the manuscript.

Ethical approval: Ethical approval were obtained from Atatürk University Animal Experiments Local Ethics Committee (Approval No: 2025/01/23).

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Explanation: Our work has not been presented anywhere before

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