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Original Article

Effect of Ciprofloxacin on Some Oxidative Stress Parameters and TNF-α, IL-6 and BDNF in Diabetic Rats with Urinary Tract İnfection Induced by *Escherichia coli*

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ABSTRACT

Background: Diabetes Mellitus (DM) and Urinary Tract Infections (UTIs) are common conditions that, especially when occurring together, lead to significant morbidity. This study aimed to investigate the effects of Ciprofloxacin (CIP) treatment on oxidative stress, antioxidant defense systems, and inflammatory markers in a rat model of experimental DM and *E. coli*-induced UTI. **Materials and Methods:** The study was conducted on rats with experimental DM and *E. coli*-induced UTI. CIP treatment was administered, and oxidative stress markers, antioxidant defense systems (including Catalase (CAT) and Glutathione (GSH) activity), and inflammatory markers (such as Malondialdehyde (MDA) and Advanced Oxidation Protein Products (AOPP)) were assessed in both serum and brain tissue. Brain-Derived Neurotrophic Factor (BDNF) levels were also measured. **Results:** The combination of DM and UTI significantly increased oxidative stress in both serum and brain tissues, as evidenced by elevated MDA levels ($p<0.05$), decreased CAT and GSH activities ($p<0.05$), and increased AOPP levels ($p<0.05$). CIP treatment significantly reduced serum MDA levels in both DM and DM+UTI groups, but did not result in significant improvements in CAT, GSH, or AOPP levels. In brain tissue, however, CIP treatment negatively affected MDA, GSH, CAT, and AOPP levels, particularly in the DM+UTI group ($p<0.05$). Additionally, CIP treatment led to an increase in BDNF levels ($p<0.05$) in brain tissue. **Conclusion:** While CIP treatment may alleviate oxidative damage in serum, it may exacerbate oxidative stress and inflammatory responses in brain tissue, particularly in the DM+UTI model. The increase in BDNF levels could act as a survival mechanism in response to CIP-induced oxidative damage. These findings suggest that CIP treatment may have undesirable neurological effects in DM and DM+UTI, emphasizing the need for further research into its impact on the nervous system. In conclusion, this study highlights the potential for CIP treatment to lead to undesirable neurological effects in DM and DM+UTI and emphasizes the need for further research into its impact on the nervous system.

Keywords: BDNF, Ciprofloxacin, Diabetüs Mellitüs, Oxidative Stress.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic condition characterized by insulin deficiency or decreased sensitivity, leading to hyperglycemia and vascular complications. According to the International Diabetes Federation, it is estimated that approximately 642 million people worldwide will be affected by DM by the year 2040.[1] DM leads to oxidative imbalance, resulting in cellular damage, inflammation, and impairment of tissue functions.[2-4] Additionally, in diabetic individuals, the immune system weakens, white blood cell count decreases, and conditions such as glucosuria increase the risk of Urinary Tract Infections (UTIs). This contributes to a higher prevalence of *E. coli*-induced UTIs in diabetic individuals, potentially exacerbating oxidative stress.[5]

Ciprofloxacin (CIP) is a fluoroquinolone class antibiotic commonly used in the treatment of *E. coli*-induced Urinary Tract Infections (UTIs).[6] CIP exerts its bactericidal effect by inhibiting bacterial enzymes, specifically DNA gyrase (type II topoisomerase and topoisomerase IV).[7] Despite its frequent use in the treatment of bacterial infections, CIP has been associated with serious side effects, including tendinopathies such as tendon rupture, joint inflammation, muscle weakness, central and peripheral neuropathies, epilepsy, and psychological disorders such as depression. It has been suggested that these side effects are linked to increased oxidative stress.[8-10] Hangas *et al.*, (2018) reported that CIP treatment inhibits mitochondrial DNA

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(mtDNA) replication, leading to a reduction in mtDNA copy number and inhibition of mitochondrial transcription.[11] This condition may lead to dysfunction of the electron transport chain and an increase in oxidative stress.[11] It has been reported that CIP increases the production of Reactive Oxygen Species (ROS), such as Hydroxyl radicals (HO^-), Superoxide anion (O_2^-), and Hydrogen Peroxide (H_2O_2), in brain tissue, potentially causing adverse effects in the Central Nervous System (CNS).[12]

Oxidative stress is a condition commonly observed in uncontrolled hyperglycemia. Prolonged, uncontrolled hyperglycemia generates dangerous by-products such as ROS through various pathways, including protein kinase C activation, glucose autoxidation, oxidative phosphorylation, and sorbitol formation.[13] When the production of ROS exceeds the capacity of the antioxidant defense mechanism, it activates pro-inflammatory signaling pathways, leading to an increase in inflammatory markers.[13] In this condition, free radicals cause dysfunction and apoptosis in various tissues, including the kidneys, liver, pancreas, brain, and eyes, leading to irreversible damage such as neuropathy, nephropathy, and retinopathy.[14] Therefore, regulating the balance between the oxidant and antioxidant defense systems is a crucial aspect of diabetes management.[15]

MATERIALS AND METHODS

Chemicals

CIP hydrochloride tablet was obtained from Biofarma İlaç San. ve Tic. A.Ş. (Istanbul, Turkey), STZ from Sigma-Aldrich, St. Louis, MO (USA), Rompun 2% (Xylazine, Bayer, United States), and Ketamine (Keta-Control, Arion, Turkey). The BDNF kit (Sunred, DZE201110477), TNF-α kit (Sunred, DZE201110765), and IL-6 kit (Sunred, DZE201110136) were also purchased. All chemicals and reagents used in this study were of analytical grade.

Experimental Animals

In this study, 40 female Wistar albino rats, aged 8-12 weeks and weighing 200-250 g, were used. The rats, obtained from the Animal Research Unit of Van Yüzüncü Yıl University, were kept in a controlled environment with a temperature of 21°C, humidity between 55-60%, and a 12-hr light/12-hr dark cycle throughout the experiment. Standard rat pellet feed and water were provided *ad libitum* for the animals. The procedures involving the experimental animals were carried out in accordance with the Ethical Committee decision 2023/13-48, dated 30.11.2023, approved by the Local Ethics Committee for Animal Experiments of Van Yüzüncü Yıl University.

Experimental Protocol

A total of 40 rats were randomly divided into 5 groups, with 8 rats in each group, and the study lasted for 20 days. No intervention was performed on the control group. In groups 2, 3, 4, and 5, Streptozotocin (STZ) was injected Intraperitoneally (IP), and the rats were monitored for 72 hr. After 72 hr, rats with blood glucose levels of 200 mg/dL or higher, measured from the tail vein were considered diabetic. Subsequently, groups 3, 4, and 5 were anesthetized, and 0.5 of mL 0.5 mL of 1.5×10^8 *E. coli* was injected intraurethrally to induce experimental Urinary Tract Infection (UTI), followed by a 48-hr waiting period. CIP, dissolved in distilled water, was administered orally via gavage for 14 days: 80 mg/kg for group 5 and 100 mg/kg for group 6. On the final day of the study, all rats were euthanized, and blood was collected via cardiac puncture to obtain serum and brain tissue. Antioxidants (MDA, CAT, GSH, and AOPP), pro-Inflammatory cytokines (TNF-α, IL-6), and BDNF levels in brain tissue were evaluated.

The groups were formed as follows

Group 1: Control Group: No special treatment was applied.

Group 2: DM Group: 45 mg/kg of STZ was injected intraperitoneally (ip).[16]

Group 3: DM+UTI Group: 45 mg/kg of STZ was injected IP,[16] followed by 0.5 mL of 1.5×10^8 *E. coli* intraurethrally.[17]

Group 4: DM+UTI+80 mg/kg Ciprofloxacin Group: DM+UTI were induced as in Group 3, followed by oral administration of 80 mg/kg ciprofloxacin for 14 days.

Group 5: DM+UTI+100 mg/kg Ciprofloxacin Group: DM+UTI were induced as in Group 3, followed by oral administration of 100 mg/kg ciprofloxacin for 14 days.

The ciprofloxacin doses employed in this study were established according to previous research.[18,19]

Experimental Diabetes Model with Streptozotocin

To establish the experimental diabetes model, rats from groups 2, 3, 4, and 5 were fasted for 12 hr. STZ (45 mg/kg) was prepared in citrate buffer (0.1 M, pH 4.5) and administered as a single Intraperitoneal (IP) dose.[16] The control group was injected with the same amount of citrate buffer. 72 hr after the STZ injection, blood samples were collected from the tail vein and assessed using the Accu-Check Active blood glucose monitor to measure fasting blood glucose levels. Rats with fasting blood glucose levels greater than 200 mg/dL were considered diabetic and included in the experiment.[20]

Induction of Experimental Urinary Tract Infection

After the experimental DM model was established, the rats were anesthetized with 10 mg/kg xylazine and 70 mg/kg ketamine administered intraperitoneally, prior to inducing the experimental UTI with *E. coli.* Under anesthesia, a 20-gauge angiocatheter was inserted into the bladder, and urine was drained from the bladder. After aspiration of the bladder urine, 0.5 mL of 1.5×10^8 *E. coli* was slowly injected into the bladder through the angiocatheter over 1 min. The angiocatheter was removed 1 hr later. The control group received an equal volume of sterile normal saline solution.[17]

Measurement of Biochemical Parameters

After all rats were sacrificed by decapitation, blood samples were collected via cardiac puncture, and brain tissues were subsequently removed and weighed. The collected blood samples were centrifuged at 4000 rpm for 10 min. Brain tissues were homogenized in a 50 mM potassium buffer (pH=7.4). The homogenate was then centrifuged at 14,000 rpm for 15 min at 4 °C.[12] The brain tissue supernatant and serum samples were stored at -20°C until the analyses were performed.

Evaluation of Oxidative Stress Markers, Inflammatory Mediators, and BDNF Levels

Brain and serum tissue samples were spectrometrically analyzed for MDA,[21] CAT,[22] GSH,[23] and AOPP.[24] Inflammatory markers (TNF-α and IL-6) and brain tissue BDNF levels were measured using ELISA kits, following the manufacturer's instructions.

Statistical Analysis

All data are presented as Mean ± Standard Deviation (SD). Statistical analyses were performed using SPSS software (v20, Chicago, IL, USA). For comparisons between groups, one-way ANOVA was applied, and significant differences were detected. Differences between groups were further examined using Tukey's *post-hoc* test. Statistical significance was set at $p<0.05$.

RESULTS

Blood Glucose Values

After the STZ application, blood glucose levels in the DM, DM+UTI, DM+UTI+80 mg/kg CIP, and DM+UTI+100 mg/kg CIP groups, excluding the control group, showed a statistically significant increase compared to pre-STZ application ($p<0.05$) (Table 1). After the STZ application, rats with blood glucose levels of 200 mg/dL or higher were considered experimentally diabetic and included in the study.

The Effect of CIP on Serum and Brain Tissue CAT, GSH, MDA, and AOPP Levels in Diabetic Rats with UTI

Serum MDA levels were found to be statistically significantly higher in the DM and DM+UTI groups compared to the control group ($p<0.05$). In the groups receiving 80 and 100 mg/kg CIP, serum MDA levels were statistically significantly lower compared to the DM and DM+UTI groups ($p<0.05$). It was observed that the serum MDA levels in both CIP-treated groups were similar to the control values ($p>0.05$) (Table 2).

Serum CAT levels were observed to be lower in the DM and DM+UTI groups compared to the control group; however, this difference was not statistically significant ($p>0.05$). Additionally, in the groups treated with 80 mg/kg and 100 mg/kg CIP, serum CAT levels were found to be lower than those in the DM and DM+UTI groups, but this reduction also did not result in a statistically significant difference ($p>0.05$) (Table 2).

Serum GSH levels showed a statistically significant decrease in the DM and DM+UTI groups compared to the control group ($p<0.05$). The serum GSH levels in both CIP-treated groups were found to be similar to those in the DM and DM+UTI groups ($p>0.05$) and exhibited a statistically significant decrease compared to the control group ($p<0.05$) (Table 2).

Serum AOPP levels showed a significant increase ($p<0.05$) in the DM and DM+UTI groups compared to the control group. Additionally, the serum AOPP values in both CIP-treated groups were found to be statistically significantly higher compared to the DM and DM+UTI group values ($p<0.05$) (Table 2).

Brain tissue MDA levels showed a statistically significant increase in the DM and DM+UTI groups compared to the control group ($p<0.05$). In both CIP-treated groups, brain MDA levels were found to be statistically significantly higher compared to the DM and DM+UTI groups ($p<0.05$), with the greatest increase observed in the 100 mg/kg CIP-treated group ($p<0.05$) (Table 3).

No statistically significant difference was found in brain tissue CAT levels between the groups ($p>0.05$). However, a decrease was observed in all groups (DM, DM+UTI, DM+UTI+80 mg/kg CIP, DM+UTI+100 mg/kg CIP) compared to the control values. The values of both CIP-treated groups were higher than those of the DM group ($p>0.05$) and similar to those of the DM+UTI group ($p>0.05$) (Table 3).

Brain tissue GSH levels were statistically significantly lower in the DM and DM+UTI groups compared to the control group ($p<0.05$). In both CIP-treated groups, brain tissue GSH levels were found to be statistically significantly higher compared to the DM and DM+UTI groups ($p<0.05$). The brain GSH levels in the 80 mg/kg CIP-treated group were similar to those in the control group ($p>0.05$), while the brain GSH levels in the 100 mg/kg CIP-treated group were significantly higher than the control values ($p<0.05$) (Table 3).

Brain tissue AOPP levels showed a statistically significant increase ($p<0.05$) in all groups compared to the control group. However, in the CIP-treated groups, the AOPP levels were found to be similar to those in the DM and DM+UTI groups ($p>0.05$) (Table 3).

The Effect of Ciprofloxacin on Serum Tissue IL-6 and TNF- α Levels in Diabetic Rats with UTI

Serum TNF-a levels showed a statistically significant increase ($p<0.05$) in the DM and DM+UTI groups compared to the control values. Although the TNF-a levels in both CIP-treated groups were found to be statistically significantly lower than those in the DM group ($p<0.05$), they remained similar to the values in the DM+UTI group ($p>0.05$) (Table 4).

Serum IL-6 levels were found to be statistically significantly higher in the DM group compared to the control group ($p<0.05$). In both CIP-treated groups, the IL-6 levels were statistically

significantly higher than those in the DM+UTI group ($p<0.05$), while they were similar to the values in the DM group ($p>0.05$) (Table 4).

The Effect of Ciprofloxacin on Brain Tissue BDNF and Proinflammatory Cytokine (TNF-α, IL-6) Levels

Brain tissue BDNF levels were found to be statistically significantly higher in the DM group and both CIP-treated groups compared to the control group ($p<0.05$). Both CIP-treated groups also showed a statistically significant increase in BDNF levels compared to the DM+UTI group ($p<0.05$), with the greatest increase observed in the 100 mg/kg CIP-treated group ($p<0.05$) (Table 5).

It was found that brain tissue TNF-a and IL-6 levels were statistically significantly higher in the DM group compared to the control group ($p<0.05$). The brain tissue TNF-a levels were elevated in both CIP-treated groups compared to the DM group ($p<0.05$), while no significant difference was observed when compared to the DM+UTI group ($p>0.05$). Additionally, brain tissue IL-6 levels were higher in the DM group ($p<0.05$) and DM+UTI group ($p>0.05$) compared to the control group. It was found that the brain tissue IL-6 levels in both CIP-treated groups were statistically significantly higher than in the DM+UTI group ($p<0.05$). The highest statistically significant brain tissue IL-6 levels were observed in the 100 mg/kg CIP-treated group ($p<0.05$), while the values in the 80 mg/kg CIP-treated group were found to be close to those of the DM group ($p>0.05$) (Table 5).

DISCUSSION

Diabetes Mellitus (DM) is defined as the most significant risk factor for the development of Urinary Tract Infections (UTI). Hyperglycemia associated with DM negatively affects immune responses, creating an environment conducive to bacterial colonization, thereby facilitating the development of UTIs.[25] UTI infections occur more frequently in individuals with DM, complicating both the complications of diabetes and the treatment process.[26] More than 80% of UTI infections are caused by *E. coli*, and this condition requires antibiotic treatment.[5] CIP is the most commonly used fluoroquinolone antibiotic for the treatment of UTI infections.[27] Recent studies have reported that CIP induces oxidative stress and increases ROS production,[28] and as a result, oxidative stress and ROS play a significant role in the emergence of undesirable effects such as tendinopathy, hepatotoxicity, cardiotoxicity, retinopathy, and neurotoxicity associated with CIP use.[10,29-31]

In this study, we aimed to investigate the effects of CIP use on antioxidant and certain cytokine levels in the brain and serum tissues of rats with experimental DM induced by STZ and *E. coli*-induced UTI. As a result of the findings obtained in the presented study, MDA levels in both serum and brain tissues were found to be significantly higher in the DM and DM+UTI groups compared to the control group ($p<0.05$).

ROS play a crucial role in cell signaling and maintaining tissue homeostasis under normal physiological conditions. However, when produced excessively, they can lead to lipid peroxidation and DNA damage. Malondialdehyde (MDA), a byproduct of lipid peroxidation, is considered an indicator of this processes.[32]

Free radicals play an active role in the process of lipid peroxidation, leading to the oxidation of polyunsaturated fatty acids. As a result of this process, the increase in MDA levels due to the effects of free radicals is considered a biomarker of oxidative stress.[4] Lipid peroxidation and oxidative stress lead to dysfunction of pancreatic β cells, causing damage to tissues.[33] In studies conducted, an increase in MDA levels was observed

Table 1: Blood Glucose Levels of the Groups before and after STZ Administration.

Group	Glucose Levels Before STZ Administration (mg/dL)	Glucose Levels After STZ Administration (mg/dL)
Control	97.33±9.07	104.33±14.51
DM	95.50±8.87	338.16±66.85 #
DM+UTI	101.16±8.89	434.66±102.48 #
DM+UTI+80 mg/kg CIP	97.66±15.66	357.50±104.75 #
DM+UTI+100 mg/kg CIP	99.00±12.05	314.00±43.40 #

#: The difference from glucose levels before STZ administration (mg/dL) is significant ($p<0.05$).

Table 2: MDA, CAT, GSH and AOPP Levels in Serum between Groups.

Group	MDA (mmol/L)	CAT (U/L)	GSH (mmol/L)	AOPP (mmol/L)
Control	2.86±0.78^{b}	743.36±90.67^{a}	266.68±24.25^{a}	6.01±0.90^{d}
DM	4.49±0.60^{a}	649.67±80.56^{a,b}	205.97±27.05^{b}	8.74±0.91^{c}
DM+UTI	5.11±0.54^{a}	697.24±41.66^{a,b}	196.54±15.19^{b}	10.18±1.24^{c}
DM+UTI+80 mg/kg CIP	2.96±0.31^{b}	677.61±112.86^{a,b}	207.28±24.77^{b}	20.44±1.26^{a}
DM+UTI+100 mg/kg CIP	3.13±0.60^{b}	616.08±82.93^{b}	209.36±17.29^{b}	16.83±1.71^{b}

Each value represents the Mean ± SD. Different letters in each row represents statistics significance. ($p<0.05$).

Table 3: MDA, CAT, GSH and AOPP Levels in Brain Tissue Between Groups.

Group	MDA (mmol/gr)	CAT (U/L)	GSH (mmol/gr)	AOPP (mmol/gr)
Control	8.64±0.95[d]	957.27±58.89[a]	404.71±29.635[b]	20.64±1.31[c]
DM	10.98±0.79[c]	887.75±73.07[a]	294.13±38.22[c]	28.75±2.75[a,b]
DM+UTI	11.69±1.06[c]	934.31±49.56[a]	275.76±17.29[c]	26.98±2.37[b]
DM+UTI+80 mg/kg CIP	14.14±0.86[b]	909.39±50.38[a]	431.97±32.85[b]	30.16±1.08[a]
DM+UTI+100 mg/kg CIP	17.45±0.96[a]	929.59±32.77[a]	522.49±99.00[a]	29.17±1.14[a,b]

Each value represents the Mean±SD. Different letters in each row represents statistics significance. ($p<0.05$).

Table 4: Serum Proinflammatory Cytokine (TNF-α, IL-6) Levels.

Group	TNF-α	IL-6
Control	34.47±5.12[c]	20.53±1.77[b]
DM	106.99±18.70[a]	38.97±4.67[a]
DM+UTI	54.29±11.85[b]	21.29±3.47[b]
DM+UTI+80 mg/kg CIP	62.89±9.89[b]	38.00±3.12[a]
DM+UTI+100 mg/kg CIP	57.47.47±7.45[b]	35.00±3.47[a]

Each value represents the Mean±SD. Different letters in each row represents statistics significance. ($p<0.05$).

in rats with experimental diabetes compared to the control group.[4,34,35] In pregnant rats treated with CIP, MDA levels in their offspring's brain tissue showed a significant increase compared to the control group, as reported by Doğan *et al.*, (2017). Youssef *et al.*, (2024) stated that MDA levels in the hippocampal tissue of rats treated with CIP significantly increased compared to the control group.[36,37] Additionally, in a depression model induced by CIP, MDA levels in the brain tissue of CIP-treated rats showed a significant increase.[12]

In this study, serum MDA levels were found to be similar to the control group after CIP treatment, whereas brain MDA levels were significantly higher compared to the DM and DM+UTI groups. The obtained results are consistent with the studies of the researchers mentioned above.

Catalase (CAT) is an enzyme that detoxifies Hydrogen peroxide (H_2O_2) by converting it into water and oxygen within cells. CAT protects cells by reducing the harmful effects of ROS, particularly hydrogen peroxide.[38] Glutathione (GSH) is a tripeptide composed of glutamic acid, cysteine, and glycine amino acids, and functions as a potent antioxidant within cells. It plays a role in the redox regulation of protein thiols and hydrogen peroxide in mitochondria. GSH is the cell's first line of defense and mitigates harmful radicals by facilitating the dismutation of superoxide radicals, making them less harmful.[39] In the DM model, a decrease in CAT[40] and GSH levels[41] has been observed in brain tissue. Additionally, it has been reported that both CAT and GSH levels are reduced in the serum of diabetic patients.[39,42] In the present study, a significant reduction in both CAT and GSH levels was observed in the serum and brain tissues of the DM and DM+UTI groups compared to the control group. The obtained results are consistent with the findings of the aforementioned researchers.

In the present study, the observed decrease in CAT and GSH levels in the serum and brain tissue of the diabetic group can be explained as a result of oxidative stress induced by hyperglycemia. In a diabetic environment, due to hyperglycemia, glucose preferentially follows the polyol pathway, which increases NADPH consumption and disrupts the synthesis of GSH. The reduction in GSH weakens the intracellular antioxidant defense mechanisms, leading to an increase in oxidative damage.[39] Additionally, increased hydrogen peroxide levels can impair the function of the catalase enzyme, leading to a decrease in CAT levels.[42] The combination of these mechanisms may cause a significant reduction in CAT and GSH levels in both serum and brain tissue in the DM and DM+UTI groups in the present study. In the study by Igbayilola *et al.*, (2020), a significant decrease in CAT and GSH levels in the serum was observed in rats treated with 20 mg/kg CIP for 7 days.[7] In other studies, it has been found that CIP reduces CAT and GSH levels in the kidneys,[43] and liver,[44] and also decreases CAT levels in brain tissue.[12] Additionally, in the study by Doğan *et al.*, (2017), it was reported that the levels of CAT and GSH in the brain tissue of the offspring of pregnant rats treated with CIP were significantly lower compared to the control group.[36] In the present study, a decrease in CAT and GSH levels in the serum tissue was observed with CIP administration, compared to the control group. Serum CAT levels showed a decrease in both CIP-treated groups compared to the DM+UTI group. Brain tissue CAT levels were lower in the CIP-treated groups compared to the DM+UTI group, but it was observed that the CAT levels between the groups were similar. The decrease in CAT levels in both serum and brain tissue following CIP treatment in the present study is consistent with the results of the researchers mentioned above. In this study, the serum GSH levels after CIP administration were found to be similar to the DM and DM+UTI groups, while the brain GSH levels were significantly higher in both CIP-treated groups compared to the DM and DM+UTI groups. Although the findings of the aforementioned researchers indicate that CIP administration decreases GSH levels in various tissues,[7,36] it has been reported that under conditions where ROS increases, the de novo synthesis of GSH is elevated,

Table 5: Brain BDNF and Proinflammatory Cytokine (TNF-α, IL-6) Levels.

Group	BDNF	TNF-α	IL-6
Control	0.69±0.15[b]	13.01±3.03[c]	25.02±4.87[c]
DM	0.84±0.11[a]	18.74±5.41[b]	80.74±5.43[b]
DM+UTI	0.69±0.10[b]	25.97±3.58[a]	32.64±6.13[c]
DM+UTI+80 mg/kg CIP	0.86±0.05[a]	30.21±1.11[a]	87.31±6.96[b]
DM+UTI+100 mg/kg CIP	0.92±0.07[a]	30.11±2.00[a]	108.48±5.87[a]

Each value represents the Mean±SD. Different letters in each row represents statistics significance. ($p<0.05$).

thereby protecting cells from the harmful effects of ROS.[45] In the present study, it was observed that CIP administration increased GSH levels in brain tissue, and this increase might be related to the upregulation of de novo GSH synthesis in the brain tissue, which could contribute to its protection against oxidative stress. Although there is insufficient research in the literature regarding the effect of CIP on GSH levels in brain tissue, this study suggests that CIP may have triggered a different response and adaptation mechanism in brain tissue.

Advanced Oxidation Protein Products (AOPP) are a class of protein products containing di-tyrosine, and they can trigger intracellular ROS production, functioning as an endogenous mediator of redox imbalance.[46] Therefore, AOPP is considered a biomarker of oxidative stress.[46] As DM progresses and vascular complications such as nephropathy begin to develop, it has been found that AOPP levels increase, and patients with diabetic vascular complications have significantly higher AOPP levels compared to those with diabetes without complications.[47] Elevated AOPP levels are particularly considered an important risk factor for the vascular complications of DM (especially diabetic nephropathy).[48] In the presented study, the significantly higher AOPP levels in both serum and brain tissue in the DM and DM+UTI groups compared to the control group indicate increased oxidative stress in these groups and a higher risk of developing vascular complications. In the literature, it has been reported that AOPP increases with the progression of diabetes, particularly in relation to vascular complications such as diabetic nephropathy.[46-48] The findings suggest that AOPP could be used as a potential biomarker for the early diagnosis and prognostic evaluation of diabetic complications. There is limited literature regarding the effect of CIP treatment on AOPP. In rats treated with CIP, increases in AOPP levels have been reported in liver tissue[18] and serum.[49] These findings indicate that CIP has the potential to increase AOPP levels as a marker of oxidative stress in both the liver and serum. In the presented study, similar increases were observed in serum tissue, but this did not result in as pronounced an increase in brain tissue. However, it is still evident that CIP can lead to an increase in AOPP levels in brain tissue, suggesting its potential role in oxidative damage. The mechanism of CIP's toxic effects on the Central Nervous System (CNS) has been explained through the evaluation of oxidative stress, which was assessed by measuring catalase, glutathione peroxidase, and MDA levels, and correlating these changes with the levels of antioxidant values.[12] In the presented study, MDA, CAT, GSH, and AOPP levels were evaluated in both serum and brain tissues. CIP increases oxidative stress by leading to the oxidation of unsaturated fatty acids in membrane phospholipids and lipid peroxidation.[36] Ilgın *et al.*, (2015) also reported that the induction of oxidative stress by CIP administration could be related to an increase in the production of electrophilic metabolites due to its CYP450-mediated metabolism.[10] It has been stated that CIP may lead to oxidative stress by causing significant dysfunction in the electron transport chain complexes of the mitochondria.[11] In the presented study, it was observed that CIP administration in the DM+UTI groups disrupted the antioxidant balance. We hypothesize that the disruption of antioxidant balance may be caused by the triggering of ROS production by CIP, which could be due to both the metabolism of the drug and the dysfunction that may occur in the mitochondrial electron transport chain in the cells.

Chronic inflammation has been identified as a risk factor in the progression of DM and the development of its complications. An increase in IL-6 levels has particularly been associated with inflammation in the pathogenesis of type 2 DM,[50] leading to insulin resistance and dysfunction in beta cells.[51] The excessive release of TNF-a in DM has been linked to microangiopathy and neuronal damage, which is associated with diabetic neuropathy.[3] Many studies have reported an increase in TNF-a and IL-6 levels in the serum and brain tissue of diabetic rats.[47,51-53] It has been reported that hyperglycemia leads to an increase in TNF-a and IL-6 levels through oxidative damage.[54] In this study, TNF-a and IL-6 levels in both serum and brain tissue in the DM and DM+UTI groups are consistent with the results of the above-mentioned studies. According to Atallah *et al.*, (2022), a study in which 80 mg/100 g of body weight CIP was administered for 14 days in mice reported an increase in serum IL-6 levels compared to the control group.[55] Salama *et al.*, (2021) reported an increase in TNF-a levels in brain tissue in their depression model induced by CIP.[12,55] It has been reported that an increase in the levels of cytokines, such as TNF-a and IL-6, which affect neuronal function, may contribute to the progression of depression.[12] In the studies conducted by Ogino *et al.*, (2009), it was reported that a 10 mg/kg CIP dose did not alter serum TNF-α levels, but that serum TNF-α levels decreased in mice treated with 50 and 100 mg/kg CIP.[56] The IL-6 levels,

however, varied depending on the CIP dose, with particularly a 100 mg/kg dose increasing IL-6 levels.[56] Additionally, in the study by Baiily *et al*., (1990), a significant increase in IL-6 production was observed in monocytes collected from volunteers treated with 25 mg/kg CIP for 14 days following *ex vivo* lipopolysaccharide stimulation.[57]

In the present study, it was found that serum TNF-α levels in the CIP-treated groups were lower compared to the DM group, but were similar to the DM+UTI group. Serum IL-6 levels were significantly higher in both CIP-treated groups compared to the DM+UTI group, but were similar to the DM group. In brain tissue, TNF-α and IL-6 levels were found to be higher in the CIP-treated groups compared to the DM and DM+UTI groups. We believe that this increase in brain tissue is due to the disruption of the redox balance resulting from the increased ROS in the brain tissue. These findings, along with the studies of the researchers mentioned above, indicate that the effect of CIP on the inflammatory response in serum tissue varies depending on the dose, clinical conditions (DM and DM+UTI), and tissue type. The effects of CIP on IL-6 and TNF-α differ depending on the dose, tissue, and clinical conditions, revealing that CIP has the capacity to modulate inflammation at different levels.

BDNF is a member of the neurotrophic factor family widely found in the central nervous system. Recent studies show that BDNF plays a role in synaptic plasticity, synaptic formation, and the maturation and development of neurons in the brain.[58] Studies have reported that changes in BDNF levels may lead to behavioral disorders, including depression, bipolar disorder, attention deficit, Autism Spectrum Disorder (ASD), and even suicidal behavior.[59,60] It is known that diabetic patients are more prone to cognitive impairments and neuropsychiatric disorders. Additionally, regarding the role of BDNF in metabolism, it is also hypothesized that circulating BDNF levels may change in diabetic patients as a result of disruptions in glucose-related pathways.[61] Although there are many studies on the relationship between BDNF, diabetes, and its complications, the results are contradictory. Some studies have reported a significant decrease in BDNF levels in diabetic patients,[62,63] while others have reported an increase in BDNF levels in diabetic patients.[64,65] Although Tekmeh *et al.*, (2023) reported an increase in both serum and brain tissue BDNF levels in diabetic rats,[66] Ahmad *et al.*, (2022) reported a decrease in BDNF levels in the brain tissue of diabetic rats.[3] In this study, it was found that the brain BDNF levels in the DM group were increased compared to the control values, while in the DM+UTI group, the BDNF levels were similar to the control values. It was observed that CIP treatment increased the brain BDNF levels in comparison to the control, DM, and DM+UTI groups. Tekmeh *et al.*, (2023) reported that the main mechanism behind the increase in brain BDNF levels was the enhanced release and expression of BDNF as a defense mechanism by astrocyte cells, which are immunomodulatory in inflammatory conditions in the brain.[66] In this study, since CIP induces both inflammation in brain tissue (as evidenced by the increased levels of inflammatory markers such as IL-6 and TNF-α) and increases ROS production, we suggest that the increase in BDNF levels may be a defense mechanism.

CONCLUSION

This study examined the effects of CIP applied against *E. coli*-induced urinary tract infection in diabetic rats, focusing on oxidative stress and the antioxidant system. The results showed that the combination of diabetes and urinary tract infection led to a significant increase in oxidative stress in both serum and brain tissues, as indicated by elevated levels of lipid peroxidation (MDA), decreased antioxidant enzymes (CAT and GSH), and increased levels of AOPP, a marker of oxidative damage. CIP treatment significantly reduced the elevated MDA levels in the serum of both DM and DM+UTI groups, but no significant improvement was observed in CAT, GSH, or AOPP levels. In brain tissue, however, CIP treatment was found to negatively affect MDA, GSH, CAT, and AOPP levels, particularly in the DM+UTI group. These findings suggest that CIP treatment could exacerbate oxidative damage in brain tissue in the DM+UTI group and lead to further intensification of oxidative stress. In terms of neurological effects, it is hypothesized that ciprofloxacin may increase the production of ROS in brain tissue, which could lead to an increase in BDNF levels. BDNF is a neurotrophic factor that plays a critical role in synaptic plasticity, neuron development, and the survival of nerve cells. In this study, it was observed that ciprofloxacin treatment increased brain BDNF levels. This increase may indicate that BDNF acts as a defense mechanism to counterbalance the oxidative stress and inflammation in brain tissue caused by CIP. In other words, the elevation of BDNF in response to oxidative damage induced by ciprofloxacin in brain tissue could be a neuroprotective response.

In conclusion, some studies in the literature suggest that CIP treatment may lead to undesirable side effects in the neurological system. However, no specific studies on the use of ciprofloxacin in the treatment of DM and DM+UTI have been found. In this context, this study is pioneering in the field and will serve as a guide for future research. It has been observed that CIP treatment in DM and DM+UTI, particularly in brain tissue, induces oxidative stress, disrupts the antioxidant balance, increases inflammation levels, and leads to an elevation of BDNF levels, which plays an important role as a survival mechanism for cells in the brain. These findings can be considered as evidence supporting the hypothesis that CIP may play a role in undesirable effects, particularly on the nervous system. Therefore, further research is needed on the neurological effects of CIP use in the treatment of DM and DM+UTI.

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ABBREVIATIONS

DM: Diabetes Mellitüs; **CIP:** Ciprofloxacin; **UTI:** Urinary tract infection; **E. coli:** *Escherichia coli*; **ROS:** Reactive oxygen species; **CNS:** Central nervous system; **BDNF:** Brain-derived neurotrophic factor; **MDA:** Malondialdehyde; **CAT:** Catalase; **GSH:** Glutathione; **AOPP:** Protein oxidation products; **IL-6:** İnterleukin 6; **TNF-α:** Tumour necrosis factor-alpha.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study investigates the effects of CIP treatment on oxidative stress, antioxidant systems, and inflammatory markers in a rat model of DM and *E. coli*-induced UTI. The results showed that DM and UTI together significantly increased oxidative stress in both serum and brain tissues. CIP treatment reduced oxidative stress in serum but did not improve antioxidant levels or inflammatory markers significantly. In brain tissue, CIP exacerbated oxidative stress and inflammation, especially in the DM+UTI group, although it increased BDNF levels. These findings suggest that while CIP may reduce oxidative damage in serum, it could worsen neurological effects in brain tissue, highlighting the need for further research on its impact on the nervous system.

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