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Research Article

Investigation of the Effects of Rutin on Sciatic Nerve Damage Induced by Colistin in Rats

Fatih Mehmet KANDEMİR[1], Hasan ŞİMŞEK[2]

[1]Aksaray University, Faculty of Medicine, Department of Medical Biochemistry, Aksaray, TÜRKİYE, ORCID ID: 0000-0002-8490-2479
[2]Aksaray University, Faculty of Medicine , Department of Physiology, Aksaray, TÜRKİYE, ORCID ID: 0000-0001-5573-4923
Corresponding Author: Fatih Mehmet KANDEMİR, fmkandemir@aksaray.edu.tr

ABSTRACT

Introduction: This study aimed to determine the protective effect of Rutin on Colistin-induced sciatic nerve injury.

Methods: Thirty-five rats were divided into five groups: control, Rutin, Colistin, Colistin+Rutin50, and Colistin+Rutin100. Biochemically, malondialdehyde (MDA), glial fibrillary acidic protein (GFAP), nerve cell adhesion molecule (NCAM), nuclear factor kappa B (NF-κB), cyclooxygenase 2 (COX-2), and neuronal nitric oxide synthase (nNOS), and parameters were analyzed.

Results: Colistin treatment caused sciatic nerve injury by increasing MDA levels ($p < 0.05$) leading to lipid peroxidation; by increasing COX-2, NF-κB, and nNOS levels ($p < 0.05$) leading to inflammation; and by increasing GFAP levels and decreasing NCAM levels ($p < 0.05$). Colistin+Rutin50 and Colistin+Rutin100 treatments were found to have therapeutic effects against sciatic nerve injury by decreasing MDA levels and lipid peroxidation, decreasing NF-κB, COX-2, and nNOS levels and inflammation, decreasing GFAP levels, and increasing NCAM levels.

Conclusion: Overall, Rutin was found to have a therapeutic effect against Colistin-induced sciatic nerve injury.

Keywords: Colistin, GFAP, inflammation, NCAM, rutin

Sıçanlarda Kolistin ile Oluşturulan Siyatik Sinir Hasarına Rutin'in Etkilerinin Araştırılması

Fatih Mehmet KANDEMİR[1], Hasan ŞİMŞEK[2]

[1]Aksaray Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya Anabilim Dalı, Aksaray, TÜRKİYE, ORCID ID: 0000-0002-8490-2479
[2]Aksaray Üniversitesi, Tıp Fakültesi, Fizyoloji Anabilim Dalı, Aksaray, TÜRKİYE, ORCID ID: 0000-0001-5573-4923
Sorumlu Yazar: Fatih Mehmet KANDEMİR, fmkandemir@aksaray.edu.tr

ÖZ

Amaç: Bu çalışmada, Kolistin kaynaklı siyatik sinir hasarında Rutin'in koruyucu etkisinin belirlenmesi amaçlanmıştır.

Materyal ve Yöntem*:* Otuz beş sıçan kontrol, Rutin, Kolistin, Kolistin+Rutin50 ve Kolistin+Rutin100 olmak üzere beş gruba ayrıldı. Biyokimyasal olarak malondialdehit (MDA), glial fibriler asidik protein (GFAP), sinir hücresi adezyon molekülü (NCAM), nükleer faktör kappa B (NF-κB), siklooksijenaz 2 (COX-2) ve nöronal nitrik oksit sentaz (nNOS) parametreleri analiz edildi.

Sonuçlar: Kolistin tedavisi siyatik sinir hasarında MDA düzeylerini artırarak ($p < 0.05$) lipid peroksidasyonuna, COX-2, NF-κB ve nNOS düzeylerini artırarak ($p < 0.05$) inflamasyona ve GFAP düzeylerini artırırken ($p < 0.05$) NCAM düzeylerini azaltarak siyatik sinir hasarına neden oldu. Kolistin+Rutin50 ve Kolistin+Rutin100 tedavilerinin, MDA düzeylerini ve lipid peroksidasyonunu azaltarak, NF-κB, COX-2 ve nNOS düzeylerini ve inflamasyonu azaltarak, GFAP düzeylerini düşürerek ve NCAM düzeyini artırarak siyatik sinir hasarına karşı terapötik etkiler gösterdiği bulunmuştur.

Sonuç: Genel olarak, Rutin'in Kolistin kaynaklı siyatik sinir hasarına karşı terapötik bir etki gösterdiği görülmüştür.

Anahtar Kelimeler: Kolistin, GFAP, inflamasyon, NCAM, rutin

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INTRODUCTION

Colistin, produced by Colistinus, is a glycopeptide antibiotic and is known as Polymyxin E. It is generally used in the treatment of gram-negative infections (Edrees et al., 2018). It is used not only for its antiendotoxic properties but also for its bactericidal properties in the treatment of gram-negative infections (Rajabalizadeh et al., 2024). Despite its use in treatments, its use is limited due to side effects dizziness, seizures, hallucinations (Çelik et al., 2020; Durdu et al., 2025). The mechanism of damage related to its clinical use is unclear due to the primary dose-limiting factor (Eronmosele et al., 2021). Due to the absence of the blood-brain barrier, peripheral nerves are sensitive to Colistin treatment (Dai et al., 2019). The most important factor limiting treatment is nerve injury (Kankılıç et al., 2024). It causes the production of reactive oxygen species (ROS) in neuronal cells, leading to apoptosis (Dai et al., 2022). ROS-induced peroxidation occurs through protein oxidation and mitochondrial deoxyribonucleic acid (DNA) (Shafik et al., 2023). The use of neuroprotective agents in combination with Colistin is of great importance to enable the clinical use of Colistin (Edrees et al., 2018).

Due to their effectiveness and lack of toxicity, herbal medicines are widely used to reduce the side effects of toxic treatments, such as depression (Foudah et al., 2022). Flavonoids, which are natural polyphenols found in foods, have a neuroprotective effect by reducing neuroinflammation, as they are effective in slowing age-related problems such as improving cognitive function (Kessas et al., 2024). Rutin, natural flavonoid, is found in plants such as buckwheat and apples (Saafan et al., 2023; Zhang et al., 2023). Rutin reduces increased ROS by binding hydrogen to superoxide anions, hydroxyl, oxygen radicals, exhibits anti-inflammatory, antidepressant, neuroprotective effects (Arowoogun et al., 2021; Zhang et al., 2023; AbdElrazek et al., 2024). The most important pharmacological effect of Rutin is its anti-inflammatory effect through the inhibition of nuclear factor kappa B (NF-κB) (Rahmani et al., 2023).

In this study, the effects of Rutin on sciatic nerve damage caused by Colistin were investigated by analyzing malondialdehyde (MDA), glial fibrillary acidic protein (GFAP), neural cell adhesion molecule (NCAM), NF-κB, cyclooxygenase 2 (COX-2), and neuronal nitric oxide synthase (nNOS) parameters.

MATERIALS AND METHODS

Chemicals

Colistin (Colimycin® 150 mg/flakon, Koçak Pharma, İstanbul, Turkey) was obtained from a local pharmacy. Rutin (≥ 94%) and other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Experimental Procedures

Male Sprague Dawley rats weighing 220-250 g were used in the study. The rats were housed in cages with free access to water and food under controlled environmental conditions (humidity 45 ± 5%, temperature 25 ± 1°C, and a 12-hour light/dark cycle). Approval for the study was obtained from the Atatürk University Animal Experimentation Local Ethics Committee (Approval Number: 56/4,2019). The rats were divided into five groups of seven animals each, and the treatments lasted for seven days.

Control: Normal saline was administered once daily.

Rutin: 100 mg/kg Rutin was administered orally (Kandemir et al., 2022).

Colistin: 15 mg/kg Colistin was administered i.p. once daily (Ajiboye, 2018).

Colistin+Rutin50: Colistin, 50 mg/kg Rutin were administered.

Colistin+Rutin100: Colistin and 100 mg/kg Rutin were administered.

One day later, the rats were euthanized under light sevoflurane anaesthesia, and the sciatic nerve was harvested. Sciatic nerve biochemical analyses were used.

Evaluation of MDA Levels

Sciatic nerve was homogenized using a homogenizer with potassium chloride solution (1.15% KCl). MDA level was determined according to the method described by Placer et al., (1966). Protein content in the sciatic nerve was determined according to the method of Lowry et al., (1951).

Evaluation of GFAP, NCAM, NF-κB, COX-2, and nNOS Levels

Sciatic nerve GFAP (201-11-0970), NCAM (201-11-1075), NF-κB (201-11-5141), COX-2 (201-11-0297), and nNOS (201-11-0543) levels were measured using an enzyme-linked immunosorbent assay kit (Shanghai, China) according to the manufacturer's protocol.

Statistical Analysis

Statistical analyses were performed using the SPSS 20.0 software package. One-way ANOVA analysis followed by Tukey's post-hoc test was used to compare groups. Results are presented as mean ± standard deviation (SD). $p < 0.05$ was considered statistically significant.

RESULTS

Effect of Colistin and Rutin Administration on MDA Levels

The MDA level, an indicator of lipid peroxidation, is shown in Figure 1. An increase in MDA levels was observed in the group treated with Colistin ($p < 0.05$). The treatments with Colistin+Rutin50 and Colistin+Rutin100 were found to reduce the increased MDA levels.

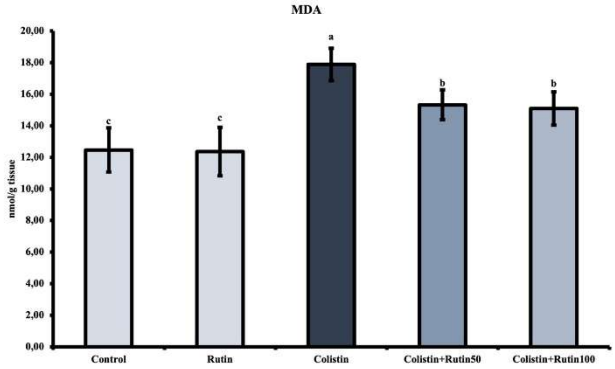

Figure 1. Effect of Rutin treatment on MDA levels in the sciatic nerve. Each group value is given as mean ± SD. Different letters (a-b-c) in the columns indicate differences between groups ($p < 0.05$).

Effect of Colistin and Rutin Administration on GFAP Levels

GFAP was analyzed using the ELISA method (Figure 2). GFAP levels in the sciatic nerves of rats treated with Colistin increased compared to the control and Rutin groups ($p < 0.05$). Rutin treatment (50-100 mg/kg) reduced GFAP levels in a dose-dependent manner.

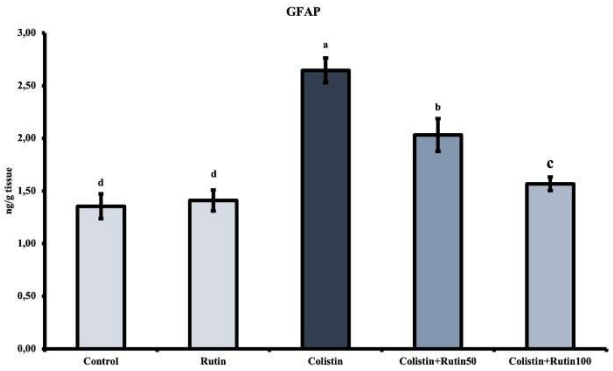

Figure 2. Effect of Rutin treatment on GFAP levels in the sciatic nerve. Each group value is given as mean ± SD. Different letters (a-b-c-d) in the columns indicate differences between groups ($p < 0.05$).

Effect of Colistin and Rutin Administration on NCAM Levels

NCAM levels are shown in Figure 3. NCAM levels in the sciatic nerves of rats treated with Colistin decreased compared to the control and Rutin groups ($p < 0.05$). Colistin+Rutin50 and Colistin+Rutin100 treatments increased NCAM levels in a dose-dependent manner.

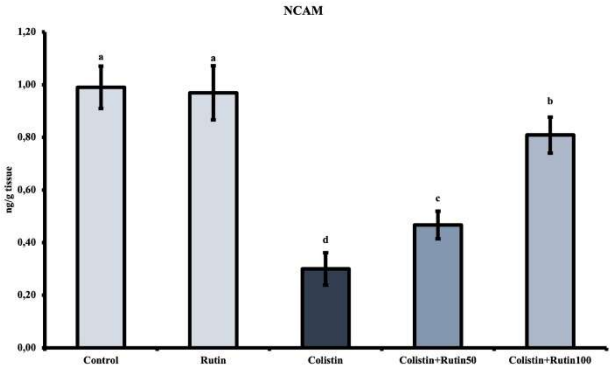

Figure 3. Effect of Rutin treatment on NCAM levels in the sciatic nerve. Each group value is given as mean ± SD. Different letters (a-b-c-d) in the columns indicate differences between groups ($p < 0.05$).

Effect of Colistin and Rutin Administration on NF-κB Levels

NF-κB levels were analyzed to determine the level of inflammatory damage in the sciatic nerve (Figure 4). NF-κB levels increased in the sciatic nerves of rats treated with Colistin ($p < 0.05$). When administered together with Colistin, Rutin reduced NF-κB levels.

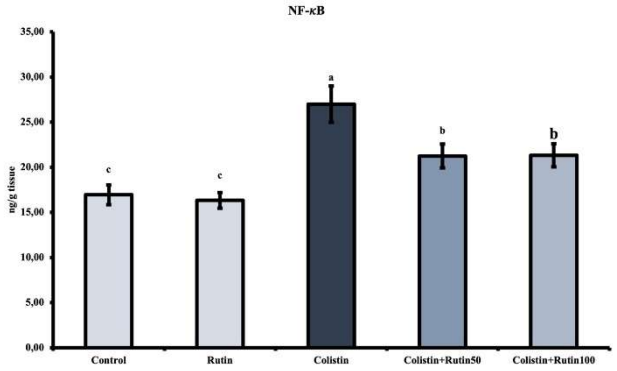

Figure 4. Effect of Rutin treatment on NF-κB levels in the sciatic nerve. Each group value is given as mean ± SD. Different letters (a-b-c) in the columns indicate differences between groups ($p < 0.05$).

Effect of Colistin and Rutin Administration on COX-2 Levels

The results for COX-2, another inflammation parameter, are shown in Figure 5. Rats treated with Colistin showed an increase in COX-2 in the sciatic nerve ($p < 0.05$). When Rutin was administered in combination with Colistin, it reduced COX-2 levels in a dose-dependent manner.

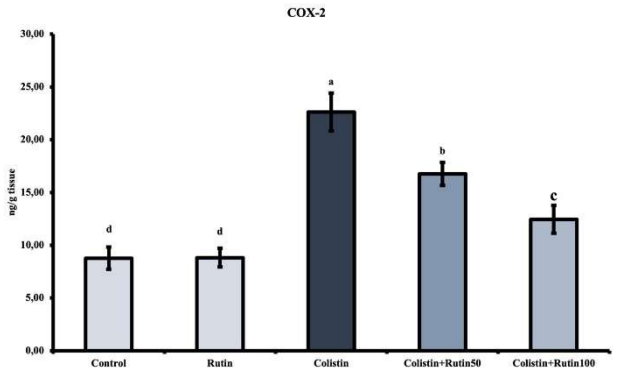

Figure 5. Effect of Rutin treatment on COX-2 levels in the sciatic nerve. Each group value is given as mean ± SD. Different letters (a-b-c-d) in the columns indicate differences between groups ($p < 0.05$).

Effect of Colistin and Rutin Administration on nNOS Levels

It was found that Colistin administration increased nNOS levels in the sciatic nerve ($p < 0.05$). However, it was found that Colistin+Rutin50 and Colistin+Rutin100 treatments reduced the increased nNOS levels (Figure 6).

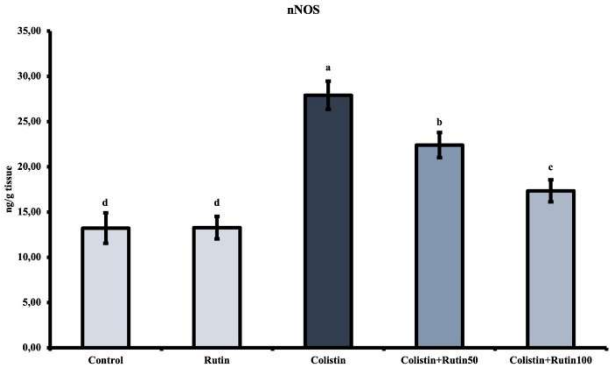

Figure 6. Effect of Rutin treatment on nNOS levels in the sciatic nerve. Each group value is given as mean ± SD. Different letters (a-b-c-d) in the columns indicate differences between groups ($p < 0.05$).

DISCUSSION AND CONCLUSION

This study, the effects of Rutin, a natural flavonoid, sciatic nerve damage caused by Colistin were investigated.

Cells exposed to harmful toxic substances produce free radicals, leading to oxidative stress (Ding et al., 2024). MDA is the most important indicator of oxidative stress (Shargh et al., 2025). Increased MDA levels cause damage to cells by increasing membrane structure, membrane function, and membrane permeability (Yu et al., 2024; Zhang et al., 2024; Kandemir et al., 2025). Increased MDA levels activate the inflammatory pathway (Shargh et al., 2025). In the present study, we found that Colistin caused ROS release in the sciatic nerve of rats, increasing MDA levels, while Rutin (50-100 mg/kg) treatment reduced lipid peroxidation and had a beneficial effect on sciatic nerve damage. Previous studies have reported that Colistin causes nerve injury by increasing MDA levels in the central nervous system (Edrees et al., 2018; Durdu et al., 2025) and sciatic nerve tissue (Dai et al., 2019). It has been stated that Rutin improves nerve injury in the central nervous system by exhibiting antioxidant effects (Çelik et al., 2020).

GFAP, an important marker for astrocytes, is a protein produced in astrocytes and composed of intermediate filaments (Samir et al., 2024; Hegab et al., 2025). GFAP significantly affects events such as synaptic signal transmission and nerve tissue development, making it important for assessing neuronal damage (Hegab et al., 2025; Okoh et al., 2025). NCAM, which is found in almost all tissues, is present at the highest

levels in peripheral nerve tissue and continues to be expressed not only in neurons but also in glial cells until adulthood (Aonurm-Helm et al., 2016; Dos Reis et al., 2024; Er et al., 2025). It also plays an important role in cell-cell and cell-extracellular interactions (Cao et al., 2016). In the present study, we found that Colistin increased GFAP levels and decreased NCAM levels in sciatic nerve tissue. We found that Colistin+Rutin50 and Colistin+Rutin100 treatments had the opposite effect on these parameters, showing improvement. It has been reported that Colistin causes damage by increasing GFAP levels and decreasing NCAM levels in sciatic nerve tissue (Yılmaz et al., 2024). It has been stated that Rutin reduces nerve injury by decreasing GFAP levels against various toxic substances (Saafan et al., 2023).

Increased ROS results in oxidative stress, which triggers cell death by causing inflammation (Kumar et al., 2021; Gencer et al., 2025). NF-κB, a transcription factor, regulates proinflammatory mediators and initiates inflammatory activation by supporting the expression of proinflammatory mediators such as COX-2 (Wang et al., 2014; Ramamoorthy et al., 2017; Jin et al., 2023). nNOS, inducible NOS (iNOS), and endothelial NOS (eNOS) are the three isoforms of nitric oxide synthase, and increased expression of nNOS plays a significant role in pathological processes such as nerve injury (Karaca et al., 2025). In the present study, it was found that Colistin causes inflammation by increasing COX-2, NF-κB, and nNOS levels, while Rutin (50-100 mg/kg) treatment not only regulates lipid peroxidation but also effectively reduces inflammation. Previous studies have reported that Colistin increases inflammation (Edrees et al., 2018; Çelik et al., 2020), while flavonoids improve inflammation caused by Colistin (Yılmaz et al., 2024).

The present study suggests that Rutin has therapeutic effects on Colistin-induced sciatic nerve damage. We can say that the therapeutic properties of Rutin stem from its anti-inflammatory, antioxidant properties.

DECLARATION OF CONTRIBUTION RATE OF RESEARCHERS

Authors' contribution rates to the study are equal.

FINANCIAL SUPPORT AND ACKNOWLEDGMENT

This study received no financial support.

CONFLICT OF INTEREST DECLARATION

There is no conflict of interest between any institution, person, or author within the scope of the study.

ETHICAL STATEMENT

Animal studies: The study was conducted in accordance with the Declaration of Helsinki and approved by the Animal Experimental Local Ethics Committee of Ataturk University (Protocol No. 56/4, 2019).

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