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The effect of quercetin, a flavonoid, on lung injury caused by sepsis

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Ethics Committee Approval
This study was carried out at Adıyaman University Experimental Animals Application and Production Center with the permission of Adıyaman University Animal Experiments Local Ethics Committee (ADYÜ-HADYEK) (2019/045).
The present study followed international, national, and/or institutional guidelines for humane animal treatment and complied with relevant legislation from the Animal Ethics Committee.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Lung injury is frequently observed in cases with sepsis, which can lead to conditions that progress to acute respiratory distress syndrome (ARDS) causing mortality. There is no specific treatment for sepsis or sepsis-induced lung injury. Antioxidant therapy has been one of the most prominent options for treatment, according to pathophysiological studies. The aim of this study was to investigate the effects of quercetin, a powerful antioxidant, on sepsis and sepsis-related lung injury.
Methods: Thirty-two adult male Sprague Dawley rats were divided into five groups. The control group (CNRL) received 1.5 ml saline via the intragastric route. The quercetin group (QUER [n=5]) underwent no sepsis procedure and received 20 mg/kg quercetin via the intragastric route starting 15 days before the procedure. The sham group (SHAM [n=6]) underwent a surgical incision and received 1.5 ml intragastric olive oil (quercetin dissolves in oil). The sepsis group (SEPS [n=7]) underwent the sepsis procedure. The sepsis and quercetin group (SEPS+QUER [n=7]) underwent the sepsis procedure and received 20 mg/kg quercetin via the intragastric route for 15 days before the procedure. Cecal ligation and puncture methods were used to induce sepsis. While ALT, AST, LDH, GGT and CRP values were analyzed from rat blood, MDA and GSH levels were analyzed from lung tissue.
Results: The results showed that quercetin reduced neutrophil infiltration (TLIS 3.5 [0.26] in the SEPS group vs TLIS 2.75 [0.29] in the SEPS+QUER group [*P*=0.01]), intra-alveolar macrophage count (SEPS vs SEPS+QUER [*P*=0.01]) and cell proliferation (SEPS vs SEPS+QUER [*P*=0.01]), and that it helped to preserve lung anatomy during sepsis. It was observed that MDA levels in the lung tissue decreased with the treatment of quercetin to septic rats (SEPS vs SEPS+QUER [*P*=0.046]).
Conclusion: These findings suggest that quercetin may be a potential treatment option for sepsis. However, more studies are needed to determine whether quercetin is a viable option as a therapeutic strategy in patients.

Keywords: sepsis, quercetin, acute respiratory distress syndrome, lung

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Introduction

Sepsis is a life-threatening response to infection, which typically starts in an organ and results in a dysregulated host response [1]. Sepsis can manifest as hypoxemia, inflammatory changes, tissue damage, or hypotension [2]. Acute lung injury (ALI) is a critical condition involving rapid-onset respiratory failure associated with intra- and extra-pulmonary causes. ALI is characterized by non-cardiogenic edema, severe systemic hypoxia, alveolar hemorrhage, pulmonary infiltration, and alveolar membrane changes. It particularly develops due to sepsis, shock, aspiration, and blood transfusion. The mortality rate for ALI is 18.0-54.7% [3].

The addition of lipopolysaccharides (LPS) stimulates the rat airways and causes the release of proinflammatory cytokines, which can result in apoptosis in epithelial and endothelial cells. This produces damage to the alveolar-capillary barrier, which causes an increase in permeability. This sequence of events instigates the migration of polymorphonuclear (PMN) cells to the lung. Tissue damage occurs through oxidative stress because activated PMN cells respond to infectious pathogens. Oxidative substances include superoxide anion, toxic metabolites, such as H_2O_2, hydroxyl radicals, and hypochlorous acid. Antioxidative enzymes work to protect the lung against the onslaught of oxidative damage [3,4]. Humans consume anti-inflammatory and antioxidant compounds such as flavonoids, which are naturally occurring and exhibit a wide range of biological effects through diet. Quercetin is a flavonoid widely found in nature, and it produces a wide anti-inflammatory, anti-proliferative, and antioxidant effect. Recent evidence suggests that quercetin can protect the lung against oxidative damage in different models of pulmonary injury [5,6]. The aim of this study was to investigate the efficacy of quercetin in sepsis-related lung injury and its protective and therapeutic effects on lung damage in sepsis.

Materials and methods

This study was carried out at Adıyaman University Experimental Animals Application and Production Center with the permission of Adıyaman University Animal Experiments Local Ethics Committee (Adyü-Hadyek) (2019/045). Thirty-two adult male Sprague Dawley rats weighing 280-300 grams were used. The sample size was identical to those in similar studies [4]. The animals were randomly divided into groups. The control group (CNRL) received 1.5 ml saline via the intragastric route. The quercetin group (QUER [n=5]) underwent no sepsis procedure and received 20 mg/kg quercetin via the intragastric route starting 15 days before the procedure. The sham group (SHAM [n=6]) underwent a surgical incision and received 1.5 ml intragastric olive oil (quercetin dissolves in oil). The sepsis group (SEPS [n=7]) underwent the sepsis procedure. The sepsis and quercetin group (SEPS+QUER [n=7]) underwent the sepsis procedure and received 20 mg/kg quercetin via the intragastric route for 15 days before the procedure. Cecal ligation and puncture methods were used to induce sepsis.

The rats in each group were kept in separate cages and housed at 22 ± 2°C with ad libitum access to food and water in a 12-hour light-dark cycle. Anesthesia was induced with the intramuscular administration of xylazine hydrochloride (20 mg/kg Rompun; Bayer Türk İlaç Ltd. Şti., Turkey) and ketamine hydrochloride (70 mg/kg Ketalar; Eczacıbaşı, Istanbul, Turkey) under veterinary supervision.

Euthanasia

The rats were euthanized 24 hours after the sepsis procedure. Prior to euthanasia, the rats were anesthetized using intraperitoneally xylazine hydrochloride at a dose of 20 mg/kg and ketamine hydrochloride at a dose of 70 mg/kg. Transcardiac perfusion using 0.9% sodium chloride was performed for the euthanasia. Intracardiac blood samples were taken after the induction of deep anesthesia for the biochemical analysis. The lung was rapidly removed following the euthanasia.

Administer of quercetin

20 mg/kg of quercetin was administered with olive oil and oral gavage (for 15 days) [7].

Sepsis model with cecal ligation

This model was described by Wichterman et al. [8] in 1980. Following induction of general anesthesia, the rat was placed in a supine position and fixed on the operating table. The skin was prepared and disinfected, and the cecum was exposed using a 2-cm abdominal incision from the front of the genital protrusion to the cranial region. The ileocecal valve was ligated distally and punctured twice with an 18 G needle from the anti-mesenteric edge. All layers were then sutured. The animals received subcutaneous fluid replacement.

Anesthesia

On the 16th day of the study, all rats scheduled for surgery were anesthetized by an intraperitoneal administration using 20 mg/kg xylazine hydrochloride (20 mg/kg Rompun; Bayer Türk İlaç Ltd. Şti., Turkey) and 70 mg/kg ketamine hydrochloride (70 mg/kg Ketalar; Eczacıbaşı, Istanbul, Turkey) under aseptic conditions.

Research parameters

Oxidant-antioxidant analysis was carried out on lung tissue samples. Blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP), and gamma-glutamyl transferase (GGT) levels were measured.

Tissue homogenates

Lung tissues were washed with 0.9% NaCl at 4°C. They were then cut into small sections according to cold chain principles and placed into Eppendorf pipettes. The tissues were homogenized with cold 1.15% KCl for MDA analysis [9].

Malondialdehyde analysis

Tissue MDA concentration is a lipid peroxidation marker. Tissue MDA was analyzed using the thiobarbituric acid reaction (TBARS) method [10-12]. After the homogenates were homogenized in 10% trichloroacetic acid, they were centrifuged. After the superficial liquid part was mixed with 0.67% thio-butyric acid in equal volumes, it was incubated in boiling water at 90°C for 15 minutes followed by cooling and centrifugation. Tissue MDA levels were measured for absorbance at 532 nm and expressed in units of nmol/g tissue.

Glutathione analysis

GSH analysis was performed according to Ellman's analysis [13]. The glutathione in the tube reacted with 5.5'-dithiobis 2-nitrobenzoic acid, producing a yellow-greenish color.

The light intensity of this color was read in the spectrophotometer at a wavelength of 410 nm. Reduced glutathione was measured.

Histopathological preparation

Lung tissues were fixed in 10% formaldehyde, embedded in paraffin, and subjected to histopathological examination. Sections 5 µm in thickness were taken from the blocks, stained with hematoxylin and eosin, and evaluated under an Olympus BX53 microscope.

The items descriptive for acute lung injury, namely interstitial edema, alveolar wall thickness, congestion, neutrophil infiltration, hemorrhage, intra-alveolar debris, and intra-alveolar macrophage and cell proliferation, were scored semi-quantitatively. Each finding was scored 0=none, 1=0-25%, 2=25-50%, 3=50-75%, or 4=75-100%. In addition, the total lung injury score (TLIS) was calculated as the average of the scores for each group divided by the number of rats in it.

Statistical analysis

The one-sample Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. Statistical comparisons were performed using one-way ANOVA or the Kruskal Wallis H test. The groups found to be significant in these tests were compared using the pairwise Mann Whitney U test or Tukey's multiple range test. Results were reported as mean, standard deviation (SD) or median (min-max). A p value less than 0.05 was considered significant. All analyses were performed using IBM SPSS Statistics 15.0 for Windows (New York; USA).

Results

One member of the quercetin group (QUER) died during the study period and was excluded from the experimental protocol.

Histopathological findings

The alveolar structure was normal in the CNRL group. Mild neutrophil infiltration, mild interstitial edema, congestion, hemorrhage, and intra-alveolar macrophages were observed in only one rat. The total lung injury score (TLIS) was 3. Very mild interstitial edema was observed in the QUER group, while the other structures were normal. No neutrophil infiltration was observed in any members of that group. The TLIS was 1.8. Slightly more interstitial edema, congestion, hemorrhage, and intra-alveolar macrophages were observed in the SHAM group compared to the CNRL and QUER groups. No neutrophil infiltration was observed. The TLIS was 5.8.

Very intense neutrophil infiltration and a significant increase in all other findings were observed in the sepsis group. The TLIS was 23.16 in the sepsis group. Decreases were determined in all findings in the SEPS+QUER group compared to the SEPS group. The TLIS was 18.5 in the SEPS+QUER group. TLIS was lower in the SEPS+QUER group than in the SEPS group. A detailed analysis of total lung scores between the SEPS and SEPS+QUER groups with the relevant p values is given in Table 1. Images reflecting the histopathological features of the groups are shown in Figure 1.

Table 1: The detailed scoring and p-values between the SEPS and SEPS+QUER groups total lung damage score

	SEPS (n=7) Mean (SD)	SEPS+QUER (n=7) Mean (SD)	*P*-value
Interstitial edema	3.33 (0.39)	2.75 (0.66)	0.19
Alveolar wall thickness	3.0 (0.43)	2.37 (0.42)	0.22
Congestion	3.16 (0.31)	2.62 (0.34)	0.24
Neutrophil infiltration	3.5 (0.26)	2.75 (0.29)	0.01
Hemorrhage	3.0 (0.27)	2.87 (0.34)	0.35
Intraalveolar debris	2.3 (0.24)	1.75 (0.25)	0.36
Intraalveolar macrophages	2.3 (0.19)	1.62 (0.17)	0.01
Cell proliferation	2.5 (0.21)	1.75 (0.18)	0.01

SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Lung oxidative stress and anti-oxidative response

Lipid peroxidation in lung homogenates was evaluated in terms of MDA levels. These increased significantly in the septic rats (CNRL vs SEPS [*P*=0.012]). Tissue MDA levels decreased significantly with the addition of quercetin to the sepsis group (SEPS vs. SEPS+QUER [*P*=0.046]).

Antioxidant activity was determined by levels of GSH in the lung tissues. GSH levels were significantly lower in the lung homogenates from septic mice (CNRL vs. SEPS [*P*=0.001]). Although the GSH levels in lung homogenates increased in the SEPS+QUER group, this was not statistically significant (SEPS compared to SEPS+QUER [*P*=0.35]).

Comparisons between the groups' tissue MDA and GSH levels are shown in Tables 2 and 3 and Figure 2.

Figure 1: Histopathological images from the study groups a- CNRL: An 40xH&E image of normal alveolar structures with mild edema. b- QUER: A 40xH&E image showing mild interstitial edema, and no neutrophils. c- SHAM: A 40xH&E image showing interstitial edema and intra-alveolar macrophages. d- SEPS: A 40xH&E image showing intense edema, neutrophilic infiltration, and intra-alveolar macrophages. e- SEPS: A 100xH&E image showing diffuse neutrophils in alveolar walls and erythrocytes in alveolar spaces. f- SEPS+QUER: A 40xH&E image showing diffuse neutrophils and edema in alveolar walls, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

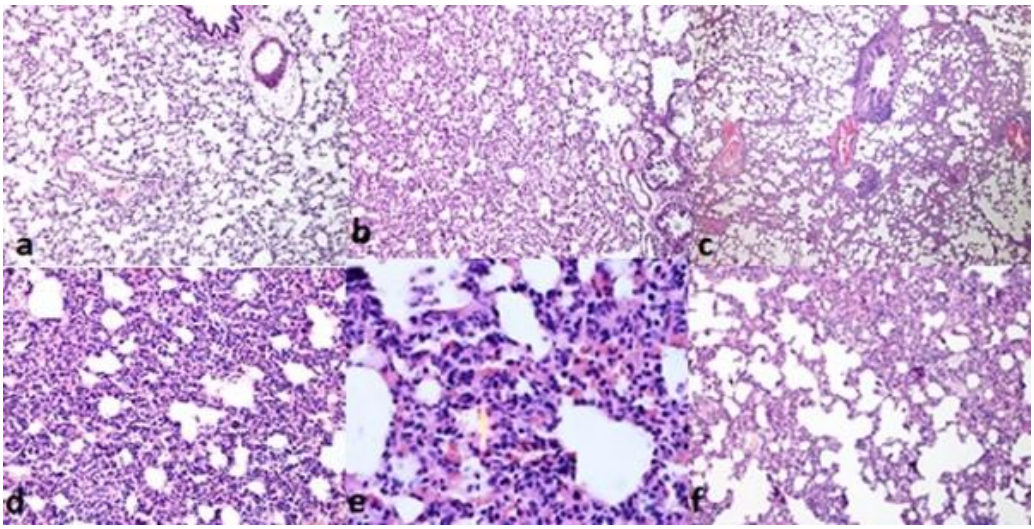
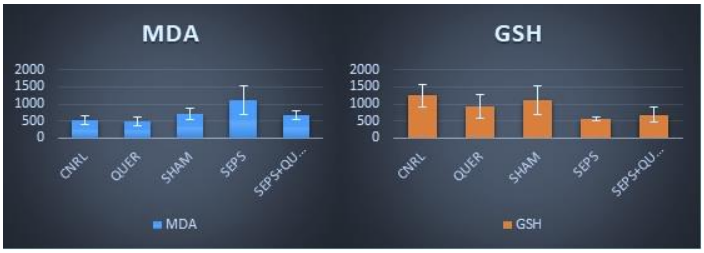


Figure 2: Tissue MDA and GSH levels in the study groups



MDA: malondialdehyde, GSH: Glutathione, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

ALT, AST, GGT, LDH, and CRP values

ALT values differed significantly between the control group and all groups except the SHAM and QUER groups. There was no significant difference between the SEPS, SEPS+QUER, CNRL, and QUER groups regarding AST values, but a significant difference was found between the other groups. The increase in LDH values in the SHAM, SEPS and SEPS+QUER groups was statistically different compared to all the other groups. No difference was observed between the SHAM, SEPS, and SEPS+QUER groups' LDH values. No difference between groups was determined in GGT or CRP values. Blood biochemistry values, intergroup comparisons, and p values are given in Tables 3 and 4.

Table 2: Comparison of MDA and GSH values between groups

	CNRL /SHAM	CNRL/SEPS	CNRL/SEPS+QUER	CNRL/QUER	SHAM/SEPS	SHAM/SEPS+QUER	SHAM/QUER	SEPS/SEPS+QUER	SEPS/QUER	SEPS+QUER/QUER
MDA	0.942	0.012	0.377	0.473	0.016	0.735	0.046	0.046	0.013	0.238
GSH	0.557	0.001	0.004	0.152	0.011	0.011	0.457	0.219	0.033	0.172

MDA: malondialdehyde, GSH: Glutathione, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Table 3: Comparison of ALT, AST, LDH, GGT, CRP, MDH and GSH values between groups

	Group (n)	Mean (SD)	*P*-value*
ALT (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	41 (15) 44 (13) 42 (11) 149 (97) 86 (21)	0.001
AST (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	121 (19) 107 (21) 170 (27) 740 (299) 672 (196)	0.001
LDH (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	713 (100) 768 (197) 1525 (495) 2243 (424) 1963 (1203)	0.001
GGT (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	8 (4) 6 (1) 6 (1) 8 (5) 5 (1)	0.38
CRP (mg/dL)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	0.15 (0.07) 0.13 (0.03) 0.13 (0.03) 0.15 (0.06) 0.18 (0.07)	0.45
MDA (nmol/g)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	524 (103) 716 (173) 1110 (420) 670 (121) 500 (121)	0.002
GSH (nmol/g)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	1244 (324) 1112 (423) 571 (50) 690 (217) 928 (345)	0.003

* One Way Anova, ALT: alanine amino transferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, GGT: gamma-glutamyl transferase, CRP: c-reactive protein, MDA: malondialdehyde, GSH: Glutathione, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Table 4: Comparison of ALT, AST and LDH between groups and *P*

	CNRT/QUER	CNTR/SHAM	CNTR/SEPS	CNRT/SEPS+QUER	QUER/SEPS	QUER/ SEPS+QUER	SHAM/QUER	SHAM/SEPS	SHAM/SEPS+QUER	SEPS/SEPS+QUER
ALT	1.00	0.818	0.001	0.001	0.003	0.005	0.931	0.001	0.002	0.097
AST	0.107	0.015	0.001	0.001	0.003	0.003	0.004	0.001	0.001	1.000
LDH	0.792	0.002	0.001	0.001	0.005	0.003	0.004	0.366	0.022	0.053

ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate Dehydrogenase, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Discussion

ALI is a sepsis-related pathological process [14]. Sepsis is one of the causes of apoptosis in the lung epithelium. Quercetin is a powerful anti-inflammatory and antioxidant [5,15]. The results of this study show that quercetin reduces the negative effects of sepsis on the lungs by lowering inflammation and oxidative stress.

ALI can occur directly as a result of lung pathologies or indirectly as a result of extrapulmonary pathologies. Sepsis, a common cause of ALI, is the leading in-hospital cause of mortality, resulting in some five million deaths per year. Sepsis increases vascular permeability and damages heart function and metabolic balance, thus leading to multiple organ failure and mortality [16,17].

LPS found in gram-negative bacteria occupies a significant place in the pathogenesis of sepsis [18-20]. Based on the current evidence, it appears that the development of sepsis is related to oxidative stress and reactive oxygen species (ROS). ROS causes cellular damage and is involved in the pathogenesis of sepsis [4]. Studies have shown that flavonoids can protect experimental animals against LPS-induced tissue damage or septic shock. Research has also shown that quercetin reduces TNF alpha and IL-1 levels and improves inflammatory responses. Studies have further reported that quercetin inhibits IL-8 production, TNF-α, and macrophages. Blockades of mitogen activated protein kinase and activation of nuclear factor-kappa B have been reported to not only protect mice from tissue damage, but also to reduce the production of proinflammatory cytokines. In addition, quercetin can inhibit nitric oxide (NO) formation, which is stimulated by activation of macrophages and microglia [16].

A previous study of the distribution of quercetin showed that it accumulates mostly in lung tissue. One study reported that quercetin blocks microglia activation and also protects neurons from inflammatory damage [21]. Yılmaz et al. [22] described that quercetin was effective against lung damage caused by aspiration. Sang et al. [23] showed that quercetin alleviated sepsis-induced ALI by suppressing oxidative-mediated ER stress by activation of SIRT1/AMPK pathways in rats with sepsis induced by the CLP method. Wang et al. [24] reported that lung injury in LPS-induced sepsis was alleviated by quercetin. Quercetin not only prevents sepsis-related lung injury but also reduces pulmonary fibrosis caused by silica dust [25], reduces oxidative damage caused by paraquat, a widely used herbicide [26], and has been shown to have the potential for use as a therapeutic agent in the treatment of *Pseudomonas aeruginosa*-induced inflammation by regulating IL-1β production in macrophages infected with the bacterium [27].

In the present study, quercetin suppressed inflammation in rats with sepsis and reduced the damage caused by ALI. Histological examination showed that quercetin reduced neutrophil infiltration, intra-alveolar macrophage numbers, and cell proliferation in rats with sepsis. Quercetin significantly reduced MDA levels in lung tissue and also lowered lipid peroxidation. However, it did not exhibit a comparable effect on GSH levels. However, an increase of GSH level, which indicates an anti-oxidative effect was observed in the present study, but there was no statistical difference. We believe that it may be depend on the quercetin dosage.

The functions of different organ systems are compromised when the severity of infection exceeds the body's ability to cope with it. Sepsis can lead to dysfunction in many organs and even death. The lungs are usually the first organ to be affected, while the organs most commonly affected by sepsis are the lungs, liver, and kidneys. There is a close relationship between the number of dysfunctional organs and mortality. Studies generally suggest that sepsis increases the levels of the enzymes described in this study [28,29]. The present study investigated the amount of quercetin, an antioxidant capable of reversing lung damage in sepsis. However, we also examined AST, ALT, and LDH values as indicators of liver damage, a common finding in sepsis. These three values were significantly higher in septic rats compared to the control group. Decreases were also observed in ALT, AST, and LDH values in rats with sepsis receiving supplementary quercetin, although these were not statistically significant.

Limitations

One possible limitation of our study might be the use of a lower dose of quercetin as compared to previous trials in the literature, which have employed much higher doses.

Conclusion

No antioxidant therapy, including quercetin use, has been approved for treating ALI caused by sepsis. However, the result of this study shows that a powerful antioxidant such as quercetin may have a place in the treatment of ALI. Therefore, further studies on quercetin use in patients with ALI are needed.

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