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Protective Effects of Luteolin on Lipopolysaccharide-Induced Acute Renal Injury in Mice

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Background: Sepsis can cause serious acute kidney injury in bacterium-infected patients, especially in intensive care patients. Luteolin, a bioactive flavonoid, has renal protection and anti-inflammatory effects. This study aimed to investigate the effect and underlying mechanism of luteolin in attenuating lipopolysaccharide (LPS)-induced renal injury.

Material/Methods: ICR mice were treated with LPS (25 mg/kg) with or without luteolin pre-treatment (40 mg/kg for three days). The renal function, histological changes, degree of oxidative stress, and tubular apoptosis in these mice were examined. The effects of luteolin on LPS-induced expression of renal tumor necrosis factor-α (TNF-α), NF-κB, MCP-1, ICAM-1, and cleaved caspase-3 were evaluated.

Results: LPS resulted in rapid renal damage of mice, increased level of blood urea nitrogen (BUN), and serum creatinine (Scr), tubular necrosis, and increased oxidative stress, whereas luteolin pre-treatment could attenuate this renal damage and improve the renal functions significantly. Treatment with LPS increased TNF-α, NF-κB, IL-1β, cleaved caspase-3, MCP-1, and ICAM-1 expression, while these disturbed expressions were reversed by luteolin pre-treatment.

Conclusions: These results indicate that luteolin ameliorates LPS-mediated nephrotoxicity via improving renal oxidant status, decreasing NF-κB activation and inflammatory and apoptosis factors, and then disturbing the expression of apoptosis-related proteins.

MeSH Keywords: Acute Kidney Injury • Inflammation • Lipopolysaccharides • Mice, Inbred C57BL

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Background

As important excretory organs, the kidneys are the preferential targets of xenobiotics such as drugs or environmental contaminants. Acute renal damage, characterized by acute tubular cell injury and kidney dysfunction, mainly develops following toxic or ischemic insults [1]. Severe sepsis and septic shock are the leading causes of acute kidney injury (AKI) in bacterium-infected patients receiving intensive care, accounting for almost 50% of AKI in these patients [2]. Septic patients with AKI have overall increased morbidity and prolonged hospital stays, consume more healthcare resources, and have increased mortality [3]. The pathophysiology of septic AKI is complex, involving multiple factors, and is distinct from that of non-septic AKI [4–8].

Lipopolysaccharide (LPS)-induced AKI is the most common model to study the septic nephropathy. So far, the mechanism of LPS-induced toxicity has not been clearly elaborated; it has been proposed to be multi-factorial in nature, with involvement of reactive oxygen species (ROS), apoptosis, and inflammation factors [9]. Enhanced production of ROS and decreased antioxidant enzymes are involved in the early stage of LPS-induced nephrotoxicity [10,11], which results in oxidative damage in different tissues and reactions with thiols in protein and glutathione that could cause cell dysfunction [12,13].

The activation of the TLR4 signaling pathway plays an important role in the pathogenesis of LPS-induced renal injury and damage [14]. This signaling pathway stimulates the expression of pro-inflammatory chemokines and cytokines such as interleukins (IL-1β, IL-18, IL-6) and tumor necrosis factor-α (TNF-α) in the kidney. Glomerular fibrin deposition occurs partially due to enhanced induction of nuclear factor-κ B and TNF-α in the kidney [15].

Luteolin is a secondary metabolite that exists widely in many plants; some used in traditional Chinese medicine e.g., honeysuckle, chrysanthemum, herba schizonepetae, and herba ajugae, are rich in luteolin. Researchers have showed that luteolin exhibits anti-inflammatory, antioxidant, and anti-carcinogenic activities [16–18]. Recent studies have shown that luteolin has a renal protective effect via attenuation of oxidative stress and inflammation in cisplatin-induced AKI in animals [19,20].

Based on previous studies, we speculated that luteolin may also be useful in ameliorating LPS-induced AKI. We also explored the possible mechanisms involved in Institute of Cancer Research (ICR) mice.

Material and Methods

Animal experiment

The experiments were carried out in accordance with the guidelines of Animal Ethics Committee of Tianjin Union Medicine Center. The ethics approval number was No. 20150137.

Healthy male ICR mice (20–22 g) were procured from SPF Laboratories (Beijing, China). The mice were caged under pathogen-free conditions with controlled temperature and humidity. Mice were given food and water ad libitum, and were divided into 4 groups (n=10 per group) after one week of acclimatization. In the control group, saline was given orally (10 mL/kg) for three consecutive days, and a single intraperitoneal (ip) injection of saline was given on the third day; the injection volume was 10 mL/kg. In the model group, saline was given orally (10 mL/kg) for three days, and a single ip injection of LPS (25 mg/kg) was given on the third day. In the LPS and luteolin group, luteolin (40 mg/kg/day) was given orally once daily for 3 days and a single ip injection of LPS was given on the third day. LPS was dissolved in the saline as 1 mg/mL. The luteolin-only group received oral administration of luteolin at a dose of 40 mg/kg. The body weight of mice was recorded each day.

Twenty-four hours after LPS injection, mice were sacrificed by decapitation at the end of the experiment, and blood samples were obtained by eye enucleation. The kidney were immediately harvested and processed; half of the samples were fixed in 4% buffered paraformaldehyde (pH 7.4) at 4°C overnight and embedded in paraffin for histopathological and immunohistochemical analysis. The remaining half were frozen in liquid nitrogen immediately for subsequent evaluation.

Laboratory examination

The obtained plasma samples were centrifuged at 900 *g* for 20 min and stored at –80°C. Serum creatinine (Scr) and blood urea nitrogen (BUN) activities were measured by the enzymatic kinetic method using commercially available kits (Jiancheng Pharmaceuticals, Nanjing, China), following the manufacturer's instructions.

Histopathology examination

Fixed renal samples were dehydrated using an alcohol series, cleared with xylene, and embedded in paraffin. Sections (5 μm) were stained with hematoxylin and eosin (H&E) and examined under light microscopy by experienced histologists in a blinded fashion. Five high-power fields of each section were assessed, and scores representing the approximate extent of necrotic area in the cortical proximal tubules were then averaged as mean ±SEM. The degree of damage was graded: 0 denoted no degeneration; 1 denoted minimal degeneration (10%

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involvement); 2 denoted mild degeneration (10–35% involvement); 3 denoted moderate degeneration (36–75% involvement); and 4 denoted severe degeneration (75% involvement).

TUNEL assay

The terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick end labeling (TUNEL) assay was used for *in situ* apoptosis with TUNEL reagent (Promega, Madison, Wisconsin, USA). In brief, 10 μm paraffin sections were treated with proteinase K 20 μg/mL and then incubated in a nucleotide mixture containing fluorescein-12-dUTP and TdT. Positive controls were pretreated with 1 U/mL DNases, and negative controls were incubated without TdT. Dark yellow apoptotic cells were counted under light microscopy (CX31, Olympus, Japan).

Measurement of oxidative and anti-oxidative parameters in kidney

Removed kidney tissues were weighed and washed with ice-cold saline, and then were homogenized in ice-cold saline (1:10, wt/vol). The homogenate was centrifuged at 12,000 g for 10 min at 4°C. The resultant supernatant was used to determine the activities of superoxide dismutase (SOD), malondialdehyde (MDA), reduced glutathione (GSH), and catalase using commercial kits (Jiancheng Pharmaceuticals, Nanjing, China) according to the instructions.

ELISA analysis of TNF-α, NF-κB, phosphorylated-NF-κB, ICAM-1, and MCP-1 in kidney tissues

Kidney levels of TNF-α, NF-κB, phosphorylated-NF-κB, ICAM-1, and MCP-1 were measured with an enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's instructions (R&D Systems, USA). Briefly, each kidney tissue was homogenized by phosphate-buffered saline (PBS) in a 1:10 concentration (1 g of tissue to 10 mL of PBS buffer). A monoclonal antibody specific for these proteins was pre-coated onto a microplate. The standards and test samples were then pipetted into the wells to allow binding of these proteins to the immobilized antibodies. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for these proteins was added to the wells. Following removal of unbound antibody-enzyme reagent through washing, a substrate solution was added to the wells and color was developed. The optical density of each well was measured at the wave length of 450 nm or 510 nm on a microreader (S190, Molecular Devices, USA). The concentration of each cytokine or chemokine was accordingly calculated.

Immunohistochemistry

After deparaffinization and rehydration, the kidney sections were treated with 3% H_2O_2 for 10 min to bleach endogenous peroxidases. After rinsing with PBS, sections were irradiated in 0.1 mol/L sodium citrate buffer (pH 6.0) in a microwave oven (medium-low temperature) for 20 min. Nonspecific binding sites were blocked with normal goat serum diluted in PBS, and the slides were then incubated overnight at 4°C with anti-mouse monoclonal antibodies against cleaved caspase 3 and BCL2 in a humid environment. They then were incubated in horseradish peroxidase (HRP)-conjugated secondary antibodies for 30 min at 37°C. After rinsing with PBS, the sections were incubated with labeled streptavidin-biotin for 30 min, then visualized with 3,3'-diaminobenzidine tetrachloride (DAB) and counterstained with hematoxyline. After rinsing, the sections were dehydrated with an alcohol series and cleared with xylene, mounted with DPX and coverslipped, and then examined by light microscopy.

Statistical analysis

Histopathology data were expressed as mean ±SEM and compared by one-way analysis of variance (ANOVA) with post hoc tests to the LPS-treated group. Data from biochemical analysis and ELISA were presented as mean ±SEM and analyzed by student's t-test. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was carried out using GraphPad Prism 5.0 (GraphPad Software, San Diego, California, USA).

Results

Luteolin improves biochemical indices of renal function

BUN and Scr levels in LPS-treated mice increased 2.93- and 2.10-fold compared with those in the normal mice (38.94±4.05 *vs.* 13.28±1.38 mg/dL, 3.68±0.37 *vs.* 1.75±0.11 mg/dL; $P<0.05$), which indicated the induction of severe septic nephropathy. Compared with the model group, SCr levels markedly decreased by 38.5% with luteolin treatment, and BUN levels decreased by 46.5% in luteolin group (Table 1). The luteolin alone did not change the renal functions.

Luteolin ameliorates oxidative stress in LPS-challenged kidney tissues

As we can see from Table 2. LPS induced a significant increase in the MDA level compared with the normal group (86.3±4.52 *vs.* 38.2±2.53 nmol/g; $p<0.01$). Meanwhile the antioxidant indices of GSH, catalase, and SOD activities showed significant reductions compared with the normal group ($P<0.05$). On the other hand, treatment with luteolin significantly maintained MDA and GSH levels compared with those in the model group, together with increased activities of catalase and SOD enzyme ($P<0.05$). The luteolin alone did not produce a significant oxidative change in the mouse kidney.

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Table 1. Blood urea nitrogen and Scr values at the post-treatment with the luteolin in LPS-induced AKI model.

Groups	Control	LPS model	LPS + luteolin	Luteolin
N	10	10	10	10
BUN (mg/dl)	13.28±1.38	38.94±4.05#	20.82±2.35**	14.74±1.52
Scr (mg/dl)	1.75±0.11	3.68±0.37#	2.26±0.24*	1.84±0.15

# $p<0.05$, compared with the normal control rats; * $p<0.05$, ** $p<0.01$, compared with the LPS-induced AKI rats.

Table 2. Luteolin improve the oxidative stress condition.

Groups	Control	LPS model	LPS + luteolin	Luteolin
N	10	10	10	10
GSH (mmol/g tissue)	5.48±0.13	2.09±0.12#	4.25±0.18**	5.35±0.14
MDA (nmol/g tissue)	38.2±2.53	86.3±4.52#	54.4±7.81**	37.5±0.89
SOD (U/mg protein)	14.3±0.96	6.96±0.78#	11.34±0.54**	13.3±0.34
Catalase (U/mg protein)	8.2±0.53	3.5±0.32#	6.7±0.45**	8.8±0.36

# $p<0.05$, compared with the normal control rats; * $p<0.05$, ** $p<0.01$, compared with the LPS-induced AKI rats.

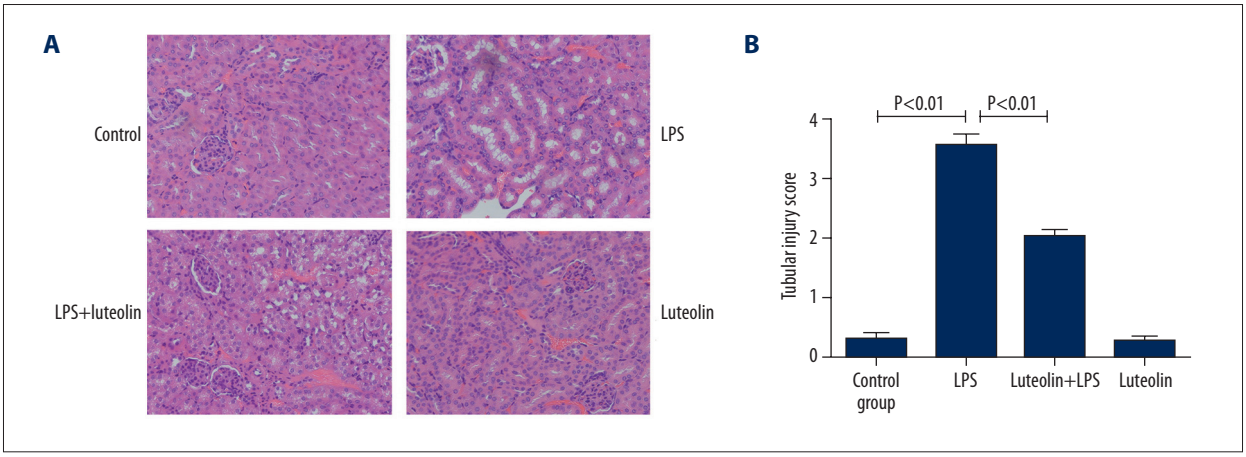

Figure 1. Effect of luteolin on LPS-induced renal tubular damage. (**A**) Histologic sections of kidney at 24 h after treatment with control buffer, LPS, and LPS plus luteolin (200×). (**B**) Histopathological scoring of tubular injury was concomitant with histologic analysis (n=10 for each experimental group). Data are expressed as mean ±SEM. # P < 0.05 *vs.* control; * P<0.05, ** P<0.01 *vs.* LPS.

Luteolin improves the histology of LPS-treated mice

The normal glomerular and tubular structure could be seen in both the cortical and medullary regions of the kidney in the control group (Figure 1A). In the LPS-treated group, we observed severe diffuse acute tubular necrosis and desquamation and parenchyma degeneration in the cortex, including tubular congestion and swelling, loss of brush border, tubular cell necrosis, tubular nuclear pyknosis, tubular cell flattening, and severe invasion of inflammatory cells within the interstitium and the perivascular and subvascular areas (Figure 1A). Mice treated with luteolin at 40 mg/kg demonstrated significant reduction of injury (Figure 1A). The histological scores also showed increased tubular injury after LPS treatment, which was significantly reversed by luteolin treatment (Figure 1B).

Luteolin attenuates LPS-induced apoptosis in the kidney

TUNEL staining apoptotic cells are shown in Figure 2. There were almost no TUNEL-positive cells in normal mice and luteolin-treated controls. The number of TUNEL-positive cells was significantly increased after LPS treatment compared with the vehicle-treated control group. Luteolin administration significantly decreased the number of LPS-induced TUNEL-positive cells.

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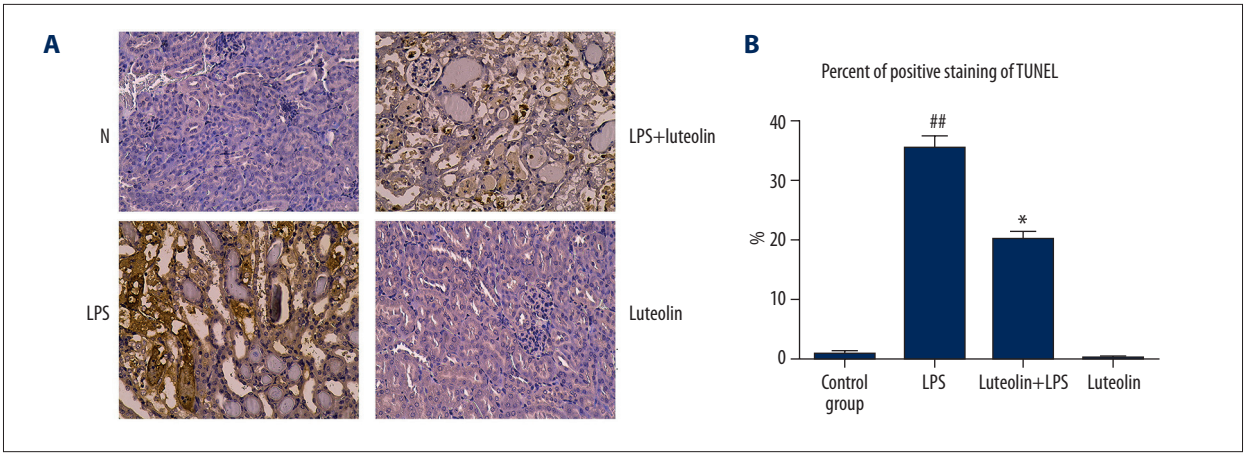

Figure 2. DNA fragmentation was visualized *in situ* by the TUNEL procedure by light microscopy. (**A**) Representative TUNEL figures. (**B**) Quantitation analysis. Data are expressed as mean ±SEM. # P<0.05 *vs.* control; * P<0.05, ** P<0.01 *vs.* LPS.

Luteolin regulates expression of TNF-α, NF-κB, ICAM-1, MCP-1 and IL-1β

As shown in Figure 3, we demonstrated by ELISA that the protein expression of inflammatory factors including TNF-α, p-NF-κB, ICAM-1, MCP-1, and IL-1β was significantly increased in the LPS-treated group compared with the normal group. However, expression of these proteins was alleviated significantly by luteolin, and luteolin alone did not cause an increase of pro-inflammatory cytokines and chemokines. Total NF-κB did not change much among these four groups.

Luteolin suppresses cleaved caspase-3 in LPS-treated mice

The distribution of cleaved caspase-3 in kidney sections was assessed by immunohistochemistry (Figure 4). We observed slight staining of cleaved caspase 3 in cortical and medullar structures of kidney in the control group. In the LPS group, diffuse and strong cleaved caspase-3 staining could be seen in all proximal and distal tubules in the renal cortex. The positively stained cells exhibited morphologic changes that were associated with apoptosis (pyknotic, shrunken cell with condensed nucleus). The activation of caspase-3 was dramatically reduced by luteolin treatment, while luteolin alone did not cause visible injury.

Discussion

In this study, we assessed the protective effects of luteolin using an LPS-induced mouse nephropathy model. Results showed that luteolin could reduce LPS-induced oxidative stress, local inflammation, and tubular apoptosis, which were aggravated in the pathogenesis of renal dysfunction. The luteolin acted through reduction of an LPS-induced increase in expression of inflammatory signals including TNF-α, p-NF-κB, MCP-1, and IL1β, and expression of apoptotic signals including caspase 3 protein.

Systemic inflammation mediates organ dysfunction during sepsis. Excessive inflammation plays a major role in the initiation of kidney damage and deterioration of kidney function4[21]. Pro-inflammatory cytokines are major mediators of sepsis-induced AKI [22]. Pro-inflammatory mediators are known to regulate acute inflammation by activating the JAK-stat3 signaling [23] and NF-κB pathways [24]. Controlling pro-inflammatory mediator production and downstream pro-inflammatory mediators could be an effective approach to treat inflammatory kidney injury [25]. However, how to regulate inflammatory signaling in sepsis-induced AKI remains largely unknown.

Antioxidants, modulators of nitric oxide, diuretics, and anti-apoptotic agents are current strategies for ameliorating or preventing LPS nephrotoxicity [26]. Nowadays, attention has focused on discovering natural, original compounds for protecting against renal injury, as well as accelerating tubular cell regeneration. Luteolin is the main bioactive component of *Epimedium brevicornum,* and it has attracted much attention due to effects on invigorating the kidney in China. Luteolin has a protective effect on the early stage of experimental diabetic nephropathy via modulating TGF-β1 and type IV collagen expression in rats [27]. There is also a report about its protective effect against LPS-induced acute inflammatory responses via the PI3K/Akt and NF-κB signaling pathway [28]. Therefore, we explored the potential pharmacological actions exerted by luteolin in mice with LPS-induced renal injury and the possible mechanism involved.

In this study, a single injection of LPS in the mouse model induced renal morphological changes, including tubular necrosis desquamation and degeneration in the proximal and distal tubules, as well as an increased number of TUNEL-positive

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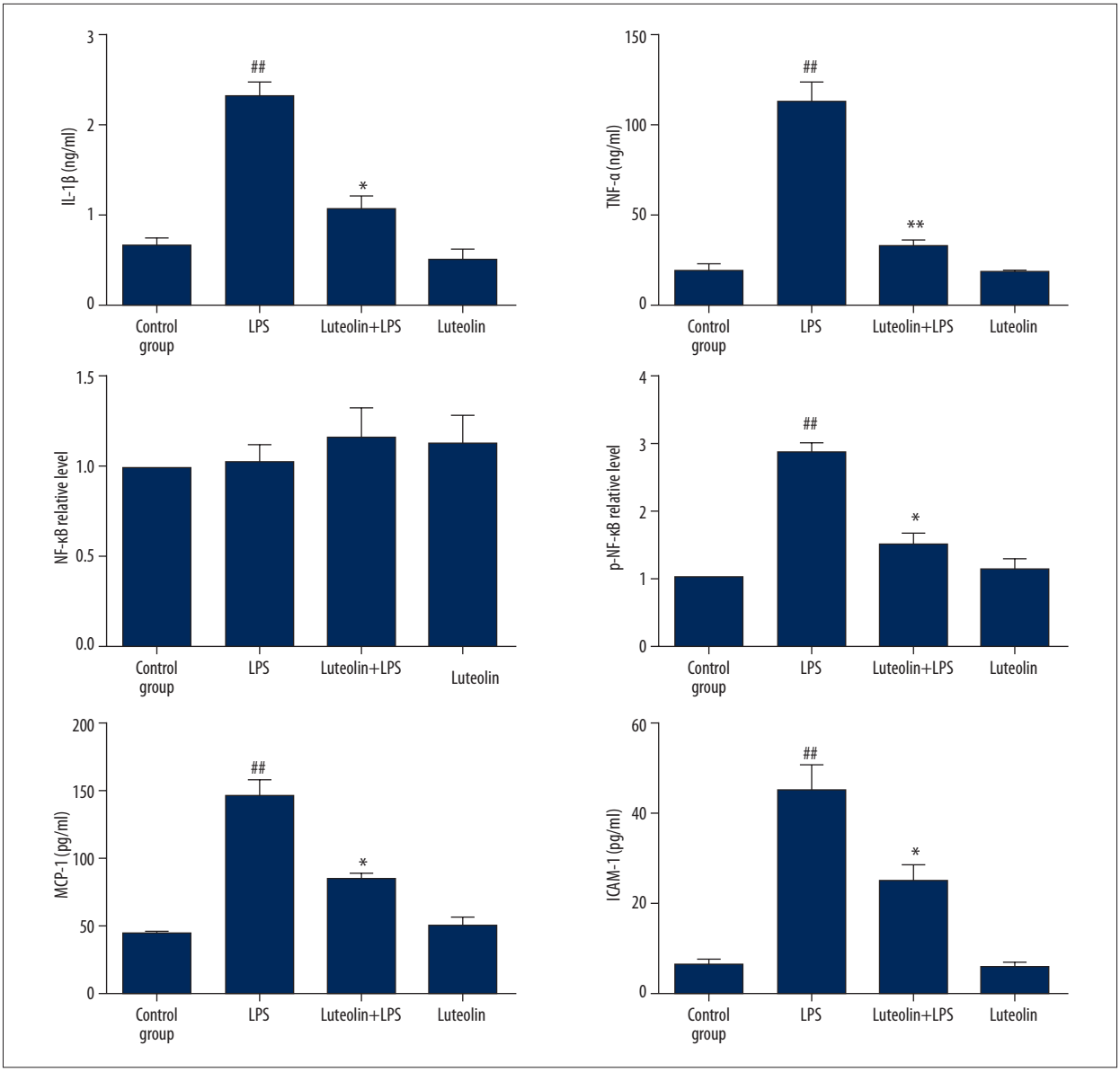

Figure 3. Effect of luteolin on LPS-induced TNF-α, total NF-κB, p-NF-κB, IL1β, MCP-1 and ICAM-1 protein expressions. Kidneys from mice treated with control buffer, LPS, and LPS plus luteolin were evaluated for protein expressions by ELISA analysis. Data are expressed as mean ±SEM. # P<0.05 *vs.* control; * P<0.05, ** P<0.01 *vs.* LPS.

cells. This usually resulted in disturbed renal function, which was also confirmed in our examination of biochemical parameters (elevated BUN and Scr levels, and renal cortical MDA level, as well as reduced kidney GSH level, catalase, and SOD activities). Induction of nephrotoxicity by LPS is a rapid process that occurs within 4 h following administration. Luteolin administration started 2 days before LPS administration in the present study. Results showed luteolin significantly shifted all the measured biochemical parameters toward normalcy, and it attenuated necrotic damage, which suggests protective effects on kidney function and histology.

Previous mechanistic studies about LPS-induced nephropathy demonstrated variously implicated key upstream events. Previous research demonstrated that increased oxidative stress was one of the earliest features that leads to lipid peroxidation and GSH depletion [10,12]. Treatment of LPS-treated mice with luteolin alleviated the disturbed renal oxidant status, which could partially be attributed to the protective action of luteolin at an early stage of LPS-induced nephrotoxicity.

NF-κB activation is associated with increased ROS generation and is pivotal in the consequent expression of pro-inflammatory cytokines like TNF-α, adhesion molecules (such as

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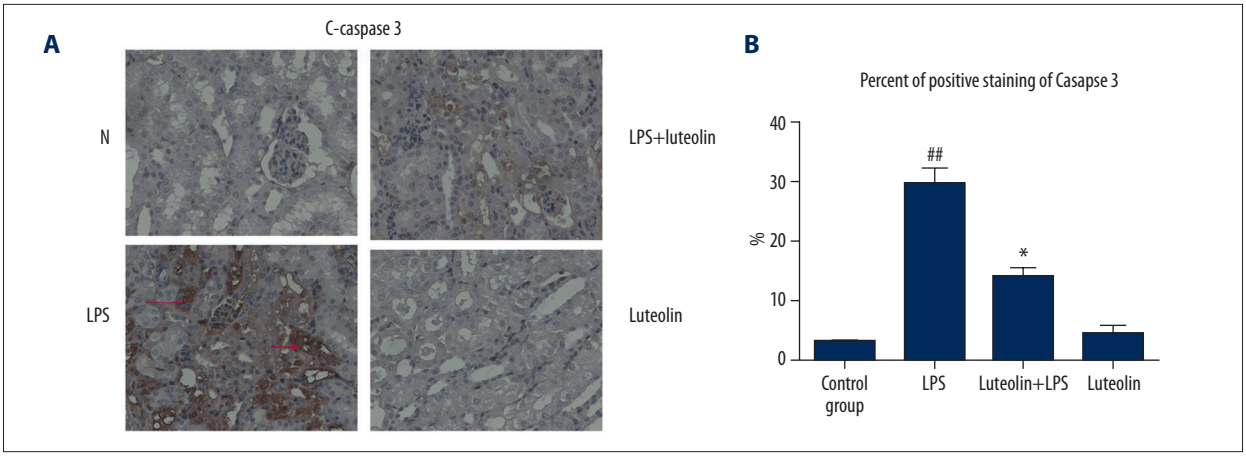

Figure 4. (**A, B**) Effect of luteolin on immunohistochemical stain of cleaved caspase 3 in LPS-induced mice. The brown area is the positive expression area, indicated by the red arrow (200×). Data are expressed as mean ±SEM. # P<0.05 *vs.* control; * P<0.05, ** P<0.01 *vs.* LPS.

ICAM-1) [29], and the pro-apoptotic proteins (caspase family) [30]. LPS treatment activated NF-κB translocation into the nucleus and increased TNF-α mRNA via p38 MAPK [31]. These chemokines may then facilitate migration and infiltration of inflammatory cells and a secondary wave of ROS generation, and further amplify the inflammatory cascade and injury [32]. In this study, luteolin suppressed the release of TNF-α from the activated immune cells through attenuating NF-κB activation. It is likely that the protective effect of luteolin is mediated in part by its anti-inflammatory effect.

NF-κB activation has been known to regulate various cellular responses, including apoptosis. It was reported that apoptosis could aggravate the pathogenesis of nephrotoxicity via caspase 3 expression [25]. In the current study, LPS-mediated activation of caspase-3 was attenuated by luteolin. All these observations indicate the protective effect of luteolin on LPS-induced renal tubular apoptosis via modulating expression of caspase 3.

There are still some limitations of the LPS-induced AKI model. Firstly, the LPS model mimics the clinical conditions of bacterium infection sepsis in young patients. However, animal models of sepsis differ from human sepsis because of age, comorbidity, and use of different supportive therapy [33]. Secondly, the LPS AKI model is a simple sepsis model; it is difficult to reflect the complicated clinical conditions, and the animal's responsiveness is different than a human's. Thirdly, in the current study, we used the pre-treatment method to prevent LPS-induced AKI, while in the clinical practice, most therapy strategies are conducted after sepsis occurrence. Fourthly, some researchers reported that immunotherapy for sepsis based on cytokine production after LPS challenge is misdirected because the LPS model does not accurately reproduce the cytokine profile of sepsis [34]. Based on these above limitations, the potential of luteolin to alleviate sepsis-induced AKI needs further study, especially in testing its efficiency in cases of delayed treatment.

Conclusions

In the present study with the LPS-induced AKI model, we found preliminary evidence that pre-treatment with luteolin can improve renal function and attenuate renal injury and apoptosis of tubular cells. Further study of the mechanism of action showed that luteolin can decrease oxidative stress and inhibit NF-κB over-activation, which probably consequently blocks the inflammation cascade and caspase 3-mediated apoptosis.

Conflicts of interest

The authors declare no conflict of interest.

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