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Comparative Analysis of Curcumin and Metformin Effects on the Kidney in a Model of Unilateral Nephrectomy and Ischemia-Reperfusion Injury

Samaneh Karimi[1], Farhad Koohpeyma[2], Layasadat Khorsandi[3,4], Armin Panahi[3], Fatemeh Rezaei-Tazangi[5], Fereshtesadat Fakhredini*[3,4]

Abstract

Background: Unilateral nephrectomy and renal ischemia-reperfusion injury (I/R) are causes of acute kidney injury that can cause renal dysfunction, decreased glomerular filtration rate, impaired homeostasis, and increased mortality. This study aimed to evaluate the combined effects of curcumin (Cur) and metformin (Met), both protective antioxidants, on renal tissue structure and Neutrophil gelatinase-associated lipocalin (Ngal) and Kidney injury molecule 1 (Kim-1) genes expression levels in rats undergoing unilateral nephrectomy and ischemia/reperfusion.

Methods: In this experimental study, 40 male rats were randomly divided into five groups. The animals underwent unilateral nephrectomy and ischemia/reperfusion and were then treated with curcumin and metformin or both for 14 days. Subsequently, histopathological and morphometric analyses were performed, and Ngal and Kim-1 gene expression levels were evaluated using real-time PCR.

Results: Histopathological damage, expression levels of blood urea nitrogen (BUN), creatinine (Cr), blood biochemical parameters and oxidative stress and expression levels of Ngal and Kim-1 genes were significantly reduced in the patient group that received metformin and curcumin simultaneously. However, total antioxidant capacity (TAC) was increased in the patient group that received curcumin + metformin. Morphometric parameters also improved in this group.

Conclusion: The results showed that the combination therapy with curcumin and metformin effectively protected the kidneys against unilateral nephrectomy and I/R injury.

Keywords: Curcuminoid, Ischemia-reperfusion injury, Metformin, Unilateral nephrectomy.

Introduction

Unilateral nephrectomy and ischemia-reperfusion injury (IRI) are important pathological conditions that occur due to obstruction of urinary tract obstruction and a reduced effective blood supply to the kidneys, respectively, and affect the morphology of the kidney tissue, especially the tubules and the expression of genes related to kidney development (1-5).

New biomarkers for the diagnosis of kidney injury are Kidney Injury Molecule-1 (Kim-1) and Neutrophil Gelatinase-Associated

1: Department of Anatomical Sciences, School of Medicine, Abadan University of Medical Sciences, Abadan, Iran.
2: Student Research Committee, Endocrinology and Metabolism Research Center, Shiraz University of Medical Science, Shiraz, Iran.
3: Cellular and Molecular Research Center, Medical Basic Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
4: Department of Anatomical Sciences, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
5: Department of Anatomy, Faculty of Medicine, Fasa University of Medical Sciences, Fasa, Iran.
***Corresponding author: Fereshtesadat Fakhredini; Tel: +98 9163474600; E-mail: ffakhredini_aot@yahoo.com.**
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Lipocalin (Ngal) (6). Kim-1 is a membrane glycoprotein expressed in epithelial cells of the damaged proximal tubules in the kidney. Under normal conditions, the kidney does not secrete this protein; it is only secreted by the kidney when injury occurs (6). Another novel biomarker for the detection of kidney injury is Ngal. It binds to neutrophils and is produced by neutrophils and epithelial cells. In addition, Ngal expression is rapidly increased in ischemic or nephrotoxic kidney injury and is also secreted by the proximal convoluted tubule, loop of Henle, and collecting duct in the kidney (7). Ngal can be measured in plasma, serum, and urine as early as two hours after renal injury, making it an early, sensitive, and non-invasive biomarker. Reports have shown that following cisplatin-induced nephrotoxic injury, urinary Ngal increases within 3 hours of cisplatin administration (8). The demand for alternative treatments and herbal medicines has risen due to the complications caused by the prolonged use of industrial drugs, as well as the high costs imposed on patients. Several research studies have been done in the field of using herbal medicines or chemical compounds with fewer side effects to improve disorders caused by kidney and liver diseases (9, 10).

Curcumin, a yellow polyphenolic pigment, is the primary active compound found in the stem of the turmeric plant. The properties of curcumin include anti-inflammatory, antioxidant, and anticancer effects. It has been shown to mitigate damage caused by ethanol, thioacetamide, cholestasis, and carbon tetrachloride poisoning. In addition, it exhibits protective properties against neurological diseases and diabetes. It also has a protective effect against cerebral ischemia due to its ability to cross the blood-brain barrier (11). A study found that gentamicin causes damage to kidney function and leads to a significant increase in the expression of Nagel and Kim-1 in the plasma of the group receiving gentamicin. The same study demonstrated that animals treated with curcumin showed significant improvement in kidney function parameters, including reduced kidney tubule damage, decreased apoptosis, and lower oxidative stress (12).

Recently, the possible effects of metformin in protecting the kidneys have attracted much attention, and many studies have proven its antioxidant properties (13, 14). Research has shown that metformin can ameliorate renal tubular damage caused by gentamicin (15, 16). A clinical trial in this area investigated the effects of metformin on markers of kidney damage, such as including Ngal in doxorubicin-induced nephrotoxicity. This study showed that metformin reduced renal Ngal levels, indicating potential protective effects on kidney function (17). Additionally, studies have demonstrated the inhibitory effects of curcumin on Ngal and Kim-1 expression in response to inflammatory stimuli, further supporting its potential anti-inflammatory properties (18, 19).

The rising number of individuals with kidney disorders or in need of kidney transplants, along with the demand for cost-effective medications with fewer side effects, underscores the necessity of this study. It is imperative to expand the knowledge of the possible effects of curcumin and metformin on improving the side effects caused by unilateral nephrectomy and ischemia/reperfusion damage on kidney tissue structure.

Materials and Methods

Animals

This experimental study was carried out on 40 adult male Sprague-Dawley rats, which were randomly selected. The animals were housed at a temperature of 20–22 °C, with a 12-hour light/12-hour dark cycle and relative humidity maintained between 40% and 60%. They were kept in polycarbonate cages with steel mesh roofs, and the bedding was covered with cloth. Cage floors were cleaned daily, and the cages were disinfected weekly.

The animals were randomly allocated into five groups of 10.

Control group: The animals had access to water and normal food.

I/R group: The animals underwent unilateral nephrectomy, followed by ischemia of the contralateral kidney using a clamp for 30 minutes. Three days later, the animals were dissected.

I/R + Cur group: In this group, the animals underwent unilateral nephrectomy, then were treated with curcumin (100 mg/kg) (20) for 14 days (21). After the treatment period, the contralateral kidney was subjected to 30 minutes of ischemia using a clamp, and the animals were dissected three days later.

I/R + Met group: In this group, the animals underwent unilateral nephrectomy and then received metformin (250 kg/mg) (22) for 14 days (23). Then, the kidney on the opposite side was ischemia for 30 minutes with a clamp, and the animals were dissected 3 days later.

I/R + Cur + Met group: The animals underwent unilateral nephrectomy and were treated with a combination of curcumin (100 mg/kg) and metformin (250 mg/kg) for 14 days. After the treatment period, the contralateral kidney was clamped for 30 minutes to induce ischemia, and the animals were dissected three days later.

Surgical Procedures

Unilateral Nephrectomy

First, the animals were anesthetized with intraperitoneal (IP) injection of ketamine (80 kg/mg) and xylazine (5 mg/kg). After making a longitudinal cutting on the abdomen of the animals, the blood vessels entering the right kidney of the animal were ligated using absorbable surgical thread. Then the kidney was removed, and finally, the surgical site was sutured.

Ischemia/Reperfusion

After 14 days of unilateral nephrectomy, to induce ischemia/reperfusion, the animals were again anesthetized by IP injection of ketamine and xylazine solution. This time, on the left side of the abdomen, after making a longitudinal incision, the blood vessels entering the left kidney were occluded using a clamp for 30 minutes. After creating ischemia, the clamp was removed, and the surgical site was sutured. Reperfusion continued for 72 hours after ischemia. Moreover, oral gavage was done during these three days.

Biochemical Analysis

To measure serum markers, blood samples were collected from the heart and centrifuged at 3500 rpm for 15 minutes. The isolated serum was evaluated by diagnostic kits to measure creatinine, BUN, uric acid, Malondialdehyde (MDA), TAC, Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1β) and lactate dehydrogenase (LDH). Following the collection of blood samples and the biochemical analyses, the animals were sacrificed for further investigation.

Histopathological studies

The kidney tissue of the animals was separated and, after being rinsed with normal saline, was placed in 10% formalin. After the fixation process, tissue processing steps were performed, and 5-µm sections were prepared. Slides were stained with hematoxylin-eosin (H&E) staining and then studied histologically under a light microscope (24).

Morphometric analysis

Tissue processing was performed using Motic software (Micro-Optic Industrial Group Co. Ltd., UK). **Subsequently**, morphometric features such as kidney volume, cortex, medulla, necrotic and inflammatory tissues, glomerulus, proximal convoluted tubule (PCT), distal convoluted tubule (DCT), collecting ducts, loops of Henle and vessels were analyzed.

Molecular Studies

The kidney tissue was separated from the surrounding tissues and placed in liquid nitrogen for molecular analysis. Subsequently, to measure the expression of genes, total RNA was extracted from kidney tissue using a **commercial** RNA extraction kit and quickly frozen at -70 °C, and then RNA quality was checked using 1% agarose gel electrophoresis. The concentration of RNA was measured using a NanoDrop device. After measuring the standard of RNA quality and quantity, cDNA synthesis was done using a cDNA strand synthesis kit. The expression levels of Ngal and Kim-1 gene was calculated relative to the Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, and finally the target genes were normalized using the internal control gene (GAPDH) and compared to other groups.

Primers for the Kim-1 gene (NM_173149, forward primer: TGGCACTGTGACATCCTCAGA; reverse primer: GCAACGGACATGCCAACATA), for NGAL gene (NM_005564, forward primer: TCCCAGAGCTGAACGG; reverse primer: GAAGTCGCGGAGACA) and the housekeeping GAPDH (NM_017008, forward primer: CCTGGAGAAACCTGC-CAAGTAT; reverse primer: AGCCCAGGATGCCCTTTAGT were used.

Statistical Analysis

The data were analyzed using SPSS (version 21.0). Subsequently, one-way ANOVA followed by the post hoc LSD test was performed. Results were presented as mean ± standard deviation (SD), and differences were considered statistically significant at $p< 0.05$.

Results

Histology

The structure of the kidney tissue in the control group was normal and no pathological damage was observed. In the I/R group, cell swelling, and degeneration were observed in the urinary tubules, along with pyknotic nuclei, and tissue necrosis and the loss of brush border (large arrow) in the kidney tissue. In addition, a significant increase of tissue inflammation (arrowhead), along with congestion and interstitial and intratubular hemorrhage (*) were observed. Hyaline casts (small arrow) were also present in the tubules of kidney tissue in the I/R group. The level of necrosis and inflammation was reduced in the groups treated with curcumin and metformin, with the most notable improvement observed in the group receiving curcumin + metformin simultaneously (Fig. 1).

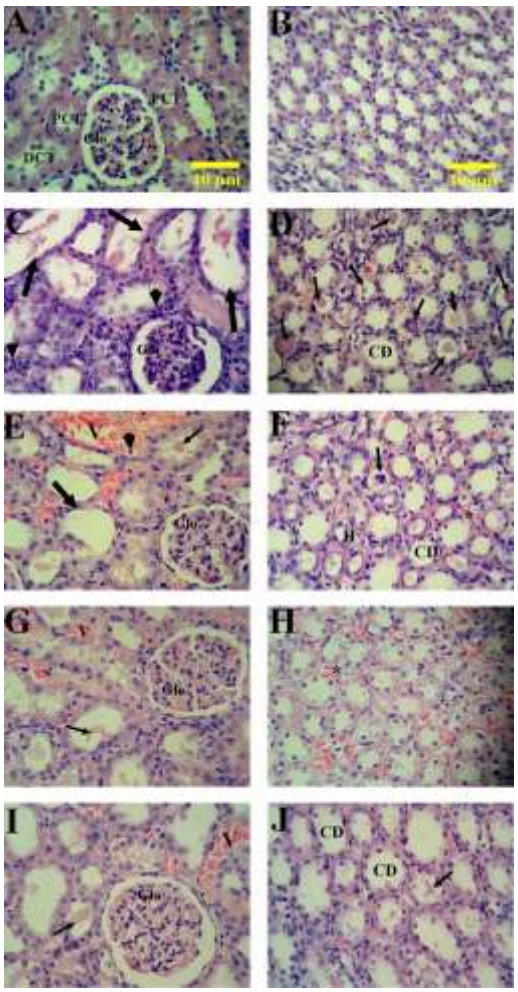

Fig. 1. Renal histopathological microscopic image in experimental groups. Hematoxylin Eosin staining ×400. A (cortex) and B (medulla): Control. C and D: I/R. E and F: Curcumin group. G and H: Metformin. I and J: Curcumin+ Metformin. Glo: glomeruli, DCT: Distal convoluted tubule; PCT: proximal convoluted tubule; H: Henle's loop; CD: Collecting ductus; V: Vessel. Big arrow: brush border; Arrowhead: tissue inflammation; Small arrow: hyaline casts.

Morphometric analysis

The kidney weight and volume in I/ R, I/R + Cur, I/R + Met, and I/ R+ Cur +Met groups were significantly more than the control group. No significant difference was seen between the weight and volume of all I/ R, I/R + Cur, and I/R + Met groups. Kidney weight and volume in the I/ R+ Cur + Met group decreased significantly compared to the I/R group.

In the I/R, I/R + Cur, I/R + Met, and I/ R+ Cur + Met groups, the volume of the cortex and the medulla increased significantly compared to the control group. While these four groups were not significantly different from each other.

The volumes of necrotic and inflammatory tissue in the I/ R, I/R + Cur, I/R + Met, and I/ R+ Cur + Met groups was significantly more than the control group. In the I/R + Cur, I/R + Met, and I/R + Cur + Met groups, the volume of necrotic tissue and the inflammatory volume were significantly lower compared to the I/R group (Fig. 2).

The volumes of the glomeruli, proximal convoluted tubules (PCTs), distal convoluted tubules (DCTs), collecting ducts, Henle's loops, and vessels in the I/R group were significantly higher than the control group. Treatment with curcumin and metformin alleviated these parameters, such that the volumes were lower in the I/R + Met group compared to the I/R + Cur group, and even lower in the I/R + Cur + Met group than in the I/R + Met group (Fig. 3).

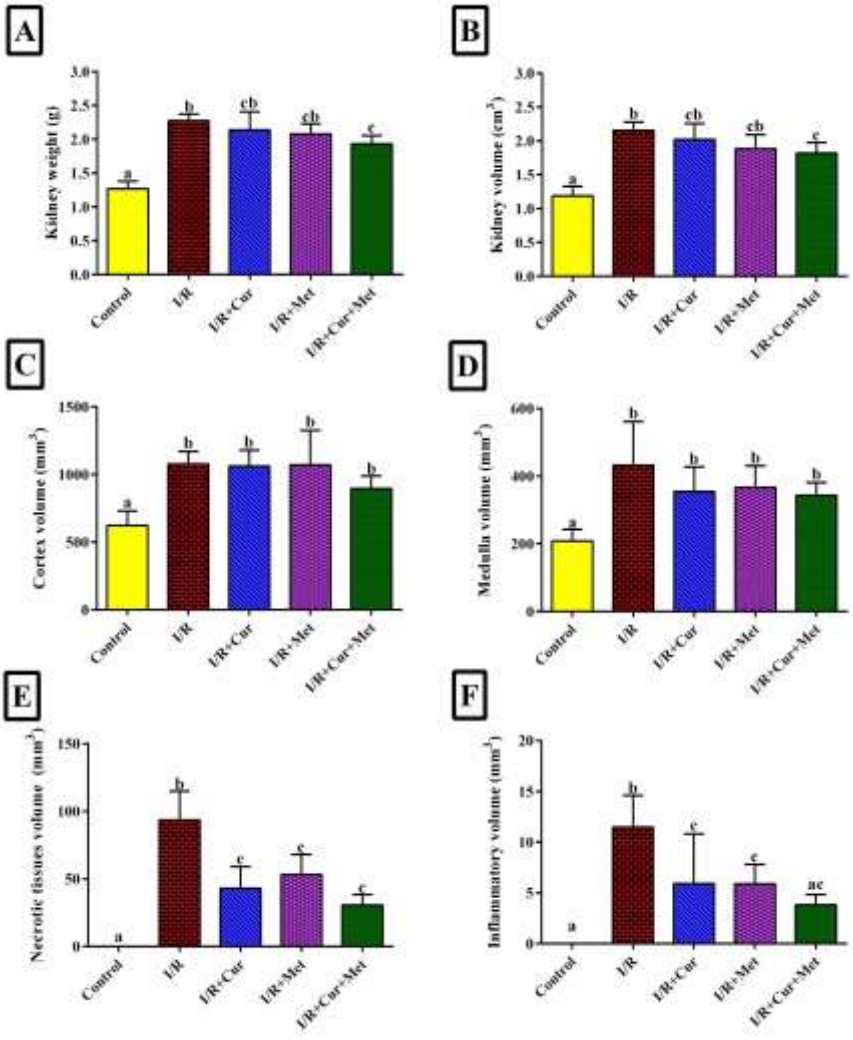

Fig. 2. Morphometric parameters in different groups. No significant difference between the groups that have at least one similar letter. Different letters indicate significant differences ($p < 0.05$).

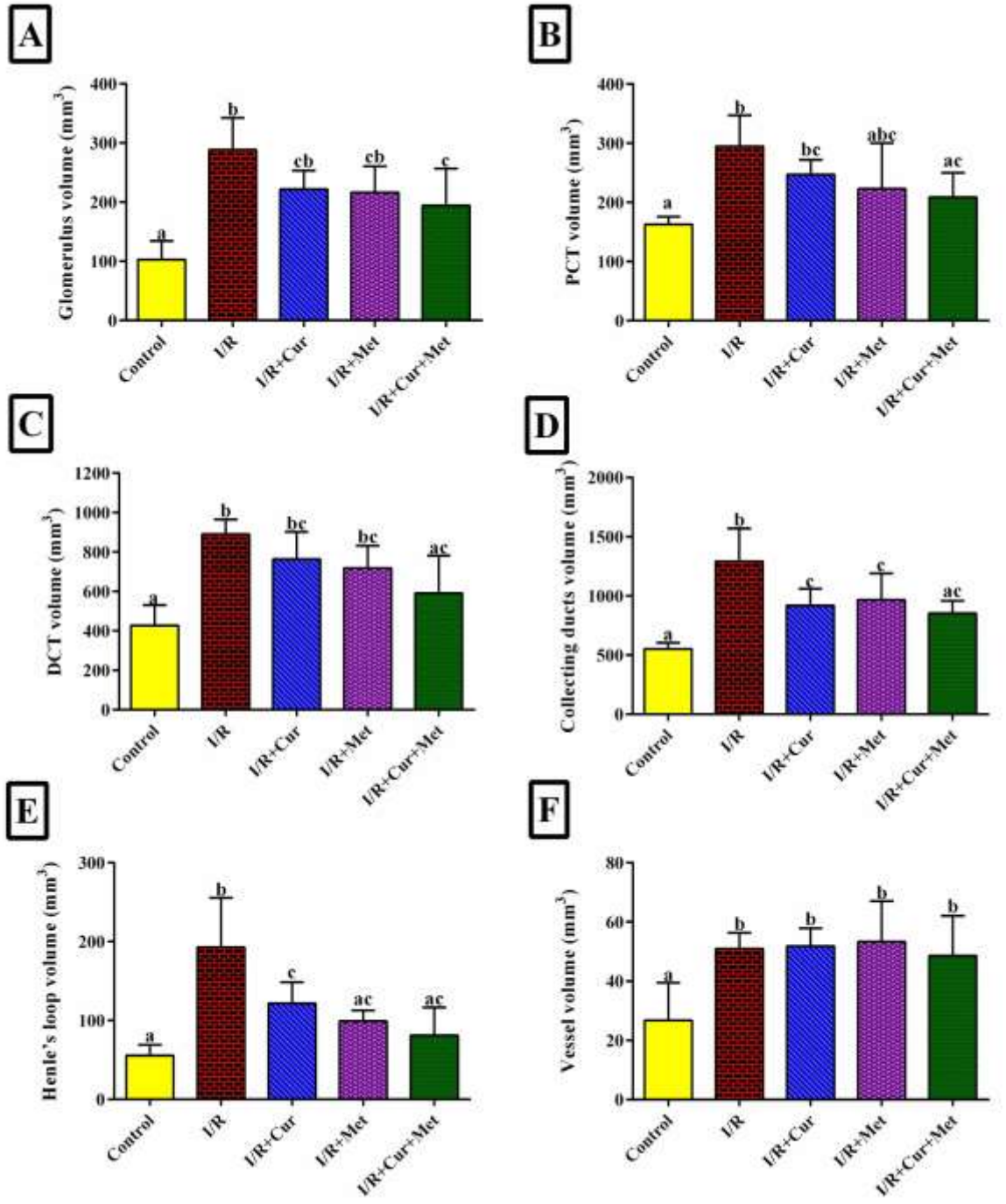

Fig. 3. Morphometric parameters in different groups. No remarkable difference between the groups with at least one similar letter. Different letters show a significant difference between different groups ($p< 0.05$).

Blood biochemistry

The levels of BUN, creatinine, LDH, MDA, TNF-α, and IL-1β in the I/R group increased significantly compared to the control group. These values declined significantly in the I/R + Cur, I/R + Met, and I/ R+ Cur +Met groups compared to I/R, with the lowest levels observed in the I/R + Cur + Met group. The level of TAC in the I/R group was significantly lower than in the control group. These values were significantly increased in I/R + Cur, I/R + Met and I/R+ Cur +Met groups, with the highest level observed in the I/ R+ Cur +Met group (Fig. 4).

Gene expression

The expression rate of Ngal and Kim-1 genes in the I/R group was significantly higher than the control group. In I/R + Cur, I R + Met and I R+ Cur +Met groups, the expression levels of these genes decreased, with the lowest levels observed in the I/R+ Cur +Met group (Fig. 5).

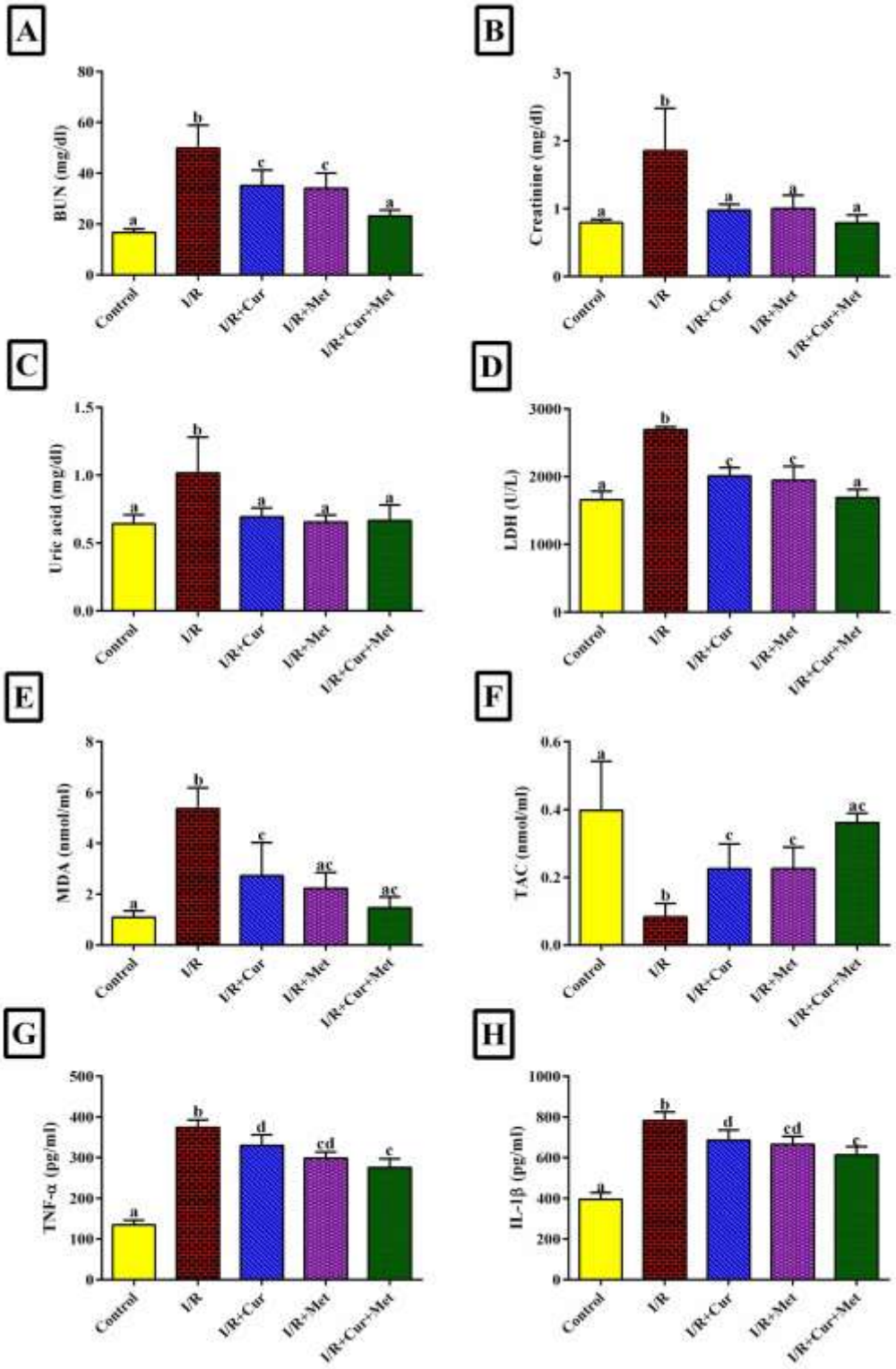

Fig. 4. The amounts of blood biochemical parameters and oxidative stress-related enzymes in different groups. Similar letters in different groups mean no significant difference between them. and different letters indicate significant differences between groups ($p < 0.05$).

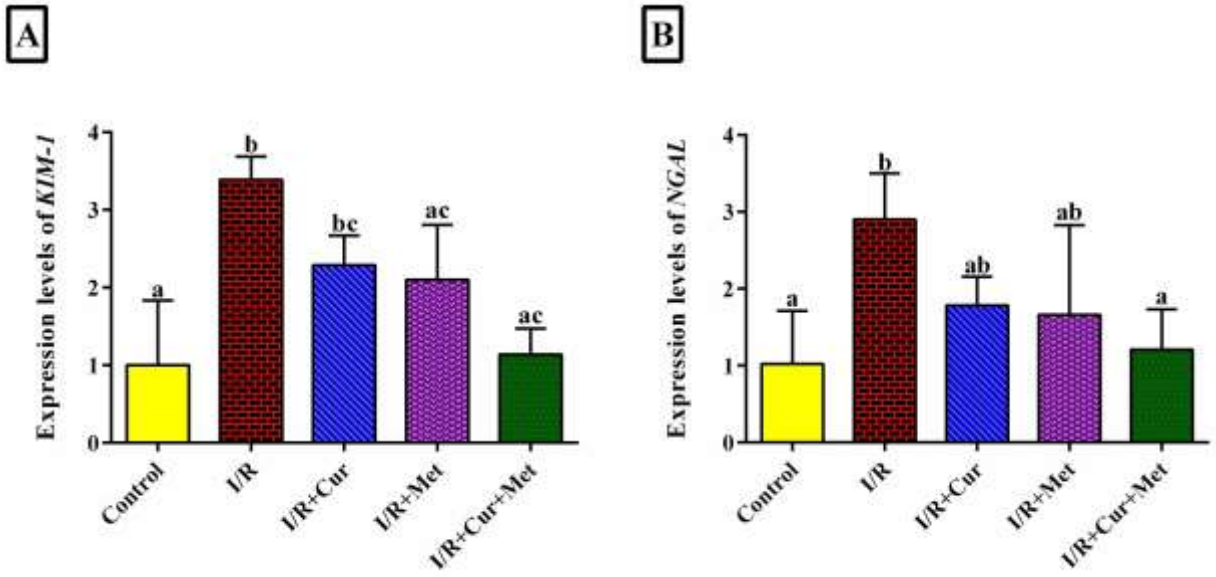

Fig. 5. The level of expression of Kim-1 and Ngal genes in different groups. One similar letter between groups means no significant difference between different groups. Different letters indicate a significant difference ($p< 0.05$).

Discussion

The purpose of this study was to investigate the effects of curcumin and metformin on damage caused by unilateral nephrectomy and renal ischemia-reperfusion in rats. Various histological, morphometric, biochemical, and genetic parameters were examined. The data showed that the simultaneous use of curcumin and metformin in rats that underwent unilateral nephrectomy and renal I/R injury reduced the amount of necrosis and inflammation. Moreover, morphometric criteria such as kidney weight and volume, cortex and medulla volume, glomerulus volume, PCT, DCT, collecting ducts, loop of Henle and vessel volume were close to the normal state of the kidney organ. According to Dare et al, the use of L-ergothioneine and metformin together prevented kidney impairment in a type 2 diabetic mouse model (25). Curcumin was shown to have beneficial effects on preventing kidney damage and renal toxicity in rats (26). Abd El-Kader et al. showed that treatment with Cur four days before and three days after cisplatin injection ameliorated renal function and significantly decreased oxidative stress, inflammatory markers, and apoptosis. According to their report, Cur resulted in a decrease in serum creatinine and BUN in the treatment group. In addition, their histopathological studies showed that Cur significantly improved tubular and brush border destruction, interstitial congestion and bleeding caused by cisplatin injection (27). It has been observed in several studies that inflammatory factors like TNF-α, IL-6, and MCP-1 increase cisplatin-induced nephrotoxicity and AKI in animal models, which can be reversed by thymoquinone or curcumin (28). Malformed tubular cells produce multiple agents that absorb inflammatory cells into the tubular interstitial area (29). Leaked cells secrete cytokines that force some tubular cells to convert to a mesenchymal phenotype and activate myofibroblasts in the tubular interstitial environment (30). These activated myofibroblasts are also able to increase the production of ECM by depositing glycoproteins, fibronectins and collagens. These deposits lead to an increase in the weight and volume of structures inside the kidney and finally the kidney itself (31), which is in line with the results of our research. On the other hand, the decrease in kidney weight and volume and morphometric structures within it after Cur and metformin treatments can be

explained by their anti-inflammatory properties. The combination treatment with curcumin and metformin also reduced the levels of BUN, Creatinine, LDH, MDA, TNF-α, and IL-1β while increasing the TAC level. These features can be attributed to the anti-inflammatory properties of these two compounds, which are well documented (32). Other research has also shown the beneficial effects of medicinal plants on other damaged organs of the body (33).

To further investigate the protective effects of curcumin and metformin on renal injury, the expression levels of Kim-1 and Ngal genes, which are good markers in proximal tubular cells during AKI, were measured (34). The results of the present study showed that the expression rate of Ngal and Kim-1 genes in the I/R group was significantly higher than the control group. In I/R + Cur, I/R + Met, and I/R + Cur + Met groups, the expression levels of these genes decreased, and the minimum level was seen in I/R+ Cur +Met group. Alfai et al. showed that the combination of thymoquinone and curcumin prevented kidney damage caused by cisplatin. They reported that these compounds reduced the expression of NFκB and Kim-1 genes and improved the Nrf2/HO-1 signaling pathway, leading to the reduction of kidney damage (35). Another study reported that curcumin significantly and dose-dependently reduced I/R-induced renal injury and significantly reduced serum creatinine and BUN levels (36). Our results were consistent with the results of this study. Zhang et al. investigated the protective effects and underlying mechanisms of cardamonin, a flavonoid with antioxidant potential, in animal models of renal I/R and unilateral ureteral obstruction (UUO). They confirmed that the administration of CAD (100 mg/kg) ameliorated tissue morphology and kidney function and decreased the overexpression of fibrotic Indicators such as col I, fibronectin, col III, and α-SMA during TGF-β1 activation. Meanwhile, constant oral administration of CAD after UUO surgery effectively decreased the expression of Ngal, Kim-1, Cr, MDA and BUN in CAD + I/R groups (37). Our results were consistent with the results of this study.

The results of the current research are also in line with their research. Thus, recognizing and targeting the common pathways or molecules appears to be hopeful and vital for recovering kidney disorders (38). Several antioxidants and anti-inflammation agents have been examined in clinical trials in patients with related kidney diseases and have reported encouraging results. There are many more candidate agents, which encourage researchers to keep on with searching for potential antioxidants and anti-inflammatory factors to prevent kidney illnesses.

Early treatment with the therapeutic combination of curcumin and metformin improved kidney function, tissue structure, and morphometric characteristics in animal models of unilateral nephrectomy and ischemia-reperfusion injury.

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Conflict of interest

All authors have no conflict of interest to report.

Ethics approval

The present investigation received ethical approval from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (ethical approval number IR.AJUMS.ABHC.REC.1401.057). Informed consent was obtained from all participants, and their participation was voluntary.

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