DMF attenuates cisplatin-induced kidney injury via activating Nrf2 signaling pathway and inhibiting NF-kB signaling pathway

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Abstract. – **OBJECTIVE:** N,N-dimethylformamide (DMF) exerts anti-inflammatory and anti-oxidant capacities. We aim to explore whether DMF could regulate cisplatin-induced kidney injury in rats via NF-E2-related factor 2 (Nrf2) pathway and nuclear factor-κB (NF-κB) pathway.

MATERIALS AND METHODS: A total of 30 Sprague Dawley (SD) rats were randomly assigned into sham group, cisplatin treatment group (DDP group) and DMF + cisplatin treatment group (DMF group), with 10 rats in each group. After 10 days of treatment, we collected serum and kidney samples of rats. Serum levels of creatinine (Cr) and urea nitrogen (BUN) were detected using relative commercial kits. Hematoxylin-eosin (HE) staining was performed to observe pathological changes of kidneys. The relevant oxidative stress indicators in the kidney homogenates of each group were detected by commercial kits, including malondialdehyde (MDA), total antioxidant capacity (T-AOC), catalase (CAT), glutathione (GSH), superoxide dismutase (SOD) and monoamine oxidase (MAO). Protein expressions of Nrf2 and NF-κB in kidney tissues were detected by Western blot.

RESULTS: Serum levels of Cr and BUN were lower in DMF group than those of DDP group. Higher activities of SOD, GSH, CAT and T-AOC were found in DMF group compared with those of DDP group. However, MAD and ROS contents were remarkably decreased in DMF group than those of DDP group. DMF pretreatment remarkably reduced renal pathological changes. Western blot analysis also indicated that DMF effectively upregulated expression levels of Nrf2, Heme Oxygenase-1 (HO-1) and NAD (P) H, quinine oxidoreductase 1 (NQO-1), while downregulated NF-κB.

CONCLUSIONS: DMF could inhibit oxidative stress by activating Nrf2 signaling pathway and reduce inflammatory response by attenuating NF-κB signaling pathway, thus protecting cisplatin-induced kidney injury.

Key Words:
N,N-dimethylformamide, Nrf2 signaling pathway, NF-κB signaling pathway, Cisplatin, Acute kidney injury.

Introduction

Acute kidney injury (AKI) is a common perioperative complication characterized by persistent oliguria and/or elevated serum creatinine level. AKI leads to lower postoperative long-term survival, higher hospital costs and higher risks of postoperative concurrent chronic kidney disease (CKD) and hemodialysis[1,2]. Drug-induced kidney injury is caused by exposure to toxins or potentially toxic drugs. The clinical manifestations of AKI include abnormal urine indicators, renal pathological changes and weakened renal function[3]. The main types of drug-induced nephrotoxicity include AKI, acute renal failure, acute interstitial nephropathy and nephrotic syndrome[3-5]. Cisplatin is a broad spectrum of highly effective anti-tumor drugs. However, the nephrotoxicity of cisplatin can also cause AKI during the treatment. Therefore, alleviation of cisplatin-induced nephrotoxicity has been well investigated[5,6]. It is of clinical significance to actively prevent and treat AKI, so as to avoid further secondary injuries[7,8]. The balance of production and clearance of oxygen free radicals exerts an important role in maintaining homeostasis[9]. However, when the body suffers from toxic damage, adenosine triphosphate (ATP) in the damaged cells is metabolized to accumulated hypoxanthine, resulting in increased xanthine oxidase formation. Subsequently, many oxygen molecules in the ischemic tissue prompt the catalysis of xanthine oxidase to hypoxanthine. Many reactive oxygen species (ROS) are generated in the above process, including superoxide anion, hydrogen peroxide and free hydroxyl groups. Chemically active ROS cause oxidative stress damage in renal cells, resulting in nephron damage and loss of renal function[10]. In recent years, the role of NF-E2-related factor 2 (Nrf2) in the regulation of oxidative stress has attracted much attention[11-14]. Nrf2

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is an important nuclear transcription factor for cell defense against oxidative stress. It has been confirmed that over 200 endogenous protective genes could be regulated by Nrf2[15-18]. In addition, nuclear factor-κB (NF-κB) is also an important transcriptional factor controlling the expressions of various pro-inflammatory genes. ROS could aggravate the inflammatory response and cause tissue damage by activating NF-κB pathway[19-21].

The influence of N,N-dimethylformamide (DMF) on the occurrence and development of organ damage caused by poisons and ischemia has been well recognized[22, 23]. In this study, we aim to investigate whether DMF could reduce cisplatin-induced kidney injury by activating Nrf2 signaling pathway and inhibiting NF-κB signaling pathway. We provide preclinical evidence for the clinical application of DMF to treat and prevent the toxin-induced kidney injury.

Materials and Methods

Chemicals and Reagents

N,N-dimethylformamide (DMF) was purchased from Sinopharm Shanghai Reagent Co., Ltd. (Shanghai, China). Cisplatin injection was provided by Jinan Qilu Pharmaceutical Co., Ltd. (Jinan, China). Malondialdehyde (MDA) test kit, total antioxidant capacity (T-AOC) test kit, catalase (CAT) assay kit, reduced glutathione (GSH) assay kit, total superoxide dismutase (SOD) assay kit, creatinine (Cr) assay kit and urea nitrogen (BUN) assay kit were obtained from Nanjing Jiancheng Biological Co., Ltd. (Nanjing, China). Ordinary balance, electronic thermometer and 721 spectrophotometer were purchased from Shanghai Analytical Instrument Factory (Shanghai, China).

Animals

A total of 30 Sprague Dawley (SD) rats weighing 180-220 g (Vital River Laboratory Animal Technology Co., Ltd., Beijing, China) were housed in a temperature-controlled room with free access to food and water. Rats in sham group were intragastrically given to distilled water (0.01 mL/g) for 10 days. Rats in DDP group were administered with distilled water (0.01 mL/g) for 7 days, followed by cisplatin (25 mg/kg) injection on the 7th day. After that, the rats were continued to be administrated with distilled water for another 3 days. Rats in DMF group were treated with isodose distilled water for the first 7 days. After cisplatin treatment, DMF was administrated for another 3 days. One hour after the last administration, blood was obtained from the orbital vein and the rats were sacrificed after anesthesia. Changes in body weight and daily activities of the rats during the entire administration period were observed and recorded. This study was approved by the Animal Ethics Committee of Qiqihar Medical University Animal Center.

Assessment of Renal Function

Body weight of rats was recorded each time before intragastrical administration. Fresh bilateral kidney tissues were harvested and weighed immediately after the rats were sacrificed. Kidney index =kidney mass / body mass. A total of 2 mL of blood sample was centrifuged at 3500 g/min for 30 min. Serum creatinine (Cr) level was measured by sarcosine oxidase method and urea nitrogen (BUN) level was measured by urease method.

Histological Examination

The renal tissues of each group were cut in coronal sections, fixed with 10% formaldehyde and paraffin-embedded. Tissues were then stained with hematoxylin and eosin. Histological changes were assessed by semi-quantitative examination of renal tubular necrosis. Evaluation criteria were as follows: 0 = no damage, 1 = 10%, 2 = 11% to 25%, 3 = 26% to 45%, 4 = 46% to 75%, 5 = > 76%. Five randomly selected fields of each sample were observed.

TUNEL Assay

Apoptosis in kidney sections was detected according to the instructions of *in situ* DNA terminal transferase (TUNEL) assay (ApopTag Plus Peroxidase *In Situ* Apoptosis Detection Kit; Chemicon, Millipore, Billerica, MA, USA). A 5-μm thick paraffin section was used for TUNEL staining and counterstained with methyl green. The number of TUNEL-positive cells in 10 random fields was counted under a high power microscope.

Biochemical Measurements

A midline abdominal incision was cut to expose the abdominal cavity. The abdominal aorta was cannulated under the branch of the renal artery. The proximal segment above the branch of renal artery was clamped and the left renal vein was then cut open. Pre-cooled saline was used to perfuse the kidneys. After the color of kidney

tissue changed from red to white, the kidney was quickly removed and placed in liquid nitrogen. Part of the tissue was homogenized and stored in a -80°C freezer. Contents of MDA, T-AOC, CAT, GSH, SOD and ROS were measured according to the instructions of corresponding detection kits.

Immunohistochemical Staining

After the paraffin-embedded tissues were dewaxed and hydrated, 50 µL of anti-rat PCNA (1:100) were added and incubated at room temperature for 1 h. After washing with PBS (phosphate-buffered saline) for 3 times, 40-50 µL of the corresponding secondary antibody were added and incubated at room temperature for another 1 h. Diaminobenzidine (DAB) (R&D Systems, Minneapolis, MN, USA) was added to develop color for 5-10 min. Deionized water was used to rinse the residual DAB. The tissue was finally dehydrated, sealed and observed under a microscope.

Western Blot

Kidney tissues were added with lysis buffer and shaken on ice for 30 min. The total protein was separated after the centrifugation at 14,000 g/min for 15 min at 4°C. Protein concentration was calculated by bicinchoninic acid (BCA) protein assay kit (Pierce, Rockford, IL, USA). The extracted proteins were separated on a 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and subsequently transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). Western blot analysis was performed according to standard procedures. The primary antibodies were Nrf2, Heme Oxygenase-1 (HO-1), NAD (P) H, quinine oxidoreductase 1 (NQO-1), NF-κB and β-actin. The secondary antibodies were anti-mouse and anti-rabbit.

Statistical Analysis

The *t*-test was used for comparing continuous variables. Categorical variables were analyzed using x^2-test or Fisher's exact probability method. Kaplan-Meier method was performed to evaluate the survival time of patients and Log-rank test was used to compare the differences between different curves. SPSS 22.0 (Statistical Product and Service Solutions) was used for data analysis (IBM, Armonk, NY, USA). The data were expressed as mean ± standard deviation ($\bar{x} \pm s$). $p < 0.05$ was considered statistically significant.

Results

DMF Pretreatment Improved Renal Function in Cisplatin-Induced Renal Injury Mice

Body weight and kidney index in DDP group were remarkably lower than those of sham group ($p < 0.05$), indicating that cisplatin-induced kidney injury model in rats was successfully established. Compared with those of DDP group, rat body weight and kidney index were remarkably improved after treatment with 20 mg/kg DMF ($p < 0.05$, Figure 1A and 1B). Besides, quantitative analysis of renal function-related indicators showed that serum levels of Cr and BUN in DDP group and DMF group were higher than those of sham group ($p < 0.05$, Figure 1C and 1D). However, serum levels of BUN and Cr in DMF group were still markedly higher than those of sham group.

DMF Preserved Renal Histologic Structure and Mitigated Neutrophil Infiltration

The microstructure of the kidney tissue in sham group was normal. Enlarged tubular lumen and flat tubular epithelium were observed in DDP group. Besides, disordered cells with granular denaturation and karyopyknosis were shown in renal tissues of DDP group. Obvious glomerular contraction, interstitial proliferation and inflammatory cell infiltration were also found in DDP group. Kidney injury in DMF group was less than that of DDP group (Figure 2A). Kidney tubules injury score in DDP group and DMF group was higher than that of sham group ($p < 0.05$, Figure 2B).

DMF Decreased Renal Tubular Cells Apoptosis and Enhanced Cell Proliferation After Cisplatin-Induced Renal Injury

The number of TUNEL-positive cells in kidneys of DDP group was higher than that of sham group ($p < 0.05$, Figure 3A, 3B). However, the TUNEL-positive cells in kidneys of DMF group were remarkably decreased compared with that of DDP group ($p < 0.05$, Figure 2C and 2D). Besides, we performed PCNA immunostaining on renal sections to evaluate whether DMF affects the proliferation of renal tubular epithelial cells. The number of PCNA-positive cells in DMF group was significantly higher than that in DDP group ($p < 0.05$, Figure 2E and 2F).

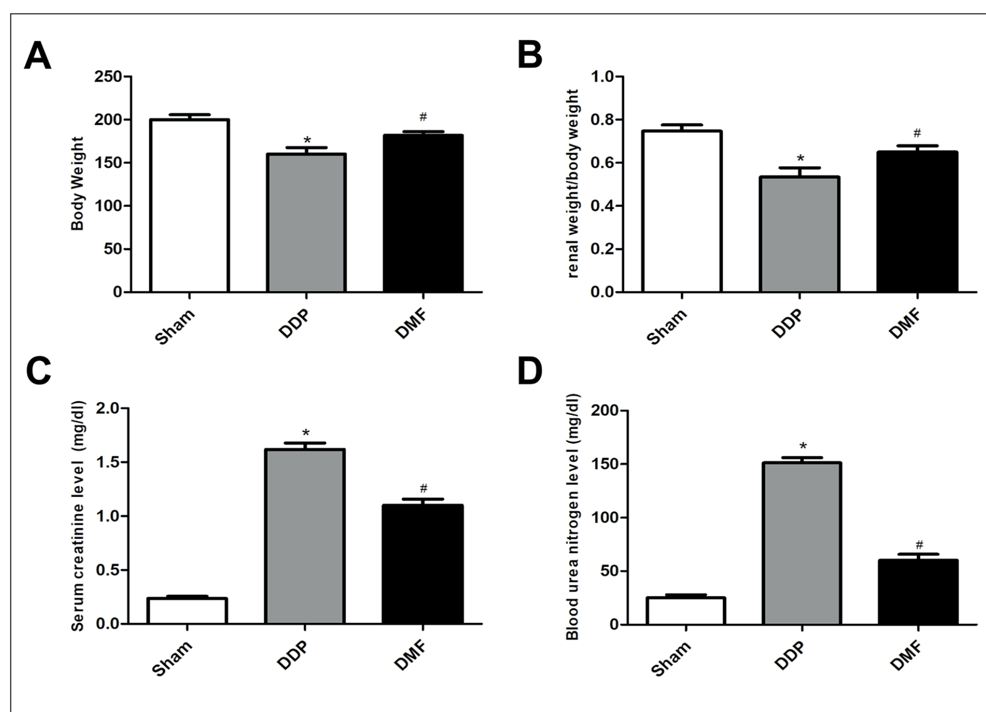

Figure 1. DMF conserved renal function in cisplatin-induced renal injury. ***A,*** Body weight of rats in sham group (n=10), DDP group (n=10) and DMF group (n=10). ***B,*** The ratio of renal weight/body weight in the different management groups. ***C,*** Serum level of Cr in the different management groups. ***D,*** BUN level from the different management groups. Data were presented as mean ± SD, *significant difference *vs.* sham group ($p < 0.05$); #significant difference *vs.* DDP group ($p < 0.05$).

DMF Decreased ROS Production and Tissue Impairment by Reinforcing Antioxidant Capacity

Our data indicated that DDP can significantly impair the anti-oxidative capacity of kidney tissues and stimulate ROS production. DMF administration effectively restored levels of antioxidant markers in kidney injury tissue homogenates, including SOD, GSH, SOD, CAT and T-AOC (Figure 3C-3F). DMF also reduced ROS production in kidney tissues (Figure 3B). In addition, the lipid peroxidation index MDA in the kidney tissue of DMF group was also markedly lower than that of DDP group (Figure 3F).

DMF Supplementation Enhanced Nrf2 Nuclear Translocation, Upregulated HO-1 and NQO-1, and Downregulated NF-κB

To explore the protective mechanism of DMF in cisplatin-induced kidney injury, we further extracted the total protein from kidney tissues. Nrf2 expression showed a remarkable increase in DMF group when compared to that of sham group and DDP group (Figure 4A). The results of Western blot also indicated that the nuclear translocation of Nrf2 in DMF group was remarkably enhanced compared with that of sham group and DDP group, respectively (Figure 4B). Enhanced Nrf2 nuclear translocation also increased the levels of HO-1 and NQO-1 in DMF group (Figure 4D and 4E). In addition, we also detected the expression level of NF-κB in each group. The findings showed that nuclear expression of NF-κB in DMF group was lower than that of DDP group (Figure 4A and 4C).

Discussion

Acute kidney injury (AKI) is a common pathological feature characterized by acute progressive loss of renal function, dramatic drop in glomerular filtration rate and azotemia, electrolyte disorders, acid-base imbalances and oliguria[2]. Toxic injury is an important cause of AKI. Clinically, the renal ischemia reperfusion after cardiac vascular surgery, kidney transplantation and shock will produce a large number of oxygen free radicals, resulting in acute tubular necrosis[3]. Nrf2 is

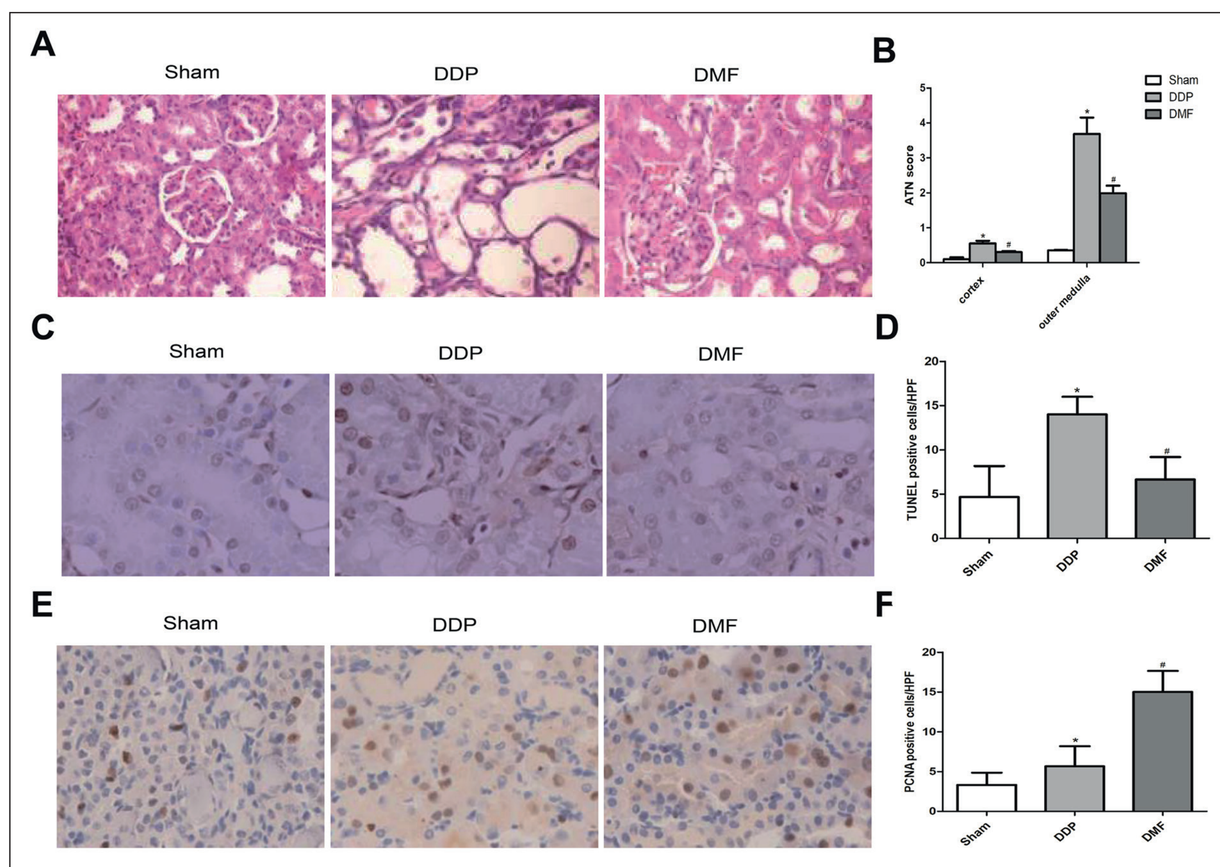

Figure 2. DMF prevented cisplatin-induced renal injury in renal morphology. Renal sections were stained with hematoxylin and eosin and examined using light microscopy (magnification 200×). ***A,*** H&E staining of kidney tissues in sham group, DDP group, and DDP group. ***B,*** Quantification of ATN score in cortex and outer medulla of three groups. ***C,*** Representative images (magnification 200×) of TUNEL immunostaining in the cisplatin-induced renal injury. ***D,*** Quantification of TUNEL-positive cells by averaging number of 5 HPF in different groups. ***E,*** Representative images of proliferating cell nuclear antigen (PCNA) in the kidney sections (magnification 200×) in the injured kidney at different time points. ***F,*** Quantification of PCNA-positive cells by averaging number of 5 HPF in different groups. Values were expressed as mean ± SD.*significant difference *vs.* sham group ($p < 0.05$); #significant difference *vs.* DDP group ($p < 0.05$).

an important nuclear transcription factor for cell defense against oxidative stress. After binding to anti-oxidation response elements (ARE) in the nucleus, Nrf2 can regulate the expressions of multiple downstream antioxidant genes[11,13,14]. DMF is a recently synthesized potent Nrf2 inducer. *In vitro* experiments have demonstrated its anti-oxidation and anti-apoptotic functions. Therefore, we speculated that DMF has a protective effect on AKI caused by ischemia reperfusion. It is of great importance for the prevention and treatment of clinical AKI, so as to find effective drugs and molecular therapeutic targets.

Oxidative stress caused by the pathological accumulation of ROS is involved in the development of renal ischemia-reperfusion injury[24,25]. The dynamic balance between enzyme and non-enzymatic antioxidant systems protects the body from ROS attack[26]. Abnormal activation of the xanthine oxidase pathway leads to increased production of ROS, further destroying the lipids, proteins and DNA in cells. Among them, lipids are the most sensitive to oxygen radical damage[27]. Oxidative stress caused by increased oxygen free radicals in toxic injury is a key event in AKI[28]. Since the renal organelle membrane and cell membrane are mainly composed of polyunsaturated fatty acids (PUFAs), the oxygen free radical-induced cell damage is the most severe activity after toxic damage in kidneys. In addition, excessive ROS can also induce the inflammasome formation, autoimmune activation and platelet activation, which further aggravate the kidney injury[29-34]. ROS-induced

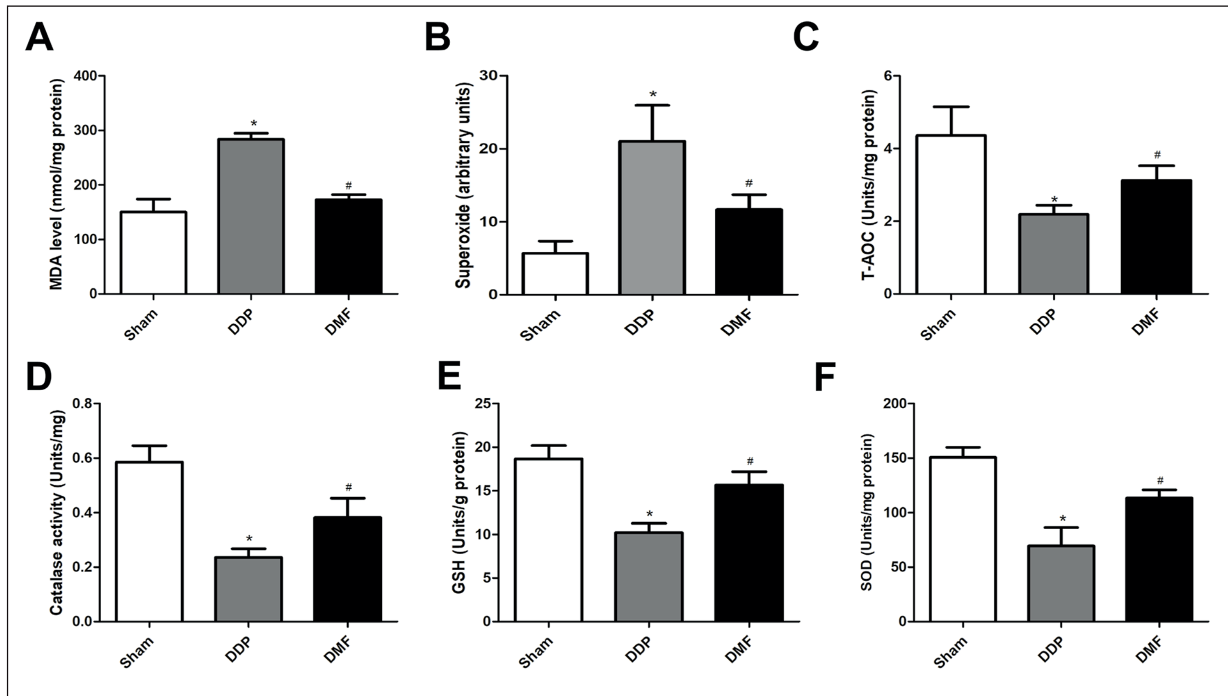

Figure 3. DMF attenuated oxidative stress injury by the assessment of biochemical parameters. ***A,*** MDA content in kidney tissues. ***B,*** ROS content was reported as arbitrary units per millimeter square field. ***C,*** T-AOC content in kidney tissues. ***D,*** CAT content in kidney tissues. ***E,*** GSH content in kidney tissues. ***F,*** SOD content in kidney tissues. Data were expressed as mean ± SD. *significant difference *vs.* sham group ($p < 0.05$); #significant difference *vs.* DDP group ($p < 0.05$).

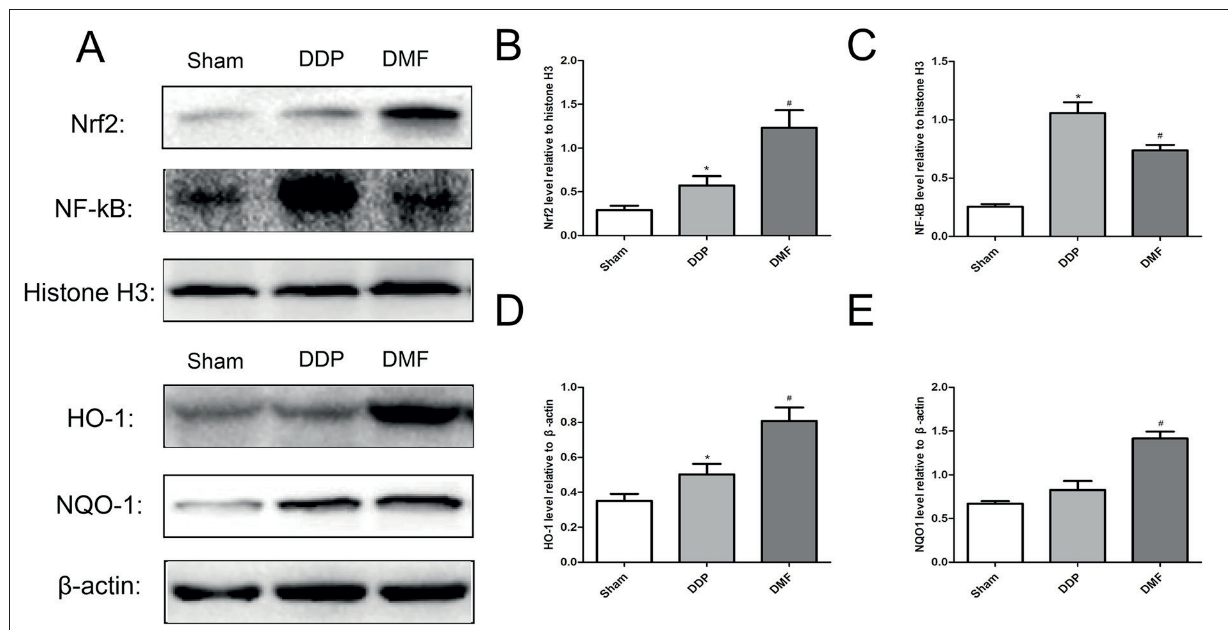

Figure 4. DMF supplementation enhanced Nrf2 nuclear translocation, increased protein expressions of HO-1 and NQO-1, and decreased protein expression of NF-κB. ***A,*** Protein expressions of Nrf2, NF-κB, HO-1, and NQO-1 in different groups. Histone H3was used as a protein control to normalize volume of protein expression. ***B-C,*** Protein levels were determined by densitometric analysis and normalized to the Histone H3 signal. ***D-E,*** Protein expressions of HO-1 and NQO1 in different groups. β-actin was used as a protein control to normalize volume of protein expression. Data were expressed as mean± SD. *significant difference *vs.* sham group ($p < 0.05$); #significant difference *vs.* DDP group ($p < 0.05$).

fibrosis also exaggerates AKI and CKD[35,36]. In summary, strengthening the cellular antioxidant defense system to combat oxidative stress is a viable option for AKI therapy.

Nrf2 maintains a low expression level in cytoplasm because it is rapidly ubiquitinated by Kelch-like ECH associated protein 1 (Keap1) and subsequently degraded by the proteasome[11,17]. Excessive ROS production results in the change of Keap1 conformation by modifying cysteine residues (Cys257, Cys273, Cys288, Cys293). The low-affinity site DLG in Nrf2 dissociates from Keap1, while the high-affinity ETGE still binds to Keap1. As a result, Nrf2 is unable to be recognized by ubiquitin ligase and still occupied. The newly synthesized Nrf2 enters the nucleus and binds to an antioxidant response element (ARE) to initiate the transcription of downstream target genes[10-15]. In this way, a series of phase II detoxification enzymes and antioxidant enzymes could be expressed, mainly including CAT, SOD, NQO1 and HO-1[13-15,17].

NF-κB is a transcription factor that suppresses expressions of many pro-inflammatory genes. NF-κB typically binds to its inhibitory protein IκB in a dimeric form. It is present in the cytoplasm in an inactive form. When the cells are stimulated by extracellular signals, activated IκB kinase (IκB kinase, IKK) phosphorylates IκB. Freely activated NF-κB rapidly enters the nucleus and binds to the specific κB sequence of the target genes, inducing transcription of related genes[19]. These upregulated genes include a variety of inflammatory cytokines such as TNF-α, IL-1β and IL-6[20, 21]. ROS-induced oxidative stress leads to phosphorylation of NF-κB subunit, resulting in activation of NF-κB signaling pathway[20]. In this study, NF-κB was overexpressed in DDP group, while DMF treatment downregulated NF-κB expression. These results indicated that cisplatin-induced ROS accumulation could activate NF-κB pathway. Our data showed that DMF reduced cisplatin-induced inflammatory responses in kidney by downregulating NF-κB and activating Nrf2, which was consistent with a previous study[30].

Conclusions

We found that DMF could inhibit oxidative stress by activating Nrf2 signaling pathway and reducing inflammatory response by attenuating NF-κB signaling pathway, thus protecting cisplatin-induced kidney damage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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