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Original article

Diacerein ameliorates kidney injury induced by cisplatin in rats by activation of Nrf2/Ho-1 pathway and Bax down-regulation

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ABSTRACT

Cisplatin is an antineoplastic medicine used for solid tumor treatment. The main side effect that limits its dose is nephrotoxicity. Diacerein has been used for the treatment of joint diseases like osteoarthritis. It also has exhibited analgesic effects and antipyretic activities in animal models so this study targets to indicate the diacerein effect on nephrotoxicity induced by cisplatin in rats. Rats were distributed into four groups: normal healthy control; diacerein, which received diacerein daily by gastric gavage (50 mg/kg/-day); cisplatin, which received only one intraperitoneal injection of cisplatin (6 mg/kg) and cisplatin and diacerein, which received diacerein daily after the cisplatin injection till 7th and 12th days, respectively. Diacerein treatment decreased kidney function markers so the cisplatin effect was reversed. Also, diacerein increased the renal antioxidants and decreased oxidative stress. Diacerein up-regulated Ho-1 (heme oxygenase 1), Nrf2 (Nuclear factor erythroid 2–related factor 2) and endothelial nitric oxide synthase (eNOS) genes expression, while down-regulated Bcl-2-associated X protein (Bax) gene expression. Furthermore, the renal transforming growth factor beta-1 (TGF-β1) decreased by the diacerein effect. Consequently, diacerein has a curative effect against cisplatin due to its anti-inflammatory, antioxidant, and antiapoptotic properties.

1. Introduction

Acute kidney injury (AKI) is the foremost severe side effect of cisplatin-induced toxicity. Cisplatin is utilized as chemotherapy for different cancers that lead to the collection of platinum inside the kidney causing DNA and RNA damage. Cisplatin produced reactive oxygen species (ROS) that were involved in its cellular injury. The improved lipid peroxidation and repressed antioxidant are trademarks in cisplatin-induced nephrotoxicity. In expansion, inflammation and apoptosis were demonstrated to play a critical role in cisplatin-induced renal injury (Michel and Menze, 2019).

Diacerein is a medicine for treating osteoarthritis as it promotes the synthesis of cartilages. Diacerein was stated to have a renoprotective impact against cisplatin-induced acute kidney injury through its anti-inflammatory and antioxidant activities (Pavelka et al., 2016). Diacerein decreases the synthesis of IL-1β and activates IκB-α/NFκB pathway. (Chueakula et al., 2018). Diacerein inhibits the nitric oxide production that explains its anti-inflammatory and anti-osteoarthritis properties (Abdelaziz et al., 2018). Rhein, an active metabolite of diacerein, has nephroprotective, antioxidant, anti-inflammatory, hepatoprotective, anticancer, chondroprotective, antimicrobial, antidiabetic activities (Zhou et al., 2015; Guo et al., 2020; de Oliveira et al., 2020) so this study targets to clarify diacerein effect on the cisplatin-induced renal injury in rats.

Abbreviations: SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; Ho-1, heme oxygenase 1; Nrf2, Nuclear factor erythroid 2–related factor 2; eNOS, endothelial nitric oxide synthase; Bax, Bcl-2-associated X protein; TGF-β1, transforming growth factor beta-1.

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2. Materials and methods

2.1. Chemicals

Cisplatin (Cat. No. PHR1624) was obtained from Sigma-Aldrich, USA, and diacerein (Cat. No. 13296) was bought from Eva Pharma Company, Egypt.

2.2. Animals and experimental design

48 male *Sprague Dawley* rats (290–340 g) gotten from and kept within the animal house of the Urology and Nephrology Center, Mansoura University, where the temperature was kept at 20 °C, and the animals were fed a standard diet containing carbohydrates 65%, proteins 20.3%, fat 5%, fiber 5%, salt mixture 3.7%, and vitamin mixture 1% (Abd El-Khalik et al., 2021) with free access to water in *ad libitum*, and live in 12-h light/dark cycle. All animals received human care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 86–23 revised 1985) and the approval of the ethical committee of Mansoura University, Faculty of Science, Egypt [MDP.21.03.63]. Rats were divided into 4 groups (N = 12). **Normal group:** Normal rats weren't injected by anything, **Diacerein group:** Normal rats were supplemented with diacerein 50 mg/kg b.w./day by gastric gavage according to Abdel-Aziz et al. (2018), **Cisplatin group:** Rats injected in intraperitoneal by cisplatin 6 mg/kg b.w. for one time according to Liu et al. (2017), **Cisplatin & Diacerein group:** Rats injected in intraperitoneal by cisplatin 6 mg/kg b.w. for one time and then supplemented with diacerein 50 mg/kg b.w./day by gastric gavage till euthanization occurred for half rats at 7th day and at the 12th day for the other half of rats.

2.3. Samples preparation

Rats were anesthetized with an overdose of halothane and euthanized after finishing the experiment. Before euthanization, A metabolic cage was used to collect the urine samples for microalbuminuria measurement, and samples of blood were collected from the heart and left to clot for 30 min. before centrifuged (JANETZKI T30, Germany) for 10 min at 4000 rpm to separate serum for renal function markers measurement. Every kidney was removed and divided by a lancet into two parts, The first half of the right kidney was homogenized in 5–10 ml cold buffer that contained 100 mM potassium phosphate, pH 7.0, and 2 mM EDTA per gram tissue according to Beutler et al. (1963) to give a 10% homogenate using a homogenizer for antioxidants and oxidative stress measurements, the other half of kidney used to measure transforming growth factor beta-1 (TGF-β1) by flow cytometry, the first half of the left kidney was preserved into 10% formalin for immunohistochemical and histopathological investigations and the other half of kidney was kept in RNAlater (Thermo fisher scientific, Lithuania) (Cat. No. AM7022) at −20 °C for real-time PCR measurement of genes expression.

2.4. Biochemical investigation

Serum creatinine, BUN, and microalbuminuria were measured on Cobas C 311 analyzer according to Toora and Rajagopal (2002), Talke and Schubert (1965), and Mogensen (1984), respectively by kits (Roche Diagnostics, USA) (Cat. No. 7D64-20, 7D75-20, and 7D53-20, respectively). While catalase (CAT), malondialdehyde (MDA), glutathione reductase, and superoxide dismutase (SOD) were measured according to Aebi (1984), Ohkawa et al. (1979), Beutler et al. (1963), and Nishikimi et al. (1972) methods respectively by colorimetric kits (Bio-Diagnostics, Egypt) (Cat. No. CA 25 17, MD 25 29, GR 25 11, and SD 25 21, respectively).

2.5. Real-time PCR evaluation

TRIzol reagent (Thermo Fisher scientific, USA) was used for RNA extraction from kidney according to manufacturer's instruction (Hummon et al., 2007) and Nanodrop spectrophotometer (München, Germany) used to quantify RNA concentration. 2 μg RNA was transformed to cDNA by kit (Thermo Scientific, USA). Primers were designed by NCBI and synthesized for gene expression evaluation at Vivantis (Malaysia) as presented in Table 1. Each sample was statistical analyzed by equation $2^{-\Delta\Delta ct}$ (Pfaffl, 2001).

2.6. Flow cytometry technique

FACS caliber flow cytometer, USA used to evaluate renal TGF-β1 as renal tissue was prepared according to Tribukait et al. (1975). The material was washed with isotone tris EDTA buffer "Ethylene-diaminetetraacetic acid" and 0.07 M sodium chloride with 0.005 M EDTA. They were dissolved in 250 ml of distilled water and then pH changed to be 7.5 by the use of normal HCl. Then, the cell suspension was centrifuged at 1800 rpm for 10 min, whereupon the supernatant was removed. After centrifugation, the cells were fixed in ice-cold 96–100% ethanol (BDH) in approximately 1 ml for each sample. The next step, Staining method of TGF-β1 according to Miyazono et al. (1993). 100 μl of cell suspension (1x106) cell/ml was prepared by isolation of mononuclear cells with Tris EDTA buffer. The cells were washed with PBS/BSA (Bovine serum albumin) with 2 ml and then centrifuged at 2000 rpm for 5 min. The pellet was resuspended in 100 μl of PBS and the supernatant was discarded. 7 μl of TGF-β1 was added and mixed well then the tube was incubated at room temperature for 30 min. in dark. Cells were washed by 2 ml PBS/BSA, and centrifuged at 2000 rpm for 5 min. and discarded the supernatant. Finally, cells were resuspended in 200 μl of 4% paraformaldehyde in PBS and then fixed until acquired by flow cytometer.

2.7. Histopathological investigations

The kidney samples were rinsed in saline solution and immediately fixed in 10% buffered formalin. The fixed specimens were dehydrated by ethanol, cleared by xylene, and embedded in paraffin at 60 °C. The kidney paraffin block was cut at 5 μm thickness by

Table 1
Sequences of primers used for Real-Time PCR evaluation.

Genes	Forward primer	Reverse primer	Accession number
Nrf2	TTGTAGATGACCATGAGTCGC	ACTTCCAGGGGCACTGTCTA	NM031789.2
HO-1	CTTTCAGAAGGGTCAGGTGTC	TGCTTGTTTCGCTCTATCTCC	NM012580.2
Bax	GGCGATGAACTGGACAACAA	CAAAGTAGAAAAGGGCAACC	NM017059.2
eNOS	CACACTGCTAGAGGTGCTGGAA	TGCTGAGCTGACAGAGTAGTA	NM021838.2
GAPDH	AGACAGCCGCATCTTCTTGT	TTCCCATTCTCAGCCTTGAC	NM017008.4

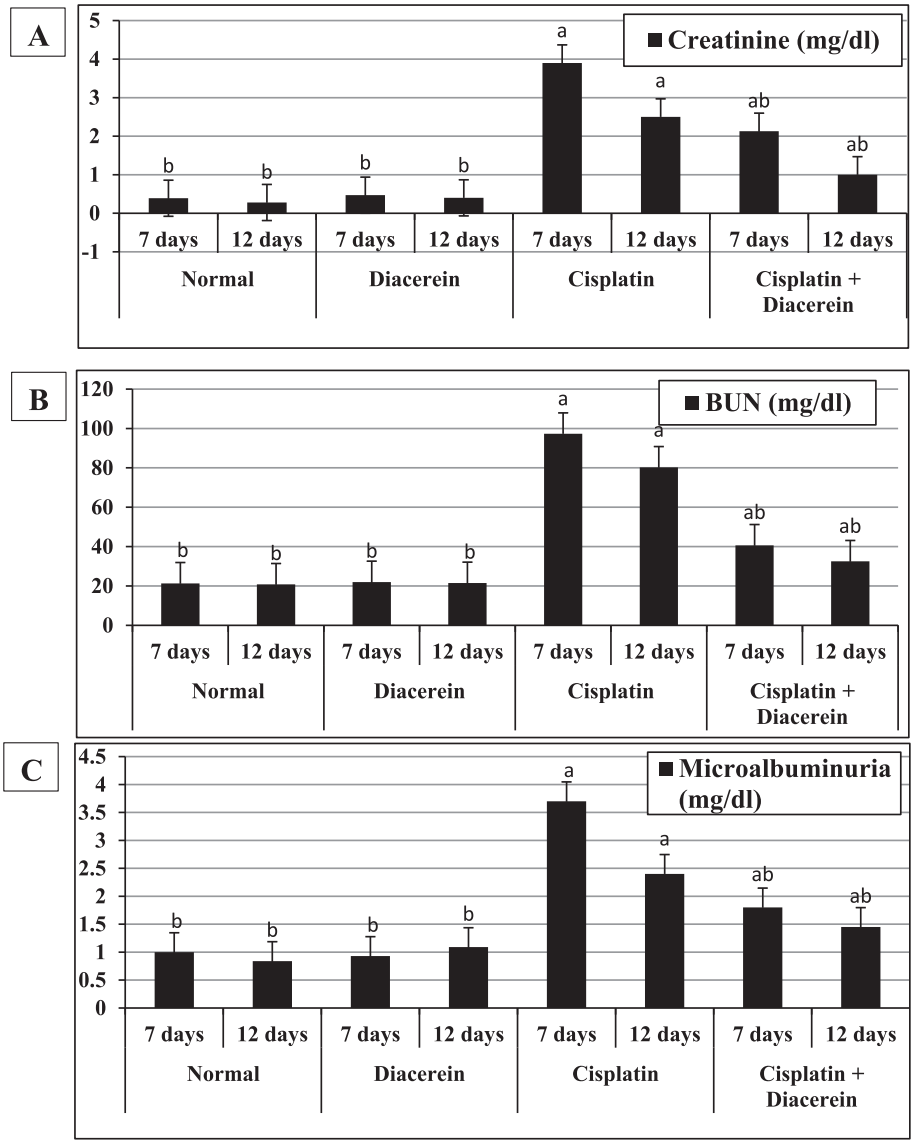

Fig. 1. (A-C). Kidney function markers of studied groups. a: significant against normal at $P \leq 0.05$b: significant against cisplatin at $P \leq 0.05$.

slidge microtome, stained with hematoxylin as well as eosin, and examined on an Olympus CX51 light microscope at 400x magnification and scale bar = 50 μm (Banchroft et al.,1996).

2.8. Statistical analysis

SPSS version 17 used for statistical analysis of results. ANOVA and Post Hoc LSD test statistically analyzed data. Differences considered significant at $P \leq 0.05$ (Harnett and Horrell, 1998).

3. Results

3.1. Diacerein effect on cisplatin-induced nephrotoxicity

Rats receiving cisplatin exposed a significant rise in BUN, creatinine, and microalbuminuria compared to normal and diacerein groups. Alternatively, the diacerein and cisplatin group exhibited a significant reduction of BUN, creatinine, and microalbuminuria compared to the cisplatin group as shown in Fig. 1.

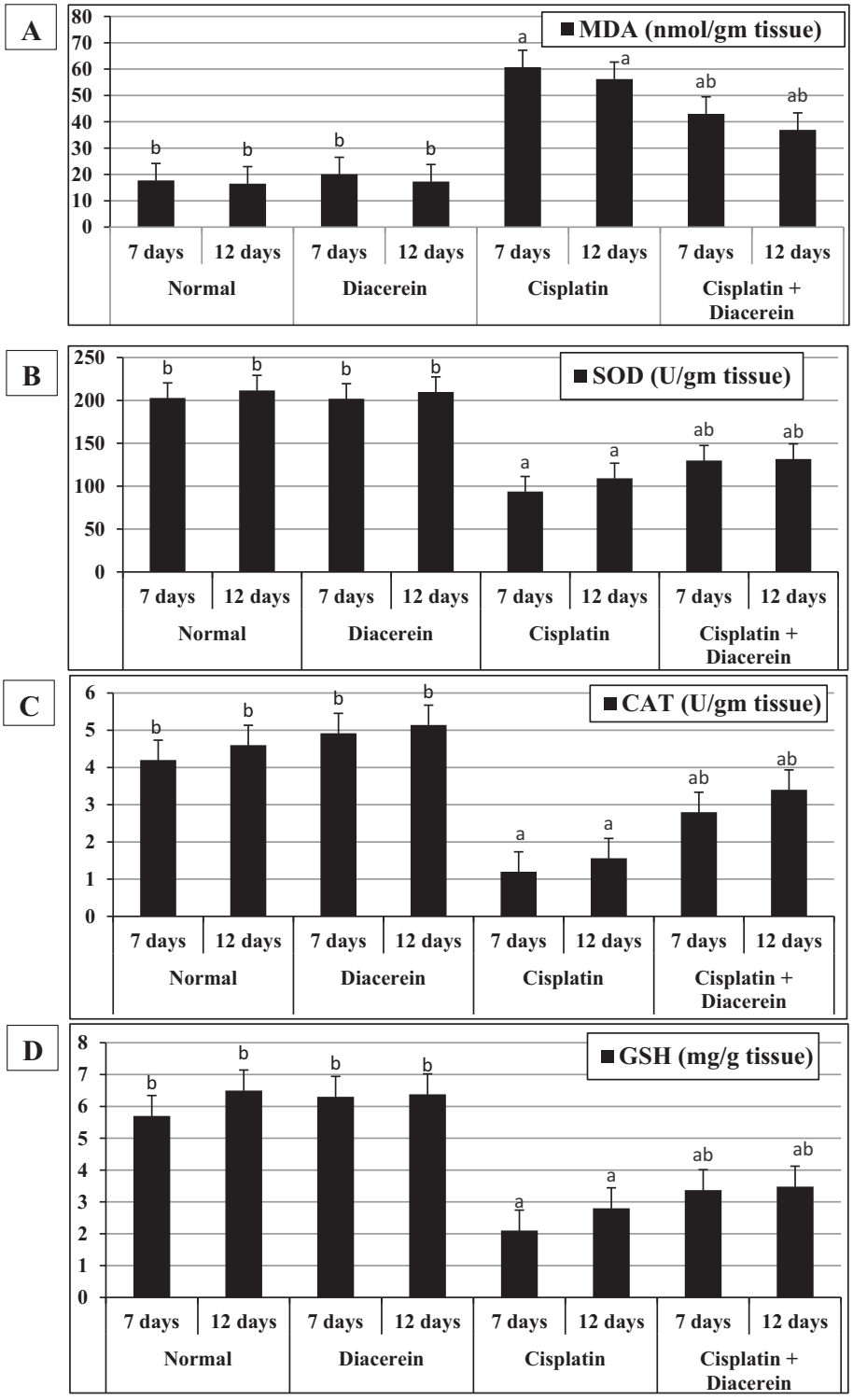

Fig. 2. (A-D). Effect of diacerein on antioxidant and oxidative stress markers. a: significant against normal at $P \leq 0.05$b: significant against cisplatin at $P \leq 0.05$.

3.2. Effect of diacerein on antioxidant and oxidative stress markers in kidney tissues

Rats injected with cisplatin exhibited a significant reduction of renal SOD, CAT, and GSH while renal MDA exposed a significant rise compared to normal as well as diacerein groups. Conversely, the cisplatin and diacerein treated group showed a significant increase in renal SOD, CAT, and GSH whereas MDA showed a significant decrease compared to the cisplatin group as shown in Fig. 2.

3.3. Effect of cisplatin and diacerein on renal Nrf2, Ho-1, Bax, and eNOS genes expression

Cisplatin down-regulated renal Nuclear factor erythroid 2–related factor 2 (Nrf2), heme oxygenase 1 (Ho-1) and endothelial nitric oxide synthase (eNOS) and up-regulated renal Bcl-2-associa ted X protein (Bax) compared to normal and diacerein groups. The diacerein treatment decreased the cisplatin effect as showed in Fig. 3 (A-D).

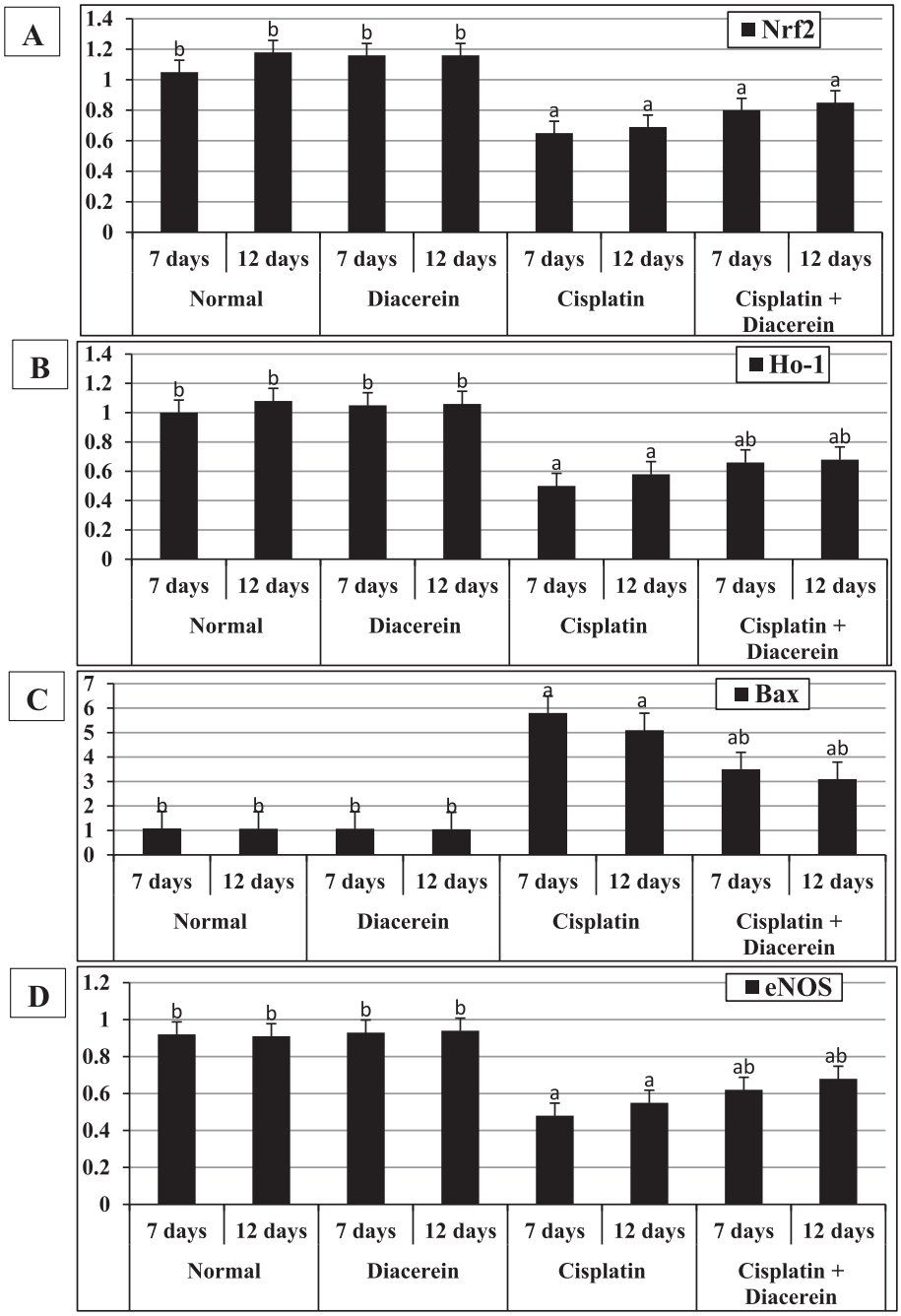

Fig. 3. (A-D). Diacerein effect on the mRNA levels of renal Nrf2, Ho-1, Bax and eNOS.a: significant against normal at $P \leq 0.05$b: significant against cisplatin at $P \leq 0.05$.

3.4. Effect of diacerein on flow cytometry measurements

The renal TGF-β1 significantly ($P \leq 0.05$) decreased after diacerein treatment that attenuated the cisplatin effect as explained in Fig. 4.

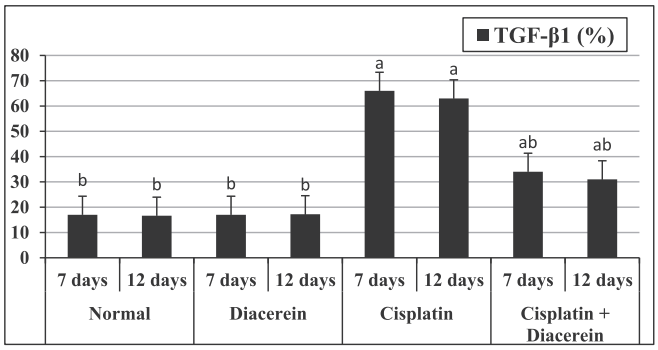

Fig. 4. Diacerein effect on renal TGF-β1. a: significant against normal at $P \leq 0.05$b: significant against cisplatin at $P \leq 0.05$.

3.5. Kidney histopathological observations

The control and diacerein groups had normal renal morphology. Cisplatin group showed more tubular dilation and epithelial cells desquamation with more interstitial fibrosis. Hydropic degeneration was seen in most renal tubules with mononuclear cells infiltration around the affected tubules with abnormally dilated lumina. On the other hand, diacerein and cisplatin group had

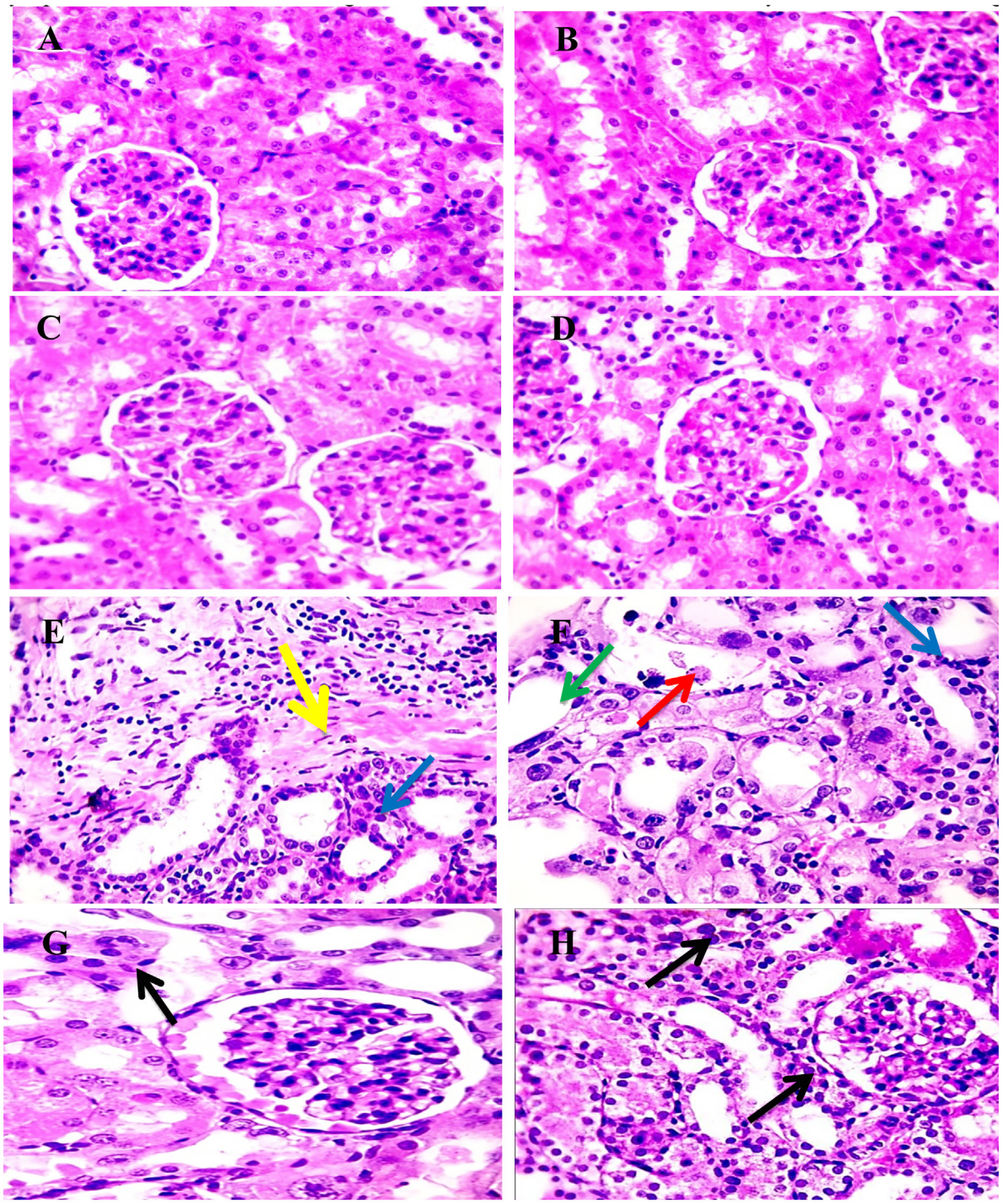

Fig. 5. Normal group at 7th **(A)** and 12th **(B)** days and diacerein group at 7th **(C)** and 12th **(D)** days had normal renal structure. Group of cisplatin at 7th **(E)** and 12th **(F)** days illustrated tubular dilation (green arrow), desquamation (red arrow), and interstitial fibrosis (yellow arrow). Hydropic degeneration was seen in most renal tubules with mononuclear cells infiltration around the affected tubules with abnormally dilated lumina (blue arrows). Cisplatin and diacerein group at 7th **(G)** and 12th **(H)** days had more regenerative changes (black arrows). X: 400 bar 50.

regenerative changes in the form of flattened to low cuboidal epithelial cells lining basophilic cytoplasm and tubular cell enlargement were detected at 7th and 12th days as illustrated in Fig. 5.

4. Discussion

Acute kidney injury (AKI) is often occured by nephrotoxins like cisplatin. Cisplatin is used as a chemotherapeutic medicine for can-

cer but nephrotoxicity is its main side effect (Wang et al., 2020). Cisplatin increases BUN, creatinine, and microalbuminuria levels. This cisplatin nephrotoxicity at the 7th day of its injection was evidenced by histopathological changes that showed more tubular dilation, epithelial cells desquamation with more interstitial fibrosis. Similar findings were reported previously by Barakat et al. (2020).

Diacerein is an anti-inflammatory analgesic medicine used to treat osteoarthritis. Rhein, an active metabolite of diacerein, has a renoprotective effect against cisplatin-induced acute kidney disease through its anti-inflammatory and antioxidant activities (Abdel-Aziz et al., 2018). Diacerein decreased BUN, creatinine, and microalbuminuria levels in diacerein and cisplatin group after 7 and 12 days from the injection. Rhein reduces interstitial inflammation, renal fibrosis, and hepatic growth factor levels (Yu et al., 2018). This was revealed by histological findings of diacerein and cisplatin group as regenerative changes increased, but at 12th day from injection regenerative changes are more than these at the 7th day. These results are in agreement with the previous findings of Abdelaziz et al. (2018).

Cisplatin leads to depletion of glutathione, mitochondrial respiration impairment, and production of ROS. Cisplatin-induced nephrotoxicity related to lipid peroxidation production. The decrease of CAT, GSH, and SOD and the increase of renal MDA are due to the effect of cisplatin (McSweeney et al., 2021). Rhein dramatically decreased ROS production and renal MDA level by downregulated the mRNA expression of MDA while it increased CAT, SOD, and GSH-Px activities (Zhong et al., 2012).

This study reported down-regulation in the level of Nrf2 gene in the kidney tissue after cisplatin injection and correlated that with HO-1 down-regulation. HO-1 has a protective response against apoptosis that occurred due to cisplatin (Cao et al., 2017). On the other hand, this study clarified some up-regulation in renal Nrf2 and HO-1gene expression after diacerein treatment. HO-1 expression upregulated in diacerein group and this is attributed to up-regulation of Nrf2 expression that induces the ARE-dependent genes expression (Chueakula et al., 2018).

Cisplatin up-regulates renal Bax gene expression. Cellular stress induced by cisplatin activates Bax and Bak causing the opening of mitochondrial permeability transition pores (MPTPs) and secretion of cytochrome *c* into cytosol from mitochondria. Caspase-9 that motivated by cytochrome *c* activates several downstream caspases that lead to apoptosis (Zakaria et al., 2019). Conversely, diacerein treatment induced relative down regulation of renal Bax gene expression. Diacerein attenuated cisplatin effect and downregulated Bax in kidney tissues and this effect upregulated the Bcl-2, anti-apoptotic protein that improved renal function and reduced apoptosis. The diacerein anti-apoptotic effect suppresses the c-Jun N-terminal kinase (JNK) pathway that is involved in apoptotic signaling activation (Abd-Ellatif et al., 2019).

Cisplatin down regulates renal eNOS gene expression. The down-regulation of eNOS is due to a decrease in renal blood flow (Bae et al., 2009). Diacerein changed the effect of cisplatin by inducing relative up-regulation of renal eNOS gene expression. NO generated by eNOS activation is important for oxidative stress defense and anti-apoptotic mechanism (Morsy and Heeba, 2016).

This study revealed that the renal TGF-ß1 level of cisplatin injected rats increased. This result was agreed with the elevation of renal and systemic levels of TGF-β1 induced by cisplatin (Bayomi et al., 2013). On the other hand, rhein abolished the expression of alpha-smooth muscle actin (α-SMA) and fibronectin in interstitial fibroblasts cells induced by TGF-β1 thus rhein inhibits renal fibrosis (Zhou et al., 2015). For this reason, treatment of experimental rats with diacerein after cisplatin administration represents a significant decrease in the level of TGF-β1 in kidney tissue when compared with cisplatin group.

5. Conclusion

Diacerein can attenuate kidney injury induced by cisplatin drug in rats and this is reflected by its anti-apoptotic, antioxidant, and anti-inflammatory properties.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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