

Ameliorative effect of desloratadine against cisplatin-induced renal and testicular toxicity in rats: Attention to TLR4/NLRP3 inflammasome signaling pathway

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ABSTRACT

Cisplatin (CIS) is a potent anticancer drug that is used in the treatment of different types of cancer. Owing to its serious side effects, its clinical use is considerably limited. Aims: This study was mapped to investigate the potential effects of desloratadine (DES) against CIS-induced nephrotoxicity and testicular injury. Main methods: DES (5 and 10 mg/kg) was orally administered for 10 days, and CIS was injected once (10 mg/kg, i.p.) in adult male rats on day 9 to induce both renal and testicular toxicity. Key findings: DES significantly attenuated CIS-induced alterations in histopathology and biomarkers. DES resulted in a significant reduction in serum levels of creatinine (Cr), urea, and blood urea nitrogen (BUN), in addition to a marked decrease in urinary levels of albumin and total protein. Additionally, DES efficiently reinstated the oxidative balance by preventing the elevation of malondialdehyde (MDA) and enhancing superoxide dismutase (SOD) activity, and increasing glutathione (GSH) levels. Moreover, DES produced a profound decrease in renal and testicular levels of nucleotide-binding domain-(NOD) like receptor 3 (NLRP3), interleukin (IL)-1 β , and caspase-1 when compared to the CIS group. Furthermore, DES significantly decreased CIS-induced elevation in toll-like receptor 4 (TLR4), tumor necrosis factor- α (TNF- α), and nuclear factor-kappa B (NF- κ B) levels in both renal and testicular tissues. Significance: DES can be used as adjuvant therapy with CIS in cancerous cases, pending further clinical studies.

1. Introduction

Cisplatin (CIS), or (cis-diamminedichloroplatinum II), is a platinum-containing anti-cancerous agent used widely to treat solid malignancies alone or in combination with others. In fact, CIS is one of the most potent, well-established, and effective chemotherapeutic agents [1], often prescribed to 10–20 % of all cancer patients to slow cancer growth and enhance the survival probability [2]. It acts by forming both intra- and inter-strand crosslinks with the purine bases of the DNA [3]. As a result, they impair the normal repair mechanisms, triggering, in process, a DNA damage response that stimulates both cell-cycle arrest and death [4]. Unfortunately, the potent anti-cancer effect of CIS on the cancer cells is often associated with severe adverse side effects on the normal tissues limiting its dose and even clinical application, most specifically, both testicular and nephro-toxicities [4].

Induced nephrotoxicity by CIS accounts for up to 20 % of all incidences of acute kidney injury (AKI) in hospitalized cancer patients [5]. In fact, in a previous study, nearly 30 % of CIS recipient patients experienced AKI within days of starting chemotherapy [5]. In a large cohort study, about one in three patients experienced AKI upon treatment with CIS. In addition, the majority of surviving patients experience a permanent decline in renal filtration capability indicating long-term chronic kidney injury, even when cis is seized [5]. This nephrotoxicity is often associated with rapid loss of excretory mechanisms within the kidney, enhancing the accretion of metabolic waste products including urea, nitrogen, and creatinine (Cr), tubular cell injury and death, aggravated by both inflammation and vascular injury [2]. Renal accumulation of CIS induces a state of oxidative imbalance triggering inflammation-led pathways, ultimately causing nephrotoxicity. Unfortunately, despite multiple successful therapy studies in rodents, CIS-

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Table 1

Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced mortality and change in body weight.

	Mortality	Change in body weight (g)
Control	0 %	26.1 ± 1.6
CIS	33.3 % [#]	-24 ± 2 [#]
CIS + DES5	16.6 % ^{#&}	-16 ± 0.3 ^{#&}
CIS + DES10	0 % ^{&*}	20 ± 1.8 ^{&*}

Data are expressed as mean ± S.E.M, mortality is expressed as a percentage (n = 4–6).

CIS, cisplatin (10 mg/kg, i.p.); DES, desloratadine (5 or 10 mg/kg, orally); S.E.M, standard error of the mean; ANOVA, analysis of variance. #, &, * significantly different when compared with control, CIS, or CIS + DES5 group, respectively, using the Chi-Square test for mortality and one-way ANOVA followed by Tukey-Kramer multiple comparisons post-hoc test for the change in body weight ($p < 0.05$).

induced AKI remains to be common in people [2], necessitating more research.

Another side effect of CIS is the observed testicular toxicity [6]. In testicular cancer, the use of CIS often results in cure rates as high as 80 %. Unfortunately, this anti-cancerous effect is associated with toxicity on the surrounding normal testicular tissue, by triggering pathways that induce apoptosis, inflammation, and oxidative stress [7,8]. The manifestations of CIS-induced testicular toxicity include the impairment of Leydig cell activity, a decrease in testosterone production, and germ cell

death. Subsequently, CIS recipients often suffer from temporary or permanent infertility [9]. Therefore, establishing adjuvant therapy against CIS-induced testicular injury has been a pressing issue.

Desloratadine (DES) is a potent and non-sedative H1-histamine receptor antagonist used to treat the symptoms of allergic rhinitis and urticaria [10]. DES has been suggested as an antioxidant [11,12], anti-inflammatory agent [13,14], and even antigrowth agent [15]. DES has been implicated as an inhibitor of the production and release of certain pro-inflammatory cytokines, for example, interleukin (IL)-6 and IL-8. Previously, DES has been suggested as a potential reno-protectant in renal ischemia/reperfusion (I/R) model [12], but not in models of drug toxicity such as CIS-induced organ injury in rodents.

Therefore, this study was mapped out to determine the probable mitigative effect of DES against CIS-induced both renal and testicular toxicity induced by a single dose of CIS in rats. In addition, we investigated the potential pathways underlying such effects.

2. Materials and methods

2.1. Animals

Twenty-four male Sprague-Dawley rats (220–270 g, aged seven to eight weeks) were supplied from the Faculty of Pharmacy, Delta University for Science and Technology, Gamasa, Egypt. Rats were housed and cared for in the animal house of the Faculty of Pharmacy, Mansoura University, Egypt. They were maintained under standard conditions; the

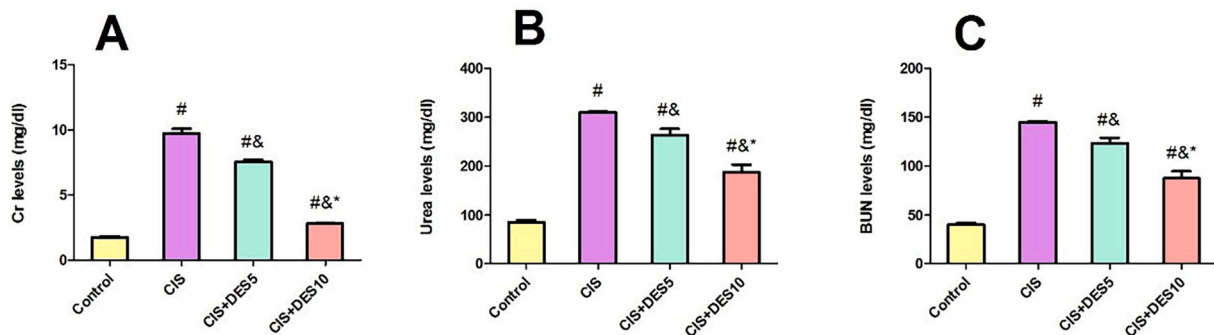


Fig. 1. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to serum renal function parameters.

Data are expressed as mean ± S.E.M, (n = 4–6).

CIS, cisplatin; DES, desloratadine (5 or 10 mg/kg, orally); S.E.M, standard error of the mean; ANOVA, analysis of variance; Cr, creatinine; BUN, blood urea nitrogen. #, &, * significantly different when compared with control, CIS, or CIS + DES5 group, respectively, using one-way ANOVA followed by Tukey-Kramer multiple comparisons post-hoc test for the change in body weight ($p < 0.05$).

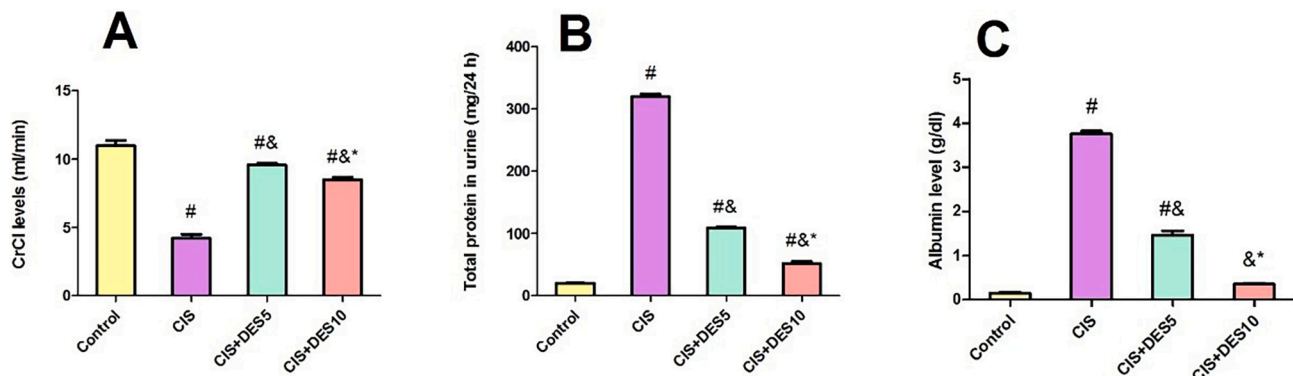


Fig. 2. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to urine parameters; A) CrCl, B) Total protein, C) Albumin.

Data are expressed as mean ± S.E.M, (n = 4–6).

CIS, cisplatin; DES, desloratadine (5 or 10 mg/kg, orally); S.E.M, standard error of the mean; ANOVA, analysis of variance; CrCl, creatinine clearance. #, &, * significantly different when compared with control, CIS, or CIS + DES5 group, respectively, using one-way ANOVA followed by Tukey-Kramer multiple comparisons post-hoc test for the change in body weight ($p < 0.05$).

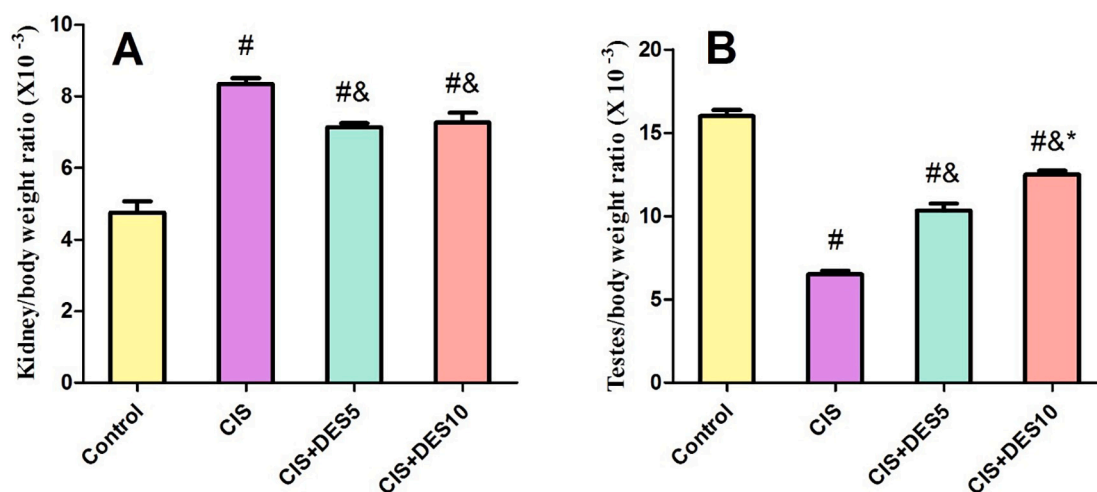


Fig. 3. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to kidney/body weight ratio and testis/body weight ratio; A) kidney/body weight ratio; B) testis/body weight ratio.

Data are expressed as mean \pm S.E.M, ($n = 4-6$).

CIS, cisplatin; DES, desloratadine (5 or 10 mg/kg, orally); S.E.M, standard error of the mean; ANOVA, analysis of variance. #, &, * significantly different when compared with control, CIS, or CIS + DES5 group, respectively, using one-way ANOVA followed by Tukey-Kramer multiple comparisons post-hoc test for the change in body weight ($p < 0.05$).

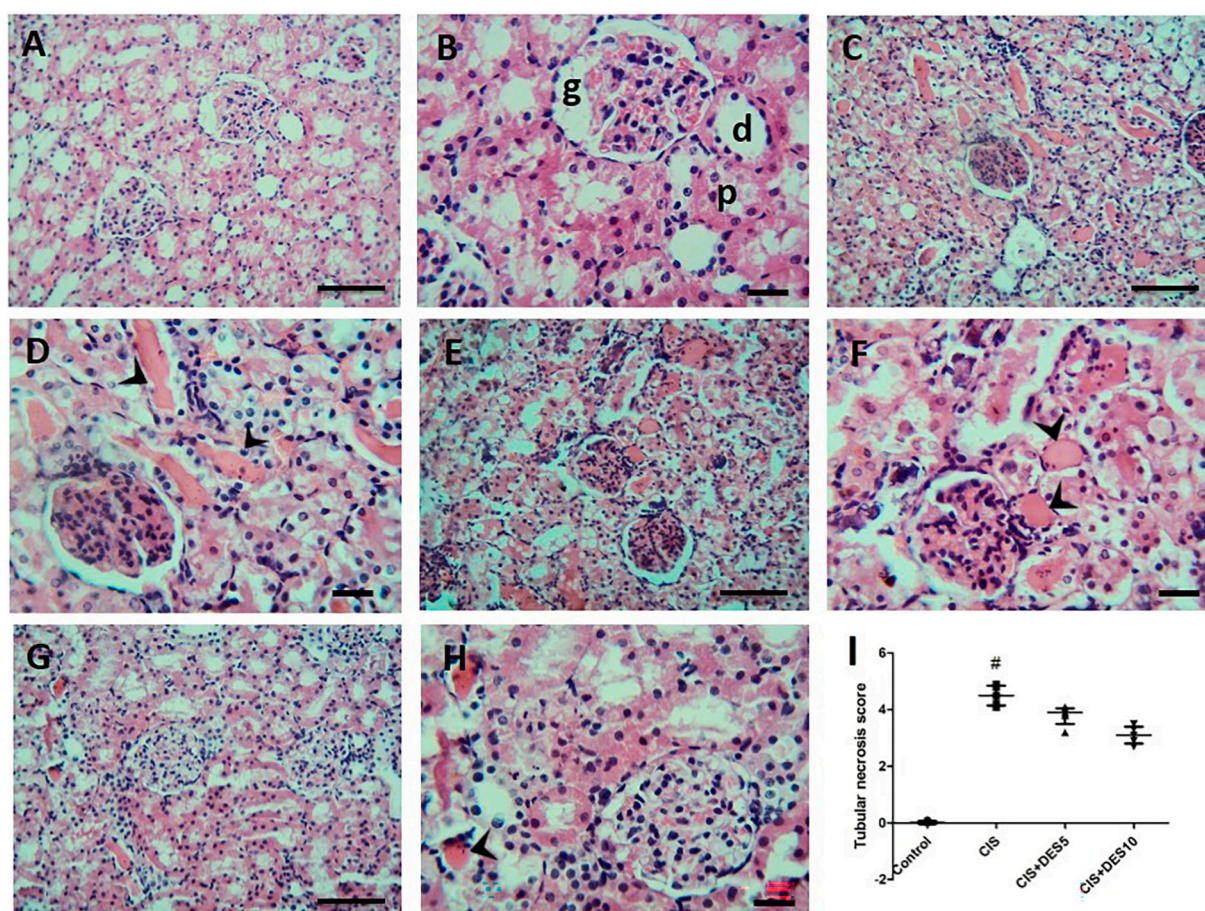


Fig. 4. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to renal histopathology by H&E.

Histological sections of rat kidney showing the cortices of the control group (A & B), CIS group (C & D), CIS + DES5 group (E & F), and CIS + DES10 group (G & H). H&E: A, C, E & G X 200 and B, D, F & H X 400. The control group shows the normal structure of the renal cortex with the glomeruli (g), proximal convoluted tubules (p), and distal convoluted tubules (d). CIS group shows severe affection of the renal tubules with signs of tubular cell lining vacuolation and intratubular cast deposition (arrowheads). I: scores of tubular necrosis, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. #, $p < 0.05$ vs. control, $n = 4$.

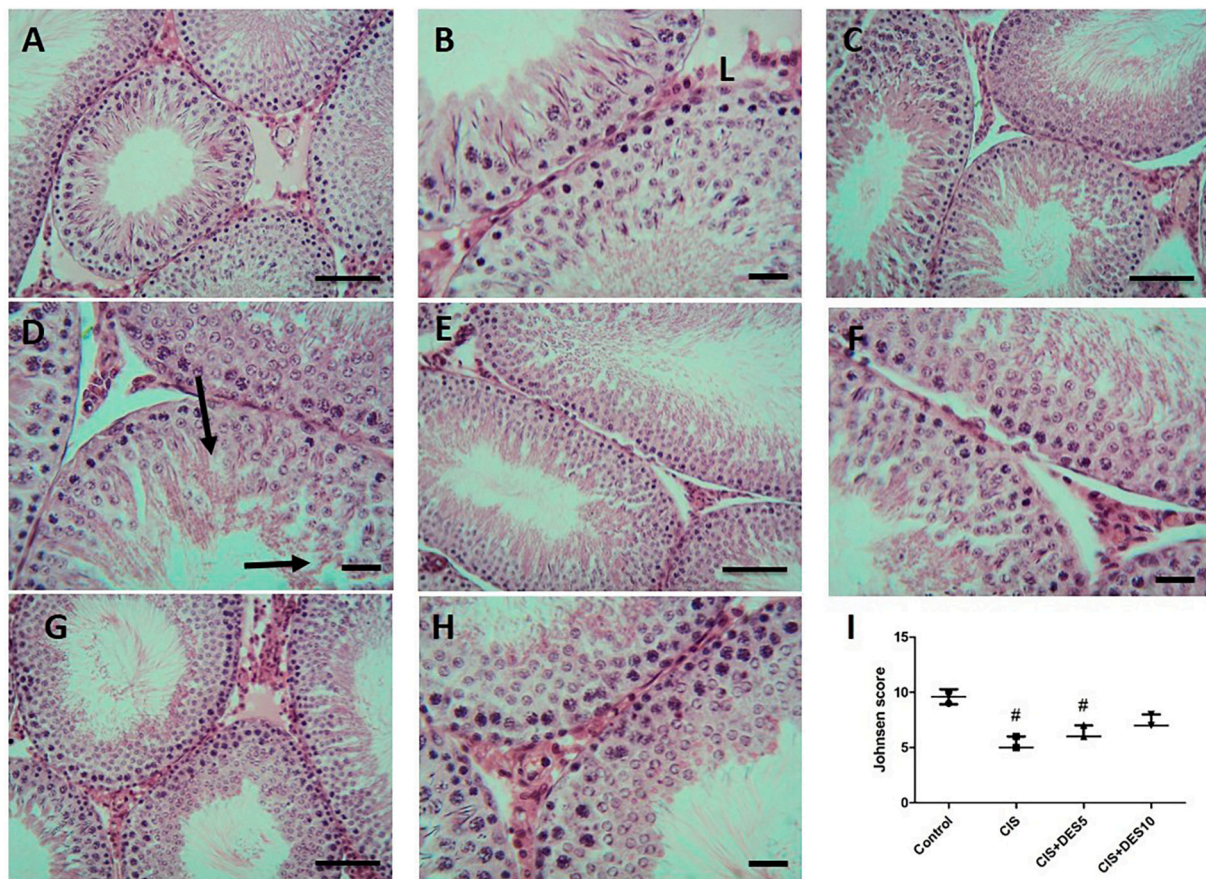


Fig. 5. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to testicular histopathology by H&E. Histological sections of rat testes showing the control group (A & B), CIS group (C & D), CIS + DES5 group (E & F), and CIS + DES10 (G & H). Hematoxylin & Eosin: A, C, E & G X 200 and B, D, F & H X 400). The control group shows the normal structure of the testis with seminiferous tubules lined with different stages of spermatogonia and separated with the Leydig cell (L). The positive group shows pathological changes in the seminiferous tubular epithelium in the form of intercellular spacing (arrows). I: Johnsen scores, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups, $n = 4$.

Table 2

Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced renal and testicular oxidative stress.

	Renal oxidative stress			Testicular oxidative stress		
	MDA (nmol/g)	GSH (mmol/g)	SOD (U/g)	MDA (nmol/g)	GSH (mmol/g)	SOD (U/g)
Control	7.4 ± 0.4	0.38 ± 0.01	54.8 ± 0.4	7.2 ± 0.01	0.51 ± 0.02	49.4 ± 0.3
CIS	15.2 ± 0.2 [#]	0.12 ± 0.001 [#]	36 ± 1.4 [#]	20.8 ± 0.3 [#]	0.16 ± 0.01 [#]	28.7 ± 1.1 [#]
CIS + DES5	8 ± 0.3 ^{&}	0.21 ± 0.01 ^{#&}	48.6 ± 2.2 ^{&}	15.2 ± 1.6 ^{#&}	0.26 ± 0.009 ^{#&}	46.8 ± 0.9 ^{&}
CIS + DES10	10.9 ± 0.3 ^{#&*}	0.28 ± 0.008 ^{#&*}	44.5 ± 2.1 ^{#&}	12.4 ± 0.9 ^{#&}	0.3 ± 0.01 ^{#&}	37.2 ± 1.3 ^{#&*}

Data are expressed as mean ± S.E.M, ($n = 4-6$).

CIS, cisplatin; DES, desloratadine; S.E.M, standard error of the mean; ANOVA, analysis of variance; MDA, malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase. #, &, * significantly different when compared with control, CIS, or CIS + DES5 group, respectively, using one-way ANOVA followed by Tukey-Kramer multiple comparisons post-hoc test for the change in body weight ($p < 0.05$).

temperature at (25 °C ± 2), and humidity (55–65 %) with consecutive cycles of 12 h of light and darkness in standard cages [$n = 3$, dimensions, 43 × 29 cm (L X W)] and unlimited access to standard pellets diet (5.7 % fat, 44.3 % carbohydrate, 19.9 % protein and small percentages of calcium, phosphorus and fibres) and tap water.

Animal care and procedures were carried out in compliance with the guidelines of ARRIVE and the National Institutes of Health (NIH) standards and authorized by the Research Ethics Committee- Faculty of Pharmacy, Mansoura University, Mansoura, Egypt (code number: 2022–213).

2.2. Drugs and chemicals

DES (CAS No: 100643–71-8), provided as Delarex® tablets (GLOBAL NAPI pharmaceuticals, Cairo, Egypt), was prepared by dissolving in sterile water and given orally. Cis (CAS No:

100,643–71-8), was provided as a 50 mg/50 ml vial (Mylan Pharmaceuticals, Mumbai, India) was given via intraperitoneal (i.p.) injection. All utilized chemicals were of the highest purity.

2.3. Experimental protocol

Rats were allowed to acclimate one week before the commencement

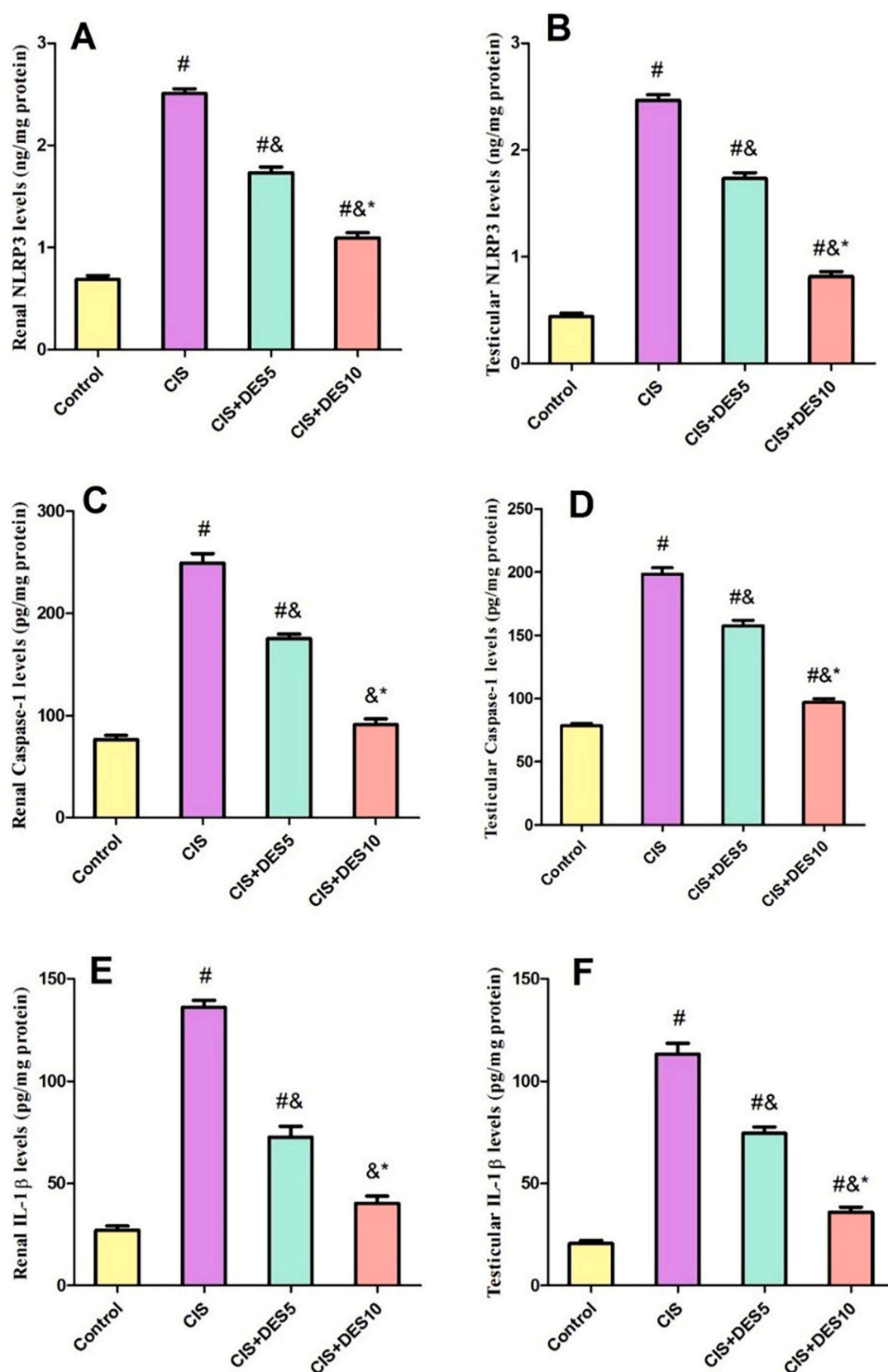


Fig. 6. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to A) renal NLRP3, B) testicular NLRP3, C) renal caspase-1, D) testicular caspase-1, E) renal IL-1 β , F) testicular IL-1 β .

Data are expressed as mean \pm S.E.M, ($n = 4-6$).

CIS, cisplatin; DES, desloratadine; S.E.M, standard error of the mean; ANOVA, analysis of variance; NLRP3: Nod-like receptor 3, IL-1 β : interleukin-1 β . #, &, * significantly different when compared with control, CIS, or CIS + DES5 group, respectively, using one-way ANOVA followed by Tukey-Kramer multiple comparisons post-hoc test for the change in body weight ($p < 0.05$).

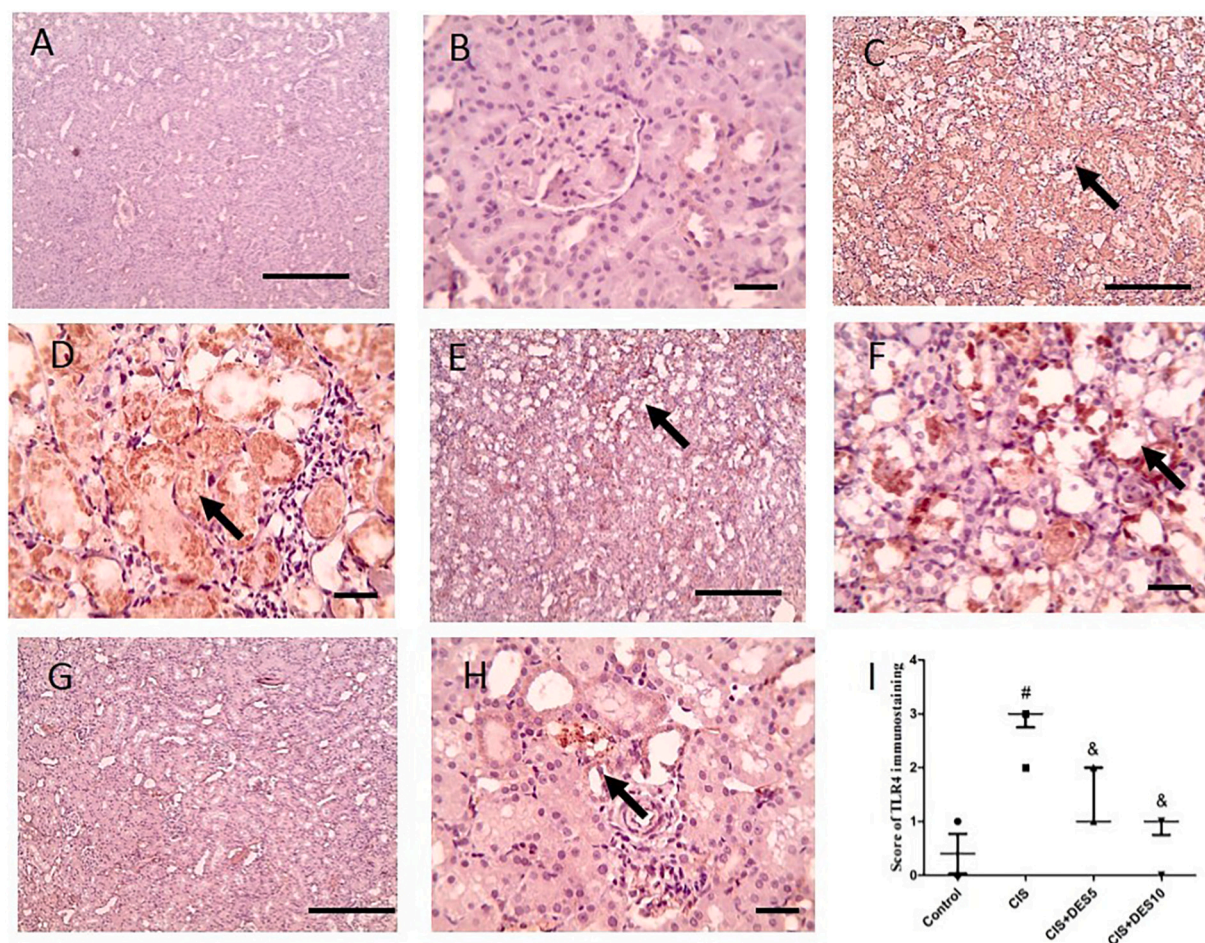


Fig. 7. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to immunohistochemically stained renal TLR4. Microscopic pictures of immunostained renal tissue against TLR4. X: 100 bar 100 (A,C,E,G) and X: 400 bar 50 (B,D,F,H). I: score of TLR4 immunostaining, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. #, $p < 0.05$ vs. control; & $p < 0.05$ vs. CIS, $n = 4-6$.

of the experiment. Rats were randomly divided into four groups; a normal Control group, to which sterile water was given orally once per day for ten days and a single i.p. injection of normal saline (0.9 % w/v) on day 9 was administered. CIS group: rats received an i.p. injection of CIS (10 mg/kg) [16,17] on day 9 to induce both renal and testicular damage in rats. CIS + DES5 and CIS + DES10 groups: rats orally received DES (5 and 10 mg/kg/day, respectively) [12] once per day for ten days and were injected with CIS (10 mg/kg, i.p.) on day 9. CIS was injected in overnight fasted rats. Drugs were administered daily at 9 a.m. CIS was injected an hour after the treatment dose on day 9.

2.4. Collection of the biological samples

24 h post the injection of rats with CIS, 24 h-urine samples were collected from all the groups. Rats were weighed and underwent thiopental anesthesia. Blood was withdrawn after a heart puncture, allowed to clot for 30 min, and then centrifuged at 3000g for 15 min at 4 °C to separate the serum to be divided into aliquots stored at -80 °C until analysis. The two kidneys and testes were dissected from each rat, washed, blot-dried, and weighed. A part of the kidney and the left testicular tissue were preserved at -80 °C for the subsequent conduction of enzyme-linked immunosorbent assay (ELISA) and oxidative stress/antioxidant assays. A part of the remaining kidney and the right testicle was preserved in 10 % (v/v) neutral-buffered formalin solution and Davidson solution (347 ml deionized water, 111 ml/l 100 % acetic acid, 320 ml/l 99 % ethanol, and 222 ml/l formalin-solution 10 % phosphate-

buffered) for 48 h, respectively, for the preparation of the paraffin blocks of these tissues for both histopathological and immunohistochemical assessments for toll-like receptor 4 (TLR4), tumor necrosis factor- α (TNF- α) and nuclear factor-kappa B (NF- κ B) proteins.

2.5. Evaluation of renal injury and function

The renal injury and function were evaluated biochemically by estimating the serum levels of creatinine (Cr), urea and blood urea nitrogen (BUN). Urinary creatinine, albumin, and total protein were also evaluated. All these parameters were measured by commercially available kits (235,001, 320,001, 210,001, 310,001, respectively, Spectrum Diagnostics, Cairo, Egypt) and following the manufacturer's guidelines.

2.6. Histopathological and immunohistochemical assessments of both renal and testicular tissues

For the histopathological assessment, both fixed renal and testicular tissues were embedded in paraffin wax, sectioned (4 μ m in thickness) by microtome, and then stained with hematoxylin and eosin (H&E). For the immunohistochemical assessment, 4 μ m-thick paraffin-embedded sections, along with an appropriate positive control section, underwent deparaffinization by heating and rehydration using xylene and descending concentrations of ethanol. Subsequently, sections were subjected to retrieval of antigens using a citrate buffered solution (pH 6.0), and blocking of endogenous peroxidases, using 3 % hydrogen

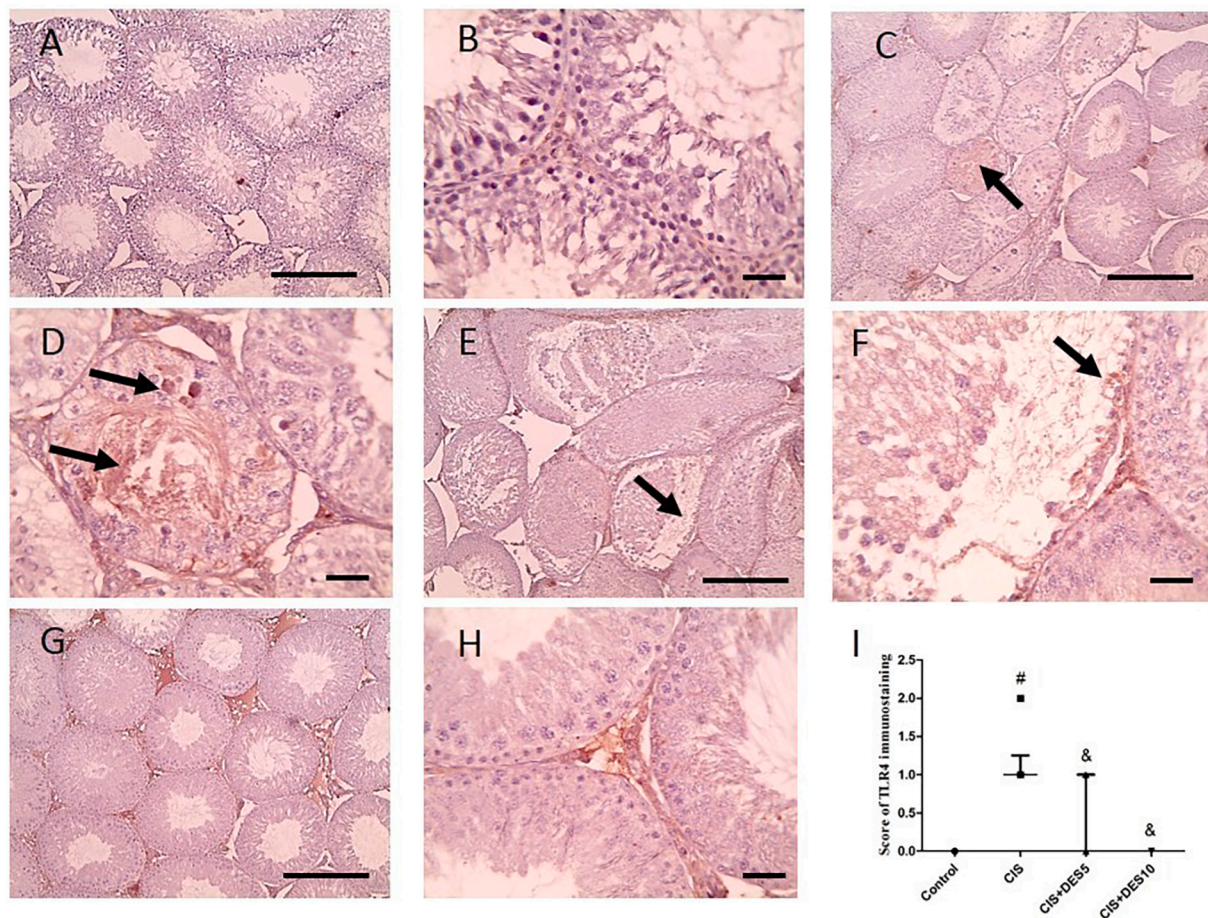


Fig. 8. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to immunohistochemically stained testicular TLR4. Microscopic pictures of immunostained testicular tissue against TLR4. X: 100 bar 100 (A,C,E,G) and X: 400 bar 50 (B,D,F,H). I: score of TLR4 immunostaining, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. #, $p < 0.05$ vs. control; & $p < 0.05$ vs. CIS, $n = 4-6$.

peroxide for 15 min, and the non-specific protein binding, using 1 % bovine serum albumin for 1 h. Slide sections were incubated with primary antibodies, followed by HRP-conjugated secondary antibodies and substrate/chromogen for color development. The primary antibody for TLR4 was provided from Wuhan Servicebio Biotechnology (Wuhan, China) at dilution 1:500, while that of TNF- α and NF- κ B were provided from ABclonal (Woburn, MA, USA) at dilution 1:200.

An unbiased researcher conducted the histopathological and immunohistochemical analysis in a blind fashion. ImageJ software (1.52a, NIH, USA) with a dedicated built-in routine for an area measuring and the quantification of the stain was used to examine the images. [18].

2.7. Enzyme-linked immunosorbent assay (ELISA) for cytokines

Renal and testicular levels of IL-1 β , caspase-1, and nucleotide-binding domain-(NOD) like receptor 3 (NLRP3) were measured in tissue lysates using ELISA kits bought from (Cloud-Clone Corp, USA), (Biovision, Milpitas, CA, USA) and (Aviva systems biology, San Diego, CA, USA), respectively. To make tissue lysates, 50 mg of tissue (from the kidney or testis) were ground in 0.45 ml of ice-cold lysis buffer (10 mM Tris pH 7.4, 150 mM NaCl, 0.5 % v/v Triton X-100). The supernatants were then separated by centrifugation at 5000g for 10 min at 4 °C. Eventually, 96-well ELISA plates were filled with tissue lysate supernatants. Using Bradford's technique, the protein content in tissue lysates was measured [19].

2.8. Determination of renal and testicular oxidative stress and antioxidant parameters

Using a Potter-Elvehjem homogenizer, portions of both the kidney and testicle (10 % w/v) were crushed in an ice-cold buffer (20 mM Tris-HCl, 1 mM EDTA, pH 7.4). Then, supernatants were collected by centrifuging the mixture at 3000g for 20 min at 4 °C and immediately used for the subsequent analysis.

Superoxide dismutase (SOD) activity and the level of reduced glutathione (GSH) were evaluated as indicators of the tissue antioxidant capacity, whereas malondialdehyde (MDA) concentration was assessed as a sign of lipid peroxidation [20]. MDA content was determined by the previously stated technique [21]. Briefly, MDA was measured through a reaction with thiobarbituric acid (TBA), and absorption was determined spectrophotometrically at 532 nm. As described by Marklund, SOD-inhabitable auto-oxidation of pyrogallol was monitored to measure the SOD activity [22]. At 420 nm, the change in absorbance was measured. The 5,5-dithiobis-2-nitrobenzoic acid and GSH reaction is the basis for GSH determination, and the product was evaluated spectrophotometrically at 412 nm [23].

2.9. Statistical analysis

Data were expressed as mean \pm standard error of the mean (S.E.M). One-way analysis of variance (ANOVA) and then Tukey's Kramer multiple comparisons test were used for the statistical evaluation of the data. Dunn's test was employed after Kruskal Wallis for non-parametric

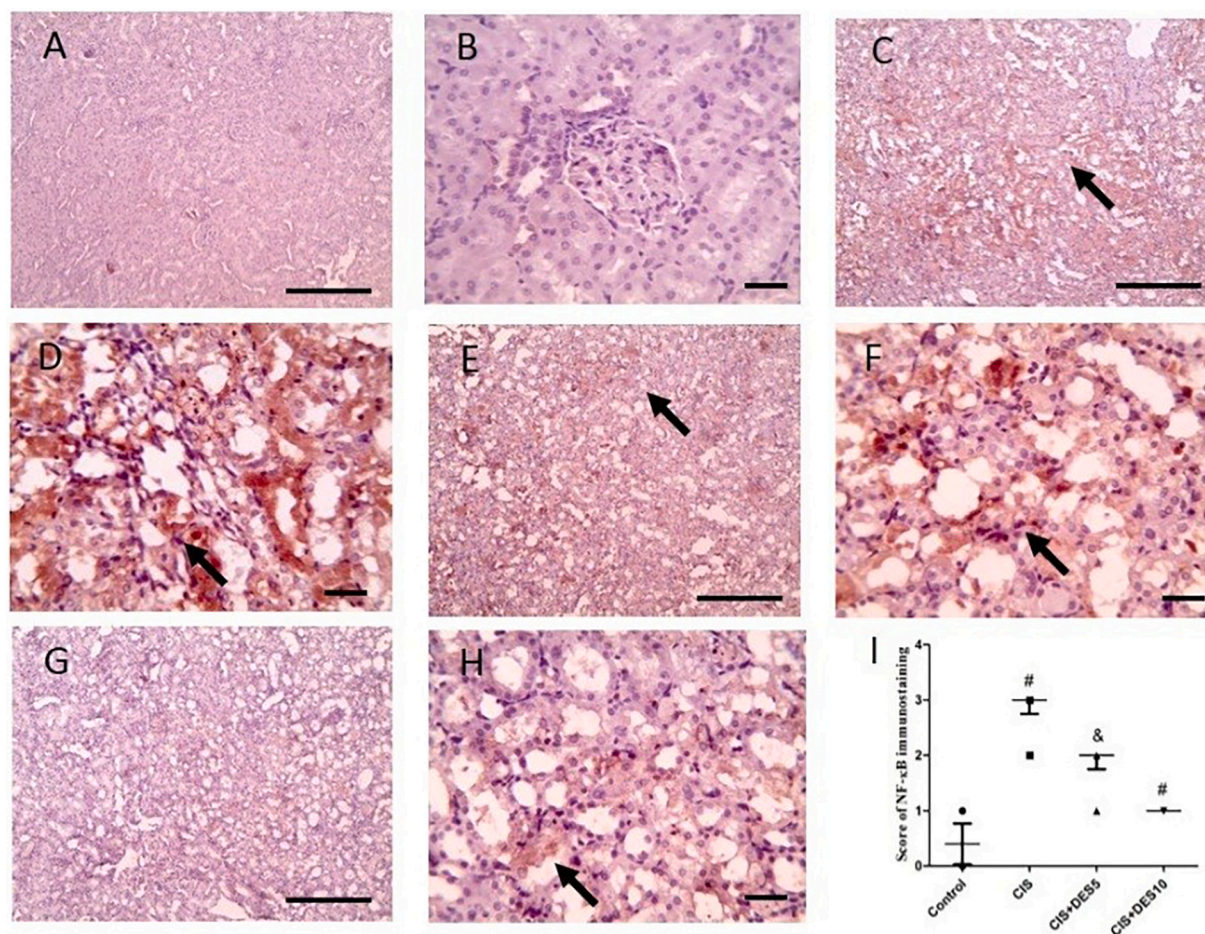


Fig. 9. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to immunohistochemically stained renal NF-κB. Microscopic pictures of immunostained renal tissue against NF-κB. X: 100 bar 100 (A,C,E,G) and X: 400 bar 50 (B,D,F,H). I: score of NF-κB immunostaining, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. #, $p < 0.05$ vs. control; & $p < 0.05$ vs. CIS, $n = 4-6$.

comparison for the histopathological score. Statistical analyses were performed by Graphpad software Prism V 5 (Graphpad Software Inc., San Diego, CA, USA). Significance was predefined as a p -value < 0.05 .

3. Results

3.1. Effect of DES on CIS-induced mortality and change in body weight

Table 1 shows that two of six rats have died after an i.p. injection of a high dose of CIS. In both the control and the CIS + DES10 groups, there was no mortality, however, in the CIS + DES5 group, one of six rats has not survived.

Injection with CIS resulted in a significant decrease the body weight upon comparison with the control group. Oral pretreatment with DES (5 mg/kg) significantly decreased this loss when compared to the CIS group. In the DES10 group, the body weight was maintained nearly as the control group (Table 1).

3.2. Effect of DES on CIS-induced alterations to serum renal function parameters

A significant build-up of metabolic waste products, Cr and urea, and subsequently BUN, was apparent in the CIS group compared to the control group. Oral administration of DES in both doses significantly decreased these elevated levels when compared to the CIS group (Fig. 1).

3.3. Effect of DES on CIS-induced alterations to urine parameters

CIS injection induced a substantial elevation in the urinary levels of total protein and albumin concomitant with a marked decrease in levels of creatinine clearance (CrCl) when compared to the control group. Pretreatment with either DES 5 or 10 mg/kg significantly reduced the levels of total protein and albumin and increased levels of CrCl in urine when compared to the CIS group (Fig. 2).

3.4. Effect of DES on CIS-induced alterations to kidney/body weight and testis/body weight ratio

In the CIS group, there was a profound rise in kidney/body weight ratio and a substantial drop in testis/body weight ratio when compared to the control group. Oral administration of DES (5 & 10 mg/kg) markedly decreased kidney/body weight ratio and increased testis/body weight ratio when compared to the CIS group (Fig. 3).

3.5. Effect of DES on CIS-induced alterations to renal and testicular histopathology

Fig. 4 illustrates that renal sections from the control group show a normal structure of the renal cortex with the glomeruli and proximal and distal convoluted tubules. The CIS group exhibited severe changes to the renal tubules with signs of tubular cell lining vacuolation and intra-tubular cast deposition. In contrast, pretreatment with DES showed

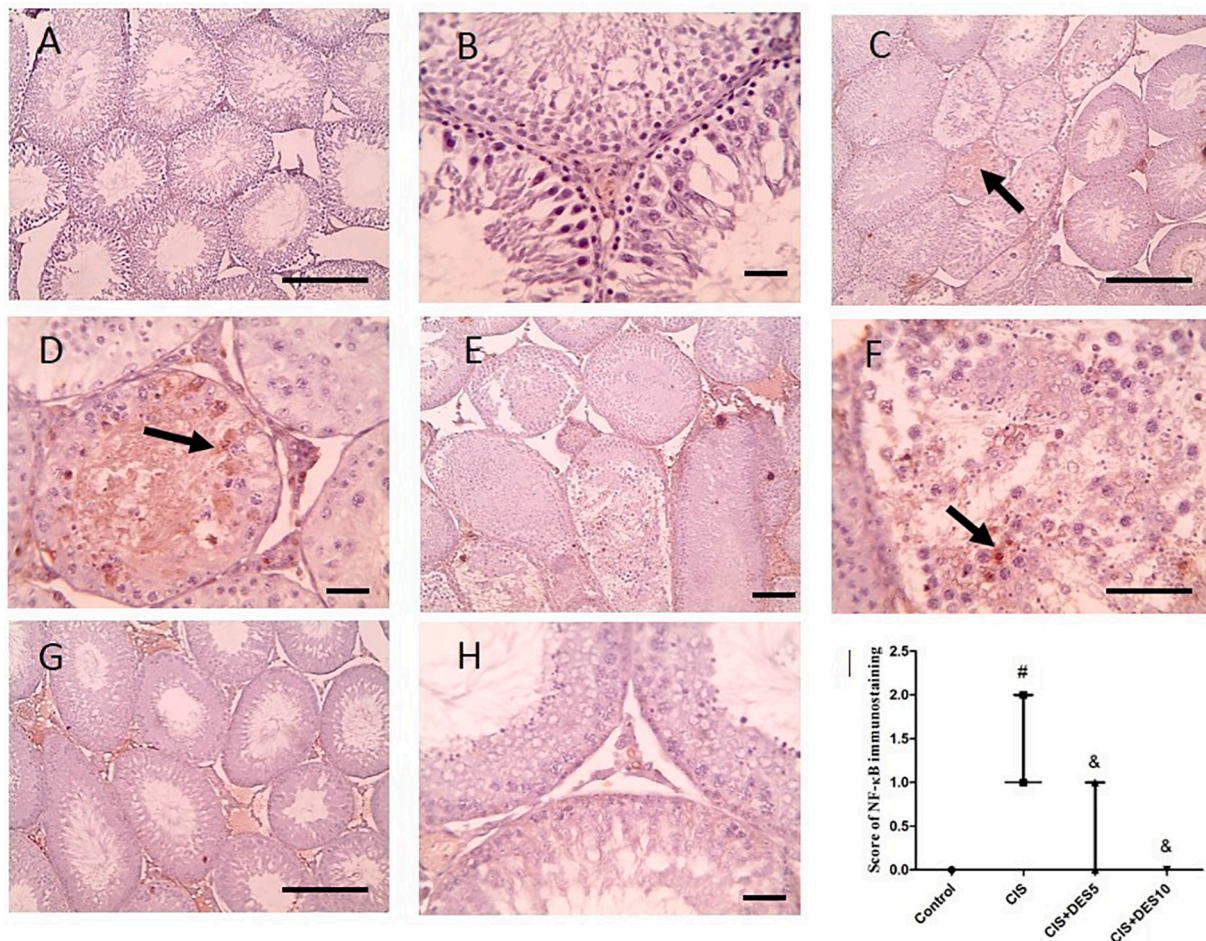


Fig. 10. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to immunohistochemically stained testicular NF-κB. Microscopic pictures of immunostained testicular tissue against NF-κB. X: 100 bar 100 (A,C,E,G) and X: 400 bar 50 (B,D,F,H). I: score of NF-κB immunostaining, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. [#], $p < 0.05$ vs. control; & $p < 0.05$ vs. CIS, $n = 4-6$.

marked improvement in the renal lesions in a dose-dependent manner.

Fig. 5 demonstrates that the control group shows the normal structure of the testis with seminiferous tubules lined with different stages of spermatogonia and average interstitium with average Leydig cells. In contrast, the CIS group exhibited marked subcapsular congestion of the blood vessel with edema. The testis from that group also shows the seminiferous tubular epithelium in the form of intercellular spacing and partial destruction of the basement membrane, necrotic germinal lining, and marked interstitial edema with Leydig cell hyperplasia. There was an obvious improvement in sections from CIS + DES5 and CIS + DES10 groups; by only showing fewer scattered tubules with a mild incidence of interstitial edema and Leydig cell hyperplasia.

3.6. Effect of DES on CIS-induced renal and testicular oxidative stress

A single injection of CIS produced a significant elevation in both renal and testicular MDA content, concomitant with a marked reduction in both renal and testicular GSH levels and SOD activities when compared with the control group. DES in both doses substantially reversed these alterations when compared to the CIS group (Table 2).

3.7. Effect of DES on renal and testicular NLRP3, Caspase-1, and IL-1 β levels

Indeed, in the CIS group, the renal and testicular levels of NLRP3 (Fig. 6A & B) were significantly elevated along with an increase in the

renal and testicular Caspase-1 (Fig. 6C & D) and consequently, an increase in the renal and testicular IL-1 β levels was observed (Fig. 6E & F) when compared to the control group. Oral treatment with DES (5 and 10 mg/kg) repressed the activation of the NLRP3/Caspase-1/IL-1 β pathway compared to the CIS group.

3.8. Effect of DES on renal and testicular TLR4 protein level

Microscopic pictures of immunostained renal and testicular sections against TLR4 showed negative expression in the renal epithelium and epithelial lining of the seminiferous tubules of the control group (Fig. 7A,B) and (Fig. 8A,B), respectively. In contrast, sections from the CIS group revealed a strong positive brown staining of the protein compared to the control group (Fig. 7C,D) and (Fig. 8C,D) respectively. In the CIS + DES5 group, TLR4 was only moderately elevated in the renal epithelium (Fig. 7E,F) and decreased in the epithelial lining of the seminiferous tubules (Fig. 8E,F). In the CIS + DES10 group, TLR4 was mildly elevated in the renal section (Fig. 7G,H), however, retained negative expression in the testicular section (Fig. 8G,H). Figs. 7I & 8I showed the results of the semi-quantitative analysis of TLR4 immunostaining in both renal and testicular tissues, confirming the previous observations.

3.9. Effect of DES on renal and testicular NF-κB protein expression

Microscopic pictures of immunostained renal and testicular sections

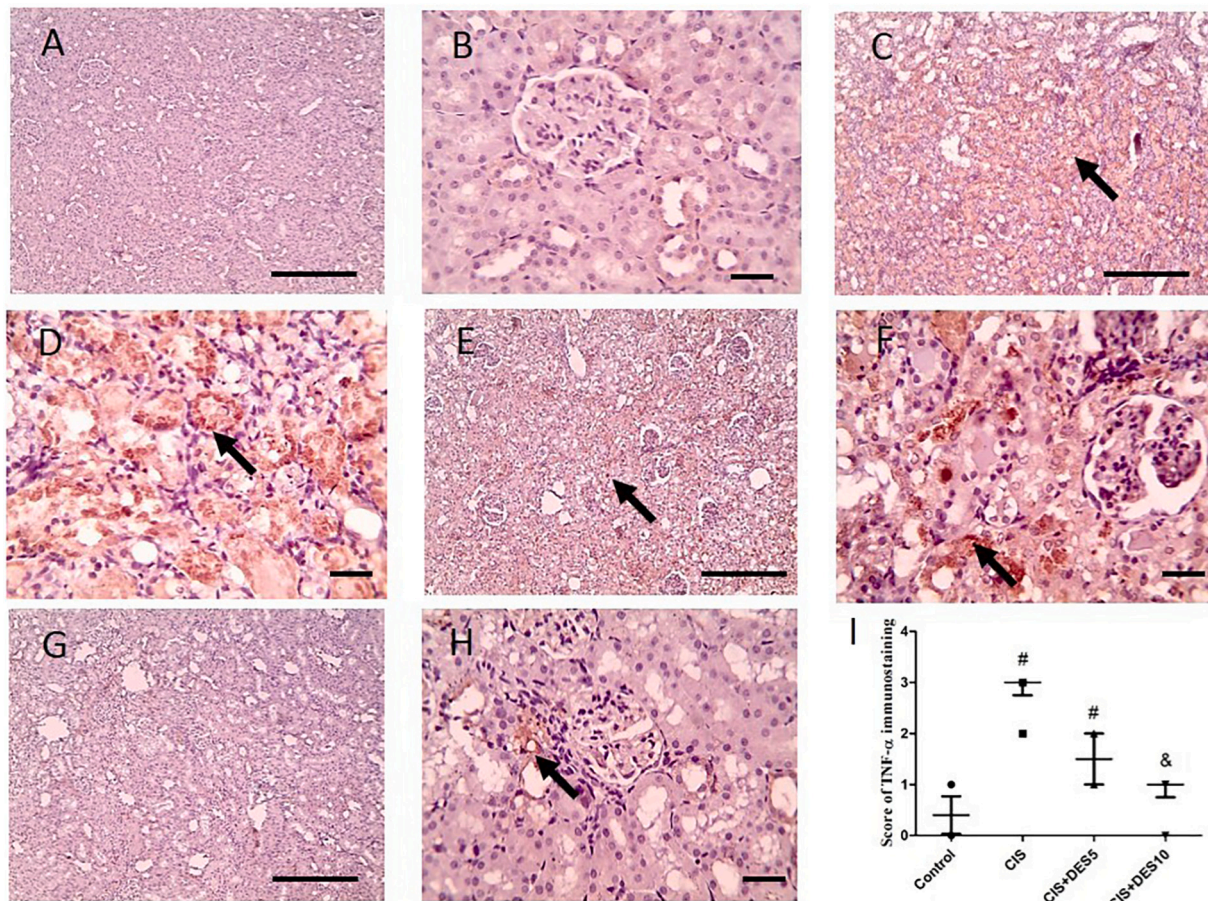


Fig. 11. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to immunohistochemically stained renal TNF- α . Microscopic pictures of immunostained renal tissue against TNF- α . X: 100 bar 100 (A,C,E,G) and X: 400 bar 50 (B,D,F,H). I: scores of TNF- α immunostaining, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. #, $p < 0.05$ vs. control; & $p < 0.05$ vs. CIS, $n = 4-6$.

against NF- κ B of the control group showed negative expression in renal epithelium and epithelial lining seminiferous tubules (Fig. 9A,B) and (Fig. 10A,B) respectively. Sections from the CIS group revealed a high expression of NF- κ B, indicated by the strong brown staining, in renal epithelium and the epithelial lining seminiferous tubules (Fig. 9C,D) and (Fig. 10C,D), respectively, when compared to the control group. In the CIS + DES5 group, the expression of NF- κ B appeared to be moderate in the renal epithelium (Fig. 9E,F) and decreased in epithelial lining affected seminiferous tubules (Fig. 10E,F). On the other hand, in the CIS + DES10 group, the NF- κ B staining was mild in the renal section (Fig. 9G,H), however, retained a negative expression in the testicular section (Fig. 10G,H). Figs. 9I & 10I showed the results of the semi-quantitative analysis of NF- κ B immunostaining in renal and testicular tissues, confirming the previous findings.

3.10. Effect of DES on renal and testicular TNF- α protein expression

Microscopic pictures of immunostained renal and testicular sections against TNF- α showed negative expression in renal epithelium and epithelial lining seminiferous tubules of the control group (Fig. 11A,B) and (Fig. 12A,B) respectively. Pictures from the CIS group exhibited a strong positive brown staining of TNF- α in the renal epithelium and epithelial lining seminiferous tubules in comparison to the pictures obtained from the control group (Fig. 11C,D) and (Fig. 12C,D) respectively. Regarding the CIS + DES5 group, the positive brown staining of TNF- α appeared to be decreased in the renal epithelium (Fig. 11E,F) and in the epithelial lining of the seminiferous tubules (Fig. 12E,F) when compared

to the CIS group. Concerning the CIS + DES10 group, both renal and testicular staining of TNF- α was the least among the groups administered CIS (Fig. 11G,H) and (Fig. 12G,H), respectively. Results of a semi-quantitative analysis of TNF- α immunostaining in renal and testicular tissues showed the same findings (Figs. 11I & 12I).

4. Discussion

Organs injuries are common side effects of chemotherapeutic agents, such as CIS, inciting dire consequences on both patient quality of life and survival [3]. CIS is a favorable anti-cancer agent in various solid tumors. However, its application is often clinically limited by the accompanied nephrotoxicity and adverse impact on the testicular tissue [4].

Unfortunately, the specific pathogenic mechanisms underlying CIS-induced damage on normal tissues, such as the kidney and testis, remain unclear [4]. However, CIS is thought to damage the cellular integrity of healthy tissue provoking vicious cycles of oxidative stress, inflammation, and cellular death. In our study, the potential repurposing of DES was investigated in ameliorating both CIS-induced renal and testicular injuries in male rats. Previous studies have shown the possible role of DES as an antioxidant and anti-inflammatory agent in other animal experimental models [24,25]. However, the usage of DES to relieve CIS-induced AKI and testis injuries has not been reported.

At first, the successful establishment of CIS-induced tissue damage was demonstrated. The CIS group exhibited a significant reduction in both renal function and the ability to filtrate metabolic toxic wastes. As previously indicated, urine excretion of CIS is mediated by the apically-

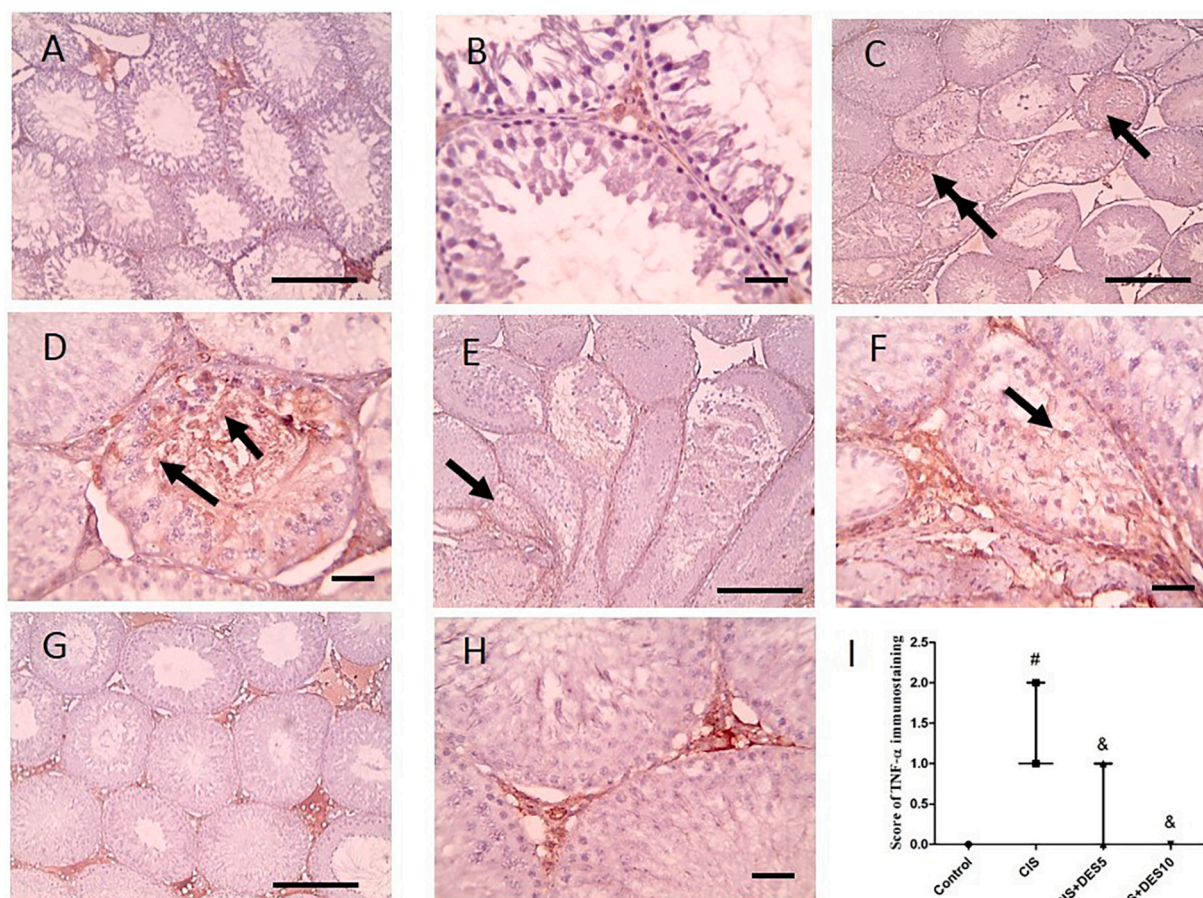


Fig. 12. Effect of DES (5 or 10 mg/kg, orally) on CIS (10 mg/kg, i.p.)-induced alterations to immunohistochemically stained testicular TNF- α . Microscopic pictures of immunostained testicular tissue against TNF- α . X: 100 bar 100 (A,C,E,G) and X: 400 bar 50 (B,D,F,H). I: score of TNF- α immunostaining, Kruskal-Wallis test was performed followed by Dunn's multiple comparison post-hoc test to test the significance between groups. [#], $p < 0.05$ vs. control; [&] $p < 0.05$ vs. CIS, $n = 4-6$.

localized efflux transporters, such as multidrug resistance-associated proteins (MRPs), and multi-antimicrobial extrusion protein (MATEs). Both transporters are highly present in the renal proximal and distal tubules [26]. As a consequence, CIS is mainly cleared through glomerular filtration and tubular excretion, in a fashion that ultimately causes its concentration to build up in the renal tissue more than any other tissue [2]. Subsequently, CIS starts to induce renal injury that progresses into acute and then chronic nephrotoxicity. In our study, a single high dose of CIS provoked both tubular cell injury and death aggravated by both inflammation and vascular injury as indicated by H&E histopathological investigation. These observations are in agreement with a previous study of the same model [27,28].

To further confirm the previous observation, the CIS group exhibited a significant elevation of serum cr, urea, and BUN compared to their levels in the control group. The formers are considered golden key diagnostic markers of renal injury by reflecting the poor capacity of nephrons to selectively remove these waste products from the blood and into the urine [29]. This was also associated, in return, with a decreased level of urinary Cr. Further, damaged nephrons in the CIS group also exhibited a non-selective and unwanted filtration of major and bulky molecules indicated by a significant elevation of both urinary total protein and albumin compared to the control group.

In contrast, pretreatment with DES (5 and 10 mg/kg) significantly reduced CIS-induced renal injury by significantly preserving the renal ability to filtrate the toxic molecule, cr; by reducing its level in the serum and enhancing its excretion in the urine. Further, DES significantly reduced both serum urea and BUN compared to those in the CIS group.

In addition, H&E-stained renal tissue indicated a significant improvement of the tissue and an obvious spare of the renal tissue from CIS. DES has been once reported to have a potential renoprotective effect in I/R injury, showing a similar observation [12].

Fortunately, DES exhibited a similar protective effect on the testicular tissue from the induced toxicity by CIS. This observation was carried out by H&E-staining of the tissue. CIS is known to cause testicular damage through the stimulation of oxidative stress and DNA damage affecting, in process, the Leydig cells and inducing the death of the germ cells [30]. In our study, DES indeed reduced CIS-induced Leydig cell hyperplasia, necrotic germinal lining, focal lack of spermatogenesis, and the observed interstitial edema observed in the CIS group.

Collectively, the observed protective effect of DES, most specifically in the dose (10 mg/kg), contributed, in return, to the improvement occurring in the animal parameters. For example, DES promoted survival in this pretreated group, showing no mortality, retention of good weight gain, and an enhancement in both renal and testicular indexes.

The study then investigated the possible underlying mechanisms of the observed protective effect of DES. As previously mentioned, the negative impact of CIS on the normal tissues as a side effect arises from the significant generation of reactive oxygen species (ROS) wreaking havoc on cellular homeostasis. As a consequence, these ROS, are thought to provoke several signaling pathways, such as NF- κ B, inducing the observed CIS injury [12].

Measuring tissue MDA has been considered a great tool to assess oxidative stress. In addition, an inadequate antioxidant defense system, led by GSH and antioxidant enzymes such as SOD, contributes to

oxidative-induced injury under inflammatory conditions [31]. In response to the high dose of CIS, both renal and testicular tissues of the CIS group exhibited a significant elevation in the levels of MDA, indicating an impaired oxidative balance, with a significant reduction in both GSH level and SOD activity, indicating limitations to the antioxidant defense system. Decreases in the level of GSH and activity of SOD, parallel to a significant increase in the level of MDA, by CIS-induced tissue toxicity, have been previously reported [32–34].

Previously, NF- κ B has been suggested as a driving force of the vicious cycle between inflammation and oxidative stress causing the adverse side effects of CIS [35–37]. Upon its activation in response to stress, cytokines, and ROS, NF- κ B p65 act as a transcription factor by phosphorylation that hinders its degradation, allowing a build-up of its concentration in the cytoplasm and subsequent translocation to the nucleus to control the expressions of a variety of proinflammatory cytokines and chemokines [38]. In agreement, significant elevations of NF- κ B levels in both renal and testicular tissues, with a significant nuclear translocation, have been observed in the CIS group in comparison to the control group.

DES has been previously reported as a possible antioxidant in both rat and human subjects [11,12,39]. Pretreatment with DES (5 and 10 mg/kg) reinstated the oxidative balance by significantly enhancing SOD activity, sparing GSH from being over-spent in return, and preventing the elevation of MDA, which ultimately reduced NF- κ B activation and localization into the nucleus. These observed effects may be related to DES antagonistic effect on histamine (H)₁-receptor, where histamine has been shown to activate NF- κ B [40], most interestingly only following induced H₁ receptor overexpression [41]. Moreover, the same study indicated the repressive effect of DES on NF- κ B activation, which could not be achieved by either H₂- or H₃-receptor antagonists [41].

As previously mentioned, NF- κ B is a major driver of inflammation by acting as a transcription factor for proinflammatory molecules [42]. Of those, TNF- α appears to play a central role in the pathogenesis of CIS-induced AKI [43]. Indeed, the CIS group, in response to the elevation of NF- κ B, exhibited a significant elevation of both renal and testicular TNF- α in comparison to the control group.

Interestingly, the secretion of TNF- α from renal tubular cells and activation of NF- κ B creates positive feedforward loops that have been suggested as a therapeutic potential for treating CIS-induced organ damage. Pretreatment with DES (10 mg/kg) significantly reduced the level of TNF- α in comparison to the CIS group. Renal tubular cell death is the cumulative consequence of cellular responses to CIS treatment. Of the mechanisms by which the cell activates cell death, during CIS assault, is TNF- α -led extrinsic apoptosis, often elevated in the impacted tissues. Previously, H₁-receptor blocker antihistamines have been suggested to have a non-histamine-related anti-inflammatory effect [44]. Targeting TNF- α has been reported as one of those underlying mechanisms. In one report, exogenous TNF- α -induced activation of NF- κ B has been repressed by DES in human lung A549 epithelial cells and even opposed its activity on another protein, RANTES, a chemokine provoked during allergy [41]. In parallel, TNF- α -deficient mice were resistant to CIS-induced AKI [43]. Moreover, the same research demonstrated that targeting TNF- α -induced expression of RANTS and other chemokines, has improved CIS-induced nephrotoxicity. DES has shown inhibition of TNF- α in the human mast cell line (HMC-1) without time- nor concentration dependency [45]. Finally, DES reduced TNF- α and induced proinflammatory cytokines in patients with chronic sinusitis [14].

Activation of NLRP-3 inflammasome is another key orchestrating multiprotein complex in CIS-induced inflammatory storms. The activation of this complex is closely associated with an overproduction of ROS during tissue injury [42], both are key events for CIS-induced organ injury. The complex is assembled from NLRP3, an adapter protein, apoptosis-associated speck-like protein containing a CARD (ASC), and pro-cysteinyl aspartate specific proteinase-1 (pro-caspase-1).

During tissue injuries such as those induced by CIS, the death-promoting signals; pathogen- and death-associated molecular patterns

(PAMPs/DAMPs) are detected by the innate transmembrane receptor, TLR4. Increasing evidence supports the important role of TLR-mediated inflammation in CIS-induced AKI [46]. In response, NF- κ B is activated inducing the transcription NLRP3 inflammasome components, NLRP3 and pro-IL-1 β [47], and other proinflammatory mediators, IL-6, and TNF- α [48]. Following danger signals, the assembly of the protein complex occurs activating procaspase-1 into caspase-1 which is responsible for the activation of IL-1 β , inducing pyroptosis [47].

The study investigated the effect of DES on CIS-induced activation of the former pathway. DES involvement in preventing the activation of NLRP3 inflammasome-led pathway remains unknown. However, a close molecule, loratadine, has been suggested to inhibit NLRP3 inflammasome in human chondrosarcoma cell line SW1353 cells, mainly through its ability to regulate ROS production and detoxification [49].

The current study suggests that the protective effect of DES against CIS-induced inflammation is potentially attributed to its ability to reduce both renal and testicular levels of TLR4, following CIS challenge, thus suggesting an additional regulator point of DES over NF- κ B. This suppression of the TLR4/NF- κ B pathway was associated with a significant reduction in the NLRP3 inflammasome levels, indicated by the significant reduction in the level of NLRP3 compared to the CIS group. Finally, DES was able to reduce the activity of NLRP3 inflammasome indicated by a reduced pyroptosis evidenced by reduced levels of both cleaved caspase-1, and subsequently IL-1 β in the pretreated groups compared to the CIS group.

5. Conclusion

The current study has investigated the potential of targeting both inflammation and oxidative stress by DES in ameliorating CIS-induced renal and testicular toxicity in rats. Indeed, pretreatment with DES (5 and 10 mg/kg) revealed significant antioxidant and anti-inflammatory properties. These effects are exerted through its ability to enhance the antioxidant defense system led by both GSH and SOD while, reducing the activation of TLR4/NF- κ B and the NLRP3/Caspase-1/IL-1 β signaling pathways. Therefore, the current study proposes the potential use of DES as adjuvant therapy in attenuating CIS-induced side effects. Future studies, however, should be conducted to investigate its beneficial use clinically during induced cancerous settings. In addition, extensive and thorough assessment of the potential protective effect of DES on the reproductive system should be considered.

CRediT authorship contribution statement

AAS, RAZ, HEK and DHE conceptualized the study and developed the protocol. AAS, RAZ, HEK and DHE carried out the experiments. AAS, RAZ, HEK and DHE analyzed the data. AAS, RAZ, HEK and DHE wrote the first draft and revised the whole manuscript.

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.

Data availability

Data will be made available on request.

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