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RESEARCH ARTICLE

Testicular toxicity of cisplatin in rats: ameliorative effect of lycopene and N-acetylcysteine

Asmaa Elsayed[1] · Ashraf Elkomy[1] · Mohamed Alkafafy[2] · Reda Elkammar[3] · Anwar El-Shafey[4] · Ahmed Soliman[5] · Mohamed Aboubakr[1]

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Abstract

Lycopene (LP) and N-acetylcysteine (NAC) protective effects were assessed for testicular toxicity mediated by cisplatin (CP) in rats. Forty-nine rats were divided into 7 groups ($n = 7$); these groups included the control group (saline, PO), LP (10 mg/kg, PO), NAC (150 mg/kg, PO), CP (7.5 mg/kg, IP) on the 27th day of the study, LP + CP, NAC+CP, and LP + NAC + CP. Serum levels of testosterone were decreased following CP injection. Malondialdehyde (MDA) has been increased with considerable glutathione (GSH), and dismutase superoxide (SOD) and catalase (CAT) decline in the testis tissues after CP injection. CP caused severe alterations in testicular tissues and elevated caspase-3 expression. Besides that, LP and/or NAC administration improved CP-induced testicular toxicity and apoptosis, probably via their antioxidant properties.

Keywords Cisplatin · N-acetylcysteine · Lycopene · Oxidative stress · Testosterone · Testes

Introduction

Cisplatin (CP) is used for the treatment of a variety of malignancies and kills cells through many processes, including the creation of reactive oxygen species (ROS), DNA damage, and activation of apoptosis (Abdel-Daim et al. 2019a, b; Abdel-Daim et al. 2020; Abo-Elmaaty et al. 2020; Elkomy et al. 2020; Sallam et al. 2021). ROS has injured the tissue by interaction with biological macromolecules resulting in the creation of oxidized substances (Aboubakr et al. 2019, 2020). Several studies recorded testicular toxicity of cisplatin (Ateşşahin et al. 2006; Abdel-Wahab et al. 2020; Azab et al. 2020; Gholami Jourabi et al. 2021). Disturbance in the balance between oxidants and antioxidants and lipid peroxidation plays a key role in testicular injuries induced by CP (Liu et al. 2015). CP attaches to the purine bases of DNA and causes ruptures in the strand. DNA repair pathways leading to apoptotic or non-apoptotic death in cells consequently activate damaged in DNA, RNA, and protein (Riddell 2018). Many investigations have shown that CP causes serious testicular injury due to impaired Leydig cell activity (testosterone production inhibition) and germ cell death induction (Mesbahzadeh et al. 2021).

Lycopene (LP) is naturally present in fruits and vegetables such as strawberries, tomatoes, cherries, and carrots (Abdel-Daim et al. 2019d). Structurally, the analog of carotenoid is a free radical destroyer (Kara et al. 2016). LP possesses anti-inflammatory (Aboubakr et al. 2021a, b), antihyperlipidemic, anti-mutagenic, immune-stimulant, and protective agents against testicular injury through suppressing oxidative stress and apoptosis (Kara et al. 2016; Ma et al. 2018; Aly 2019; Kaya et al. 2019; Xu et al. 2019; Zhao et al. 2020), which makes it a potential reproductive dysfunction therapy option for males. LP reduces disruption to the vital cell components (Soleymaninejad et al. 2017).

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✉ Mohamed Aboubakr
mohamed.aboubakr@fvtm.bu.edu.eg

[1] Department of Pharmacology, Faculty of Veterinary Medicine, Benha University, Moshtohor, Toukh, Qalyubiyya 13736, Egypt

[2] Department of Biotechnology, College of Science, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia

[3] Department of Histology, Faculty of Veterinary Medicine, Benha University, Moshtohor, Toukh, Qalyubiyya 13736, Egypt

[4] Anatomy Department, Faculty of Veterinary Medicine, Benha University, Moshtohor, Toukh, Qalyubiyya 13736, Egypt

[5] Pharmacology Department, Faculty of Veterinary Medicine, Cairo University, Giza 12211, Egypt

N-acetylcysteine (NAC) is a glutathione precursor that has a thiol group with antioxidant and anti-inflammatory effects (Abdel-Daim et al. 2019c; Tras et al. 2021). By enhancing cellular GSH, NAC performs its powerful antioxidant action and consequently protects from lipid peroxidation (El-Maddawy and El-Sayed 2018; Elsayed et al. 2021). The powerful antioxidant effects of NAC make it a potential control for disorders related to free radical damage (Owumi et al. 2021). It has potent anti-inflammatory effects via inhibiting the cyclooxygenase enzyme (Farshid et al. 2010). NAC has been reported to protect against dysfunction and testicular damage (Elnagar et al. 2018; Mohammadi-Sardoo et al. 2018; Kheradmandi et al. 2019; Turkmen et al. 2019; Owumi et al. 2021; Soliman et al. 2021).

This study aimed to investigate the preventive role of LP and/or NAC in rats against testicular toxicity due to CP via examining testosterone level, oxidative stress indicators, caspase-3 expressions, and morphometrical parameters.

Materials and methods

Chemicals

The chemicals used were as follows: CP (50 mg/ml; EIMC Pharmaceuticals CO, Cairo, Egypt), natural LP (Sigma Aldrich Co, USA), and NAC (SEDICO, 6th October City, Egypt).

Experimental rats

Male Wister albino rats (49; 180–200 g, 2 months) were obtained from Biological Products and Vaccines Organization, Egypt. All rats have a standardized pellet diet and free water access and have been kept in a light/dark cycle of 25 ± 2 °C and 12:12 h. The rats had been acclimated for a week before the trial started. Animals have been divided into 7 groups: 1st group (control, saline only); 2nd group (10 mg LP/kg, PO) (Wang et al. 2018); 3rd group (150 mg NAC/kg, PO) (Feng et al. 2015); 4th group (saline, PO + CP (7.5 mg/kg, IP single dose; on the 27th day)) (Adeyemi et al. 2017); 5th group (LP + CP); 6th group (NAC + CP), and 7th group (LP + NAC + CP). The treatments (LP, NAC) were administered for 30 days (once daily).

Sampling (blood and tissues)

Rats were anesthetized 24 h after the ending of the trial with isoflurane. Blood was collected from the retroorbital plexus, and the serum was centrifuged for 15 min at 1200 g, for testosterone analysis; the serum was kept at –20 °C. Tests were excised rapidly and saline washed. In phosphate buffer tissue, tissues (1 gram) were homogenized (pH 7.4). Homogenated tissues were centrifuged for about 20 min at 1200 × g at 4 °C. Before use in oxidative stress indicators, assessment in testicular tissues, the supernatants were kept at −20°C. For histological and immunohistochemical (IHC) examinations, a portion of testicular tissue was quickly preserved in formalin.

Testosterone estimation

Serum levels of testosterone were analyzed using ELISA kits (Immunometrics Ltd., London, UK) (Tietz 1995).

Oxidative stress

Using diagnostic kits (Biodiagnostic Co., Egypt), the levels of malondialdehyde (MDA) (Ohkawa et al. 1979) and activities of catalase (CAT) (Aebi 1984), superoxide dismutase (SOD) (Nishikimi et al. 1972), and glutathione reductase (GSH) (Richardson and Murphy 1975) were estimated.

Histopathology, lesion scoring, and immunohistochemistry (IHC)

The testes were fixed using 10% formaldehyde, embedded in paraffin wax. Sections of paraffin blocks (5 µm thick) were cut using a microtome. Sections were put on glass slides and deparaffinized before staining with H&E stain. Spermatogenic disturbance degree was evaluated using Johnsen's scoring, which ranged from a score of 1 (no cells in the seminiferous tubules) to 10 (complete spermatogenesis) (Johnsen 1970) and were illustrated in Table 2.

The immunostaining was performed using caspase-3 according to Porter and Jänicke (1999). Tissue sections were dehydrated and dewaxed in sequential ethyl alcohol graded for immunohistochemical evaluation. Antigen retrieval by EDTA solution in flood, pH 8, was completed. Afterward, use 3% H_2O_2 in methanol solution for 5 min and wash 3 times, for 5 min, in PBS for each of the endogenous peroxidases blocks. The slide was then blocked for 20 min at BSA (5%) and thereafter treated at a temperature of 37 °C for 1 h with a primary monoclonal antibody-caspase-3 (Santa Cruz Biotechnology Inc., Dallas, USA, 1:100). Subsequently, the slide was washed with PBS three times and heated to secondary IgG anti-mouse antibodies (Dako, Japan 1:1000 dilution) at 37 °C for 45 min. In the end, 3,3-diaminobenzidine tetrahydrochloride made the brown stain visible (DAB; Dako, Japan). The immunohistochemical expressions of caspase-3 in the testes were scored as outlined by Aboubakr et al. (2021a, b). An intensity score (IS), 0–4 representing no staining to very strong staining, respectively, was scored to the examined cells. In addition, a proportional score (PS), 0–5 for no positive cells to greater than 65% positive cells, respectively, was recorded. The total score (TS) was

Table 1 Effect of LP, NAC, and/or CP on serum testosterone and antioxidant parameter testicular tissues. Data are expressed as the mean ± SE ($n = 7$)

Parameters	Control	LP	NAC	CP	LP + CP	NAC + CP	LP + NAC + CP
MDA (nmol/g)	52.89 ± 0.61^{d}	51.75 ± 1.21^{d}	53.62 ± 1.41^{d}	123.94 ± 3.26^{a}	101.61 ± 2.01^{b}	98.43 ± 1.97^{b}	73.82 ± 1.91^{c}
CAT (U/g)	16.91 ± 0.23^{a}	17.52 ± 0.43^{a}	17.04 ± 0.42^{a}	8.21 ± 0.07^{d}	11.10 ± 0.26^{c}	11.51 ± 0.29^{c}	13.42 ± 0.26^{b}
SOD (U/g)	20.39 ± 0.13^{b}	20.11 ± 0.22^{ab}	21.2 ± 0.28^{a}	10.22 ± 0.20^{f}	13.21 ± 0.32^{e}	15.50 ± 0.13^{d}	18.61 ± 0.45^{c}
GSH (mg/g)	3.91 ± 0.13^{a}	4.13 ± 0.75^{a}	4.04 ± 0.16^{a}	0.87 ± 0.01^{d}	2.87 ± 0.05^{c}	2.79 ± 0.02^{c}	3.52 ± 0.08^{b}
Testosterone (ng/ml)	2.17 ± 0.04^{a}	2.19 ± 0.04^{a}	2.24 ± 0.05^{a}	0.87 ± 0.01^{d}	1.31 ± 0.05^{c}	1.26 ± 0.04^{c}	1.81 ± 0.05^{b}

calculated by the addition of IS to PS and then scored at 1–3, 4–6, and 7–9 representing weak, moderate, and strong grades, respectively, and was recorded in Table 3.

Statistical analysis

The data were found to be mean ± SE in this study. The SPSS software (version 21) was utilized for the analysis of the data using one-way ANOVA. Duncan's post hoc test was employed for group comparisons. $P < 0.05$ has been accepted for statistical significance.

Results

Effect on serum testosterone levels

Testicular toxicity induced by CP was demonstrated by the reduced testosterone levels compared to those of control rats. In particular, when combined treatment with LP and NAC was applied in rats intoxicated by CP, a significant rise in the value of testosterone is observed, which was significantly lower in comparison to the control group. These data demonstrated that LP and NAC combination improved protection against testicular damage by CP than each alone (Tables 1, 2 and 3).

Effect on oxidative damage parameters

The effects of CP poisoning, LP, NAC, and their combination treatment on oxidative parameters were shown in Table 1. Remarkable increases (MDA levels) and a marked decline in (GSH, CAT, SOD) levels in testicular tissues of the CP group were observed. Consequently, the toxic effects of CP on testicular MDA, CAT, SOD, and GSH were substantially returned towards normal by the administration of LP or NAC alone; however, these values have still differed markedly from control. Also, LP + NAC + CP group revealed a marked enhancement in testicular oxidative damage induced by CP in especially in comparison to LP + CP) and NAC + CP groups.

Table 2 Johnsen score of seminiferous tubular cross-sections in control and treated groups

Groups	Johnsen scores
Control	9.90 ± 0.11^{a}
LP	9.70 ± 0.15^{a}
NAC	9.80 ± 0.13^{a}
CP	4.30 ± 0.47^{d}
CP + LP	6.30 ± 0.36^{c}
CP + NAC	6.10 ± 0.43^{c}
CP + LP + NAC	7.50 ± 0.26^{b}

Table 3 PS, IS, and TS ± SE for caspase-3 immunohistochemical expressions in the testis

Groups	PS	IS	TS
Control	1.16 ± 0.04^{d}	0.52 ± 0.03^{d}	1.68 ± 0.07^{d}
LP	1.20 ± 0.03^{d}	0.56 ± 0.02^{d}	1.76 ± 0.04^{d}
NAC	1.18 ± 0.02^{d}	0.54 ± 0.04^{d}	1.72 ± 0.05^{d}
CP	4.54 ± 0.05^{a}	3.84 ± 0.04^{a}	8.38 ± 0.07^{a}
CP + LP	3.96 ± 0.04^{b}	2.46 ± 0.08^{b}	6.42 ± 0.11^{b}
CP + NAC	3.88 ± 0.09^{b}	234 ± 0.09^{b}	6.22 ± 0.14^{b}
CP + LP + NAC	3.26 ± 0.09^{c}	1.76 ± 0.05^{c}	5.02 ± 0.12^{c}

Values are expressed as the mean ± SE. *IS*, intensity scores; *PS*, proportional scores; *TS*, total scores

Histopathology and lesion scoring

Testis sections of saline-treated rats had normal histological structure, seminiferous tubules lined by stratified germinal epithelium, and in between tubules interstitial tissue with Leydig cells (Fig. 1A). Also, LP- or NAC-treated rats (Fig. 1B, C) showed normal testicular criteria as described in the control group. In contrast, CP-induced severe degenerative changes in the testis are represented by intertubular edema and necrosis of spermatic cells of seminiferous (Fig. 1D, E). LP (Fig. 1F) or NAC (Fig. 1G), with CP, showed a moderate effect on the testis notably by presence of patent spermatogonia with mild vacuolatic spermatocytes and mild degenerated spermatogonia and spermatocytes. By using LP and NAC combined with CP, the testicular architecture was restored (Fig. 1H).

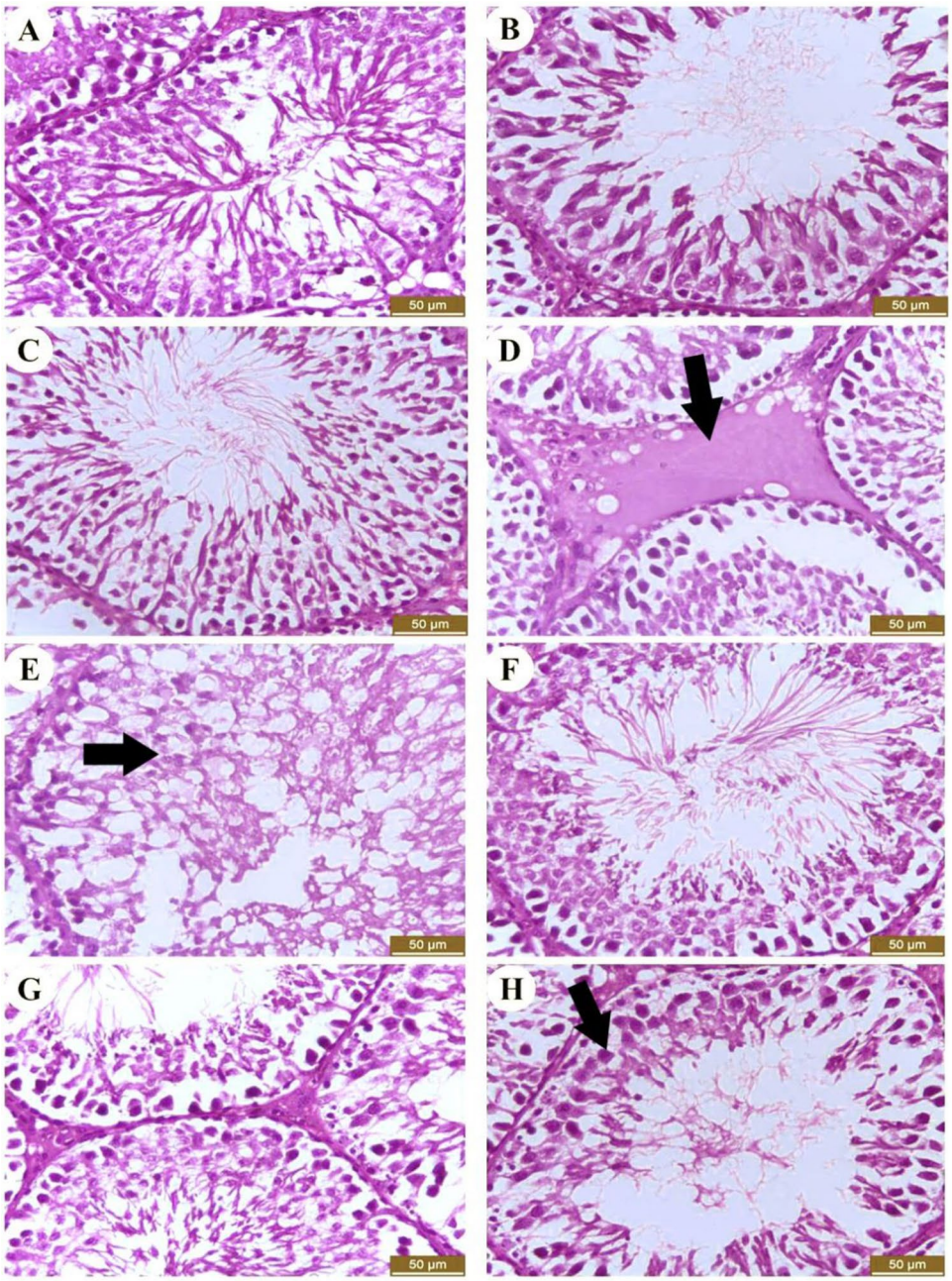

Fig. 1 Changes in the histopathology of the testes. **A** (saline), **B** (LP), and **C** (NAC), nearly normal spermatogonia and spermatocytes were seen in the seminiferous tubules. Intertubular edema (black arrow) (**D**) and necrosis of spermatic cells of seminiferous (black arrow) (**E**) were evident in the testes of CP-treated rats. The seminiferous tubules of CP + LP-treated rats showed patent spermatogonia with mild vacuolatic spermatocytes (**F**). Mild degenerated spermatogonia and spermatocytes were seen in CP + NAC-treated group. Marked restoration of spermatogonia (black arrow) with mild degenerated spermatocytes were noticed in most of the seminiferous tubules of CP + LP + NAC-treated group

Immunohistochemistry

Shown in Fig. 2, the immunohistochemical staining of the testicular cells was varied according to the cellular condition. CP-treated rats showed severe expression of caspase-3 in testicular cells when compared to control and LP- and NAC-treated rats which showed faint positive immunostaining. A minimal improvement of the caspase-3 expression was noticed in CP-LP and CP-NAC groups. CP-LP-NAC intensely lowered CP upregulation of caspase-3.

Discussion

CP induces sperm dysfunction, testicular damage, abnormalities in Leydig cells, and germ cell apoptosis (Azab et al. 2020; Azarbarz et al. 2020**;** Gholami Jourabi et al. 2021). These findings were reliable with the results obtained, including the role of oxidative stress and apoptotic pathways in testicular damage caused by CP. Most drugs used for treating cancer induce toxicity and oxidative injury in different organs as testes (Azarbarz et al. 2020). Testicular damage due to CP is attributed to oxidative stress induced by

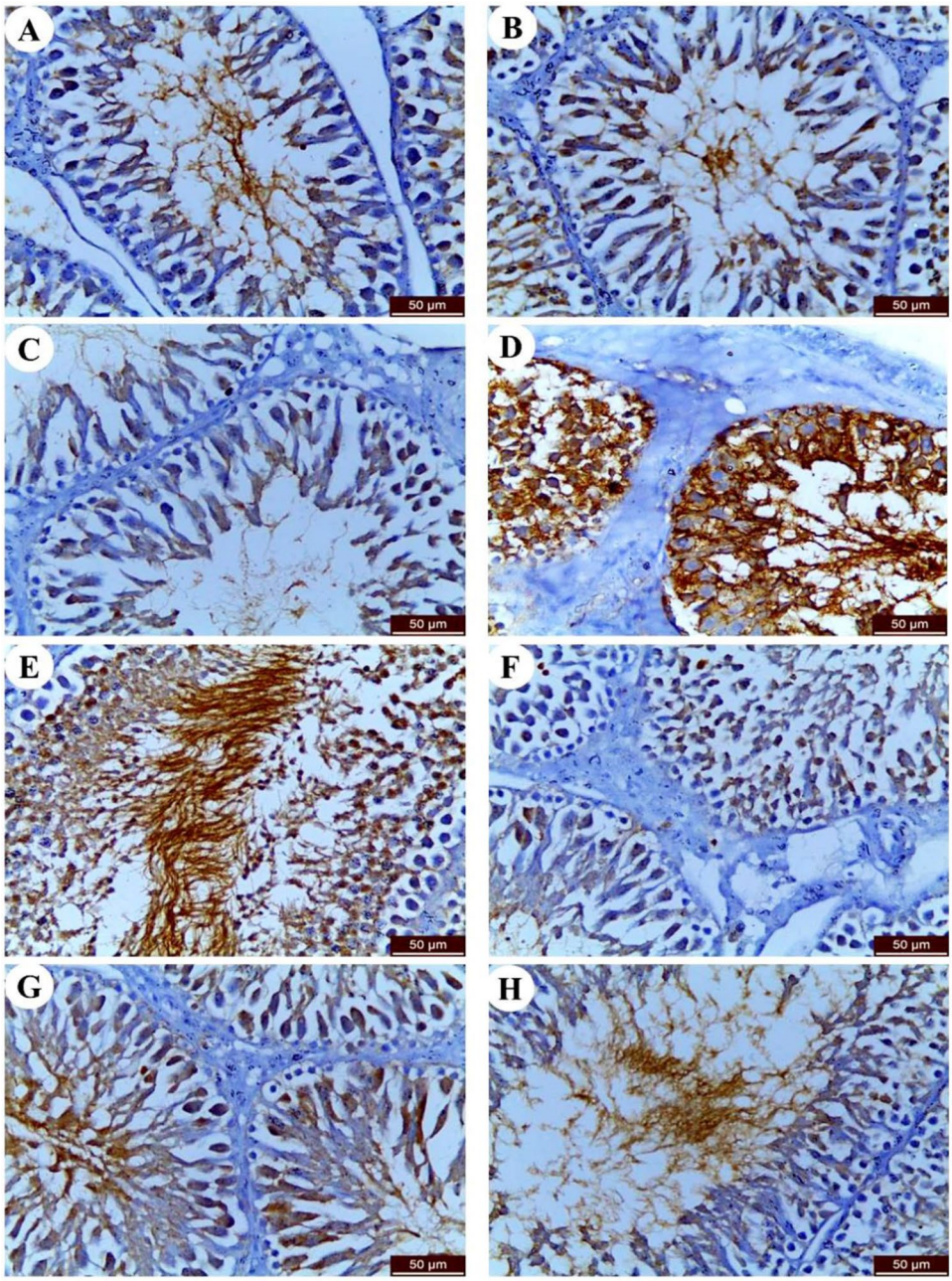

Fig. 2 Caspase-3 immunohistochemical micrographs of the testes in control and treated rats. Mild caspase-3 expression was seen in control (**A**), LP (**B**), and NAC-treated rats (**C**) evidenced by faint cytoplasmic DAB staining. **D–E** Strong extensive intracytoplasmic caspase-3 protein expression was evident in the CP-treated rats. Mild (**F**) to moderate (**G**) cleaved caspase activity was detected in CS + LP- and CP + NAC-treated rats, respectively. A marked decline in caspase-3 expression in the spermatogonia and spermatocytes of seminiferous tubules in CP + LP + NAC-treated rats (**H**)

the increased free radical formation and antioxidant depletion (Sallam et al. 2021). Free radicals have been noticed to induce reactions which is important for a broad range of damage induced by CP (Abdel-Wahab et al. 2020; Azab et al. 2020).

Testosterone, the most important male sexual hormone, is secreted by the testes and plays an important role in testicular development as well as in spermatogenesis (Zhao et al. 2018).

In this study, CP injection substantially reduced the level of testosterone hormone. This is attributed to Leydig cells dysfunction, which is responsible for gonadotropin production and decreases mitochondrial and cytochrome P-450 activity (Garcia et al. 2012). Also, CP reduces the expression of androgen-binding proteins and induced disorders in hormones which is attributed to its effects on the hypothalamic–pituitary–gonadal axis (Almeer and Abdel Moneim 2018). Published investigations have shown a drop in testosterone levels following CP injection (Abdel-Wahab et al. 2020; Azab et al. 2020; Azarbarz et al. 2020; Gholami Jourabi et al. 2021).

With regard to oxidative/antioxidant indicators, CP revealed a drastic increase in testicular MDA (enhanced lipid peroxidation) and declined activities of testicular GSH,

CAT, and SOD. Similar results were given by Jahan et al. (2018), Yadav (2019), and Sallam et al. (2021). Such reduction of antioxidant enzymatic molecules might be because of an uncontrollable generation of H_2O_2, which impairs the antioxidant defense systems of the testis. Results of the present work come along with those of previous investigations (Yadav 2019; Sallam et al. 2021). CP increases the level of ROS and lowers antioxidant enzymes (Jahan et al. 2018).

Interestingly, pretreatment with LP or NAC with CP showed an improvement in testicular functions (testosterone level, histological, and IHC alterations). This suggests that LP and NAC are capable of stabilizing the integrity of cell membranes or improving the regeneration of damaged cells. Thus, these molecules appear to be promising agents in alleviating CP cellular damage. In addition, the capacity of both LP (Salem et al. 2012; Aly 2019; Kaya et al. 2019; Xu et al. 2019) and NAC (Anand et al. 2015; El-Maddawy and El-Sayed 2018; Shittu et al. 2019) to prevent testicular dysfunction may be because they possess free radical scavenging potentials and antioxidant activity. These findings showed that LP and NAC prevented cell death due to oxidative stress.

CP's success in cancer treatment is limited to adverse reactions as it has a significant gonadotoxic effect. These findings go in hand with Fouad et al. (2017) and Kohsaka et al. (2020) who recorded decreased body weight of the testis due to parenchymal atrophy of germinal cells in CP-treated rats. Our results showed thinning in seminiferous tubule walls due to sloughed spermatogenic cells; these findings lead subsequently to oligo- or azoospermia, and these findings go in line with Cherry et al. (2004).

CP caused observable histological injuries in testicular tissue. Histological changes were noted by severe degenerative changes in the wall of seminiferous tubules, interstitial edema, degenerated and desquamated spermatogenic cells, and congested blood vessels. Numerous investigations previously reported that the administration of CP has deleterious effects on testicular tissue (Azarbarz et al. 2020; Gholami Jourabi et al. 2021).

Immunohistochemical analysis using in the epithelium after CP injection. Oxidative stress and tissue damage by CP result in elevated expression of the caspase-3, leading to apoptosis (Abdel-Wahab et al. 2020; Gholami Jourabi et al. 2021). The IHC results revealed that LP and/or NAC decreases the caspase-3 protein expression in testicular tissues.

CP treatment showed overexpression of caspase-3 as it promotes intracellular ROS production, which is very strong oxidants that stimulates DNA fragmentation and enters the cells in stages of apoptosis (Henkel 2005). Combined treatment with LP lowers the histopathological adverse effect of CP as LP has antioxidant properties that can attenuate oxidative stress and exert anticancer effects as mentioned by Kara et al. (2016) and Antonuccio et al. (2020). NAC lowers the histopathological lesions and caspase-3 expression caused by CP. Combined LP or NAC treatment with CP restored normal histological architecture indicating that combination of LP + NAC was more efficient than each alone due to their dual antioxidant actions and their abilities to recover the enzymatic antioxidant activity.

Conclusion

Overall, the research indicates that CP caused marked testicular damage resulting from oxidative stress and apoptosis. LP + NAC combination might be employed as a potential protective effect against CP-induced testicular damage.

Author contribution Elsayed A, Alkafafy M, El-Shafey A, Soliman A, Elkomy A, and Aboubakr M made design, analysis, and writing. Elkammar R performed pathology and IHC.

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Data availability All relevant data are within the paper.

Declarations

Ethics approval Ethical Committee of the Fac. Vet. Med., Benha University (BUFVTM 03-03-21).

Consent to participate Not applicable

Consent for publication

The manuscript is not previously published in any journal.
The manuscript is not currently under consideration in other journals

Conflict of interest The authors declare no competing interests.

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