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Evaluation of Protective Role of Date Palm Pollen against Cisplatin-Induced Reproductive Toxicity in Rats

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Abstract

Date palm pollen (DPP) is herbal mixture that widely used in traditional medicine to improve fertility. The current study aimed to determine the protective role of the DPP extract against cisplatin-induced reproductive toxicity in rats. Sixty rats were used (30 of each sex) and allocated to normal, negative, and test control groups of males and females (10 animals per group). Reproductive toxicity was induced by an intraperitoneal injection of cisplatin (4.5 mg/kg/72 hour) in the negative and test groups, whereas the test groups also received daily oral doses of DPP methanolic extract (250 mg/kg). At the end of the experimental period (30 days), the rats were sacrificed to determine the fertility parameters. The obtained results showed that, oral administration of DPP extracts exhibited protective effects as demonstrated by a prominent increase in serum estradiol concentration, recovery from reduction in gonads weight, and a considerable enhancement on histological observations among male and female rats. Moreover, elevation in epididymal sperm count and motility in male animals was observed compared to that in cisplatin-treated rats. DPP had a significant effect on estradiol levels, as well as protective effects against cisplatin-induced reproductive toxicity in both male and female rats.

Keywords: Cisplatin, date palm, epididymal characteristics, *Phoenix dactylifera*

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1 Introduction

Infertility is defined as the inability of a couple to conceive naturally after one year of regular unprotected sexual intercourse, and it affects approximately 13% to 15% of couples worldwide [1]. Reported causes of infertility include pelvic inflammatory diseases, sexually transmitted infections, and some personal habits (excess alcohol intake and cigarette smoking), in addition to some environmental and occupational hazards [2], [3]. Some chemotherapeutics, such as cisplatin, are known to cause damage to the ovaries as well as Sertoli cells and Leydig cells of the testis, leading to premature ovarian failure and anti-spermatogenic and anti-steroidogenic effects, respectively [4], [5]. Cisplatin is used for the treatment of many types of cancers, including sarcomas, lymphomas, breast, lung, and bladder cancer [6], [7]. The precise mechanism by which cisplatin causes testicular toxicity and germ cell apoptosis is not fully known; however, numerous studies have shown that drug exposure can disrupt the redox balance of tissues, suggesting that biochemical and physiological disturbances may result from oxidative stress [8].

Phoenix dactylifera L. (Date palm) belongs to the Aracaceae family is called Nakhla and the tree of life by the Arabs [4], [9]. It is native to the North Africa and Persian Gulf regions with the top producers including Iraq, Egypt, Saudi Arabia, Tunisia, Algeria, UAE, Oman, Libya, Pakistan, Sudan, and USA [10]. It is a dioeciously (male and female flowers being produced in clusters on separate palms), medium-sized tree (tall tree up to 36 meters in height) occasionally found cultivated or self-grown [11], [12]. In the review of published data, it is found that the plant possesses numerous curative potentials as antioxidant, anti-cancer, anti-diabetic, anti-hyperlipidemic and antimicrobial along with protection of various cells against different environmental toxic chemicals and side effects of chemotherapy [13]. Suspension of date palm pollen (DPP) is widely used for curing male infertility [14]. Currently, there are no scientific reports that address the accurate doses or dose range of DPP that have effects as traditional medicine, and the most popular form used traditionally is the pollen powder (about 2–5 grams) mixed with milk, bee honey or other herbal extracts, daily (at least 2 hours before breakfast) for 1 to 2 months [15].

The plant kingdom serves as a valuable source of new medicinal agents, and it has been reported that approximately 25% of modern medications are derived from plant materials [16], [17]. Additionally, large numbers of plants-derived drugs (about 74%) that are commonly used in some countries were discovered as a result of chemical studies directed at the isolation of the active constituents of the plants used in traditional medicine [18]. Taken together, being a product of an indigenous plant and the previously reported studies, these could imply DPP to be a promising agent against a range of exogenous fertility toxic stimuli. Therefore, the aim of this study was to determine the protective role of the DPP extract against cisplatin-induced reproductive toxicity in rats.

2 Materials and Methods

2.1 Plant material

The plant material (white powder) was obtained from the flower cluster of a male date palm plant. Extraction of DPP was performed based on the method described by Musab *et al*., [19], through methanolic (70%) maceration for 72 hours, with intermittent shaking, and then filtered under vacuum. The filtrate was allowed to evaporate at room temperature and the extract was collected, freeze-dried, and stored in an amber glass container (in a refrigerator) until used.

2.2 Experimental animals

Healthy and sexually mature Wister albino rats of males and females (12–15 weeks old) were obtained from the animal house of the Faculty of Pharmacy, University of Gezira, Sudan, and were housed in polyacrylic cages, and maintained under standard laboratory conditions (temperature, 25 ± 2°C; dark and light cycle, 12/12 h). Rats received a standard diet and water ad libitum. The animals were acclimatized to laboratory conditions for 15 days before the commencement of the experiment.

2.3 Effects on cisplatin-induced reproductive toxicity

The effects of DPP extract on cisplatin-induced reproductive toxicity in rats were investigated based on the methods described by Gabr *et al*., [4], John *et al*., [5], and Marah *et al*., [9]. Sixty rats (30 males and 30 females) were selected. The animals were divided into six groups (three of males and three of females) of 10 rats each as follows:

- Groups I and II were considered as normal control groups of males and females, respectively (received distilled water).
- Groups III (males) and IV (females) were considered negative control groups.
- Group V and VI (test control groups of male and females respectively).

The treatment duration was 30 days, and the plant material was administered at an oral daily dose of 250 mg/kg based on the average doses used in the studies conducted by Gabr *et al*., [4], Fouad *et al*., [20], and Wafaa *et al*., [21], to the test control groups (V and VI). Reproductive toxicity was induced in groups III, IV, V, and VI by intraperitoneal injection of cisplatin at a dose of 4.5 mg/kg every 72 h.

The final body weight of the animals was determined at the end of the experimental period. The rats were sacrificed to determine the following fertility parameters.

1) Body to sex organs weight ratio: Testicular tissues and ovaries were removed and weighed, and the relative weight of the organs (%) was calculated as g/100 g body weight.
2) Serum hormones concentration assays: Blood samples obtained from all animals after decapitation were left to clot, and serum was separated by centrifugation to estimate testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and prolactin levels by enzyme-linked immunosorbent assay (ELISA) using an auto-analyzer according to the manufacturer's instructions.
3) Epididymal sperm characteristics: The methods described by Arun *et al*., [22], and Jennifer *et al*., [23], were used. The right cauda epididymis was quickly removed (after the animals were killed). The epididymis was placed in a Petri dish containing pre-warmed nutrition medium then placed on a hot-stage at 37 °C (after adherent fat, blood vessels, and connective tissue were cut away). Sperm were released by cutting the cauda epididymis longitudinally with fine-pointed scissors and compressed with forceps. Sperm motility was assessed by dripping the sperm solution (with a micropipette) onto a clean glass slide (covered with a cover glass) and captured using a light microscope. Sperm solution was dripped into a hemocytometer (covered with a cover glass) under a light microscope to assess the count and abnormality (assessment of the ratio of spermatozoa with complete head and tail from the total number).
4) Histopathological examination: Following abdominal incision, ovarian and testicular tissues were dissected, preserved in 10% formalin, subjected to histopathological examination using routine paraffin embedding, sectioned using a rotary microtome, stained with hematoxylin and eosin, and observed under a light microscope by a histopathologist.

2.4 Statistical analysis

The obtained data were statistically analyzed using a paired t-test and expressed as the mean ± standard error. For comparisons with group data, differences were considered significant if *P*-value was < 0.05.

3 Results and Discussion

In female rats, cisplatin administration (4.5 mg/kg) every 72 hours significantly reduced the serum levels of estradiol (the other studied serum hormone concentration assays for testosterone, FSH, LH, and prolactin showed no significant differences between the animal groups), along with a reduction in the sex organ weight ratio to the total body weight of the negative control group compared with the normal control group (*P-value* < 0.05), which indicated the presence of gonadotoxic effects after exposure to the drug. However, the group that was co-administered DPP was largely spared from this reducing effect on serum estradiol and gonad weight caused by cisplatin administration (*P-value* < 0.05).

In the male group, serum estradiol, serum testosterone, sex organ weight ratio to total body weight, sperm count, and motility were notably decreased by cisplatin administration compared to the normal control group (*P-value* < 0.05), whereas sperm abnormality determinations showed no significant differences between the normal control and the other groups. DPP co-administration (to the test group) significantly counteracted the effect of cisplatin on serum estradiol and gonad weight and preserved the integrity of some sperm characteristics compared to the negative group (*P-value* < 0.05), without a significant change in serum testosterone compared to the negative group. The results for the female and male groups are presented in Tables 1 and 2, respectively.

Table 1 Effect of oral administration of DPP on some fertility parameters in female rats

Group (N = 10)	Ovaries weights (g/100 g body weight)	Serum estradiol level (pg/ml)
Normal control	0.11 ± 0.01	219.03 ± 13.68
Negative control (Cisplatin)	0.09 ± 0.006 [a]	99.71 ± 7.86 [a]
Test control (Cisplatin + DPP)	0.095 ± 0.003 [b]	140.87 ± 8.3 [b]

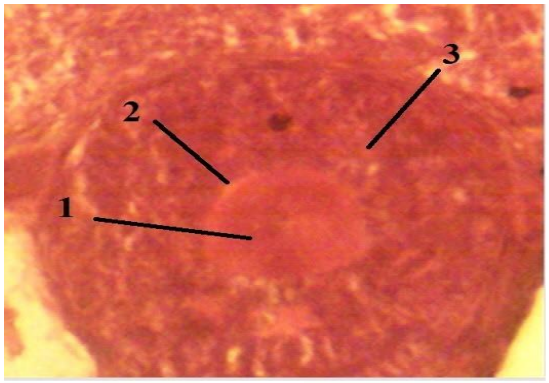
N: number of animals / group.
[a] Significant differences compared to the normal control.
[b] Significant differences compared to the negative control.

Table 2 Effect of oral administration of DPP on some fertility parameters in male rats

Group (N=10)	Sperm characters		Serum testosterone level (ng/ml)	Serum estradiol level (pg/ml)	Sex organ weights (g/100 g body weight)
	Count	Motility (%)			
Normal control	354.75± 21.59	83.33 ± 1.18	4.32 ± 0.41	31.16 ± 5.30	1.52 ± 0.05
Negative control (Cisplatin)	106.75± 0.85 [a]	27.33 ± 2.10 [a]	2.52 ± 0.19 [a]	17.13 ± 1.39 [a]	1.10 ± 0.10 [a]
Test control (Cisplatin + DPP)	283.00± 23.16 [b]	73.33 ± 1.18 [b]	2.18 ± 0.16	24.18 ± 3.86 [b]	1.31 ± 0.03 [b]

N: number of animals / group.
[a] Significant differences compared to the normal control.
[b] Significant differences compared to the negative control.

For histopathological examination, different histological sections of the ovaries from the female control group showed good development of ovarian follicles, normal blood vessels, and normal stromal cells. The pre-ovulatory follicle showed a typical morphology of oocytes and euchromatin nuclei, which were surrounded by a typical zona pellucida and several layers of granulosa cells. Well-developed primary follicles and normal luteal cells of corpus luteum are also evident in these sections. The most evident histopathological changes in the ovaries of females administered cisplatin alone were congestion and reduction in the number of ovarian follicles. Other changes include vacuolation in the luteal cells, ooplasm, and granulosa cells of pre-ovulatory follicles. Moreover, the histological changes indicated a thin and irregular zona pellucida, while the oviducts showed congestion of the blood vessels. For the group that was administered DPP in addition to cisplatin, the results demonstrated that the plant material caused a considerable enhancement in the mean number of primary, secondary, and graph follicles with less congestion compared to the negative control group. The pre-ovulatory follicle also showed less vacuolation in the ooplasm, with minimal irregularities in the zona pellucida and granulosa cells, compared to the cisplatin alone group. Figures 1 show histological sections of ovarian tissues from the normal, negative, and test groups, respectively.



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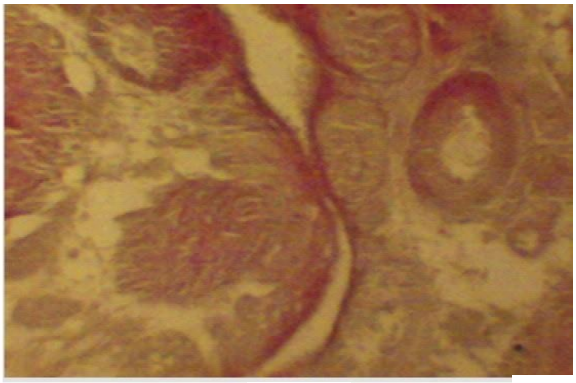

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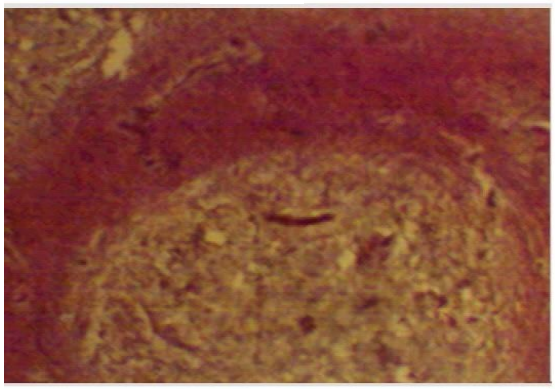

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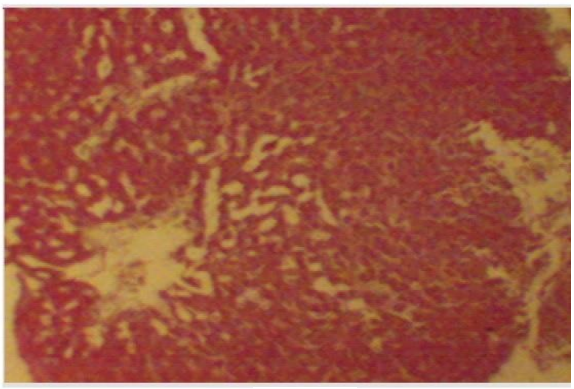

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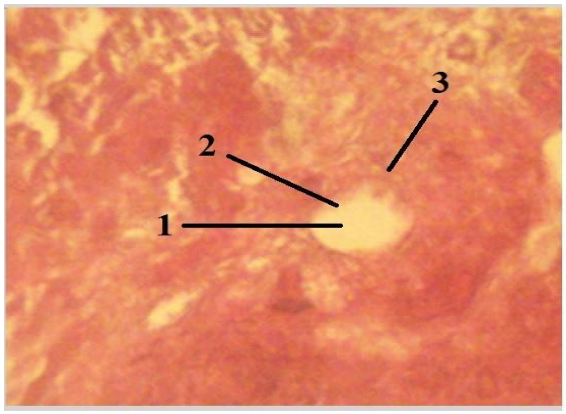

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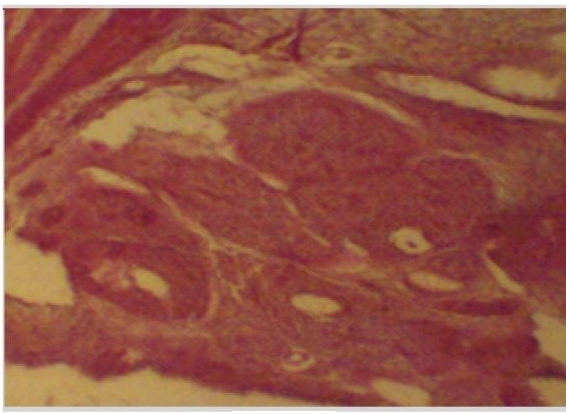

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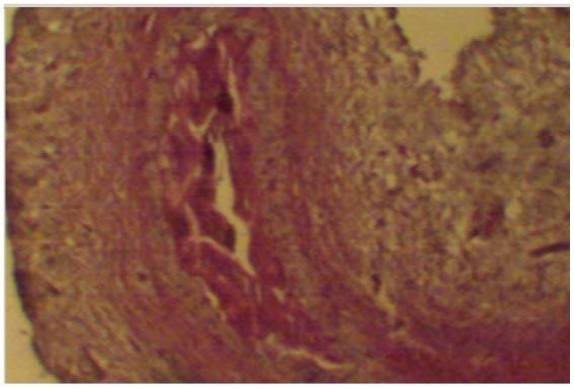

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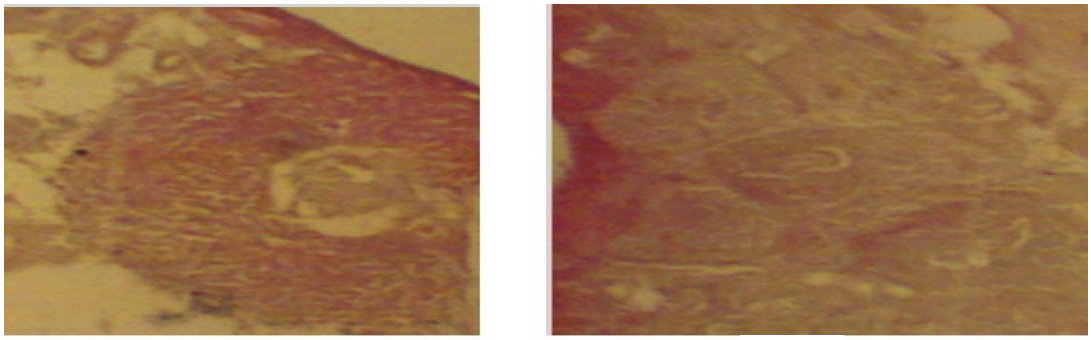

Figure 1 Ovarian sections from the female normal control group (I), negative group (II), and test group (Cisplatin + DPP) (III). (1A) Normal morphology of pre-ovulatory follicle with mature oocyte (line 1) surrounded by normal zona pellucida (line 2) and several layers of granulosa cells (line 3) 40x; (1B) Well developed primary follicles 25x; (1C) Corpus luteum showing normal luteal cells 40x; (1D) Oviducts showing normal blood vessels 40x. (IIA) Pre-ovulatory follicle showing vacuolation in ooplasm (line 1) with irregular zona pellucida (line 2) and granulosa cells perform strong contact with oocyte (line 3) 40x; (IIB) Primary follicles showing congestion and reduction in number 25x; (IIC) Corpus luteum showing vacuolation in luteal cells 40x; (IID) Oviducts showing congestion of blood vessels 40x. (IIIA) Pre-ovulatory follicle showing less vacuolation in ooplasm with minimal irregularities of zona pellucida and granulosa cells compared to the Cisplatin group 40x; (IIIB) Primary follicles showing less congestion and enhancement of the mean number compared to the Cisplatin group 25x.

On the other hand, for the male groups, the histopathological sections of testicular tissues of the normal control group showed regular seminiferous tubules with sperm in the lumina of tubules. Additionally, typical features of cell morphology were observed, such as a narrow intertubular space, and tubules lined by stratified germinal epithelium with spermatogonia, spermatocytes, round spermatids, and elongated spermatids. In addition, a cluster of Leydig cells was observed around the blood capillaries, indicating a normal seminiferous epithelium. Cisplatin-treated rats showed many distorted, disorganized seminiferous tubules with decreased sperm and were separated by wide interstitial spaces. Some tubules also showed a marked reduction in germinal epithelium thickness. DPP co-treatment resulted in preserved testicular morphology, in which the cells appeared with less deterioration than those treated with cisplatin alone, and few spermatogenic cells showed vacuolated cytoplasm, supplementing the protective effect of the plant extract. The results are shown in Figures 2.

Cisplatin (the first platinum-containing anti-cancer drug) is widely used to treat various types of cancers, including sarcomas, carcinomas, lymphomas, and germ cell tumors. These platinum complexes of the drug react through binding to DNA and causing crosslinking which ultimately triggers apoptosis [24]. Despite its potent antineoplastic action, Cisplatin treatment is coupled with several toxic effects including nephrotoxicity, oxidative stress injury and testicular damage, and several studies suggested that the drug affects Sertoli cells and Leydig cells of testis, thereby causes anti-spermatogenic and anti-steroidogenic effects in males [25]. In females, cisplatin and other chemotherapeutics have been known to cause damage to the ovaries, leading to premature ovarian failure in approximately 40% of female patients who undergo chemotherapy [5].

Based on the published literature, fertility studies assessment may generally include sex organ weights, hormonal assay, macroscopic and histological examination of sex organs, evaluation of sperm characters in males, as well as the optimal treatment period to optimize the parameters used [26]. It was also reported that, for animal experimental designs it is critical to use control groups as an integral part of the study for comparison of data in the animals given the treatment to non-treated ones, this aims to minimize the impact of a plethora of variables, validates the experiment, provide the basis for data analysis and comparisons, and can also discriminate outcomes caused by the treatment or intervention from those caused by other factors [15].

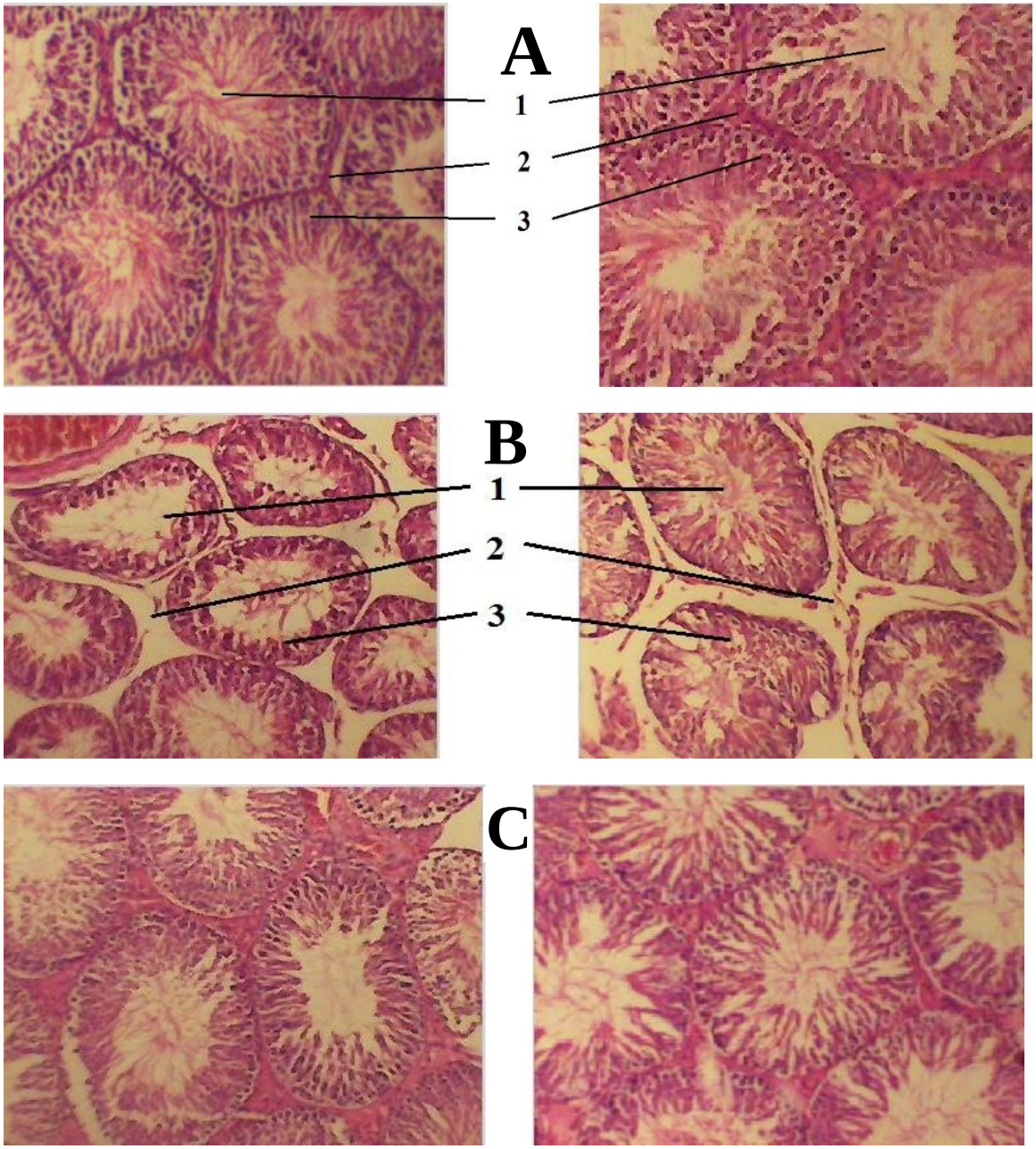

Figure 2 Testicular sections from the male normal control group 40x (A), negative group (Cisplatin) 40x (B), and test group (Cisplatin + DPP) 40x (C). (A1) Regular seminiferous tubules and sperms in the lumina of tubules; (A2) Narrow inter-tubular space; (A3) Tubules are lined by stratified germinal epithelium with spermatogonia, spermatocytes, round spermatid and elongated spermatids. (B1) Distorted disorganized seminiferous tubules and decreased sperms; (B2) Wide interstitium spaces; (B3) Some show marked reduction in the thikness of the germinal epithelium.

Based on these findings, cisplatin administration caused remarkable weight loss in the sex organs, reduction in epididymal sperm count, suppression of sperm motility, decline in estradiol and testosterone concentrations (in male rats), and histological deterioration. The current study demonstrated that DPP treatment caused a prominent increase in estradiol concentration associated with an elevation in epididymal sperm count and motility, along with considerable enhancement in histological observations.

In agreement with the findings of Musab *et al*., [19], DPP could possibly elevate the serum level of estradiol due to the presence of sterol compounds, such as estrone, detected by

phytochemical analysis of the plant material, and it could also be attributed to the protective effect of DPP against cisplatin-induced dysfunction through its antioxidant characteristics. Estrogenic potency of estrone is mainly due to its conversion to estradiol within the body [27]. Estrogens are responsible for some physiological functions in males (fertility, reproduction and bone health) as well as early sexual development, sexual behavior, and spermatogenesis process [28], [29].

The results obtained were in accordance with those reported by Gabr *et al*., [4], in terms of increased sperm count, sperm motility, and genital organ weight. The current study has also clearly demonstrated the impact of DPP in improving several reproductive parameters and is confined to other reported works that address its ability to treat the toxic effects caused by many toxicants, such as lead acetate, cadmium chloride, carbofuran, and electromagnetic fields [9], [21], [30], [31].

4 Conclusions

Oral administration of DPP extract exhibited protective effects against cisplatin-induced reproductive toxicity in rats, as demonstrated by a prominent increase in serum estradiol concentration, recovery from reduction in gonad weight, considerable enhancement in histological observations among male and female rats, and elevation of epididymal sperm counts and motility in male animals. This plant material could provide a candidate source for new drugs to treat disorders resulting from the low concentration of estradiol, in addition to its protective effect against some reproductive toxicants. However, further studies are necessary to confirm this finding.

5 Declarations

5.1 Acknowledgements

The researchers express their appreciation and gratitude to the Department of Pharmacology, Faculty of Pharmacy - University of Gezira for their technical support and experimental facilities.

5.2 Author contribution

All authors contributed equally in concept, design, resources, experiments, and critical review of the study.

Writing, literature search, and data interpretation were done by the corresponding author.

5.3 Funding

There is no funding body, and the study was carried out by self-financing.

5.4 Etic

The study was approved by the Faculty of Pharmacy, University of Gezira Ethical Committee, and the experimental protocol and procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals of The National Academies [32].

5.5 Conflict of Interest

The authors declared that, there are no any conflict of interest regarding the current study.

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