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Histomorphological evaluation of docetaxel effects on testes and epididymides in Wistar rats

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ABSTRACT
Background: Chemotherapy drugs, such as Docetaxel, which are crucial for treating cancer, frequently cause unknowingly damage to healthy tissues.
Aim: To investigate the histomorphological effects of docetaxel chemotherapy on certain parameters in testes and epididymides.
Method: For this purpose, 24 Wistar Albino rats were divided randomly into one control group and three treatment groups. The treatment groups were administered 2.5, 5, and 10 mg/kg of the drug. The experiment lasted for 28 days. The weights of the testes and epididymides were measured. The testicular and epididymal samples were subjected to histological analysis and were examined under a light microscope.
Result: The results revealed that the dose of DX1 (2.5 mg/kg) of docetaxel had no adverse effect on the process of spermatogenesis; however, the highest doses of DX2 and DX3 penetrated the blood-testis barrier and disrupted the structural and functional system of spermatogenesis. The results of the present study indicate that the highest dose of docetaxel leads to adverse effects on testes, epididymides, and their fertility parameters. In addition, the testicular tissues of DX2 and DX3 displayed adverse histomorphological changes. The process of spermatogenesis was interrupted, and a progressive decrease in the height of the germinal epithelium was observed. On this basis, the weight of the testes and epididymides decreased.
Conclusion: A dose of 2.5 mg/kg of Docetaxel was the drug of choice for chemotherapy. Further studies are needed to investigate the long-term effects of Docetaxel on male fertility.
Keywords: Docetaxel, Testis, Epididymis, Histomorphology, Wistar rat, Male fertility.

Introduction

The seminiferous tubules comprise the bulk of the testes (King, 2023; Khalaf *et al*., 2024). They are essential for spermatogenesis, the production of sperm. Sperms produce spermatozoa through a complicated developmental process. Sperm cells grow with structural support from Sertoli cells. A complex network of blood arteries, lymphatic cells, neurons, and hormone-secreting cells surround seminiferous tubules. Spermatogenesis requires nutrition, oxygen, and hormones, which are transported by interstitial spaces. Leydig cells in the interstitial compartment synthesize testosterone, the primary male sex hormone for male reproductive tissue development and secondary sexual features. These tubules are embedded in sparse interstitial tissue surrounded by a thin layer of contractile myoid cells that play multiple roles (Zhao *et al*., 2021). These cells support the tubules and maintain their shape. At various stages of spermatogenesis, sperm and fluids are transported inside tubules. Additionally, the contractile properties of these cells facilitate the movement of sperm from the seminiferous tubules to the epididymis, where sperm matures and is stored (Rogers, 2010; Zhao *et al*., 2021). Male fertility is the ability to produce viable offspring and the high ability to provide semen and sperm traits, in addition to multi-factorial characteristics including (immunological, hormonal, genetics, nutritional, seasonal, and behavioral) (Hussin and Al-Haaik, 2018; Leslie *et al*., 2025); however, the decreased capacity of viable offspring production may lead to infertility (El-Newary *et al*., 2022). Infertility is the most critical

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global problem; furthermore, different reasons lead to decreased fertility rates (Al Chalabi *et al*., 2020). Infertility is estimated to occur in 8%–12% of couples worldwide, with a male component being the primary contributing reason in approximately 50% of couples. The causes of male subfertility can vary significantly and may be attributed to inherited, acquired, or idiopathic factors that hinder the process of spermatogenesis (Agarwal *et al*., 2021). Generally, epididymal sperm counts serve as a sensitive and frequently used measure to assess the impact of male reproductive toxicants on the epididymis and testicles (Wang, 2003; Khalaf *et al*., 2022).

Chemotherapy is widely used for the treatment of various cancers. However, side effects can cause severe complications, including infertility. Infertility is a significant issue for patients with cancer, as chemotherapy treatment protocols may lead to long-term health implications (Abdullahi, 2022). Furthermore, chemotherapy drugs may cause metabolic and hormonal alterations due to stress, malnutrition, and fever (Saruhan, 2020).

Docetaxel is a chemotherapy drug commonly used to treat various cancers, including breast, prostate, lung, and ovarian (Imran *et al*., 2020). Moreover, previous studies have shown that docetaxel altered the expression of apoptosis-related genes in mRNA expression in mouse genital organs (Lopes *et al*., 2014). Docetaxel caused testes damage due to its systemic toxicity (Yardım *et al*., 2021). Chemotherapeutic drugs are one of the common causes of infertility, such as Filgrastim (Tuimah Alabedi *et al*., 2021) and Cadmium Chloride (Ali Hameed *et al*., 2022). Docetaxel commonly damages the male reproductive system, leading to decreased epididymal sperm counts, alive sperm, motility, and abnormal sperm morphology (Zhang *et al*., 2014). However, the specific effects of Docetaxel on epididymal sperm quality and histological changes in testicular tissue in Wistar rats are not fully understood.

This study aimed to focus on the adverse effects of docetaxel on some parameters of the testes and epididymis and to observe changes in the histological characteristics of the testes in Wistar Albino rats. The objective of this study was to better understand the precise changes in reproductive organs caused by docetaxel treatment. This will help us to identify the various pathways contributing to male infertility caused by chemotherapy. This understanding has implications for patients with cancer receiving treatment and for broader initiatives focused on protecting reproductive health.

Methods

Experimental design

The present experiment utilized 24 healthy adult male Wistar Albino rats. These rats were purchased from a research center in Najaf, Iraq. The rats were housed in hygienic cages in an animal facility. All rats were exposed to a 12-hours light/dark cycle and were provided by standard food and water ad libitum.

Group allocation

The animals were divided randomly into four groups (six each), one control (C), and three treatment groups (DX.1, DX.2, and DX.3). The control group received intraperitoneally normal saline. A single dose of (2.5, 5, and 10) mg/kg of Docetaxel was administered to each group. DX dosages were selected according to Sandström *et al*. (1999); Engels *et al*. (2004).

Experimental duration

The experiment lasted for 28 days to evaluate the effect of docetaxel on the reproductive parameters of the testes and epididymis.

Ethical approval

All experiments were performed according to the guidelines of the Implementing Health Research at the Institutions of the Ministry of Health, Iraq (2018), the WHO Code of Conduct for Responsible Research (2017), and Principles of Human Experimental Techniques (Russell and Burch, 1959), for the Use of Experimental Animals (EC-1, 4-3-2024).

Measurements

Evaluation of sperm parameters

At the end of the treatment period, the rats were anesthetized with xylazine and ketamine (5 and 50 mg/kg). The epididymal sperm parameters (Table 1) were studied using standard methods (Al Chalabi *et al*., 2020). After euthanasia, the cauda epididymides were promptly cut into two halves to discharge the epididymal contents into a 35-mm Petri dish containing 2 ml of RPMI-1640 (pH 7.4). A drop of fluid was placed on a slide to measure sperm motility. The percentage of viable and morphologically aberrant sperm was determined by counting sperm from five random fields. The average was multiplied by 10^6 according to Tegelenbosch and de Rooij (1993); Wang (2003). To preserve viable sperm activity, all experimental instruments, containers, and surfaces were maintained at 37°C. Sperm motility and numbers were measured by mincing 100 mg of the caudal epididymis in 1 ml of RPMI-1640. A drop of the mixed sample was applied to a slide under a cover slip to measure sperm motility. The index was calculated by counting motile and immotile spermatozoa per unit area. Epididymal counts were also performed and were expressed as millions/ml of suspension. Sperm vitality was assessed by mixing 40 µl of freshly liquefied semen with 10 µl of eosin-nigrosin (Merck-Germany). One drop of the mixture was placed on a clean slide, and 100 sperm were counted at ×100 magnification (Olympus Japan). Sperms dyed pink or crimson were considered dead, whereas unstained ones were considered alive according to Khalaf *et al*. (2024).

Measurement of testicular and epididymal weight

The testes and epididymides weights were determined in all four groups to assess the possible effects of

docetaxel (Table 2). The data were collected and analyzed using statistical analysis.

Histomorphological examination

At the end of the experiment, histomorphological examination was performed on the testes and epididymides samples. Tissues were fixed in a 10% formalin solution for 48 hours (Hammodi and Al Aamery, 2022; Khaleel and Alkhazraji, 2022). The routine histological processes were carried out according to Luna (1968), and they involve three steps: dehydration, clearing, and infiltration. Dehydration was performed by immersing the specimens in a series of ethyl alcohol (from 50%, 70%, 90% to 100%) alcohol, 30 minutes for each. The clearing step was Xylene. This solvent displaces the alcohol in the tissue. The clearing process lasted for 30 minutes. In the third step, infiltration was performed using Molten paraffin to displace xylene. Immediately after tissue embedding, the wax was rapidly cooled to reduce the wax crystal size. Multiple changes of the paraffin wax were performed to completely displace the clearing agent xylene. The samples were sectioned using a 7-micron rotary microtome and then stained with hematoxylin and eosin. The stained sections were examined under a light microscope at different magnifications, and photomicrographs were taken using a digital camera (Sony A7RM4A, 26 megapixels) attached to the microscope. The main fertility parameters are sperm motility, alive sperm, normal appearance, and sperm concentration in the epididymis (Bustani and Baiee, 2021; Ali Hameed *et al.*, 2022). For sperm parameter evaluation, the tail of the epididymis was rinsed and incubated in 2 ml of normal saline at 37°C, then segmented into small sizes via the microscissor to release the epididymal sperms from the epididymal tubules for testes evaluation using the protocol (Tuimah Alabedi *et al*., 2021; Al-Mousaw *et al*., 2022).

Statistical analysis

The data were tabulated in a datasheet of the Statistical Package for the Social Sciences (IBM, SPSS) version 25.0, which was used for statistical analysis. The mean and standard errors of continuous variables were reported, and significant differences were tested using the analysis of variance test, followed by the least significant difference test. These tests were used to determine the differences between the various concentrations of treatment and control groups in terms of spermatogonia counts, weights of testes, and epididymides (SAS, 2012).

Results

The current results showed that the low dose (2.5 mg/kg) docetaxel (DX1) had no adverse effects on the fertility of male rats, as shown in Figures 1a and b, 2a and b.

Furthermore, histological examination of the testes showed little effect in the seminiferous tubules of the

Table 1. Morphological findings of docetaxel effect on motility, alive sperm, normal appearance, and concentrations of epididymal sperms

Group	C	DX1	DX2	DX3	*p-value*
Motility (%)	89.22 ± 0.31^{a}	60.36 ± 0.54^{b}	46.05 ± 0.62^{c}	32.59 ± 0.35^{d}	0.000^{abcd}*
Alive sperm (%)	92.11 ± 0.07^{a}	62.14 ± 0.21^{b}	50.51 ± 0.54^{c}	30.46 ± 0.54^{d}	0.000^{abcd}*
Normal appearance (%)	95.50 ± 0.23^{a}	82.30 ± 0.28^{b}	70.98 ± 0.30^{c}	60.68 ± 0.24^{d}	0.000^{abcd}*
Epididymal sperm concentrations x 50 x 10^{6}	12.93 ± 0.17^{a}	10.13 ± 0.16^{b}	6.83 ± 0.39^{c}	3.51 ± 0.02^{d}	0.000^{abcd}*

Values Mean ± SE of 24 adult male Wistar rats.
C = control group; DX1, DX2, and DX3 = treatment groups.
^{abcd}Mean values between groups.
*Significant differences at a probability value ($p \leq 0.05$).

Table 2. Histomorphological findings of docetaxel effect on weight of testes in g and epididymides in mg, and spermatogonia count 10^{6} per g of testis

Group	C	DX1	DX.2	DX3	*p-value*
Testes (g)	1.62 ± 0.02^{a}	1.56 ± 0.02^{b}	1.49 ± 0.01^{c}	1.34 ± 0.03^{d}	0.000–0.033^{abcd*}
Epididymides (mg)	589.00 ± 4.64^{a}	578.83 ± 0.87^{b}	566.67 ± 1.54^{c}	556.50 ± 2.32^{d}	0.000–0.016^{abcd*}
Spermatogonia Count (10^{6} per g of testis)	82.83 ± 0.83^{a}	68.17 ± 1.62^{b}	52.50 ± 1.86^{c}	40.17 ± 1.86^{d}	0.000–0.000^{abcd*}

Values Mean ± SE of 24 adult male Wistar rats.
C = control group; DX1, DX2, and DX3 = treatment groups
^{abcd}Means values between groups.
*Significant differences at a probability value ($p \leq 0.05$).

Table 3. Histomorphological findings of docetaxel effect on total area in µm2, diameter in µm, and germinal epithelium height in µm of the seminiferous tubules.

Group	C	DX1	DX2	DX3	*p-value*
Area of the seminiferous tubules (μm^2)	92.65 ± 8.83[a]	77.59 ± 6.00[a]	69.62 ± 2.31[c]	56.44 ± 4.17[d]	0.073[cd] 0.000–0.007[aa]
Diameter of seminiferous tubules (µm)	338.25 ± 13.76[a]	310.61 ± 11.14[a]	297.01 ± 4.91[c]	264.93 ± 9.46[d]	0.062[aa] 0.000–0.006[cd]
Length of the germinal epithelium (µm)	88.22 ± 2.67[a]	72.15 ± 2.64[b]	57.82 ± 2.56[c]	44.08 ± 1.30[d]	0.000–0.000[abcd]

Values Mean ± SE of 24 adult male Wistar rats. [abcd]Means values between groups.
C = control group; DX1, DX2, and DX3 = treatment groups
[a]Significant differences at a probability value ($p \leq 0.05$).
[bcd]Non-significant differences at a probability value ($p > 0.05$).

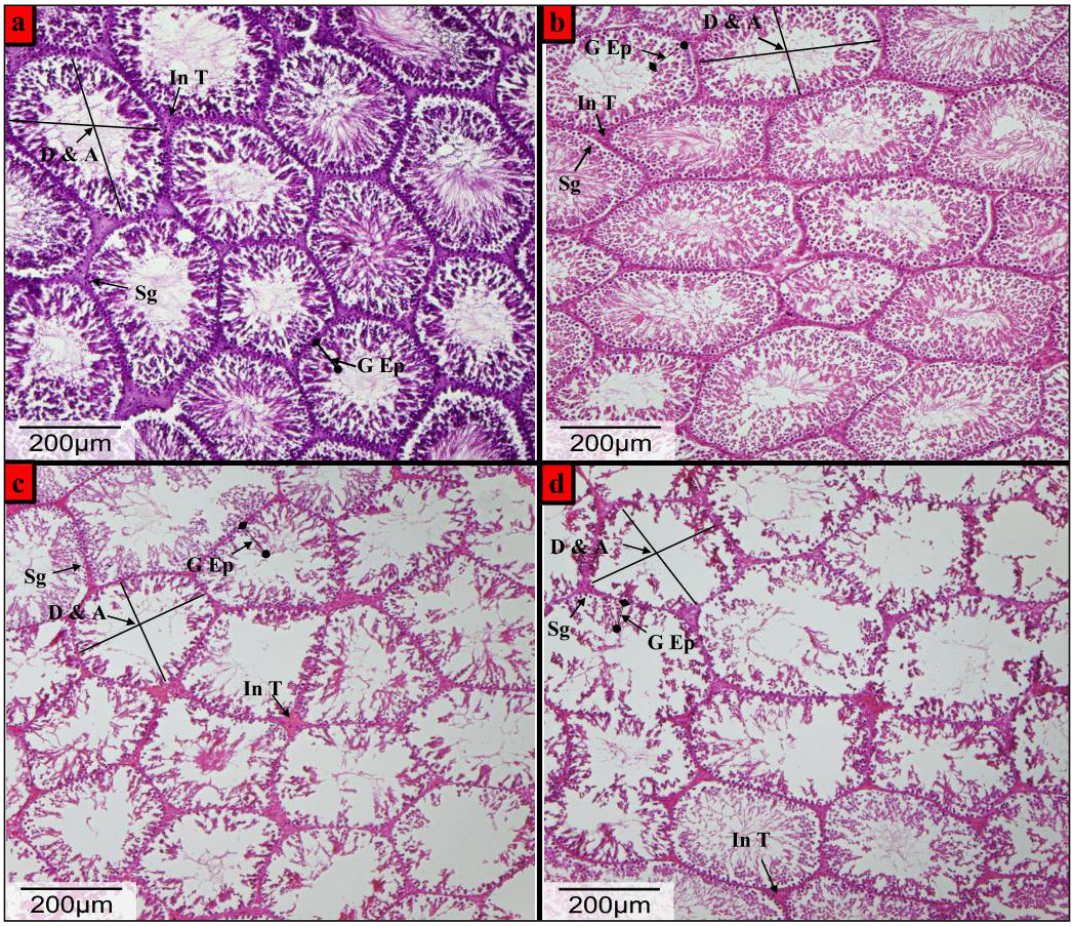

Fig. 1. Photomicrographs of Hematoxylin and Eosin (H&E)-stained testis from the Wistar male rats (a) control group, (b) DX1 group, (c) DX2 group, and (d) DX3 group, showed: Germinal epithelium (G Ep), diameter & total area (D & A), interstitial tissue (In T), spermatogonia (Sg). (b) showing relative histological changes in the height of germinal epithelium and general architecture of the testis. No significant reduction in the area and diameter of seminiferous tubules, and (c and d) showed a progressive adverse effects of chemotherapy on the spermatogenic epithelium, a reduction in total area and diameter of the seminiferous tubules, and damage in the architecture of the testis. H&E-Stain, X-100 x 26-megapixels.

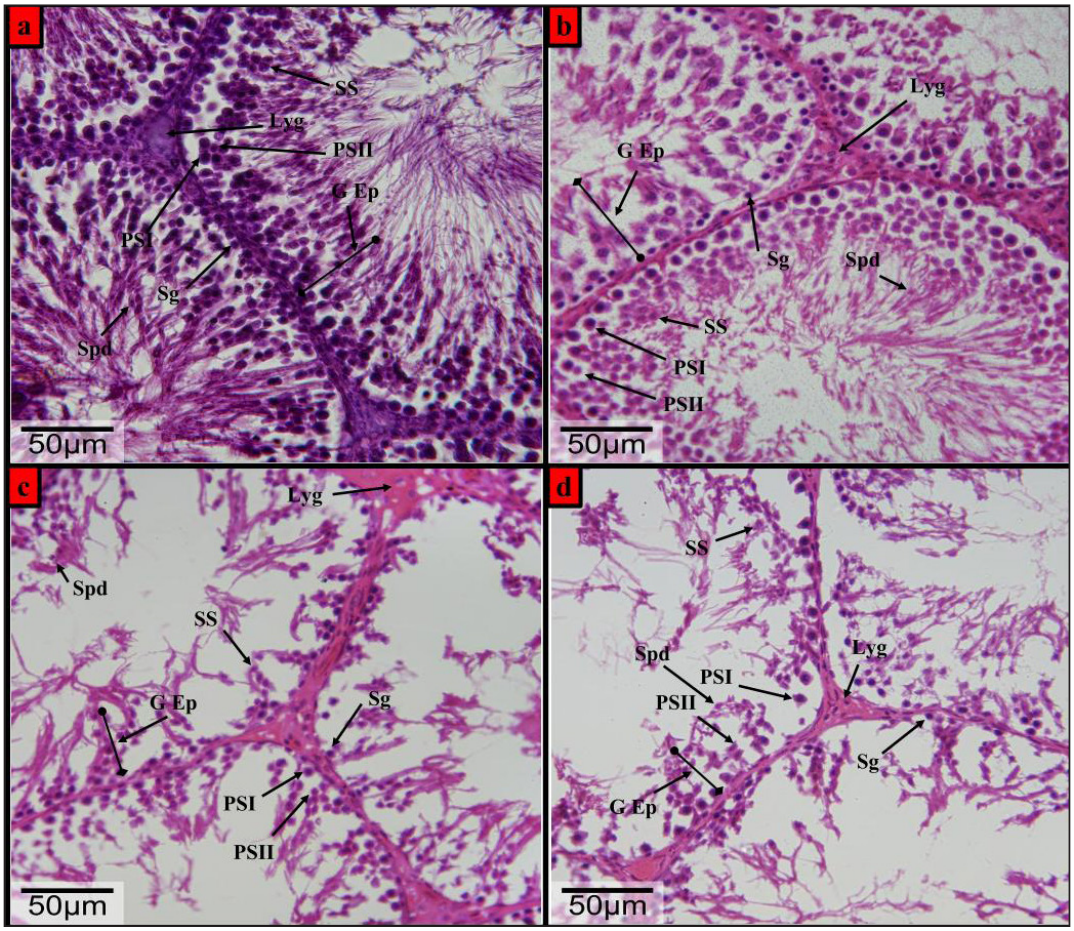

Fig. 2. Photomicrographs of H&E-stained testis from the wistar male rats (a) control group, (b) DX1 group, (c) DX2 group, and (d) DX3 group, showed: Germinal epithelium (G Ep), spermatogonia (Sg), leydig (Lyg), primary spermatocyte-I (PSI), primary spermatocyte-II (PSII), secondary spermatocyte (SS), and spermatid (Spd). (b) showed a relative histological change in the height of germinal epithelium and the general architecture of seminiferous tubules, and there was a significant reduction in the number of spermatogonia. (c and d) showed adverse effect of chemotherapy, a progressive decrease in the height of the germinal epithelium, and damage in the architecture of the seminiferous tubules. H&E-Stain, X-400 x 26-megapixels.

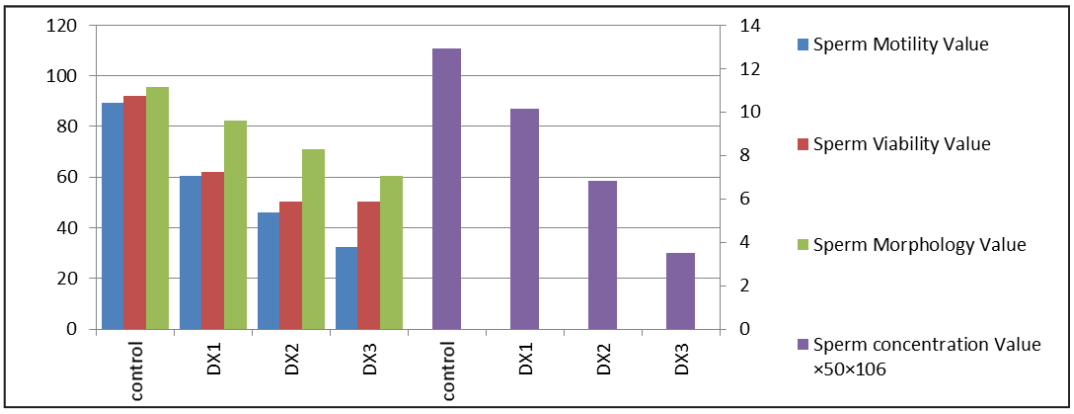

Fig. 3. Showed a statistical comparison among means of the groups: Control, DX1, DX2, and DX3. There was a progressive decrease in the values of motility, alive sperm, sperm morphology, and concentration of epididymal sperms. DX2 and DX3 showed a significant effect of Docetaxel.

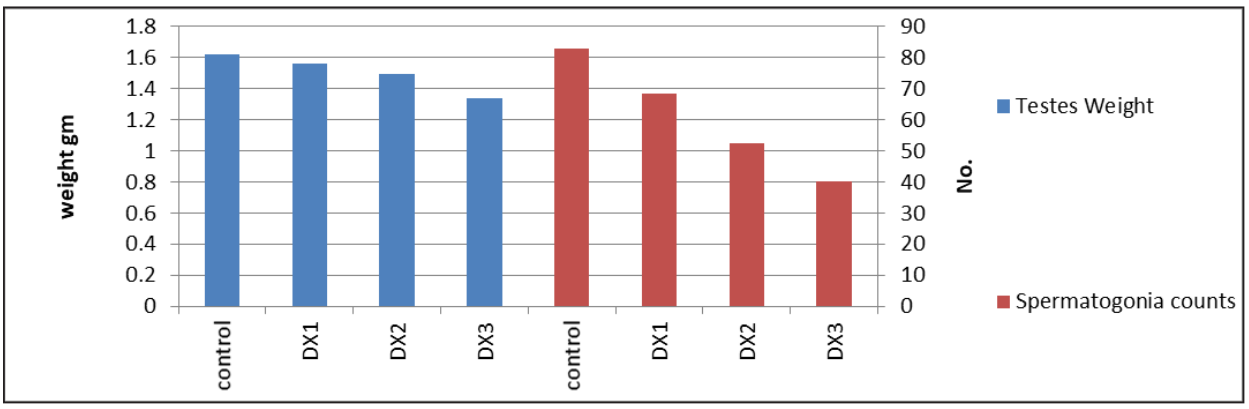

Fig. 4. Showed a statistical comparison among means of the groups: Control, DX1, DX2, and DX3. There was a progressive decrease in the values of the weight of testes in g and spermatogonia count 10^6 per g of testis. DX2 and DX3 showed a significant effect of Docetaxel.

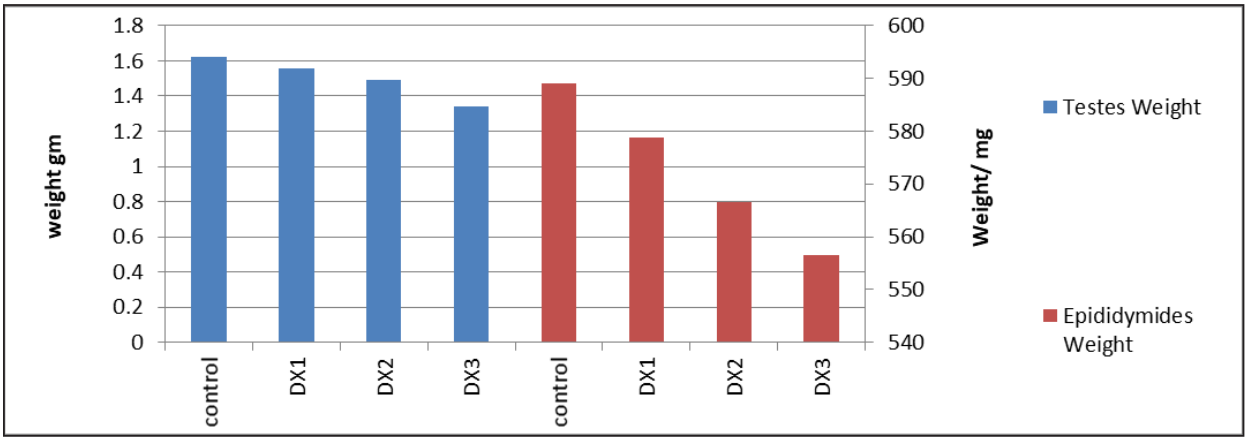

Fig. 5. Showed a statistical comparison among means of the groups: Control, DX1, DX2, and DX3. There was a progressive decrease in the values of the weights of testes in g, and epididymides in mg. DX2 and DX3 showed a significant effect of Docetaxel.

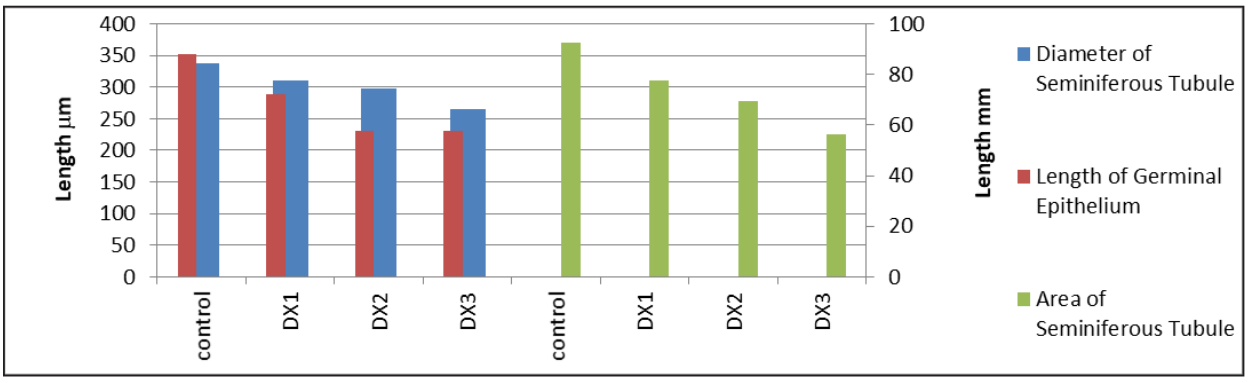

Fig. 6. Showed a statistical comparison among means of the groups: Control, DX1, DX2, and DX3. There was a progressive decrease in the values of total area in μm^2, and diameter in µm of the seminiferous tubules, and germinal epithelium length in µm. DX2 and DX3 showed a significant effect of Docetaxel.

control and DX1 groups compared with DX2 and DX3 groups. In DX2 and DX3 groups, the periphery of the seminiferous tubules appeared thinner and polygonal compared with control group, as shown in Figures 1 and 6 and Table 3.

In addition, the germinal epithelium was degenerated compared with control group, as shown in Figures 2b–d

and 6 and Table 3. Histological examination of the testes revealed significant changes in DX1, possibly due to apoptosis. However, no significant histological damage was noticed in DX1 group, as shown in Figures 1b and 2b. Table 2 and Figures 4 and 5 showed a progressive decrease in the weight of the testes and epididymides in DX 2 and DX3 groups. Spermatogonia counts decreased in all treatment groups, especially in DX1 group, as shown in Figures 2 and 4 and Table 2. The administration of docetaxel at the highest doses caused a significant decrease in epididymal sperm parameters. The Testes of control group showed normal testicular architecture with well organized seminiferous tubules and Leydig cells, as shown in Figures 1a and 2a. In contrast, the testicular tissues of rats treated with the highest doses of Docetaxel showed degeneration of seminiferous tubules, atrophy, and reduced Leydig cell counts (Figures 1c and d, 2c and d).

Discussion

The study found that Docetaxel at a low dose (2.5 mg/kg) did not affect rats' fertility negatively (Figures 1a and b, 2a and b). The treatment groups (DX2 and DX3) had lower epididymal parameters and less effect on the seminiferous tubules (Figures 3–6 and Tables 1 and 2). However, the DX1 group did not present any significant damage or changes. However, considerable damage occurred in DX2 and DX3 groups (Figures 1c and d, 2c and d). This is consistent with the findings of (Zhang *et al*., 2014; Altintas *et al*., 2015; Sarıözkan *et al*., 2017). Docetaxel had chemotherapeutic properties represented by the induction of apoptotic cell death and the inhibition of mitosis by promoting the phosphorylation of Bcl-2, a protein known for its antiapoptotic properties, in malignant cells (Sarıözkan *et al*., 2017). Hence, these findings in DX2 and DX3 suggest that docetaxel may have detrimental effects on male reproductive health and should be used with caution in clinical practice.

Docetaxel administration resulted in a significant decline in epididymal sperm parameters, particularly in DX2 and DX3 groups, indicating a progressive decrease in testes and epididymides (Table 2 and Figures 4 and 5). These findings were consistent with those of previous studies showing chemotherapy-induced infertility in male rats (Abdelaziz *et al*., 2020). The mechanism underlying the reduction in epididymal sperm parameters could be the direct toxic effects of the drug on the testicular and epididymal tissues. Chemotherapeutic drugs, i.e., Docetaxel, have been shown to induce apoptosis and oxidative stress in different cell types (Al Chalabi *et al*., 2020; Al-Mousaw *et al*., 2022). The findings of the present study agreed with the findings of (Gelmon, 1994), who demonstrated a reduction in sperm parameters. In addition, Altintas *et al*. (2015) reported that the administration of Docetaxel leads to a significant decrease in sperm count, motility, and abnormal sperm morphology in rats (Altintas *et al*., 2015).

Furthermore, Sariözkan *et al*. (2016) reported that docetaxel administration resulted in significant histopathological changes in the testes of adult rats (Sariözkan *et al*., 2016). The present results were also typically correlated with Moradi *et al*. (2021), who reported a progressive decline in the spermatogonia count in rodents affected by chemotherapy. A previous study reported a proportional relationship between the spermatogonia count and the weights of the testes and epididymides; thus, a reduction will follow any upgrading decrease in spermatogonia in the diameter of the seminiferous tubules (Robb *et al*., 1978). This result was similar to the findings in (Tables 2 and 3, Figures 1b–d, 4 and 5). On the other hand, Takzare *et al*. (2016) reported that the highest doses of morphine and naloxone led to a progressive statistical decrease in the spermatogonia count and the weights of testes and epididymides, consistent with the herein results.

The control group's testes exhibited normal structure (Figures 1a and 2a), whereas rats treated with high doses of Docetaxel showed degeneration of seminiferous tubules, atrophy, and reduced Leydig cell counts (Figures 1c and d, 2c, and d). The current results agreed with prior research that confirmed the occurrence of testicular degeneration after chemotherapy treatment (Altintas *et al*., 2015; El-Amir *et al*., 2019; Özyilmaz Yay *et al*., 2019). The findings of this study revealed that the administration of Docetaxel at doses of 5 and 10 mg/kg could be lead to testicular injury and damage to male reproductive parameters within 28 days. The alterations in the structure of testicular tissue could be ascribed to the direct harmful impact of Docetaxel on Leydig cells and the epithelium responsible for spermatogenesis (Boekelheide, 2005; Sarıözkan *et al*., 2017). Additionally, it is possible that the damaged testis was influenced by docetaxel-induced oxidative stress and apoptosis.

The results of the current study were consistent with several other publications that have assessed the effects of chemotherapy on fertility parameters and testicular tissue (Huyghe *et al*., 2004; Chatzidarellis *et al*., 2010; Jacobs and Vaughn, 2012; Meistrich, 2013; Altintas *et al*., 2015; Polland and Berookhim, 2016; Sarıözkan *et al*., 2017; Tue Nguyen *et al*., 2018; Ghafouri-Fard *et al*., 2021). The effect of doxorubicin, a chemotherapy medication, on male fertility parameters in Wistar rats was explored by (Badkoobeh *et al*., 2013). Their findings demonstrated a decrease in the number, movement, and survival of sperm. Moreover, histological analysis demonstrated testicular degeneration in the testis of Wistar rats administered doxorubicin (Lee *et al*., 2012). Similarly, the effects of cisplatin, another chemotherapy drug, on male fertility parameters in Wistar rodents were assessed (Aksu *et al*., 2016). Sperm parameters decreased, and histological alterations, such as seminiferous tubule atrophy and germ cell apoptosis, were observed in testicular tissue.

In their study, Khoei *et al*. (2018) examined the impact of methotrexate on various parameters associated with male Swiss albino mice's fertility. The findings revealed a decline in the number, movement, and survival of sperm. Furthermore, a histological study found that testicular degeneration was characterized by an increase in apoptosis and a reduction in the proliferation of germ cells. Prior research has examined the impact of crocin, a saffron extract, on various aspects of male fertility in adult male rodents. These studies had shown a decline in sperm numbers, mobility, and cell survival (Al-Fartwsy *et al*., 2022; Mohammadpour *et al*., 2023). Both of these results aligned with the outcomes of this current research, suggesting that the administration of chemotherapy medications at large doses could elicit an adverse effect on testicular health, epididymides, and male fertility parameters.

Conclusion

The current study showed that administering docetaxel at large doses harms the reproductive indices and histology of testicular tissue in male Wistar rats. The findings indicate that the testicular toxicity of docetaxel is associated with oxidative stress and may vary depending on the dosage. The implications of the study findings have significant importance for the therapeutic application of docetaxel in patients with cancer within the reproductive age group who may face potential long-term fertility concerns. Additional research is required to examine the mechanisms underlying the harmful impact of Docetaxel on testicular tissue and to devise methods to reduce or prevent its adverse effects. Furthermore, novel treatment approaches should be developed to alleviate the reproductive toxicity of chemotherapy. The formation of collaborative partnerships between oncologists, reproductive specialists, and fundamental scientists holds significance in advancing the understanding of the impact of chemotherapy on male fertility and devising accurate interventions to safeguard reproductive well-being during cancer treatment. It is crucial to adopt a proactive and comprehensive approach to obtain the most favorable treatment outcomes and mitigate adverse reproductive consequences. The objective of this approach is to offer comprehensive healthcare services to individuals diagnosed with cancer, including their oncological and reproductive health.

Conflict of interest

The authors declare that they have no competing interests.

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No funding was received.

Authors' contributions

Conceptualization, M.S.A.; Methodology, M. S.A.; Validation, M. S.A.; Formal Analysis, H.H.K.; Investigation, A.A.H.; Data Curation, E.H.A.A.; Writing—Original Draft Preparation, M.S.A.; Writing—Review and Editing, M.S.A.; Supervision, A.M.H.; Project Administration, H.H.K.; Funding Acquisition, M.S.A. All authors have read and agreed to the publication of the manuscript.

Ethical approval

All experiments were performed according to the guidelines of the Implementing Health Research at the Institutions of Ministry of Health, Iraq (2018), the WHO Code of Conduct for Responsible Research (2017), and Principles of Human Experimental Techniques (Russell and Burch, 1959), for the Use of Experimental Animals (EC-1, 4-3-2024).

Data availability

The authors confirm that data supporting the findings of this study are available in the manuscript.

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