



The Effect of *Diplotaenia turcica* Root Extract on Sperm Parameters and Antioxidant Parameters in Doxorubicin-administered Rats

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ABSTRACT

This experimental study was designed to evaluate the potential toxic effects of Doxorubicin (DOX), a commonly used antineoplastic agent, on sperm parameters and antioxidant markers in rats, as well as the potential protective role of the root extract of *Diplotaenia turcica*, an endemic plant species native to Türkiye. A total of 21 male Wistar albino rats, divided into three groups of seven animals each, were used in the study. The experimental period lasted 7 days. The control group received only physiological saline solution. In the DOX group, a single intraperitoneal dose of DOX (15 mg/kg) was administered. In the DOX + *Diplotaenia turcica* root extract group, the animals received the plant extract orally at a dose of 150 mg/kg daily following DOX administration. Within 24 hours after the final treatment, the rats were anesthetized with ketamine, and testicular tissues were collected for analysis. Sperm concentration and the percentage of abnormal sperm were evaluated using samples obtained from the cauda epididymis. Additional testicular tissue samples were preserved for biochemical analysis. Levels of malondialdehyde (MDA), reduced glutathione (GSH), and catalase (CAT) activity were measured using commercial ELISA kits. All animals were humanely sacrificed at the end of the experiment in accordance with ethical guidelines. The findings of this study demonstrated that DOX induced significant impairments in both sperm parameters and antioxidant status, as evidenced by a marked decrease in sperm concentration, GSH levels, and CAT activity, along with a significant increase in the percentage of abnormal sperm and MDA levels. However, co-administration of *Diplotaenia turcica* root extract appeared to mitigate these adverse effects, suggesting a protective role in preserving testicular function. These results highlight the potential biomedical value of endemic plant species and underscore the importance of further research into their therapeutic applications.

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Introduction

Doxorubicin (DOX) is a highly potent chemotherapeutic agent belonging to the anthracycline class of drugs. It is widely used as a standard treatment option for various malignancies, particularly breast cancer, certain lung tumors, acute leukemia, and lymphomas (Carvalho et al., 2009; Vatsyayan et al., 2009; Jamialahmadi et al., 2021). However, despite its therapeutic efficacy, the clinical application of DOX is significantly limited by its pronounced toxicity in non-target organs such as the heart, kidneys, brain, and, notably, the testes (Alafifi et al., 2023). Testicular toxicity induced by DOX involves complex pathological mechanisms, including impaired autophagy, increased oxidative stress, inflammatory responses, activation of cell death pathways, and morphological alterations in spermatozoa and testicular tissue (Oyovwi et al., 2022). While the

antineoplastic effect of DOX is associated with the generation of reactive oxygen species (ROS), it concurrently suppresses the antioxidant defense system in various organs, including testicular tissue. This oxidative stress can damage sperm cell membranes, DNA structure, and protein content, ultimately compromising male reproductive capacity (Takeshima et al., 2021). Both short- and long-term administration of DOX has been shown to increase the risk of male infertility by causing structural damage to testicular tissue, disrupting spermatogenesis, inducing hormonal imbalances, and significantly reducing sperm quality (Shati and Khalil, 2023; Alshuwayer et al., 2025).

Diplotaenia turcica belongs to the Umbelliferae (Apiaceae) family, which, according to GENOM data, comprises 464 genera, predominantly distributed across

Central Asia. In Türkiye, the family is represented by 109 genera and approximately 450 species. Various studies on Umbelliferae species have demonstrated their antihyperglycemic, hypolipidemic, and antioxidant properties (Razavi et al., 2010; Ahmed et al., 2011; Farkhad et al., 2012; Duran et al., 2015). Originally classified as *Diplotaenia cachrydifolia* until 2011, *Diplotaenia turcica* was described as a distinct species by Pimenov and colleagues (Pimenov et al., 2011). The plant holds cultural and medicinal importance due to its traditional use in herbed cheese and folk medicine, where it is employed in the treatment of conditions such as snake and scorpion bites, diabetes, and rheumatism (Kaval et al., 2014; Uce and Tunçtürk, 2014). A review of the literature indicates that the root extract of *Diplotaenia turcica* increases antioxidant enzyme levels, reduces blood glucose levels, and mitigates pancreatic β -cell damage. Notably, a 200 mg/kg dose was reported to produce stronger effects than glibenclamide (Özdek et al., 2020). Additionally, the same extract has been shown to enhance follicular development and significantly increase the number of Graafian follicles in rat ovarian tissue (Colcimen et al., 2019).

This study was designed to evaluate the potential toxic effects of DOX on the male reproductive system and to investigate the protective role of the root extract of *Diplotaenia turcica*, an endemic plant species native to Türkiye. By examining alterations in sperm parameters and the antioxidant defense system, the study aimed to elucidate the potential benefits of the plant extract in preserving testicular function. Ultimately, the research sought to provide scientific evidence supporting the use of natural products in the management of chemotherapy-induced reproductive toxicity.

Materials and Methods

Extraction of Plant Material

The root portions of *Diplotaenia turcica*, harvested in May and June following taxonomic identification, were initially rinsed thoroughly with physiological saline solution. The cleaned roots were subsequently cut into small fragments, shade-dried, and pulverized into a fine powder using a mechanical grinder. A 100 g sample of the obtained powder was subjected to maceration in 1000 mL of 96% ethanol for 24 h. After the incubation period, the mixture was filtered to obtain the filtrate. This filtrate was concentrated using a rotary evaporator at 50°C and 70 rpm. The residual extract was then further dried in a water bath at 40°C until complete solvent evaporation occurred (Farkhad et al., 2012).

Animals

This study utilized 21 male Wistar albino rats weighing approximately 250–300 g. The animals were supplied by the Experimental Research Center of Van Yüzüncü Yıl University. During the experimental period, the rats were maintained in suitable cages under standard laboratory conditions, with an ambient temperature of 22±2°C and a 12 h light/12 h dark cycle. The cages were cleaned daily, and the animals were provided ad libitum access to fresh food and water throughout the study.

Experimental Design

Ethical approval for this study was granted by the Local Animal Ethics Committee of Van Yüzüncü Yıl University (Ethics Committee Approval No: 2025/06-26). Prior to the commencement of the experimental procedures, the animals underwent a 10-day acclimatization period to adapt to the laboratory conditions. Throughout the entire study, all procedures were conducted with careful consideration of animal welfare and in compliance with international ethical guidelines.

The rats were randomly divided into three experimental groups, each comprising seven animals (n = 7):

Control group: The animals were administered physiological saline solution orally for 7 consecutive days.

DOX group: A single intraperitoneal injection of Doxorubicin (15 mg/kg) was given (Alshuwayer et al., 2025).

DOX + *Diplotaenia turcica* root extract group: After a single intraperitoneal administration of DOX (15 mg/kg), the rats received *Diplotaenia turcica* root extract orally at a dose of 150 mg/kg once daily for 7 days.

At the conclusion of the experimental period, all animals were subjected to 12 h of fasting. Anesthesia was subsequently induced by intraperitoneal administration of ketamine at 75 mg/kg. While under anesthesia, one testis from each rat was surgically removed for biochemical assessments and preserved under suitable conditions in a deep freezer. The collected tissues were examined for oxidative stress and antioxidant parameters, including MDA levels, GSH content, and CAT activity. The cauda epididymis from the opposite testis was utilized for spermatological analysis.

Semen Collection and Evaluation of Spermatological Parameters

Sperm samples were obtained from the cauda epididymis to evaluate spermatological parameters. The collection procedure was carried out in accordance with the method reported by Aksu et al. (2015). Briefly, the cauda epididymis was carefully dissected and separated. The removed tissue was placed in a sterile Petri dish containing 2 mL of physiological saline solution pre-warmed to 37°C. The tissue was then finely cut at multiple sites using a sterile scalpel to promote the release of spermatozoa into the medium. Subsequently, the preparation was incubated at 37°C for approximately 15 min. The obtained suspension was homogenized and utilized for spermatological assessments, including sperm concentration and morphological analysis.

Sperm concentration was assessed with minor modifications to the method described by Sönmez et al. (2005), replacing the conventional hemocytometer with an Eppendorf tube. A 10 μ L sample of the sperm suspension, prepared by mincing the cauda epididymis in physiological saline, was pipetted into an Eppendorf tube containing 990 μ L of Hayem's solution. The mixture was vortexed for 15 s, and approximately 10 μ L of the diluted suspension was subsequently placed into the counting chambers of a Thoma slide. After allowing a 5 min settling period for the sperm cells, enumeration was carried out under a phase-contrast microscope at 400× magnification.

The assessment of abnormal spermatozoa was performed based on the method described by Türk et al. (2008). Briefly, a drop of the homogenized sperm suspension was applied onto a clean, dry slide and evenly spread to obtain a thin smear. After air-drying at room temperature, the smears were stained with 1% eosin–nigrosin solution. Once staining was completed, the slides were examined under a microscope at 400× magnification. For each specimen, a minimum of 200 sperm cells were analyzed, and those displaying morphological abnormalities were documented. The proportion of spermatozoa with normal morphology was calculated and compared among the experimental groups.

Evaluation of Biochemical Parameters

Commercial ELISA kits were employed for the biochemical analyses conducted in this study. All procedures were carried out in strict accordance with the manufacturers' instructions.

The GSH ELISA kit (Cat No: ELK8577) was utilized to determine GSH levels, the MDA kit (Cat No: YLA0029RA) was used for the measurement of MDA levels, and the CAT kit (Cat No: YLA0123RA) was applied to assess CAT activity.

Statistical Analysis

In the statistical assessment of biochemical parameters, the normality of continuous variables was assessed using the Shapiro–Wilk test. Variables demonstrating a normal distribution were compared among groups using one-way analysis of variance (ANOVA). A p value <0.05 was accepted as statistically significant. All statistical procedures were performed using SPSS software (Version 20.0; SPSS Inc., Chicago, IL, USA). Group comparisons for sperm parameters were likewise conducted using one-way ANOVA. In cases where a significant difference was identified, Tukey's Honestly Significant Difference (HSD) post hoc test was employed to determine which groups accounted for the observed variation.

Results

Spermatological Findings

Analysis of sperm concentration data presented in Table 1 revealed a significant decrease in the DOX- administered group compared with the control group ($P < 0.001$). In contrast, the group administered with DOX in combination with *Diplotaenia*

turcica root extract exhibited a significant increase in sperm concentration relative to the DOX-only group ($P < 0.001$). Similarly, assessment of sperm morphology indicated a significant rise in the percentage of abnormal sperm in the DOX group compared to the control group ($P < 0.001$). However, administration of both DOX and *Diplotaenia turcica* root extract resulted in a significant reduction in the proportion of abnormal sperm compared with the DOX- administered group ($P < 0.001$).

Biochemical Findings

Analysis of the biochemical data presented in Table 2 demonstrated a significant increase in MDA levels in the DOX- administered group compared with the control group ($P < 0.001$). In contrast, the group receiving both DOX and *Diplotaenia turcica* root extract showed a significant decrease in MDA levels relative to the DOX-only group ($P < 0.001$). Regarding CAT enzyme activity, the DOX group exhibited a significant reduction compared to the control group ($P < 0.001$), whereas the DOX + *Diplotaenia turcica* root extract group displayed a significant increase in CAT activity compared with the DOX- administered group ($P < 0.001$). Similarly, GSH levels were markedly lower in the DOX group relative to controls ($P < 0.001$), while co-administration of *Diplotaenia turcica* root extract with DOX led to a significant elevation in GSH levels compared to the DOX-only group ($P < 0.001$).

Discussion

Cytotoxic effects of chemotherapeutic agents, particularly on testicular tissue, pose a significant clinical challenge to male reproductive health, highlighting the need for supportive strategies to preserve fertility during treatment. In recent years, natural compounds have shown potential in alleviating chemotherapy-induced testicular toxicity due to their antioxidant, anti-inflammatory, and cytoprotective properties. Several plant extracts have been reported to reduce ROS levels, thereby mitigating oxidative stress-induced cellular damage, supporting spermatogenesis, and positively affecting testosterone production (Alshuwayer et al., 2025; Korkmaz et al., 2025; Yeni et al., 2025). In this context, the results of our study using a botanical agent indicate that herbal supplements may offer a promising approach to preventing testicular damage associated with chemotherapeutic treatments.

Table 1. Effect of *Diplotaenia turcica* root extract on sperm parameters in doxorubicin-administered rats

Groups	Sperm Density ($\times 10^6$)	Abnormal Sperm Rate (%)
Control group	83.85 ± 1.57^a	9.57 ± 0.78^c
DOX group	46.71 ± 1.11^c	47.28 ± 1.60^a
DOX + <i>Diplotaenia turcica</i> root extract group	56.00 ± 1.82^b	14.12 ± 1.95^b

a, b, c: Statistical differences between groups with different letters in the same column are significant ($P < 0.001$).

Table 2. Effects of *Diplotaenia turcica* root extract on testicular tissue MDA and GSH levels and CAT enzyme activity in DOX-administered rats

Groups	MDA (nmol/ml)	CAT (ng/ml)	GSH (pg/ml)
Control group	4.18 ± 0.11^b	1358 ± 67^a	18191 ± 621^a
DOX group	9.81 ± 0.96^a	640 ± 45^c	207 ± 271^c
OX + <i>Diplotaenia turcica</i> root extract group	5.30 ± 0.75^b	923 ± 50^b	11807 ± 244^b

Each value is presented as mean $\pm$ SE ($n = 7$). $p < 0.05$; a, b, c: Mean values in the same row marked with different letters indicate a statistically significant difference between groups.

Based on the data from our study, DOX administration exerted significant detrimental effects on male reproductive health. Specifically, the DOX group exhibited a pronounced reduction in sperm concentration compared with the control group ($P < 0.001$), indicating that DOX-induced testicular toxicity disrupts spermatogenesis and decreases sperm production. Similarly, analysis of sperm morphology showed a significant increase in the percentage of abnormal sperm in the DOX- administered group ($P < 0.001$), suggesting that DOX may inflict structural damage on germ cells, thereby impairing normal sperm development. Previous studies have reported that DOX disrupts testicular cellular architecture and induces apoptosis in spermatocytes and spermatids, compromising the structural integrity of seminiferous tubules and leading to increased abnormal sperm formation (AbdRabou et al., 2021). Our observations regarding sperm parameters align with findings reported in the literature (Mustafa et al., 2022; Shati and Khalil, 2023; Alshuwayer et al., 2025; Aribo et al., 2025; Jaiyeoba-Ojigbo et al., 2025).

In the group receiving DOX in combination with *Diplotaenia turcica* root extract, a significant increase in sperm concentration ($P < 0.001$) and a significant reduction in the percentage of abnormal sperm ($P < 0.001$) were observed. These results are consistent with previous studies (Belhan et al., 2020) and suggest that *Diplotaenia turcica* root extract may provide protective effects against DOX-induced testicular toxicity. It is proposed that the plant's potential antioxidant compounds reduce ROS-mediated cellular damage, thereby preserving germ cells and supporting spermatogenesis.

The primary mechanism underlying DOX-induced testicular damage involves the generation of ROS and the resulting biochemical and physiological disruptions caused by oxidative stress. In this study, CAT enzyme activity, as well as GSH and MDA levels, were measured in the testicular tissues of all experimental groups to assess the effects of DOX and the potential protective role of *Diplotaenia turcica* root extract. The results showed a significant decrease in CAT activity and GSH levels ($P < 0.001$), accompanied by a marked increase in MDA levels ($P < 0.001$) in the DOX- administered group. These observations are in agreement with previous studies (Mustafa et al., 2022; Shati & Khalil, 2023; Alshuwayer et al., 2025; Aribo et al., 2025; Jaiyeoba-Ojigbo et al., 2025; Korkmaz et al., 2025; Yeni et al., 2025; Toraman and Ceylan, 2025). The reduction in GSH following DOX administration reflects a weakened antioxidant defense system, rendering cells more vulnerable to free radical-induced damage. At the same time, the elevated MDA levels indicate increased lipid peroxidation due to DOX exposure, suggesting oxidative damage to cellular membranes.

In the DOX + *Diplotaenia turcica* root extract group, GSH levels, CAT enzyme activity, and MDA levels were restored to near-normal values, closely resembling those of the control group. The administration of *Diplotaenia turcica* root extract appears to enhance endogenous antioxidant defenses by increasing GSH levels, likely due to GSH's ability to scavenge free radicals. GSH interacts directly with peroxides and free radicals, thereby preventing oxidative stress-induced damage (Arulselvan and Subramanian, 2007). Likewise, *Diplotaenia turcica*

root extract was observed to reduce MDA levels, suppressing lipid peroxidation and oxidative cellular injury. These results indicate a protective effect of *Diplotaenia turcica* root extract against DOX-induced testicular toxicity. The ameliorative effects of the extract on biochemical parameters are consistent with previous reports (Özdek et al., 2020).

Conclusion

This study demonstrates that DOX can exert detrimental effects on testicular function and the antioxidant system, while highlighting the potential protective role of *Diplotaenia turcica* root extract in mitigating these effects. The results indicate that DOX causes changes in sperm parameters and oxidative stress markers, whereas the plant extract shows promising potential to alleviate these alterations and support testicular health. These findings emphasize the value of endemic plants from Türkiye in biomedical research and suggest their potential as complementary agents in oncological treatment regimens. Further studies are warranted to elucidate the mechanisms of action of *Diplotaenia turcica* root extract and to assess its potential applicability in clinical settings.

Declarations

Ethical Approval Certificate

The study protocol was approved by Van Yuzuncu Yil University Animal Experiments Local Ethics Committee (Approval number: 2025/06-26, Date: 29.05.2025).

Author Contribution Statement

Saadet Belhan: Data collection, investigation, formal analysis, and writing the original draft.

Uğur Özdek: Data collection and investigation, review and editing.

Fund Statement

The authors declared that this study has received no financial support.

Conflict of Interest

The authors declare no conflict of interest.

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