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Original article

Cypermethrin's Consequences on the Male Reproductive System of Swiss Albino Mice

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Abstract
Infertility is a prevalent issue impacting millions of individuals of reproductive age globally. The reduction in male fertility has been linked to various factors, including exposure to environmental pollutants like pesticides. Cypermethrin, a type II synthetic pyrethroid insecticide commonly used in Libya, is the focus of this study, which aims to evaluate its effects on the male reproductive system in mice. The research involved three groups of adult male Swiss albino mice (Mus musculus), each consisting of eight individuals. The control group received distilled water, while the treatment groups were administered cypermethrin at doses of 65.7 mg/kg (CYP I) and 93.86 mg/kg (CYP II) of body weight (bw). All treatments were delivered orally via gavage over a period of 28 days. At the end of the experiment, measurements were taken for body and testicular weights, as well as serum levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Additionally, semen parameters, including sperm count, motility, and morphological abnormalities, were assessed. Histopathological evaluations of testicular tissue were conducted using histological cross-sections. Results indicated no significant differences in body weight between the treatment and control groups. However, the higher dose (CYP II) led to a marked reduction in testicular weight, sperm count, motility, and normal sperm morphology, alongside all histopathological criteria, Johnsen's score, testosterone, and LH levels, while FSH levels increased. These findings suggest that cypermethrin induces testicular toxicity and adversely affects male fertility in mice
Keywords. Cypermethrin, Infertility, Sperm Parameters, Reproductive Toxicity.

Introduction

Infertility is a major global issue, affecting over 15% of the world's population [1]. It describes the failure to conceive following 12 months of regular, unprotected intercourse [2]. Male factor infertility accounts for 40% of all infertility cases [3,4] and affects around 7-10% of the male population worldwide [5, 6]. Since 1992, there has been a considerable reduction in male fertility [7-9], raising worries about the influence of modern environmental variables on fertility [10], since it is thought to be one of the key causes of male infertility [5,11,12]. Numerous studies have connected pesticide exposure to reproductive abnormalities and male infertility [13-19]. Unfortunately, the increase in the production and consumption of pesticides in agriculture in order to meet the high demands of the rising population has led to crossing the tolerance level, causing severe environmental and health problems. These chemical toxicants affect male reproductive organs by damaging steroidogenesis and deteriorating sperm quality. These negative effects depend on the type of pesticide, the exposure dose, and the duration period [20].

In the meantime, the Swiss albino mouse (*Mus musculus*) serves as a valuable and widely accepted model organism in toxicological research due to its physiological similarities to humans, well-characterized reproductive biology, ease of handling, and genetic uniformity. Studies utilizing this model provide crucial insights relevant to understanding potential human health risks [21]. Studies on occupational exposure as well as animal experiments support the idea that environmental contaminants are contributing to fertility issues [22,23]. Pesticides such as Amitraz [24], Chlorpyrifos [25], malathion [26], acetochlor [27], and dimethoate [28] have shown adverse effects on mouse test models, proving the reproductive toxicity caused by pesticides.

Synthetic pesticides known as pyrethroids have been developed as substitutes for their natural counterparts, pyrethrins, due to their slower photodegradation. Pyrethroids target and disrupt the nervous systems of insects, leading to hyperactivity, paralysis, and eventual death. However, they can also be harmful to non-target species like crustaceans and fish [29]. Over the past decade, the use of pyrethroids has increased while other types of insecticides, like organochlorines, organophosphates, and carbamates, have decreased due to advantages such as their effectiveness against insects, rapid biodegradation, and low toxicity to mammals [30]. Cypermethrin, a type II synthetic pyrethroid insecticide, is widely utilized in commercial agriculture worldwide, including Libya [31]. Studies have demonstrated the adverse effects of cypermethrin on the nervous system [32-34], the lungs [35], liver and kidneys [36-42], as well as reproductive toxicity, molecular toxicity, endocrine disruption and decreased fertility in both sexes of experimental animals[43-53], leading to reduced weight of various male reproductive organs, decrease in serum testosterone levels, reduced sperm count, changes in sperm motility, abnormalities in sperm morphology, testicular lesions, impairments of the seminiferous tubule structure, impairments of spermatogenesis, and genotoxic effects [44,54-63]. These negative consequences could be linked to its antiandrogenic effects [64]. herefore, this study aims to systematically investigate the consequences of

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commercial formulation of cypermethrin exposure on the male reproductive system of Swiss albino mice. This study will specifically evaluate its effects on key endpoints, including testicular histoarchitecture, sperm parameters (count, motility, morphology), reproductive hormone levels (testosterone, LH, FSH), and potential apoptotic changes. Understanding these effects is critical for a comprehensive assessment of cypermethrin's reproductive toxicity profile and its implications for environmental and occupational health.

Methods

Preparation of pesticide doses

The study utilized Cyper-kal 40% EC pesticide, which is widely used in agriculture in Libya. It contains Cypermethrin [cyano-(3-phenoxyphenzyl) methyl]3-(2,2-dichloroethenyl)-2,2-dimethyl cyclopropan-1-carboxylate] as its active component. It was obtained from the local market and appropriately diluted in distilled water to administer doses of 65.7 and 93.86 mg/kg bw. These doses represent 1/10 and 1/7 of the LD50 value of the aqueous solution of cypermethrin as stated in previous studies [65,66].

Experimental design

Mature male Swiss albino mice (*Mus musculus*) aged between 12 - 16 weeks and weighing 25 to 30 grams were bred in the animal house at the Zoology Department of the Faculty of Science at Tripoli University. The mice were kept under a natural light/dark photoperiod at a room temperature of 22 ± 3°C and were fed a standard mice diet and had access to drinking water *ad libitum*. The study received ethical approval from the Scientific Research and Ethics Committee at the University of Tripoli (SREC-UOT 20-2022). The mice were divided into three groups, consisting of eight animals each. The control group received distilled water, while the treatment groups were administered 65.7 mg/kg (bw) cypermethrin (CYP I) and 93.86 mg/kg (bw) cypermethrin (CYP II). All treatments were administered orally via gavage for a duration of 28 days. Throughout the study, the mice were observed daily to monitor their survival and identify any potential signs of toxicity. At the end of the treatment period, the mice were weighed and then euthanized for further analysis.

Weighing and preserving samples

The mice were weighed at the beginning of the experiment and then after 24 hours of the final treatment. On the 29th day, the mice were weighed, and the change in body weight was calculated. Blood samples were collected and centrifuged, and the serum was stored at -20 °C for hormonal analysis. Subsequently, the sperm were isolated from the vas deferens and subjected to sperm analysis for evaluation. The testes were then quickly removed, weighed, and fixed in 10% neutral buffered formalin for histological examination.

Sperm count, motility, and morphology evaluation

Semen was collected by gently squeezing each vas deferens in a Petri dish containing 1 mL of physiological normal saline (0.9% NaCl), which was incubated for 10 minutes at 37 °C before being completely mixed using a small pipette. A Neubauer hemocytometer counting chamber was used, and the motile and immotile sperm cells were counted under a light microscope at 400X magnification using the counting system described by [67] and [68].

The results were expressed as a percentage of motility, and the total sperm count was determined and expressed as sperm x 10^6/mL. Sperm smears were created from the sperm suspension, which was stained with 1% eosin, for the assessment of sperm morphology using 400X magnification of a standard light microscope.

Biochemical analysis

Testosterone, LH, and FSH were quantified according to established protocols using chemiluminescence immunoassay (CLIA) kits (Snibe maglumi, China) and the Cobas e 411 platform (Roche Cobas e 411, Switzerland).

Histological procedures

Fixed tissue specimens were dehydrated in ethanol, then cleared with xylene and embedded in paraffin. They were sectioned to a thickness of 5-µm. Then, tissue sections were stained with hematoxylin and eosin (H&E). Sections were examined under a microscope, and photographs were taken for histological evaluation and Johnsen's scoring. Two hundred round or nearly round seminiferous tubule cross sections were examined at 100X magnification per animal to evaluate histological alterations, including detachment of spermatogenic cells, sloughing of germ cells, and vacuolization in the germinal epithelium. The average percentage was calculated for each specimen as the method described by [69]. Furthermore, the level of maturation of the germinal epithelium was assessed utilizing Johnsen's scoring method [70].

Statistical analysis

The variables were tested for normal distribution, and homogeneity. Results were presented as the mean ± standard deviation (SD) of eight mice. The statistical software package (SPSS version 23) was employed to

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analyze variance ANOVA – One way, followed by post-hoc pairwise comparison applying the Duncan test for inter-group comparisons involving more than two groups. Furthermore, a p-value of less than 0.05 was considered statistically significant ($p < 0.05$).

RESULTS

Body and testicular weight

The study found no significant differences in body weight between the treatment and control groups ($P > 0.07$). Furthermore, there were no significant differences in testis weight between the control and CYP I group (P=0.056). Meanwhile, the CYP II group showed a significant reduction in testicular weight (P=0.00) compared to the control group (Table 1).

Table 1. Body weight and testis weight of male mice treated with cypermethrin

Groups	Body Weight (G)	Testis Weight (G)
Control	28.01±2.13^{ab}	0.11±0.01^{a}
CYP I	28.90±0.99^{a}	0.11±0.00^{a}
CYP II	26.90±1.20^{b}	0.09±0.01^{b}

Data represent the mean ± SD of eight mice in each group. Values in the same column for a compartment, not sharing the same superscript, are significantly different from each other at $p < 0.05$.

Hormonal assay

The testosterone level was significantly reduced in the groups treated with CYP I and CYP II (P=0.00). While the LH level was significantly reduced only in the CYP II group (P=0.001) in comparison to the control group. In contrast, FSH levels were significantly elevated in the CYP I (P=0.03) and CYP II (P=0.00) groups compared to the control group (Table 2).

Table 2. FSH, LH, and testosterone concentration in male mice treated with cypermethrin

	FSH	LH	Testosterone
Control	2.09±0.19^{b}	9.78±0.56^{a}	6.6±1.7^{a}
CYP I	2.75±0.87^{a}	8.43±1.08^{ab}	3.4±1.5^{b}
CYP II	3.36±0.34^{a}	6.84±1.63^{b}	2.2±0.9^{b}

Data represent the mean ± SD of eight mice in each group. Values in the same column for a compartment, not sharing the same superscript, are significantly different from each other at $p < 0.05$.

Sperm parameters

According to the findings, exposure to CYP I and CYP II significantly reduced sperm parameters (P=0.00). Cypermethrin toxicity decreased sperm count and motility percentage, while elevating the percentage of morphologically abnormal sperm (Table 3). Various abnormalities were discovered in the sperm heads, midpieces, and tails, as shown in (Figure 1). There was no significant difference in the percentage of abnormal sperm between the control and CYP I groups (P=0.083), while there was a significant increase in abnormal sperm in the CYP II group when compared to the control and CYP I groups (P=0.00) (Table 3). The percentage of head abnormalities, such as amorphous head and hookless head, was significantly higher in the CYP II group compared to other treatment groups (P=0.00), while sperms with bent tails were significantly increased in the CYP I and CYP II groups compared to the control group (P=0.00, P=0.039, respectively) (Figure 2).

Table 3. Sperm count, motility, and morphological abnormality in mice treated with cypermethrin

Variables	Motility percentage (%)	Sperm count (106/ml)	Percentage of normal sperm (%)
Control	0.62±0.06a	74.8±3.9a	0.42±0.05a
CYP Ⅰ	0.43±0.05b	37.6±5.4b	0.39±0.03a
CYP Ⅱ	0.33±0.04c	33.0±4.7c	0.26±0.05b

Data represent the mean ± SD of eight mice in each group. Values in the same column for a compartment, not sharing the same superscript, are significantly different from each other at p < 0.05.

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Figure 1. Normal and abnormal sperm shape in control and cypermethrin-treated groups. (A) normal morphology. (B) amorphous head. (C) hookless head. (D) hammer head. (E) bent head. (F) hairpin loop. (G) bent mid-piece. (H) bent tail. 1.0% eosin stain, 40X.

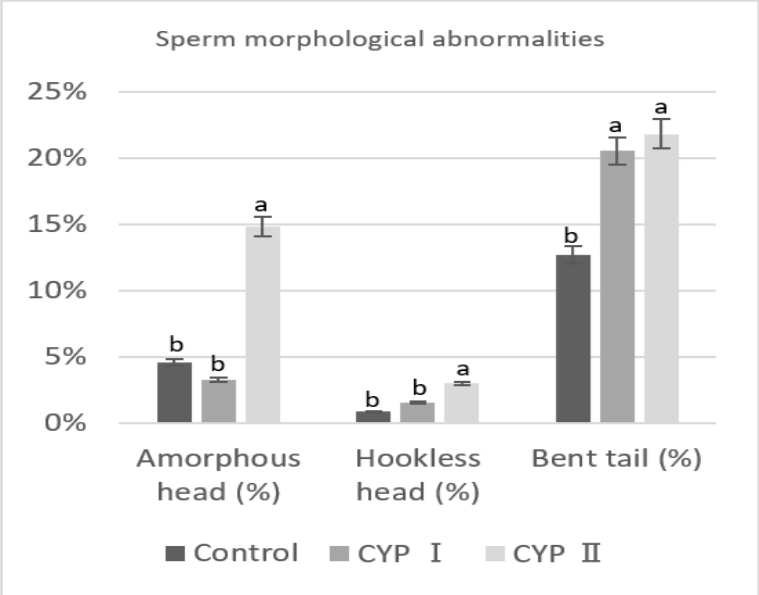

Figure 2. Percentage of morphologically abnormal sperm in mice treated with cypermethrin. Data represent the mean ± SD of eight mice in each group. Bars not bearing the same alphabet as superscript are significantly different from each other at p < 0.05.

Histological cross sections

The results of histology assessments demonstrate that testes from the control group had normal histological structure, a normal pattern of seminiferous tubules with orderly arranged spermatogenic cells, a high spermatozoa abundance in the lumen, and restricted interstitial space with numerous Leydig cells. The germinal epithelium was made up of concentric layers of germ cells, spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa, indicating normal spermatogenesis with a very low incidence of detached, sloughed, or vacuolized seminiferous tubules, as shown in (Table 4) and (Figure 3). Meanwhile, the testes of CYP-treated groups showed marked damage in histological architecture and organization of seminiferous tubules as compared to the control group, as well as varying degrees of degenerative alterations. The low dose CYP I (65.7 mg/kg) caused the amount of sperm in the lumen to decrease and the interstitial tissue to thicken in some areas, as well as sloughing of germ cells (Figure 4).

The CYP II (93.86 mg/kg) group's seminiferous tubule lumens were wider and nearly devoid of sperm (Figure 5), and germ cell degenerative changes occurred, such as detachment, sloughing, scattered spermatids, severe vacuolization of the seminiferous tubule cells, and spermatocyte exfoliation into the lumen. There was a significant decrease in normal histology criteria in the CYP I and CYP II groups in comparison to the control group (P=0.00), as well as a significant decrease in the CYP II group when compared to the CYP I group (P=0.00), as shown in (Table 4). Normal spermatogenesis was observed in both the control and CYP I groups, and there was no significant difference in the mean Johnsen's score (P=1.00). Meanwhile, in the CYP II group, nearly all tubules showed maturation arrest, and the mean Johnsen's score was significantly lower than that in the control group (P=0.00) (Table 4).

Table 4. Testis histology assessment and Johnsen's score of mice treated with cypermethrin

Variables	Percentage of seminiferous tubules				Johnsen's score
	Normal%	Detached%	Sloughed%	Vacuolized %	
Control	87.67±1.53^{a}	11.33±1.53^{a}	1.00±0.00^{c}	0.33±0.58^{c}	10.00±0.00^{a}
CYP I	54.67±1.53^{b}	7.00±1.73^{b}	14.67±2.89^{b}	23.33±1.53^{b}	10.00±0.00^{a}
CYP II	1.67±0.58^{c}	7.00±2.65^{b}	52.33±2.52^{a}	40.00±4.00^{a}	4.67±0.58^{b}

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Data represent the mean ± SD of eight mice in each group. Values in the same column for a compartment, not sharing the same superscript, are significantly different from each other at $p < 0.05$.

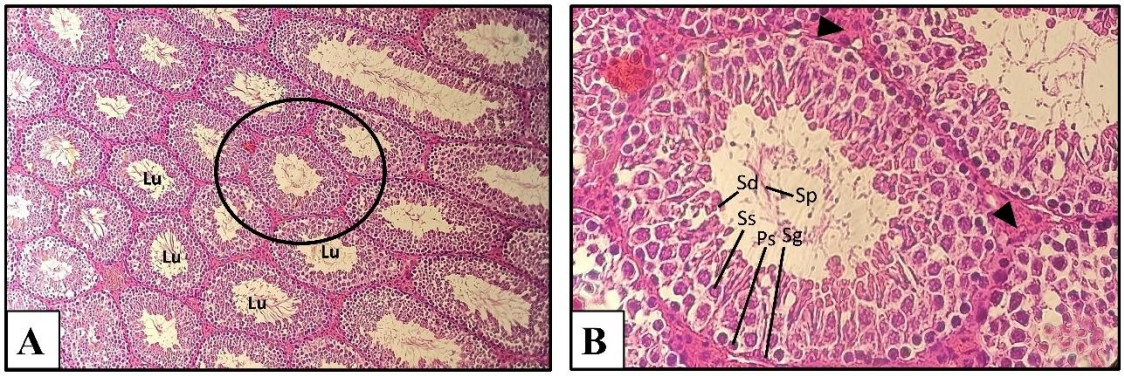

Figure 3. Photomicrograph of a histological section of the control group mouse testis, showing normal histological structure, normal pattern of seminiferous tubules with orderly arranged spermatogenic cells consisting of concentric layers of spermatogonia (Sg), primary (Ps) and secondary (Ss) spermatocytes, spermatids (Sd) and spermatozoa (Sp). High spermatozoa concentration in the lumen (Lu) and little interstitial space with abundant Leydig cells (arrowhead). (H and E stain, A:10X and B:40X).

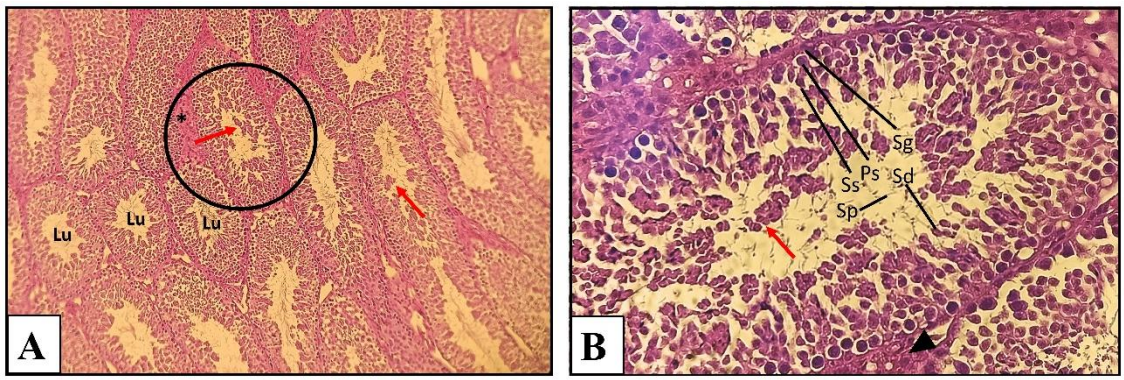

Figure 4. Histological sections of the testes of male mice treated with 65.7 mg/kg cypermethrin. The number of sperm in the lumen (Lu) tended to decrease, and the germ cells began to slough (red arrows). At the same time, spermatogenic cells, spermatogonia (Sg), primary (Ps) and secondary (Ss) spermatocytes, spermatids (Sd) and spermatozoa (Sp), as well as Leydig cells (arrow head), are still observed. While interstitial tissue appears to be thicker in some areas (*). (H and E stain, A:10X and B:40X).

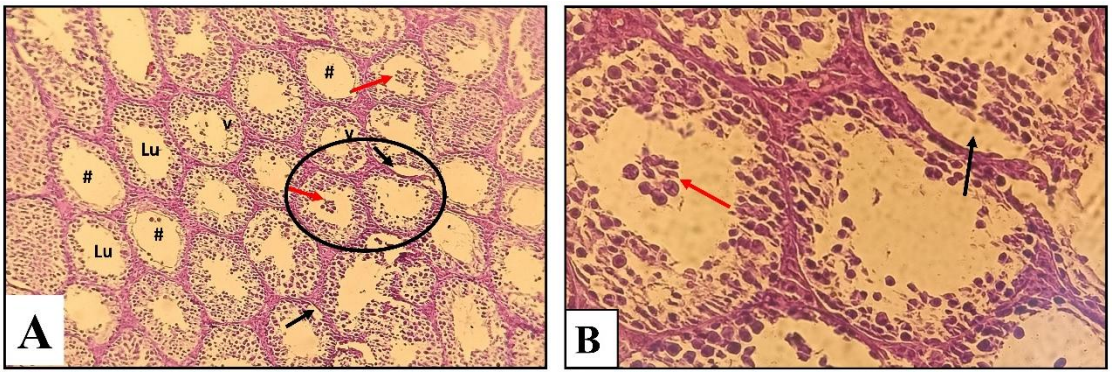

Figure 5. Histological sections of testes of male mice treated with 93.86 mg/kg cypermethrin. (A) The lumens of the seminiferous tubules were increased in size and nearly devoid of sperm (#), and varying degrees of germ cell degenerative changes occurred, such as sloughing of germ cells (red arrows), vacuolation (v), and detachment of germinal epithelium (black arrows). (H and E stain, A:10X and B:40X).

Discussion

Differences in body and reproductive organ weights are a useful indicator of reproductive health. The body weight of the mice appeared unaffected by the various treatments applied in this study. However, the

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testicular weight significantly decreased when treating mice with CYP II (93.86 mg/kg bw). The observed reduction in body and testis weight aligns with a well-established body of literature documenting similar losses in overall and reproductive organ mass [44,59,60,63,71]. In contrast, Elbetieha et al. [54] observed a low body weight gain despite a significant increase in the weights of the testes, seminal vesicles, and preputial gland. The accumulation of interstitial connective tissue observed in the testes may have caused these increases. According to Crumpton et al. [72] and Mandal and Das [73], a reduction in testis weight is an accepted indicator of testicular and reproductive toxicity. This reduction can be attributed to several factors, including decreased food intake [74], testicular degeneration resulting from cypermethrin toxicity [75], or cell apoptosis [76], leading to enhanced pro-apoptotic activity and consequent cell death [77]. Previous studies revealed that CYP significantly up-regulated apoptotic genes such as p53 and Cas3 in the brain and testis tissues, while down-regulating the expression of the Bcl-2 gene, which is an anti-apoptotic gene [78]. This mechanism provides a plausible explanation for the testicular weight loss seen in our CYP II-treated group.

Within the present research, after administering cypermethrin to mice, the amount of testosterone level was considerably reduced, whereas FSH levels were significantly increased. This finding was consistent with the results of [61], which revealed a significant reduction in serum testosterone level and a significant increase in serum FSH concentration in male rats treated daily with cypermethrin at a dose of 60 mg/kg body weight. While, [79] revealed that cypermethrin significantly lowered serum testosterone level while elevating LH level, without altering serum FSH hormone level. Meanwhile, other reports noted that testosterone, as well as FSH and LH levels, have shown a significant reduction when exposing mice [44,59] and rats [54,60,62,80] to cypermethrin. Furthermore, researchers reported similar testosterone level results in male animals exposed to other synthetic pyrethroids like fenvalerate in rats [81] and permethrin in mice [82]. In a study by Zhang et al. [82], damage to the Leydig cell mitochondrial membrane in adult mice was shown to disrupt steroidogenesis, resulting in decreased testicular testosterone biosynthesis. Disruption of Leydig cell viability can impair testicular steroidogenesis, leading to disturbances in spermatogenesis and fertility issues. Studies indicated that steroidogenic acute regulatory protein (StAR) expression decreased significantly in cypermethrin-treated rats [64]. Further research demonstrated that cypermethrin significantly down-regulated the expression of Leydig cell genes, *Lhcgr*, *Star*, *Cyp11a1*, and *Cyp17a1* and their proteins, leading to the conclusion that cypermethrin inhibits the development and function of Leydig cells in male rats in late puberty [79]. On the other hand, testosterone treatment in cypermethrin-treated rats ameliorated its toxic effects by restoring testosterone biosynthesis, spermatogenesis, and sperm maturation events [64].

These findings indicate that cypermethrin has a detrimental effect on sperm quality. The administration of two doses of cypermethrin resulted in a significant reduction in sperm count, motility, and normal morphology, alongside an increase in sperm abnormalities. These results are supported by the studies of Wang et al. [44], Elbetieha et al. [54], Joshi et al. [60], Li et al. [61], Sharma et al. [62], Abdel-Razik, et al. [63], Katragadda, et al. [64] Abd- Ellaah, et al. [80] and Zhang et al. [82], In a study by Zhang et al. [82], it was proposed that diminished levels of testosterone could be a key factor contributing to the observed decline in sperm concentration and movement, alongside structural defects in the testes of mice exposed to cis-permethrin. On the same side, Yao and Wang [83] revealed that pyrethroids can reduce sperm count and sperm motility, increase the abnormal sperm count, and cause deformity of the sperm head. Other studies explain that cypermethrin's effects are due to the overproduction of free radicals. For example, oxidative stress has been proposed to play an essential role in cypermethrin-induced reproductive dysfunction [44, 62]. Chronic exposure to CYP increased levels of certain cytochrome P450 enzymes and decreased glutathione S-transferase activity, indicating prolonged toxicological impact [84]. Furthermore, Agarwal et al. [85] found a correlation between increased production of reactive oxygen species and reduced sperm motility.

In the CYP I group, histopathology assessments revealed that some seminiferous tubule germ cells began to slough, detach, and vacuolize, and the number of sperm in the lumen tended to decrease. In the group treated with CYP II, the lumens of the seminiferous tubules were larger and almost empty of sperm. Additionally, nearly all tubules showed maturation arrest, and the average Johnsen's score was notably lower than in the control group. This led to a significant decrease in all histopathology criteria in both the CYP I and CYP II groups compared to the control group. Additionally, there was a significant decrease in the CYP II group compared to the CYP I group. According to several studies [44, 59, 60, 61, 71], prolonged exposure to cypermethrin harms the testes by changing their tissue structure and disrupting sperm production. These negative effects may be the result of lowered plasma testosterone or the formation of free radicals in the testicular tissue [72,73,86,87]. Fascinatingly, Ravula and Yenugu [88] observed that prolonged exposure to pyrethroids disrupts the expression of genes. These genes regulate apoptosis, spermatogenesis, steroidogenesis, and male gamete genetic reprogramming.

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Conclusion

This study indicates that cypermethrin has considerable harmful effects on the male reproductive system, as seen by hormonal alterations, sperm suppression, and unfavorable effects on semen parameters in mice treated with cypermethrin. This study implies that pesticides should not be used excessively.

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Conflicts of Interest

The authors declare no conflicts of interest.

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