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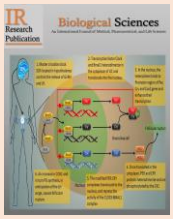

Ameliorative Effects of Curcumin on Ciprofloxacin-Induced Testicular Toxicity: A Study on Reproductive Hormones, Oxidative Stress, and Histological Changes in Adult Male Mice

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ABSTRACT

Ciprofloxacin, a widely used fluoroquinolone antibiotic, has been associated with testicular toxicity, characterized by oxidative stress and hormonal imbalances that impact male reproductive health. Curcumin, a natural antioxidant and anti-inflammatory agent, has shown potential in mitigating these effects. This study aimed to evaluate the ameliorative effects of curcumin on ciprofloxacin-induced testicular toxicity in adult male mice, focusing on reproductive hormones, oxidative stress, and histological changes. Thirty mice were divided into six groups, receiving varying doses of ciprofloxacin and curcumin over 30 days. Hormonal assays for testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were performed, alongside assessments of oxidative stress markers like malondialdehyde (MDA) and histopathological analyses of testicular tissue. Results showed a significant reduction in FSH and testosterone levels in ciprofloxacin-treated mice, with curcumin ameliorating these effects in co-treatment groups. MDA levels, an indicator of oxidative stress, were elevated in ciprofloxacin-only groups but significantly reduced in curcumin-treated groups. Histological examination revealed that curcumin protected against ciprofloxacin-induced testicular damage. In conclusion, curcumin demonstrated significant protective effects against ciprofloxacin-induced testicular toxicity by normalizing reproductive hormone levels, reducing oxidative stress, and preserving testicular architecture. These findings suggest curcumin as a potential therapeutic agent for preventing fluoroquinolone-related reproductive toxicity.

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Introduction

The testes, housed within the scrotum, serve as the primary male reproductive organs, playing pivotal roles in sperm production (spermatogenesis) and androgen synthesis, particularly testosterone (steroidogenesis) [1]. Measuring approximately 4–6 centimeters in length, the testes originate retroperitoneally during fetal development before descending into the scrotum [2]. Their function is

finely regulated by the hypothalamic-pituitary-testicular axis, wherein Luteinizing Hormone (LH) promotes testosterone production, and Follicle Stimulating Hormone (FSH) stimulates spermatogenesis [3].

In recent years, substantial progress has been made in understanding male reproductive physiology, particularly the role of male factors in infertility [4]. Male reproductive function is broadly classified into three domains: spermatogenesis, sexual performance, and the hormonal regulation of reproductive activities [5]. These domains are vital not only for reproduction but also for their systemic effects, as male sex hormones influence accessory sexual organs, metabolism, growth, and other physiological processes [4].

Infertility, defined as the inability to conceive after two years of regular unprotected intercourse, has emerged as a significant global concern, with male-factor infertility accounting for a substantial proportion of cases [2, 6]. Among the contributors to male infertility, the use of certain drugs, especially when taken chronically has drawn considerable attention [7]. Some medications disrupt the hypothalamic-pituitary-testicular axis, thereby reducing testosterone levels and impairing spermatogenesis [8]. Others exert direct toxic effects on sperm cells or suppress spermatogenic activity [9, 10].

Curcumin, a bioactive compound derived from turmeric, has gained widespread recognition for its diverse medicinal properties [10]. Traditionally used for its therapeutic benefits, curcumin is well-documented for its potent antioxidant and anti-inflammatory effects [11]. Additional studies have revealed its hepatoprotective and hypoglycemic properties [12, 13], which further underscore its potential role in mitigating oxidative stress and inflammation.

Ciprofloxacin, a widely prescribed broad-spectrum antibiotic, has been associated with testicular toxicity, a condition that compromises male reproductive health [6, 8]. This toxicity is characterized by oxidative stress and impaired spermatogenesis, highlighting the urgent need for effective protective interventions [11]. Curcumin, with its robust antioxidant and anti-inflammatory properties, has shown promise as a therapeutic agent capable of mitigating such adverse effects [7, 12].

This study seeks to investigate the protective effects of curcumin on ciprofloxacin-induced testicular toxicity in adult male mice. By assessing reproductive hormone levels, oxidative stress markers, and histological changes, this research aims to elucidate the potential ameliorative effects of curcumin across varying doses.

Materials and Methods

Ethical approval for study

All the procedures in this research shall be conducted in accordance with the standard procedures as set by the Ethical Committee of the College of Health Sciences, Benue State University, Makurdi.

Study material procurements

Experimental animals

Thirty (30) adult male mice were obtained from the Animal House, College of Health Sciences, Benue State University, Makurdi. The mice were housed in standard conditions with free access to food and water ad libitum throughout the duration of the study. Prior to experimentation, the animals were allowed to acclimatize to their environment for one week. Body weights were recorded before the commencement of treatment and subsequently at weekly intervals.

Experimental plant

Turmeric leaves, the source of curcumin, were procured from a local vegetable market in the High-Level area of Makurdi. The leaves were thoroughly cleaned, dried, and ground into powder. An aqueous extract of the powdered turmeric leaves was prepared and stored in a refrigerator at an appropriate temperature until required for administration during the experiment.

Experimental drug

Ciprofloxacin tablets were purchased from Mernax Pharmacy, located opposite the College of Health Sciences, Gboko Road, Makurdi. The tablets were dissolved in distilled water to prepare a solution at the desired concentration, which was stored at the recommended temperature and used throughout the study period.

Housing and caging

Six (6) plastic cages, each measuring 30×20 cm, were provided by the Animal House. Each cage housed five mice, with animals grouped according to experimental conditions. The mice were maintained under standard laboratory conditions,

with free access to food and water, throughout the experiment.

Other materials

Additional materials used during the study included sterile gloves, syringes, needles, dissecting boards, fixative solution (10% formal saline), histological stains (Hematoxylin & Eosin, Periodic Acid-Schiff), cover slips, glass slides, microscopes, a microtome, a centrifuge, distilled water, feeding plates, and water bottles.

Preparation of experimental drug solution

Ciprofloxacin (100 mg) was dissolved in 500 mL of distilled water to create the solution used for the study. The prepared solution was stored under appropriate temperature conditions and administered as per the experimental design.

Preparation of experimental plant extract

Dried turmeric leaves were weighed, ground into a fine powder, and dissolved in 500 mL of distilled water to form an aqueous extract. The extract was stored at the recommended temperature and administered during the experiment as outlined in the study design.

Experimental design

The thirty (30) adult male mice were randomly divided into six (6) groups, with five mice in each group, housed in individual cages. The treatment regimen for each group was as follows:

Group A (Control): 5 mg/kg body weight of normal saline for 30 days.

Group B: 100 mg/kg body weight of ciprofloxacin for the first 15 days.

Group C: 3 mg/kg body weight of curcumin for the first 15 days.

Group D: 100 mg/kg body weight of ciprofloxacin + 3 mg/kg body weight of curcumin for the first 15 days.

Group E: 3 mg/kg body weight of curcumin for the first 15 days, followed by 100 mg/kg body weight of ciprofloxacin for the last 15 days.

Group F: 6 mg/kg body weight of curcumin for the first 15 days, followed by 100 mg/kg body weight of ciprofloxacin for the last 15 days.

Animal sacrifice

At the end of the 44 day study period, all the 30 adult male mice will be fasted overnight and then euthanized humanely. Blood samples shall be collected in sterile bottles for biochemical analysis, and the testes and epididymis will be harvested and fixed in 10% formal saline for histological analysis and tissue processing.

Serum Hormonal Assay: Leutinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and Testosterone

The blood that was collected into plain containers was allowed to clot. Each sample was centrifuged at 1000 rpm for 10 min to achieve separation. The serum obtained was put into aliquots in each case, labeled and stored at – 200C) [13]. One aliquot of each specimen was taken at a time, to avoid repeated freezing and thawing, and the samples were analyzed for hormone estimation using enzyme immunoassay (EIA), according to the World Health Organization (WHO) matched reagent programme protocol (manual) for EIA kits (protocol/ version of December 1998 for Luteinizing Hormone) [11]. The kids were supplied by NIADDK – NIH (USA).

Testosterone concentrations in plasma were determined by the enzyme immunoassay technique based on the principle of competitive binding between Testicular Testosterone (TT) and TT-horseradish peroxidase conjugate for a constant amount of rabbit anti-TT, as previously described [14]. Briefly, goat anti-rabbit Immunoglobulin G (IgG)-coated wells were incubated with TT standards, controls, samples (blood sera and supernatants of testicular homogenates), TT-horseradish peroxidase conjugate reagent and rabbit anti-TT reagent at 37□C for 90 minutes. Unbound TT peroxidase conjugate was removed and the wells washed. Tetramethylbenzidine was added and incubated, resulting in the development of a blue colour. The colour development was stopped with the addition of 1N hydrochloric acid, and the absorbance measured spectrophotometrically at 450nm. A standard curve was obtained by plotting the concentration of the standard versus the absorbance and TT concentrations calculated from the standard curve.

Estimation of Lipid Peroxidation (Malondialdehyde)

Lipid peroxidation in the tissue was estimated colorimetrically by thiobarbituric acid reactive substances (TBARS) method of Buege and Aust [15]. A principle component of TBARS being malondialdehyde (MDA), a product of lipid

peroxidation. In brief, 0.1 ml of tissue in Tris-HCl buffer, pH 7.5 was treated with 2 ml of (1:1:1 ratio) TBA-TCA-HCl reagent (thiobarbituric acid 0.37%, 0.25 N HCl and 15% TCA) and placed in water bath for 15 min, cooled. The absorbance of clear supernatant was measured against reference blank at 535 nm. Concentration was calculated using the molar absorptivity of malondialdehyde which is 1.56 x105 M-1 cm-1 and expressed as nmol/mg protein.

Histological tissue processing

Histological processing of the testicular tissue was carried out following the protocol described by Mohammed et al. [16]. The testes were harvested and promptly fixed in 10% buffered formalin to preserve tissue morphology and prevent autolysis. Subsequently, the tissues were embedded in paraffin wax to provide structural support for thin sectioning. Sections were cut at a thickness of 5-7 µm and stained with Hematoxylin and Eosin (H&E) for microscopic evaluation.

Data analysis

Statistical data obtained in this research shall be analyzed using the Statistical Package for the Social Sciences (IBM SPSS). Mean and Standard Error in Mean (S.E.M) shall be calculated for all the values. Comparison between the control and treated groups shall be done using one-way Analysis of Variance (ANOVA) with appropriate post-hoc tests. Differences shall be considered statistically significant at $p < 0.05$.

Results

Reproductive Hormones: Follicle Stimulating Hormone (FSH), Testosterone and Luteinizing Hormone (LH)

Figure 1 shows the mean reproductive hormone levels across groups compared on one – way ANOVA. For the FSH levels; groups B – F all showed a statistically significant decrease in mean at $p \leq 0.05$ when compared to the control group, groups A and E showed a statistically significant increase in mean when compared to the Ciprofloxacin – only group. For the testosterone levels; groups B – D and F all showed a statistically significant decrease in mean when compared to the control group, while groups A and E showed a statistically significant increase in mean when compared to the Ciprofloxacin and Curcumin – only groups respectively.

For the luteinizing hormone levels; no group showed a statistically significant difference in mean. The result in figure 1 shows that both Ciprofloxacin and Curcumin had a significant decreasing effect on the follicle stimulating hormone and testosterone levels as observed in groups B and C respectively, while Curcumin showed significant protective effect against the effect of Ciprofloxacin as observed in groups E and D of this research.

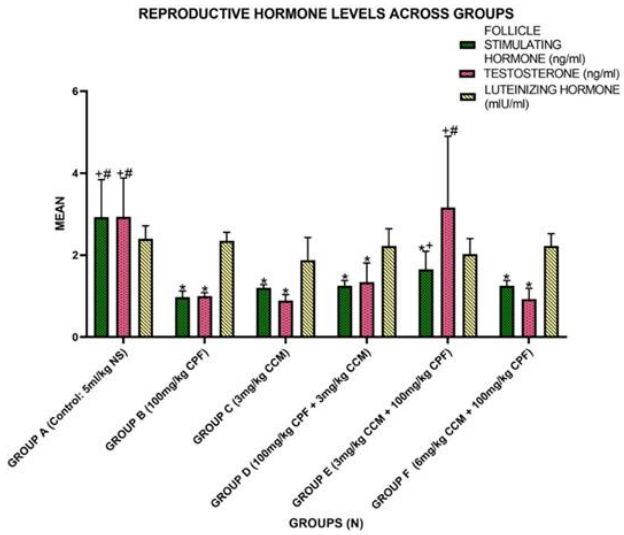

Figure 1: Simple Bar Chart Showing the Mean Reproductive Hormones Levels across Groups. N = 5; NS – Normal Saline; CPF – Ciprofloxacin; CCM – Curcumin * = Statistically Significant Difference at $p<0.05$ in Mean when compared to the Control Group + = Statistically Significant Difference at $p<0.05$ in Mean when compared to the Ciprofloxacin-only Group # = Statistically Significant Difference at $p<0.05$ in Mean when compared to the Curcumin-only Group

Oxidative Stress: Malondialdehyde (MDA)

Figure 2 shows the mean MDA level across groups compared on one – way ANOVA. Groups B, C and F showed a statistically significant increase in mean when compared to the control group, while groups A, D and E showed a statistically significant decrease in mean when compared to the Ciprofloxacin and Curcumin – only groups respectively. The result in figure 2 shows that independent administration of Ciprofloxacin and Curcumin showed a significant increasing effect on the oxidative stress level of the testicular cells of the experimental animals, while combined administration showed a decreasing effect on the MDA level (oxidative stress) of the animals.

Histological Examination

The examination of testicular tissues across the all groups through histopathological analysis revealed a generally normal histological state in the control group and the groups treated with curcumin. This normalcy was characterized by typical features,

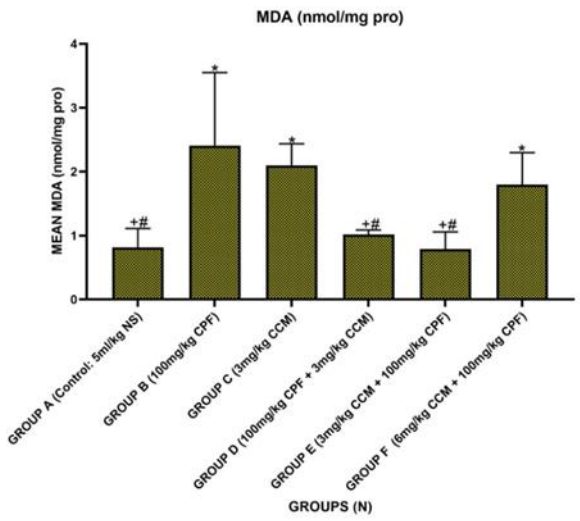

Figure 2: Simple Bar Chart Showing the Mean MDA Levels across Groups. N = 5; NS – Normal Saline; CPF – Ciprofloxacin; CCM – Curcumin. * = Statistically Significant Difference at $p<0.05$ in Mean when compared to the Control Group. + = Statistically Significant Difference at $p<0.05$ in Mean when compared to the Ciprofloxacin-only Group. # = Statistically Significant Difference at $p<0.05$ in Mean when compared to the Curcumin-only Group

including a prominent presence of spermatozoa extending towards the lumen. Additionally, the Leydig cells exhibited an intact morphology, and the seminiferous tubules displayed evidence of spermatid retention. These combined findings pointed towards a healthy and functional testicular environment.

However, a few noteworthy deviations were observed in the ciprofloxacin group, including spermatid retention, tubular atrophy, and a diffuse disorganization of germ cells. In these instances, the testicular profile indicated pathological conditions marked by the absence of interstitial space, degeneration of testicular architecture, and necrosis. Notably, the interstitial tissues showed the presence of maturing spermatogenic cells within the seminiferous tubules, with some cells displaying a ruptured nuclear membrane and nucleus fragmentation (karyorrhexis).

This histological profile suggests the curcumin showed some ameliorative potential against the testicular histo-toxic effect of ciprofloxacin administration.

Discussion

This study highlights the protective effects of curcumin against ciprofloxacin-induced testicular toxicity in adult male mice, particularly its influence on reproductive hormones, oxidative stress, and testicular histology. The findings provide valuable insights into curcumin's therapeutic potential in mitigating drug-induced reproductive damage.

Ciprofloxacin treatment (Group B) resulted in significant reductions in follicle-stimulating hormone (FSH) and testosterone levels. These results align with previous studies demonstrating that fluoroquinolones like ciprofloxacin impair testicular function by disrupting spermatogenesis and reducing serum hormone levels. For instance, Sudhakar et al. [17] reported that high doses of ciprofloxacin in rats caused a decline in testosterone and FSH levels, likely due to oxidative stress-induced Leydig cell damage, which impairs hormone synthesis.

Interestingly, curcumin administration alone (Group C) also reduced FSH and testosterone levels. This outcome might reflect the biphasic action of curcumin, as its effects can vary depending on dose and exposure duration [9]. While some studies, such as Kumar et al. [18], have reported curcumin's ability to enhance testosterone levels, its oxidative stress-modulating properties may lead to hormonal variations under specific conditions. The observed recovery of FSH and testosterone levels in Groups D and E, where curcumin was co-administered with ciprofloxacin, underscores curcumin's protective role. This finding concurs with Kumar et al. [19], who demonstrated curcumin's efficacy in mitigating fluoroquinolone-induced reproductive toxicity through its antioxidative and protective effects on the testicular microenvironment.

Luteinizing hormone (LH) levels remained unchanged across all groups, suggesting that neither ciprofloxacin nor curcumin directly impacts the hypothalamic-pituitary-gonadal axis at this level. This result contrasts with findings from Tanyildizi et al. [20], who observed significant reductions in LH levels in antibiotic-treated animals. The discrepancy could be attributed to species-specific differences or variations in experimental design, such as the duration of exposure. damage, was evident from the significant increase in malondialdehyde (MDA) levels in the ciprofloxacin-treated group (Group B). Elevated MDA levels, a hallmark of lipid peroxidation, corroborate previous studies that identified ciprofloxacin-induced oxidative damage in testicular tissues [21]. Notably, curcumin co-administration in Groups D and E significantly reduced MDA levels, highlighting its antioxidative properties. These results are consistent with the findings of Yadav et al. [22], who reported that curcumin mitigates oxidative stress by upregulating antioxidant enzymes and inhibiting lipid peroxidation, thereby preserving cellular integrity in

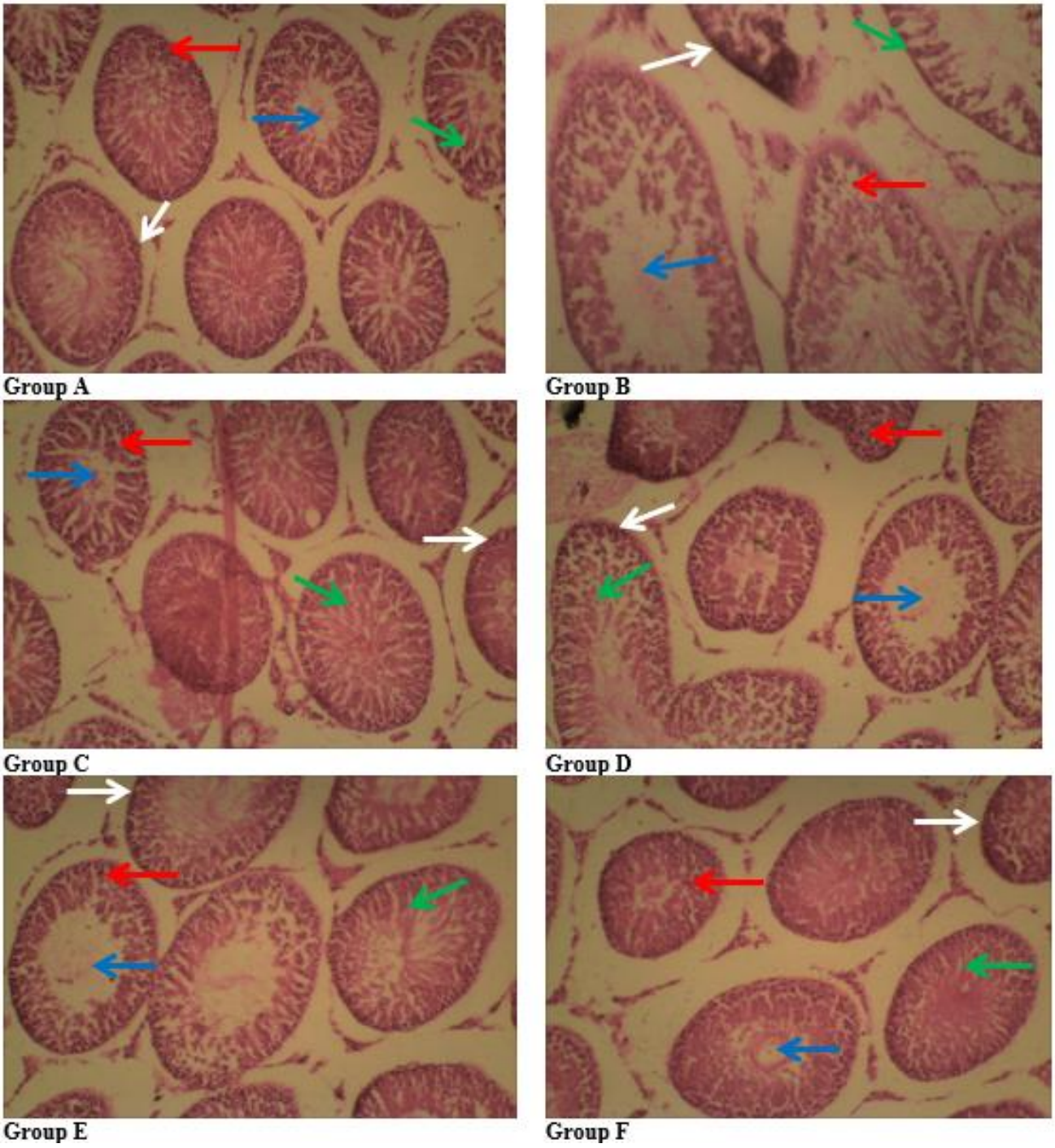

Figure 3: Photomicrographs of Testes from Groups A – F showing Lumen (Blue Arrow), Spermatocytes (Red Arrow), Spermatogonia (Green Arrow), and Basement Membrane (White Arrow). Group A: Showing prominent spermatozoa extending towards the lumen, intact Leydig cells, seminiferous tubule integrity, and normal basement membrane (H & E x40). Group B: Showing degeneration of testicular architecture, ruptured nuclear membrane, spermatid retention, tubular atrophy, and diffuse disorganization of germ cells (H & E x40). Group C: Showing prominent spermatozoa extending towards the lumen, intact Leydig cells, seminiferous tubule integrity, and normal basement membrane (H & E x40). Group D: Showing prominent spermatozoa extending towards the lumen, intact Leydig cells, seminiferous tubule integrity, and normal basement membrane (H & E x40). Group E: Showing prominent spermatozoa extending towards the lumen, intact Leydig cells, seminiferous tubule integrity, and normal basement membrane (H & E x40). Group F: Showing prominent spermatozoa extending towards the lumen, intact Leydig cells, seminiferous tubule integrity, and normal basement membrane (H & E x40).

the testes. Curcumin's protective effects likely stem from its ability to neutralize free radicals and enhance the activity of endogenous antioxidant systems, such as superoxide dismutase and catalase. This dual action mitigates oxidative stress and preserves cellular homeostasis, as demonstrated by the reduced MDA levels and improved antioxidant profiles in the curcumin-treated groups [12, 17].

Histological analysis further corroborated the protective role of curcumin. The ciprofloxacin-treated group (Group B) exhibited significant testicular damage, including tubular atrophy, germ cell disorganization, and necrosis, which are hallmarks of impaired spermatogenesis and testicular dysfunction. These observations align with findings from Aldarmahi [23], who described similar testicular alterations in response to ciprofloxacin exposure. Conversely, the curcumin-treated groups (Groups C, D, E, and F) showed substantial histological improvement, with preserved seminiferous tubule morphology and intact Leydig cells. This structural protection reflects curcumin's ability to enhance tissue repair mechanisms and mitigate cellular damage.

Comparable histological protection by curcumin has been documented in prior studies. For example, Kocahan et al. [17] demonstrated that curcumin alleviates testicular histopathological changes caused by drug-induced toxicity, primarily through its anti-inflammatory and antioxidative properties. The present study reinforces these findings, emphasizing curcumin's therapeutic potential in preserving testicular health during ciprofloxacin exposure.

These results collectively underscore curcumin's promise as an ameliorative agent against ciprofloxacin-induced testicular toxicity, with implications for managing drug-induced reproductive health challenges.

Conclusion

The results of this study suggest that curcumin exerts significant protective effects against ciprofloxacin-induced testicular toxicity. It ameliorates disruptions in reproductive hormone levels, reduces oxidative stress, and preserves testicular histology. Given the growing use of fluoroquinolones and the risk of reproductive side effects, curcumin presents a promising therapeutic option to mitigate these adverse effects.

Contribution of authors

Edache Daniel Abah conceptualized and designed the research protocol, carried out literature review, analyzed the result and drafted manuscript. Eriba Daniel David carried out curcumin extract and drug solution preparation, animal care and management, and the treatment protocol. Omirida Oda Paul carried out literature review and reference resource compilation. Ukase Monday Francis performed animal treatment protocol and recorded observation data. Maikyo Fabian Deungwan performed animal weights measurements, treatment protocol, and recorded observation data.

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Conflict of Interest

The authors state that there are no conflicts of interest to this research, and that all reference sources have been duly cited and listed in the bibliography section.

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