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Original Research Article

Effect of White Turmeric (*Curcuma zedoaria*) Rhizome Ethanol Extract on Fertility in Male Diabetic Wistar Rats

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia, and affects testicular function and spermatogenesis, causing sexual dysfunction and fertility disorders in men. Traditional medicines, such as white turmeric rhizome, can interfere with normal function of the seminiferous tubules, and affects fertility; hence, the administration of white turmeric rhizome to diabetic patients may worsen infertility. This study aimed to assess the effect of white turmeric (*Curcuma zedoaria*) rhizome ethanol extract on fertility in diabetic male Wistar rats. The study employed a laboratory-based experimental approach with a post-test only control group design. Twenty male Wistar rats were divided into five groups of four animals each, consisting of negative control (K-): untreated normal rats, positive control (K+): untreated diabetic rats, treatment groups (P1, P2, and P3): diabetic rats treated with white turmeric rhizome ethanol extract at doses of 20, 40, and 60 mg/200 g body weight, respectively. The treatment was administered orally once daily for 28 days. At the end of the treatment period, the rats were euthanized, their testes were removed, evacuated, and the testicular volume was measured. Thereafter, the testes were prepared for microscopic examination. Immunohistochemical staining was conducted to assess the expressions of androgen receptor, and p53. The results showed that the ethanol extract of white turmeric rhizome affects fertility through a significant ($P < 0.05$) decrease in androgen receptor expression, and reduction in testicular volume compared to the control. Thus, the administration of white turmeric rhizome extract may have adverse consequences on fertility in male diabetic patients.

Keywords: Diabetes, White Turmeric Rhizome, Streptozotocin, Androgen Receptor, p53, Testicular Volume.

Introduction

Indonesia, a tropical country rich in medicinal plants, has for a long time been using traditional medicine as an alternative treatment due to its affordability and minimal side effects. White turmeric (*Curcuma zedoaria*) (CZ) is a widely used herbal remedy from the Zingiberaceae family. The plant is native to Bangladesh and the East Himalaya, but commonly cultivated in South and Southeast Asia.[1,2] CZ is a perennial herb that grows up to 1.5 meters in height in the lowlands.[3] Its leaves are developed in a 35-60 cm sheath, and in the mature stage, the leaves have an oblong shape, 25-75 cm long by 8-20 cm wide.[3] CZ also has pseudostem and brown rhizomes with yellowish-white flesh.[3] CZ is known for its active biochemical compounds, including essential oils, curcumin, and tannins, which exhibit anticancer, antibacterial, antifungal, antioxidant, and hepatoprotective properties.[4] In recent years, there has been a rise in CZ consumption due to its health benefits, especially in the treatment of non-infectious diseases like cancer.[5–8] However, several studies found that CZ possibly possesses anti-fertility properties in males, significantly impacting quality of life.[5,6] Diabetes mellitus (DM), a global health concern with a prevalence of 6.4%, has increased fourfold over the past three decades. DM contributes to male reproductive dysfunction, including erectile and ejaculatory disorders, structural changes in reproductive organs, and impaired sperm quality.[9] DM also reduces testicular blood flow, disrupting endothelial function and microcirculation, leading to morphological changes.[10]

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Androgens, essential for male reproduction, exert their effects by binding to androgen receptors, primarily in the testes. The absence of these receptors leads to incomplete germ cell development, azoospermia, and infertility.[11] Additionally, p53, a tumor suppressor protein, regulates cell cycles and plays a role in spermatogenesis. Its absence is linked to increased sperm abnormalities.[12] This study aims to evaluate the effects of CZ on fertility by assessing androgen receptor expression, p53 expression, and testicular volume in a diabetic rat model, providing new insights into its potential reproductive benefits.

Materials and Methods

Chemicals and Equipment

Sterile neutral pH saline, sterile distilled water, alcohol, 10% formalin, paraffin (Parafflakes, Indonesia), Canada balsam (Merck, Germany), xylol (Merck), streptozotocin (Santa Cruz Biotechnology, USA), mouse monoclonal antibody (Sigma-Aldrich, USA), p53 rabbit polyclonal antibody (Sigma-Aldrich), DAB (3.3'-diaminobenzidine) (Bloom Tech, China), and streptavidin peroxidase. The equipment used include digital weighing balance (OneMed, Indonesia and Boeco, Germany), micropipettes (Socorex, Switzerland), forceps (Renz, Pakistan), surgical scissors (Renz), scalpels and blades (OneMed), microtome (Leica, Germany), water baths (Cypress Diagnostics, Belgium), hot plates DLAB MS H280 (DLAB, China), deck glasses (OneLab, China), object glasses (OneLab), and binocular microscopes (Leica, Germany).

Collection of plant sample and extract preparation

White turmeric rhizomes in the form of white turmeric rhizome ethanol extract powder were obtained from UPT Materia Medica Batu, East Java, Indonesia. The extract powder was identified and authenticated at the Department of Mathematics and Natural Sciences, Universitas Sumatera Utara, where a voucher number 1588/MEDA/2024 was assigned. The powdered sample (100 mg) was macerated in 500 mL of 95% ethanol at room temperature for 3 days and filtered through Whatman No.1 filter paper. The residue was macerated in another 500

mL of 95% ethanol for another three days and filtered. The solvent was removed using a rotary evaporator.

Animals

Twenty (20) healthy male Wistar rats aged 2-3 months, weighing between 200-250 g were procured from Focus Medikal Indonesia, Indonesia. The rats were housed at the Integrated Research Laboratory, Universitas Sumatera Utara and assigned unique identification codes from 01 to 20. Each rat was placed individually in stainless steel ventilated cages (150 cm^2 base area x 15 cm height). They were acclimatized to the laboratory condition for a minimum period of five days at a temperature of 20-27°C, and a humidity of 40-70%. The lighting condition was maintained at 12 h light/12 h dark cycle. Each cage was labeled with the test animal code, arrival date, initial weight, treatment group, and planned termination date. The rats were fed with pelletized chicken feed, and allowed access to drinking water *ad libitum*. The body weight of the rats was measured every three days, and the animals were maintained until they met the study criteria.

Ethical approval

The study was approved by the Research Ethics Committee of the Universitas Prima Indonesia, with approval reference number 006/KEPK/UNPRI/1/2025.

Study design/Animal grouping

This study was laboratory-based experimental research using a post-test only control group design, where measurements were taken after treatment and compared with a control group. The research was conducted at the Integrated Research Laboratory (Laboratorium Penelitian Terpadu), Universitas Sumatera Utara (USU), Indonesia, for animal experiments, while the immunohistochemical analysis was performed at the Anatomical Pathology Laboratory, Royal Prima General Hospital, Medan. The study was carried out from November 2024 to February 2025.

Wistar rats were randomly divided into five groups of four rats per group. The groups included a negative control group consisting of normal rats with no treatment (K-), a positive control group consisting of diabetic rats (K+) with no treatment, and three diabetic groups receiving white turmeric rhizome extract at doses of 20 mg, 40 mg, and 60 mg per 200 g body weight (P1, P2, and P3, respectively). The white turmeric rhizome extract doses were determined using a conversion factor method; thus, doses were set at 20 mg, 40 mg, and 60 mg per 200 g of rat body weight. The extract was administered orally once daily for 28 days

Streptozotocin induction of diabetes mellitus

Prior to treatment with the extract, rats in the positive control and extract treatment groups were induced with diabetes using streptozotocin. The initial blood glucose levels of the rats were measured by collecting a drop of blood from the tail and testing with a glucometer. Rats with normal blood glucose levels were injected intraperitoneally with streptozotocin at a dose of 100 mg/kg body weight to induce diabetes, followed by a three-day adaptation period. Blood glucose levels were reassessed after three days.[13]

Immunohistochemical examination of the testes

After the treatment period, the rats were euthanized using ether. The testes were surgically removed, and preserved in a 10% formalin solution. The androgen receptor immunohistochemistry staining was conducted at the Anatomical Pathology Laboratory of Royal Prima General Hospital. Paraffin-embedded tissue blocks were sectioned using a Leica RM 2125 microtome to obtain 3 µm-thick sections, which were mounted on poly-L-lysine-coated glass slides with dimensions of one inch in width, three inches in length, and 1.2 mm in thickness. The tissue sections were dried at 75°C for 15 minutes and then stained using the Leica Bond-Max system. The slides were rehydrated using graded ethanol (70%, 80%, and 95%) for 15 minutes, then cleared in xylol I, II, and III for another 15 minutes. The sections were then mounted for microscopic examination.[14]

Androgen receptor expression was evaluated by assessing the percentage of positively stained testicular cells at 40x magnification, and evaluating the staining intensity at 400x magnification, using prostate tissue as a positive control.[16] The staining intensity and percentage were recorded, and androgen receptor expression in the testicular cell nuclei was scored based on the numerical scale: (% strong intensity × 3) + (% moderate intensity × 2) + (% weak intensity × 1).[14]

For p53 immunohistochemical staining, the same procedure was applied as for androgen receptor staining. The p53 expression was assessed by evaluating the percentage of positively stained tumor cells at 40x magnification and the staining intensity at 400x magnification. The staining intensity and percentage were recorded, and p53 expression in testicular cell nuclei was assessed qualitatively as either negative (-) or positive (+).[15]

The measurement of testicular volume was scored based on the numerical scale: (4π x ½ length x ½ width x ½ height)/3.[16,17]

Statistical analysis

Data were presented as mean ± standard deviation (n = 4). Data were analyzed using one-way ANOVA, followed by LSD post-Hoc test for multiple comparisons using SPSS 25.00 software. Significant difference was established at $P < 0.05$.

Results and Discussion

Characteristics of the study sample

The characteristics of the rats which met the study inclusion criteria are presented in Table 1. From the results, the mean age of the rats in the different groups were 2.37 ± 0.47, 2.55 ± 0.44, 2.55 ± 0.12, 2.52 ± 0.12, and 2.62 ± 0.30 months for groups K-, K+, P1, P2, and P3, respectively. For gender, all samples used were male rats. The body weights of the rats in the K-, K+, P1, P2, and P3 groups were 230.00 ± 11.88, 235.50 ± 9.71, 222.20 ± 16.41, 219.70 ± 16.76, and 244.00 ± 6.68 g, respectively. The Shapiro-Wilk normality test revealed a p-value > 0.05, which is indicative of a normal distribution.

Table 1: Characteristics of the experimental rats

Group	Mean Age (months)	Mean Body Weight (grams)
K-	2.37 ± 0.47	230.00 ± 11.88
K+	2.55 ± 0.44	235.50 ± 9.71
P1	2.55 ± 0.12	222.20 ± 16.41
P2	2.52 ± 0.12	219.70 ± 16.76
P3	2.62 ± 0.30	244.00 ± 6.68

K-: Negative control; K+: Positive control; P1: White turmeric extract at 20 mg/ 200 gram; P2: White turmeric extract at 40 mg/200 gram; P3: White turmeric extract at 60 mg/200 gram

Effect of white turmeric rhizome extract on androgen receptor expression

The androgen receptor expression levels are shown in Table 2, whilst the comparative appearance presented in Figure 1. The androgen receptor H-scores in the rats' testes were 247.50 ± 19.37 in the K- group, and 162.50 ± 17.08 in the K+ group. In the treatment groups (P1, P2, and P3), the H-score of the androgen receptor decreased to 138.75 ± 14.36, 97.50 ± 17.08, and 86.25 ± 14.93, respectively.

The post-hoc LSD test results indicated significant differences in the decline of androgen receptor H-score between K- and K+, P1, P2, and P3 ($P < 0.05$); K+ and P2 and P3 ($P < 0.05$); as well as P1 and P2 and P3 ($P < 0.05$). Thus, the findings from the study revealed a statistically significant decrease in the androgen receptor H-score in diabetic rats, and treatment groups. These findings align with the study of Kotian *et al*. (2019)[18] which reported that diabetic animals exhibit a reduction in seminiferous tubule diameter, decreased spermatogenesis, and a decline in Sertoli and Leydig cells, ultimately leading to a decrease in androgen receptor expression.[18] This finding is also consistent with O'Hara and Smith (2015)[11], Wang *et al*. (2022)[19], and Messner *et al*. (2017)[20], who reported that the curcumin content in *Curcuma zedoaria* (white turmeric) rhizome can lead to reduced spermatogenesis, a decrease in seminiferous tubule diameter, and lower testosterone levels, which subsequently affect androgen receptor expression.[11,19,20]

Table 2: Effect of white turmeric rhizome extract on androgen receptor expression in testes of male diabetic rats

Group	H-score	LSD post-hoc				
		K-	K+	P1	P2	P3
K-	247.50 ± 19.37	-	0.000	0.000	0.000	0.000
K+	162.50 ± 17.08	0.000	-	0.062	0.000	0.000
P1	138.75 ± 14.36	0.000	0.062	-	0.003	0.000
P2	97.50 ± 17.08	0.000	0.000	0.003	-	0.355
P3	86.25 ± 14.93	0.000	0.000	0.000	0.355	-

K-: Negative control; K+: Positive control; P1: White turmeric rhizome ethanol extract (20 mg/200 g); P2: White turmeric rhizome ethanol extract (40 mg/200 g); P3: White turmeric rhizome ethanol extract (60 mg/200 g).

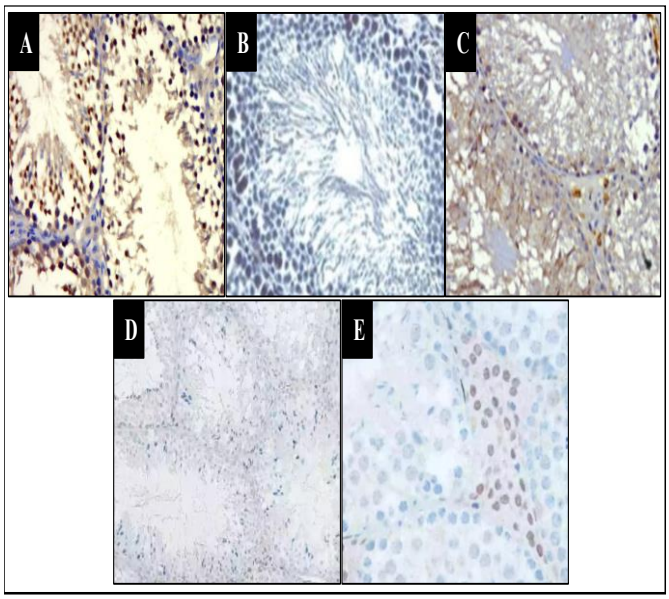

Figure 1: Effect of white turmeric rhizome extract on the testes of male diabetic Wistar rats through androgen receptor expression. **(A)** Negative control group, **(B)** Positive control group, **(C)** White turmeric rhizome ethanol extract (20 mg/200 g), **(D)** White turmeric rhizome ethanol extract (40 mg/ 200 g), **(E)** White turmeric rhizome ethanol extract (60 mg/ 200 g)

The decline in androgen receptor expression in the testes of diabetic rats is influenced by various biological mechanisms related to metabolic and hormonal disturbances caused by diabetes. The testes are a primary target organ for androgens, and changes in androgen receptor expression can impact various physiological functions, including sperm production and sexual function. The androgen receptor H-score measures the level of androgen receptor expression in tissues, which can be affected by diabetes. In diabetes, reduced androgen hormone sensitivity may lead to decreased androgen receptor expression in target tissues. This reduction could indicate physiological changes in hormonal responses due to diabetes.[19]

The decrease in androgen receptor expression in the testes of diabetic rats results from a combination of endocrine, metabolic, inflammatory, and epigenetic factors. Disruptions in testosterone levels, oxidative stress, inflammation, and damage to Sertoli and Leydig cells contribute to the decline in androgen receptors in the testes, affecting reproductive function, including spermatogenesis, and fertility.[11]

The endocrine factors include endocrine dysfunction in diabetes, such as reduced testosterone levels and impaired gonadal function. Diabetes is associated with a decline in testosterone levels. Testosterone is the primary ligand that activates androgen receptors, and if testosterone levels decrease due to diabetes, stimulation of androgen receptors will also be reduced, leading to decreased androgen receptor expression in the testes.[18] Inflammation is another condition observed in diabetes, linked to systemic inflammation caused by elevated pro-inflammatory cytokines such as TNF-α and IL-6. This inflammation can alter gene expression, including genes encoding androgen receptors in the testes. The inflammatory process can also damage Sertoli and Leydig cells, crucial for testosterone production and spermatogenesis. Diabetes can also influence gene expression epigenetically, affecting androgen receptor genes in the testes. Epigenetic modifications, such as DNA methylation and histone modifications, may suppress androgen receptor expression without altering the DNA sequence.[10]

Curcumin in *Curcuma zedoaria* rhizome has antioxidant properties that can reduce oxidative stress, which is associated with testicular cell damage, and impaired spermatogenesis. However, *Curcuma zedoaria* also contains many compounds that are possibly implicated in inhibiting spermatogenesis. The atrophy or shrinkage of seminiferous tubules may result from reduced Sertoli cells or damage to Leydig cells, which play a role in testosterone production. Testosterone binds to androgen receptors and triggers gene transcription necessary for spermatogenesis. If testosterone levels are low, stimulation of androgen receptors is also reduced, leading to a decline in androgen receptor expression in the testes.[11]

Effect of white turmeric rhizome extract on p53 expression

The results obtained from the immunohistochemical staining for p53 expression are presented in Table 3. The p53 expression in rat testes was positive in all rats in the K- group (Figure 2), while in the K+ group, it was positive only in one rat. In the treatment groups (P1, P2, and P3) which received white turmeric rhizome extract at doses of 20 mg, 40 mg, and 60 mg/200 g of rat, respectively, p53 expression decreased, with a positive result in one rat in the P1 group, and negative results in all rats in the P2 and P3 groups.

Table 3: Effect of white turmeric rhizome extract on p53 expression in the testes of male diabetic rats

Group	p53 Expression				p-value
	Positive		Negative		
	n	%	n	%	
K-	4	100.0	0	0.0	
K+	1	25.0	3	75.0	
P1	1	25.0	3	75.0	0.12
P2	0	0.0	4	100.0	
P3	0	0.0	4	100.0	

K-: Negative control; K+: Positive control; P1: White turmeric rhizome ethanol extract (20 mg/200 g); P2: White turmeric rhizome ethanol extract (40 mg/200 g); P3: White turmeric rhizome ethanol extract (60 mg/200 g).

The study also observed a decline in p53 expression in the diabetic rats and treatment groups, but this was not statistically significant ($p > 0.05$). There were also no significant differences ($p > 0.05$) in p53 expression between diabetic rats and control groups, despite increased oxidative stress in the affected tissues. These results suggest that while diabetes affects multiple molecular pathways, the DNA damage response via p53 may not always be evident in diabetic rats, and additional treatments did not significantly alter p53 expression.[21]

These findings contrast with the findings from previous studies which reported that positive p53 expression indicates active apoptosis in germ cells, ensuring normal testicular function. In contrast, loss of p53 expression suggests impaired apoptosis, potentially leading to testicular developmental abnormalities.[12,21,22]

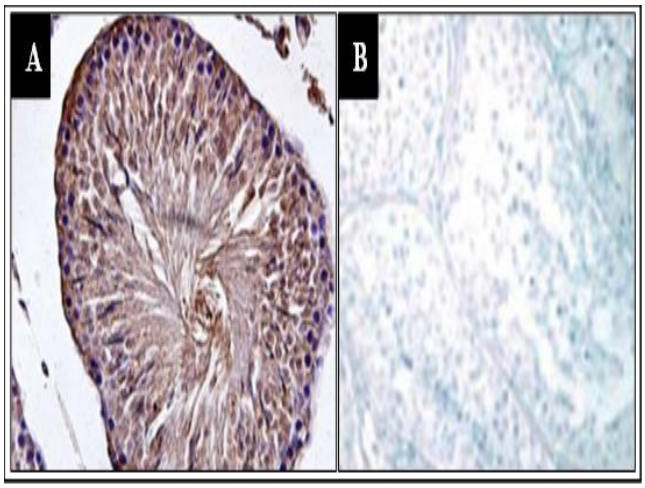

Figure 2: Effect of white turmeric rhizome extract on the testes of male diabetic Wistar rats through p53 expression. **(A)** Positive expression in the negative control group, **(B)** Negative expression in the positive control group, and the treatment groups

The decrease in p53 expression in diabetic rats is an intriguing topic because p53 plays a crucial role in cell cycle regulation, DNA repair, and apoptosis. p53 is typically activated in response to cellular stress, including oxidative stress, which is common in diabetes. A reduction in p53 expression may disrupt these processes, allowing damaged or stressed cells to survive instead of undergoing apoptosis. This reduction may contribute to changes in reproductive tissues such as the testes, potentially affecting fertility. The effect of diabetes on p53 expression may vary depending on the diabetes model and the severity or duration of the condition. Mild or short-term diabetes models may not show significant changes in p53 expression, whereas severe or long-term conditions could lead to a more apparent reduction in p53 expression.[21] Curcumin in *Curcuma zedoaria* rhizome can modulate p53 expression through multiple signaling pathways. In diabetic rats, *Curcuma zedoaria* supplementation may reduce inflammation and oxidative stress, decreasing p53 activation. A reduced p53 expression may sometimes indicate reduced cellular damage, lowering the need for p53-mediated repair responses. In diabetic rats treated with *Curcuma zedoaria*, the decline in p53 expression could indicate that curcumin reduces cell damage and regulates apoptosis, potentially maintaining a better balance between cell repair and survival while mitigating diabetes-related stress. The decrease in p53 expression in diabetic rats treated with *Curcuma zedoaria* may result from the combined antioxidant and anti-inflammatory effects, which reduce cellular damage and the need for p53-mediated repair responses. Several studies suggest that when oxidative stress is controlled, p53 expression may decline because the damage that typically triggers p53 activation is reduced.[12,22]

Effect of white turmeric rhizome extract on testicular volume

The results of the testicular volume measurements are shown in Table 4. The testicular volume in the K- group was 1.05 ± 0.33 cm^3, while in the K+ group, it was 0.92 ± 0.05 cm^3. In the treatment groups (P1, P2, and P3) which received white turmeric rhizome ethanol extract at doses of 20 mg, 40 mg, and 60 mg/200 g, respectively, the testicular volume decreased to 0.91 ± 0.03 cm^3, 0.86 ± 0.03 cm^3, and 0.82 ± 0.01 cm^3, respectively.

Similar to H-score for androgen expression, post hoc LSD test also revealed a statistically significant decline in testicular volume in diabetic rats and treatment groups ($P < 0.05$). This decrease in volume aligns with the findings from several other studies which reported that diabetes and curcumin present in *Curcuma zedoaria* rhizome can cause a reduction in seminiferous tubule diameter, ultimately leading to a decline in testicular volume.[11,18,19]

The reduction in testicular volume in diabetic rats is a common finding in experimental studies examining the impact of diabetes on the reproductive system. Damage to Sertoli and Leydig cells due to diabetes can disrupt spermatogenesis and reduce testicular volume. Diabetes is often accompanied by increased oxidative stress, characterized by elevated reactive oxygen species (ROS), which can damage testicular cells and trigger chronic inflammation, leading to tissue damage and reduced testicular volume. Although, the antioxidant properties of white turmeric rhizome might counter the oxidative stress caused by hypoglycemia in diabetes, its toxicity toward the testicular cells and organelles is more substantial. Chronic inflammation exacerbates Leydig and Sertoli cell damage, resulting in testicular shrinkage. Diabetes also affects blood microcirculation, leading to ischemia or reduced blood flow to the testes, depriving the cells of oxygen and nutrients, and reduce testicular volume.[19]

Table 4: Effect of white turmeric rhizome extract on testicular volume in male diabetic rats

Group	Testicular Volume (cm^3)		LSD post-hoc				
			K-	K+	P1	P2	P3
K-	1.05 0.33	±	-	0.000	0.000	0.000	0.000
K+	0.92 0.05	±	0.000	-	0.776	0.024	0.001
P1	0.91 0.03	±	0.000	0.776	-	0.042	0.002
P2	0.86 0.03	±	0.000	0.024	0.042	-	0.143
P3	0.82 0.01	±	0.000	0.001	0.002	0.143	-

K-: Negative control; K+: Positive control; P1: White turmeric rhizome ethanol extract (20 mg/200 g); P2: White turmeric rhizome ethanol extract (40 mg/200 g); P3: White turmeric rhizome ethanol extract (60 mg/200 g).

Conclusion

From the findings of the present study, it can be concluded that the administration of white turmeric (*Curcuma zedoaria*) rhizome extract has a significant adverse effect on fertility through the reduction of androgen receptor expression and testicular volume. However, its impact on fertility by reducing p53 expression was not statistically significant.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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