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The Histomorphometric Alterations in Male Sprague-Dawley Rats Following Exposure to Dextromethorphan and Antioxidants Administration

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Abstract

Background Morphometric evaluation of seminiferous tubules and epididymis is a common parameter used to assess male fertility. This study aimed to evaluate the morphological changes in male rats following exposure to dextromethorphan.

Methods A total of 80 male rats (150 ± 30 g) were divided into four groups (N = 20; A-D) for the study. Group A received distilled water; group B received 20 mg/kg, group C received 40 mg/kg, and group D received 80 mg/kg of DM for a duration of four weeks. At the end of the treatment period, five rats were selected from each group and the following histomorphometric parameters were analyzed: diameter and height of the seminiferous tubule and epididymes, volume of testes, and the number of spermatogonia, spermatocytes, and spermatids within the seminiferous tubules. The remaining 15 rats were divided into three groups (N = 5; E-G). They received Rutin (25 mg/kg), Quercetin (50 mg/kg), and DW, respectively, for four weeks to ascertain the recovery rate.

Results All histomorphometric parameters decreased compared to the control group; however, when comparing the recovery-alone group to the treatment groups, a slight increase was observed. The morphometric measurements showed an increase when Rutin and Quercetin were compared to both the treatment and recovery-alone groups. The comparison between Rutin and Quercetin showed no substantial difference in their effects.

Conclusion Dextromethorphan has showed to have deleterious effect on the epididymal and testicular morphometry and this could culminate into infertility in males, however, these damages were significantly improved upon the administration of Rutin and Quercetin as antioxidants.

Keywords Dextromethorphan, Histomorphometry, Rutin, Quercetin

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1 Introduction

In recent years, there has been an increasing concern regarding the negative impact of various environmental exposures and certain substances on male reproductive health.[1, 2] While some of these agents are promoted for their therapeutic benefits, there is mounting evidence that they can disrupt normal hormonal balance in males.[3] The testis plays a central role in the male reproductive system, functioning as both an exocrine and endocrine gland. Its exocrine function involves the production of male germ cells (sperm), while its endocrine role centers on the secretion of male sex hormones, particularly testosterone. Exposure to xenobiotics, foreign chemical substances not naturally produced by the body, can interfere with critical processes such as sperm maturation by disrupting regular changes in the sperm membrane.[4] Toxic substances targeting the testis can significantly alter both the quantity and quality of sperm produced during spermatogenesis, ultimately affecting the population of sperm entering the epididymis. Additionally, toxicant-induced changes in testicular fluid, whether in volume or composition, may impair the function of epididymal epithelial cells and, consequently, sperm maturation. Chemicals that suppress testosterone production by Leydig cells can have further adverse effects on the epididymis. Testosterone deficiency leads to a reduction in both the number and quality of sperm entering the epididymis, causes regression of the epididymal epithelium, and impairs androgen-dependent aspects of sperm development. Furthermore, some chemicals can directly disrupt the structural integrity and function of the epididymis itself, impacting both the interstitial tissue and epithelial lining. These changes can alter the composition of the luminal fluid and, by extension, the condition of the sperm within the lumen.[5]

There have been numerous studies on the reproductive organs, particularly those of morphological structure and physiological functions of reproductive organs that were affected by certain substances from diets and/or consumption.[6-9] Yet, there remains a notable lack of comprehensive morphometric studies, as most histological literature focuses on photomicrographs rather than providing detailed quantitative measurements. In response to this gap, the present study examines morphological changes in male reproductive organs following exposure to dextromethorphan, utilizing Sprague-Dawley rats as the experimental model. Dextromethorphan (DM), a widely used antitussive agent, is present in over 150 over-the-counter medications. Chemically, DM is the dextrorotatory enantiomer of the methyl ether of levorphanol, an opioid analgesic, and it serves as a stereoisomer of levomethorphan, another opioid analgesic. DM is synthesized from benzylisoquinoline through a process known as Grewe's cyclization, which converts the compound into a three-dimensional morphinan structure. Specifically, 1,2,3,4,5,6,7,8-octahydro-1-(4-methoxybenzyl) isoquinoline is transformed into an N-formyl derivative, cyclized to N-formyl normorphinan, and subsequently reduced to an N-methyl group, producing 3-methoxy-17-methylmorphinan (racemethorphan).[10] Pharmacologically, dextromethorphan acts primarily by suppressing the cough reflex, decreasing activity within the brain's cough center either directly or by numbing cough receptors. Beyond its antitussive properties, it has demonstrated efficacy in alleviating pain in cancer patients,[11-13] managing symptoms of Parkinson's disease,[14] reducing the severity of pseudobulbar affect,[15] and treating cerebral ischemia.[16, 17]

2 Methods

Drug

Dextromethorphan was sourced from Fairy Pharmaceuticals in Zhuhai, Guangdong Province, China. Rutin was obtained from Pharmtex Pharmaceuticals, Lagos, Nigeria. Quercetin was purchased from Sigma Chemical Company, St. Louis, USA.

Animals

A total of 80 healthy male Sprague-Dawley rats weighing between 150 ± 30 g were used for this study. They were housed in standard well-ventilated wire-mesh plastic cages in the Animal House of the Department of Anatomy, College of Medicine, University of Lagos under standard room temperature. The rats were exposed to a 12-hour light and a 12-hour dark cycle and were left to acclimatize for a period of 2 weeks before the commencement of the experiment. The drugs used in this study were administered orally, delivered through a feeding tube. The rats were identified by different ear tags. All experimental procedures and techniques were approved by the Health Ethics committee of the College of Medicine, University of Lagos, Nigeria, with strict compliance with the guiding principles for research involving animals.[18]

Experimental Design

The experimental design involved dividing the rats into four groups, labeled A through D, with 20 rats in each group. Group A functioned as the control and received 1 ml of distilled water (DW), while Groups B, C, and D were administered 20 mg/kg, 40 mg/kg, and 80 mg/kg of DM, respectively, over four weeks.[19] At the end of the treatment, five rats from each group were randomly selected and euthanized. Their testes and caudal epididymis were collected for analysis. The researchers measured several histomorphometric parameters,

including the diameter and height of the seminiferous tubules and epididymis, testicular volume, and the counts of spermatogonia, spermatocytes, and spermatids within the seminiferous tubules.

The remaining 15 rats were divided into three subgroups (E–G), with five animals in each group. Group E received 25 mg/kg of Rutin, group F received 50 mg/kg of Quercetin, and group G received 1 ml of DW for four weeks to ascertain the recovery rate. At the end of the treatment period, the animals were all euthanized. [19] The testes and caudal epididymis were harvested and the following histomorphometric parameters were analyzed: diameter and height of the seminiferous tubule and epididymis, volume of testes, and the number of spermatogonia, spermatocytes, and spermatids within the seminiferous tubules.

Evaluation of histomorphometric analysis

The prepared slides were examined under a light microscope at 10X magnification. Key parameters—seminiferous tubular diameter, seminiferous tubule height, epididymal tubular diameter, and epididymal epithelial height—were measured within the epididymis. For accuracy, 10 measurements were taken for each parameter per section using a calibrated eyepiece micrometer (Graticules Ltd., Toubridge, Kent). The mean of these measurements was calculated and recorded for each animal. Testicular volume (V) was determined using a vernier caliper. Following dissection, testes were placed in Petri dishes and their length (L), width (W), and thickness (T) were measured. These values were applied to the Setchell and Waites formula: $V = 4/3 \times \pi \times (L/2) \times (W/2) \times (T/2)$, where π is a constant (3.141). For histomorphometric (stereological) evaluation, analysis was conducted using ImageJ®, an open-source image processing software designed for scientific applications. Tissue sections (5 µm thick) were stained with hematoxylin and eosin (H&E) for stereological studies. Data collection involved a Leica DM 750 digital microscope (Leica Microsystems, Switzerland), which was connected to a computer for image capture and measurement.

3 Results

No rat died during the course of the experiment. Throughout the study, all animals remained healthy and exhibited normal behavior.

Effect of dextromethorphan on the diameter of the seminiferous tubule of adult male Sprague-Dawley rats

When the treatment group was compared to the control, a clear dose-dependent decrease was observed—meaning the higher the dose was, the greater the reduction was, with significant differences, not just between medium and low, but also between high and medium doses. The same trend appeared in the recovery group, where both medium and high doses produced a notable decrease compared to the low dose, and the high dose again showed a significant reduction compared to the medium. Interestingly, the recovery group exhibited a significant increase when compared to the treatment group. Turning to the Rutin and Quercetin groups, this dose-dependent decrease persisted. Medium and high doses both resulted in substantial reductions compared to the low dose, and the high dose showed a further decline compared to the medium. However, when these groups were compared to the treatment and recovery groups, there was an increase, although it was not pronounced. Finally, direct comparison between Quercetin and Rutin revealed a slight increase in the Quercetin group (Table 1).

Effect of dextromethorphan on the height of the seminiferous tubule of adult male Sprague-Dawley rats

When the treatment group was compared to the control, there was a notable reduction that intensified with higher doses—so, both medium and high doses led to a greater decrease than the low dose, and the high dose reduced things even further than medium. Thus, there is a pretty clear dose-response relationship. For the recovery group, the medium and high doses resulted in a significant drop compared to the low dose, and high dose still outperformed the medium dose. However, when comparing the recovery group to the treatment group, a slight increase was observed— minor but noticeable. Moving to the Rutin and Quercetin groups, it's a similar pattern. Both medium and high doses led to a greater decrease than the low dose, and the high dose had a stronger effect than the medium. When Rutin and Quercetin were compared with the treatment and recovery groups, there was a significant increase. Between Quercetin and Rutin, Quercetin showed a slight—but noticeable—increase over Rutin (Table 2).

Effect of dextromethorphan on the epididymal luminal diameter of adult male Sprague-Dawley rats

When comparing the treatment group to the control, a notable dose-dependent reduction was observed, with greater decreases corresponding to higher doses. This trend persisted when medium and high doses were compared to the low dose, and again when comparing the high dose to the medium dose—each step up in dosage led to a significant decline in values.

In the recovery group, both the medium and high doses also resulted in significant decreases compared to the low dose, and the high dose showed a further reduction

compared to the medium dose. Interestingly, when the recovery group was compared to the treatment group, values actually increased. For the Rutin and Quercetin groups, administration of medium and high doses, as opposed to the low dose, led to a reduction in measured values; the same was true when moving from medium to high dose. However, when Rutin and Quercetin groups were compared with both the treatment and recovery groups, an increase in values was noted (Figure 1).

Effect of dextromethorphan on the epididymal height of adult male Sprague-Dawley rats

Based on the study findings, there was a notable reduction in values corresponding to increasing doses; the treatment group, when compared to the control, exhibited a clear dose-dependent decrease. This trend persisted when medium and high doses were compared to the low dose, and even further when the high dose was compared to the medium dose. Within the recovery group, significant decreases were also observed: both medium and high doses resulted in lower values than the low dose, with the high dose again showing a further decrease relative to medium. Interestingly, when the recovery group was compared to the treatment group, an increase in values was observed rather than a decrease. In the Rutin and Quercetin groups, a similar dose-dependent reduction was observed, with medium and high doses resulting in lower values compared to the low dose. Additionally, values at the high dose were further reduced relative to the medium dose. However, when comparing both the

Table 1 Effect of dextromethorphan on the diameter of the seminiferous tubule of adult male Sprague-Dawley rats

Diameter of the seminiferous tubule (µm)				
Duration	Four weeks			
Group	Control (CL)	Low dose (LD)	Medium dose (MD)	High dose (HD)
DM-alone	279.60 ± 0.93	270.20 ± 0.66a	262.40 ± 1.63ab	250.80 ± 1.71abc
Recovery-alone	279.60 ± 1.96	271.60 ± 0.93a	267.40 ± 0.93ab*	256.00 ± 0.71abc*
Rutin	278.40 ± 1.81	271.20 ± 0.73a	266.20 ± 1.62ab*	259.20 ± 0.66abc*
Quercetin	278.80 ± 1.07	275.60 ± 0.75a*	268.80 ± 0.37ab*	260.40 ± 0.51abc*

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose; *p < 0.05 significant compared to DM-alone.

Table 2 Effect of dextromethorphan on the height of the seminiferous tubule of adult male Sprague-Dawley rats

Height of seminiferous tubule (µm)				
Duration	Four weeks			
Group	Control (CL)	Low Dose (LD)	Medium Dose (MD)	High Dose (HD)
DM-alone	87.40 ± 0.51	82.60 ± 0.40a	79.20 ± 0.37ab	75.00 ± 0.45abc
Recovery-alone	88.80 ± 1.02	84.20 ± 0.37a	80.40 ± 0.24ab	77.40 ± 0.24abc
Rutin	87.60 ± 1.36	85.00 ± 0.63a*	83.40 ± 0.24ab*	80.40 ± 0.24abc*#
Quercetin	89.60 ± 0.24	84.40 ± 0.24a*	83.60 ± 0.24ab*	81.60 ± 0.24abc*#

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose; *p < 0.05 significant compared to DM-alone and #p < 0.05 significant compared to recovery-alone.

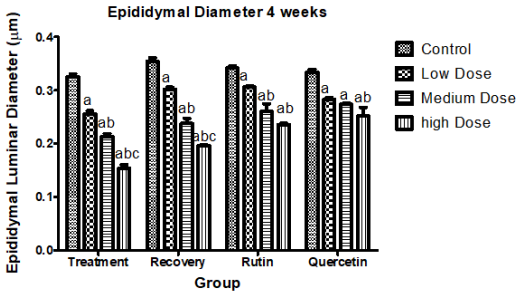

Figure 1 Effect of dextromethorphan on the epididymal luminal diameter in adult male Sprague-Dawley rats

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose.

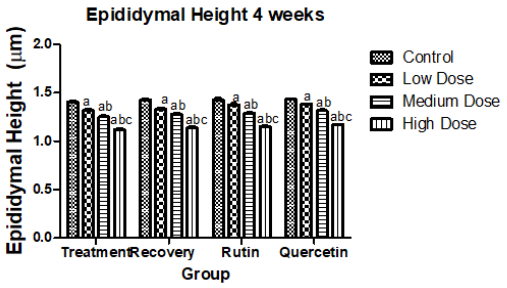

Figure 2 Effect of dextromethorphan on the epididymal height of adult male Sprague-Dawley rats

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose

Rutin and Quercetin groups to the treatment and recovery groups, an increase in values was recorded (Figure 2).

Effect of dextromethorphan on the volume of the testicular component tubule of adult male Sprague-Dawley rats

A significant, dose-dependent reduction was observed when the treatment group was compared to the control group. Notably, both medium and high doses resulted in a greater decrease than the low dose, with the high dose showing a more pronounced effect than the medium. In the recovery group, medium and high doses also produced lower values compared to the low dose, and the high dose again showed a significant reduction relative to the medium dose. Interestingly, values increased when the recovery group was compared to the treatment group. For the Rutin and Quercetin groups, both medium and high doses were associated with significantly greater decreases compared to the low dose, and the high dose again outperformed the medium. When these groups were compared to the treatment and recovery groups, a significant increase was observed. Lastly, a slight increase was noted in the Quercetin group compared to the Rutin group (Table 3).

Effect of dextromethorphan on spermatids of the seminiferous tubule of adult male Sprague-Dawley rats

When the treatment group was compared to the control, a notable decrease was observed. This downward trend continued as medium and high doses were compared to the low dose, with the most significant reduction appearing at the high dose relative to the medium. In the recovery group, both medium and high doses resulted in a considerable decrease compared to the low dose, and the high dose demonstrated a more pronounced effect than the medium dose. Interestingly, when evaluating the recovery group against the treatment group, there was a slight increase detected. Regarding the Rutin and Quercetin groups, both exhibited decreases as doses increased from low to medium and high, and the high dose consistently produced the most significant reduction. When either of these groups was compared with the treatment and recovery groups, increases were observed, especially at medium and high doses, where the differences reached statistical significance. Finally, a modest increase was noted when comparing the Quercetin group directly to the Rutin group (Table 4).

Effect of dextromethorphan on spermatocytes of the seminiferous tubule of adult male Sprague-Dawley rats

There was a marked reduction in values for the treatment group compared to the control group. Furthermore, both medium and high doses resulted in decreased values compared to the low dose, with the high dose showing a significantly greater decrease than the medium dose. In the recovery group, medium and high doses also led to notable reductions compared to the low dose, and the high dose was significantly lower than the medium dose. When comparing the recovery group to the treatment group, a slight increase in values was observed. For the Rutin and Quercetin groups, both medium and high doses produced significant decreases in values relative to the low dose, and the high dose was significantly lower than the medium dose. When these groups were compared to the treatment and recovery groups, there was an increase in values, particularly at medium and high doses, reaching statistical significance. Finally, comparing the Quercetin group to the Rutin group, a

Table 3 Effect of dextromethorphan on the volume of the testicular component tubule of adult male Sprague-Dawley rats

Volume of the testicular component (µm)				
Duration	Four weeks			
Group	Control (CL)	Low Dose (LD)	Medium Dose (MD)	High Dose (HD)
DM-alone	0.51 ± 0.01	0.41 ± 0.00a	0.37 ± 0.00ab	0.29 ± 0.01abc
Recovery-alone	0.54 ± 0.01	0.42 ± 0.01a	0.42 ± 0.01a*	0.33 ± 0.01abc*
Rutin	0.53 ± 0.01	0.45 ± 0.01a*	0.42 ± 0.01ab*#	0.40 ± 0.01ab*#
Quercetin	0.51 ± 0.01	0.47 ± 0.00a*#	0.43 ± 0.01ab*#	0.42 ± 0.00ab*#

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose; *p < 0.05 significant compared to DM-alone and #p < 0.05 significant compared to recovery-alone.

Table 4 Effect of dextromethorphan on spermatids of the seminiferous tubule of adult male Sprague-Dawley rats

Spermatids (µm³)				
Duration	Four weeks			
Group	Control (CL)	Low Dose (LD)	Medium Dose (MD)	High Dose (HD)
DM-alone	107.60 ± 0.68	94.40 ± 0.51a	89.40 ± 0.68ab	80.60 ± 0.51abc
Recovery-alone	108.00 ± 0.89	95.60 ± 0.51a	93.00 ± 0.32ab	82.40 ± 0.40abc
Rutin	108.60 ± 0.51	98.80 ± 0.58a*	95.40 ± 0.60*	88.60 ± 0.51abc*#
Quercetin	108.40 ± 0.81	99.80 ± 0.58a*#	97.40 ± 0.40*#	88.00 ± 0.71*#

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose; *p < 0.05 significant compared to DM-alone and #p < 0.05 significant compared to recovery-alone

slight increase was noted in the former (Table 5).

Table 5 Effect of dextromethorphan on spermatocytes of the seminiferous tubule of adult male Sprague-Dawley rats

Spermatocytes (µm³)				
Duration	Four weeks			
Group	Control (CL)	Low Dose (LD)	Medium Dose (MD)	High Dose (HD)
DM-alone	121.40 ± 0.51	117.20 ± 0.66a	106.60 ± 0.93ab	96.40 ± 0.51abc
Recovery-alone	122.40 ± 0.51	115.80 ± 1.07a	109.80 ± 0.37ab	99.20 ± 0.58abc
Rutin	123.60 ± 0.81	119.20 ± 0.58a	115.00 ± 0.55ab*#	106.80 ± 0.58abc*#
Quercetin	124.20 ± 0.86	119.00 ± 0.71a	113.80 ± 0.66ab*#	107.40 ± 0.40abc*#

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose; *p < 0.05 significant compared to DM-alone and #p < 0.05 significant compared to recovery-alone

Effect of dextromethorphan on spermatogonia of the seminiferous tubule of adult male Sprague-Dawley rats

A notable decrease was observed in the treatment group compared to the control. This reduction persisted when medium and high doses were compared to the low dose, with the high dose showing a significant decrease relative to the medium dose. In the recovery group, both medium and high doses also demonstrated a significant decline compared to the low dose, and the high dose further decreased relative to the medium. Comparing the Recovery group to the treatment group, there was a significant increase at both the low and high doses. In the Rutin group, significant decreases were seen for both medium and high doses versus the low dose, as well as for high versus medium doses. However, when the Rutin group was compared to both the treatment and recovery groups, an increase in values was noted. For the Quercetin group, both medium and high doses displayed a significant increase compared to the low dose, as did the high dose relative to the medium. Furthermore, Quercetin showed a significant increase when compared to the treatment and recovery groups, and a slight increase when compared to the Rutin group (Table 6).

4 Discussion

Epithelial height and tubule diameter in the seminiferous tubules and epididymis serve as key indicators of male reproductive health. In this study, reductions in epididymal epithelial height were observed, likely tied to decreased testosterone levels.[20] When testosterone drops, existing epididymal cells attempt to compensate, but overall cell height still declines, which aligns with previous research.[21] The treatment group also showed a notable decrease in epididymal diameter, suggesting disruptions in spermatogenesis that could stem from increased apoptosis among interstitial cells—those responsible for producing testosterone. This disruption appears to alter steroidogenesis, ultimately impacting the whole process of sperm production.[22] Additionally, the study recorded a decrease in the density of the seminiferous tubules, a change associated with impaired sperm physiology and reduced sperm motility.[23] Tubular diameter is commonly used in experimental and toxicological research as a marker of spermatogenic activity, with a well-established positive relationship between tubule size and sperm production. Here, males treated with dextromethorphan showed significantly reduced tubule diameter.[24,25]

Table 6 Effect of dextromethorphan on spermatogonia of the seminiferous tubule of adult male Sprague-Dawley rats

Spermatogonia (µm³)				
Duration	Four weeks			
Group	Control (CL)	Low Dose (LD)	Medium Dose (MD)	High Dose (HD)
DM-alone	47.20 ± 0.58	38.80 ± 0.37a	36.40 ± 0.51a	23.80 ± 0.86abc
Recovery-alone	46.20 ± 0.80	41.80 ± 0.58a*	37.40 ± 0.40ab	28.80 ± 0.37abc*
Rutin	48.40 ± 1.21	42.80 ± 0.71a*	37.80 ± 1.02ab	31.20 ± 0.37abc*#
Quercetin	48.20 ± 0.37	43.20 ± 0.37a*#	40.80 ± 0.37ab*	32.40 ± 0.51abc*#

Values are expressed as Mean ± Standard Error of Mean. ap < 0.05 significant compared to control; bp < 0.05 significant compared to low dose; cp < 0.05 significant compared to medium dose; *p < 0.05 significant compared to DM-alone and #p < 0.05 significant compared to recovery-alone.

This reduction may be due to cytoplasmic shrinkage within the cells[26,27] or a decrease in the number of spermatogenic cells, both of which are consistent with impaired spermatogenesis. Overall, these findings suggest that dextromethorphan negatively affects multiple parameters essential to male fertility.[28]

Animals treated with Dextromethorphan exhibited a noticeable reduction in the area of their seminiferous tubules. This decrease appears to be linked to a reduction in spermatogenic cells, with the absence of spermatozoa in the lumen clearly demonstrated in the corresponding micrographs.[29] Testicular volume, a well-established indicator of male fertility, was also found to be diminished in the treated group compared to controls. This reduction is likely associated with a decreased number of germ cells; as testicular volume is mainly dependent on the presence of differentiated spermatogenic cells [30,31]. Previous studies have shown that inhibited differentiation and a decrease in the diameter of seminiferous tubules can contribute to reduced testicular volume. [32-34] Furthermore, quantifying germ cells within the seminiferous tubules is considered a reliable approach for detecting testicular toxicity, with different germ cell populations such as spermatogonia, spermatocytes, and spermatids, displaying varying sensitivities to toxicants. [35] The height of the seminiferous epithelium, which is regulated by hormonal factors like follicle-stimulating hormone (FSH), was also reduced in the treatment group. This finding suggests varying degrees of degeneration among spermatogonia, accompanied by an increased presence of apoptotic cells.[36]

This study revealed a noticeable reduction in the numbers of spermatids, spermatocytes, and spermatogonia within the seminiferous tubules of the treatment group compared to the control group. The main culprit appears to be free radicals produced by dextromethorphan (DM), which are toxic and disrupt both the quantity of spermatogenic cells and the overall structure of the seminiferous tubules.[37-39] DM seems to interfere with the normal spermatogenic cycle and cellular division, ultimately leading to fewer spermatogenic cells.[40] On a more positive note, flavonoids such as Rutin and Quercetin, thanks to their unique structural features like hydroxyl groups on the C ring, have demonstrated protective effects on the male reproductive system.[41-43] Research has documented their beneficial impact on testicular function and the process of steroidogenesis.[44,45] In this study, when Rutin and Quercetin were administered, there was a significant improvement in all measured histomorphometric parameters compared to the DM treatment group alone. These antioxidants exhibited their protective abilities by preventing apoptosis and supporting the continued proliferation of cells within the seminiferous tubules, thereby maintaining the functional integrity of the testis against the harmful effects of DM. This protective effect seems to be linked to the downregulation of apoptotic proteins, which in turn promotes cell survival.[46,47] Supporting evidence from other studies also suggests that Quercetin and Rutin can suppress apoptosis and inflammation, even in cases of Doxorubicin-induced toxicity.[48]

5 Conclusion

The decline in male reproductive health due to toxic exposures has become a significant global concern. This study demonstrated that dextromethorphan administration adversely affected male reproductive function, as evidenced by reductions in histomorphometric parameters. Interestingly, the findings suggest that the antioxidants Rutin and Quercetin may mitigate the harmful effects induced by dextromethorphan toxicity. These outcomes were observed in male Sprague-Dawley rats, emphasizing the potential protective role of these compounds in preserving reproductive health amidst toxic challenges.

Declarations

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Artificial Intelligence Disclosure
The authors confirm that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

Authors' Contributions
All the authors have contributed to this study.

Availability of Data and Materials
None declared.

Conflict of Interest
All authors have declared no conflict of interest.

Consent for Publication
All the authors give consent to the publication of this manuscript.

Ethical Considerations
All experimental procedures and techniques were approved by the Health Ethics committee of the College of Medicine, University of Lagos, Nigeria, under the Code of Ethics CM/HREC/09/16/054, with strict compliance with the university's guiding principles for research involving animals.

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