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Histomorphological changes and alterations in the reproductive parameters of male wistar rats following exposure to ethanolic leaf extract of *Datura stramonium* (GEGEMU)

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Abstract
Datura stramonium is commonly called Jimson weed, thorn apple, or Gegemu. It is a medicinal plant that is utilized traditionally for various therapeutic purposes. Its potential health benefits have attracted attention in recent years, thus the increased exploration of its pharmacological properties. Though Gegemu holds lots of promise in traditional medicine, its effect on reproductive organs is relatively understudied. A key component of the male reproductive system is the testis which is responsible for androgen production and spermatogenesis. Any disruptions in the histological structure of the testis can profoundly impact male reproductive health. This study was carried out to elucidate the possible effects of Gegemu on the histological architecture of the testis in male Wistar rats. A total of twenty adult male Wistar rats that weighed between 200 – 250 g were used for this study. The animals enjoyed natural light and dark cycles; food and water were available ad libitum. The animals were divided into four (4) groups (A-D) of five rats each. Group A served as control and was given 1ml of distilled water, while groups B, C, and D were given 50 mg/kg, 100 mg/kg, and 150mg/kg of the extract per os, daily for six weeks. The body weight of the animals was taken before and at the end of the experiment. The animals were then sacrificed, and blood and testicular tissue were taken for analysis. The results obtained from this study showed significant (p<0.05) increases in weight across the treated groups and a reduction in the population of luminal spermatozoa with evident spermatogenic arrest. There were significant (p<0.05) decreases in the levels of the hormones assayed in this study. These findings collectively highlight the adverse impact of Gegemu on testicular histomorphology and hormonal balance, implicating potential reproductive toxicity.

Keywords: *Datura stramonium*, testis, histology, reproductive toxicity, testosterone

1. Introduction
Datura stramonium, a member of the Solanaceae family, stands as a significant medicinal plant [1]. *Datura stramonium*, commonly referred to as Jimson weed, is a readily accessible weed known for its ability to thrive in diverse environmental conditions and proliferate rapidly. It is characterized by its trumpet-shaped flowers and sweet fragrance. Throughout history, indigenous communities and tribes globally have incorporated Datura into religious ceremonies, divination rites, witchcraft rituals, and medicinal applications for numerous generations [2]. It is utilized across indigenous and traditional medicinal practices globally, grows in all the geographical regions of Nigeria, and is mostly found on roadsides, undeveloped areas, and grassy fields. This plant typically grows to a height of 2-4 feet and often spreads to a diameter of 4-6 feet. Its flowers are notable for their size, with corollas reaching lengths of 6 cm. The fruit takes the form of a large, four-oval ovate capsule, characterized by its pronounced thorns and containing numerous black to dark brown seeds. Stems are typically simple, stout, and predominantly erect. Its leaves are large, measuring approximately 20 cm in length. The root, on the other hand, is long, thick, tapering, and somewhat branched. When crushed or bruised, the leaves release an unpleasant odor [3, 4]. The plant possesses potent narcotic properties, yet it exhibits a unique effect on humans that makes it highly valuable in medicine. Symptoms of acute poisoning from the overuse of

Jimson weed include mouth dryness, intense thirst, skin dryness, dilated pupils, blurred vision, difficulty urinating, rapid heartbeat, confusion, agitation, hallucinations, as well as unconsciousness [5]. Its wide array of biological functions encompasses larvacidal, anti-asthmatic [6], antibacterial, antifungal, anti-inflammatory, antispasmodic, antioxidant, antinociceptive [7], anti-rheumatoid, and anti-ulcer properties [8]. The dried leaves of *Datura stramonium* have been historically utilized in the treatment of asthma [9].

Fig 1: Picture of *Datura stramonium* plant showing leaves and fruit.

Some reports of phytochemical screening showed the presence of glycosides, alkaloids, phenols, steroids, saponins, tannins, and steroid hormones. Though all parts of the plant are considered toxic, the mature seeds have the highest concentration of alkaloids [10, 11, 12]. This wild-growing flowering plant was studied for its tropane alkaloids, which contain methylated nitrogen atoms (N-CH3) and include the anticholinergic drugs atropine and scopolamine. Its anti-inflammatory properties, stimulation of the central nervous system, respiratory decongestion, treatment of dental and skin infections, alopecia, and toothache are some of its medicinal uses [13]. Previous reports originating from the United States have highlighted instances, primarily among adolescents and young adults, where ingestion of large quantities of the Gegemu plant resulted in fatalities or severe illness. Consequently, it is acknowledged that consumption of any part of the plant can lead to a pronounced anticholinergic reaction, occasionally posing diagnostic challenges and potentially inducing toxicity. Additionally, various studies have documented the toxic effects of *Datura stramonium* extracts on the Central Nervous System (CNS), liver, and kidneys. The presence of atropine in the seeds and leaves of the plant is believed to be the primary cause of its toxicity [14] 15, 16]. It has also been observed that ingestion and absorption of atropine by the body trigger vomiting and diarrhea in grazing animals, along with biochemical alterations in rats fed with Datura seeds [17]. Nonetheless, numerous therapeutic and medicinal benefits have been linked to the plant *Datura stramonium.*

The testes function in spermatozoa production and testosterone synthesis. These functions are controlled by the pituitary gland which is in turn influenced by the hypothalamus. The pulsatile release of gonadotropin-releasing hormone (GnRH) of the hypothalamus triggers the secretion of the pituitary gonadotropins, thus representing an elegant feedback loop with modulations by testicular hormones [18]. Any disruption to testicular histology or function could have significant implications for fertility and overall reproductive health. While previous studies have examined the toxic effects of the Gegemu plant on various organs and systems, its impact on testicular histology and function may not have been adequately explored. Filling this knowledge gap is essential for a comprehensive understanding of the plant's toxicity profile. Investigating the effects of the Gegemu plant on testicular histology and function is important for further understanding its toxicity profile, protecting reproductive health, and informing public health interventions and regulatory actions. This study was therefore aimed at investigating the effects of various doses of the aqueous extract of the leaves of *Datura stramonium* on the histomorphology of the testis, sperm parameters, and hormonal milieu in adult male *Wistar* rats.

2. Materials and Methods

2.1 Reagents/Chemicals

All reagents used were of analytical grade and products of British Drug House (BDH) England, E. Merck, Darmstadt, Germany and Aldrich Chemical Company

2.2 Collection, Identification, and Extraction of Plant Materials

The fresh leaves of *Datura stramonium* were collected from Okada town, Benin City, Edo State. It was identified and authentication was done at the College of Natural and Applied Sciences, Igbinedion University, Okada. The leaves were air-dried at room temperature, after which they were crushed and ground into powder using an electrical grinder. The ground crude sample was macerated in ethanol, filtered, and concentrated using a rotary evaporator to obtain the ethanolic extracts.

2.3 Animal Grouping and Handling

A total of twenty adult male Wistar rats that weighed 200 – 250 g were obtained from the animal house of the Department of Anatomy, School of Basic Medical Sciences, Igbinedion University, Okada, Edo State, Nigeria, and housed in the same facility for the study. The animals enjoyed natural light and dark cycles; food and water were available ad libitum. The animals were divided into groups

A, B, C, and D of five rats each. Group A served as control and was given 1 ml of distilled water, while groups B, C, and D were given 50 mg/kg, 100 mg/kg, and 150 mg/kg of the extract as oral doses daily for six weeks. At the end of the experiment, the animals were sacrificed and vital tissues were taken for analysis.

2.4 Sperm Analysis

2.4.1 Sperm count

The epididymis was minced and incubated in 5ml of physiological saline for 2 minutes. The resulting fluid was diluted 1:100 with a solution containing sodium bicarbonate and formalin. A 10ml sample of the diluted fluid with sperm cells was loaded onto a counting chamber and examined under a microscope. The total sperm count was determined using the enhanced Neubauer's counting chamber.

2.4.2 Motility

Caudal epididymal fluid was mixed with Tris buffer to a volume of 0.5ml. A portion of this mixture was examined under a microscope at 400x magnification. The average motility from the three assessments was adopted as the main motility rating.

2.4.3 Morphology

The motility assessment utilized the initial dilution method, followed by a 1:20 dilution with 10% neutral buffered formalin. A smear was then created from a drop of sperm suspension, fixed with absolute ethanol, and stained with Diff-Quik Stain I and II for 5 minutes each. Microscopic examination enabled the determination of the percentage of morphologically normal and abnormal sperm, following the protocol outlined by Pal *et al.*, [19].

2.5 Hormonal Analysis

Blood samples were obtained from the heart by cardiac puncture and allowed to clot for 2 hours at room temperature. Following a 5-minute centrifugation at 3000 revolutions per minute (rpm), the resulting supernatant (serum) was obtained for hormonal analysis. Testosterone, luteinizing hormone, and follicle-stimulating hormone levels were determined using the ELISA method with rat FSH ELISA kits.

2.6 Histological Studies

The testes were excised from the treated and control rats and were weighed and examined for gross and pathological changes. The tissues were fixed in 10% formal saline and processed by routine method for paraffin sections. Sections were cut using a microtome and stained with Erlich's Haematoxylin (H) and Eosin (E). The slides were examined using a light microscope.

2.7 Statistical Analysis

The statistical analysis carried out on data obtained was done using the IBM statistical package for social science, SPSS version 23. Thereafter test for significance was done by applying the analysis of variance (ANOVA). To determine significant differences between groups, the Duncan post- hoc was applied at $P<0.05$

3. Results

3.1 Effect of varied doses of the ethanol leaf extract of *Datura stramonium* on the weight of male *Wistar* rats

Weight changes in *Wistar* rats treated with varied doses of ethanolic extract of *Datura stramonium* leaf showed significant ($p<0.05$) increases across the treated groups relative to the control. The increases are expressed as percentage weight changes and occurred in a dose-dependent manner.

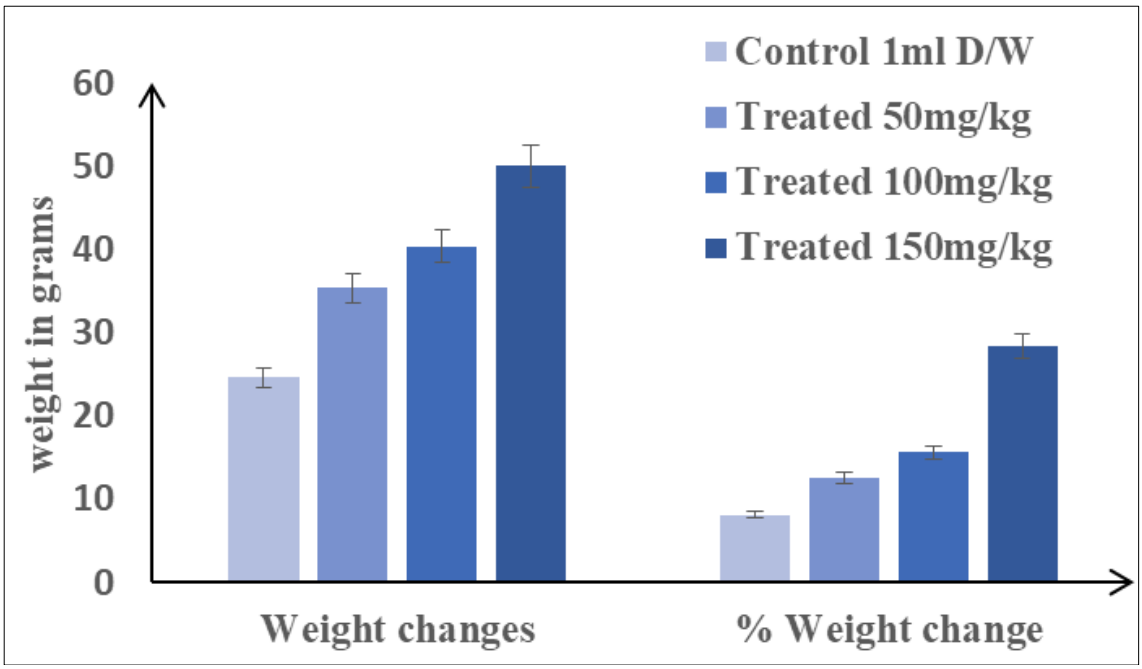

Fig 2: Weight changes

3.2 The effect of *Datura stramonium* ethanolic leaf extract on sperm parameters including sperm count, sperm motility, and morphology

Figure 3 reveals a significant ($p<0.05$) dose-dependent reduction in sperm count in male rats administered ethanolic extract of *D. stramonium* leaf relative to the control. The results in Figure 4, of the sperm motility studies carried out in the research recorded significant ($p<0.05$) dose-dependent reductions in the progressive motility of all the treated groups; 40%, 36%, and 20% for treated 50mg,

100mg and 150mg per kilogram body weight respectively, when compared with the control which was 80%. Non-progressive motility also increased across the treatment groups but in no particular manner. The percentage of immotile sperm significantly (p<0.05) increased across the treatment groups (50%, 56%, and 65% for 50mg, 100mg, and 150mg per kilogram body weight respectively, and in a dose-dependent manner, against 15% recorded in control. The results of the morphological studies showed dose-dependent significant (p<0.05) reductions in the percentages of morphologically normal sperm cells as well as significant (p<0.05) increases in percentages of morphologically abnormal sperm cells across the experimental groups as shown in Figure 5.

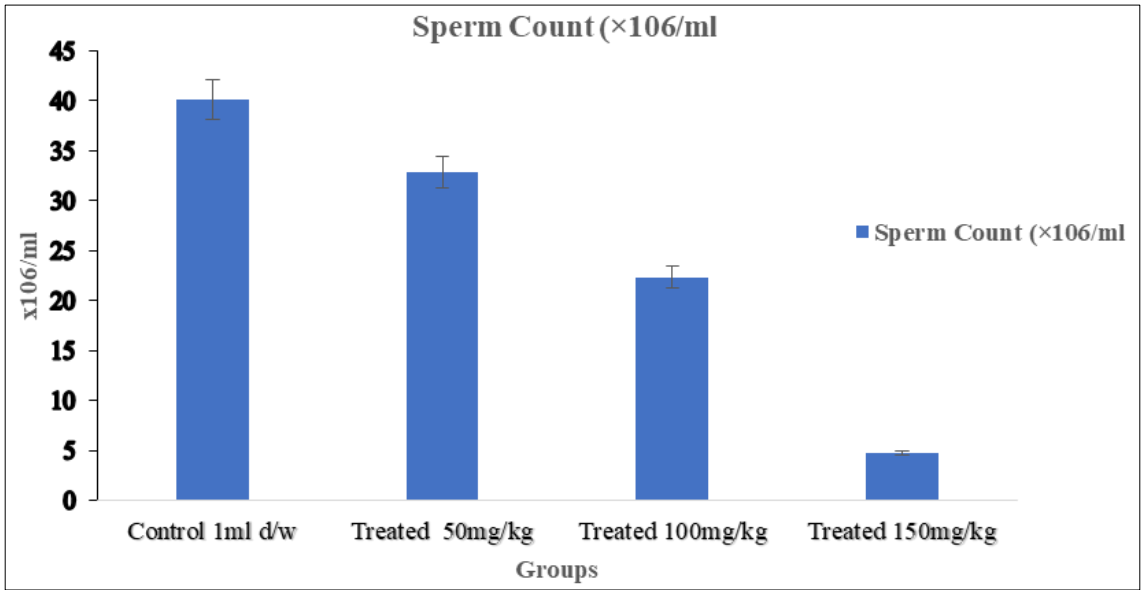

Fig 3: Sperm motility for extract-treated male rats. Values are Mean ± SEM

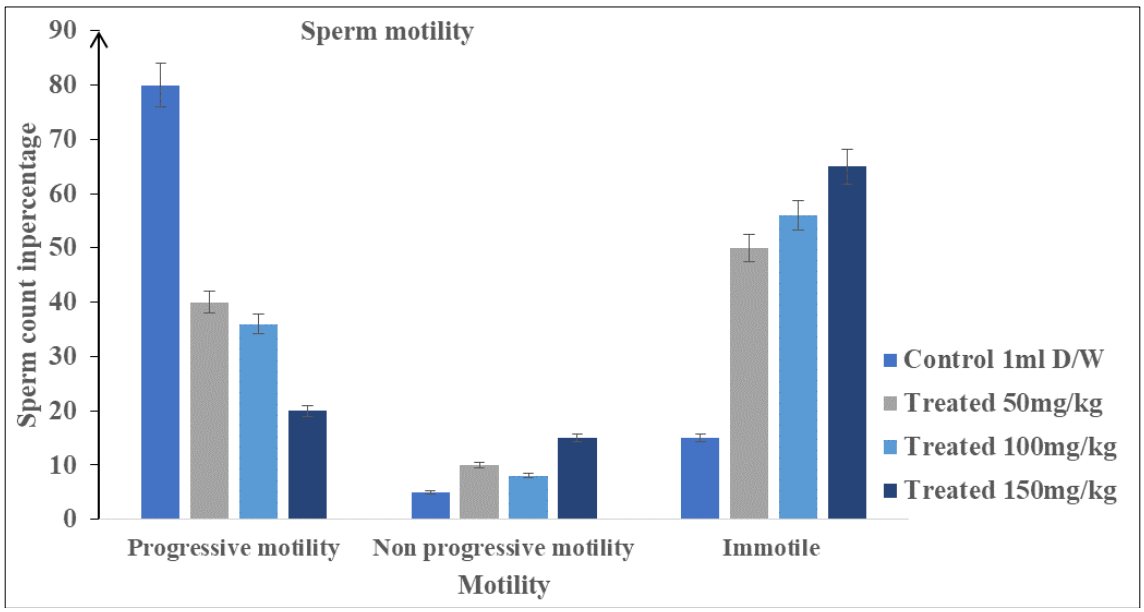

Fig 4: Sperm motility for extract-treated male rats. Values are Mean ± SEM

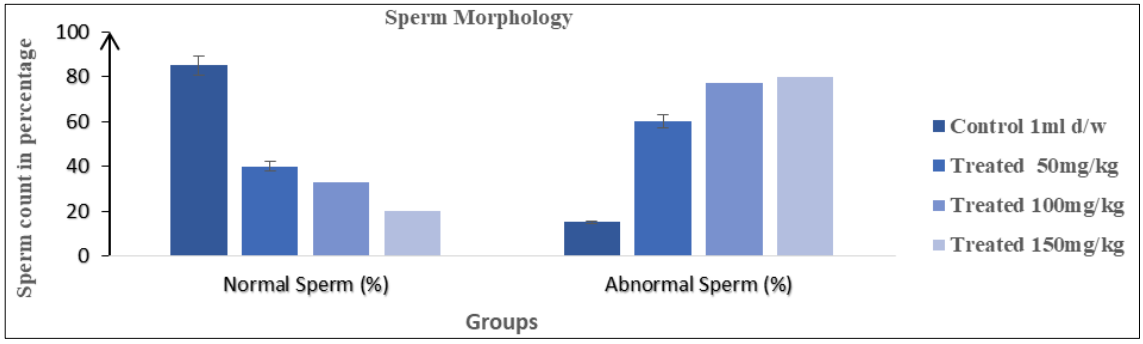

Fig 5: Sperm morphology for extract-treated male rats. Values are Mean ± SEM

3.3 The effect of *Datura stramonium* ethanolic leaf extract on the hormonal levels including Luteinizing hormone, Follicle stimulating hormone and testosterone.
Results of hormonal assay to determine serum levels of testosterone, Follicle stimulating and luteinizing hormones, revealed a significant ($p<0.05$) dose-dependent reductions in the levels of the hormones in the experimental groups relative to the control group.

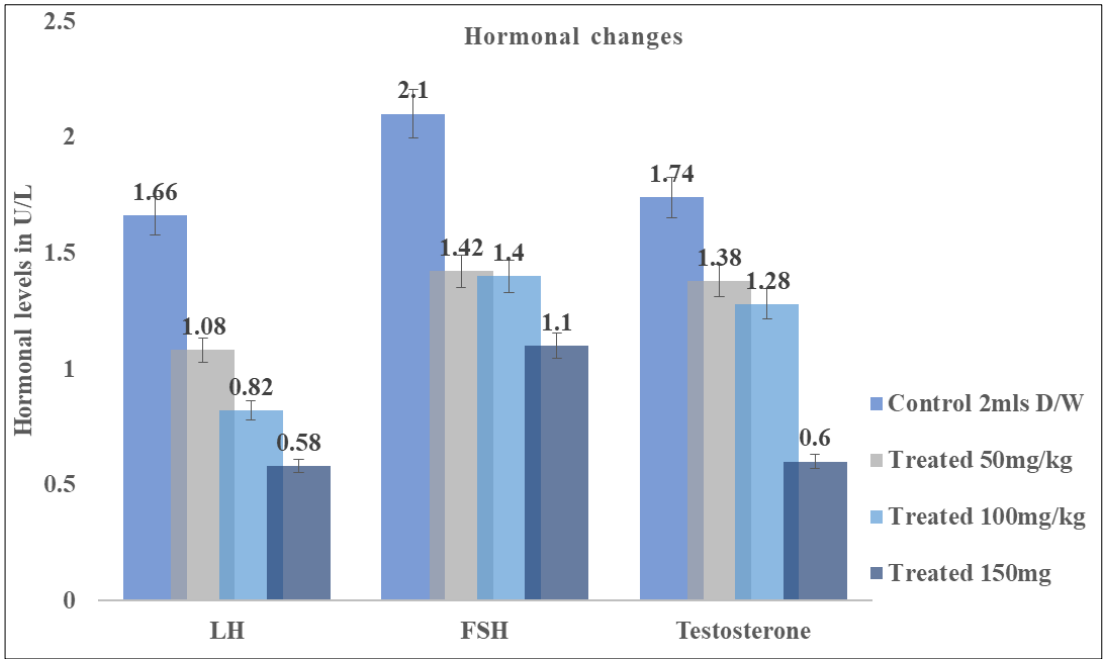

Fig 6: Hormonals levels of LH, FSH and testosterone. Values are Mean ± SEM

3.6 Histology of the Testis/ Seminiferous tubules

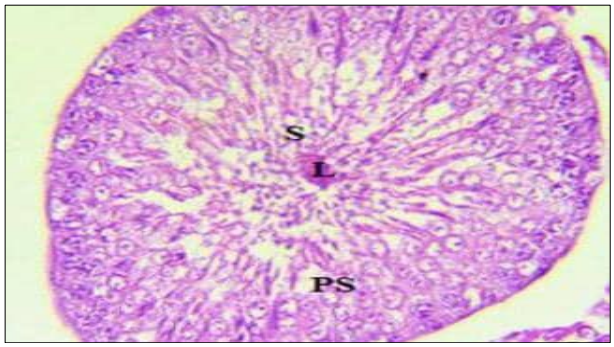

Plate 1: Photomicrograph of control testis showing normal histo-architecture of the seminiferous tubule with intact seminiferous tubular epithelium and the cells of the spermatogenic lineage (S, PS) and abundant luminal sperm cells (L). Magnification x400

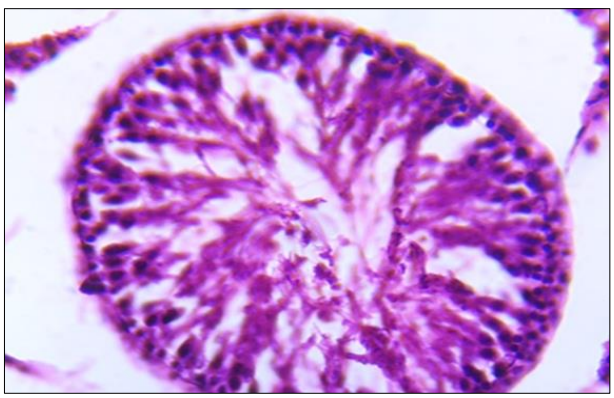

Plate 2: Photomicrograph of testis treated with 50mg/kg^{-1} of *D. Stramonium* showing fairly disrupted seminiferous tubular epithelium and very mild depletion of luminal spermatozoa. Magnification x400

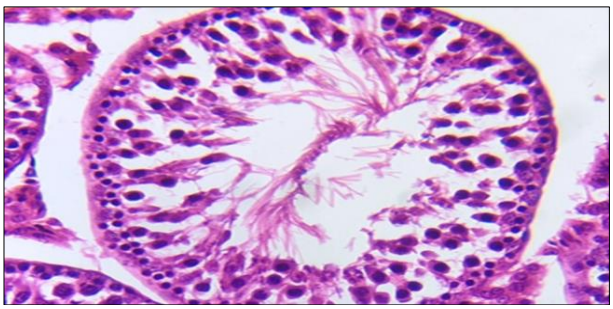

Plate 3: Photomicrograph of testis treated with 100mg/kg-1 of *D. stramonium* showing fairly disrupted histo-architecture of the seminiferous tubule and moderately reduced luminal sperm cells. Magnification x400

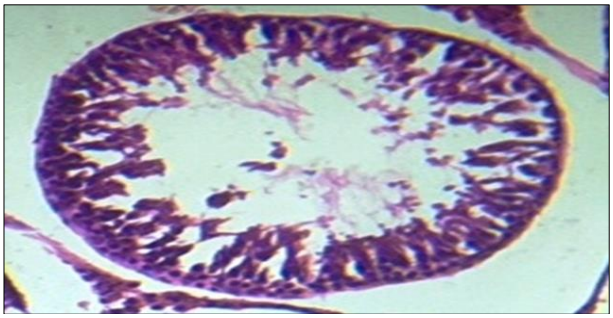

Plate 4: Photomicrograph of testis treated with 100mg/kg-1 of *D. stramonium* showing fairly disrupted histo-architecture of the seminiferous tubule and severe reduction in the population of luminal sperm cells. Magnification x400.

4. Discussion

A "herbal high" typically refers to the use of herbal substances or products to achieve altered states of consciousness or psychoactive effects, often mimicking the

effects of illicit drugs. These substances are usually derived from plants or plant-based materials and may be marketed as natural or herbal alternatives to traditional drugs like cannabis, ecstanmsy, or cocaine. Herbal highs can include herbal smoking blends, herbal pills or capsules, or extracts made from various plants known for their psychoactive properties. However, it's important to note that herbal highs can also carry significant health risks, including adverse reactions, addiction, and potential long-term harm to physical and mental health [20]. *Datura stramonium* is considered a herbal high due to its potent psychoactive properties. It is known for inducing hallucinogenic and deliriant effects, making it a substance that alters one's mental state and perception. Despite its traditional medicinal uses for conditions like asthma, *Datura stramonium's* tropane alkaloids can lead to intense visions and altered consciousness, categorizing it as a substance that can produce a "high" when consumed. However, it is crucial to highlight that the hallucinogenic properties of *Datura stramonium* come with significant risks, as its toxic alkaloids can be fatally poisonous, leading to hospitalizations and even deaths when used carelessly or inappropriately [21]. This study was designed to investigate the possible systemic consequences of exposing male albino rats of the Wistar strain to varied doses of *Datura stramonium* ethanol leaf extract. The results obtained from this study showed a significant increase in the weight of the animals across the treatment groups when compared to the control. This result compares favorably with the reports of Ejeh *et al.* [22] who reported weight gain in animals exposed to *Uvaria chamae* leaf extract. According to them, weight gain indicates that the extract is nontoxic and therefore had no interference with appetite, digestion, and assimilation of food in the experimental animals. Ademuluyi *et al.*, [23] also reported significant increases in the body weights of animals treated with Datura fruit extract. The weight gain recorded in this study may be due to increased appetite in the animals as opined by Taziebou *et al.* [24], initiated by the psychoactive properties of the extract that qualifies *Datura stramonium* as a “herbal high”.

The results of the sperm analysis revealed a significant ($p<0.05$) decrease in sperm count across the experimental groups compared to the control. Other parameters were also adversely affected as there were significant ($p<0.05$) decreases in motility as indicated by the high percentage of immotile and morphologically abnormal sperm cells. These findings are in line with the findings of Alabi *et al.*, [25]. According to their report, a high dose of *Musa paradisiaca* affected all the sperm parameters adversely, by reducing sperm count and percentage of morphologically normal sperm cells. The diminished sperm population within the seminiferous tubules and increased percentage of morphologically abnormal sperm cells carry substantial implications for male fertility. A decline in sperm numbers within these tubules and a reduction in morphologically normal sperm cells as well increased percentage of immotile spermatozoa directly influence both the overall sperm count and quality, potentially contributing to male infertility. Sperm production, maturation, and transport throughout the reproductive system hinge upon the presence of a sufficient quantity of viable spermatozoa. Consequently, a reduction in the sperm population within the seminiferous tubules can lead to diminished sperm output, thereby affecting the likelihood of successful fertilization and reproduction.

The critical factor contributing to male fertility is the development of morphologically normal mature sperm cells. Hormones from the anterior pituitary gland, specifically Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), play a pivotal role in regulating spermatogenesis and testosterone production. FSH governs spermatogenesis and prompts Sertoli cells to release Androgen-Binding Hormone (ABP), while LH stimulates testosterone production by binding to Leydig cells. Testosterone supports spermatogenesis and inhibits the hypothalamus from secreting Gonadotropin-Releasing Hormone (GnRH) and the anterior pituitary gland from producing LH and FSH through a negative feedback loop [26]. In this study, the levels of testosterone, follicle-stimulating hormone, and luteinizing hormone were significantly ($p<0.05$) decreased relative to the control. This result is similar to the findings of Okafor *et al.*, [27] who reported no significant changes in hormonal levels, with significant reduction in the sperm parameters of male rats treated with ethanolic extract of *Portulaca Oleracea*. Okwuonu *et al.*, [28] reported a significant ($p<0.05$) dose dependent decline in sperm count, progressive motility and an increased percentage of morphologically abnormal sperm cells following exposure to the aqueous extract of *Aspilia Africana* flowers. The significant decrease in levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) compared to the control group indicates a notable impact on male reproductive hormones due to exposure to the ethanolic extract of *Datura stramonium*. This decline in hormonal levels suggests a potential disruption in the endocrine system, which could affect male fertility and reproductive function. The decline in testosterone level may have affected the supposed progressive process of spermatogenesis which may have resulted in spermatogenic arrest, as were evident in the morphologic alterations observed, impaired motility, and general sperm quality.

The studies on the histology of the testis showed moderate disruptions of the seminiferous tubular epithelium and a dose-dependent reduction in the population of luminal spermatozoa across the experimental groups when compared to the control and aligns favorably with the reports of Okwuonu and colleagues [29], who reported decreases in the population of luminal spermatozoa in both the testis and epididymis of experimental animals exposed to varied doses of the ethanolic extract of *Aspilia africana* flowers. This result indicates significant alterations in the testicular structure and sperm production. When the seminiferous tubular epithelium is moderately disrupted, it implies damage to the lining of the tubules where spermatogenesis occurs [30] this disruption can lead to impaired sperm production and maturation [31]. Reductions in the population of luminal spermatozoa suggest a decrease in the number of mature sperm cells present in the tubules, which can impact fertility.

These histological changes can result from various factors such as infections, hormonal imbalances, genetic abnormalities, or environmental toxins. Understanding the extent of disruption in the seminiferous tubules and the decrease in sperm population is crucial for diagnosing and treating conditions that affect male fertility. Histological evaluation of testicular tissues plays a vital role in assessing spermatogenesis disturbances and guiding appropriate interventions to address these issues.

Conclusion

The research underscores the significance of histological examination in detecting testicular structural irregularities that may influence male reproductive well-being. Through the evaluation of seminiferous tubules and spermatozoa count, scientists and healthcare providers can acquire a crucial understanding of the root causes of male infertility and formulate precise therapeutic approaches to tackle these challenges efficiently. The outcomes of this investigation reveal that *Datura stramonium* adversely affects the morphology and functionality of the male reproductive system in rats, emphasizing the necessity to avoid its usage to prevent detrimental impacts on reproductive health.

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