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ANTI-INFLAMMATORY ROLE OF *ANNONA MURICATA* FRUIT EXTRACT ON CYTOARCHITECTURE OF TESTOSTERONE INDUCED PROSTATIC HYPERPLASIA IN MALE WISTAR RAT

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ABSTRACT

An increase in the prostate's size that is not malignant is identified as benign prostatic hyperplasia (BPH), characterized by proliferation of the cellular membranes of the prostate, which leads to constriction of urine flow, abdominal pain, dysuria, urinary hesitancy, urinary intermittency, and nocturia. Hence, this study is designed to investigate the curative effect of Annona Muricata Extract (AME) on the prostate of testosterone-induced prostate hyperplasia and prostate as an organ. 20 male Wistar rats were randomly grouped into four groups of 5 animals per group. Group A used as control were given 0.5 ml normal saline (NS), Group B were administered 15mg/kg testosterone + extract (TEST + AME), Group C were administered 15mg/kg testosterone + extract (Recovery), Group D were administered 15mg/kg testosterone only (TEST). Statistical analysis was done using GraphPad Prism. The result revealed a considerable change in body weight of group treated with testosterone and Annona muricata (p value<0.001), prostatic (p value<0.0001) weight and testicular weight (p value<0.0014). Morphologically, prostatic collagen deposition and thick prostatic epithelium caused by testosterone administration were significantly reversed. There is regeneration of seminiferous tubules and interstitial spaces in testicular architecture after the administration of Annona muricata. In conclusion, this study has shown that Annona muricata with its rich antioxidants, makes it a strong alternative therapy in reversing the inflammation of any source in the system, as it is evident in the outcome of statistical analysis and histology.

Keywords: Anti-oxidant, Prostatic, Hyperplasia, Annona muricata, Testosterone

INTRODUCTION

Testosterone is the main hormone circulating in men, secreted almost entirely by the testes, plays a key role in the development of male reproductive tissues such as penis and the development of the scrotum in the fetus, prostate, improving secondary sexual characteristics such as increased muscle, bone mass, and growth of body hair in potency. In women, it is secreted by the ovaries, adrenal glands, as well as through the peripheral conversion of dehydroepiandrosterone and androstenedione, the weak adrenal androgens. Only about 10% of men's testosterone, which is secreted nearly exclusively by the testes, is normally present in women's serum(Leje *et al*., 2924).

Additionally, to its role as a common hormone, testosterone is used as a medication in the treatment of low testosterone levels in men and breast cancer in women. Since testosterone levels decline with age, it is occasionally used in older men to counteract this insufficiency. It is also abused in enhancing physique and performance in athletes and many others. The use of testosterone as a supplement, both in low and high doses, has been known to lead to prostate hyperplasia.

Benign prostatic hyperplasia (BPH) is a noncancerous increase in size of the prostate, it is the most common cause of lower urinary tract symptoms (LUTS), which includes involuntary urination, urge incontinence, urinary hesitancy, intermittency, involuntary interruption of voiding, weak urinary stream, and post-micturition dribbling, these symptoms may be accompanied by pain while urinating, dysuria (Jin *et al.,*2021). Risk factors include a family history, obesity, type 2 diabetes, lack of exercise, and erectile dysfunction. Treatment options including lifestyle changes, medications, a number of procedures and surgery, patients with mild symptoms weight loss, exercise, and decreasing caffeine intake is recommended, while patients with more significant symptoms, medications may include alpha blockers such as terazosin or 5α-reductase inhibitors such as finasteride (Zheng *et al.*, 2024). Surgical removal of part of the prostate may be carried out in those who do not improve with other measures.

According to age, the prevalence of BPH in men worldwide was recorded, it said to be present in about 50% of those in the age range of 51 to 60, 70% in the range of 61 to 70 years, and 90% in the range of 81 to 90 years (Lim, 2017). Current conventional treatment regimens for both BPH and its related cancer have produced very adverse effects **(**Ng *et al*., 2024). Apart from being expensive, causing urinary incontinence and erectile dysfunction, some of the adverse effects of conventional therapy include toxicity and growth inhibition to normal cells (Mbiantcha *et al*., 2018).

The search for alternative therapy for the treatment of benign prostatic hyperplasia has lead use of natural Products, which are easy to assess, cheap, and affordable.

Annona muricata is one of the natural products used traditionally for the treatment of benign prostatic hyperplasia. Because of its somewhat acidic flavor when ripe, the edible fruit of this species of the genus Annona, which belongs to the Annonaceae family of custard apple trees, is known as soursop. Annona muricata can be found in Latin America, the Caribbean, Africa, Southeast Asia, and the Pacific. soursop and its derivative products are ingested across the world. It is a modest upright evergreen tree that can grow to about 9.1 m tall, Its juvenile limbs are fuzzy, its foliage is elongated to elliptical, about 8 cm to 16 cm long and 3 cm to 7 cm wide.

The flesh of the fruit consists of an edible, white pulp, some fiber, and a core of indigestible black seeds. The pulp is also used to make fruit nectar, smoothies, fruit juice drinks, as well

as candies, sorbets, and ice cream flavorings. The fruit contains significant amounts of phytochemicals such as vitamin C, vitamin B1 and vitamin B2. The leaves of *Annona muricata* contain annonamine, which is an aporphine-class alkaloid featuring a quaternary ammonium group (Mutakin *et al.,*2022).

MATERIALS AND METHODS

The study design was an experimental study where testosterone was injected intramuscularly into the Wistar rat and extracts of *Annona muricata* were obtained, and induced orally.

Ethical Approval

This was obtained from the ethical committee of the Faculty of Basic Medical Sciences, College of Health Sciences, Osun State University.

Chemicals and Extract

Testosterone was purchased from Akol Pharmaceutical Company, Oshogbo. *Annona muricata* was purchased in a local store in Igbona market, Oshogbo, Osun State, Nigeria. The plant was identified and authenticated at the Department of Plant Biology, Osun State University, Osogbo.

The *Annona muricata* was extracted in the laboratory in Osun State University. The *Annona muricata* fruit was first washed, peeled with hands, and then cut into tiny pieces. Liquidized into the soursop fruit extract (SFE) using Mammonlex juice extractor; model; JD 1004. The SFE (or juice) was stored in glass bottles and preserved in a refrigerator at 2-4 ºC until used for experiment (Rho *et al*., 2019).

Animal Treatments

7 weeks old male rats (*Rattus novergicus*), weighed about (130-170) g at the beginning of the experiments were used. The rats were procured from the animal holdings of Osun State University, Osogbo. These animals were allowed to acclimatized for one week to their new environment (animal house of the Osun state university, Osogbo) before the commencement of experimental work. The animals were kept in plastic cages with controlled humidity, wood shavings for bedding, and a 12-hour light-dark cycle. They were also provided with food and water.

Twenty(20) male Wistar rats were randomly grouped into four groups, 5 animals per group. Group A used as control were given 0.5 ml normal saline (NS) 6 weeks, Group B were administered a single dose of 15mg/kg testosterone daily and treated with Soursop fruit extract (TEST + AME) 6 weeks, Group C were administered a single dose of 15mg/kg testosterone daily + extract (TEST + AME) for 4 weeks then withdrawn to recover for two weeks, Group D were administered 15mg/kg testosterone only (TEST) daily for 6 weeks as used by Ojewole *et al.* (2021)

Animal Slaughter and Samples Collection

The animals were slaughtered on the sixtieth (43rd day) week after the administration of both testosterone and *Annona muricata*, being anaesthetized with 0.5ml/kg of ketamine hydrochloride and fixed by transcardial perfusion method using 4% paraformaldehyde as fixative agent, the prostate and the testis was excised, weighed on a weighing balance and then fixed in Bouin's fluid for histological analysis, blood samples were immediately using collected 5 ml syringes from the apex of the heart and the blood samples were placed in heparinized bottles, centrifuged at 3,000 rpm for 15 minutes to collect the blood plasma.

Determination of the weight of each organ

At sacrifice, the weight of the testes and prostate were determined using a top loader sensitive balance (Metler Toledo, Germany). To deduce the individual body weight differences, the relative weight (%) was calculated from the body weight at sacrifice and the absolute weight of each organ as follows;

Body weight at sacrifice $=\frac{body\ weight}{organ\ weight}$ x100

Morphological observations (body weight)

The animals' body weights were recorded on the first day of acclimatization, every week of administration and on the day of sacrifice, and the final day of sacrifice. The difference between the animal's starting and ending weights was used to calculate the weight gain.

Histological examination

Routine histological processing using hematoxylin and eosin dyeing method was carried out. The testes were preserved in Bouin's fluid, dried in increasing levels of alcohol, cleared in xylene, and infiltrated in molten paraffin wax before finally inserted in molten paraffin wax to form block. The paraffin block containing the material was then sliced by the rotary microtome at 4µm thickness. The sections were then floated in liquid basin at 40°C and moved to a transparent plate and stained with hematoxylin and eosin stains. The slides were then viewed under light microscope at × 100 and × 400 magnification and photomicrographs were taken in at both magnifications.

Statistical Analysis

All data are presented as the mean ± standard error of the mean (SEM). Statistical significance was determined using analysis of variance (ANOVA) followed by a multiple comparison procedure and a Dunnett post hoc test. Differences in P values <0.05 or <0.01 were considered statistically significant

RESULTS AND DISCUSSION

Group A (Normal control) Weight remained relatively stable throughout the six weeks. Initial weight was approximately 150 grams. Slight fluctuations observed, but no significant changes noted. Group B (Testosterone + Soursop) Initial weight was around 160 grams. A gradual increase in weight was observed over the six weeks. By week six, the weight had increased to approximately 180 grams. Group C (Testosterone +soursop recovery): Initial weight was the highest among all groups, starting at about 170 grams. A significant increase in weight was observed, peaking at around 220 grams by week three. After week three, the weight slightly decreased but remained higher than the initial weight. Group D(Testosterone only) Initial weight was similar to Group A, starting at approximately 150 grams. A gradual increase in weight was observed, similar to Group B. By week six, the weight had increased to about 170 grams.

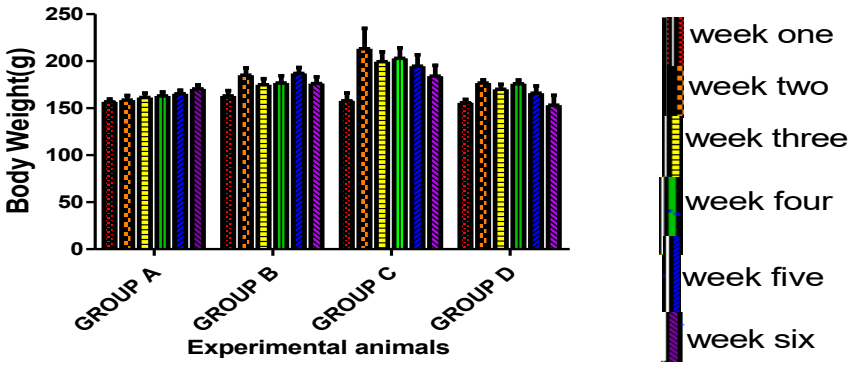

Figure 1: Chart showing body weight changes across the groups over six weeks

Testis Organ Weight

Group A (Control): Displays moderate testicular weight, representing physiological baseline. Statistically significant (*p < 0.05) higher weight than Group B (testosterone + AME). Group B (Testosterone + Soursop) Shows lowest testicular weight. Indicates marked testicular atrophy, likely due to combined suppressive effect of testosterone and AME. Significantly different from both control (*p < 0.05) and testosterone-only group (**p < 0.01). Group C (Testosterone + Soursop Recovery): Displays a partial restoration of testicular weight compared to Group B. Suggests reversibility of testicular atrophy post-Soursop treatment. Still significantly lower than Group D (**p < 0.01), indicating incomplete recovery. Group D (Testosterone only) Exhibits the highest testicular weight among all groups. Reflects androgen-induced hypertrophy or retention of testicular mass. Statistically significant compared to Group B and Group C.

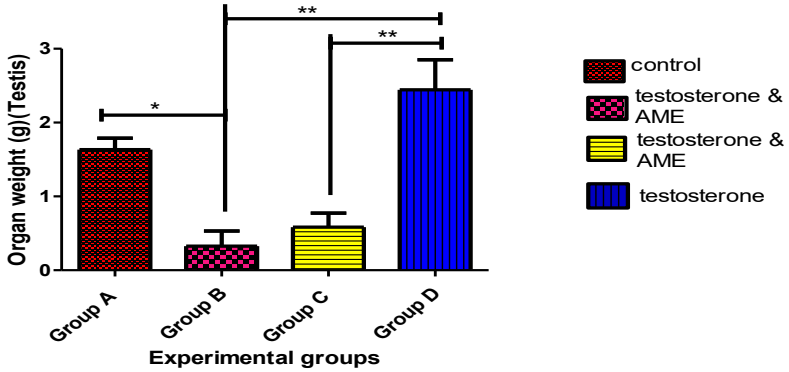

Figure 2: Chart showing prostate organ weight differences across the groups

Report on Prostate Organ Weight Across Experimental Groups

Group A (Control) Moderate prostate weight. Serves as the baseline for comparison. Significantly different from all other groups (*p < 0.05 to ***p < 0.001) Group B (Testosterone + Soursop). Lowest prostate weight among all groups. Suggests a suppressive or atrophic effect of AME when co-administered with testosterone. Statistically significant reduction compared to control (**p < 0.01) and Group D (***p < 0.001). Group C (Testosterone + Soursop Recovery). Slight increase in prostate weight compared to Group B. Indicates partial recovery post-treatment cessation. Still significantly lower than control and testosterone-only group. Group D (Testosterone only). Highest prostate weight observed. Indicates androgen-induced prostate hypertrophy. Highly significant difference from all other groups (*p < 0.05 to ***p < 0.001)

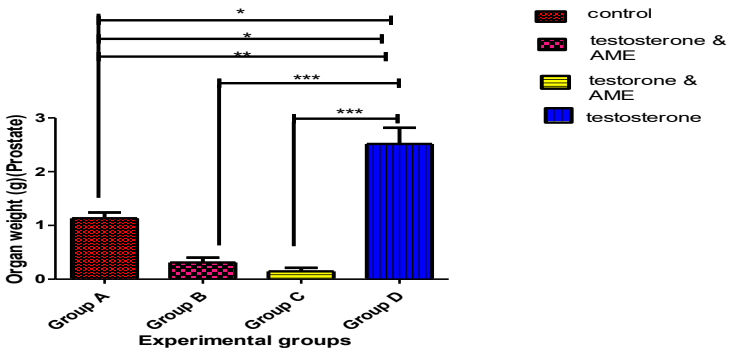

Figure 3: Prostate organ weight differences across the groups

Histology of the Prostate (H&E)

Group A(normal control) Multiple prostatic acini with well-developed connective tissue cores (CA). Lamina propria (LP) appears vascular and supportive. Smooth muscle bundles (M) are visible, typical of the prostate's fibromuscular stroma. Group B **(**testosterone + AME) Highly folded glandular epithelium (E), indicating active secretory or proliferative state. Prominent connective core (CA), supporting epithelial projections. Lamina propria (LP) seen with some stromal expansion. Group C (Testosterone + Soursop) Recovery Complex glandular infoldings with abundant epithelial lining (E). Thick lamina propria (LP) and connective axis (CA), supporting the glandular architecture. Group D **(**Testosterone only) Moderately folded epithelial layer (E) with well-developed connective tissue axis (CA). Lamina propria (LP) shows prominent stromal features.

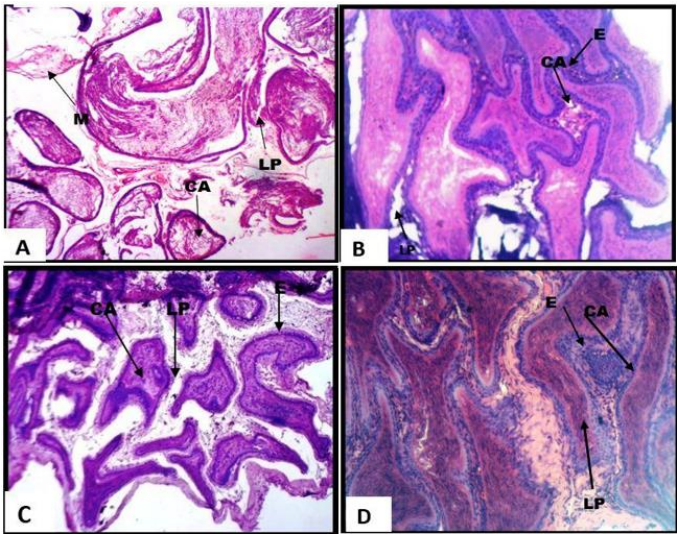

Plate 1: Photomicrograph of histomorphological presentation of the prostate gland across the groups (H& E X 100) M=Smooth muscle bundles CA=Connective tissue axis LP=Lamina propria E=Epithelial layer

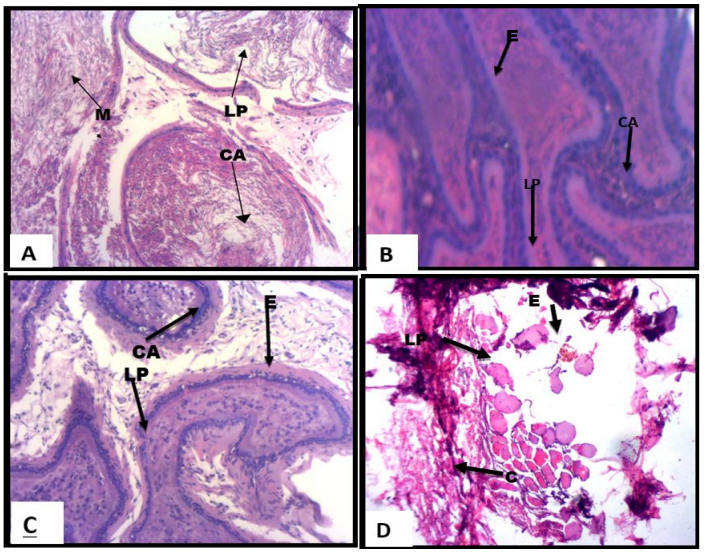

Plate 2: Photomicrograph of histomorphological presentation of the prostate gland across the groups (H& E x400) M=Smooth muscle bundles CA=Connective tissue axis LP=Lamina propria E=Epithelial layer

Histology of the testis (H&E)

Group A (Control) The seminiferous epithelium is tall, densely populated with layers of spermatogenic cells at various stages (spermatogonia, spermatocytes, spermatids). The basement membrane is well defined and intact. Sertoli cells present and supporting spermatogenesis. Spermatogonia is clearly located at the basal lamina. Interstitial cells Leydig cells visible between tubules, indicating androgen production. This panel shows normal active spermatogenesis, typical of a healthy testis. Group B (Testosterone + Soursop) Seminiferous tubules are more dilated lumens and densely packed germinal epithelium. Leydig cells is prominent in interstitial spaces — suggestive of hormonal stimulation. Spermatogenic Activity appears hyperactive with more defined layers and abundant spermatozoa. There are signs of increased spermatogenesis, possibly testosterone-induced testicular stimulation. Group C (Testosterone + Soursop) Tubular structure appears disorganized; seminiferous tubules

show reduced germinal epithelium. Red Circled Area indicates vacuolation or degenerative changes. Connective Tissue may appear more prominent due to germ cell loss. Therefore, there is evident testicular degeneration or suppressed spermatogenesis, likely due to toxic or inhibitory effects of treatment. Group D (Testosterone) The seminiferous tubules is partially restored architecture. Red Circle: Still indicates some localized degeneration or incomplete recovery. Spermatogonia (SG): Detected, indicating renewed spermatogenic activity. Partial histological recovery of testicular architecture post-treatment — regeneration is evident but not fully complete.

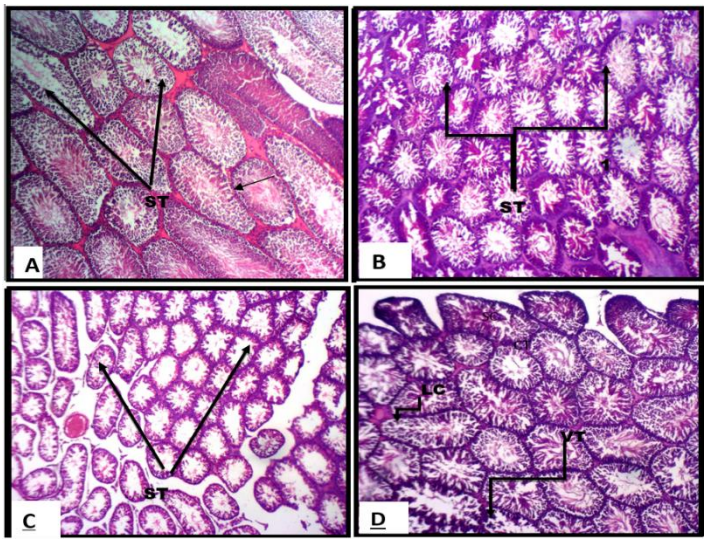

Plate 3: Photomicrographs of the testicular Histomorphology of male Wistar rats (H& E x100). SC=Sertoli cells BM=Basement membrane L=Lumen CT=Connective tissue SG=Spermatogonia

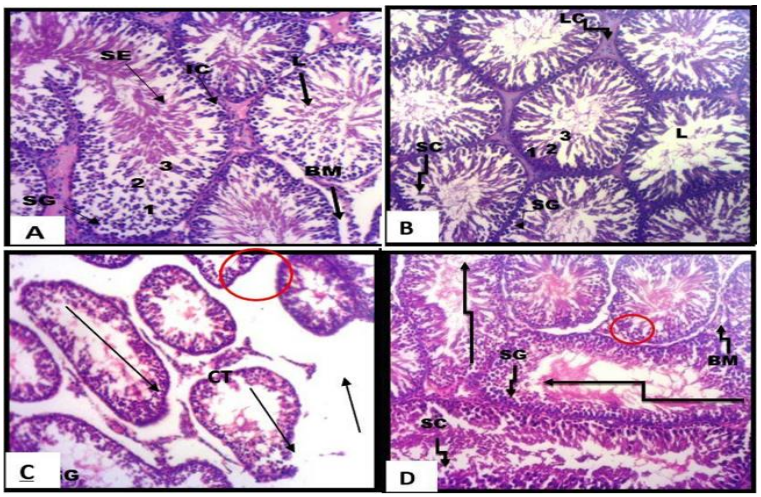

Plate 4: Photomicrographs of the testicular Histomorphology of male Wistar rats (H& E x100 & x400). SC=Sertoli cell BM=Basement membrane L=Lumen CT=Connective tissue SG=Spermatogonia

Discussion

This study investigated the effects of testosterone and *Annona muricata* extract (Soursop) on body weight, relative organ weights (testes and prostate), and histological architecture of reproductive tissues in male subjects across four experimental groups. The findings demonstrate significant physiological and morphological alterations in response to these treatments, with clear distinctions among the control, co-treatment, and recovery groups (Leje., 2024) (Ezirim., 2024).

Normal Control maintained relatively stable body weights throughout the six-week period, consistent with normal physiological regulation and metabolic homeostasis. In contrast, Groups B and D, which received testosterone with or without Soursop, showed a gradual increase in body weight, aligning with testosterone's known anabolic effects that promote muscle and tissue growth. Interestingly, Group C (Testosterone + Soursop Recovery) exhibited the highest initial weight and a rapid gain peaking at week three, followed by a slight reduction, suggesting a possible initial over-compensatory response or fluid retention phase that later normalized during recovery.(Geary., 2019).

Marked differences in testicular weights across the groups were evident. Group A served as the physiological baseline. Testosterone treated with soursop showed the lowest testicular weight, indicating pronounced atrophy. This supports previous literature that highlights the suppressive effects of both exogenous testosterone and phytochemical agents like soursop on the hypothalamic–pituitary–gonadal axis, leading to reduced endogenous testosterone production and testicular shrinkage. Testosterone only, however, had the

highest testicular weight, potentially reflecting androgen-induced hypertrophy or retention of testicular mass. Recovery group demonstrated partial restoration of testicular weight, suggesting that the testicular atrophy caused by co-treatment is at least partially reversible upon cessation of soursop(Muller., 2018).

A similar trend was observed in prostate weights. The control group presented moderate weight, serving as the baseline. The lowest prostate weight was observed in group administered with testosterone and Soursop strongly suggesting that Soursop exerts an inhibitory or atrophic effect on the prostate, possibly through anti-androgenic or antioxidant mechanisms. Recovery group demonstrated a partial recovery in prostate weight post- Soursop withdrawal, indicating the potential reversibility of Soursop -induced changes. Group D again showed the highest prostate weight, reinforcing the hypertrophic influence of testosterone on androgen-sensitive tissues such as the prostate(Kohestani., 2020).

The histological findings further validate the morphometric data. On the Prostate, group A showed typical architecture with well-developed connective tissue and smooth muscle bundles. Group B presented highly folded glandular epithelium and expanded lamina propria, suggesting hyperplasia or heightened secretory activity, possibly induced by testosterone, although Soursop seems to modulate this activity. Recovery group displayed partial restoration with complex glandular infoldings and thick supporting structures, while the group given testosterone only retained moderately folded epithelium, indicative of ongoing androgen influence(Ng., 2024). On the Testis, the baseline displayed classic features of active spermatogenesis with intact seminiferous tubules, spermatogenic layers, and Leydig cell presence. Hyperplasia treated with Soursop, surprisingly, showed increased spermatogenic activity and densely packed tubules, likely due to testosterone stimulation, although the long-term health of these structures remains questionable. Conversely, the Recovery group exhibited tubular disorganization, vacuolation, and germ cell loss, underscoring the testicular damage from Soursop. The group given testosterone only showed signs of architectural recovery, with spermatogonia present and localized degeneration—suggestive of partial but incomplete testicular restoration post-treatment(Adamczewska., 2024)..

CONCLUSION

Overall, this study underscores the regenerative role of Soursop when co-administered with testosterone: while it exhibits suppressive effects on reproductive organ weight and structure, indicative of toxicity or endocrine disruption, it also permits partial recovery upon cessation. Testosterone alone exerts hypertrophic/hyperplasia effects on both the testes and prostate but may also induce overstimulation and possible tissue remodeling.

These findings suggest that while Soursop may hold therapeutic potential, particularly as an anti-androgenic agent, its co-administration with exogenous testosterone could compromise reproductive health. Recovery post-treatment highlights a degree of reversibility, but further studies are warranted to determine the long-term implications and safe dosage thresholds for Soursop in reproductive contexts.

RECOMMENDATION

Further research should be carried out on the anti-inflammatory properties of Soursop to ascertain the effect on the prostate and other organs.

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