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DETERMINATION OF EFFECTIVE DOSE OF TESTOSTERONE PROPIONATE FOR THE INDUCTION OF BENIGN PROSTATIC HYPERPLASIA IN WISTAR RATS

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ABSTRACT

Benign prostatic hyperplasia (BPH) refers to the nonmalignant growth or hyperplasia of prostate tissue and is a common cause of lower urinary symptoms (LUTS) in older men. The incidence of the condition and clinical burden has inspired the search for intervention strategies and deepened the study for better understanding of the disease etiology, epidemiology, pathophysiology and possible cure. Thirty-five Wistar rats were randomly divided into seven groups (n=5). Group 1 received normal rat chow and water ad libitum, and served as the normal control. Groups 2 and 3 received 3 mg/kg b.wt of TP for 11 days and 22 days respectively. Groups 4 and 5 received 6 mg/kg b.wt of TP for 11 days and 22 days respectively. Groups 6 and 7 received 9 mg/kg b.wt of TP for 11 days and 22 days respectively. Following euthanasia, blood was collected and serum decanted for biochemical assay. The prostate gland was harvested and prepared for histological study. The serum testosterone level increased significantly ($p<0.05$) from 3.67±0.81 ng/ml in group 1(normal control) to 6.67±1.16 ng/ml, 9.80±2.47 ng/ml and 8.20±2.14 ng/ml respectively for groups treated with 3 mg/kg b.wt, 6 mg/kg b.wt and 9 mg/kg b.wt of TP for 22days. PSA concentration was also significantly elevated in the TP treated groups. Histological sections showed alterations in the histoarchitecture of the prostate gland treated with TP, particularly at doses of 6 mg/kg b.wt and 9 mg/kg b.wt. TP treatment led to increase in prostate index. The biochemical changes and the typical adenosis seen in the histomorphology of the test groups proves that TP synthetically induces BPH. Duration above 10 days and up to 22 days show lasting BPH signs in experimental model. Doses of up to 9 mg/kg b.wt of TP should not be used for experimental purposes owing to the severe physical changes observed in the group treated with 9 mg/kg b.wt of TP for 22 days.

INTRODUCTION

Benign prostatic hyperplasia (BPH) refers to the nonmalignant growth or hyperplasia of prostate tissue and is a common cause of lower urinary symptom (LUTS) in older men. Disease prevalence has been shown to increase with advancing age. Cumulated evidence shows that histological prevalence of BPH at autopsy is as high as 50% to 60% for males in their 60s, while older men in their 70s and above have a prevalence rate of 80% to 90%. (Roehrborn, 2005). BPH involves increases in the number of both stromal and epithelial cells in the transitional zone of the prostate. Conditions associated and leading up to BPH

include bladder outlet obstruction (BOO), lower urinary tract symptoms (LUTS), benign prostatic enlargement (BPE), and benign prostatic obstruction (BPO) (Abrams, 1994). Whereas benign prostatic enlargement refers to increase in size of the gland, BOO describes blockage to urinary flow whereas BPH is best described by histological changes (Abrams, 1999; Silvermann, 2004). LUTS manifests in various clinical presentations including urgency, frequency, dysuria, incontinence and suprapubic pain (Abdelmoteleb et al., 2020; Common, 2016). BPH and its correlative symptoms, LUTS greatly reduces patients' quality of life (QoL). The incidence of the condition and clinical burden has inspired the search for intervention techniques and deepened the study for better understanding of the disease etiology, epidemiology, pathophysiology and possible cure.

In a bid to understand the mechanistic process of BPH and treatment options, animal models are employed. For efficacy of induction, various animal models are employed, particularly the use of Wistar rats. The role of androgens in the maintenance of prostate disease is well established. BPH being an age-related disease requires the participation of mTOR which is involved in cellular senescence (Choi et al., 2000; Blagosklonny, 2014). There are two main methods widely engaged in BPH induction. Testosterone and prolactin stimulate development of BPH (Sluczanowska-Glabowska et al., 2010). In testosterone-induced model, administration of testosterone causes hyperplasia in ventral lobes of the rat prostate, analogous to morphological changes in human BPH (Rick et al., 2013). In sulpiride-induction model, sulpiride stimulates prolactin production by the pituitary gland, thus causing hyperplasia in the lateral and dorsal prostate lobes. Testicular androgens are essential to develop BPH as dihydrotestosterone (DHT) promotes tissue growth and cellular proliferation by interacting directly with prostatic epithelium and stroma (Roehrborn, 2008; Foster, 2000). Testosterone is converted to DHT by 5-alpha-reductase 2 in prostatic stromal cells and accounts for 90% of total intraprostatic androgens (Uckert et al., 2020). DHT directly influences prostatic stromal and adjacent cells, which affect cellular proliferation and apoptosis (Banerjee et al., 2018). Exogenous supply of androgen as TP sustains and promotes the proliferation and apoptotic process

Various researchers have reported using various doses of testosterone propionate (TP) in modelled BPH studies. Liu et al., (2023) reported using a dose of 7.5 mg/kg b.wt of TP given to 7 weeks old male mice to induce BPH. In a similar study, 60 mice were randomly divided into six groups, and the experimental groups were daily subcutaneously injected with 7.5 mg/kg b.wt of TP for 14 days. (Huang et al., 2017). Some other studies have equally reported 7.5 mg/kg/d subcutaneous injection with TP to induce BPH. (Solanki et al., 2021; Zou et al., 2017). However, there are studies that have stated different doses of TP for experimental BPH. Lim et al., (2018) in their study used 3 mg/kg b.wt of TP for 28 days. In BPH dog model, the animals were subcutaneously injected with testosterone propionate (TP) at a dose of 10 mg/kg/day for 8 weeks for BPH induction. (Li et al., 2018). Obisike et al., (2019) asserted that there has been controversy over the specific dose of TP that can synthetically induce BPH and for how long the biochemical, clinical and histological manifestation can last.

MATERIALS AND METHODS

Experimental Animals

Thirty-five (35) male Wistar rats which were 9 weeks old and weighing between 180-200 g were procured for this study. The rats were purchased from the animal house, Faculty of Basic Medical Sciences, University of Port Harcourt. The animals were acclimatized for two weeks. The laboratory conditions were maintained, temperature- 25°C, relative humidity- 35-60 %, 12 hr light dark cycle. Rats were allowed rat chow and drinking water *ad libitum***.**

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Drugs and Chemicals

Testosterone propionate injection (25mg/1ml) was purchased from Laborate Pharmaceuticals India Ltd (Industrial, Area, Paints Salub, India). ATC CODE: GO3BAO3. NAFDAC Ref No: A4-3348

Experimental Design

After the acclimatization period, the rats were randomly placed in 7 groups with 5 rats per group. Apart from group 1 which served as the normal control, every other group was subcutaneously injected with different doses of testosterone (TP) and for varying durations. The protocol for the groups was as follows:

Group 1: Normal Control – Normal rat chow and water *ad libitum.*

Group 2: 3 mg/kg b.wt of TP for 11 days

Group 3: 3 mg/kg b.wt of TP for 22 days

Group 4: 6 mg/kg b.wt of TP for 11 days

Group 5: 6 mg/kg b.wt of TP for 22 days

Group 6: 9 mg/kg b.wt of TP for 11 days

Group 7: 9 mg/kg b.wt of TP for 22 days.

The weights of the rats were taken before the experimental procedure, and the weights of the rats and prostate tissues were taken at sacrifice.

Calculation of Prostatic Index

Prostate Index was calculated using the formula below:

$$\text{Prostate Index} = \frac{\text{Prostate Weight (PW) in g}}{\text{Body Weight (BW) in g}}$$

Sample Collection

At the end of treatments, the animals were anaesthetized with chloroform and blood samples collected through cardiac dislocation into plain tubes for the determination of biochemical parameters.

Biochemical Assays

Testosterone concentration was determined by competitive enzyme immunoassay method using AccuBind ELISA kits (manufactured by Monobind Inc, Lake Forest, CA 92630 USA), adopting the method of Chen et al., (1991). The evaluation of the concentration of follicle stimulating hormone (FSH) and the level of luteinizing hormone was carried out according to the method of Uotila et al., (1981) and Beastall et al., (1987) respectively.

Determination of Prostate Specific Antigen

The PSA concentration in serum was determined according to the method described by Adhyam and Cupta (2012). The ELISA kit uses the sandwich – ELISA principle. The micro ELISA plate in the kit has been precoated with an antibody to PSA. 25 µl of standard and samples were pipetted into the assigned wells. 100 µl of tPSA enzyme reagent was added to each well. The microplate was swirled gently for 30 seconds to mix and incubated for 30 minutes at room temperature. The contents were discarded by decantation, 350 µl of the wash buffer added. Sequel to this the stop solution was added and mixed gently for 20 seconds. Absorbance was read at 450 nm using a microplate reader (Biotek ELx 800 UV Absorbance Microplate Reader, ON, Canada).

Histology

The prostate glands were fixed in 10% neutral-buffered formalin, then dehydrated in increasing concentrations of ethanol, washed with xylene, and finally embedded in paraffin. The blocks bearing tissues were stained with haematoxylin and eosin in thin section. The stained slides were captured at 100x magnifications using light microscope, and the resulting histomicrograph was evaluated for alterations in histoarchitectural structure.

Statistical Analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS), window version 23.0 USA, and expressed as Mean $\pm$ standard Error of Mean (SEM). One way ANOVA followed by Post Hoc Tukey test was performed to evaluate differences among multiple groups and $p < 0.05$ was considered statistically significant.

RESULTS

Effect of TP Treatment on Physical Parameters

The effect of TP on physical parameters such as weight gain or loss, frequency of micturition, fur discoloration or loss, loss or gain to appetite, mortality as well as other parameters were observed. (Table 1). For the 22 days treatment with 9 mg/kg b.wt dose, fur discoloration and loss as well as diarrheic stool was observed.

Table 1: Effect of TP Treatment on Physical Parameters of Rats for Determination of Effective Dose for BPH Induction

S/No	Parameter	Grp 1	Grp 2	Grp 3	Grp 4	Grp 5	Grp 6	Grp7
1	Weight gain	-	-	+	+	+	+	+
2	Frequent micturition	-	-	+	+	+	+	+
3	Fur Discoloration & loss	-	-	-	-	-	-	+
4	Loss of Appetite	-	-	-	+	+	+	+
5	Diarrheic stool	-	-	-	-	-	+	+
6	Mortality	-	-	-	-	-	-	-

+ = Sign observed/present

- =Sign not observed/ absent

Hormonal Profile in the serum of TP Treated Rats

There was a significant ($p< 0.05$) increase in serum testosterone level of TP treated rats, compared to the normal control. However, there was an observed decrease in the levels of Luteinizing hormone (LH) and follicle stimulating hormone (FSH) for the TP treated rats when compared to the normal control ($p< 0.05$).

Prostate Specific Antigen (PSA) Level in the serum of Rats Treated with TP

The concentration of PSA was assessed in the serum as shown in Figure 2. The level of PSA for TP treated groups were significantly ($p< 0.05$) elevated when compared to the normal control. The PSA level of group 2 was elevated 10 folds (1000 %) when compared to the normal control.

Weight of Testis, Prostate, and Prostate Index of Rats Treated with TP

Results on the effect of TP on weights of testis, prostate and prostate index are shown in Figure 3. TP treatment significantly ($p< 0.05$) reduced the weight of the testis while significantly ($p<0.05$) increasing the weight of the prostate and prostate index when compared to the normal control.

Histoarchitectural Alteration

As represented in Plates 1-7, rats treated with TP showed histoarchitectural alterations. The group treated with TP for a longer period showed adenosis or atypical adenomatous hyperplasia of the prostate gland. However, the normal control shows normal prostate with secretory epithelium with more cuboidal cells, lumen is also indicated.

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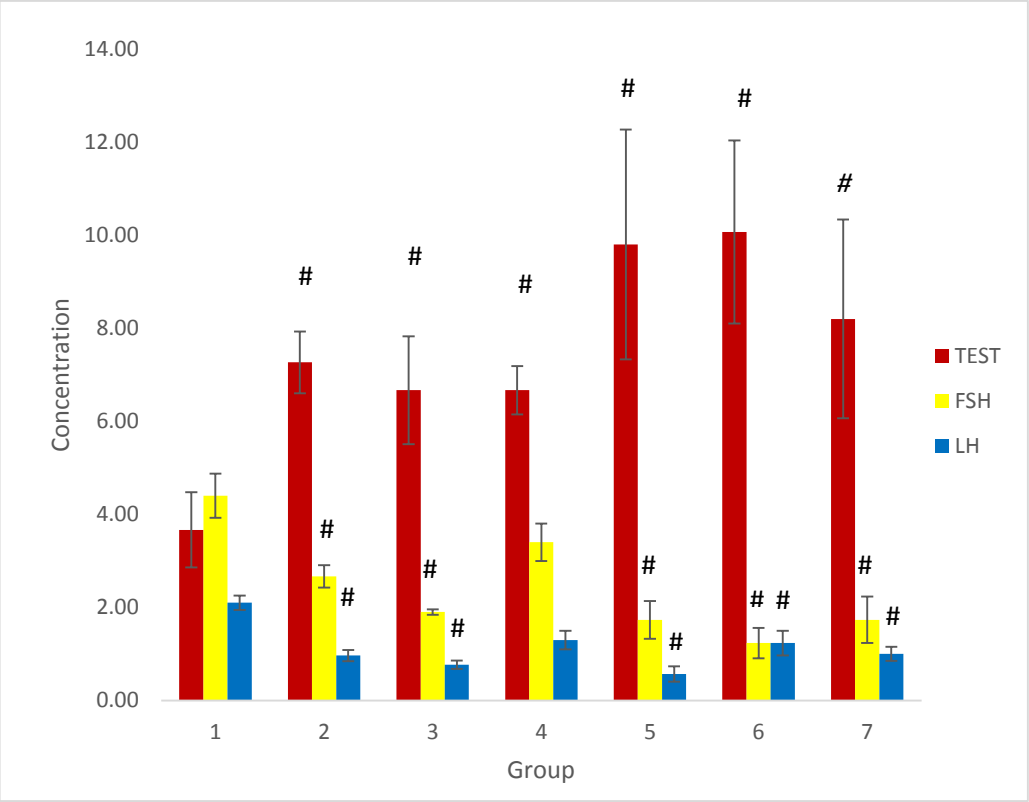

Fig. 1: Hormonal Profile of TP treated rats. All values are expressed as mean ± SEM, (n=5). #(p<0.05) differed significantly when compared to the normal control.

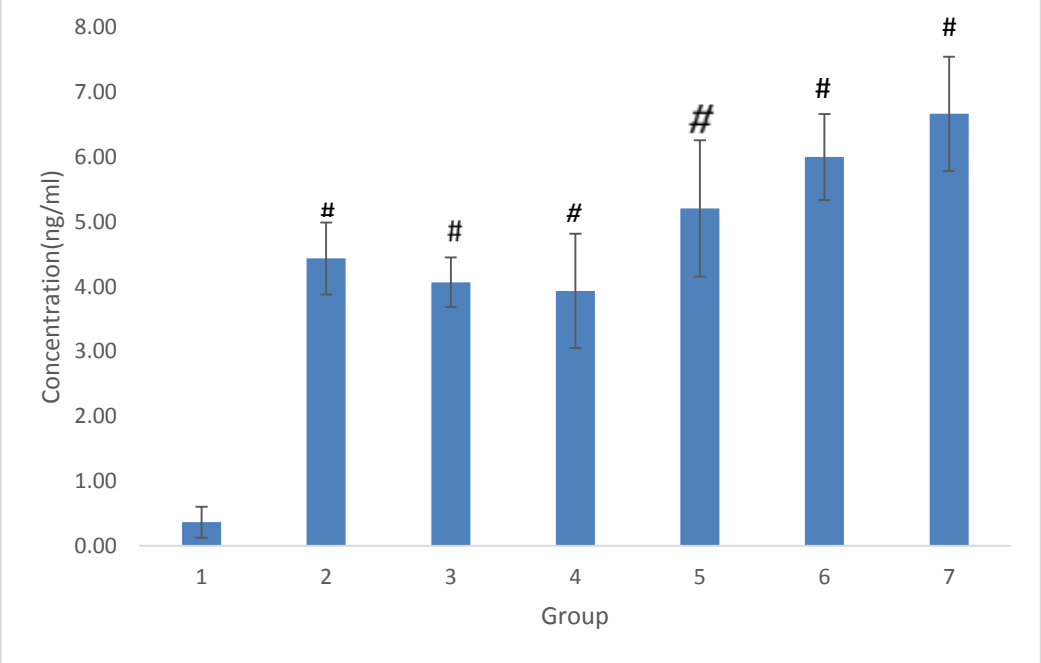

Fig. 2: Prostate Specific antigen (PSA) Level of TP treated rats. All values are expressed as Mean ± SEM, (n = 5). #(p<0.05) differed significantly when compared to the normal control.

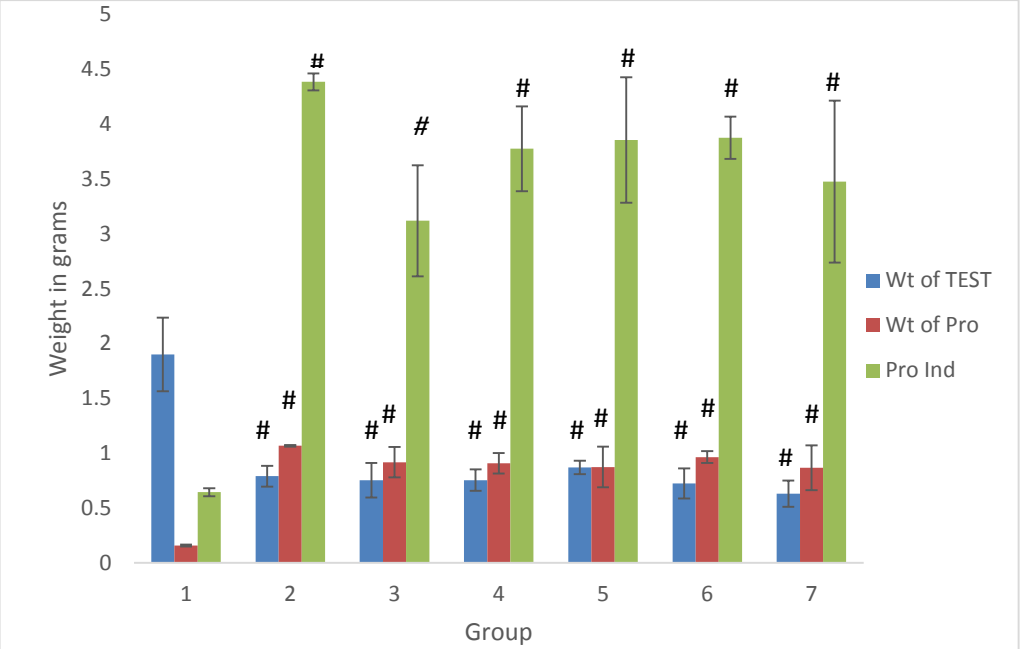

Fig. 3: Weight of Testis, Prostate and Prostatic Index of TP treated rats. All values are expressed as mean ± SEM, (n=5). #(p<0.05) differed significantly when compared to the normal control.

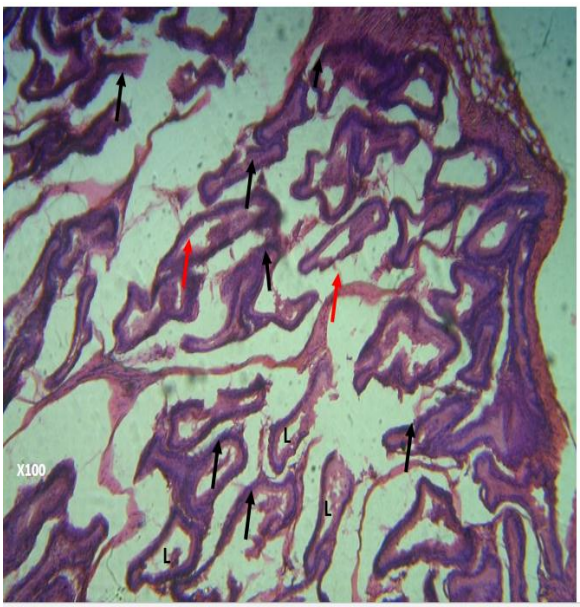

Plate 1: Photomicrograph of Prostate of Normal control. Shows normal architecture with secretory epithelium. There is presence of cuboidal cells (black arrow)

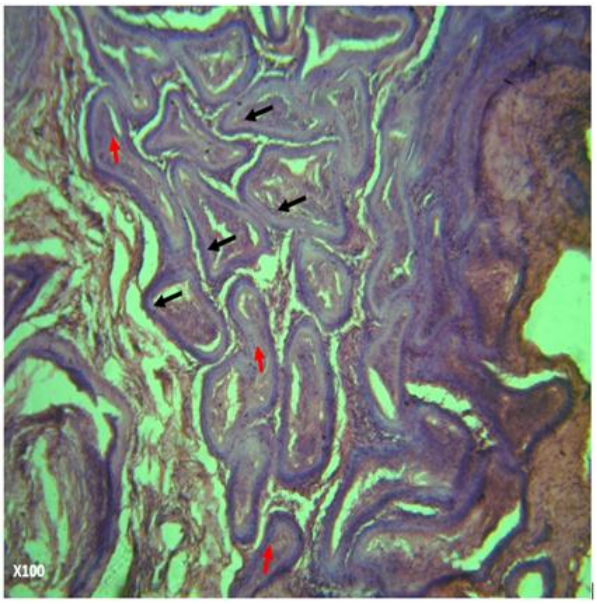

Plate 2: Photomicrograph of rat treated with 3 mg/kg b.wt TP for 11 days. Prostate is normal with cuboidal-columnar secretory epithelium. The lumen of some of the tubuloalveolar gland contains corpora amylacea

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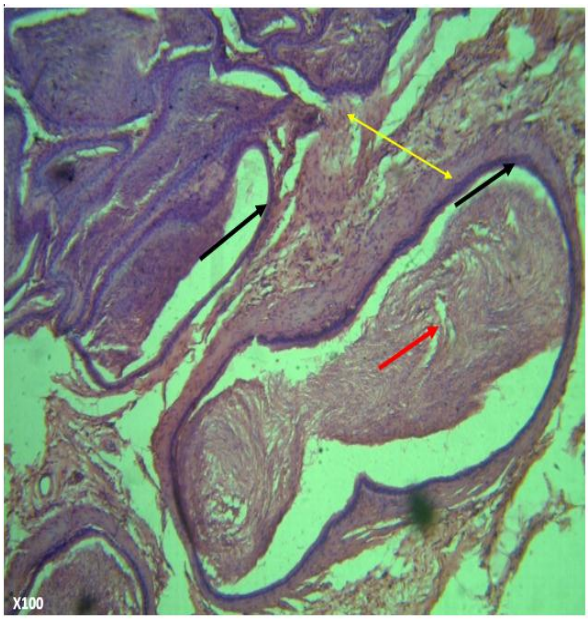

Plate 3: Photomicrograph of rat treated 3 mg/kg TP for 22 days. There is slight architectural distortion. Prostate shows cuboidal columnar secretory epithelium. Tubuloalveolar gland contains corpora amylacea

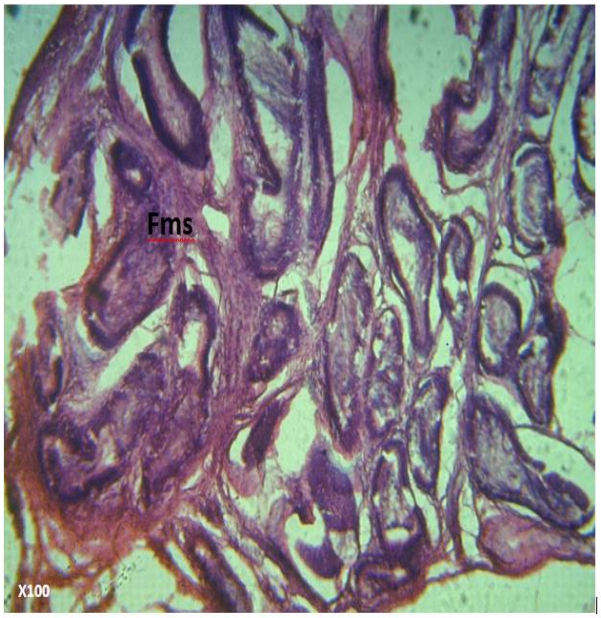

Plate 4: Photomicrograph of rat treated with 6 mg/kg b.wt TP for 11 days. Prostate has increased fibromuscular mass with slight distortion of the histoarchitecture.

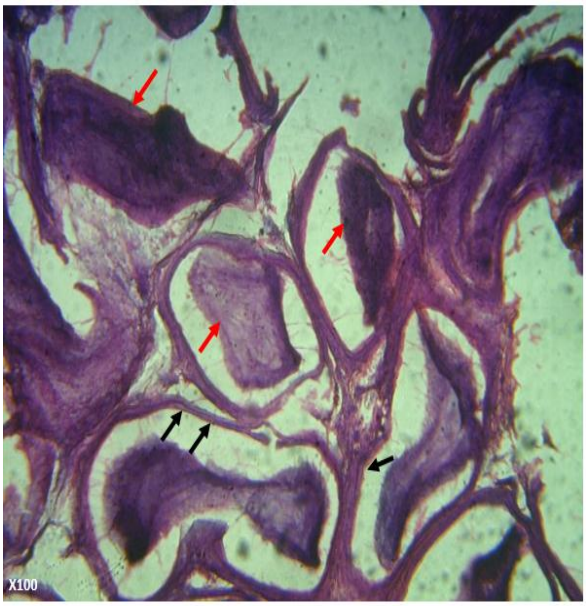

Plate 5: Photomicrograph of rat treated with 6 mg/kg TP for 22 days. Prostate has acini with cystic atrophy appearance indicated by low secretory epithelium (black arrow)

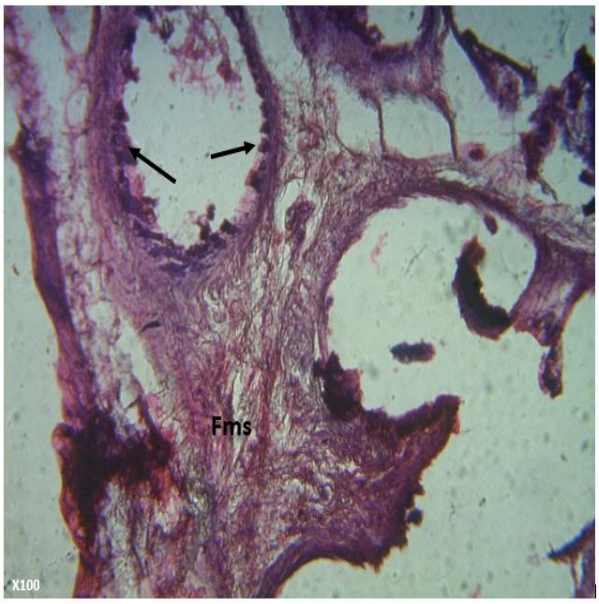

Plate 6: Photomicrograph of rat treated with 9 mg/kg b.wt TP for 11 days. There is hyperplasia of the secretory epithelium with mild disruption (black arrow)

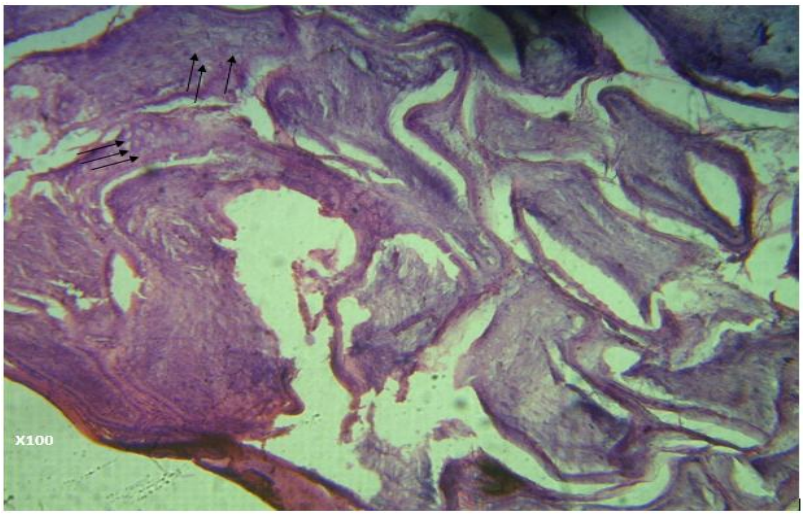

Plate 7: Photomicrograph of rat treated with 9 mg/kg b.wt TP for 22 days. There is adenosis or atypical adenomatous hyperplasia of the prostate gland and reduction in the secretory epithelium

DISCUSSION

Benign prostatic hyperplasia is a multifocal, non-malignant, hyperplastic and progressive histopathological change in stromal and epithelial cells in the transitional zone of the prostate, resulting in discrete prostatic nodules, inflammation, fibrosis and changes in smooth muscle activity which can cause partial or complete obstruction of the urethra (McVary et al., 2011). Awedew et al., (2022) reported that globally, there were 94.0 million prevalent cases of BPH in 2019, compared with 51.1 million cases in 2000. The age-standardized prevalence of benign prostatic hyperplasia has been placed at 2480 per 100,000 people. The global number of prevalent cases increased by 70.5% between 2000 and 2019. This rising statistic is worrisome, hence the various research, studies and investigation into the etiology and progression of the disease. Although BPH may be non-malignant, it greatly reduces and diminishes the quality of life (QoL) of the sufferers. In order to gain better understanding of this urological disease, many controlled studies are initiated by artificially reproducing a human-like condition of the disease in animal models. One vital agent utilized in this procedure is TP. To effectively ascertain what dose and duration of administration of TP to create a condition parallel to human BPH, studies are conducted with different doses of TP administered for varying duration to animal models. The goal being to establish what dose and for how long a BPH case can be sustained. The BPH in the animal model closely mirrors what is observed in human BPH cases.

In the current study, we sought to determine the dose and duration of TP administration that can cause lasting BPH in Wistar rats. For a period of 11 days and 22 days daily treatment with TP was maintained while observation was made of physical changes and some biomarkers were assayed to understand changes that happened in the urogenital system. Rats treated with TP showed increase in body weight for all doses of TP administered for 22 days treatment period. Other observed changes include frequent micturition in the test groups. For a duration of 22 days at a dose of 9 mg/kg b.wt fur discoloration and loss of fur were observed. Animals were also observed to be passing diarrhea-like stool. Levels of testosterone were observed to be significantly elevated in the test groups, particularly at 6 mg/kg b.wt and 9 mg/kg b.wt. However, the levels of FSH and LH were declined in the test groups. Choi et al., (2019) stated that subcutaneous injection

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of TP, either following castration or without castration increases testosterone level. Subcutaneously injected testosterone and its metabolite, DHT bind to the androgen receptor (AR) in the prostate. Upon activation, the AR functions as a transcription factor of growth factor, consequently accelerating prostate stromal and epithelial cell proliferation (Lee et al., 2004). The lowered level of FSH and LH in the test groups could be attributed to a compensatory response, a negative feedback to exogenous TP administration. The results also reveal an increase in PSA concentration of the test groups. This is in accordance with similar reports from Hans et al., (2021). Other studies have revealed TP treatment causes increase in prostate weight, PSA and prostate index (Babu et al., 2010; Tang et al., 2014). The findings of the current study agrees with these published findings above.

A histomorphological investigation of the prostate tissues reveals a lot about the etiology and progress of BPH. The tissues of the prostate are directly impacted by both the enlargement and obstruction of the prostate seen in BPH. Constantinou (1996) asserted that hormonal treatment induces prostate growth and hardens the ventral lobe of the prostate. It has also been stated that the dorsal lobe of the rodent prostate is ontogenetically comparable to human prostate (Mahapokai et al., 2000). The histological changes seen in the prostate of the test group in the current study reveals pronounced alterations at the doses of 6 mg/kg b.wt and 9 mg/kg b.wt. Atypically adenomatous hyperplasia of the prostate gland is also present as indicated by the presence of uniform round glands arranged in a circumscribed nodule. Thickening of the fibromuscular stroma and enlargement of the lumen are also seen.

TP administration could induce clinical and histological BPH from doses above 3 mg/kg b.wt, and a daily subcutaneous injection for a period above 10 days could cause the on set of BPH in experimental models.

CONCLUSION

Various studies have established the role of testosterone in prostate enlargement in human males. The biochemical changes and histomorphology of the test groups particularly those which received 6 mg/kg b.wt and 9 mg/kg b.wt of TP proves that TP synthetically induces BPH. Duration above 10 days and up to 22 days prove to show lasting BPH signs in the experimental model. However, it is recommended that doses of up to 9 mg/kg b.wt of TP should not be used for experimental purposes owing to the severe physical changes observed in the group treated with 9 mg/kg b.wt of TP for 22 days.

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