World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Biochemical evaluation of *Ceiba pentandra* leaf on the amelioration of testosterone induced-benign prostatic hyperplasia in Wister rats

Oyom Bright Bassey [1,*], Halima Suleiman [2], Kwasau Blessing Shiyin [3] and Alabi Olufemi Solomon [4]

[1] *Federal Polytechnic Daura, Department of Science Laboratory Technology, Katsina State, Nigeria.*
[2] *Nile University of Nigeria, Department of Biochemistry, Abuja, Federal Capital Territory, Nigeria.*
[3] *Federal Polytechnic Daura, Department of Science Laboratory Technology, Katsina State, Nigeria*
[4] *Federal Polytechnic Daura, Department of Science Laboratory Technology, Katsina State, Nigeria.*

World Journal of Advanced Research and Reviews, 2023, 18(01), 476–487

Publication history: Received on 27 February 2023; revised on 10 April 2023; accepted on 12 April 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.18.1.0623

Abstract

Benign prostatic hyperplasia (BPH) is a considerable public health problem prevalent among older men. Despite its eminent prevalence, the etiology of BPH is not well understood. Accumulating evidence indicates that modifiable risk factors of cardiovascular disease may also increase the risk of BPH and potentially contribute to BPH development. This study evaluated the ameliorative effect of *Ceiba pentandra* leaf on some lipids profile indices and bilirubin concentration of rats induced BPH. Thirty six Wistar rats were divided randomly into six groups (n = 6). All the experimental groups except the normal control were induced benign prostatic hyperplasia using testosterone propionate and estradiol valerate at a dose of 400 µg and 80 µg respectively, for 21 days. After induction, rats in the negative control (BPH Control) group received no treatment. Rats in the standard control group received finasterides (1mg/kg body weight), while rats in the low dose extract, medium dose extract and high dose extract groups received the plant extract according to their body weights in kilogram at 500 mg/kg, 1000 mg/kg, and 1500 mg/kg respectively. Normal Control group received only feed without any special treatment. The animals in all the groups were allowed access to water and feed *ad libitum* for 28 days. The rats were anaesthetized after treatment period. Blood samples were collected and serum harvested for analyses using standard methods. Result showed that *Ceiba pentandra* leaf had ameliorative effect on the lipids profile analyzed.

Keywords: *Ceiba pentandra*; Benign Prostatic Hyperplasia; Amelioration; Testosterone propionate**.**

1. Introduction

Benign prostatic hyperplasia (BPH), commonly referred to as benign enlargement of the prostate, is an age- and hormone-related condition that causes varying enlargement of the prostate and histological alterations in the prostate gland. Urinary urgency, slow stream, nocturia, and increased daytime frequency are only a few of the symptoms brought on by prostate enlargement (Djavan, 2003; Lee *et al*., 2012). The quality of life for BPH sufferers is severely impacted by these symptoms (Sagnier *et al*., 1995; Lee *et al.*, 2016). The mechanism underlying the pathogenesis of BPH remains largely unidentified, however, a number of overlapping and complementary theories have been proposed. The pathophysiology of BPH involves hormonal changes in an aging man, albeit the exact mechanism is not yet entirely understood (Veeresh et al., 2010).The development and growth of normal prostate mainly depends on androgen stimulation, by dihydrotestosterone (DHT), which is produced from the prostrate by 5α-reductase enzyme (Cho *et al.*, 2013; Carson and Rittmaster, 2003).

* Corresponding author: Oyom Bright Bassey

Funding: This research was funded by Tertiary Education Trust fund (TETFUND) 2022 Intervention through the Institutional Based Research Grant, (Federal Polytechnic Daura, Katsina State, Nigeria) reference number: FPDRA/CA/R/CTETFUND/006/1.

There are two primary types of treatment for BPH patients: α1-adrenergic receptor antagonists to reduce smooth muscle tone in the prostate and the bladder neck, and 5α-reductase inhibitors to reduce prostate size (Fine and Ginsberg, 2008). The most often prescribed drugs for treating BPH historically have been tamsulosin and finasteride (Lee, 2003). Only 64% of men receiving both medications, according to McConnell *et al.* (2003) showed a decreased risk of clinical progression, which is indicated by symptoms getting worse, acute urine retention, and incontinence and urinary tract infection. Additionally, these medications caused unpleasant side effects including low libido, erectile dysfunction, postural hypotension, asthenia, and occasional syncope (Akiyama *et al.*, 1999; Lee eta l., 2014). It is highly desirable to develop a α1-adrenergic antagonist or other medication that can selectively suppress the smooth muscle tone of lower urinary tract without vascular effects and decrease prostate volume without sexual dysfunction for the treatment of urinary outlet obstruction in BPH (Akiyama *et al*., 2002)

Natural compounds produced from plant sources have long been the primary sources of novel medications for the treatment of a variety of ailments (Dharmani *et al.*, 2006). The multi-purpose *Ceiba pentandra plant*, which is native to northern Nigeria, and other tropical West African locations, has been found to have a variety of pharmacological applications. It is a plant from the *Bombacaeae* family. The presence of secondary metabolites like polyphenol, flavonoids, alkaloids, and saponins in *Ceiba pentandra plant* is responsible for its promising medicinal properties. Some of these compounds have been identified to possess antioxidant properties; scavenging free radicals produced by oxidation –reduction reactions (Nandeesh *et al.*, 2008). Previous research on the plant's morphology in different areas has confirmed that the plant is also utilized as a hypoglycemic agent and has been proven to be a successful treatment for rheumatism, headaches, and vertigo (Ngounou *et al.*, 2000). Typically, monitoring the progression of BPH involves evaluating specific biochemical markers (Kellogg, 2007). This study evaluated how extract of *Ceiba pentandra* leaf affected some lipids profile indices in testosterone propionate and estradiol valerate- induced benign prostatic hyperplasia in male Wistar rats.

2. Materials and methods

2.1. Collection and preparation of *Ceiba pentandra* leaf extract

The plant leaves were purchased from a local market in Okuku Local Government Area, Cross River State. The plant were authenticated by a Botanist, Prof. S. Udoh of the Department of Biology, Cross River University of Technology (CRUTECH), Calabar with a voucher number BOT/PA/2022/017. The sample were deposited in the herbarium of the same department. The fresh leaves of *Ceiba pentandra* were washed with distilled water and then allowed to get dried in a dust-free environment for ten days. The dried leaves were blended using an electronic blender.

2.2. Experimental animals

A total of thirty six (36) male Wistar rats weighing 185 – 220 grams were obtained from the Department of Medical Biochemistry, Cross River University of Technology, Okuku Campus, and transferred to the Animal House of the Department of Biochemistry Cross River University of Technology (CRUTECH) Calabar, Nigeria. The animals were acclimatized for 7days on pelletized rat chow and water *ad libitum* and maintained under standard housing conditions of adequate ventilation and room temperature ($25^0C \pm 5^0C$) and relative humidity (46% ±5%) with a natural 12hr light-dark regimen.

2.3. Chemicals and reagents

2.3.1. Drug/Chemicals

Testosterone (Testosterone Propionate)

Testosterone propionate (brand name **Testost –** manufactured by Laborate Pharmaceuticals India Limited) was purchased from Bez Pharmarcy and stores, No. 27 Etta-Agbor Street, Calabar, Nigeria, after full explanation of the purpose for procurement.

Ketamine Injection (Ketamine hydrochloride)

Ketamine is a medication mainly used for starting and maintaining anaesthesia (brand name **Ketalar –** manufactured by Sular Pharmaceuticals, India) was purchased from Bez Pharmacy and Stores, No. 27 Etta-Agbor Street, Calabar and was used to anaethesize the rats prior to bilateral orchiectomy.

2.4. Extraction of Plant Materials

The powdered material (500 g of *C. pentandra*) was weighed and soaked in 650 ml distilled water and allowed to macerate at room temperature for 48 hours. The solution was filtered after 48 hours into a beaker using Whatman filter paper No 4. The suspension was filtered through Whatman filter paper No 4 and dried in water bath at 55°C. The dried extract was weighed and stored in a clean reagent bottle, then preserved in a refrigerator at 4°C until its use.

$$\%\ Recovery\ = \frac{crude\ extract\ obtained}{Weight\ of\ grounded\ leaves} \times \frac{100}{1}$$

$$= \frac{10g}{500g} \times \frac{100}{1} = 2\%$$

Aqueous concentration of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg of *C. pentandra* extract was prepared using distill water and used as administrative doses

2.5. Experimental design

The animals weighing 185 and 220g were divided into six (6) groups with six (6) animals each. The six groups were: Group 1 (Normal), Group 2 (benign prostatic hyperplasia control), Group 3 (administered 3 mg/kg b. wt. testosterone + 5 mg/kg finasteride), Group 4 (administered 3 mg/kg b. wt. testosterone + 500 mg/kg of *C. pentandra* leaves extract), Group 5 (administered 3 mg/kg b. wt. testosterone + 1000 mg/kg of the extract), Group 6 (administered 3 mg/kg b. wt. testosterone + 2000 mg/kg of the extract). Benign prostatic hyperplasia was induced in Wistar rats using testosterone propionate for 28 days. Administration of extract was done for another 28 days, and then followed by accurate measurement of the changes. The animals were anesthetized using chloroform, and the blood samples of each animal were collected through the cardiac puncture method. The blood samples were aliquoted into the appropriate sample bottles (Plain and EDTA bottles), liver, kidney, and testes of Wistar rats were harvested into universal bottles containing formalin and transported to the laboratory. The design of the experimental procedure used in the study is shown in Table 1.

Table 1 Design of experimental procedure

Groups	Groups category	Treatment and dosage
Groups 1	**Normal group**	**Distilled water**
Groups 2	BPH control	3 mg/kg b. wt. testosterone
Groups 3	Standard control	3 mg/kg b. wt. testosterone + 5 mg/kg Finasteride
Groups 4	Low dose	3 mg/kg b. wt. testosterone 500 mg/kg of the leaves extract
Groups 5	Medium dose	3 mg/kg b. wt. testosterone + 1000 mg/kg of the extract
Groups 6	High dose	3 mg/kg b. wt. testosterone 2000 mg/kg of the extract

2.6. Ethical approval

Ethical approval for the treatment and handling of experimental animal and human subjects was obtained from the Faculty Animal Research Ethics Committee on Use and Care of Experimental Animals, Faculty of Basic Medical Sciences, Cross River University of Technology (CRUTECH) Ogoja Campus with the approval number/code; CRUTECH/FBMS/IREC/2022-A1102.

2.7. Evaluation of biochemical parameters

The rats received treatment for 28 days, and on the first and 28th days, their weights were recorded. They underwent anesthesia at the conclusion of the experiment. The prostate glands were removed and weighed. Half of the group's prostate were sent to the toxicology lab for biochemical analyses, including lactate dehydrogenase (LDH), superoxide dismutase (SOD), malondialdehyde (MDA), and follicle stimulating hormone (FSH) the remaining halves were put in containers with 10% formalin and stained for histology with hematoxylin and eosin.

2.7.1. PSA content

After anesthetizing the rats, blood samples were collected from their hearts and sent to an associate laboratory to evaluate free prostate specific antigen (PSA) in the blood using the PSA ELISA kit Akanni OO, et al., (2017).

2.7.2. Body weight and prostate weight

Body weight were measured in the beginning and the end of the experiment. Also, prostate heights were measured after ketamine hypochlorite combination was used to anesthetize the animals at a dose of 0.15 ml/kg of body weight administered intraperitoneally and removing prostate gland.

The prostate weight to body ratio can be calculated using the prostate index formula. Any changes in this index, when compared between each group and the normal and illness groups, show the degree to which the disease is being prevented from progressing. Prostate index and inhibitory prostate weight are computed using the two measured weights and these formulas.

$$\text{. Prostate index} = \frac{\text{Prostate weight}}{\text{Body weight}}$$

Percentage of inhibition = 100

$$\frac{Treatment\ group - normal\ group}{sease\ group - negative\ control}$$

2.8. Histopathological examination

To investigate the morphological changes, the tissue was cut into 4-nM sections using a rotatory microtome, stained with eosin and hematoxylin and was observed under a 40x microscope (Kim, Sk, Seok H et al., 2015).

2.9. Statistical analysis

Data obtained were analyzed using one-way ANOVA followed by least square difference (LSD) post-hoc comparison test to evaluate significant difference between the mean values of the experimental and control groups. Differences at $P < 0.05$ were regarded as significant. Graphpad prism version 7 and SPSS software package version 23.0 were used for the statistical analyses.

3. Results

Effect of aqueous leaf extract of *C. pentandra* on semen parameters of testosterone propionate- induced benign prostatic hyperplasia in male rats

Table 2 displays the findings on the impact of *C. pentandra* aqueous leaf extract on the semen parameters of testosterone propionate-induced benign prostatic hyperplasia in male rats. In comparison to the negative control, male rats in Groups 3 to 6 had considerably larger amounts of semen ($p > 0.05$). In comparison to the negative control, groups 4 to 6 exhibit an increase in viability, normal activity, and sperm count that is not statistically significant ($p > 0.05$). When compared to the negative control, Group 3's viability (82.00%), normal (85.00%), activity (86.00%), and sperm count (710.00 ml/106) all increased significantly ($p > 0.05$). Group 4 to 6 had a non-significant decrease ($p > 0.05$) in abnormal, Sluggish, and dead sperm cells analyzed when compared to control while Group 3 had a significant decrease ($p > 0.05$) in abnormal (14.00 %), Sluggish (6.00 %), and dead (8.00 %) sperm cells compared to the negative control.

3.1.1. Effect of aqueous leaf extract of C. pentandra on oxidative stress and hormone levels of testosterone propionate-induced benign prostatic hyperplasia in male rats

Table 3 displays the findings of the study on the impact of *C. pentandra* aqueous leaf extract on oxidative stress and hormone levels of testosterone propionate-induced benign prostatic hyperplasia in male rats. Male rats in Groups 3 to 6 had non-significantly higher levels of lactate dehydrogenase (LDH) (u/l) compared to the positive and negative controls ($p > 0.05$). When compared to the negative and positive controls, Superoxide Dismutase (SOD) levels in Groups 3 to 6 were considerably lower ($p > 0.05$). When compared to the negative and positive controls, malondialdehyde (MDA) levels in Groups 3 to 6 were considerably higher (p 0.05), while Group 5 exhibited a significant rise when compared to Groups 3, 4, and 6. Findings revealed that male rats' levels of Follicle Stimulating Hormone (FSH) (miu/ml).

A significant increase ($p < 0.05$) in testosterone level was observed in Group 2. However, Groups 4 to 6 also showed a significant decrease ($p < 0.05$) in testosterone level compared to Group 2.

Table 2 Effect of aqueous leaf extract of *C. pentandra* on semen parameters of testosterone Propionate-induced benign prostatic hyperplasia in male rats

Groups	Volume (ml)	Viable %	Normal %	Abnormal %	Activity %	Sluggish %	Dead %	Sperm count (ml x 10^6)
1	0.14 ± 0.05	81.50 ± 2.50	74.00 ± 5.00	24.00 ± 5.00	66.50 ± 2.50	9.00 ± 0.00	21.00 ± 2.50	448.00 ± 50.00
2	0.09 ± 0.00	66.23 ± 4.21	63.00 ± 2.67	33.00 ± 2.50	61.67 ± 1.67	11.67 ± 1.67	26.67 ± 3.33	300.00 ± 57.74
3	0.36 ± 0.02	82.00 ± 1.75	85.00 ± 1.50	12.00 ± 1.67	86.00 ± 1.87	6.00 ± 1.00	8.00 1.23	710.00 ± 74.83
4	0.24 ± 0.04	70.50 ± 5.00	70.31 ± 5.46	24.25 ± 5.46	71.25 ± 7.74	8.75 ± 1.25	20.00 ± 7.07	537.50 ± 143.43
5	0.32 ± 0.05	73.67 ± 4.21	72.49 ± 4.21	21.33 ± 4.41	75.00 ± 7.64	10.00 ± 2.89	15.00 ± 5.00	550.00 ± 104.08
6	0.23 ± 0.03	76. 12 ± 4.31	73.00 ± 5.71	27.00 ± 5.39	67.00 ± 6.44	11.00 ± 1.87	22.00 ± 4.90	510.00 ± 112.25

Values are presented as mean ± SD of triplicate determinant (n = 3).

Table 3 Effect of aqueous leaf extract of *C. pentandra* on oxidative stress and hormone levels of testosterone propionate-induced benign prostatic hyperplasia in male rats

Groups	LDH (u/l)	SOD (u/l)	MDA (u/l)	FSH (miu/ml)	TESTOSTERONE (ng/ml)
1	33.10 ± 7.90	0.67 ± 0.12	0.37 ± 0.06	3.00 ± 0.40	2.35 ± 0.30
2	25.30 ± 0.50	0.69 ± 0.01	0.31 ± 0.02	3.27 ± 0.24	2.93 ± 0.20
3	22.15 ± 2.15	0.29 ± 0.04	0.59 ± 0.02	1.98 ± 0.31	2.16 ± 0.20
4	23.10 ± 2.90	0.29 ± 0.01	0.62 ± 0.02	1.80 ± 0.24	1.58 ± 1.14
5	24.46 ± 0.80	0.18 ± 0.01	0.72 ± 0.00	1.47 ± 0.23	1.91 ± 0.29
6	30.75 ± 4.05	0.37 ± 0.06	0.55 ± 0.04	1.80 ± 0.11	2.00 ± 0.15

3.2. Effect of aqueous leaf extract of *C. pentandra* on hematological indices of testosterone propionate-induced benign prostatic hyperplasia in male rats

The results of the effect of aqueous leaf extract of *C. pentandra* on hematological indices of testosterone propionate-induced benign prostatic hyperplasia in male rats presented in Table 4 showed that there was no significant difference ($p < 0.05$) in the PCV and HB levels of the test groups compared to the positive and negative control. The same non-significant decrease ($p < 0.05$) was obtained in PLT, MCH, MCV, MCH, RBC, Leucocyte, Neutrophils, Mesophiles, Basophils, and Eosinophils.

Table 4 Effect of aqueous leaf extract of *C. pentandra* on haematological indices of testosterone propionate-induced benign prostatic hyperplasia in male rats

GROUPS	PCV (%)	HB (g/dl)	WBC (x 10^9/L)	PLT (x 10^9/L)	MCV (FL)	MCH (Pg)	MCHC (g/dL)
1	47.00 ± 3.00	15.50 ± 0.50	9.10 ± 0.90	383.50 ± 63.50	53.35 ± 0.45	17.80 ± 0.20	33.35 ± 0.15
2	44.50 ± 3.50	14.15 ± 1.15	10.90 ± 4.10	482.00 ± 266.00	53.30 ± 0.90	17.60 ± 0.60	33.23 ± 0.52
3	43.50 ± 1.50	15.50 ± 0.50	13.10 ± 0.70	376.00 ± 128.00	53.42 ± 0.67	17.68 ± 0.46	32.62 ± 0.68
4	45.69 ± 0.50	14.45 ± 0.15	16.90 ± 1.50	353.00 ± 157.00	53.45 ± 0.27	16.83 ± 0.85	32.58 ± 0.94
5	42.50 ± 4.50	14.05 ± 1.45	23.30 ± 0.10	529.00 ± 109.00	53.83 ± 0.97	15.93 ± 0.72	33.93 ± 0.47
6	44.00 ± 2.0	14.65 ± 0.65	18.35 ± 4.05	503.00 ± 59.00	51.38 ± 1.28	17.80 ± 0.39	33.48 ± 0.49

Values are presented as mean ± SD (n = 3). Mean values with same superscript letters along the column are not statistically significant at $p < 0.05$.
PCV - Packed Cell Volume, HB – Hemoglobin, WBC – White blood cell-, MCV - mean corpuscular volume, MCH - mean corpuscular hemoglobin, MCHC - mean corpuscular hemoglobin content

3.3. Effect of aqueous leaf extract of *C. pentandra* on cardiac and cancer markers (ng/ml) of testosterone propionate-induced benign prostatic hyperplasia in male rats

The results of the effect of aqueous leaf extract of *C. pentandra* on cardiac markers (ng/ml) of testosterone propionate-induced benign prostatic hyperplasia in male rats presented in Table 4 showed a non-significant decrease ($p < 0.05$) of CKMB concentration in Groups 3 to 6. D-DIMER concentration showed a non-significant increase ($p < 0.05$) in Groups 3 to 6. Myoglobin concentration showed a non-significant decrease ($p < 0.05$) in Groups 3 and 6, and a non-significant increase ($p < 0.05$) in Groups 4 and 5. Prostate-Specific Antigen (PSA) (ng/ml) of male rats in Groups 3 to 6 show a significant increase ($p > 0.05$) when compared to the positive and the negative control. Similarly, there was a non-significant decrease ($p > 0.05$) in the level of Carcinoembryonic antigen of rats in Groups 3 to 6 when compared to the positive and negative controls.

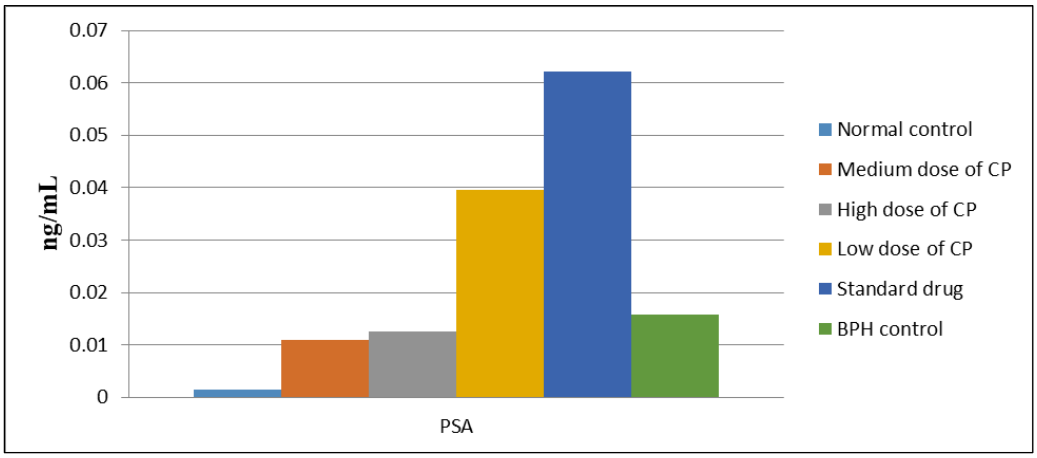

Figure 1 Prostate Specific Antigen

3.3.1. Effect of aqueous leaf extract of C. pentandra on liver markers of testosterone propionate-induced benign prostatic hyperplasia in male rats

Results of the effect of *C. pentandra* aqueous leaf extract on the liver of testosterone propionate-induced benign prostatic hyperplasia in male rats are shown in Table 5. When compared to the negative control, the ALP concentration in male rat Groups 3 to 6 was significantly lower (p 0.05). When compared to the negative control, the AST concentration increased significantly (p 0.05) in Groups 3 and 4 and non-significantly (p > 0.05) in Groups 5 and 6. When compared to the negative control, ALT concentration results showed a substantial increase (p 0.05) in Groups 3 and 4 and a non-significant decrease (p > 0.05) in Groups 5 and 6. Total-Protein concentration showed a non-significant increase (p>0.05) in Groups 3 and 4, a significant increase in Groups 5, and a non-significant decrease in Group 6 compared to the negative control. Albumin concentration in Groups 3 and 4 showed a non- significant decrease (p > 0.05). However, there was a non-significant increase in Groups 5 and 6 when compared to the negative control.

Table 5 Effect of aqueous leaf extract of A. muricata on liver markers of testosterone propionate-induced benign prostatic hyperplasia in male rats

GROUPS	ALP (IU/L)	AST (IU/L)	ALT (IU/L)	T-PROTEIN (g/L)	ALBUMIN (g/L)
1	283.85 ± 10.75	66.50 ± 10.50	53.00 ± 4.00	69.95 ± 0.65	40.75 ± 0.55
2	289.03 ± 0.88	65.33 ± 4.18	50.00 ± 1.73	66.53 ± 2.34	38.17 ± 1.37
3	134.40 ± 4.88	87.20 ± 6.59	74.40 ± 6.70	68.12 ± 2.39	41.18 ± 1.00
4	165.18 ± 8.74	82.50 ± 2.66	68.50 ± 2.33	69.43 ± 1.90	40.70 ± 1.09
5	139.97 ± 7.91	68.33 ± 3.28	48.33 ± 2.73	76.27 ± 1.21	44.33 ± 1.21
6	149.80 ± 8.09	65.80 ± 2.48	45.80 ± 2.97	66.44 ± 1.66	43.18 ± 2.13

Values are presented as mean ± SD of the triplicate determinant (n = 3). Mean values with the same superscript letters along the column are not statistically significant at p < 0.05. AST=Aspartate aminotransferase, ALT=Alanine Aminotransferase, ALP= Alkaline Phosphatase

3.4. Effect of aqueous leaf extract of *C. pentandra* on the kidney of testosterone propionate-induced benign prostatic hyperplasia in male rats

The results of the Effect of aqueous leaf extract of *C. pentandra* on the kidney of testosterone propionate-induced benign prostatic hyperplasia in male rats presented in Figure 1 shows a non-significant increase (p > 0.05)) in creatinine and urea concentration in Groups 3 to 6 of male rats compared to the negative control. There was a non-significant increase (p > 0.05) in potassium concentration in Groups 3 to 4 compared to the negative control, and a non-significant decrease (p > 0.05) in potassium concentration in Groups 5 to 6. Results showed a non-significant decrease (p > 0.05) in sodium concentration in Groups 3 to 6 compared to the negative control.

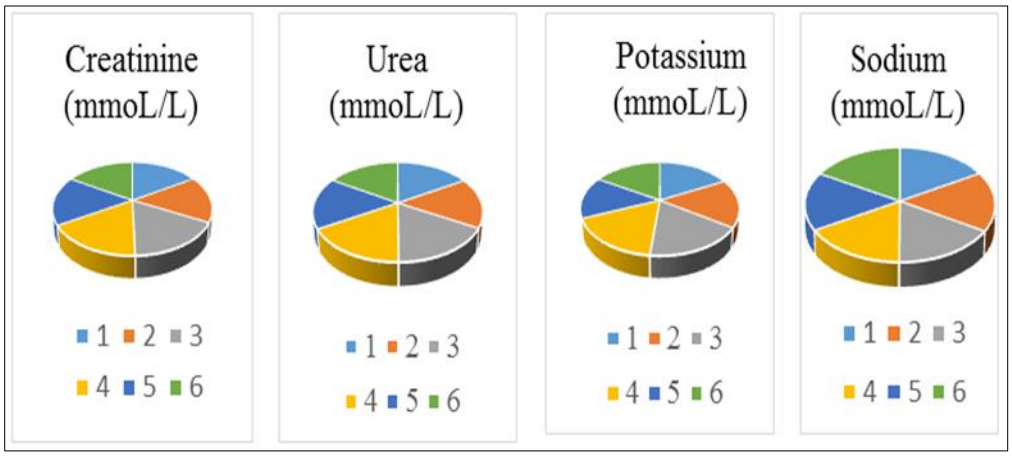

Figure 2 Effect of aqueous leaf extract of *C. pentandra* on the kidney of testosterone propionate-induced benign prostatic hyperplasia in male rats from Groups 1-6.

4. Discussion

The results of Amadi et al. [16] who investigated the potential ameliorative effects of *C. pentandra* on sodium fluoride-induced toxicity on hematological indices and fecundity of adult male Wistar rats and discovered that leaf extracts of *C. pentandra* have no toxic effect on testes of male rats corroborated the findings of *C. pentandra* having no toxic effect on testes of male rats.. *C. pentandra* is antioxidative, anticancer, antimalarial, antihelmintic, piscicidal, antiviral, and antibacterial properties, implying a wide range of possible applications. Asimicin, bullatacin, and bullatalicin are three significant acetogenins found in ripe *C. pentandra*

Hormonal level of testosterone propionate-induced benign prostatic hyperplasia in male rats administered with aqueous leaf extract of *C. pentandra* showed a significant decrease ($p > 0.05$) in FSH levels for male rats in Groups 3 to 6 treated with *C. pentandra* compared to the negative control. This agrees with the study of Amadi et al. [16] who investigated the potential ameliorative effects of aqueous leaf extract of *C. pentandra*. There was a decrease in testosterone and FSH concentrations in Groups 4 to 6 compared to the negative control. This decrease in FSH may be due to *C. pentandra* toxic effect on the anterior pituitary gland, causing oxidative damage to the anterior pituitary gland's architecture, responsible for the generation of FSH (glycoprotein hormone) and luteinizing hormone. The decline in testosterone levels in groups administered with aqueous leaf extracts of *C. pentandra* suggested that its phytochemical composition may reduce the effect of the pituitary gland and testosterone synthesis [19]

The effect of aqueous leaf extract of *C. pentandra* on oxidative stress of testosterone propionate-induced benign prostatic hyperplasia in male rats had a non-significant increase ($p > 0.05$) in Lactate Dehydrogenase (LDH) activity in Groups 3 to 6 compared to the positive and negative control. Superoxide Dismutase (SOD) concentration in Groups 3 to 6 was significantly decreased ($p > 0.05$) compared to negative and positive control. Malondialdehyde (MDA) in Groups 3 to 6 was significantly increased ($p > 0.05$) compared to the negative and positive control, and Group 5 had a significant increase compared to Groups 3, 4, and 6. This is in agreement with the findings of Agu et al. [20] who worked on "protective effect of ethanol extract of soursop (annona muricata linn) leaves on cycad induced oxidative stress in male albino wistar rats", and discovered an increase in LDH and MDA concentration in rats administered with *C. pentandra* compared to that of the negative control, and that the SOD concentration decreased compared to that of the negative control. The observed increase in LDH concentration of Groups 3 to 6 compared to negative control is owing to tissue damage produced by rats' exposure to testosterone propionate, a well-known toxin as described above. Malondialdehyde (MDA) is a measure of polyunsaturated lipid peroxidation caused by reactive oxygen radicals (ROS). These lipids are essential components of biological membrane structures. Membrane lipids are predominantly attacked by free radicals, resulting in their peroxidation [21]. This causes membrane instability, breakdown of membrane proteins and other macromolecules, and cellular damage [22]. The increased levels of oxidative stress caused by testosterone propionate were reduced in rats administered with *C. pentandra*. This reduction was via the reduction in levels of SOD, LDH, and MDA in the rats, supporting the findings of Lolodi and Eriyamremu [23] who found a decrease in SOD activity in rats given Cycads.

There was a decrease ($p > 0.05$) in PSA level in male rats of Groups 3 to 6 compared to the positive and the negative control. Testosterone propionate-induced benign prostatic hyperplasia is a pointer to the ameliorative impact of testosterone propionate-induced benign prostatic hyperplasia. As a direct result of inhibiting 5-reductase, a decrease in PSA levels is linked to the reduction in prostatic hyperplasia [24] Furthermore, the fact that the PSA level in the negative control group remained high indicates that the observed decline in PSA in treated rats was due to the ameliorative effect of *C. pentandra*. This corroborates the findings of Ogbu et al. [25] who discovered dutasteride and acetogenin-rich fraction isolated from Annona muricata leaves reduced the levels of PSA in rats with testosterone propionate-induced benign prostatic hyperplasia.

The Effect of aqueous leaf extract of *C. pentandra* on hematological indices of testosterone propionate-induced benign prostatic hyperplasia in male rats showed normal hematology indices in the test groups when compared to the negative control. Previous studies have shown that some plant extracts including leaf extract of A. muricata have the potential to positively affect the erythropoietic system [16, 26, 27, 28].

The effect of aqueous leaf extract of *C. pentandra* on cardiac markers of testosterone propionate-induced benign prostatic hyperplasia in male rats revealed there was a non-significant decrease ($p < 0.05$) of CKMB concentration in Groups 3 to 6 compared to that of the negative control. D-DIMER concentration had a non-significant increase ($p < 0.05$) in Groups 3 to 6 compared to the negative control. Myoglobin concentration had a non-significant decrease ($p < 0.05$) in Groups 3 and 6, and a non-significant increase ($p < 0.05$) in Groups 4 and 5. The result of CKMB, D-DIMER, and Myoglobin from this study indicates the aqueous leaf extract of A. muricata has no deleterious effect on the functional integrity of the cardiac system. This corroborates the findings of Niu et al. [29] who worked on "Hyperbaric oxygen

improves survival in heatstroke rats by reducing multiorgan dysfunction and brain oxidative stress" and discovered there was an increase of D-dimer concentration in heatstroke rats.

The liver which is responsible for xenobiotic metabolism and detoxification is also susceptible to hepatotoxic chemicals [30]. The effect of aqueous leaf extract of *C. pentandra* on the liver of testosterone propionate-induced benign prostatic hyperplasia in male rats revealed a significant decrease in ALP concentration in Groups 3 to 6 of male rats compared to the negative control, which agrees with the study of Syahida et al. [28] on "Soursop (Anonna muricata): Blood hematology and serum biochemistry of Sprague-Dawley rats" who discovered ALP concentration in rats treated with *C. pentandra* was significantly decreased compared to their negative control. The AST concentration was significantly increased ($p > 0.05$) in Groups 3 and 4 and Groups 5 and 6 showed a non-significant increase compared to the negative control. The result showed that ALT concentration was significantly increased ($p > 0.05$) in Groups 3 and 4. However, there was a non-significant decrease ($p < 0.05$) in Groups 5 and 6 compared to the negative control. T-Protein had a non-significant increase ($p > 0.05$) in Groups 3 and 4, a significant increase in Group 5, and a non-significant decrease in group 6 compared to the negative control. Albumin concentration in Groups 3 and 4 had a non-significant decrease ($p < 0.05$) and a non-significant increase in Groups 5 and 6 compared to the negative control. This liver-function investigation revealed that aqueous leaf extract of *C. pentandra* has no acute hepatotoxic effect. The enzymes AST and ALT are crucial in the breakdown of amino acids channeled into the Krebs cycle and electron transport chain [31] Because ALT and ALP are concentrated in the liver, they are considered accurate indicators of liver disease [27, 32]. Changes in membrane-bound ALP negatively impact membrane permeation, disrupting the transportation of metabolites [31]. When the liver is diseased, these enzymes are released into the system in excess of a critical concentration [32].

By measuring the serum levels of urea, creatinine, potassium, and sodium, renal dysfunction was examined. In the blood serum of patients with defective kidneys, these indicators are found above normal levels, according to Edmund and David [32]. When urea, creatinine, sodium, and potassium levels in groups 3 through 6 were compared to the positive and negative controls, there was no statistically significant difference ($p > 0.05$) between them and the kidneys of testosterone propionate-induced benign prostatic hyperplasia in male rats. The renal function investigation on groups treated with aqueous leaf extract of *C. pentandra* compared to that of the negative control revealed a non-toxic effect on kidney and renal function. Onyegeme-Okerenta et al. [34] in their study on the ameliorating potential of Annona muricata on sodium Fluoride-induced toxicity on lives and kidneys of male Wistar rats concluded that concomitant treatment of NaF leaf extract of Annona muricata resulted in mild/moderate amelioration and generation of damaged hepatic and renal tissues

5. Conclusion

The findings of this study shows that testosterone propionate-induced benign prostatic hyperplasia in male rats might be ameliorated by aqueous leaf extract of *C. pentandra* when taken over an extended period of time. On testosterone propionate-induced benign prostatic hyperplasia in male rats, the aqueous leaf extract of *C. pentandra* showed improved sperm count, volume, normalcy, and viability, while decreasing the amount of abnormal, slow, and dead sperm cells. The sex hormones (Follicle Stimulating Hormone and Testosterone) in male Wistar rats may be brought back to normal by *C. pentandra*. Moreover, it promotes spermatogenesis, which improves the quality of the semen. The administration of *C. pentandra*'s aqueous leaf extract also demonstrated potential for improving hematological indicators, cardiac, renal, and cancer outcomes.

Compliance with ethical standards

Acknowledgments

The first author is grateful to the Tertiary Education Trust Fund (TETFUND) Abuja, Nigeria for the award of a grant which facilitated the execution of this study. The authorities of Federal Polytechnic Daura, Katsina State are appreciated for providing the enabling environment.

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

Ethical approval for the treatment and handling of experimental animal and human subjects was obtained from the Faculty Animal Research Ethics Committee on Use and Care of Experimental Animals, Faculty of Basic Medical Sciences, Cross River University of Technology (CRUTECH) Ogoja Campus with the approval number/code; CRUTECH/FBMS/IREC/2022-A1102.

Funding

This research was funded by Tertiary Education Trust fund (TETFUND) 2022 Intervention through the Institutional Based Research Grant, (Federal Polytechnic Daura, Katsina State, Nigeria).

Authors' Declaration

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

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