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The Effects of Ethanolic Extracts of *Polyalthia longifolia* Seeds on Experimentally Induced Benign Prostatic Enlargement in Adult Male Wistar Rats (*Rattus norvegicus*)

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a prevalent condition among older men, often accompanied by lower urinary tract symptoms and erectile dysfunction that impair quality of life. Although surgical and pharmaceutical options exist, limited research has explored alternative therapies such as *Polyalthia longifolia*. This study investigated the effects of ethanolic seed extracts of *P. longifolia* on experimentally induced prostate enlargement in adult male Wistar rats. Twenty mature rats were acclimatised for two weeks and then divided into four groups. BPH was induced in groups 1–3 using subcutaneous testosterone (2.5 mg/kg bw) and ethinylestradiol (0.5 mg/kg bw) on alternate days for two weeks. By week three, treatment was commenced: Group 1 - high dose received 2.5 ml/kg bw of P. longifolia ethanolic extract (PLEE), Group 2 -low dose 1.25 ml/kg bw PLEE, Group 3- treated control, and Group 4- normal control received distilled water. After two weeks of treatment, prostate and testis tissues were excised for histology, and blood samples were collected for biochemical analysis. Hormonal induction significantly increased prostate and seminal vesicle weight while reducing testicular weight and sperm count ($p \leq 0.05$). Treatment with *P. longifolia* extract reduced prostate epithelial and acinar structures in a dose-dependent manner. Histological analysis revealed widening of prostatic acini, reduced epithelial thickness, and improved concretions. Additionally, extract administration modulated lipid profiles and increased serum protein levels. In conclusion, ethanolic extracts of *P. longifolia* seeds demonstrated therapeutic potential against BPH, alleviating prostate enlargement and histopathological changes in a dose-dependent fashion, warranting further clinical investigation.

Keywords: *Polyalthia longifolia* seed, induced BPH, sperm count, lipid profile

INTRODUCTION

The prostate is an accessory gland of the male reproductive system, located just beneath the urinary bladder. It is about walnut-sized and typically weighs between 20 and 30 g. From around the fourth decade of life, it commonly begins to enlarge, reaching an average of 40–50 g by the age of 80[1]. Benign prostatic hyperplasia (BPH) is a slowly progressive condition involving epithelial and fibromuscular overgrowth of the prostate gland. Evidence indicates that androgens, particularly the active metabolite dihydrotestosterone (DHT), play a central role in this process. Sometimes referred to as benign prostatic hypertrophy, BPH is a histological diagnosis defined by excessive proliferation of prostatic cellular components[2]. Enlargement of the gland may arise from epithelial and stromal expansion, impaired programmed cell death (apoptosis), or both. The condition typically originates in the periurethral and transitional zones of the prostate, where hyperplasia leads to glandular enlargement that can obstruct urinary outflow[3,4].

Herbal or botanical medicine employs roots, leaves, seeds, stems, flowers, and other plant parts to treat ailments, support immunity, relieve discomfort, and promote vitality or relaxation. While Western medicine may often regard such approaches as experimental, it is well established that many modern pharmaceutical products have their origins in medicinal plants[5]. The application of medicinal herbs containing non-nutritive, health-promoting properties for the management of urinary symptoms linked to BPH has drawn global attention mainly because they are associated with fewer side effects than synthetic drugs such as dutasteride and finasteride, and because patients desire more autonomy over their treatment [6,7].

Polyalthia longifolia var. pendula (family *Annonaceae*), commonly known as "Ashoka," is native to the arid regions of India and is also widely cultivated across India, Pakistan, and Sri Lanka[8]. In Ayurveda, the term "Ashoka" refers to a plant traditionally used for the treatment of gynecological disorders[9]. The oil obtained from *P. longifolia* seeds is reddish, a property that likely reflects the presence of carotenoids, vitamin A, tocopherols, and vitamin D - all of which are fat-soluble, particularly in oleic acid, the most abundant fatty acid in the oil. The seed oil has a specific gravity of 0.875, pH of 5.37, and viscosity of 1.026. Analysis shows that *P. longifolia* seeds contain saturated fatty acids (9.04–10.79%), monounsaturated fatty acids (16.64–20.29%), and polyunsaturated fatty acids (11.55–12.78%). Hexadecanoic acid was identified as the predominant saturated fatty acid[10].

Therapeutic activities attributed to *P. longifolia* include anticancer, antitumor, antimicrobial, anti-inflammatory, hypotensive, antiulcer, antioxidant, and hypoglycaemic properties[8,11]. Both the leaves and seeds are rich in phytochemicals, macro- and micro-elements, and essential oils with significant medicinal potential. Moreover, adverse effects often linked to synthetic drugs used in the management of BPH are rarely reported with herbal remedies. This suggests that *P. longifolia* seed and leaf may represent a promising natural alternative in addressing BPH. Given the limited knowledge available, the present study was designed to evaluate the differential effects of ethanolic extracts of *Polyalthia longifolia* seeds on hormone-induced prostate enlargement in adult male Wistar rats.

MATERIALS AND METHODS

Ethical clearance was obtained from the Departmental Ethical Committee, conforming to the Declaration of Helsinki and the Guiding Principles in the Use of Animals (American Physiological Society, 2002).

Animal handling

Adult male Wistar rats were supplied by the animal house of the Department of Anatomy, Olabisi Onabanjo University, Ikenne Remo, Ogun State, Nigeria. The rats were kept in the rat control room of the Anatomy department and acclimatized for two weeks before the experiment commenced. The rats were fed a standard diet (Top feed Nig. plc.), given water, and maintained under standard conditions. The room was well ventilated with a temperature range of about 25°C-27°C under day or night, 12-12hours photo periodically. A total of 20 (control and treated) adult male Wistar rats weighing between 91.1 g and 175.3 g were used for the experiment. Hormones Testosterone (T) and Ethinylestradiol (E) were also used in the experiment.

Seeds collection

The seeds were collected from *Polyalthia longifolia* trees at OOU Ikenne campus, Ikenne area of Ogun State, Nigeria, and authenticated by staff of the plant science department, Olabisi Onabanjo University. A voucher specimen was deposited at the departmental herbarium.

Induction of BPH

Dilution of the Hormone Testosterone (T): 1 ml, i.e., an ampoule containing (25 mg/ml) Testosterone was added to 9 ml of cholesterol-free vegetable oil (soya oil), thus 25 mg of Testosterone was equivalent to the 10 ml of Testosterone and soya oil to give a 10 ml solution of 2.5 mg/ml. Dilution of the Hormone Ethinylestradiol (E_2): 10 mg/ml of Ethinylestradiol was used. 1 ml, i.e., an ampoule of Ethinylestradiol was added to 9 ml of cholesterol-free vegetable oil (soya oil). The new concentration was 1mg/ml. Benign Prostatic Hyperplasia (BPH) was induced by giving 2.5 mg/kg bw T and 0.5 mg/kg bw E_2 subcutaneously in the inguinal region on alternate days for 2 weeks in all animals in groups 1-3.

Preparation of the extract

The seeds of *Polyalthia longifolia* were separated from the seed coats manually, and then sun-dried for 3 days because they were picked almost dry. The seeds were granulated into coarse particles using an electronic blender to give them a fine texture. 50 g of the ground seeds was soaked in 300mls of ethanol for 24-hours, after which it was then filtered using Whatman's filter paper, the filtrate was then taken to the College of Pharmacy of Olabisi Onabanjo University, Sagamu, Ogun State, Nigeria, for the extraction of *Polyalthia longifolia* seed oil. This yields an oily crude extract (18.3%). 10 ml of the ethanolic seed oil extracts were prepared, 0.5 ml were given to the high dose animals, and 0.25 ml of the seed oil extract were given to the low dose animals.

Animal groups: The adult male Wistar rats were divided into four groups, in which Hormonal induction and extract treatment lasted for about two weeks. Each subgroup of the animals was: Group 1, 2, and 3 had BPH-induced (IBPH) animals, while Group have normal (un-induced) animals.

Group 1: IBPH and High dose (HDPL) -The animals in this group received - 1.25 ml/kg bw *Polyalthia longifolia* seed oil extract.

Group 2: IBPH and Low dose (HDPL) -The animals in this group received- 0.625 ml/kg bw of *Polyalthia longifolia* seed oil extract.

Group 3: I BPH control (HTC)-The animals in this group received- 0.5 ml/kg bw distilled water

Group 4: Normal control (UTC)-The animals in this group received- 0.5 ml/kg bw distilled water

Animal sacrifice

The animals were sacrificed under anesthesia using a covered jar filled with cotton wool immersed in chloroform. Precautions were taken to avoid the complete death of the animal to get blood and tissue samples under normal conditions of the body before any autolysis or putrefaction occurs. The accessory organs were harvested and free from fascia, weighed in a torsion balance, and fixed in a formal saline solution. Blood was collected via cardiac puncture from each animal as described in our previous study[12]. The blood was collected into sterile bottles and centrifuged at 4000 × g for 10 min using a MSE tabletop centrifuge machine (Minor Gallenkamp). The extracted serum of each rat was stored in the freezer at -20 °C for biochemical assay.

Determination of biochemical lipid parameters

The concentration of serum total cholesterol and triglyceride was measured enzymatically by using kits and standards supplied by Sigma Diagnostics (St. Louis, MO). HDL-cholesterol was measured by using an EZ HDL-Cholesterol Kit as previously described[12]. However, we calculate the non- HDL-Cholesterol concentration by subtracting HDL-Cholesterol from total cholesterol. The intra-assay CVs were 2.2, 2.6, and 1.7% for total cholesterol, HDL cholesterol, and triglycerides, respectively.

Data analysis

Statistical data analysis was done using SPSS for Windows 14.0. Values are expressed as Mean $\pm$ Standard Deviation, n =20 (five per group). Comparison of the means was carried out using a one-sample t-test and one-way ANOVA (analysis of variance), and Tukey's HSD post-hoc test at $p \leq 0.05$ was considered significant. Experimental rats were compared with normal rats.

RESULTS

Effects of ethanolic extracts of Polyalthia longifolia on body weight

A two-way analysis of variance (ANOVA) was conducted to examine the effects of Time (weeks 1 to 2) and Treatment Group (UTC, HTC, LDPL, HDPL) on body weight, $F(3, 64) = 0.1034$, $p = 0.9578$. We observed that time had no significant effect on body weight, whereas the treatment group significantly influenced body weight across the study period ($p < 0.05$) (Figure 1).

Effects of ethanolic extracts of Polyalthia longifolia on testis and accessory sex glands

In this study we observed a significant differences in prostate weight ($p = 0.0011$), where HTC had a higher weight than UTC, HDPL was also higher than UTC, while LDPL was lower than HTC; testicular weight also differed significantly ($p = 0.0074$), with both LDPL and HDPL showing reductions compared to UTC, whereas seminal vesicle weight ($p = 0.1262$) and sperm count ($p = 0.0712$) showed no significant differences among the groups (Figure 2).

Histological effects of ethanolic extracts of Polyalthia longifolia on induced BPH

Histological analysis of the prostate showed an increase in the size of acinar and glandular tissue; epithelial height in the inter-acinar connective tissue in the hormone-treated control compared to the untreated control. While the treatment groups showed a reduction in the epithelial size and a reduction in the number of acinar cells. There was an increase in the number of acinar cells per reference area, which is evidence that the extracts caused the shrinking of the gross prostate, reduction of the prostate cells' size, and the inter-acinar connective tissue (Figure 3).

Biochemical parameters

Lipid profile of treated and untreated animals at the end of 2 weeks of treatment. We observed no significant differences in TG and LDH across groups ($p \geq 0.05$), whereas TP ($p = 0.0183$), HDL ($p = 0.0009$), and CHOL ($p < 0.0001$) differed significantly. Post-hoc analysis showed elevated TP in HTC and HDPL, while both HDPL and LDPL exhibited significantly higher HDL and CHOL relative to UTC and HTC.

Electrolyte, urea, and globulin levels

At the end of 2 weeks of treatment, we observed a significant increase in S, P, U, and GLB ($p < 0.05$); however, no significant difference was observed in CL ($p = 0.1088$), which varied among groups. Post-hoc analysis revealed that HTC and HDPL exhibited elevated S, whereas HDPL showed significantly higher P, U, and GLB levels compared with UTC and HTC.

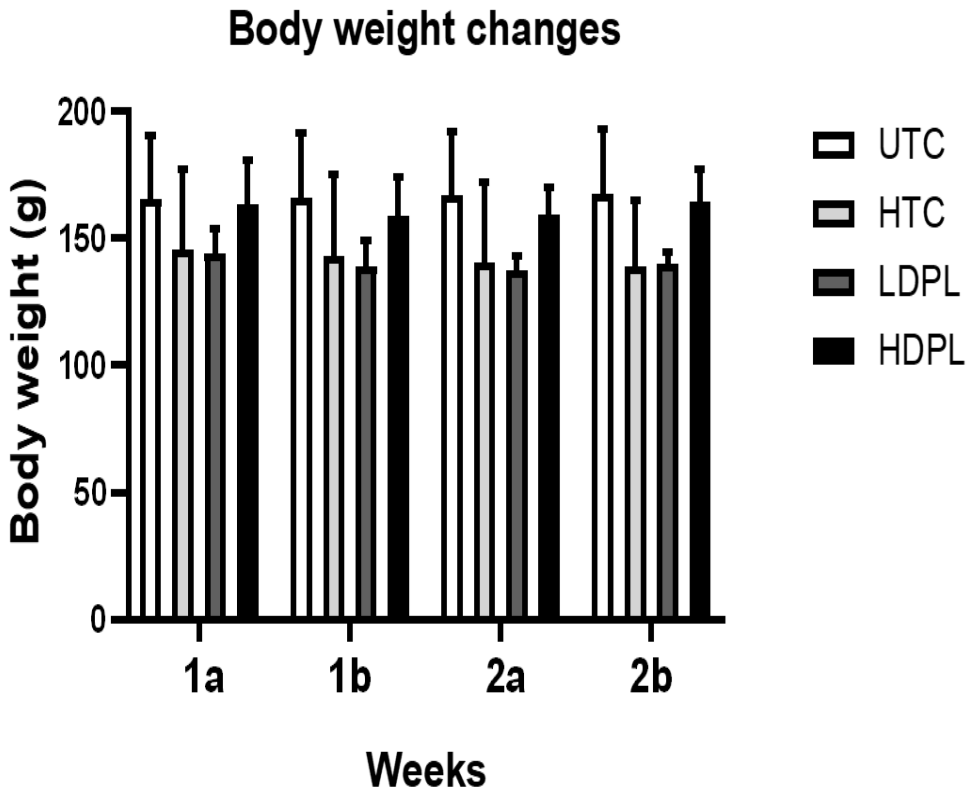

Figure 1: Data is presented as mean ± SD, and the differences in weight are statistically significant at P< 0.05. UTC- Untreated BPH induced control, Hormone treated control-HTC, LDPL- Induced BPH treated with low dose extracts, HDPL- Hormone treated with high dose extracts

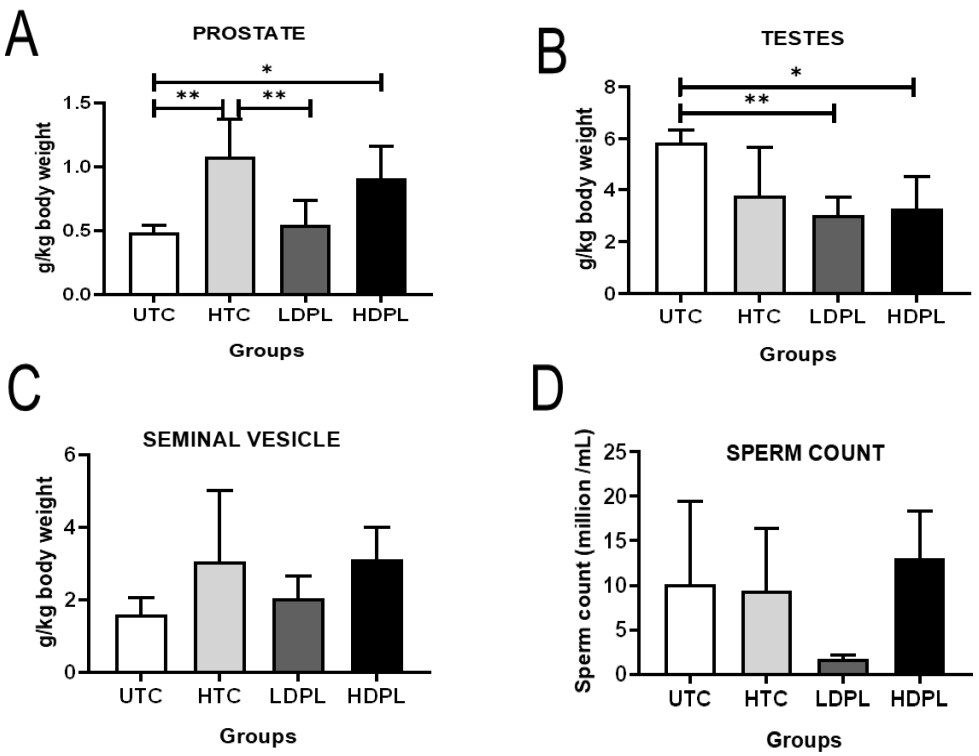

Figure 2: Data is presented as mean ± SD, and the differences in weight are statistically significant at P< 0.05. UTC- Untreated BPH induced control, Hormone treated control-HTC, LDPL- Induced BPH treated with low dose extracts, HDPL- Hormone treated with high dose extracts

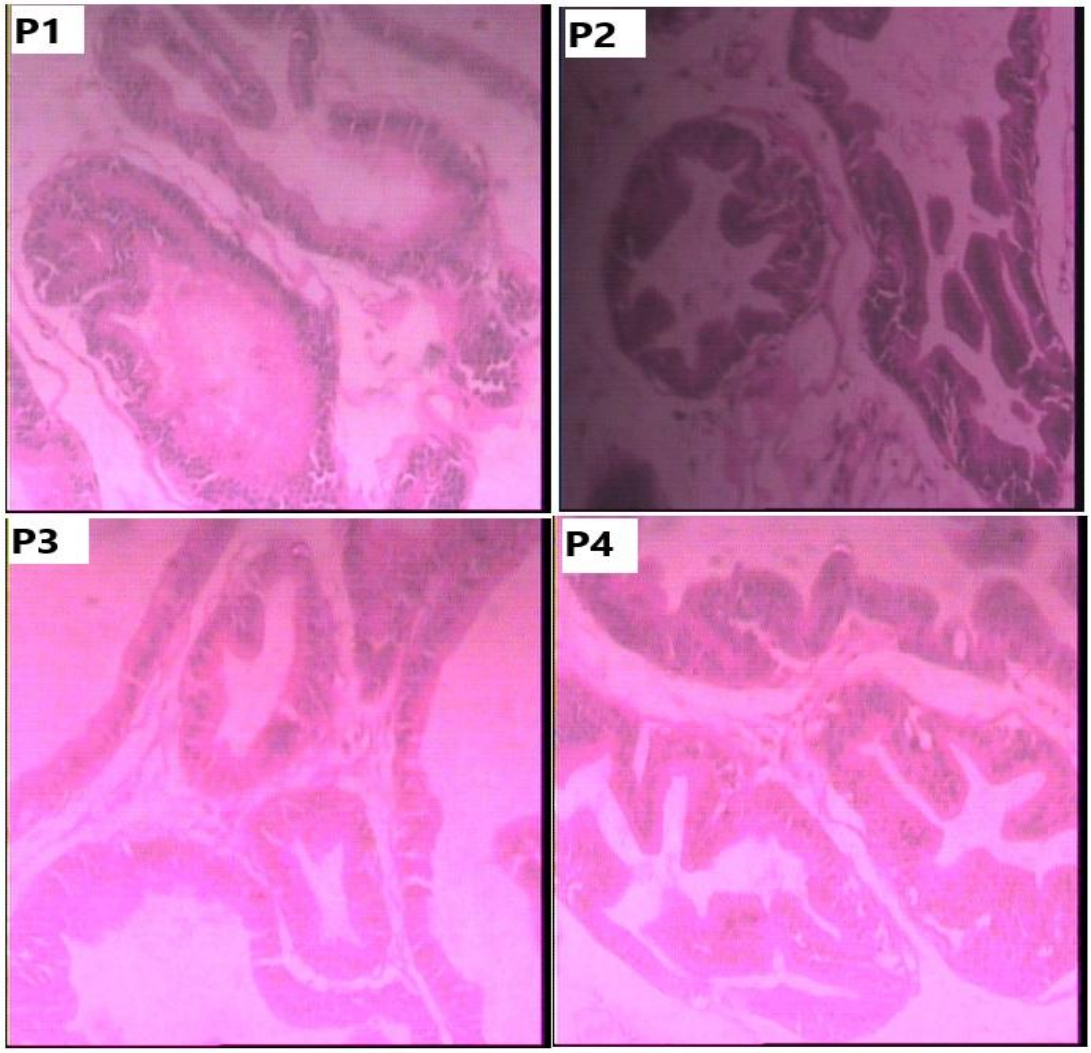

Figure 3: Photomicrograph of Prostate (H&E, X400). P1: Prostate normal control (UTC) group; **P2:** Prostate hormonal induced (HTC) group; **P3:** Prostate of high dose *Polyalthia longifolia* seed extracts treated (HDPL); **P4:** Prostate low dose of PL seed extracts treated (LDPL).

Table 1: Effects of Ethanolic Extracts of *Polyalthia longifolia* on Lipid Profile and LDH

Treatment	**UTC**	**HTC**	**LDPL**	**HDPL**	**SIG LEVEL**
TP (mg/dl)	6.9 ± 0.1	7.1 ± 0.1	7.05 ± 0.1	7.1 ± 0.1	0.0183* Yes
LDH (mg/dl)	122 ± 10.4	123± 10.1	125.5 ± 2.5	134± 10.7	0.1853 No
HDL (mg/dl)	44 ± 0	44 ± 1.6	46.5 ± 1	46.5 ± 1	0.0009*** Yes
CHOL(mg/dl)	97.7±4.0	96.5 ± 4.0	126.5± 7.5	126.5 ± 7.5	0.0001*** Yes
TG (mg/dl)	81.3 ± 4.6	67.9 ± 8.9	79.3 ± 2.5	85.5 ± 4.4	0.2723 No

Differences in weight are statistically significant at P< 0.05. UTC- Untreated BPH induced control, Hormone treated control-HTC, LDPL- Induced BPH treated with low dose extracts, HDPL- Hormone treated with high dose extracts. HDL-high density lipoprotein, TP- total protein, LDH-lactate dehydrogenase, CHOL- cholesterol, TG- triglyceride.

Table 2: Electrolyte, urea, and globulin Test. Data is presented as mean ± standard deviation

Treatment	UTC	HTC	LDPL	HDPL	SIG LEVEL
CL (mmol/dl)	97.3 ± 1.2	97 ± 1.2	98.5 ± 1.0	98 ± 0.0	0.0188 No
S (mmol/dl)	137.3 ± 1.2	137.± 1.2	139. ± 1.2	138.5± 1	0.0428* Yes
P (mmol/dl)	3.8 ± 0.1	4.1 ± 0.1	4. ± 0	4.1 ± 0.5	0.0357* Yes
U (mg/mol)	33.6 ± 2.9	37.3 ± 8.6	26.8 ± 3.8	41. ± 1.2	0.0591* Yes
GLB (g/dl)	2.9 ± 4.6	3 ± 0	3 ± 0	3.05 ± 0.1	0.0275* Yes

Differences in weight are statistically significant at P< 0.05. UTC- Untreated BPH induced control, Hormone treated control-HTC, LDPL- Induced BPH treated with low dose extracts, HDPL- Hormone treated with high dose extracts. CL- chloride ion. S- sodium, U-urea, P- potassium, GLB-globulin.

DISCUSSION

In several developing countries, such as Nigeria, herbal medicines are usually adopted for the management of different ailments. Medicinal plants are also currently accepted in many developed countries in Europe, Australia, and North America, where they are labelled as complementary or even alternative medicines[14]. The lack of scientific data to support the use of the herbs has remained a cause for concern, and the lack of scientific justification or poor-quality control may culminate in toxicity from bioactive constituents of the herbs[15,16,17].

Presently, this investigation assessed the potential of *P. longifolia*, a well-known medicinal plant, to restore or alleviate abnormalities in an experimentally induced BPH model. The lack of a significant time effect implies that body weight remained largely unchanged throughout the study duration, regardless of treatment group. This may suggest that the two-week observation window was too brief to capture measurable weight alterations, or that body weight in this model is not particularly responsive to change within such a short period. The significant overall treatment effect shows that body weight varied among the groups, yet the absence of notable pairwise differences in the post-hoc Tukey analysis indicates that these variations were minor or possibly attributable to individual variability rather than a consistent treatment effect. It is also possible that higher doses of *P. longifolia* did not translate into stronger effects on body weight under this experimental design, or that the sample size was insufficient to detect meaningful differences. The lack of a treatment -time interaction further suggests that treatment did not alter the trajectory of body weight across the study. This could mean that the treatment (whether low or high doses of *P. longifolia*) exerted a stable effect or no effect at all over the observation period, or that any potential outcomes may require a longer timeframe to become apparent. Similar to our findings, Nair *et al.*,[18] reported no gross behavioral alterations in mice administered *P. longifolia* extracts. Our results also suggest that neither high nor low doses of the extract suppressed food intake in the rats.

In this study, BPH was confirmed by a marked increase in relative prostate weight within the HTC group compared with the UTC group. Interestingly, the lower dose of *P. longifolia* produced a notable reduction in prostate weight, whereas the higher dose failed to significantly counter the prostate enlargement. In addition, neither dosage was able to restore relative testicular weight when compared with the UTC group. Histological analysis revealed that the extract reduced epithelial thickness and the number of acinar cells relative to the hormone-treated group, suggesting a partial restorative effect. Data from prostate and testis weights reinforce our earlier observations that prostate size increases significantly while testicular size decreases in this BPH animal model[18]. Consistent with earlier reports, our study confirms *P. longifolia* as a relatively non-toxic plant[19]. In previous work, we also demonstrated an increase in seminal vesicle weight accompanying prostate enlargement following hormonal treatment[19]. Although the increase in seminal vesicle weight was not statistically significant in this study, the trend resembled that observed for the prostate. Sperm count likewise did not vary significantly, though animals receiving the low dose showed the lowest values, likely reflecting inter-animal variability, as suggested by the wide standard deviations.

Total protein is often assessed in hepatic and renal disorders and is recognized as a biomarker of various metabolic imbalances. Albumin, the predominant plasma protein, contributes to vascular homeostasis and acts as a carrier for diverse molecules[20]. Reduced albumin levels have been documented in liver pathologies such as necrosis, impaired hepatic function, insulin resistance, and diminished oxidative phosphorylation[22]. In our experiment, both doses of *P. longifolia* significantly elevated total protein and

albumin levels, suggesting that the extract may support normal metabolic processes. These results align with Chanda *et al*.[20], who reported that methanolic extracts of *P. longifolia* did not compromise renal or hepatic function. Additionally, we observed that the higher dose significantly elevated globulin levels. Globulin is the second most abundant protein in the blood. Previous authors[23,24] reported significant decreases in total protein, albumin, and globulin concentrations in rats induced with BPH. In agreement with these findings, our results align with the work of Oyeyemi *et al*.[25], who demonstrated the hepatoprotective effects of *P. longifolia* aqueous and methanolic leaf extracts against cadmium-induced hepatotoxicity. The authors attributed these protective effects to the inhibition of oxidative stress in rats. Similarly, Jothy *et al*.[26] reported that the abundant phenols and flavonoids in *P. longifolia* restored liver health following paracetamol-induced injury in rats, further supporting the extract's effectiveness in maintaining normal liver functions.

Total Acid Phosphatase (TAP) was significantly increased in extract-treated groups compared with the control. Like most enzymes, TAP levels rise in response to injury in tissues rich in the enzyme[27]. Although the prostate contains the highest concentration of acid phosphatase, other organs, including the liver, also harbor appreciable amounts[28]. Elevated prostatic acid phosphatase (PAP) in patients with BPH has been linked to prostate enlargement and increased enzyme synthesis or expression[29]. Acid phosphatase activity in prostatic cancers is reported to be nearly threefold higher than normal.

Our findings indicate that both low and high doses of the extract significantly increased TAP levels, though values remained less than half of those recorded in the untreated and hormone-treated groups. Since TAP, and not PAP, was assayed in this study, it is likely that the observed elevation reflects enhanced protein output from the liver rather than prostatic changes. Alkaline phosphatase levels were not significantly altered, although higher values were observed in extract-treated groups, with the highest level recorded in rats receiving the high dose. By contrast, Adaramoye *et al*.[30] reported increased serum and prostatic acid phosphatase as well as elevated serum and prostatic alkaline phosphatase. The differences may be attributable to their use of a castrated rat model and a longer treatment period of four weeks, which may have amplified the hormonal effects on phosphatase activities. Collectively, these findings suggest that *P. longifolia* promotes hepatic protein release, including albumin and globulin, although the precise mechanisms remain to be elucidated.

Assessment of renal function frequently relies on urea accumulation, a by-product of protein catabolism excreted by the kidneys[31]. In our study, *P. longifolia* did not significantly alter urea levels at either dose; in fact, the lowest urea values were recorded in rats treated with the low dose. Chanda *et al*.[20] similarly reported no significant changes in urea levels in male rats administered varying doses of *P. longifolia* extract, consistent with our observations. These findings suggest that *P. longifolia* may suppress protein catabolism while enhancing protein synthesis.

Furthermore, Chanda *et al*.[20] observed a reduction in cholesterol levels in rats treated with the methanolic extract of *P. longifolia*, proposing that the plant exerts hypolipidemic effects and may confer protection against cardiovascular risk factors. However, closer scrutiny of their data reveals that the reduction in cholesterol was inconsistent and not dose-dependent. Results from gender-specific toxicological studies have shown that cholesterol levels were not significantly altered in male rats treated with varying doses of *P. longifolia* extract. In the present study, the extract did not significantly affect LDL cholesterol or triglyceride levels. However, both low and high doses significantly elevated total cholesterol and HDL cholesterol at the end of the experimental period. Since HDL cholesterol is widely regarded as the "good cholesterol"[32], this finding suggests that *P. longifolia* may confer cardiovascular protection and reduce the risk of atherosclerosis, stroke, and other cardiovascular abnormalities. Our data also suggest that *P. longifolia* contributes to homeostatic stability by protecting key electrolyte levels. Sodium, potassium, and chloride are the principal electrolytes responsible for fluid balance. While chloride levels were unaltered, sodium and potassium levels showed statistically significant differences; however, Post Hoc analysis revealed no intergroup differences, indicating that the observed changes were marginal and of limited physiological consequence.

In conclusion, the findings from this study suggest that *P. longifolia* is relatively safe, preserves prostate microstructure, and does not significantly alter body weight or key electrolyte levels. Importantly, it appears to enhance blood protein concentrations and modulate lipid profiles in Wistar rats with induced prostate enlargement within a two-week period. Further investigations, particularly with larger sample sizes and extended treatment durations, are warranted to provide greater insight into the mechanisms underlying the beneficial effects of *P. longifolia* in BPH.

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Conflict of interest

The authors declare no conflicts of interest.

Authors' contributions

Study conception, design, and supervision were carried out by OAA and AKA. JA performed the animal experiments, collected data, and drafted the initial manuscript. FNU and OJO contributed to data acquisition, analysis, interpretation, design modification, and co-drafting of the manuscript. SLAJ reviewed the data analysis and prepared the final draft. All authors contributed to the article and approved the submitted version.

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