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Hydroalcoholic Extract and Fractions of *Ficus sur* (Forssk) Ameliorate Pathophysiological Alterations Associated with Testosterone-Induced Benign Prostatic Hyperplasia in Male Wistar Rats

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Abstract: Medicinal plants possess a rich and diverse array of bioactive natural products. This study examined the effects of *Ficus sur* hydroalcoholic stem bark extract (FSSE), its ethyl acetate (EtOAc) and *n*-butanol (BuOH) fractions, in reversing physiological and histological abnormalities associated with testosterone-induced benign prostatic hyperplasia (BPH) in Wistar rats. The acute oral toxicity of the extract and the effect of FSSE and its EtOAc and BuOH fractions on BPH using the testosterone-induced BPH model in male Wistar rats over a 28-day treatment period were evaluated using established methods. Changes in prostate organ weight (PW) and indices (PI), biochemical indices such as serum testosterone, prostate-specific antigen (PSA), malondialdehyde (MDA), and superoxide dismutase (SOD) levels, and tissue histology were assessed following standard protocols. FSSE did not cause any toxic manifestations or mortality after 14 d of observation. Treatment with FSSE and its fractions significantly reduced ($P < 0.05$) PW and PI, and also produced a dose-dependent restorative decrease ($P < 0.05$) in serum testosterone and PSA levels. Also, a significant reduction ($P < 0.05$) in MDA and an increase ($P < 0.05$) in SOD levels, reflecting improved oxidative defense was observed in the extract- and fraction-treated groups. Key hepatic enzyme activities were unaltered, while the histological integrity of the prostate was preserved in the FSSE-treated groups. These findings establish the efficacy of *F. sur* hydroalcoholic stem bark extract and its fractions in reversing pathophysiological abnormalities associated with BPH in experimental rats, thereby providing scientific support for its ethnomedicinal application in urinary-related disorders.

Introduction

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate gland that manifests as lower urinary tract symptoms (LUTS), including urgency, frequency, and nocturia, which substantially impair urinary function and quality of life in affected men. The condition predominantly occurs in individuals over 60 years of age, with histological evidence of BPH present in nearly all men beyond the age of 80 (1 – 3). Although its precise etiology remains uncertain, multiple pathological mechanisms have been implicated, such as age-related hormonal alterations, structural changes within prostatic tissue, chronic inflammation, and metabolic dysregulation (4). Androgens play a pivotal role in the development and maintenance of the male reproductive system by stimulating the differentiation and proliferation of stromal and epithelial cells within the prostate. Two isoforms of the 5α-reductase enzyme are expressed in the prostate: type 1 and type 2, with the latter predominating in stromal cells. Type 2 catalyzes the conversion of testosterone into dihydrotestosterone (DHT), the principal androgen in prostatic tissue (5). DHT subsequently binds to androgen receptors, inducing conformational changes that modulate gene expression and promote cellular proliferation, thereby contributing to prostatic enlargement (6). Furthermore, emerging evidence highlights a correlation between inflammatory processes, prostate volume, and tissue mass, suggesting that inflammation may represent a

critical factor in the pathogenesis of BPH (7 – 9).

Standard therapeutic approaches for localized prostatic disorders, including benign prostatic hyperplasia (BPH), encompass surgical intervention, pharmacological management, and watchful waiting (1). Pharmacotherapy options comprise selective α1 A-adrenergic (ADRA1A) antagonists such as tamsulosin; 5α-reductase type 2 (5αR2) inhibitors including finasteride and dutasteride; antimuscarinic agents such as tolterodine and oxybutynin; β3-adrenergic agonists like mirabegron; and phosphodiesterase type 5 (PDE5) inhibitors, notably sildenafil and vardenafil. Dutasteride, a widely utilized 5α-reductase inhibitor, suppresses both isoforms (types 1 and 2), whereas finasteride selectively inhibits type 1 (10). Although these agents demonstrate efficacy in mitigating BPH-related symptoms, their use has been associated with adverse effects, including erectile dysfunction, cardiovascular complications, and, in some cases, acute urinary retention (11). These limitations have stimulated growing interest in phytotherapeutic interventions for BPH and related lower urinary tract symptoms (LUTS). The increasing adoption of herbal medicines may be attributed to their perceived effectiveness, favorable tolerability profile, and minimal impact on reproductive and cardiovascular functions compared to conventional pharmacotherapy (11). Experimental studies have documented beneficial effects of plant extracts in animal models of BPH (12, 13). Phytochemicals—naturally occurring, non-nutrient bioactive compounds—play a central role in mediating the therapeutic properties of plants (14). Classes of phytochemicals such as alkaloids, flavonoids, polyphenols, tannins, terpenoids, and saponins have demonstrated potential in drug discovery and the development of novel therapeutic agents for BPH (15, 16). Mechanistic investigations reveal that anti-BPH medicinal plants exert their effects through inhibition of 5α-reductase activity, modulation of androgen receptor signaling, attenuation of oxidative stress, and suppression of prostatic inflammation (16).

Ficus sur (synonym: *Ficus capensis*), commonly referred to as broom cluster fig, cape fig, or bush fig, belongs to the Moraceae family and is widely distributed across tropical regions of Africa. Traditionally, it has been employed in the management of diverse ailments, including disorders of the digestive, respiratory, endocrine, reproductive, urinary, and integumentary systems (17, 18). Ethnobotanical evidence indicates that various parts of *F. sur* are utilized in treating swellings and urinary tract disorders characteristic of benign prostatic hyperplasia (BPH) (19). In Ethiopia's Dugda district, a folkloric preparation comprising crushed fresh leaves and stem bark of *F. sur* was reported to alleviate urinary retention and enhance urine output (20). The observed improvement in urinary function may be attributable to the plant's phytoconstituents, which are presumed to exert modulatory effects on neuromuscular activity and excretory pathways within the urinary tract. Previous investigations have documented the presence of diverse phytochemicals in *F. sur*, alongside a broad spectrum of biological activities—including antioxidant, antimicrobial, cytotoxic, diuretic, and anti-inflammatory properties—demonstrated in both *in vivo* and *in vitro* models (21, 22). Despite its longstanding use in traditional medicine for urinary disorders, pharmacological validation of these claims remains limited. This underscores the need for rigorous scientific evaluation of *F. sur* in experimental models to establish its therapeutic potential in the management of BPH and associated urinary conditions.

Methodology

Plant Materials, Collection, and Extraction

The stem bark of *F. sur* was harvested from its natural habitat in Ibadan, Oyo State, Nigeria (**Figure 1**), by a Taxonomist at the Forest Research Institute of Nigeria (FRIN), Ibadan. Botanical authentication was conducted at FRIN, and a voucher specimen (FHI113940) was deposited in the institute's herbarium. The collected stem bark was air-dried, pulverized, and subjected to exhaustive extraction with 80% ethanol (7.50 L) by maceration at ambient temperature (26 – 32 °C) for 3 d. The resulting mixture was filtered through Whatman No. 4 filter paper, and the filtrate was concentrated under reduced pressure at 50 °C to yield the crude hydroalcoholic extract of *F. sur* stem bark (FSSE), with a final weight of 286.00 g, corresponding to a 5.72%$^{w}/_{w}$ yield.



Figure 1. *F. sur* in its natural habitat showing the stem bark and fruits (A) and the peeled, dried stem bark (B).

Fractionation of *F. sur* Hydroalcoholic Extract

The modified Kupchan solvent partitioning method, as outlined by Van-Wagenen *et al.* (23), was employed to fractionate the crude extract. Briefly, the extract was suspended in a 2 L separating funnel containing 200 mL of a water/methanol mixture (90:10, $^{v}/_{v}$) and sequentially partitioned with dichloromethane (3 × 500 mL), ethyl acetate (4 × 500 mL), and *n*-butanol (4 × 500 mL). Each solvent fraction was subsequently concentrated under reduced pressure at 40 °C, except for the *n*-butanol fraction, which was concentrated in a thermostatic water bath at 50 °C. This process yielded dichloromethane (DCM) (15.80 g, 6.32%), ethyl acetate (EtOAc) (45.96 g, 16.78%), and *n*-butanol (BuOH) (52.69 g, 21.08%) fractions. The EtOAc and BuOH fractions were selected for subsequent biological screening.

Pharmacological Screening

Experimental Animals

Male Wistar rats (180 – 220 g) were employed for the biological investigations. Animals were housed in well-ventilated cages under controlled environmental conditions at 22 ± 3 °C, with a 12-h natural light/dark cycle, and acclimatized for 14 d before experimentation. Standard rodent chow and water were provided *ad libitum*. All procedures involving animals were conducted in accordance with the ethical guidelines for the care and use of laboratory animals established by the National Research Council (24). Ethical approval for the study was obtained from the Ethics Committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria (Approval No. EC/FP/024/02).

Acute Oral Toxicity Study

The acute oral toxicity assessment was performed in accordance with the OECD (Organization for Economic Co-operation and Development) Test Guideline No. 423 (25). Ten male Wistar rats were randomly assigned to experimental and control groups. Animals in the treatment group received a single oral limit dose of *F. sur* extract at 2000 mg/kg body weight, while the control group was administered distilled water (10 mL/kg body weight). Before dosing, rats were fasted for 3 – 4 h with free access to water. Following administration, animals were observed continuously for 30 min and subsequently monitored for 4 h to detect any immediate toxic responses. After confirming survival of the initially treated rat, four additional rats were dosed under identical conditions. Clinical signs of toxicity, adverse effects, or mortality were recorded daily throughout the study. All animals were further observed for 14 d to identify any delayed toxic manifestations or deaths.

Testosterone-induced Benign Prostatic Hyperplasia Activity

The *in vivo* testosterone-induced benign prostatic hyperplasia (BPH) model in male Wistar rats, as described by Mbaka *et al.* (26), was employed to evaluate the efficacy of the crude extract and its solvent fractions. A total of 60 male Wistar rats (180 – 220 g) were randomly assigned into ten groups (n = 6). Group 1 (positive control) received the vehicle (10 mL/kg body weight, b.w.); Group 2 (negative control) served as the BPH-disease group without treatment; Group 3 was administered finasteride (standard drug) at 10 mg/kg b.w.; Groups 4 – 6 received graded doses of the crude hydroalcoholic extract (FSSE) at 100, 200, and 400 mg/kg b.w., respectively; Groups 7 and 8 were treated with 200 and 400 mg/kg b.w. of the ethyl acetate (EtOAc) fraction; while Groups 9 and 10 received 200 and 400 mg/kg b.w. of the *n*-butanol (BuOH) fraction. To induce prostatic hyperplasia, all groups except Group 1 were administered testosterone enanthate subcutaneously at 5 mg/kg b.w. daily for 28 d. At the end of the experimental period, rats were euthanized under ketamine anesthesia, and the prostate glands were excised, weighed, and subjected to histopathological examination. Blood samples were collected via cardiac puncture for biochemical analyses, including prostate-specific antigen (PSA), serum testosterone, superoxide dismutase (SOD), lipid peroxidation (malondialdehyde, MDA), and liver function tests (LFT).

Body and Prostate Weight Changes of Rats

The rats' body weight was taken at the beginning and end of the study. The prostate index, also known as the prostate weight to body weight ratio, was determined by dividing prostate weight in milligrams by the animal's body weight in grams (27).

Biochemical Analysis

Following anesthesia, blood samples were collected via cardiac puncture. Serum prostate-specific antigen (PSA) and testosterone concentrations were determined using Accubind ELISA kits (Monobind, Lake Forest, CA92630, USA) in accordance with the manufacturer's instructions. Prostate tissues were excised, homogenized in 0.03 M phosphate buffer (pH 7.4), and centrifuged at 10,000 rpm for 15 min at 4 °C to obtain supernatants for biochemical analysis to determine oxidative stress markers (28). Lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels through the thiobarbituric acid-reactive substances (TBARS) assay, wherein MDA reacts with thiobarbituric acid to form a chromogen with absorbance measured at 532 nm using an ELISA reader (29). Superoxide dismutase (SOD) activity was evaluated using commercial assay kits (Elabscience, USA) according to the manufacturer's protocol.

Tissue Histology

Histological evaluation of the prostate tissues from the experimental animals was performed following the method described by Drury *et al.* (30) as reported by Ekeyi *et al.* (31). Briefly, excised prostate samples randomly collected from each group were fixed in 10% phosphate-buffered formalin for approximately 48 h and subsequently processed using standard histopathological techniques. Microscopic examination and photomicrographic documentation were carried out using a Biobase® light microscope.

Evaluation of Liver Status

Liver function parameters were assessed using Randox diagnostic kits (UK). Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by the colorimetric method of Reitman and Frankel (32). Alkaline phosphatase (ALP) activity was

measured following the protocol of Walter *et al.* (33), which is based on the enzymatic hydrolysis of colorless phosphate esters of alcohols and phenols by alkaline phosphatase, yielding *p*-nitrophenol. In alkaline solution, *p*-nitrophenol appears as the yellow nitrophenolate ion, enabling spectrophotometric quantification.

Statistical Analysis

Statistical comparisons between groups were conducted using One-way ANOVA. To compare the means between the test and control groups, the *post hoc* Dunnett's test was used. The results were presented as mean ± standard

Table 1. Effect of FSSE and fractions on prostate weight changes and index in BPH-induced rats.

Extracts and fractions	Body weight			Prostate weight (g)	Prostate index (mg/g)
	Initial (g)	Final (g)	Change		
Group 1	184.2 ± 8.176	225.8 ± 9.436	41.6 ± 3.894	0.4618 ± 0.015*	2.021 ± 0.172*
Group 2	188.2 ± 21.14	214.6 ± 20.13	26.4 ± 5.105	0.9522 ± 0.051[a]	5.228 ± 0.356[a]
Group 3	159.2 ± 8.726	183.0 ± 11.08	23.8 ± 7.819	0.5688 ± 0.018*	2.824 ± 0.148*
Group 4	179.4 ± 2.088	198.6 ± 4.654	19.2 ± 4.271	0.649 ± 0.026*[a]	3.625 ± 0.141*[a]
Group 5	165.6 ± 8.687	201.8 ± 9.233	36.2 ± 8.027	0.6632 ± 0.045*[a]	3.276 ± 0.102*[a]
Group 6	180.6 ± 8.536	218.2 ± 8.552	37.6 ± 8.232	0.604 ± 0.022*	2.710 ± 0.095*
Group 7	191.2 ± 10.1	219.0 ± 8.301	27.8 ± 4.641	0.6866 ± 0.035*[a]	2.991 ± 0.153*
Group 8	191.6 ± 4.19	205 ± 12.320	18.00 ± 9.783	0.6502 ± 0.065*[a]	2.643 ± 0.371*
Group 9	179.8 ± 10.41	211 ± 11.550	31.2 ± 4.454	0.6876 ± 0.052*[a]	3.384 ± 0.321*[a]
Group 10	204.8 ± 9.795	216.6 ± 8.304	11.8 ± 10.450*[a]	0.649 ± 0.040*[a]	2.655 ± 0.322*

Note: Data represent mean ± SEM (n = 6); Values with '*' are significantly different compared to BPH-control, while values with the letter 'a' are significantly different compared to normal control ($P < 0.05$). Group 1 = Normal control (not BPH-induced and no treatment). Group 2 = BPH-control (BPH-induced but no treatment). Group 3 = Standard control (induced and treated with finasteride). Groups 4, 5, and 6 = induced and treated with 100, 200, and 400 mg/kg of FSSE, respectively. Groups 7 and 8 = induced and treated with 200 and 400 mg/kg of EtOAc fraction, respectively. Groups 9 and 10 = induced and treated with 200 and 400 mg/kg of BuOH fraction, respectively.

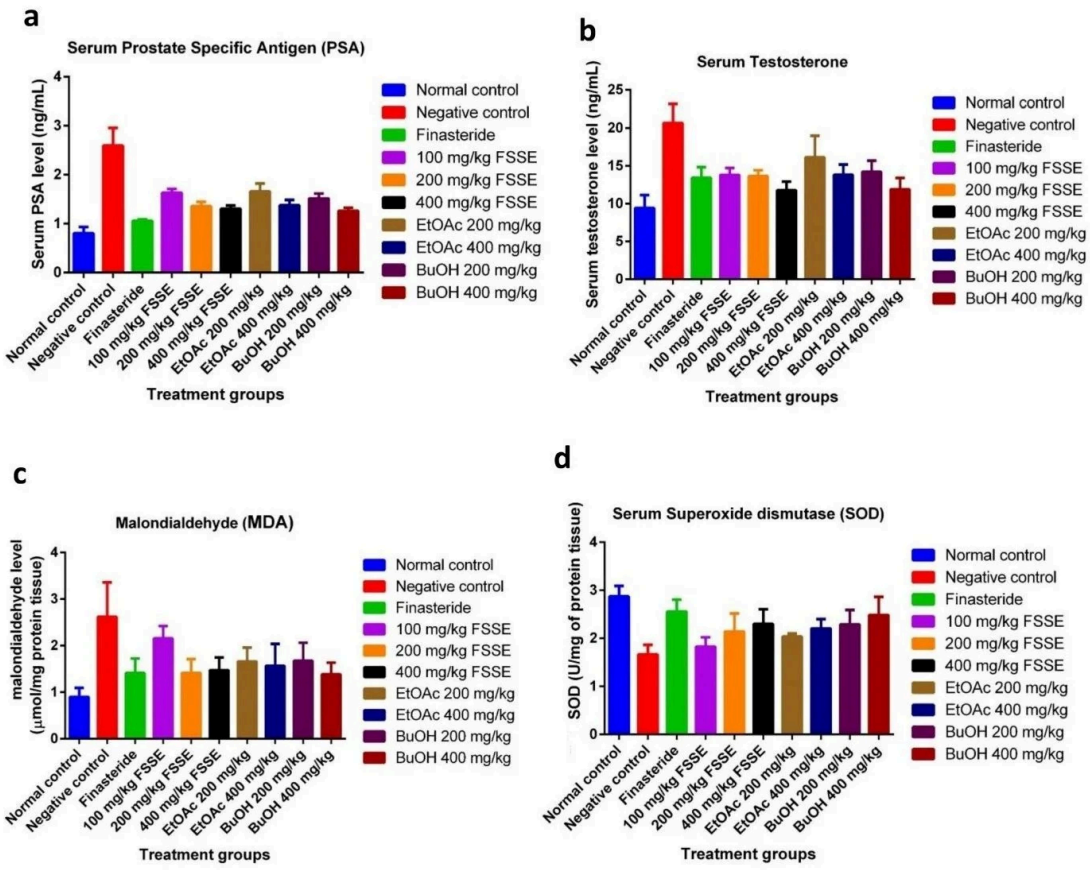


Figure 2. Effect of FSSE and fractions on biochemical parameters in testosterone-induced BPH study. Legend: a – serum prostate-specific antigen (PSA); b – serum testosterone; c – malondialdehyde (MDA); d – serum superoxide dismutase (SOD). Data represent mean ± SEM (n = 6); Values with '*' are significantly different compared to BPH-control, while values with the letter 'a' are significantly different compared to the normal control group; $P < 0.05$ is considered significantly different.

error of the mean (SEM), and the significance level was set at $P < 0.05$. All statistical analyses were done using GraphPad Prism Software Version 9.0 (GraphPad Software Inc., United States).

Results

Acute Oral Toxicity

The hydroethanolic extract of *F. sur* stem bark did not elicit any toxic manifestations or mortality at a single oral dose of up to 2000 mg/kg body weight in Wistar rats of both sexes. Throughout the 14-day observation period, no treatment-related behavioral alterations, morbidity, or mortality were recorded. Accordingly, the extract was considered non-toxic at the tested dose and deemed safe for subsequent pharmacological evaluation.

Effect of FSSE and the Fractions on Prostate Weight and Prostatic Index

Table 1 presents the changes in body weight, prostate weight (PW), and prostate index (PI) of the experimental rats. PW and PI are recognized as critical indicators of the onset and progression of benign prostatic hyperplasia (BPH). Administration of testosterone significantly increased PW in the BPH-disease control group compared to the normal control. Treatment with the crude hydroalcoholic extract (FSSE) at 200 and 400 mg/kg, as well as its solvent fractions (EtOAc and BuOH), produced a dose-dependent reduction in PW relative to the BPH-disease group. A comparable effect was observed in the finasteride-treated group. Furthermore, extract- and fraction-treated rats exhibited a significant decrease ($P < 0.05$) in PI compared to the negative control group, underscoring the protective effect of *F. sur* against testosterone-induced prostatic enlargement.

Evaluation of Biochemical Parameters

Prostate-specific antigen (PSA), a key biomarker in the clinical diagnosis of BPH, was markedly increased ($P < 0.05$) in the disease group compared to the normal control. Extract-and fraction-treated groups demonstrated significant reductions ($P < 0.05$) in PSA levels relative to the BPH-disease group, indicating protective effects against prostatic hyperplasia. The testosterone-induced BPH-disease group exhibited a significant elevation ($P < 0.05$) in serum testosterone levels compared to the normal control (**Figure 2b**). Conversely, treatment with the crude extract, solvent fractions, and finasteride resulted in a significant reduction ($P < 0.05$) in serum testosterone relative to the negative control group. These findings suggest that elevated serum testosterone contributes to the development and progression of BPH via the androgen signaling pathway. Malondialdehyde (MDA), a marker of lipid peroxidation, was significantly elevated ($P < 0.05$) in the BPH-disease group compared to the normal control. Treatment with finasteride, FSSE, and its fractions significantly reduced ($P < 0.05$) MDA levels relative to the

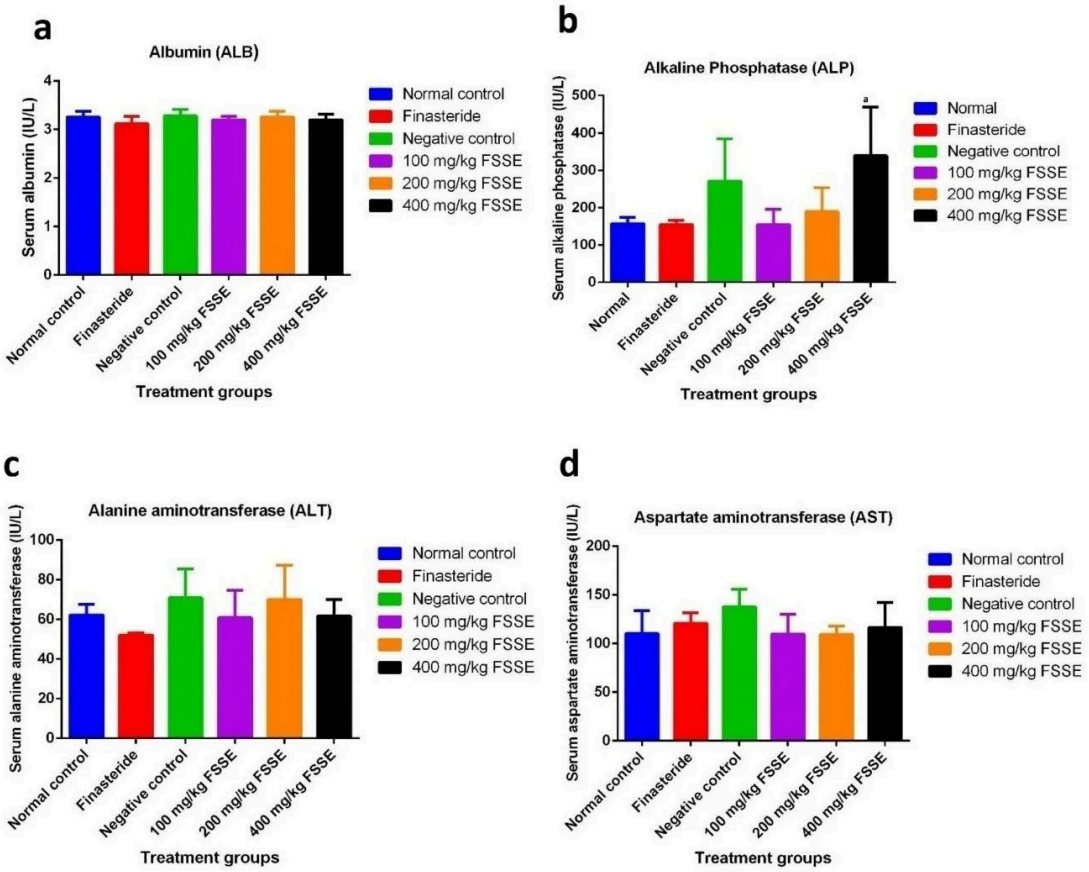


Figure 3. Effect of FSSE on the liver status of BPH-induced male Wistar rats. Legend: a – albumin (ALB), b – alkaline phosphatase (ALP), c – alanine aminotransferase (ALT), d – aspartate aminotransferase (AST). Data represent mean ± SEM (n = 6); Values with 'a' are significantly different compared to normal control ($P < 0.05$).

negative control group (**Figure 2c**), highlighting their antioxidative potential. *In vivo* antioxidant activity, assessed by serum superoxide dismutase (SOD) levels, revealed that extract-and fraction-treated groups exhibited significantly increased ($P < 0.05$) SOD activity compared to the negative control group (**Figure 2** d). This suggests that the treatments may mitigate oxidative stress pathways implicated in BPH pathogenesis.

Effect of the Extract on Liver Function Status

The activities of liver marker enzymes (ALP, AST, ALT, and ALB) in the extract-treated groups did not differ significantly from those of the normal control (**Figure 3**). However, Group 6, which received 400 mg/kg of FSSE, exhibited a significant elevation ($P < 0.05$) in ALP levels compared to the normal control. Elevated serum activities of these enzymes are commonly associated with hepatic injury or dysfunction and may serve as clinical indicators of compromised liver function (34).

Histological Examination

Histological examination of prostate tissues revealed distinct morphological differences across the experimental groups (**Figure 4**). In the normal control group, the prostate displayed regular acini and intact stromal architecture, lined by columnar epithelial cells with clear basal nuclear polarity (**Figure 4a**). In contrast, the BPH-disease (negative control) group exhibited marked epithelial proliferation and stromal infiltration by inflammatory cells, consistent with prostatic hyperplasia (**Figure 4b**). Treatment with finasteride (**Figure 4c**) and FSSE at 100 and 200 mg/kg (**Figure 4d** – **f**) resulted in moderate epithelial proliferation with preserved acinar structures and slight dilation, indicating partial amelioration of hyperplastic changes.

Discussion

Notable variations in BPH burden across regions highlight its substantial impact and underscore its significant public health impact and highlight the urgent need for effective management strategies (35). This study investigated the therapeutic potential of the hydroalcoholic stem bark extract of *F. sur* (FSSE) and its ethyl acetate (EtOAc) and *n*-butanol (BuOH) fractions in a testosterone-induced BPH model in male Wistar rats. Prostatic hyperplasia was induced by continuous administration of testosterone for 28 d, and disease progression was evaluated through behavioral parameters (urination frequency and prostate-to-body weight ratio), biochemical assays, and histopathological analysis, as previously described by Akbari *et al.* (27) and Ekeyi *et al.* (31).

Although the etiology of benign prostatic hyperplasia (BPH) is multifactorial, substantial evidence implicates androgens—particularly testosterone and its more potent metabolite, dihydrotestosterone (DHT)—in the pathogenesis of the disease via the androgen-signaling axis (4, 36). Elevated systemic testosterone enhances intraprostatic conversion to DHT, which drives abnormal

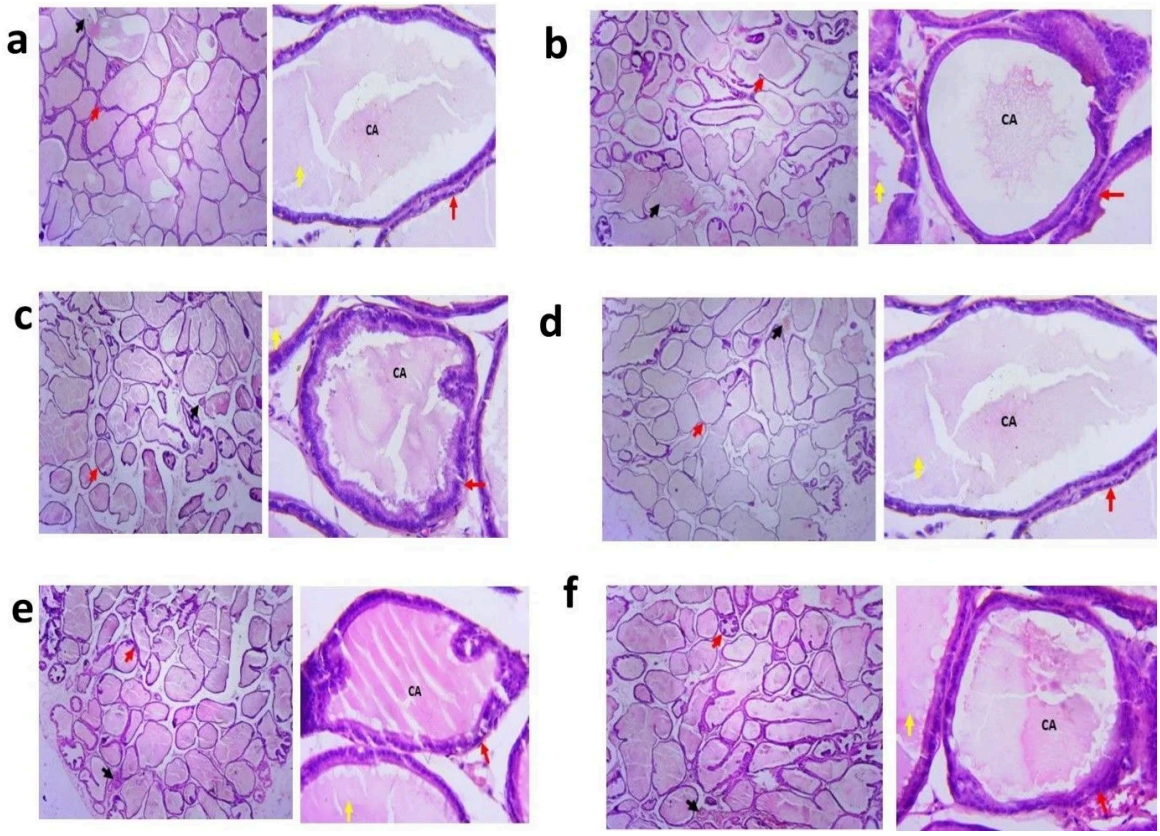


Figure 4. Photomicrographs showing the histoarchitecture of the prostate stained with H and E (Mag. x 800). Legend: Red arrow – secretory epithelium; Black and Yellow arrows – corpora amylacea; CA - corpora amylacea; a - normal control group; b – negative control group; c - finasteride group; d - FSSE (100 mg/kg) group; e - FSSE (200 mg/kg) group; f - FSSE (400 mg/kg) group.

prostatic growth and hyperplasia (36). The testosterone-induced BPH model employed in this study is a well-established experimental framework for assessing the efficacy of candidate agents against prostate-related disorders, as it replicates key pathological features of the human condition, including increased prostate weight, histological hyperplasia, and altered urinary dynamics, largely mediated by heightened intraprostatic DHT activity (37). Treatment with FSSE and its fractions significantly mitigated prostatic enlargement, reducing prostate indices in a manner comparable to finasteride, the standard reference drug. In contrast, the untreated BPH-disease group exhibited marked increases in body and prostate weights, likely attributable to water retention secondary to transient elevations in testosterone. These findings are consistent with established evidence that exogenous testosterone administration in rodents promotes prostate gland growth and enlargement (38).

Pharmacological modulation of 5α-reductase type 2 (5αR2) activity reduces intraprostatic DHT concentrations, thereby attenuating prostate enlargement. Similarly, adrenergic receptor subtype ADRA1A and phosphodiesterase-5 (PDE5) are directly involved in regulating smooth muscle tone and urinary flow (39). In the present study, the significant reduction in serum testosterone levels observed in the extract- and fraction-treated groups underscores the potential of *F. sur* to modulate androgen signaling pathways. This hormonal regulation likely contributed to the attenuation of prostatic enlargement mediated by excessive testosterone activity, aligning with the mechanistic basis of current therapeutic strategies for BPH. However, more elaborate *in vivo* investigations targeting these molecular pathways, coupled with rigorous symptomatic assessments of experimental rats—a component lacking in the present study—would provide a more comprehensive evaluation of both disease-modifying and symptom-relieving effects of the extract and its fractions. Such an approach would bridge mechanistic insights with physiological outcomes, thereby strengthening the translational relevance of the findings.

Monitoring biochemical markers is essential for evaluating the onset and progression of benign prostatic hyperplasia (BPH). A consistent feature reported in BPH studies is the altered status of key antioxidant enzymes within prostatic tissue. Extensive evidence demonstrates that enzymes such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) are markedly reduced in patients with BPH, thereby exacerbating oxidative stress and contributing to cellular apoptosis and DNA damage. Conversely, upregulation of these enzymes mitigates BPH progression by enhancing the clearance of reactive oxygen species (ROS), attenuating chronic inflammation, and restoring physiological cell turnover (40, 41).

SOD plays a pivotal role in endogenous antioxidant defense by catalyzing the conversion of superoxide radicals into hydrogen peroxide, which is subsequently detoxified by glutathione peroxidase and catalase into water and oxygen. In the present study, SOD activity was dose-dependently enhanced in the extract- and fraction-treated groups, suggesting an improvement in antioxidant capacity. This enhancement likely contributed to the mitigation of BPH progression by counteracting oxidative stress arising from excessive ROS accumulation within the prostate gland. In contrast, a reduced activity of this enzyme, as observed in the untreated BPH-disease group, reflects a diminished capacity to neutralize ROS, promoting oxidative stress, cellular dysfunction, and eventual cell death. This observation aligns with previous reports that individuals with benign prostatic hyperplasia experience systemic oxidative stress triggered by an imbalance between the production of reactive oxygen species (ROS) and diminished antioxidant defenses (40–42).

Malondialdehyde (MDA), a by-product of lipid peroxidation, is widely employed as a biomarker of oxidative damage (43). The progression of BPH has been strongly linked to increased lipid peroxidation, heightened inflammatory responses, and diminished antioxidant defenses (40, 44). Elevated MDA levels reflect enhanced lipid peroxidation and tissue injury, both of which contribute to BPH pathogenesis (45). The protective effects observed with FSSE and its fractions may be attributed to their rich content of secondary metabolites, including polyphenols, flavonoids, and terpenoids, which are well-documented for their antioxidant properties. These phytochemicals can attenuate lipid peroxidation by scavenging free radicals and preventing oxidative damage (46).

Prostate-specific antigen (PSA), a protein secreted by prostate epithelial cells, serves as a critical biomarker for monitoring BPH progression, prostate cancer, and therapeutic efficacy. Elevated PSA levels are indicative of prostatic enlargement and dysfunction (47). In this study, PSA levels were significantly reduced in testosterone-induced BPH rats treated with FSSE and its fractions, suggesting inhibition of pathological processes associated with BPH development. This finding corroborates earlier reports demonstrating that plant extracts and fractions can reverse BPH-related anomalies, including elevated PSA levels, thereby improving prostate health (48–50).

Several synthetic medications have been linked to hepatotoxicity, often resulting in treatment complications and discontinuation. In this study, the reduction in serum activities of AST, ALT, and ALP observed in BPH-induced rats treated with *F. sur* stem bark extract suggests that the extract is unlikely to exert hepatotoxic effects. Typically, elevated serum levels of these enzymes are indicative of liver injury caused by hepatotoxins (34). Hepatic damage is characterized by increased hepatocyte membrane permeability, congestion, cellular rupture, leakage of intracellular components into the bloodstream, bile duct obstruction, or direct injury to liver tissue (51). Importantly, treatment with FSSE did not produce significant elevations in liver enzyme activities across the experimental groups. Although a slight increase in ALP was noted at the highest dose (400 mg/kg body weight), such an isolated change is not considered a reliable marker of hepatotoxicity unless accompanied by additional physiological or behavioral abnormalities. Collectively, these findings indicate that the doses of FSSE administered in this study can be regarded as safe with respect to liver function.

Histological evaluation revealed distinct differences in prostatic architecture across the experimental groups (**Figures 4a – f**). In the normal control group,

photomicrographs displayed well-preserved stromal tissue and typical acini lined by columnar epithelium with nuclei exhibiting clear basal polarity. In contrast, the BPH-disease group demonstrated pronounced epithelial proliferation and a reduction in prostatic tubules, consistent with hyperplastic changes. These alterations align with previous reports by Akbari *et al.* (27) and Ikeyi *et al.* (48), which documented the impact of exogenous testosterone administration on prostatic tissue in BPH-induced male Wistar rats. Treatment with FSSE and its fractions resulted in minor acinar dilation and moderate epithelial proliferation, suggesting partial restoration of normal histological structure. The mechanism underlying this protective effect may involve modulation of androgen signaling, particularly the interaction between dihydrotestosterone (DHT) and androgen receptors. Such modulation enhances protein synthesis, cellular differentiation, and the maintenance of prostatic cell integrity, thereby contributing to improved tissue architecture and function (52 – 54).

Conclusion

This study established the efficacy of the hydroalcoholic stem bark extract and fractions of *F. sur* in attenuating pathological alterations associated with testosterone-induced benign prostatic hyperplasia in male Wistar rats. Treatment with the extract and fractions normalized key biochemical parameters—including testosterone, prostate-specific antigen (PSA), malondialdehyde (MDA), and superoxide dismutase (SOD)—and improved histological profiles, thereby confirming significant anti-BPH activity. To the best of our knowledge, this represents the first comprehensive evaluation of *F. sur* stem bark extract and fractions in a testosterone-induced BPH model, providing experimental validation for its ethnomedicinal use in urinary disorders. Future research should emphasize detailed mechanistic investigations, together with the isolation and characterization of bioactive constituents, and the conduct of well-designed clinical studies. Such efforts would advance novel drug discovery strategies for the management of benign prostatic hyperplasia and other urinary-related disorders.

Abbreviations

BPH= Benign Prostatic Hyperplasia; DHT = Dihydrotestosterone; LUTS = Lower Urinary Tract Symptoms; PSA = Prostate Specific Antigen; ROS = Reactive Oxygen Species.

Declaration

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

All data generated during and/or analyzed during the current study are presented within this article.

Ethics Statement

All animal procedures adhered to ethical guidelines for the care and welfare of research animals as stipulated by the National Research Council (NRC, U.S.). Ethical approval was granted by the Ethics Committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria (EC/FP/024/02).

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Additional Information

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