Research Article Open Access

A clinical investigation to determine the safety and efficacy of a novel, patented prunus domestica extract in benign prostatic hyperplasia

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Submission Date: January 15th, 2025; **Acceptance Date:** February 25th, 2025; **Publication Date:** February 28th, 2025

Please cite this article as: Sankhwar. S. N., Verma N., Patel N., Kumar P., Goel A., Rungta M. A clinical investigation to determine the safety and efficacy of a novel, patented prunus domestica extract in benign prostatic hyperplasia. *Functional Foods in Health and Disease* 2024; 15(2): 129-143. DOI: https://doi.org/10.31989/ffhd.v15i2.1556

ABSTRACT

Background: Benign Prostate Hyperplasia (BPH) is defined as a non-cancerous enlargement of the prostate gland that is frequently observed in males over 50 years. The major symptoms of the disease involve difficulty urinating, urine dripping, incomplete bladder emptying, and, in severe cases, urine backflow that may lead to kidney infections. Conventional treatments, such as alpha-adrenergic receptor antagonists and Type 2 5-alpha reductase inhibitors, are often associated with significant side effects. In contrast, conventional drugs are based on alpha-adrenergic receptor antagonists or Type 2 5-alpha reductase inhibitors; phototherapeutics —especially phytosterols from the plum family, *Prunus domestica* and *Prunus africana*—have shown promise in BPH treatment by lowering prolactin and cholesterol levels in the prostate.

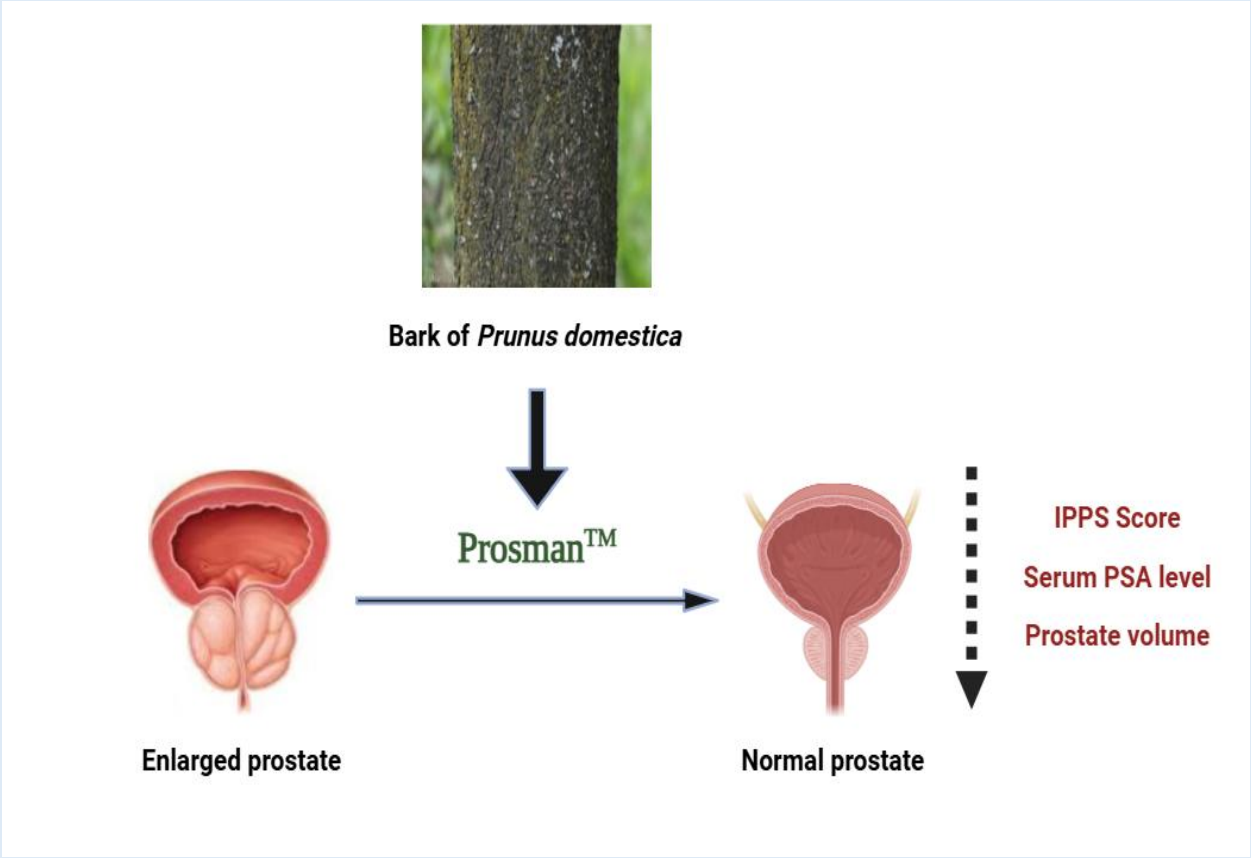
Objectives: This research aimed to conduct a robust clinical trial to evaluate the effects of Prosman™, a novel patented and standardized extract of *Prunus domestica*, in patients aged 40–65 years with BPH

Material and Methods: An open-labeled single-armed study on 140 male patients of BPH aged 40-65 years. Prosman™ was administered in a dosage of 100 mg twice a day for 12 weeks, with follow-ups at weeks 4, 8, and 12. Efficacy was evaluated through biochemical tests, including blood tests for Prostate-Specific Antigen (PSA), ultrasound, and urinary flow tests. Safety was assessed through analysis of various blood parameters, including hemoglobin, total leukocyte count, differential leucocyte count, SGOT, SGPT, and ALP levels, along with monitoring urea and creatinine levels.

Results: *Prunus Domestica* extract (Prosman™) was efficacious and effective in alleviating BPH in subjects, as confirmed, evidenced by a reduction in IPSS score, prostate volume, and serum PSA levels. No significant adverse changes were observed in the hematological parameters.

Conclusion: *Prunus Domestica* extract (Prosman™) can, therefore, be explored as a safe and effective phototherapeutics for the development of novel treatment procedures for BPH.

Keywords: Benign Prostatic Hyperplasia (BPH); *Prunus domestica*; Clinical Investigation; Urinary dysfunction, prostate enlargement; Prostate specific antigen (PSA); Ultrasound; Safety



INTRODUCTION

The prostate gland, located just below the bladder and in front of the rectum, is associated with several vital physiological functions. This includes Prostate-specific secretion of Prostate-specific antigens vital for maintaining the optimal viscosity of the semen, conversion of testosterone into dihydrotestosterone to augment male sexual desire, and mediating contraction of the urethral muscle for the ejaculation of semen through the urethra. Benign prostate hyperplasia (BPH) is a condition in which the prostate gland is enlarged without any cancerous transformation. This condition is believed to occur due to multiple factors ranging from changes in hormonal balance [1], chronic cardiovascular diseases [2], and, most frequently, aging [3]. As evidenced by histopathological changes, BPH has been found to affect more than 50% of the population aged between 50 and 60 years [4]. The pathophysiology of the disease has not been extensively studied to date [5]. The primary effect of an enlarged prostate, affecting both stromal and epithelial components, is the development of Lower Urinary Tract Symptoms (LUTS), characterized by the progressive blockage of the proximal urethra, and obstruction in the urethral release of both urine as well as semen. This incomplete emptying of the urinary bladder results in an urge for frequent urination, a hallmark of the disease, which, in more advanced cases, may lead to backflow of urine, increasing the risk of bladder or kidney infections.

The molecular basis of the disease has been primarily linked to the loss of testosterone's regulation of androgens, specifically testosterone itself. The central hypothalamic-pituitary-gonadal axis regulates serum testosterone's age-dependent physiological concentration [6]. During the reproductive years, serum testosterone levels are maintained at approximately 600 ng/ml, after which they gradually decline. About 10% of testosterone is converted into Dihydrotestosterone inside the prostate gland by the enzyme Type 2 5α-reductase, the more predominant isoform as compared to the Type II enzyme. Dihydrotestosterone is the most important hormone involved in male sexual differentiation and also mediates normal growth of the prostate gland [7]. However, the excessive activity of this hormone has been identified as the major reason for the proliferation of the prostate gland beyond its normal physiological volume, a hallmark of BPH [8].

The preferred first-line of treatment in the affecting bladder management of BPH is the use of alpha-adrenergic–-receptor antagonists like terazosin, doxazosin, tamsulosin, and alfuzosin [9]. These drugs promote smooth muscle relaxation in the bladder, facilitating urine flow [10]. However, they are associated with significant side effects, including dizziness, headache, asthenia, postural hypotension, rhinitis, and retrograde ejaculation [9]. The only other therapeutic approach for managing BPH is the use of Type 2 5-alpha reductase inhibitors to bring down the serum and intraprostatic concentration of DHT [11]. The most commonly used drugs in this regard are finasteride and dutasteride, two synthetic steroids that are also effective in treating scalp hair loss [12-13]. However, they too carry notable adverse effects, including decreased sexual desire, reduced ejaculation, depression, and anxiety [14].

Given the numerous potential side effects associated with conventional BPH treatments, phytotherapeutics have gained significant popularity. Saw palmetto (*Serenoa repens*), obtained from the berry of the American dwarf palm tree, *Pygeum africanum* (African Cherry) have shown promise in effectively

managing BPH [15]. Although *Prunus Africana* (family Rosaceae) is the most widely recognized for BPH treatment and is listen in the United States Pharmacopoeia (USP). However, its overexploitation across the globe has led to its serious depletion, necessitating a shift toward alternative sources with similar phytotherapeutic properties. One such alternative, Prunus domestica, a small deciduous tree from the same family, predominantly found in temperate regions worldwide. Rich in vitamin C, potassium, and dietary fiber, *Prunus domestica* is commonly consumed in dried form or processed into jams, jellies, and sauces.

Beyond its nutritional benefits, *Prunus* is also a strong reservoir of phytosterols, known for their anti-inflammatory activity, via inhibition of pro-inflammatory prostaglandins production in the prostate [16-17]. It also contains pentacyclic triterpenes (ursolic and oleanic acids) with anti-edema properties [18] and ferulic acid esters (n-docosanol and tetracosanol) responsible for normalizing prolactin levels and preventing the deposition of cholesterol in the prostate gland [19]. Since prolactin enhances testosterone uptake by the prostate [20] and cholesterol amplifies dihydrotestosterone (DHT) activity [21], these compounds may help mitigate prostate enlargement [21].

Extracts of Prunus domestica have been effectively used alleviating prostate enlargement, regulating urination, and improving overall patient health improvement [22-23]. Its primary phytotherapeutic components, beta-sitosterol and docosyl ferulate, play key roles in BPH management. Beta-sitosterols help in the complete emptying of the urinary bladder and thus alleviate urination problems [24], whereas docosyl ferulate is associated with the management of cholesterol levels, especially in the prostate.

Although Prunus shows great potential in managing, the number of robust clinical trials to ensure the safety and efficacy of this formulation, in comparisom to conventional therapeutic approaches have been inadequate. This paper presents a human clinical trial of a patented extract of Prunus domestica, Prosman™, on post-reproductive male patients (between the age of 40 to 65 years) suffering from BPH for at least the last six months.

MATERIALS AND METHODS

Standardized *Prunus domestica* extract (Prosman™)

Prosman™ contains phytosterols, such as beta-sitosterol, which demonstrate potent anti-inflammatory benefits by lowering the prostate-specific prostaglandins involved in the augmentation of inflammatory response. Moreover, Prosman™ comprises pentacyclic triterpenes (ursolic and oleanolic acids) with anti-edema properties, as well as ferulic acid esters (n-docosanol and tetracosanol), which has been shown to decrease the prolactin levels and prevent cholesterol build-up in the prostate. Prolactin also plays an integral role in boosting testosterone uptake by the prostate, while cholesterol enhances the number of dihydrotestosterone (DHT) docking sites. Prosman™ is a patented *Prunus domestica* extract, standardized to **β-sitosterol (0.431 mg/g) and docosyl ferulate (0.16 mg/g)** (Batch No. CR/SITO/14-15/APR/01; Mfg date: June 2015). It hold multiple patents including, US Patent: 9,314,495 B2 (April 19, 2016), Chinese Patent: CN103153324B (September 16, 2015), Japanese Patent: JP6101690B2 (March 22, 2017), European Patent: EP2734215A1 (June 5, 2019), South Korean Patent: KR10-1811097B1 (January 25, 2018), and Indian Patent: 389375 (July 22, 2011). Manufactured in an **ISO 9001:2015, ISO**

22000:2018 certified facility, Prosman™ also meets Kosher, Halal, NSF-US GMP, WHO-GMP, and ZED - Gold standards.

Ethical Conduct and Regulatory Approvals: The medical and clinical procedures of this single-center study were conducted in full compliance and accordance with the International Council for Harmonization (ICH) guidelines for Good Clinical Practices (GCP). All essential clinical study documents were maintained and archived in accordance with the International Ethical Standards as outlined by the Declaration of Helsinki and its subsequent amendments. Strict confidentiality of all enrolled subjects was maintained. Subject recruitment followed preapproved inclusion and exclusion criteria, as approved by the Institutional Review Board (IRB).

Institutional Ethics Committee (IEC) of the King George's Medical University, Lucknow, UP, India (Ethics Committee Registration # ECR/262/Inst/ UP/2013) approved this study protocol (Protocol #CR/BPH/11/13 dated Mar 27, 2014, Ref: IRB Proposal "Evaluation of *Prunus domestica* extract on benign prostate hyperplasia (BPH): An Add-On Study"). This study was also issued by the Drugs Controller General (India), Directorate Generate of Health Services (New Delhi, India) under Rule 122DD of the Drugs & Cosmetic Rules, 1945 (File #ECR/421/George's/Inst/UP/2013 dated June 5, 2013) . It is also registered on clinicaltrials.gov (NCT02702947).

Patient Information and Consent: Consent forms were distributed to enrolled patients prior to their involvement in the study. These were subsequently signed by either the enrolled patient or his/her legal representative and submitted along with the protocol to the Institutional Ethics Committee for approval. The consent form was signed by the subject or legally accepted representative, and the investigator-designated research professional obtained the consent.

Project Compliance and Ethical Conduct: The entire study complied with the ICH guidelines for Good Clinical Practices (GCP). Important documents related to including the archiving of essential documents as per International Ethical Standards guaranteed by the Declaration of Helsinki and its subsequent amendments. Patient confidentiality was maintained throughout the study.

Project Confidentiality: In order to prevent any possible selection bias, allocations were concealed from all stakeholders of the study, including patients, investigators, and co-coordinators. A pack of 60 transparent cellulose capsules in sealed aluminum pouches, each containing 100 mg of Prosman (investigational product), was given to each patient, and a BD dosage was advised for oral (BD) administration.

Project Discontinuation Criteria: As defined in the safety assessment clause, it is clearly stated that the trial would only be terminated due to serious adverse side effects (as defined in the safety assessments clause).

Subject Recruitment: Clinical examination, evaluation, and screening were conducted for all enrolled and recruited subjects per IRB-approved inclusion and exclusion criteria (Table 1). A total of 140 male subjects were recruited in this single-center one-arm clinical investigation.

Table 1. Inclusion and exclusion criteria

A.	**Inclusion criteria**
1.	Male subjects (age: 40-65 years)
2.	Patients affected BPH (and its clinical manifestations) for the last 6 months before participation.
3.	Patients identified by ultrasound who have a prostate volume between ≥ 20 ml and ≤ 70 ml.
4.	Patients who have IPSS ≥ 8 during baseline screening.
5.	Patients agree to sign the informed consent.
B.	**Exclusion criteria**
1.	Patients identified as having neurogenic bladder dysfunction.
2.	Patients suffering from bladder neck contracture or urethral stricture.
3.	Patients exhibiting acute or chronic prostatitis or urinary tract infection.
4.	Patients who have been identified to have prostate cancer or prostate carcinoma identified by digital rectal exam.
5.	Patients who have joined in any other clinical study within the last 30 days.
6.	Patients who have resting systolic blood pressure (SBP) > 160 mmHg or < 90 mmHg or diastolic blood pressure (DBP) > 90 mmHg or < 60 mmHg at screening.
7.	Patients who have urine flow < 5 ml/sec.
8.	Patients who have used any other nutraceutical or botanical supplements for BPH treatment or associated symptoms and erectile dysfunction in the past 1 month.
9.	Patients suffering from hematuria of unidentified etiology.
10.	Patients who had radiation treatment or therapy previously.

All study participants were advised to consume two capsules containing the test product daily for a period of twelve consecutive weeks. They were also advised to maintain daily diaries which were monitored and endorsed on a regular basis both by the PI and the co-coordinator of the study.

Demographic Parameters: This study was conducted in male subjects only. The average age of the recruited subjects was 56.08 years, the minimum age was 40 years, and the maximum age was 65 years. The maximum and minimum heights of the subjects were 177 cm and 154 cm, respectively, with the average height of the study population being 166.81 cm. Similarly, the average body weight and BMI of the study participants were 68.73 kg and 24.68 kg, respectively. However, in this study population, not much variation in BMI was observed, as seen with a standard deviation of only 2.83 (Table 2).

Following the treatment, both systolic blood pressure (SBP) & diastolic blood pressure (DBP) were brought down. The variation among the study population was also reduced on completion of the treatment, suggesting blood pressure got normalized (Table 2). Table 2 displays the demographic data of this investigation.

Table 2. Demographic data

Parameters	Baseline	Completion of 12-Weeks of Treatment
Body Weight (Kgs)	68.73 ± 8.38	
BMI (Kg/m^2)	24.68 ± 2.83	
Age (Years)	56.08 ± 7.65	
Height (cms)	166.81 ± 3.09	
Systolic Blood Pressure mmHg	123.87 ± 10.14	120.22 ± 1.91 (p = 0.000**)
Diastolic Blood Pressure mmHg	84.02 ± 8.01	81.46 ± 3.93 (p = 0.001**)

Study Compliance and Accountability Procedure: The investigational product was kept under proper storage conditions without exposure to heat, light, and humidity. Allocation permission for the product was limited to authorized personnel of the site. They also recorded the distribution in the IP accountability log with the date and signature of the Principal Investigator and study co-coordinators. Additionally, it was mandatory for all recruited and enrolled participants to keep a record of their consumption along with other physiological changes they felt (if any) in daily diaries provided by the PI and other study co-coordinators. Whenver asked, the PI was tasked with maintaining and producing the accountability before the technical audit committee.

Concomitant Médication: All concomitant prescription medications taken during the study participation were recorded on the case report forms (CRFs). Reported medications included concomitant prescription medications, over-the-counter medications (OTC), and non-prescription medications taken at the time of adverse events (all grades).

Safety Assessment: The safety of enrolled study participants receiving the investigational supplements during the study was routinely monitored. All enrolled subjects regularly visited the clinical study center in intervals of 4 weeks for routine physical check-ups and received capsules for the following 4 weeks. A physical check-up was conducted to detect any manifestation of an adverse drug reaction or apparent discomfort due to administration. Laboratory investigations were conducted at baseline and follow-up visits (12 weeks) to evaluate and record any adverse events in the participants. Detailed blood chemistry analyses, including hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), serum glutamic pyruvic transaminase activity (SGPT), serum glutamic oxaloacetic transaminase (SGOT) activity, serum alkaline phosphatase (ALP) activity, serum bilirubin, blood urea nitrogen (BUN) level, and serum creatinine levels were performed at the initiation (0 week) and after completion of the 12 consecutive weeks of supplementation.

Efficacy Assessment: The efficacy of Prosman™ (standardized *Prunus domestica* extract) was assessed through a PSA blood test, ultrasound [25], and urinary blood flow in all enrolled study participants suffering from benign prostate hyperplasia (BPH) at baseline, follow-up visits (4 and 8 weeks), and completion of the study (12 weeks).

The International Prostate Symptom Score (IPSS): IPSS is a written questionnaire that determines the severity of lower urinary tract symptoms (LUTS) in men suffering from benign prostatic hyperplasia (BPH). All recruited

subjects' clinical histories were taken, and subjective symptoms were evaluated by "modified Boyarsky score" and IPSS questionnaire. IPSS score and time-dependent urinary flow were recorded and assessed at weeks 0, 4, 8, and 12 of treatment.

Effect on Prostate Volume: Prostate volume was assessed at weeks 0, 4, 8, and 12 (on completion) of treatment using ultrasound.

Effects on Serum Prostate Specific Antigen Levels (PSA) and Serum Testosterone Levels: PSA and serum testosterone levels were assessed during a total blood chemistry assay

Sonographic Evaluation: Sonographic evaluation of the prostate is performed using the transrectal ultrasound (TRUS) method, where a small ultrasound probe is inserted into the rectum to obtain detailed images of the prostate gland. This procedure allows for an accurate assessment of the size, shape, and presence of any abnormalities, such as tumors or lesions.

Adverse events: The study participants routinely maintained daily diaries to record and document any adverse medical occurrences during this investigation. Moreover, the study coordinators regularly questioned all study participants to ensure that any physiological discomfort during the study was investigated during the conduction of the routine visits to the clinical study center.

Ethical Justification: The entire cost of the study, including expenses towards the management of any unwanted condition, including adverse medical consequences, was borne by the sponsor. This ensured that no additional financial liability was imposed on the enrolled study participants.

Statistical Analyses: All statistical analyses were conducted using Microsoft Excel tools. A comparison of the baseline parameters was carried out using Student's t-test. Data was expressed as mean ± standard deviation (S.D.). Parametric and non-parametric tools were also used as and whenever needed, according to the nature of the data. Appropriate parametric and non-parametric tests, including chi-square tests, were used to evaluate the efficacy and safety of Prosman™ in subjects suffering from benign prostrating hyperplasia.

RESULTS

Efficacy Evaluation

Time-dependent effect of Prosman™ on International Prostate Symptom Score (IPPS) score: Time-dependent significant incremental increases (p=0.000) in IPPS scores were observed following 4-, 8- and 12-weeks of Prosman™ treatment (Table 3), as compared to the baseline value. Prosman™ supplementation exhibited efficacy within the first four weeks of the treatment. Furthermore, all enrolled patients reported a decrease in IPPS scores following the completion of the treatment.

Table 3. Time-dependent effect of Prosman™ on IPPS score

IPPS Score	Data (mean ± SD)	p-value (t-value)
Baseline	19.14 ± 5.77	
After 4-Weeks (Visit 1)	12.42 ± 4.87**	0.000** (t-value = 21.13)
After 8-Weeks (Visit 2)	7.37 ± 3.27**	0.000** (t-value = 29.47)
After 12-Weeks (Visit 3)	3.86 ± 2.09**	0.000** (t-value = 32.02)

Data are expressed as mean ± S.D. **Significant reduction. A paired t-test was adopted for the Data are expressed as mean ± S.D. *Significant reduction.

Time-dependent effect of Prosman™ on prostate volume: Following treatment with Prosman™, a time-dependent significant reduction in the prostate volume was observed at 4 weeks, 8 weeks, and 12 weeks of treatment, respectively. The reduction in prostate volume was 29.46% at the end of 12 weeks of treatments, and 94% of the enrolled subjects exhibited a reduction in prostate volume.

Table 4. Time-dependent reduction in prostate volume following supplementation of Prosman™

Prostate Volume	Data (mean ± SD)	p-value (t-value)
Baseline	33.33 ± 11.36	
After 4-Weeks (Visit 1)	29.49 ± 10.20**	0.000** (t-value = 7.658)
After 8-Weeks (Visit 2)	26.42 ± 8.87**	0.000** (t-value = 11.864)
After 12-Weeks (Visit 3)	23.51 ± 8.63**	0.000** (t-value = 15.682)

Analysis within the group was ascertained using a paired t-test, and an unpaired t-test was used for analysis between the groups as elaborated in the methodology. Data are expressed as mean ± S.D. **Significant reduction.

Sonographic evaluation: Beneficial effect of Prosman™: Sonographic evaluation of the enrolled subjects exhibited remarkable improvements in the percentage of patients getting normalized following the time-dependent progression of the treatment. At baseline, 93% of the subjects had mildly enlarged prostate, which decreased upon completion of the treatment, whereas 43% of the subjects showed normal prostate (Table 5)

Table 5. Data of sonographic evaluation in enrolled subjects

	Baseline (%)	Visit 1 (%)	Visit 2 (%)	Visit 3 (%)
Normal	2.5	14.7	28.1	43.0
Borderline	1.9	0.7	2.2	2.2
Mildly Enlargement	93	84.6	69.6	54.8
Moderately Enlarged	1.9	0	0	0
Severely Enlarged	0.6	0	0	0

Effect of Prosman™ on the serum testosterone and prostate-specific antigen (PSA) levels: Following supplementation of Prosman™ over a period of 12 consecutive weeks, a significant increase of 17.28% was observed in the serum testosterone levels (Table 6). However, the mean serum testosterone levels were within the normal permissible limit.

Following 12 consecutive weeks of Prosman™ supplementation, Serum PSA levels were reduced by 56% (Table 6). Approximately 76% of subjects showed a reduction in the serum PSA levels following completion of 12 consecutive weeks of treatment.

Table 6. Effect of Prosman™ on serum testosterone and PSA levels

Parameters	Treatment	Baseline	12-Weeks of Treatment	p-value
Serum Testosterone Levels (ng/ml)	Prosman™	4.34 ± 2.03	5.09 ± 1.81**	0.000** (t-value = 5.188))
Serum Prostate Specific Antigen (PSA) Levels (ng/ml)	Prosman™	2.87 ± 9.17	1.26 ± 1.59**	0.041** (t-value = 2.064)

The statistical significance of data between groups was evaluated using an Unpaired t-test. Data are expressed as mean ± S.D. *Significant reduction.

Safety Evaluation

Effect of Prosman™ on the Clinical Biochemistry and Immuno-Hematological Parameters: Serum SGOT activity dropped significantly following completion of the treatment within normal physiological (Table 7). Serum SGPT, ALP, BUN, and creatinine levels were mostly unaffected (Table 7). Blood hemoglobin levels improved following the completion of 12 weeks of treatment as compared to the baseline value. However, both values were within the normal range (Table 7). Total leukocyte, lymphocyte, monocyte, neutrophil, and basophil count were also unaltered following the completion of the 12 weeks of treatment as compared to the baseline values. A significant decrease within the specified limit in the eosinophil count was observed compared to the baseline values.

Table 7. Influence of Prosman™ on total blood chemistry and immuno-hematological parameters

Parameters	Groups	Baseline	12-Weeks of Treatment	p-value (Between groups)
SGOT (AST) U/L)	Prosman™	36.91 ± 13.66	34.04 ± 11.52	0.002* (t-value = 3.23)
SGPT (ALT) (U/L)	Prosman™	38.77 ± 17.41	36.69 ± 15.08	0.091 (t-value = 1.702)
ALP (U/L)	Prosman™	93.60 ± 37.66	92.22 ± 34.29	0.091 (t-value = 0.727)
Serum Urea Level (U/L)	Prosman™	24.66 ± 7.57	25.04 ± 7.22	0.548 (t-value = 0.602)
Creatinine (mg/dl)	Prosman™	0.97 ± 0.25	0.94 ± 0.27	0.275 (t-value = 1.095)
Hemoglobin (g/dl)	Prosman™	13.07 ± 1.55	13.47 ± 1.22	0.000* (t-value = 4.246)
Total Leukocyte Count	Prosman™	6.77 ± 1.72	6.69 ± 1.14	0.595 (t-value = 0.533)
Neutrophil Count	Prosman™	60.73 ± 8.59	62.05 ± 5.22	0.122 (t-value = 1.56)
Lymphocyte Count	Prosman™	32.59 ± 8.68	32.42 ± 3.72	0.825 (t-value = 0.22)
Eosinophil Count	Prosman™	3.51 ± 3.77	2.74 ± 2.13	0.034* (t-value = 2.15)
Monocyte Count	Prosman™	2.55 ± 2.26	2.40 ± 2.61	0.565 (t-value = 0.58)
Basophil Count	Prosman™	0.402 ± 0.75	0.396 ± 0.55	0.69 (t-value = 0.40)

The statistical significance of the data between groups was ascertained using an unpaired t-test. Data are expressed as mean ± S.D.

Adverse event reporting: In the present study, no significant adverse events were reported.

DISCUSSION

Both *Prunus domestica and Prunus africana* have well-established potential in alleviating prostate enlargement associated well-established potential in alleviating prostate enlargement-associated urinary tract complications [22-23,26-27]. In addition to their role in the management of BPH, *P. africana* and related members of the plum family have also shown strong anti-inflammatory activity chiefly by virtue of their potential to arrest the formation of pro-inflammatory prostaglandins inside the prostate [28]. However, a lack of robust and systematic clinical trials had plausibly deterred the exploitation of these herbal extracts in producing safe and effective phytotherapeutic formulations. Jena et al. (2016) [23] investigated the efficacy of five different medicinal species of Prunus, namely *Prunus amygdalus* Stokes*, Prunus armeniaca* L.*, Prunus cerasoides* Buch.-Ham. ex D. Don*, Prunus domestica* L., *Prunus persica* (L.) Batsch and *P. Africana (Hook.f.) Kalkman (Pygeum) against testosterone-induced prostatic hyperplasia with respect to the* prostatic index, testicular index, creatinine, testosterone levels; antioxidant and anti-inflammatory evaluation. *Prunus domestica* possessed the highest level of the biological effector molecule β-sitosterol (Jena et al.

2016), with all five species showing potential for managing BPH [23]. In another study carried out in Wistar rats modeled with prostatic hyperplasia, bark extract of *P. domestica* was demonstrated to significantly bring down the size of the prostate gland [29]. A systematic dosage-dependent study carried out on male Wistar rats with a proprietary formulation of *Prunus domestica* bark against a reference *Prunus africana* (also known as *Pygeum africanum*) extract indicated that the therapeutic efficiency of P. domestica (at a dosage of 200 mg/day/kg body weight) was comparable to *P. africana* [22]. In a separate study, William and Russa demonstrated that 400 mg/day/kg body weight was essential to show anti-BPH activity [30]. Moreover, multiple anti-inflammatory food and crude drugs [31], blackberry (*Rubus glaucus* B.), soursop (*Annona muricata* L.)[32], and palmetto [33] were also reported to prevent prostate enlargement and allied urinary tract complications. As can be seen, most of the studies have been conducted on animal models, and there is still a scarcity of data from actual human clinical trials.

The hallmark of BPH is an enlargement of the prostate gland following hyperactivity of dihydrotestosterone, a prostate-specific version of testosterone that is normally associated with the growth of the prostate gland. β-sitosterol, one of the primary effectors of the anti-BPH activity of Prunus, is believed to exert its effect by a) blocking 5-alpha reductase, which carries out the conversion of testosterone into dihydrotestosterone b) alleviating lower urinary tract symptoms [19] and c) promoting anti-inflammatory activity by blocking the formation of prostate-specific prostaglandins [34]. It is probably for this reason that *Prunus domestica* can achieve its intended biological effect at a lower dosage. The other effector molecule involved in mediating the therapeutic potential of Prunus is docosyl ferulate, a ferulic acid derivative and a commonly occurring plant secondary metabolite that is primarily known for its anti-oxidative potential [35]. Although the exact mechanism of the action of docosyl ferulate is unknown, it most possibly synergistically augments the activity of β-sitosterol (Figure 1).

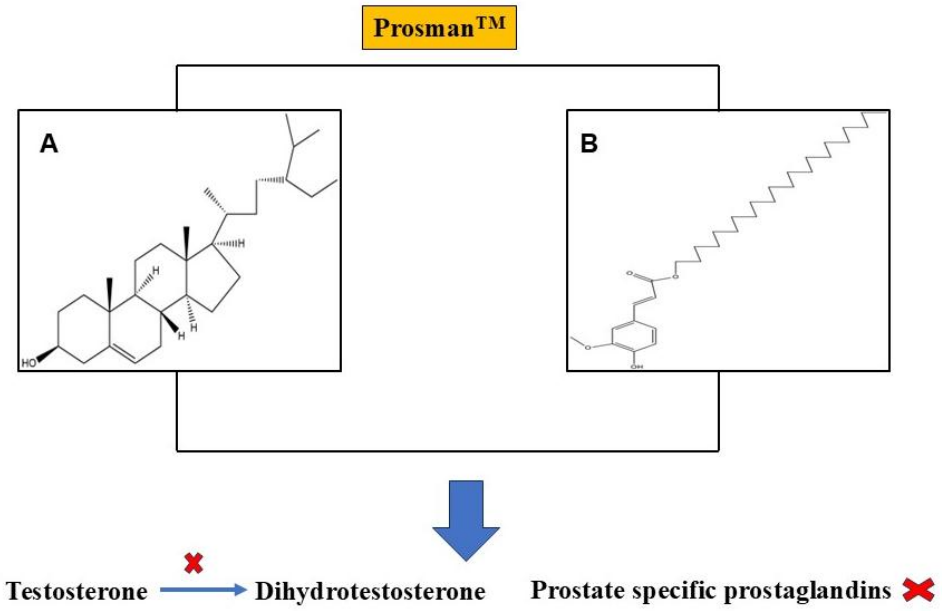


Figure 1: The two abundant biological effectors of Prunus domestica extract Prosman™ A) Beta-sitosterol and B) Docosyl ferulate, which exert their action mainly via inhibition of 5 alpha reductase, the enzyme responsible for testosterone to dihydrotestosterone conversion and arresting formation of prostate-specific prostaglandin, a major pro-inflammatory molecule

Administration of Prosman resulted in a significant reduction of IPPS score and a decrease in prostate volume with a drop in levels of prostate-specific antigens. However, serum testosterone levels rose significantly. This suggests that the effect of Prosman was to promote holistic rejuvenation of the male reproductive system, rather than merely alleviating the symptoms of BPH by reducing dihydrotestosterone activity. It is also worthwhile to state here that one of the many physiological functions of testosterone is to augment the body's anti-inflammatory defense mechanism [36]. The safety of the administration of Prosman was ensured through immunohistological parameters. Additionally, the absence of significant changes in the levels of SGOT, SGPT, and ALT confirmed that the formulation was not associated with any adverse side effects.

CONCLUSION

An emerging concern regarding the use of phytotherapeutics for the treatment of BPH has been the overexploitation of *Prunus africana* species. The rampant use of the bark of this plant by several rising pharmaceuticals has led to serious threats towards the bark of this plant by several rising pharmaceuticals has led to serious threats to the survival and sustainability of this species [37-38]. This has also adversely affected the ecosystem of the place, threatening the co-existence of several forest flora and fauna. Under the circumstances, the emergence of *Prunus domestica* answered many questions together. It has a broader geographical distribution than *P. africana* making it more abundant than the former [39]. Additionally, it also most likely has a higher content of β-sitosterol than the former making it therapeutically more viable. The present studies represent one of the handful of comprehensive human clinical trials carried out on the benefits of *Prunus domestica* on BPH. The demonstrated efficacy of Prosmanarea, as reported in the study, is thus believed to go a long way toward the widespread adaptation of Prunus extract as a safer and more effective option for the treatment of BPH as opposed to conventional approaches.

Abbreviations: BPH: Benign Prostate Hyperplasia; PSA: Prostate Specific antigen; SGOT: Serum glutamic-oxaloacetic transaminase/ aspartate aminotransferase (AST); SGPT: Serum glutamate pyruvate transaminase/ alanine transferase (ALT); ALP: alkaline phosphatase; IPSS: International prostate symptom score; DHT: Di dihydrotestosterone; Hb: Hemoglobin; TLC: Total leukocyte count; DLC: Differential leukocyte count; BUN: Blood urea nitrogen; ICH: International Council for Harmonization; GCP: Good Clinical Practices; IRB: Institutional review board; SD: Standard deviation

Funding: The present study was funded by Chemical Resources [CHERESO], Panchkula, Haryana, India.

Competing Interests: P.K., A.G., and M.R. are employees of Chemical Resources (CHERESO), Panchkula, Haryana, India; Dr. S.N. Sankhwar, Dr. Narsingh Verma and Dr. Naresh Patel are professors of King Georges' Medical Center, Lucknow, UP, India, who conducted the study independently. Dr. S.N. Sankhwar served as the project's principal investigator, while Dr. Narsingh Verma and Dr. Naresh Patel served as the project's co-principal investigator. Chemical Resources [CHERESO] funded the study for conducting the project independently.

Author Contributions: Conceptualization: S.N.S. and N.V.; Data curation: S.N.S., N.V., and N.P.; Formal analysis: S.N.S., N.V., and N.P.; Funding acquisition: S.N.S. and N.V.; Investigation S.N.S., N.V., and N.P.; Methodology: S.N.S. and N.V.; Project administration: S.N.S. and N.V.; Resources: N.P.; Supervision: S.N.S. and N.V.; Visualization: S.N.S. and N.V.; Writing-original draft

S.N.S. and N.V.; Writing-review and editing: S.N.S., N.V., and N.P.

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