ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-7 | JULY-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A CLINICAL STUDY TO EVALUATE EFFECT OF PRUNUS DOMESTICA (PROSMAN™) ON BENIGN PROSTATE HYPERPLASIA (BPH)

Clinical Research

Dr S.N.Sankhwar Professor and Head, Department of Urology, King George's Medical University, Lucknow, U.P, India. - Corresponding Author

Dr.Narsingh Verma Professor, Department of Physiology, King George's Medical University, Lucknow. U.P, India

Pravin Kumar Gangwar Research Assistant, Department of Urology, King George's Medical University, Lucknow, U.P, India

Kiran Tiwari R & D, Chemical Resources, Panchkula, Haryana, India.

Gopesh Lamgora R & D, Chemical Resources, Panchkula, Haryana, India.

ABSTRACT

Background: Benign prostate hyperplasia (BPH) is a non-malignant enlargement of the prostate. The majority of men over the age of 60 are considered to have urinary symptoms attributable to BPH. The active constituents of *Prunus Domestica* extract (Prosman™) include phytosterols (e.g., beta-sitosterol) that have anti-inflammatory effects by inhibiting production of pro-inflammatory prostaglandins in the prostate. *Prunus* also contains pentacyclic triterpenes (ursolic and oleanic acids) that have anti-edema properties, and ferulic acid esters (n-docosanol and tetracosanol) that reduce prolactin levels and block the accumulation of cholesterol in the prostate.

Objectives: The aim of the study was to evaluate the safety and efficacy of *Prunus Domestica* extract (Prosman™), in humans suffering from benign prostate hyperplasia (BPH).

Material and Methods: This was an open labeled and single armed study. The study was carried out on Indian population suffering from BPH. The study was conducted at King George's Medical University (KGMU), Lucknow. Study population comprised of males in between 40-65 years. A total of 140 subjects were included in the study. The investigation product *Prunus Domestica* extract (Prosman™) 100mg was given twice a day for 12 weeks and was allotted after screening and enrolment of the study subject. The subjects were followed up after 4 weeks, 8 weeks and 12 weeks. Safety was assessed at each follow-up visit. The efficacy of investigational product *Prunus Domestica* extract (Prosman™) in BPH subjects was evaluated by the laboratory investigations which included PSA blood test, Ultrasound and Urinary flow test. A prior ethical clearance was taken from Institutional Ethical Committee of KGMU. Statistical analysis was done by SPSS 17.0. T test was applied and a p-value of <0.05 was considered as significant.

Results: The study was conducted on 140 male study subjects in between age group 40-65 years. Average age of the study population was 56.08 years, with minimum age as 40 years and maximum age as 65 years. *Prunus Domestica* extract (Prosman™) was effective in BPH patients as reduction in the IPSS score, prostate volume and serum PSA levels were observed.

Conclusion: *Prunus Domestica* extract (Prosman™) can be labeled safe for human consumption.

KEYWORDS:

Benign Prostate Hyperplasia, Prunus Domestica, PSA levels, IPSS score.

Introduction:

Benign prostate hyperplasia (BPH) is a non-malignant enlargement of the prostate. Symptoms related to BPH are one of the most common problems in older men. Histological evidence of BPH is found in more than 10% of men in their 30s, 20% of men in their 40s, reaches 50% to 60% of men in their 60s, and is 80% to 90% of men in their 70s and 80s. The majority of men over the age of 60 are considered to have urinary symptoms attributable to BPH [1].

The proliferative disorder resulting in BPH affects both the stromal and the epithelial portions of the prostate. The enlarging prostate results in the progressive occlusion of the proximal urethra and can result in both obstructive and irritative urinary tract symptoms. The common signs and symptoms of BPH of this condition usually start after the age of 50 [2].

Benign prostatic hyperplasia represents a substantial challenge to public health. The prevalence of BPH rises sharply at the age of 35 years, reaching 50% by the age of 60 years and approaching 100% by the age of 80-85 years. The occurrence of this disease in men who are 60 to 69 years old is estimated to be almost 3 of 4 with approximately 6.5 million of 27 million men 50 to 79 years old affected. In United States, it has been estimated that BPH treatment costs approximately $4 billion annually. An analysis has revealed that from 38.1 million men with BPH, 12.2 million BPH men are managed each year [3]. The management of BPH has two goals: to reduce the trouble of symptoms and to prevent or delay the progression of BPH related symptoms. Different levels of the treatment exist for the prevention and further development of BPH. Treatment choices are guided by severity of BPH symptoms and how much these symptoms are bothering the patient. The preferred medical treatment for many men with symptomatic benign prostate hyperplasia is either an alpha-adrenergic–receptor antagonist (alpha-blocker), which reduces smooth-muscle tone in the prostate, and bladder neck, or a 5-α-reductase inhibitor, which reduces prostate volume by inducing epithelial atrophy. These drugs have side effects including dizziness, fatigue, hypotension, headache, insomnia, gynecomastia and retrograde ejaculation [4] [5] [6].

Usage of plant extracts is common in many countries of the world and is increasing across the globe. Phytotherapeutic agents represent nearly half of the medications dispensed for BPH in Italy, compared with 5% for alpha blockers and 5% for 5-alpha reductase inhibitors. In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate urinary obstructive symptoms and represents > 90% of all drugs prescribed for the treatment of BPH [7].

Prunus domestica is a small deciduous tree in the Rosaceae (rose) family that is an ancient domesticated species, known only in the cultivation. It is now cultivated in temperate areas worldwide for its fruit. *Prunus domestica* is high in potassium and vitamin C & K and are a good source of dietary fiber. It is eaten fresh, dried or prepared into jams, jellies, and juices. It is used in various alcoholic beverages, especially in Central and Eastern Europe, including the plum brandy.

The active constituents of *Prunus domestica* extract include phytosterols (e.g., beta-sitosterol) that have anti-inflammatory effects by inhibiting production of pro-inflammatory prostaglandins in the prostate. *Prunus* also contains pentacyclic triterpenes (ursolic and oleanic acids) that have anti-edema properties, and ferulic acid esters (n-docosanol and tetracosanol) that reduce prolactin levels and block the accumulation of cholesterol in the prostate. Prolactin is purported to increase the uptake of testosterone by the prostate, and cholesterol increases binding sites for dihydrotestosterone (DHT). Furthermore,

Prunus Domestica extract (Prosman™), inhibits fibroblast production, increases adrenal androgen secretion, and restores the secretory activity of prostate and bulbourethral epithelium.

Aim and objectives:

Aim

The aim of the study was to evaluate the effect of *Prunus Domestica* extract (Prosman™), in humans suffering from benign prostate hyperplasia (BPH) which was achieved by considering following given objectives:

Objectives

Primary objective of study was to evaluate the efficacy of *Prunus Domestica* extract (Prosman™) in patients with benign prostate hyperplasia (BPH) whereas secondary objective was evaluation of its safety in patients with BPH.

Material and methods:

This was an open labeled and single armed study. The study was carried out on Indian population suffering from BPH. The study was conducted at King George's Medical University, Lucknow. Study population comprised of males in between 40-65 years. A total of 140 subjects were included in the study. Key inclusion and exclusion criteria were as follows:

Inclusion Criteria

1. Age between 40 and 65 years
2. Only male patients were included
3. Patients suffering from symptoms of BPH for at least 6 months before screening.
4. Patients having prostate volume ≥ 20 mL and ≤ 70 mL as assessed by ultrasound.
5. Patients having IPSS ≥ 8 at screening and baseline.
6. Patients willing to give informed consent in writing.

Exclusion Criteria

1. Patients having neurogenic bladder dysfunction.
2. Patients having bladder neck contracture or urethral stricture.
3. Patients having acute or chronic prostatitis or urinary tract infection.
4. Patients having history of prostate cancer or carcinoma of the prostate suspected on digital rectal exam.
5. Patients participated in any other clinical trial within last 30 days.
6. Patients having resting systolic blood pressure (BP) > 160 mmHg or < 90 mmHg, or diastolic BP > 90 mmHg or < 60 mmHg at screening.
7. Patients having urine flow < 5 ml/sec.
8. Patients using other herbal medications for treatment of BPH, associated symptoms and Erectile Dysfunction in past 1 month.
9. Patients having hematuria of unknown etiology.
10. Patients gone through radiotherapy previously.

The subjects were screened for the clinical study on the basis of given inclusion/exclusion criteria. The investigation product *Prunus Domestica* extract (Prosman™) 100mg was given on twice daily basis and was allotted after screening and enrolment of the study subject. The subjects were followed up after 4 weeks, 8 weeks and 12 weeks. Safety was assessed at each follow-up visit. Subjects complaining of significant symptoms following administration of investigational product were planned to be evaluated for objective parameters of adverse drug reactions. Investigational product was considered to be discontinued in case of any serious adverse drug reaction.

The efficacy of investigational product *Prunus Domestica* extract (Prosman™) in BPH subjects was evaluated by the laboratory investigations which included PSA blood test, Ultrasound and Urinary flow test. These investigations were done at baseline, followed-up monthly (4 and 8 weeks) and at end of the study (12 weeks). The **International Prostate Symptom Score (IPSS)** which is an 8 question (7 symptom questions + 1 quality of life question) written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of the disease benign prostatic hyperplasia (BPH) was also used as a tool for efficacy assessment over various study visits.

A prior ethical clearance was taken for **Institutional Ethical Committee of KGMU**. Statistical analysis was done by SPSS 17.0. T test was applied and a p-value of <0.05 was considered as significant.

Results:

The study was conducted on 140 male subjects in between age group 40-65 years. Average age of the study population was 56.08 years, with minimum age as 40 years and maximum age as 65 years. Average height of the study population was 166.81 cm, with minimum height as 154cm and maximum height as 177 cm. Average body weight & BMI of the study population was 68.73 kg and 24.68. There was not much variation in BMI of the study population as standard deviation was 2.83 only.

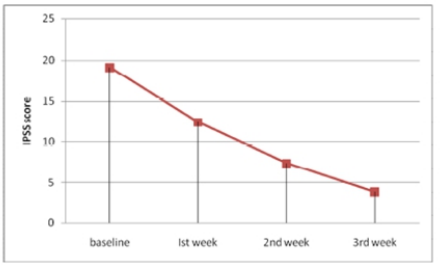
Demographic Parameters	Mean ± Std. Deviation	Minimum	Maximum
Age (years)	56.08 ± 7.65	40	65
Height (cm)	166.81±3.09	154	177
Weight (Kg)	68.73 ± 8.38	50	95
BMI (Kg/m^2)	24.68 ± 2.83	16.92	34.89

Efficacy Evaluation

a) IPPS Score

A highly significant decrease (p=0.000) in IPSS score was observed after 4 weeks, 8 weeks and on completion of the treatment as compared to baseline value. Product showed efficacy within first four weeks of the treatment. All enrolled patients reported decrease in IPPS score on completion of the treatment.

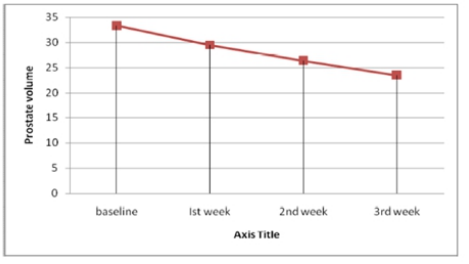
IPPS score	Mean ± Std. Deviation	t-value	p-value
Baseline	19.14 ± 5.767		
After 4 weeks (Visit 1)	12.42±4.865	21.130	.000**
After 8 weeks (Visit 2)	7.37±3.268	29.466	.000**
After 12 weeks (Visit 3)	3.86±2.094	32.018	.000**



b) Effect on Prostate Volume

Highly significant decrease in the prostate volume was observed after 4 weeks, 8 weeks and on completion of the treatment. The decrease in prostate volume was 29.46%. 94% of the patients showed decrease in prostate volume.

Prostate Volume	Mean ± Std. Deviation	t-value	p-value
Baseline	33.33 ± 11.355		
After 4 weeks (Visit 1)	29.49±10.199	7.658	.000**
After 8 weeks (Visit 2)	26.42±8.871	11.864	.000**
After 12 weeks (Visit 3)	23.51±8.628	15.682	.000**



c) Effect on Serum Prostate Specific Antigen Levels (PSA)

A significant decrease in the serum PSA levels was observed. The decrease in serum PSA levels was 56%. 76% of the patients showed decrease in the serum PSA levels on completion of treatment.

Prostate Specific Antigen Level (ng/ml)	Mean ± Std. Deviation	t-value	p-value
Baseline	2.87 ± 9.172		
After 12 weeks (Visit 3)	1.26±1.591	2.064	.041**

d) Sonographic evaluation

Sonographic evaluation of the patients showed marked improvement in the percentage of patients getting normalized on completion of the treatment. At baseline, 93% of the patients had mildly enlarged prostate, whereas on completion of the treatment 43% of the patients showed normal prostate.

	Baseline (%)	1st visit (%)	2nd visit (%)	3rd visit (%)
Normal	2.5	14.7	28.1	43.0
Borderline	1.9	0.7	2.2	2.2
Mildly enlarged	93	84.6	69.6	54.8
Moderately enlarged	1.9	0	0	0
Severe enlargement	0.6	0	0	0

e) Serum Testosterone levels

A highly significant increase in the serum testosterone levels was observed. The increase was 17.28%. The mean serum testosterone levels were within normal range on completion of treatment.

Testosterone Level (ng/ml)	Mean ± Std. Deviation	t-value	p-value
Baseline	4.34 ± 2.0338		
After 12 weeks (Visit 3)	5.09±1.812	5.188	.000**

Safety evaluation

On completion of the study, following safety conclusions were made:

a. No significant change in the liver function tests (serum SGOT, SGPT & ALP activities) was observed.

b. No significant change in the serum urea levels and creatinine levels were observed.

c. No significant change in the hematological parameters was observed on completion of the treatment.

Discussion:

Benign prostatic hyperplasia—also called BPH—is a condition in men in which prostate gland is enlarged and not cancerous. Benign prostatic hyperplasia is also called benign prostatic hypertrophy or benign prostatic obstruction.

The prostate goes through two main growth periods as a man ages. The first occurs early in puberty, when the prostate doubles in size. The second phase of growth begins around age 25 and continues during most of a man's life. Benign prostatic hyperplasia often occurs with the second growth phase.

As the prostate enlarges, the gland presses against and pinches the urethra. The bladder wall becomes thicker. Eventually, the bladder may weaken and lose the ability to empty completely, leaving some urine in the bladder. The narrowing of the urethra and urinary retention—the inability to empty the bladder completely—causes many problems associated with benign prostatic hyperplasia

The cause of benign prostatic hyperplasia is not well understood; however, it occurs mainly in older men. Benign prostatic hyperplasia does not develop in men whose testicles were removed before puberty. For this reason, some researchers believe factors related to aging and the testicles may cause benign prostatic hyperplasia. Throughout their lives, men produce testosterone, a male hormone, and small amounts of estrogen, a female hormone. As men age, the amount of active testosterone in their blood decreases, which leaves a higher proportion of estrogen. Scientific studies have suggested that benign prostatic hyperplasia may occur because the higher proportion of estrogen within the prostate increases the activity of substances that promote prostate cell growth. Another theory focuses on dihydrotestosterone (DHT), a male hormone that plays a role in prostate development and growth. Some research has indicated that even with a drop in blood testosterone levels, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage prostate cells to continue to grow. Scientists have noted that men who do not produce DHT do not develop benign prostatic hyperplasia.

In the present study, 100mg BD dose of Prosman™ capsules prepared from *Prunus domestica extract* were used to evaluate its effect on BPH. In the present study male patients suffering from BPH were enrolled. The mean age of the study population was 56 years and mean BMI was 24.68.

International Prostate Symptom Score (IPSS)

The **International Prostate Symptom Score (IPSS)** is an 8 question (7 symptom questions + 1 quality of life question) written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of the disease benign prostatic hyperplasia

A highly significant decrease (p=0.000) in the IPSS score was observed after 4 weeks, 8 weeks and on completion of the treatment as compared to baseline value. Product showed efficacy within first four weeks of the treatment. All enrolled patients reported decrease in IPPS score on completion of the treatment.

Prostate Volume

A man's prostate gland usually starts to enlarge after he reaches 40 years of age. This condition is called benign prostatic hyperplasia (BPH). The condition has also been referred to as benign prostatic hypertrophy. The prostate gland secretes a fluid that helps to nourish sperm. The gland itself surrounds the urethra, which is the tube that carries urine from the bladder out through the tip of the penis.

As the prostate grows larger, it may press on the urethra. This narrowing of the urethra can cause some men with prostate enlargement to have trouble with urination. Prostate enlargement may be the most common health problem in men older than 60 years of age.

In the present study, highly significant decrease in the prostate volume was observed after 4 weeks, 8 weeks and on completion of the treatment. The decrease in the prostate volume was 29.46%. A total of 94% of the patients showed decrease in the prostate volume.

Prostate-specific antigen

Prostate-specific antigen (PSA) is a protein produced by normal prostate cells. This enzyme participates in the dissolution of the seminal fluid coagulum and plays an important role in fertility. The highest amounts of PSA are found in the seminal fluid; some PSA escapes the prostate and can be found in the serum. The PSA level also tends to rise in men with benign prostatic hyperplasia (BPH) and is a good marker for prostate volume.

In the present study, a significant decrease in the serum PSA levels was observed. The decrease in the serum PSA levels was 56%. 76% of the patients showed decrease in the serum PSA levels on completion of the treatment, correlating well with decrease in prostate volume and IPSS score.

Three groups of active constituents of *Prunus Domestica* extract (Prosman™), are: phytosterols (including beta-sitosterol), pentacyclic triterpenoids (including ursolic acid and oleic acid) and ferulic esters of longchain fatty alcohols (including ferulic esters of docosanol and tetracosanol) [8] [9].

The phytosterols, particularly β-sitosterol, are found in numerous plants and are antiinflammatory, inhibiting the synthesis of prostaglandins. β-sitosterol has been shown to be useful in the case of BPH by helping to reduce the normally elevated levels of prostaglandins. The elimination of the excess blood and vasal congestion helps to reduce the size of prostate adenomas. Other mechanism by which the phytosterols in *Prunus Domestica* extract (Prosman™), work is by inhibiting the production of androgenic steroid hormones such as testosterone and dihydrotestosterone (DHT). Since these androgenic hormones stimulate the growth and development of the prostate through hyperplasia (proliferation of prostatic cells), they are regarded as one of the main causes of BPH.

The phytosterols compete with the precursors of these androgens and, therefore, interfere with their synthesis. Therefore, by inhibiting the production of these androgens, *Prunus Domestica* extract (Prosman™),reduces the effects of testosterone, and the more potent dihydrotestosterone, on the prostate. In this way, *Prunus Domestica* extract (Prosman™), is able to relieve the symptoms of BPH [8]. The pentacyclic triterpenoids also help to inhibit inflammation by blocking enzymatic activity. They are effective anti-edema agents and also help increase the integrity of small veins and capillaries [10].

The third active group, the ferulic esters of long-chain fatty acids, act by inhibiting the absorption and metabolism of cholesterol. One of the ways, these esters work is, by reducing the activity of prolactin, which

is involved in the uptake of testosterone in the prostate. However, these esters can also inhibit androgen synthesis in the prostate just like the phytosterols do. The ferulic acid esters are also known to lower cholesterol levels in the prostate. Cholesterol in turn is required in the biosynthesis of androgens. By inhibiting androgen production through cholesterol, these esters reduce the activities of testosterone and DHT on the prostate.

The combination of the two mechanisms by which ferulic acid esters act prevents the enlargement of the prostate and relieves body from the symptoms of BPH [8] [10]. Different studies suggest that these phytochemicals appear to work synergistically to improve the symptoms of BPH. However, the most bioactive phytochemicals in pygeum are the phytosterols. Therefore, these components of *Prunus Domestica* extract (Prosman™), are believed to exert the most important therapeutic effect in the treatment of BPH in the present study.

Conclusion:

Prunus Domestica extract (Prosman™), was effective in BPH patients as reduction in the IPSS score, prostate volume and serum PSA levels were observed. Thus **Prosman™** can be labeled safe for human consumption.

Funding

The study was funded by Chemical Resources, Panchkula, Haryana, India.

Consent to Publish

All authors have read, consented and approved the final manuscript for publication. This manuscript doesn't contain any individual person's data.

Availability of Data and Material

SNS & NSV have appropriately stored all the data in their Laboratories Storage Facility in Kings Georges Medical University, Lucknow, U.P, India.

Conflict of Interest

SNS is the principal investigator and NSV is the co-principal investigator, organized, coordinated the study.PG is Research Assistant, KT and GL are coordinators from Funding Agency

Acknowledgement:

We extend our sincere thanks to Dr Abhishek Arun (MD) for his assistance in medical writing. We are also thankful to junior doctors and staff of Urology / Physiology Department King George's Medical University, Lucknow. Special thanks to everyone who participated in the study. Very Special Thanks to Dr Shashank Tiwari OSSINC ,On Site Services Incorporation

References:

1. Paolone D. R. Benign prostatic hyperplasia. Clin Geriatr Med. 2010; 26: 223–239
2. Lamson T. C. Devices, systems and methods for treating benign prostatic hyperplasia and other conditions. Google Patent. US8900252B2. 2014
3. Parsons J. K. Modifiable Risk Factors for Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms: New Approaches to Old Problems. American UrologicalAssociation 2007; 178: 395-401,
4. Vuichod C. and Loughlin K. R. Benign prostatic hyperplasia: epidemiology, economic and evaluation. The Canadian Journal of Urology 2015; 22(51):1 – 6
5. Thorpe A. and Neal D. Benign prostatic hyperplasia. The Lancet 2003; 9366(361): 1359-1367
6. Messina R. and Mirone V. Benign prostatic hyperplasia – An economic assessment offixed combination therapy based on a literature review. Arch Ital Urol Androl. 2015;87(3):185-9
7. Shrivastava A. and Gupta V. B. Various treatment options for benign prostatic hyperplasia: A current update. J Midlife Health 2012; 3(1):10–19
8. Tewari K. And Sharma A. Process for pygeum extraction. Google Patents.US20130236574A1. 2013
9. Mehta S., Soni N., Satpathy G. and Gupta R. K. Evaluation of nutritional, phytochemical, antioxidant and antibacterial activity of dried plum (Prunus domestica). Journal of Pharmacognosy and Phytochemistry 2014; 3 (2): 166-171
10. Nyamai et al. Phytochemical profile of Prunus africana stem bark from Kenya. J Pharmacogn Nat Prod 2015, 1:1