



PROSTALUBAN - A NOVEL REMEDY FOR BENIGN PROSTATE HYPERPLASIA

Dr. Luay Rashan¹, Dr. Mohammed Rishan¹ and Dr. Rafie Hamidpour*^{1,2}

¹Biodiversity Center, Medicinal Plants Division, University of Dhofar OMAN.

²Department of Herbal Medicine, Pars Bioscience Research Center, Leawood, Kansas, United States.

***Corresponding Author: Dr. Rafie Hamidpour**

Biodiversity Center, Medicinal Plants Division, University of Dhofar OMAN.

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ABSTRACT

Benign prostatic hyperplasia also called prostate gland enlargement, is a non-malignant enlargement hyperplasia, is one of the most common diseases in ageing men, which can lead to lower urinary tract symptoms. An enlarged prostate gland can cause uncomfortable urinary symptoms, such as blocking the flow of urine out of the bladder. It can also cause bladder, urinary tract or kidney problems. The prevalence of BPH increases after the age of 40 years, with a prevalence of 8%-60% at age 90 years. Although the exact cause is unknown, however, the prevalence of benign prostatic hyperplasia depends on many factors such as, age, race, hormones, persistent inflammation, genetics, lifestyle, bacterial infection, obesity. Recent reports suggest the strong relationship of clinical BPH with metabolic syndrome and erectile dysfunction. A wide variety of treatments are available for enlarged prostate, including medication, minimally invasive therapies and surgery. Among medications there are two main medication classes for benign prostatic hyperplasia management, these are the alpha-blockers and 5 α -reductase inhibitors. On the other hand, there are also natural remedies that may work to combat enlarged prostate symptoms such as using saw palmetto, stinging nettle, beta-sitosterols and others. However, the evidence is debatable on whether these treatments actually work, and research continues to look into a multi-targeted and multi-channel molecule with potential anti-inflammatory activity that modulate several targeting properties. ProstaLuban is a novel synergistic composition that combines potentially multi targeted well-researched standardized extract from Omani frankincense *Boswellia sacra* oleogum resin with other know researched ingredients such as pygeum, saw palmetto extracts, nettle extracts and zinc oxide. This product is significantly better as an anti-inflammatory agent compared with other available natural remedies.

INTRODUCTION

Clinical benign prostatic hyperplasia (BPH) also refers to a non-malignant enlargement hyperplasia^[1], is one of the most common diseases in ageing men, which can lead to lower urinary tract symptoms (LUTS). The relation between clinical BPH and LUTS is complex, because not all men with clinical BPH develop LUTS and not all men with LUTS have clinical BPH. It is a chronic, slowly progressive disease, characterized by growth of epithelial and stromal cells from the transition zone and periurethral areas. It is almost physiological process, present in most men after 50 years and gets larger in most men as they get older. For a symptom-free man of 46 years, the risk of developing BPH over the next 30 years is 45%. Incidence rates increase from 3 cases per 1000 man-years at age 45–49 years, to 38 cases per 1000 man-years by the age of 75–79 years. While the prevalence rate is 2.7% for men aged 45–49, it increases to 24% by the age of 80 years. Globally, benign prostatic hyperplasia affects about 210 million males as of 2010 (6% of the population). The prevalence of clinical PBH depends on many factors including:

1. Age

(Last Ref.) Several studies indicated that the prevalence

of BPH rises markedly with increased age. Observational studies from Europe, US, and Asia have also demonstrated older age to be a risk factor for clinical BPH onset and progression.

2. Race

Although, no clear patterns have emerged with respect to BPH risk and race. However, observational studies comparing black, Asian and white men have produced variable results. Studies of black men in the US have observed an increased prostate transition zone and total volume compared with white men. Some data have suggested a decreased risk of clinical BPH in Asian compared with white men.

3. Hormones

Most experts consider androgens (testosterone and related hormones) to play a permissive role in the development of BPH. This means that androgens must be present for BPH to occur, but do not necessarily directly cause the condition. Dihydrotestosterone (DHT), a metabolite of testosterone, is a critical mediator of prostatic growth. DHT is synthesized in the prostate from circulating testosterone by the action of the enzyme 5 α -

reductase, type 2.

4. Inflammation

Inflammation plays a role in the development and progression of BPH as evidenced by the strong links between BPH and histological inflammation in specimens obtained from prostate biopsies and BPH surgery. Persistent inflammation causes ongoing production of large quantities of pro-inflammatory cytokines and both oxygen and nitrogen reactive species, with consequent activation of transcription factor nuclear factor-kappa B (NF- κ B) and genes encoding for further production of pro-inflammatory cytokines, chemotactic factors, and growth factors. Furthermore, inflammatory cytokines are over-expressed in BPH tissue.

5. Bacterial Infection

BPH can be caused by infection with bacteria, or other non-infective causes. However, the cause of prostatic infection, in most cases, is bacterial, the most common germs are Gram-negative bacteria, particularly *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Serratia*, *Pseudomonas*, and *Proteus* species, but Gram-positive bacteria, particularly *Enterococcus*, can be responsible for prostatic infection. Microorganisms responsible for sexually transmitted diseases can also cause prostatic infection; these include *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Trichomonas vaginalis*, and *Gardnerella vaginalis*.

6. Regeneration

Benign prostatic hyperplasia is an age-related disease. Misrepair-accumulation aging theory^[23,24] suggests that development of benign prostatic hyperplasia is a consequence of fibrosis and weakening of the muscular tissue in the prostate.

7. Genetics

Evidence suggests a strong genetic component to BPH. A case control analysis, in which men below 64 years underwent surgery for BPH, noted that male relatives and brothers had a 4-fold and 6-fold increase, respectively of age-specific risks for BPH surgery.

8. Lifestyle

It has increasingly been observed that modifiable lifestyle factors substantially influence the natural history of BPH. These include:

9. Diet

There are some indications that both macronutrients and micronutrients may affect the risk of BPH although the patterns are inconsistent. With respect to micronutrients, higher circulating concentrations of vitamin E, lycopene, selenium and carotene have been inversely associated with BPH. Zinc has been associated with both increased and decreased risk.

10. Physical activity

Increased physical activity and exercise have been consistently linked to decreased risks of BPH surgery, clinical BPH, histological BPH and LUTS.

11. Alcohol

Like exercise, moderate alcohol intake also appears to be protective against multiple outcomes related to BPH. A meta-analysis of 19 published studies (n = 120 091) observed up to a 35% decreased likelihood of BPH among men who drank daily.

12. Metabolic syndrome

13. Obesity

Studies have consistently observed that increased adiposity is positively associated with prostate volume—the greater the amount of adiposity, the greater the prostate volume.

14. Diabetes and disruptions in glucose homeostasis

Physician-diagnosed diabetes, increased serum insulin and elevated fasting plasma glucose have been associated with increased prostate size and increased risk of prostate enlargement, clinical BPH and BPH surgery.

15. Lipids

There are relatively little data on potential associations between lipids and BPH.

16. Erectile dysfunction

There is overwhelming evidence to support that erectile dysfunction (ED) and LUTS are related. The clinical diagnosis of BPH is based on a history of LUTS (lower urinary tract symptoms).

Diagnosis

1. A digital rectal examination. An enlarged prostate gland on rectal examination that is symmetric and smooth supports a diagnosis of BPH.
2. Urinalysis is typically performed when LUTS are present and BPH is suspected to evaluate for signs of a urinary tract infection, glucose in the urine (suggestive of diabetes), or protein in the urine (suggestive of kidney disease).
3. Prostate specific antigen (PSA) to evaluate for kidney damage and prostate cancer, respectively. However, checking blood PSA levels for prostate cancer screening is controversial and not necessarily indicated in every evaluation for BPH. Benign prostatic hyperplasia and prostate cancer are both capable of increasing blood PSA levels and PSA elevation is unable to differentiate these two conditions well.

Medications

The two main medication classes for BPH management are alpha-blockers and 5 α -reductase inhibitors.

Alpha-blockers

Selective α_1 -blockers are the most common choice for

initial therapy. They include alfuzosin, doxazosin (49), silodosin, tamsulosin, and terazosin.

They relax smooth muscle in the prostate and the bladder neck, thus decreasing the blockage of urine flow.

5 α -Reductase inhibitors

The 5 α -reductase inhibitors finasteride and dutasteride may also be used in men with BPH (50). These medications inhibit the 5 α -reductase enzyme, which, in turn, inhibits production of DHT, a hormone responsible for enlarging the prostate. Effects may take longer to appear than alpha-blockers, but they persist for many years.

Self-catheterization

Self-catheterization is an option in BPH when it is difficult or impossible to completely empty the bladder.

Surgery

- Transurethral resection of the prostate (TURP)
- Transurethral incision of the prostate (TUIP)
- Photo selective (laser) vaporization of the prostate (PVP): common treatment

Endovascular

The latest alternative to surgical treatment is arterial embolization, an endovascular procedure performed in interventional radiology.

Alternative medicine

Saw palmetto extract from *Serenoa repens*, beta-sitosterol from *Hypoxis rooperi* (African star grass) and pygeum (extracted from the bark of *Prunus Africana*), pumpkin seed (*Cucurbita pepo*) and stinging nettle (*Urtica dioica*) root. A systematic review of Chinese herbal medicines found that the quality of studies was insufficient to indicate any superiority over Western medicines.

Description

ProstaLuban (Figures 1 & 2) is a new class of herbal-based evidenced that combines potentially multi targeted well-researched standardized extract from Omani frankincense *Boswellia sacra* oleogum resin with other know researched ingredients such as pygeum, saw palmetto extracts, nettle extracts, zinc oxide and excipients. Several in vitro and in vivo studies were conducted to study the efficacy and safety of this product both in vitro and in vivo. For in vitro studies, several human and murine cell lines were used including primary murine microglia, raw mouse macrophages, primary human monocytes and primary human fibroblasts to test the efficacy of ProstaLuban on prostaglandin E2, interleukin 1-beta (IL-1 Beta), tumor necrosis factor (TNF) and interleukin6 (IL6). These studies showed that the product possess significant anti-inflammatory properties at concentration ranging from 1-10 ug/ml. Furthermore, the in vitro antimicrobial activity was studied using different strains of Gram-positive and Gram-negative bacteria such as Aureus

ATCC 25923; Aureus ATCC 6538. The results showed very interesting activity against most of them with an MIC ranging from 6.2-50 ug/ml (Rashan et al. Unpublished data).



Figure (1).

For in vivo studies, the activity of the product was studied in albino rats using two different pharmacological screening tests, these are:

- a. Inhibition of ascites using albino rats
- b. Freund's adjuvant using albino rats

ProstaLuban exhibited a potential anti-inflammatory activity compared to phenylbutazone drug in causing a diminution of ascites fluid. Further, another confirmatory result from Freund's adjuvant test, which clearly showed that ProstaLuban is more active, compared with the standard drugs used in this test represented by brufen and aspirin.

Further, the analgesic property of OsteoLuban was evaluated using two pharmacological screening tests, these are:

- a. Writhing induced by chemicals using albino mice
- b. Hot plate test using albino mice

ProstaLuban was more potent as analgesic in both tests compared with the reference standard used in the two above tests represented by paracetamol.

On the other hand, the oral acute toxicity of ProstaLuban was investigated in vivo utilizing healthy experimental mice as a model. A single dose was administered to the animals followed by monitoring for a period of 14 days after dosing and recording death and changes in animal behavior and any other physical variables.

The results obtained indicated that the oral LD50 of ProstaLuban is at least greater than 2000 mg/ kg in balb/c mice. In addition, ProstaLuban neither induced any death nor caused any abnormal behavior when tested at a dose of 2000 mg/ kg.

Properties of ProstaLuban:

- Lowering urinary tract symptoms secondary to BPH stage I and II
- Help in shrink the prostate to relief urinary

problems such as poor urine flow and nighttime urination.

- Has anti-inflammatory and analgesic effect
- Treating symptoms of BPH for pain caused by inflammation
- Has antioxidant effect

Critical Overview

Healing paradigm:

The healing paradigm of ProstaLuban as shown below is that its uses encourage a person to maintain a steady improvement in micturition and to ensure lower urinary tract symptoms secondary to BPH.

- Frankincense contains six boswellic acids, these are, alpha-keto boswellic acid (AKBA), Keto-Boswellic acid (KBA), Beta-boswellic acid, acetyl-beta-boswellic acid, alpha- boswellic acid and acetyl-alpha boswellic acid plus two lupeolic acid and other triterpenoid compounds .The pharmacological action documented for AKBA, KBA and acetyl-beta boswellic acids are the main active principles that manage the inflammatory response function through leukotrienes inhibition and also managed the analgesic effect . Further, it has been indicated that B-boswellic acid has enzyme cathepsin and

microsomal prostaglandin E synthase as demulcent.

- Pygeum Africanum extract contains phytosterols, saturated and unsaturated fatty acids, pentacyclic triterpenoids and others. These chemicals help in shrink prostate to relief poor urine flow and nighttime symptoms consistent with benign prostatic hyperplasia.
- Saw palmetto extract contains phytosterols, fatty acids such as lauric, myristic, palmitic fatty acids plus many other minor compounds. These compounds may have antiandrogenic effects (Nettle extract contains polyphenols, phenolic acids, fatty acids and other compounds. It helps in the treatment of LUTS associated with BPH Symptoms.
- Nettle leaves extract contains polyphenols, fatty acids such as lauric, oleic, myristic, palmitic, fatty alcohols, triterpenes, carotenoids and other minor compounds, which may help block certain effects of certain hormones in the body and has anti-inflammatory action.
- Zinc (oxide) an essential trace element required for normal prostatic function.

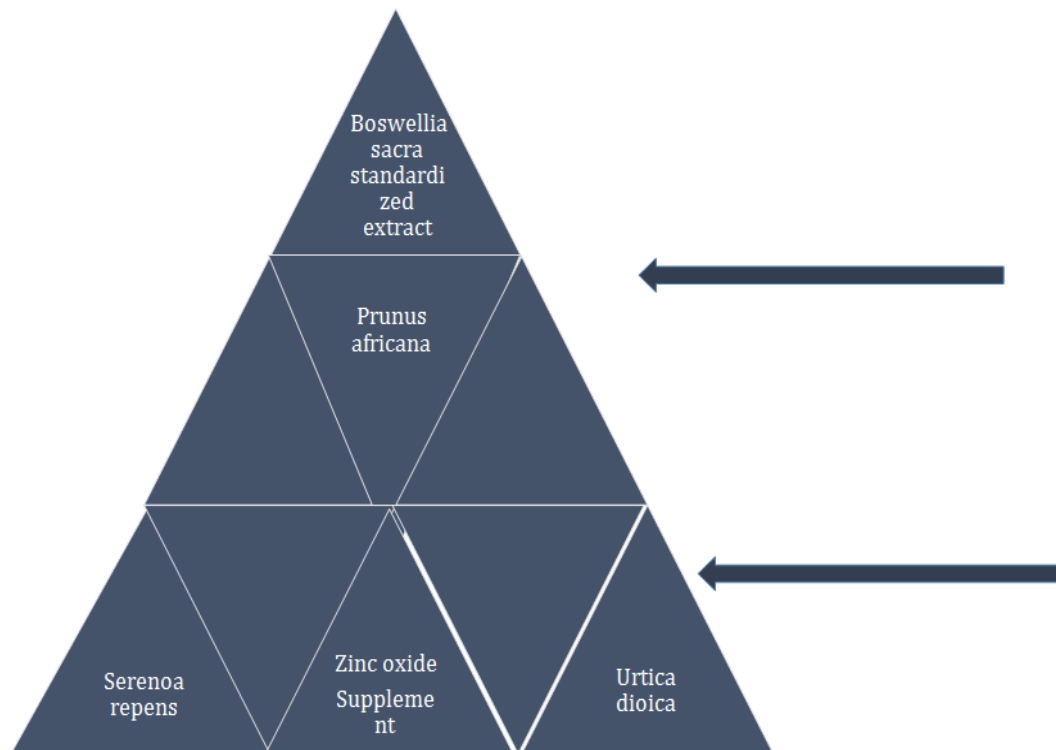


Figure (2).

RESULTS

ProstaLuban product consists of a unique combination of selected four monographic and well- researched medicinal herbs (Boswellia sacra, Prunus Africana, Serenoa repens and Urtica dioica extracts) plus zinc as essential trace element required for normal prostatic function. It is clear from the above combination that this

product has diversified actions since it contains six boswellic and two lupeolic acids, free fatty acids such as lauric, oleic, myristic and palmitic acids, phytosterols, polyphenols, phenolic acids, sterols, carotenoids, zinc and other compounds and minerals. It seems that the ingredients of this compound potentiate each other in a synergistic way to produce its multi-effect on the body.

According to some feedback from clinicians who tested this product on patients suffering from BPH, this product possessed a multi-targeted effect on these patients. It helps in shrink the prostate to relief urinary problems such as poor urine flow and nighttime urination; has strong anti-inflammatory action and this can be attributed to its action on the pro-inflammatory cytokines, chemotactic factors, antibacterial and growth factors. Furthermore, ProstaLuban relief of lower urinary tract symptoms associated with BPH and finally, it may play a significant role in restoring the urine flow and nighttime urination and treat symptoms of BPH for pain caused by inflammation.

Properties and Uniqueness of ProstaLuban

Prosta Luban is a unique, safe and effective natural health product in treatment of BPH. It is composed of an extract obtained from *Boswellia sacra* gum resin using special extraction procedure and was characterized using HPLC/MS/MS (39). The pharmacological action of this extract showed potential anti-inflammatory, analgesic and antibacterial effects when compared with standard drugs used in clinics. Further, it contains *Pygeum* extract, which contains phytosterols, fatty acids, and others that may help shrink the prostate to relief urinary problems such as poor urine flow. It also contains nettle leaves extract with polyphenols, phenolic acids and other compounds and *Saw palemotto* extract with which contains free fatty acids like lauric, oleic, myristic, palmitic, phytosterols that may block certain effects of certain hormones in the body and its anti-inflammatory action. Finally, the product contains zinc as essential trace element required for normal prostatic function. Therefore, the medicinal ingredients in ProstaLuban work in an effective and synergistic way to support each of the above claims, which on the other hand, support the healing paradigm.

Side effects

No serious side effects were reported except some patients (12%) showed some abdominal pain.

Contraindications: None

Direction for use

Three capsules daily in three dividing doses with meals.

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