THE EFFICACY OF *PRUNUS AFRICANA* IN THE MANAGEMENT OF SYMPTOMATIC BENIGN PROSTATE HYPERPLASIA AT MUHIMBILI NATIONAL HOSPITAL, A PILOT STUDY

By

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A Dissertation Submitted in the Partial Fulfillment of the Requirements for the Degree of Master of Medicine (General Surgery) of Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: "***The Efficacy of Prunus africana in the Management of Symptomatic BPH"*** in partial fulfillment of the requirements for the award of Degree of Master of Medicine (General Surgery) of Muhimbili University of Health and Allied Sciences

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I **Jichola J.J. Masanja,** declare that this dissertation is my own original work and that it has not been presented and will not be to any other University for a similar or any other degree award.

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DEDICATION

This work has been dedicated to my parents, my wife, and my Daughter.

Abstract

A Pilot Study, placebo controlled, double blind randomized Clinical trial was conducted among patients with symptomatic Benign Prostatic Hyperplasia (BPH) at Muhimbili National Hospital from April 2006 to January 2007. The aim of the study was to evaluate the efficacy, and safety of *Prunus africana* (also known as *Pygeum africanum*) in the treatment of symptomatic Benign Prostatic Hyperplasia. The main end points were improvement in the IPSS and the quality of life from the baseline. Patient were divided into two groups in order to compare the drug to a "placebo". Patients allocation to treatment and placebo were done by permuted blocks randomization.

A total of 82 patients were enrolled and followed for a period of 10 months. Each patient was followed 4-weekly for a duration of 3 months. Four patients lost to follow up and were excluded from the study and therefore analysis was done among 78 patients. Among patients who were lost to follow up 3 of them were in the placebo group. The highest number of the patients 29(37.2 %), were in the mean age 65.5.

In the treatment group, there were 26(65.0%) patients who reported improvement in IPSS from the baseline and 21(52.5%) patients reported improvement in quality of life.

In the placebo group there were 28 (73.7%) patients who reported improvement in

IPSS from the baseline and 22 (57.9%) patients reported improvement in quality of life. Among all patients, the proportion of patients who reported improvement in IPSS in the treatment group was 26(48.1%) as compared to 28 (51.9%) in the "placebo" group; The difference was not statistically significant (95% C.I, P=0.47). There were also no significant difference in proportion of patients with improvement in quality of life between the treatment group 21(48.8%) as compared to 22 (51.2 % in the "placebo" group (95% C.I, P=0.66).

No any adverse drug reaction were reported in either group and there were no deaths reported. There were no significant difference in conversion rate to surgical intervention in the treatment group 9 (52.9%) patients as compared to 8 (47.1%) patients in the placebo group (95% C.I, P=1.00). The reasons for conversion to surgery were due to patients' desire and 7 patients complicated to acute urinary retention. Among the patients who complicated to urinary retention 4(10.5%) of them were in the treatment group.

Generally the trend of the results in this initial pilot phase of this study showed that the drug is not superior over the placebo.

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List of Abbreviations

ALBA: A code for placebo in the control group

AMEST: A drug code in the treatment group

AR : Androgen receptor

BOO: Bladder Outflow Obstruction

BPH: Benign Prostatic Hyperplasia

ER : Estrogen receptor

FBP: Full Blood Picture

Hb : Haemoglobin

IMT: Institute of Traditional Medicine

IPSS: International Prostate Symptom Score

MNH: Muhimbili National Hospital

MUHAS: Muhimbili University of Health and allied Sciences

NEDLIST: National Essential Drug List

P. africana: *Prunus africana*

PSA: Prostatic Specific Antigen

QoL: Quality of Life

TURP: Transurethral Resection of the Prostate

Introduction

The prostate is a walnut-sized gland that develops from the primitive urethra as a series of solid epithelial buds which become canalized. The surrounding mesenchyme forms the stroma. It is divided into 5 lobes (anterior, posterior, middle, and two lateral lobes). There are several regions that are enclosed by an outer layer of connective tissue (capsule).[1,2] The prostate is located in front of the rectum and just below the urinary bladder. It can be examined or felt by inserting a gloved finger into the rectum. Only the posterior superficial surface of the gland can be examined this way. For a short distance, the prostate surrounds the urethra, the tubular structure that carries urine from the bladder to the outside of the body. The different zones (regions) are the peripheral, central, anterior fibromuscular stroma, and transitional. The transitional zone, which surrounds the urethra, enlarges with age in a hormonally dependent manner.[2,3,4]

The prostate forms part of the male reproductive system. It is an accessory reproductive organ and secretes about 70% of seminal fluid thus aiding transport and nourishment of sperms.[1,5] As a man matures, the prostate goes through two main periods of growth. The first growth phase occurs early in puberty, when the prostate doubles in size. At around 25 years of age, the gland begins to grow

again. The second growth phase often results, years later, in BPH.[5,6]

Androgens acting via androgen receptors (AR) play essential roles in the prostate development, growth and pathogenesis of benign prostate hyperplasia and prostate cancer. Over the last three decades, intensive studies have been carried out to elucidate the molecular basis of androgen action in the prostate. It has been realized that there are two natural potent androgens in the mammal including humans.[7]

Although testosterone is the major androgen secreted from the testes, dihydrotestosterone (DHT) is the main androgen in the prostate that mediates the androgen action via the AR.[8,9] Only one AR has been identified up to date, a member of the steroid/nuclear receptor superfamily, which is a ligand-dependent nuclear transcription factor. When androgens bind to the AR, this results in a conformational change within the AR, leading to the recruitment of co-regulators and transcription factors which mediate androgen-target gene expression. Androgen actions in the prostate can also be modulated by other hormones such as estrogens via estrogen receptors (ER).[9,10]

There are two known isoforms of the ER, ERα and ERβ, which are both co-expressed with AR in the prostate and prostate tumor cells, which provides an anatomical basis for a direct interplay between AR and ER. Although it is well known that androgens are

important for prostate development and for the pathogenesis of BPH and prostate cancer, the precise mechanisms as to how androgens control these processes are not yet fully understood. Nevertheless, there is evidence that AR action can be modulated by other hormones within the prostate or prostate tumor cells.[9, 10]

Benign prostatic hyperplasia (BPH) is one of the most common condition affecting men over 50 years of age.[11,12] The hyperplastic process begins in the periurethral and/or transitional zone of the prostate, this is contrary to prostate cancer which preferentially develops in the peripheral zone.[6,12] BPH results from proliferative process of the cellular elements of the gland. Cellular accumulation and glandular enlargement may be due to epithelial and stromal proliferation and there is also impaired apoptosis in the prostate.,[12,13]

Clinical BPH is defined as prostate weight more than 20g by transrectal/transabdominal ultrasound, urinary flow rate less than 15ml/sec. BPH presents with restriction of urinary flow with symptoms of dysuria, increased urinary frequency, urgency, hesitancy, weak urinary stream, and nocturia.[3,4,6] Long term stasis of the urine leads to urinary tract infections and possibly damage to the kidneys. More often, BPH interferes with quality of life and disturbing normal sleep. Frequent interruption of sleep leads to daytime tiredness. BPH rarely improves spontaneously, it usually either remains the same for years or gradually gets worse.[4,12]

The rationale and efficacy of phytotherapeutic agents in the treatment of lower urinary tract symptoms secondary to BPH are continuously debated.[14,15] Prunus bark extract has been used in Europe since the mid-1960s to treat men suffering from benign prostatic hyperplasia.[15] Currently, Prunus is the most commonly used medicine in France for BPH, backed by many double-blind studies pointing to its efficacy for reducing BPH symptoms.[16,17]

While plant extracts are prescribed and reimbursable treatment options in Europe, they are officially classified merely as dietary supplements in the United States.[15,16,17] The most commonly used preparations originate from various species including; *Serenoa repens, Pygeum africanum, hypoxis rooperi*, pinus, picea, urtica dioica, and *secale cereale*. Combination extracts derived from two or more plants are also used. Various components have been suggested to be active, and different mechanisms of action are being supposed.[5,18,19]

With the above context, the investigator conducted a study to evaluate the efficacy of P. africana in the treatment of symptomatic BPH at MNH. This study shows encouragement to increase the use of medical options in the treatment of BPH instead of watch and wait.

2.0 Literature Review

2.1 Overview

Medical treatment for BPH has played a major role in the improvement of symptoms associated with bladder outlet obstruction.[1,2,3] Medical therapy focuses on two aspects of the pathophysiology of BPH. A dynamic (physiologic, reversible) component related to the tension of prostatic smooth muscle in the prostate, prostate capsule and bladder neck. A fixed (structural) component related to the bulk of the enlarged prostate impinging on the urethra.The general mechanism of action of the drugs is either to relax the smooth muscle tone and/or reduce the size (bulk) of the prostate.[3, 4]

The era of medical therapy evolved in mid 1970s with the use of nonselective alpha-blockers such as phenoxybenzamine.[5,6] The medical therapeutic options for BPH have arisen over the last 3 decades, giving rise to the receptor-specific alpha-blockers that comprise the first line of therapy.[6,7,20]

Hormonal Therapy

Medical studies have shown that one of the major triggering factors for BPH is dihydrotestosterone, which is produced from the male hormone testosterone by the action of the enzyme 5-alpha-reductase. Compounds that inhibit this enzyme are expected to have a beneficial effect on alleviating symptoms of BPH. One of such compounds is finasteride. Unfortunately, clinical studies have found this drug is only marginally effective.[7]

The discovery of a congenital form of pseudohermaphroditism secondary to DHT deficiency due to a lack of 5-alpha reductase activity support the action of 5-alpha reductase on testosterone metabolism on the prostate gland.. This deficiency resulted in a hypoplastic prostate. Type II 5-alpha reductase is responsible for the conversion of testosterone to DHT. The 5-alpha reductase inhibitors block the conversion of testosterone to DHT, thus lowering intraprostatic levels of DHT. This leads to apoptosis, inhibition of prostatic growth, and involution.[9,15,16]

Alpha-1 Receptor Blockade

Smooth muscle tension in the prostate stroma, urethra, and bladder neck is mediated by the alpha1-adrenergic receptors; The alpha receptors blockers decrease resistance along the bladder neck, prostate, and urethra by relaxing the smooth muscle and allowing passage of urine.[7,10]

The 3 subtypes of the alpha-1 receptor are 1a, 1b, and 1c. The alpha-1a receptor is most specifically concentrated in the prostate, bladder neck and urethra. Drugs that are selective for this receptor (e.g., tamsulosin) may have a potential therapeutic advantage. Tamsulosin has highest relative affinity for alpha1a-receptor subtype.

The alpha-blocking agents can be subgrouped according to receptor subtype selectivity and the duration of serum elimination half-lives as follows;

- Nonselective alpha-blockers include phenoxybenzamine.
- Selective short-acting alpha-1 blockers include prazosin, alfuzosin, and indoramin.
- Selective long-acting alpha-1 blockers include Terazosin and doxazosin.
- Partially selective agents (alpha-1a blocker) e.g. Tamsulosin, which has highest relative affinity for alpha1a-receptor subtype.

The 5-Alpha-Reductase Inhibitors

The inhibition of 5-alpha reductase selectively blocks androgen action in tissues whose function is dependent on continuing production of DHT. Finasteride inhibits 5 alpha-reductase enzyme thus preventing conversion of testosterone to DHT.[7,21] This effect causes a profound decrease in the concentration of DHT in plasma, which, in turn, results in a consistent decrease in prostate size. A newer drugs e.g. dutasteride, has affinity for both type I and type II 5-alpha-reductase receptors. Both drugs actively reduce serum DHT levels by more than 80%. The medical response is symptomatic improvement, and reducing incidence of urinary retention; However these drugs may not work in all men and may take several months before activity is noted.[9,22] A third of men treated with this drugs exhibit improvements in urine flow and symptomatology.[9,22]

Phytotherapy

Pharmaceuticals derived from plant extracts are widely used throughout the world for the treatment of various medical conditions. The attraction to phytotherapeutic agents appears to be related to the perception of therapeutic healing powers of natural herbs, their availability, and the lack of adverse effects.[15,23,24] Most of the phytotherapeutic agents used in the treatment of lower urinary tract symptoms

(LUTS) secondary to BPH are extracted from the roots, seeds, barks, or fruits of plants.[15,23,24]

The suggested active components in plant extracts include; phytosterols, fatty acids, lectins, flavonoids, plant oils, and polysaccharides.[15,23,24]

Some preparations are derived from a single plant while others contain extracts from two or more plants and each agent has one or more proposed modes of action.[15,24]

Origins Of Phytotherapeutic Agents

- African plum tree barks (*Prunus africana; Pygeum africanum*),
- Saw palmetto, ie, American dwarf palm fruit (*Serenoa repens, Sabal serrulata*),
- South African star grass (*Hypoxis rooperi*) roots,
- Stinging nettle (*Urtica dioica*) roots,
- Rye (*Secale cereale*) pollen,
- Pumpkin (*Cucurbita pepo*) seeds.

2.2 *Prunus africana*

Geographical Distribution

The Plant is found in mountain forests of equatorial Africa including Angola, Cameroon, United Republic of Tanzania, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Mozambique, Republic of Congo, South Africa, Uganda, Zambia and Zimbabwe.[15,24,25] In Tanzania, the plant grows in *Mufindi, Lushoto, and Tukuyu*, (Documentation from the Institute of Traditional Medicine -MUHAS)

Other Names

Pygeum africanum, African Plum tree[15,24] Tadenan®, pygenil®l

Description

African plum trees are tall evergreens species that are found across the entire continent of Africa at altitudes of 3,000 feet or higher. They can grow up to 150 feet or higher.[15,24] They grow in forested upper highland regions across Africa, often providing shade for the lower-growing coffee or cocoa bushes, which may be planted under African plum deliberately. After flowering in the summer (which corresponds to winter months in the Northern hemisphere), the trees bear large red or brownish fruits resembling plums. The fruits which ripen in June, July,

and August in Northern Africa, and later on in countries that are more southern are used for food by natives of the area as well as by birds and animals. The hard wood of the African plum tree is used or buildings and making furniture.[15,25] The bark of African plum is harvested from living trees or from branches that have been cut for other uses. The bark is powdered and made into capsules or in liquid formulation. Initially the extracts are mashed plant barks. They are soaked in water and then boiled. After boiling the mixture is filtered of solid particle. The remaining filtrate is concentrated and dried.[15,,25] The dried powder is filled in capsules and stored ready for use.

African plum is used mainly to relieve the symptoms of prostate cancer and BPH. Numerous studies have been done to test the effectiveness of African plum for prostate enlargement and study results have been positive. [15,16,23]
African plum contains a number of different active ingredients; including fatty acid derivatives such as phytosterols (e.g. beta-sitosterol) that have anti-inflammatory effects by inhibiting production of pro-inflammatory prostaglandins in the prostate.[16,26] Prunus extracts 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[26]. Prolactin potentiates the uptake of

testosterone by the prostate, and cholesterol increases formation of binding sites for DHT.[26,27,28]

In animal studies, African plum has increased the amount and viability of semen, possibly alleviating some causes of male infertility.[29,30] Some unconfirmed reports seem to indicate that it may also be moderately effective in stimulating hair growth. *Prunus africana* extracts have been used for more than 30 years in France, Germany, and Austria for patients suffering from prostate enlargement.[15,24,28]

Mechanism of Action

Extracts have anti proliferative effects on fibroblasts and inhibits bladder hyper-reactivity, which are overproduced in BPH. Phytosterols competes with androgen precursors and inhibits prostaglandin biosynthesis to reduce prostatic cholesterol levels.[28,29,30]

Triterpenes have anti-inflammatory activity by inhibiting enzymes involved in the depolymerisation of proteoglycans in prostate connective tissue; e.g. blocking of leukotriene synthesis by inhibiting 5-lipo-oxygenase enzyme and reduces oedema by inhibition of glycosyl transferase and -glucuronidase enzymes. It also prevents conversion of testosterone to dihydrotestosterone by inhibiting 5-alpha reductase enzyme.[28,30] Conversion of testosterone to DHT stimulates prostatic glands growth.

The drug also prevents conversion of dihydrotestosterone to androstandiol by inhibiting aromatase enzyme; thus blocking synthesis of oestrogen and estradiol.[26,30] Preparation from *P. africana* improves symptoms of BPH by altering contractile protein in bladder muscle (thus decreases frequency, residual urine volume, nocturia, and increases urine flow rate and voided urine volume). *P. africana* inhibits fibroblast production, increases adrenal androgen secretion, and restores the secretory activity of prostate and bulbourethral epithelium so improving prostatic secretions and seminal fluid composition.[5]

Basic fibroblast growth factor (bFGF) is hypothesized to play a role in the development of BPH and Prunus has been shown to have a significant inhibitory effect on cell proliferation induced by bFGF.[26,27,30]

Extracts from *P. africana* are known to stimulate prostatic secretion of a normal physiological composition which would enable the spermatozoa to mature under optimal conditions.[5,31] Improvement of seminal fluid composition should lead to a better maturation of spermatozoa. Also in patients with abnormally low prostatic acid phosphatase activity, *P. africana* extract can restore acid phosphatase activity and total protein secretion, although it is more effective in patients without prostatic inflammation.[5,32,33]

Indications

(i) Common use in BPH and prostatic adenoma with voiding and filling bladder symptoms (LUTS).[15,18,19,32,33,]

(ii) Other use; [5,23,34,35]

- Fertility disorders and sexual dysfunction,
- Urinary tract infection,
- Prostatitis,
- Malaria,
- Aphrodisiac,
- Mental disorders,
- Male baldness,
- Bladder sphincter disorders.

Efficacy

Breza J, et al found 31-40% reduction in international prostate symptoms score in patients with Benign Prostatic Hyperplasia following institution of *P. africana* at dosage of 50 mg twice daily for two-month duration. He also found 31-34% improvement in quality of life. This was statistically significant ($p<0.001$). There were 89% (76/85) patients reported improvement and satisfaction in their sexual function.[32]

Chatelain C, et al, performed a study on *P. africana* extract in patients with BPH comparing once daily dosing (100mg) and twice daily dosing (50mg); and found more than 40% reduction in the mean IPSS from the baseline. Patients also reported improvement in quality of life and improvement of their sexual function.[33]

Lucchetta G, et al, conducted a study focused on men with reduced Prostatic secretion in the ejaculate at two successive examinations.[5] Results showed that, *P. africana* extract improves prostatic secretion in patients with reduced fertility and diminished prostatic secretion.[5]

In another placebo-controlled, double-blind studies (n=263), Prunus administered at a dosage of 100 mg per day for 60 days improved urinary maximum flow by 17.2%, increased voided volume by 12%, decreased residual volume by 24.5%, decreased nocturia by 31%, decreased daytime frequency by 19.4%, and resulted in overall improvement of 50%. Sixty-five percent of the subjects reported an improvement in this study as compared to 31% in the placebo group.[20,36] (no statistical parameters given)

In a recent literature review analyzed studies from 1966-2000 containing a total

of 18 randomized, controlled clinical trials involving 1,562 men. The reviewers concluded that, compared with placebo, *P. africana* provided a significant improvement in the combined outcome of urological symptoms and flow measures. It was also observed that, subjects taking Prunus extract were more than twice as likely to report an improvement in overall symptoms; nocturia was reduced by 19% and residual urine volume by 24%; and peak urine flow was increased by 23%.[19,20,37] In a lengthy (1995) literature review of the use of Prunus extract for BPH also yielded positive findings for its efficacy. In this series twelve double-blind, placebo-controlled studies of *P. africana* extract were analyzed in which 358 patients received *P. africana* extract and 359 received a placebo. The results showed a statistically significant benefit for *P africana* extract over placebo.[20,37] Unfortunately, most of the studies had small patient numbers, although one study with 126 subjects showed a statistically significant benefit for Prunus extract in maximum urinary flow rate, voided volume, residual volume, nocturia, daytime frequency, and impression of improvement scored by physicians and patients.[17,20,38]

As stated earlier on, the obstructive component of the enlarged prostate often results in bladder outflow obstruction (BOO) due to increased outlet resistance.[4,39,40] BOO results in detrusor muscle hypertrophy, hyperplasia, and instability, as well as collagen

deposition.[4,6,40] An experiment with 209 subjects with BPH using a parallel-group, double-blind, comparative phase (group A, 50 mg twice daily; group B, 100 mg once daily) and a ten-month open phase (100 mg once daily). The result showed an average impromentof IPSS by 38% in group A and 35% in group B. The quality of life index improved by 28% in both groups, and the maximum urinary flow rate (Qmax) increased 16 % in group A and 19 % in group B.[33] After 12 months, the IPSS decreased by an average of 46% and the Qmax increased by 15%.[33] In another open clinical trial testing the efficacy of Tadenan® (an extract from Prunus), 85 patients had significant improvements in IPSS (40%) and QoL (32%), and nocturnal frequency (32%). Improvements in Qmax, average urinary flow, and urine volume were also statistically significant.[32] In another series, Tadenan® was tested in four groups of New Zealand white rabbits to determine its ability to protect the bladder from contractile dysfunction caused by experimentally-induced BOO. In this study, Tadenan® had a significant outcome of reducing the effect of BOO on bladder mass and reversing the contractile response secondary to urethral obstruction.[41] These improvements are associated with the ability of Prunus extracts to alter the expression of myosin isoforms (the contractile proteins in muscle fibers).[18,41] A similar study also found that Tadenan® was able to reverse bladder dysfunction induced by mild BOO and improve bladder function with severe BOO.[42] Tadenan® has also been proven effectively

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protective when administered as a pretreatment to rabbits prior to experimentally induced BOO.[43]

In a review of four relatively small studies, *P. africana* was compared with: (1) sitosterin (n=53), (2) *Urticae urtae* radix extract (n=42), (3) non-steroidal anti-inflammatory or anti-infective treatment (n=39), or (4) non-steroidal anti-inflammatory treatment only (n=49). Although the results favored *P. africana* extract over the other treatment groups, only a small number of patients were studied, and no statistical comparisons were made among treatments.[17,20,37] In another study, *P. africana* extract (100 mg/d for 5-7 weeks) was used to treat 47 patients with chronic prostatitis (8 septic, 39 non-septic) in an open-label study. Eighty-nine percent of patients experienced complete remission of symptoms; whereas, there were no improvements in three septic patients and two non-septic patients.[17,37]

In another study, *P. africana* extract (200 mg/d for 60 days) was used either alone or in combination with antibiotics to treat 18 patients suffering from sexual disturbances due to either BPH or chronic prostatitis. Prunus improved all the urinary parameters investigated by medical history and prostatic transrectal echography, and improved sexual function despite the fact there were no significant differences found between hormonal levels and nocturnal penile tumescence and rigidity monitoring before and

after therapy. The authors stated that the results should be confirmed by other investigators but suggested that *P. africana* extract may be beneficial in the treatment of patients with sexual/ reproductive dysfunction.[38]

Dosage Formulation

P. africana is an alternative treatment for patients with uncomplicated symptoms of BPH. As mentioned earlier, Prunus is the most commonly used medicine in France for BPH, backed by many double-blind studies pointing to its efficacy for reducing its symptoms.[17,19,36]

Traditionally, bark infusions are taken orally. *P. africana* extract is usually administered at a dose (standardized to contain 14% triterpenes including beta-sitosterol and 0.5 % n-docosanol) of 50-100 mg twice daily. The recommended regimen is 100 mg daily or 50 mg twice daily for 12 months.[23,33] The efficacy of Prunus extract at 50 mg twice daily and 100 mg once daily has been shown to be equivalent.[33] Beneficial effects can be seen after one month of therapy with a tendency towards further improvement by the second month.[19]

At our centre, the preparation from *P. africana* is made by grinding the bark of the tree and then dissolving in distilled water and boiling. The mixture is then filtered of solid particles. The filtrate is concentrated and dried resulting in a powder product. The

resultant powder is filled in capsules in a weight of 100 mg/capsule and then stored ready for use.

Safety and Toxicity

The safety and efficacy of prunus extracts has been demonstrated in numerous short-term clinical trial (mean duration 8 weeks) in men to improve fertility problems and reduce benign prostatic hyperplasia. The majority of the studies reported absence of any significant adverse effects of Prunus, although there may be rare complaints of diarrhea, constipation, dizziness, gastric pain, and visual disturbances.[17,23] One study demonstrated continued satisfactory safety profiles in 174 human subjects after 12 months of 100 mg daily doses.[33] Toxicological studies have likewise shown very good tolerability after oral administration. Administration of Prunus to dog and rat subjects equivalent to 560 times the therapeutic dose for six-month periods resulted in no adverse effects on hematological, biochemical, or anatomical/ pathological parameters. The extract had no effect on fertility in male rats and rabbits at doses up to 80 mg/kg/day (gave a safety margin of 50 times the therapeutic dose). Furthermore, in vivo and in vitro mutagenicity studies showed a complete absence of mutagenic or carcinogenic potential. In fact, many of the constituents of Prunus have anticarcinogenic and antimutagenic properties in vitro and in vivo.[44,45,46] Drug interaction is unknown due to inadequate human data available. No studies have been undertaken in pregnancy, lactating

women and children under 12 years of age. Therefore the drug is contraindicated in these population groups due to unavailable data and with regard to its effects on estrogen and androgen metabolism.[7,34] Currently there is insufficient reliable information available about the use of prunus extracts for the other indications.[34,47]

Formulations Available

i. Powder,

ii. Capsule, and

iii. Tablets. [14,15]

Precaution

The preparations from Prunus extracts are contraindicated in cases of known allergy to members of Rosaceae, as well as during pregnancy, lactation and in children under the age of 12 years because of effects on androgen and oestrogen metabolism.[7] Lipophilic bark extracts appear to be well tolerated in humans. A few cases of minor and transient gastrointestinal side effects e.g. diarrhoea, nausea and gastric pain have been reported and single cases of constipation, dizziness and visual disturbance.[15,23,47]

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Other Treatment Modalities for BPH

Prostate surgery is still considered the "treatment of choice" by many urologists.[48]

However, prostate surgery carries its own risks including perforation of the bladder, injury to the rectum, infection, hemorrhage, persistent urinary incontinence, and even permanent impotence. Surgical options, include;

- Open prostatectomy.[49]
- Transurethral resection of the prostate.[48]
- Transurethral incision and electrovaporization.[50,51,52]
- Transurethral electrovaporization of the prostate.[53,54]
- Laser coagulation and vaporization.[53,55]
- Laser surgery.[56,57]

Thermal therapies;

- Transurethral microwave therapy.[58]
- Transurethral needle ablation.[59,60]
- High-intensity ultrasound energy therapy.[61]
- Water-induced thermotherapy.[62]
- Mechanical devices (e.g. Stenting and balloons), These have been abandoned.[63,64]

2.3 Statement of the Problem

BPH is common from the age of 50s. The incidence increases with ageing.[4,6] This condition is among the commonest cause of admission at MNH (Monthly Morbidity and mortality rate reports, unpublished data). Morbidity results from complications; and, its urinary symptoms thus interfering much with quality of life.[4,40,67] For the past decades the mode of treatment in Tanzania has been conservative in patients with mild to moderate urinary symptoms with no complications. Surgery is indicated when there is intolerable urinary symptoms and other complications. In Europe, medical treatment has been used in many centers for treating BPH in men and has shown to be safe and effective.[15,17]

In Tanzania, no data has been reported on efficacy and safety of this drug and the drug is not accessible. Other medical therapies are also not readily available and are expensive. The drug is also not in the National Essential Drug List (NEDLIST) or Standard Treatment Guidelines. Nevertheless the percentage of patients who are being treated with medical therapy is increasing elsewhere.[15,16,17]

2.4 Study Rationale

The rationale of this study is to evaluate the efficacy and safety of *P. africana,* in order to increase use of medical therapy for BPH than surgery by employing a locally produced drug. The hypothesis is to change the watchful waiting care in men with symptomatic BPH to medical therapy and minimize surgical intervention in our population. Nevertheless, Medical treatment in expensing herbs are the best alternative popular form of treatment for many other diseases in our culture. Currently, remedies from *P. africana* is being prepared at the Institute of Traditional Medicine at Muhimbili University of Health and Allied Sciences; and therefore the drug is readily available and accessible to patients. However the drug has to be tested at the National Hospital to have its credibility and enable us to set up a treatment protocol. This research is also complementary for the award of degree of Masters of Medicine (Surgery) of Muhimbili University of Health and Allied Sciences.

3.0. Study Objectives

3.1. Broad Objective:

To evaluate the efficacy and safety of *Prunus africana* among patients with symptomatic Benign Prostatic Hyperplasia at Muhimbili National Hospital during the study period.

3.2. Specific objectives:

3.2.1 To compare the changes in IPSS between the treatment group and the placebo group.

3.2.2. To compare the changes in QoL between the treatment group and the placebo group.

3.2.3. To evaluate the side effects of *P. africana* in the treatment group during the study period as compared to the placebo group.

3.2.4. To compare the rate of conversion to "surgery" in the treatment group and the placebo group.

4.0 Methodology

4.1. Study Design:

A randomized double blind placebo controlled clinical trial was conducted from April 2006 to January 2007. The study population were divided into two arms of 'treatment' in which one group received a new drug and the other group received a placebo. Both the new drug and the placebo were made in capsules with similar color (red) and ("coded") by different names. One codes were "***ames***t" for a drugand "***alba***". The brands were made by the Manufacturer at the Institute of Traditional Medicine. The disclosure of the codes was done by the manufacturer after the analysis

4.2. Study Area:

At Muhimbili National Hospital, Dar es Salaam, Tanzania.

4.3. Study Population:

Male patients with diagnosed of BPH presenting with uncomplicated urinary symptoms. It involved patients attending General Surgical and Urology outpatient clinic.

4.4. Patients Selection:

Male patients above 40-years old attending outpatient Clinic presenting with urinary symptoms due to BPH without complications. Patients with urine retention requiring indwelling catheterization were excluded as these patients have severe urinary obstruction and definitely required other modality of therapy including surgical intervention. Patients with evidence of urinary stones, hydronephrosis and deteriorating renal function were also excluded. Patients with these findings were considered having complications. Patients with clinical suspicious of prostatic malignancy or other malignant diseases were invariably excluded. Patients who refused consent and those who were lost to follow up were also exclude from the study.

Diagnosis was made by history taking, clinical evaluation determined at digital-rectal examination and in some patients was complemented by abdominal sonography.

4.5. Sample Size, n; sample was estimated using the formula below

$n = (z_{\alpha}/2+z_{\beta})^2[p1(1-p1)+p2(1-p2)]/(p1-p2)^2$

where

n = sample size per group

z_x =point on standard normal distribution such that area to the right of it is x p1=(estimat

true success rate on group 1, =40%

p2=(estimated) true success rate on group 2, =50%

α =type 1 error rate

β =type 2 error rate

$z_{\alpha}/2=1.96$

z_{β} =1.28

n = 514 per group.

4.5. Recruitment:

Recruitment was done at surgical outpatient clinic at MNH. All doctors attending urology and general surgical clinic were requested to refer to Dr. Masanja all male patients with BPH symptoms, without complications.

4.6. Enrollment:

Initial assessment was done during enrollment. History taking and physical evaluation performed and the initial findings including laboratory tests were recorded. A focused physical examination to assess the suprapubic area for signs of bladder distention and a cursory neurological examination for overall sensory and motor deficits was performed. Digital-rectal examination was done at initial visit in order to have clinical findings on the prostate status. Patients were positioned in lithotomy. The prostate was examined using the index finger of the dominant hand. The finger was placed through the anus after relaxation of the anal sphincter, and the prostate was palpated circumferentially (analogous to a windshield wiper movement). During this portion of examination, prostate size and contour was assessed.

The normal prostate volume in a young adult is approximately 20 g. Estimation of the number of index finger pads that sweep over the rectal surface of the prostate during a DRE is a useful way for estimating the size of the gland. Anecdotally, each finger breadth correlates to approximately 15-20 g of tissue and the prostate size may be reported as "2-3 fingerbreadths wide. Most asymptomatic men have glands less than or equal to 2 fingerbreadths.

Other investigations done as supportive were FBP, Serum creatinine and blood sugar as part of the general care of the patient.

Abdominal sonography was done to some patients to help determining protate echotexture. BPH has homogenous echogenicity. Other radiological investigations were performed in patients with other Co-morbid conditions

4.7. Randomization:

Patients allocation to treatment group were performed by Permuted blocks randomization and block lengths were changed accordingly. As mentioned earlier, The drug and the placebo were coded in two different names. As mentioned earlier the breaking of codes were done after the analysis of which the "amest" represented a drug and "alba" being a placebo as coded by the Manufacturer from the Institute of Traditional Medicine at MUHAS.

4.8. Dosage.

Treatment regimen was 100 mg twice daily for 3 months.

4.9. Instruments and Equipments:

Data were entered in a structured questionnaire made in Swahili version. Patients were requested to answer some questions and the responses were filled in the questionnaire by the author except for the IPSS and QoL where as the responses were completed by the patients however being guided by the investigator.

During follow up, assessment of IPSS and quality of life were completed using IPSS chart (appendix 3b) and QoL chart (appendix 3c) respectively. As already mentioned above this part of assessment were completed by patients. Assessment of any adverse drug reaction were done in the subsequent visits. The findings were summarized in the study visit chart and entered in the computer.

4.10. Follow up and Study Duration:

The study period took place from April 2006 to January 2007. Patients were expected to be followed up for 4-weekly for 3 months period. Most patients attended two subsequent follow up visits. Data analysis included patients who attended at least one follow up visit. Four patients did not turn up even at once and were regarded as drop up from the study.

Patients were considered improved on Quality of Life and International Prostate Symptoms if their subsequent Score were lower than the previous Values

4.11. Data Management

Data were entered and stored in the computer and movable disks. Analysis was done using SPSS 13.0 version Statistical significance testing were done using Fischer's exact test (P value).

4.12. Medico-legal Issues.

Ethical clearance was granted by the Research Ethical Committee. Informed consent was obtained from the patient before enrollment. Patients were explained of the purpose of study. Drugs were issued free of charge. No special risks were anticipated.

Results

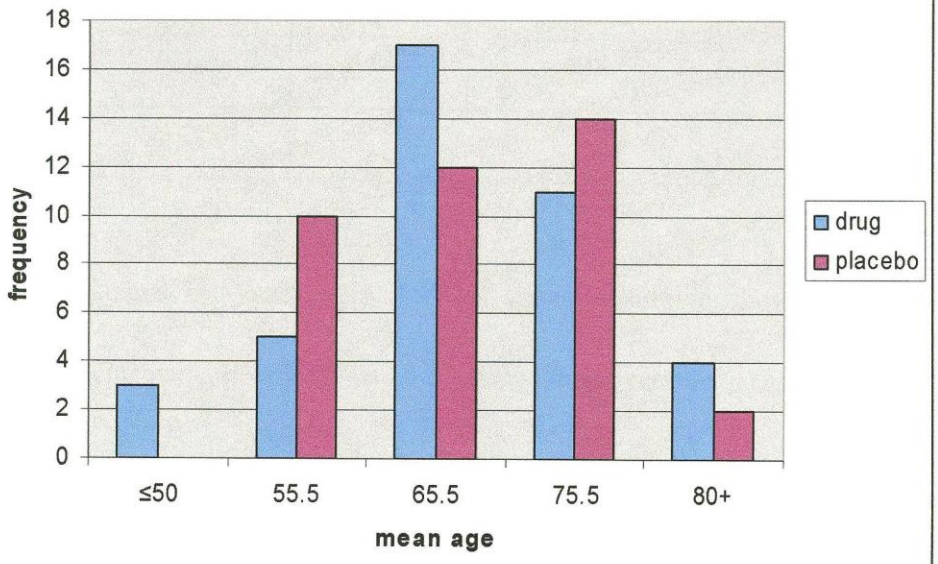
Table 1. Distribution of study population by mean age and treatment group

Mean age(years)	Drug	Placebo	Total
≤ 50	3	0	3 (3.8%)
55.5	5	10	15 (19.2%)
65.5	17	12	29 (37.2%)
75.5	11	14	25 (32.2%)
> 80	4	2	6 (7.7%)
Total	40(51.3%)	38(48.7%)	78(100.0%)

The majority number of patients 29(37.2 %), were in the mean age 65.5 years.

Among the sample population, 40(51.3 %) patients were allocated to treatment group.

Figure 1: A bar chart representing frequency distribution of the study population by mean age and group allocation



Pictorial representation of frequency distribution of mean age and "treatment" group allocation.

The majority of patients in the treatment group were in the mean age 65.5 years old.

In the placebo group, the majority of patients were in the mean age 75.5.

Table 2(a). Serum Creatinine levels among the study population

Creatinine	drug	placebo
Normal	37 (50%)	37 (50%)
Elevated	3 (75%)	1 (25%)
Total	40	38

Only 4 patients had marginally elevated serum creatinine above normal range. These patients had no clinical feature of uremia, however one of them had low Haemoglobin as well. These patients were not excluded from the study.

Table 2(b) haemoglobin measurement among the study population

Haemoglobin	drug	placebo
Normal	37 (50.7%)	36 (49.3%)
Low	3 (60.0%)	2 (40.0%)
	40	38

Five patients had anemia of varying severity. Possible causes of anemia could be nutritional deficiencies as well as infestations. These patients were equally dewormed and supplemented with oral haematenics in their 'treatment'. No any patient who received blood transfusion.

There were 2 patients with Diabetes Mellitus and both of them were in the placebo group. Their blood sugar level were under control, one of them was on dietary control and the other was on Daonil tablets 10 mg once daily.

It was not possible for most patients to undergo Ultrasonographic measurement for prostate size. Most of them could not afford and those who came with their report, most of the reports were not specific on prostate parameters and therefore it was not feasible to evaluate changes in prostate size.

Table 3. Baseline Score in Quality of Life among the study population by group allocation

QoL score	Drug	Placebo	Total
4	14 (43.8%)	18 (56.3%)	32
5	18 (52.9%)	16 (47.1%)	34
6	8 (66.7%)	4 (33.3%)	12
Total	40	38	78

There were no significant difference in quality of life baseline scores between the two groups at baseline (95% C.I, P = 0.38). There were no QoL Score below 4

Table 4. Quality of Life Score among the study population by group allocation at 3 months

QoL score	Drug	Placebo	Total
4	17 (45.9%)	20 (54.1%)	37
5	13 (48.1%)	14 (51.9%)	27
6	10 (71.4%)	4 (28.6%)	14
Total	40	38	78

At 3 months, there were no significant difference in quality of life Scores between the two groups (95% C.I, P =0.39).

Table 5. Baseline Score in IPSS among the study population by group allocation

Baseline IPSS	Drug	Placebo	Total
0-7	6 (37.5%)	10 (62.5%)	16
8-19	33 (54.1%)	28 (45.9%)	61
20-35	1 (100.0%)	0 (0.0%)	1
Total	40	38	78

There were no significant difference at baseline scores in IPSS between the two groups. (95% C.I, P = 0.31)

Table 6. IPSS Score among the study population by group allocation at 3 months

Baseline IPSS	Drug	Placebo	Total
0-7	9 (40.9%)	13 (59.1%)	22
8-19	29 (56.9%)	22 (43.1%)	51
20-35	2 (40.0%)	3 (60.0%)	5
Total	40	38	78

At 3 months, there were no significant difference in IPSS Scores between the two groups. (95% C.I, P=0.24)

Table 7. Comparison in improvement in IPSS between the treatment group and the placebo group

	Treatment allocation		
IPSS:	Drug	Placebo	Total
Improved	26 (48.1%)	28 (51.9%)	54
Not improved	14 (58.3%)	10 (41.7%)	24
Total	40	38	78

There were no significant difference in the proportion of patients who reported improvement in international prostate symptom score between the treatment group and the placebo (95% C.I, P=0.47).

Table 8. Comparison in improvement in quality of Life between the treatment group and the placebo

	Treatment allocation		
QoL:	Drug	Placebo	Total
Improved	21 (48.8%)	22 (51.2%)	43
Not improved	19 (54.3%)	16 (45.7%)	35
Total	40	38	78

There were no significant difference in the proportion of patients who reported improvement in Quality of Life between the treatment group and the placebo (95% C.I, P=0.66)

Three patients in the treatment group and one patient in the placebo reported improvement in their sexual function. However, improvement in sexual function was not among the primary outcome measure in this study.

Table 9. Side effects of the drug among the study group as compared to a placebo

Group allocation	Drug	Side effect	Total
drug	38	-	38
placebo	40	-	40
Total	78	-	78

No side effects reported in either group, neither deaths reported

Table 10. Comparison of conversion rate to surgery ("prostatectomy") between the treatment group and the placebo

	Group allocation		
Surgery:	Drug	Placebo	Total
Converted	9 (52.9%)	8 (47.1%)	17
Not converted	31 (50.8%)	30 (49.2%)	61
Total	40	38	78

There were no significant difference in conversion rate to surgical intervention between the treatment group and the placebo group. (P=1.00)

There were no surgical complications.

Discussion

A total of 82 patients were enrolled and followed for a period April 2006 to January 2007. Each patient was followed 4-weekly for a period of 3 months. Four patients lost to follow up and were excluded from the study, and therefore analysis was done among 78 patients. Among the 4 patients who were lost to follow up 3 of them belonged to the placebo group.

Among the sample population the majority of the patients 29(37.2 %), were in the mean age 65.5 (table 1 and a figure1). Among patients who completed the study, 51.3 % (40) of them were allocated to treatment group.

Among patients who were allocated to treatment group, 26(65.0%) of them reported improvement in IPSS (table 6) and 22(52.5%) reported improvement in QoL (table 7). Among patients who were allocated to the placebo group, 28(73.7%) of them reported improvement in IPSS (table 6) and 22(57.9%) patients reported improvement in QoL (table 7) .

Among all patients in the sample population, the results showed no significant difference in improvement in IPSS from the baseline between the treatment group 26 (48.1%) patients as compared to 28 (51.9%) patients in the "placebo" group (95% C.I, P=0.47). see table 6.

The results also showed no significant difference in improvement in the Quality of life

between the treatment group 21(48.8%) patients as compared to 22 (51.2%) patients in the "placebo" group (95% C.I, P=0.66). see table 7.

Three patients in the treatment group and one patient in the placebo, unexpectedly reported improvement in their sexual function. However, improvement in sexual function was not among the primary outcome measure in this study. This came about when patients attending on their subsequent visits reported to have improvement in their sexual function following the use of the drug and were coming for more drugs for their sexual function.

The results showed that the efficacy of the drug is not superior over the placebo as compared with the findings by other authors. However the proportion of patients with improvement in IPSS by 48.1% and the proportion of patients with improvement in quality of life by 48.8% showed satisfactory outcome with the treatment. As stated above these research findings are comparable with results reported by other authors in the previous studies.[5,19,32,33]

The question here arise, that we may not encourage watchful waiting since the drug showed an acceptable degree of efficacy.

In a study done by Breza J. et al, it was found 31-40% reduction in IPSS in patients with Benign prostatic hyperplasia following institution of *P.africana* at dosage of 50mg twice daily for two-month duration. It was also found 31-34% improvement

in quality of life. This as statistically significant ($p<0.001$) and there were 89% (76/85) patients reported improvement and satisfaction in their sexual function.[32] The result findings in this study showed 48.8% improvement in quality of life higher than that reported by Breza J. at al.

Chatelain C, et al, also performed a study on *P. africana* extract in patients with BPH comparing once daily dosing (100mg) and twice daily dosing (50mg); and found more than 40% reduction in the mean IPSS from the baseline. Patients also reported improvement in quality of life and their sexual function.[33.] In this study, there is 48.1% patints who reported improvement in IPSS from the baseline using 100 mg twice daily dosing.

In a study with 209 subjects with BPH using a parallel-group, double-blind, comparative phase with *P. africana* (group A, 50 mg twice daily; group B, 100 mg once daily) and a ten-month open phase (100mg once daily), the average International Prostate Symptom Score improved by 38% in group A and 35% in group B. The quality of life (QoL) index was improved by 28% in both groups. The maximum flow rate (Qmax) increased 16% in group A and 19% in group B.[17,37] After twelve months of therapy, the IPSS decreased an average of 46%.[19,37,]

In another open Clinical trial testing the efficacy of Tadenan®, a plant extract from *P .africana*, 85 patients had significant improvements in IPSS (40%) and QoL (32%).[21] A lengthy 1995 literature review of the use of *P .africana* extract for BPH also yielded positive findings for its efficacy.[20] Twelve double-blind, placebo-controlled studies of *P. africana* extract were analyzed in which 358 patients received *P. africana* extract and 359 received a placebo. The results showed a statistically significant benefit for *P. africana* extract over placebo. However, most of the studies involved small number of patients, although one study with 126 subjects showed a statistically significant benefit for *P.africana* extract in maximum urinary flow rate, voided volume, residual volume, nocturia, daytime frequency, and impression of improvement scored by physicians and patients.[19,37]

In another open clinical trial testing the efficacy of Tadenan, a an extract from Prunus, 85 patients had significant improvements in IPSS (40%) and QoL (32%), and nocturnal frequency (32%). Improvements in Qmax, average urinary flow, and urine volume were also statistically significant.[20,37] However in my study, there were no measurement of urinary flow rate due to lack of Uroflowmeter at the Hospital; and also most patients could not afford for abdominal ultrasonogram in order to estimate post voidal residual urine volume.

No any adverse drug reaction were reported in either group (table 8) and there were no death report. There were no significant difference in conversion rate to surgical intervention between the treatment group 9 (52.9%) as compared to 8 (47.1%) in the placebo group (95% C.I, P=1.00), table 9.

The reasons for conversion to surgery were due to patients desire in 10 of them, however 7 patients complicated to urinary retention. Among patients who complicated to urinary retention 4(10.5%) were in the treatment group.

Conclusion

The treatment did not show much difference in efficacy over the placebo in the treatment of early BPH. There were no significant difference in proportion of patients who reported improvement in IPSS and improvement in quality of life between the two groups. Three patients in the treatment group and one patient in the placebo group reported improvement in their sexual function.

No any adverse effect reported and were no death report in either group. Surgery is still an alternative treatment in a few cases with failure in medical response. The rate to surgical intervention between the treatment group 52.9% as compared to 47.1% in the placebo group.

Generally the trend of results in this study showed that the drug is not superior over the placebo and the difference is not statistically significant and therefore inconclusive results. However the 48.1% reduction in IPSS from the baseline and 48.8% improvement in QoL are satisfactory outcome with the treatment.

Limitations of the Study

Limitation of this study is the small sample size due to short period of study and 4 patients were lost to follow up.

Inadequate allocation of fund to pay for some investigations. The majority of patients could not afford for some investigations such as abdominal ultrasonograghy which could have been useful in measuring residual urine volume and estimation of prostate size.

This research requires team work including laboratory technician, pathologist and Sonographer/radiologist.

The estimation of prostate size and urine volume could have been possible with abdominal ultrasonograghy and if these were performed to all patients, it could have added parameters for outcome measures for the treatment response. Absence of Uroflowmetry at the Hospital which could have been used to estimate urine flow rate which is a useful indicator for treatment response.

Recommendation

The trend of the initial pilot phase in this study showed that the drug is not superior over the placebo; however this is only a fraction of estimated sample size for completion of the study. The department of Surgery in collaboration with the Institute of Traditional Medicine has already planned for continuation of this study to reach the minimum estimated sample size and therefore continuation of the study is recommended for interim comparison of results. We should therefore set a protocol for *P. africana* in the treatment of symptomatic BPH. Either we should compare *P. africana* with a known α-adrenergic blocker (e.g. tamsulosin) and with a combined therapy of *P. africana* and an α-adrenergic blocker.

This research should incorporate laboratory technician, pathologist and sonographer/radiologist for their relevant involvement.

Urology unit has to be strengthened to have uroflowmetry as there is a significant number of patients with BOO at the Hospital reported from morbidity and mortality data.

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