Chapter 5

Botanicals and the Treatment of BPH

Phytotherapy uses a naturally occurring plant or plant extracts as basis for treatment. Plant derived chemicals are now being used widely in Europe as a remedy for BPH, however these substancs have not enjoyed widespread use in the United States primarily due to the Western clinician's desire to utilize the pharmaceutical armamentarium. Plant extracts used for treatment of benign enlargement of the prostate are called *phytosterols*, which may be defined as plant derived compounds. The most commonly used of these is LSESr, or Saw Palmetto Berry Extract.

5A

Introduction

Historically, the medical community outside of the United States has long supported alternative therapies for somatic as well as genetically inherited ailments. As previously noted, this has been changing quite rapidly, with a burgeoning market for these substances recently taking hold in this country.

In consideration of this phenomenon it must be recognized that a large amount of scientific literature supporting the medical efficacy of naturally occurring substances has already been published. For example, two

botanicals which have been used successfully in the treatment of BPH are saw palmetto berry extract, or the liposterolic extract of serenoa repens (LSESr) and Pygeum africanum.

5B

LSESr

Saw palmetto is a small palm tree native to the West Indies and the Atlantic coast of North America from South Carolina to Florida. The plant grows from 6 to 10 feet high with a crown of large, 2- to 4-foot high, spiny-toothed leaves that form a circular, fan-shaped outline. The berries are used for medicinal purposes. The deep red-brown to black berries are wrinkled, oblong, and 0.5 to 1 inch long with a diameter of 0.5 inch (1).

5C

Chemical composition

Saw palmetto berries contain about 1.5 percent of a fruity-smelling oil containing saturated and unsaturated fatty acids and sterols (2). About 63 percent of this oil is composed of free fatty acids including capric, caprylic, caproic, lauric, palmitic, and oleic acids. The remaining portion is composed

of ethyl esters of these fatty acids and sterols, including beta-sitosterol and its glucoside.

The lipid-soluble compounds are thought to be the major pharmacological components. Other components of the berries include carotenes, lipase, tannins, and sugars. The purified fat-soluble extract is used medicinally and contains between 85 and 95 percent fatty acids and sterols. It is made up predominantly of a complex mixture of saturated and unsaturated free fatty acids, their methyl and ethyl esters (approximately 7 percent), long-chain alcohols in free and esterified form, and various free and esterified sterol derivatives.

The free fatty acids in this extract are identified by gas chromatography and mass spectrometry as caproic acid (six-carbon chain, C6), capric acid (C8), caprylic acid (C10), lauric acid (C12), myristic acid (C14), isomyristic acid (C14), palmitic acid (C16), oleic acid (C18:1), and stearic acid (C18). Lauric and myristic acid are the major fatty acids, accounting for approximately 30 percent of the fatty acid content. The identified alcohols include those with *n*-C22, *n*-C23, *n*-C24, *n*-C26, *n*-C28, and *n*-C30 chains, phytol, farnesol, and geranylgeraniol, in addition to high molecular weight unsaturated polyphenols. The sterolic fraction is composed of beta-sitosterol,

stigmasterol, cycloartenol, lupeol, lupenone, and 24-methylcycloartenol. Many of these sterols are esterified with the fatty acids of the extract (3).

5D

History and folk use

The American Indians used saw palmetto berries in the treatment of genitourinary tract disturbances and as a tonic to support the body nutritionally. It was administered to men to increase the function of the testicles and relieve irritation in mucous membranes, particularly those of the genitourinary tract and prostate. It has been given to women with disorders of the mammary glands: long-term use was reputed to slowly cause the mammae to enlarge. Many herbalists consider it to be an aphrodisiac.

5E

Pharmacology

A standardized liposterolic saw palmetto berry extract demonstrates numerous pharmacological effects relating to its primary clinical application in the treatment of BPH. The primary therapeutic action LSESr in this disorder is to inhibit the intraprostatic conversion of testosterone to DHT, and to inhibit DHT's intracellular binding to androgen receptor and transport to the cell

nucleus. As previously described, this occurs via competitive and uncompetitive inhibition (4).

The main constituents include carbohydrates (invert sugar, mannitol, high-molecular-weight polysaccharides with galactose, arabinose, and uronic acid), fixed oils (free fatty acids and their glycerides), steroids, flavonoids, resin, pigment, tannin, and volatile oil. The fruits and seeds are rich in triacylglycerol-containing oil (50% of the fatty acids contain 14 or less carbons) (5).

Saw palmetto has been reported to contain diuretic, urinary antiseptic, endocrinological, and anabolic properties (6). The fruit of saw palmetto has been shown *in vitro* to inhibit the 5-alpha-reductase and aromatoase, significant in the development of BPH (Koch and Biber, 1994). A recent animal study has shown anti-exudative and anti-inflammatory effects as well (7). Additional research to confirm the purported hormonal and anti-inflammatory effects of saw palmetto is required.

5F

Clinical applications

Currently, the primary clinical application of LSESr is in the treatment of BPH. However, on the basis of its pharmacology, we believe this extract may also be of benefit in other disorders of steroid hormone metabolism, such as hirsuitisim, androgenic alopecia, and polycistic ovarian disease.

5G

LSESr and BPH

As noted earlier, approximately 50 to 60 percent of men between 40 and 59 years of age present symptoms of BPH. This disorder is characterized by increased urinary frequency, nighttime awakening to empty the bladder, and reduced force and caliber of urination.

Finasteride (Proscar™) is currently the only approved drug in the treatment of BPH. Finasteride blocks the transformation of testosterone to DHT by competitively inhibiting the activity of 5-alpha-reductase. DHT has been shown to stimulate the overproduction of prostate cells, ultimately resulting in prostatic enlargement.

Proscar™ has been shown to be much less effective in the treatment of BPH (on the basis of results of several well designed and controlled clinical trials) than LSESr (8). For example, fewer than 50 percent of those taking

Proscar™ report clinical improvement after taking the drug for 1 year; and it must be taken for at least 6 months before any improvement can be expected.

Proscar™, a prescription required drug, has a cost of approximately $75 per month, not including the cost of clinician involvement and follow up. Nevertheless, Merck Pharmaceutical, the manufacturer of Proscar™, has predicted sales will soon reach $1 billion dollars annually. However, clinical studies suggest that men with BPH could achieve far better results from LSESr. Numerous studies on LSESr have shown it to be effective in nearly 90 percent of BPH patients, usually in a period of 4-6 weeks (9).

In one large double blind study involving 110 outpatients suffering from BPH, impressive clinical results demonstrating the superiority of LSESr for the treatment of BPH, were obtained. Nocturia decreased by over 45 percent, flow rate (in mm. per second) increased by over 50 percent, and postmicturition residue (in mm.) decreased by 42 percent in the LSESr treatment group. In contrast, those on placebo showed no significant improvement in nocturia or flow rate, and postmicturition (bladder fluid retained after urination) residue actually worsened (10).

Significant improvements were also noted in self-rating by the patients and global rating by the investigators. Of the fifty treated subjects completing

the 30-day study, physicians rated fourteen as greatly improved, thirty-one as improved, and only five as unchanged or worsened. In contrast, no subjects in the placebo group had greatly improved, sixteen showed some improvement, and twenty-eight remained unchanged or worsened (11). From this data it is apparent that LSESr has demonstrated efficacy in the treatment of BPH (table 3).

Although LSESr has shown excellent results in numerous double-blind, placebo-controlled clinical trials, results from a recent open multi-center study are perhaps even more compelling (12). A total of 305 patients fulfilled inclusion criteria.

Table 3: Clinical studies demonstrating the efficiency of LSESr in the treatment of BPH

Each patient was given a dosage of 160 mg. twice daily. The subjective evaluations of treatment made by patients after 45 and 90 days of treatment were quite favorable. At day 45, 83 percent of patients estimated the drug was effective. However, after 90 days, the percentage increased to 88 percent. Similarly, global evaluations made by investigator physicians after 45 and 90 days demonstrated 81 and 88 percent effectiveness, respectively. As in previous research of LSESr, there were no serious adverse reactions reported from this study.

The objective evaluations demonstrated remarkable improvements in all measurements. Maximum urinary flow (mm. per second) increased from 9.78 to 12.19; mean urinary flow rate (mm. per second) increased from 5.83 to 7.41; prostatic volume (in cubic mm.) decreased from 40,348 to 36,246; and the international prostate symptom score decreased from 19 to 12.4. An equally impressive finding was that LSESr had no demonstrable effect on serum prostatic specific antigen levels (PSA) (13).

In another three month open trial, 505 patients with mild to moderate symptoms of BPH were treated with Prostaserene®, an oral preparation of LSESr at a daily dosage of 160 mg twice daily. Three hundred five patients were available for evaluation at the end of the three month period. Using the International Prostate Symptom Score, the quality of life score, urinary flow rates, residual urinary volume, and prostate size, patients taking saw palmetto showed significant improvement after only 45 days of treatment. After 90 days, 88 percent of the patients and 88 percent of physicians considered the therapy successful. Serum prostate-specific antigen (PSA) concentration was not modified by taking saw palmetto, thus reducing the chance of masking potential prostate cancer. Side effects were reported in only 5 percent of the patients completing the three month study (14).

5H

Dosage

To achieve the benefit with LSESr, it is recommended that the extract contain 85-95 percent fatty acids and sterols. It is also suggested that this level be delivered at a dosage of 160 mg. twice daily as LSESr has a half-life of approximately 12h (15).

5I

Toxicity

LSESr is completely safe, as no significant side effects have ever been reported in the clinical trials of the extract or with saw palmetto berry ingestion. Detailed toxicology studies on LSESr have been carried out on mice, rats, and dogs, and indicate that the extract has no toxic effects. Further, unlike finasteride, LSESr has never been linked to teratogenic effects. It has been used safely by women in the treatment of infertility, painful menstruation and difficulties with lactation.

5J

Pygeum

General description

Pygeum africanum, an evergreen tree native to Africa, can grow to a height of 120-150 feet. It has pendulous branches with thick, oblong-shaped, leather-like, dark green-colored leaves and creamy white flowers. The fruit resembles a cherry when ripe. The dark-brown to gray bark of the trunk is used for medicinal purposes.

5K

Chemical composition

The major active components of the bark are fat-soluble compounds such as pentacyclic triterpenes, sterolic triterpenes, fatty acids, and esters of the ferulic acid (figure 15A -15B).

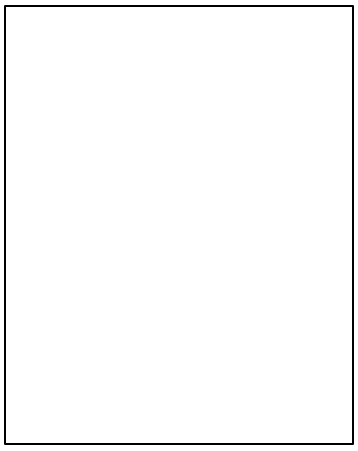

Figure 15A: Ferulic acid

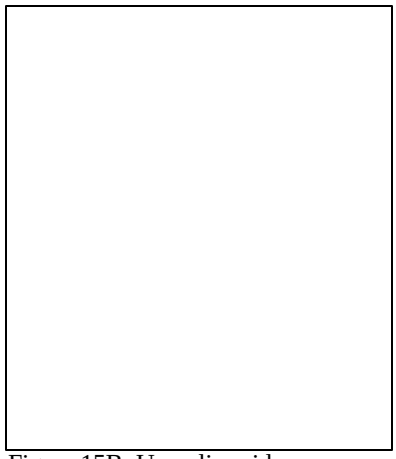

Figure 15B: Urosolic acid

The pentacyclic triterpenic components include ursolic acid, oleanolic acid, crataegolic acid, and their glucosides. The sterolic fraction is composed mainly of beta-sitosterol and beta-sitosterone (figure 16).

Figure 16: Beta-sitosterone

The fatty acids are twelve to twenty-four carbons in length (C12 to C24) and the important ferulic acid esters are those bound to *n*-tetracosanol and *n*-docosanol (16).

5L

History and folk use

The powdered bark of Pygeum is used by the natives of tropical Africa as a treatment for urinary disorders. It is often administered with palm and other oils. Traditionally the bark of the tree was collected and powdered, then drunk as a tea for genito-urinary complaints. Recently numerous clinical trials have demonstrated the usefulness of a standardized extract of pygeum for prostatic dysfunction, particularly BPH (17).

5M

Pharmacology

Pharmacological screening of various extracts prepared with solvents of differing degrees of polarity indicates that the highest activity is found in lipophilic extracts. Virtually all of the pharmacological research has featured a pygeum extract standardized to contain 14 percent triterpenes including beta-sitosterol and 0.5 percent *n*-docosanol. This extract has been extensively studied in both experimental animal screens as well as clinical trials involving human subjects.

The primary target organ for the effects of pygeum in males is the prostate gland. The three major active components of pygeum appear to exert differing, yet complimentary, effects in BPH. Chemical analysis and pharmacological studies indicate that the lipophilic extract of pygeum bark has three categories of active constituents. The phytosterols, including beta-sitosterol, have anti-inflammatory effects by interfering with the formation of pro-inflammatory prostaglandins that tend to accumulate in the prostate of men with BPH (18). The pentacyclic terpenes have an anti-edema or decongesting effect. The last group are the ferulic esters. These constituents reduce levels of the hormone prolactin and also block cholesterol in the prostate. In addition, pygeum has been shown to enhance the secretions of the prostate and bulbourethral glands, both in terms of quantity and quality.

5N

Ferulic acid esters

The esters of ferulic acid act primarily on the endocrine system. Studies in animals have shown that *n*-docosanol reduces levels of leutinizing hormone and testosterone while raising adrenal secretion of both androgens and corticosteroids. *n*-Docosanol also significantly reduces serum prolactin levels. This reduction is quite significant, as prolactin increases uptake of testosterone and increases synthesis of DHT within the prostate (19).

The accumulation of testosterone within the prostate as well as its subsequent conversion to DHT is thought to be a major contributing factor to the hyperplasia observed in BPH. Although traces of *n*-docosanol are present in pygeum, the esterification with ferulic acid results in greater bioavailability and activity (20).

Fat-soluble components in pygeum exert a systemic cholesterol-lowering action and reduce the intraprostatic cholesterol content. Breakdown products of cholesterol accumulate in prostate tissue affected with either BPH or cancer. These metabolites of cholesterol initiate degeneration of prostatic cells, which can promote prostatic enlargement.

Drugs that lower cholesterol levels may exert a favorable influence on BPH by preventing the accumulation of cholesterol in the prostatic cells and limiting subsequent formation of damaging cholesterol metabolites. The lowering of intraprostatic cholesterol content is an important aspect of the pharmacology of pygeum.

In addition, the sterols of pygeum have also been shown to reduce inflammation by preventing the intraprostatic formation of inflammatory prostaglandins (21).

5O

Other components

The pentacyclic triterpenes found in pygeum exhibit anti-inflammatory effects within the prostatic epithelium and may be responsible for stimulation of the secretory cells of the prostate, seminal vesicles, and bulbourethral glands. Finally, the fatty acid components are similar to those of LSESr and may exert similar effects as well as improve the oral bioavailability of other components of the lipophilic extract.

5P

Pygeum and prostate disorders

The pharmacological actions of the standardized pygeum extract supports its use in prostate disorders, BPH in particular. Adding further support are the results from numerous clinical trials of over 600 patients (22). Consistently, these studies have demonstrated pygeum to effectively reduce the symptoms and clinical signs of BPH, especially in early cases. However, it must be pointed out that improvement is largely symptomatic (i.e. quality of life assessment scores vs urinary output and flow) as the results on reducing the size of the prostate or the residual urine content of the bladder are modest. The results of the clinical trials on pygeum are given below, followed by a discussion of some of the most important aspects of these studies.

One of the major challenges in evaluating the effectiveness of pygeum in BPH has been the high rate of responders to placebo. However, it should be noted that evaluating new treatments for benign prostate growth is intrinsically difficult. BPH is a chronic condition that varies over time --symptoms may gradually get worse or better, or they may resolve only to reappear months later. Some men whose prostate enlarges never develop any symptoms, while others with only minimal prostate growth are terribly bothered by symptoms.

These factors suggest that any study attempting to prove or disprove the

value of a new remedy must be of sufficient duration and control in order to overcome the placebo effect. However, to date, few studies published on pygeum have been of long duration. Many studies lasted only a few weeks or included only a small number of men, and few included a placebo group as a control, or randomly assigned men to either the active remedy or placebo.

One recent study does highlight the importance of double-blind methodology featuring both objective and subjective findings. In this study, both patients and physicians rated the placebo and pygeum extract to be effective in improving subjective symptoms of daytime frequency, nocturia, weak stream, after dribbling, hesitation, and interruption of flow (23). However, urodynamic variables (flow, frequency, and histogram) clearly demonstrated the superiority of pygeum over placebo.

One of the shortcomings of some of the clinical research on pygeum is the lack in many of the studies of objective measures such as urine flow rate (ml/sec), residual urine content, and prostate size. Studies that have used objective measurements have shown some good results (table 4).

Table 4: Results of the most significant open and double-blind studies of the last 20 years on outpatients treated with Pygeum africanum for 1 to 3 months

For example, in one open trial, thirty patients with BPH given 100 mg/day of the pygeum extract for 75 days demonstrated significant improvements in objective parameters: maximum flow rate increased from 5.43 ml/sec to 8.20 ml/sec and the residual urine volume dropped from 76 ml to 33 ml (24).

It should be pointed out that in a double-blind study which compared the pygeum extract with the extract of saw palmetto, the saw palmetto extract produced a greater reduction of symptoms and was better tolerated (25). In

addition, the improvement of objective parameters, especially urine flow rate and residual urine content, is better in the clinical studies with LSESr.

However, there may be circumstances where pygeum is more effective than LSESr (ref). For example, LSESr has not been shown to produce the effects that pygeum has produced on prostate secretion. Although the two extracts have somewhat overlapping mechanisms of actions, they can be used in combination.

5Q

Male infertility and impotence

Pygeum may be effective in improving fertility in cases where diminished prostatic secretion plays a significant role. Pygeum has been shown to increase prostatic secretions and improve the composition of the seminal fluid. Specifically, pygeum administration to men with decreased prostatic secretion has led increased levels of total seminal fluid plus increases in alkaline phosphatase and protein.

Pygeum appears to be most effective in cases where the level of alkaline phosphatase activity is reduced (i.e., less than 400 IU/cm3) and there is no

evidence of inflammation or infection (i.e., absence of white blood cells or IgA). The lack of IgA in the semen is a good predictor of clinical success. In one study, the patients with no IgA in the semen demonstrated an alkaline phosphatase increase from 265 to 485 IU/cm3. In contrast, in those subjects with IgA showed only a modest increase from 213 to 281 IU/cm3.

Pygeum extract has also shown an ability to improve the capacity to achieve an erection in patients with BPH or prostatitis as determined by nocturnal penile tumescence in a double-blind clinical trial (26). BPH and prostatitis are often associated with erectile dysfunction and other sexual disturbances. Presumably by improving the underlying condition, pygeum can improve sexual function.

5R

Dosage

The dosage of the lipophilic extract of *Pygeum africanum* standardized to contain 14% triterpenes including beta-sitosterol and 0.5% n-docosanol is 100 to 200 mg per day in divided doses. The crude herb is not used.

5S

Toxicology

Acute and chronic toxicity tests in the rat and mouse have shown that the standardized extract of *Pygeum africanum* bark is non toxic. Increasing doses from 1 to 6 g/kg in the mouse and from 1 to 8 g/kg in the rat caused no deaths within 48 hours.

In chronic toxicity studies, dosing the animals from 60 to 600 mg/kg for eleven months did not produce any negative effects. In the human clinical trials, the pygeum extract also demonstrated no significant toxicity. The most common side effect is gastrointestinal irritation resulting in symptoms ranging from nausea to severe stomach pains, however, rarely does the presence of these side effects result in discontinuation of therapy.

5T

Conclusions

Benign prostatic hyperplasia (BPH), a non-malignant abnormal enlargement of the prostate gland can cause a significant disruption of lifestyle due to urinary outflow obstructive and irritative symptoms. Two botanicals which have been used successfully in the treatment of BPH are the liposterolic extract of serenoa repens a.k.a. saw palmetto berry extract (LSESr) and

Pygeum africanum. The advantages over pharmaceutically derived alternatives are a high level of success and freedom from negative side effects.

As previously noted, BPH shares a strikingly similar hormonal metabolism with AGA. For the author, the clue that both LSESr and beta-sitosterol repeatedly demonstrated benefit in the treatment of BPH under double blinded, placebo controlled, conditions was a critically important element leading to the central hypothesis of this dissertation.

5U

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