Complementary and alternative medications for benign prostatic hyperplasia

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KEEHN A, LOWE FC. Complementary and alternative medications for benign prostatic hyperplasia. *Can J Urol* 2015;22(Suppl 1):18-23.

Introduction: *The use of complementary and alternative medications has become a multi-million dollar business in the United States and comprises more than half of all filled prescriptions for benign prostatic hyperplasia (BPH) in Europe. For the practicing urologist, understanding the phytotherapeutic agents available, their proposed mechanism of action, the research supporting their use, and their safety profiles has become increasingly important as more patients inquire into their use.*
Materials and methods: *A comprehensive literature search was conducted to identify pertinent articles pertaining to alternative and complementary treatment options for the management of BPH. Treatments demonstrating adequate clinical data, including Serona repens, Pygeum africanum, and Secale cereal, were selected for in depth review.*
Results: *Small clinical trials for each of the agents demonstrated mixed results while larger more soundly constructed studies found no significant benefit for the use of phytotherapy in the treatment of BPH.*
Conclusions: *Based on the available literature, there is no evidence that phytotherapy significantly improves symptoms of BPH against placebo, despite being largely safe for ingestion. In patients with mild BPH symptoms who are reluctant to take standard pharmaceutical medications may try these agents provided that the patient understands their current limitations. Those with moderate or severe BPH should be discouraged from alternative and complementary treatments.*

Key Words: BPH, phytotherapy, Serona repens, Pygeum africanum, Secale cereal

Introduction

Benign prostatic hyperplasia (BPH), the non-malignant enlargement of the prostate, is one of the most common urological diseases worldwide and is responsible for almost 8 million medical office visits annually in the United States.[1] Given the prevalence of the condition and the lower urinary tract symptoms (LUTS) that accompany it, treatment for BPH both medical and surgical has been well described. Over the past 20 years, the use of complementary and alternative medications has become a multi-million dollar business in the United States with the expansion of health food stores, vitamin shops, and internet companies selling these agents for the treatment of BPH. In Austria, France, and Germany, phytotheraputic agents are considered first line treatment for moderate LUTS and comprise roughly 90% of all prescriptions filled for BPH management.[2] In the United States, about 40% of men opting for non-surgical therapy for BPH use herbal supplements alone or in conjunction with other medical preparations, and that number continues to grow.[3]

For the practicing urologist, understanding the phytotherapeutic agents available, their proposed mechanism of action, the research supporting their use, and their safety profiles has become increasingly important as more patients inquire into their use. There have been more than 30 phytotheraputic compounds described for the management of BPH, Table 1. Of those, the saw palmetto berry (SPB), also known as Serona repens, has been one of the most widely used and studied supplements and will thus be emphasized in this review. Additionally, two other studied agents, Pygeum africanum, and Secale cereal will be reviewed.

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TABLE 1. **List of phototherapies known to be used for BPH management**

Phytotherapy	Description and locale
Allium sativum	Garlic extract, found internationally
Althea officinalis	Root extract of this perennial species native to Africa
Arctostaphylos uva-ursi	Extract of this shrub found in mostly northern latitudes
Asteracantha longifolia	Seed and root extract of this plant found mostly in India
Cucurbita pepo	Extract from pumpkin seeds found in multiple locales
Curculigo orchioides	Extract of flowering plant species found in Asia
Echinacea spp	Root extract of flowering plant found in North America
Epilobium spp	Extract of flowering plant found in temperate tropical areas
Equisetum arvense	Extract of herbaceous plant fund in northern hemisphere
Ganoderma lucidum	Extract of the fruit of the plant found in Asia
Hypoxis rooperi	Extract of plant native to South Africa
Lactuca scariola	Extract of biennial plant native to Europe and North Africa
Lycopersicum esculentum	Compound within the common tomato plant also known as lycopene
Opuntia ficus-indica	Extract of cactus plant found in semi-arid regions of the world
Orbignya speciosa	Extract of bark and root of Brazilian native palm tree
Parmellia perlata	Extract of lichen species found in temperate climate zones
Phellodendron amurense	Bark extract of deciduous trees native to eastern Asia
Pinus pinaster	Extract of pine tree native to Southwest Mediterranean region
Pygeum africanum	Extract of evergreen tree native to regions of sub-Saharan Africa
Roystonea regia	Extract of palm native to Florida and Mexico
Saxifraga stolonifera	Extract of perennial flowering plant native to Asia
Secale cereale	Extract of this common grass gown as grain in fields internationally
Serenoa repens	Extract of saw palmetto berry found in the southeastern USA
Telfairia occidentalis	Extract of this vine and seeds grown in West Africa
Urtica dioica	Extract of flowering plant found in Europe and Asia
Vaccaria segatalis	Extract of herbaceous plant found in Eurasia
Zea mays	Extract of common corn found in multiple locales

Saw palmetto

SPB, also known by its botanical name Sabal serrulatum is the most common phytotherapeutic agent used for the management of BPH. In fact, the SPB has become so popular that it has become one of the 10 top selling supplements in the United States.[4] A primary difficulty in evaluating the efficacy of SPB is the absence of a standard formulation. Since phytotherapies are listed as foods by the United States Food and Drug Administration, there is little regulation in their production and distribution. The result is that the various brands marketing SPB have marked variation in content due to both variability of the extraction process, and the plant itself.[5] The most extensively studied preparation of SPB is manufactured in France and marketed as the drug Permixon (Pierre Fabre Medicament, Castres, France). In 2004, Habib et al analyzed 14 products for free fatty acid (FFA) content, esters, and glycerides.[6] The FFA content, which has been suggested as the primary source of clinical benefit, was noted as high as 80.7% for Permixon down to 40.7% for Solaray (Nutraceutical Corp., Park City, UT, USA). Methyl and ethyl esters were noted at 16.7% for Prosta-urgenine (Hoyer-Madaus, Mannheim, Germany) and at 2.5% for Permixon. Permixon was also noted to have the lowest content of glycerides at 6.8%, whereas Solaray was highest at 52.15%. It is clear, therefore, that product

content variability could skew results of the various trials evaluating SPB.

Mechanism of action

Although not clearly defined, multiple mechanisms of action have been proposed for SPB based on various in-vitro studies, including: alterations in cholesterol metabolism,[7] anti-androgen effects,[8] anti-inflammatory effects,[9] pro-apoptotic properties,[9] relaxation of detrusor and prostate smooth muscle,[10] and even placebo effect.[10] SPB may serve as an anti-androgen supplement via the inhibition of the type 1 and type 2 iso-enzymes of 5-alpha reductase noted in multiple studies.[11] Although, other investigations have pointed out that the inhibition is weak, less potent that finasteride, and present at sub-physiologic levels.[12] SPB may effect relief of BPH via anti-inflammatory properties derived from a decrease in sex-hormone binding globulin, and in-vitro inhibition of synthesis of cyclooxygenase, and by modulating the expression of pro-inflammatory genes.[13] Several studies have found that SPB suppresses growth and induces apoptosis of prostatic epithelial cells by inhibition of signal transduction pathways.[14] SPB may lead to smooth muscle relaxation via blockade of alpha-1 receptors and calcium channels during in-vitro experiments.[15] Despite this, more recent reports from rat prostates have in fact found that SPB might induce, rather than inhibit the activity alpha-1 receptors.[16] Clearly, the actual mechanism of action of SPB has yet to be elucidated.

Clinical studies

There have been multiple meta-analyses integrating results from the many studies reported on SPB and their effect on BPH. Many of the early systematic reviews including those by Wilt et al in 1998 of all products and then by Boyle in 2004 of Permixon products suggested that SPB conferred a modest to moderate improvement in urinary symptoms against placebo. An additional study suggested it acted similarly to finasteride but with less sexual side effects.[17] Yet, one of the major criticisms of these early reviews was that the studies included were relatively small, underpowered, and contained short follow up data. Additionally the data within was possibly inaccurate secondary to variability in study products, and the flawed methodology utilized for interpreting the diverse data.

In 2006, Bent et al published an NIH funded study; the first non-company funded clinical trial looking at the efficacy of SPB.[18] They utilized a carbon dioxide extract of SPB (Rexall-Sundown Bohemia, NY, USA) and manufactured one lot of product for patient distribution in order to control for product variation that contained 92.1% total fatty acids as seen on gas chromatography. In this 12 month, randomized, double blinded, placebo controlled, trial in 225 men, the authors reported no significant difference in the change in IPSS score (mean difference of 0.04 points, 95% CI -0.93 to 1.01) and Qmax (mean difference of 0.43 mL/minute, 95% CI -0.52 to 1.38) compared to placebo. Additionally, prostate size, post void residual (PVR), serum prostate-specific antigen (PSA) levels, and quality of life also were not different between the groups. At that time, it was speculated that the lack of efficacy was possibly secondary to low levels of active ingredient in the used product.

In response to this speculation, the NIH sponsored the Complimentary and Alternative Medicine for Urinary Symptoms (CAMUS) trial whose results were reported in 2011.[19] In this long term dose escalation trial of 72 weeks, two batches of SPB were prepared with 85%-95% FFA levels (Rottapharm/Madaus, Cologne, Germany). Results showcased that double and triple doses of SPB did not alter symptom scores compared with placebo. Additionally, the proportion of clinical responders (defined as ≥ 3 point decrease in the IPSS score) were similar at 43% for SPB versus 44% for placebo - with an associated risk ratio of 0.96 (95% CI 0.76-1.22). The results here, along with the results of the initial NIH funded study highlighted that SPB likely did not confer benefit over placebo for the treatment of BPH/LUTS. Despite the lack of efficacy, SPB was found to be safe even at double and triple doses compared to placebo.

Since the CAMUS trial, two recent systematic reviews have looked at the overall efficacy of Permixon and non-Permixon SPB. In 2012, MacDonald et al systematically reviewed the literature on the use of SPB for treatment of BPH.[20] In all, 17 randomized controlled trials (n = 2008) assessing SPB monotherapy (typically 320 mg/day) versus placebo were included. A meta-analysis of three high quality trials (n = 661) showed that SPB therapy was equivalent to placebo in reducing LUTS based on IPSS score (WMD -0.16 points, 95% CI -1.45 to 1.14) and Qmax (WMD 0.40 mL/s, 95% CI -0.30 to 1.09). Tacklind et al also reviewed the SPB literature in 2012.[21] While previous reviews from the same team in 1998, 2000, and 2002 touted clinical response with the use of SPB, the addition of well-constructed long term studies starting in 2006 led their results to reverse in a Cochrane review published in 2008. In their 2012 Cochrane update of 32 trials and 5666 patients the authors reported no significant difference between treatment arms (MD -0.25 points, 95% CI -0.58 to 1.07) and heterogeneity was nonexistent (I2 = 0%)

Safety profile

Clinical trials of SBP have consistently demonstrated that therapy at a dose of 320 mg/day is well tolerated with a side effect profile similar to that of placebo. Some reported side effects are generally mild and include headache, decreased libido, and gastrointestinal problems.[20] Other outlying case reports have been noted in the literature attributing more serious side effects to SPB including coagulopathy, hepatitis and pancreatitis.[22-24] The CAMUS trial confirmed that SPB is safe even in double and triple usual dosages.

An important fact concerns is the effect SBP might have on PSA. In 2013, Andriole et al reported on results from the CAMUS trial demonstrating that SPB did not alter PSA compared to placebo.[25] PSA was shown to be similar at baseline between treatment groups and the mean change during the trial for SPB and placebo was 0.23 and 0.16 respectively (p = 0.5). They concluded that even at relatively high doses. SPB did not affect serum PSA levels. Thus, there is no concern that taking SPB may mask the ability to detect prostate cancer via PSA screening.

Pygeum africanum

P. africanum of the Rosaceae family has been used in Europe under the trade name of Tadenan (Fournier, Dijon, France), and has been prescribed for BPH there for several decades.[26,27] The active compounds implicated in the treatment of BPH consist of N-N-butylbenzenesulfonamide, and atraric acid.[28]

Mechanism of action

Three proposed mechanisms of action have been hypothesized for P. africanum's effect on BPH symptoms based on in vitro studies. Firstly, it may inactivate androgen receptors via inhibition of nuclear translocation.[26] Secondly, P. africanum has shown to inhibit cellular growth factors such as fibroblast and epidermal growth factor.[29] And finally, P. africanum has been shown to have anti-inflammatory properties related to the inhibition of 5-lipoxygenase and consequent decrease of leukotriene production and other 5-lipoxygenase metabolites.[30]

Clinical studies

In 2000, Ishani et al reported the results of 18 clinical trials investigating P. africanum.[26] A total of 1562 men were analyzed with a mean trial duration of 61 days with a SD of 21 days. Doses ranged from 75 mg/day to 200 mg/day. Significant results of the analysis included that P. africanum decreased PVR by 24% in a total of 264 men in two studies (WMD -13 mL, 95% CI -23 to 3), and men taking the supplement had increased Qmax compared to placebo by 23% in 363 men over four studies (WMD 2mL/per second, 95% CI 0.3 to 4.7). Overall the results point to a modest benefit for the use of P. africanum over placebo. Yet, this meta-analysis must be interpreted with caution. Many of these studies had short study durations, varying dose protocols, did not compare P. africanum to placebo or to standard therapies and did not have IPSS scores and offered no information on long term complications. A multicenter placebo controlled trial (T-IPSS study) was undertaken in early 2000's, however, the results were never released nor published. Thus, in 2015, the efficacy of P. africanum is still questionable with further well-designed clinical trials needed to validate this agent.

Safety profile

P. africanum dosing has been reported at 75 mg/day-200 mg/day with 100 mg/day found with most frequency.[26] A study comparing 100 mg/day split in two doses of 50 mg showed equivalence to the 100 mg daily dosing option in terms of efficacy and side effects.[31] P. africanum induced adverse effects have been reported as mild and consisted of gastrointestinal problems and headache.[32]

Secale cereal

S. cereale, also known as rye pollen, is an extract made from the microbial digestion of the plant pollen. The most studied formulation is Cernilton (AB Cernelle. Engelholm, Sweden).

Mechanism of action

Several mechanisms of action have been proposed for S. cereale, including relaxation of urethral and bladder smooth muscle via antagonism of alpha adrenergic receptors. Additional mechanisms include induction of apoptosis in prostatic epithelial cells and inhibition of prostaglandin and leukotriene biosynthesis.[33]

Clinical studies

A meta-analysis of S. cereale literature was published in 2000 by MacDonald et al looking at four trials, of which two were placebo controlled. The analysis included 444 men with study durations of 24 weeks or less.[34] The authors reported that Cernilton reduced nocturia compared with placebo with a weighted RR of 2.05 (95% CI = 1.41 to 3.00). Yet, Cernilton was not more effective than placebo in improving urinary flow rates, residual volume or prostate size. A more recent randomized trial suggested that administration of 750 mg of

Cernilton could improve and arrest the progression of BPH symptoms more efficiently and effectively than 375 mg of the same product.[35] Two hundred and forty patients with IPSS scores > 7 were treated with 750 mg Cernilton for the first year and 375 mg for the next three. After the first year of treatment prostatic volume, episodes of retention, and surgical interventions were all decreased while Qmax PVR, and IPSS score were only affected after 4 years of treatment. No adverse effects were observed.

Despite this, the clinical trials utilized in the systematic review were limited by short duration, small patient numbers, gaps in reported outcomes, and variances in agent purity/preparation. The comparative trials did not provide a proven active control. In 2011, Wilt et al withdrew an update to the 2000 Cochrane review citing lack of adequate information to make a significant update. Thus, all that can be concluded based on the available evidence is that Cernilton is well tolerated.

Safety profile

Dosing of Cernilton ranges from 375 mg-1500 mg daily and is generally well tolerated. Common side effects have been reported as allergic respiratory reactions, skin hypersensitivities, and gastrointestinal symptoms.[36]

Combination trials

Numerous companies have manufactured combination pills for BPH in order to have a proprietary product. However, there is very limited clinical trial data available to make any definitive statement about these combination products. None of them have enough extensive data to recommend.

Conclusions

What to tell your patients

Currently, there is no standard of care regarding the management of patients with symptomatic BPH using phytotherapeutic agents. This is primarily so because the current literature has not been able to consistently prove the efficacy of these supplements. While in years past, data showed a modest benefit with use of these agents (like SPB), more recent and methodologically sound investigations have shown otherwise. Individuals should be advised that while many of these agents demonstrate acceptable safety profiles, the efficacy and mechanisms of action are still not defined. In patients with mild BPH symptoms who are reluctant to take standard pharmaceutical medications, phytotherapeutic agents are reasonable option, provided that the patient understands the current limitations of these agents. In patients with moderate to severe symptoms, including those with recurrent infections, bladder stone disease, or renal dysfunction, phytotherapy should be discouraged and traditional medical or surgical management should be advocated.

Disclosure

Dr. Aryeh Keehn has no disclosure.
Dr. Franklin C. Lowe is a consultant for Boehringer Ingelheim. □

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