THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 8, Number 6, 2002, pp. 813–821

Flavonoid and Botanical Approaches to Prostate Health

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common problem among aging men that produces significant morbidity and health care costs. Contention exists as to whether currently available surgical and pharmacologic options for BPH are appropriate for men in the watchful-waiting stage. Recently, the possible benefits of phytotherapies (plant-derived preparations) in treating BPH and prostate cancer are being considered. Several phytotherapies, including saw palmetto, *Pygeum africanum*, curbicin, and isoflavone-containing supplements (red clover [*Trifoleum pratense*] and soy), are widely used in patients with BPH. Evidence suggests that the consumption of isoflavones found in legumes is related to lower rates of BPH and prostate cancer among Asian men. When evaluating natural therapies, the physician should look for a product that relieves symptoms and is safe, contains a health-conferring ingredient with a defined mechanism of action, and is standardized for that ingredient. Phytotherapies, particularly isoflavone-containing supplements, are likely to have an important role in the management of patients in the watchful-waiting stage of BPH.

OVERVIEW OF ISSUES IN PROSTATE HEALTH

Benign prostatic hyperplasia (BPH) is a common problem; its prevalence among elderly men is estimated to be as high as 90% (Barry, 1990). Men with BPH have reduced quality-of-life measures and tend to seek professional care as the symptoms worsen and as the fear of more severe consequences, such as prostate cancer, increases.

Symptoms related to BPH do not correlate well with diagnostic measurements of prostate size, uroflowmetry, postvoid residual volume, and degree of bladder trabeculation. For this reason, considerable professional disagreement exists regarding BPH diagnosis and treatment methods. Symptoms of BPH can be classified as irritative (urgency, nocturia, frequency) or obstructive (dribbling, urinary hesitancy, straining to void, decreased force of or interruption of the stream, retention). Irritative symptoms appear to have more significant effects than obstructive symptoms on quality-of-life measures (Department of Veterans Affairs, 1993).

CONVENTIONAL MEDICAL THERAPIES FOR BPH

Most physicians agree that patient preference should be the dominant factor in the choice of therapy, particularly regarding sur-

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gery, for BPH. Patients with less severe symptoms may elect or be advised by their physicians to undergo watchful waiting, but many watchful-waiting patients continue to be symptomatic and eventually elect to undergo surgery to relieve their symptoms. Treatment with finasteride or an α-blocker such as terazosin (Flomax,® Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT), or tamsulosin (Hytrin® Abbott Laboratories, North Chicago, IL), may be more effective for symptom relief than watchful waiting (Altwein, 1998). However, accurate assessment of the benefits of BPH pharmacotherapy has been difficult because of the high placebo effect of therapies for this disease (Nickel, 1998).

Transurethral resection

Transurethral resection of the prostate (TURP) is the primary treatment for BPH. Initially, TURP was used to correct complete urinary obstruction, but because of its increased safety and availability, TURP is commonly used to alleviate less severe symptoms of BPH to improve quality of life. However, transurethral resection is not appropriate for all patients (Graversen et al., 1989). The need to perform TURP is undeniable when an elderly man has severe outlet obstruction leading to chronic urinary retention, large residual volume, or evidence of hydroureter or hydronephrosis, which may result in concurrent urinary tract infections, renal failure, and death (Barry et al., 1988; Department of Veterans Affairs, 1993; Graversen et al., 1989). Most men with symptoms of BPH are not at risk for obstructive uropathy or acute urinary retention, so the need for TURP in these patients is questionable. While TURP is successful in approximately 85% of cases (Graversen et al., 1989), many men are reluctant to undergo TURP, and the potential sequelae of TURP, such as operative risk among older men and retrograde ejaculation in younger men, are often unacceptable. Less invasive therapies to alleviate BPH symptoms, such as laser therapy and thermotherapy, may be alternative options for patients (Altwein, 1998; Servadio et al., 1990). In patients undergoing thermotherapy, 51% of cases showed improvement in objective and subjective signs and symptoms (Servadio et al., 1990). The advantages of laser therapy, as compared with TURP, are less clear because of dissatisfaction with current laser equipment and the long-lasting, irritative symptoms that follow laser ablation of the prostate (Altwein, 1998).

Pharmacotherapy

Finasteride shrinks the prostate by inhibiting the activity of 5-α-reductase, the enzyme necessary for converting testosterone to dihydrotestosterone (DHT), the active androgen in prostatic tissue. In a large-scale, placebo-controlled study conducted in 613 men, finasteride (compared to placebo) improved symptoms of BPH, increased urinary flow, and decreased prostate volume. However, improvement occurred slowly: symptom scores did not differ between placebo- and finasteride-treated patients during the first 8 months of treatment (Nickel et al., 1996). The most common adverse effects of finasteride are impotence or ejaculatory failure (8.1%), decreased libido (6.4%), and gynecomastia (0.5%) (Proscar®; Merck & Co., Whitehouse Station, NJ). Finasteride is contraindicated in women who are or may potentially be pregnant because it may cause developmental abnormalities in a male fetus (Proscar [package insert], 2001). To date, no drug interactions of clinical importance have been identified with finasteride. The cost of finasteride is approximately $68 for 30 tablets and $200 for 90 tablets. Finasteride lowers prostate-specific antigen (PSA) values by approximately 50% in patients with BPH. Finasteride did not appear to alter the rate of prostate cancer detection in patients with BPH and elevated PSA who were monitored in controlled clinical trials (Proscar, 2001). Currently, there is a large clinical trial underway in the United States that is investigating the role of finasteride in reducing the incidence of prostate cancer.

Terazosin and tamsulosin relieve symptoms of BPH by blocking α-1-adrenoceptors in the bladder neck and prostate, leading to relaxation of smooth muscle (Flomax [package insert], 1999; Hytrin [package insert], 1996). The effects are rapid; however, the patient should undergo dose supervision while the dose is titrated up. The most common adverse effects

of α-blockers include fatigue (7.4%, terazosin), postural hypotension (0.6%, terazosin; 0.2%, tamsulosin), dizziness (9.1%, terazosin; 15%, tamsulosin), nasal congestion/rhinitis (1.9%, terazosin; 13.1%, tamsulosin), and impotence (1.6%, terazosin) (Flomax, 1999; Hytrin, 1996). Terazosin and tamsulosin are contraindicated in patients known to be hypersensitive to these drugs. No clinically important drug interactions have been identified with terazosin, but the coadministration of tamsulosin and cimetidine has been shown to result in a significant decrease in the clearance of tamsulosin (Flomax [package insert], 1999; Hytrin [package insert], 1996). Tamsulosin and terazosin cost approximately $50 for 30 capsules and $141 to $147 for 90 capsules.

RATIONALE FOR NATURAL THERAPIES

Many patients are not satisfied with available surgical or pharmacologic therapies for BPH because of potential adverse effects. Patients who have heightened consumer awareness are beginning to request natural products. One study demonstrated that as many as 34% of people use unconventional therapies (medical interventions not taught widely at U.S. medical schools or generally available at U.S. hospitals), mostly for chronic conditions (Eisenberg et al., 1993). Other advantages of natural therapies may include better patient compliance, less anxiety among patients, improved safety, and lower cost.

The importance and practicality of investigating the use of natural therapies in treating medical disorders have been recognized by the National Institutes of Health, which has allocated funding for alternative medicine research. Thus, the field of alternative medicine has grown considerably. Numerous peer-reviewed publications now exist that examine the safety, efficacy, and mechanism of action of a number of natural therapies. Before prescribing a natural therapy for BPH, a number of criteria should be analyzed. Of premier importance for physicians selecting a natural therapy is that the therapy relieves patients' symptoms, is safe, provides sufficient quantities of the ingredient conferring a beneficial effect, and has a mechanism of action that is understood. Several isoflavone-containing botanic supplements possess these characteristics and have shown promise in the management of BPH and prostate cancer.

SCIENTIFIC EVIDENCE OF A ROLE FOR ISOFLAVONES IN PROSTATE HEALTH

Flavonoids are a family of plant-derived substances (phytochemicals) that are also termed phytoestrogens because of their estrogenic activity. Seven flavonoid subfamilies, including isoflavones, constitute the principal dietary source of phytoestrogens. Isoflavones are found primarily in legumes, including soybeans, red clover, chickpeas, lentils, grams, beans, and groundnuts. Isoflavones occur unconjugated (aglycone forms) or conjugated to sugars (glucoside forms). The aglycone isoflavone forms are biologically active at the receptor level. The four main aglycone isoflavones are formononetin and its demethylated product, daidzein, and biochanin A and its demethylated product, genistein.

Genistein has been well studied because of its function as a tyrosine kinase inhibitor (Akiyama et al., 1987). Genistein inhibits growth of human breast and prostate cancer cells, inhibits angiogenesis, and is a potent antioxidant (Peterson and Barnes, 1993; Record et al., 1995).

The diet issue

Several epidemiologic studies have linked a low incidence of BPH and prostate cancer with consumption of diets rich in isoflavones. Jacobsen et al. (1998) demonstrated a correlation between high consumption of soy milk and reduced risk of prostate cancer among Seventh Day Adventist men. A study by Hebert et al. (1998) showed that prostate cancer mortality was inversely associated with consumption of cereals, nuts and oilseeds, fish, and soy products.

Adlercreutz and coworkers (1993) have found that Japanese men have high plasma levels and urinary excretion of isoflavone phytoestrogens. High isoflavone concentrations, par-

ticularly genistein, correlate with a high intake of soy products, which is part of the traditional Japanese diet. Morton and colleagues (1997) found that men from Hong Kong had higher levels of the isoflavones daidzein and a metabolite of daidzein, equol, in their plasma and prostatic fluid compared to men from Britain and Portugal. Based on a large body of epidemiologic evidence, the increased risk of BPH and prostate cancer among Western men has been postulated to be a result of decreased consumption of isoflavone-containing foods (Adlercreutz et al., 1993; Jacobsen et al., 1998; Morton et al., 1997).

Documented mechanisms of isoflavone action

Isoflavones have been shown to have both effects on glandular epithelium in the prostate involving 5-α-reductase inhibition and increased UDP-glucuronosyltransferase activity and stromal effects including 17-β-hydroxysteroid dehydrogenase inhibition, aromatase inhibition, and estrogen-receptor antagonism. Using isoflavone doses much higher than those found *in vivo*, Evans and coworkers (1995) demonstrated that the isoflavones formononetin, daidzein, biochanin A, genistein, and the metabolite equol were effective at inhibiting 5-α-reductase activity in genital skin fibroblasts. These data suggest that isoflavones may decrease prostate size by a similar mechanism to that of finasteride. Biochanin A and its demethylated product genistein were highly effective at inhibiting 17-β-hydroxysteroid dehydrogenase at concentrations of 100 μmol (greater than 80% inhibition). At the same concentration, formononetin and daidzein were less effective inhibitors (between 30% and 40% inhibition) of 17-β-hydroxysteroid dehydrogenase. Keung (1995) also found that all 4 isoflavones inhibited 17-β-hydroxysteroid dehydrogenase activity equally.

UDP-glucuronosyltransferase is an enzyme responsible for conjugating steroid hormones with UDP-glucuronic acid, thereby inactivating the hormone and expediting its elimination from tissues (Sun et al., 1998). Sun and colleagues (1998) reported that all four isoflavones stimulated the UDP-glucuronosyltransferase activity of prostate cancer cells in vitro, increasing the amount of testosterone conjugated to UDP-glucuronic acid. Biochanin A was the isoflavone with the most potent activity. Biochanin A decreased prostate-specific antigen (PSA) levels less in the presence of increased levels of glucuronidated testosterone (Sun et al., 1998), suggesting a link between this metabolic pathway and prostate cancer.

Aromatase is an enzyme responsible for estrogen synthesis. Increased aromatase activity in adipose tissue has been linked to the promotion of breast cancer, and aromatase inhibitors have been given successfully to women with advanced estrogen-dependent breast cancers (Campbell and Kurzer, 1993). A study by Campbell and Kurzer (1993) demonstrated that biochanin A inhibited aromatase activity while daidzein, genistein, and equol had no effect. Decreasing aromatase activity may also affect levels of estrogen in smooth muscle cells in the vicinity of the stroma. Growth of these cells is stimulated by estrogen (Matzkin and Soloway, 1992).

Estrogens are known to promote the growth of a number of hormone-dependent cancers, such as breast cancer and prostate cancer. Researchers have begun looking at the potential mechanisms by which isoflavones that possess estrogenic activity may inhibit the growth of such cancers by binding to the estrogen receptor, thus inhibiting the biologic activity of estradiol. Collins and coworkers (1997) showed that biochanin A was capable of inhibiting estradiol-dependent activity by inhibiting dimerization of the estrogen receptor that is required for the biologic activity of estradiol. Similarly, genistein, at concentrations expected to be circulating in the human body, competed with estradiol for binding to the estrogen receptor on a human breast cancer cell line. Prolonged genistein exposure of this cell line resulted in downregulation of estrogen receptor mRNA and a decreased response to estradiol stimulation (Wang et al., 1996).

Demonstrated activity in vivo

Several studies in animals indicate a role for isoflavonoids in prostate health. A significantly higher incidence of prostatitis occurred in the lateral lobe of the prostate in rats who were fed

a soy-free diet compared with rats fed a standard commercial diet or one with added soy ($p < 0.05$). Furthermore, urinary excretion of daidzein, genistein, and equol was significantly reduced in animals receiving a soy-free diet compared with animals fed a standard commercial diet ($p < 0.05$) (Sharma et al., 1992). Pollard and Luckert (1997) reported that the incidence of prostate-seminal vesicle tumors induced by methylnitrosourea in Lobund-Wistar rats was reduced in rats fed diets containing high concentrations of genistein and daidzein compared with rats fed low-isoflavone diets (51% versus 60%, respectively). In addition, the disease-free period was extended by 27% in the rats fed the high-isoflavone diet (Pollard and Luckert, 1997).

In 1997, Stephens reported a case study of a patient with moderately high-grade adenocarcinoma of the prostate who took a phytoestrogen isoflavone preparation derived from red clover (160 mg daily) for 1 week before prostatectomy. Remarkably, the tissue had undergone significant apoptosis and the tumor had regressed, suggesting a therapeutic role for phytoestrogens in prostate cancer (Stephens, 1997).

SELECT PHYTOTHERAPIES AVAILABLE FOR TREATMENT OF BPH

A number of phytotherapies are currently available for treatment of BPH. Although some scientific evidence exists for their efficacy in treating BPH, considerably more work, including placebo-controlled clinical trials and comparison studies with pharmacotherapies, must be done to prove their efficacy. Because of the more receptive atmosphere for natural therapies in Europe, much of the investigative work on the use of phytotherapies for BPH has been performed there.

Saw palmetto

Saw palmetto (*Serenoa repens*) is a small palm tree indigenous to the southeastern coastal states of North America that produces berries that have a history of use in botanical medicines for disorders of the urinary tract (Janson, 1999). The liposterolic extracts from these berries have been examined in Europe for treating prostate diseases (Janson, 1999). Saw palmetto has been shown to inhibit 5-α-reductase activity (Délos et al., 1995), block α-1-adrenoreceptors (Goepel et al., 1999), and possess antiestrogenic activity (Di Silverio et al., 1992). A study at the University of Chicago demonstrated that saw palmetto was well tolerated by patients and relieved BPH symptoms, but measures of bladder obstruction did not significantly change after 6 months. In addition, symptom scores were not assessed until 2 months, so it is unknown whether symptom relief occurred earlier (Gerber et al., 1998). The active ingredient in saw palmetto has not been identified, and the many different formulations available may have differing amounts of active ingredients (Janson, 1999).

Pygeum africanum

Pygeum africanum is an extract of an African tree bark that may help relieve prostate symptoms by reducing prostate swelling (Janson, 1999). In a European multicenter trial, *P. africanum* improved International Prostate Symptom Score and uroflowmetry parameters more than placebo and was well tolerated (Breza et al., 1998). *P. africanum* inhibited growth factor–induced proliferation of rat prostatic fibroblasts, suggesting that inhibition of growth factors in humans may be a possible mechanism by which *P. africanum* reduces prostate overgrowth. An Italian study found that *P. africanum* improved BPH symptoms and urinary parameters in 18 patients treated for 60 days. However, *P. africanum* use did not correlate with a reduction in serum levels of 17-β-estradiol or testosterone (Carani et al., 1991).

Curbicin

Another therapy that has shown promise in the treatment of symptoms of BHP is curbicin, an agent derived from pumpkin seeds (*Cucurbita pepo* L) and the fruits of dwarf palms (*Sabal serrulata*) (Carbin et al., 1990). While the exact mechanism of action is unknown and data on curbicin are limited, results of a study by Carbin et al. (1990) showed significant im-

provement in patients treated with curbicin compared with placebo.

Soy

Soy contains a high concentration of the conjugated isoflavones genistin and daidzin. Foods containing soy include soy milk, tofu, soy yogurt, miso, soy flour, and soy protein extract. Eight ounces (approximately 230 g) of soy products are recommended for daily consumption. However, consuming this amount of soy is impractical for most people and may produce gas and other adverse effects. A soy supplement may be taken instead and should contain 12 to 20 mg of the aglycone form of genistein and daidzein for maximal effect (Gaynor and Hickey, 1999).

Red clover

The extract of *Trifolium pratense* (red clover) has been used historically by Asians and Europeans as a medicinal herb. Unlike the extracts from other medicinal herbs described above, the formulation of red clover, extracted from red clover leaves and flowers, is well established and is a rich source of all four isoflavones: genistein, formononetin, daidzein, and biochanin A. A pharmacologic study recently demonstrated that a commercial tablet consisting of 40 mg of aglycone isoflavones was well tolerated and produced plasma levels of isoflavones similar to those found in populations consuming high-isoflavone diets. The study offered evidence suggesting that biologically significant levels of isoflavones are maintained during once-daily administration of red clover supplement from isoflavone accumulation over long-term therapy and the relatively long plasma half-lives of the isoflavones supplied by red clover (Howes et al., 2002). In a clinical trial conducted by Gerber, 35 men were randomized to receive either 40 or 80 mg of formulated isoflavones extracted from red clover. After 3 months of treatment, urinary flow rates increased by 9.8%, International Prostate Symptom Score decreased by 23.3%, and quality-of-life score improved by 17%. Changes in symptomatology were most rapid within 1 month of beginning therapy and continued at a slower rate over the following 2 months. No significant differences were observed between the two red clover dosage arms.*

A RATIONAL APPROACH TO CHOOSING THERAPIES

Of the phytotherapies discussed, those containing isoflavones are the most promising because of the strong dietary link with prostate health and the defined mechanisms of action. The issue then becomes choosing the best supplement to deliver these agents. A comparison of various isoflavone preparations that are currently available was recently conducted (Table 1) (Setchell et al., 2001). Table 1 lists several different isoflavone preparations that can be used to promote prostate health and the concentrations of aglycone isoflavones they actually deliver. Supplements containing the highest quantities of aglycone isoflavones per capsule, tablet, or serving are likely to be the most effective phytotherapies for maintaining prostate health.

CONCLUSION

Aging men are at risk of developing BPH, which produces significant morbidity and health care costs. The benefits of phytotherapies in treating BPH and prostate cancer are becoming realized as our knowledge of alternative and complementary medicine increases. As a result, many patients are exploring natural therapies for the prevention and treatment of BPH. The advantages of natural therapies over conventional treatments may include better patient compliance, improved safety, and lower cost. The informed physician can help direct patients to appropriate therapies that are likely to be effective. Good scientific evidence links isoflavones to improved prostate health. Isoflavone, particularly red clover extract, supplements are likely

*G. S. Gerber, MD, PhD, unpublished data, April 2000.

TABLE 1. SUMMARY OF THE ISOFLAVONE COMPOSITION OF VARIOUS COMMERCIALLY AVAILABLE PHYTOESTROGEN SUPPLEMENTS

Product	*Total isoflavones (mg/g)*	*% Aglycones*	*Total isoflavones per capsule, tablet, or serving (mg)*	*Claimed isoflavone content per capsule (mg)*
Carlson Easy Soy[b]	17.52 ± 0.38	7.3	10.2	12.5
Carlson Easy Soy Gold[b]	46.91 ± 0.69	14.9	36.2	50.0
Erdic (Busting Out[c])[d]	—	—	—	Not stated
Estroven[e,f]	7.63 ± 0.04	10.8	7.8	50.0
Solgar[g]	6.56 ± 0.32	1.4	9.4	15.0
Kudzu root extract[f]	35.89 ± 0.17	13.0	11.5	3.0
PhytoEstrin™[h]	16.83 ± 0.26	5.5	10.3	14.0
PhytoSoya[i]	31.97 ± 0.54	2.0	12.5	17.5
Soy extract	32.32 ± 1.05	12.1	11.3	13.0
H & B Soya isoflavones[j]	20.81 ± 0.44	2.1	16.2	16.7
Soyamax™[h,i]	1.96 ± 0.01	9.2	58.0	60 mg/29 g
Soy Care[k]	66.02 ± 5.07	4.2	23.2	25.0
N Resources soy isoflavones[l]	96.21 ± 0.94	5.9%	43.4	50.0
SoyPLUS[m]	37.21 ± 1.82	5.3%	18.1	20.0
Naturally Preferred Soy Germ[n]	24.03 ± 0.51	5.7%	12.3	10.0
Trinovin[o,p]	73.59 ± 1.33	95.6%	36.9	40.0
Basic soy isoflavones	27.74 ± 0.3	8.5%	16.6	25.0
NovaSoy®[q]	66.80 ± 2.43	5.1%	40.8	50.0
New Phase, Sunsource[r]	7.03 ± 0.15	26.0%	8.6	80.0
Spring Valley[s]	24.27 ± 1.13	10.1%	12.7	7.0
Sundown®[t]	82.77 ± 1.03	5.5%	39.2	40.0
PhytoSoy™[u]	10.21 ± 0.35	47.2%	3.4	4.0
Soy Choice Vitanica[v]	70.05 ± 1.23	8.9%	25.8	56.0
Revival[i,u]	1.78 ± 0.02	9.6%	8.9	13.8
Nutri Soy®[q,x]	2.84 ± 0.01	8.1%	2.8	Not stated
Soy Life 25[y,z]	20.22 ± 0.31	1.7%	20.2	25.0

Adapted from: Table 3 in Setchell KDR, et al. 2001.

[a]A number of manufacturers indicate a range for isoflavone content, in which case the minimum amount was selected. Values shown are means ± standard error of the mean (SEM).

[b]J.R. Carlson Laboratories, Inc., Arlington Heights, IL.

[c]Busting Out, LLC.,

[d]Questionable peaks detected by mass spectrometry but too low for reliable quantification.

[e]Amerifit Nutrition, Bloomfield, CT.

[f]Measurement does not include puerarin glycosides because of lack of pure standards for quantification.

[g]Solgar, Leonia, NJ.

[h]USANA Health Sciences, Salt Lake City, UT.

[i]Powdered supplement, values expressed per serving.

[j]Arkopharma, Laboratoires Pharmaceutiques, Carros, France.

[j]H & B,

[k](Soy Care)

[l](N Resources)

[m]West Central Soy, Ralston, IA.

[n](Naturally Preferred Soy Germ)

[o]Novogen, Inc., Stamford, CT.

[p]Supplement contains mainly methoxylateed isoflavones from clover as its aglycones.

[q]Archer Daniels Midland Company, Decatur, IL.

[r](New Phase or Sunsource New Phase)

[s](Spring Valley)

[t]Rexall Sundown, Boca Raton, FL.

[u](PhytoSoy)

[v](Vitanica)

[w]Physicians Laboratories, Kernersville, NC.

[x]Toasted soy flour ingredient.

[y]

[z]Soy germ extract used as an ingredient

to be important therapies for promoting prostate health during the watchful-waiting period in patients with BPH.

ACKNOWLEDGMENT

This manuscript was supported by an unrestricted educational grant from Novogen, Inc.,

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