Nutraceuticals in Prostate Disease: The Urologist's Role

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Interest in and use of complementary and alternative therapies, especially nutraceuticals, is high in prostate disease. These therapies have shown potential in benign prostatic hyperplasia (BPH), prostatitis, and prostate cancer. Some have produced results equal to or better than pharmaceuticals currently prescribed for BPH. In category III prostatitis, some nutraceuticals may offer relief to patients who get little from standard therapy. Because it is becoming apparent that inflammation may play a role in the progression of BPH and development of prostate cancer, nutraceuticals, which commonly have anti-inflammatory properties, may play a role. These therapies have also shown potential in prostate cancer treatment and prevention, especially those that also reduce cardiovascular events or risk. Nevertheless, uses of some nutraceuticals in prostate disease have had less desirable consequences, showing lack of efficacy, adulteration, and/or severe side effects or drug interactions. By ensuring that these therapies undergo careful study for effectiveness, quality, and safety, urologists can look forward to adding them to their evidence-based armamentarium for prostate disease.
[Rev Urol. *2008;10(3):192-206*]

Key words: Complementary or alternative medical therapy • Nutraceuticals • Benign prostatic hyperplasia • Prostatitis • Prostate cancer

In North America, at least 30% of men diagnosed with prostate disease use some complementary and alternative medical (CAM) therapy,[1,2] primarily herbal biological agents, vitamins, supplements, and dietary intervention. Clearly, patients have embraced the concept, so urologists managing prostate disease should be prepared to offer advice on the risks and benefits and play a role in ensuring that safe and effective therapies are developed.

North American urologists have been slower than their European colleagues to understand and use these therapies. In Italy, for example, 50% of the medications used for benign prostatic hyperplasia (BPH) are phytotherapies, and in Germany and other European countries, phytotherapies are first-line treatment for mild-to-moderate benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS).[3] In most European countries, many phytotherapies must be prescribed. In Europe and, as of 2006, in Canada, new phytotherapies and nutraceuticals must undergo the same scrutiny and approval process as pharmaceuticals.

The best-studied CAM therapies for prostate disease include dietary modification; the phytotherapies *Serenoa repens* (saw palmetto), *Pygeum africanum*, phytosterols, rye pollen extract (eg, Cernilton®, Graminex LLC, Saginaw, MI), and others; and vitamins and minerals, such as vitamin E and selenium. Nevertheless, many of the studies are small, short, not randomized, and/or not placebo controlled. In addition, results can be difficult to measure, especially in preventive trials.

North American urologists' reluctance to use these therapies stems not only from the lack of an evidence base for benefit, but also from concerns about safety and quality. Indeed, none of the CAM therapies with more than $100 million in sales 5 years ago is commanding as much in sales and attention today. Interest surges and wanes as products are found after marketing to be ineffective or show significant side effects or drug interactions. Because the Dietary Supplements Health and Education Act (DSHEA) of 1994 defined these products as dietary supplements, manufacturers do not have to demonstrate effectiveness to the Food and Drug Administration (FDA) before marketing, nor are the products subject to the premarket safety evaluations to which new food ingredients or pharmaceuticals are subject. Manufacturers are not required to demonstrate that the product contents match the labeling before marketing.

The potential risks are significant. For example, St. John's wort can interact with some 50% of prescription medications.[4] In addition, many nutraceuticals used in prostate disease contain concentrations of ingredients different from the advertised amount and contaminants.[5] Because of such problems, the American Urological Association (AUA) now recommends that patients stop taking most nutraceuticals 2 to 3 weeks before undergoing any surgical or radiation procedure.

Nevertheless, these therapies appear to be here to stay. As a result, the AUA has taken steps to encourage careful study of supplements used for urologic problems. The urological community should continue to encourage regulation and work with manufacturers to provide not only quality control but also efficacy and safety data. Although it is easy to level charges at CAM, traditional medicine is guilty of many of the same faults. Urologists do not necessarily treat BPH or prostatitis pharmaceutically based only on objective parameters. In fact, we typically treat these conditions empirically. Therapies recommended for prostate cancer prevention and treatment do not have controlled, randomized trials to back them, only anecdotal evidence and large series. The majority of randomized, controlled trials that have supported BPH or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) therapies are typically short—3 and 6 months in BPH and 6 and 12 weeks in CP/CPPS. And, although the FDA requires adequate safety data for marketing, estimated deaths for all adverse drug reactions and medication errors make these a leading cause of death (estimated to be the fifth leading cause of death in the United States).[6,7]

Clinical trials in prostate disease have taken urology to the forefront of CAM research. The urological community does need to proceed with more caution to avoid the kinds of problems that occurred with PC-SPES, a purported wonder herb (actually a concoction of various herbs) that had demonstrable benefit in prostate cancer treatment. After complications were reported, the product was found to be tainted with estrogens, warfarin, and indomethacin, was recalled from the market, and clinical trials were stopped. There are tremendous opportunities, however, in CAM for BPH, CP/CPPS, and prostate cancer, especially because emerging evidence indicates that prostate inflammation, which plays a role in some cases of CP/CPPS, may have a crucial role in the genesis and progression of BPH and prostate cancer.[8-12] This article reviews the CAM research so far and highlights the opportunities for future CAM research in prostate disease.

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BPH

To truly understand the benefits that may be derived from nutraceuticals in terms of BPH symptom improvement, one must be cognizant of the literature in regard to the results of medical intervention. With any of the

recommended medical BPH therapies—alpha-blockers, 5-alpha-reductase inhibitors, or the combination—the International Prostate Symptom Score (IPSS) typically improves 3 to 6 points, but patients are not always satisfied with that improvement. For example, in the Hytrin Community Assessment Trial,[13] it took at least a 4-point improvement for patients with the lowest baseline scores (10 to 15) to say they felt good and at least a 16-point improvement for those with the highest baseline scores (30 to 35) to say so. Clearly, medical therapy of BPH does not produce the result that surgery does, and patients many times demand more. At least from the patients' standpoint, phytotherapies can play a role in achieving that result.

All interventions for BPH/LUTS have a strong placebo effect, but that effect is not exclusively based on what is usually thought of as placebo phenomena—the white-coat effect, conditioning, expectations, and so on. Without therapy, BPH patients, in fact, are remarkably consistent in their flow rates and reporting of symptoms, as a 2-week lead-in study in a BPH/LUTS treatment trial showed.[14] Before selection and randomization, 150 patients were asked to come to the clinic twice within 2 weeks and complete the BPH symptom index questionnaire and undergo a flow-rate study each time. The correlation between the first and second measurements was very high.

These were unselected symptomatic patients, however, and not all symptomatic patients are typically included in clinical trials. Instead, patients are screened and entered into trials with a minimum threshold AUA Symptom Index (AUASI) or IPSS score, voided volume, or flow rate. The investigators found that setting a threshold symptom score did, indeed, affect the result. Patients tended to have a lower AUA/IPSS symptom score on a second measurement. The reason is regression to the mean, which is a trend in the direction opposite that of the restriction imposed by the selection process, with more regression ("improvement") when thresholds are set higher. For example, setting an AUASI threshold at 7 points induced a regression of 1 point, setting it at 10 points induced a regression of 1.1 points, and setting it at 15 points induced a regression of 1.4 points.[14] The regression effect was also apparent in the BPH Impact Index, voided volume, and peak urinary flow rate. Urologists need to keep this effect in mind when they evaluate clinical trials of BPH therapy, whether of pharmaceuticals or phytotherapies.

Phytotherapies used in BPH include extract of the berries of *Serenoa repens* (saw palmetto), *Pygeum africanum* (from the bark of the African plum tree), pumpkin seed, rye pollen (also known under the brand name Cernilton), stinging nettle, South African star grass, and quercetin (Table 1). Often, the effects suggested for these phytotherapeutic agents mimic the activities of

Table 1
Phytotherapies Used for Benign Prostatic Hyperplasia

Origin/Name	Components	Suggested Effects
Serenoa repens = *Sabal serrulata* American dwarf palm tree/saw palmetto berry	Free fatty acids Phytosterols (beta-sitosterol and others) Aliphatic alcohols	Antiandrogen ↓ 5-alpha reductase ↓ growth factor Anti-inflammatory
Pygeum africanum African plum tree	Phytosterols (beta sitosterol, beta sitosterone) Triterpenes Long-chain fatty acids	↓ bFGF and EGF (induce fibroblast proliferation) ↓ inflammation/edema ↓ LH, testosterone, prolactin ↓ detrusor contractility Alters bladder function Inhibits growth factors
Cucurbita pepo Pumpkin seed	Sterols, carotinoids, minerals (Se, Mg)	Antiandrogen Anti-inflammatory
Secale cereale Rye pollen	Alpha amino acids, phytosterols, carbohydrate	↓ urethral resistance ± alpha receptor ↓ 5-alpha reductase ↓ growth factors ↓ ATPase ↓ cell growth Modulates SHBG
Urtica dioica Stinging nettle	Lectins, phenol, sterols, lignans	
Hypoxis rooperi South African star grass	Beta-sitosterol, other phytosterols	
Quercetin (extract from onions, tea, spices, red wine, cranberry, and citrus fruits)	Bioflavonoid	↑ TGF beta (enhances apoptosis) Anti-inflammatory ↓ inflammation Antioxidant Inhibits inflammatory cytokines ↓ DHT

ATPase, adenosine triphosphatase; bFGF, basic fibroblast growth factor; DHT, dihydrotestosterone; EGF, epidermal growth factor; LH, luteinizing hormone; Mg, magnesium; Se, selenium; SHBG, sex hormone–binding globulin; TGF beta, transforming growth factor beta.

currently marketed pharmaceuticals. The best clinical evidence for the effectiveness of each of these is summarized below.

Saw Palmetto

Extract of the berries of the saw palmetto or the American dwarf palm tree (*Serenoa repens*) has been the best studied of the phytotherapies for BPH. It is believed to have antiandrogenic effects, to inhibit 5-alpha-reductase types 1 and 2 and prolactin growth factor, to induce proliferation, and to have antiestrogenic, antiedematous, and anti-inflammatory effects. Preparations have been plagued with poor reliability and inaccurate statements of content. In fact, in a study of commonly used supplements in prostate disease, 3 of 6 tested saw palmetto compounds contained less than 20% of the stated dose, and 1 contained more than twice the stated dose.[5] A meta-analysis of 18 studies involving 2900 patients taking saw palmetto products, including mixtures, showed a significant improvement in overall symptom score (1.41 points), peak flow rate (1.93 mL/s), and nocturia (0.76 episodes/night) compared with placebo.[15] In these trials, ratings for self improvement all favored saw palmetto over placebo, but the results for nocturia and peak flow rate were not all significant.

An analysis of 14 placebo-controlled and 3 open-label trials of one saw palmetto preparation (Permixon®, Pierre Fabre, Castres, France)[16] involved 4280 patients followed up for 21 days to 24 months. It showed a significant improvement in peak flow rate and reduction in nocturia above placebo and a 5-point reduction in the IPSS overall. But other analyses are troublesome. Gerber and colleagues[17] treated 50 men with LUTS with saw palmetto 160 mg bid for 6 months. Although the reduction in the IPSS was significant (7 points), there were no significant changes in objective urodynamic parameters—peak urinary flow rate, postvoid residual urine volume, or detrusor pressure at peak flow. Willetts and colleagues[18] did a careful, placebo-controlled, 6-month trial in 100 men that showed no difference in IPSS, peak flow rate, or International Index of Erectile Function scores.

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The most rigorous trial of saw palmetto for BPH was published in 2006 in *The New England Journal of Medicine*.[19] The trial, which included 225 typical BPH patients, is the longest (1 year) and most rigorously performed placebo-controlled, randomized trial published to date. The investigators found no significant differences between active treatment and placebo for any of the outcome parameters—AUASI score, maximal urinary flow rate, prostate size, residual urine volume, quality of life, or prostate-specific antigen (PSA) levels.

African Plum Tree

The bark of the African plum tree (*Pygeum africanum*, also *Prunus africanum*) is not thought to have any 5-alpha-reductase activity. It inhibits various growth factors, has anti-inflammatory and antiedematous as well as phytoestrogenic effects, and reduces luteinizing hormone (LH), testosterone, and prolactin. It has been shown to reduce detrusor contractility and alter bladder function.[20] A Cochrane meta-analysis including 1500 men in 18 trials (6 placebo controlled) showed moderate improvement in the combined outcome of symptoms and flow rate, especially nocturia.[21] A review of the published experienced with a *P africanum* preparation (Tadenan®, Debat Laboratories, Paris, France) identified 2262 patients treated with the extract, including 12 double-blind, placebo-controlled studies. Only 1 study, however, included more than 100 patients, and no study followed up patients for longer than 12 weeks. None of the trials meet the guidelines recommended by the International Consultation Conferences on BPH, and, therefore, the data on *P africanum*'s efficacy are not conclusive.[22]

Pumpkin Seed

A randomized, placebo-controlled, 1-year trial examined the effect of pumpkin seeds (*Cucurbita pepo*), which are popular in Germany, in 476 patients with LUTS and BPH. The IPSS improved 6.8 points with active treatment, 1.2 points better than placebo, which was reported as a statistically significant difference.[23] An improvement in IPSS this large is rarely achieved with an alpha-blocker or 5-alpha-reductase inhibitor.

Rye Pollen

A Cochrane review of rye pollen extract (Cernilton)[24] included data on 440 men who were studied in 2 placebo-controlled and 2 direct comparative trials lasting 12 to 24 weeks. The weighted mean relative risk (RR) for self-rated improvement was 2.40 (range, 1.2-4.25) versus placebo and 1.42 (range, 1.2-4.75) versus Tadenan, a *P africanum* extract. The weighted mean RR for nocturia was 2.05 (range,

1.41-3.00) versus placebo and Paraprost® (an amino acid combination) (Nikken Kagakusha, Japan). Cernilton did not improve urinary flow rate, residual urine, or prostate size compared with placebo or either comparator treatment. Withdrawal because of adverse events was 4.8% for Cernilton versus 4.2% for Paraprost and 2.7% for placebo.

Stinging Nettle

The German stinging nettle (*Urtica dioica*) preparation Prostagutt® (Schwabe Pharma AG, Karlsruhe, Germany) was tested in a 12-month (489 patients) double-blind, comparative trial versus finasteride with dramatic improvements in symptom score (4.8-7.5 points) and a similarly dramatic improvement in the urinary flow rate of 2 to 3 mL/s. Prostagutt was as effective as finasteride in a comparison, although no placebo group was included in the study.[25]

South African Stargrass

Two preparations of South African stargrass (*Hypoxis rooperi*) have been studied in randomized, placebo-controlled trials. The Harzol trial,[26] which included 200 patients randomized to 20 mg tid or placebo for 6 months, showed substantial and significant improvements compared with placebo in IPSS (7.3 points) and peak flow rate (5.2 mL/s). The Azuprostat trial[27] included 177 patients randomized to 65 mg per day versus placebo over 6 months and showed similarly impressive, statistically significant results (8.3 points on the IPSS, 8.8 mL/s in Qmax). These improvements are greater than those achieved with most alpha-blockers, 5-alpha-reductase inhibitors, or even combination therapy. Wilt and colleagues'[28] meta-analysis of 4 randomized, placebo-controlled trials including 519 men (lasting from 4-26 weeks) showed a weighted mean difference of 4.9 points in the IPSS and 3.9 mL/s in peak flow rate, both significantly different from placebo.

Quercetin

Quercetin is a bioflavonoid with anti-inflammatory properties commonly found in foods such as apples, tea, onions, red grapes and wine, leafy greens, and various berries. It has documented antioxidant and anti-inflammatory properties and inhibits inflammatory cytokines implicated in the pathogenesis of CP/CPPS.[29-31] In Shoskes and colleagues' prospective, double-blind, placebo-controlled trial, the urinary component of the National Institutes of Health (NIH) Chronic Prostatitis Symptom Index (CPSI) improved by 2.7 points versus 1.5 for placebo,[31] although it isn't clear in this study whether that is a clinically significant change. The effect on urinary symptoms hints at a potential use in BPH.

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In an animal study of quercetin, finasteride, and the combination,[32] quercetin did not affect wet prostate weight, but it did decrease dihydrotestosterone (DHT) in a dose-dependent fashion. Testosterone, however, rose only at the highest dose, so the mechanism may not be similar to that of 5-alpha-reductase inhibitors, which increase testosterone in a stepwise fashion by preventing breakdown of DHT. Adding quercetin to finasteride did not increase finasteride's effect. The authors speculated that quercetin has some androgen-independent effect, but further studies need to be done to clarify quercetin's mechanism of action and utility in BPH.

Interpretation

Studies of phytotherapies for BPH have yielded mixed results, with some indicating dramatic improvements with both the placebo and active treatment and others indicating no effect with the same treatment. Analyzing the trials by length, placebo control, or number of centers still does not resolve the discrepancies or clarify the results. The proposed NIH study to test saw palmetto in a classical, phase II, dose-finding study may address some of these concerns.[33]

One possible explanation for these variable results with saw palmetto or other phytotherapies is that they may have different activity in different populations. Such effects prompted the FDA approval of the combination hydralazine and isosorbide dinitrate (BiDil®, NitroMed, Inc., Lexington, MA) for African Americans with heart failure, for example. An as-yet undiscovered or unexamined characteristic might define a population and explain the variability of effect in BPH.

One understudied but important parameter characteristic of BPH may be histologic inflammation. It is becoming apparent that asymptomatic inflammation associated with BPH may predict clinical progression and future complications such as acute urinary retention.[34] Inflammation in the prostate may also be implicated, at least in part, in the pathogenesis of BPH. Prostate inflammation may explain some of the variability of effect of doxazosin, finasteride, and the combination seen in the 5-year Medical Therapy of Prostatic Symptoms (MTOPS) trial.[35] A post-hoc analysis[35] showed that inflammation in biopsy

specimens, which would be categorized as chronic prostatitis type IV (found incidentally in transurethral resection of the prostate or biopsy specimens in asymptomatic patients), occurred in about 40% of patients. Inflammation did not correlate with BPH symptoms or urodynamic parameters, but it did correlate with higher PSA values and somewhat higher prostate volume. In patients with no inflammation who received placebo, only 13% had symptoms progress, only 4% had surgery, and none had urinary retention. In contrast, among those who did have inflammation at baseline, 21% had symptoms progress, 6% went into retention, and nearly 12% had surgery. Clearly, inflammation influenced the natural history of BPH, with inflammation-positive patients having a far worse natural history of the disease over time.

Inflammation also influenced therapy. In those with no inflammation, combination therapy had no effect on progression, whereas combination therapy reduced the risk of progression by more than 50% in those with inflammation. In addition, in patients without inflammation, finasteride did not improve flow rate or symptom score, whereas in patients with inflammation, results with finasteride were similar to those with the alpha-blocker. Inflammation is a condition that many of the phytotherapies do affect. It may be this effect on prostate inflammation that results in the benefits seen with phytotherapy in research trials and in clinical practice. It may be worthwhile to stratify BPH patients for phytotherapy studies based on histologic criteria instead of traditional criteria, such as prostate size, age, symptom score, and flow rate.

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Prostatitis

Prostatitis is common and a major clinical problem. Worldwide prevalence, depending on the definition, is from 5% to 14% of men,[36,37] and the condition typically accounts for 3% to 12% of the urologist's male outpatient practice.[38,39] The effect of prostatitis on quality of life is great, with impact scores similar to those of myocardial infarction, angina, or Crohn's disease.[40] Its economic impact is great as well, with total mean annual costs per patient estimated in 2004 to be $4397, nearly double the cost of rheumatoid arthritis.[41]

Pain is this syndrome's most common feature, affecting 97% of patients and having the greatest impact on quality of life.[40,42] The pain can be general, perineal, abdominal, low back, or associated with ejaculation. The syndrome's urinary symptoms are common LUTS symptoms (both storage or obstructive and voiding or irritative). Erectile dysfunction, including low libido, insufficient rigidity, and premature ejaculation, is also common.[43]

Based on a consensus conference, the National Institute of Diabetes and Digestive and Kidney Diseases developed a new classification system for prostatitis[44] (Table 2). Because the etiology is unclear, the new classification avoids etiologic expressions such as "nonbacterial prostatitis."

Category I

Alternative or phytotherapies should be actively discouraged for category I, acute bacterial prostatitis, which is a potentially life-threatening systemic infection. Cure rates are near 100% with antibiotics and appropriate supportive care.

Category II

Patients with category II prostatitis have recurrent episodes of bacterial urinary tract infection (UTI) by the same organism. Treatment usually involves long-term therapeutic or suppressive doses of antibiotics.

In this category, complementary therapy can play a supportive role. Prolonged antibiotic use can disrupt the normal gastrointestinal flora, and there is some evidence that probiotic formulations and lactobacilli culture-active yogurt can prevent or lessen gastrointestinal symptoms associated

Table 2
National Institute of Diabetes and Digestive and Kidney Diseases Consensus Classification of Prostatitis Syndromes

I. Acute bacterial prostatitis
II. Chronic bacterial prostatitis
III. Chronic prostatitis/chronic pelvic pain syndrome
A. Inflammatory
B. Noninflammatory
IV. Asymptomatic inflammatory prostatitis

Data from Krieger et al.[44]

with antibiotic therapy.[45] There is also evidence that some probiotic treatments may lessen recurrent UTIs, at least in women.[46-48] If probiotics could lessen our antibiotic use in these patients, we could avoid the common and considerable side effects of long-term antibiotics. With quinolones, the risk of Achilles tendon rupture is high.[49]

Thought to have antibacterial potential in the prostate, zinc is known to be a component of antibacterial factor in seminal fluid, and early studies of chronic prostatitis showed reduced levels in semen,[50] although a more recent study found no difference.[51] In addition, supplementation does not increase prostatic fluid levels,[50] so there is no convincing evidence that zinc helps treat infection or symptoms or prevent recurrence in category II prostatitis.

Cranberry juice is commonly thought to protect against UTIs. It may block adherence of *Escherichia coli* to the uroepithelial cells[52] and may reduce the biofilm load.[53] No placebo-controlled studies have confirmed a protective effect, and no evidence shows cranberry juice reduces UTIs in men with category II prostatitis. In addition, dangerous interactions with warfarin have been reported.[54] Because the juice is highly acidic and many men with prostatitis are sensitive to acid loads in their diet, it may make symptoms worse.

Category III

Phytotherapies have shown the greatest potential in category III prostatitis, termed CP/CPPS, which is the most common of the clinical prostatitis syndromes. The symptoms may be similar to those experienced by patients with chronic bacterial prostatitis (category II) but without infection and probably with more pain and discomfort (certainly with more durable and sustained discomfort). The etiology is unknown, but there are many theories, including persistent, occult prostate infection or inflammation, possibly as a response to infection or a dysregulated immune response or a true autoimmune disease. All the symptoms of CP/CPPS, however, can be caused by pelvic muscle spasm and can be extrinsic to prostate tissue. In some patients who underwent radical prostatectomy for CP/CPPS or prostate cancer, CP/CPPS symptoms did not resolve. In these cases, disease may never have been in the prostate or, because of long-term prostatic inflammation and pain, an autonomous neuromuscular condition developed.

Even though the term *prostatitis* is often applied to category III, there is often no evidence of inflammation. Only about 50% of symptomatic patients have leukocytes in expressed prostatic secretions (EPS),[55,56] and only about 33% have any apparent inflammation in biopsy specimens, with only 5% having moderate to severe inflammation.[57] Leukocytes, however, are not the only indicators of inflammation in EPS and seminal fluid. Various investigators have found evidence of elevated oxidative stress[58,59] and elevated levels of certain cytokines and chemokines that are inflammatory mediators in EPS and semen of men with category III prostatitis.[60]

Interestingly, some of these cytokines are blocked directly by quinolone and macrolide antibiotics, which may account for the reduction in symptoms with antibiotics even when patients have no proven infection. Typically, symptoms return within a day or 2 of stopping the antibiotics, which is not characteristic of infection because bacteria remain suppressed for weeks after antibiotic therapy is stopped.

Many phytotherapies have antioxidant and anti-inflammatory characteristics, and it might be by these mechanisms that these compounds produce their clinically beneficial effects. The best-studied phytotherapies in this category are quercetin, rye and other pollen preparations, and saw palmetto.

Quercetin. Quercetin has anti-inflammatory and antioxidant properties and may be lacking in the diet of category III prostatitis patients because levels of this bioflavonoid are high in many of the very foods patients tend to avoid—onions, tea, spices, red wine, cranberry, and citrus fruits—because they prompt symptoms.

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In a preliminary, unblinded study of quercetin in an unselected group of prostatitis patients, 75% had improvement if EPS cultures were negative.[30] This led to a randomized, placebo-controlled study in which 30 men with category III prostatitis received either a supplement containing quercetin 500 mg bid or placebo for 1 month. In an unblinded follow-up study, 17 patients received a supplement containing quercetin as well as bromelain and papain, which enhance absorption of the bioflavonoid, as well as saw palmetto and cranberry. Response was assessed with the CPSI, a validated symptom score. The placebo group had a 7% improvement, whereas the quercetin group had a 35% improvement. Twenty percent of patients taking placebo had an improvement of at least 25%, whereas

67% of those receiving the supplement had that level of improvement. Leukocyte counts dropped more in the active treatment group than in the placebo group.[31] (A 25% improvement in the CPSI score has since been validated as the threshold of clinical significance.[61]) In the follow-up, 82% of the men had at least a 25% improvement in symptom score.[31]

Isoprostanes were also measured before and after treatment in some of these patients. These compounds produced in the prostate are stable markers of oxidative stress, specifically of nonenzymatic lipid peroxidation. They have some limited biological functions in the kidney, causing some afferent arterial restriction, and in rodents they promote bladder contraction.[62]

Eight patients in this study had isoprostane levels in EPS determined before and after treatment, and each experienced dramatic reductions in these levels.[31] In addition, levels of endorphins, known natural painkillers, rise, and levels of prostaglandin E2, a potent inflammatory molecule, drop dramatically in EPS with administration of this supplement.[58] Interestingly, at sites of inflammation, leukocytes produce endorphins.[63,64]

Why some patients improve with quercetin therapy whereas others do not is not entirely clear, but genetic polymorphisms that alter cytokine gene expression may help answer the question. A study of 11 responders and 17 nonresponders to Prosta-Q[65] (Farr Laboratories, Los Angeles, CA) showed marked differences in tumor necrosis factor alpha expression. All 11 nonresponders had a low-responder genotype, whereas only 5 (30%) of the responders did. About half of those who did respond had high expression of IL-10. It is unclear whether expression of these genes is related to quercetin's activity, a question that deserves further investigation.

Common side effects of quercetin products include mild nausea or tingling, usually when the products are taken on an empty stomach. Orange pigment in some preparations may show up in semen, and patients can be reassured that this is the dye and not an infection. Because quercetin binds to the DNA gyrase site on *E coli*,[66] where quinolone antibiotics bind, quercetin could theoretically interfere with quinolone antibiotics, so the 2 should not be used together. Quercetin may safely be combined with nonquinolone antibiotics, however. Another concern is that, at high doses, antioxidants have pro-oxidative activity.[67]

This may be why patients taking multiple, multicompound nutraceuticals may have worsening of their symptoms, so it is wise to advise patients against this practice.

Rye and grass pollen. The rye pollen preparation Cernilton has been studied more extensively for BPH, but a few studies have been done in prostatitis. Unblinded studies without validated end points have claimed improvement in chronic prostatitis and prostatodynia patients.[68-72] Interestingly, in an open-label trial of Cernilton in 90 patients, 78% of patients without complicating factors such as urethral strictures and prostatic stones improved, whereas only 1 of 18 patients with complicating factors did so.[69] Prostatic calcification may play an important role in the disease.[73] The first controlled, randomized study of Cernilton in CP/CPPS using a validated symptom score was presented at the AUA meeting in 2006.[74] Patients with type IIIa (inflammatory) prostatitis were randomly assigned to placebo (63) or Cernilton (59). Those taking Cernilton had statistically significant improvements in the pain and quality-of-life components of the CPSI and improvement in urinary symptoms that was not statistically significant. A controlled, randomized study of a similar preparation, Prostat/Poltit (grass pollen extract, including rye pollen)[75] in 60 patients showed greater symptom improvement in patients on active treatment after 6 months. The researchers did not use an accepted, validated outcome index, so it is difficult to compare these results with other studies examining treatments in CP/CPPS.

Saw palmetto. Experience with saw palmetto in prostatitis is limited. It was compared with finasteride in a randomized, controlled trial with 64 men.[76] After 1 year, there was no symptom change in the saw palmetto group. A randomized, placebo-controlled study using the saw palmetto preparation Permixon in 61 patients[77] found mild improvement in CPSI scores in 75% of patients and moderate to marked improvement in 55% of patients on active treatment versus 20% and 16% of control patients, respectively. The study, presented at the AUA meeting in 2004, has not been published.

Category IV

Although category IV prostatitis is asymptomatic, new evidence of the role inflammation may play in the progression of BPH and in prostate cancer makes this category, defined almost as an afterthought, one of the most important and interesting for study and a potential target of treatment. Here, too, phytotherapy may have a role. Many of the proposed mechanisms for the phytotherapies in the prostate are anti-inflammatory. It is beyond the scope of this review to examine the potential role of phytotherapies in the management of category IV prostatitis, but this will likely become an important topic in the near future.

Prostate Cancer

Complementary and alternative medical therapies present great opportunities in prostate cancer, especially in the watchful waiting population. Although many older men with well-differentiated tumors will not die of prostate cancer,[78,79] they do have a 20% to 25% chance of dying of the disease in 15 to 20 years.[80,81] Patients recommended for watchful waiting want to do something to keep their cancer from progressing, so many are using off-label medications and CAM therapies.

Urologists need to give them and all our patients advice that will stand the test of time. Patients have a right to know what the best evidence is for different CAM therapies and, most important, how to increase their chance of survival. Following is a summary of the current evidence on CAM therapies of interest to patients seeking to prevent prostate cancer and/or its progression.

CAM Therapies in Prostate Cancer

PC-SPES and imitators. PC-SPES, a mixture of 8 Chinese herbs, came on the market in 1996 and looked very promising for prostate cancer. Anecdotal studies showed improvement and PSA reductions. Moreover, the company that produced it was reputable, the supplement was standardized by chemical analysis, and the manufacturer ensured batch-to-batch consistency. Numerous laboratory and clinical studies were published, and the consensus was that the formulation reduced prostate cancer growth and decreased PSA. The National Center for Complementary and Alternative Medicine and others supported 5 clinical trials that were either being planned, funded, or had actually begun when complications began to be reported. Independent laboratory analysis showed PC-SPES was contaminated with diethylstilbestrol, warfarin, and indomethacin. The FDA issued a warning, the product was recalled, production was stopped, trials were halted, and the manufacturer went out of business. Nevertheless, numerous copycats have replaced PC-SPES, and patients are taking them. For this reason, it is wise to check prostate cancer patients' androgen levels.

Zinc. Because zinc levels were found to be low in prostate tissue in men with prostate disease, deficiency was assumed. But studies of doses much higher than the reference daily intakes (RDI) of 11 mg per day are very concerning. In the Health Professionals Follow-up Study, which followed up 46,974 men over 14 years, there was no increased prostate cancer risk in men taking doses of up to 100 mg per day. In men taking more than that, however, the relative risk of new cases of advanced prostate cancer was 2.29, and in men taking supplemental zinc for at least 10 years, it was 2.37.[82] In a trial published in 2007, men and women taking 80 mg of zinc per day had significant increases in hospital admissions for genitourinary complications ($P = .0003$).[83]

Vitamin E. Enthusiasm long ran high for vitamin E as a preventive for a number of diseases and helped prompt the still-ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT). But multiple trials showed no cardiovascular risk reduction, and the HOPE TOO trial actually showed an increased risk of heart failure as well as no decreased risk of cancer.[84,85] In addition, high doses of vitamin E were shown to substantially increase the risk of a second primary cancer or recurrence in head and neck cancer patients and also to increase all-cause mortality significantly in those who underwent radiation therapy.[86,87] The vitamin still has potential, but its benefits may depend on the dosage or form. Gamma tocopherol, the major form in the diet, was found more effective than alpha tocopherol, the synthetic form usually found in dietary supplements, at controlling growth of a human prostate cancer cell line,[88] but no controlled trials have been completed in humans. Vitamin E phosphate, the recently discovered natural form of vitamin E, is being tested in a small preliminary trial to determine its impact on prostate cancer.[89]

Selenium. Data showing reduced risk of cancers in areas of the United States with the highest levels of selenium in the soil[90] prompted numerous studies of selenium supplements as a cancer preventive, including a randomized, controlled trial in basal and squamous cell carcinoma patients in Arizona, where soil levels of selenium are low. That study showed a reduction in prostate cancer as a secondary end point,[91] but only in patients with low serum selenium levels. In addition, patients with higher blood levels of selenium had a significant increased risk of recurrence of squamous cell carcinoma of the skin, which was the primary end point of the trial.[92] This is just another example of the importance of treating supplements like medications, which have a window of dosage effectiveness and potential for deleterious results beyond the normal range of intake. We can look forward to more definitive conclusions from SELECT.[93]

Patients recommended for watchful waiting want to do something to keep their cancer from progressing, so many are using off-label medications and CAM therapies.

Calcium. Based on observational data, urologists have long advised men against using supplemental calcium to reduce their prostate cancer risk. But one of the little-publicized findings of the Prostate Cancer Prevention Trial was that PSA velocity slowed in men taking calcium supplements.[94,95] In addition, the only randomized trial of calcium supplements to follow prostate cancer incidence found a reduced risk in the supplement group compared with the placebo group.[96] For this reason, and because we treat men at risk of osteoporosis—older men and men undergoing androgen deprivation therapy—supplemental calcium can be recommended to these patients.

Vitamin D. Interest in vitamin D is high, and many trials are ongoing, including the Androgen-independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT). This trial in patients with androgen-independent cancer aims to determine whether high-dose calcitriol increases the proportion of those who have a better-than 50% reduction in PSA with docetaxel.[97] Even without these results, we have reason to correct our patients' vitamin D deficiency because normal serum levels lower the risk of fracture in men. Patients in Northern latitudes, those who use sunscreen diligently, and obese patients often have deficiency. Recent research shows that vitamin D intake is abnormally low in prostate cancer patients.[98] Supplementation should be based on need, and levels can be determined easily with a 25-hydroxy vitamin D test. A serum level of at least 32 ng/mL is considered normal, but recent evidence suggests that a value of 35 to 40 ng/mL (90-100 nmol/L) is optimal, based on a summary of past clinical trials.[99] Supplementation with more than 400 IU per day (the usual level in multivitamins) is often not sufficient to correct deficiency. An intake of 800 IU or more per day will take several months to normalize blood levels of vitamin D. It seems prudent to check prostate cancer patients' serum levels and recommend vitamin D supplements if appropriate, calcium supplements, and weight-bearing exercise before we prescribe bisphosphonates. There is also an opportunity to improve clinical trial findings in prostate cancer by normalizing vitamin D levels before randomization.

Multivitamins. The largest randomized trial of multivitamin and mineral supplementation in men's health, Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX), included 7876 women and 5141 men who were followed up for a median of 7.5 years.[100] Participants receiving active therapy took a single daily capsule containing ascorbic acid 120 mg, vitamin E 30 mg, beta carotene 6 mg, selenium 100 μg, and zinc 20 mg, very near the RDIs and amounts typical of daily multivitamins. Men on active treatment had a 31% reduction in the relative risk of cancer, a 37% reduction in the relative risk of all-cause mortality, and a 48% reduction in the relative risk of prostate cancer. However, men with higher PSA values who took the supplement may have had an increased risk of prostate cancer, which suggests that tumors may utilize certain antioxidants or nutrients from pills once the tumor itself has become clinically significant.[101] Whether a daily multivitamin for prostate cancer risk reduction should be recommended will become clearer when the Harvard Physician's Health Study II is complete, because prostate cancer is one of the end points.

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Lycopene. Studies of lycopene for prostate health have shown variable results. Two small studies indicated benefit in reduction of PSA and other markers and in progression postorchidectomy,[102,103] but 2 other studies showed no PSA response.[104]

Pomegranate. An uncontrolled trial of pomegranate juice in men with rising PSA after definitive local therapy showed reduction in PSA doubling time, and an in vitro study showed positive effects on cell proliferation and apoptosis.[105] Pomegranate and many other fruit and berry juices, however, can act like grapefruit juice on CYP3A[106] and may interact with a number of medications. In addition, this juice has a high calorie content (approximately 120-140 calories per 8 oz), so patients who consume this juice must be careful about the amount they drink. Further study is needed before pomegranate juice supplementation should be recommended for prostate health.

Low fat. Ever since an animal study was published in 1995 showing a fat-restricted diet could slow prostate cancer growth,[107] many urologists have advised their patients to eat a low-fat diet, but primary prevention trials of low-fat diets in hormone-sensitive cancers have not been compelling. In the Women's Health Initiative, 20,000 women on a low-fat diet for 8 years had no reduced risk of breast cancer. Nor was there any effect on cardiovascular disease, colorectal cancer, or the global index. A Memorial Sloan-Kettering trial including 1300 men showed no effect of a low-fat, high fruit and vegetable

consumption diet on PSA slope or the incidence of prostate cancer over 4 years.[108] In the Ornish trial[109] with watchful waiting, prostate cancer patients who adopted a no-fat diet and lifestyle changes and took high-dose supplements, experienced small PSA reductions, and patients' high-density lipoprotein (HDL) levels, in fact, decreased significantly ($P < .001$) by 5 mg/dL.

Cardiovascular and Prostate Health

As myriad studies have shown, the leading cause of death in men and women is cardiovascular disease, and that is also true in cancer prevention trials. The Prostate Cancer Prevention Trial,[94] which was a primary prevention trial, had 10 documented deaths from prostate cancer among 18,000 men, but 1113 men died of other causes. In fact, in the first 10 years of treatment for prostate cancer, one of the leading causes of death was a cardiovascular event, and the number 1 cause of death in cancer prevention trials for men and women is cardiovascular disease.[110,111] Clearly, the real-world impact of preventive medicine goes beyond prostate cancer, and unless we can help our patients institute measures that affect more than prostate cancer, we will not have the greatest impact we can on their survival.

A study of African American men presenting for prostate cancer screening highlights that opportunity for urologists. At a traditional, annual PSA screening offered in Chicago, IL, and Baltimore, MD, men were also offered cholesterol and high-sensitivity C-reactive protein (hsCRP) tests. Fewer than 10% of the men had elevated PSA levels, but about 50% had high total cholesterol levels, 25% had abnormally low HDL levels, 20% had abnormally high low-density lipoprotein (LDL) levels, and 30% had abnormally high levels of hsCRP. More than 25% of men reported alternative medicine use.[112] When we recommend CAM to our patients, we will do them a great service by emphasizing approaches that can affect both their cardiovascular and prostate health. Following are some approaches that hold promise in both.

Lifestyle Risk Reduction

INTERHEART, a 52-country study including 15,152 cases and 14,820 controls, found that 9 modifiable lifestyle features could predict 90% to 95% of the population-attributable risk of heart attack no matter what sex, age, or region: smoking, raised ApoB/ApoA1 ratio, hypertension, diabetes, abdominal obesity, psychosocial factors (including clinical depression), low consumption of fruits and vegetables, absence of regular (moderate) alcohol use, and lack of physical activity.[113] Each positive lifestyle factor we can help our patients to undertake will lower their cardiac risk 10%, and we can advise our prostate cancer patients that the best way to improve their chance of survival is to reduce their cardiac risk to zero.

Diet/Caloric Restriction

Although extreme low-fat diets have not been shown to improve prostate health dramatically, "heart healthy" diets that improve lipid profiles, lower blood pressure, and promote weight loss for obese patients are likely to reduce the risk of cardiovascular disease, prostate cancer, and often other health risks that are concerns for our patients, such as Alzheimer's disease and erectile dysfunction.[110,111] Overall caloric restriction is another diet strategy with potential for our patients. In the Prostate Cancer Prevention Trial, the only dietary change with a documented affect on PSA was caloric reduction, no matter whether it was from protein, carbohydrate, or fat.[95]

Omega-3 Fatty Acids/Fish Oil

Trials of supplemental fish oil are encouraging in cardiovascular health, showing triglyceride reduction, HDL increases, and heart rate and blood pressure reductions. A meta-analysis of omega-3 fatty acid trials also showed reduced risk of cardiac events and death from any cause.[114] Some limited data indicate that fish consumption may lower prostate cancer recurrence as well.[115] Supplements are inappropriate for your patient, however, if they cause easy bruising.

Fiber

Soluble fiber reduces the risk of cardiovascular disease[116] and is, therefore, valuable for your patients even without evidence of improvement in prostate health. Flaxseed, which contains fiber as well as plant estrogens and omega-3 fatty acids, has shown promising early results in prostate cancer. Animal studies found flaxseed inhibited the growth and development of prostate cancer,[117] and pilot human studies found ground flaxseed supplementation produced significant reductions in PSA and cholesterol.[118] A larger trial of neoadjuvant ground flaxseed (1-3 tablespoons a day) is ongoing, and we should hear about the results before the end of 2008.

Clearly, the real-world impact of preventive medicine goes beyond prostate cancer, and unless we can help our patients institute measures that affect more than prostate cancer, we will not have the greatest impact we can on their survival.

Bioflavonoids

Recent results with soy protein–based products suggest that they are at least heart healthy for patients who want to include them daily in their diets.[119] In addition, preliminary research on bioflavonoids such as quercetin, which are natural, plant-based anti-inflammatories, suggests that they may have an impact on prostate cancer,[120] but the research needs to be followed up by a clinical trial. Quercetin is already an option for men with chronic nonbacterial prostatitis, so there should be some attention given to its ability to prevent prostate cancer if, indeed, tissue inflammation increases the likelihood of prostate carcinoma.

Conclusion

Nutraceuticals pose great challenges and present tremendous opportunities in prostate disease. In a market without the rigorous clinical trials and regulation that can ensure efficacy and safety, the dangers are high, and failures, such as with PC-SPES, can be spectacular. But nutraceutical research shows that some of these compounds present opportunities to manage prostate disease that may even exceed those afforded by today's pharmaceuticals. Clinical and basic research is demonstrating that inflammation may play a crucial role in the genesis and progression of BPH and prostate cancer. That hints at even more potential for nutraceuticals in prostate disease because so many have anti-inflammatory properties.

A number of nutraceutical preparations tested in BPH, such as African stargrass, have produced results equal to or better than finasteride or alpha-blockers and deserve rigorous study and testing. The proposed NIH study to test saw palmetto in a classical, phase II dose-finding study, and more studies like this for other nutraceuticals in BPH, could not only address our concerns but bring new, more effective BPH therapies. In category III prostatitis (CP/CPPS), the category we understand least and for which we have no therapies that are consistently or robustly effective, some nutraceuticals, especially quercetin, may offer patients some relief of symptoms that we have been unable to provide otherwise. Urologists can look to successes with nutraceuticals and other CAM approaches in cardiovascular disease to increase the chance of success in prostate cancer prevention and treatment. Indications are that the CAM therapies that reduce cardiovascular events and improve lipid profiles and other cardiovascular risk factors may also reduce PSA, prostate cancer cell growth, and the prevalence of prostate cancer. Even if a CAM therapy that reduces cardiovascular risk does not reduce prostate cancer risk, we will still improve our patients' chance of survival.

Urologists can look forward to including CAM therapies, including

Main Points

- Urologists must be aware that at least 30% of their patients diagnosed with prostate disease use some complementary and alternative medical (CAM) therapy.
- Urologists should include a discussion of CAM therapy with all their patients diagnosed with prostate disease.
- Urologists must educate themselves about the efficacy and risks of the complementary alternatives available for their patients with prostate disease.
- Buyer beware: Many studies have confirmed that herbal preparations from different producers may have drastically different composition, durability, contaminants, and even efficacy.
- The best-studied CAM therapies for benign prostatic hyperplasia (BPH) include the phytotherapies *Serenoa repens* (saw palmetto), *Pygeum africanum*, phytosterols, and rye pollen extract (eg, Cernilton®).
- The most clinical evidence for a CAM therapy being effective in BPH is for extract of the berries of the saw palmetto or the American dwarf palm tree (*Serenoa repens*), and even that evidence is not conclusive.
- Of all the prostatitis syndromes, CAM therapies hold the most promise for category III chronic prostatitis/chronic pelvic pain syndrome, and the most effective candidates appear to be quercetin, pollen extract, and saw palmetto.
- CAM therapies are attractive (for both patients and physicians) in men on watchful waiting or active surveillance protocols.
- The best-studied vitamin and mineral CAM therapies for prostate cancer include vitamin E and selenium.
- The leading cause of death in prostate cancer trials is cardiovascular disease. CAM therapy for the heart appears to be the most effective therapy for the prostate.

nutraceuticals, in their evidence-based armamentarium for prostate disease if they help ensure that these therapies undergo careful study for effectiveness, quality, and safety. ■

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