

Review

Complementary and Alternative Medicine for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Jillian L. Capodice, Debra L. Bemis, Ralph Buttyan, Steven A. Kaplan and Aaron E. Katz

Department of Urology, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA

To discuss challenges concerning treatment for chronic prostatitis/chronic pelvic pain syndrome (CP/ CPPS) and review complementary and alternative medical (CAM) therapies being evaluated for this condition, we performed a comprehensive search of articles published from 1990–2005 using the PubMed, Medline databases. Data from the articles were abstracted and pooled by subject. Keywords cross-searched with CP/ CPPS included: complementary, alternative, integrative, therapies, interventions, nutrition, antioxidants, herbs, supplements, biofeedback and acupuncture. Listed articles with no abstracts were not included. Various CAM therapies for CP/ CPPS exist including biofeedback, acupuncture, hyperthermia and electrostimulation. Additionally, a variety of *in vitro* and *in vivo* studies testing herbal and nutritional supplements were found. Saw palmetto, cernilton and quercetin were the most frequently tested supplements for CP/ CPPS. Although many CAM therapies demonstrate positive preliminary observations as prospective treatments for CP/ CPPS, further exploratory studies including more randomized, controlled trials are necessary for significant validation as treatment options for this complex disorder.

Keywords: acupuncture – alternative medicine – biofeedback – chronic prostatitis – complementary medicine – herbs – hyperthermia – supplements

Introduction and Characterization of Prostatitis

Chronic prostatitis/chronic pelvic pain syndrome (CP/ CPPS) is of significant interest in urology and accounts for up to 2 million office visits per year (1). Currently, there are multiple approaches to the management of CP/ CPPS depending on the classification of the related symptoms. However, there are no absolute findings or laboratory tests employed and diagnosis is often one of exclusion.

In 1995, the National Institutes of Health established an International Prostatitis Collaborative Network in order to construct a new classification of prostatitis syndromes and better define chronic prostatitis (2,3). The categories are now

documented as follows:

Category 1. Acute bacterial prostatitis

Category 2. Chronic bacterial prostatitis

Category 3. Chronic prostatitis/chronic pelvic pain syndrome

A. Inflammatory

B. Non-inflammatory

Category 4. Asymptomatic inflammatory prostatitis.

While most patients report a primary subjective symptom of local pain and/or dysuria, the clinical presentation of acute versus chronic prostatitis varies. Laboratory cultures are standardly employed to detect bacterial involvement and this testing along with other diagnostic criteria determines each classification. Men with Category 1, acute prostatitis, frequently present with dysuria, fever, malaise, myalgia (non-specific) and positive culture analysis that often reveals coliform bacteria. This imparts to standard antibiotic treatment with good prognosis for recovery and minimal recurrence.

For reprints and all correspondence: Jillian L. Capodice, MS, L.Ac., Department of Urology, College of Physicians and Surgeons, Columbia University Medical Center, Herbert Irving Pavilion, 11th Floor, 161 Fort Washington Avenue, New York, NY 10032, USA. Tel: +1-212-305-5727; Fax: +1-212-305-1564; E-mail: jc2346@columbia.edu

Patients with Category 2, chronic bacterial prostatitis, present with similar symptoms as those with acute prostatitis. However, the frequency of symptoms (duration >3 months), recurrent urinary tract infections and additional diagnostic tests including analysis of lower urinary tract cultures contribute to its diagnosis as Category 2 prostatitis (2).

Men with Category 4, asymptomatic inflammatory prostatitis, do not present with subjective symptoms. This diagnosis is often discovered via laboratory findings such as the positive presence of white blood cells in prostatic secretions or in prostate tissue during routine evaluation for other disorders (1).

Comparative to the total number of prostatitis cases reported, the majority of representative cases are Category 3, CP/CPPS (1,4). This diagnosis is usually one of exclusion, as bacterial etiology acute or chronic is ruled out. Other exclusion criteria include urogenital cancer, urethral stricture and neurologic disease affecting the bladder. However, the patient may still present with polyuria, dysuria, generalized myalgia or specific pelvic pain, urethral discharge, voiding dysfunction, sexual dysfunction and negative impact on quality-of-life (QOL). The presentation of this symptom set is now termed Category 3, CP/CPPS. Categories 3A and 3B are further differentiated by the presence or absence of inflammatory blood cells in prostatic secretions and seminal fluid, respectively (4,5). Table 1 further outlines the characteristics and treatment options of Category 3 prostatitis.

Due to the complexity in diagnosing CP/CPPS, the National Institutes of Diabetes and Digestive and Kidney Diseases funded the Chronic Prostatitis Collaborative Research Network (CPCRn) in 1995 (2,3). This network was fundamental in the construction and validation of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), which was implemented in 1999 (3). The index has become a valid measure that quantifies the qualitative experience of men with CP/CPPS and addresses three different aspects of CP/CPPS: pain, function and QOL (3,6).

The formation of the CPCRn and the advent of the NIH-CPSI have better characterized diagnosis and treatment for CP/CPPS, but challenges still exist. While standard treatment options including anti-inflammatory agents, analgesics and alpha-blockers are often prescribed, impact on QOL is another factor often overlooked in the treatment and management of CP/CPPS (1,4,5,7). The focus on QOL, anecdotal data, epidemiological studies and the increased popularity and validation of herbal, complementary and alternative medicine (CAM) has led to exploration of the utility of CAM therapies as treatments for CP/CPPS (8). CAM therapies including biofeedback, acupuncture, heat therapy, electrostimulation, herbal and nutritional supplements will be discussed below.

CAM Background

CAM, as defined by the National Center for Complementary and Alternative Medicine (NCCAM), is a group of diverse medical and health care systems, practices and products that are not presently considered part of conventional medicine. Conventional medicine is further defined as medicine as practiced by holders of MD (medical doctor) or DO (doctor of osteopathy) degrees (9). Though the list of what therapies or practices considered to be CAM changes continually, the pool of both practitioners of CAM modalities and patients utilizing CAM services continues to grow within the United States and globally (9).

The inclusion of CAM practices in urology is also being implemented in the clinic. Many groups such as the Committee of Complementary and Alternative Medicine within the American Urological Association (AUA) recognize the integration of non-conventional therapies into urological clinical practice. Additionally, both public demand for CAM therapies and their testing and validation within health science research centers has increased (8,10,11). It has been suggested that many urological conditions possessing subjective and QOL

Table 1. Characteristics and treatment options for CP/CPPS*

Category 3 prostatitis	Definition	Standard options	CAM options
Category 3: Chronic prostatitis/chronic pelvic pain	≥3 months pain/discomfort in the pelvic region, no bacterial involvement, inconsistent micturition and/or sexual function complaints	Antibiotics	Acupuncture
A. Inflammatory	A. Presence of white blood cells in semen, EPS or VB3	Alpha-blockers	Biofeedback
B. Non-inflammatory	B. Absence of white blood cells in semen, EPS or VB3	Analgesics	Electrical stimulation
		Anti-inflammatory drugs	Heat therapy
		5-Alpha reductase inhibitors	Herbal and nutritional agents
		Muscle relaxants	
		Pentosan polysulfate	
		Prostatic massage	
		Physical therapy	

CAM, Complementary and alternative medicine; EPS, expressed prostatic secretions; VB3, voided urine after prostatic massage.

*As adapted from the National Institutes of Health/National Institutes of Diabetes and Digestive and Kidney Diseases (1–3).

components such as in benign prostatic hyperplasia (BPH), chronic prostatitis, voiding, erectile dysfunction and cancer prevention and survivorship might be particularly amenable to CAM treatment strategies (10). This review will focus on current CAM therapies found in the literature for CP/CPSP.

CAM Therapies for CP/CPSP

Biofeedback

Biofeedback therapy is considered a mind–body technique that utilizes a monitoring machine to assist people in controlling bodily functions such as heart rate, blood pressure and muscle tension. This therapy has been studied for its efficacy in urological conditions such as incontinence, prolapse, pediatric voiding dysfunction and CP/CPSP (12–17). The hypothesis of biofeedback's mechanism of action in treating CP/CPSP is based on the principle that maximum muscle contraction prompts maximum muscle relaxation. This mechanism addresses the chronic pain aspect of CP/CPSP and focuses on muscular reeducation, which may ultimately provide symptom relief (13–15).

Two studies testing the value of biofeedback therapy for CP/CPSP yielded positive results. The first study assessed 62 patients who were refractory to conventional therapy (such as antibiotics and/or alpha-blockers) for greater than half a year. These patients were treated utilizing the Urostym Biofeedback equipment five times a week for 2 weeks with a stimulus intensity of 15–23 mA and duration of 20 min. The NIH-CPSI index noted a significant overall reduction in score ($P < 0.01$) and no side effects were reported during the trial (13).

A second pilot study evaluated biofeedback therapy in 19 men with pelvic floor tension and CP/CPSP. These results demonstrated significant improvement in pain scores as measured by the AUA symptom index ($P = 0.001$). While this study focused on testing the effect of biofeedback therapy in treating the symptoms associated with CP/CPSP, it also implicated the presence of pelvic floor tension contributing to pain and the paramount importance of muscular reeducation for its treatment (15). These initial, positive biofeedback studies may warrant larger randomized clinical trials to confirm safety and efficacy as well as explore the mechanism of action of biofeedback therapy.

Acupuncture

Acupuncture is a traditional Chinese method of medical treatment involving the insertion of fine, single-use, sterile needles in acupoints according to a system of channels and meridians that was developed by early practitioners of Traditional Chinese Medicine (TCM) over 2000 years ago. The needles are stimulated by manual manipulation, electrical stimulation or heat (18). Currently, acupuncture is often used with TCM and it is a recognized health profession with strict licensure and regulatory status in 40 states (19). Common applications include acupuncture as a complementary therapy for cancer

patients undergoing chemotherapy or radiotherapy, for conditions involving pain such as migraines and back pain, and for relieving the impact of stress among patients with chronic conditions. The precise physiological mechanism of action of acupuncture is unknown but a variety of hypotheses exist. For example, acupuncture analgesia is thought to be mediated by central nervous system (CNS) mechanisms of pain control via the release of specific neurotransmitters, such as endorphins (20–23). Additionally, there are significant data which suggest that acupuncture treatment can decrease inflammation and relieve pain (24,25).

Data suggesting the ability of acupuncture treatment to decrease pain, positively impact QOL and potentially modulate inflammation and/or affect the CNS has suggested it as potential therapeutic option for men with CP/CPSP. While a number of studies listed in other journals test the utility of acupuncture treatment for CP/CPSP (26) only two medline listed pilot studies are shown testing acupuncture treatment in patients with CP/CPSP.

The first study examined whether acupuncture improved pain, voiding symptoms and QOL in 12 men with CP/CPSP. This study reported a significant decrease in total NIH-CPSI pain, urinary and QOL scores ($P < 0.05$) over 6 weeks of treatment and an average 33 weeks of follow-up (27). The mechanism of action addressed in this paper suggests a neuro-pathic model of CP/CPSP and the hypothesis that acupuncture, if considered a neuromodulatory therapy, may provide a therapeutic option for men with CP/CPSP (27).

A second study tested acupuncture treatment for CP/CPSP patients with intrapelvic venous congestion. This study of 10 patients receiving 5 weeks of acupuncture treatment also reported a significant decrease in NIH-CPSI pain and QOL scores ($P < 0.05$, $P < 0.01$). While the study reported no serious adverse events, the mechanism of action was not addressed (28). The promising clinical outcome of both studies testing acupuncture for CP/CPSP implies that larger studies are required to confirm the utility of acupuncture in this patient population.

High Frequency Electrostimulation

Only one study in English was found utilizing electrostimulation for chronic prostatitis. This study tested a new, high frequency, urethral–anal prototype stimulation device in men with CP/CPSP twice weekly for 5 weeks. The results demonstrated a significant decrease in the NIH-CPSI ($P = 0.0002$) with no urethral, anal complaints or other side effects (29). The authors suggest that due to the positive results, simple technology and ability to be self-administered, this new device may have utility in the treatment of CP/CPSP. However, further studies and standardization of the electrostimulation device are essential.

Hyperthermia

Anecdotal evidence and a few clinical trials have suggested heat therapy or hyperthermia as a treatment option for men

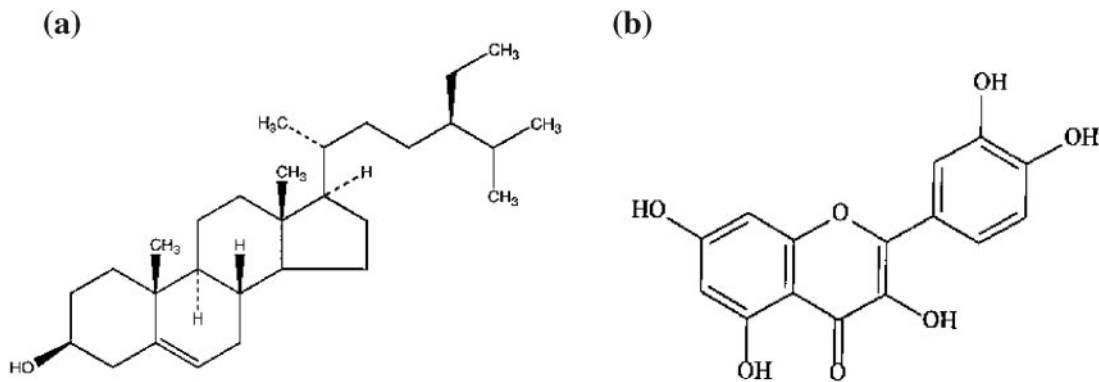


Figure 1. Chemical structures of components found in herbal or nutritional supplements. (a) Structure of beta-sitosterol an active component of *S. repens* (41). (b) Structure of quercetin (41).

with CP/CPPS. Its mechanism of action is based on the application of heat to the prostate to relieve pain. An excellent review by Zeitlin (30) discusses the lack of literature concerning hyperthermia and CP/CPPS. The review notes a variety of pitfalls in hyperthermia research including variation and lack of standardization of treatment. These concerns are applicable to both the type of heat utilized such as interstitial heat or microwaves and variation in its application, either transrectally or transurethrally. The review also suggests that the hyperthermia instruments used were not validated and outcome measures were subjective. However, the review implies that utilization of a quantitative assessment tool, applied statistics and greater documentation of therapy type may offer hyperthermia a better opportunity to be evaluated as a potential therapy for CP/CPPS (30).

We also discovered the paucity of literature described by Zeitlin and only three listed clinical trials utilizing hyperthermia. The first study analyzed a group of 45 men with chronic abacterial prostatitis or prostatic dysuria who underwent 6 weekly, 1 h sessions of local deep microwave hyperthermia ($42.5 \pm 0.5^\circ\text{C}$) to the prostate. Although the authors report encouraging results in the decrease of pain, these subjective patient assessments were not quantified by the NIH-CPSI or other index for CP/CPPS (31).

A second abstract discussed a randomized, sham-controlled comparative study utilizing transrectal microwave hyperthermia in 80 men with CP/CPPS. While this abstract noted a 75% symptomatic improvement in the treatment group, the study was available as an abstract only with no statistical significance or descriptive methodology reported (32). A third study also tested transrectal microwave hyperthermia for both chronic non-infectious and infectious prostatitis. While the study design incorporated obtaining measurement of prostatic secretions, uroflowmetry and transrectal color Dopplerographic mapping, the results from the study were not abstracted as the article was in Russian (33).

Herbal and Nutritional Supplements

Herbal and nutritional supplement therapies have been most widely investigated for their utility in CP/CPPS and other

prostate conditions such as BPH (34–40). While many formulations have been cited for their use in a wide variety of urological conditions, saw palmetto, pollen extract and quercetin were the supplements found with specific application to CP/CPPS. While most herbal and nutritional supplements contain a wide variety of synergistic ingredients upon compositional analysis, some of the active components such as phyosterols or antioxidants are listed in Fig. 1.

Saw palmetto

Saw palmetto (*Serenoa repens*) garnered much attention in urology based on a great deal of anecdotal evidence regarding its prostate specific properties. It is widely used in many Asian, African and European countries and compositional analysis of the berry of *S. repens* exhibits sterols and free fatty acids as its major constituents (41). Initial studies suggested that the efficacy of saw palmetto may be similar to that of the pharmaceutical enzyme inhibitors such as finasteride. This preliminary data prompted the exploration of mechanism, utility and efficacy of saw palmetto in *in vitro* analysis and in clinical trial settings. While a number of trials have examined saw palmetto use for symptoms related to BPH (34–39), only a few have focused on it specifically for CP/CPPS (42–44).

The first study compared the safety and efficacy of saw palmetto berry supplement versus finasteride in men with Category 3, CP/CPPS. This prospective, open label 1 year study randomized 64 men to the saw palmetto or finasteride group, respectively. After 1 year of treatment, the NIH-CPSI score decreased from 23.9 to 18.1 in the finasteride group ($P < 0.003$) and from 24.7 to 24.6 in the saw palmetto group ($P = 0.41$). While significance was only achieved in the finasteride treatment arm, it was notable that at the end of the trial 41 and 66% of participants opted to continue the therapies of saw palmetto and finasteride, respectively, regardless of achieved statistical significance (42).

The second clinical trial from China examined the effects of prostatic gland capsules containing saw palmetto berry in patients with CP/CPPS. While 125 men reported positive outcome and the NIH-CPSI was used as a primary end point, the article is only available in Chinese and the manufacturer,

active constituents of the capsules and statistical significance was not reported (43).

A third multicenter study testing a saw palmetto abstract called Permixon analyzed the response of Permixon therapy in 61 patients with Category 3B prostatitis. While 65% of the Permixon group reported improvement based on the Patients Subjective Global Assessment (SGA), the total NIH-CPSI and the pain, voiding and QOL/impact domains of the NIH-CPSI, statistical significance was not reported (44). Additionally, prostate volume was unchanged in both the treatment and control groups. While this multicenter study suggests that Permixon may provide clinical benefit for CP/CPPS 3B, the dosages and components of the Permixon product were not listed in the abstract.

The assessments of saw palmetto studies for CP/CPPS are far fewer than those for BPH. However, marked and continued progress in molecular studies, increased mechanistic data and more clinical trials in CP/CPPS are warranted to ascertain the utility and reproducibility of saw palmetto use in men with chronic prostatitis.

Pollen Extract: Cernilton

Pollen extract is traditionally collected from the flowers of various plant types and it contains carbohydrates, fat, protein, vitamins and minerals (41). The particular pollen extract named cernilton has been suggested to benefit a variety of urological conditions. Anecdotal evidence and references from traditional herbal texts have implicated cernilton's potent anti-inflammatory properties and potential in treating symptomatic relief of urinary pain and dysfunction often present in both CP/CPPS (41) and BPH (45,46). *In vitro* studies demonstrate a variety of experimentation on this particular extract including histopathological analysis of its effect on cell proliferation, apoptosis, serum cytokines and testosterone (47,48). The literature also lists quite a few clinical trials on pollen extract; however, five are in the Japanese language and one in the German language (45,48–52). While many of these studies report the positive activity of pollen extract and suggest its usefulness for CP/CPPS, data from these studies were not abstracted due to unavailability and translation of the articles.

One available study testing pollen extract reported a 78% favorable response of men with chronic prostatitis taking Cernilton[®] pollen extract at a dosage of 1 tablet TID for 6 months (53). While this study reported favorable results, the study was published in 1993 and similar subsequent larger phase clinical trials are not evident to further elucidate the possible utility of pollen extract in men with CP/CPPS.

Quercetin

Quercetin is known chemically as a mixture of 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one and 3,3',4',5,7-pentahydroxy flavone. It belongs to a group of polyphenolic substances known as flavonoids and is a member of the class of flavonoids called flavonols. It is commonly found in the plant kingdom in the rinds and barks of certain foods

such as onions, grapes and green tea (41). Since quercetin is thought to have antioxidant, anti-inflammatory, antiviral, immunomodulatory, anticancer, gastroprotective and anti-allergy activities it has been studied for a variety of conditions (54–56).

One prospective, randomized, double-blind, placebo-controlled trial was performed to test the action of this bioflavonoid in men with CP/CPPS. This placebo-based study assessed 30 men with CP/CPPS to receive the bioflavonoid quercetin, 500 mg twice daily or the placebo pill for 1 month. Significant change in the NIH-CPSI score was observed in the quercetin ($P = 0.003$) versus the placebo group, who had an insignificant mean improvement in the NIH-CPSI score (57). While this was the only clinical trial found testing quercetin for CP/CPPS, the positive outcome supports the need for further study including cost analysis of quercetin therapy in this patient population.

Other Herbal Agents for Prostatitis

Finally, a wide variety of herbal compounds not previously discussed were found during this review, many of which are commonly used in the TCM herbal material medica. Some of the compounds are Nan mi qing capsules containing *Rheum palmatum* and *Rx. astragalus memberanaceus*, Ye Ju Hua Shuan, an herbal suppository of *Flos Chrysanthemi Indici* and a variety of other formulae or capsules of which the ingredients were not listed (58–62).

Initial *in vitro* studies examining some of the herbal compounds effects on markers of inflammation such as thromboxanes (TBX2) and 6-keto-PGF1- α are promising as the link between chronic inflammation in CP/CPPS is still under investigation (58). While the preliminary reports of additional herbal compounds are encouraging, a number of difficulties exist in the extraction of this data. Namely, the articles are in the Chinese or other language and data including the ingredients, constituents and other practices including good manufacturing are unable to be assessed. While this conundrum exists for many herbal agents despite their historical use in a variety of traditional herbal medicine systems, testing of safety and utility are still necessary. However, the variety of herbal agents available offers a large source to draw from and the possibility that other herbal products might be beneficial in the treatment of CP/CPPS.

Conclusions

A summary of the reviewed literature is outlined in Table 2 and a variety of CAM modalities tested in patients with CP/CPPS include practitioner-based therapies such as biofeedback, hyperthermia, acupuncture and electrostimulation, and biological-based therapies including herbal and nutritional supplements. As the challenges in treating this complex and chronic disorder remain, further evidence of efficacious CAM treatment options for men with CP/CPPS is needed. Thus far, promising data on the function and efficacy of certain

Table 2. Summary of CAM therapies for prostatitis/chronic pelvic pain syndrome

CAM therapy	Total number of studies	Positive outcome significance achieved	Positive outcome	Negative outcome	Data not assessed*
Biofeedback	n = 2	2			
Acupuncture	n = 2	2			
High frequency electrostimulation	n = 1	1			
Hyperthermia	n = 3		1		2*
Saw palmetto	n = 3		2	1**	
Pollen extract	n = 7	1			6*
Quercetin	n = 1	1			
Other herbal extracts	N/A				

*Data not abstracted in our review.

**Significance not achieved; however, 41% of patients opted to continue saw palmetto therapy.

CAM therapies suggest their potential as treatment options for this patient population. Further exploratory studies including more *in vitro* studies of herbal products, mechanistic data, cost analysis and randomized, controlled trials will assist in validation of certain CAM therapies as permanent treatment options for men with CP/CPPS (63,64).

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