



# Phytotherapy and physical therapy in the management of chronic prostatitis–chronic pelvic pain syndrome

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## Abstract

Chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) is one of the four category prostatitis, and the prevalence is over 90–95% in prostatitis. Because of its pain and obstructive voiding difficulties, it severely affects the quality of life of the patient. However, the standard treatment is still unclear. Given the lack of proven efficacy of conventional therapies (such as antibiotics, anti-inflammatory medications, and alpha-blockers), many patients have turned to phytotherapy and other alternative treatments. In recent years, phytotherapy and physical therapy have advanced a lot because of the safety, efficacy and high compliance. This review covers phytotherapy (quercetin, bee pollen, pumpkin seed oil, eviprost, terpene mixture) and physical therapy (acupuncture, shock wave, thermobalancing, transurethral needle ablation, transcutaneous electrical nerve stimulation sono-electro-magnetic therapy) commonly used in chronic prostatitis to help the clinician and researchers.

**Keywords** Chronic prostatitis · Alternative therapies · Phytotherapy · Physical therapy · Quality of life

## Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is one of the four categories of chronic prostatitis. It is a prevalent and poorly understood disease. The widespread presence of CPPS is over 90–95% in the four cases of prostatitis [1]; the syndrome of CPPS includes pelvic pain, genital pain, obstructive voiding difficulties, ejaculatory pain, plasma semen [2] and erectile dysfunction [3], which severely affects the people's quality of life. So it is essential to find an appropriate treatment for CP/CPPS.

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is an uncertain condition, and patients mostly choose multiple treatments. The classical theory of pain as a simple response to a noxious stimulus has some merit, but current research reveals that the response is much more intricate,

and we must look at a patient's psychology and physiology to be able to understand each individual's pain response [4]. There are different theories about the pain of CPPS. Westesson et al. believed that the most important reason is the pelvic floor spasm. The pelvic floor spasm can be the only etiology and also can be the secondary reason through infection or inflammation. In the first condition, the pain symptom can be resolved by relieving the muscle spasm, but in the secondary condition, the symptom can be relieved to some degree [5]. The pelvic floor spasms may cause voiding dysfunction and pain and, this, in turn, increases the stress and worsens the condition [6]. Some authors believe that the inflammation in the prostate is the most important factors. It can increase sensitivity and activity of neurons in the dorsal root ganglion, which releases neurotransmitters and chemokines, and induces inflammation in the spinal cord and conveys the pain signal to the brain [7].

The management should be multimodal, of suitable duration and incremental. However, there is no “golden standard” to treat the disease because pathogenesis is still unclear and some researchers think CP/CPPS is a multifactorial disease, such as autoimmunity, genetic predisposition, infection, neuromuscular problem, and intraprostatic ductal reflux [4]. Even that, some comprehensive treatments to relieve the syndrome are used to reduce the pain of the patient and improve the quality of life, including the antibiotics,

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anti-inflammatory medications, alpha-blockers, neuromodulators, phytotherapy, pelvic floor physical therapy (PFPT) and cognitive behavior therapy [8, 9]. However, the use of antibiotics is still arguable in that there has no isolated bacterium [10]. Even the anti-inflammatory medications that can decrease pain and alpha-blockers which improve outflow obstruction should be taken for a limited time for the commonness of adverse effects [11]. Most recently, it is increasing attention to the phytotherapy and physical therapy for the little adverse effect and high patients acceptance [12].

With the development of science and technology, some new phytotherapy and physical therapies were invented. For the treatment of CP/CPPS alternative therapies have been investigated and have shown some success in improving the symptoms of chronic prostatitis. This review will discuss the phytotherapy agent and physical therapy in the treatment of CP/CPPS.

## Phytotherapy

Phytotherapy, the use of plants extracts as therapeutic agents for the maladies for various urological disorders. These alternative therapies are gaining more attention in the treatment of chronic prostatitis due to its low adverse effects, high efficacy, and potency and improve the sign and symptoms than other traditional therapies. Phytotherapy and the possible effect are summarized in Table 1.

### Pollen extract (cernilton)

Cernilton, which is a standardized pollen extract mixture, has been prescribed almost 20 years for the treatment of CP/CPPS [13]. Cernilton is composed of water soluble and fat

soluble ingredients [14]. In some studies, Morais et al. verified that pollen collected by honeybee appears to the antioxidant properties and antimicrobial activity [15]. Maruyama et al. demonstrated that pollen extract has a strong anti-inflammatory action which was achieved by inhibiting NO production and activity of COX-2 [16]. Some clinical studies have been done to explore the effect of pollen extract for the treatment of CP/CPPS.

Exploring the effect of pollen extract to the CP/CPPS, Wagenlehner et al. conducted a multicenter, randomized, double-blind study and showed that pollen extract resulted in a significant symptom improvement compared to placebo and more acceptance in 12 weeks. The pain relief was significantly different from the baseline, which brought a considerable increase in the total NIH-CPSI score and the QoL subdomain [13]. However, the precise mechanism of cernilton to the CP/CPPS therapy is currently unclear. Kamijo et al. developed a rat model of CP/CPPS by castrating and administering estradiol. They divided those rats into seven groups consisting of sham-operation (sham-castration and no drugs), control, four kinds of CN-009 (pollen extract) and TS (testosterone) with five or six animals in each group. The research demonstrated that pollen extract could protect acinar epithelial cells and inhibits stromal proliferation by enhanced apoptosis [17]. Cai et al. conducted another study; they found that pollen extract and vitamins for CP/CPPS are linked to decrease in the proinflammatory cytokine IL-8 which highlights that cytokine IL-8 could be a useful marker for response to the treatment [10].

### Quercetin

Quercetin, a kind of bioflavonoids, can be found in many fruits, vegetables, leaves, and grains [18]. It has anticancer

**Table 1** The phytotherapy effect and possible mechanism

Phytotherapy agent	Significant effect	Possible mechanism
Cernilton	Relieve pain QoL subdomain Total NIH-CPSI score	Anti-inflammatory
Quercetin	Relieve pain	Reduce the expression of proinflammatory cytokines Antioxidant ability Suppress the phosphorylation of NF- $\kappa$ B and MAPKs
Pumpkin seed oil	Residual urine Flow rate WBC count NIH-CPSI	Reduce the inflammation of prostatic tissues
Eviprostat	Total scores Pain scores Urinary scores QOL scores	Mediated oxidative stress and bladder inflammation Suppresses the stromal predominance Anti-inflammatory effect
Terpene mixture (rowatinex)	Total NIH-CPSI score pain domains quality of life	Anti-inflammatory effect Reduce pain and swelling

properties [19] and can ameliorate all markers of inflammation, and oxidative stress measured [20]. It has been used to treat prostate cancer and chronic prostatitis. Some clinical trials have been carried out to identify its effect on the CP/CPPS. A prospective, double-blind, controlled trial was conducted by Shoskes et al. They found a mean improvement of 35% of the quercetin group and only 7.2% in the placebo group. Moreover, a significant increase in pain relief and quality-of-life score was observed between the groups [21]. Regarding the precise mechanism, there is some progress. Meng et al. establish a novel CP/CPPS model and harvested the prostates and blood specimens to identify the mechanism after the measurement of quercetin for 4 weeks. They found that Quercetin can reduce the expression of proinflammatory cytokines, improve antioxidant ability, and more importantly suppress the phosphorylation of NF- $\kappa$ B and MAPKs. So they believed that quercetin treats CP/CPPS at least partly through NF- $\kappa$ B and MAPK signaling pathways to have anti-inflammatory and antioxidant effects [22].

### Pumpkin seed oil

Pumpkin seed oil extracted from *Cucurbita pepo* L. is a common oil in southern Austria, Slovenia, and Hungary [23]. It is a highly unsaturated oil, with major oleic and linoleic acids present [24]. Evidence suggested that pumpkin seed oil can block prostate growth in rats and has been used to treat benign prostatic hyperplasia (BPH) [25, 26]. Because of these effects on the prostate, Tantawy et al. conducted research about the pumpkin seed oil for chronic nonbacterial prostatitis. By administrating PSO combined with phonophoresis or low-intensity ultrasound, they found that PSO has a significant difference in the residual urine, flow rate, WBC count, and NIH-CPSI before and after the treatment [27]. However, the reason why PSO is effective for CP/CPPS is still unknown.

### Eviprostat

Eviprostat, a phytotherapeutic agent, is most widely prescribed for the treatment of BPH, and has over 40 years of history in Japan and Germany [28]. It consists of five components [29]. Also, the effect of improving bladder function [30] and potent antioxidant and anti-inflammatory activities [29] have attracted strong research interest.

Moreover, it also has an effect on CP/CPPS. Iwamura et al. conducted a random and prospective clinical trial to study the efficacy of Eviprostat to the CP/CPPS. Pollen extract, a standard treatment for CP/CPPS in Japan, was used as a control. In the result, there was no significant difference between the two groups in the total pain, urinary, and QOL scores of the NIH-CPSI at 8 weeks. So they verified that the eviprostat is an effective phytotherapy for the CP/CPPS-like pollen

extract [31]. Many researchers studied the mechanism to treat CP/CPPS. Tsunemori et al. found that eviprostat significantly suppressed the level of macrophage infiltration, Mic1 (macrophage inhibitory cytokine-1) gene expression, and proinflammatory cytokines/chemokines in the prostate in a rat NBP model, which may reduce the pain and inflammatory syndrome of CP/CPPS [32]. Shibuya et al. believed that partly owing to inhibit CCL2/MCP-1 production in the prostate, eviprostat suppresses stromal proliferation and inflammation [33].

### Terpene mixture

Terpenes are chemicals composed of isoprene [34]. Rowatinex is a terpenic complex composed of pinene, borneol and so on [35]. Borneol has the effect of reducing pain and swelling, which has been used widely in injuries, burns and muscle pain [36]. Lee et al. designed and conducted a prospective trial to evaluate the effect of rowatinex. Twenty-five patients of CP/CPPS were treated with rowatinex, and 25 patients of CP/CPPS were treated with ibuprofen. Baseline scores were similar between the two groups. After 6 weeks of treatment, both groups had a significant difference in the mean total NIH-CPSI score, pain domains and quality of life, but rowatinex has significantly more improved patients. So rowatinex may be an alternative treatment for the CP/CPPS, especially for the pain relief [35]. The pinene is the most significant ingredient in rowatinex [35] and Zhou et al. found that pinene inhibited the NF- $\kappa$ B nuclear translocation. The activation of NF- $\kappa$ B can lead to the expression of proinflammatory cytokines, chemokines, inflammatory enzymes. So the inhibition of NF- $\kappa$ B by pinene has the anti-inflammatory effect [37], which may be positive for CP/CPPS.

### Physical therapy

Physical therapy is an alternative treatment and has been used for many years. It can relieve the pain of the patients and has little effect. Recently, it has been attracting increasing attention. Physical therapy and the possible effect are summarized in Table 2.

### Acupuncture

Acupuncture is an alternative treatment approved in many countries and is widely used in traditional Chinese medicine for chronic pain. According to traditional Chinese medicine theory, acupuncture activates the Qi flow or energy flow through the meridians. Some studies reported that acupuncture had the effect of anti-inflammatory, immune modulation, and neuromodulation. Acupuncture can improve pain

**Table 2** The effect of physical therapy and possible mechanism

Physical therapy	Significant effect	Possible mechanism
Acupuncture	NIH-CPSI total score Relieve pain	Stimulate pudendal nerve Inhibit the spinal cord Enhance immune
Shock wave	Pain QoL Voiding condition	1.reduce muscle tone Hyperstimulate nociceptors Interrupt the flow of nerve impulses Affect the neuroplasticity of the pain memory Anti-inflammatory
Thermobalancing	Mean pain score Decrease prostate volume (PV) Improve QoL	Terminate the “micro-focus”
Transurethral needle ablation	Symptom scores	Accelerate inflammation recovery Change mucosal permeability
Transcutaneous electrical nerve stimulation	Pain score	Relieve pain
Sono-electro-magnetic therapy	No difference in the total score of NIH-CPSI, but patients had better effect	?

symptoms and can bring better results regarding NIH-CPSI, and quality of life for chronic prostatitis [38].

A random and controlled study with 68 patients of CP/CPPS was conducted to compare the effect of acupuncture versus sham acupuncture for 8 weeks treatment and 24 weeks follow-up. The result showed a significant decrease in total NIH-CPSI score between the two groups at 8th, 20th, 32nd weeks. Acupuncture group was statistically better in the pain and quality of life subscale scores or IPSS(International Prostate Symptom Score) [39]. Another study by Sahin et al. showed that acupuncture and sham acupuncture are 92% and 48% NIH-CPSI responders(50% decrease of total NIH-CPSI), respectively. The acupuncture group had a significantly greater decrease in pain relief even both groups showed a significant decrease in NIH-CPSI during the follow-up [40]. The different result of the pain syndrome between the two studies may be due to the number of acupoints and different acupuncturists. The more acupoints may relate to higher effect [40]. One report case demonstrated that one 35-year-old patient who received eight courses treatment of acupuncture and Chinese herbs experienced long-lasting relief [41]. Moreover, no adverse events were found. A Cochrane systematic review also demonstrated that acupuncture has a meaningful reduction in prostatitis symptoms [2]. However, the mechanism of acupuncture therapy is still exploring. Different acupoints may have different mechanisms. For example, the acupoints of BL30 and BL35 are related to stimulation of the pudendal nerve. The pudendal nerve is the main sensory and motor nerve of the perineum and provides genital sensation and control of the urethral sphincter and anal sphincters. BL30 and BL35 are close to the pudendal nerve. So when BL30 and BL35 are stimulated, the pudendal nerve is also stimulated and prevents local sensations passing to the central

nervous system, which can reduce the pain [42]. BL-33, BL-34 and BL-54 acupoints are located in the third and fourth posterior sacral foramen, which can inhibit the spinal cord and then have a predominant analgesic effect [40]. The CV1-huiyin, CV4-guanyuan, and SP6-sanyinjiao can enhance immune and prevent urinary retention [40]. Lee et al. chose CV1, CV4, SP6, and SP9 acupoints to conduct a study and they demonstrated that the natural killer cell levels of acupuncture group increased 5% compared to the sham group, supporting the immune mechanism [43].

### Shock wave therapy

The shock wave is single sound pulses and can form cavitation due to high pressure and variable negative pressure [44]. Shock wave as a therapy has been used in some diseases, such as diabetic wounds [45] and tendinitis [46]. Extracorporeal shock wave therapy (ESWT) is an effective and safe treatment and used in CP/CPPS [47]. Zimmerman et al. implemented a randomized, double-blind study. Thirty patients received ESWT, and thirty patients received sham ESWT without shock wave energy transmission. The treatment frequency was four times (once per week), each by 3000 impulses. The follow-up was carried out at week 1st, 4th, and 12th. The study showed a significant improvement in pain, QoL, and voiding condition in the ESWT group, whereas sham group went through a continuous deterioration during the follow-up period [48]. The longest follow-up period study conducted by Al Edwa et al. showed that all parameters were significantly improved at the period of 12 months. At 2nd-week IPSS and NIH-CPSI urination, domain showed maximum improvement and stabilized until 12th month. However, the AUA QOL\_US (American Urological Association Quality of Life Due

to Urinary Symptoms) and IIEF (International Index of Erectile Function) parameters showed the max effect at the 2nd week and appeared mild deterioration at the 6th month and 12th month but no significant changes after the 2nd week [49]. Guu et al. designed an ESWT study to those who failed the traditional medical treatment (antibiotics, alpha-blockers, and anti-inflammatories) and found significant clinical improvement after the treatment of ESWT with three kinds of medicines therapy for 4 weeks and most patients maintained a good efficacy for 3 months [50]. Although the mechanism of ESWT is still unclear, few hypotheses are being discussed: it can reduce muscle tone, hyperstimulate nociceptors, interrupt the flow of nerve impulses, and affect the neuroplasticity of the pain memory [51]. Mariotto et al. found that ESWT can increase NO production and suppress NF- $\kappa$ B activation, so they believed immunological pathogenesis of CPPS [52].

### Thermobalancing therapy

Thermobalancing therapy (TT) is a non-invasive and safe treatment invented by Dr. Simon Allen, which was enabled by the use of a therapeutic device for treating the CP/ CPPS. It applies a special mixture of waxes (thermoelement) to the skin [53]. Simon Allen conducted a clinical trial to verify the efficacy. The 45 patients of the treatment group received TT permitted by Dr. Allen's therapeutic device (DATD), and the control group did not receive TT. After 6 months of monotherapy, the mean pain score of the treatment group was significantly different, which declined from 10.38 to 3.58, while the control group just decreased from 10.49 to 9.71. Moreover, this study also found the improvement of QoL and the reduction of prostate volume (PV) [54]. Transrectal microwave thermotherapy was also tried to explore the therapeutic effect. It was an effective choice for CP/ CPPS patients supported by the total NIH-CPSI scores were significantly different from baseline. The results also showed that the sperm count was decreased by 23.8% in the 3 months after the treatment, but 6 months after treatment, the sperm quality recovered and the deformity rate was also lower [55]. Similarly, the effect of transrectal radiofrequency hyperthermia (TRFH) was explored by Gao, Mingdong, et al. They found that TRFH or TRFH with tamsulosin plus clarithromycin group was significantly different in pain relief, improved quality of life and urination domains [56]. Simon Allen, the inventor of TT, believed the trigger of CP/ CPPS related to capillaries, which can form "micro-focus" of hypothermia and ischemia and the use of TT can spread energy through the prostate gland and terminate the "micro-focus", so it can reduce the pressure of gland and relieve the pain [57].

### Transurethral needle ablation

Transurethral needle ablation (TUNA) was initially to cure benign prostatic hyperplasia (BPH). In 2004, a phase II prospective trial was conducted by Chiang and Chiang to explore the efficacy and safety of the treatment. They constituted two planes of four ablation sites in each lobe. One plane was located 0.5–10.0 mm distal to the bladder neck and the other plane was located 0.5–10.0 mm proximal from the verumontanum. The sheath was retracted on each needle to provide a shield for the urethra. The temperature increased with increasing power. The urethral temperature was maintained below 43 °C. Thirty-two patients were accessed in the third month; because of loss to follow-up, only twenty patients were accessed during the sixth month. The decrease in the mean symptom scores at the third and the sixth months was statistically significant from the baseline. So the transurethral needle ablation may also be an alternative measurement [58]. This effect was achieved probably by intraprostatic sympathectomy and coagulative areas of necrosis, which can accelerate inflammation recovery and change mucosal permeability [59].

### Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) can reduce pain in adults with chronic pain [60] and has the potential to decrease cancer bone pain [61]. Two studies were conducted to test the efficacy of TENS for CP/ CPPS. The first study assessed 24 patients. These patients were equally divided into TENS, analgesics and placebo group. The TENS treatment carried out five times a week for 4 weeks with frequency, intensity, pulse width and duration of 60 Hz, 100  $\mu$ S, 25 mA and 20 min, respectively, and the result revealed a significant difference in pain score [62]. The second study assessed 60 patients treated with TENS for 12 weeks. The study demonstrated that low pain visual analog scale declined significantly. After treatment, 29 patients recovered and 21 patients remained a positive effect during the 43.6 months of follow-up. The quality of life of the patients also considerably changed. No adverse event was reported [63]. TENS has the advantage in relieving chronic pain and widely accepted by the patients. The precise mechanism of this effect is unintelligible.

### Sono-electro-magnetic therapy

Kessler implemented a randomized controlled, double-blind trial to identify the impact of sono-electro-magnetic. Thirty patients received sono-electro-magnetic treatment, and thirty patients were the placebo group. The result showed that both groups had no difference in the total score of NIH-CPSI after 12 weeks of treatment. However, patients with symptoms

lasting 12 months or less had a better effect from sono-electro-magnetic therapy [64]. Considering the potential effect on CP/CPPS, sono-electro-magnetic therapy may be a novel research direction.

## Conclusion

Chronic prostatitis/chronic pelvic pain syndrome is still poorly understood. The regular pharmacotherapy treatment can relieve the syndrome to some extent. However, because of adverse events, people are looking for a more safe and effective measure. So in recent years, some phytotherapy draws their attention, such as cernilton, quercetin, pumpkin seed oil, eviprost, and rowatinex. Moreover, some safe and invasive physical therapy has also advanced, such as acupuncture, shock wave, thermobalancing, transurethral needle ablation, transcutaneous electrical nerve stimulation and sono-electro-magnetic. These therapies have little adverse effect; at the same time, they are safe, effective and more accepted by patients. Further experimental studies of herbal products, mechanistic data, cost analysis and randomized, controlled trials will assist in the validation of phytotherapies and physical therapies as alternative management options for men with CP/CPPS.

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## Compliance with ethical standards

**Conflict of interest** All authors declare no conflict of interest.

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