Green therapies for a grey disease

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Abstract

Phytotherapeutic agents are used for many years as an adjunctive therapy of benign prostatic hypertrophy. The similarity of the symptoms of the lower urinary tract associated with chronic prostatitis with those caused by benign prostatic hypertrophy and the anecdotally observed efficacy of the phytotherapeutic agents in the improvement of pelvic pain justifies their use in the treatment of chronic nonbacterial prostatitis. Many clinicians and researchers have investigated the role of herbal medicinal products against the symptoms of the lower urinary tract however a careful review of the reported studies showed that specific studies for nonbacterial prostatitis are limited. Even if in these studies the target, the material and the methods varies, most support their usefulness. Despite the general belief that phytotherapeutic agents have a dual mechanism of action (both hormonal and anti-inflammatory) it seems that they actually exhibit a moderate anti-inflammatory effect the exact mechanism of which is not fully investigated.

Introduction

Chronic nonbacterial prostatitis or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is considered the most common form of prostatitis, accounting for almost 90% of all the prostatitis cases. It can affect men of all ages. It manifests as a combination of mild prostatism (irritant or obstructive symptoms) and pain in the prostate and in various other locations such as the perineum, the scrotum, testicles, penis or even the bladder. The intensity of discomfort may be initially mild and it worsening gradually over a period of time (usually longer than three months). Up to 50% of the patients experience sexual dysfunction. The symptoms sometimes persist and sometimes disappear. Although signs of inflammation are present, patients have no bacteria in their urine and prostatic secretion. Actually no causative agent has been implicated with certainty therefore, treatment is basically symptomatic. For the above reasons CP/CPPS remains a grey disease.

Current pharmacotherapy of CP/CPPS is multidi-
tion and includes alpha - adrenergic blockers, muscle relaxants, nonsteroidal anti - inflammatory drugs, 5 - alpha - reductase inhibitors, antibiotics and herbal medicines. However, the use of - most of - the above medications is not fully justified and documented.

With regard to phytotherapeutic drugs, some have been proven effective in improving symptoms of the lower urinary tract associated with benign prostatic hypertrophy. Given that several symptoms are common in CP/CPPS and prostatic hypertrophy and since these conditions overlap in pathological substrate, many clinicians and researchers investigated the role of phytotherapy in the treatment of CP/CPPS. This article presents the existing published data on the efficacy of the most usually used phytotherapeutic agents in the treatment of prostate diseases and discusses the pathophysiological basis of phytotherapy in CP/CPPS.

Material and methods
A database and a manual search were conducted in the MEDLINE database of the National Library of Medicine, Pubmed, Cochrane Library and other libraries using the terms: “prostate”, “prostatitis”, “chronic prostatitis/chronic pelvic pain syndrome”, “non - bacterial prostatitis” “phytotherapy”, combined with the key words: “Saw palmetto”, “Pygeum Africanum”, “Equisetum arvense”, “Chimaphila umbellata”, “Populus tremula”, “Pulsatilla pratensis”, “Quercetin”, “Cernilton” in various combinations. Bibliographic information in the selected publications was checked for relevant publications not included in the initial search. Because of the close relationship between inflammation and prostatic hypertrophy and the fact that these two conditions share similar symptoms, we also took into consideration studies examining the efficacy of phytotherapy in the treatment of symptoms secondary to benign prostatic hyperplasia (BPH) that are common to CP/CPPS.

Results
A variety of phytotherapeutic agents are used worldwide for the management of lower urinary tract symptoms (LUTS) and some of them have been also tested in CP/CPPS treatment. The most commonly used preparations originate from the species serenoa repens, rye - grass and pygeum africanum.

Serenoa repens (Saw palmetto, Serenoa serrulata) is the best known phytotherapeutic as it has been used in traditional and alternative medicine to treat a variety of conditions. Not only the fruits but also the husk and leaves of this palm - like plant are highly enriched in fatty acids and phytosterols. Their extract has been the subject of intensive research for the treatment of symptoms of BPH and recently, prostatitis. In both cases its efficacy has been investigated either in combination or in comparison with other phytotherapeutic, antibiotics, alpha - blockers, anti - inflammatories and inhibitors of 5 - alpha reductase. There are more studies examining the role of saw palmetto as add - on therapy to other agents and less as monotherapy.

With regard to studies using S. repens extract as monotherapy for men with confirmed CP/CPPS, these of Lopatkin et al., and Giulianelli et al., showed significant improvement in symptoms (as measured in IPSS and NIH - CPSI questionnaires) over the six month treatment and follow up period. Moreover, an improvement in both erectile and voiding function (as demonstrated by the increase in the scores for the IIEF - 5 questionnaire and uroflowmetry results respectively) was also achieved. This efficacy appears to increase by the addition of supplements such as lycopene and selenium: Morgia and colleagues evaluated the effectiveness of this combination (S. repens, lycopene and selenium) versus S. repens alone and found a significant decrease in PSA and white blood cell count after eight weeks of treatment only in the group of patients who received combined therapy. Of note, IPSS improvement was slightly higher in the group of combined therapy and the mean NIH CPSI score reduction in the group of combined therapy was twice as much as that of monotherapy. Similarly, a placebo controlled randomized trial of combinational treatment (S. repens, selenium and lycopene) from the same authors showed greater changes in IPSS scores, serum PSA levels and peak urine flow rates in the treatment than in control group. The mean NIH CPSI score reduction in the treatment arm was twice as much as that of placebo. Interestingly, while combination of S. repens with selenium and lycopene achieved high
success rates in both studies that of S. repens alone
in the previously mentioned trial was comparable to
that of placebo in the last mentioned study.

Magri et al., who tested the combination of S.
repens with α - blockers with or without supple-
ments (lycopene and selenium), found a similarly
significant improvement in urinary flow (Qmax),
pain and quality of life (questionnaires NIH - CPSI,
QoL) over the 18 month follow - up period. Kaplan
and colleagues in a prospective, 1 - year trial com-
pared the effects of S. repens treatment with that of
finasteride. According to their results, patients
treated with S. repens showed no significant long -
term improvement (as measured in NIH/CPSI, AUA
Symptom Score, QoL and MPS), while those treat-
ed with finasteride had significant and long - term
improvement in all studied parameters except that
of urinary flow rate. Finally, a multicentre study of
the Italian Society of Oncological Urology compared
the efficacy of the combination S. repens plus alpha
- blocker versus that of S. repens alone, and found
similar changes in the uroflowmetry after 6 months
of follow - up. The mean urine flow rate was slight-
ly increased while there were no changes in sexual
function during the observation time. Notably, there
was a substantial decrease in the amount of patients
presenting severe prostatic symptoms and an im-
provement of inflammatory findings on ultrasound
examination, clinical examination and biopsy mate-
rial. In none of the studies mentioned above were
observed significant side effects.

Regarding studies focusing on LUTS of various ae-
tiologies accompanied or not by chronic pelvic pain,
two synchronous comparative placebo controlled
trials found no difference in the effectiveness of S.
repens versus placebo in the long term study period.
In accordance to these findings, a large multicentre randomized trial by Barry
et al., showed that - even - higher doses of S. repens
cannot influence neither the impact of LUTS nor the
quality of sexual performance over the placebo. On
the other hand, Sinescu et al., demonstrated a sta-
tistically significant improvement of mild or moder-
ate LUTS (as measured in IPSS questionnaire) induced
by BPH in a cohort of patients treated with S. repens.
Further improvements were observed in QoL, urinary
flow (Qmax), residual urinary volume and erectile
function (as measured in IIEF questionnaire) during
the long term study period. In accordance to the
above, Reissigl et al., in a randomized placebo con-
trolled study found an overall 30% reduction of pain
(as measured in NIH - CPSI questionnaire) and an 18% decrease of PSA levels in the S. repens group which
were significantly different of that of the control
group. A prospective multicenter double - blind ran-
domized study comparing tamsulosin (0.4mg/24h)
with S. repens (320mg/24h) in a sufficient number
of patients (542) with symptomatic prostatic hyper-
trophy (IPSS≥10) found no differences in IPSS (with
a corresponding improvement in both of irritative
and obstructive complaints), after 12 months of fol-
low up. Notably, Qmax and PSA improvement was
similar in both groups. Both treatments were equally
well tolerated. Pavone et al., administered a combi-
nation of S. repens, Urtica dioica and Pinus pinaster
(IPBTRE) either alone or in association with antibiotics
or α - blockers for a minimal duration of 30 days to a
maximum of a year. They found a remarkable reduc-
tion of pain and LUTS induced discomfort in 85% of
the evaluated cases (especially in relation to irritative
symptoms). Of note, meta - analyses found the ef-
effectiveness of saw palmetto inferior of that of finas-
teride and tamsulosin but clearly higher than that of
placebo in the treatment of mild and moderate LUTS,
nocturia and discomfort, while there was no compa-
range efficacy for pain management.

Controversy exists with regard to the ability of S.
repens to reduce prostate size. While Debruyne et
al. observed a slight reduction in prostate size after
12 months of follow up of patients treated with
S. repens, most clinical trials found S. repens extract
no more effective than placebo in blocking benign
prostate growth. Experimental evidence suggests
that it is rather the association of S. repens with some
natural compounds (such as lycopene, other carote-

The bark of the plant Pygeum Africanum contains
phytosterols (e.g. beta - sitosterol) pentacyclic trit-
erpenes (ursolic and oleanic acids) and ferulic acid
esters (n - docosanol and tetracosanol). It has been
used for ages in Africa and since the mid - 1960s in Eu-
rope to treat BPH. Despite the long experience with
pygeum, it actually has been the subject of very few studies. Some of them shows efficacy in symptoms regression (either as experienced by patients or as measured by IPSS) and micturition parameters (maximum urine flow and volume of urination)\textsuperscript{22, 23}. This efficacy appears to persist over time\textsuperscript{24, 25}. Frequency of nocturia and quality of life were found to improve further with long - term pygeum administration\textsuperscript{25}. However residual urine, prostate size and quality of sexual performance were not improved\textsuperscript{24}. In contrast to BPH patients, patients with CP/CPPS treated with pygeum - alone or in association with antibiotics - significantly improved in sexual function\textsuperscript{26}. In none of these studies undesirable effects were observed.

Quercetin is a natural bioflavonoid found in many fruits, vegetables, grains and leaves. Although it has been widely used for years, there are quite few studies examining its efficacy in the treatment of LUTS and prostatitis\textsuperscript{27}. In a large cohort of patients with CP/CPPS, Shoskes et al., administered phenotypical treatment (UPOINT) and found greater improvement (as measured in NIH - CPS questionnaire) with quercetin compared with other treatments after at least 6 months of therapy\textsuperscript{28}. In a smaller study from the same centre, quercetin administrated alone, achieved high improvement rates (from at least 25 to 100%) in the 67% of the patients. Of note, when administrated in combination with papain (which enhances the absorption of bioflavonoids); it achieved even higher improvement rates in 82% of the patients. In contrast, the placebo controlled group showed lower improvement rates in only 25% of the patients\textsuperscript{29}.

The rye - grass pollen extract (Cernilton) contains carbohydrates, aminoacids, vitamins, minerals and vegetable fats. The last are believed that increase plasma antioxidants, reduce insulin and confine local inflammation, limiting thus the development of both prostatitis and BPH. Since the early 90s, when Cernilton was first introduced in clinical practice, few studies examined its clinical effects and safety. More precisely, before 2000 only two placebo - controlled, two comparative trials and two trials with no control groups were published. All these studies lasted 3 - 14 months\textsuperscript{30, 31, 32, 33, 34, 35}. In all, Cernilton improved self - rated urinary symptoms but did not improved urinary flow rates, residual volume or prostate size compared with placebo or the comparative study agents\textsuperscript{36}. When studied in cohorts of patients with CP/CPPS improved self - rated urinary symptoms\textsuperscript{37, 38} and showed a clear therapeutic advantage over placebo\textsuperscript{39}. However, in an interesting study of patients with BPH who underwent surgery and were diagnosed with chronic nonspecific prostatitis upon biopsy, administration of Cernilton improved the persistent symptoms from the lower urinary tract and sexual dysfunction, according to the degree prostatitis\textsuperscript{40}. Other researchers found an overall 74.2% improvement in subjective symptoms and 65.6% in the objective findings\textsuperscript{39} while other reported complete cure of only 36% of the treated population\textsuperscript{41}. Notably, according to these authors, in the presence of aggravating or alleviating factors, the response to Cernilton treatment was practically null\textsuperscript{42}. Reasons explaining the abovementioned disparities are unknown. One possible explanation is that the therapeutic effect of Cernilton may be time and dose dependent: Long - term administration of cernilton (6 months of treatment) resulted in a significant improvement rate of 76 - 78\%\textsuperscript{37, 42}. Correspondingly, a daily dose of 750 mg promoted a faster and more noticeable improvement in subjective (NIH - CPSI, Sex - 4, IPSS, QoL) and objective criteria (leukocyte count in prostatic exudation) compared with that induced by the dose of 375 mg\textsuperscript{43, 44}. Both doses were equally well tolerated.

Equisetum arvense (field horsetail or common horsetail) is an herbaceous perennial plant. It was long used in the treatment of various diseases and it has specific use for BPH, prostatitis and prostate oedema\textsuperscript{45}. It is rich in silicic acid and silicates, which provide approximately 2 - 3% elemental silicon. Silicon stimulates leucocyte activity, helps preserve elasticity of connective tissue and promotes the repair of tissue. The abovementioned properties are of outmost importance for the treatment CP/CPPS. In the few existing reports, Equisetum arvense's extract is being using in the treatment of LUTS and chronic prostatitis in combination with other phytotherapeutic agents (extracts from the plants Chimaphila umbellata, Populus tremula, Pulsatilla pratensis, Willow bark) and wheat germ oil as well, under the brand name Eviprostat. Tamaki et al., reported gradual improvement in symptoms of prostatism and dysuria.
prostatic secretion was found a significant reduction in the number of leukocytes in Chinese Medicine Syndrome Score) and a similarly improvement in NIH - CPSI score, TCMSS (Traditional in patients with CP/CPPS. A statistically significant astrágalo, Salvia púrpura, Gardenia and Houttuynia) lin herbal mixture (Genciana, Bambú, Poria cocos, evaluated the therapeutic effect of the Longjintong lie herbal and plant extracts products of the Far East to re treatment achieved higher rates in NIH - CPSI score significantly lower than that of the control group). Differences of 50 µg/mL prevented inflammatory activity (IPSS), improvement in quality of life scores (QoL) and significant nocturia reduction during treatment. The drug was well tolerated. Iwamura et al., compared the efficacy of equisetum arvense with that of rye pollen extract in the treatment of patients with CP/CPPS and found no significant differences.

The root extract of African potato (Hyposis hemerocallicida) was used for centuries in Africa for relieving diseases of the urinary tract. Epilobium parviflorum is an herbaceous perennial plant belonging to the Onagraceae family. Its flower - petal - extract was traditionally used in Central Europe for the treatment of prostate disorders. Despite their popularity there are no clinical studies demonstrating any efficacy in the treatment of CP/CPPS for both herbs and plant extracts products of the Far East to re.

Paeoniflorin is one of the main components of the root of herbaceous plant Paeonia lactiflora (white peony) which is used by the traditional medicine of Korea, China and Japan for its soothing properties. It is believed that it is effective in the treatment of prostate complaints. A clinical study evaluated its efficacy in the treatment of CP/CPPS based on the improvement in NIH - CPSI score and the number of lecithin particles (SPL) in the prostatic fluid. Moreover it was examined whether and if a - blockers enhance its efficacy. According to the authors, treatment with Paeoniflorin (Qianlieping Capsule) alone increased the number of lecithin particles by 46.9% and improved the NIH - CPSI score by 24.4%. However, the combination of paeoniflorin and tamsulosin increased the number of lecithin particles by 61.4% and improved the NIH - CPSI score by 42.3%. Of note, combinational treatment achieved higher rates in NIH - CPSI score than those of tamsulosin alone (33.7% and 28.6% respectively).

Traditional Chinese medicine uses mixtures of herbs and plant extracts products of the Far East to relieve discomforts from urinary tract. A focused study evaluated the therapeutic effect of the Longjintonglin herbal mixture (Genciana, Bambú, Poria cocos, astrágalo, Salvia púrpura, Gardenia and Houttuynia) in patients with CP/CPPS. A statistically significant improvement in NIH - CPSI score, TCMSS (Traditional Chinese Medicine Syndrome Score) and a similarly significant reduction in the number of leukocytes in prostatic secretion was found.

Discussion

For most of the abovementioned phytotherapeutic drugs no comparative or placebo - controlled studies further evaluating their efficacy exist and the few existing clinical trials have methodological problems and omissions in the reported results. Regarding the most known of them - saw palmetto and cernilton - published studies weren't based on a single clinical trial formulation. In addition the clinical trials are limited by their short duration, the limited number of participants and the unknown quality of the preparations used. However the main reason for the low adoption of phytotherapeutic drugs in the everyday clinical practice is the fact that their mechanism of action remains unclarified. They generally believed to have anti - androgenic and anti - inflammatory properties. Although the latter explain the pain recession, the exact mechanism that improves complaints of urination and sexual function remains unknown.

Three different mechanisms of action have been proposed for Saw palmetto: inhibition of the androgenic receptor (antiandrogenic), inhibition or blocking the action of growth factors (antiproliferative) and reduction of the production of 5 - lipoxygenase metabolites (anti - inflammatory). The latter has been proved both clinically and pathologically: the percentage of inflammatory pattern in biopsy material and prostatectomy specimens from patients receiving serenoa repens and quercetin was significantly lower than that of the control group. In contrast, the existing evidence on an antiandrogenic action by inhibiting Salpha - reductase activity is rather contradictory. It has been proved both clinically and pathologically: the percentage of inflammatory pattern in biopsy material and prostatectomy specimens from patients receiving serenoa repens and quercetin was significantly lower than that of the control group. In contrast, the existing evidence on an antiandrogenic action by inhibiting Salpha - reductase activity is rather contradictory. In support of this, a relatively new study on androgen - independent prostate epithelial PC - 3 cells demonstrated that the anti - proliferative, anti - inflammatory and anti - oedematous effects of serenoa repens are taking place in absence of androgens. Infact, serenoa repens at effective concentrations of 50µg/mL prevented inflammatory activity on human epithelial prostate cells by suppressing signaling growth factors such as IGF - I (Insulin - Like Growth Factor). Furthermore, it exerts an inhibitory effect on the expression of the inflammation factors COX - 2, 5 - LOX, iNOS, on the binding activity of NF - kB and on the replication of TNF - a. Notably, the combination of serenoa repens, selenium and lyco-
pene exhibits greater inhibitory activity than that of the serenoa repens alone. Notably, the combination serenoa repens, selenium and lycopene increases the pro-apoptotic molecules Bax and caspase - 9, blocks the mRNA of the anti - apoptotic Bcl - 2, and limits the expression of the epidermal and vascular - endothelial growth factors. Therefore it could be hypothesized that the significant decrease in mast cell concentration and the rapid fall of histamine levels as well as the reduction in the inflammatory oedema (resulting from the above sequelae) allow relaxation of muscle layer and gradually lead to the relief of chronic prostatitis symptoms. Of note, although antiandrogenic activity of serenoa repens has not been experimentally demonstrated, it has been suggested that long term administration causes atrophy of the epithelium of the central region of the prostate gland. This finding provides evidence of an antiandrogenic action and also explains the limited efficacy of serenoa repens in sexual dysfunction complain. Quercetin is considered an anti-allergenic and natural anti-inflammatory that inhibits the formation of bruises and the development of oedema. These properties have been histologically demonstrated in the prostate gland. There are no sufficient laboratory studies investigating the exact mechanism but it appears to exhibit a strong antioxidant activity. It is able to down-regulate the inflammatory response of bone marrow - derived macrophages in vitro. Moreover, it inhibits cytokine and inducible nitric oxide synthase expression through inhibition of the NF - kappaB pathway. This property indicates that quercetin reduce or even help prevent some of the damage free radicals cause. Importantly, it is also considered a non-specific inhibitor of protein kinase through which inhibits activation of inflammatory mediators and enzymes such as lipoxygenase. Through this effect quercetin decreases levels of inflammatory prosta-glandin and increases levels of prostatic endorphins which are natural pain - relieving molecules. Moreover, it also prevents the release of histamine which causes concentration of basophils and mast cells. The abovementioned effects can cause oedema reduction and relaxation of muscle stroma. These properties explain both the pain recession and complaints of urination improvement following long term (eight - week) quercetin administration. A poorly investigated hormonal action with presumably anti-testosterone effects is also reported. According to Prossnitz and Barton quercetin activates the alpha and beta estrogen receptors (Erα & Erβ) and acts as an agonist of the G coupled estrogen receptor protein (GPER). However, it is about two to three times less potent than the endogenous 17β - estradiol.

Rich in phytosterols, cernilton (pollen extract) is thought to have anti-inflammatory properties. It is believed that exhibits a strong antioxidant activity and blocks the formation of inflammatory prostaglandin and leukotriene molecules. Chen et al studied the levels of oxygen free radicals in the prostate during occurrence, development, and recovery of CP/CPPS. A significant reduction of free radicals levels in the after treatment period was found in the biological material from patients received pollen extract (EA - 10, P5), while no changes observed in the control group.

In an experimental investigation of the anti-inflammatory activity of pollen extract cernilton in mice Kamijo et al., found that it clearly inhibits the proliferation of the stromal cells, and, in combination with increased apoptosis protects epithelial cells from inflammation spread.

Similarly, another experimental study of hormonally induced chronic nonbacterial prostatitis in rats by Asakawa et al., found that pollen extract significantly reduced the elevated levels of cytokines in a dose-dependent manner. Moreover, the histopathological changes associated with inflammation were all resolved with treatment. According to these researchers the above offer a strong evidence of a hormonally mediated anti-inflammatory action. Interestingly, patients with chronic non-bacterial prostatitis whose treatment failed were found to bear genotype which predisposes to the production of low levels of interleukin 10. This fact suggests autoimmunity as a probable aetiology of this disease and provides evidence that pollen extract has an anti-inflammatory activity rather due to the inhibitory effect on inflammatory cytokines of prostatic tissue than hormonally mediated.

The stems of equisetum arvense (horsetail) contain 5% to 8% of silica and silicic acids. The size of silicified structures varies accordingly to the location within
the plant: thicknesses of 3 - 7 µm and 0.2 - 1.0 µm are observed in the stem and leaf, respectively. The plant contains about 5% of a saponin called equisetin, in addition to the flavone glycosides isoquercitrin, equisetin, and galuteolin. It also contains phenolic acids, tannin, alkaloids. Of note, the alkaloid nicotine is present in minute amounts (less than 1 ppm) but may account for a portion of the pharmacologic activity of the plant. The sterol fraction of equisetum arvense contains beta - sitosterol, campesterol, isofucosterol, and trace amounts of cholesterol72. The plant also contains more than 15 types of bioflavonoids, as well as manganese, potassium, sulfur, and magnesium while the cytokinin isopentenyladenosine has been identified in fertile fronds73. Populus tremula contains popoulini, salicin and gallic acid. Chimaphila umbellata contains large quantities of erikolinis, arbutin and methyl - arbutin, tannin and gallic acid. Most of the above exhibit some anti - inflammatory activity. The most intriguing of Equisetum arvense's components is silica. It is well known that silica is a fibrogenic factor which has been associated with chronic inflammation of the lungs and thus it could aggravate prostatic inflammation when administered in CP/CPPS patients. However it was shown that silica - activated macrophages promote high expression of the anti - inflammatory and fibrotic cytokine IL - 10. Therefore the fibrotic formation can either accompany by a pronounced anti - inflammatory reaction or a progressive inflammation73. Studies showed that silica particle size impacts immune responses, with submicron amorphous silica particles inducing higher inflammatory responses than silica particles over 1000 nm in size, which is ascribed not only to their ability to induce caspase - 1 (IL - 1) activation but also to their cytotoxicity73.

Salicin is the precursor of aspirin and it is considered responsible for the anti - inflammatory properties of the plants Populus tremula and Willow bark. The extract from the bark of the above - mentioned trees was found to be at least as effective as aspirin in reducing inflammatory exudates and in inhibiting leukocytic infiltration as well as in preventing the rise in cytokines, and was more effective than aspirin in suppressing leukotrienes, but equally effective in suppressing prostaglandins. The fact that the extracts of the plants Populus tremula and Willow bark have lower "salicin" content than that of an equivalent dose of aspirin may lead one to speculate that other constituents of the extract contribute to its overall activity74. According to Khayyal et al., the presence of polyphenols in the extract of Willow bark probably plays a significant role in enhancing its free radical scavenging properties76. Independently to the controversy regarding long term salicin induced anti - inflammatory properties, its role in the reduction of pain is not to be doubted.

The ester of epigallocatechin and gallic acid (epigallocatechin gallate - 3) is a polyphenol with strong antioxidant activity that can neutralize free radicals and reduce cell damage. Moreover it has immunostimulatory properties77. Arbutin and methyl arbutin are transformed in hydroquinone into the intestine. The last inhibits tyrosinase, thereby helping to reduce the amount of free radicals. Furthermore, arbutin exerts an antiseptic effect on the mucous membrane of the urinary tract78. Tannin is a phenol with astringent and antiseptic properties. It is believed to form a protective layer around cells which reduces the increased secretion of inflamed gland79. The flower extract of Pulsatilla pratensis contains a lactonic glycoside called ranunculin, triterpenoid saponins, tannin and volatile oil. Ranunculins' product protoanemonin is a toxin with antibacterial, antiviral and cytopathogenic properties. When comes into contact with air and dimerizes to anemonin, which is further hydrolyzed to a non - toxic carboxylic acid that exhibits anti - inflammatory and anti - neuralgic properties76.

An experimental study in rats with induced nonbacterial prostatitis has shown that this combination of the abovementioned components (Eviprostat) significantly reduced levels of cytokines and malondialdehyde (oxidative stress marker)80.

Pygeum contains numerous constituents, including phytosterols such as beta - sitosterols, which were thought to inhibit of the androgenic receptor (antiandrogenic) in a fashion similar with that of finasteride (by interfering with the binding sites for dihydrotestosterone). However, the fact that hormone mediated effects (such as sexual dysfunction and prostate gland size reduction) are rare in patients
receiving pygeum suggests a different mechanism of action. In fact, sitosterols exhibit a clear anti-inflammatory action by inhibiting the production of prostaglandins in the prostate. Pygeum contains also ferulic esters, which reduce levels of prolactin (a hormone that promotes testosterone uptake in the prostate gland) and cholesterol (which increase the binding sites for dihydrotestosterone). The extent of their impact is unknown. Actually the esters of ferulic acid act on the endocrine system: experimental studies showed docosanol to reduce levels of LH and testosterone while raised adrenal steroid secretion of both androgens and corticosteroids. Stimulation of adrenal androgen secretion enhances anti-inflammatory effects and contribute to the restoring of the secretory activity of prostate epithelium. Other pygeum components include pentacyclic triterpenes, which inhibit an enzyme involved in inflammation and help reduce edema and oleic acid that also has anti-edematous effects. In a laboratory study, pygeum extract demonstrated also a poorly investigated anti-proliferative effect on prostate cells derived from rats, which was in part mediated by inhibition of basic fibroblast growth factor. Experimentally it has been shown that pygeum reduce the production of the metabolites of 5-lipoxygenase (especially leukotrienes) and inhibits the production of fibroblasts (through repression of bFGF - basic fibroblast growth factor). An additional neurotropic effect is not to be excluded since pygeum administration in experimental animal models modified bladders’ contractility by reducing the sensitivity to electrical stimuli, to phenylephrine, to adenosine triphosphate and carbachol as well.

Most of the components of Paeoniflorin are monoterpenic glycosides. Of these, paeoniflorin is the major (>90%) component and it is responsible for the pharmacological effects both in vitro, and in vivo. It has anti-inflammatory effects involving the inhibition of acute and sub-acute inflammation by suppressing the increase of intracellular calcium ions concentrations and by inhibiting the production of PGE2, LTB4 and NO (mediators of inflammation). Moreover it acts on lymphocyte proliferation, differentiation of Th/ Ts lymphocytes and the production of proinflammatory cytokines and IgM antibodies.

The ethanol extract of dried leaves of Gardenia contains a sufficient amount of genipin which has anti-inflammatory effects. This effect was found to be proportional to the concentration of genipin. However, the nature and the exact mechanisms of action are not well understood.

Leaves of Salvia contain saponins, resins, terpenes, tannins and flavonoids for which exhibits anti-inflammatory and antiseptic properties. Bamboo leaves have also anti-inflammatory and antioxidant properties which are probably associated to the presence of abundant silica. Houttuynia has antibacterial properties and fungus Poria Cocos has a diuretic effect therefore its role is probably auxiliary. No studies investigating the underlying mechanisms and their effects on prostate exist for these herbs.

**Conclusions**

Several clinicians and researchers have investigated the effectiveness of phytotherapeutics in the treatment of benign prostatic hypertrophy related lower urinary tract symptoms, however specific studies clearly focusing on nonbacterial prostatitis are very rare. Most of the published studies demonstrate a significant improvement in LUTS and CP/CPPS symptoms associated with a satisfactory safety profile. The exact mechanism of action remains unknown however they generally exhibit anti-inflammatory properties. Due to the heterogeneity of the products of this class of medicines and the methodological problems associated with the existing studies it is not easy to draw definitive conclusions about their role in CP/CPPS treatment.

**Abreviations**

Chronic nonbacterial prostatitis or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH).
Τα φυτοθεραπευτικά χρησιμοποιούνται εδώ και πολλά χρόνια ως συμπληρωματική θεραπεία στην καλοήθη υπερτροφία του προστάτη. Η ομοιότητα των συμπτώματων του κατώτερου ουροποιητικού στη χρόνια προστατίτιδα με αυτά που προκαλούνται από την καλοήθη υπερτροφία του προστάτη και η παρατηρούμενη αποτελεσματικότητα των φυτοθεραπευτικών στη βελτίωση του πυελικού πόνου δικαιολογεί τη χρήση τους στη θεραπεία της χρόνιας μη βακτηριακής προστατίτιδας. Πολλοί κλινικοί γιατροί και ερευνητές έχουν διερευνήσει το ρόλο των φυτικών φαρμακευτικών προϊόντων κατά των συμπτώματος του κατώτερου ουροποιητικού συστήματος, ωστόσο μια προσεκκική εξέταση των υφιστάμενων μελετών έδειξαν ότι οι εξειδικευμένες για τη μη βακτηριακή προστατίτιδα είναι περιορισμένες. Ακόμα και αν σε αυτές τις μελέτες ο στόχος, το υλικό και οι μέθοδοι ποικίλουν οι περισσότερες υποστηρίζουν τη χρησιμότητά τους. Παρά τη γενική πεποίθηση ότι τα φυτοθεραπευτικά έχουν διπλό μηχανισμό δράσης (ορμονικό και αντι-φλεγμονώδη) φαίνεται ότι εμφανίζουν μία μέτρια αντιφλεγμονώδη δράση της οποίας ο ακριβής μηχανισμός δεν έχει πλήρως διερευνηθεί.

Περίληψη

Λέξεις ευρετηριασμού
χρόνια μη βακτηριακή προστατίτιδα, σύνδρομο χρόνιου πυελικού άλγους, συμπτώματα από το κατώτερο ουροποιητικό σύστημα, φαρμακοθεραπεία, φυτοθεραπευτικά

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