Review

Serenoa repens and Pygeum Africanum in the treatment of BPH

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Abstract

INTRODUCTION /AIM: Serenoa repens (SR) and Pygeum Africanun (PA) exhibit marked anti-inflammatory, anti-androgenic and anti-proliferative effects. For this reason, they have been subject of research as potential treatment of benign prostatic hypertrophy (BPH). The aim of this study is to present current knowledge on the topic.

METHODS: A non-systematic search was performed in electronic libraries for clinical trials, experimental studies and systematic reviews on the topic using the terms: "prostate", "benign prostatic hypertrophy", "lower urinary tract symptoms" combined with the key words: "phytotherapy", "Saw palmetto", "Serenoa repens", "Serenoa serrulata", "Pygeum Africanum", "Prunus africana" in various combinations.

RESULTS: A sufficient number of studies of the efficacy of SR for the treatment of LUTS and BPH exists. Most of them examine the role of saw palmetto as add-on to other agents and less as monotherapy. Few similar studies for PA have been published up to date. Almost all examine its role as monotherapy. According to our research, there is no clear evidence of clinical superiority of phytotherapy over conventional treatment however a potent synergistic effect was shown. SR seems to be more efficient than PA though non produce some of the therapeutic effects of PA.

CONCLUSIONS: Combination of SR and PA with other medications can offer significant improvements of urinary status while having a favourable safety profile and for this reason may be considered a viable therapy for treating LUTS in certain groups of patients.

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Introduction

Benign prostatic hyperplasia (BPH) is often accompanied by lower urinary tract symptoms (LUTS) that can significantly affect the quality of life (QoL) of the patients. A variety of phytotherapeutic agents are widely used in traditional and alternative medicine to treat LUTS. The most commonly used preparations originate from the species of palm-like tree Serenoa repens (SR), commonly known as saw palmetto (Serenoa serrulata) and from the African prune tree Pygeum Africanum (PA) also known as Prunus Africana. The extract of the fruits and the husk of these plants is highly enriched in fatty acids and phytosterols and exhibit anti-inflammatory anti-androgenic and antiproliferative effects [1-3]. For this reason, they have been the subject of clinical and experimental research in the treatment of symptoms of BPH. In this paper we aim to review relevant published data in order to compare their efficacy in this field.

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", "benign prostatic hypertrophy", "lower urinary tract symptoms" combined with the key words: "phytotherapy", "Saw palmetto", "Serenoa repens", "Serenoa serrulata", "Pygeum Africanum", "Prunus Africana" 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 in consideration few studies examining the efficacy of phytotherapy in the treatment of symptoms secondary to prostatitis in BPH patients.

Results

SR in the treatment of symptoms of BPH has been tested either alone or in combination or in comparison with other phytotherapeutic, alpha-blockers and inhibitors of 5-alpha reductase (5-ARI). 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 SR extract as monotherapy for men with BPH related LUTS, these of Lopatkin et al, and Giulianelli et al, showed significant improvement in symptoms (as measured in IPSS questionnaire) over the six-month treatment and follow up period. Improvement in both erectile and voiding function was also achieved [4, 5]. Sinescu et al., demonstrated a statistically significant improvement of mild or moderate LUTS and improvements in overall QoL, urinary flow (Qmax), residual urinary volume (RV) and erectile function (EF) during the long-term study period [6]. Others found that higher doses of SR cannot additionally improve neither LUTS nor EF [7, 8].

When compared with placebo, SR extract demonstrated a statistically significant difference in improvement of mild or moderate LUTS. However, SR treatment showed no measurable effect on Qmax [9]. Recently, Ye et al, in a placebo-controlled study found significant improvements in Qmax, IPSS, QoL and EF in the SR extract group. Adverse events were very rare and comparable between the two groups (1.89 and 1.18% in the study and the placebo group respectively)[10]. Finally, Giannakopoulos et al, found significant improvements in the IPSS quality-of-life scores, Qmax and RV over the placebo. In contrast, Helfand et al, found no differences between improvements in urinary symptoms between SR extract and placebo group at 72 weeks of follow-up [8, 11]. Two similar synchronous trials found no difference in the effectiveness of SR versus placebo [12-13]. In none of the abovementioned studies were observed significant side effects.

Efficacy of SR was also compared to that of established BPH treatments. Alcaraz et al, found that in real-life practice, SR shows an equivalent efficacy to alpha-blockers and 5-ARI in LUTS improvement with fewer side effects [14]. In accordance to these findings, Pytel et al. (2002 and 2004) enrolled patients with documented BPH and LUTS. Outcome was estimated upon IPSS, QoL, index of sexual function (MSF-4), size of the prostate, urodynamic and biological parameters. Follow-up lasted 24 months. Apart from the abovementioned parameters, plasma hormones (testosterone, DHT, estradiol, LH, androstenedione) did not change [15,16]. A prospective multicentre double-blind randomized study comparing tamsulosin (0.4mg/24h) with SR (320mg/24h) in a sufficient number of patients with symptomatic BPH (IPSS≥10) found no differences in IPSS improvement after 12 months of follow up. Nota-

bly, Qmax and PSA improvement was similar in both groups. Both treatments were equally well tolerated [17]. Ryu et al showed that the combination SR and tamsulosin was more effective than tamsulosin monotherapy, only in reducing storage symptoms after 6 months of treatment. Adverse events were comparable (16.9 and 20% for the monotherapy and combinational therapy groups) [18]. Statistically significant difference in clinical improvements in LUTS/BPH severity was found between Silodosin plus SR and SR alone, and Silodosin plus SR and Silodosin alone as well [19]. In contrast, according to Argirović and Argirović, in the treatment of BPH, none of SR and tamsulosin had superiority over another and, combined therapy (tamsulosin + SR) does not provide extra benefits. In this study, adverse events occurred only with tamsulosin [20]. Similar conclusions were provided by Glemain et al. and Hizli & Uygur [21, 22]. Finally, a multicentre study compared the efficacy of the combination SR plus alpha-blocker versus SR alone and found similar changes in the uroflowmetry after 6 months of follow-up [23].

Cai et al found greater improvement of patient's quality of life, with the combination SR, Pinus massoniana Bark Extract and Crocus sativus when compared with SR alone [24]. Morgia and colleagues evaluated the effectiveness of the combination SR, lycopene and selenium (SR, LY, SE) versus SR alone in patients with LUTS/BPH/CNBP. They found a slightly higher IPSS improvement in the group of combined therapy after eight weeks of treatment [25]. Again, Morgia and colleagues evaluated the effectiveness of the combination SR, LY, SE (group A), versus tamsulosin alone (group B) and versus the combination SR, LY, SE and tamsulosin (group C). At one year from baseline, the changes of IPSS and Qmax were greater for Group C versus monotherapies [26].

According to some authors a two-month period of treatment with PA extract 50mg twice daily induced significant improvement in IPSS and uroflowmetry parameters [27, 28]. Positive effects were accompanied by a satisfactory safety profile and a substantial improvement in QoL [28]. PA extract administration (200 mg/24h), for 60 days improved urinary sexual and and prostatic echographical parameters with no significant alteration in serum hormonal levels (testosterone, DHT) before and after therapy [29]. In contrast, a small similar study by Donkervoort et al., found no significant effect [30].

In a placebo-controlled study, Pygeum extract given for 6 weeks in a daily dose of 2x100 mg showed significantly better improvement in IPSS over placebo [31]. In another placebo-controlled study a daily dose of 4x 50 mg provided greater improvement in all the subjective and objective parameters than the placebo [32]. A similar multicenter study found a significant difference between the PA group and the placebo group with respect to therapeutic response as measured by IPSS (55 versus 31% respectively) after two months of treatment [33]. Mild side effects (diarrhea, constipation, dizziness and visual disturbance) were observed in 2.3% of PA group patients.

Of note, comparison of once and twice daily dosage forms of Pygeum africanum showed equal effectiveness and safety at 2 months [34].

Several authors investigated the efficacy and safety of the combination of PA with other phytotherapeutic agents: An orally dosed herbal preparation containing Cucurbita pepo, Epilobium parviflorum, lycopene, Pygeum africanum and Serenoa repens provided significant reduction in IPSS median score (36% in the active group vs 8% for the placebo group), during the 3-months intervention. The day-time and night-time urinary frequency were also reduced in the active group [35]. Krzeski et al., compared the standard dose of an Urtica dioica/PA preparation (300/25mg) with half the standard dose twice daily for 8 weeks and found no difference in Qmax, RV and nycturia improvement [36].

Main outcomes of the comparative studies included in this review are displayed in table 1.

Discussion

Evaluation of SR and PA efficacy in BPH related LUTS treatment is actually difficult for two main reasons. First, the exact mechanism by which they treat BPH remains unknown. Among mechanisms proposed to explain SR's and PA's effects is the inhibition of the activity of the enzyme 5-a reductase (5-aR), the impediment of apoptotic processes in prostate's cells and the hindrance of inflammatory mediators [37, 38]. The above have been attributed by specific studies to different compounds and chemical ingredients included in the extracts. However, the mechanism of action is yet to be thoroughly and fully specified.

5-aR is a basic modulator of the conversion of testosterone to dihydrotestosterone (DHT), which is responsible for the overgrowth of the prostate's epithelial cells. When compared with the most known 5-aR inhibitor, finasteride, SR shows similar or inferior effectiveness in the treatment of mild and moderate LUTS, nocturia

Table 1 *Main outcomes*

	Placebo	SR	5ARI	alpha-blockers	IDIProst plus SR	SR, LY, SE	alpha-blocker SR, LY, SE	alpha-blocker SR	PA
Dedhia	+	+							
Bent	+	+							
Ye	+	++							
Barry	+	+							
Alcaraz		+	+	+					
Debruyne		+		+					
Cai		+			++				
Morgia		+				++			
Morgia				+		+	++		
Ryu				+				++	
Boeri		+		+				++	
Argirović		+		+				+	
Bertaccini		+						+	
Gerber	+	++							
Helfand	+	+							
Glemain		+		+				+	
Hizli & Uygur		+		+				+	
Dufour	+								++
Bassi	+								++
Barlet	+								++

and discomfort [39-41]. However clinical trials found SR extract no more effective than placebo in blocking benign prostate growth [42]. Evidence suggests that the main activity of SR is anti-apoptotic and it is rather the association of SR with some natural compounds (such as lycopene, other carotenoids and selenium) that reduce prostate size than SR alone [43]. This happens as the Ly-Se-SR association is more effective than SR in augmenting the pro-apoptotic Bax and caspase-9 and blunting the anti-apoptotic Bcl-2 mRNA. In addition, Ly-Se-SR more efficiently suppresses the EGF and Vascular Endothelial Growth Factor (VEGF) expressions in hyperplastic prostates [44]. Finally, research suggests an anti-inflammatory activity of SR, provided by beta-sitosterols, which inhibits the production of prostaglandins in the prostate. A strong anti-inflammatory is also achieved through the inhibition of inflammatory mediators MCP-1/CCL2 and VCAM-1 [45].

Despite slight decrease in levels of testosterone associated with PA administration, inhibition of 5-aR by PA is considered minimal and not clinically significant [46]. Antiandrogenic and antiestrogenic effects (which may block the initiation of hyperplasia), were also achieved through the activity of ferulic esters which decrease prolactin (which stimulates intraprostatic dihydrotestosterone synthesis and testosterone uptake) and cholesterol (which increases the binding sites for dihydrotestosterone), though such effects do not appear to reverse the progression of BPH [47]. An anti-inflammatory effect attributed to several contents of PA extract -such as pentacyclic triterpenes and ferulic esters- was proposed to explain -in part- the in vitro therapeutic effect of Pygeum [48]. In confirmation to the above, a significant downregulation of genes involved in inflammation and oxidative-stress pathways has been recently shown [49]. According some investigators, a powerful anti-proliferative effect on prostate cells, resulting from inhibition of epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor 1 (IGF-I) counteract the structural and biochemical changes associated with BPH [50, 51].

Research suggests that PA reverses altered myosin isoform expression and causes a decrease in the contractility of the detrusor muscle by reducing its sensitivity

to electric stimulants such as phenylephrine, adenosine triphosphate and carbachol [52].

The abovementioned properties of SR and PA explain in part their effects on BPH however remains a gap between in vivo and in vitro studies. Especially for PA most studies are old and out-dated.

Second, due to the heterogeneity of the existing herbal formulations, the short duration of most studies, the variability in study design and variation in outcome measures, the literature is somehow limited. In fact, most SR extracts vary considerably in composition, effectiveness and supporting evidence, since their activity depends on the concentration of free fatty acids and the method of extract preparation [53]. Unfortunately, most studies provided generic or inadequate descriptions of the preparations used with regards to the free fatty acid and phytosterol percentage of the extract and no study gave extra information on the method of SR extraction and the pivotal aspect of the preparation's lauric acid content that would show compliance with the European Pharmacopoeia recommendation. On the other hand, it is possible that placebo effect influenced by positive patients' expectation on phytotherapeutic agents alter the findings of questionnaire based clinical studies [54].

This review didn't find evidence of superiority of SR and PA over conventional BPH treatment and no direct comparison between the two phytotherapeutic agents exists. According to this research, both SR and PA offer improvements of urinary status while having a favorable safety profile. However, it should be also noted that most PA studies are old and include small numbers of patients while there are no studies comparing its efficacy and safety to that of established BPH treatments. For this reason, it could be assumed that SR effects on urine flow rate and residual urine content might be better. Both have a favourable safety profile though, SR is better tolerated. On the other hand, SR seems not to produce the effects of PA on bladder detrusor.

Since initial clinical trials examining SR with other phytotherapeutic agents and micronutrients have shown a potent synergistic effect [55], the above combination with a-blockers may offer an alternative (other than finasteride and alpha blocker) combination therapy to patients with moderate symptoms. The combination of PA with a- blockers could be investigated as an alternative (other than anticholinergic and alpha blocker) combination therapy for patients with irritative symptoms. Finally, SR and PA exhibit remarkable anti-inflammatory and anti-proliferative effect and therefore they may have a crucial role in delaying the development of clinical BPH. For this reason, it could be important to study their effect in younger patients with early symptoms. Such a study may be carried out for each extract separately, depending on the method of preparation and brand.

Conclusions

Despite the amount of preclinical and clinical studies, a definite evaluation of the efficacy of SR and PA in the treatment of BPH related LUTS is actually difficult for methodological reasons. Current data provides no clear evidence of clinical superiority of phytotherapy over conventional treatment. However, combination of SR and PA with other medications can offer significant improvements of urinary status while having a favourable safety profile and for this reason may be considered a viable therapy for treating LUTS in certain groups of patients.

Περίληψη

ΕΙΣΑΓΩΓΗ/ΣΚΟΠΟΣ: Το εκχύλισμα των Serenoa repens (SR) και Pygeum Africanun (PA) διαθέτει αντιφλεγμονώδεις, αντιανδρογονικές και αντιπολλαπλασιαστικές ιδιότητες. Για το λόγο αυτό έχει αποτελέσει αντικείμενο έρευνας για την θεραπεία της υπερτροφίας του προστάτη. Σκοπός αυτής της μελέτης είναι να παρουσιάσει την τρέχουσα γνώση πάνω σε αυτό το θέμα.

ΜΕΘΟΔΟΙ: Πραγματοποιήθηκε μια μη συστηματική έρευνα σε ηλεκτρονικές βιβλιοθήκες για κλινικές δοκιμές, πειραματικές μελέτες και συστηματικές ανασκοπήσεις θέμα χρησιμοποιώντας τους όρους: «προστάτης», «καλοήθης υπερτροφία του προστάτη», «συμπτώματα κατώτερου ουροποιητικού» σε συνδυασμό με τις λέξεις: «φυτοθεραπεία», «Saw palmetto», «Serenoa repens», «Serenoa serrulata», «Pygeum africanum», «Prunus Africana» σε διάφορους συνδυασμούς.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Στην βιβλιογραφία υπάρχει επαρκής αριθμός μελετών για το SR στην θεραπεία των συμπτωμάτων της καλοήθους υπερτροφίας. Οι περισσότερες από αυτές εξετάζουν το ρόλο του ως πρόσθετο σε άλλους παράγοντες. Λίγες μελέτες έχουν δημοσιευθεί μέχρι σήμερα για το PA. Σχεδόν όλες εξετάζουν το ρόλο του ως μονοθεραπεία. Σύμφωνα με αυτήν την έρευνα, δεν υπάρχουν σαφή στοιχεία κλινικής ανωτερότητας της φυτοθεραπείας σε σχέση με τις συμβατικές φαρμακοθεραπείες. Ορισμένες κλινικές δοκιμές που χρησιμοποιούν το SR συνδυαστικά με άλλα φυτοθεραπευτικά ή με συμβατικά φάρμακα ανέδειξαν μια ισχυρή συνεργική επίδραση. Από την άλλη πλευρά αυτό στερείται ορισμένων θεραπευτικών ιδιοτήτων του PA.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Ο συνδυασμός SR με το PA και άλλα φυτοθεραπευτικά μπορεί να προσφέρει σημαντικές βελτιώσεις στην λειτουργία του ουροποιητικού συστήματος ενώ έχει ευνοϊκό προφίλ ασφάλειας και γι 'αυτό το λόγο μπορεί να θεωρηθεί ως μια βιώσιμη θεραπεία σε ορισμένες κατηγορίες ασθενών.

Λέξεις ευρετηριασμού

**φυτοθεραπεία,
Serenoa repens,
Pygeum Africanum**

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