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Nutraceuticals in Prostate Disease: The Urologist's Role
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Table 1

Phytotherapies Used for Benign Prostatic Hyperplasia

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

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

SERENOA

Cochrane Database Syst Rev. 2002;(3):CD001423.
Serenoa repens for benign prostatic hyperplasia.
Wilt T[1], Ishani A, Mac Donald R.

Abstract

BACKGROUND:
Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. The extract of the American saw palmetto or dwarf palm plant, Serenoa repens (also known by its botanical name of Sabal serrulatum), is one of the several phytotherapeutic agents available for the treatment of BPH.

OBJECTIVES:
This systematic review aimed to assess the effects of Serenoa repens in the treatment of LUTS consistent with BPH.

SEARCH STRATEGY:
Trials were searched in computerized general and specialized databases (MEDLINE, EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting manufacturers and researchers.

SELECTION CRITERIA:
Trials were eligible if they (1) randomized men with BPH to receive preparations of Serenoa repens (alone or in combination) in comparison with placebo or other BPH medications, and (2) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements. Eligibility was assessed by at least two independent observers.

DATA COLLECTION AND ANALYSIS:
Information on patients, interventions, and outcomes was extracted by at least two independent reviewers using a standard form. The main outcome measure for comparing the effectiveness of Serenoa repens with placebo or other BPH medications was the change in urologic symptom scale scores. Secondary outcomes included changes in nocturia and urodynamic measures. The main outcome measure for side effects was the number of men reporting side effects.

MAIN RESULTS:
In this update, 3 new trials involving 230 additional men (7.8%) have been included. 3139 men from 21 randomized trials lasting 4 to 48 weeks were assessed. 18 trials were double-blinded and treatment allocation concealment was adequate in 11 studies. Compared with placebo, Serenoa repens improved urinary symptom scores, symptoms, and flow measures. The weighted mean difference (WMD) for the urinary symptom score was -1.41 points (scale range 0-19), (95%CI = -2.52, -0.30, n = 1 study) and the risk ratio (RR) for self rated improvement was 1.76 (95%CI = 1.21, 2.54, n = 6 studies). The WMD for nocturia was -0.76 times per evening (95%CI = -1.22, -0.32; n = 10 studies). The WMD for peak urine flow was 1.86 ml/sec (95%CI = 0.60, 3.12, n = 9 studies). Compared with finasteride, Serenoa repens produced similar improvements in urinary symptom scores (WMD = 0.37 IPSS points (scale range 0-35), 95%CI = -0.45, 1.19, n = 2 studies) and peak urine flow (WMD = -0.74 ml/sec, 95%CI = -1.66, 0.18, n = 2 studies). Adverse effects due to Serenoa repens were mild and infrequent. Withdrawal rates in men assigned to placebo, Serenoa repens or finasteride were 7%, 9%, and 11%, respectively.

REVIEWER'S CONCLUSIONS:
The evidence suggests that Serenoa repens provides mild to moderate improvement in urinary symptoms and flow measures. Serenoa repens produced similar improvement in urinary symptoms and flow compared to finasteride and is associated with fewer adverse treatment events. The long term effectiveness, safety and ability to prevent BPH complications are not known. The results of this update are in agreement with our initial review.

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Fitoterapia in urologia

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Introduzione

Negli ultimi anni il numero di coloro che scelgono di curarsi con prodotti “naturali” o “alternativi” è cresciuto costantemente. Molti pazienti si rivolgono alle terapie naturali perché intolleranti o allergici ad alcuni farmaci o, a volte, per la convinzione, per lo più errata, che il prodotto naturale sia comunque meno dannoso ed esente da effetti collaterali o tossici per chi lo assume. D’altra parte i medici si avvicinano alle cosiddette medicine complementari o “non convenzionali” spinti dalla curiosità scientifica, dal numero sempre maggiore di pazienti che vi fanno autonomamente ricorso e dalla crescente attenzione dimostrata verso tali prodotti, o trattamenti, da parte dei media. La medicina moderna trae le sue origini dall’uso secolare delle piante medicinali, gran parte dei principi attivi dei farmaci usati attualmente derivano, infatti, da queste e tutt’oggi si giunge alla scoperta di nuove molecole studiando l’uso delle piante nell’ambito delle medicine tradizionali. Anche per questo l’interesse per i prodotti a base di ingredienti vegetali da parte delle aziende farmaceutiche e delle Istituzioni è grande. Al proposito le autorità sanitarie di tutto il mondo, attraverso l’Organizzazione Mondiale della Sanità (OMS), prestano la loro attenzione alle piante medicinali, cercando di selezionare quelle attive, che presentano un rapporto rischio/beneficio favorevole, regolamentando il settore normativo e promuovendone un uso terapeutico su basi scientifiche.

L’urologia, dal canto suo, è da decadi in prima linea nell’uso dei fitoterapici: riteniamo pertanto utile fornire un moderno inquadramento normativo ed applicativo sulla fitoterapia in urologia. Questa review si basa sulle normative vigenti in Italia e sulle evidenze scientifiche. Serenoa repens (Saw palmetto o Sabal serrulata (Michaux) Nichols, frutto) La pianta, della famiglia delle Palmeae, è originaria della parte meridionale degli Stati Uniti dove cresce al limite delle foreste di pini e sulle dune semisabbiose dalla Carolina alla California, in posizione soleggiata. Era utilizzata dagli indiani della Florida per curare numerosi disturbi urologici. Costituenti e meccanismo d’azione. La “droga vegetale” è costituita dal frutto maturo essiccato, ricchissimo di acidi grassi a catena media: acido oleico, laurico, miristico, linoleico, linolenico, palmitico, caprilico e caprico, per 2/3 in forma libera e per 1/3 esterificati. Sono presenti poi steroli, prevalentemente L-sitosterolo e il suo 3-glucoside, campestrolo e stigmasterolo; trigliceridi, triterpenio, polisaccaridi, flavonoidi, olio essenziale e acido antranilico (2). Viene impiegato generalmente l’estratto lipido-sterolico che contiene dall’85% al 95% di acidi grassi (4). Sebbene il meccanismo d’azione non sia ancora del tutto chiarito, l’estratto ha dimostrato un effetto antiandrogenico, dovuto principalmente alla componente fitosterolica e di acidi grassi. L’effetto si esplica soprattutto attraverso l’inibizione dell’enzima 5-alfa-reduttasi che converte il testosterone in diidrotestosterone (DHT). Sembra inoltre che i costituenti della droga vegetale si leghino ai recettori per gli androgeni situati nel tessuto prostatico e nel prepurzio, riducendo così il legame del testosterone. Questo effetto antiandrogenico avviene selettivamente nel tessuto prostatico, senza influenzare la concentrazione di testosterone, LH e FSH nel plasma e senza disturbare il sistema degli ormoni sessuali (18). L’estratto di Serenoa repens è in grado di inibire, in vitro, gli effetti della prolattina sulla conduttanza del potassio, sulla protein chinasi C e sulle concentrazioni intracellulari di Ca+ in cellule ovariche di hamster. Ciò potrebbe suggerire una sua azione di inibizione sulla proliferazione del tessuto prostatico indotta dalla prolattina (19). Inoltre l’estratto di Serenoa repens riduce in modo statisticamente significativo i livelli dell’Epidermal Growth Factor (EGF) nel tessuto prostatico di pazienti portatori di IPB (20). Ciò indica che l’estratto di Serenoa repens può inibire la crescita delle cellule prostatiche epiteliali indotta da fattori di crescita.

La droga vegetale presenta anche un’azione antiflogistica che sembra dovuta ai polisaccaridi presenti nel fitocomplesso. Un certo ruolo potrebbe essere svolto anche dai fitosteroli che sarebbero capaci di inibire la fosfolipasi A2 e di conseguenza la trasformazione dell’acido arachidonico in prostaglandine ad azione flogogena ed in leucotrieni. Recenti ricerche indicano che l’estratto lipidico della droga vegetale inibisce anche la 5-lipo-ossigenasi e in parte anche la ciclo-ossigenasi.

Dose giornaliera

1-2 g di droga vegetale o 320 mg di estratto lipofilo al giorno, il trattamento può essere proseguito senza limitazione, secondo necessità.

Controindicazioni ed effetti avversi

Nessuna controindicazione nota. In alcuni casi può provocare epigastralgie, talvolta con senso di nausea (2).

Interazioni

Non segnalate.

Studi clinici
Una metanalisi della Cochrane del 2005 ha analizzato 18 studi clinici controllati, per un totale di 2939 pazienti di cui circa 1100 verso placebo e circa 1800 verso farmaco (21). In alcuni studi la Serenoa repens era associata con altri fitoterapici. È risultato che i soggetti trattati con l'estratto avevano avuto un miglioramento della sintomatologia rispetto a quelli che avevano ricevuto il placebo, in particolare miglioramenti statisticamente significativi riguardo la nicturia, il flusso massimo urinario, il residuo post-minzionale.
Debruyne in uno studio randomizzato, a 12 mesi, ha paragonato l'effetto dell'estratto lipido-sterolico di Serenoa repens (Permixon) e la tamsulosina (22). Sono stati arruolati 704 pazienti con un International Prostate Symptom Score (IPSS) >0 = a 10, che hanno ricevuto 320 mg/die di estratto di Serenoa repens o 0.4 mg/die di tamsulosina per 1 anno. Si valutavano il punteggio dell'IPSS, il volume prostatico e l'attività sessuale pre e post terapia. Lo studio non ha rilevato differenze significative tra tamsulosina ed estratti di Serenoa repens nei punteggi di valutazione dei sintomi e nel picco di flusso urinario a 12 mesi. Entrambi i prodotti erano ben tollerati, tuttavia i disturbi di eiaculazione erano più frequenti con la tamsulosina. Il limite dello studio è la mancanza di un gruppo di controllo con placebo.
Uno studio randomizzato che ha coinvolto 352 soggetti non ha rilevato differenze significative nei punteggi dell'IPSS fra tamsulosina e tamsulosina più estratti di Serenoa repens (miglioramento 5.2 con tamsulosina vs 6 con tamsulosina più Serenoa repens; valore di P riportato come non significativo). Sulla base di questi dati Clinical Evidence (scheda aggiornata a maggio 2005) ha classificato gli estratti di Serenoa repens come "probabilmente utili" nel trattamento dell'IPB (16). Non ci sono differenze significative nei sintomi tra estratti di Serenoa repens e tamsulosina o finasteride (21). Un altro studio randomizzato non ha rilevato differenze significative nei sintomi fra estratti di Serenoa repens più tamsulosina e solo tamsulosina.
Una metanalisi pubblicata nel 2004 ha analizzato la letteratura clinica esistente sull'azione di Serenoa repens in pazienti affetti da ipertrofia prostatica benigna (23). Sono stati analizzati 14 studi clinici controllati e 3 studi clinici in aperto, che hanno coinvolto 4280 pazienti. Gli endpoints primari erano il flusso urinario massimo e la nicturia. Si è notato che Serenoa repens causava una riduzione nell'IPSS di 4.78, con un aumento del flusso urinario massimo di 2.22 mL/s versus 1.20 ottenibile col placebo. Il placebo causava una riduzione delle minzioni notturne di 0.63, mentre Serenoa repens portava ad un valore 1.01 ($p<0.001$). La metanalisi conclude affermando che Serenoa repens è significativamente migliore del placebo nel ridurre la nicturia e nell'aumentare il flusso urinario massimo, senza causare rilevanti effetti collaterali.

QUERCETINA

QUERCETIN IN MEN WITH CATEGORY III CHRONIC PROSTATITIS: A PRELIMINARY PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract
Objectives. The National Institutes of Health (NIH) category III chronic prostatitis syndromes (nonbacterial chronic prostatitis and prostatodynia) are common disorders with few effective therapies. Bioflavonoids have recently been shown in an open-label study to improve the symptoms of these disorders in a significant proportion of men. The aim of this study was to confirm these findings in a prospective randomized, double-blind, placebo-controlled trial.
Methods. Thirty men with category IIIa and IIIb chronic pelvic pain syndrome were randomized in a double-blind fashion to receive either placebo or the bioflavonoid quercetin 500 mg twice daily for 1 month. The NIH chronic prostatitis symptom score was used to grade symptoms and the quality-of-life impact at the start and conclusion of the study. In a follow-up unblind, open-label study, 17 additional men received 1 month of a supplement containing quercetin, as well as bromelain and papain (Prosta-Q), which enhance bioflavonoid absorption.
Results. Two patients in the placebo group refused to complete the study because of worsening symptoms, leaving 13 placebo and 15 bioflavonoid patients for evaluation in the blind study. Both the quercetin and placebo groups were similar in age, symptom duration, and initial symptom score. Patients taking placebo had a mean improvement in NIH symptom score from 20.2 to 18.8 (not significant), while those taking the bioflavonoid had a mean improvement from 21.0 to 13.1 (P ! 0.003). Twenty percent of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25%. In the 17 patients who received Prosta-Q in the open-label study, 82% had at least a 25% improvement in symptom score.
Conclusions. Therapy with the bioflavonoid quercetin is well tolerated and provides significant symptomatic improvement in most men with chronic pelvic pain syndrome.

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Randomised, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia. Beta-sitosterol Study Group.

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Abstract
Medical treatments have become available for benign hypertrophy of the prostate, including alpha-receptor blocking agents and 5-alpha-reductase inhibitors. Drugs derived from plants, for which no precise mechanism of action has been described, are widely used for this purpose in Europe. In a randomised, double-blind, placebo-controlled multicentre study, 200 patients (recruited between April and October 1993) with symptomatic benign prostatic hyperplasia were treated with either 20 mg beta-sitosterol (which contains a mixture of phytosterols) three times per day or placebo. Primary end-point was a difference of modified Boyarsky score between treatment groups after 6 months; secondary end-points were changes in International Prostate Symptom Score (IPSS), urine flow, and prostate volume. Modified Boyarsky score decreased significantly with a mean of -6.7 (SD 4.0) points in the beta-sitosterol-treated group versus -2.1 (3.2) points in the placebo group $p < 0.01$. There was a decrease in IPSS (-7.4 [3.8] points in the beta-sitosterol-treated group vs -2.1 [3.8] points in the placebo group) and changes in urine flow parameters: beta-sitosterol treatment resulted in increasing peak flow (15.2 [5.7] mL/s from 9.9 [2.5] mL/s), and decrease of mean residual urinary volume (30.4 [39.9] mL from 65.8 [20.8] mL). These parameters did not change in the placebo group ($p < 0.01$). No relevant reduction of prostatic volume was observed in either group. Significant improvement in symptoms and urinary flow parameters show the effectiveness of beta-sitosterol in the treatment of benign prostatic hyperplasia.

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Management of Benign Prostatic Hyperplasia: Could Dietary Polyphenols Be an Alternative to Existing Therapies?

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Abstract

The incidence of benign prostatic hyperplasia (BPH) is gradually on the increase. While conventional drugs such as the α1-adrenergic receptor antagonists and 5α-reductase inhibitors have been found to be useful in the treatment of BPH, the adverse side effects associated with their usage, have led to increased search for alternative means of managing this disease. Furthermore, although surgery has also been suggested to be a sure method, the cost and risks associated with it excludes it as a routine treatment. Dietary polyphenols have gained public interest in recent times due to their roles in the prevention of various diseases that implicate free radicals/reactive oxygen species. However, their roles in the management of BPH have not been explored. Hence, this review on their prospects in the management of BPH and their mechanisms of action. Literature search was carried out in several electronic data bases such as PubMed, Google Scholar, Medline, Agora, and Hinari from1970 to 2017 to identify the current status of knowledge on this concept. The findings from these data bases suggest that while dietary polyphenols may not replace the need for the existing therapies in the management of BPH, they hold promise in BPH management which could be explored by researchers working in this field.

Quercetin for Chronic Prostatitis/Chronic Pelvic Pain Syndromes

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KEYWORDS: Prostatitis, Chronic pelvic pain syndrome, Quercetin, Phytotherapy
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The prostatitis syndromes are some of the most prevalent conditions in urology but also the most poorly understood. Although little controversy exists over the therapy for documented acute or chronic bacterial infections, most patients fall into the nonbacterial or prostatodynia group, now referred to as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) or National Institutes of Health (NIH) category III. The origin, natural history, and appropriate therapy for these patients are unclear. Patient and physician dissatisfaction with these syndromes is high, making it an area ripe for patient interest in nontraditional and alternative therapies. The polyphenolic bioflavonoid quercetin is a phytotherapeutic compound that has antiinflammatory and antioxidant properties. Its mechanism of action could be of value for several potential pathways in the origin of CP/CPPS. This article discusses the current understanding of CP/CPPS and how treatment with quercetin can be used alone or as part of multimodal therapy.

EFFICACY OF QUERCETIN IN TREATMENT OF BENIGN PROSTATIC HYPERPLASIA IN A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL IN IRAN — 2011

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Objectives: Benign prostatic hyperplasia (BPH) is an enlargement of the prostate gland that occurs commonly as men age. Nowadays, many treatments for this disease are used, but these treatments are not quite effective yet. In this study, we assessed the efficacy of quercetin drop in alleviating BPH symptoms.
Method: In a double-blind randomized clinical trial, 200 men over 50 years with BPH symptoms who were hospitalized in Ahvaz hospitals were randomly divided in two groups and treated with quercetin (40 drop, TDS) and placebo (40 drop, TDS). AUA symptom score, prostate-specific antigen (PSA) levels, prostate volume, post-voidal residue (PVR) by sonograms and uroflowmetry results were determined before and 3 months after treatment. Data were analyzed by SPSS software.
Results: Before treatment, there were no significant differences in age, PSA, PVR, AUA symptom score, prostate volume and uroflowmetry between the two groups. After treatment, the mean of PSA levels, prostate volume and PVR did not differ between the two groups. In the quercetin group, the mean of AUA symptom score was 4.6 less (pb.0001) and the mean of maximal urine flow rate was 3.2 ml/s more than the placebo group (pb.0001). Conclusions: According to the results of this study, it seems that quercetin drop against placebo has better effects on reduction of BPH symptoms and increases urine flow rates.

BETASITOSTEROLO

Clinical Trial

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Treatment of symptomatic benign prostatic hyperplasia with beta-sitosterol: an 18-month follow-up

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Abstract

Objectives: To determine the long-term effects of phytotherapy with beta-sitosterol (the trade name for beta-sitosterol used in this study is Harzol(R)) for symptomatic benign prostatic hyperplasia (BPH). Patient and methods At 18 months after enrolment in a 6-month multicentre double-blind placebo-controlled clinical trial with beta-sitosterol (reported previously), patients were re-evaluated using the modified Boyarsky score, the International Prostate Symptom Score and quality-of-life index, the maximum urinary flow rate (Qmax) and postvoid residual urine volume (PVR). In this open extension of the original trial (after 6 months of treatment or placebo), patients were free to chose their further treatment for BPH.

Results: In all, 117 patients (59%) were eligible for analysis during the follow-up. Of the formerbeta-sitosterol group, 38 patients who continued beta-sitosterol treatment had stable values for all outcome variables between the end of the double-blind study and after 18 months of follow-up. The 41 patients choosing no further therapy had slightly worse symptom scores and PVR, but no changes in Qmax. Of the former placebo group, 27 patients who started beta-sitosterol after the double-blind trial improved to the same extent as the treated group for all outcome variables. The 18 patients choosing no further therapy showed no signs of improvement.

Conclusion: The beneficial effects of beta-sitosterol treatment recorded in the 6-month double-blind trial were maintained for 18 months. Further clinical trials should be conducted to confirm these results before concluding that phytotherapy with beta-sitosterol is effective.