

Literaturservice I-GAP

BPH and Sabal serulata

1: Planta Med 2009 Jan;

Analysis of the Hydrodistillate from the Fruits of *Serenoa repens*.

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The chemical composition of the hydrodistillate won by steam distillation from the fruits of *SERENOA REPENS* (W. Bartram), a well known phytomedicine against benign prostatic hyperplasia (BPH), was analyzed by GC-MS. It resulted in the identification of 144 steam-volatile components including about 100 structures which have not been described as constituents of the fruits from *S. REPENS* so far. The main component detected was lauric acid (40.4 %).

2: Actas Urol Esp 2008 Oct;32(9):916-25

[Economic evaluation of medical treatment of benign prostatic hyperplasia (BPH) in the specialised care setting in Spain. Application to the cost-effectiveness of two drugs frequently used in its treatment]

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OBJECTIVES: To develop a pharmacoeconomic study in order to know the average cost of BPH diagnosis and follow-up in Spain in the Urology Department setting from the perspective of the public health system, considering two frequently used drugs in the Spanish Healthcare environment, an alpha-blocker (tamsulosin) and the lipido-sterolic extract of *Serenoa repens* (Permixon). **MATERIAL AND METHODS:** Direct healthcare costs of BPH diagnosis and treatment were determined for each clinical stage according to the International Prostate Symptom Score (IPSS): mild, moderate and severe. Data on the usage and unit costs of healthcare resources were obtained from a semi-structured interview with clinical experts. The clinical efficacy of the medical treatments was obtained from the PERMAL clinical study, where therapeutic equivalence between the two studied drugs was observed. **RESULTS:** For patients treated in the Urology Department setting, the average annual cost of diagnostic tests and medical visits related to mild, moderate or severe BPH symptoms were, respectively, Euro 124, Euro 207, and Euro 286. The average annual cost of the drugs, including adverse effects treatment, was Euro 211 for Permixon and Euro 346 for tamsulosin. **DISCUSSION:** Costs of medical care of BPH increases with symptom intensity. Pharmacological treatment makes up a significant part of the disease's cost. According to the model used, treatment with Permixon is considerably more cost-effective than with tamsulosin, offering average yearly savings of Euro 135 per patient.

3: Pharmacology 2008;82(4):270-5

Comparison of the potency of different brands of *Serenoa repens* extract on 5 α -reductase types I and II in prostatic co-cultured epithelial and fibroblast cells.

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BACKGROUND: *Serenoa repens* extract is the phytotherapeutic agent most frequently used for the treatment of the urological symptoms caused by benign prostatic hyperplasia. There are many extracts in the market and each manufacturer uses different extraction processes; for this reason, it's possible that one product is not equivalent to another. The aim of this study was to compare the activity of different extracts of *Serenoa repens* marketed in Italy. **METHODS:** The following extracts were tested on 10 day co-cultured epithelial and fibroblast cells by a 5 α -reductase activity assay: Permixon, Saba, Serpens, Idiprost, Prostamev, Profluss and Prostil. In order to assess the variability in *Serenoa repens* products, 2 different batches for each brand were evaluated. **RESULTS AND CONCLUSIONS:** All extracts tested, albeit variably, are able to inhibit both isoforms of 5 α -reductase. However, the potency of the extracts appears to be very different, as well as the potencies of 2 different batches of the same extract. This is probably due to qualitative and quantitative differences in the active ingredients. So, the product of each company must be tested to evaluate the clinical efficacy and bioactivity.

4: Arch Ital Urol Androl 2008 Jun;80(2):65-78

Activity of *Serenoa repens*, lycopene and selenium on prostatic disease: evidences and hypotheses.

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An increasing number of preclinical data, epidemiological evidences and clinical trials point to a potential role of natural compounds like herbal extracts, carotenoids and specific metals in the prevention and/or treatment of different prostate conditions, like hyperplasia, inflammation, cancer. The present article reviews some of the major and most recent findings on the therapeutic properties of three of the most widely used compounds, i.e. *Serenoa repens*, lycopene and selenium. Although the mechanism of action of these compounds ought to be further characterized by focused investigation, it appears that a common feature of these agents may be a dual activity on proliferative disorders as well as on inflammatory conditions at the level of the prostate gland.

5: Bull Exp Biol Med 2007 Nov;144(5):699-701

Comparative study of pharmacological activity of afala on the model of hormone-induced prostatitis in rats.

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Afala (ultralow-dose antibodies to prostate-specific antigen) injected for 60 days to rats with hormone-induced prostatitis caused by sulphiride prevented the development of prostatic hyperplasia and reduced the severity of histological changes. The effect of Afala was superior to that of the reference drug (*Serenoa repens* extract).

6: Complement Ther Med 2008 Jun;16(3):147-54

A detailed safety assessment of a saw palmetto extract.

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BACKGROUND: Saw palmetto is commonly used by men for lower-urinary tract symptoms. Despite its widespread use, very little is known about the potential toxicity of this dietary supplement. METHODS: The Saw palmetto for Treatment of Enlarged Prostates (STEP) study was a randomized clinical trial performed among 225 men with moderate-to-severe symptoms of benign prostatic hyperplasia, comparing a standardized extract of the saw palmetto berry (160 mg twice daily) with a placebo over a 1-year period. As part of this study, detailed data were collected on serious and non-serious adverse events, sexual functioning, and laboratory tests of blood and urine. Between-group differences were assessed with mixed-effects regression models. RESULTS: There were no significant differences observed between the saw palmetto and placebo-allocated participants in the risk of suffering at least one serious adverse event (5.4% vs. 9.7%, respectively; $p=0.31$) or non-serious symptomatic adverse event (34.8% vs. 30.1%, $p=0.48$). There were few significant between-group differences in sexual functioning or for most laboratory analyses, with only small differences observed in changes over time in total bilirubin ($p=0.001$), potassium ($p=0.03$), and the incidence of glycosuria (0% in the saw palmetto group vs. 3.7% in the placebo group, $p=0.05$). CONCLUSIONS: Despite careful assessment, no evidence for serious toxicity of saw palmetto was observed in this clinical trial. Given the sample size and length of this study, however, these data do not rule out potential rare adverse effects associated with the use of saw palmetto.

7: Tidsskr Nor Laegeforen 2008 May;128(11):1293-4

[*Serenoa repens* in benign prostatic hyperplasia]

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Serenoa repens is one of many herbal products used to treat benign prostatic hyperplasia. The treatment has been studied extensively, but the methodological quality has often been poor. Metaanalysis of early studies

indicate that the treatment may have favourable effects on patients with benign prostatic hyperplasia, but more recent investigations of better methodological quality have questioned these results. The available documentation does not support use of products containing *Serenoa repens* for these patients. *Serenoa repens* is associated with mild adverse effects comparable to that of placebo.

8: J Urol 2008 Jun;179(6):2119-25

Phytotherapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia.

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PURPOSE: We examined the available data from clinical trials for certain botanicals used for lower urinary tract symptoms secondary to benign prostatic hyperplasia, including *Serenoa repens* (saw palmetto), *Pygeum africanum* (African plum), *Secale cereale* (rye pollen) and *Hypoxis rooperi* (South African star grass). **MATERIALS AND METHODS:** MEDLINE and The Cochrane Library searches were done in June 2007 using the terms benign prostatic hyperplasia, lower urinary tract symptoms, phytotherapy, saw palmetto, *Serenoa*, *Permixon*, *Pygeum africanum*, *Tadenan*, *Cernilton*, *Cernitin* and *Hypoxis*. Search results were assessed for relevance and the inclusion of placebo controlled trials. **RESULTS:** Two systematic reviews and 3 clinical trials were examined in the evaluation of *Serenoa repens*. Data from the systematic reviews showed an improvement in flow rates and symptoms. The results of 1 clinical trial were equivocal and the remaining 2 trials clearly showed equivalence to placebo. Systematic reviews were used in the evaluation of *P. africanum*, *Secale cereale* and *Hypoxis rooperi*. *P. africanum* and *H. rooperi* showed an improvement in flow rates and symptoms compared to placebo, while *S. cereale* showed an improvement in symptoms but not flow rates compared to placebo. **CONCLUSIONS:** Most clinical trials of investigating the efficacy of botanicals suffer from well documented methodological flaws. Saw palmetto has been clearly shown as comparable to placebo in a trial of sound methodology. While preliminary results appear promising, to our knowledge the remaining botanicals have yet to be evaluated in a trial of similar quality.

10: Int Urol Nephrol 2007;39(4):1137-46

Efficacy and safety of a combination of Sabal and Urtica extract in lower urinary tract symptoms--long-term follow-up of a placebo-controlled, double-blind, multicenter trial.

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In an open-label extension of a randomized, double-blind clinical trial, the long-term efficacy and tolerability of a fixed combination of 160 mg Sabal fruit extract WS 1473 and 120 mg Urtica root extract WS 1031 per

capsule (PRO 160/120) were investigated in elderly men with moderate or severe lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH). Two hundred and fifty-seven patients were randomly treated with 2 x 1 capsule/day PRO 160/120 or placebo for 24 weeks, followed by a 24-week control period and a 48-week follow-up period in which all patients received PRO 160/120. Efficacy measures included the assessment of LUTS [International Prostate Symptom Score ((I-PSS) self-rating questionnaire) and uroflow and sonographic parameters. Two hundred and nineteen subjects participated in the follow-up. Between baseline and end of observation (week 96) the I-PSS total score was reduced by 53% ($P < 0.001$), peak and average urinary flow increased by 19% ($P < 0.001$), and residual urine volume decreased by 44% ($P = 0.03$). The incidence of adverse events during follow-up was one in 1,181 treatment days; in only one event a causal relationship with intake of PRO 160/120 could not be excluded. Treatment with PRO 160/120 thus provides a clinically relevant benefit over a period of 96 weeks.

11: Arch Ital Urol Androl 2007 Jun;79(2):84-92

Reduction of PSA values by combination pharmacological therapy in patients with chronic prostatitis: implications for prostate cancer detection.

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We identified from our clinical database a total of 471 patients affected by cat. II chronic bacterial prostatitis (CBP), cat. III (IIIa and IIIb) chronic pelvic pain syndrome (CP/CPSP), or cat. IV asymptomatic inflammatory prostatitis (AIP), according to NIH criteria. 132 intent-to-treat patients, showing levels of PSA $>$ or $= 4$ ng/mL, were subjected to a 6-week course of combination pharmacological therapy with 500 mg/day ciprofloxacin, 500 mg/day azithromycin (3 days/week), 10 mg/day alfuzosin and 320 mg b.i.d. *Serenoa repens* extract. At the end of treatment, 111 per-protocol patients belonging to all categories of prostatitis showed a total 32.5% reduction of PSA levels. In the same group, 66 patients (59.4%) showed "normalization" of PSA values under the 4 ng/mL limit. Patients affected by cat. IIIb CP/CPSP showed the highest PSA reduction and normalization rates (40% and 68.4%, respectively). Follow-up data show that, after a marked, significant reduction at completion of therapy, PSA levels, urine peak flow rates and NIH-CPSI symptom scores remained constant or decreased throughout a period of 18 months in patients showing normalization of PSA values. Prostatic biopsy was proposed to 45 patients showing persistently high PSA values ($>$ or $= 4$ ng/mL) at the end of treatment. Fourteen patients rejected biopsy; of the remaining 31, 10 were diagnosed with prostate cancer. Four months after a first biopsy, a second biopsy was proposed to the 21 patients with a negative first diagnosis and persistently elevated PSA levels. Three patients rejected the procedure; of the remaining 18, four were diagnosed with prostatic carcinoma. In summary, combination pharmacological therapy decreased the number of patients undergoing prostatic biopsy from 111 to 45. Normalization of PSA values in 59.4% of patients--not subjected to biopsy--increased the prostate cancer detection rate from 12.6% (14/111) to 31.1% (14/45). The reduction of PSA after a 6-week course of therapy was calculated in patients affected by cat. II, IIIa, IIIb and IV prostatitis after stratification with respect to the concomitant presence or absence of benign prostatic hyperplasia (BPH). PSA was reduced by 41% in cat. II CBP patients without BPH, compared to a

12.7% reduction in patients affected by BPH. Cat. IIIa CP/CPPS patients without BPH showed a 58.3% reduction of PSA levels, compared to a 20.7% reduction observed in CP/CPPS/BPH patients. These data show that the presence of BPH may prevent the reduction of PSA induced by combination pharmacological therapy, and suggest that care has to be taken in the adoption of PSA as a marker of therapeutic efficacy in the presence of confounding factors like BPH. PSA should in our opinion be used as a significant component of a strategy integrating multiple diagnostic approaches.

13: Anticancer Res 2007 Mar-Apr;27(2):873-81

Evaluation of cell death caused by an ethanolic extract of *Serenoa repens* fructus (Prostasan) on human carcinoma cell lines.

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BACKGROUND: Phytotherapy is a third approach for treating lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). The lipido-sterolic extract of the fruit of *Serenoa repens* is one of the more widely used phytotherapeutic agents in this regard. MATERIALS AND METHODS: The effect of an ethanolic extract of *S. repens* (10-1000 microg/ml) was tested in hormone-sensitive LNCaP, MCF-7 and hormone-insensitive DU 145, MDA MB231 prostate, breast carcinoma cell lines, renal Caki-1, urinary bladder J82, colon HCT 116 and lung A 549 cancer cells. Its cell growth inhibitory and apoptosis-inducing effects were tested using WST-1 assay and flow cytometry (Annexin V/PI stain) and/or by colorimetric assay (APOPercentage assay). RESULTS: The *S. repens* extract induced a dose-dependent antiproliferative effect on all human malignant cells tested, with GI50 values between 107 and 327 pmicro/ml. In hormone-sensitive prostate LNCaP and breast MCF-7 cell lines, the effect of extract expressed in GI50 was 2.2- and 2.5-fold more potent ($p < 0.01$) than in hormone-insensitive DU 145 and MDA MB231 cells. The proportion of apoptotic cells, except in A549 cells, lay between 22.5-36.3%. *S. repens* extract did not induce apoptosis in lung cancer A 549 cells. CONCLUSION: This study showed that the antiproliferative effect exerted by the ethanolic extract of *S. repens* is at least triggered by induction of apoptosis. These in vitro data provide some information that may be useful for clinical use and render *S. repens* extract an interesting tool for new applications.

14: Int Urol Nephrol 2007;39(3):879-86

A prospective study of the efficacy of *Serenoa repens*, tamsulosin, and *Serenoa repens* plus tamsulosin treatment for patients with benign prostate hyperplasia.

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INTRODUCTION: Increasing attention has been focused on the use of phytotherapeutic agents to alleviate the symptoms of benign prostatic hyperplasia (BPH) in recent times. The best described and studied phytotherapeutic agent is *Serenoa repens* (SR). MATERIALS AND METHODS: This prospective study was designed to have 3 arms including SR 320 mg per day (N = 20), Tamsulosin (TAM) 0.4 mg per day (N = 20) and SR + TAM (N = 20) to reveal the superiority or equivalence between these treatment regimens in BPH. RESULTS: The groups were not statistically different with regard to increase in maximal urinary flow rate (Q (max)) and decrease in International Prostate Symptom Score (I-PSS) (P > 0.05). No adverse effect was detected in SR therapy group. CONCLUSION: Treatment of BPH by both SR and TAM seems to be effective alone. None of them had superiority to another and additionally, combined therapy (SR + TAM) does not provide extra benefits. Furthermore SR is a well-tolerated agent that can be used alternatively in the treatment of LUTS due to BPH.

15: Integr Cancer Ther 2006 Dec;5(4):362-72

Effects of homeopathic preparations on human prostate cancer growth in cellular and animal models.

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The use of dietary supplements for various ailments enjoys unprecedented popularity. As part of this trend, *Sabal serrulata* (saw palmetto) constitutes the complementary treatment of choice with regard to prostate health. In homeopathy, *Sabal serrulata* is commonly prescribed for prostate problems ranging from benign prostatic hyperplasia to prostate cancer. The authors' work assessed the antiproliferative effects of homeopathic preparations of *Sabal serrulata*, *Thuja occidentalis*, and *Conium maculatum*, in vivo, on nude mouse xenografts, and in vitro, on PC-3 and DU-145 human prostate cancer as well as MDA-MB-231 human breast cancer cell lines. Treatment with *Sabal serrulata* in vitro resulted in a 33% decrease of PC-3 cell proliferation at 72 hours and a 23% reduction of DU-145 cell proliferation at 24 hours (P<.01). The difference in reduction is likely due to the specific doubling time of each cell line. No effect was observed on MDA-MB-231 human breast cancer cells. *Thuja occidentalis* and *Conium maculatum* did not have any effect on human prostate cancer cell proliferation. In vivo, prostate tumor xenograft size was significantly reduced in *Sabal serrulata*-treated mice compared to untreated controls (P=.012). No effect was observed on breast tumor growth. Our study clearly demonstrates a biologic response to homeopathic treatment as manifested by cell proliferation and tumor growth. **This biologic effect was (i)significantly stronger to *Sabal serrulata* than to controls and (ii)specific to human prostate cancer. *Sabal serrulata* should thus be further investigated as a specific homeopathic remedy for prostate pathology.**

16: J Soc Integr Oncol 2006;4(4):170-86

Evidence-based systematic review of saw palmetto by the Natural Standard Research Collaboration.

Ulbricht, Catherine, Basch, Ethan, Bent, Steve, Boon, Heather, Corrado, Michelle, Foppa, Ivo, Hashmi, Sadaf, Hammerness, Paul, Kingsbury, Eileen, Smith, Michael, Szapary, Philippe, Vora, Mamta, Weissner, Wendy

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Here presented is an evidence-based systematic review including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

17: Eksp Klin Farmakol 2006 Jul-Aug;69(4):66-8

[Effect of biologically active substances of animal and plant origin on prooxidant-antioxidant balance in rats with experimental prostatic hyperplasia]

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The effect of biologically active complexes of animal (prostatilen) and plant (permixon) origin on physiological indices of prostate and prooxidant-antioxidant balance in prostate and blood was studied in rats with the hyperprolactinemia-induced prostatic hyperplasia. It was shown that both prostatilen (1 mg of the total peptides per kg) and permixon (100 mg of *Serenoa repens* extract per kg) prevent increase in the prostate mass and volume, in the content of lipid hydroperoxides, and in the glutathione peroxidase activity in prostate. Prostatilen, in contrast to permixon, **normalized the content of lipid hydroperoxides (increased under hyperplasia conditions) and increases glutathione peroxidase activity (reduced under hyperplasia conditions).**

19: Curr Urol Rep 2006 Jul;7(4):260-5

Saw palmetto and lower urinary tract symptoms: what is the latest evidence?

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The use of dietary supplements for treating a wide range of health conditions has grown rapidly in the United States. In the field of men's health, the most common dietary supplement used is an extract of the berry of the saw palmetto plant, with which men commonly self-medicate in order to treat lower urinary tract symptoms. Throughout the past two decades, substantial literature has emerged examining the biologic and clinical effects of saw palmetto extracts. Several lines of evidence suggest that saw palmetto may exert physiologic effects consistent with a beneficial clinical effect on the mechanisms of benign prostatic hyperplasia. Although most clinical studies tend to suggest a modest efficacy benefit of saw palmetto, more recent studies are less consistent and the precise clinical value of saw palmetto for treating lower urinary tract symptoms remains

undefined. Overall, there appear to be few safety concerns with short-term use of this herbal medicine, although large-scale and longer-term safety studies have not been performed. Higher-quality studies are currently underway to better define the potential benefits and risks of plant-based extracts for treating symptoms related to benign prostatic hyperplasia.

21: *Phytomedicine* 2007 Feb;14(2-3):204-8

Hepatotoxicity potential of saw palmetto (*Serenoa repens*) in rats.

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Saw palmetto (*Serenoa repens* L.) is an herbal drug used to treat symptoms of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). There has been a report that a preparation containing this herb has caused cholestatic hepatitis in one person and some indications exist that it may have the potential to produce liver toxicity. The purpose of this study was to evaluate the effect of saw palmetto on rat liver function by measuring its effects on several enzymes and formation of malondialdehyde (MDA), a byproduct of lipid peroxidation. A significant increase in these parameters is considered an indication of liver toxicity. Thirty-six rats were divided into 6 groups of 6 animals each. They were treated for 2 or 4 weeks with a placebo or saw palmetto at doses of 9.14 or 22.86 mg/kg/body wt./day; that is, 2 x and 5 x the maximum recommended daily human dosages. After 2 or 4 weeks, the animals were sacrificed and blood was collected to prepare serum for enzyme assays, which were performed using commercially available kits. A portion of the liver was removed, and a homogenate prepared for the lipid peroxidation assay. Results showed no significant difference in animal body weight, enzyme activity, or MDA formation at either time or dosage level, as compared to controls. The data indicate that at the doses and time periods tested, saw palmetto did not produce any significant effect on the normal biological markers of liver toxicity.

22: *Eur Urol* 2007 Jan;51(1):207-15; discussion 215-6

The efficacy of drugs for the treatment of LUTS/BPH, a study in 6 European countries.

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OBJECTIVES: This paper profiles the usage and effectiveness of various LUTS/BPH drugs in real-life practice. **METHOD:** The TRIUMPH study recorded the treatment and outcomes of 2351 newly-presenting LUTS/BPH patients in 6 European countries over a 1-year follow-up period. At each visit the clinician recorded the treatment, co-morbidities, complications and drugs prescribed, and the patient completed an IPSS questionnaire. The results were analysed using change in IPSS as the primary outcome measure. **RESULTS:** Over the study period 74.9% of patients were prescribed medication, the majority (83% of those medicated) were prescribed only a single drug. Tamsulosin was the most commonly prescribed drug in all countries (38% of medicated cases), although with national variation from 24% in Poland to

70% in Italy. The alpha-blockers were the most effective, with a mean reduction of 6.3 IPSS points. Finasteride was slightly less effective (4.1 points). Significant improvements were seen in 43% of patients on phytotherapy with *Serenoa repens* or *Pygeum africanum* compared to 57% of those on finasteride and 68% on alpha-blockers. The only combination therapy found to produce a statistically significant improvement over the use of individual drugs was finasteride+tamsulosin (8.1 points compared to 6.7 for tamsulosin alone and 4.2 for finasteride alone). CONCLUSIONS: All drug treatments showed some improvement over watchful-waiting for most patients over the study period: the alpha-blockers were found to be the most effective. There were marked national differences in prescribing patterns, both in individual drug choice and in the use of combination therapies.

23: South Med J 2006 Jun;99(6):611-2

Saw palmetto-induced pancreatitis.

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Saw palmetto is a frequently used botanical agent in benign prostatic enlargement (BPH). Although it has been reported to cause cholestatic hepatitis and many medical conditions, Saw palmetto has not been implicated in acute pancreatitis. We report a case of a probable Saw palmetto induced acute hepatitis and pancreatitis. A 55-year-old reformed alcoholic, sober for greater than 15 years, presented with severe non-radiating epigastric pain associated with nausea and vomiting. His only significant comorbidity is BPH for which he intermittently took Saw palmetto for about four years. Physical examination revealed normal vital signs, tender epigastrium without guarding or rebound tenderness. Cullen and Gray Turner signs were negative. Complete blood count and basic metabolic profile were normal. Additional laboratory values include a serum amylase: 2,152 mmol/L, lipase: 39,346 mmol/L, serum triglyceride: 38 mmol/L, AST: 1265, ALT: 1232 and alkaline phosphatase was 185. Abdominal ultrasound and magnetic resonance cholangiography revealed sludge without stones. A hepatic indole diacetic acid scan was negative. Patient responded clinically and biochemically to withdrawal of Saw palmetto. Two similar episodes of improvements followed by recurrence were noted with discontinuations and reinstatement of Saw Palmetto. Simultaneous and sustained response of hepatitis and pancreatitis to Saw palmetto abstinence with reoccurrence on reinstatement strongly favors drug effect. "Natural" medicinal preparations are therefore not necessarily safe and the importance of detailed medication history (including "supplements") cannot be over emphasized.

24: Drugs R D 2006;7(4):233-41

Effect of D-004, a lipid extract from the Cuban royal palm fruit, on atypical prostate hyperplasia induced by phenylephrine in rats.

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BACKGROUND AND OBJECTIVE: Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that results in obstructive lower urinary tract symptoms. Saw palmetto (*Serenoa repens*), the dwarf American palm (Arecaceae family), is commonly used to treat BPH. The Cuban royal palm (*Roystonea regia*) also belongs to the Arecaceae family, and 200-400mg of D-004, a lipid extract from its fruits, administered orally for 14 days has been shown to prevent testosterone- but not dihydrotestosterone-induced prostatic hyperplasia in rats. D-004 (125-250 microg/mL) added to preparations of rat vas deferens caused a marked, dose-dependent and significant inhibition of noradrenaline-induced smooth muscle contraction, a response mediated through alpha(1)-adrenoceptors, and was more effective in these respects than Saw palmetto. However, the in vivo effects of D-004 and Saw palmetto on the hypertensive response induced by noradrenaline were modest (albeit significant), and neither treatment affected resting blood pressure or heart rate in rats. The differential effects of D-004 in in vitro and in vivo models could be related to a differential affinity for adrenoceptor subtypes or to different bioavailabilities in vascular and urogenital targets. Phenylephrine injected into rodents induces prostatic hyperplasia with all the characteristic morphological changes of the condition but does not result in enlargement of the prostate. Therefore, this phenylephrine-induced change in rat prostate tissue is called atypical prostatic hyperplasia. It serves as an in vivo model of prostatic hyperplasia induced by stimulation of alpha(1)-adrenoceptors. The objective of this study was to determine whether D-004 can inhibit induction of atypical prostatic hyperplasia by phenylephrine in rats. **METHODS:** Rats were randomly distributed into five groups (ten rats/group). One group was a negative control and received oral vehicle only. The other four groups were injected subcutaneously with phenylephrine (2 mg/kg): of these groups, one was a positive control receiving the vehicle, and the other three groups were treated with D-004 or Saw palmetto (both 400 mg/kg) or tamsulosin 0.4 mg/kg. All active treatments were given orally for 28 days. After completion of treatment, rats were placed unrestrained in metabolic cages and micturition studies were performed. The rats were later killed and their prostates removed and weighed. Prostate samples were processed for histological study, with histological changes being assessed according to a scoring system. Bodyweight was measured at baseline and at weekly intervals. **RESULTS:** Histological examination of positive control rats revealed features of atypical prostatic hyperplasia, with piling-up, papillary and cribriform patterns and budding-out of epithelial cells. Micturition assessment revealed that phenylephrine significantly lowered both the total volume of urine in 1 hour and the volume per micturition; the latter was considered the main efficacy variable. D-004 and Saw palmetto extracts significantly prevented this reduction in volume per micturition by 70.5% and 68.6%, respectively, while tamsulosin totally abolished the reduction in micturition induced by phenylephrine (100% inhibition). Tamsulosin, D-004 and Saw palmetto significantly reduced the histological changes of atypical prostatic hyperplasia induced by phenylephrine by 73.1%, 61.2% and 50.0%, respectively. **CONCLUSIONS:** Administration of D-004 resulted in marked and significant prevention of phenylephrine-induced impairment of micturition and histological changes in rat prostate. These findings indicate that, in vivo, D-004 effectively opposes these responses to phenylephrine, which are mediated through urogenital alpha(1)-adrenoceptors. In this respect, D-004 was moderately more effective than Saw palmetto, a phytotherapeutic standard used to treat BPH, but less effective than tamsulosin, a selective alpha(1A)-adrenoceptor antagonist.

Extracts from *Pygeum africanum* and other ethnobotanical species with antiandrogenic activity.

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Extracts from *Pygeum africanum*, *Serenoa repens* and *Cucurbita pepo* are used in the treatment of benign prostatic hyperplasia (BPH) and prostate cancer (PCa). The activity of the androgen receptor (AR) is known to control growth of the prostate. Here, we examined extracts of these plants for their antiandrogenic activity using an AR responsive reporter gene assay for drug discovery. A selective dichloromethane extract from the stem barks of *Pygeum africanum* revealed the highest antiandrogenic effect. Bioactivity-directed fractionation of this extract led to the isolation of N-butylbenzenesulfonamide (NBBS) indicating that extracts of the stem bark of *P. africanum* harbour androgen antagonistic activity. This compound may provide a novel approach for the prevention and treatment of BPH and human PCa.

26: *Urologia* 2006 Mar-Apr;(2):12, 14-9

[Combined extract of Sabal palm and nettle in the treatment of patients with lower urinary tract symptoms in double blind, placebo-controlled trial]

Lopatkin, N A, Sivkov, A V, Medvedev, A A, Walter, K, Schlefke, S, Avdeichuk, Iu I, Golubev, G V, Mel'nik, K P, Elenberger, N A, Engelman, U

A multicenter, prospective clinical trial was performed to study efficacy and tolerance of a compound drug PRO 160/120 in the elderly men with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). A total of 257 patients were randomized into two groups. Group 1 of 129 patients received PRO 160/120; group 2 of 128 patients received placebo. In 2-week induction blind phase of placebo the patients received for 24 weeks 1 capsule of the drug or placebo twice a day in conditions of double blind study. The double blind phase was followed by an open control period for 24 weeks when all the patients received PRO 160/120. Treatment efficacy evaluation was based on I-PSS, quality of life index, urodynamic and ultrasonography evidence. PRO 160/120 was superior to placebo by attenuating LUTS assessed by I-PSS, improved obstructive and irritative symptoms, was effective in patients with moderate and severe symptoms. Tolerance of the plant extract was good.

30: *Arzneimittelforschung* 2006;56(3):222-9

Efficacy and safety of a combination of sabal and urtica extract in lower urinary tract symptoms. A randomized, double-blind study versus tamsulosin.

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The aim of this prospective, randomized, double-blind, double-dummy, multicenter clinical trial was to investigate the efficacy and safety of PRO 160/120 (Prostagutt forte), a fixed combination preparation of 160 mg Sabal fruit extract WS 1473 and 120 mg Urtica root extract WS 1031 per capsule, in comparison to the alpha-adrenoceptor antagonist tamsulosin (CAS 106463-17-6) in lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH). 140 elderly out-patients suffering from LUTS caused by BPH, with an initial score \geq 13 points in the International Prostate Symptom Score (I-PSS), received 2 x 1 capsule/d PRO 160/120 or 1 x 0.4 mg/d tamsulosin and were treated for 60 weeks with interim visits at weeks 8, 16, 24, 36, and 48. The primary outcome measure for efficacy was the change in I-PSS total score, the percentage of patients with an I-PSS score \leq 7 points at endpoint ('responders') was analyzed as well. During 60 weeks of randomized treatment the I-PSS total score was reduced by a median of 9 points in both groups. In total, 32.4 % of the patients in the PRO 160/120 group and 27.9% in the tamsulosin group were responders (test for non-inferiority of PRO 160/120: $p = 0.034$; non-inferiority margin 10%). Both drugs were well tolerated, with one adverse event in 1514 treatment days for PRO 160/120 and one event in 1164 days for tamsulosin. The study supports non-inferiority of PRO 160/120 in comparison to tamsulosin in the treatment of LUTS caused by BPH.

31: Pol Merkur Lekarski 2005 Nov;19(113):710-5

[Modern pharmacotherapy of benign prostatic hyperplasia]

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Benign prostatic hyperplasia is the most common medical problem affecting elderly men throughout the world. With increasing awareness of health issues amongst males, the morbidity caused by this disease is not longer being accepted as just part of growing old. Until about 10 years ago, surgery was the only effective treatment for symptomatic benign prostatic hyperplasia. Now, many men suffering from this disorder may be effectively treated with a medical therapy. This article provides an overview of the efficacy and safety of 5alpha-reductase inhibitors, alpha-adrenoceptor antagonists and herbal remedies, putting special emphasis on the current place of these agents in the modern therapy of benign prostatic hyperplasia. **Wherever possible, our opinion is based on the detailed analysis of the results of available clinical trials.**

33: N Engl J Med 2006 Feb;354(6):557-66

Saw palmetto for benign prostatic hyperplasia.

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BACKGROUND: Saw palmetto is used by over 2 million men in the United States for the treatment of benign prostatic hyperplasia and is commonly

recommended as an alternative to drugs approved by the Food and Drug Administration. METHODS: In this double-blind trial, we randomly assigned 225 men over the age of 49 years who had moderate-to-severe symptoms of benign prostatic hyperplasia to one year of treatment with saw palmetto extract (160 mg twice a day) or placebo. The primary outcome measures were changes in the scores on the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate. Secondary outcome measures included changes in prostate size, residual urinary volume after voiding, quality of life, laboratory values, and the rate of reported adverse effects. RESULTS: There was no significant difference between the saw palmetto and placebo groups in the change in AUASI scores (mean difference, 0.04 point; 95 percent confidence interval, -0.93 to 1.01), maximal urinary flow rate (mean difference, 0.43 ml per minute; 95 percent confidence interval, -0.52 to 1.38), prostate size, residual volume after voiding, quality of life, or serum prostate-specific antigen levels during the one-year study. The incidence of side effects was similar in the two groups. CONCLUSIONS: In this study, saw palmetto did not improve symptoms or objective measures of benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00037154.).

34: Drugs Exp Clin Res 2005;31(5-6):193-7

Therapeutic effect of D-004, a lipid extract from *Roystonea regia* fruits, on prostate hyperplasia induced in rats.

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Benign prostatic hyperplasia (BPH) is a nonmalignant growth of prostate leading to difficulty in urinating. Drug therapy, phytotherapy included, is frequently used to treat BPH. D-004 is a lipid extract from *Roystonea regia* fruits, and previous studies have shown that oral treatment with D-004 for 14 days prevented prostate hyperplasia (PH) induced by testosterone in rats. No information is available, however; about the effects of D-004 in reverting already established PH. This study investigated whether D-004 could improve PH after oral dosing with testosterone in rats. Rats were distributed in five groups (10 rats/group). One group was injected with soy oil (negative control) and four groups were injected with testosterone: one was orally treated with the vehicle (positive control), two with D-004 (200 and 400 mg/kg) and the other with Saw palmetto (400 mg/kg). At study completion, the rats were sacrificed and the prostates were removed and weighed. D-004 (200 and 400 mg/kg) significantly and dose-dependently decreased prostate enlargement by 85% and 98%, respectively, versus the positive control. Likewise, Saw palmetto (400 mg/kg) significantly reduced prostate weight by 73% versus the positive control. D-004 (400 mg/kg) was more effective ($p < 0.05$) than Saw palmetto (400 mg/kg) in lowering prostate enlargement. D-004 and Saw palmetto also decreased the prostate weight to body weight ratio, but did not affect body weight. In conclusion, D-004 (200 and 400 mg/kg) orally administered was effective for reducing PH after testosterone dosing. D-004 (400 mg/kg) was more effective than Saw palmetto (400 mg/kg). Further studies, however, are needed to corroborate the present results.

35: Geriatrics 2005 Nov;60(11):32, 34

Herb-drug interactions. Interactions between saw palmetto and prescription medications.

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Patients over age 50 typically present with one chronic disease per decade. Each chronic disease typically requires long-term drug therapy, meaning most older patients require several drugs to maintain health. Simultaneously, use of complementary and alternative medicine (CAM) has increased in the United States in the last 20 years, reaching 36% in 2002; herbal medicine use accounts for approximately 22% of all CAM use. Older adults often add herbal medicines to prescription medications, yet do not always inform their physicians. The drug metabolizing enzyme systems process all compounds foreign to the body, including prescription and herbal medications. Therefore use of both medicinals simultaneously has a potential for adverse interactions. This review, which discusses saw palmetto, is the last in a series covering the documented interactions among the top 5 efficacious herbal medicines and prescription drugs.

36: MMW Fortschr Med 2005 Oct;147 Suppl 3:103-8

[Efficacy of a combined Sabal-urtica preparation in the symptomatic treatment of benign prostatic hyperplasia. Results of a placebo-controlled double-blind study]

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This re-evaluation of a double-blind placebo-controlled therapeutic study of the combined sabal-urtica preparation PRO 160/120 investigates the changes in the irritative symptoms of benign prostatic hyperplasia (BPH) under the test substance in comparison with placebo. It was found that, over the study period of 24 weeks, the micturition symptoms frequency and urgency were statistically significantly improved under the well-tolerated PRO 160/120 in comparison with placebo. The patient's quality of life was also significantly better under PRO 160/120 in comparison with placebo. CONCLUSION: The often distressing symptoms of BPH can be effectively ameliorated already after only a few weeks of treatment with the sabal-urtica preparation PRO 160/120. In particular those patients with the stigmatizing symptoms urinary urgency and frequency benefit from such treatment.

37: MMW Fortschr Med 2005 Oct;147(40):52-3

[Benign prostatic syndrome. Urinary urgency and micturition frequency reduced with plant preparation]

PMID: 16255520 [found with GoPubMed]

38: World J Urol 2005 Sep;23(4):253-6

Progression delay in men with mild symptoms of bladder outlet obstruction: a comparative study of phytotherapy and watchful waiting.

Djavan, Bob, Fong, Yan Kit, Chaudry, Aziz, Reissigl, Andreas, Anagnostou, Theodore, Bagheri, Fariborz, Waldert, Matthias, Fajkovic, Harun, Marihart, Sibylle, Harik, Mike, Spaller, Simone, Remzi, Mesut

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To determine the effect of phytotherapy (Serona repens) on the clinical progression in men with mild symptoms of bladder outlet obstruction (BOO). A total of 189 patients with mild symptoms of BOO, recruited from four different European clinics, were included in the analysis. Age, prostate specific antigen (PSA), international prostate symptom score (IPSS), quality of life (QOL), maximum urinary flow rate (Qmax) and total prostate and transitional zone volume were recorded. Clinical progression was defined as change from the mild-IPSS group into the moderate or severe group or the occurrence of urinary retention and need of surgery. Cumulative progression rate was 1, 7, 9 and 16% at 6, 12, 18 and 24 month, respectively, for the active group (Serona repens) as compared to 6, 13, 15 and 24% for the watchful waiting group. (P=0.03) significant improvements in the Qmax, IPSS and QOL were seen in the group receiving Serona repens. Serona repens significantly reduced the clinical progression rates in men with mild symptoms of BOO. It also led to improvements in urinary symptoms, QOL scores and urinary flow rates.

40: J Herb Pharmacother 2005;5(1):17-26

A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro.

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Inhibition of 5alpha-reductase has been reported to decrease the symptoms of benign prostate hyperplasia (BPH) and possibly inhibit or help treat prostate cancer. Saw Palmetto berry lipid extract (SPLE) is reported to inhibit 5alpha-reductase and decrease the clinical symptoms of BPH. Epidemiologic studies report that carotenoids such as lycopene may inhibit prostate cancer. In this investigation the effect of the carotenoid astaxanthin, and SPLE were examined for their effect on 5alpha-reductase inhibition as well as the growth of prostatic carcinoma cells in vitro. These studies support patent #6,277,417 B1. The results show astaxanthin demonstrated 98% inhibition of 5alpha-reductase at 300 microg/mL in vitro. Alphastat, the combination of astaxanthin and SPLE, showed a 20% greater inhibition of 5alpha-reductase than SPLE alone in vitro. A nine day treatment of prostatic carcinoma cells with astaxanthin in vitro produced a 24% decrease in growth at 0.1 mcg/mL and a 38% decrease at 0.01 mcg/mL. SPLE showed a 34% decrease at 0.1 mcg/mL. **CONCLUSIONS: Low levels of carotenoid astaxanthin inhibit 5alpha-reductase and decrease the growth of human prostatic cancer cells in vitro. Astaxanthin added to SPLE shows greater inhibition of 5alpha-reductase than SPLE alone in vitro.**

41: Curr Urol Rep 2005 Jul;6(4):290-5

Saw palmetto and finasteride in the treatment of category-III prostatitis/chronic pelvic pain syndrome.

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Chronic nonbacterial prostatitis/chronic pelvic pain syndrome is a common entity for which a standardized management has not been established. Patients often have a significant symptom complex and impact on quality of life, but very little is known about the efficacy of second- and third-line treatments, such as the use of herbal supplements. Many treatments studied in recent literature include antibiotics, alpha-blockade, anti-inflammatory agents, and cognitive behavioral interventions such as biofeedback and psychotherapy.

42: Eur Urol 2005 Aug;48(2):269-76

Evaluation of male sexual function in patients with Lower Urinary Tract Symptoms (LUTS) associated with Benign Prostatic Hyperplasia (BPH) treated with a phytotherapeutic agent (Permixon), Tamsulosin or Finasteride.

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OBJECTIVES: Sexual function is one of the aspects in the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) that has gained increasing attention. We compared the influence on men's sexuality of Permixon, a lipido-sterolic extract of *Serenoa Repens*, with Tamsulosin and Finasteride using a specific validated questionnaire exploring patient's sexual functions. **METHODS:** A database was created comprising patients from 3 main double-blind, randomized studies - Permixon vs. Finasteride, Permixon vs. Tamsulosin and Permixon 160 mg vs. 320 mg including a total of 2511 patients. Three hundred fifty four were on Tamsulosin, 545 on Finasteride and 1612 patients on Permixon. LUTS were assessed using the I-PSS questionnaire. Peak flow rates and prostate volume were recorded. The MSF-4 questionnaire, including 4 items that explore the patient's interest in sex, quality of erection, achievement of orgasm and ejaculation, was used across the studies. This questionnaire was demonstrated as highly reproducible and both psychometrically and clinically valid across different cultures. Correlation coefficients were given to assess the linear relationship between continuous variables. **RESULTS:** At 3 months, there were no statistically significant differences between the three treatment groups in terms of I-PSS or Qmax evolutions (all p values > 0.05). At 6 months, as compared to pretreatment data, there was a slight increase in sexual disorders in Tamsulosin (+0.3) and Finasteride (+0.8) treated patients while it slightly improved with Permixon therapy (-0.2). Ejaculation disorders were the most frequently reported side effects after Tamsulosin or Finasteride (both +0.2 on the specific MSF-4 question 4). There was no correlation between the evolution of the MSF-4 scores and the evolution in I-PSS neither in patients treated with Permixon, Finasteride or Tamsulosin. However, there was a slight

correlation between the MSF-4 score at baseline and the I-PSS at baseline ($r^2 = 0.032$). Although there was a correlation between the MSF-4 and age at baseline ($r^2 = 0.1452$), there was no correlation between the evolution in MSF-4 during therapy and the age of the patients. CONCLUSION: The present study demonstrates that Permixon therapy has no negative impact on male sexual function. Both Finasteride and Tamsulosin had a slight impact on sexual function, especially on ejaculation, although these effects were rare and in line with previous reports about these two drugs.

43: World J Urol 2005 Jun;23(2):139-46

Long-term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms--a placebo-controlled, double-blind, multicenter trial.

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The efficacy and tolerability of a fixed combination of 160 mg sabal fruit extract WS 1473 and 120 mg urtica root extract WS 1031 per capsule (PRO 160/120) was investigated in elderly, male patients suffering from lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia in a prospective multicenter trial. A total of 257 patients (129 and 128, respectively) were randomized to treatment with PRO 160/120 or placebo (127 and 126 were evaluable for efficacy). Following a single-blind placebo run-in phase of 2 weeks, the patients received 2 x 1 capsule/day of the study medication under double-blind conditions over a period of 24 weeks. Double-blind treatment was followed by an open control period of 24 weeks during which all patients were administered PRO 160/120. Outcome measures for treatment efficacy included the assessment of the patients' LUTS by means of the I-PSS self-rating questionnaire and a quality of life index as well as uroflow and sonographic parameters. Using the International Prostate Symptom Score (I-PSS), patients treated with PRO 160/120 exhibited a substantially higher total score reduction after 24 weeks of double-blind treatment than patients of the placebo group (6 points vs 4 points; $P=0.003$, one tailed) with a tendency in the same direction after 16 weeks. This applied to obstructive as well as to irritative symptoms, and to patients with moderate or severe symptoms at baseline. Patients randomized to placebo showed a marked improvement in LUTS (as measured by the I-PSS) after being switched to PRO 160/120 during the control period ($P=0.01$, one tailed, in comparison to those who had been treated with PRO 160/120 in the double-blind phase). The tolerability of PRO 160/120 was comparable to the placebo. In conclusion, PRO 160/120 was clearly superior to the placebo for the amelioration of LUTS as measured by the I-PSS. PRO 160/120 is advantageous in obstructive and irritative urinary symptoms and in patients with moderate and severe symptoms. The tolerability of the herbal extract was excellent.

44: Contemp Clin Trials 2005 Jun;26(3):397-401

Use of an embedded N-of-1 trial to improve adherence and increase information from a clinical study.

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Withdrawal of participants from randomized trials can occur because of symptoms thought to be related to the study medicine, but the causal relationship between the study medicine and the symptoms is often unclear. Single-patient trials ("N-of-1 trials"), developed to identify optimal therapy for an individual patient in the clinical setting, may provide a means of resolving some of these dilemmas. We describe here the use of an N-of-1 study embedded within a placebo-controlled trial of saw palmetto for a participant who considered withdrawing because he believed the study medication caused an increase in his blood pressure. In this case, the N-of-1 study not only reassured the patient, who decided to remain in the study, but provided potentially useful new information regarding the study medication. Wider use of formal N-of-1 studies may be a valuable tool for improving adherence and determining whether observed side effects are caused by study medication in clinical trials.

45: Aging Male 2004 Jun;7(2):155-69

Preventing diseases of the prostate in the elderly using hormones and nutraceuticals.

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The prostate has only one function, namely to secrete fluid containing substances that are needed for reproduction. This requires an extremely high concentration of androgens in the tissues. Benign prostatic hypertrophy (BPH) seems to be related to the long-term exposure of the prostate to the strong androgen 5alpha-dihydrotestosterone (DHT) and, possibly, to estrogens. The relation between prostate cancer and androgens is suggested to be U-shaped, with both extremes of androgen concentrations being associated with increased risk of invasive cancer. In the treatment of patients with BPH, the lipidic liposterolic extracts of *Serenoa repens* were as effective as the pharmaceutical inhibitors of the 5alpha-reductase enzyme or alpha1-adrenergic blockers in relieving urinary symptoms. In addition to moderately inhibiting the 5alpha-reductase activity, *Serenoa* seems to exert anti-inflammatory and complementary cellular actions with beneficial effects on the prostate. Unlike the pharmaceutical 5alpha-reductase inhibitors, finasteride and dutasteride, *Serenoa* does not suppress serum PSA, facilitating the follow-up and the early detection of prostate cancer. We suggest a strategy to prevent prostate cancer that aims at providing men with partial androgen deficiency correct testosterone substitution with a sustained release buccal bio-adhesive tablet. In addition, food supplementation with extracts of *Serenoa repens* and a combination of the antioxidants selenium, (cis)-lycopene and natural vitamin E, together with fish oil rich in long-chain polyunsaturated essential fatty acids of the omega-3 group seems warranted. Clearly, a holistic approach including careful clinical and biological monitoring of the aging man and his prostate remains mandatory.

47: J Urol 2005 Feb;173(2):507-10

Serenoa repens treatment modifies bax/bcl-2 index expression and caspase-3 activity in prostatic tissue from patients with benign prostatic hyperplasia.

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PURPOSE: Permixon is a lipidosterolic extract of *Serenoa repens* (SR) widely used to treat men with benign prostatic hyperplasia (BPH). We tested the effect of this drug on molecular mechanisms associated with apoptosis, such as the Bax-to-Bcl-2 expression ratio and caspase-3 activity, in prostatic tissue from men with symptomatic BPH treated for 3 months before surgery. **MATERIALS AND METHODS:** An open, multicenter pilot study of 2 parallel groups of patients with BPH was done. They were randomized to be followed for 3 weeks without any treatment before surgery (control group) or to receive 160 mg SR orally twice daily for a 3-month period preceding the same surgery. Surgery was ultimately performed in 17 controls and 12 patients by transurethral prostate resection or retropubic adenectomy. Bax and Bcl-2 expression, and caspase-3 activity were determined by Western blot in 15 controls and 10 patients, and reported in blinded fashion. **RESULTS:** The Bax-to-Bcl-2 ratio, which is used as an apoptotic index, was significantly increased in the prostatic tissue of treated patients. The level of the intact 116 kDa poly (adenosine diphosphate-ribose) polymerase form, an enzyme involved in the cell death apoptotic pathway, was also found to be decreased in prostatic tissue from SR treated patients, suggesting increased caspase 3 activity in the prostate. **CONCLUSIONS:** Permixon increased molecular markers involved in the apoptotic process, ie the Bax-to-Bcl-2 expression ratio and caspase-3 activity. This could have clinical relevance due to the improvement in symptoms produced by treatment with this drug.

48: Curr Opin Urol 2005 Jan;15(1):45-8

Role of phytotherapy in men with lower urinary tract symptoms.

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PURPOSE OF REVIEW: *Serenoa repens* extract is a popular phytotherapeutic agent in men with lower urinary tract symptoms. Although the exact mechanism of action is unknown, the agent is generally well accepted for its easy availability and good tolerability. This paper reviews the evidence of its efficacy in comparison with placebo, 5-alpha reductase inhibitor and alpha-1 adrenoreceptor antagonist. **RECENT FINDINGS:** *Serenoa repens* extract is comparable with 5-alpha reductase (finasteride) and alpha-1 antagonist in the treatment of benign prostatic hyperplasia in terms of symptom score and peak urinary flow rate improvement, but has a lower incidence of associated sexual dysfunction. Furthermore, long-term usage (36 months) of *Serenoa repens* decreases the progression rate of the condition as compared with watchful waiting. In addition, the efficacies of *Serenoa repens* are proven in several placebo-controlled trials. **SUMMARY:** *Serenoa repens* has proven its role in the management of benign prostatic hyperplasia and will remain as a viable first-line treatment option.

49: Urologia 2004 Sep-Oct;(5):10-6

[Morphological changes in prostatic tissue of patients with benign prostatic hyperplasia treated with permixon]

Sivkov, A V, Kudriavtsev, Iu V, Medvedev, A A, Razumov, S V, Kochetov, S A

A pilot trial has been performed to assess effects of permixon on prostatic tissue in patients with benign prostatic hyperplasia (BPH). A total of 49 BPH and control patients entered the trial. 36 patients of the study group were randomized into 3 subgroups of 12 patients each. Permixon was taken in a standard dose of 320 mg/day for 3, 6 and 12 months, respectively. Mean duration of BPH was 3.7 years (0-8 years). Mean value of PCA was 6.0 ng/ml. The control group of 13 patients were not given permixon. Multifocal prostatic biopsy was performed in all the patients before and after the treatment or follow-up. Stromal-parenchymatous correlation in the study group significantly increased (by 59%)--from 3.28 (0.25-9.61) to 5.22 (1.20-10.67) ($p = 0.0002$). For the control group this correlation was insignificant. Permixon-treated patients demonstrated inhibition of prostatic epithelium proliferative activity by 32% ($p = 0.0001$) and a rise in the stage of proliferative centers development from stage II-III to IV-V. Intensity of inflammation in prostatic tissue decreased by 53% in the study group and insignificantly in the control group. Thus, permixon treatment of BPH leads to a significant rise in stromal-parenchymatous correlation due to inhibition of proliferative activity of prostatic epithelium and attenuation of inflammation.

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51: J Urol 2004 Nov;172(5 Pt 1):1792-9

Is there a scientific basis for the therapeutic effects of serenoa repens in benign prostatic hyperplasia? Mechanisms of action.

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PURPOSE: The huge resurgence of interest in herbal remedies has spawned a global industry that now competes with conventional drugs as adjuncts and/or alternatives for various conditions. The medical treatment of benign prostatic hyperplasia (BPH) is no exception. Along with alpha-blockers and 5alpha-reductase inhibitors the extract of the American dwarf palm, *Serenoa repens*, is unquestionably the most widely used. Together with *Pygeum africanum*, an extract from the bark of the African plum tree, it is licensed in Germany, France and other European countries for symptomatic BPH. This review was done to analyze the large number of in vivo and in vitro laboratory studies that have been performed with extracts of *Serenoa repens* to elucidate mechanism(s) of action. **MATERIALS AND METHODS:** A literature search (MEDLINE) revealed more than 30 publications relating to laboratory studies with extracts of *Serenoa repens*, addressing the question of a mechanism of action. It would appear that the n-hexane lipidosterolic extract of *Serenoa repens*, namely Permixon (Pierre Fabre Medicament, Boulogne, France), is a product that has uniquely been subjected to more scientific investigation than any other such preparation. **RESULTS:** Placebo controlled and comparative clinical studies of Permixon indicate its efficacy for BPH/lower urinary tract symptoms. Numerous mechanisms of action have been proposed, including an antiandrogenic action, an anti-inflammatory effect and an antiproliferative influence through the inhibition of growth factors. **CONCLUSIONS:** Set against the background of

our current knowledge of the pathophysiology of the aging prostate, the results of these studies suggest a wide spectrum of activity. However, precise mechanism(s) of action remain obscure. Balance and caution are needed when extrapolating the results of in vitro laboratory studies to the complex human situation.

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[Evaluation of the clinical benefit of Permixon and tamsulosin in severe BPH patients--PERMAL study subset analysis]

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OBJECTIVE: To compare the efficacy of the lipido-sterolic extract of *Serenoa repens*, Permixon, to that of the α -blocker, tamsulosin, in the treatment of severe low urinary tract symptoms (LUTS) of benign prostatic hyperplasia (BPH). **METHODS:** In a 12-month, double-blind, randomized study that showed equivalent efficacy of Permixon 320 mg/day and tamsulosin 0.4 mg/day ("PERMAL study"), 685 BPH patients with IPSS > 10 had been analyzed for efficacy. Of these, the 124 patients with severe LUTS (IPSS > 19) at randomization were retained for this subset analysis. After a 4-week run-in period, 59 and 65 patients had been randomized to tamsulosin and Permixon groups, respectively. Both treatment groups were compared regarding the evolution from baseline of total IPSS and its irritative and obstructive subscores. LUTS-related QpL, prostate volume, Qmax and MSF-4 (sexual activity questionnaire) at different time points over 1 year. An analysis of variance of changes from baseline to end point was performed for all the parameters. The over-time evolutions of total, irritative and obstructive IPSS were further compared using a variance analysis for repeated measurements. **RESULTS:** At 12 months, total IPSS decreased by 7.8 with Permixon and 5.8 with tamsulosin ($p = 0.051$); the irritative symptoms improved significantly more ($p = 0.049$) with Permixon (- 2.9 versus - 1.9 with tamsulosin). The superiority of Permixon in reducing irritative symptoms appeared as soon as month 3 and was maintained up to month 12 ($p = 0.03$). **CONCLUSION:** Permixon 320 mg/day was shown to be slightly superior to tamsulosin 0.4 mg/day in reducing LUTS in severe BPH patients after 3 months and up to 12 months of treatment.