

## Premenstrual Syndrome and Menstrual Irregularities

## ABSTRACTS

- Bartsch W., 1979. Hormone blood levels and their inter-relationships in normal men and men with benign prostatic hyperplasia (BPH).
- Boehm S., 1998. Estrogen suppression as a pharmacotherapeutic strategy in the medical treatment of benign prostatic hyperplasia: evidence for its efficacy from studies with mepartricin.
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- Chia S.J., 1999. Is staging of benign prostatic hyperplasia (BPH) feasible?
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### **Hormone blood levels and their inter-relationships in normal men and men with benign prostatic hyperplasia (BPH).**

Bartsch W, Becker H, Pinkenburg FA, Krieg M.

Acta Endocrinol (Copenh) 1979 Apr;90(4):727-36

In 128 non-hospitalized men (age range 36-65 years) rectal palpation revealed in 54 cases an enlargement of the prostate (group II), which was very distinct in 20 cases (group III). The measurement of testosterone (T), 5alpha-dihydrotestosterone (DHT), 5alpha-androstane-3alpha,17beta-diol (3alpha-diol) oestradiol (Oe2), sex-hormone-binding-globulin binding capacity (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (Prl) in the blood of normal men (group I) and those with BPH (group II or III) demonstrated no significant differences between the three groups when respective age ranges were compared. A significant increase of FSH and decrease of 3alpha-diol with age was seen in the normal group (I), which was similar but less pronounced in BPH (groups II and III). A distinct increase of DHT with age was found in BPH (group II), which was not so dominant in normal men (group I). From these data it is concluded that the conversion of DHT to 3alpha-diol might be reduced in older males independent from the occurrence of BPH and that the hyperplastic prostate possibly secretes significant amounts of DHT into the circulation. These results are discussed with respect to their possible role in the pathogenesis of BPH.

### **Estrogen suppression as a pharmacotherapeutic strategy in the medical treatment of benign prostatic hyperplasia: evidence for its efficacy from studies with mepartricin.**

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Wien Klin Wochenschr 1998 Dec 11;110(23):817-23

Estrogen suppression has been introduced as a pharmacotherapeutic strategy in the medical treatment of benign prostatic hyperplasia. Recent negative results obtained in placebo-controlled trials with the aromatase inhibitor atamestane raised doubts about the efficacy of estrogen reduction. However, inhibition of aromatase not only reduces estrogens but also increases androgens which promote prostatic growth. In order to reevaluate the therapeutic efficacy of estrogen suppression, we summarize clinical trials investigating the therapeutic effects of mepartricin in the treatment of uncomplicated benign prostatic hyperplasia. Mepartricin has been reported to lower the levels of circulating estrogens without causing changes in other hormones such as androgens. By applying stringent inclusion criteria, 23 studies (including 7 placebo-controlled trials, 3 post-marketing surveillance studies, and 13 open trials) published between 1982 and 1996 were selected to be included in this report. In 79.9% of 4635 patients treated with mepartricin, its therapeutic effect was rated "good" or "excellent". In 6 out of 7 placebo-controlled trials, the therapeutic efficacy of mepartricin was significantly superior to that of placebo. Comparison of these data with results obtained with alpha 1-adrenoceptor antagonists or with the 5 alpha-reductase inhibitor finasteride indicates that mepartricin is as efficient as these widely accepted medical treatments for benign prostatic hyperplasia. Since mepartricin acts selectively upon estrogens, the present results show that estrogen suppression may be considered an efficient pharmacotherapeutic strategy in the medical treatment of uncomplicated benign prostatic hyperplasia.

### **The extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: a multicenter open study.**

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Current Therapeutic Research 55 ( 7 ): p 776-785 1994

Because prostatic surgery is not the treatment of choice for most patients with benign prostatic hyperplasia (BPH), the therapeutic effect of a 160-mg, twice-daily, oral dose of *Serenoa repens* extract was studied during a 3-month open trial in 505 patients with mild-to-moderate symptoms of BPH. The efficacy of the regimen was evaluated in 305 of these patients. Traditional parameters for quantifying prostatism, such as the International Prostate Symptom Score, the quality of life score, urinary flow rates, residual urinary volume, and prostate size, were found to be significantly improved after only 45 days of treatment. After 90

of treatment, a majority of patients (88%) and treating physicians (88%) considered the therapy effective. In addition, the serum prostate-specific antigen concentration was not modified by the drug, thus limiting the risk of masking any possible development of prostate cancer during treatment. The incidence of side effects (5%) was low and compares favorably with that reported for existing medical therapies used in BPH patients. The extract of *Serenoa repens* appears to be an effective and well-tolerated pharmacologic agent in treating the mictional problems accompanying BPH.

### **Efficacy and safety of the extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: therapeutic equivalence between twice and once daily dosage forms.**

Braeckman, J.; Bruhwylter, J.; Vandekerckhove, K.; Geczy, J. Department of Urology, A. Z. VUB, Laarbeeklaan 103, 1090 Brussels, Belgium.

Phytotherapy Research 1997 vol. 11 ( 8 ): p.558-563

The efficacy and safety of 2 dosage forms (160 mg twice/day or 320 mg once/day) of the extract of *S. repens* fruits (Prostaserene) were compared during a 1-year treatment in 132 patients suffering from benign prostatic hyperplasia (BPH). Both dosage forms induced a significant improvement in the efficacy variables: international prostate symptom score (60% after 1 year), quality of life score (85% of patients were satisfied after 1 year of treatment), prostatic volume (12% after 1 year), maximum flow rate (22% after 1 year), mean flow rate (17% after 1 year) and residual urinary volume (16% after 1 year). No significant differences were found between the 2 dosage forms. The percentage of patients or investigators evaluating that the treatment had a medium or bad tolerance was never >4%. Nineteen side effects were observed in 16 patients (12.1%), 8 patients in each group. The majority of these side effects (at least 75%) were related to the natural evolution of the disease itself rather than to the medication.

### **Anti-inflammatory activity of sabal fruit extracts prepared with supercritical carbon dioxide. In vitro antagonists of cyclooxygenase and 5-lipoxygenase metabolism. [Article in German]**

Breu W, Hagenlocher M, Redl K, Tittel G, Stadler F, Wagner H. Institut fur Pharmazeutische Biologie, Ludwig-Maximilians-Universitat Munchen.

Arzneimittelforschung 1992 Apr;42(4):547-51

The extract SG 291 (Talso, Talso uno) from the fruits of *Sabal serrulata* (syn.: *Serenoa repens*) prepared by supercritical fluid extraction with carbon dioxide is used for the treatment of benign prostatic hyperplasia (BPH) and non bacterial prostatitis. In the present work, the Sabal extract SG 291 was analyzed by gas chromatography and investigated for its inhibitory influence on the biosynthesis of inflammatory arachidonic acid metabolites. The extract SG 291 was found in vitro to be a dual inhibitor of the cyclooxygenase (IC50-value: 28.1 micrograms/ml) and 5-lipoxygenase pathway (IC50-value: 18.0 micrograms/ml). By alkaline hydrolysis, ether extraction and preparative thin layer chromatography the extract SG 291 was separated in three fractions containing acid lipophilic compounds (A), fatty alcohols (B) and sterols (C) as main components. Fraction A inhibited the biosynthesis of cyclooxygenase (CO) and 5-lipoxygenase (5-LO) metabolites in the same intensity as the native extract SG 291, while the fractions B, C and beta-sitosterol showed no inhibitory effect on both enzymes of the arachidonic acid pathways. Therefore, the CO and 5-LO inhibiting principle of *Sabal serrulata* extract SG 291 must be localized in the acidic lipophilic fraction (SLF). The CO and 5-LO inhibitory effects may give an explanation for the in vivo observed antiphlogistic and antiedematous activity of the lipophilic *Sabal serrulata* extract SG 291.

### **Is staging of benign prostatic hyperplasia (BPH) feasible?**

Chia SJ, Foo KT. Department of General Surgery, Tan Tock Seng Hospital, Singapore.

Ann Acad Med Singapore. 1999 Nov;28(6):800-4

With better understanding of the natural history of benign prostatic hyperplasia (BPH), the treatment can be tailored to the severity of the disease. The aims of this study were to determine the feasibility of staging BPH according to its severity and choose the optimal therapeutic tool for each category, and for comparing results of various modalities of treatment. Two hundred and twenty-five patients with clinical BPH were seen between October 1994 and July 1995. Initial assessment included the International Prostatic Symptom Score, and the quality of life index, digital rectal examination, urinalysis, prostate specific antigen, uroflow and residual urine estimation. Patients were then divided into: Stage 1, those with no bothersome symptoms and no significant obstruction, they can generally be watched. Stage 2, those with bothersome symptoms but without significant obstruction, they can be treated with pharmacotherapy/thermotherapy. Stage 3, those with significant obstruction defined as uroflow of less than 10 ml/s with persistent residual urine of > 100 ml, transurethral prostatic resection (TURP) would be recommended. Stage 4, those with complications of BPH such as chronic retention of urine and bladder stone, they would need TURP. One hundred and fifty-nine patients had complete follow up data of at least 2 years. Of the 70 patients who were originally

in Stage 1, 59 (89%) remained in status quo, 6 patients developed acute retention of urine and only 1 required TURP. Of the 38 patients in Stage 2, 24 were down-staged to Stage 1 after medication and thermotherapy but 4 still remained in Stage 2 and the other 10 had worsening of symptoms requiring surgery. Of the 46 patients in Stage 3, 30 (65%) had TURP and all except 1 were down-staged to Stage 1. All patients in Stage 4 had TURP and improved. We conclude that staging of patients with clinical BPH is feasible. It serves as a useful guide for management and improves cost effectiveness.

### **Chemical and pharmacological study on hypercritical CO<sub>2</sub> extracts of *Serenoa repens* fruits.**

Cristoni A.; Morazzoni P.; Bombardelli E. E. Bombardelli, Indena S.p.A., Direzione Scientifica, Viale Ortles 12, 20139 Milan Italy

Fitoterapia ( FITOTERAPIA ) (Italy) 1997, 68/4 (355-358)

From the fruits of *S. repens* some extracts have been prepared with a procedure involving CO<sub>2</sub> in hypercritical conditions at different sets of temperature and pressure. The obtained oils showed in castrated prepuberal rats a significant anti-androgenic activity, in agreement with what reported in the literature for other lipophilic extracts. The best results were observed with the extract arising from hypercritical CO<sub>2</sub> at 45°C and 220 bar.

### **Roles of estrogen and SHBG in prostate physiology.**

Farnsworth WE. Department of Urology, Northwestern University Medical School, Chicago, Illinois, USA.

Prostate. 1996 Jan;28(1):17-23

Heretofore, the function of estrogen in the prostate, other than as an antiandrogen, has been unclear. In this review of a growing fund of knowledge about both estrogen and the plasma protein, sex hormone-binding globulin (SHBG), or testosterone-estradiol binding globulin (TeBG), the hypothesis is proposed that estrogen, mediated by SHBG, participates with androgen in setting the pace of prostatic growth and function. It is suggested that the estrogen not only directs stromal proliferation and secretion, but also, through IGF-I, conditions the response of the epithelium to androgen.

### **A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia.**

Gann PH, Hennekens CH, Longcope C, Verhoek-Oftedahl W, Grodstein F, Stampfer MJ. Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Prostate 1995 Jan;26(1):40-9

We assessed the relation of plasma hormone levels and nonhormonal factors with subsequent occurrence of surgical treatment for benign prostatic hyperplasia (BPH) among participants in the Physicians' Health Study. Frozen plasma samples, collected at the study onset, were available for 320 men who developed surgically treated BPH up to 9 years later and for 320 age-matched controls. Plasma testosterone (T), dihydrotestosterone (DHT), androstenedione, estradiol (E2), and estrone (E1) were measured for each case-control pair. In unadjusted analyses, none of the hormones or hormone ratios were associated with BPH; for example, for T and E2 the odds ratios (OR) comparing the highest quintile (Q5) with the lowest (Q1) were 0.74 (95% CI = 0.42, 1.30) and 1.07 (95% CI = 0.51, 2.22), respectively. However, in multivariate analyses controlling diastolic blood pressure, exercise, alcohol, E1, and DHT:T ratio, we observed a strong trend for increasing risk across quintiles for E2 (Q5 vs. Q1 OR = 3.56, P trend = 0.009), and a weak inverse trend for E1 (Q5 vs Q1 OR = 0.51, P trend = 0.07). The excess risk associated with E2 was confined to men with relatively low androgen levels. Three nonhormonal factors previously suspected as risk factors were independently associated with surgical BPH in these data. The OR for a 1-mm Hg difference in diastolic blood pressure was 1.04 (95% CI = 1.01, 1.07). Alcohol use and infrequent exercise were inversely associated with risk of BPH surgery; however, risk estimates were not consistent across categories of exercise and alcohol frequency. Our results indicate that normal variation in circulating androgen levels does not influence development of BPH, but that variation in estrogen levels might be important.

### **Saw palmetto berry extract inhibits cell growth and Cox-2 expression in prostatic cancer cells.**

Goldmann WH, Sharma AL, Currier SJ, Johnston PD, Rana A, Sharma CP. Boston BioProducts Inc., Ashland, MA 01721, USA.

Cell Biol Int 2001;25(11):1117-24

The cytotoxicity of a commonly used material to alleviate the symptoms of benign prostatic hyperplasia (BPH), Saw Palmetto Berry Extract (SPBE), was examined as neat oil using a set of prostatic cell lines; 267B-1, BRFF-41T and LNCaP. Proliferation of these prostatic derived cell lines is inhibited to different degrees when dosed for 3 days with SPBE. The amount of SPBE required to inhibit 50% growth (IC50) of these cell lines was 20-30 nl equivalents of SPBE per ml of medium for cell lines 267B-1 and BRFF-41T and approximately 10-fold more for the LNCaP cell line. The effect of SPBE dosing on these cell lines is not irreversible, since a 30 min treatment with SPBE at an IC50 concentration does not inhibit their growth. Normal prostate cells were inhibited by 20-25% when grown in the presence of 200 nl SPBE equivalent per ml media. Growth of other non-prostatic cancer cell lines, i.e. Jurkat and HT-29, was affected by approx. 50% and 40%, respectively. When LNCaP cells were grown in the presence of dihydrotestosterone and SPBE, the IC50 concentration decreased significantly compared to LNCaP cells grown in the presence of serum and SPBE. Reduced cellular growth after SPBE treatment of these cell lines may relate to decreased expression of Cox-2 and may be due to changes observed in the expression of Bcl-2. Expression of Cox-1 under similar conditions is not affected because of its constitutive expression. Since increased Cox-2 expression is associated with an increased incidence of prostate cancer, and decrease in its expression by SPBE would provide a basis for further investigation of its use against BPH and in prostatic cancer chemoprevention.

### **Mechanisms involved in the spasmolytic effect of extracts from *Sabal serrulata* fruit on smooth muscle.**

Gutierrez M, Garcia de Boto MJ, Cantabrana B, Hidalgo A. Departamento de Medicina, Laboratorio de Farmacologia, Oviedo, Spain.

Gen Pharmacol 1996 Jan;27(1):171-6

The effects of two extracts from *Sabal serrulata* fruits [total lipidic (L) and saponifiable (S)] on smooth muscle contractions have been assayed. 2. Both extracts (0.1-1 mg/ml) relaxed the tonic contraction induced by norepinefrine (30 nM) on rat aorta [EC50, 0.53 +/- 0.05 mg/ml (L) and 0.5 +/- 0.04 mg/ml (S)] and by KCl (60 mM) on rat uterus. The Sabal extracts (0.3-1 mg/ml) also antagonized the dose-response curve of contractions induced by acetylcholine (0.1-100 microM) on urinary bladder. 3. dL-Propranolol (1 microM) but not the inactive (R)-(+)-propranolol(1 microM) potentiated the Sabal extracts relaxant effect by lowering the EC50 (0.35 +/- 0.2 vs 0.20 +/- 0.01 mg/ml for L and 0.43 +/- 0.02 vs 0.19 +/- 0.02 mg/ml, P < 0.01, for S extract). 4. Cycloheximide (10 micrograms/ml) antagonized the effect of extracts from Sabal. However, actinomycin D (5 micrograms/ml) significantly (P < or = 0.01) antagonized the effect of the total lipidic extract without modifying that of the saponifiable extract. 5. The relaxant effect of both extracts was not modified by the tyrosine kinase inhibitor genistein (10 microM) or the ornithine decarboxylase inhibitor alpha-difluoromethyl-ornithine (10 mM).

### **Rationale for using aromatase inhibitors to manage benign prostatic hyperplasia. Experimental studies.**

Habenicht UF, el Etreby MF. Research Laboratories of Schering AG, Berlin, Germany.

J Androl 1991 Nov-Dec;12(6):395-402

Today, human benign prostatic hyperplasia (BPH) is considered primarily to be a disease of the stroma, in which estrogens are thought to play a considerable causative or permissive role. The growing incidence of BPH with increasing age coincides with a shift in the androgen:estrogen ratio in favor of estrogens, not only in terms of serum hormone values, but also in the prostate itself. Furthermore, evidence has been provided for a preferential accumulation of estrogens in the stroma of human hyperplastic tissue, and the presence of an estrogen receptor satisfying the classical criteria of high affinity and low capacity has been demonstrated. Also, animal studies have emphasized the potential role of estrogens in the pathogenesis of BPH. Experimentally, stimulation of the stroma, particularly of smooth muscle, can be induced by aromatizable substrates, such as androstenedione, in the prostates of beagles and cynomolgus monkeys. These effects can be antagonized by aromatase inhibitors, such as atamestane. In addition, the increase in intraprostatic estrogen concentrations and immunohistochemically detectable estrogen receptor content induced by androstenedione in intact dogs is completely reversed by simultaneous treatment with atamestane. In conclusion, clinical data, as well as that from animal models, emphasize an important role for estrogens in the development of BPH. Estrogen deprivation might, therefore, represent a useful treatment for human BPH.

### **The effect of extracts of the roots of the stinging nettle (*Urtica dioica*) on the interaction of SHBG with its receptor on human prostatic membranes.**

Hryb DJ, Khan MS, Romas NA, Rosner W. Department of Medicine, St. Luke's/Roosevelt Hospital Center, New York, N.Y. 10019.

Planta Med 1995 Feb;61(1):31-2

Extracts from the roots of the stinging nettle (*Urtica dioica*) are used in the treatment of benign prostatic hyperplasia. The mechanisms underlying this treatment have not been elucidated. We set out to determine whether specific extracts from U.

dioica had the ability to modulate the binding of sex hormone-binding globulin to its receptor on human prostatic membranes. Four substances contained in *U. dioica* were examined: an aqueous extract; an alcoholic extract; *U. dioica* agglutinin, and stigmasta-4-en-3-one. Of these, only the aqueous extract was active. It inhibited the binding of 125I-SHBG to its receptor. The inhibition was dose related, starting at about 0.6 mg/ml and completely inhibited binding at 10 mg/ml.

### **Comparison of the effects of chlormadinone acetate-pellet implantation and orchidectomy on benign prostatic hypertrophy in the dog.**

Kawakami E, Tsutsui T, Shimizu M, Orima H, Fujita M, Ogasa A. Department of Reproduction, Nippon Veterinary and Animal Science University, Tokyo, Japan.

Int J Androl 1995 Oct;18(5):248-55

Five beagles out of 11 dogs aged 7-10 years with benign prostatic hypertrophy (BPH) were implanted subcutaneously with pellets of the synthetic anti-androgen chlormadinone acetate (CMA) at a dose of 10 mg/kg bodyweight. The remaining six dogs (one beagle and five mongrel dogs) underwent bilateral orchidectomy. Changes in prostatic volume, histological findings in the prostate and the testis, and peripheral plasma levels of LH, testosterone and oestradiol-17 beta (E2) were assessed up until 24 and 4 weeks after CMA-implantation and orchidectomy, respectively. Measurements of the size of the prostate and biopsies of the prostate were performed by laparotomy. Mean prostatic volume had decreased to 71% and 41%, respectively, of its pretreatment volume, by 4 weeks after CMA-implantation and orchidectomy, and was 49% and 47%, respectively, of pretreatment volume at 12 and 24 weeks after CMA-implantation. The clinical signs of BPH, e.g. haematuria, resolved within 2 weeks after either treatment. When the prostate was examined histologically 4 weeks after either treatment, hardly any evidence of active secretion (e.g. glandular epithelium projecting markedly into the lumen), was observed in CMA-implanted dogs, alveolar diameter and height of the glandular epithelium had decreased markedly and the glandular lumen had become very small in the orchidectomized dogs. By 12 weeks after CMA-implantation, degenerative and atrophic glands were observed in the prostate nearly the same as at 4 weeks after orchidectomy. In the testis the number of germ cells in the seminiferous tubules decreased markedly after CMA-implantation. The mean level of plasma LH at 4 weeks after orchidectomy had increased to 14.9 ng/ml, twice the value before operation. The mean levels of plasma testosterone and E2 at 4 weeks after CMA-implantation had decreased to 0.7 ng/ml and 9 pg/ml from 1.5 ng/ml and 15 pg/ml, the values before treatment, respectively. CMA-implantation resulted in poor semen quality. The results indicate that CMA-implantation at a dose of 10 mg/kg results in the same prostate-shrinking effect as orchidectomy.

### **Effect of aging on endogenous level of 5 alpha-dihydrotestosterone, testosterone, estradiol, and estrone in epithelium and stroma of normal and hyperplastic human prostate.**

Krieg M, Nass R, Tunn S. Institute of Clinical Chemistry and Laboratory Medicine, University Clinic Bergmannsheil, Bochum, Germany.

J Clin Endocrinol Metab 1993 Aug;77(2):375-81

It is widely believed that benign prostatic hyperplasia (BPH) is associated with aging. Thus, the question arises whether or not a correlation exists between the well known prostatic androgen and estrogen accumulation and aging. To address this question, we measured 5 alpha-dihydrotestosterone (DHT), testosterone, estradiol, and estrone in epithelium and stroma of six normal (NPR) and 19 BPH and correlated the values with the age of the donors (26-87 yr). The mean DHT level in NPR epithelium was significantly higher than in NPR stroma, and also significantly higher than in epithelium and stroma of BPH. The epithelial DHT level of NPR and BPH decreased with age, the correlation being statistically significant. The stromal DHT level of NPR and BPH showed no correlation with age. Concerning testosterone, generally rather low values were found which showed no correlation with age. The mean levels of estradiol and estrone were significantly higher in BPH stroma as compared to BPH epithelium as well as to NPR epithelium and stroma. In NPR, the mean levels of estradiol and estrone were significantly higher in epithelium than stroma. In NPR and BPH, the stromal estradiol and estrone levels increased significantly with age. In epithelium such a correlation between the estrogen levels and age was not found. Our results indicate that the prostatic accumulation of DHT, estradiol, and estrone is in part intimately correlated with aging, leading with increasing age to a dramatic increase of the estrogen/androgen ratio particularly in stroma of BPH.

### **The inhibiting effects of components of stinging nettle roots on experimentally induced prostatic hyperplasia in mice.**

Lichius JJ, Renneberg H, Blaschek W, Aumuller G, Muth C.

Planta Med 1999 Oct;65(7):666-8

Direct implanting of fetal urogenital sinus (UGS) tissue into the ventral prostate gland of adult mice led to a 4-fold weight

increase of the manipulated prostatic lobe. The induced growth could be reduced by the polysaccharide fraction (POLY-M) of the 20% methanolic extract of stinging nettle roots by 33.8%.

### **Retgression of the symptomatology of prostate adenoma under conservative treatment with ERU-capsules.**

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Fortschritte der Medizin (Germany) 1987, 105/1 (50-52)

Patients suffering from prostate adenoma with hyperplasia in the stages I to III responded after six months so satisfactorily to the conservative treatment with extractum radicis urticae (ERU) that only two patients exhibiting stage III (5.1% of the case material) had to be operated. In the remaining 37 patients the levels of uroflow and residual urine as well as the rectal palpation, frequency of nycturia and pollakisuria in most of the cases improved, i.e. there was a marked improvement in 86% of the cases already after three months of treatment.

### **Tissue effects of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic androgens.**

Marks LS, Hess DL, Dorey FJ, Luz Macairan M, Cruz Santos PB, Tyler VE. Urological Sciences Research Foundation, Culver City, California, USA.

Urology 2001 May;57(5):999-1005

**OBJECTIVES:** To determine the effects of a saw palmetto herbal blend (SPHB) compared with finasteride on prostatic tissue androgen levels and to evaluate needle biopsies as a source of tissue for such determinations.

**METHODS:** Prostate levels of testosterone and dihydrotestosterone (DHT) were measured on 5 to 10-mg biopsy specimens (18-gauge needle cores) in three groups of men with symptomatic benign prostatic hyperplasia: 15 men receiving chronic finasteride therapy versus 7 untreated controls; 4 men undergoing prostate adenectomy to determine sampling variability (10 specimens each); and 40 men participating in a 6-month randomized trial of SPHB versus placebo, before and after treatment.

**RESULTS:** Prostatic tissue DHT levels were found to be several times higher than the levels of testosterone (5.01 versus 1.51 ng/g), that ratio becoming reversed (1.05 versus 3.63 ng/g) with chronic finasteride therapy. The finasteride effect was statistically significant for both androgens ( $P < 0.01$ ), and little overlap of individual values between finasteride-treated and control patients was seen. In the randomized trial, tissue DHT levels were reduced by 32% from 6.49 to 4.40 ng/g in the SPHB group ( $P < 0.005$ ), with no significant change in the placebo group.

**CONCLUSIONS:** For control versus finasteride-treated men, the tissue androgen values obtained with needle biopsy specimens were similar-both for absolute values and the percentage of change-to those previously reported using surgically excised volumes of prostatic tissue. The quantification of prostatic androgens by assay of needle biopsies is thus feasible and offers the possibility of serial studies in individual patients. The SPHB-induced suppression of prostatic DHT levels, modest but significant in a randomized trial, lends an element of support to the hypothesis that inhibition of the enzyme 5-alpha reductase is a mechanism of action of this substance.

### **Effect of the lipidosterolic extract of *Serenoa repens* (Permixon) and its major components on basic fibroblast growth factor-induced proliferation of cultures of human prostate biopsies.**

Paubert-Braquet M, Cousse H, Raynaud JP, Mencia-Huerta JM, Braquet P. Bio-Inova Euro Lab Research Laboratories, Plaisir, France.

Eur Urol 1998;33(3):340-7

**OBJECTIVE:** To assess the effect of the lipidosterolic extract of *Serenoa repens* (LSESr) on in vitro cell proliferation in biopsies of human prostate

**MATERIAL AND METHODS:** Cell proliferation was assessed by incorporation of [ $^3\text{H}$ ]thymidine followed by autoradiography.

**RESULTS:** Basic fibroblast growth factor (b-FGF) induced a considerable increase in human prostate cell proliferation (from +100 to +250%); the glandular epithelium was mainly affected, minimal labeling being recorded in the other regions of the prostate. Similar results were observed with epidermal growth factor (EGF), although the increase in cell proliferation was not recorded in some cases. Lovastatin, an inhibitor of hydroxymethylglutaryl coenzyme A, antagonized both the basal proliferation and the growth factor-stimulated proliferation of human prostate epithelium (EGF, mean inhibition approximately 80-95%; b-FGF,

mean inhibition approximately 40-90%). Geraniol, a precursor of both farnesyl pyrophosphate and geranylgeranyl pyrophosphate, and farnesol, the precursor of farnesyl pyrophosphate, increased cell proliferation only in some prostate specimens, this effect being antagonized by lovastatin. LSESr did not affect basal prostate cell proliferation, with the exception of two prostate specimens in which a significant inhibition of basal proliferation was observed with the highest concentration of LSESr (30 micrograms/ml). In contrast, LSESr inhibited b-FGF-induced proliferation of human prostate cell cultures; this effect was significant for the highest concentration of LSESr (30 micrograms/ml). In some prostate samples, a similar inhibition was also noted with lower concentrations. Unsaturated fatty acids (UFA), in the range 1-30 ng/ml, did not affect the basal prostate cell proliferation, only a slight increase in cell proliferation was noted in 1 prostate specimen. UFA (1, 10 or 30 micrograms/ml) markedly inhibited the b-FGF-induced cell proliferation down to the basal value. Lupenone, hexacosanol and the unsaponified fraction of LSESr markedly inhibited the b-FGF-induced cell proliferation, whereas a minimal effect on basal cell proliferation was noted.

**CONCLUSIONS:** Despite the large variability in the response of the prostate samples to b-FGF, these results indicate that LSESr and its components affect the proliferative response of prostate cells to b-FGF more than their basal proliferation.

### **Prostate-specific antigen in the diagnosis of organ-confined treatable prostate carcinoma. [Article in German]**

Recker F. Departement Chirurgie, Kantonsspital Aarau.

Schweiz Med Wochenschr 1996 Nov 2;126(44):1881-90

Prostate cancer is now the most common cancer and the second most common cause of death from cancer among men. Several studies have shown a frequency of autopsy-detected cancer of 40% in men over 50 years of age. In contrast, the lifetime probability of prostate cancer being diagnosed clinically is only 8%. Thus histologically documented prostate cancer only becomes clinically relevant if the tumors are > 0.5 cm<sup>3</sup> and the life expectancy exceeds 10 years. Therapy with curative intention is only possible for organ confined disease. Because disease specific survival is about 80-90% after 10 years for conservative treatment of organ confined disease, early detection of prostate cancer is useful for patients with a life expectancy > 10 years. Organ confined prostate cancer is usually asymptomatic. The use of prostate specific antigen (PSA) combined with digital rectal examination (DRE) results in a 2-3 fold increase in prostatic carcinoma detection rate, especially of organ confined disease, by PSA. In men with a minimally elevated PSA-value of 4-10 ng/ml (Hybritech Assays), 25% will have a prostatic carcinoma regardless of the finding of the DRE, which would have reached clinical significance in the follow-up. The indication for biopsy should be established at an early date. There is no support for the common opinion that early detection programs detect clinically unimportant cancers. 95% of tumor volumes are > 0.5 cm<sup>3</sup>. Furthermore only 3-5% of subjects show prostate cancer in detection programs though 8% will develop clinical symptoms of prostate cancer during their lifetime. This difference is a reason for longitudinal programs with PSA and DRE control once a year, as proposed by the American Cancer Society and the American and Canadian Urological Association, in contrast to other health care organizations, which would wait with general screening until data from prospective randomized trials with beneficial effects of screening are available. To introduce prostate cancer therapy with curative intention for symptomatic patients as well, the cancer should be detected below a PSA level of 10 ng/ml. Insufficient specificity of PSA (2-4 patients have to undergo biopsies to detect one cancer patient) is still an unsolved problem.

### **Lignans from the roots of *Urtica dioica* and their metabolites bind to human sex hormone binding globulin (SHBG).**

Schottner M, Gansser D, Spiteller G. Lehrstuhl Organische Chemie I, Universitat Bayreuth, Germany.

Planta Med 1997 Dec;63(6):529-32

Polar extracts of the stinging nettle (*Urtica dioica* L.) roots contain the ligans (+)-neoolivil, (-)-secoisolariciresinol, dehydrodiconiferyl alcohol, isolariciresinol, pinoresinol, and 3,4-divanillyltetrahydrofuran. These compounds were either isolated from *Urtica* roots, or obtained semisynthetically. Their affinity to human sex hormone binding globulin (SHBG) was tested in an in vitro assay. In addition, the main intestinal transformation products of plant lignans in humans, enterodiol and enterolactone, together with enterofuran were checked for their activity. All lignans except (-)-pinoresinol developed a binding affinity to SHBG in the in vitro assay. The affinity of (-)-3,4-divanillyltetrahydrofuran was outstandingly high. These findings are discussed with respect to potential beneficial effects of plant lignans on benign prostatic hyperplasia (BPH).

### **Interaction of lignans with human sex hormone binding globulin (SHBG).**

Schottner M, Gansser D, Spiteller G. Lehrstuhl Organische Chemie I, Universitat Bayreuth, Germany.

Z Naturforsch [C] 1997 Nov-Dec;52(11-12):834-43

Lignans bind to sex hormone-binding globulin (SHBG). The lignan with the highest binding affinity is (+/-)-3,4-divanillyltetrahydrofuran. In a double Stobbe condensation--without use of protecting groups--a wide variety of lignans with different substitution pattern in the aromatic and aliphatic part of the molecule was synthesized. These lignans were tested in a SHBG-binding assay which allowed to deduce the following relationship between structure and activity: 1) (+/-)-diastereoisomers are more active than meso compounds 2.) the 4-hydroxy-3-methoxy (guajacyl) substitution pattern in the aromatic part is most effective 3.) the activity increases with the decline in polarity of the aliphatic part of the molecule.

### **Lignans interfering with 5 alpha-dihydrotestosterone binding to human sex hormone-binding globulin.**

Schottner M, Spitteller G, Gansser D. Lehrstuhl für organische Chemie, Universität Bayreuth, Germany.

J Nat Prod 1998 Jan;61(1):119-21

The natural lignans (-)-3,4-divanillyltetrahydrofuran (1), (-)-matairesinol (2), (-)-secoisolariciresinol (3), (+/-)-enterolactone (4), (+/-)-enterodiol (5), and nordihydroguaiaretic acid (NDGA) (6) reduce the binding of 3H-labeled 5 alpha-dihydrotestosterone (DHT) to human sex hormone-binding globulin (SHBG). (-)-3,4-Divanillyltetrahydrofuran (1) has the highest binding affinity ( $K_a = 3.2 \pm 1.7 \times 10^6 M^{-1}$ ) of all lignans investigated so far; the reversibility of its binding and a double reciprocal plot suggest a competitive inhibition of the SHBG-DHT interaction. Increasing hydrophobicity in the aliphatic part of the lignans (butane-1,4-diol-butanolide-tetrahydrofuran structures) leads to higher binding affinity. In the aromatic part, a 3-methoxy-4-hydroxy substitution pattern is most effective for binding to SHBG.

### **Changes in the endocrine environment of the human prostate transition zone with aging: simultaneous quantitative analysis of prostatic sex steroids and comparison with human prostatic histological composition.**

Shibata Y, Ito K, Suzuki K, Nakano K, Fukabori Y, Suzuki R, Kawabe Y, Honma S, Yamanaka H. Department of Urology, Gunma University School of Medicine, Maebashi, Japan. yshibata@akagi.sb.gunma-u.ac.jp

Prostate 2000 Jan;42(1):45-55

**BACKGROUND:** It is well-known that the incidence of benign prostatic hyperplasia (BPH) increases with aging. The age-dependent changes in the ratio of serum sex steroid concentrations may play a role in BPH development. To clarify the relationship between the prostatic tissue concentrations of these steroids and age, we established a precise method of simultaneous quantitative analysis for prostatic sex steroids and used this method to investigate the tissue concentrations of three major sex steroids (testosterone, dihydrotestosterone, and estradiol) in the human prostate.

**METHODS:** The methodology for the simultaneous quantitative analysis of prostatic sex steroids was established using castrated rat prostatic tissue, coupled with internal standards, for androgen-deprived medium, and the validation of the method was examined. Human prostatic tissues were collected during surgery and immediately frozen at -70 degrees C. Using our method, the steroidal fractions were extracted, purified, and quantified. The proportions of stroma, epithelium, and glandular lumen were measured on each histological specimen, using an image analyzer.

**RESULTS:** The validation tests showed that our method of quantitative analysis was precise and sensitive enough for the quantification of testosterone, dihydrotestosterone, and estradiol in the prostate. In humans, the prostatic dihydrotestosterone concentration decreased with age, but the concentrations of testosterone and estradiol showed no relation with age. Therefore, the ratio of estradiol to dihydrotestosterone concentration (E2/DHT) in prostate increased with age. The E2/DHT ratio showed a significant positive correlation with the proportion of stroma.

**CONCLUSIONS:** The age-dependent decrease in prostatic dihydrotestosterone and constant estradiol concentration lead to a relatively estrogen-dominant environment compared to that at younger ages. We assume that this relatively estrogen-dominant status induces stromal proliferation by some mechanism and leads to the development of BPH. Copyright 2000 Wiley-Liss, Inc.

### **Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome.**

Sokeland J. Urological Clinic of Dortmund, Training Hospital of the University of Munster, Germany.

BJU Int 2000 Sep;86(4):439-42

**OBJECTIVE:** To test the hypothesis that in patients with benign prostatic hyperplasia (BPH), the outcome of drug therapy with finasteride may be predictable from the baseline prostate volume and that positive clinical effects might be expected only in patients with prostate volumes of > 40 mL, using a subgroup analysis of results from a previously reported clinical trial of

finasteride and phytotherapy.

**PATIENTS AND METHODS:** A subgroup of 431 patients was analysed from a randomized, multicentre, double-blind clinical trial involving 543 patients with the early stages of BPH. Patients received a fixed combination of extracts of saw palmetto fruit (*Serenoa repens*) and nettle root (*Urtica dioica*) (PRO 160/120) or the synthetic 5 $\alpha$ -reductase inhibitor finasteride. The patients assessed had valid ultrasonographic measurements and baseline prostate volumes of either  $\leq$  40 mL or  $>$  40 mL. All 516 patients were included in the safety analysis. The results of the original trial showed equivalent efficacy for both treatments.

**RESULTS:** The mean (SD) maximum urinary flow (the main outcome variable) increased (from baseline values) after 24 weeks by 1.9 (5.6) mL/s with PRO 160/120 and by 2.4 (6.3) mL/s with finasteride. There were no statistically significant group differences ( $P = 0.52$ ). The subgroups with small prostates ( $\leq$  40 mL) showed similar improvements, with mean values of 1.8 (5.2) mL/s with PRO 160/120 and 2.7 (7.4) mL/s with finasteride. The mean values for the subgroups with prostates of  $>$  40 mL were similar, at 2.3 (6.1) and 2.2 (5.3) mL/s, respectively. There were improvements in the International Prostate Symptom Score in both treatment groups, with no statistically significant differences. The subgroup analysis showed slightly better results for voiding symptoms in the patients with prostates of  $>$  40 mL, but there were also improvements in the subgroup with smaller prostates. The safety analysis showed that more patients in the finasteride group reported adverse events and also there were more adverse events in this group than in patients treated with PRO 160/120.

**CONCLUSION:** The present analysis showed that the efficacy of both PRO 160/120 and finasteride was equivalent and unrelated to prostate volume. However, PRO 160/120 had better tolerability than finasteride.

### **Endocrine environment of benign prostatic hyperplasia-relationships of sex steroid hormone levels with age and the size of the prostate. [Article in Japanese]**

Suzuki K, Inaba S, Takeuchi H, Takezawa Y, Fukabori Y, Suzuki T, Imai K, Yamanaka H, Honma S. Division of Urology, Shakai Hoken Mishima Hospital.

Nippon Hinyokika Gakkai Zasshi 1992 May;83(5):664-71

To determine the influence of endocrine factors on benign prostatic hyperplasia (BHP), the levels of three sex steroid hormones i.e., total testosterone (Total-T), free testosterone (Free-T) and estradiol (E2), were measured in serum of healthy 154 men. Their ages ranged from 18 to 91 years old. In 59 men, prostatic size was estimated by digital examination and was subdivided into three groups: smaller than or equal to walnut size, small hen's egg size and equal to or larger than hen's egg size. Firstly, relationships of sex hormone levels with age were studied. There was a slight decrease in Total-T over 60 years old, a significant decrease in Free-T, and no change in E2 with age. Thus, E2/Total-T and E2/Free-T ratio increased significantly after middle-age. Secondly, relationships of hormone levels with prostatic size were studied. In the larger prostate group, a significantly lower level of Total-T and significantly higher level of E2 were detected. But there was no difference in Free-T. Thus, the prostatic size was correlated positively with E2 level, E2/Total-T and E2/Free-T ratio. These suggest that the endocrine environment tended to be estrogens-dominant with age, in particular, after middle-age, and that patients with large prostates have more estrogens-dominant environments. We conclude that estrogens are key hormones for the induction and the development of BPH.

### **Induction of apoptosis and inhibition of cell proliferation by the lipido-sterolic extract of *Serenoa repens* (LSESr, Permixon) in benign prostatic hyperplasia.**

Vacherot F, Azzouz M, Gil-Diez-De-Medina S, Colombel M, De La Taille A, Lefrere Belda MA, Abbou CC, Raynaud JP, Chopin DK. Groupe d'Etude des Tumeurs Urologiques, Centre de Recherches Chirurgicales, Inserm EMI 99.09, Faculte de Medecine, Creteil, France.

Prostate 2000 Nov 1;45(3):259-66

**BACKGROUND:** To determine the mechanism by which prostate volume increases during the development of BPH and to evaluate the effect of LSESr (Permixon), a phytotherapeutic agent, we investigated apoptosis and cell proliferation in the stroma and epithelium of normal prostate and of BPH tissues from patients treated with or without LSESr.

**METHODS:** MIB-1 staining and the in situ end-labeling assay were used to evaluate the proliferative-apoptotic balance in normal prostates and in BPH tissues. Quantitative assessment was performed using an image analysis system.

**RESULTS:** In normal prostates, there was no significant difference between apoptotic and proliferative indices. Cell numbers and proliferative indices were higher in BPH than in normal prostates, while apoptosis values were similar. In the BPH treated group, LSESr significantly inhibited proliferation and induced cell death in both epithelium and stroma.

CONCLUSIONS: Induction of apoptosis and inhibition of cell proliferation are likely to be the basis for the clinical efficacy of LSESr. Copyright 2000 Wiley-Liss, Inc.

### **Eds. Campbell's Urology, Seventh Edition,**

Walsh, P.C., Retik, A.B., Vaughan, E.D.,

Volumes 1-3 1997 Oct. London: Harcourt Brace.

### **Pygeum africanum for benign prostatic hyperplasia.**

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Cochrane Database Syst Rev. 2002;(1):CD001044

**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 African prune tree, *Pygeum africanum*, is one of the several phytotherapeutic agents available for the treatment of BPH.

**OBJECTIVES:** To investigate the evidence whether extracts of *Pygeum africanum* (1) are more effective than placebo in the treatment of Benign Prostatic Hyperplasia (BPH), (2) are as effective as standard pharmacologic BPH treatments, and (3) have less side effects compared to standard BPH drugs.

**SEARCH STRATEGY:** Trials were searched in computerized general and specialized databases (MEDLINE (1966-2000), EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting relevant manufacturers and researchers.

**SELECTION CRITERIA:** Trials were eligible if they (1) were randomized (2) included men with BPH (3) compared preparations of *Pygeum africanum* (alone or in combination) with placebo or other BPH medications (4) 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 were extracted by at least two independent reviewers using a standard form. The main outcome measure for comparing the effectiveness of *Pygeum africanum* with placebo and standard BPH medications was the change in urologic symptoms scale scores. Secondary outcomes included change in urologic symptoms including nocturia and urodynamic measures (peak and mean urine flow, prostate size). The main outcome measure for adverse effects was the number of men reporting adverse effects.

**MAIN RESULTS:** A total of 18 randomized controlled trials involving 1562 men met inclusion criteria and were analyzed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double-blinded. There were no studies comparing *Pygeum africanum* to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors. The mean study duration was 64 days (range, 30-122 days). Many studies did not report results in a method that permitted meta-analysis. Compared to men receiving placebo, *Pygeum africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI), -1.4, -0.3 (n=6 studies)]). Men using *Pygeum africanum* were more than twice as likely to report an improvement in overall symptoms (RR=2.1, 95% CI = 1.4, 3.1). Nocturia was reduced by 19%, residual urine volume by 24% and peak urine flow was increased by 23%. Adverse effects due to *Pygeum Africanum* were mild and comparable to placebo. The overall dropout rate was 12% and was similar between *Pygeum Africanum* (13%), placebo (11%) and other controls (8%).

**REVIEWER'S CONCLUSIONS:** A standardized preparation of *Pygeum africanum* may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia. However, the reviewed studies were small in size, were of short duration, used varied doses and preparations and rarely reported outcomes using standardized validated measures of efficacy. Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. These trials should be of sufficient size and duration to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

### **Serenoa repens for benign prostatic hyperplasia.**

Cochrane Database Syst Rev 2000;(2):CD001423

**OBJECTIVES:** This systematic review aimed to assess the effects of Serenoa repens in the treatment of Benign Prostatic Hyperplasia (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:** 2939 men from 18 randomized trials lasting 4 to 48 weeks were assessed. 16 trials were double-blinded and treatment allocation concealment was adequate in 9 studies. Compared with placebo, Serenoa repens improved urinary symptom scores, symptoms, and urinary 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 1.75 (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 1.93 ml/sec (95%CI = 0.72, 3.14, n = 8 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 improves urologic symptoms and flow measures compared with placebo. 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.

### **Open study of conservative treatment of prostatic adenoma.**

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Therapiewoche ( THERAPIEWOCHE ) (Germany) 1980, 30/13 (2244-2251)

After 8 weeks' treatment with 2 x 2 capsules of prostagutt per day, 82% of subjective disorders such as pollakisuria, nycturia, dysuria, delayed onset of micturition, weak jet, after-dripping and prolonged duration of micturition were reported improved or eliminated. Prior to treatment, 72% of the subjects showed a clearly reduced uroflow. After the treatment, this could be demonstrated in only 26%. Prolonged duration of micturition was present in 80% before and in 50% after the treatment. 46% of the patients with prostatic adenoma had a rest urine over 30 ml before treatment, as against 12% after the treatment.

### **Antiproliferative effect of Pygeum africanum extract on rat prostatic fibroblasts.**

Yablonsky F, Nicolas V, Riffaud JP, Bellamy F. Laboratoires Debat, groupe Fournier, Garches, France.

J Urol 1997 Jun;157(6):2381-7

The effect of a Pygeum africanum extract (Tadenan) (Pa), used in the treatment of micturition disorders associated with BPH, has been examined on the proliferation of rat prostatic stromal cells stimulated by different growth factors. EGF, bFGF, and IGF-I but not KGF are mitogenic for prostatic fibroblasts in culture. Pygeum africanum inhibits both basal and stimulated growth with IC50 values of 4.5, 7.7 and 12.6 micrograms./ml. for EGF, IGF-I and bFGF, respectively, compared to 14.4 micrograms./ml. for

untreated cells, the inhibition being stronger towards EGF. Pygeum africanum inhibited the proliferation induced by TPA or PDBu in a concentration-dependent manner with IC50 values of 12.4 and 8.1 micrograms./ml. respectively. The antiproliferative effects of Pa were not ascribed to cytotoxicity. These results show that Pygeum africanum is a potent inhibitor of rat prostatic fibroblast proliferation in response to direct activators of protein kinase C, the defined growth factors bFGF, EGF and IGF-I, and the complex mixture of mitogens in serum depending on the concentration used. PKC activation appears to be an important growth factor-mediated signal transduction for this agent. These data suggest that therapeutic effect of Pygeum africanum may be due at least in part to the inhibition of growth factors responsible for the prostatic overgrowth in man.

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