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Original Articles

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Prostasan in the treatment of benign prostatic hyperplasia (BPH)

A plant remedy with a wide clinically confirmed action spectrum

Prostasan capsules contain the native extract obtained from the dried seeds of the saw palmetto *Serenoa repens* or *Sabal serrulata* with the aid of ethanol 96% by volume. Using this method of extraction, not only the fat-soluble constituents but also the hydrophilic components of the plant, can be made available for therapeutic purposes. Characteristic effects are the antiandrogenic, antiphlogistic, antiproliferative and anti-oedematous actions on the diseased prostate gland. The first-mentioned effect can be explained biochemically by the inhibition of both 5α-reductase and the binding of 5α-dihydrotestosterone (DHT) to receptors, while the second effect is based on an inhibition of 5-lipoxygenase and cyclo-oxygenase, the central enzyme of arachidonic acid catalysis to leukotrienes and prostaglandins. The causality of the two last-mentioned – and certainly salutary – effects, in contrast, is unspecific or does not involve hormones. In particular the mild forms of BPH, VAHLENSIECK stages I and II, respond well to treatment with this ethanolic extract of dried Sabal seeds when it is administered constantly over a period of years. With respect to tolerability, no reservations apply, even over this necessarily long-term application.

The function of the prostate gland, which surrounds the urethra at the base of the bladder, is to produce, beginning at puberty, seminal fluid to augment the motility of the sperm during insemination. After puberty, this gland attains its normal size of about 3.5×5×2.5 cm, at which it remains until the age of 50. According to McNEAL (1988), the gland is divided into a central, peripheral and transitional zone with androgen receptors that respond to stimulation by 5α-dihydrotestosterone (DHT), and drive the production of the specific prostatic secretion. The male sex hormone, DHT, is produced through the action of 5α-reductase on the testosterone produced in the testicles, and is considerably more potent than the latter. To protect it from being broken down into inactive metabolites, DHT is coupled in the plasma to the sex hormone-binding globulin (SHBG) until it binds to the androgen receptors of the prostate.

Beginning at about the age of 30, the cells of the gland in the region of the transitional zone occasionally undergo hyperplastic growth to produce benign prostatic hyperplasia (BPH), and beyond the age of 80, virtually every man is affected by the condition. The result of this hypertrophy is restriction of the urethra with progressive functional disorders and symptoms affecting the efferent urinary system which, depending on their severity, are divided by VAHLENSIECK into four, and by ALKEN into three, stages **(Table 1)**.

Aetiology and pathogenesis

The aetiology of BPH which, apart from the glandular overgrowth, is also accompanied by an increase in, and inflammatory changes to, the stroma, has not yet been finally clarified, although the hormonal changes taking place in old age, together with a reduction in the testosterone-oestrogen ratio must be considered to be one of

Vahlensieck classification		Alken classification	
Stage	Symptoms	Stage	Symptoms
I	No micturition disorder Uroflow > 15 ml/sec No residual urine No trabeculated bladder	I	Increased urinary frequency Pollakiuria Nocturia Hesitancy in starting micturition Weak stream
II	Variable micturition disorders Uroflow between 10-15 ml/sec Some residual urine possible Incipient trabeculation possible	II	Incipient decompensation of bladder function with residual urine and urgency
III	Persistent micturition disorders Uroflow < 10 ml/sec Residual urine > 50 ml Trabeculated bladder	III	Decompensation of bladder function with urinary retention or overflow bladder and hydronephrosis
IV	Persistent micturition disorders Uroflow < 10 ml/sec Residual urine > 100 ml Distended bladder Upper urinary tract stasis		

Table 1: Classifications of benign prostatic hyperplasia (BPH).

the underlying causes. In this connection, an important role is played by the diminishing gonadal function accompanied by a constant further production of oestrogens in the interstitial cells of Leydig in the testicles, as also in the adrenal cortex, and a constant conversion of testosterone into oestrogens by aromatase.

By way of compensation of this situation, an increase in the activity of the enzyme 5α-reductase occurs, leading to an increase in the production of DHT and thus to an increasing occupation and stimulation of the prostatic androgen receptors **(Figure 1)**. The clearly elevated tissue levels of prostaglandins (in particular PG F2α) and leukotrienes in the prostate gland as 5-lipoxygenase/cyclo-oxygenase metabolites of arachidonic acid, might also act on the hyperplastic growth of the prostate via their cell-proliferative and secretion-enhancing effects. The hypertrophy of the prostate will not necessarily give rise to any symptoms, as long as the urethra is not obstructed and the function of the bladder is not disturbed.

A useful aid for assessing the subjective complaints of a patient is the «International Prostatic Symptom Score IPSS», which takes into account signs of obstruction (hesitancy in starting micturition, slowed micturition, weak, intermittent urine stream, dribbling) and disorders (sense of incomplete emptying of the bladder, progressive urinary frequency, nocturia, tenderness in the lower abdomen, urinary incontinence), and also the resulting problems that give the patient the feeling that his quality of life has decreased.

Objectifiable criteria for determining the severity of the disease include, initially, rectal palpation to determine the approximate size and the consistency of the prostate gland and to distinguish BPH from carcinoma, and then uroflowmetry with measurement of the volume voided per unit of time, and, in particular, suprapubic determination of the amount of residual urine with the aid of ultrasound.

Differential diagnostic considerations must include hypocontractility of the detrussor muscle, infections of the lower urinary tract, urinary calculi, neurological disorders in the lower abdominal segments, diabetes mellitus and, last but not least, also the use of medications which may influence or even hinder voiding of the bladder. These latter include α-adrenergic agonists and parasympatholytic agents.

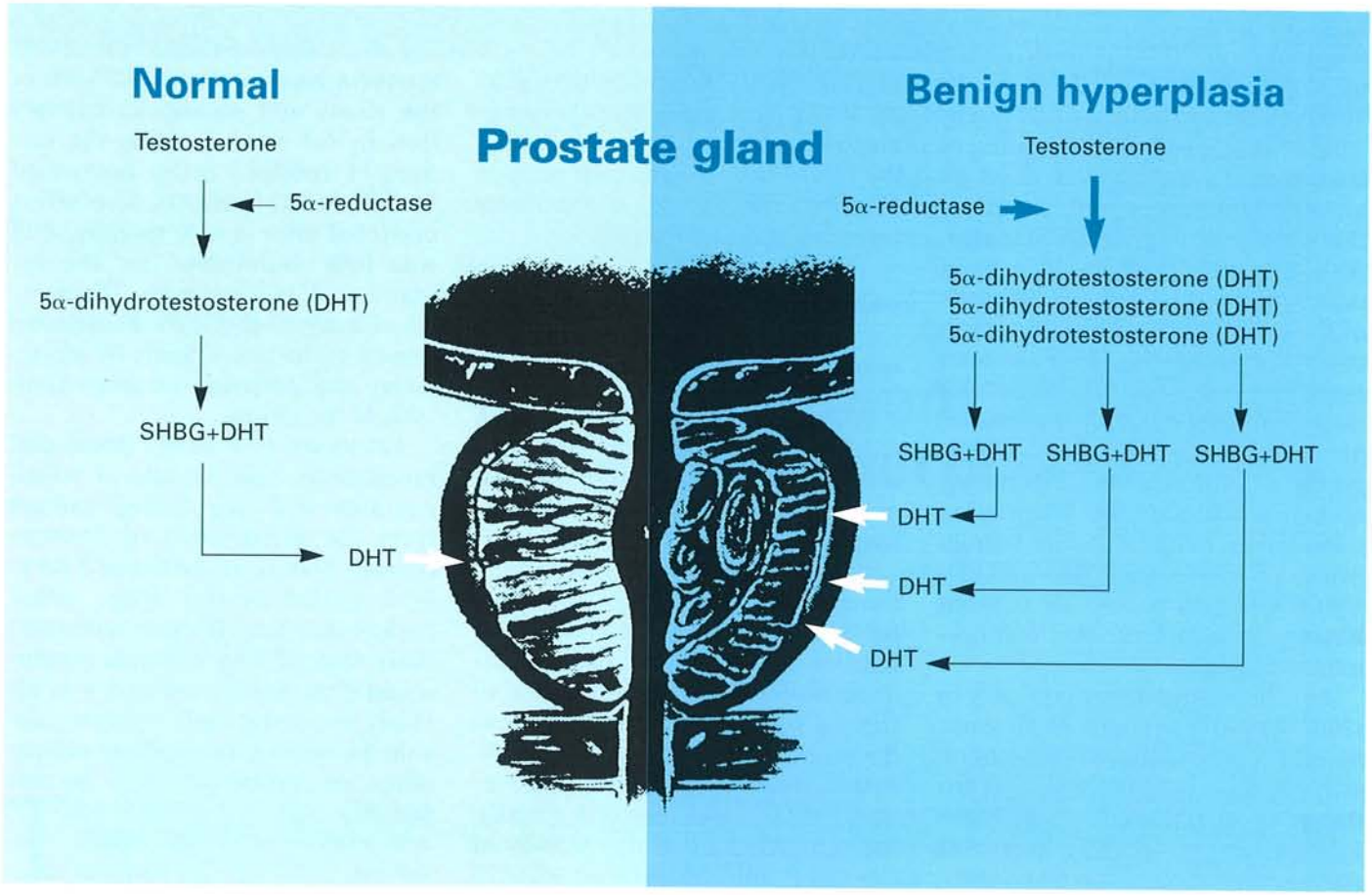

Figure 1: Benign prostatic hyperplasia (BPH) in comparison with healthy prostate (modified from S. Heinzl, 1990). DHT = 5α-dihydrotestosterone as a stimulant of fluid secretion and glandular hyperplasia; SHBG = sex hormone-binding globulin.

Therapeutic possibilities

Therapeutic medications are used not merely in the early stages; alpha-receptor blockers, acting via a reduction in the tone of the smooth muscles, have a dilatory effect on the urethra, but also on the blood vessels. The associated risk of undesired hypotensive circulatory reactions has been considerably reduced by the development of selective alpha-1-blockers.

The antiandrogen medications presently available lack a selective character and are associated with a hardly tolerably loss of male sex characteristics and behaviour. Although the inhibitors of aromatase prevent the conversion of testosterone to oestrogens, they do not interfere with the body's own production of oestrogen. The agonists of the gonadotropin releasing hormone produced by the hypothalamus first cause an increase in the production of the sex hormones in the testicles. On longer administration, however, this hyperstimulation results in chemical castration. In men, therefore, these GnRH agonists are more suitable for the treatment of prostate cancer. Among the synthetic chemical agents, the most successful have proved to be the inhibitors of 5α-reductase with their modified androgen deprivation effect.

In severe cases the *ultima ratio* continues to be surgery. However, at least in the case of the commonly employed transurethral resection of the prostate (TUR-P), despite an anatomically successful procedure, 18% of the patients continue to complain of voiding problems. Furthermore, the postoperative mortality rate is still around 0.5%. Since the beginning of the nineties, therefore, alternative instrumental procedures have been developed, of which, in addition to the intra-urethral implantation of spirals and urethral stents, balloon dilatation, transurethral incision of the prostate (TUIP), transurethral ultrasound-guided laser-induced prostatectomy (TULIP), and transurethral microwave thermotherapy (TUMT) are worthy of mention.

Phytotherapy

In the medical treatment of BPH, plant remedies have a long tradition and, in comparison with synthetic drugs, have the particular advantage of having a wide spectrum of action. The fruits of the saw palmetto *Serenoa repens* (*Sabal serrulata* in the old botanical

nomenclature) that grows in marshy coastal areas in the southern states of North America as well as in Mediterranean countries and North Africa, have, since the beginning of the present century been used as an antiphlogistic agent in infections of the urinary tract, and also, for a number of decades, have been successfully used to treat diseases of the prostate. In the monograph of the Commission E of the German Federal Health Office, extracts of these fruits, for example, Prostasan, are identified as having antiandrogen and antiphlogistic effects and as being «suitable for eliminating micturition complaints in benign prostatic hyperplasia in VAHLENSIECK's stages II and III without having an effect on the enlargement of the gland».

For the assessment of efficacy in studies taking account of all commercial preparations containing only *Serenoa repens* extract, in addition to the patient's subjective micturition symptoms, objective parameters such as uroflowmetry, determination of residual urine and prostate size were also employed. Published data are available from a total of five open observational studies involving 2,416 patients and a treatment duration of between 12 and 48 weeks, 9 placebo-controlled studies involving 583 patients, and a treatment duration of between 4 and 12 weeks, as also two long-term studies in 477 patients and a treatment duration of between 12 and 36 months. In all of these studies, the daily dose of *Serenoa repens* extract was, without exception, 320 mg.

In terms of the effect on the subjective micturition symptoms, a reduction of nocturia by more than 50% was reported throughout, while treatment overall was recorded as successful in 80 to 88% of the cases. Among the objectifiable parameters, the volume of residual urine was also clearly reduced by between 50 and 60%, while urinary flow increased by between 4 and 7 ml per second. In addition, HELPAP et al. (1995) reported a significant reduction in oedema, both periglandular and within the stroma of the prostate vis-à-vis placebo. With respect to tolerability, it can be stated that no recognizable risk was observed during the entire follow-up period of up to 3 years, and 98% of the patients reported good tolerability.

Conclusions

Although the exact mechanism of the mixture of active constituents in *Serenoa repens* extract remains unclear, it may nevertheless be noted that:

The aqueous fraction containing the polysaccharides is responsible for the antiphlogistic and anti-oedematous action, while the antiandrogen effect and the inhibition of the 5α-reductase, and thus a reduction in the production of 5α-dihydrotestosterone may be attributed to the lipid fraction. Finally, an enhancement of the activity of the enzymatic breakdown of DHT by the intraprostatic 3α-hydroxysteroido-oxidoreductase (3α-HSOR) is under consideration. In accord with this are the statements contained in the monograph issued by Commission E based on the results of the studies showing a significant improvement in the quality of micturition and a clear reduction in the volume of residual urine.

Follow-up observations have shown that, over a period of up to 5 years, the symptoms of benign prostatic hyperplasia can improve spontaneously in a third of the cases. For this reason, since May 1995 the requirement established at the conference «International Consultation on Benign Prostatic Hyperplasia» held in Monte Carlo, and subsequently accepted by the WHO, namely that therapeutic studies should be designed to run for a period of at least one year, now applies.

For all commercial preparations containing *Serenoa repens* extract, the prospective long-term observation over a period of three years employing the test extract IDS 89 by BACH (1995) can be used for comparative purposes. In this study, nocturia was improved in 75.3% of the cases and maximum urinary flow by 6.1 ml/sec., while the volume of residual urine decreased by 50% in 315 patients. This effect occurred after 3 to 6 months, and was fully maintained for the remaining 30 to 33 months. The overall efficacy of this extract was assessed to be good, both by physicians and patients, in more than 90% of the cases.

Prostasan is a newly developed medication, one capsule of which contains 320 mg native extract from the dried seeds of *Serenoa repens*. This corresponds to 2.88 to 3.52 grams of the drug, which means that the effective minimum daily dose of 1 to 2 grams recommended in the monograph E is already exceeded with a single capsule. In view of its excellent tolerability, no problems need be expected.

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A list of further references may be requested from the author.

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