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Botanical derivatives for the prostate

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Abstract

The prostate, after the age of 45 years, may undergo benign hyperplasia (BPH). Its etiology has not yet been completely explained, but different factors play a major role in its occurrence, among them, the sexual hormones (with a fundamental role of 5α reductase). The 5α reductase activity and inflammatory aspects in the prostate tissue can be effectively controlled with the use of highly standardized plant extracts (*Pygeum africanum*, *Serenoa repens,* etc.), which yield excellent results in the prophylaxis and treatment of the symptoms linked to prostate hypertrophy. The prostate tissue is not affected only by benign diseases but may also be subject to neoplastic transformation. From an epidemiological point of view, a vegetable derivative, lycopene, was linked with a lower occurrence of prostate carcinoma. A recent clinical study demonstrated that lycopene might not only prevent prostate cancer but also have therapeutic effects.

Keywords: Benign prostatic hyperplasia; Prostatic neoplasm; *Pygeum africanum*; *Serenoa repens*; Lycopene

1. Introduction

The prostate is a gland, only present in males, which is placed immediately below the bladder triangle. Its function is to secrete a milky fluid containing citrate ions, calcium ions, phosphate ions and profibrinolysin. During the emission of the seminal fluid, the prostatic gland contracts rhythmically following the contractions of the ductus deferens and releases its secretion, which thus enriches the seminal fluid.

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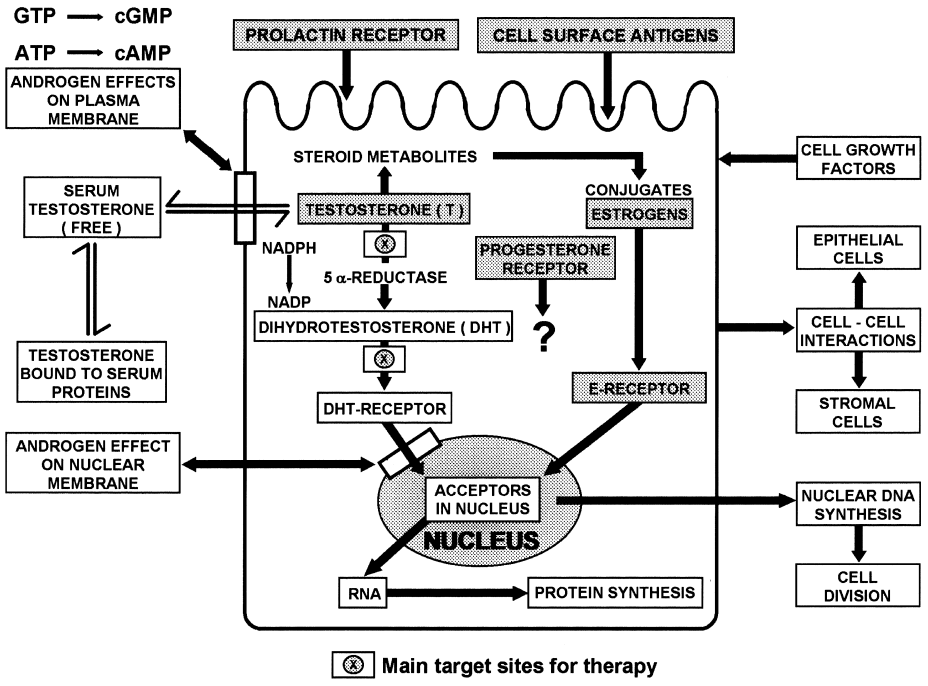

Fig. 1. Factors regulating prostatic growth at a cellular level.

The prostate is often subject to pathological processes of various kinds and seriousness. A slight prostatitis (inflammation of the prostate with or without infection) is quite likely to occur around the age of 45 years. In addition, benign prostatic hypertrophy (BPH) occurs in more than 50% of men over 50. BPH is a slow, progressive enlargement of the fibromuscular and epithelial structures of the gland. This process may lead to ureteral obstruction with urine retention and consequent urinary disorders (e.g. frequent, painful urinations, painful perineal stress, incomplete emptying of the bladder, decrease in urine volume and flow). This disease may be so serious as to require operative procedure.

Vahlensieck [1] classified BPH in four different stages based on its symptoms. A surgical intervention is considered indispensable in stage IV of BPH, in which obstruction and irritation symptoms lead to a marked worsening of the patient's quality of life. In stages II and III, pharmacological treatment may successfully help to control BPH.

Although this disease is widely spread, its etiology has not yet been completely explained. Different kinds of factors play a major role in the occurrence of BPH [2], e.g. sexual hormones, stromal–epithelial interaction, growth factors, insulin and prolactin (Fig. 1). Sexual hormones — above all male sexual hormones — certainly play a major role. In particular, testosterone is transformed in the more active

dihydrotestosterone (DHT) by the action of 5α reductase. DHT combines with androgen receptors, thus promoting protein synthesis with consequent cell growth. In this sense, any anomalous hyperactivity of 5α reductase should be related to BPH, as DHT levels in patients suffering from BPH are four to six times higher than normal [3]. Cholesterol, as well as its metabolite, 5α, 6α-epoxycholesterol, also seem to play an important role in the etiopathogenesis of prostate diseases. Cholesterol and its esters are involved in the metabolism of androgens and, therefore, are responsible for the increased number of androgen receptors [4].

2. Phytotherapy

The role of 5α reductase, cholesterol and inflammation in the prostate tissue can be effectively controlled with the use of highly standardized plant extracts (*Pygeum africanum*, *Serenoa repens,* etc. [5]), which yield excellent results in the prophylaxis and treatment of the symptoms linked to prostatic hypertrophy. The use of plant derivatives as drugs against prostate diseases is very common in Germany, but there are also examples in other European countries. At present, European plant-based drugs are being extensively introduced in the USA as dietary supplements, although it cannot be excluded that in the end they will be classified as drugs.

These plant extracts, for their nature, may show similarities in their composition, containing various active ingredients, such as phytosterols, phytoestrogens, triterpenes, free or esterified fatty acids, long-chain fatty alcohols, lectins and lignans (flavonoids). These substances possess anti-androgenic and anti-inflammatory activity, inhibit prostaglandin synthesis and cell proliferation, and relax smooth muscle. The effects of these extracts, therefore, are not related to the activity of one component, but are more likely based on the additive and/or synergic action of all their components [6,7].

3. *Pygeum africanum*

The standardized *P. africanum* (*Prunus africana*) extract has been used clinically for BPH treatment since 1969 [8]. Characterized by the presence of phytosterols (with anti-inflammatory effects), pentacyclic triterpenes (with anti-edematous activity) and ferulic acid esters (possessing a powerful hypocholesterolemic activity), *Pygeum* extract has been tested altogether in thousands of patients suffering from BPH with much better results than those exhibited by controls. In a highly reliable and significant clinical trial [9], conducted in double-blind pattern against placebo on over 100 patients per group, statistically significant variations were observed in all the most important urinary parameters affected by BPH after 2 months' treatment (Fig. 2).

Of the various pharmacological tests aimed at studying the mechanism of action in depth, the castrated rat model proved to be of particular interest [10]. It resulted

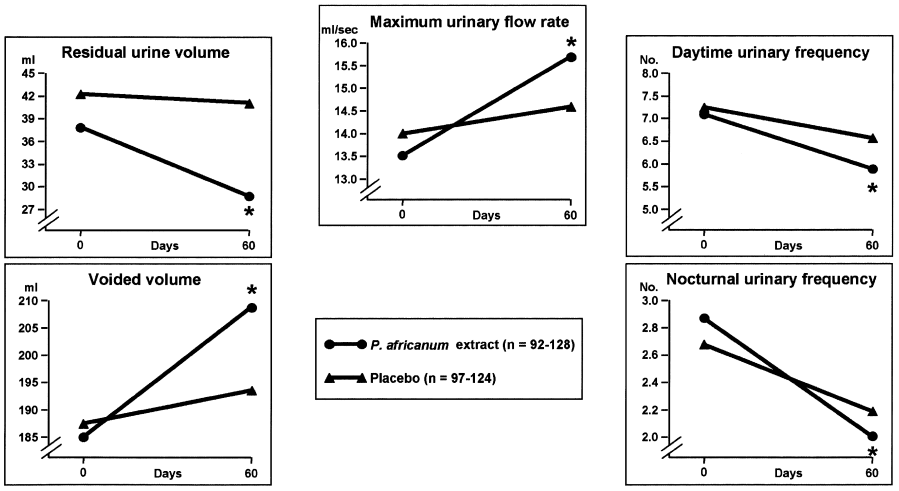

Fig. 2. Effect of *P. africanum* bark extract on urinary parameters in patients suffering from BPH. Mean values before treatment (day 0) and after its end (60 days); $^{*}P < 0.05$ vs. placebo.

from this test that *Pygeum*, following its intraperitoneal administration, antagonized testosterone in the prostate and seminal vesicles (Table 1).

More recently, it was reported that *Pygeum* inhibited the production, induced by the 5-lipoxygenase enzyme, of such metabolites as chemotactic leukotriens by human polymorphonuclear cells stimulated by means of calcium ionophore A23187 (Fig. 3). This means that *Pygeum* can prevent the inflammatory cells — that appear to be involved in the BPH development — from infiltrating into the prostate [11].

Table 1
Effects of *P. africanum* bark extract on prostate and seminal vesicles weights in castrated rats[a]

Treatment	Dose (mg/kg i.p. for 20 days)	Initial body weight (g)	Body weight gain (g)	Prostate (mg)	Seminal vesicles (mg)
Castrated controls	–	87 ± 2	103 ± 4	4.6 ± 1.2	13.3 ± 1.5
Testosterone s.c. 0.2 mg/rat/day	–	90 ± 2	126 ± 4	244.6 ± 12.8[b]	503.9 ± 43.1[b]
P. africanum	1	87 ± 2	110 ± 3	4.9 ± 1.1	13.3 ± 0.9
	10	88 ± 3	15 ± 4	7.0 ± 1.4	14.7 ± 0.8
P. africanum + testosterone	1	88 ± 2	117 ± 4	172.0 ± 17.9[b]	329.2 ± 35.3[c]
	10	92 ± 2	120 ± 5	214.8 ± 20.6	370.9 ± 33.8[c]

[a] Values are mean ± S.E.; $n = 12$.
[b] $P < 0.05$ vs. castrated controls.
[c] $P < 0.05$ vs. testosterone.

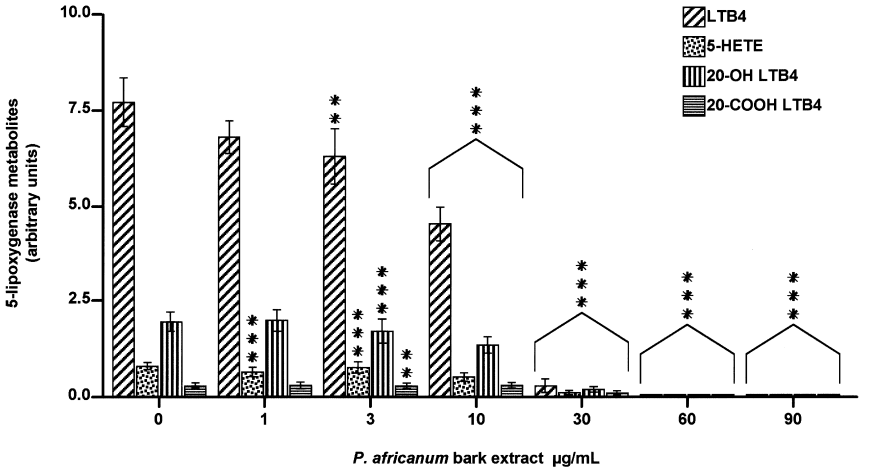

Fig. 3. Effect of *P. africanum* bark extract on the production of 5-lipoxygenase metabolites stimulated by calcium ionophore A23187 in human polymorphonuclear cells. Arbitrary units = peak area of the metabolite/peak area of the internal standard (19-OH PGB_2). Values are mean ± S.E.; $n = 5$; $^{**}P < 0.01$, $^{***}P < 0.001$, Dunnett's *t*-test vs. controls (0).

4. *Serenoa repens*

The efficacy and non-toxicity of the standardized *S. repens* extract (in particular that obtained from extraction with CO_2 in supercritical conditions, i.e. without using organic solvents [12]) have been demonstrated by pharmacological, toxicological and clinical trials, with the latter having been conducted in thousands of patients and, in some cases, according to the double-blind pattern against placebo [13]. The extract is characterized by the presence of fatty acids (in particular oleic and lauric acids), sterols (including β-sitosterol) and long-chained alcohols. The mixture of these components and, above all, the presence of lauric acid, gives the

Table 2
5α reductase activity in isolated hypertrophic prostate tissues in presence of *S. repens* extract and fatty acids[a]

Substance	Epithelium	Stroma
Controls	100	100
Serenoa repens extract	72 ± 8.4	55 ± 4.3
Palmitic acid	98 ± 8.0	100 ± 5.2
Oleic acid	96 ± 2.3	102 ± 3.6
Lauric acid	49 ± 1.8	58 ± 2.3
Myristic acid	57 ± 2.8	66 ± 1.0

[a] Values are mean ± S.E.; $n = 6$. Testosterone: 580 nM; extract: 500 μg/ml; fatty acids: 2 mM.

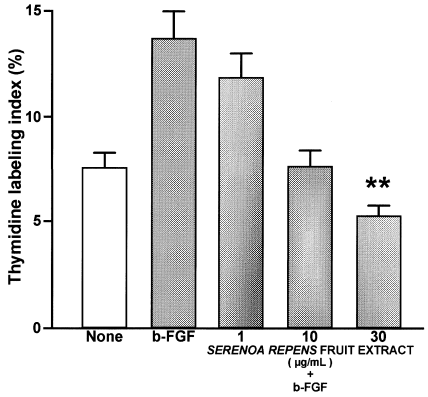

Fig. 4. Effect of *S. repens* fruit extract on b-FGF-induced prostate (glandular epithelium) cell proliferation. Proliferating cells labeled by [^{3}H]thymidine and cultures stopped after 72 h. Results expressed as thymidine labeling index (percentage of cells marked after autoradiographic revelation). Values are mean ± S.E.; $n = 5$; $^{**}P < 0.01$ vs. cells incubated with b-FGF, F test of Fisher (ANOVA).

extract properties capable of inhibiting 5α reductase (Table 2); as mentioned above, this enzyme is involved in testosterone metabolism and is partly responsible for BPH [14].

A number of other mechanisms of action have been observed in the whole extract. For example, the extract can interfere with the synthesis of inflammatory metabolites of arachidonic acid by inhibiting the activity of cycloxygenase and lipoxygenase [15]. Another in-vitro experiment (Fig. 4) demonstrated that the extract can, depending on its concentration, inhibit prostate cell proliferation, induced by the presence of the basic fibroblastic growth factor in the culture medium [16].

The clinical use of *Serenoa* has highlighted its capability of improving urodynamic parameters, urine flow values, residual urine volume and all the other symptoms typical of BPH to a similar degree to that obtained with a synthetic-specific drug (e.g. finasteride) [17]. It should also be noted that the use of this extract rarely causes the onset of such side effects as a decreased libido or sexual power (which are quite common in the treatment of this benign form), nor does it modify the PSA value (the prostate soluble antigen that is the marker of prostatic neoplasms), thus allowing the immediate identification of any neoplastic transformation of the gland [18].

5. Lycopene

The prostate tissue, however, is not affected only by benign diseases, but like other tissues, may be subject to neoplastic transformation. Prostate neoplasms —

Table 3
Comparison of carotenoid concentration in paired normal and tumoral tissues from human prostates[a]

Substance	Normal tissue (nmol/g)	Tumoral tissue (nmol/g)
Lycopene	0.63 ± 0.09	0.91 ± 0.13[b]
All-*trans* β-Carotene	0.48 ± 0.06	0.60 ± 0.08[b]
9-*cis* β-Carotene	0.38 ± 0.06	0.40 ± 0.07
α-Carotene	0.35 ± 0.06	0.35 ± 0.05
Lutein	0.26 ± 0.05	0.33 ± 0.05
cis ± *trans* α-Cryptoxanthin	0.22 ± 0.03	0.29 ± 0.03
Zeaxanthin	0.19 ± 0.04	0.29 ± 0.06
β-Cryptoxanthin	0.14 ± 0.02	0.18 ± 0.03
Total carotenoids	2.65 ± 0.25	3.35 ± 0.32[b]

[a] Values are mean ± S.E.; $n = 25$.
[b] $P < 0.05$ (pairwise comparison).

which are quite common after the age of 65–70 years — may originate as such or be the consequence of a malignant degeneration of a previous BPH.

From an epidemiological point of view, a vegetable derivative, lycopene, was recently linked to a lower occurrence of prostate carcinoma [19]. This red pigment extracted from tomato peel (*Lycopersicum aesculentum*) is an acyclic carotenoid. The biological properties of lycopene — a highly lipotropic molecule which, unlike beta-carotene, does not have any provitamin A activity — are several and range from a 'simple' antioxidant activity (lycopene is the most powerful antioxidant known so far and acts at an extremely low molarity) to neoplasm growth control and a recently hypothesized hypocholesterolemia-inducing effect capable of reducing the risk of atherosclerosis. A study indicated that this substance (Table 3) is more abundant in neoplastic than in healthy prostate tissue taken from the same subject [20]. Lycopene probably exerts its preventive action against neoplastic growth by reducing IGF-I (insulin-like growth factor I) levels, this being a molecule often reported to be responsible for cancer formation [21].

A recent clinical study demonstrated for the first time that lycopene might not only prevent prostate cancer — as had been thought so far — but may also have therapeutic effects [22].

6. Conclusions

To sum up, although there are objections that botanical derivatives are generally not supported by double-blind trials conducted over long periods (some years), it should be recognized that they are effective in the treatment of the first stages of benign prostate hyperplasia and prospectively useful also in the treatment of prostate neoplasms, thus making this field one of the finest examples of phytotherapy.

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