SABALSELECT™

A NATURAL REMEDY FOR THE RELIEF OF UROLOGICAL DISORDERS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA

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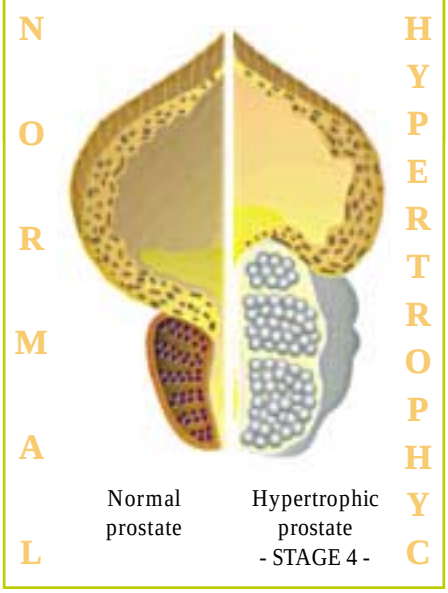
BENIGN PROSTATIC HYPERPLASIA

The prostate represents one of the largest glands in the human body and it supplies a great number of biological components to the seminal plasma.
The size of the prostate increases slowly from the time of birth until puberty.[1]
A rapid increase then occurs until the third decade is reached.
After this period the size of the organ remains constant until about the age of 45 years. Starting at this time the prostate may either not show any pathological change or it may undergo a progressive enlargement (Fig. 1) with the development of the clinical feature of the benign prostatic hyperplasia (BPH)[1-5] (Table 1).
Different factors seem involved in the etiology of BPH such as sexual hormones, stromal-epithelial interactions, stem cells, growth factors, prolactin.[4]
Among these, sexual hormones, in particular testicular androgens and estrogens are recognized to control the prostate growth. In the normal male the major circulating androgen is testosterone which is almost exclusively of testicular origin. Circulating testosterone diffuses across plasma membrane and then it is transformed into dihydrotestosterone (DHT) within the prostatic gland by 5α-reductase.

DHT binds to cell androgen receptors at level of epithelial and stromal structure, promoting the synthesis of nuclear mRNA and consequently the production of proteins in cytoplasm and cell replication.[2,4]
Estrogens, which are formed in men by the aromatase system from testosterone and androstenedione, may contribute to the proliferation of stromal cells.
Also stromal growth factors seem to play a role in the pathogenesis of BPH, in particular the basic fibroblastic growth factor (b-FGF).[4]

Fig. 1 Benign Prostatic Hyperplasia.



The urinary symptomatology associated with BPH is due both to mechanical and dynamic factors: growth of the glandular mass and increase of the smooth muscle tone of the prostate and urethra, due to stimulation of α-adrenergic receptors.[6,7]
In addition inflammatory processes may contribute to the development of BPH: prostaglandins and leukotrienes are reported to be involved as mediating agents and also in the evolution of inflammatory symptoms.[7,8]
The therapy of BPH has the main goal of reducing the urological disorders and delaying surgery.
According to Table 1, at the 4th stage the only effective therapy is surgical whereas, at the 2nd and 3rd stages, the pharmacological approach has been proved to be a valid help in the management of BPH.
Among the pharmacological remedies for BPH, some active principles obtained from the plant kingdom today play a very remarkable role.[7,9]
This is the case of lipophilic extracts of *S. repens* fruits (namely obtained by supercritical CO_2 or n-hexane) which are today widely used in clinical practice.

Table 1 Vahlensieck's classification of benign prostatic hyperplasia (BPH).

	Pharmacological approach		Surgical approach
STAGE 1	**STAGE 2**	**STAGE 3**	**STAGE 4**
• Normal micturition	• Periodic disorders of micturition	• Permanent disorders of micturition	• Permanent disorders of micturition
• Moderate hyperplasia	• Moderate hyperplasia	• Hyperplasia	• Hyperplasia
• Uroflow over 15 mL/sec	• Uroflow between 10 and 15 mL/sec	• Uroflow under 10 mL/sec	• Uroflow under 10 mL/sec
• No residual urine	• Residual urine under 50 mL	• Residual urine over 50 mL	• Residual urine over 100 mL
• No "trabecula" bladder	• No or only initial evidences of "trabecula" bladder	• "Trabecula" bladder	• Dilated bladder
			• Residual urine in the upper urinary tract

SERENOA REPENS

Serenoa repens (Bartram) J.K. Small (syn: *Sabal serrulatum* Schult. f.) named also saw palmetto, is a low shrubby palm native to North America where it grows in pine woods and among the sandy dunes in the coastal lands of South Carolina, Louisiana, Georgia and Florida.[10]

The partially dried, ripe fruits were used in traditional American medicine to produce a drug useful for treatment of troubles of the bladder, urethra and prostate.[11]

The first observations concerning the therapeutic applications of *S. repens* are contained in an exhaustive review by A.L. Marcy that appeared in a number of American Journal of Urology of the year 1892.

The full description of the drug is given in "The dispensatory of the United States of America" - The 23rd Edition (1943).

A monograph on the *S. repens* fruit is reported in the British Herbal Pharmacopoeia (1979).

In 1989 the Commission E for Phytotherapeutic Substances of the German Federal Health Office published a positive monograph on the *Sabal fructus* (Bundesanzeiger No. 43, 2nd February 1989).

SABALSELECT™

The fruits of *S. repens* are extracted with supercritical CO_2.[12,13]

The pressure and temperature conditions of extraction are critical for the pharmacological effect.[13]

This extractive procedure, conducted at 45 °C / 220 bar, directly produces a pharmacological product (SABALSELECT™) which can be used without further purifications.

Table 2 shows the chemical composition of SABALSELECT™ with the percentages of fatty acids, alcohols and sterols.

PHARMACOLOGICAL ST

The earliest *in vitro* pharmacological studies proved that *S. repens* fruit extract inhibited the 5α-reductase activity in human foreskin fibroblasts and the binding of androgens to the specific receptor.[14,15]

The inhibition of 5α-reductase activity has more recently been confirmed,[16,17] whereas the block of DHT binding with the prostatic receptor is still controversial.[9,16]

S. repens extract can influence the synthesis of inflammatory metabolites through a dose related inhibition of cycloxygenase and lipoxygenase activities (IC_{50} values: 28 and 18 µg/mL)[12] (Fig. 2).

Moreover it has recently been reported that the extract (5 µg/mL) is able to inhibit the production of chemotactic leukotrienes by human polymorphonuclear cells, stimulated with the calcium ionophore A23187.[18]

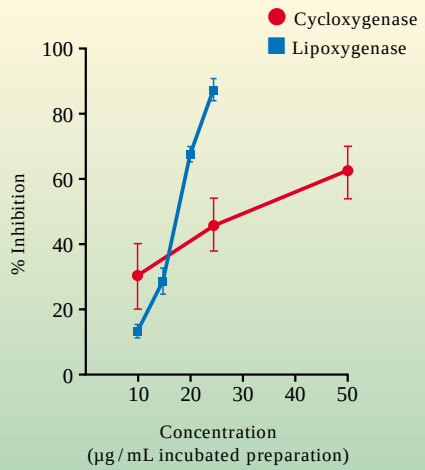
The inhibiting activity showed by *S. repens* extract on both 5α-reductase activity and the enzymes of arachidonic acid metabolism appeared localized in the acidic lipophilic fraction of the extract.[12,19]

An inhibition of b-FGF-induced proliferation of human prostate cell

Table 2 Chemical composition of SABALSELECT™.

Fatty acids	Content (%)	Fatty alcohols and sterols	Content (%)
Total fatty acids	**93.5**	**Fatty alcohols**	**0.20**
		Hexacosanol	0.017
Saturated	**59.8**	Octacosanol	0.146
Caproic acid	1.5	Tetracosanol	0.004
Caprylic acid	2.3	Triacontanol	0.033
Capric acid	2.5		
Lauric acid	30.2	**Sterols**	**0.32**
Myristic acid	12.0	Campesterol	0.07
Palmitic acid	9.5	Stigmasterol	0.03
Stearic acid	1.8	ß-Sitosterol	0.22
Unsaturated	**33.7**		
Oleic acid	28.5		
Linoleic acid	4.6		
Linolenic acid	0.6		

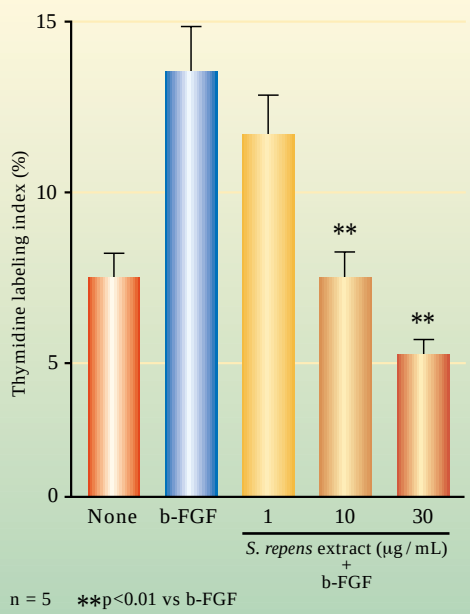
Fig. 2 *In vitro* concentration-dependent inhibition of the cycloxygenase and lipoxygenase activities by the *S. repens* fruit extract prepared with CO_2.



TUDIES

cultures has also been reported for the extract and for some of its components (unsaturated fatty acids, hexacosanol and the unsaponified fraction) (Fig. 3).[20]
Spasmolytic and smooth muscle relaxing activities have recently been described for a *S. repens* extract.[21,22]
These effects seem due to an activation of the sodium/calcium exchanger, an interference with intracellular calcium mobilization possibly cAMP-mediated, and also an α-adrenoceptor antagonistic property.
In vivo experimental studies in mice and rats confirmed that *S. repens* extracts have peripheral antiandrogenic activity as well as anti-inflammatory and antiedema properties.[15,23,24] In a model of transplantation of human BPH tissue into athymic nude mice, systemic therapy with an extract of *S. repens* fruit significantly inhibited the tissue growth.[25]
The *S. repens* extract turned out to be well tolerated orally in rats and in dogs up to the dose of 2 g/kg daily for 6 months.
The extract is also devoid of mutagenic and teratogenic effects and has no effect either on fertility or libido.[26]

Fig. 3 Effect of *S. repens* fruit extract on basic fibroblastic growth factor (b-FGF)-induced prostate cell proliferation.



PHARMACOKINETICS

The pharmacokinetic parameters obtained in a bioequivalence study, between two oral formulations, carried out on 12 healthy subjects, indicated that *S. repens* extract (320 mg or 160 mg capsules) was rapidly absorbed with peak times of 1.50-1.58 h, and peak plasma levels of 2.5-2.7 µg/mL. The area under curve values ranged from 7.99 to 8.42 µg • h/mL.[27]
The tissue distribution of some of the main chemical constituents of the *S. repens* extract was investigated in rats after administration of *S. repens* extract supplemented with [^{14}C]-labeled oleic and lauric acids or β-sitosterol.
The whole-body autoradiographic investigation demonstrated that the highest uptake of radioactivity was found in prostatic tissues of the rats which were treated with the extract supplemented with [^{14}C]-labeled oleic acid.[28]

CLINICAL USE

The clinical efficacy of the *S. repens* extract in mitigating the urological disorders associated with BPH and its good tolerability are documented by several clinical studies, carried out on patients suffering from mild to moderate BPH.[29-31] In Table 3 are reported the main double-blind placebo-controlled studies.[32-39] The efficacy and safety of the liposteroidal extract (160 mg p.o., twice a day), obtained by supercritical CO_2 have recently been evaluated in a multicenter double-blind, placebo-controlled study carried out on 238 BPH-patients.[39]
The extract was well tolerated and significantly improved, in comparison with the placebo group, the total symptomatological score (daytime and nocturnal urinary frequency, dysuria, urgency, hesitancy), the quality of life score and the urinary volume.
Side effects, mainly gastrointestinal, were observed in 2.5% of the verum patients and in 3.7% of the placebo patients. The same extract proved to be a safe and effective treatment for mictional troubles associated with BPH in two 3-month open studies[40,41] carried out on 505 and 356 patients suffering from BPH, respectively. A study of therapeutic equivalence between two oral dosage forms (160 mg, b.i.d. and 320 mg o.d., for 1 year), has been carried out on 132 patients.[42]
Both dosage forms significantly improved the clinical symptomatology, evaluated by the international prostate symptom score (I-PSS), quality of life score, prostatic volume, and urodynamic parameters. The results of the most recent clinical studies confirm those obtained in the previous studies carried out on large number of patients.[9,43,44]
In a 6-month multicenter double-blind equivalence study[45] the efficacy of a *S. repens* extract (320 mg p.o., daily) appeared comparable with that of finasteride (5 mg p.o., daily), with regard to the symptomatology associated with BPH, evaluated by I-PSS, the peak urinary flow rate and quality of life score. Unlike finasteride, the extract did not modify the serum prostate specific antigen concentration and had minimal effects on the prostate volume. Furthermore, the patients treated with *S. repens* extract complained minimal changes in the sexual function.

Table 3 *S. repens* fruit extract. Double-blind clinical trials carried out on benign prostatic hyperplasia (BPH) patients.

Number of reference	Number of patients	Period of treatment (days)[a]	Improvement in urodynamic parameters and clinical symptomatology (% difference vs baseline)	Comparison vs placebo	Tolerability
32	22	60	Voided volume (+43), maximum and mean flow (+43, +55), dysuria (-37), nocturia (-59)	Statistically significant differences	Excellent
33	30	30	Maximum and mean flow (+33, +29), residual urine (-51), daytime and nocturnal urinary frequency (-32, -50), strangury in 92% of cases	Clearly different	Excellent
34	110	28	Voiding rate (+50)•, residual urine (-42)•, dysuria, nocturia (-46)•	Statistically significant differences	Excellent
35	30	31-90	Maximum and mean flow (+26, +61)*, voided volume (+19)*, daytime and nocturnal urinary frequency (-42, -74)	Clearly different	Excellent
36	80	12 weeks	Urinary flow rate (+35)**, nocturnal urinary frequency (-36)•, urgency (-36)**, hesitancy (-59)•, terminal dribbling (-37)•	No statistically significant differences	Good
37	40	90	Residual urine (-59)**, daytime and nocturnal urinary frequency (-42, -67)**	Statistically significant differences	Excellent
38	176	30	Maximum flow (+29)•, daytime and nocturnal urinary frequency (-11, -32)•, dysuria in 31% of cases	Statistically significant differences	Excellent
39	238	3 months	Urinary volume, daytime and nocturnal urinary frequency (-51, -67), urgency (-57), dysuria (-44)	Statistically significant differences	Good

[a] Unless otherwise specified. Dosage: 320 mg / day p.o. in two divided doses. * p <0.05, ** p <0.01, • p <0.001 vs baseline.

CONCLUSIVE REMARKS

The bulk of the results obtained in several double-blind placebo-controlled clinical trials and in multicenter open clinical studies demonstrates that *S. repens* extract is an effective and safe treatment for the relief of urological disorders associated with BPH.[46]

Because of the complex composition of the extract, a multiple mechanism of action seems underlie to its therapeutic activity:

- Inhibition of 5α-reductase activity[16,17]
- Double blocking of cycloxygenase and lipoxygenase activities[12]
- Inhibition of chemotactic leukotriene production by inflammatory cells[18]
- Attenuation of proliferative response of prostate cells to growth factors[20]
- Inhibitory effect on nuclear estrogen receptors[47]
- α-Adrenoceptor antagonistic properties[22]
- Interference with the action of prolactin[48]

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