

An original CO₂ *Serenoa repens* fruit extract

Specifically developed for improving symptoms associated with BPH

Clinical and pharmacological data support its efficacy

A safe product, devoid of any side effect

Sabalselect®

Serenoa repens fruits

■ **Benign Prostatic Hyperplasia (BPH)**, a non-malignant overgrowth of the prostatic tissue surrounding the urethra, can ultimately constrict the urethral opening and give rise to associated **Lower Urinary Tract Symptoms (LUTS)** such as urgency, frequency, nocturia, incomplete bladder emptying, and weak urine stream. In fact, urologists today consider the treatment of LUTS that have been associated with BPH to be at the main aim of therapy since many of these symptoms are not due to an enlarged prostate.

If not treated, serious complications can occur in men with BPH, including acute urinary retention, renal insufficiency and failure, urinary tract infection, and also bladder stones.

The exact etiology of BPH is not known; however, the similarity between this pathology and the embryonic morphogenesis of the prostate has led to the hypothesis that BPH may result from a “reawakening” of embryonic induction processes in adulthood.

Histologically distinguishable BPH is present in about 8% of men aged 31 to 40 years, and this prevalence increases markedly with age to **about 90%** by the ninth decade of life establishing this pathology as a chronic disease that spans decades.¹

The therapy of what is generally termed BPH has the main goal of reducing the urological symptoms associated with the condition and delaying surgery.

The evaluation of the urological symptoms associated with BPH are mainly measured by three similar scores: the Vahlensieck, the AUASI and the I-PSS rating. All these methods are based on a limited number of questions associated with a numbered



score: the total score is an evaluative index of BPH associated urinary severity which can be from “mild” to “moderate” or “severe”. Severe symptoms that are associated with a very large prostate may require surgery.

The same mild to moderate urinary symptoms may be caused by infections or other more severe conditions including prostate cancer, and therefore should always be evaluated by a health care professional before any self treatment.

Serenoa repens extract is indicated to **improve symptoms** associated with **mild form of BPH**, and in particular, symptomatology should be considered before any treatment. Among the pharmacological remedies for the BPH, some active principles obtained from plant kingdom today play a very remarkable role.^{2,3}

Clinical Use

The BPH treatment goals are an **improvement of micturition disorders**, the decrease of urinary frequency and the decrease of residual urine volume. The clinical efficacy of Sabalselect® in mitigating the urological symptoms associated with BPH has been documented by several clinical studies (Table 1), carried out on patients suffering from mild to moderate BPH³⁻¹⁰ but has not been demonstrated to be effective in case of severe BPH symptoms.¹¹

There is evidence that Sabalselect® carries out its action specifically in the prostate tissue, without effecting systemic changes of hormone levels.¹² The clinical efficacy and tolerability of Sabalselect® has been assessed in 2000 men affected by mild or moderate BPH.³ The treatment with 160 mg twice a day for 12 weeks resulted in a significant reduction of volume of residual urine (-46%); half of the patients reached normal values at the end of treatment.

Table 1. Sabalselect®. Clinical trials carried out on Benign Prostatic Hyperplasia (BPH) patients.

Reference number	Number of patients	BPH Severity	Period of treatment	Improvement in urodynamic parameters and clinical symptomatology (% difference vs baseline)	Comparison vs placebo	Tolerability
3	2000	Mild/Moderate	3-6 months	Residual urine (-46) dysuria, nocturia in about 60% of cases	Not available	Very good
4	40	Medium/Moderate	90 days	Residual urine (-59) daytime and nocturnal urinary frequency (-42, -67)	Statistically significant	Excellent
5	238	Moderate	3 months	Urinary volume, daytime and nocturnal pollakiuria (-51), nocturia (-67), urgency (.57), dysuria (-44)	Statistically significant	Very good
6	505	Mild/Moderate	3 months	International Prostate Symptom Score (I-PSS) (-35), quality of life score (QoL), urinary flow rates, residual urinary volume, prostate size residual urinary (-20), maximum and mean flow (+25, +27), prostate volume (-11)	Not available	Very good
7	356	Mild/Moderate	3 months	I-PSS, QoL, toucher rectal score	Not available	Very good
8	132	Mild/Moderate	1 year	Maximum and mean flow (+22, +17), residual urine (-12), I-PSS (-60), QoL in 85% of cases	No significant differences between the two dosage forms (160 vs 320 mg/day)	Very good
9	578	Mild/Moderate	3 months	Residual urine (-48), flow rate (+52), nocturia in 59% of cases	Not available	Good - Very good
10	1334	Mild/Moderate	3 months	Residual urine (-50), pollakiuria (-37), nocturia (-54) dysuria in 38% of cases	Not available	Very good
11	225	Moderate/Severe	1 year	American Urological Association Symptoms Index (AUASI) (-0.68), urinary flow rate (+ 0.42 ml/min)	No significant differences vs placebo	Very good

Nocturia (having to wake up to urinate at night) decreased in about 60% of cases while dysuria (painful or difficult urination) has been relieved in up to 62.5% patients. Same results have been obtained in another arm where 320 mg has been given for 6 months. The product was very well tolerated proving to be safe for chronic use.

Sabalselect® (160 mg twice a day), in a multicenter double-blind, placebo controlled study carried out on 238 BPH-patients⁵ significantly improved, in comparison with the placebo group, the total symptomatology score (daytime and nocturnal urinary frequency, dysuria, urgency, hesitancy), the quality of life score and the urinary volume. It was very well tolerated, 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 urinary symptoms associated with BPH in two 3-months open studies^{6,7} 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.⁸ Both dosage forms significantly improved the clinical symptomatology, evaluated by the International Prostate Symptom Score (I-PSS), i.e. quality of life score, prostatic volume, and urodynamic parameters. Clinical trials involving a large number of

BPH patients^{9,10} confirmed the efficacy of Sabalselect[®] in alleviating the urological disorders with an equivalent extent of improvement.

Unlike finasteride, the BPH prescription drug, the extract did not modify the serum prostate specific antigen concentration, and all the patients treated had no or minimal changes in the sexual function.

A meta-analysis published by the Cochrane Collaboration showing 21 clinical trials involving over 3,000 men concluded that *S. repens* provides improvement in urinary symptoms and flow measures in patients with mild to moderate

symptoms associated with BPH.¹³

Serenoa repens showed benefits compared to placebo and compared to the prescription drug finasteride with significantly fewer adverse treatment events.

The clinical overall experiences have clearly shown that **Sabalselect[®]** is as safe as placebo and can be a rational **first line of treatment for mild symptoms** before more potent pharmacological therapies are needed and after any more serious illness as the underlying cause has been excluded.

Pharmacokinetics

The pharmacokinetic parameters obtained in a bioequivalence study of two oral formulations, carried out on 12 healthy subjects, indicate 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 AUC values ranged from 7.99 to 8.42 µg•h/ml.¹⁴ The tissue distribution of some of the main chemical

constituents of the *S. repens* extract was investigated in rats after administration of the extract itself supplemented with [¹⁴C] 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 [¹⁴C] oleic acid.¹⁵

Serenoa repens

Serenoa repens (Bartr.) Small (also named 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 Florida¹⁶; it is also reported to be very well-adapted to surviving fires.^{17,18,19}

The partially dried, **ripe fruits** were used in traditional American medicine to produce a drug useful for treatment

of bladder, urethra and prostate disorders.²⁰

Recently, full descriptions of the drug are given in "World Health Organization's Monographs on Selected Medicinal Plants, Volume II (2002)", in the "ESCOP Monographs, Second Edition (2003)", and on "Encyclopedia of Dietary Supplements (2005)".

Furthermore, *Serenoa repens* fruits used by Indena are in **compliance with European Pharmacopoeia 5.0.**

Chemical profile

There are several possibilities to prepare lipophilic extracts, but those involving ethanol, normal hexane and CO₂ as solvents are the most used.

Indena focussed on the last extractive procedure to prepare an **highly standardized extract**, with particular and **reproducible phytochemical characteristics**.

The operative conditions such as pressure and temperature are crucial for the pharmacological effect²¹, as it was possible to demonstrate, for example, administering Sabalselect[®] and an other CO₂ extract (35 °C/250 bar), in castrated prepuberal rats (Table 2).

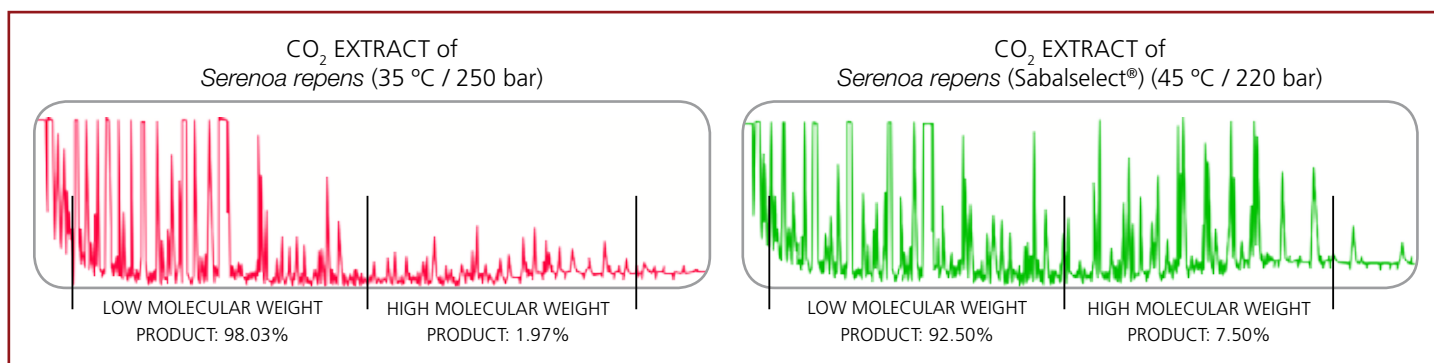


Table 2. Effect of orally administered (10 days) Hypercritical CO₂ *Serenoa repens* fruit extract in castrated prepuberal rats.

Substances	Dose (mg/day)	Body weight (g)		Prostate weight (mg)
		Initial	Final	
Normal control (olive oil)	-	58.1 ± 2.6	91.1 ± 3.2	20.6 ± 2.4
Castrated control (olive oil)	-	56.2 ± 1.8	87.2 ± 2.2	3.0 ± 1.2*
Testosterone propionate -15 µg/day, s.c. (olive oil)	-	62.3 ± 3.1	95.2 ± 2.5	17.4 ± 1.8
Testosterone propionate -15 µg/day, s.c. (olive oil) + 35 °C / 250 bar CO ₂ extract	300	65.1 ± 2.7	92.3 ± 2.5	11.7 ± 1.3 ●
Testosterone propionate -15 µg/day, s.c. (olive oil) + 45 °C / 220 bar CO ₂ extract Sabalselect®	150	63.1 ± 2.7	94.2 ± 2.5	11.9 ± 1.6 ●●
	300	64.1 ± 1.7	93.6 ± 2.4	6.5 ± 1.2 ●●
Testosterone propionate -15 µg/day, s.c. (olive oil) + 50 °C / 280 bar CO ₂ extract	300	66.2 ± 2.2	94.1 ± 2.5	11.1 ± 1.1 ●

Values are mean ± S.E.; n = 15; *p < 0.01 vs normal control; ● p < 0.05, ●● p < 0.01 vs testosterone propionate; Duncan's test

Table 3. Chemical composition of Sabalselect®.

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

Table 3 shows the chemical composition of Sabalselect® with the composition in fatty acids, alcohols and sterols,

elucidated by a **validated GLC method**.

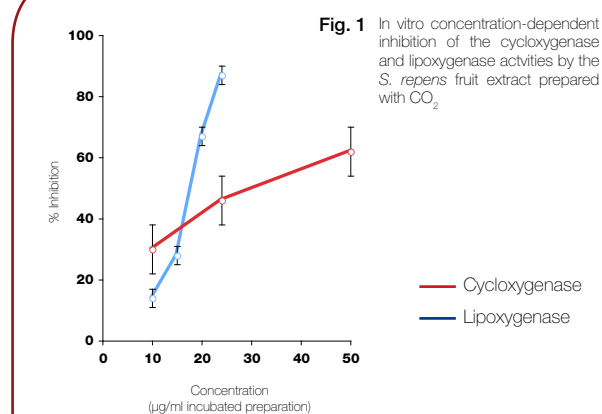
The **standardized** extract is produced under **strict GMP's**.

Pharmacology

In mild to moderate BPH, to reduce androgen stimulation, **5α-reductase** are clinically used. In *in vitro* studies *S. repens* fruit extract proved to inhibit the activity of this enzyme²² and the binding of androgens to the specific receptors²³.

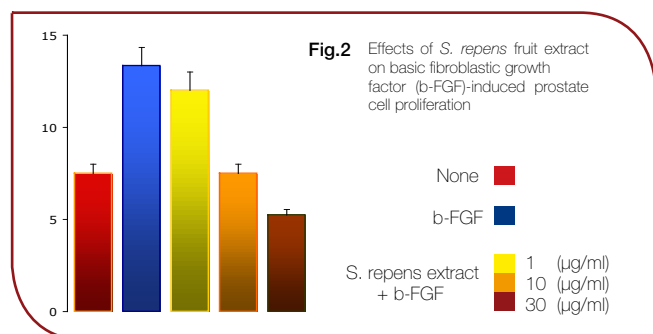
The inhibition of 5α-reductase activity has been confirmed^{24,25}, whereas the block of DHT (dihydrotestosterone) binding with the prostatic receptor is still controversial.^{3,24} The inhibiting activity showed by *S. repens* on both 5α-reductase activity and the enzymes of arachidonic acid metabolism appeared localized in the acidic lipophilic fraction of the extract.^{26,27}

S. repens extract can influence the synthesis of **inflammatory metabolites** through a dose related inhibition of cyclooxygenase and lipoxygenase activities (IC₅₀ values: 28 and 18 µg/ml, Fig. 1).²⁶



Moreover it has been reported that the extract (5 µg/ml) is able to inhibit the production of chemotactic leukotrienes by human polymorphonuclear cells, stimulated by the calcium ionophore A23187.²⁸

An inhibition of b-FGF-induced proliferation of human prostate cell cultures has also been reported for the extract and for some of its components (unsaturated fatty acids, hexacosanol and the unsaponified fraction, Fig. 2).²⁹



Sabalselect[®] treatment may be effective in relieving symptoms of BPH, in part, by inhibiting specific components of the IGF-I signalling pathway, and inducing JNK activation thus mediating antiproliferative and proapoptotic effects on

prostate epithelia.³⁰

Spasmolytic and smooth muscle relaxing activities have been described for a *S. repens* extract.^{31,32}

These effects seem to be 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.^{23,33,34}

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.³⁵

It has been shown that Sabalselect[®] was able to alleviate the urodynamic symptoms in hyperactive rat bladders by increasing bladder capacity and subsequently prolonging the micturition interval. This data sustained the observed clinical efficacy of Sabalselect[®] in the treatment of lower urinary tract symptoms.³⁶

Toxicology³⁷

- Acute toxicity in mice, rats and dogs
- 13- and 26-week oral toxicity in the Sprague Dawley rat at different dosage levels
- 13- and 26-week Oral Toxicity in the Beagle Dog at different dosage levels
- Genetic toxicology evaluation
- Teratogenicity study in the rat and the rabbit
- Fertility study in the rat
- Peri-postnatal toxicity studies in the rat

Conclusive remarks

The bulk of the results obtained in several double-blind placebo-controlled clinical trials and in multicenter open clinical studies demonstrates that Sabalselect[®] is an effective and safe treatment for the relief of urological disorders associated with mild BPH.³⁶

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

- Inhibition of 5 α -reductase activity^{24,25}
- Double blocking of cyclooxygenase and lipoxygenase activities²⁶
- Inhibition of chemotactic leukotriene production by inflammatory cells²⁸
- Attenuation of proliferative response of prostate cells to growth factors²⁹
- Inhibitory effect on nuclear estrogen receptors¹³
- α -Adrenoceptor antagonistic properties³²
- Interference with the action of prolactin³⁸

Sabalselect[®] is produced under strict GMP's with a specific CO₂ extraction process, has a defined chemical profile as demonstrated by validated GLC method of analysis. Sabalselect[®] is **safe**, and supported by a **full toxicological package** and has been extensively evaluated *in vitro*, *in vivo* and **nine clinical studies** are underlining its **effective activity for the relief of the urinary symptoms associated with mild BPH**.

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