A.Vogel

Bioforce Monograph

A.Vogel Prostasan®

Saw Palmetto

Serenoa repens

Contents

Saw Palmetto

1.1. Botany

Saw Palmetto (Sabal serrulata, Serenoa repens) belongs to the family of betel palm plants and is native to the southern coastal states of North America (North Carolina, Florida), Central America and tropical South America. The low-stemmed dwarf palm grows from a creeping rootstock and forms leafstalks of up to 1.5m in length. The characteristic fan-shaped, serrate leaves are split into as much as 24 segments. The olive-sized, dark red, bluish or black berry fruits contain the pharmacologically active ingredients.[1]

1.2 Traditional Use

The fruits of Saw Palmetto have been eaten by humans for thousands of years. According to Hale[2], they were the basic foodstuff of the Seminole Indians who dried the fruit so that it was available to them throughout the whole year. The Indians obtained the healing effect by means of the fruit tincture and the crushed seeds, which were used at that time to treat enlarged prostates, cystitis, gonorrhea, and irritation of the mucous membrane. The natives of Central and South American countries also used the Saw Palmetto as a medicine. They primarily had faith in its diuretic, tonic and relaxing properties. The sweetened seed oil is particularly soothing and was used mainly for sleeplessness, severe coughing and bronchitis.[3]

1.3 Contemporary Use

Nowadays, Saw Palmetto extract is primarily used to treat the early and intermediate stages of benign prostatic hyperplasia (BPH).

1.4 Prospect of other possible uses

Newer research results are opening up new indication areas. It is proven, for example, that androgenic alopecia is caused by the same mechanism as BPH, which is why the Saw Palmetto can be used to treat it.[4, 5]

1.5 Pharmacology

The broad spectrum of active contents allows comprehensive treatment of the diversified symptom complex of BPH. The inhibition of 5α-reductase and the mode of action which inhibits cyclooxygenase and 5-Lipoxygenase both originate from the acid lipophilic fraction of the extract, whereby lauric acid in particular plays a key role.[6]

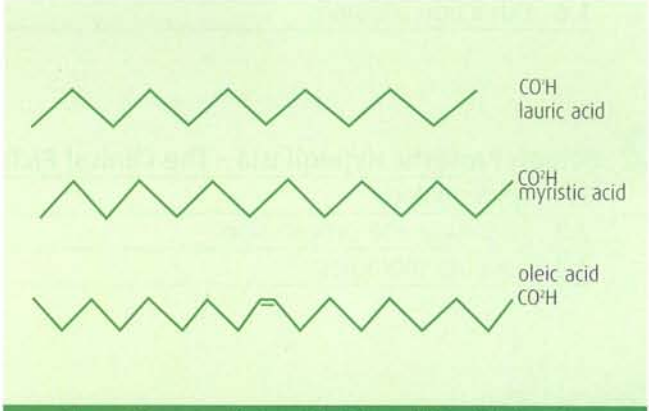


Figure 1: Important fatty acids of the acid lipophilic fraction of the Saw Palmetto extract.

1.5.1 Specific anti-androgenic effect

The specific anti-androgenic effect is accomplished by inhibiting both the 5α-reductase and the receptor binding of 5α-dihydrotestosterone (DHT) (see Figure 2). The acid lipophilic fraction of the Saw Palmetto extract has a selective anti-androgenic effect on the prostate, without affecting the hypothalamic-pituitary regulatory system or the Leydig cells.[7, 8, 9] This also explains the lack of undesirable effects, such as gynaecomastia and loss of libido, which are a part of the other anti-androgenic therapies because they affect the higher-ranking hormonal regulatory systems due to their active mechanisms.[7, 10]

1.5.1.1 Inhibition of 5α-reductase

The Saw Palmetto extract reduces the activity of 5α-reductase, which catalyses the metabolisation of testosterone into its active metabolites DHT.[8, 11, 12, 13] This leads to a lowering of the DHT level and thus to involution of the glandular epithelial portions of the prostate.[14] Various

in-vitro experiments have documented the inhibiting effect of the extract on 5α-reductase in the epithelial tissue and stroma of human hyperplastic prostate. There are two isoforms of 5α-reductase, which are expressed in both the healthy prostate and in the pathologically changed prostate.[15] While therapeutic doses of the 5α-reductase inhibitor finasteride only inhibit isoform II[16], it is proven that Saw Palmetto extract acts as an efficient inhibitor of both isoforms.[17] This inhibiting influence was also proven in human foreskin fibroblasts [18, 19, 20], which have a particularly high 5α-reductase content.[8]

Saw Palmetto extract exerts its anti-androgenic effect without preventing the prostate cells from secreting PSA (prostate specific antigen), for which reason PSA can continue to be used as a marker for prostate cancer screening.[17] This finding is also in contrast to most 5α-reductase inhibitors which suppress the PSA production and change the corresponding values.

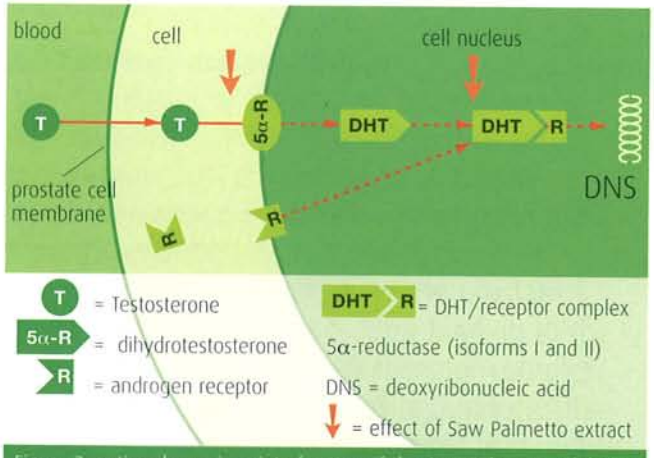


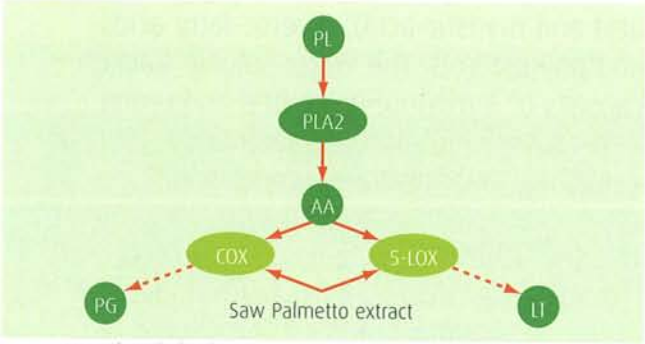
Figure 2: anti-androgenic point of action of the Saw Palmetto. Inhibition of 5α-reductase and inhibition of the DHT receptor binding

1.5.1.2 Inhibition of DHT receptor binding

The binding of DHT to androgen receptors trigger a transcription cascade which induces cell proliferation and thus growth of the prostate. The lipophilic Saw Palmetto extract competitively inhibits nuclear and cytosolic DHT-receptor bindings[12, 20, 21], which prevents the DHT-receptor complex from forming, reaching into the nucleus and triggering transcription (see Figure 2).[8, 22]

Excessive cell growth is therefore inhibited and further growth of the prostate is prevented.

1.5.2 Anti-oedematous and anti-inflammatory effect



PL = phospholipids
PLA2 = phospholipase A_2
AA = arachidonic acid
PG = prostaglandins
5-LOX = 5-lipoxygenase
COX = cyclooxygenase
LT = leukotrienes

Figure 3: Schematic depiction of the inhibition of cyclooxygenase and 5-lipoxygenase using Saw Palmetto

The increased tissue level of 5-lipoxygenase/cyclooxygenase metabolites which act to proliferate cells and to increase secretion during the BPH disorder can consequently be lowered using Saw Palmetto extract. The dose-dependent inhibition of cyclooxygenase and 5-lipoxygenase has an anti-oedematous and anti-inflammatory effect (see figure 3).[23] The anti-inflammatory effect is due to the inhibition of both enzymes, cyclooxygenase and 5-lipoxygenase. This dual inhibition of the arachidonic acid cascade also prevents the so-called substrate shift which occurs when only one of the two enzymes is inhibited.[21]

1.6 Extraction methods

Saw Palmetto extracts can be obtained using several methods, for example by hypercritical CO2 extraction or by hexane extraction. In this last case, polysaccharides cannot be used as an active agent because they are not soluble therein due to their hydrophilicity.[25] In addition, for toxicological reasons, hexane must be removed again during manufacture of the pharmaceutical, which is not always completely possible.[26]

An ethanol extract from the fruit of Saw Palmetto offers the advantage that both lipophilic and hydrophilic fractions can be isolated. The fat-soluble portion contains fatty oil (mainly esters of oleic acid, lauric acid and myristic acid), diverse fatty acids and phytosterols. The water-soluble fraction consists of a mixture of neutral and uronic acid-containing heteropolysaccharides, such as galactose, arabinose and uronic acid.[27]

The Saw Palmetto extracts available today are manufactured using similar but not identical methods. Manufacturing can be carried out with extraction means having a different concentration but results in comparable fatty acid, fatty acid ethyl ester, and effectiveness profile[26] (see figure 4)

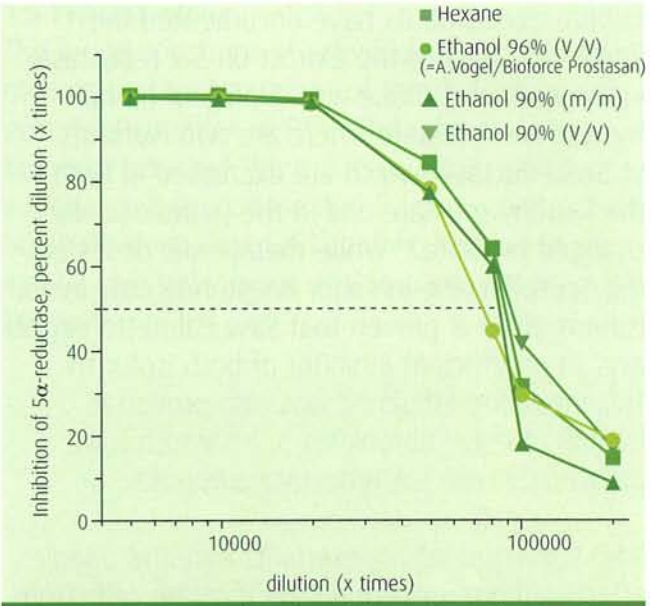


Figure 4 concentration-dependent inhibition of 5α-reductase using different Saw Palmetto extracts[26]

Benign Prostatic Hyperplasia - The Clinical Picture 2

2.1 Epidemiology

BPH, the benign enlargement of the epithelial and fibromuscular portions of the stroma of the prostate, is the most frequent cause of male bladder evacuation disorders.[28] As a result of their frequency, BPH presents a public health and socio-economic problem which will become even more serious as life expectancy increases. Around 50% of men aged over 50 show the symptoms of BPH and in men over 80, almost 100% are affected.[29] It is recommended that validated questionnaires, such as the International Prostate Symptom Score (IPSS), be used in order to carry out standardised recording.[30]

In addition to obstructive complaints (difficulty starting urination, weak and interrupted urinary flow), the main symptoms of BPH also include irritative complaints (feeling of residual urine, polyuria, nocturia and urinary incontinence) which must be conservatively or operatively treated in the case of progressive development.[30]

2.2 Aetiology and progression

The development of prostatic hyperplasia is due to raised activity of 5α-reductase and to increased DHT concentration. After the absorption of the testosterone formed in the testicles into the cell, it is metabolised in certain tissues, for example in the prostate, into DHT by 5α-reductase. After binding to the androgen receptor, this DHT-receptor complex migrates into the cell nucleus and induces the formation of messenger ribonucleic acid, which influences cell proliferation and leads to growth of the prostate.[7, 31] An age-related shift in the androgen/oestrogen ratio in favour of oestrogen, which promotes a proliferation of prostate tissue, is also considered to be a cause.[32]

The raised tissue levels of prostaglandins (particularly PGF 2α) and leukotrienes in the prostate as 5-lipoxygenase metabolites and cyclooxygenase metabolites of arachidonic acid can also have an influence on the hyperplastic growth of the prostate due to their cell-proliferating and secretion-increasing effect.[32] The clinical manifestation of BPH can be divided into three stages according to Alken[28] (see table 1) or 4 stages according to Vahlensieck (see table 2).

I. irritation stage	Obstructive and irritative symptoms
II. residual urine stage of the bladder	Beginning of decompensation evacuation system residual urine 100-150ml, polyuria
III. decompensation stage	Bladder decompensation: chronic total urinary retention, uninhibited neurogenic bladder; restricted kidney function; final state: uremia

Table 1: Division of BPH into stages according to Alken (1955)

I. irritation stage	No urinary disorders Uroflow: maximum urinary flow above 15ml/s No residual urine, no trabeculated bladder
II. residual urine stage	Changing urinary disorders Uroflow: 10-15ml/s Possibly already a small amount of residual urine (<50ml) Possibly already the beginning of
III. trabeculated bladder	Permanent urinary disorders Uroflow: <10ml/s Residual urine >50ml; trabeculated blad-
IV. renal congestion	Permanent urinary disorder Very pronounced BPH Uroflow: maximum urinary flow below 10ml/s Residual urine above 100ml; uninhibited neurogenic bladder; Congestion of the upper urinary tract

Table 2: Division of BPH into stages according to Vahlensieck (1985)

2.3 Possible therapies

In the case of symptomatic treatment of BPH, the therapeutic focus is primarily aimed at:

- reducing the residual urine volume
- minimising the urination complaints
- reducing the urination frequency.

In stages I and II according to Alken and Vahlensieck and in inoperable cases a conservative therapy is indicated, with phytotherapy, particularly Saw Palmetto extracts,

being suitable as the primary therapy (see Figure 5).[33]

BPH patients in stage III according to Alken or stage IV according to Vahlensieck must be surgically treated.

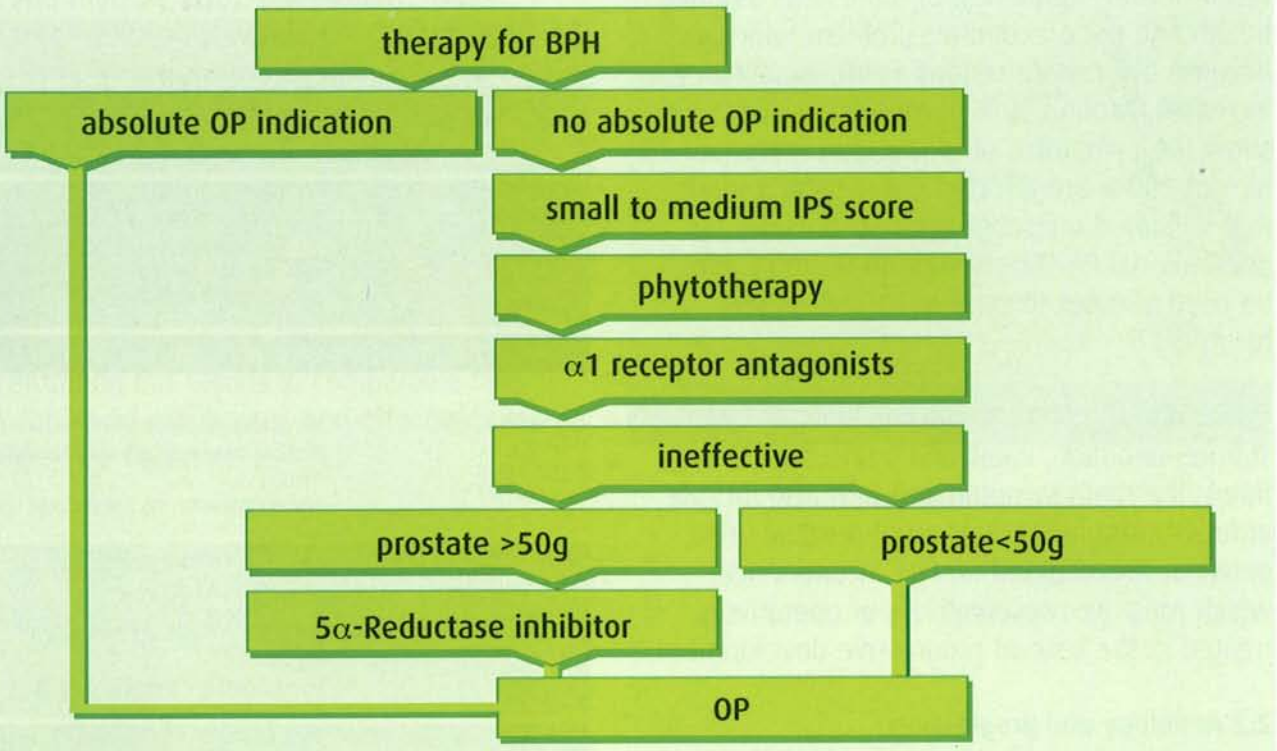


Figure 5: Therapy regime for BPH. Phytotherapeutics, particularly Saw Palmetto extracts, are suitable primary therapy.[33]

3.1 Dosage and use

Several studies have been carried out to determine the optimal dose and administration method (once-daily vs. twice-daily).[34, 35, 36] A study of 49 patients over 6 months compared daily doses of 320mg and 960mg in terms of effectiveness and tolerance. No significant difference was found between the two doses of the extract. Optimal effectiveness was achieved with a dose of 320mg.[35]

In another study, the once-daily (320mg) dose of Saw Palmetto extract was compared with twice-daily administrations (of 160mg each).[38] Both doses significantly reduced the International Prostate Symptom Score (-6.4±5.4 vs. - 6.4±5.9; p-value<0.0001) and no difference was established between the two administration methods. For compliance reasons, it is to be recommended that a once-daily dose of 320mg be taken.

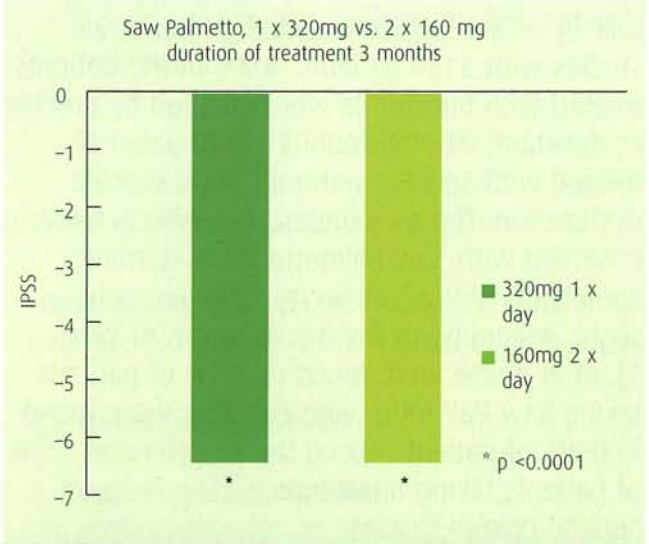


Figure 6: Once-daily (320mg) vs. twice-daily (160mg) administration of Saw Palmetto extract[38]

3.2 Effectiveness

Many different studies have tested the effectiveness of Saw Palmetto extract, and have proven that use of this botanical is indicated in cases of BPH. In these studies, which in some cases lasted for up to 48 weeks,[22, 35, 37] Saw Palmetto, in comparison with a placebo, significantly improved both the signs and the symptoms of the complaint. The course of the illness, measured on the IPSS and in terms of the improvement in quality of life and the uroflow parameters was decisively optimised.

3.2.1 Saw Palmetto vs. placebo

The double-blind, placebo-controlled, randomised study by Tasca et al.[38] tested the effectiveness of Saw Palmetto in BPH patients (n=30) over 60 days. Uroflow parameters were primarily measured, such as maximum urinary flow rate, average urinary flow rate, urinary volume and urination time, whereby the verum group displayed a significant improvement in all parameters compared to the placebo group (see Figure 7).

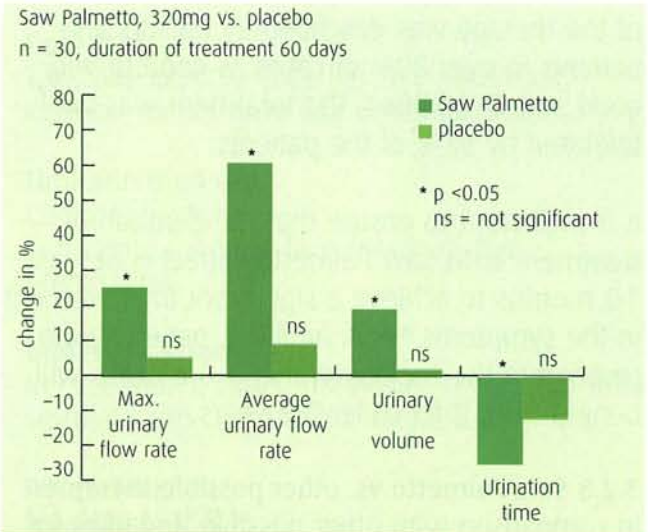


Figure 7: Effect of Saw Palmetto vs. placebo in BPH patients[38]

3.2.2 Long-term study of Saw Palmetto vs. placebo

Cukier et al.[39] also confirm the effectiveness of Saw Palmetto vs. placebo over a treatment period of 90 days for a larger patient group containing 148 patients. As well as a significant improvement of dysuria ($p < 0.001$) and nocturia ($p<0.001$) with Saw Palmetto, it was also possible to reduce the residual urine volume in the verum group by 42%; from 94.7ml to 55.1ml, whereas in the placebo group it increased by 8.7%.

Lastly, a long-term study of 542 patients over a period of therapy of up to 15 months also recorded a continuous improvement in urinary symptoms over 6 to 9 months and continuing effectiveness when the treatment was extended for up to a year. This continuing therapeutic effect was confirmed by the continually increasing number of good or very good effectiveness assessments undertaken by doctors (from 68% to 89%) and patients (from 75% to 95%).[40]

The longest study[41] so far carried out tested 435 patients with BPH in stages II and III according to Vahlensieck over 3 years. At the end of the study, the residual urine amount was still 50% of the starting value and the maximum urinary flow rate increased by 6.1ml/s. The effectiveness of the therapy was described by doctors and patients in over 80% of cases as good to very good and, in addition, the treatment was well tolerated by 98% of the patients.

It is important to ensure that the duration of treatment with Saw Palmetto extract is at least 1-2 months to achieve a significant improvement in the symptoms.[22, 37] In addition, patients who respond to the therapy within 3-6 months will benefit from it for at least 3 years.

3.2.3 Saw Palmetto vs. other possible therapies

In comparison with other possible therapies for BPH (α1-antagonists [42], 5α-reductase inhibitor [43]), Saw Palmetto extract demonstrated equal effectiveness with a lower rate of side effects. The double-blind, randomised, multicentre study by Carraro et al.[43] involving 1098 patients showed a practically equal effect with respect to BPH symptoms for both Saw Palmetto and finasteride (a 5α–reductase inhibitor). In both study groups, the IPSS, the quality of life and the urinary flow rate clearly improved, with there being no significant differences between the two preparations. This fact was also confirmed by Wilt T.J. et al. in Cochrane Review on Saw Palmetto for BPH.[37]

3.3 Tolerability

Saw Palmetto is better tolerated than both 5α-reductase inhibitors (finasteride) and α1-antagonists.[34]

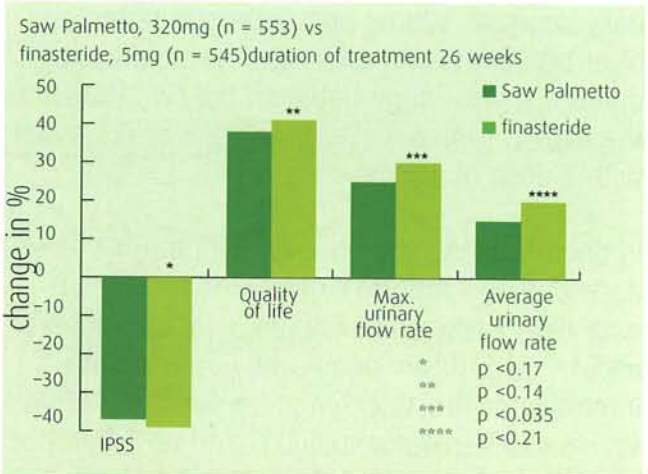


Figure 8: Effectiveness of Saw Palmetto vs. finasteride in BPH patients.[41]

Studies show that Saw Palmetto extract causes significantly less erectile dysfunction than finasteride. According to the metaanalysis by Wilt T.J. et al.[37], which included a total of 21 studies with 3139 patients, 4.9% of the patients treated with finasteride were affected by erectile dysfunction, whereas only 1.1% of patients treated with Saw Palmetto reported erectile dysfunction. The only undesirable effects hitherto observed with Saw Palmetto were stomach complaints[9, 38, 44] which were, however, only slight. According to the metaanalysis of Wilt T.J. et al. these were found in 1.3% of patients taking Saw Palmetto, whereas they were found in 0.9% of patients taking the placebo and 1.5% of patients taking finasteride.[37]

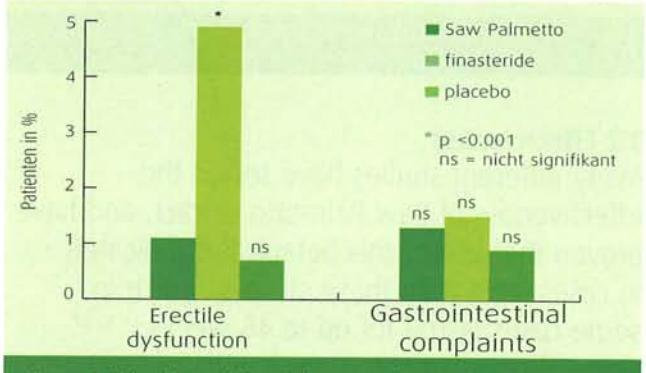


Figure 9: Side effects of Saw Palmetto vs. finasteride and placebo37

Product profile - A. Vogel Prostasan

4

Prostasan, the Saw Palmetto product from Bioforce AG, meets the highest qualitative demands required of a modern pharmaceutical. The Saw Palmetto fruit originate from controlled organic cultivation in Florida and are harvested when totally ripe in September and then gently dried. Many substances are contained in one plant, and these only exert their curative effect when they come together. The amount and the concentration of the individual contents depend on: the location, harvesting time/conditions, climatic conditions and cultivation conditions.

In order to guarantee a constant concentration of all contents, the following 3 measures are used to standardise Bioforce products:

- The controlled organic cultivation at the same location guarantees constant plant quality
- The validation of all critical manufacturing stages permits thorough production control and regulation
- The mixing of different batches to create mixtures of different years results in constant concentrations of active ingredients.

These measures together guarantee constantly high product quality with optimal effectiveness.

4.1 Technical Information

A. Vogel Prostasan Capsules
Urination complaints in cases of benign prostatic hyperplasia (BPH)

Composition
1 capsule of A.Vogel Prostasan contains 320mg (±5%) native extract (extractum ethanol spissum) drug extract ratio 9-12:1 of dried sabal fruits (Serenoa repens fructus) from controlled biological cultivation, corresponding to 2.88-3.84g drug or at least 270mg fatty acids, calculated as heptadecanoic acid.

Properties/Effects
Serenoa repens extracts possess anti-oedematous, anti-inflammatory and anti-androgenic properties due to the inhibition of the biosynthesis of prostaglandins and leukotrienes and the inhibition of the 5α-reductase without affecting the plasma concentrations of testosterone, FSH and LH. They reduce both the irritative and the obstructive symptoms of BPH and lead to an improvement in urination quality, uroflow and residual urine.

Pharmacokinetics
As yet, there is no data available on absorption, distribution, metabolism and elimination.

Indications/Possible uses
Urination complaints in cases of benign prostatic hyperplasia in stages II and III according to Vahlensieck (stages I and II according to Alken).

Dose/Use
Take one capsule once per day after food. Regular, longer term use is recommended.

Limitations on use
Contraindications
Sensitivity (allergy) to contents of the preparation.

Undesired effects
In exceptional cases, medicines containing sabal serrulata can cause slight flatulence.

Interactions
No data available.

Other Advice
Shelf life
The medicine may only be used up to the expiry date on the container.

Swiss pharmaceutical authority IKS number
54010.

Packs
of 30, 60 and 120 capsules. .

Summary

5

With a prevalence of 50% in men aged over 50 and practically 100% in men over 80, BPH is a public health problem which will increase further as life expectancy in society increases. It is important that the diverse symptoms be diagnosed and treated as soon as possible as this can have a decisive effect on the quality of life of an ageing man.

There is demand for an effective therapy that can be easily tolerated and which, if used in time, can have a beneficial effect on the progressive development of BPH.

A. Vogel Prostasan , made from standardised Saw Palmetto extract is a highly effective treatment for BPH in its initial and moderate stages and is practically free of side effects.

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