EUROMED Herbal Extract Series

Saw Palmetto Lipidic Extract

For the Treatment of BPH

EUROMED

Introduction

EUROMED is a company that specializes in making botanical extracts and active principles used as phytomedicines in pharmacy. EUROMED develops and produces therapeutically active raw materials.

The botanical raw materials are subject to strict selection and inspection, and products are manufactured according to methods developed by the EUROMED company. They include inspections to guarantee a standard quality from both analyticochemical and therapeutical points of view and take into consideration the state of art in different fields: research and development, analyses, processes and devices and therapeutic applications.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.

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1 Saw Palmetto Lipidic Extract: General Information

1.1 Description

All natural

The lipidic extract of Saw Palmetto is a standardized herbal extract of *Sabal serrulata* berries (*Sabal fructus*).

Herbal remedy to prevent or treat BPH

The extract of Saw Palmetto berries is a herbal preventive and therapeutic agent for benign prostatic hyperplasia (BPH). It results in relief of symptoms, such as:

- pollakisuria (frequent urination),
- nocturia (frequent nocturnal urination) and
- urinary urgency.

Residual urine is reduced and urinary outflow is improved.

The Saw Palmetto extract from EUROMED gives most patients some relief of symptoms within the first 30 days.

The extract of Saw Palmetto does not interact with other drugs.

1.2 Indications

The lipidic extracts of Saw Palmetto manufactured by EUROMED are used in the treatment of prostatic diseases, especially benign prostatic hypertrophy (international stages I-II, stages II-III according to VAHLENSICK), and for the stabilization of the urodynamic of the patient.

1.3 Extract Specifications

Saw Palmetto extract is a lipidic extract of *Sabal serrulata* containing between 85 to 95 % cent of fatty acids. Finished preparations usually contain about 160 - 320 mg *Sabal serrulata* berry extract (as available from EUROMED) corresponding to 1 - 2 g of the berries.

1.4 Dosage and Methods of Administration

A daily oral dose of 320 mg Saw Palmetto extract is common practice. Table 1 (page 6) gives a survey of popular European Saw Palmetto-preparations available on the market.

1.5 Contraindications and Interactions

There are no known contraindications to the long-term use of Saw Palmetto extract. There are no known interactions with drugs usually prescribed.

1.6 Side-effects

Well tolerated

Saw Palmetto extract is generally well tolerated. Side-effects are rare when the standardized extract is taken. In exceptional cases gastric complaints may occur.

Tab. 1: European preparations containing Saw Palmetto extract.

Preparation Name	**Method of extraction**	**Content of *Sabal* Extract [mg]**	**Total Extract/day [mg]**
Prosta Urgenin Uno	ethanolic	320	320
Prostagutt uno/ -mono	ethanolic	320/160	320
Prostamol uno	ethanolic	320	320
Prostata Kapseln	ethanolic	160	320
Prostess/ -uno	ethanolic	320/160	320
Remiprostan uno	ethanolic	320	320
Serenoa-ratiopharm/ -uno	ethanolic	160/320	320
Strogen S/ -uno		320/160	320
Sita	lipophilic	320	320
Steiprostat	alcoholic	160	320
Talso/ -Uno	lipophilic	160/320	320
Eviprostat-S	ethanolic	160	320
Belluran	ethanolic	2,1 g drug/ml	1,05-2,1 g drug

2 From Plant to Extract

2.1 Saw Palmetto (*Sabal serrulata*): Botanical Data

Saw Palmetto berries

The fruits of Saw Palmetto originate from *Sabal serrulata* MICH. [13], a small species of palms native to the USA. Synonyms are *Serenoa repens* (BARTR.) SMALL or *Serenoa* (*Serenaea*) *serrulata*, *Sabal serrulatum* or *Chamerops serrulata*. Its dispersal area are the pine forests and dunes from North-Carolina to Florida. There it grows in large tracts of bushland covering many square kilometres.

Sometimes *Sabal serrulata* (syn. *Serenoa repens*) is a tree with a stem up to 4 m height. The palm leaves are divided in 18 to 24 segments and sit on petioles of about 1 m [24, 36]. The petioles are toothed. That led to the Latin name *serrulata* = toothed and to the English name Saw Palmetto. The small growth of the plant led to the designation „shrub Palmetto“ [24]. Because of the tonic effect on the neck of the bladder and the prostate Saw Palmetto is also given the name „herbal catheter“ [54].

The flowers are small with axillary inflorescences. They develop into oval and about 2 to 3 cm long and up to 1.5 cm thick berries of black to dark blue-red colour. They contain one single hard brownish seed. The taste is initially sweet and then strong to acrid [24, 26, 31].

The officinal berries, used therapeutically consist of skin, pulp and a large seed.

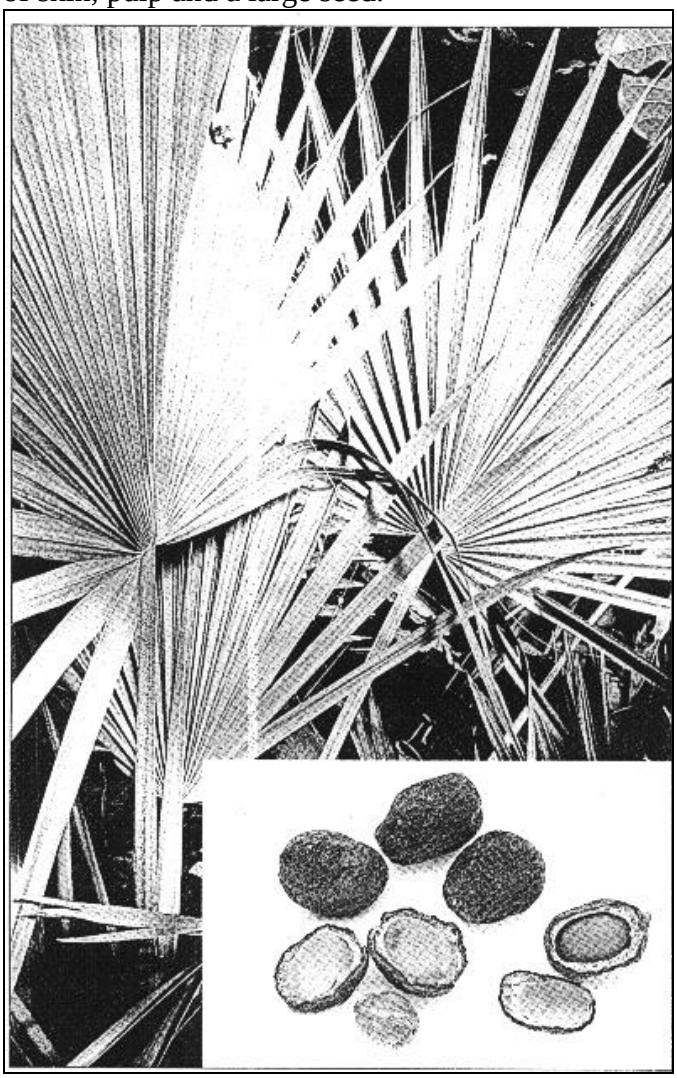

Fig. 1: Saw Palmetto (*Sabal serrulata*).

2.2 Historic Use

The berries, rich in fat, serve as food for the animals living in Florida and are collected by hunters. The American Indians used the berries as a sexual tonic, a diuretic and as a sedative. The steam from cooking berries was inhaled for diseases of the nose.

The American physicians READ and SALOMONS from Savannah introduced the plant into scientific medicine. They name a variety of indications, such as prostatitis, prostatic hypertrophy, cystitis, enuresis, testicular atrophy, proctitis and dysmenorrhoea. The efficacy in benign prostatic hyperplasia has been shown in numerous investigations and is also mentioned as a main indication by MADAUS [31].

2.3 Chemistry of Saw Palmetto Berries

The most important constituents of the berries are different sterols, fats and free fatty acids, carotenoids, essential oils and polysaccharides. [15, 26]. In the 1960's three phytosterols were detected by thin-layer chromatography [25].

Figure 2 shows some plant sterols contained in the extract of the berries compared to testosterone and 5-α-dihydrotestosterone. The antiandrogenic effects of these constituents can be illustrated by their structural alliance.

The free fatty acids and their ethyl esters are thought to be responsible for an inhibition of 5-α-reductase [37]. In pharmacological experiments an antiphlogistic effect has been shown for the acid polysaccharides isolated from extracts of Saw Palmetto berries [26].

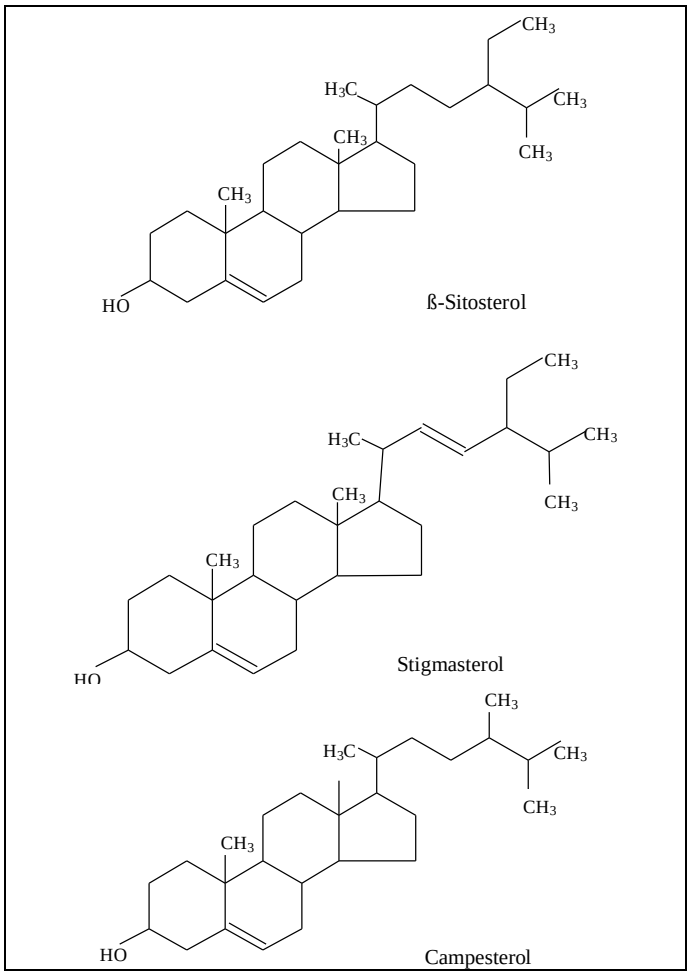

Fig. 2: Phytosterols of Saw Palmetto (*Sabal serrulata*).

The following table gives a general review of the substances found in Saw Palmetto berries.

Tab. 2: Substances found in Saw Palmetto berries [23, 24, 26, 27, 29, 41, 54].

Active and Other Substances

• Phytosterols: δ-5- and δ-7-sterols:
  • β-sitosterol
  • β-sitosterol-3-O-β-D-glycoside
  • β-sitosterol palmitate, myristate, laurate, also as β-D-glycoside
  • liposterols
• Triglycerides and fatty acids: fat oil with medium-chain, saturated fatty acids and unsaturated fatty acids, 2/3 as free forms and 1/3 as ethyl esters:
  • oleic acid
  • lauric acid
  • myristic acid
  • palmitic acid
  • n-caprylic acid
  • caproic acid
  • capric acid
• Carbohydrates: acid polysaccharide, mannitol
• Essential oil
• Carotene
• Flavonoids: isoquercitrin, kaempferol-2-O-glycoside, rutin
• Tannins
• Enzymes
• Resins

2.4 Preparation of the Extract and Quality Control

The plant material used for EUROMED Saw Palmetto extract is primarily cultivated.

Herbal crops grown in regions adjacent to their natural habitats, e.g. in Ecuador, are standardized in conjunction with collections of wild plants. This way the extract quality of EUROMED Saw Palmetto is maintained. Permanent professional botanical inspections are part of the growth of the crops.

After an average of 7 years the usable berries of Saw Palmetto can be picked. The harvest time varies by region and is usually in later summer. Adequate size and condition of the berries are of great importance to the quality of the extract of EUROMED Saw Palmetto. The collection of the berries, which is exclusively by hand, is made more difficult by the sawteeth of the palm stems. Subsequently the collected berries are rapidly dried and made into lipophilic extract.

Inspection of the drug upon its arrival at EUROMED

When the plant material arrives at EUROMED an exhaustive inspection of the raw material according to the current methods guarantees the quality of the final product .

Furthermore EUROMED evaluates the possible contamination of the drug. In doing so the company assures that the limits fixed by international standards or literature are not exceeded.

Pesticides: in compliance with the limits established in Ph. Eur. 3rd ed., 2.8.13 (1997)

Aflatoxins: the contamination with these mycotoxins is controlled by legal limits world-wide

Heavy metals: the contamination with heavy metals is controlled by atomic absorption spectrophotometry

Microbiology: in compliance with the limits established in Ph. Eur. 3rd ed., 5.1.4 (category 4B), (1997)

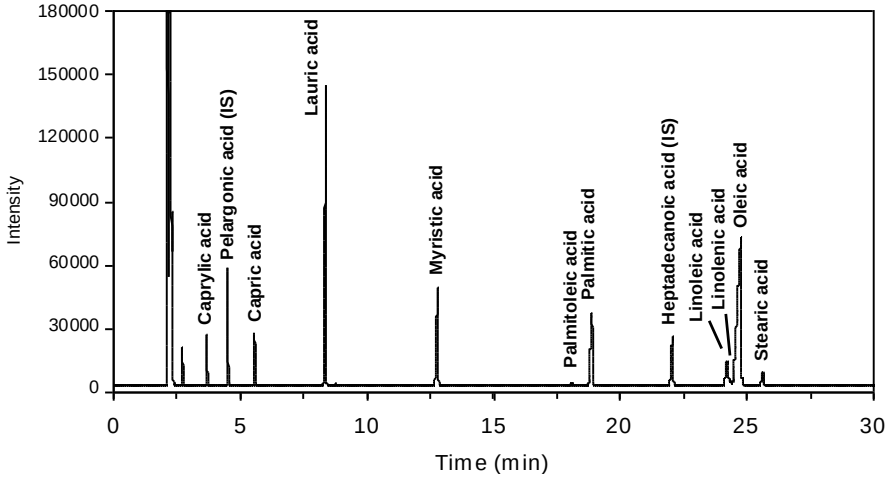

Fig. 3: Standard-gas chromatogram of Saw Palmetto lipidic extract from EUROMED.

Only high-quality raw plant material, selected according to the strictest criteria, is used.

Patented process

EUROMED applies a patented extraction process to obtain the extract. This procedure patent of EUROMED meets the indications of the Commission E monograph [13] for an ethanolic extract. It provides a high yield of valuable constituents and a high-grade extract in a careful way [19].

According to the original processes EUROMED produces a lipidic extract from the fruits of Saw Palmetto:

EXTR. SABALAE SERRULATAE E FRUCT. OLEOSUM (SAW PALMETTO LIPIDIC STEROLIC EXTRACT)

Lipidic extract, oily liquid, dark green-brown colour and characteristic smell of the drug.

EUROMED Saw Palmetto extract satisfies the highest quality standards of the various European regulatory systems. It meets and exceeds all European requirements for approved European medicinal use.

2.5 Standardization

Consistent batch to batch quality

The consistent batch to batch quality of the EUROMED Saw Palmetto extract is guaranteed by the standardized production process. The EUROMED extract of Saw Palmetto berries is standardized to a content of 85 - 95 % of fatty acids.

The analytical specifications of the EUROMED Saw Palmetto extract are:

* Aspect	Dark green-brown colour, oily liquid with aromatic odour
* Identification	GC Fingerprint
* Solubility	Insoluble in water, soluble in organic solvents
* Density at 20° C	0.850 - 0.950
* Loss on drying	Max. 5.0 %
* /n/20/D	1.4 - 1.5
* Content of fatty acids	85 - 95 %
* Saponification value	220 - 240
* Iodine value	30 - 60

* Microbiology: according to Ph. Eur. 3rd ed., 5.1.4., category 3B

3 Benign Prostatic Hyperplasia (BPH)

3.1 Morphology of the Prostate and of the BPH

The prostate is a single, doughnut-shaped gland about the size of a chestnut. It is below the bladder and surrounds the urethra [36] (see Fig. 4).

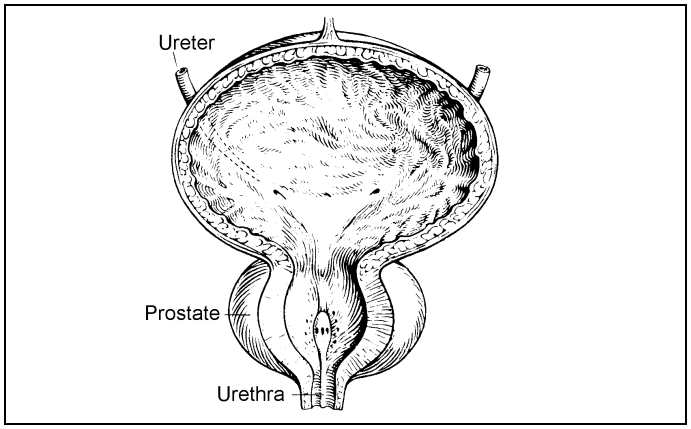

Fig. 4: Profile of the urinary bladder and the prostate.

Benign Prostatic Hyperplasia (BPH) develops primarily in those parts of the prostate directly adjacent to the urethra. Unlike this, carcinoma of the prostate develops mainly in the peripheral parts of the gland [33].

The proliferation of glandular and stroma cells in the periurethral and transitional zones increases after the 50th year of a man's life (Fig. 5). The glandular nodes in the transitional zone have a increased tendency to grow with advancing years [2, 7].

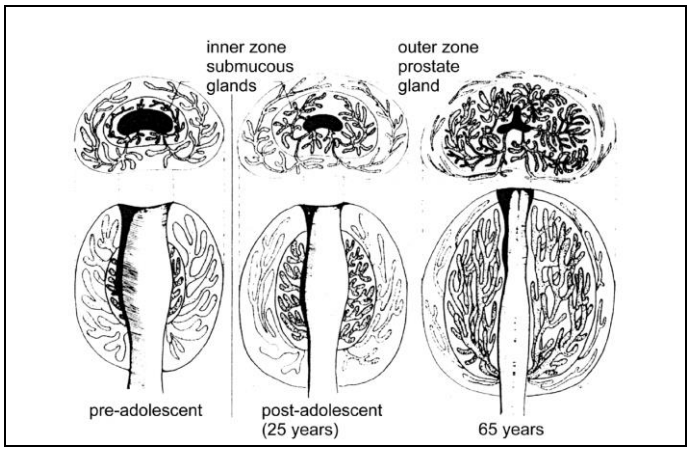

Fig. 5: Cross and longitudinal sections of the developmental phases of the BPH.

The expanded central part of the prostate spreads to the bladder, which responds to the increased resistance with a hypertrophy of the detrusor. Later residual urine and vesicorenal reflux result in dilatation of the upper urinary tract. On a long-term basis hydronephrosis, affections of the renal parenchyma and renal insufficiency may develop [2].

3.2 Epidemiology

More than 50% of men over 50 years and 80% of men over 70 years suffer from Benign Prostatic Hyperplasia (BPH). Fig. 6 shows the incidence of BPH in relation to age. Hence BPH is the most frequent urologic disease of the aging man [1, 35, 41, 47]. It is a world-wide disease [34]. Racial, genetic and environmental influences seem to be responsible for the world-wide variance of incidence [4].

BPH is a world-wide disease

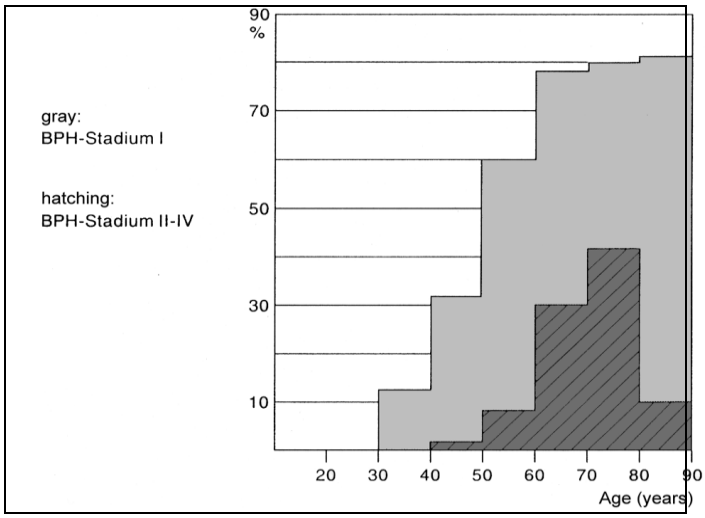

Fig. 6: The percentage of BPH in the male population.

The growing average life expectancy increases the need for therapy, since more and more patients reach the symptomatic stage of the disease [7].

3.2 Endocrinology

Development, growth and functional differentiation of the prostate are endocrinically controlled. They are influenced by the hypothalamus-hypophysis-gonads axis [44]. The excretion of gonadotrophin-releasing hormones (GnRH) from the hypothalamus stimulates the release of other hormones. Subsequently the Leydig-interstitial cells of the testicles are activated to synthesize and to secrete testosterone. In the prostatic cell testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-α-reductase. DHT has an affinity for the androgen receptors 3 to 10 times higher than testosterone. Growth and maturation of the prostate are controlled via androgen receptors [43].

The etiology is not yet clear, but there are indications that a hormonal imbalance may be involved [38]. Fig. 7 shows the androgenic aspect of the BPH genesis as well as the possible points of action of Saw Palmetto berries extract (e. g. as available from EUROMED) .

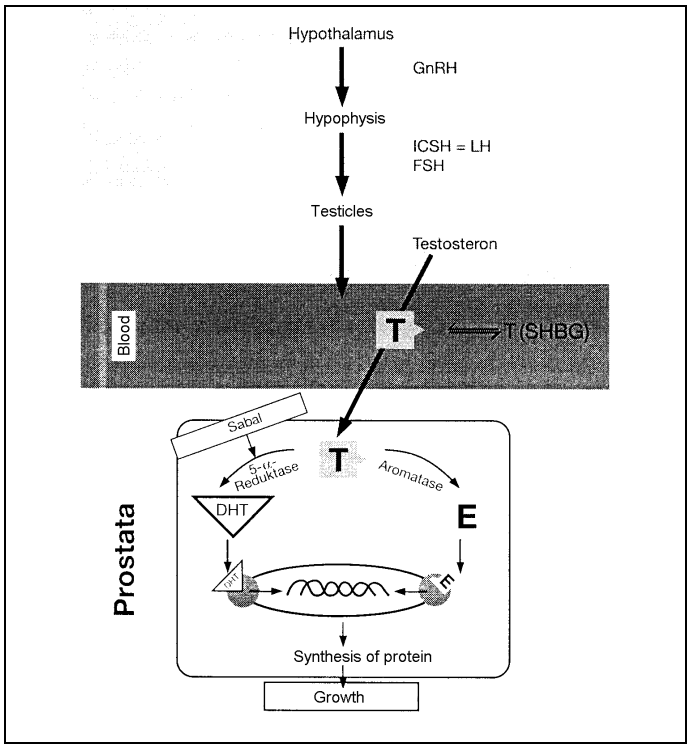

Fig. 7: Antiandrogenic action of Saw Palmetto berries extract (as available from EUROMED) with BPH.

Testosterone is metabolized into estrogens stimulating the growth of the fibromuscular tissue of the prostate [55]. In a man growing older the estrogen-androgen ratio changes in favour of the estrogens. Consequently two preconditions for BPH to arise are:

- no reduction of the male gonad function
- an advanced age of the patient.

DHT plays a crucial part in the pathogenesis of the BPH [43]: The activity of 5-α-reductase is increased in the hyperplastic prostatic tissue. That's why more DHT is produced [34]. DHT binds to the androgen receptors and induces the biosynthesis of protein and the growth of the prostate.

Prostaglandins and leucotrienes can also contribute as mediators to the development of the BPH. In addition to their inflammatory characteristics and their ability to induce edemas they also lead to an increased cellular proliferation [34].

3.4 Symptoms

Initially symptoms affect the patient's lifestyle. They consist primarily of unwanted change in urination. Later symptoms of increased urinary obstruction occur as disease progresses [17, 18].

The irritative symptoms are assumed to be induced by an instability of the bladder detrusor. The obstructive symptoms are caused by an exclusively mechanical stricture of the urethra (Tab. 3).

Tab. 3: BPH Symptoms [7, 17, 34, 36, 41].

Irritative Symptoms
• Nocturia (frequent nocturnal urination) • Pollakisuria (frequent diurnal urination) • Urinary urgency • Incontinence • Feeling of incomplete voiding of urine • Dysuria (difficulty and pain in urination)
Obstructive Symptoms
• Weakened urinary stream • Urinary stammering • Ischuria (urinary retention) • Terminal dribbling of urine • Formation of residual urine in the bladder • Delayed micturition start

The symptoms can cause a strong emotional crisis and affect the general condition as well as the quality of life of the patients considerably [18, 51].

Frequently it is the acute urinary retention, which causes the patient to consult an urologist. An acute erythrocyturia (blood in the urine) may make the matter more complicated.

3.5 Stages

The classification according to VAHLENSIECK [49] comprises four clinical stages of the BPH:

Tab. 4: Stages of prostatic hyperplasia.

Stage I
No voiding disorder of the bladder • More or less developed BPH • Urinary outflow more than 15 ml/s • No residual urine • No trabecular bladder
Stage II
Changing voiding disorder of the bladder (Frequency and strength of the urinary streams) • More or less developed BPH • Urinary outflow between 10 and 15 ml/s • No or only little residual urine (up to 50 ml) • No or beginning trabecular bladder
Stage III
Steady voiding disorders of the bladder (Frequency and strength) • More or less developed BPH • Urinary outflow less than 10 ml/s • Residual urine more than 50 ml • Trabecular bladder
Stage IV

Steady voiding disorders of the bladder

- More or less developed BPH
- Urinary outflow less than 10 ml/s
- Residual urine more than 100 ml
- Dilated bladder
- Urinary stasis of the upper urinary tract

A clinical interpretation of the symptoms and findings of the BPH in three clinical stages is also of general international use. This method is preferred in the Anglo-Saxon countries [28]:

- In stage I (irritation, compensatory stage) the bladder can be voided without residual urine and with normal or slightly weakened urinary stream. Urinary urgency, pollakisuria and nocturia may occur.
- Stage II (stage of beginning decompensation) is characterized by increasingly obstructive symptoms and the formation of residual urine up to about 10 ml.
- In stage III (stage of decompensation) the increasing amounts of residual urine lead to overflow incontinence. Later hydrouretro-nephroses with chronic postrenal kidney insufficiency may develop.

3.6 Therapy

In Stage IV according to VAHLENSIECK resection or ectomy is frequently the treatment method chosen, but in the Stages II and III (according to VAHLENSIECK, and I or II according to the international classification, resp.) a conservative medicamentous treatment is preferred [51].

Today conservative BPH therapy has obtained a high rank. Micturition difficulties and the formation of residual urine decrease in 60 to 70 % of the patients [50].

To-date mainly estrogens, gestagens and antiandrogens have been used. Recently 5-α-reductase inhibitors and the antagonists of the α_1-receptors have been used. However, the rank of these medications in BPH therapy has not been finally identified [1].

Phytopharmaceutical agents have been used successfully for a long period of time. Use of these agents have seen resurgence due to the emergence of additional data regarding their mechanisms of action and clinical application [51].

Among all the mechanisms discussed, phytosterols are considered as active and have been found in experimental as well as in clinical investigations to interfere with either reduction of testosterone to dihydrotestosterone, the sex-hormone binding globulin or aromatisation of testosterone. Additional effects are documented in experiments indicating immunomodulation and anti-inflammatory qualities [38].

Quick relief of symptoms is mostly due to free fatty acid fraction

Also the free fatty acids in the standardized EUROMED Saw Palmetto extract have shown anti-inflammatory and α-antagonist actions that result in quick relief of symptoms.

Saw Palmetto extract in 81 % of European BPH products

Having an 81 % share of the European herbal prostatic drug market, Saw Palmetto products (as available from EUROMED) are one of the most prescribed and sold OTC preparations in Europe. Clinical tests conducted during the last 10 years have boosted *Sabal* preparations to first place among all the herbal prostatic drugs [41].

The available surgical procedures are the open adenectomy, the transurethral resection (TUR-P) and the bladder incision [17]. This surgery is associated with complications and can aggravate the matter. That's why it should be avoided unless absolutely necessary [36].

Because of their unfavourable benefit-risk ratio the TUR-P is not the therapy chosen by patients having irritative symptoms or slight to moderately severe obstructive complaints. First the application of a phytopharmaceutical agent (e. g. a Saw Palmetto extract as available from EUROMED) should be taken into consideration [1].

In the stages I and II (international) [28] or II and III according to VAHLENSIECK [49] the conservative therapy is preferred today. The necessity of a preventive treatment in stage I is still being discussed.

4 Pharmacology

4.1 Pharmacodynamics of Saw Palmetto Extract

Many different mechanisms account for efficacy

The therapeutic benefit of Saw Palmetto extract in treating micturition symptoms of BPH is essentially based on antiandrogenic and antiphlogistic effects. However, new findings show that contraction inhibition may also be involved. The separate effects and hypotheses which are discussed to be responsible for the efficacy of Saw Palmetto are: .

- Antiandrogenic
  - Competitive inhibition of the testosterone-receptor
  - Inhibition of 5-α-reductase
- Antiphlogistic and anti-exudative
  - Membrane-stabilizing
  - Inhibition of phospholipase A_2
  - Inhibition of 5-lipoxygenase and cyclooxygenase
- Myo-relaxant, spasmolytic

4.1.1 Antiandrogenic Effect

Lipophilic extracts from the berries of Saw Palmetto have an antiandrogenic effect because of their content of phytosterols [23].

The antiandrogenic effect is selectively developed in the prostatic tissue without influencing the concentrations of testosterone, FSH and LH in the plasma and without affecting the sex-hormone system [51].

The pharmacological examination of the antiandrogenic effect of Saw Palmetto extract (as available from EUROMED) was conducted with several species of animals [45]. Castrated rats and mice were treated either with testosterone, pure excipient or testosterone with Sabal berries extract.

Antiandrogenic effect

Two weeks later the weight of the genital organs of the animals treated with the testosterone and the sabal berries extract combination was significantly smaller in comparison to those animals treated with testosterone alone. The additional administration of Sabal berries extract decreased the proliferative effect of testosterone significantly [45].

These findings were confirmed by an additional test: The genital organs of male mice and rats were stimulated by the administration of gonadotropin. Saw Palmetto extract antagonized the increase in weight of prostate and preputial glands in a constant and dose-related way. However, the weights of gonads, thymus or suprarenal glands was not changed [45].

Competitive inhibition of the testosterone-receptor

There is a discussion that the constituents of *Sabal* attach themselves to the androgen receptors and competitively inhibit the binding of testosterone to the receptor [6, 9]. In-vitro experiments with Sabal berries extract applied to human preputial fibroblasts proved the inhibition of the binding of androgen to the specific receptors in the plasma and especially in the nucleus.

Inhibition of 5-α-reductase

Furthermore Saw Palmetto extract reduced the metabolism of testosterone into the more active dihydrotestosterone (DHT) by inhibiting of the catalytic enzyme 5-α-reductase [30, 42, 46].

4.1.2 Antiphlogistic and Anti-exudative Effects

Saw Palmetto extract (as available from EUROMED) showed an antiphlogistic effect on the locally Dextran-induced edema on the rat's pad and on the UV erythema of the guinea pig: The oral pre-administration of Saw Palmetto extract brought about a distinct, dose-related reduction of the developing edema, which was plethysmo-graphically determined [48].

The antiphlogistic effect of the hydrophilic Saw Palmetto extract is mainly attributed to an acid polysaccharide isolated from Sabal berries extract. This polysaccharide also reduced cardiac edema by more than 50%.

Membrane-stabilizing effect

A membrane-stabilizing effect with the reduction of the capillary permeability is supposed to be the working mechanism. The phytosterols contained in the Saw Palmetto extract (as available from EUROMED) have a sterane skeleton similar to the corticosteroids. They are able to inhibit the enzyme phospholipase A_2 and consequently the arachidonic-acid cascade into prostaglandins and leucotrienes (Fig. 8) [53]. Results obtained in *in-vivo* tests have been confirmed *in-vitro* [52].

Inhibition of phospholipase A_2

Inhibition of 5-lipoxygenase and cyclooxygenase

Furthermore the inhibition of 5-lipoxygenase and cyclooxygenase has been studied. The inhibitory principle lies in the acid, lipophilic fraction of the Saw Palmetto extract [5].

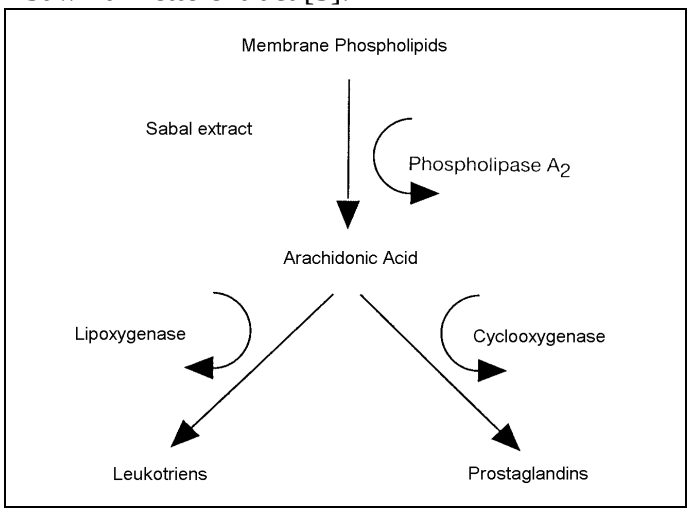

Fig. 8: Arachidonic-acid cascade and point of impact of Saw Palmetto extract.

An alcoholic extract of Saw Palmetto berries reduced the release of the prostaglandins PGI_2 and PGE_2 significantly (Fig. 9) [27].

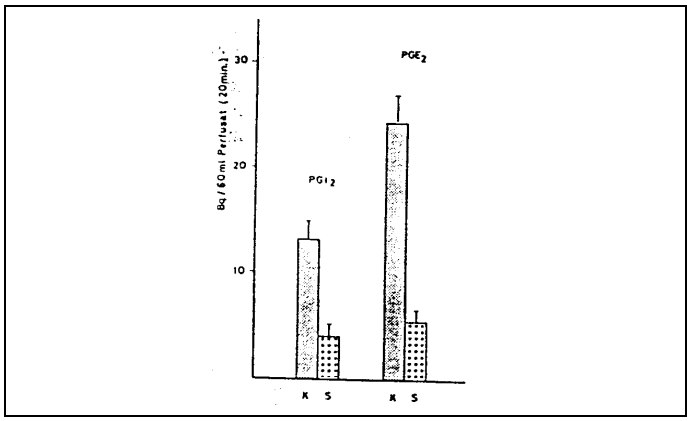

Fig. 9: The influence of alcoholic extracts of Saw Palmetto berries on the biosynthesis of prostaglandin; 1 ml extract equivalent to 250 mg drug; K = control; S = alcoholic Sabal extract; Bq = Bequerel; SEM (n=3) [27].

4.1.3 Myo-relaxant Effect

There is a great number of α-adrenergic receptors in the neck of the bladder, in the stroma of the prostate and in the prostatic capsule controlling the tone of the unstriped musculature in the prostatic urinary tract. Following an α-adrenergic stimulation the tone is raised and the urethral resistance increases. Correspondingly a relaxation of the unstriped musculature may be obtained by a blockage of the α-receptors [18].

Investigations on isolated spermatic ducts of rats have shown, that Saw Palmetto extract (as available from EUROMED) is able to antagonize contractions provoked by the administration of noradrenalin or by electrostimulation as a function of the concentration. When increases in contractions were caused in ileum and bladder dissections of guinea pigs by the application of KCl, then a concentration-related relaxation of the increased tone of the unstriped musculature could be obtained by the administration of Saw Palmetto extract also in these experiments (Figures 10 and 11) [40].

Spasmolytic effect on different smooth muscle contractions

Further experiments have shown that a lipophilic extract from Saw Palmetto fruits relaxes vanadate-induced contractions on rat uterus [22]. The total lipidic extract as well as the saponifiable fraction relax the tonic contraction induced by norepinephrine on rat aorta, by KCl on rat uterus, and by acetylcholine on urinary bladder [21].

The relaxation effects described can be explained as antagonization of α-adrenergic and Ca^{2+} related mechanisms by means of the reference substances used [21, 22, 38, 39, 40].

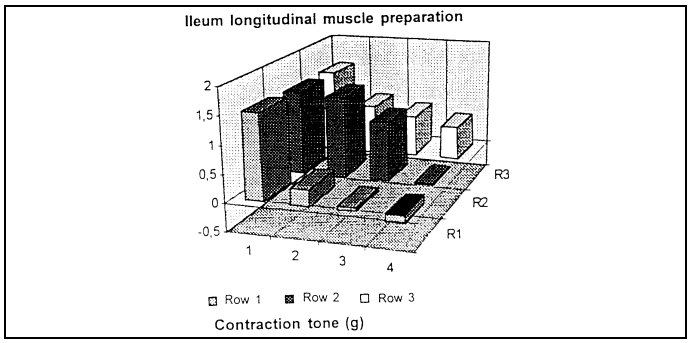

Fig. 10: First row: Significant decrease in KCl spasm (column 1) in response to 0.15, 0.22 and 0.33 mg/ml Sabal extract (columns 2-4). Second row: Effect of 10^{-9} to 10^{-7} M/L Verapamil. Third row (behind): Partial relaxant effect of the solubiliser Tween 80 in concentrations equivalent to those of the *Sabal* extract [40].

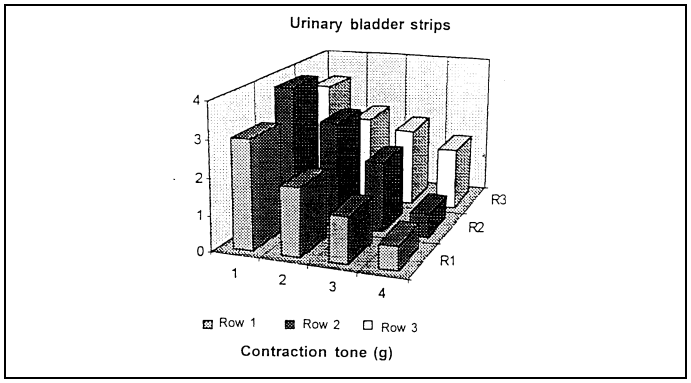

Fig. 11: First row: Significant decrease in KCl spasm produced by 0.15, 0.22 or 0.50 mg/ml *Sabal* extract. Second row: Effect produced by 10^{-9} to 10^{-7} M/L Verapamil. Third row: Relaxant effect of the solubiliser Tween 80 in concentrations equivalent to those in the Saw Palmetto extract [40].

This increase in the resistance of the unstriped musculature in micturition difficulties in connection with BPH is well known [8].

In contrast to the quick action (days) achieved with the Saw Palmetto extract, the 5-α-reductase inhibitors like finasteride need several months to start relieving the symptoms.

The antiphlogistic and anti-edematous factors of action have a clinical importance, since the BPH is often accompanied by a congestion and a sterile prostatitis.

The relaxant properties of Saw Palmetto extract (as available from EUROMED) lead to a reduction of the micturition difficulties also due to an increased adrenergic muscle tone.

4.2 Pharmacokinetics

The extract of Saw Palmetto berries is a complex compound. Therefore pharmacokinetic experiments are difficult and data are not yet available.

5 Toxicology

The toxicity of Saw Palmetto extract (as available from EUROMED) is generally very low.

Acute Toxicity

The acute oral toxicity of Saw Palmetto extract has been studied in different species of animals.

The LD_{50} in mice, rats and guinea pigs can be classified as >10 g/kg body weight. High doses up to 5 g Saw Palmetto extract per kg body weight given to dogs did not result in any intoxications.

Subacute Toxicity

High doses of Saw Palmetto extract were orally given to rats and dogs for 6 weeks. The clinical, hematological, biochemical and histological parameters were studied. Doses 360 and 16 times over the therapeutic dose administered to rats and dogs, respectively, did not show any toxic effects.

Chronic Toxicity

In long-term studies conducted for 6 months rats and dogs were given daily doses of Saw Palmetto extract up to 80 times (400 mg/kg) and 40 times (200 mg/kg), respectively, over the therapeutic doses. Cases of death or clinical symptoms did not occur. Saw Palmetto extract did not show any influences on laboratory parameters (hematology, blood chemistry, urinary findings) and histopathologic criteria.

Reproduction Toxicology

Saw Palmetto extract (400 mg/kg, i.e. 80 times over the therapeutical dose) had no effect on the fertility of rats.

Genotoxicity/Carcinogenicity

There are no data available.

6 Clinical Pharmacology

A controlled double-blind study was performed with 35 BPH patients. The probands received 160 mg extract for 3 months. The control group was given a placebo. The steroid receptors in the nuclear and cytosolic fractions were determined by means of the saturation analysis technique for androgen and estrogen receptors and the enzyme immunoassay for estrogen and progesterone receptors. Estrogen and prostaglandin receptors in the nuclear fraction were significantly ($p<0.01$) lower in the proband group than in the control group. The determination of androgen receptors in the nuclear fraction were positive in only 1 of 10 cases (6 of 10 in the control group). Saw Palmetto extract (as available from EUROMED) contains at least two fractions, i.e. one with antiandrogenic and the other with antiestrogenic effects [16].

The extract of Saw Palmetto berries does not work via systemic changes of hormone levels. As a result of the treatment with 320 mg extract given for 30 days no changes were found in the plasma levels of testosterone and follicle-stimulating and luteinising hormones [11].

7 Proof of Clinical Efficacy

7.1 Clinical Trials with Placebos

Several clinical tests with more than 800 patients were conducted to study the efficacy of Saw Palmetto extract (as available from EUROMED) in treating BPH. The Saw Palmetto extract led to a reduction of the subjective micturition symptoms, improved the urinary outflow and reduced the residual urine volume.

More than 20 double-blind studies

More than 20 controlled double-blind studies have demonstrated that the lipidic extract of the berries standardized to contain 85 to 95 % fatty acids and sterols is effective in relieving all the major symptoms of BPH including increased night-time urinary frequency, the most bothersome complaint [36].

Champault G, Patel JC, Bonnard AM. Brit. J. Clin. Pharmacol. 18: 1984, 461-462

In a controlled double-blind study 110 BPH patients in stage I and II (international) were given *Sabal* berries extract or a placebo for 30 days [12]. The success of the therapy was illustrated by the parameters nocturia, dysuria, urinary outflow and residual urine volume as well as by overall evaluations by the patients and the attending physician. The proband group was significantly better with respect to all the subjective and objective parameters than the control group. Nocturia and the residual urine volume decreased by more than 45 % and 42 % resp., the urinary outflow rate increased by more than 50 % in the Saw Palmetto treated group.
The tolerance was equally good in both groups. Changes in the clinicochemical parameters did not occur. 47 patients continued the therapy by an average of 14.6 months. Efficacy continued during this period and the extract was well tolerated [12].

Gabric V, Misckic H. Therapiewoche 37: 1987, 1775-1788

Symptoms remit

A distinct improvement of functional disorders, urinary bladder capacity, urinary outflow and micturition periods by Saw Palmetto extract (2 x 160 mg/d) could be demonstrated in a controlled comparison study conducted for two months. 42% of the patients of the proband group but only 15% of the control group indicated an improvement of their complaints. The tolerance of the Saw Palmetto extract was good. The therapy had to be stopped due to gastric complaints in one case only [20].

Cukier D. La Gazette Médicale Supplément 1: 1986, 34-38

160 BPH stage I and stage II (international classification) patients were treated with Saw Palmetto extract or placebo in a multicentric control study for 2 to 3 months. The criteria of efficacy were dysuria, diurnal and night pollakisuria and the residual-urine volume determined sonographically. Saw Palmetto extract led to an improvement of dysuria by about 50% on the range of complaints. Also pollakisuria was reduced by more than 30% compared to the placebo control. The residual urine volume decreased by 14% to the initial value in the proband group, whereas it slightly increased in the control group. The tolerance was evaluated as good in 95% of the cases [14].

Carreras JO. Arch. Esp. de Urol. 40(5): 1987, 310-313

Another study showed that the treatment of benign prostatic hypertrophy with extract of Saw Palmetto was effective with most of the patients: it was excellent in 67% and good in 25%. The efficacy is ascribed to its antiandrogenic (inhibitor of DHT formation) and antiedematous properties. Side-effects or toxicity from its application were not found. The gastric tolerance was excellent in all patients [10].

Mattei, F.M.; Capone, M.; Acconcia, A.: Medikamentöse Therapie der benignen Prostatahyperplasie mit einem Extrakt der Sägepalme. TW Urol. Nephrol. 2/5: 1990, 346-350

40 BPH patients (stage II and III according to VAHLENSICK) of an average age of 59 years were treated with Saw Palmetto extract or placebo in a controlled study for more than 3 months. Diurnal and night micturition frequencies, dysuria, the feeling of incomplete urination and complaints in the perineal or suprapubic areas were determined after 0, 30, 60 and 90 days of therapy. The residual urine volume and the size of the prostate as objective quantities were measured by sonography at the beginning and at the end of the study. A good result of the treatment could be seen in the proband group after only 30 days. The residual urine volume measured sonographically was reduced by Saw Palmetto extract by 59%, whereas placebo did not show any effect. A distinct improvement of diurnal (Fig. 13) and night (Fig. 14) pollakisuria could be seen after 30 days of therapy.

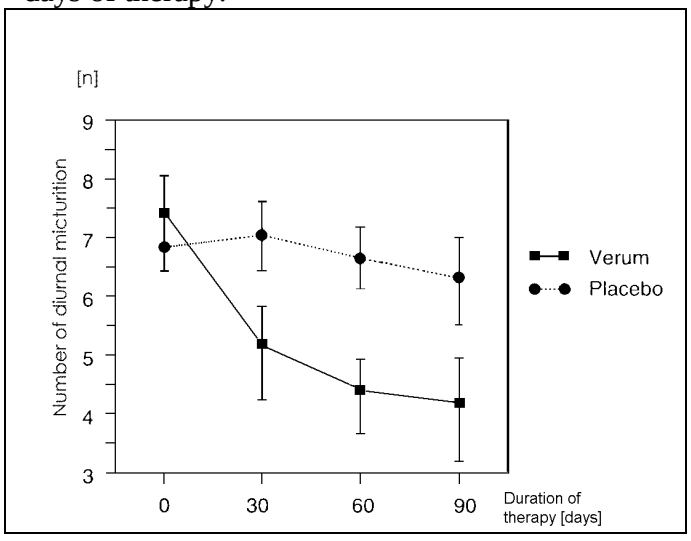

Fig. 13: Reduction of pollakisuria „diurnal“ during the Saw Palmetto extract or placebo therapies.

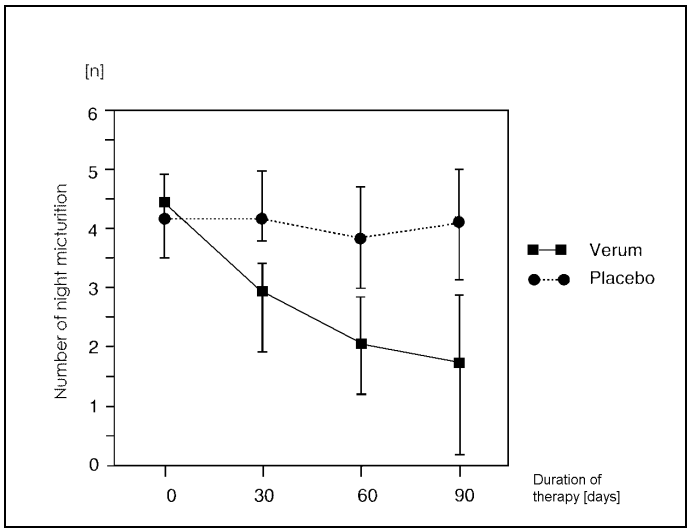

Fig. 14: Reduction of nocturia during the Saw Palmetto extract and placebo therapies.

The micturition frequency decreased significantly compared to the placebo group. Dysuria, the feeling of incomplete urination as well as pains and pressure symptoms were also distinctly improved (Fig. 15). The only side effects were gastro-intestinal complaints with one patient of the proband and control groups each. Altogether both the treatments were well tolerated. There was no influence on the laboratory findings [32].

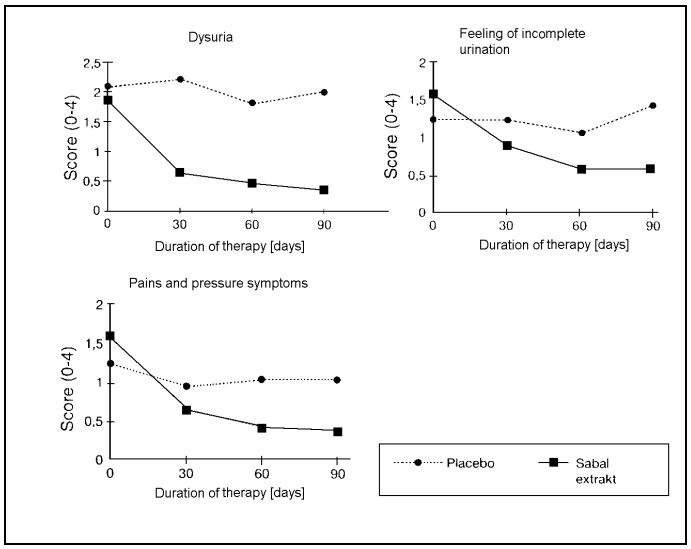

Fig. 15: Changes of subjective parameters (mean values) by Saw Palmetto extract and placebo therapies.

7.2 Drug Monitoring Trials

Vahlensieck W, Völp A, Lubos W, Kuntze M. Fortschr. Med. 111: 1993, 323-326

The good results of the clinical studies were confirmed by a twelve-week drug monitoring trial with 1.334 male BPH patients treated with Saw Palmetto extract. The residual urine volume decreased by 50%. The average number of pollakisurias and nocturias decreased by 37 and 54%, respectively. The portion with dysuric complaints decreased from 75 to 37%. The efficacy and compatibility in more than 80 and 95% of the cases, respectively, were evaluated as good or very good [51].

Bach D. Urologie [B] 35: 1995, 178-183

Improvement of the quality of life

The longest published study to date is a three-year prospective multicentric study [3]. The maximum urinary outflow rate increased by an average of 6.1 ml/s during the three-year treatment. The residual urine volume was reduced by 50%. The improvement of the quality of life turned out to be decisive to the success of the therapy. 80% of the physicians and patients judged the efficacy as very good or good. Only 1.8% of the patients stopped their participation in the study because of side-effects [3, 18].

Summary

The treatment with Saw Palmetto extract is an effective therapy in the stages I and II (international) or II or III (according to VAHLENSIECK). micturition complaints, urinary outflow and residual urine volume are improved. However, the size of the prostate is not measurably influenced. Saw Palmetto extract is tolerated well with minimal side effects.

Hence Saw Palmetto extract (as available from EUROMED) is of great importance to the phytotherapy [26]. The evaluation of the Bundesgesundheitsamt/ Federal Public Health Department (today: Bundesinstitut für Arzneimittel und Medizinprodukte/ Federal Institute for Drugs and Medical Devices) on efficacy and harmlessness of Saw Palmetto in treating BPH is given in a positive monograph [13].

7.3 Therapeutic Safety

High level of therapeutic safety

Saw Palmetto extract is notable for its particularly high level of clinical safety. To-date acute cases of Saw Palmetto extract poisoning have not been reported.

High level of compliance

Particular emphasis should be put on the high tolerance of Saw Palmetto preparations leading to a high level of treatment compliance because of the extremely low incidence of side-effects.

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