New perspectives on saw palmetto

(Serenoa repens):
a medico historical/analytical comparison
of preparations derived from it and a clinical
pilot trial in patients with benign prostatic
hyperplasia and sexual dysfunctions

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Submitted for degree of Doctor of Philosophy
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For my parents

and

Maja and Matthias
This thesis describes research conducted in the School of Pharmacy, University of London/University College of London between May 2008 and April 2012 under the supervision of Professor Michael Heinrich.

I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

______________________________  30th of October 2012
Signature                          Date

Andy Suter
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Andy Suter
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<th>Definition</th>
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<td>AOAC</td>
<td>Association of Official Analytical Chemists</td>
</tr>
<tr>
<td>AP</td>
<td>Sum of area of fatty acids in a sample</td>
</tr>
<tr>
<td>ASEX</td>
<td>Arizona Sexual Experience Scale</td>
</tr>
<tr>
<td>AST</td>
<td>Area of internal standard</td>
</tr>
<tr>
<td>AUASI</td>
<td>American Urological Association Symptom Index</td>
</tr>
<tr>
<td>AUR</td>
<td>Acute urinary retention</td>
</tr>
<tr>
<td>B.C.</td>
<td>Before Christ</td>
</tr>
<tr>
<td>BfArM</td>
<td>Bundesinstitut für Arzneimittel und Medizinprodukte</td>
</tr>
<tr>
<td>BPH</td>
<td>Benign Prostatic Hyperplasia</td>
</tr>
<tr>
<td>bSFI</td>
<td>Brief Sexual Function Inventory</td>
</tr>
<tr>
<td>bw</td>
<td>Body weight</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
</tr>
<tr>
<td>CRF</td>
<td>Case record form</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome</td>
</tr>
<tr>
<td>DAN-PSSsex</td>
<td>Danish Prostatic Symptom Score questionnaire for sexual dysfunction</td>
</tr>
<tr>
<td>DER</td>
<td>Drug extractant ratio</td>
</tr>
<tr>
<td>DHT</td>
<td>Dihydrotestosterone</td>
</tr>
<tr>
<td>DISF/DISF-SR</td>
<td>Derogatis Interview for Sexual Functioning</td>
</tr>
<tr>
<td>EC_{50}</td>
<td>Half maximal effective concentration</td>
</tr>
<tr>
<td>ED</td>
<td>Erectile dysfunctions</td>
</tr>
<tr>
<td>ESCOP</td>
<td>European Scientific Cooperative on Phytotherapy</td>
</tr>
<tr>
<td>FAME</td>
<td>Fatty acid methyl esters</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FID</td>
<td>Flame ionization detector</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HPTLC</td>
<td>High performance thin layer chromatography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Half maximal inhibitory concentration</td>
</tr>
<tr>
<td>iD</td>
<td>Internal diameter</td>
</tr>
<tr>
<td>IIEF</td>
<td>International Index of Erectile Function Questionnaire</td>
</tr>
<tr>
<td>IIEF-5</td>
<td>Short version of the International Index of Erectile Function Questionnaire with only 5 questions</td>
</tr>
<tr>
<td>IIEF-ED</td>
<td>International Index of Erectile Function Questionnaire-erectile dysfunction subscale</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukine</td>
</tr>
<tr>
<td>INF</td>
<td>Interferone</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prostate Symptom Score</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat population</td>
</tr>
<tr>
<td>kPa</td>
<td>kiloPascal</td>
</tr>
<tr>
<td>LNCaP</td>
<td>Human prostate adenocarcinoma cell line</td>
</tr>
<tr>
<td>LOX</td>
<td>Lipoxygenase</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>MSHQ-EjD</td>
<td>Male Sexual Health Questionnaire to assess ejaculatory dysfunction</td>
</tr>
<tr>
<td>MTOPS</td>
<td>Medical Therapy of Prostatic Symptoms study</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non steroidal antiinflammatory drug</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal component analysis</td>
</tr>
<tr>
<td>PDE</td>
<td>Phosphodiesterase</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol population</td>
</tr>
<tr>
<td>PRV</td>
<td>Post-void residual urine</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostatic specific antigen</td>
</tr>
<tr>
<td>Q&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum Urinary Flow Rate</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised clinical trial</td>
</tr>
<tr>
<td>R&lt;sub&gt;r&lt;/sub&gt;</td>
<td>Retardation factor</td>
</tr>
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>SDys</td>
<td>Sexual dysfunctions</td>
</tr>
<tr>
<td>SHGB</td>
<td>Sex hormone binding globulin</td>
</tr>
<tr>
<td>SP</td>
<td>Sample (for the phytochemical analysis)</td>
</tr>
<tr>
<td>TID</td>
<td>Three times daily</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>Urolife QoL-9</td>
<td>Urolife BPH Quality of Life 9-questionnaire</td>
</tr>
<tr>
<td>Urolife QoL-9 sex</td>
<td>Urolife BPH Quality of Life 9-questionnaire subscale for 'patient's perceived sexual life'</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>Vklin</td>
<td>Verordnung für klinische Studien</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WIT</td>
<td>Weight of internal standard</td>
</tr>
<tr>
<td>WS</td>
<td>Weight of sample</td>
</tr>
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Abstract

Saw palmetto berries (*Serenoa repens*) are used today for treatment of symptoms of benign prostatic hyperplasia (BPH) which is an age dependent disease leading to lower urinary tract symptoms (LUTS) and impacts negatively sexual functions.

I carried out the first clinical pilot trial to assess if a saw palmetto treatment in patients with BPH and concomitant sexual dysfunctions (SDys) is effective and safe in both groups of symptoms. After 8 weeks of treatment with 320mg saw palmetto extract daily, BPH symptoms measured with the International Prostate Symptom Score IPSS were reduced from $14.4 \pm 4.7$ to $6.9 \pm 5.2$ ($p<0.0001$). At the same time SDys measured with the brief Sexual Function Inventory bSFI improved from $22.4 \pm 7.2$ to $31.4 \pm 9.2$ ($p<0.0001$), and with the Urolife BPH QoL-9 sex questionnaire from $137.3 \pm 47.9$ to $195.0 \pm 56.3$ ($p<0.0001$). The treatment was very well tolerated and accepted by the patients.

Another subject of this thesis was to examine the quality of commercial preparations from eight countries which contained saw palmetto and are sold as treatments for BPH symptoms. For each of the 46 analysed products the amount of the main active constituents, the fatty acids was determined using gas chromatography. The quantity of fatty acids per daily dosage varied widely between the products and also the composition of the samples was very heterogeneous.

A medico-historical investigation how saw palmetto was introduced firstly into U.S. American medicine and how the plant became popular as a treatment in Germany was the last aspect of the thesis. The eclectic physicians pioneered in using this plant in the United States supported by homeopathic doctors and pharmacists. In Germany, mainly the homeopaths favoured the use of saw palmetto and were the trailblazers making it a popular treatment for BPH symptoms.

In conclusion, this thesis shows comprehensively how saw palmetto made its way into medical practice in the United States and Germany, that preparations on the markets containing saw palmetto differ widely in their content of the main active constituents, the fatty acids, and thus higher quality demands from regulatory authorities are warranted, and in a pilot trial it could be shown that saw palmetto is not only an effective and safe treatment for BPH symptoms but also for concomitant SDys.
Aims

In this thesis new data on historical, phytochemical, and clinical aspects of saw palmetto as a medical treatment should be presented. This includes in more detail:

- A historical review how saw palmetto became a popular treatment in the United States and how the plant made it into the medical practice in Germany, this all embedded in the historical context of treatment of benign prostatic hyperplasia (BPH)

- A phytochemical analysis of 46 commercial preparations containing saw palmetto on their amount of the main active constituents, the fatty acids

- A clinical pilot trial with a standardised saw palmetto product in patients with BPH and sexual dysfunctions to assess if this treatment may improve not only urinary symptoms but also concomitant sexual disorders
The Chapter 1 presents a general introduction into botanical, pharmacological, toxicological, and clinical particulars of saw palmetto and provides also an introduction into the disease benign prostatic hyperplasia (BPH).

In Chapter 2 the history of treatments for BPH are laid out, followed by a comprehensive review on the history of the use of saw palmetto. This includes the traditional use by the indigenous population of the Florida region, the first mentioning of the plant in Western literature and how the plant became a popular treatment in the United States. The last part of this chapter depicts how saw palmetto was introduced into the German scientific community and when the plant was acknowledged as a medical treatment for BPH.

The Chapter 3 provides a phytochemical analysis of 46 commercial preparations which contain saw palmetto and are sold as treatments for BPH.

Chapter 4 shows results from a clinical pilot trial in patients with BPH and concomitant sexual dysfunctions.

Finally, Chapter 5 includes the final discussion and conclusions of all results gathered in this PhD thesis.
Chapter 1

An introduction to saw palmetto, the plant, its pharmacology and efficacy
and
to benign prostatic hyperplasia BPH, the disease, its diagnosis, and treatments
Chapter 1: General Introduction

1.1 Saw palmetto – the plant (*Sabal serrulata, Serenoa repens*)

1.1.1 Discovery and taxonomic description

The first European mentioning of a tree which could have been saw palmetto was in 1575 by Hernando Descalante Fontaneda, a Spanish shipwreck survivor who lived with the Indians of Florida for 17 years (5). In his memoirs he called the shrubs ‘palma’ and ‘palmito’ and how important they were to the indigenous people of Florida (6). Later then, the quaker merchant Jonathan Dickinson, another shipwreck survivor, named a tree around 1690 a ‘shubby palmetto’. This could have been with a high certainty also saw palmetto as he fed from the berries to avoid starvation (7, 8).

It was the botanist William Bartram in 1792 who was the first to give an accurate description of saw palmetto. In his botanical book ‘Travels’, which is a comprehensive report of the flora of North and South Carolina, Georgia, and Florida, he wrote about a ‘dwarf saw palmetto’ and *Coryphha repens*. This is considered today as the first description in literature which can be attributed with great certainty to *Serenoa repens* (9).

Today the two most commonly used botanical names are *Sabal serrulata*, referring to the fan-shaped serrated leaves and *Serenoa repens* which goes back to the botanist J.D. Hooker. The genus is named in honour to Sereno Watson (1826-1892) an assistant of Asa Gray, a well known botanist who in the 19th century described the flora of the south-eastern coastal areas of the United States (10).

The accepted taxonomical name is now *Serenoa repens* (W. Bartram) Small (11). It belongs to the genus Serenoa, family Arecaceae (palm trees), the subfamily Coryphoideae, tribe Coryphea, and subtribe Lvistoninae (12). *Serenoa repens* is the only representative of the genus Serenoa (13).

Nevertheless, the first official botanical name was *Chaemerops serrulata* (Michx.) which was issued in 1803 (14) but this name was sometimes also mistakenly taken for the
cabbage palm, a tree often to find in the same regions where saw palmetto grows (15). Other common names for the plant are saw palmetto, in older literature the plant was also often cited as dwarf palm (16) or *Brahea serrulata* (Michx.) or *Diglossophyllum serrulatum* (Michx.) (14).

In the following only the term *Serenoa repens* will be used as it is the accepted name in the botanical literature (17).

### 1.1.2 Botanical Description

The name of the saw palmetto is due to the saw-like leaves. These characteristic fan shaped leaves are bright green and are up to one meter wide. Approximately three to seven leaves are produced each year and remain alive on the plant for about two years. The plant bears a densely cluster of white flowers, the so called spadix, which is shorter than the leaves (18). The palm has a creeping and branching prostrate stem, which can occasionally reach the height of two meters (Figure 1) (19, 20).

Saw-palmetto produces one to three prominent spadices during spring, and fruits mature during summer. However, individual plants may flower throughout the year, but fruit seldom matures outside the summer period.

The drupes are about the size of an olive, in its mature stages of green to orange colour and harbour the pharmacologically active constituents. During ripening, the fruits turn in colour from green (May-June) to yellow (mid-August), to orange (September), and to bluish-black (September-October). Fruit production can be variable among years. Annual average number of seeds per plant has been measured to vary between 100 and 500 in mid to late June, but decrease rapidly until mid-October when no fruits remain on the plants (21).

Saw palmetto flowers are in densely-branched, interfoliar inflorescences, which are about half a meter in size. The trees commonly produce one to three, at maximum five inflorescences at the time whereas one contains several thousand individual flowers (22).
By judging from their leaf scars and the length of their growing stems, it has been estimated that the oldest saw palmetto plants in Southern Florida have an age of about 500 to 700 years (23).

**Figure 1:** Saw palmetto plant with ripe berries (Source: A.Vogel Bioforce AG)

### 1.1.3 Distribution and Ecology

*Serenoa repens* is one of the most abundant plants in the Southeastern United States. It can be found in pine flatwoods, which are special soils formed from marine sediments, prairies, and scrubs as well as in dunes and maritime forests but seems to be sensitive to salt spray. Interestingly, saw palmetto is well adapted to fire and is one of the most fire-tolerant among the pyric species (19).
Chapter 1: General Introduction

The plant is endemic in Florida and according to the plant database of the United States Department of Agriculture can be found also in the states of Texas, Louisiana, Mississippi, Alabama, Indiana, Georgia, and South Carolina (24). In a similar database of the United States Geological Survey, the same states as above are mentioned except Texas. The map of the distribution shows that *Serenoa repens* occurs mainly in Florida and in the other mentioned states mainly in the Southern coastal areas (2) (Figure 2).

**Figure 2**: The local distribution of *Serenoa repens* indicated with green colour, after United States Geological Survey USGS, 2006 (2).

The Catálogo de las Plantas Vasculares de Panamá describes the occurrence of *Serenoa repens* also in Panama, which would be contradictory to the data above (25).

Generally, the plant grows best in regions with an average annual rainfall of 100-163 cm and a minimum to maximum temperature range of -4° to 36°C. It seems to be cultivated only in Northern America (13).
1.1.4 Wildlife Use

A wide variety of species use saw palmetto either as a source for food or for nesting or protective cover.

Animals known to use it for nesting cover are the endangered Florida grasshopper sparrow (*Ammodramus savannarum*), the Florida woodrat (*Neotoma floridana*), the wild turkey (*Meleagris gallopavo*), the Florida panther (*Felis concolor*) (26), and the Florida black bear (*Ursus americanus ssp. floridanus*) (19). As escape cover or bedding cover during windy, cold days it is used by the white-tailed deer (*Odocoileus virginianiana*) (27).

Not only the berries but also the apical meristem, the so-called heart of the plant are eaten. It is physically extracted and eaten by black bears and feral pigs (*Sus scrofa*). They usually eat on the freshly regrown plants after a fire (26). Cattle are known to consume the leaves only if there is no better forage (28) or they consume the fronds during winter (26).

However, generally, the herbal parts or the stem of the plant has little value as livestock forage (29), in particular since the frond is less than 30% digestible even though its phosphorous content is relatively high (26).

Over 300 species of insects have been observed visiting saw palmetto flowers. Some of these flower visitors collect nectar and/or pollen, while others find mates or prey near or on the flowers. The main visitors of the flowers and thus the primary pollinators appear to be bees; the other most frequently observed insects were mostly dipterans or hymenopterans (30).

The berries are the main source of food from saw palmetto for animals. A large variety of animals have been observed consuming them, such as raccoons, foxes, rats, gopher tortoises, white tail deer, black bears, feral hogs, and even fish and waterfowl (19). The fruit or more precisely the drupe is an excellent source for carbohydrates and oils. In late summer when the fruits are ripe, they are eaten extensively by black bears. A road killed adult female bear was found to have more than 13.5 kg of saw palmetto fruit in its stomach (26). White tailed deer favour the berries as an important late autumn and
early-winter food, whilst given to cows it has been observed that they produce more and better milk (19).

Generally, the animals eating the drupes serve as dispersal agents as the seeds are distributed throughout the landscape in faeces (26). The fruit’s endocarp and seed coat are impermeable to oxygen and it takes four to six months for these tissues to deteriorate (24).

In total, the plant itself provides food or cover for more than 100 bird, 27 mammal, 25 amphibian, and 61 reptile species (31).

### 1.2 Pharmacological data of saw palmetto

#### 1.2.1 Constituents

The dried saw palmetto berries consist to about 36% of pericarp, 16% pulp, 10% testa of the seed, and 38% of the seed. The pulp contains a highly active lipase which dissociates triglycerides during ripening and drying to single fatty acids (32). The fruits primarily contain free fatty acids such as capric, caproic, caprylic, lauric, myristic, oleic, linoleic, linolenic, stearic, and palmitic acids (17) and their ethyl esters and glycerides (33) which occur most likely during the extraction process (17). This process is catalysed by an esterase which is to be found in the pulp (32). An analysis of 14 saw palmetto berry extracts showed that up to 52.15 % of the total extract were methyl- or ethyl esters and glycerides (34), while an investigation of the pressed juice of the berries estimated that about one third of the oil were ethyl esters (32). Schantz et al. found in an analysis of the saw palmetto fruit and a hexane/acetone (4:1 v/v) extract that the ratio of triglycerides to free fatty acids in the fruit and the extract was about 2:1 (35). A more extensive description of the fatty acids with the structure formulae is given in chapter 3.3.2.

Further sterols (17) and specially the phytosterols such as β-sitosterol and β-sitosterol 3-O-D-glucoside, (33) campesterol and stigmasterole can be found (Figure 3) (36). The amount of phytosterols is rather low compared to the whole extract, the analyzed amounts are in the range from 0.45 (35) to 0.1% of total mass in ripe fruits (37) to 1.9-55.4mg campesterol, 4–28.6mg stigmasterol, and 6.9–174mg β-sitosterol per 100g in
several investigated saw palmetto preparations like powdered berries, aqueous, ethanolic, and CO₂ extracts (36).

An investigation on the substances of the hydrodistillate of saw palmetto berries identified 144 compounds whereas lauric acid was with an amount of 40.4% the main detected component (38).

Other constituents are carbohydrates such as mannitol and polysaccharides with galactose and arabinose (33), triterpenes (17), aromatic acids like ferulic and vanillic acid (33), β-carotens, the vitamin E derivates γ-tocopherol and δ-tocopherols (35), and the monoamine tyramine which was reported to be 0.72% of the total mass of an ethanolic saw palmetto extract (Figure 3) (39).

In total, in lipophilic saw palmetto berry extracts, the fatty acids and its esters are predominant and comprise to about 75-95% of the total extract (40).

It is assumed that the fatty acids together with the phytosterols are the main active principles of saw palmetto, particularly in treatment of prostate problems (41).

Since the main use of saw palmetto preparations is in benign prostatic hyperplasia (BPH), the majority of the pharmacological experiments have been carried out targeting this disease. These are primarily investigations on anti-androgenic, anti-inflammatory and on muscle relaxation or vasodilatative effects where always lipophilic saw palmetto berries extracts were used. They are abbreviated in the following as saw palmetto extracts.
1.2.2 Antiandrogenic properties

In human foreskin fibroblasts, a saw palmetto extract inhibited the binding of $[^3H]$-DHT to both cytosolic and nuclear androgen receptors by 90% and 70%, respectively (IC$_{50}$ 7.1 units/mL). 100mg/mL of the total extract inhibited the 5-alpha-reductase activity in the rat ventral prostate by 50%, and reduced conversion of testosterone into dihydrotestosterone (DHT) in human foreskin fibroblasts by 90% (42). 

Another study showed only marginal effects of several saw palmetto extracts on the activity of 5-alpha-reductase from human prostate or on DHT binding to the rat prostatic androgen receptor. In concentrations up to 100mg/mL, various saw palmetto preparations (Permixon, drug extractant ratio (DER) 6-12:1, extractant hexane; Talso, DER 10:1, lipophilic extract; Strogen Forte, DER 10:1, lipophilic extract, and Prostagutt, DER 11.8:1, lipophilic extract) showed in vitro weak 5-alpha-reductase compared to finasteride (43).
The mode of action of saw palmetto and finasteride appears to be different. While the addition of saw palmetto extract inhibited metabolism of $[^{3}H]$-testosterone (0.1 μM) in human prostate epithelial cells and fibroblasts to all metabolites (DHT, androst-4-ene-3,17-dione, 5α-androstane-3,17-dione), finasteride blocked conversion of $[^{3}H]$-testosterone (0.1 μM) to DHT and 5α-androstane-3,17-dione, but not androst-4-ene-3,17-dione. If this difference is relevant in the in vivo situation is questionable (44). The inhibition of the two isoforms of 5-alpha-reductase by saw palmetto extract seems to be non-competitive and less potent with a Ki level about ten times higher than finasteride, which was a competitive inhibitor (45).

Of a fractioned saw palmetto extract – i) saponifiable, ii) non-saponifiable, and iii) hydrophilic sub fractions - only the saponifiable sub-fraction (consisting mainly of lauric, oleic, myristic and palmitic acids) was active in inhibiting 5-alpha-reductase.

Of the fatty acids investigated, lauric acid was the most active: It inhibited epithelial and stromal 5-alpha-reductase activity by 51% and 42%, respectively, non-competitively and dose dependently up to a concentration of 0.2mmol/L. The non-saponifiable fraction, consisting mainly of phytosterols, was weakly active, while the hydrophilic sub fractions, containing carbohydrates, amino acids and polysaccharides, were inactive (46). Raynaud, 2002 confirmed these findings, he showed that the dual inhibitory activity of saw palmetto extract on 5-alpha-reductase type 1 and type 2 can be attributed to its high content in free fatty acids (47). Also, lipophilic saw palmetto extract effectively inhibited in LNCaP prostate cancer cell lines 5-alpha-reductase activity (48).

A further confirmation of the in vitro results was seen in a rat model of prostate hyperplasia induced by androgen stimulation. After oral administration of saw palmetto extract, 200mg/d for six days, the hormone-induced increase in prostate weight was stopped (49). Another trial showed similar findings: 50mg/kg bw/d saw palmetto extract inhibited hormone-induced prostate weight as well. The maximum effect was reached after 60 and 90 days for the dorsal and lateral regions of the rat prostate, and for ventral region after 30 days and 60 days, respectively (50). Furthermore, in rats a saw palmetto extract decreased testosterone-induced prostate weight by 38% (150mg extract/d) or 76% (300mg extract/d) (51). Similar effects were reported by de Lourdes,
2007 for 400mg/kg/d for 14 days, also in a rat model (52). The reduction of prostate weight was 44%, while Talpur, 2003 reported a reduction to the size of the control group (53).

In dogs with asymptomatic mild to moderate prostate enlargement, a dose of 1,500 mg/d TID saw palmetto extract which is about five times of the human dose of 320mg or 300mg/d TID for 90 days did not affect prostatic weight, volume or histology. In a similar trial set up saw palmetto extract did not affect the prostate in the same way as finasteride (54).

The *in vitro* results suggest that saw palmetto inhibits the 5-alpha-reductase due to its content of fatty acids. But the interaction with the enzymes seems to be different from that of finasteride. To which extent the inhibition is clinically relevant is still part of discussion and needs further investigation but animal testing showed that this mode of action could be of relevance for saw palmetto. In trials with biopsies of BPH patients no clear confirmation of these findings could be observed. Di Silverio, 1992, saw small antiandrogenic and antiestrogenic effects (55) and in removed prostate tissue after saw palmetto berries treatment, effects on oestrogen, progesterone and androgen receptors were seen in the nuclear, but not in the cytosolic fraction. In a subsequent trial the decrease of DHT – as marker of 5-alpha-reductase activity *in vivo* - in that region correlated with clinical improvements (56).
1.2.3 Anti-inflammatory activity

As will be shown below (Chapter 2), saw palmetto preparations were used traditionally for diseases with a certain inflammatory component like cough or epididymitis. Even though an anti-inflammatory activity could be of therapeutical relevance, only few experimental data on this subject is available.

An older experiment showed moderate antiinflammatory activity. In a guinea pig model lipophilic 1-5ml/kg bw saw palmetto extract one hour before exposure to UV light inhibited erythema. But carrageenan induced rat paw oedema was not reduced, in line with this that saw palmetto extract did not inhibit platelet cyclooxygenase (57).

Adult male Wistar rats, receiving 50 or 100mg/kg bw saw palmetto extract for 90 days displayed a reduced accumulation of mast cells in proximal stroma in a dose dependent manner (58) and Sabal extract prepared with supercritical carbon dioxide inhibited cyclooxygenase and 5-lipoxygenase \textit{in vitro} (IC$_{50}$ 28.1 and 18.0\mu g/mL, respectively) (59).

Further evidence of the antiinflammatory activity could be shown \textit{in vitro} using LPS-induced IL-12 formation with androgen-independent human prostate cancer PC-3 cells. Saw palmetto extract 50\mu g /mL reduced this LPS-induced IL-12 formation by 40% (60).

Anti-inflammatory activity \textit{in vivo} was investigated by Vela-Navarrete, 2005. The pilot study showed a significant reduction of inflammatory parameters in prostatic tissues of patients treated with saw palmetto extract. Interestingly, a correlation with clinical improvement was observed (61).
1.2.4 Muscle relaxation and vasodilatative effects

The traditional use of saw palmetto particularly in bladder problems in women as will be described in chapter 2, points to the possibility that extracts of the plant could also interaction with specific receptors in the bladder. To some extent, positive results have been seen but there is clear evidence yet lacking.

A saw palmetto extract inhibited specific binding of [H]-[N-methyl-H] scopolamine methyl chloride (bladder) and [H]-prazosin (prostate) with IC\(_{50}\) values of 46.1 and 183 \(\mu\)g/ml, respectively (62). Another study showed that various saw palmetto extracts inhibited radioligand binding to human prostatic alpha1-adrenoceptors and agonist-induced \[^{3}H\]inositol phosphate formation \textit{in vitro} noncompetitively (63). But the results could not be confirmed in a subsequent clinical trial in 12 healthy volunteers (64).

In a series of \textit{in vitro} experiments, saw palmetto extract inhibited the muscarinic M3 receptor with an IC\(_{50}\) of 3-30\(\mu\)g/ml but not on the M1 and M2 receptor. The M3 receptor is seen as the relevant receptor which needs to be inhibited to influence overactive bladder syndrome (65).

Saw palmetto extract exerted significant binding activity on autonomic receptors in the lower urinary tract under \textit{in vitro} and \textit{in vivo} conditions. Oral administration of saw palmetto extract to rats significantly changed the maximal number of binding sites for prostatic \[^{3}H\]-prazosin binding and for bladder \[^{3}H\]NMS binding. This alteration by saw palmetto extract was selective to the receptors in the lower urinary tract (66).

A single dose of 60mg/kg saw palmetto extract caused in a hyperactive rat bladder model a significant improvement of the micturition interval, micturition volume and bladder capacity during intravesical saline infusion. Also, doses of 12 and 20mg/kg significantly reversed the reduced micturition interval as well as the decreased micturition volume and bladder capacity due to 0.1% acetic acid infusion dose dependently. Repeated administration to conscious, freely moving rats of 6mg/kg saw palmetto extract daily constantly increased the micturition interval and concomitantly decreased voiding frequency. These experiments showed that saw palmetto worked, at least in the animal model, also in overactive bladder (62).
1.2.5 Interactions with P450 enzymes

Based on in vitro and in vivo trials there are almost no signals for a relevant interaction potential for saw palmetto. These findings correspond well with the clinical situation as in patients so far no cases have been reported (17). The majority of BPH patients are older than 60 years of age (67) and usually use more than only one medication (68). The findings from the P450 studies imply that patients with concomitant medication which is metabolised by P450 enzymes are not at risk of any interactions by taking alongside a saw palmetto preparation.

Yale, 2005 reported a slight inhibition in vitro of CYP3A4, CYP2D6, and CYP2C9 with a lipophilic saw palmetto extract which contained 85-95% fatty acids and sterols and 0.1-0.3% β-sitosterol (producer PhytoPharmacia, Green Bay, U.S.A.). For the experiments the extract was drained and diluted 1:10 in 2% methanol. The IC\textsubscript{50} for the test items were 0.8% of the enzyme activity for CYP2D6, 0.14% or 0.24% for CYP3A4 depending on substrate, and 0.43% for CYP2C9 calculated from the inhibitory concentrations of the undiluted primary test samples (69). Budzinski, 2000 found only moderate inhibitory potential on CYP3A4 when compared to the test substance 7-benzyloxyresorufin. Among 21 investigated herbal products, the assessed saw palmetto preparation was ranked 13\textsuperscript{th} regarding its interaction potential, Hydrastis canadensis and Hypericum perforatum had the lowest inhibitory concentrations. The tested saw palmetto product was only described as a commercial product available in Canada. Echinacea purpurea herb and ginkgo biloba, which were tested by both groups, had comparable results like saw palmetto in both trials (69, 70).

An investigation on the ability of different herbal preparations to inhibit UDP-glucuronosyltransferase showed a moderate inhibitory potential of 55.2 ± 9.2μg/ml for a 96% ethanolic saw palmetto extract with more than 85% fatty acids and more than 0.1% sterols (Finzelberg and Co. KG, Andernach, Germany), but the clinical relevance of this finding is unclear (71).
In two clinical trials this topic was addressed in twelve healthy subjects of both sexes in each trial. Markowitz, 2003 showed that 320mg saw palmetto extract four times daily for 14 days did not change the enzyme activities of CYP2D6 and CYP3A4. There were no significant differences between the mean ratios at baseline and after saw palmetto exposure for dextrometorphane (CYP2D6 activity) and alprazolam (CYP3A4 activity). The authors conclude that when taken at the recommended doses, saw palmetto extracts are unlikely to lead to interaction with other medication which use the same cytochromes for clearance (72).

Gurley, 2004 administered 320mg saw palmetto extract twice daily, containing 85 – 95% of fatty acids, for 28 days. The extract had no influence on the activity of CYP1A2, CYP2E1, CYP2D6 and CYP3A4. The authors stated as well that prolonged use of saw palmetto poses a minimal risk of drug interactions related to interference with these CYP enzymes (73).

1.3 Toxicological assessment of saw palmetto

1.3.1 Acute Toxicity

In experiments to determine the anti-oedematous effect of a hexane extract of saw palmetto maximum an oral dose of 10mL/kg exerted no ‘toxic effects’. The calculated LD50 added up to 54mL/kg in male rats. However, no details were provided in support of this statement. A dosage of 50mL/kg lead mice to no deaths after oral administration of a saw palmetto extract (57).

1.3.2 Repeat Dose Toxicity

Following a report that a product containing a saw palmetto preparation caused cholestatic hepatitis, the effect of saw palmetto on rat liver function was assessed. Investigated were the effects of a saw palmetto extract on several enzymes and formation of malondialdehyde (MDA), a by-product of lipid peroxidation. A significant increase in these parameters is considered to be an indicator of liver toxicity. Thirty-six rats were treated for two or four weeks with a placebo or saw palmetto at doses of...
9.14 or 22.86mg/kg/bw/day; that is, 2 x and 5 x the maximum recommended daily human dosages. After two or four weeks, the results showed no significant difference in animal body weight, enzyme activity, or MDA formation at either time or dosage level, as compared to controls. The data indicate that saw palmetto is not involved in a mechanism causing liver toxicity (74).

These results are in line with reports on animal toxicity. In male Wistar rats 50 and 100 mg/kg bw saw palmetto extract given by oral gavage, showed no toxicity. Also, no changes in body and prostate weight at necropsy, and macroscopic examination of prostate were noted (58).

No adverse effects were observed at higher levels for a shorter period of time. Rats tolerated 100, 320 and 640mg/kg/d saw palmetto extract in 2.5% ethanol well for 30 days (75).

1.3.3 Reproductive and developmental toxicity

There is only limited data available on reproductive toxicity. In an in vitro study with hamster oocytes and sperm, a lipophilic saw palmetto extract produced no significant effect on sperm motility at doses of 0.9mg/mL. The extract had no inhibitory effect on the penetration of oocytes by sperm nor were denaturations or mutations of DNA detected after prolonged exposure to this herb (76). Also, a newer study showed no influence of saw palmetto in a mice model to induce DNA damage (77) nor did they observe any mutagenic signals in Ames tests (78, 79).

Overall, saw palmetto extract appears to be safe for use in men with BPH in particular in the recommended daily dosage of 320mg. In the period of January 2003 to December 2007, 61.4 million daily dosages of Prostasan®, the preparation used in the trial in this thesis, have been sold worldwide. During this time, only one minor case was reported to the Pharmacovigilance Department of A.Vogel Bioforce AG (80).
1.4 Clinical efficacy and safety of saw palmetto

More than 90 publications on clinical trials with saw palmetto extracts are available; all were carried out in benign prostatic hyperplasia (BPH).

Thus, in the following the disease BPH will be explained before discussing the results of the studies with saw palmetto. The next chapters will give information on the aetiology and course of the disease, its diagnosis and the therapy options. A more detailed description of the history of BPH and its treatments are given in chapter 2.

1.4.1 Benign Prostatic Hyperplasia – the disease

1.4.1.1 Aetiology of the disease

Generally, benign prostate hyperplasia (BPH) is defined by a non-malignant overgrowth of the prostatic tissue surrounding the urethra. This finally leads to a constriction of the urethra and then to lower urinary tract symptoms (LUTS) such as urgency, frequency, nocturia (synonym: nycturia), incomplete bladder emptying, and weak urine stream (3). It is the most commonly occurring neoplastic disease in men (67).

The exact aetiology of BPH is not yet understood. The main theories are that the disease is a result from reactivation of embryonic induction processes in the prostatic tissue which originates in the innermost aspect of the prostate gland - the so called transition zone which is located along the axis of the urethra (81). The prostate itself is a male fibromuscular sex gland about the size of a chestnut with exocrine but no established endocrine secretory function. It produces a volume expanding vehicle for sperm, which seems to be the only function of this gland and the secretions provide fluid that constitutes less than 20% of the ejaculate (82). The seminal fluid is excreted by ejaculatory ducts, which pierce the posterior surface of the urethra (83) (Figure 4).
As mentioned the reason for the prostatic growth is not yet clearly understood. The central factor is certainly age as it affects men above the age of 40 (67). There are some theories for the reasons of the prostate growth postulated so far:

One is the hyperactivity of the membrane-bound 5-alpha-reductase, the enzyme that converts testosterone to DHT, which in the end then leads to an increased cell proliferation. Patients suffering from a 5-alpha-reductase deficiency show prostatic volumes, which are approximately $1/10^{10}$ of age-matched normal controls highlighting the importance of DHT for the normal formation of the prostate (84). On the other hand, there is certainty that the development of BPH is exclusively dependent on androgens since BPH does not occur in men castrated prior to puberty (85). The reasons why the two isoforms of the 5-alpha-reductase should be overexpressed can not be explained yet (86).
Another influence on the prostate growth may be the shift in the balance of testosterone to oestrogen, which tends towards oestrogen in the aging men. The reason for this is that more testosterone is converted to DHT and bioavailable testosterone levels decline due to decreased production by the testis and increased sex hormone binding globulin (SHGB) levels which combine to lower free circulating testosterone (87). However, circulating levels of free estradiol which is secreted mainly by the adrenal gland remain constant in the aging male due to an age-related increase in body weight and adipose cells which express high levels of aromatase and convert androgens to oestrogens. The outcome is a significant increase in the oestrogen/testosterone ratio allowing the balance of prostate growth to shift towards oestrogen dominance. It has been proposed that increased estrogenic stimulation of the prostate in the aging male may lead to reactivation of growth and subsequent neoplastic transformation (88) mainly by activation of estrogenic receptors in the prostatic tissue (89).

Another theory, which has received increasing attention postulates that BPH may be triggered or at least catalysed by inflammatory conditions (90). Histologically, the association of BPH and inflammation is well recognised. Already in 1979, it was noted that 98% in a series of 162 resected prostates had inflammatory lesions (91). There is also clinical evidence for this hypothesis, two studies found a clear correlation between inflammatory stages such as prostatitis and either the prostate size (92) or symptom progression and prostate resection (93). A long term study carried out between 1988 and 1994 in 2337 men in the United States revealed that those having an increased C-reactive protein level of 3mg/l which acts as a marker of acute inflammations were 1.47 times more likely to have more BPH symptoms than those with lower values (94).

There are a lot of cytokines such as IL-2, IL-4, IL-6, IL-8, IL-15, IL-17 and INF-γ involved in inflammatory processes in BPH and have been found with rates of increased expression and higher amounts at all in enlarged prostates. This lead to the hypothesis that BPH is not only an inflammatory but as well an immuno-inflammatory disease since some of the cytokines are not inflammatory at all but rather immune modulatory like IL-4 or INF-γ (95).
So far there is one clinical trial available which has investigated the influence of an anti-inflammatory drug on BPH symptoms. Patients suffering from BPH taking the COX-2 inhibitor celecoxib had, after only one month of treatment, significantly less nocturia and a significantly lower score in the International Prostate Symptom Score IPSS than those taking placebo (96). This trial indicated that the inhibition of the inflammatory component of the BPH may lead to fast symptom relief for the patients.

The latest theory postulates that the prostate growth is a secondary condition caused by insufficient veins in the testicles. Because of the inadequate transport of blood from the testicular veins to the upper body, the prostate which is penetrated by this vein, is exposed to blood which contains up to 130-fold the serum level of testosterone. This testosterone is then converted to DHT and leads subsequently to prostatic cell proliferation (97). This theory is plausible as it is the only one explaining why and how an increased amount testosterone is available in the prostate as in elderly men the serum levels of this hormone are decreasing (98). First results from 28 patients where the insufficient veins were obliterated showed good treatment results in reducing their BPH symptoms (97).

1.4.1.2 Course of the disease and diagnosis

BPH symptoms occur in men over the age of 40 who have testosterone-producing testes, whereas morphologically it can already be detected in men over 30 years of age (99). The main symptoms which have static and dynamic components (100) are increased frequency of urination with nocturia, difficulty starting and stopping urination, weak urine stream, feeling that the bladder has not emptied completely with residual urine and in later stages urinary retention and painful urination (101).

The symptoms may not progress over time. Studies have shown that in populations over a period of three years about 25% of all patients who had primary symptoms of BPH respectively lower urinary tract symptoms (LUTS) had an improvement in their symptoms without treatment (99).
BPH is not a life threatening disease except when urinary retention is not treated since this could lead to renal failure (102). Nevertheless, it may affect the quality of life of patients in many ways be it by causing lack of sleep by nocturia, pressure to visit the toilet very frequently or fear of urine smell due to terminal dribbling.

The disease is mainly diagnosed by assessment of the symptoms. The standard instrument is a validated questionnaire, the International Prostate Symptom Score IPSS (99) or the American Urological Association (AUA) symptom score (103). The difference to the IPSS is that there is an additional quality of life question amended (99).

The severity of the disease is furthermore defined in two classifications, one from Alken, 1955 (104) and the other from Vahlensieck, 1985 (105), which are mostly used in Germany. Whereas Alken defines the three stages mild, moderate and severe as the irritative, the residual urine and the decompensation-stages, in the definition of Vahlensieck there are four stages with the first three being similar to the Alken definition, but he adds an initial stage where no symptoms occur at all.

A common diagnosis of BPH is via rectal examination, but it is important to note that enlargement does not correlate with the severity of symptoms (106). With the physical exam prostatic cancer can be excluded since cancerous tissue is different at palpation than smooth BPH-tissue. A marker for prostatic cancer is additionally the measurement of the prostate-specific antigen PSA, even though its values may be influenced by other conditions like for example inflammations (107).

Optional tests for the evaluation of the BPH or LUTS include urinary flow rate measurements, post void residual urine measurements, pressure flow studies and ultrasonography to determine the size of the prostate (106).
1.4.1.3 Epidemiology

Histologically BPH is shown in 8% of men aged 31 to 40 years. This number rises progressively with age and can be distinguished in the 9th decade in about 90% of all men. Figure 5 shows the frequency of histologic BPH in different age groups (3).

**Figure 5**: Presence of histologic BPH at autopsy by age group (3)

Prostatic enlargement is a necessary but not sufficient condition for the development of LUTS. This means that not all men having an enlarged prostate finally also suffer from the symptoms of a BPH as mentioned previously (67).

Epidemiological studies have shown that nearly 50% of all men of age 80-90 suffer from symptoms (108). The prostate size nevertheless seems to be the main factor for inducing the symptoms: The odds to develop moderate to severe symptoms after the age of 50 were 3.5 higher in men with a prostate volume >50mL than those with smaller prostate volume (109).
Comparison of data for development of microscopic BPH from the USA, England, Denmark, Austria, India, and Japan showed that there is almost no difference in frequency related to age group (67). Another large epidemiological study indicated that black and Hispanic men were at higher risk of having BPH symptoms (110) whereas in a large survey in the United States no difference in frequencies for BPH surgery between Black, Asian and White males could be found (111).

In the study of Kristal with 5667 BPH patients obesity, particularly abdominal obesity, was one of the main risk factors leading to BPH symptoms (110). Another survey detailed that in addition intake of alcohol, lack of physical activity, and diabetes were risk factors, it could not be established if smoking, diet, hypertension, and environmental factors were connected to increased BPH symptoms (112). Genetic factors and diet may nevertheless have an important influence on the progression of BPH. The occurrence of BPH is less frequent in Asian countries as compared to the United States. However, on entering the USA, Asians immigrants develop BPH mirroring the rates of US American men (101).

Because of its high prevalence in the older male population, BPH is an increasing burden for the health systems. It is the fourth most diagnosed disease in men older than 50 years with a prevalence rate of 13.5%, which is in the same range as osteoarthritis (113). For the U.S.A., the direct costs of medical services for treatment of BPH are estimated to about 1.1 billion $ per year (114) whereas a Spanish study assessed the costs for only medicine for one BPH patient per year to about 300 Euro (115).
1.4.1.4 Treatment of BPH

1.4.1.4.1 Watchful waiting

The first treatment option for patients with an IPSS up the total score of seven points is watchful waiting (106). Studies have shown that for these patients medical treatments are not better than placebo. The patient needs to be monitored during this phase as well as spontaneous exacerbations and remissions of BPH may occur (116).

1.4.1.4.2 Medical treatments

1.4.1.4.2.1 Herbal preparations

Even though not stated in any of the actual treatment guidelines on BPH such as the U.S. American, British, Australian, European, and Canadian guidelines (117) phytomedicinal products are often applied as first line treatments to reduce BPH symptoms.

The main used herbal products are saw palmetto preparations or combinations of saw palmetto with stinging nettle which provide good treatment results in patients with mild to moderate symptoms of BPH also showing good tolerability (118). Since there is a strong patient demand for saw palmetto it is stated in one treatment guideline that doctors nevertheless should become familiar with this treatment (106).

There are further herbal treatments available for the treatment of BPH.

Preparations made from African plum (Pygeum africanum) showed positive effects on the symptoms of BPH. The authors of a Cochrane analysis including 18 controlled clinical trials concluded that despite of weak methodologies, small number of patients in the trials, and the short study durations a small but significant improvement compared to placebo could be observed. In these studies lipophilic extracts containing mainly fatty acids with a daily amount of 100mg were applied (119, 120).
Since men in Asia suffer less from BPH it is assumed that probably a soy-rich diet may be a treatment option for BPH or its prevention. A short term clinical trial (one month) with an isoflavone product derived from red clover ('Trinovin') showed in dosages of 40 mg and 80mg per day a rapid relief of BPH symptoms with a very good safety profile (121).

In several placebo controlled studies β-sitosterol exerted promising effects in patients with BPH (122-126). A shortcoming of these trials is their big heterogeneity regarding the investigated products and the number of participants which ranged from 62 (122) to 200 (124). The used preparations contained pure β-sitosterol or β-sitosterol-glucoside of diverse origin, with different daily dosages. In the trial of Berges 60mg β-sitosterol from Cucurbita pepo were applied daily which were described as ‘containing a variety of phytosterols’ (124), Kadow used 0.3mg of a β-sitosterol glucoside (122) and Fischer 195mg β-sitosterol (126) per day, and Klippel 130mg free β-sitosterol from Hypoxis rooperi, Pinus pinaster, and Picea abies (125). Except for the lowest dose of 0.3mg β-sitosterol glucoside, the trials showed good efficacy and safety. A Cochrane analysis (2000) carried out on the use of β-sitosterol in the treatment of BPH symptoms based on these few trials suggested that the use of non-glucosidic β-sitosterol could improve urinary symptoms and flow measurements but gave no recommendation on the daily dosage (127).

Three placebo controlled clinical trials have been carried out with a rye-grass pollen extract. The available evidence suggests that rye pollen extract was well tolerated and modestly improved overall urological symptoms, including nocturia. In one trial rye grass pollen was superior in its efficacy to a Pygeum africanum preparation. Since the trials were mostly not carried out with state of the art parameters and were of short treatment duration, currently a conclusive statement if rye-grass pollen extract is a reasonable treatment option cannot be made (128).
1.4.1.4.2.2 Alpha blockers

For patients with an IPSS > 7 or bothersome symptoms, the main treatment prescribed are α-blockers. This therapy is based on the concept that LUTS are partly caused by α1-adrenergic-mediated contraction of prostatic smooth muscle and bladder neck (129). The main substances used are doxazosin, tamsulosin, alfuzosin, and terazosin. They all have been widely studied in the treatment of BPH and LUTS (117).

The most selective of these four substances is tamsulosin since it targets the α-1A adrenoreceptor subtype which accounts for 70% of all adrenoreceptors in the prostate and is 13 times more specific in targeting these prostatic receptors than those in the urethra (130).

Meta-analytical data on alpha-blockers derived from the AUA guideline showed that all four substances have about the same efficacy whereas tamsulosin was slightly better leading to an improvement of 4 to 6 points on the IPSS. The main advantage of α-blockers is the fast onset of activity (131).

Side effects of these medications may differ; orthostatic hypotension, dizziness, weakness, nasal congestion and abnormal or retrograde ejaculation were reported most frequently (132).

1.4.1.4.2.3 5-alpha-reductase inhibitors

Currently, there are two 5-alpha-reductase inhibitors available, finasteride and dutasteride. Dutasteride is selective for both isoforms of the 5-alpha-reductase whereas finasteride more selectively blocks the isoform type 2 (133). Both treatments lead to a symptom relief after 6-9 months of therapy and to a shrinking of the prostate size by about 20% (106). The advantage of these therapies is that they significantly prevent the incidence for surgery and urinary retention whereas α-blockers can only lead to a delay of 2-2.5 years of these two items (134). The disadvantages are the long onset of action, the efficacy seen on BPH symptoms are lower than with α-blockers or surgery (116), and that PSA values are decreased by about 50% (135).
If long term use of 5-alpha-reductase inhibitors is favourable for chemoprevention (prevention of prostatic cancer in particular) is still a topic for discussion. The Prostate Cancer prevention trial with 19'000 men receiving either placebo or finasteride revealed a significantly lower frequency of cancers in the finasteride groups but the tumours were more aggressive than those found in the placebo group (136).

Which of the two 5α-reductase inhibitors is more efficacious is still a matter of discussion. A large study with 5090 patients found a significant difference regarding acute urinary retention (AUR) and prostate-related surgeries in favour of dutasteride. Even though the differences were statistically significant they may not have been clinically relevant as they were quite low (12% for dutasteride vs. 14.7% for finasteride) (137).

Most often cited side effects were ejaculatory dysfunction, erectile dysfunction, and decreased libido (138).

Regarding the choice for the right medication to treat BPH it seems that finasteride and dutasteride are most favourable for patients with a large prostate (>50mL) whereas α-blockers can be used in patients with all kind of prostate sizes (106).

1.4.1.4.2.4 Combination therapy

The largest trial, evaluating if a combination of an alpha blocker with a 5-alpha-reductase inhibitor is useful in the treatment of BPH was the Medical Therapy of Prostatic Symptoms (MTOPS) study. More than 3000 men received either placebo, doxazosin, finasteride, and a combination of doxazosin and finasteride. After 4.5 years, in the placebo group the AUA score had declined to a median value of 4, with doxazosin to six points, with finasteride five points and with the combination seven points were reached (p<0.05). With the combination the risk of progression was reduced by 66% compared to a 39% reduction with doxazosin and 34% with finasteride (134).
The overall outcome from this study was that the combination was more effective not only in treatment but also in terms of a favourable progression of the BPH. The combined use of 5-alpha-reductase inhibitors and α-blockers is generally used in everyday practice (106).

1.4.1.4.3 Surgical treatments

1.4.1.4.3.1 Open prostatectomy

This is the oldest and most effective treatment for relieving BPH symptoms (106). It is still performed and recommended for large prostates (138) and the symptomatic improvement occurs in 98% of all patients (106).

1.4.1.4.3.2 Transurethral resection of the prostate (TURP)

The method was developed in the 1920's (106) and is still the gold standard for surgical treatment of BPH. It is a surgical procedure in which portions of the prostate gland are removed through the urethra with a unipolar wire loop-electrocautery device. Sterile glycine irrigation fluid is used to distend the bladder and urethra during the procedure. After the surgery, which lasts about one hour, a catheter is placed for about one day (138).

TURP reduces symptoms of BPH by 88% (116) and is the most effective treatment for BPH with respect to the improvement of symptoms and flow rates (138) but morbidity associated with the procedure is still an important issue (139). Immediate postoperative side effects include bleeding, and urinary tract infections (139), whereas long term complications comprise retrograde ejaculation (70% of the treated patients), impotence (14%; range 3-32%), partial incontinence (6%) and total incontinence (1%) (140). About one in ten patients needs retreatment within five years after surgery (116).
1.4.1.4.4 Other surgical treatment options

Since many elderly patients are poor surgical candidates and younger patients find the risk of sexual dysfunction unacceptable, ‘minimally invasive’ surgical techniques have been developed (106).

The transurethral microwave thermotherapy is a method where by insertion of a device the temperature within the prostate (via the urethra) is increased to above 45°C, which leads to necrosis of the prostatic tissue (139). The advantage of this method is that long term complications such as impotence and retrograde ejaculation occur much less frequently than with TURP (141) and the surgery can be performed in an ambulatory setting (138). However, only a small patient population is eligible for this treatment (139).

Transurethral needle ablation is a further non-invasive method where low-level radiofrequency is delivered via a needle into the prostatic tissue. The results of this treatment may be limited since the bladder neck and the median prostate lobe cannot be treated but it is safe and generally well tolerated without further long term side effects (106).

Instead of using a electrocautery device to resect the prostate tissue, laser is also applied (laser prostatectomy). This method seems to be as effective as TURP (142) by leading to less long term side effects but the method is not easy to apply and needs ‘significant endoscopic skills’ (139).

The latest minimally surgical intervention is the above mentioned so called Gat-Goren method which aims at sclerosing insufficient testicular veins and reduces thus the venular hypertension in the prostatic tissue and subsequently the extensive testosterone concentration. This method is still in a pilot phase and should be established with larger clinical trials (97).

In summary, the medical treatments fall short of achieving a patient perception of more than fair to good improvement in most cases. The awareness of very good to excellent improvement is reserved for surgical interventions. Patients, who are dissatisfied with
the efficacy or safety of their medical treatment, are initially advised to seek minimal
invasive surgical treatment and then TURP (143).
A treatment layout for BPH patients which summarises the knowledge of the actual urological guidelines is given in Table 1 (100) with modifications after Geavlete (144) and Gregorin (145).

Table 1: Treatment scheme for BPH patients with regard to their LUTS, prostate size, severity of symptoms, and complications after Issa, 2007 (100) with modifications regarding the use of saw palmetto after Geavlete (144) and Gregorin (145).

<table>
<thead>
<tr>
<th>LUTS severity</th>
<th>Prostate size</th>
<th>Bothersome symptoms</th>
<th>Complications</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUASI≤7</td>
<td></td>
<td></td>
<td></td>
<td>Watchful waiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saw palmetto</td>
</tr>
<tr>
<td>AUASI≥8</td>
<td>≤30 cc (ml)</td>
<td>No</td>
<td></td>
<td>Watchful waiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saw palmetto</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td>Watchful waiting</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Alpha blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saw palmetto</td>
</tr>
<tr>
<td></td>
<td>&gt;30 cc (ml)</td>
<td>No</td>
<td></td>
<td>Watchful waiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-α-reductase inhibitor (SARI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Watchful waiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alpha blocker</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>(monotherapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SARI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alpha blocker + SARI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minimally invasive therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgical therapy</td>
</tr>
</tbody>
</table>

| Yes | Surgical therapy |
1.5 Clinical data from saw palmetto preparations

Monographs and meta analyses are the two major sources which give an assessment on the clinical efficacy and safety of a treatment. The main difference between these two documents is that monographs for herbal medicines consider also the traditional use of a plant, whereas meta analyses rely only on published clinical data.

In the following, a short summary on the present monographs on saw palmetto and the most recent important reviews is given.

1.5.1 Monographs on saw palmetto, recommended preparations and daily dosages

Currently, there are four monographs available on saw palmetto, an older German Commission E monograph (146), a WHO (147) and an ESCOP monograph (17) and one from the Canadian health authority (40). They all recommend the use of saw palmetto in mild to moderate forms of BPH. As side effects stomach problems, nausea, diarrhoea or other minor gastrointestinal complaints are cited. No interaction with other medications are quoted nor any restrictions of use or contraindications.

As daily dosage 320mg of a lipophilic saw palmetto berry extract are recommended in all monographs, the WHO monograph advices to apply this dosage as a single dose or twice daily at 160mg (147). The monographs advise to use extractants such as hexane (40, 146, 147), ethanol 90% (40, 146, 147), supercritical CO₂ (147) or equivalent agents (17, 40, 146, 147). Only the Canadian monograph addresses further requirements on the extract quality i.e. it should contain between 70-95% free fatty acids and corresponding ethyl esters (40). Table 2 summarises the data from the monographs on the different extractants and recommended daily dosages.
Table 2: Requirements on daily dosages and extractants from the monographs on saw palmetto

<table>
<thead>
<tr>
<th>Reference</th>
<th>Daily dose</th>
<th>Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada (40)</td>
<td>320mg lipidosterolic extract</td>
<td>Extracted with lipophilic solvents such as hexane or ethanol 90 % v/v</td>
</tr>
<tr>
<td></td>
<td>with 320mg lipophilic ingredients</td>
<td></td>
</tr>
<tr>
<td>ESCOP (17)</td>
<td>320mg lipophilic extract</td>
<td>No details on solvents provided; equivalent preparations acceptable</td>
</tr>
<tr>
<td>WHO (147)</td>
<td>320mg (as a single dose or 160mg twice daily) of a lipidosterolic extract</td>
<td>Extracted with n-hexane, ethanol 90 %, or supercritical fluid carbon dioxide to contain between 70 and 95% free fatty acids and corresponding ethyl esters or equivalent preparations</td>
</tr>
<tr>
<td>German Commission E Monograph (146)</td>
<td>320mg lipophilic extract</td>
<td>Extracted with solvents such as hexane or ethanol 90 % v/v; equivalent preparations</td>
</tr>
</tbody>
</table>

1.5.2 Clinical studies with saw palmetto preparations

Based on Medline, EMBASE and the Cochrane more than 90 clinical trials available on saw palmetto and BPH have so far been published. In a meta analyses on saw palmetto only randomised controlled clinical trials which fulfil a defined quality level, measured either with the Jadad score (148) or the criteria from Schulz (149), are usually included. For example, the latest reviews on saw palmetto by the Cochrane Collaboration included only 21 studies in 2002 (118) and 30 trials in 2009 (150). These Cochrane reviews are regarded as the gold standard among meta-analyses and are the basis to assess if a treatment can be called evidence-based.

In all trials lipophilic saw palmetto extracts with a daily dosage of 320mg were applied with treatment durations from 4 to 60 weeks. The studies were placebo-or reference-controlled; reference compounds were alpha blocking agents like tamsulosin or 5-alpha-reductase inhibitors like finasteride. As endpoints either BPH symptoms, measured with the IPSS or the AUA score or urinary flow parameters were chosen (150).
In 2000 and 2002 the reviews from the Cochrane Collaboration gave a positive statement on the efficacy and safety of saw palmetto in treatment of BPH symptoms. LUTS and flow parameters were assessed as having improved significantly compared to placebo and were as good as under finasteride treatment (118, 151).

After a large placebo controlled clinical trial, carried out in the United States, with negative outcome was published (152), the next Cochrane review in 2009 regarded the efficacy of saw palmetto as doubtful but paradoxically still as good as finasteride or an alpha blocking agent in longer term treatment of more than 16 weeks (150).

The findings from this review are thus often cited to question the efficacy of saw palmetto like in the latest BPH treatment guideline from the American Urological Association (153). In all trials, the safety of the saw palmetto preparations was excellent, the treatments were very well tolerated and no severe side effect occurred (154).

The conclusions from the Cochrane analyses are debatable since these reviews had a restricted view on a treatment. They neglected not only the traditional use of the plant but also personal experiences from urologists which regard saw palmetto as a good symptomatic first line treatment for BPH patients (144, 145). Also the trials which were chosen in the analyses may have shortcomings as well. It is for instance not explainable why trials from France (155-157), Italy (158, 159) or Germany (160, 161) yielded positive results but why the latest U.S. American studies on saw palmetto in BPH produced only negative outcomes (152, 162).

1.6 Final remarks

In conclusion, there is sufficient scientific evidence from in vitro testings and animal experiments to explain the mode of action of saw palmetto in patients with BPH. Furthermore, there are plenty of clinical trials and personal experiences showing that saw palmetto acts as a very well tolerated and efficacious treatment in patients with mild to moderate BPH symptoms; this is also widely accepted and used in the recommendations by four respected monographs.
Chapter 2

A short history of the treatments for BPH, the use of saw palmetto in the United States until the 1930's and the introduction of saw palmetto into Germany
Chapter 2: Historical part

A short history of the treatments for BPH, the use of saw palmetto in the United States until the 1930's and the introduction of saw palmetto to Germany

2.1 Introduction

Today saw palmetto is a well known treatment option for mild to moderate symptoms of BPH. In the United States, Sabal ranks third among the food supplements with an annual sales volume of 200 million dollars (163) and an estimated number of 2.5 million users (164). The worldwide turnover is likely to be 700 million dollars per annum (163) reaching almost blockbuster status in pharmaceutical terms and in Germany half of the urologists prescribe herbal treatments for BPH symptoms with saw palmetto being the favourite one (164). The same situation is reported for France (165) and Italy where five times more saw palmetto products are prescribed than alpha antagonists for treatment of BPH symptoms (166).

Surprisingly, despite of the status as being one of the most popular phytomedicines little is known about the origins of saw palmetto as a treatment for BPH. Only two publications dealt so far to some extent with the history of the use of saw palmetto. The book by David Winston (167) and the review by Bennett (19) give some details on how the plant was applied by the indigenous population of the Florida region as well as the first medical uses of saw palmetto among white settlers in the United States. Bennett gives a good and comprehensive description of the indications where saw palmetto was used traditionally but lacked historical data on when, how and by whom the species was used nor did it assess the timeline of its introduction into medical practice. Winston quotes interesting sources documenting the first use of saw palmetto among white settlers but the historical part in his book is rather short and is not the main scope of the book which lies in the medical use of the plant.
A coherent review on how saw palmetto made its way to become an acknowledged treatment in the United States is lacking. The same applies also for Germany where the plant has a special status as it is not a traditional European medicinal plant but was introduced from the United States. There are no data who introduced saw palmetto into Germany, how it became known and who used it first as a medical treatment or as a food. Additionally there is no literature available which puts saw palmetto as a treatment for BPH into the context to available and generally applied cures for this disease until 1930.

With the medical historic part of my thesis I aimed to provide new insights about these topics. The goal was to find out how saw palmetto was used among the Indians of the Florida region, then how the white settlers gained knowledge about the plant, for which indications they used it and how it was described in literature. One main interest was further to assess if a group of practitioners favoured the use of saw palmetto and then how this treatment became popular and made its way into the official U.S. American compendiums.

In a last step I wanted then to find out how saw palmetto made its way over the Atlantic and became known in Germany. The goal was to show how the knowledge grew about saw palmetto in Germany over time, how was the plant used and who were the first practitioners to use it as a remedy.

### 2.2 Research Strategy and Methods

#### 2.2.1 Research strategy

In order to understand how the disease BPH evolved in medical literature first I searched for publications on the history of BPH and checked all available medical standard textbooks from 1870 to 1930 on the treatment of the prostate disorders in the Wellcome Library in London as well as in the library of the Medical Historic Institute of the University of Zurich.
Secondly, literature searches on when saw palmetto was first mentioned in the medicinal literature of English language allowed an understanding of how it was introduced into medical or alternative practice. The timeframe 1870 to 1930 was chosen as saw palmetto was apparently first mentioned in American medical literature in the period after the American civil war, i.e. post 1870 (167) and in 1926 it was included in the official U.S. formulary, showing that the plant had an official status as medical agent (19).

In a third step, the relevant literature was assessed to determine how and when saw palmetto appeared for the first time in popular, medicinal or scientific German literature. This country was chosen as subject of research as I am of German mother tongue and since saw palmetto is today an important herbal remedy in this country. I also preferred Germany to the other German speaking countries Austria or Switzerland as it is the biggest country and the majority of literature was assumingly published there.

As a framework how to find historical sources I used the methodology and considerations given by Brundage in his book ‘Going to the Sources’ (168). He divides the most important research material, the primary sources in two classes. The first are manuscript sources like handwritten records which were not intended for publication, the others published sources. These encompass two categories, manuscript materials such as letters, diaries which were later published and materials that were intended to be made public like newspaper articles, annual reports, books or the like (168).

For this research I used almost only published sources like journal articles and books but no manuscript sources or archive material. Like this, my work is a comprehensive medico-historical collection of published material on saw palmetto covering how the plant was used first in the United States by indigenous people and physicians and its introduction into German medical society.
To assess the quality of a source I used the guidance given for source criticism in the book of Howell and Prevenier, ‘From reliable sources - an introduction to historical methods’ (169). This involves the evaluation of the genealogy, genesis, originality, and interpretation of a document as well as the authority of its author and his or her competence and trustworthiness. Regarding the genealogy, genesis, and originality I tried to find out if the document was an original or copy and where, by whom and when the source was produced. In a second step I interpreted the document by understanding its intended meaning, for example was it a research article to inform the scientific community or rather intended to promote a commercial product.

At last I assessed the authorial authority of a document by finding out who was its writer and what was the competence and trustworthiness of the author regarding the content of the article or document. For these evaluations I carried out in the majority internet searches by using the name or institution of the author as search term, which often provided good background information.

All literature searches were carried out either online or in the named libraries from January 2010 until January 2012. A literature was marked as a hit when it provided sufficient evidence for the use of saw palmetto as a medicinal treatment or as a hint that the saw palmetto was known but not used as a medicinal treatment (but for example as a garden plant).

Table 3 lists the libraries or resources I used for my searches with the search terms, limitations in year of publication and the hits. When a hit was of special interest or needed further clarification, then the biggest historical U.S. online library, Hathi Trust (170) or in case of a German reference, the ‘Karlsruhe virtual catalog’ (171), the biggest German library resource were searched or individual libraries where a certain reference was kept in original.

In the end I had assessed more than 1700 documents for use in this medico-historical overview.
Table 3: Libraries and online resources for the literature search from January 2010 until January 2012 with search terms, limits on publication dates, number of hits, and the hits which could be used for the analysis.

<table>
<thead>
<tr>
<th>Library/Resource</th>
<th>Search terms</th>
<th>Period</th>
<th>Number of hits</th>
<th>Usable hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZVAB (Zentrales Verzeichnis Antiquarischer Bücher [central register of antiquarian books]) zvab.com</td>
<td>Serenoa ; Sabal ; Sägepalme</td>
<td>1870-1920</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Google books (books.google.com)</td>
<td>Sägepalme</td>
<td>1870-1930</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Google books (books.google.com)</td>
<td>Serenoa</td>
<td>1870-1930</td>
<td>342 german hits</td>
<td>13</td>
</tr>
<tr>
<td>Google books (books.google.com)</td>
<td>Sabal</td>
<td>1870-1930</td>
<td>6750 german hits, viewed around 1000</td>
<td>14</td>
</tr>
<tr>
<td>Medical historic library university of Zurich</td>
<td>Serenoa, Sabal, Sägepalme</td>
<td>1870-1930</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>The Wellcome library, London</td>
<td>Prostate, prostatic hyperplasia ; saw palmetto</td>
<td>1870-1930</td>
<td>200</td>
<td>15</td>
</tr>
<tr>
<td>Swissbib.ch (all Swiss libraries)</td>
<td>Sabal, Sägepalme, Serenoa, Hagers Handbuch, Homöopathisches Arzneibuch, Homöopathische Arzneibücher</td>
<td>1870-1930</td>
<td>80 ca. 20</td>
<td>20</td>
</tr>
<tr>
<td>Zentralbibliothek Zürich (central library Zurich, it combines the libraries of the ETH Zurich, University of Zurich and the Canton of Zurich)</td>
<td>Hagers Handbuch, Homöopathisches Arzneibuch, Sägepalme, Prostata</td>
<td>1870-1930</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>American Botanical Council ABC</td>
<td>Literature on traditional use of saw palmetto, sent on request by Roy Upton, president of the American Herbal Pharma – copoeia and David Winston, American Botanical Council</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Google books (books.google.com)</td>
<td>Chaemerops serrulata, Brahea serrulatum, Diglossophyllum serrulatum</td>
<td>1800-1930</td>
<td>200</td>
<td>10</td>
</tr>
</tbody>
</table>
2.3 Results

2.3.1 The history of benign prostatic hyperplasia and its treatment

2.3.1.1 The discovery of the prostate and benign prostatic hyperplasia

The first mentioning of the prostate in medicinal literature is credited to Herophilus of Alexandria (ca. 300 B.C.) but it is questionable if the organ he described as 'parastates' (172) or as 'prostateae glandulosae' and 'prostateae cirsoideae' was really the prostate and were not the seminal vesicles and the ampulae of the ductus deferens (173). Erasistratos, a Greek anatomist living from 320-250 B.C., wrote about the prostate in the same manner several years later as Herophilus. It was then Rufus of Ephesos, a physician who lived between the 2nd and the 1st century B.C. who was apparently the first author to give a good description of the glandular nature of the prostate. He was followed by the dominant medical doctor of this era, Galen (131-201 B.C.) who gave in his explanations of anatomical procedures an account of the prostate as 'spongy flesh at the side of the neck of the urinary bladder' (174). Interestingly, benign prostatic hyperplasia as a disease was not mentioned by earlier ancient authors, be it by Hippocrates (ca. 406-377 B.C.) who was considered to be first urologist nor by ancient Egypt authors (172).

Surprisingly from the Hippocratic period to the 16th century, the prostate or prostatic hyperplasia were only vaguely portrayed in medical literature (175). The famous anatomist Vesalius (1514-1564) reported the existence of the prostate only in very general terms and Leonardo da Vinci (1452-1519) ignored the prostate in his drawings of the male urogenital tract completely (173).

Nicolo Massa of Padua is believed to be the author who around 1550 'rediscovered' the prostate as an organ (175) and in 1648 Jean Riolan, the younger (1577-1657), was the first person to find the relationship between an enlarged prostate and urinary problems (176). Previously the French surgeon Ambroise Paré (1510-1590) had observed that male urinary problems occurred more frequently in the elderly and that these LUTS arose age-dependently (172).
That the prostate or BPH symptoms were not more frequently a topic in medical books during the 16th to the 17th century may be attributed to only few men reaching the 'prostate-age of sixty years' as the historian Shelley names it and the average life-span of forty years at that time (173). But there is evidence that BPH was apparent in medieval times as could be shown with the autopsy of the mummy from one of the leading figures of the Italian Renaissance, Pandolfo III Malatesta (1370-1427). Macroscopic and histological findings showed that he suffered from an enlarged prostate which is the first paleopathological record (177).

Even though several physicians and anatomists like Thomas Bartholin (1616-1680), Pierre Dionis (1650-1718) or Giovanni Domenico Santorini (1681-1737) tried to dissolve the mechanism behind BPH it was until 1761 that the Italian anatomist Giovanni Battista Morgagni gave in his comprehensive work 'De sedibus et causis morborum per anatomen indagatis' a proper account of prostatic hypertrophy and he realised the relationship between retention symptoms and pathological findings. His mechanical view on the disease that an enlarged prostate leads to urinary problems was a breakthrough since until then it was believed that urinary symptoms in elderly men were caused by a paralysis of the bladder or leniency of the urinary tract (176).

Although several anatomists tried thereafter to explain the real nature of prostatic growth, it was in 1862 Rudolf Virchow who established that prostatic hypertrophy was a hyperplastic disease (178). In 1911 Lendorf set a milestone in BPH research confirming the concept that the hyperplastic growth was in fact a growth in the periurethral glands (176) which is the actual understanding of the disease (3).
2.3.1.2 The history of BPH treatments

2.3.1.2.1 Catheterisations and surgical interventions in BPH in history until 1930

Not many treatments for patients suffering from BPH symptoms have been reported until the beginning of the 20th century. Mainly catheterisations or needle punctuations of the distended bladder were recommended indicating that only patients with moderate to severe obstructive symptoms were treated (173).

Already in ancient Greek catheterisations were carried out, Erasistratos was the first to describe one with an S-shaped catheter. In the 16th to the 19th century catheterisations became popular again and different catheters and methods were developed and tried out (175). Major milestones were then the invention of the gum-elastic catheter in 1777 by Theden (179), around 1840 the bladder catheter of Mercier called the 'cathéter condé' and in 1853 the balloon catheters by Reybard (176). At the end of the 18th and until the begin of the 20th century catheterisation was the general accepted treatment for prostatic problems; for one patient in the early nineteenth century even the number of 6892 catheterisations is documented (173).

The first operative procedure on the prostate was performed by the French surgeon Ambrose Paré in 1575 using a genius punch-type instrument to cut out tissue. His method of inserting a hollow tube with a cutting or crushing implement into the urethra to remove prostate tissue was the same construction as is used today in endoscopes for prostatic surgery (175). On the principle of the Paré's method different approaches with dilating, compressing or cutting the prostate were exercised until the end of the 19th century (176).

In the last quarter of the 19th century bladder puncture was carried out often where a coarse needle was inserted via the transrectal, perineal, or suprapubic route and the bladder was then emptied through the punctuation (173). A further development was open adenectomy which was performed from the end of the 19th century when anaesthetics and antiseptic surgery were established. The transurethral procedures were further developed, leading to the method of transurethral resection of the
prostate (TURP) with an electrocautery device. This surgery first was tried out in 1926 and is the gold standard for prostatic surgery today (175).

In the late 19\textsuperscript{th} century castration was also advocated as a treatment because of observations made with animals and the apparent similarity of prostatic adenoma and uterine myoma which decreased in volume after oophorectomy (175). This treatment attained a 'short and hectic period of glory' (176) but soon disappeared as method of choice because of the lack of efficacy and the obvious mental and aesthetic burden for the patients (175).

2.3.1.2.2 Medication used for BPH from 1820 until 1930

Non-surgical therapies for BPH were rarely ever mentioned in medicinal literature. The leading opinion at the end of the 19\textsuperscript{th} century was that BPH was an 'incurable disease' (180) and earlier, in 1874 it was stated by the doctors van Buren and Keys that 'In the present state of our knowledge, hypertrophy of the prostate is not curable by any means that have yet been used' (181).

The main medical books on genitourinary diseases in the period of 1870 to 1930 recommended in the majority catheterisations or surgical interventions as efficacious treatments particularly for moderate to severe BPH symptoms (181-190).

In 1810 Hunter advocated sea bath cures, blistering to the perineum, opiate blisters against pain, and drugs such as hemlock (most probably \textit{Conium maculatum}) or mezereon (\textit{Daphne mezereum}) which was often used as powder or decoction to treat syphilis (191). The British surgeon Henry Thompson described in his book 'The enlarged prostate' a holistic treatment regimen for the patients affected by BPH which included moderate and well digestible food and beverages, sufficient physical activity, modest sexual behaviour, and a positive mind-set. He also discussed the use of hemlock as proposed by Hunter but was more sceptical about the efficacy of the plant in BPH as it was then used successfully 'in enlargements of the lymphatic and mammary glands'. Furthermore, he opposed the use of mercury in BPH patients, a treatment which was obviously administered quite often these days. He also promoted the use of 'the
hydrochlorate of ammonia' which was a treatment administered in Germany and France where 4-12 grams had to be taken for a duration of 4-8 weeks (192).

A further treatment was the application of iodine either as suppository, orally or as topical treatment on the 'urethral surface of the prostate'. Thompson cited the findings of Stafford, who reported good efficacy in treatment of enlarged prostates (193) but also advocated the use of bromine but both, iodine and bromine should only be administered cautiously (192). He was impressed by the waters of the springs of Kreuznach in Germany which were rich in iodine and bromine. He had visited the baths and subsequently, recommended hip baths to British patients suffering from BPH using the Kreuznach waters from the Elizabeth-Quelle which could be bought then in the United Kingdom. The spring water contained also other minerals such as sodium, calcium and carbonic acid gas (192).

The treatment with iodine and bromide was also described later by the physician William T. Belfield and he proposed further an injection to the bladder containing a solution of tannin in glycerine and water with 0.5-1% zinc citrate as treatment of BPH (185). Van Buren and Keys regarded the treatment with iodine and bromide as not efficacious and wrote that 'the advocates of these and other methods have failed to establish their claims' (181).

The U.S. American urologist Eugene Fuller recommended for BPH patients as medicamentous treatments mild diuretics such as 'sweet spirits of nitro, terpentine, and juniper' where citrate of potash, buchu (Barosma betulina) and a fluid extract of corn silk (Stigmatis maidis) should be added for best efficacy (187).

Another American urologist, Robert W. Taylor endorsed only few non-surgical treatments, aside from hot bathes and lifestyle changes like a balanced diet or enough physical activity. He suggested 'strychnine, quinine, and tonics ... in run down and debilitated subjects' (188). The American urologist Hugh Cabot advised not to use 'palliative measures' but promoted catheterisation or operations (189). Abrahams and Morson, two American urologists, were even stricter by declaring that 'the correct treatment for this disease is removal of the whole gland by operation' (194).
Among German urologists medications or palliative treatment, as it was called, was not highly regarded as method of choice. This is also shown in the standard work of Schlagintweit, 1921 who recommended catheterisation and then surgery but no medicamentous or other treatments (190).

In summary, until 1930 no standard medications for BPH patients were available and saw palmetto was never mentioned in the standard books on urology. Catheterisation and surgery were the methods of choice and the medicamentous breakthrough was achieved in the late 1970's after the discovery that alpha blocking agents like phenoxybenzamine, a nonselective \( \alpha \)-adrenoreceptor antagonist, were effective in treating BPH symptoms (195). In 1992, then the first 5-alpha-reductase inhibitor, finasteride, was granted marketing authorisation by the U.S. Food and Drug Administration for treatment of BPH symptoms (196).

These two classes of drugs are at the time the main synthetical drugs for BPH symptoms (197). Further details of current treatments of BPH were already given in chapter 1.4.1.4.
2.3.2 History of human use of saw palmetto

2.3.2.1 Use as material and wax

The fibres were important to Florida’s indigenous people, the Seminole. Since saw palmetto leaves and stems are rich in fibres, they were used to fabricate brushes (19), served as basic material for the production of paper (7), and in some specialised cases during World War II even for cartridge plugs and wallboards (198). The Seminole made thatches for their houses and constructed huts and used the fibre to braid fruit collecting, corn sifting and ritual baskets (7) either for their own use or these days mainly as souvenirs for tourists (199). Further use of the fibres of saw palmetto was made for production of fire fans and ceremonial dance fans. Even baby rattles were produced from the leaves by producing a little closed basket, which held pieces of charcoal (19) and with the fibres also mattresses and straw hats were manufactured (20).

Palmetto leaves may also be a source of wax. Wilder and Kitzke described a yield of 1.4 to 2.7g of the free flaking wax per 100g of leaves. But as most of the palm wax of other species is also free flaking and easy to collect, the costs for collecting and processing saw palmetto wax is economically questionable (28).

2.3.2.2 Use as food

Since saw palmetto berries are rich in oils, they formed an important part of the diet of Florida’s indigenous people and the berries are ubiquitous in archaeological sites in Florida. In the 1990’s older Seminole Indians still ate the fruit raw but they advised not to eat more than five fruits per day since they are bitter and moreover it is recommended not to eat them with hot liquids as this may burn the mouth (19). The Indians also prepare a sweetened traditional drink with the berries, which is called ‘shiopee sofkee’ (33).
The use among non-indigenous residents was detected in settlements from the 16th century from Spanish Florida (200) and there in particular at Lake Okeechobee (8). Generally, records of the plant have been found among the indigenous groups of the Timucua and Apalachee, the Cochtaw living near the Mississippi river who used the dried berries for winter use, and also among the Sioux Indians (8).

The known first record of non-indigenous habitants of America eating saw palmetto fruit was by a young Quaker merchant, Jonathan Dickinson, who wrote in a book 1796 about the misadventures of a boat full of Quakers shipwrecked on August 23, 1696 on Florida’s east coast. They were captured by indigenous people and kept as prisoners for several weeks. They almost starved and all they could eat were fish and saw palmetto berries. He describes this often cited experience of eating saw palmetto fruits: ‘We tasted them, but not one among us could suffer them to stay in our mouths, for we could compare the taste of them to nothing else but rotten cheese steeped in tobacco juice.’ (7).

The botanist Bartram to the other hand, wrote in 1792 that the berries were ‘delicious and nourishing food’ but as he interviewed later the Creek Indians about the berries they defined them as ‘bitterish and stinging on the palate, at first using it, but soon become familiar and desirable’ (8, 9).

The mentioning of the species’ use as a beverage by white settlers or in later centuries by the inhabitants of Florida is firstly as a soft drink, which in the early 1900’s was sold by Miami pioneers. This drink was called ‘metto’ and was a mixture of saw palmetto berries with carbonated water (201). Secondly, it was tried as an aromatic in cognac (202).

In 1866, a German book already mentioned that the saw palmetto tree was used to get a starch flour (203). In 1888, the same was described in detail in an article where the production of a flour used by the Seminole Indians made from the root of saw palmetto was detailed (204). A newer source, the book ‘Field Guide to Edible Wild Plants’ explained further that the palm heart is ‘tender and makes an excellent salad or cooked vegetable’ (205).
2.3.2.3 Use as a medicine

2.3.2.3.1 Medical uses by indigenous people

The indigenous people of Florida knew saw palmetto as a medication with diuretic, sedative and aphrodisiac properties. The steam from cooking fruits was inhaled as a treatment for bronchitis, as expectorant and to soothe irritated mucous membranes (206). Infusions of the leaves and roots were taken to treat dysentery and stomach pains by 'Gulf Coast Indians' (most probably referring to the Seminole Indians) and they applied the inner trunk bark as a dressing or poultice for insect and snakebites and skin ulcers. The indigenous group of the Houma (Louisiana) administered a decoction of the root for sore eyes, high blood pressure, and kidney problems (207).

2.3.2.3.2 Use in U.S. American, Non-indigenous medicine

The first mentioning of the use of saw palmetto in Western medicine appeared in an article published in the journal 'The Medical Brief' from St. Louis by Dr. J. B. (James Bond) Reed of Savannah, Georgia in 1877 (208). Despite of an extensive search, I could not find the original literature as the first issues available in the largest American library catalogue, Hathi Trust from this journal are from 1882 on onwards (209) and libraries in St. Louis hold no old issues of this journal either. His real name was actually James B. Read and he was from 1878 to 1879 president of the Georgia Medical Society (210), in the following he will be named as 'Read' and not Reed.

The article from Read was cited in the journal 'New Preparations' under the title 'a new remedy-Sabal serrulata-Saw palmetto' in 1879. He wrote that 'settlers of the South' observed that animals feeding from the berries 'grew sleek and fat' and noticed that the animals were in a 'marked health'. The settlers seemingly prepared a decoction of the fruits for medical purposes. In his neighbourhood several people tried preparations of the berry and obviously Read tried them also in humans and reported that the berries improved digestion, increased 'flesh, strength and weight' and relieved irritations of the mucous tissues, in particular of the airways and were a good remedy for bronchial coughs and common colds (211). In 1911, the same article was also cited
in a publication called ‘History of the vegetable drugs of the pharmacopeia of the United States’ by John Uri Lloyd. He was an influential pharmacist and follower of the eclectic philosophy of that time and owned together with his brothers one of the biggest factories for production of herbal medicines, the Lloyd Brothers, Pharmacists, Inc. in Cincinatti, Ohio (212). He confirmed the cited data from ‘Reed’ in his article and also mentioned that saw palmetto was before 1879 practically unknown in medicine (213).

‘Reed’ was later often cited correctly as J.B. Read and appears like this in the Archiv der Pharmazie, 1879 (214), in the Materia Medica, 1900 (215) and the books of Madaus, 1938 (216); Read is regarded as the first person bringing saw palmetto into the U.S. medical society of these days.

In the same year, 1879, a description of saw palmetto berries of J.B. Read was given in the American Journal of Pharmacy (217) and in ‘The Planter’s Gazette’ (218) with a broad description of the plant, its appearance, where it grows. He reported that he observed three imiscible phases as the expressed liquid from the fresh fruits settled: A volatile yello essential oil, a brown lipidic oily phase, and an aqueous yellowish phase with sugary taste. The articles cite the medical use, adding that indigenous people like the berries as food and that even fish ate the berries greedily once the fell into the water. The article cited here is not the original article but a German translation which was published the same year in a German journal (219).

Further reports of medicinal uses of saw palmetto were mainly from eclectic doctors. Eclectic medicine combined herbal medicine with physical therapy practices and was a direct reaction to the academic medicine of that time which, as described above, involved a lot of harmful therapies like the application of mercury-based remedies or excessive bloodletting (220). The term eclectic was first used by Constantine Samuel Rafinesque (1783-1840), a French polymath who lived among native Northern American Indians and observed their use of medicinal herbs (221). The word ‘eclectic’ was derived from the Greek word ‘eklegeto’ meaning ‘to choose from’ and should refer to physicians who chose anything beneficial to help their patients (220).
In 1829, a medical doctor called Wooster Beach founded in New York the ‘Reformed Medical College’ to teach eclectic medicine. This school was soon followed by about a dozen other privately funded eclectic medical schools, generally located in the Midwestern United States. The best known college was the ‘Eclectic Medical Institute’ in Worthington, Ohio, which later moved to Cincinnati; this was also the last eclectic institution to teach students and closed in 1939.

Eclectic medicine expanded during the 1840’s and peaked in the 1880’s and 1890’s and was described as a ‘large populistic, anti-regular medical movement in North America’ (222).

The eclectic schools failed to gain approvement by the ‘Flexner Report’ in 1910, which was used to decide on accreditation of medical schools in the United States (223). This forced the eclectic colleges either to change their curriculum and to become ‘normal’ medical schools or they had sooner or later to close down (220).

In 1879, saw palmetto was introduced to the eclectic community by a doctor called I.J.M. Goss of Marietta, Georgia (220, 224). He recommended the use of the plant for the same indications previously mentioned by Read.

In the Kings dispensatory, the main book of the eclectic doctors the plant was already mentioned in 1894 demonstrating its wide spread recognition and semi-official use (225). Saw palmetto was indicated for irritated mucous membranes, such as caused by coughs, pertussis, sore throats, acute catarrh, and asthma. For genitourinary conditions, it was found to be effective for irritations associated with gonorrhoea, epididymitis, and ovarian pain. It was also recommended for the treatment of enlarged prostates as well as for atrophied breasts, testes, and ovaries (225, 226).

Other eclectic physicians such as Herbert T. Webster from California gave details about the use of saw palmetto berries for an indication called ‘the relaxation of the urinary organs of the nervous system’ which included frequent urination and vesical irritation with BPH. He also mentioned administration of Sabal for female reproductive problems such as ‘dragging sensation in the pelvis and abdominal tenderness’ (227). A further eclectic physician, Eli G. Jones, later well known for his books on herbal medicines and
cancer (228) wrote that he considered palmetto useful for ‘deficient sexual performance/drive, loss of libido, infertility due to overwork, exhaustion and excessive childbearing’ (229).

Around 1895 Dr. A. L. Davidson from Mount Pleasant, Utah, also an eclectic physician wrote an article describing a single case of a man of 51 years who had lost his sexual potency (given the description of the symptoms most probably due to BPH) and that he could not satisfy his ‘wife, a buxom blonde, several years his junior’ any longer. Having prescribed him 15 drops of a saw palmetto tincture four times daily, the patient noticed within two weeks an improvement of his urine flow, an increase of his testicle size and his ‘vigor of life’ had returned (230). In 1896, Dr. William. E. Bloyer, a professor at the Eclectic Medical Institute in Cincinnati wrote in the Eclectic Medical Journal an article on saw palmetto describing its medical uses ranging from bronchitis to treatment of BPH (231).

An interesting view on the use of saw palmetto can also be found in the Journal of the North American Eclectic Materia Medica Association (around 1895 to 1900, edition unknown). Here the tonsils and the prostate were described as being similar in tissues and therefore, saw palmetto was recommended not only for genitourinary ailments but also for the treatment of tonsillitis, croup, for snoring, and chronic sore throat (167). In the book of Winston, a J.W. Fyfe is cited who advocated the use of saw palmetto also for respiratory tract symptoms and a J.D. Hatton published in 1897 in the ‘Medical Gleaner’, an eclectic medical journal, on saw palmetto recommending it for ‘prostatic troubles of old men’ and for symptoms of chronic gonorrhoea (232).

But it was not only among the eclectic community that saw palmetto gained already soon after the publication of Read attention. A pharmacist, J.M. Dixon made around 1880 the first mention of saw palmetto as a treatment for disorders of the genitourinary tract. He described a special effect of the fluid extract on the reproductive glands, the ovaries, prostate, and testes, for ‘sexual debility’ but said that ‘the remedy seems to have a special affinity to the prostate, and a specific effect upon it’ (167, 233).
Also in 1880 a physician, Stephen F. Dupore of Savannah, Georgia wrote that saw palmetto worked well in affections of the throat, bronchial tubes, lungs, and even in haemorrhage of the lungs (234).

Around 1885 a doctor F. A. Evans wrote in the journal ‘The Medical Brief’ that he found approximately 15 drops of the fluid extract to be effective against paroxysms of migraine. In addition to the already mentioned effects on the genitourinary system, he also promoted saw palmetto for ‘all cases of wasting of the testes’ which in his view was often a cause for impotence. Even though he favoured also the use in gynaecological practice to promote the use of the mammae, he believed that the best effects were generally seen on enlarged prostates (167). The same indications were also reported in an article in the Western Druggist by Dr. H. Knapp who thought it had the action of a ‘great vitalizer’ (235).

In the same year, 1895, in the ‘Proceedings of the American Pharmaceutical Association’ a pharmaceutical chemist gave a comprehensive description of saw palmetto, the plant, the chemistry of different extracts of the drug as well as different accounts of medical use citing Read, Dixon, the below mentioned Evans and a Dr. Kinnicut who had published in 1892 in the New York Medical Journal that saw palmetto was in his view a good remedy for patients suffering from tuberculosis and in laryngitis (236). Two years later in the same journal, saw palmetto berries were discussed with an extensive description of the appearance of the fruit and some data on its chemistry (237).

Interestingly, some of the medicinal standard text books of the United States of that time such as Drugs And Medicines of North America by Lloyd, 1884 (238) and the Specific Medication and Specific Medicines, 1870 (239) made no notice yet of saw palmetto nor did the earlier works from Jonathan Pereira in 1842 and 1852 about the ‘Elements of the Materia medica and Therapeutics’ (240, 241) which described the plants in use in the United States.
By the late 1890's, the use of saw palmetto in eclectic, homeopathic, and allopathic medicine in the United States became widespread. Pharmaceutical companies like Wyeth Laboratories, Lilly, Squibb, and Merck all produced saw palmetto preparations (242).

In 1898, the homeopathic physician Edwin Moses Hale from Chicago published his standard book on saw palmetto which was a milestone as this was a comprehensive compendium on the history, the use and the preparations of saw palmetto which were available in the United States. They included the whole range of watery to oily preparations of the berries such as tinctures, fluid extracts, pure oil, saccharated oil, malto-sabal (saw palmetto oil mixed with maltose), aqua oleum sabal, and suppositories (7).

The most detailed portrayal those days on the use of *Sabal serrulata* in a standard book was given soon after the book of Hale, in 1900, in the 'Dictionary of Materia Medica' by J.H. Clarke. He referred mainly to the book of Hale, but also discussed several cases in women where overactive bladder, kidney problems, irregular menses and breast atrophies and peritonitis were treated successfully with saw palmetto. He described a wide variety of indications for saw palmetto with main emphasis on urinary problems but recommended it also as a remedy to improve sexual dysfunctions, such as erectile dysfunction and lack of drive in men, as well as to increase libido in women and as a treatment for ovarian pain (215).

The homeopath William Boericke issued in 1901 his own 'Boericke's Materia Medica (Materia medica: the Tinctures)' where he described the use of saw palmetto mainly for 'irritability of the genito-urinary organs' and in particular for 'prostatic troubles' but indicated the plant also for various disorders like a 'confused, full head; makes her angry' (243).

In 1903 John William Fyfe gave in an eclectic manual of a modern materia medica for saw palmetto the dosage recommendation of 10-30 drops thrice daily in water, mainly for treatment of BPH and 'functional inactivity of the reproductive system' (244).
The journal ‘Kew Bulletin’ reported 1899 that in this year 250 tons of liquid extracts of saw palmetto berries were consumed in the United States as a remedy (245).

The widespread use of saw palmetto found at the begin of the 20th century recognition by the U.S. American health authorities and the plant gained an official status as a remedy: From 1906 onwards it was listed and then mentioned in the United States Pharmacopeia (1916) and then in the National Formulary from 1926 until 1950 (19). These official records were a milestone for saw palmetto as a treatment in the United States. The plant was not any further a treatment solely favoured by a special and marginal group of physicians like the eclectics but were an officially accepted medication of that time.
An overview on the use of saw palmetto in the United States and the first mentioning in monographs and pharmacopeia in chronological order is given in Table 4.

**Table 4:** Documented use of the whole plant of saw palmetto in history in the United States and first mentioning in monographs and pharmacopeia.

<table>
<thead>
<tr>
<th>Date</th>
<th>Use of saw palmetto and mentioning in scientific literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>15th (or earlier) to 16th century</td>
<td>Use as food among Native Indians of Florida region. Probably also use as material for construction of huts, basket, fans, etc.</td>
</tr>
<tr>
<td>Traditional use by Indians</td>
<td>Medicinal use by Native Indians of Florida region: steam from cooking fruits, inhalations for treatment of bronchitis, expectorant, irritated mucous membranes. Infusions for treatment of dysentery, stomach pains; dressing and poultice for insect and snakebites, skin ulcers; use for sore eyes, high blood pressure, kidney problems.</td>
</tr>
<tr>
<td>1877</td>
<td>Dr. Read, Savannah, Georgia: Use in respiratory tract infections like common colds or bronchitis</td>
</tr>
<tr>
<td>1879</td>
<td>Two further articles from Read, description of the plant and of its chemistry, use in respiratory tract infections like common colds or bronchitis described</td>
</tr>
<tr>
<td>Around 1880</td>
<td>J.M. Dixon: use of saw palmetto in genito-urinary disorders and as a sexual stimulant</td>
</tr>
<tr>
<td>1880</td>
<td>Treatment of bronchitis and upper respiratory tract infections</td>
</tr>
<tr>
<td>1885?</td>
<td>Use in BPH</td>
</tr>
<tr>
<td>1892</td>
<td>Dr. Kinnicut: Treatment of tuberculosis and laryngitis</td>
</tr>
<tr>
<td>1892</td>
<td>Saw palmetto described as a 'great vitalizer' (Knapp)</td>
</tr>
<tr>
<td>1894</td>
<td>Saw palmetto cited in the King’s dispensatory</td>
</tr>
<tr>
<td>1894</td>
<td>Description of the plant in the Proceedings of the American Pharmaceutical Association</td>
</tr>
<tr>
<td>1896</td>
<td>Description of the appearance of the berries and their chemistry</td>
</tr>
<tr>
<td>1896</td>
<td>Portrayal of saw palmetto in the Eclectic Medical Journal (Bloyer)</td>
</tr>
<tr>
<td>1898</td>
<td>Standard book of Hale on saw palmetto</td>
</tr>
<tr>
<td>1900</td>
<td>Chapter in the Dictionary of the Materia Medica by Clarke</td>
</tr>
<tr>
<td>Early 1900</td>
<td>Soft drink of Miami pioneers, called ‘metto’</td>
</tr>
<tr>
<td>1906</td>
<td>First mentioned in the United States pharmacopeia</td>
</tr>
<tr>
<td>1926</td>
<td>First mentioned in the U.S. National Formulary</td>
</tr>
</tbody>
</table>
2.3.2.3.3 The appearance of saw palmetto in German scientific literature

In 1835, a plant was described in a German book on general botany under the name 'Chaemerops palmetto' as an example for a palm tree without thorns but it is not clear if really saw palmetto was meant (246). In the 'Nomenclator botanicus hortensis', an enumeration of 'European cultivated plants' from 1840, Chaemerops was named 'Zwergpalme' [dwarf palm] and 'Chaemerops serrulata' as the finely serrulated [feingesägt] dwarf palm tree, growing in Georgia, USA (247). In a story about the garden show 1850 in Gent, Belgium, the same palm tree, 'Chaemerops serrulata' was mentioned as being one of the objects in a special exhibition on palm trees (248).

The first mentioning of saw palmetto in German literature as 'Sägepalme' is from a description of a journey to Effingham County in Georgia, U.S.A, in 1862 (249). The author mentioned that 'the ground is covered for hours with saw palmetto (Chaemerops serrulata)' ['..der Boden stundenweit mit Säge-Palme, Chaemerops serrulata, als Unterholz bedeckt']. And in a book on Northern-American agriculture, 'Sägepalme Chaemerops serrulata' was cited as a tree used from Indians to gain a starch flour from it (203).

'Sabal serrulata' appeared around the same time also in a book on palm trees, the origins of the plant were stated as Georgia and Florida (250). Later, the plant was described in an account of the flora of Northern America as 'Sabal palmetto, serrulata' (251).

In 1879 the first citation of saw palmetto in non botanical but medicinal German literature appeared. In the journal 'Archiv der Pharmazie', a journal for German pharmacists, the article from the above mentioned American Journal of Pharmacy on saw palmetto was published as a German translation (219).

In 1890, the plant 'Sabal serrulata' was quoted in the 'Real-encyclopädie der gesammten pharmacie', a dictionary for pharmacists and physicians (252).
A year later, in 1891, the medical use of saw palmetto was described for the first time: Brestowski cited in his book ‘Die neueren und neusten Arzneimittel’ a plant he called ‘Sabiana serrulata’. He referred in the description of the drug to Dixon, meaning by this maybe not only the pharmacist named from the article of Davis, 1892 (233), but probably ‘Dixon’s saw palmetto’, a saw palmetto preparation sold those days by the Dixon saw palmetto medicine company from Jacksonville, Florida (253). Brestowski wrote that the berries were ‘calming, sleep-inducing and at the same time diuretic’ and that they had a positive effect on the digestion and a ‘specific action’ on the glands of the sexual organs. The fluid should be used in weakness of the sexual organs, muscle atony, nervous disorders which leads to digestive complaints, male impotence and vaginal balls made with cocoa butter and saw palmetto fluid should be applied in proplapsus uteri, leucorrhea, exhaustion caused by frequent parturation or sexual excesses (254).

In 1897, the well known German chemist and pharmacognost Carl Hartwich gave details on ‘Sabal serrulata’. He described the appearance of the fruits and that they could be used for phthisis and diseases of the lung and that they may have a diuretic effect (255).

In his posthumously published standard work on healing plants Dragendorff mentioned 1898 also ‘Sabal serrulatum’ shortly and wrote about the medical use of the ‘fruit nutritivum [Frucht nutritivum] by phthisis, bronchitis, etc.’ and to use a as a ‘diurectic, sedativum and stimulant remedy for the glands of the genitals’ (256).

Also homeopathic standard books of that time from two of the German opinion leaders in homeopathy, Carl Heinigke and Arthur Lutze (265) the ‘Handbuch der homöopathischen Arzneiwirkungslehre’, 1880 by Heinigke (266) or ‘Dr. Lutze’s Lehrbuch der Homöopathie’, 1860, 1878, 1887 (267-269) did not quote Sabal nor was it included in the ‘Arzneibuch für das deutsche Reich’, the German pharmacopoeia, of the years 1891 and 1900 (270, 271) or on a pharmacognostic map of the world of 1899 (272).

For a short period of time, the stem of saw palmetto gained some interest as a tanning agent in German literature. In 1896, ‘palmetto extract from Serenoa serrulata’ was described as a new tanning agent in a German chemical technical repertory with reference to an U.S. American publication (273), in 1898 the content of tannins of ‘Serenoa serrulata’ was discussed in another scientific publication (274), and in 1899 a botanical annual report detailed the tannin content of the stem and roots of ‘Serenoa serrulata’ (275). Later, the use of saw palmetto for tanning appeared no longer in literature.

In 1900, in the ‘Zeitschrift des Berliner Vereines Homöopathischer Aerzte’ the journal of the homeopathic doctors of Berlin cited under the chapter ‘Lesefrüchte aus homöopathischen Zeitungen’ [News from (literally ‘reading fruits’) homeopathic journals] a lecture given on the 7th of December 1899 by a Dr. E. M. Madden at the British Homeopathic Society on saw palmetto (the article was entitled as ‘Sabal serrulata oder Saw palmetto’). He gave a description of the fruits and recommended the use for enlargement of the prostate, explained one case of successful treatment of enuresis in a boy and cited then some cases from the book of Hale (276). In the meantime, the book from Hale had seemingly been translated to German by F.G. Oehme, then a well known homeopathic scientist. I could not find the book itself but only a citation that he had translated the book and used himself saw palmetto with success (277).
A year later, in 1901, saw palmetto was to be found in the German homeopathic dispensatory (Homöopathisches Arzneibuch) issued by the Association of German Pharmacists. Under 'Sabal serrulata' a description of the fruits was given and the receipt for the preparation of a mother tincture: one part of the fruit and two parts 'spirit of wine' [Weingeist] (278). In the 'Pharmacopoea homoeopathica polyglotta' by Willmar Schwabe which came out in the same year, saw palmetto was interestingly not mentioned (279).

At the same time, in a book on homeopathic remedies, 'Sabal serrulata' was discussed using mainly Hale, 1898 as source, for urinary problems as well as a therapy causing 'a curious juvenilisation with return of the potency and increase of the vitality'. The author recommended silicea as an antidote in 'excited states' under saw palmetto (280).

In 1903 the book 'Deutsche homöopathische Arzneimittellehre' stated that a catheter may not be used any longer after having taken a saw palmetto remedy (281).

Later on in the book 'Handbuch der homöopathischen Arzneiwirkungslehre' of 1905 by the homeopath Karl Heinigke the medical use of 'Sabal serrulata' was explained in detail with reference to the existing Northern American knowledge of Hale. Heinigke recommended five drops of a mother tincture in water taken several times daily for treatment of prostate disorders, lack of drive, testicular inflammations in men and in women for ovarian inflammations, urethritis, mastitis, and dysmenorrhea; furthermore for venereal diseases, enuresis, and inflammations of the bladder in men and women (282).

The journal of the customs of the Germany ('Reichszollblatt') demanded 1906 for 1 deciliter of 'saw palmetto fruits drenched in wine spirit ' [mit Weingeist getränkte Früchte der Sägepalme] a duty rate of 80 German mark indicating that saw palmetto fruits had been imported on a regular basis (283).
In 1908, saw palmetto was described as a remedy for nycturia in a homeopathic book which was published by the homeopathic doctors of Berlin (284) and in 1909 the plant was cited as an aphrodisiac in a journal of German pharmacists (285). Sabal was also briefly quoted that it appeared in Northern America in a book on pharmacognosy by Tschirch but no further information on the plant or its use was given (286).

In 1914 saw palmetto was mentioned in an article about an exam in a university or school [Lehranstalt] in Hamburg where fruit kernels had to be determined and saw palmetto was among one of those (287).

During World War I, saw palmetto was several times a topic in German scientific literature; at a time when no saw palmetto could be delivered from the United States because of the British naval blockade (288). In 1916 the ‘Chemisches Zentralblatt’ described the fluid extract of saw palmetto, its appearance and main constituents (289), and in 1917 the berries and the plant were characterised in the ,Zeitschrift für angewandte Chemie’ (290), in the ,Therapeutische Monatshefte’ a short description of Sabal was alluded (291), the ,Zeitschrift für Untersuchung der Nahrungs- und Genussmittel’ gave a morphological description of the berries (292), and ,the Hygienische Rundschau’ gave details on the plant (293). In 1918 saw palmetto was depicted in the ‘Jahresbericht der Pharmazie’ as a ,little known preparation which was mentioned in literature as an aphrodisiac’ (294).

In 1922, Rosenberg cited saw palmetto in a guide to the different official compendiums (295) and in 1924 Sabal serrulatum was quoted in Dr. Wilmar Schwabe’s homeopathic compendium for the first time but only in the appendix under ‘seldomly used homeopathic remedies’ very shortly with name and that with ripe fresh berries an essence with 90% ethanol should be prepared (296).

In 1928, the use of saw palmetto berries to aromatise cognac could be found in a book on etheric oils (297).
These citations show that saw palmetto between 1901 to 1930 was known among homeopathic doctors, pharmacists, chemists, and nutrition scientists in Germany.

However, the use may not have been that widespread as several homeopathic standard books of that time make no reference to saw palmetto, like the 'Arzneiwirkungslehre neuerer homöopathischer Heilmittel by Voorhoeve', 1910 (298), the 'Kurze Anleitung zum richtigen Gebrauch der wichtigsten homöopathischen Arzneimittel' in 1913 (299), the 'Lehrbuch der homöopathischen Therapie' in 1914 (300), 'Ottinger's Homöopathie' in 1921 (301) or the 'Handbuch der homöopathischen Arzneiwirkungslehre' from 1922 (302), and 1927 the 'Lehrbuch der Homöopathie' (303).

The plant was also not too well known among herbalists and in the pharmacognostic society since most pharmacognostic or herbal books of that time make no quote of saw palmetto such as 1909 the 'Vergleichende Volksmedizin' (304), 1911 'Schröters Schatzkästlein der Pflanzenheilkunde' (305), 1914 the book 'Volkstümliche Namen der Arzneimittel, Drogen und Chemikalien' (300), 1920 'Schreibers kleiner Atlas der wichtigeren Heilpflanzen' (306) and 1924 'Pharmakognosie als Vademecum für Ärzte' (307).

Also until 1930 in academic medicine, among general practitioners or medicinal authorities saw palmetto was not well known and accepted generally as a treatment.

Books on new pharmaceutical drugs like 'Die neueren Arzneimittel in der ärztlichen Praxis', 1908 (308), the 'Arzneimittel der heutigen Medizin', 1919 (309), and 'Neue Arzneimittel und pharmazeutische Spezialitäten', 1926 (310) make no mentioning of the plant nor does the official German Pharmacopeia, the 'Arzneibuch für das deutsche Reich', 1910 (311), its supplement 1916 (312) and the issue of the Arzneibuch of 1926 (313).
In 1938, Madaus described saw palmetto in his work on ‘biological remedies’ as a good treatment for BPH and that homeopaths used the plant mainly for this indication. He showed the results of a survey he had carried out among ‘outstanding adepts of medicinal plants’ [hervorragende Heilpflanzenkenner] which included not more than hundred persons but also ‘heads of clinics and sanatoria’. Of them, 41.2% stated that they used saw palmetto for the treatment of BPH as the primary treatment, followed by Populus tremulus with 12.4% and Pareira brava with 9.4%. This survey showed that among at least a certain group of German doctors saw palmetto was broadly applied in patients with BPH (216).

The most comprehensive German book on herbal drugs and medications, ‘Hagers Handbuch’ also reflected the status of saw palmetto as a well known treatment as the plant was first mentioned in the issue of 1944 (314) whereas it was not cited in any previous editions of the book in 1903 (315), 1913 (316), 1925 (317), 1927 (318), and 1930 (319).

The chapter on saw palmetto gives a description of the partially dried, ripe berries and their use as a ‘diureticum, sedativum, stimulant; and a fluid extract for lung disorders’ with reference to the National Formulary, sixth edition, 1938 of the United States. The chapter cites the production of an essence according to the homeopathic dispensatory (‘Homöopathisches Arzneibuch’), the production of an elixir with sandalwood and of a fluid extract of saw palmetto also according to the National Formulary (314).

I regard this first mentioning of saw palmetto in Hagers Handbuch as the breakthrough of the plant as a remedy in Germany. A quotation in this standard book reflects that saw palmetto was used as a treatment in Germany and an acceptance as an important medication. This might have also been the trailblazer for its general introduction and recognition to the pharmaceutical and medical community in Germany after World War II until today.

A chronological description of the citations of saw palmetto in German literature is given in Table 5.
**Table 5: Documented historical use of saw palmetto in German scientific literature**

<table>
<thead>
<tr>
<th>Time</th>
<th>Reference of saw palmetto in German literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1835</td>
<td>First mentioning of ‘Chaem erops palmetto’ in a book on general botany</td>
</tr>
<tr>
<td>1840, 1850, 1862, 1866, 1863, 1878</td>
<td>Botanical description of saw palmetto and its habitat as ‘Chaem erops serrulata’ or ‘Sagepalme’</td>
</tr>
<tr>
<td>1879</td>
<td>First citation of saw palmetto in a pharmaceutical journal, translation of an U.S. American article</td>
</tr>
<tr>
<td>1890</td>
<td>‘Sabal serrulata’ cited in a dictionary for pharmacists and physicians</td>
</tr>
<tr>
<td>1891</td>
<td>First description of medical use of saw palmetto (‘Sabiana serrulata’) as a calming, sleep inducing, diuretic treatment with effects on the sexual organs in men and women, and as therapy for prolapsus uteri and others in women</td>
</tr>
<tr>
<td>1897</td>
<td>Mentioning by a pharmacognost, Carl Hartwich for phthisis and diseases of the lung, with diuretic properties</td>
</tr>
<tr>
<td>1898</td>
<td>Quotation by Dragendorff, same indications as Hartwich and as a ‘stimulatory remedy’ for the genitals</td>
</tr>
<tr>
<td>1896, 1898, 1899</td>
<td>Discussion in literature of saw palmetto as a tanning agent</td>
</tr>
<tr>
<td>1900</td>
<td>Article on the use of saw palmetto in a homeopathic journal of homeopaths from Berlin</td>
</tr>
<tr>
<td>1900</td>
<td>German translation of the book of Hale</td>
</tr>
<tr>
<td>1901</td>
<td>‘Sabal serrulata’ in the German homeopathic dispensatory, issued by pharmacists</td>
</tr>
<tr>
<td>1901</td>
<td>Description of ‘Sabal serrulata’ in a book on homeopathic remedies. Silicea recommended as antidote in excited states from saw palmetto</td>
</tr>
<tr>
<td>1903</td>
<td>Saw palmetto cited in a book on homeopathic drugs, with use in BPH</td>
</tr>
<tr>
<td>1905</td>
<td>Detailed information on saw palmetto, use as mentioned in Hale but also for enuresis, venereal diseases and bladder inflammations</td>
</tr>
<tr>
<td>1906</td>
<td>Mentioning of saw palmetto in the journal of the customs of Germany</td>
</tr>
<tr>
<td>1908</td>
<td>Saw palmetto for nycturia described in a homeopathic book from homeopaths from Berlin</td>
</tr>
<tr>
<td>1909</td>
<td>Quoting of saw palmetto as an aphrodisiac drug in a journal of German pharmacists</td>
</tr>
<tr>
<td>1914</td>
<td>Article on the exam in Hamburg where saw palmetto had to be determined</td>
</tr>
<tr>
<td>1916</td>
<td>Information in a chemistry journal on saw palmetto and the fluid extract</td>
</tr>
<tr>
<td>1917, 1918</td>
<td>Details about saw palmetto in medical, food, and pharmaceutical scientific journals</td>
</tr>
<tr>
<td>1924</td>
<td>Saw palmetto in Willmar Schwabe’s homeopathic compendium</td>
</tr>
<tr>
<td>1938</td>
<td>Chapter on saw palmetto in Madaus’ book on biological remedies</td>
</tr>
<tr>
<td>1944</td>
<td>Hagers Handbuch cites saw palmetto for the first time</td>
</tr>
</tbody>
</table>
2.4 Discussion

Being a patient suffering from BPH at the end of the 19th century in the Western world was a miserable thing. The disease itself was quite new, it was not well understood nor was properly known how it developed. As medicamentous treatments baths, some herbal medicines or iodine, bromide or even mercury were applied which in the end might have done more harm than being any good at all. The standard treatment were catheterisations, an often painful procedure and if it was not carried out under sterile conditions secondary infections of the bladder or prostate regularly occurred (320). This again impaired the quality of life of a patient, not to talk about the mental burden of this intervention.

As a final procedure surgeries were carried out but the operation techniques were not very advanced and involved castration or the total resection of the prostate. Severe side effects must have occurred frequently regarding the still high rate of side effects in TURP these days (81).

Regarding the circumstances a BPH patient was in around 1870, it was no surprise that saw palmetto soon was tested in this patient group. Interestingly, it was not the traditional knowledge of the Indians on saw palmetto that was copied by practitioners but the observation of settlers that the berries had a positive effect on animals feeding them. Thanks to the settlers and Dr. Reads curiosity, openness and attention, saw palmetto was tried out as a new remedy which soon spread among the eclectic medical community.

And it is no wonder that the eclectic doctors were the ones trying out saw palmetto and evaluating whether it worked best in common colds, bronchitis, in BPH, in urogenital inflammations and disorders for men and women, and that the plant had vitalizing and aphrodisiac properties. The eclectic philosophy based on the use of herbal medicine and physical therapy with the goal to find new treatments in alignment with nature which were well tolerated and in a way ‘softer’ than the existing often harming medication and surgical treatments (220). Therefore the eclectic doctors were open to try out new herbal treatments and since they were well connected, had their own journals and even medical schools, they could teach and spread their knowledge widely.
and rapidly (222). It is thanks to them and also the coincidence that the eclectics were most popular in the time saw palmetto was rediscovered that within 20 years saw palmetto became a broadly used treatment in the United States. The number of 250 tons of saw palmetto tincture produced in the U.S.A. in 1900, which equals to 50 million daily dosages of 5ml and this in a population of then of 76 million people shows this clearly.

The second group of practitioners which helped saw palmetto to become a well known treatment in the United States were the homeopaths. Their medication consisted mainly of herbal medicines and as they were not part of academic medicine they were by their nature more open to new therapies. By having their own journals and medical schools, the homeopaths, too, could spread the knowledge on saw palmetto effectively like the eclectics. Hale for example, who wrote the standard book on saw palmetto was a homeopath himself, teaching at the Hahnemann Medical College of Chicago (321).

And the third group of groundbreakers for saw palmetto in the United States were the pharmacists as they occupied themselves as early as 1879 with saw palmetto. They were experts on the production and quality of saw palmetto preparations and played thus an important role that the plant was soon mentioned in the official U.S. pharmacopeia and then in the National Formulary.

So, in short, the combination of the eclectics as the discoverers and pioneers on saw palmetto, the homeopaths as the catalysts, and the pharmacists as the ones who had the pharmaceutical quality and production of the tincture in their scope made saw palmetto an officially acknowledged treatment.

In Germany in the meantime, it took some years longer until saw palmetto became a well known remedy. The plant was known in German literature in botanical terms and some scientific knowledge was summarised soon after its publication in the United States. However, it was not until the turn of the century that the scientific community showed a wider interest in the plant. Until 1900 the use of saw palmetto was not widespread and the knowledge about the plant confined to some experts as shown by the fact that it was only rarely mentioned in scientific books and articles.
In the time from 1900 to 1910 saw palmetto was mainly included in homeopathic books. It looks thus as if the homeopaths were the ones giving saw palmetto a special attention as a remedy but that the pharmacists knew already earlier about the plant. Both together then were the ones making saw palmetto known and popular as a treatment. This is corroborated by the fact that in 1901 the German Homeopathic Dispensatory issued by the Association of German Pharmacists mentioned saw palmetto but that the Homeopathic Pharmacopoeia (also 1901) by Schwabe, an enthusiastic homeopath himself, did not mention saw palmetto.

However, by the end of World War I the plant was known and investigated in Germany also by chemists and nutritional scientists. It looks that they became interested in saw palmetto as German practitioners used it more frequently and it was more often a topic in U.S. scientific journals. Taken as a whole, by the 1920’s there were plenty of people in the scientific community who had worked on saw palmetto and there was sufficient knowledge on the plant available in Germany. I suppose this assisted saw palmetto further to become an acknowledged treatment.

To which extent saw palmetto was used in medical practice as a remedy between 1920 and the 1930’s is difficult to assess with the public sources available. In 1924 Schwabe cited saw palmetto in the chapter of ‘seldomly used remedies’ (296), but Madaus showed in his survey in 1938 that saw palmetto was the favourite herbal treatment for BPH at least among practitioners he had asked (216). It seems that between 1920 and 1930 saw palmetto became popular resulting in the mid 1940’s in the standard book on German drugs and pharmaceutical preparations, the Hagers Handbuch (314).

Nevertheless, I could not identify a single brand, company or a practitioner which was the main promoter of saw palmetto in Germany. I had asked several German phytomedical companies like Schwabe for data on their product portfolio between 1900 to the 1930’s but none had any archive material available (322). The only saw palmetto preparation I found was a fresh plant trituration of saw palmetto berries from Madaus in 1938, one of his so called ‘Teep’ products which were a mixture between a homeopathic and a herbal remedy containing 0.025 g Sabal fruits per tablet.
The reason why not more saw palmetto brands were identified could be because the available public sources were limited in its number and content or that due to the volatile economic situation in Germany after World War I with several phases of hyperinflation (323) it was difficult to market sustainably a saw palmetto product and create a strong Sabal brand. To verify these hypotheses searches in archives are mandatory.

What made saw palmetto as a treatment popular in the end is difficult to say but it must have been primarily the same reasons as in the United States: There was no medication for BPH, by the standards of the period saw palmetto was obviously efficacious and safe - and probably also that it was a remedy from another continent piquing people's curiosity might have helped as well. The strong interest in Germany that time for foreign plants is reflected by the fact that in 1933 for more than 20 million Reichsmark different herbal drugs were imported (324).

Further, German homeopathy was significantly influenced at least until 1900 by the American homeopaths and their publications. Like this, knowledge about treatments was extensively exchanged between the two homeopathic communities and it is highly likely that a new therapy like the use of saw palmetto was promoted by this channel (265).

The success of saw palmetto in treating BPH could not have been foreseen. The Indians used inhalations from the berries for infections of the respiratory tract such as bronchitis and for treatment of irritated mucous membranes (206). Further, external treatments made from the inner trunk bark against insect or snake bites or skin ulcers were applied or teas from the leaves and roots for treatment of gastrointestinal disorders. From one Indian tribe even the treatment of sore eyes or kidney problems were reported (207). The settlers trying out saw palmetto concentrated themselves only on the use of the berries. There were no records that parts of the stem or the leaves were applied by the settlers, thus confirming the story of Read.
One major difference between the preparations used by the Indians and those by the settlers were that the latter used alcohol as an extractant. Therefore the tinctures were rich in lipophilic substances which are today considered as the main active constituents (41). These tinctures were certainly more potent than watery preparations as they contain substances with good anti-inflammatory (59), anti-gonadotropic (48), muscle relaxing (62) and vasodilating effects (66).

Interestingly, the settlers used preparations from the berries like the Indians firstly for treatment of infections of the respiratory tract, even though some positive effects on digestive function were observed as well (208). It was already three years later, 1880, that the first mention of saw palmetto as a therapy of genitourinary ailments appeared: Its effects on ovaries, the prostate and testes were described and the aphrodisiac properties of the plant. Remarkably, already in this publication it was noted that the best effect was seen in BPH (167, 233). But from then on until the 1920’s, saw palmetto was seen as a remedy for three main indications: Severe infections of the respiratory tract like bronchitis, genitourinary diseases in women and men like prostate problems or inflammations of the ovaries, and, finally, sexual dysfunctions like erectile dysfunctions or testicular atrophy in men, infertility and breast atrophy in women and as a sexual stimulant for both, men and women (7, 19, 167, 215, 226).

Why saw palmetto in the end became a treatment indicated today only for mild to moderate stages of BPH (17) is obvious. The plant showed in this indication a very good efficacy and at the same time almost no other medicamentous treatments were available. Moreover, BPH is a disease where improvements can be observed well and fast (99), contrarily to other indications where the plants was used for example like inflammations of the genitourinary tract (325).

But nevertheless, looking at the successful use of saw palmetto in other indications than BPH, further or new research is warranted to confirm the reported findings. Therefore, I carried out a clinical pilot trial in BPH patients with sexual dysfunctions to assess if saw palmetto is efficacious in this indication and to see if old knowledge could thus be confirmed.
Even though I presented in this chapter a wealth of data, this historical part has several shortcomings.

First of all, I have no training in historical research nor any education in historical sciences. My searches were carried out and assessed according to my best knowledge, helped by two standard books (168, 169) and sometimes with tips from the people from the medical historic library in Zurich.

Secondly, I carried out the majority of the searches and views of the literature via the internet using public online resources. Even though historians recommend the use of internet searches as they are faster, more comprehensive and lead in the end to same results as visiting libraries and looking at original literature (326, 327), it still not seen as state of the art in historical research (168). Furthermore, the view of original literature is due to copyright problems and fraudulent behaviour of users issuing reprints form online books more and more limited to so called snippet views where only parts of the literature can be viewed (328).

Thirdly, this use of only public material is a further important limitation of the whole medico-historical part. For almost any aspect of this investigation, like which were in the U.S.A. or in Germany the most important saw palmetto products, who were the key promoters of Sabal or where and how many preparations of the plant were sold in both countries until 1930, deeper research using archive material is warranted. Since this historical investigation forms only a third of this thesis and time was limited, I could not address all these additional questions.

Fourthly, it was difficult for me sometimes to assess the importance of a single reference and to carry out a proper source criticism. How far spread was a journal for example, who read it and how did it influence practitioners or how important was the opinion of a certain author is difficult to judge and would need also further and deeper research, mainly in archives.
Yet, with this research I could show for the first time, embedded in the treatment context for BPH until the beginning of the 20th century, at least trends which groups of practitioners pioneered in using saw palmetto in the United States and in Germany and how it became a popular treatment.

And, finally, that saw palmetto was quoted for the first time in Hagers Handbuch in 1944, at a time when Germany was at war with the United States, gives this research chapter an almost political or maybe at least a philosophical final twist. The boldness of the authors to include saw palmetto with reference to the U.S. National Formulary shows that on one hand the plant must have been a really good remedy but to the other hand that scientific evidence is in the end stronger than political ideology.
Chapter 3

The phytochemical analysis of 46 commercial preparations containing saw palmetto by using thin layer and gas chromatography
Chapter 3: Phytochemical analysis

The phytochemical analysis of 46 commercial preparations containing saw palmetto by using thin layer and gas chromatography

3.1 Introduction

As described in the previous chapters, saw palmetto preparations are the most popular herbal therapies for treatment of BPH. In general, they are produced by using a lipophilic extractant like N-hexane, 90-96% V/V ethanol or supercritical carbon dioxide (17, 40). For example, a common extraction procedure using ethanol is to crush the fruits in a mill, then macerate them for 1-2 days in the extractant. After this an exhaustive extraction for 4-5 hours is performed using percolation and hot ethanol at a temperature of about 55°C. In the end, the percolate is concentrated to an ethanolic spissum extract which will be encapsulated (329).

For supercritical fluid with carbon dioxide conditions which equal or exceed its critical temperature of 31.1° C and its critical pressure of 73.8 bar (330) are used. Therefore, extraction conditions like, for example, of at least about 500 bar and a temperature of less than 80° C are used (331).

The majority of these products are at the time sold worldwide as food supplements (332, 333) and only in a few countries like Germany or Switzerland they are registered and have to fulfil high quality requirements regarding the amount of active constituents and their stability (334). Therefore, I intended to assess the composition and quality of different preparations containing saw palmetto which are marketed for treatment of BPH symptoms.

Currently, there are only a few publications available which address the quality of different saw palmetto products even though in 2000 a consultation paper on treatments for BPH demanded further research on this topic (335).
The four monographs on saw palmetto all demand a daily amount of 320mg lipophilic saw palmetto extract (17, 40, 146, 147). As the main active constituents of these extracts free fatty acids and their ethyl esters are seen as well as phytosterols (17, 40, 62, 146, 147, 336). The only official quality marker so far for saw palmetto preparations is to be found in the European Pharmacopeia which requires lauric acid to be at least 20% of the total fatty acid (336). Thus, the quantity of fatty acids in saw palmetto preparations may serve as an important good quality marker. A more detailed description of the fatty acids in saw palmetto are given in chapter 3.3.2.

Feifer et al. examined six commercial preparations analytically and compared the amount of total fatty acids per unit with the information given on the package. They could show that there were large differences for three of the products between the stated information and the quantity of fatty acids determined in this analysis (337). In another publication, fourteen Sabal products were compared regarding their content of free fatty acids, methyl, ethyl, and long chain esters, triglycerides, and unsaponified matter. The results indicated large differences in the proportion of free fatty acids and their esters and the authors concluded that only those products with sound clinical data can be seen as effective (34).

In two further series of experiments the difference on bioactivity of different saw palmetto preparations was investigated. Scaglione et al. tested eight commercially available saw palmetto products on their ability to inhibit the two isoforms of the 5-alpha-reductase in vitro. The EC$_{50}$ for both isoforms differed widely for the products and in the majority also between different batches of a product. Nevertheless, the authors were cautious to relate these data to clinical efficacy (338).

In 2004 the German authority BfArM initiated a comparison of the bioactivity of three different saw palmetto extracts produced with ethanol 90%, ethanol 96% and hexane. The three preparations were similar in this in vitro setting in their activity to inhibit the 5-alpha-reductase (339).

The cited investigations focussed always on products from one country and the sample number was at all times small. Therefore, I wanted to carry out a broader investigation which included many test products from different countries to assess the daily amount of fatty acids and the composition of fatty acids in each product.
I collected 46 preparations containing saw palmetto from eight countries worldwide, with 19 of these products containing saw palmetto only as active constituent (mono preparations) and the other 27 where combined with other components such as vitamins, herbal extracts or minerals (combi preparations).

As quality reference, in each preparation the amount of the fatty acids lauric acid, capric acid, caprylic acid, myristic acid, palmitic acid, linolenic acid, oleic/linoleic acid, and stearic acid was determined using gas chromatography.

With this investigation I wanted to evaluate if the analysed products varied in their daily amount of total fatty acids and if these differences were country-specific or related to the regulatory status of a product.

Of further interest was, if the preparations differed in their proportion of fatty acids and if there were general differences between mono and combination products regarding their composition of fatty acids.

An additional goal was to assess how conform the measured fatty acid values were with the requirement of the monographs, the European Pharmacopeia, and the information given on the package.

In total, an overview on the quality of commercial preparations containing saw palmetto from different countries should be presented in the end.

The method of choice for this assessment was gas chromatography. This is a robust and uncomplicated method but the outcome is limited to the determination of nine fatty acids.
Chapter 5: Phytochemical analysis

Even though the fatty acids are the group of the active constituents to be found in the highest amount in saw palmetto extracts (40) there are also other active constituents in the extract like the phytosterols $\beta$-sitosterol, campesterol or stigmasterol, (340) polysaccharides (17) $\beta$-carotens, tocopherols (35) or the monoamine tyramine (39).

As it was not possible, due to lack of time and too few available test samples to carry out further analysis to quantify other active constituents, a further analytical investigation was carried out on the same samples using proton-NMR-spectroscopy in a Master thesis with a metabolomic approach using Principal Component Analysis (PCA) as statistical method (341). The goal of this thesis was to establish a fast and reproducible method to analyse saw palmetto products which should give a comprehensive answer on the characteristics of the products by using PCA (342). The results from the NMR-analysis are compared in the end with the gas-chromatographic analysis.
3.2 Material and Methods

3.2.1 Reference samples

Forty-six commercial products containing saw palmetto, indicated for treatment of BPH and which were known to sell well in their country were obtained from retail outlets or pharmacies. The preparations came from eight different countries, namely Canada, Finland, Germany, the Netherlands, the United Kingdom, South Korea, Spain, Switzerland, and the United States. Only the products from Switzerland were registered herbal products which needed to fulfill quality standards as demanded in the ESCOP monograph (17) and the European Pharmacopeia (336). The samples from Finland and Canada were also registered but no strict quality requirements have to be fulfilled, the registration acts rather as an official sales license.

The 46 products were tablets, soft gel or hard gel capsules, and the combination partners in combi products were mostly pumpkin seed oil (Cucurbita pepo), preparations from Pygeum africanum or stinging nettle (Urtica dioica) or single plant-derived substances like β-sitosterol or lycopene. Further from vitamins in the majority vitamins D and E and as minerals selenium or zinc were supplemented.

The daily dosages of all preparations were heterogeneous. Regarding the minimal daily dosage this was one unit per day for 20 products, for 21 products twice and for one preparation thrice daily, for three products there was a 4 x daily and for one product even a six times daily consumption. From the products containing only saw palmetto as active constituent only eight products were dosed once daily and six brands twice daily. Also the amount of saw palmetto extract declared for one tablet or capsule varied widely reaching from 2.5mg to 500mg per unit.

The extracts were in the majority not well declared on the packages or package leaflets, so only for a few products proper drug extractant ratios (DER) and the extractant were available. The given declarations showed that the greater number of the saw palmetto extracts were highly lipophilic, at least one (SP 14) contained also crude saw palmetto berry powder. None of the investigated products had reached expiry date.
Table 6 gives details on the test products, a more comprehensive description of each item including additionally the brand name, manufacturer, drug-extractant ratio, other active substances, and batch number is given in Appendix 1.

In the following the test samples can be identified with their reference number given in Table 6, abbreviated as SP and the number whereas SP stands for specimen.
Table 6: Details of the 46 preparations containing saw palmetto which were included in the analytic comparison

<table>
<thead>
<tr>
<th>Sample nr. (SP)</th>
<th>Country</th>
<th>Regulatory status</th>
<th>Food supplement (FS)</th>
<th>mono or combination</th>
<th>Tablet (T), capsule (C)</th>
<th>Tablet or capsule weight [mg]</th>
<th>Daily dosage (units/d)</th>
<th>Amount of saw palmetto per unit [mg] as given on package</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAN</td>
<td>R</td>
<td>combi</td>
<td>C</td>
<td>1800</td>
<td>160</td>
<td>2x1</td>
<td>150mg SP extract, 132mg SP berry</td>
</tr>
<tr>
<td>7</td>
<td>UK</td>
<td>FS</td>
<td>combi</td>
<td>C</td>
<td>450</td>
<td>80</td>
<td>4x1</td>
<td></td>
</tr>
<tr>
<td>8</td>
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<td>T</td>
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<td>80</td>
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</table>
3.2.2 Thin layer chromatography (TLC) for identification

3.2.2.1 Main principle

TLC is a simple and well known chromatographic technique to analyse drugs quickly and with great certainty (343) and is known to be 'the workhorse' for screening tests in laboratories (344). The method was first established by Izmailov and Srabber in 1938 who separated galenic formulations using loose layers of aluminium oxide on glass plates by continuously dropping a solvent on the point of application. The breakthrough for TLC was achieved when Stahl in 1958 developed high quality equipment for preparation and separation together with a standardised fine-grained silica gel. He was also the first person to propose the name TLC for this analytic method (345).

The method is based on the principle that the flat layer of the material serves as a stationary phase and that the mobile liquid phase is moved by capillary forces across this layer. Like this, compounds in mixtures are separated by their migration speed on the plate. The distance they migrate per time depends on the adsorption of the specific molecule to the stationary phase and, therefore, depends on its distribution between the two phases. The more a substance is adsorbed, the slower it moves (343, 344).

The detection is carried out by locating the spots on the plate and identifying the substances (344). Several methods are available to locate the spots on the plate. This can be by exploiting the luminescence characteristics of the analyte either by a fluorescence or phosphorescence or by impregnating the layer bed with a fluorescent indicator substance and afterwards inspection under UV light. Furthermore the layer can be sprayed with a nonspecific strong oxidant or with a group – or substance specific reagent solution (344, 346). A substance is much easier to identify when an authentic reference substance is applied as well and the separated spots can be compared to it (344).

Like this, TLC is the standard method for identification of herbal drugs which can also give answers on the quality and even on the quantity of certain compounds (343). Furthermore, the procedures and results are documented in pharmacopoeias (336, 343) and are easy to reproduce.
3.2.2.2 Protocol for analytical TLC

The method applied was in accordance with the requirements of the European Pharmacopoeia on thin layer chromatography, chapter 2.2.27 and the monograph on saw palmetto fruit (336). The principle of this TLC method was that with an apolar, acidic mobile phase the lipophilic substances of the saw palmetto preparation were separated on a silica gel layer. After spraying with anisaldehyde reagent and heated to 110°C, the zones were analysed at daylight.

This TLC method was already used routinely at A.Vogel Bioforce AG quality assurance for identification of the saw palmetto preparation Prostasan®. This is a registered product containing 320mg saw palmetto extract per capsule extracted with ethanol 96% V/V and fulfils the requirements of the European pharmacopoeia and the monographs (17, 40, 146, 147, 336). The amount of each test preparations for TLC was calculated using a modified formula after having carried out previous experiments.

The formula for Prostasan® is as follows:

\[ \frac{0.25 \times 320}{485} = 0.16 \left[ \frac{g \times mg}{mg} \right] = [g] \]

0.25 = [g] necessary Prostasan® content
320 = [mg] Saw Palmetto extract per Prostasan® capsule
485 = [mg] Prostasan® capsule weight

The adjusted formula for soft gel capsules and tablets was:

\[ x = \frac{0.16 \times b}{a} \]

x = [g] necessary capsules (tablets) content
a = [mg] Saw Palmetto per capsule (tablet) as given on the package
b = [mg] capsule (tablet) weight

for hard gel capsules the formula was adjusted to

\[ x = \frac{0.4 \times b}{a} \]
The amount of a capsule content or tablet was dissolved in 4ml toluol. As reference substances 10mg β-sitosterol and 4mg β-amyrin were separately dissolved in 10ml ethanol (96%). 4μl of the saw palmetto preparation, which was a clear yellow solution as well as 2μl each of the reference solutions and additionally also Prostasan® as a reference saw palmetto product were applied to a silica gel F<sub>254</sub> HPTLC plate with 60nm pore size from Merck.

As mobile phase acted a mixture of toluene, ethylacetate and acetic acid mixed in the ratio of 70:30:1 V/V. The runtime was about 20 minutes and the dried plate was thereafter sprayed with anisaldehyde reagent. After heating the plate up for 5-10 minutes to 110°, the zones were visible and the plate could be analysed.

The method applied here serves only for the identification and not for quantification of substances.

3.2.3 Gas chromatography for analysis of fatty acids

3.2.3.1 Main principle

In gas chromatography (GC), the mobile phase is an inert carrier gas which is generally helium, argon, or nitrogen which has no significant interactions with the analyte. The main function of the carrier gas is to transport the compounds to be analysed from the injector to the detector. The stationary phase is either solid or liquid where the constituents to be separated can be adsorbed (344).

GC is applicable to substances or their derivatives which can be volatilised under the temperatures which are applied (336), mainly organic and anorganic materials with molecular weight ranging from 2 to 1000 Daltons and is the premier technique to separate and analyse volatile compounds (347). The method is based on the works of Prior and Cremer who were the first to develop a solid gas chromatography method in 1947 which was published officially in 1951 (348).
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The basic principle of a gas chromatograph is quite simple and the differences in gas chromatographic systems lay generally in the use of the carrier gases. The system is that gas is directed through the injector to the column and the sample is injected either into a special injector or to the column itself. The analytes are then separated in the column which is heated by an oven and usually temperature gradients are used to improve the separation. The separated compounds are then recognised in the detector (344, 349).

The choice of the gas is often important, even though it is inert, as it determines by its molar mass, density, and viscosity how long the analytes stay in the column. A longer diffusion time leads in the end to a better peak broadening and a better resolution (344).

Also, there are several injection systems used but the oldest and most popular is split injection. Here, a small proportion of the sample is transferred to the column with a standard syringe on the heated injection port which contains a deactivated glass liner. The sample is rapidly evaporised and the major part is discharged as waste through the split which is an opening right at the top of the column (347).

There are a wide variety of columns in use for GC like packed columns where the stationary phase is coated on a granular support material or capillary columns with a liquid stationary phase deposed on the column wall. Depending on the type of column they differentiate in their diameter and length, whereas capillary columns are generally narrower and much longer, up to 100 m, than the packed ones (344).

More than 60 detectors have been tried out in GC (347) but most often flame ionization detectors (FID) are used. The principle of this detection system is the measurement of the electric conductivity of a hydrogen flame between two electrodes. When an organic compound enters the flame the substance is ionised causing an electric current and this allows to detect this compound (344, 350).

The advantages of GC is that it is a fast, efficient, and sensitive analysis providing a high resolution. Further the method is non destructive making it possible for online-coupling for example to a mass spectrometer and is easy to apply, reliable and inexpensive (347).
3.2.3.2 Protocol for fatty acids analysis with GC

The method used was based on the principle that the lipophilic constituents of the saw palmetto preparations were extracted with hexane, then saponified with sodium-hydroxide and finally esterified to fatty acid methyl esters (FAME) with boron trifluoride-methanol complex. The FAME were then separated with GC and analysed using heptadecanoic acid as internal standard. Like this the esters and free fatty acids are determined together, counted as free fatty acids.

This was a modified standard method of the German Society for Fat Science for fatty acid methyl esters (351) which is in alignment with the recommendations of the European Pharmacopoeia for gas chromatography and for determination of fatty acids in saw palmetto products (336). Tablets, soft and hard gel capsules had each to be prepared with different protocol for GC as will be shown in the following.

a) Preparation of tablets

For tablets this formula was applied to determine the amount needed for analysis:

\[ x = \frac{1000 \times 0.16 \times b}{a} \]

x = [mg] necessary tablet content

a = [mg] Saw Palmetto extract per tablet as given on the package

b = [mg] tablet weight as given on the package

1000 = coefficient on mg

0.16 = calculations coefficient based on preliminary experiments

The corresponding amount of tablets were pulverised and combined with 4ml ethanol 40%, 8ml water and 5ml internal standard solution in a 40ml centrifuge tube. Afterwards the mixture was extracted with 3 times with 15ml hexane. The hexane phases were then combined and dried with sodium sulphate and then concentrated in a rotary evaporator.
b) Preparation of soft gel capsules

The amount of the content of soft gel capsules needed for the analysis was calculated as follows:

\[
x = \frac{1000 \times 0.13 \times b}{a}
\]

\(x\) = [mg] necessary capsule content

\(a\) = [mg] Saw Palmetto per capsule as given on the package

\(b\) = [mg] capsule weight as given on the package

1000 = coefficient in mg

0.13 = calculations coefficient based on preliminary experiments

From each soft gel capsule the calculated capsule content was added to a 50ml centrifuge tube and mixed with 5ml of the internal standard solution (300mg heptadecanoic acid dissolved in 50ml petroleum ether) and then dissolved in 10ml petroleum ether. After addition of 1g water-free sodium sulphate the tube was centrifuged for 5 minutes at 3000U/min. Of the supernatant, 10ml were then concentrated to dryness in a rotary evaporator.

c) Hard gel capsules

The quantity from the content of hard gel capsules mandatory for the GC analysis was calculated using the following formula:

\[
x = \frac{1000 \times b}{a}
\]

\(x\) = [mg] necessary capsule content

\(a\) = [mg] Saw Palmetto extract per capsule as given on the package

\(b\) = [mg] capsule weight as given on the package

1000 = [g] amount of herb for the analysis
The calculated amount of the capsule content was transferred to a Soxhlet extraction thimble, covered with wool and extracted for 45 minutes with 70ml hexane and 5ml internal standard solution. The extraction solution was thereafter concentrated on the rotary evaporator to ca. 2ml and then dried with water-free sodium sulphate. The clear solution was then evaporated until dry on the rotary evaporator.

The next preparatory steps were the same for all investigated galenic forms.

Six ml of 2% methanolic sodium hydroxide-solution were added to the residue and heated up to the boiling point for 10 minutes, then 5ml boron trifluoride-methanol complex were added and the whole mixture was boiled for another 2 minutes. Finally, 20ml heptane were added, stirred and cooled down.

Afterwards saturated sodium chloride solution was added until the heptane phase ascended into the flask neck. About 1ml of the resulting heptane phase was dried in a centrifuge tube with water-free sodium sulphate; the clear yellowish green solution was used for the chemical analysis.

The analysis was performed twice for each test preparation with a gas chromatograph (Trace GC ultra, Thermo electro-cooperation) using an Optima 5 capillary column, 25m x 0.32mm iD with 0.25μm layer thickness.

The column was held isothermally at 100°C, then the temperature was programmed to increase at a rate of 5°C /min to 190°C where it was kept for 5 minutes. The injector was set to 250°C and an amount of 1μl solution was injected using the split mode with hydrogen as carrier gas at a constant pressure of 40 kPa.

The system suitability was given when in the chromatogram the resolution between the main peak lauric acid and myristic acid amounted to at last ten. The single fatty acids which were assigned according to the retention time of the peaks and were calculated in reference to the area of heptadecanoic acid. The areas were integrated by using Chromcard software. The methods precision is 0.9% and the correlation in linearity 0.998.

Fig. 6 shows a typical chromatogram of an analysis with the identification of the peaks.
For capric acid, caprylic acid, lauric acid, myristic acid, palmitic acid, linolenic acid, oleic/linoleic acid, and stearic acid the amount was calculated in reference to heptadecanoid acid as follows:

\[ \text{Fatty acid [mg/unit]} = \frac{\text{AP} \cdot \text{WIT}}{320} \cdot \frac{\text{AST}}{10 \cdot \text{WS}} \]

- \( \text{AP} \) = sum of area of fatty acids in a sample
- \( \text{AST} \) = area of internal standard
- \( \text{WIT} \) = weight of internal standard [mg]
- \( 10 \) = dilution of internal standard
- \( \text{WS} \) = weight of sample [mg]
- \( 320 \) = standard weight of capsule content

Each test preparations was analysed twice. The corresponding mean value of every product was used for the analysis. All analyses were carried in the analytical laboratories of A.Vogel Bioforce AG, Roggwil, Switzerland with the assistance of laboratory technicians.

\[ \text{Andy Suter} \]
3.3 Results

3.3.1 Identification of the test samples with TLC

The products were applied grouped together according to their galenic form, means tablets, soft and hard gel capsules on separate silica gel plates.

On Figure 7 and 8 are the TLC fingerprints of the tablet samples. Except for the preparation on position 2 in Figure 7 and the reference substance Prostasan® on position 7, these were all combination products. The two products on lane 5 and 6 were sold by different manufacturers but had the same composition given on the package containing a large variety of herbal substances, vitamins and minerals. The fingerprint identifies them as similar products.

Figure 7: TLC fingerprint profile of six different tablets on band 1-6, band 7 is the reference product Prostasan capsules, band 8 are the reference substances β-sitosterol (upper band) and β-amyrin (lower band)

1 = SP 57, Spasmo-Urgenin, Madaus, Spain
2 = SP 8, Sereprostat, Robapharm España S.A., Spain
3 = SP 55, Prosta-Fort, GSN, Spain
4 = SP 23, Saw Palmetto Complex, Nature's Aid Ltd., UK
5 = SP 38, Prostaat, Phital, Netherlands
6 = SP 42, Prosta Totaal, Distributie care bv, NL
7 = SP 10, Prostasan, Bioforce AG, Switzerland
8 = Reference solution: β-Sitosterol; β-Amyrin
Figure 8: TLC fingerprint profile of the tablet preparation SP56 on band 1, band 2 is the reference product Prostasan capsules, band 3 are the reference substances β-sitosterol (upper band) and β-amyrin (lower band, barely visible)

Among the hard gel capsule products, Figure 9 shows that all the mono preparations presented almost the same TLC fingerprint (lane 1, 3, 4, 5, 7). The fingerprints of the two Dutch products in Figure 9 on lane 8 and 9 indicated that they were combination products. The products in lane 2 and 6 were also combinations but they were for this assay maybe not sufficiently concentrated. The three further hard capsule preparations in Figure 10 were all combination products whereas the product on lane 2, a combination product with vitamin D and minerals showed almost the same pattern like the reference product Prostasan.
Figure 9: TLC fingerprints of nine products in hard gel capsules, on position 10 is the reference product Prostasan capsules, on position 11 are the reference substances β-sitosterol (upper band) and β-amyrin (lower band).

1 = SP 12 Permlxon, Pierre Fabre Iberica S.A., Spain
2 = SP 22 Biprostat, Dietéticos Intersa S.A., Spain
3 = SP 13 Saw Palmetto Berries, , Natural Factors, Canada
4 = SP 45 Saw Palmetto, Homeocan, Canada
5 = SP 14 Saw Palmetto Berries, Solgar Vitamin and Herb, UK
6 = SP 11 Saw Palmetto, Holland and Barret, UK
7 = SP 24, ProstaFleur Extra Forte, Bloem Natuurprodukten NL
8 = SP 41, Prostalife, Bloem Natuurprodukten NL
9 = SP 35, Prostasan, Bioforce AG, Switzerland
10 = SP 24, ProstaFleur Extra Forte, Bloem Natuurprodukten NL
11 = Reference solution: β-Sitosterol, β-Amyrin

Figure 10: TLC fingerprints of three hard gel capsules on lane 1-3, the reference substance Prostasan on lane 4 and on lane 5 β-sitosterol (upper band) and β-amyrin (lower band).

1 = SP 15, Saw Palmetto & Pygeum Bark, Higher Nature, UK
2 = SP 17, Prostate Health, Schiff Nutrition Group Inc, USA
3 = SP 47, Saw Palmetto & Pygeum Extract, Country Life, USA
4 = SP 10, Prostasan, Bioforce AG, Switzerland
5 = Reference solution: β-Sitosterol, β-Amyrin
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The majority (n=29) of the commercial preparations were made with soft gel capsules. Figure 11 shows the fingerprints of the six saw palmetto brands from Switzerland. All except the sample on position 4 which contained also an \textit{Urtica dioica} extract were mono preparations. They displayed an almost uniform TLC fingerprint and could evidently be identified as a lipophilic saw palmetto preparation when compared to the reference product Prostasan® (Figure 11).

\textbf{Figure 11:} TLC fingerprint of the six Swiss saw palmetto preparations which were all made with soft gel capsules. On lane 7 are the reference substances \(\beta\)-sitosterol (upper band) and \(\beta\)-amyrin (lower band)

1 = SP 30, Prosta Urgenin, Max Zeller Söhne AG, CH  
2 = SP 31, SabCaps, Vifor SA, CH  
3 = SP 27, Prostagutt Uno, Schwabe Pharma AG, CH  
4 = SP 40, Prostagutt F, Schwabe Pharma AG, CH  
5 = SP 36, Prostadyn, Dr. Dünner AG, CH  
6 = SP 10, Prostasan, Bioforce AG, CH  
7 = Reference solution: \(\beta\)-Sitosterol; \(\beta\)-Amyrin
In Figure 12, 13, and 14 the mono preparations always showed similar signals as compared to the reference product Prostasan®. Combination samples produced in four cases no clear bands but rather big black spots (Fig. 12, SP46; Fig. 13, SP51; Fig. 14, SP 44, SP 21). These could be due to either to the concentration being too high but also to pumpkin seed oil extracts in SP 44, 46, and 51 which usually in TLCs evokes signals similar to the ones seen here (343).

Two combination products in Figure 12 on position 12 and 13 showed displayed almost the same pattern like the reference product Prostasan® even though they contained additionally pumpkin seed or soy oil.

**Figure 12:** TLC fingerprints of 14 different saw palmetto preparations with soft gel capsules. On lane 15 is the reference product Prostasan, on lane 16 are the reference substances \( \beta \)-sitosterol (upper band) and \( \beta \)-amyrin (lower band).

1 = SP 37, Saw Palmetto, Swiss Herbal Remedies Ltd., CAN
2 = SP 34, Saw Palmetto Extract, Now Foods, USA
3 = SP 19, Prost-Force, Prairie Naturals, Canada
4 = SP 1, Prostate Perform, New Roots Herbal, Canada
5 = SP 48, Saw Palmetto & Pygeum, Preferred Nutrition, CAN
6 = SP 20, Life Extension, Quality Supplements and Vitamins Inc., USA
7 = SP 33, Curfsal, Pharbio, Finland
8 = SP 43, Prostaian Forte, VSM, Netherlands
9 = SP 53, Saw Palmetto Berry Extract, Solaray, USA
10 = SP 46, Prostavital, Healt Aid, UK
11 = SP 29, Saw Palmetto Mono Product 1 (HFS), CJ Nutra, Korea
12 = SP 16, Saw Palmetto Combination Product 1 (HFS), CJ Nutra, Korea
13 = SP 18, Saw Palmetto Combination Product 2 (HFS), Chung Wae Pharma Corporation, Korea
14 = SP 32, Saw Palmetto Mono Product 2 (HFS), Chong Kun Dang Health, Korea
15 = SP 10, Prostasan, Bioforce AG, Switzerland
16 = Reference solution: \( \beta \)-Sitosterol; \( \beta \)-Ammrin
Chapter 3: Phytochemical analysis

**Figure 13:** TLC fingerprints of two preparations made with soft gel capsules. On lane 3 is the reference product Prostasan, on lane 4 are the reference substances $\beta$-sitosterol (upper band) and $\beta$-amyrin (lower band)

1 = SP 44, Prostavit, Bional, Netherlands  
2 = SP 21, Prostavit Forte, Bional, Netherlands  
3 = SP 10, Prostasan, Bioforce AG, Switzerland  
4 = Reference solution: $\beta$-Sitosterol; $\beta$-Amyrin

**Figure 14:** TLC fingerprint of five saw palmetto preparations with soft gel capsules. On lane 6 is the reference product Prostasan, on lane 7 are the reference substances $\beta$-sitosterol (upper band) and $\beta$-amyrin (lower band)

1 = SP 49, ProstActive, Nature's Way, USA  
2 = SP 50, Prostate SLX, New Chapter Inc., USA  
3 = SP 51, Prostate Advantage, Enzymatic Ther., USA  
4 = SP 52, Saw Palmetto & Pygeum, Nature's Way, USA  
5 = SP 54, Saw Palmetto Extract, Source Nat., USA  
6 = SP 10, Prostasan, Bioforce AG, Switzerland  
7 = Reference solution: $\beta$-Sitosterol; $\beta$-Amyrin
In conclusion, the results show that the applied concentrations were sufficient to cause a good signal strength. The TLC fingerprints displayed that the saw palmetto mono preparations could well be identified when compared to the reference product Prostasan® no matter the galenic form of a product. Also, in general the mono preparations could be differed from the combination products. Answers on quantity of the saw palmetto extracts or which were the components in a combination product could not be given with this TLC methodology. Methodological aspects, how ß-sitosterol could be determined qualitatively and quantitatively by also using TLC are presented in the discussion section.
3.3.2 Analysis of fatty acids

For each of the tested products the amount of the fatty acids lauric acid, capric acid, caprylic acid, myristic acid, palmitic acid, linolenic acid, oleic acid, linoleic acid, and stearic acid were determined whereas for oleic and linoleic acid the sum for both were assessed since the resolution of the peak was not satisfactory. The chosen fatty acids are known to form the majority of lipophilic constituents of saw palmetto fruits and are thus a good marker for the botanical drug’s active constituents (352). A detailed description of the fatty acids analysed is given in Table 7.

Table 7: The elemental formula, lipid number, structure, and pharmacological activities of the gaschromatographically analysed fatty acids

<table>
<thead>
<tr>
<th>Fatty acid (IUPAC name)</th>
<th>Elemental formula/lipid number</th>
<th>Structure</th>
<th>Pharmacologically known activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caprylic acid (octanoic acid)</td>
<td>C8H16O2 C8:0</td>
<td></td>
<td>Antibacterial (353-357)</td>
</tr>
<tr>
<td>Capric acid (decanoic acid)</td>
<td>C10H20O2 C10:0</td>
<td></td>
<td>Antiviral (358)</td>
</tr>
<tr>
<td>Lauric acid (dodecanoic acid)</td>
<td>C12H24O2 C12:0</td>
<td></td>
<td>Antibacterial (359), insulinotropic (360), increasing high density lipoprotein (HDL) (361), antimuscarinic, antiandrogenic (41, 46, 47)</td>
</tr>
<tr>
<td>Myristic acid (tetradecanoic acid)</td>
<td>C14H28O2 C14:0</td>
<td></td>
<td>Antibacterial (362), antiparasitic (363), hypercholesterolaemic (364)</td>
</tr>
<tr>
<td>Palmitic acid (hexadecanoic acid)</td>
<td>C16H32O2 C16:0</td>
<td></td>
<td>Hypercholesterolaemic (364, 365)</td>
</tr>
<tr>
<td>Stearic acid (octadecanoic acid)</td>
<td>C18H36O2 18:0</td>
<td></td>
<td>anti-adipogenic (366-368)</td>
</tr>
<tr>
<td>Oleic acid ([9Z] octadec-9-enoic acid)</td>
<td>C18H32O2 18:1</td>
<td></td>
<td>Anticarcinogenic (369), hypotensive (370) antimuscarinic, antiandrogenic (41)</td>
</tr>
<tr>
<td>Linoleic acid (cis, cis-9,12-octadecadienoic acid)</td>
<td>C18H30O2 18:2</td>
<td></td>
<td>anti-adipogenic (371), inflammatory (?) (372, 373)</td>
</tr>
<tr>
<td>α-linolenic acid ([9Z,12Z,15Z] octadec-9,12,15-trienoic acid)</td>
<td>C18H28O3 18:3</td>
<td></td>
<td>Antinflammatory, immune modulatory, anti-adipogenic, radical scavenger, increasing lipoprotein peroxidation, anticarcinogenic (374)</td>
</tr>
</tbody>
</table>
3.3.2.1 Total daily amount of fatty acids per preparation

The test samples varied widely in their amount of saw palmetto extract as declared by the producer, the capsule or tablet weight, and the daily dosages (Table 6). Thus in the following the results of the fatty acid analysis will be shown for the lowest daily dosage as given on the package as this is the amount of tablets or capsules which the manufacturer of the product still considers to be efficacious.

The results showed there great heterogeneity between the products in the amount of fatty acids per day as can be seen in Figure 15 for the lowest daily dosage per preparation. The concentrations were in the range between 8.43mg for the product with the lowest daily amount of fatty acids to 1473mg for the item with the highest value. The mean reached 372.4 ± 333.7mg fatty acids per day and the median value was 283.5mg/d.

Mono and combination products differed slightly in the average when looking at all test items regarding the content of fatty acids but the combinations displayed a larger variability. Products containing only saw palmetto result in 230.5 ± 127.2mg fatty acids per day with values ranging from 30.89 to 1473.2mg, combination products in 261.0 ± 247.5mg with a range from 8.34 to 1173.02mg daily; the corresponding median values were 271.9mg for mono preparations, respectively 239.3mg per day for combinations (Figure 15).
Figure 15: Amount fatty acids per day of the lowest daily dosage given on the package for each analysed product [mg/d] of all 46 investigated commercial preparations. White bars indicate mono preparations containing only saw palmetto as active constituent, red bars combination products.
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The differences in the daily amount of fatty acids per product were more pronounced when looking at the country of origin. The mono preparations from Switzerland and South Korea showed all similar concentrations while the highest dosed U.S. American product contained 2.7 times the amount of the preparation with lowest dose, for Canada this ratio was 3.0, and for Spain even 13.3 (Figure 16).

Figure 16: Total amount of fatty acids per minimal daily dosage [mg/d] for mono products sorted by their country of origin

Combination products when analysed by their country of origin showed an even more ambiguous picture regarding the amount of total fatty acids. The mean values were highest for the Canadian products (n=3) with 1008.5 ± 219.6mg/d, followed preparations from the U.S.A (n=7) with 378.3 ± 288.6mg/d, and South Korea (n=2) with 358.7 ± 61.1mg/d. The lowest average value for the total fatty acid content displayed the Spanish products (n=3) with 129.2 ± 193.7mg/d.

The enormous standard deviations highlight that there was a large variability between the daily amount of fatty acids between the preparations within one country. The highest dosed brand in Spain contained 42.3 times more fatty acids than the lowest dosed, for the products from the United Kingdom this factor was 27.9, for those from the Netherlands 14.4, from the U.S.A. 9.0, from Canada 1.6, and from South Korea 1.3.

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The total amount of fatty acids in combination products cannot be explained by other botanical drugs included in a preparation. Samples containing one or both of these extracts could contain high amounts of fatty acids like for example for the Canadian SP19 with 1173.02mg/d but also very low daily concentrations like 26.64mg of the Spanish sample SP 15 (Figure 17).

**Figure 17:** Daily amount of total fatty acids for combination products according to the minimal dose of every preparation [mg/d], divided by country of origin. The darker bar indicates for each country the mean value with standard deviation.
3.3.2.2 Comparison of measured fatty acid quantities to the amounts given on the packages of mono preparations

The differences in the total amount of fatty acids between the products might not be that relevant for a customer when the quantities of extract are declared correctly. Thus for the mono preparations I compared the measured quantities of fatty acids to the amounts given on the packages or the package leaflet. For the calculation of the difference between the stated and measured amount I assumed that an extract would consist of 100% fatty acids.

There were large dissimilarities between the measured values and the package information ranging from about 10 times less fatty acids up to 4.6 more fatty acids than what was stated by the manufacturer.

Usually lipophilic saw palmetto extracts contain 70-95% fatty acids (147, 352). Only for eight of the analysed 19 preparations a percentage of fatty acids per capsule or tablet in this range could be calculated by comparing the measured amount of fatty acids to the written quantity of extract by the manufacturer. Interestingly, all registered Swiss products were among these eight products as well as the also registered Finnish product and one Korean product. The only U.S. American preparation (SP49) which was in the calculated range is actually a German preparation similar to SP 27 as both are produced by the same manufacturer, Schwabe Pharma in Germany (375).

Surprisingly, for SP12, Permixon®, a saw palmetto product with a good preclinical and clinical background and known to be a reputed product (34, 338) only a value of 34.8% fatty acids of the extract could be determined (Table 8).
Table 8: Differences between the amount of saw palmetto extract as stated on the package and the measured concentration of total fatty acids per tablet or capsule assuming the extract consists of 100% of fatty acids.

<table>
<thead>
<tr>
<th>Sample nr.</th>
<th>Country</th>
<th>Unit</th>
<th>Amount of saw palmetto extract per unit [mg] as declared on package</th>
<th>Total fatty acids [mg] per unit measured</th>
<th>Difference in % of information on package vs. measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP 8</td>
<td>ESP</td>
<td>t</td>
<td>80</td>
<td>368.3</td>
<td>460.4%</td>
</tr>
<tr>
<td>SP 37</td>
<td>CAN</td>
<td>c</td>
<td>80</td>
<td>253.06</td>
<td>316.3%</td>
</tr>
<tr>
<td>SP 34</td>
<td>USA</td>
<td>c</td>
<td>160</td>
<td>378.2</td>
<td>236.4%</td>
</tr>
<tr>
<td>SP 53</td>
<td>USA</td>
<td>c</td>
<td>160</td>
<td>354.61</td>
<td>221.6%</td>
</tr>
<tr>
<td>SP 54</td>
<td>USA</td>
<td>c</td>
<td>320</td>
<td>444.31</td>
<td>138.8%</td>
</tr>
<tr>
<td>SP 36</td>
<td>SWI</td>
<td>c</td>
<td>160</td>
<td>151.56</td>
<td>94.7%</td>
</tr>
<tr>
<td>SP 33</td>
<td>FIN</td>
<td>c</td>
<td>320</td>
<td>290.24</td>
<td>90.7%</td>
</tr>
<tr>
<td>SP 49</td>
<td>USA</td>
<td>c</td>
<td>320</td>
<td>285.68</td>
<td>89.3%</td>
</tr>
<tr>
<td>SP 35</td>
<td>SWI</td>
<td>c</td>
<td>320</td>
<td>281.34</td>
<td>87.9%</td>
</tr>
<tr>
<td>SP 27</td>
<td>SWI</td>
<td>c</td>
<td>320</td>
<td>274.53</td>
<td>85.8%</td>
</tr>
<tr>
<td>SP 31</td>
<td>SWI</td>
<td>c</td>
<td>320</td>
<td>274.45</td>
<td>85.8%</td>
</tr>
<tr>
<td>SP 32</td>
<td>Korea</td>
<td>c</td>
<td>320</td>
<td>271.9</td>
<td>85.0%</td>
</tr>
<tr>
<td>SP 30</td>
<td>SWI</td>
<td>c</td>
<td>320</td>
<td>271.82</td>
<td>84.9%</td>
</tr>
<tr>
<td>SP 29</td>
<td>Korea</td>
<td>c</td>
<td>320</td>
<td>237.74</td>
<td>74.3%</td>
</tr>
<tr>
<td>SP 12</td>
<td>ESP</td>
<td>c</td>
<td>160</td>
<td>55.68</td>
<td>34.8%</td>
</tr>
<tr>
<td>SP 45</td>
<td>CAN</td>
<td>c</td>
<td>350</td>
<td>51.01</td>
<td>14.6%</td>
</tr>
<tr>
<td>SP 14</td>
<td>UK</td>
<td>c</td>
<td>300</td>
<td>34.5</td>
<td>11.5%</td>
</tr>
<tr>
<td>SP 13</td>
<td>CAN</td>
<td>c</td>
<td>500</td>
<td>56.8</td>
<td>11.4%</td>
</tr>
<tr>
<td>SP 11</td>
<td>UK</td>
<td>c</td>
<td>450*</td>
<td>44.57</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

*Contains also saw palmetto powder
3.3.2.3 The relative amount of the single fatty acids per preparations giving and indicator for their inner composition

a) Combination products

For each of the analysed products the relative amount of every single fatty acid was assessed compared to the total amount of fatty acids. Like this, a fingerprint on the composition for each product can be produced.

For the combination preparations, the relative amount of fatty acids and the resulting pattern varied widely. For example, only eleven products had a lauric acid content of more than 20% of the total fatty acids, three test items, SP44, SP46, and SP56 contained almost none at all. To link the amount of certain fatty acids to extracts like Pygeum africanum, soy, or pumpkin seeds which were part of the combinations was not possible (Figure 18).

Figure 18: Relative amount of the analysed single fatty acids compared to the total fatty acid content for each investigated combination product. The bar at the very right shows the average value of all investigated combi products (n=27).
b) Mono products

The composition of the saw palmetto mono extracts was in the majority comparable as can be seen in Figure 19. The percentage of the eight different single fatty acids was more or less comparable in about 14 of the mono preparations, the samples SP54, 34, 53, 8, and 37 differed the most from the average values.

Saw palmetto fruits contain high amounts of oleic and lauric acid, each is present with around 30-40% of the total fatty acids (352), the above mentioned 14 preparations showed high concentrations of lauric and oleic/linoleic acid as well. The amount of 20% lauric acid per saw palmetto extract as demanded in the European Pharmacopeia (336) was reached by all but four mono preparations. Three of these four products, SP34, SP54, and SP8 had larger amounts of oleic and linoleic acid and one item, SP37, contained a very high concentration of linolenic acid which is unusual for saw palmetto berries and gave raise to a suspected adulteration with another plant oil.

In general the pulp of the saw palmetto fruit contains more myristic acid compared to the whole drupe (352). None of the test items had increased values of this fatty acid which indicates that in all cases the whole fruits were extracted.

The extractant was available from the package or patient information leaflet for SP27, 30, 31, 33, 35, and 36; either 90% or 96% ethanol was used and all these products had comparable drug extractant ratios. These ethanolic preparations showed the same relative amount of the fatty acids compared to the only product extracted with hexane, SP12 (Figure 19).
Figure 19: Relative amount of the analysed single fatty acids compared to the total fatty acid content for each investigated mono product. The bar at the very right shows the average value of all investigated mono products (n=19)

In summary, on average the combination products showed a different pattern compared to saw palmetto preparation. They contained less lauric, oleic/linoleic, and myristic acid but higher concentrations of palmitic, linolenic and stearic acid. Among the mono items, four products displayed different patterns compared to the other extracts whereas one contained a high amount of linolenic acid which is not a main constituent of saw palmetto berries.

The chromatograms of the investigated samples are displayed in the appendix.
3.3.2.4 Main results from proton-NMR-analysis from the master thesis of Tony Booker (2010)

In the NMR analysis the test items SP1 to SP37, except SP8 were analysed and additionally four saw palmetto mono tinctures and one German lipophilic mono extract (Prostess uno, TAD Pharma) and a British product from Chapmans which contained saw palmetto powder extract.

For better comparison of the two analytical methods, GC and NMR-spectroscopy, I focus in the following only on products which were analysed using both techniques.

For sample preparation, the test items were first extracted with methanol and then analysed, but as with this extraction method the soft extracts dissolved insufficiently, deuterated chloroform was used thereafter as extractant.

With the NMR analysis the compounds gallic acid, absorbic acid, galactose, sitosterol, stigmasterol, caproic acid ethyl ester, and oleic acid could be analysed. The latter two substances could be positively identified from the spectra of the methanolic sub extracts from the saw palmetto products and could be used for quantitative work.

In general, the analysis showed that tinctures and preparations containing dried saw palmetto powder could be differentiated with the principal component analysis (PCA) from powder extracts.

Among the soft gel extracts, the hexane extract Permixon (SP12) presented a different metabolomic fingerprint than the others which partly might be due to the excipient polyoxethylene glycol but it contained also more methyl and ethyl esters.

Three other preparations, SP26, SP34, and SP37 were different from the main group of soft gel extracts.
Further small differences between the test items, also between combination and mono products could not be detected with NMR nor were at this stage any quantifications of constituents in the extracts possible. But the NMR-method, here used for the first time for a metabolomic approach for different saw palmetto preparations proved to be robust and reproducible and the clustering allowed well to identify outliers.

A good example for a PCA is shown in Figure 20 for soft extracts in chloroform. The saw palmetto mono extracts build in the majority one cluster whereas combi preparations deviated from it (Figure 20).

**Figure 20:** Ellipse scores of saw palmetto soft extracts (SP25-37) versus combination products (SP16-SP21) in chloroform.
3.4 Discussion

This phytochemical analysis of 46 commercial preparations from eight different countries which contain saw palmetto is at the time the most comprehensive investigation of saw palmetto products carried out so far.

The study showed that with the TLC methodology lipophilic saw palmetto mono-extracts could be identified well and that the total amounts of fatty acids measured with GC were very heterogeneous between all analysed products. The relative amounts of the nine investigated fatty acids were similar in ethanolic mono preparations but rather different in combinations. Furthermore, this investigation provided evidence that the mono preparations sold as food supplements displayed large differences between the declared and the measured amount of fatty acids.

The analysis confirmed that the TLC method of the European Pharmacopoeia (336) showed good results in identifying saw palmetto mono products.

With this TLC method saw palmetto preparations with different extractants could be distinguished since SP12, the only investigated hexane-based extract, showed a different TLC fingerprint than the ethanolic mono extracts. More test samples with hexane as extractant for comparison would be needed to confirm this finding.

Otherwise, the TLC fingerprints were very heterogeneous and only in some cases the saw palmetto component was to some extent identifiable. Also for preparations containing same combination partners like Pygeum africanum- or pumpkin seed extracts no uniform fingerprints which could be related to one of the components could be observed. Thus, this TLC method is best applied in saw palmetto mono preparations and solely for identification and not for quantification or qualitative determination of substances like $\beta$-sitosterol.

A better method to evaluate the quality of a product with Sabal is the analysis of its amount of fatty acids which are seen as the main active constituents in saw palmetto preparations (17, 40) and are known to influence positively pathological mechanisms of BPH (41, 48, 52, 376).

With the applied GC standard method nine fatty acids were analysed which comprise more than 95% of the fatty acids of saw palmetto berries. Other fatty acids not
determined in this analysis like tridecanoic acid, pentadecanoic acid, arachic acid, behenic acid, and lignoric acid are only to be found in very low quantities in saw palmetto extracts of less than 0.2% each (35). Caproic acid which also could not be analysed with the applied GC methodology, accounts for about 3% of all fatty acids in saw palmetto (352, 377).

The analysis demonstrated that the total amount of these nine fatty acids per lowest daily dosage were very heterogeneous between the test samples and that they varied widely with a factor of about 177 between the minimum and maximum concentration in mono products, respectively with a factor of 38 for combinations.

In general saw palmetto monographs recommend a daily dosage of 320mg lipophilic berry extract with 70-95% fatty acids (17, 40, 146, 147). When this daily dosage of 224-304 mg fatty acids is taken as an acceptable quality standard, then only nine mono-preparations were in this range. Sixteen combinations and five saw palmetto only brands displayed higher daily fatty acid values, five mono and eleven combination items lower quantities.

A too low daily amount of fatty acids may lead to a lack of efficacy, too high concentrations may not results in immediate health hazards as these fatty acids have a very low toxicity (378) and higher dosages of saw palmetto extract for example were still very well tolerated (162) but it makes it impossible to compare these products in terms of their efficacy. If a higher daily dosage of these fatty acids would result in improved efficacy in BPH patients is unclear as clinical data is lacking.

In general there is no need to exceed the recommended dosages for these fatty acids as with 320mg lipophilic saw palmetto extract and with 100mg lipophilic Pygeum africanum extract satisfying results in BPH patients were achieved (17, 40, 119, 146, 147).

A higher dosed long term supplementation with some fatty acids may have negative health effects. Palmitic acid and myristic acid are suspected to be a risk factor for cardiovascular disease (364) and linoleic acid as it is a precursor of arachidonic acid which is converted to prostaglandins can also be pro-inflammatory (372, 373).
Whether increasing the amount of fatty acids by combining saw palmetto with another herbal extract like *Pygeum africanum* or *Urtica dioica* or by fortifying it with vitamins and mineral leads to a better efficacy in treatment of BPH symptoms is doubtful. Studies of products containing saw palmetto and urtica, saw palmetto and *Pygeum africanum* or even a combination of saw palmetto with cernitin, β-sitosterol, and vitamin E showed no better efficacy in reducing BPH symptoms than what is known from saw palmetto mono-preparations (379-381).

The total daily amount of fatty acids is one important quality marker to assess the investigated products. Another one is the relative concentration of each investigated fatty acid to know about the composition of the total fatty acids.

The only quality requirement for the composition of saw palmetto extracts is the demand of the European Pharmacopoeia that saw palmetto extracts must contain at least 20% lauric acid (336). The majority of the evaluated mono preparations fulfilled this criterion, from the combination products only twelve did. There was no clear differentiation between registered and unregistered brands concerning the amount of lauric acid; two food supplements from the UK, SP14 and SP11, presented the highest relative concentrations of lauric acid, one licensed product from Canada, SP37, the lowest ones.

The composition of fatty acids acts like a fingerprint for a preparation and can thus be compared to other products. In Table 9 the mean frequency of the single fatty acids are given for seven ethanolic saw palmetto mono products who fulfilled the criteria of the monographs (SP27, SP30, SP31, SP33, SP35, SP36, SP49; Table 9)(17, 40, 146, 147). For comparison further fatty acid compositions for saw palmetto fruits, other saw palmetto extracts, the average values of all combination products, and other herbal extracts are listed as well.
### Table 9: The frequency of nine fatty acids in different saw palmetto preparations, the whole fruit, and extracts from *Pygeum africanum*, pumpkin seeds, olive, and coconut oil as comparison.

<table>
<thead>
<tr>
<th>%</th>
<th>Capric acid</th>
<th>Caprylic acid</th>
<th>Lauric acid</th>
<th>Myristic acid</th>
<th>Palmitic acid</th>
<th>Linolenic acid</th>
<th>Oleic+/Linoleic acid</th>
<th>Stearic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average monographed saw palmetto mono products (n=7)</td>
<td>2.4</td>
<td>1.93</td>
<td>30.41</td>
<td>12.37</td>
<td>9.76</td>
<td>6.28</td>
<td>35.16</td>
<td>1.69</td>
</tr>
<tr>
<td>Average all saw palmetto mono products (n=19)</td>
<td>2.28</td>
<td>1.69</td>
<td>27.2</td>
<td>10.52</td>
<td>9.92</td>
<td>7.64</td>
<td>37.83</td>
<td>2.91</td>
</tr>
<tr>
<td>Saw palmetto whole fruit (352) (n=143 sites)</td>
<td>2.7</td>
<td>2.7</td>
<td>31.7</td>
<td>12.86</td>
<td>9.79</td>
<td>3.92</td>
<td>34.41</td>
<td>1.83</td>
</tr>
<tr>
<td>Saw palmetto ethanolic extract (382)(Indena)</td>
<td>1.82</td>
<td>2.11</td>
<td>30.86</td>
<td>13.68</td>
<td>10.06</td>
<td>0.92</td>
<td>39.04</td>
<td>1.51</td>
</tr>
<tr>
<td>Saw palmetto CO$_2$ extract (382)(Indena)</td>
<td>2.78</td>
<td>2.36</td>
<td>33.3</td>
<td>12.51</td>
<td>9.26</td>
<td>0.99</td>
<td>36.89</td>
<td>1.9</td>
</tr>
<tr>
<td>Permixon SP12</td>
<td>2.59</td>
<td>1.99</td>
<td>32.04</td>
<td>12.97</td>
<td>9.64</td>
<td>4.2</td>
<td>34.99</td>
<td>1.69</td>
</tr>
<tr>
<td>Hexane/acetone saw palmetto extract 4:1 (v/v) (35)</td>
<td>-</td>
<td>1.2</td>
<td>11.9</td>
<td>10.6</td>
<td>13.5</td>
<td>1.5</td>
<td>59.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Average all combination products (n=27)</td>
<td>2.34</td>
<td>2.55</td>
<td>16.61</td>
<td>6.32</td>
<td>16.05</td>
<td>13.93</td>
<td>31.35</td>
<td>10.85</td>
</tr>
<tr>
<td>Pygeum africanum(382)</td>
<td>-</td>
<td>-</td>
<td>0.38</td>
<td>0.94</td>
<td>28.3</td>
<td>4.3</td>
<td>55.5</td>
<td>10.58</td>
</tr>
<tr>
<td>Cucurbita(382)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.24</td>
<td>-</td>
<td>79.76</td>
<td>-</td>
</tr>
<tr>
<td>Cucurbita (383)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4-14</td>
<td>-</td>
<td>0:21-47</td>
<td>L:35-59</td>
</tr>
<tr>
<td>Coconut oil (383)</td>
<td>6.4</td>
<td>8.0</td>
<td>48.5</td>
<td>17.5</td>
<td>8.4</td>
<td>1.5</td>
<td>6.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Olive oil (383)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12.2</td>
<td>0.9</td>
<td>84.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Andy Suter* 125
Interestingly, the average fatty acid frequencies of the seven mono products comply almost exactly with the values given for the whole fruit by Bubrick et al. (352) who investigated saw palmetto berries collected from 143 sites in Florida. An ethanolic and a CO₂ saw palmetto extract analysed by Ganzera et al. also showed similar results like the average frequencies of the seven mono preparations only with a smaller linolenic acid content (382).

The hexane extract Permixon® displayed in our analysis an almost congruent fatty acid pattern compared to the seven ethanolic extracts and similar values for lauric, myristic, oleic, and linoleic acid as reported in literature (47).

Only a hexane/acetone standard extract which was developed by the U.S. American National Institute of Standards and Technology in cooperation with the Food and Drug Administration FDA presented a different fingerprint than the mentioned extracts. It had almost threefold less lauric acid than the ethanolic extracts but almost twice as much oleic and linoleic acids and more palmitic acid (35).

Mature saw palmetto fruits yield twice as much lauric acid than immature fruits, very mature fruits contain more oleic acid than lauric acid (377). The pattern from the eight ethanolic preparations showed that the majority of the manufacturers of the extracts obviously used the same mixture of immature and mature fruits and that they were a mixture from all regions of Florida as the fatty acid pattern varies significantly between the different regions in Florida (352). The only samples that differed from the average fatty acid content were SP34, SP54, and SP8 which contained more oleic/linoleic acid than the other test items. This could be due to using more very mature fruits and/or that they were from one cultivation where the berries contain more oleic acid. In an unpublished report Berries from central Florida displayed a twice as high laureate to oleate ratio compared to samples from northern Florida (377). Bubrick et al. found also geographic variation in the content of oleic to lauric acid throughout Florida, they observed the highest ratio in a cultivation towards central Florida but the lowest ratio in a plantation on the East coast of Florida. Interestingly, the amount of β-sitosterol, campesterol, and stigmasterol remained throughout the saw palmetto berries samples of 143 investigated sites in Florida almost the same (352).
One test item, SP37, showed a very high concentration of linolenic acid which is unusual for saw palmetto berries, this product was suspected to be adulterated with another plant oil (383). A later inspection of the package showed that it contained soy bean oil which was mentioned as an excipient but not as an active, this oil is rich linolenic acid (384).

With this fingerprint, the mono preparations could well be distinguished from combination products as they offered in the average a different fatty acid pattern. In general combination products had lower amounts of lauric and myristic acid but higher amounts of palmitic, linolenic, and stearic acid. These differences could be mainly contributed to fatty oils from Pygeum africanum and Cucurbita pepo extracts which are known to contain more linolenic and stearic acid than saw palmetto extracts.

Saw palmetto is unique in its composition of fatty acids if one compares it for example with the amount of fatty acids of coconut and olive oils (Table 9).

In summary, an extract can well be characterised by its composition of fatty acids which acts like a fingerprint for a product.

Thus, to guarantee a good extract quality I would propose that not only the minimum percentage of lauric acid should be recommended by the pharmacopoeia but also minimum relative amounts from other important fatty acids like oleic and myristic acid. A broader analysis of saw palmetto mono preparations with known extraction conditions could define where the margin would lie. This analysis and data from literature in Table 9 show that for ethanolic extracts an amount of at last 30% oleic and 10% myristic acid could be suitable.

Nevertheless, the GC method applied is limited as only fatty acids could be analysed. Other substances like β-sitosterol (127, 385) or β-carotene (386) which influence symptoms associated with BPH positively should also be determined in these extracts and a certain amount could be required as quality marker as well. In particular β-sitosterol which exerted in vitro a positive influence on several mechanism associated with BPH as showing antiandrogenic (385), apoptotic (387), and antiinflammatory (388)
activity and for which at least in higher dosages also clinically significant improvements of BPH symptoms could be shown (127) is a good further quality marker besides the fatty acids. As a clinical trial with 0.3mg β-sitosterol per day showed no clinical efficacy in BPH patients (122) the amount of about 1mg β-sitosterol/g which can be found in saw palmetto extracts (340) is obviously not the main active principle of a berry extract but may have an positive supportive role in improving LUTS.

Whether β-sitosterol was present in the test items could not have been detected using our TLC-system, the method used in this thesis was solely for the identification of saw palmetto preparations. The majority of the preparations showed a signal with similar Rf of the β-sitosterol reference but they were often rather large dark spots in contrast to the the violet-pink zone which is characteristic for β-sitosterol (336), they contained most probably fatty acids and their esters.

A more precise way by using TLC to determine the presence of β-sitosterol would be to quantify its amount densitrometrically. Numerous validated TLC methods are described in literature but mainly for plants containing only a small amount of fatty acids or triglycerides. To use one of these methods, our test items must have been prepared previously to omit the fatty acids and its esters for example by extraction with hexane. These prepared test items could be applied on silica gel plates (F254 HPTLC plate with 60Å pore size) using toluene:chloroform:methanol (4:4:1 [v/v/v]) as mobile phase with β-sitosterol as control. After derivatisation with anisaldehyde-sulphuric acid reagent Murthy et al. could quantify the amount of β-sitosterol from the Indian medical plant Mucuna pruriens densitographically at 527nm by comparing it to a calibration curve with β-sitosterol (389). A similar technique was described by Sparzak et al. who showed a robust and validated method for identification and quantification of β-sitosterol in Phyllanthus species by using the same plates as mentioned above with a mobile phase consisting of chloroform:hexane:methanol (65:30:5 [v/v/v]) and subsequent derivatisation with vanillin reagent. Compared to a calibration curve with different β-sitosterol concentrations densitrometrically at 525nm wavelength they determined the amount of β-sitosterol in each test item (390).
Also, various HPLC (391, 392) and gas chromatographic methods are available for the separation, identification, and quantification of phytosterols whereas GC, often combined with mass spectrometry is the method of choice these days to determine phytosterols. There are several standardized GC methods for phytosterol analysis available which are approved by for example the German government (393), the Association of Official Analytical Chemists (AOAC)(394) or the International Organisation for Standardisation (ISO)(395). A common principle for the analysis of phytosterols is that the test samples are saponified at high temperature with ethanolic KOH solution to obtain the free sterols. The unsaponifiable fraction containing phytosterols is then extracted with toluene, reduced and the phytosterols are derivatized to trimethylsilyl (TMS) ethers so they become volatile. They are then quantified by gas chromatography (GC) with hydrogen flame ionization detection (FID) (36). Samples that contain 50-150μg of a mixture of phytosterols can well be analysed (396).

A survey on the concentration of the phytosterols campesterol, stigmasterol, and β-sitosterol in different preparations containing saw palmetto has already been carried out by Sorenson et al. in 2006 (340). Since the amount of these three phytosterols is similar in saw palmetto berries from all over Florida (352) the major influencing factor in saw palmetto mono-preparations is the extraction method used (Table 10). An alcohol-free extract and a liquid extract had the lowest phytosterol quantities, a CO₂ extract the highest amounts. Two ethanolic extracts, Prostasan and ProstActive capsules, also investigated in our survey, exerted similar phytosterol values. The combination with pygeum increases the amount of β-sitosterol but seemingly not of campesterol and stigmasterol (340).
Table 10: Mean content of the phytosterols campesterol, stigmasterol and β-sitosterol in different preparations containing saw palmetto according to (340).

<table>
<thead>
<tr>
<th></th>
<th>Campesterol</th>
<th>Stigmasterol</th>
<th>β-sitosterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saw palmetto 45% powdered extract</td>
<td>0.35</td>
<td>0.17</td>
<td>1.09</td>
</tr>
<tr>
<td>Alcohol-free saw palmetto</td>
<td>0.025</td>
<td>0.013</td>
<td>0.069</td>
</tr>
<tr>
<td>Liquid herbal extract: saw palmetto</td>
<td>0.019</td>
<td>0.014</td>
<td>0.076</td>
</tr>
<tr>
<td>ProstActive once daily (A SP49)</td>
<td>0.363</td>
<td>0.193</td>
<td>1.07</td>
</tr>
<tr>
<td>ProstActive Plus saw palmetto with stinging nettle</td>
<td>0.334</td>
<td>0.099</td>
<td>1.22</td>
</tr>
<tr>
<td>Prostasan capsules (A SP10)</td>
<td>0.395</td>
<td>0.201</td>
<td>1.12</td>
</tr>
<tr>
<td>Pygeum and saw palmetto</td>
<td>0.223</td>
<td>0.087</td>
<td>2.73</td>
</tr>
<tr>
<td>Saw palmetto pygeum lycopene complex tablets</td>
<td>1.17</td>
<td>1.04</td>
<td>2.76</td>
</tr>
<tr>
<td>Saw palmetto CO₂ extract</td>
<td>0.554</td>
<td>0.286</td>
<td>1.74</td>
</tr>
<tr>
<td>Saw palmetto berry</td>
<td>0.054</td>
<td>0.040</td>
<td>0.322</td>
</tr>
</tbody>
</table>

Even though the quantification of another active substance like β-sitosterol in the test samples would have given additional information, we decided to use a different approach for further assessment of the preparations.

Our method of choice was proton-NMR-spectroscopy and PCA for statistical evaluation. This allows not only to focus on one or two substance groups like fatty acids or phytosterols but on all with NMR detectable constituents. By using the statistical procedure of PCA, preparations with similar characteristics can be grouped in clusters. In the Master thesis of Tony Booker which was the first to use this methodology to evaluate different products containing saw palmetto, he could arrange preparations with similar compositions and could identify outliers. He showed that SP12, SP26, SP34, and SP37 did not belong to a cluster. The difference to other extracts was most probably explicable as SP12 contained polyoxethylene glycol as excipient, SP26 used super critical fluid extraction, SP34 had added extra, glycerine, carob, and zinc oxide,
and SP37 additionally to the saw palmetto extract soy bean oil and glycerine as was already discussed in the fatty acid analysis.

For a broad analysis of saw palmetto products the method is superior to GC-analysis as it is not only robust, easy to apply but has the asset that with PCA a statistical method is applicable with which in short time relationships between different preparations can be assessed.

To compare the results from the NMR-analysis from single substances with the ones from the GC analysis is difficult as one identified substance, caproic acid ethyl ester was not determined with GC. However, in general, the ethanolic mono-preparations which were similar in the GC analysis were also related in the PCA of the proton-NMR-analysis.

Further work on the NMR-methodology is thus recommended with more products to have more data to form more and clearer clusters to differentiate the various products on the markets as well as outliers.

However, whether an extract with a certain composition is efficacious can in the end only be shown in a clinical trial. *In vitro* testing of preparations, focussing mostly on one assay only like inhibition of the 5-alpha-reductase may give an idea about the clinical efficacy but can not exclude nor predict a clinical outcome (34, 338).

Looking at it from a patient's perspective, the results of this phytochemical study are even of greater importance. A BPH patient buying an unregistered food supplement containing saw palmetto which is marketed for treatment of prostate problems has no certainty what kind of quality or quantity of active constituents he receives as they are mostly not declared on the package. And when they are stated, then in case of the saw palmetto mono preparations sold as food supplements they were in the majority faulty. This finding is in accordance with the analysis of Feifer et al. (337) who showed that only three of six investigated saw palmetto preparations from the U.S.A. presented the amount of fatty acids correctly. Another survey published in the American journal 'Consumer Reports' reported that of 13 assessed brands containing saw palmetto only eight complied with the declared amount (397).
Saw palmetto serves consequently as a good example for discussion if herbal preparations should be on the market as unregulated food supplements or as registered medicinal products.

From a legal perspective, in Europe food supplements are defined as 'concentrated sources of nutrients or other substances with a nutritional or physiological effect, whose purpose is to supplement the normal diet' (398), they are not intended for treatment of diseases but to maintain 'functions of the organism or to support health' (399). Medicinal products are by definition of the European Union 'substances or combination of substances for treating or preventing disease in human beings or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions' (400).

Saw palmetto preparations are used to treat symptoms of BPH which is a disease (401) and therefore should be regarded at least from a legislative point of view as medicinal products and be registered. This regulatory framework applies not only for prescription but also for non-prescription medication, the over-the-counter (OTC) products to which herbal medicines belong (402).

Nevertheless, one could still argue that food supplements and herbal products are both moderately efficacious and well tolerated and for that reason phytomedical preparations should be available as food supplements. This would reflect for example the U.S. American or Dutch situation for herbal medicinal products.

Regarding the heterogeneous results from this phytochemical analysis of saw palmetto products I favour the approach to register these preparations also based on the following considerations.

A registration allows not only to use an herbal product in a certain indication but demands from the manufacturers to adhere to high quality requirements. The quality part of a registration dossier for a traditional herbal medicinal product demands the same data on quality as for any synthetical medication. This includes not only validated production processes but also that a manufacturer has to provide stable products with same uniformity of dose (402).
Like this, the customer is protected from incorrect declarations on the packages and is assured to obtain a good quality product for his or her disease. With the situation present in many countries where herbal products are unregulated, patients are often mislead regarding the amount of active constituents and declarations as could be shown in this phytochemical analysis.

An often heard argument from opponents of a regulation for herbal medicinal products is that this would confine the patient’s freedom of choice for natural medicines and that rather the public needs to be educated to differentiate between good and low quality products instead of registering them (403). These arguments are in reality nothing more than excuses from companies which cannot provide good quality nor clinical data for their preparations. A registration would answer the question about the quality of a product and is much easier to carry out than a public education of consumers.

Another reason why I advocate the registration of Sabal preparations and herbal medicinal products is that they show generally moderate efficacy with a very good safety profile. To guarantee this at least mite efficacy a good product quality is mandatory, this can be reached best by registrations.

With this good benefit/risk ratio, herbal medicinal products could become at least in Europe an interesting treatment alternative to synthetical drugs for several mild to moderate disorders. It would be a pity if patients could not profit from this therapy option - due to lack of quality.
Chapter 4

A clinical pilot study with saw palmetto in patients with BPH and concomitant sexual dysfunctions
Chapter 4: Clinical pilot study

A clinical pilot study with saw palmetto in patients with BPH and concomitant sexual dysfunctions

4.1 Introduction

The first U.S. American physicians using saw palmetto discovered that the plant was not only efficacious in respiratory tract infections and genitourinary disorders but also as treatment for sexual dysfunctions (SDys).

As outlined in chapter 2.3.2.3.2, already in 1880 the pharmacist Dixon indicated the use of Sabal for ‘sexual debility’ (233), in 1885 a doctor Evans wrote that the plant had a good effect on ‘wasting of the testes’, in his view the reason for impotence (167), and Knapp in 1892 (235) and Davidson in 1895 (230) substantiated Sabal as treatment of male SDys such as impotence or lack of drive. Also in current literature saw palmetto is often cited as a herbal treatment for testicular atrophy (404, 405) and for erectile dysfunctions (406) or as an aphrodisiac (407).

Nevertheless, even though the properties of saw palmetto on SDys are known only a few clinical studies assessed this topic. Therefore I carried out a clinical pilot trial in BPH patients with concomitant SDys to evaluate if a saw palmetto treatment could improve BPH and SDys symptoms as well.

In the following, an overview is given about the epidemiology of male SDys, their relation to BPH, the possible underlying pathophysiology, the detrimental effect of BPH standard medication on SDys, and clinical data of saw palmetto in SDys.
4.1.1 Epidemiological data of SDys in the elderly male population

Generally, sexual functions are divided into the four domains desire (libido), erection (arousal), ejaculation (force, volume) and orgasm/satisfaction (408). Until the beginning of the new millennium, it was assumed that SDys, meaning dysfunctions of one of the above mentioned four domains in men are a natural consequence of the ageing process. Recent studies showed that a decrease in sexual functions is not inevitably a consequence of ageing (409). A variety of large-scale epidemiological studies showed that BPH in particular is an important factor for SDys.

In a large epidemiological survey with 15’496 men aged between 40-69 years a clear correlation between age and erectile dysfunctions and lack of libido was shown. Whereas more than 60% of men aged 40 stated no erectile problems, only about 10% of all men in the age group of 65-69 years were in the identical situation. The same went for libido where 60% of all around 40 year old faced no problems but only around 18% of all men aged 65-69 years had still a good libido. The study did not investigate the prevalence of LUTS as well but acts as a good marker for the general prevalence of SDys. Interestingly, men with moderate to severe sexual problems were up to three times more frequently seeing a doctor than those with none or light symptoms (410).

The most comprehensive trial to date which investigated LUTS and SDys was the Multinational Survey of the Ageing Male (MSAM-7) study in 2003 with 12’815 men aged between 50 and 80 years from the USA and six European countries. About 49% of all men experienced erectile dysfunctions with a higher proportion in the USA (55%) compared to Europe (45%) and around 45% of all patients suffered from ejaculatory dysfunctions. LUTS were prevalent in around 90% of all patients. The more severe the symptoms of LUTS, the more frequent and more severe the mentioned SDys occurred. Age and LUTS were stronger risk factors for erectile dysfunction and ejaculatory disorders than diabetes, hypertension, heart disease, or hyperlipidaemia (411).
In a large study carried out in Germany, the Cologne Male Survey, which examined 4489 men between 30 to 80 years, the overall prevalence of erectile dysfunctions was 19%. Interestingly, the incidence of LUTS was 72% in patients with erectile dysfunctions versus 38% in those without erectile dysfunctions. In addition to age, diabetes, hypertension, and pelvic surgery, LUTS was seen as an independent risk factor for erectile dysfunction (412).

The same findings were observed in the UrEpik study which assessed the relationship between erectile dysfunction and LUTS in 4800 men from the United Kingdom, the Netherlands, France, and Korea. Erectile disorders were present in 21% of all men which was significantly associated with age (p>0.001) and LUTS was seen as an important co-factor for erectile dysfunctions and lack of libido (413).

LUTS as an important and independent comorbidity for erectile dysfunction was also shown in a survey investigating 2476 men between 25-70 years in Spain (414) and a study with 2412 men from Brazil, Italy, Japan and Malaysia aged 50 to 78 years also reported that LUTS were the most significant predictor of moderate to severe erectile dysfunctions (415).

Overall, the epidemiological studies presented a clinically significant association between LUTS and various types of SDys in ageing men worldwide.

Rosen assumed from the epidemiological data that the relative risk of developing erectile dysfunction is 3.7 higher in patients with BPH-symptoms than those without symptoms in a time period of two years after first reporting them (409).
4.1.2 Pathophysiology of sexual dysfunctions and BPH

The pathophysiologic mechanisms which lead to erectile dysfunction, ejaculatory disorders, and lack of libido after enlargement of the prostate are still not clear and yet not very well investigated.

There are several hypotheses on possible mechanisms of action for SDys caused by BPH. One theory assumes that an imbalance in the autonomic control of smooth muscle contraction may lead to SDys. The main reason for this might be an over­presence of α1-adrenergic receptors in patients with LUTS in the prostatic capsule and the bladder neck which results in an increased smooth muscle tone (416). Noradrenaline is involved in the contraction of the penile tissues, in particular the corpus cavernosum smooth muscle, via activation of α1-adrenergic receptors which are most probably regulated by androgens (417). Any impairment of these receptors may therefore lead to erectile dysfunctions and ejaculatory disorders (409), also since contraction and growth of vascular smooth muscle cells are mediated by α1-adrenergic receptors (418).

Another hypothesis states that endothelial dysfunction is a possible mechanism which refers to impaired endothelium dependent relaxation (i.e. vasodilatation) due to decreased activity of nitric oxide (NO) (419). Noradrenaline acts as the major sympathetic neurotransmitter, whereas NO is the major parasympathetic neurotransmitter. To produce an erection, the balance has to change: The noradrenaline effect must be minimised and the NO effect increased (420).

In prostatic tissue from men with BPH, the innervation which leads to NO secretion (nitrergic innervation) is decreased compared to normal prostatic tissue assuming that this change in the endothelium leads to erectile dysfunctions (421).

A further risk factor to decrease endothelial function is chronic inflammations (422). Since low grade systematic inflammations seem to be the connection between metabolic syndrome, coronary artery diseases and erectile dysfunctions, anti-inflammatory therapy might be an additional treatment option for erectile problems (423).
Another theory assumes that a change in sex hormones impacts sexual functions. Data from a longitudinal study, the Massachusetts Male Aging Study, with 1290 men aged 40 to 70 years, showed that the serum levels of total testosterone, dehydroepiandrosteron, cortisol, and oestrone decreased, whilst the levels of DHT, sex hormone binding globuline, luteinizing hormone and prolactin increased during an observation period of seven to ten years (424). Since hormones itself are produced and secreted in one tissue but have the ability to regulate or induce signal cascades in their target tissues either by enzyme activities or by the receptors (425) it is assumed that a change in the concentration of these hormones may have an influence in the pathophysiology of BPH and sexual dysfunctions (409).

If it is correct, that LUTS/BPH and SDys share a common mechanism, the optimal treatment strategy would be a single agent which improves both conditions (411). Our pilot study with saw palmetto tried to assess if saw palmetto could be one of these desired therapies.

4.1.3 Sexual adverse events of BPH standard medication

As outlined in chapter 1.4.1.4, the main medical treatments for BPH symptoms include alpha blockers such as tamsulosin, doxazosin, and alfuzosin (117) which provide fast relief of LUTS symptoms (131) or the 5-alpha-reductase-inhibitors finasteride and dutasteride, which lead to symptom relief after 6-9 months and are most favourable in patients with large prostates (106). Both treatment options show beneficial effects on BPH symptoms; however, they also each have a significant negative impact on sexual functions.

The main SDys reported under alpha blocker therapy were retrograde or abnormal ejaculation, which occurred in 4-18% of patients taking tamsulosin, with rise to 30% during long term use (426), under silodosin treatment a rate of ejaculatory disorders of 28% ensued (427). Studies on 5-alpha-reductase inhibitors stated SDys with a frequency of 2.1% to 38%, with erectile dysfunctions being most prominent, followed by decreased libido and ejaculatory disorders (428). SDys were the most often observed
adverse events under 5-alpha-reductase-inhibition, with similar frequencies reported for finasteride and dutasteride (429).

The latest American Urological Association guideline on treatment of BPH recommended the combination of an alpha blocking agent with a 5-alpha-reductase-inhibitor for better efficacy but neglecting safety (197). Two trials assessing combination treatments, one with dutasteride and tamsulosin (430), the other with finasteride and doxazosin (134) showed that the incidence of sexual adverse events was higher in the combinations than with monotherapy alone.

Summarised, a BPH patient is at a significant risk to cause or deteriorate existing SDys by taking one or a combination of these standard therapies for prostate problems.

4.1.4 Data from clinical studies on saw palmetto in SDys

Five previous clinical trials of saw palmetto treatment for BPH also evaluated changes in SDys as a secondary parameter, with mixed results. However, patients in these trials had mainly BPH symptoms, not necessarily SDys as well. Using the International Index of Erectile Function (IIEF), Willetts, 2003 observed a trend of improvement, with an increase from 51.5 to 55.1 after 12 weeks of saw palmetto treatment compared to a small decrease from 49.4 to 48.7 with placebo (431), and Sinescu et al. reported under saw palmetto a significant improvement of the IIEF from 44.4 to 50.8 after 24 months of treatment (432). In the trial conducted by Gerber (2001) patients had to fill out a non-specified “sexual function questionnaire” which did not change either with placebo or saw palmetto (433). In an open study, Bauer (1999) asked if the treatment had an influence on patient’s “sexual activity”; responses indicated that it mostly remained unchanged with two patients reporting an increase (160). The placebo controlled Sabal study from Barry et al. observed after 72 weeks of treatment no change in IPSS and urinary flow rates and also not in the IIEF erectile function subscale (p=0.29) and in the Male Sexual Health Questionnaire to assess ejaculatory dysfunction MSHQ-EJD (p=0.16) (162).

Taken together, data from these trials is insufficient to show convincingly that saw palmetto had a positive influence on BPH-related SDys.
4.1.5 Summary and Study Rationale

Epidemiological studies gave evidence that BPH is one of the strongest co-factors to cause SDys in the ageing male population. Standard therapies for BPH symptoms like alpha-blockers or 5-alpha-reductase inhibitors cause frequently sexual adverse events and may so deteriorate existing SDys. Thus, therapies are sought which are efficacious and safe in the treatment of BPH symptoms and SDys as well.

Historically saw palmetto was also used as treatment of male SDys but clinical trials could not confirm efficacy in this indication so far for Sabal. In all the above discussed saw palmetto studies, BPH symptoms were always the primary parameter which means the patients could have suffered from SDys but they were never mandatory an inclusion criterion.

Thus, the pilot trial presented here is the first study ever to investigate if saw palmetto is efficacious and safe as treatment of SDys in BPH patients.
4.2 Material and Methods

4.2.1 Study design

The trial was initiated by the urologist Dr. Eugen Riedi, then head of the urology department at the Kantonsspital Chur, Switzerland. He observed that BPH patients he had prescribed a saw palmetto treatment often reported an improvement in their concomitant SDys. Together with him and Prof. Reinhard Saller, head of the Institute of Complementary Medicine of the University hospital of Zurich, the study design was set up (Table 11).

As this was a pilot trial to gain data for generation of hypotheses for a larger study an uncontrolled study design was chosen. This open design was in accordance with other pilot studies on SDys in BPH patients, for example from alpha blocking agents (434, 435).

The study period for our trial consisted of a one-week untreated run-in phase and a subsequent treatment period of eight weeks. At each visit, efficacy parameters were recorded as detailed below. The run-in phase was carried out to observe if BPH symptoms and SDys remained stable. The treatment duration of eight week was chosen since in other saw palmetto trials after this period already good results were observed (118, 436).
Table 11: Study design of the pilot study with saw palmetto on SDys in BPH patients (Prostasan® Libido trial)

<table>
<thead>
<tr>
<th>Title</th>
<th>Clinical pilot trial to investigate the influence of a saw palmetto berry preparation (Prostasan®) on sexual functions in patients with benign prostatic hyperplasia (Prostasan® Libido trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>IV (IIib)</td>
</tr>
<tr>
<td>Study number</td>
<td>920'136</td>
</tr>
<tr>
<td>Principal investigator</td>
<td>Dr.med. Eugen Riedi, urologist, Chur, Switzerland</td>
</tr>
<tr>
<td>Other study centres</td>
<td>About ten GPs or urologists in the cantons of Zurich, Berne, Grisons, St. Gallen and Zug in Switzerland</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>For each investigator: 500 Swiss francs/patient; for each patient: 100 Swiss francs/patient</td>
</tr>
<tr>
<td>Study duration per patient</td>
<td>1 week untreated, run-in phase; 8 weeks with treatment (56 ± 5 days), total 9 weeks</td>
</tr>
<tr>
<td>Number of patients</td>
<td>At least 40 patients</td>
</tr>
<tr>
<td>Medication, dosage</td>
<td>1x1 capsule Prostasan® daily (320mg extract per capsule, 96%V/V ethanolic Serenoa repens berries extract)</td>
</tr>
<tr>
<td>Study design</td>
<td>Open multicentric clinical trial (planned to generate hypothesis for a larger trial, thus a pilot trial)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Patients with BPH and sexual dysfunctions (erectile dysfunction and/or decrease of libido) which existed for at least two months and are defined by:</td>
</tr>
<tr>
<td></td>
<td>• Age 18-80 years old</td>
</tr>
<tr>
<td></td>
<td>• International Prostate Symptom Score IPSS Score &gt;7</td>
</tr>
<tr>
<td></td>
<td>• Sexual drive from bSFI (brief Sexual Function Inventory) &lt;5</td>
</tr>
<tr>
<td></td>
<td>• Patient is not satisfied with his sexual performance</td>
</tr>
<tr>
<td></td>
<td>• Notion and possibility to practise his sexuality (masturbation, intercourse)</td>
</tr>
<tr>
<td></td>
<td>• No organ-dependent damages which rule out the performance of sexual activities.</td>
</tr>
<tr>
<td></td>
<td>• Willingness to answer honestly to questions on sexuality</td>
</tr>
<tr>
<td></td>
<td>• Written informed consent</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>- Lack of libido which is due to a psychiatric disease or a depressive mood</td>
</tr>
<tr>
<td></td>
<td>- Lack of libido in the judgment of the investigator within the last two months</td>
</tr>
<tr>
<td></td>
<td>- Patients with severe vascular disorders (microangiopathies)</td>
</tr>
<tr>
<td></td>
<td>- Severe diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>- Patients with hypertension who are on a stable antihypertensive medication for less than two months</td>
</tr>
<tr>
<td></td>
<td>- Known neuropathies</td>
</tr>
<tr>
<td></td>
<td>- Known bad compliance of the patient</td>
</tr>
<tr>
<td></td>
<td>- Participation in a clinical trial within the last 2 month before study start</td>
</tr>
<tr>
<td></td>
<td>- Alcohol, drugs-abuse</td>
</tr>
<tr>
<td></td>
<td>- Planned surgeries within the observation time</td>
</tr>
</tbody>
</table>
## 4.2.2 Investigators

More than 50 physicians in Switzerland were asked with a letter to participate in the trial and followed up with a personal contact, in the end nine doctors agreed to take part. Together with the main investigator, the urologist Dr. Eugen Riedi, a total of three urologists and seven general practitioners were the study centres.

## 4.2.3 Patients

Eligible were ambulatory patients with a confirmed BPH diagnosis with at least moderate symptoms measured with an IPSS>7 and not older than 80 years. They had to fulfil the inclusion and the exclusion criteria as given in Table 11 and sign the informed consent form after having read the detailed patient information on the study. The participants were recruited by their physician, in each practice leaflets and a poster about the trial were displayed to attract study participants.

<table>
<thead>
<tr>
<th>Not allowed concomitant medication:</th>
<th>Illicit concomitant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>with the exception of stable application since at least 3 months:</td>
<td>All of the following medication is not permitted if it has not been taken stable for at least during three months:</td>
</tr>
<tr>
<td>- Application of 5-alpha-reductase inhibitors</td>
<td>- 5-alpha-reductase-inhibitors</td>
</tr>
<tr>
<td>- Application of alpha-antagonists</td>
<td>- alpha-blockers</td>
</tr>
<tr>
<td>- Long-term application of NSAIDs (synthetics and phytochemicals) and paracetamol</td>
<td>- long term intake of synthetical and herbal NSAID and paracetamol as well as synthetical antidepressants</td>
</tr>
<tr>
<td>- Application of synthetic antidepressive agents</td>
<td>- Continuous intake of phosphodiesterase-inhibitors, defined as more than one unit/ two weeks, and intake of a phosphodiesterase-inhibitor less than four days prior to the first study visit</td>
</tr>
</tbody>
</table>
4.2.4 Study medication

The patients received at the second visit a brown glass with 90 capsules of Prostasan®. One capsule contained 320mg saw palmetto berry extract (batch: 025070) which was extracted with 96% ethanol (V/V) and had a DER of 9.0-12.0 : 1. The berries were from A.Vogel Bioforce's own organic certified cultivation in Florida, USA. Patients had to take one capsule daily after eating, the time point for intake was not defined. The compliance was checked by counting the remaining tablets at the final study visit.

4.2.5 Questionnaires

4.2.5.1 Questionnaire for BPH symptoms

The main symptoms of BPH, which include static and dynamic components (100), are increased frequency of urination with nocturia, difficulty starting and stopping urination, weak urine stream, feeling that the bladder has not emptied completely with residual urine, and in later stages urinary retention and painful urination (101). The International Prostate Symptom Score IPSS is the validated standard instrument to measure the severity of these symptoms (99) (Table 12). The investigator needed to fill it out with the patient which takes about 10-15 minutes time. A validated German version was available and used in this trial (437).
Table 12: The International Prostate Symptom Score IPSS (99)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incomplete emptying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>had a sensation of not emptying your</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bladder completely after you finish</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urinating?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>had to urinate again less than two hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>after you finished urinating?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Intermittency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>found you stopped and started again</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>several times when you urinated?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Urgency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the last month, how difficult have</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>you found it to postpone urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Weak stream</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>had a weak urinary stream?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Straining</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>had to push or strain to begin urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Nycturia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, many times did you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>most typically get up to urinate from the</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time you went to bed until the time you</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>got up in the morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A total score of 0-7 indicates mild, 8-18 moderate, and above 18 points severe BPH symptoms. To assess irritative symptoms the points of questions 2, 4, and 7 are summarised and for the obstructive symptoms the scores are added of the questions 1, 3, 5, and 6. Nocturia is evaluated only with the single score of question 7.
4.2.5.2 Questionnaires for sexual dysfunctions

Attempts to measure human sexual functions appeared first in literature in the early 1960's (438). The central problem lied first in the definition of a SDys since sexual functioning, hypoactive sexual desire disorder, and sexual satisfaction are merely hypothetical constructs. Therefore the measurement of these parameters and the instruments used are generally not as powerful as those used in physical sciences (439). The current instruments, namely questionnaires, are mostly a product of the thinking of Masters and Johnson (440, 441), a team which pioneered in the research of diagnosis and treatment of SDys, and Helen Kaplan who examined hypoactive sexual desire and so called 'inhibited sexual desire' (442). With their knowledge the sexual response cycle was defined which strongly emphasized on the above mentioned phases of desire, arousal, orgasm, and resolution (408). In this model a dysfunction or disturbance may occur in any or multiple phases of the cycle and the diagnosis is usually made without statement of the aetiology (439).

For setting up the design of this clinical trial, I investigated and compared available validated questionnaires for male SDys which are discussed in the following.

4.2.5.2.1 The Derogatis Interview for Sexual Functioning (DISF/DISF-SR)

The Derogatis Interview for Sexual Functioning (DISF/DISF-SR) is an instrument designed to assess an individual current sexual functioning. It consists of 25 questions and is available for men and women as separate issues and covers five separate domains which are sexual cognition/fantasy, sexual arousal, sexual behaviour/experience, orgasm and sexual drive (443). As this score is also dedicated to areas such as relationship and behaviour but not mainly on male SDys and is with 25 questions too long to apply, it was not selected for the planned clinical trial.
4.2.5.2.2 The Arizona Sexual Experience Scale (ASEX)

The Arizona Sexual Experience Scale (ASEX) is a self-reporting inventory to evaluate SDys in men and women covering the items drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm (444). The limitations of this instrument are that it was developed for patients taking psychotropic drugs and not many epidemiological data is available.

4.2.5.2.3 The International Index of Erectile Function (IIEF)

The International Index of Erectile Function (IIEF) has become the standard questionnaire in assessing erectile dysfunctions and was used so far in more than 50 clinical trials (439). Patients have to fill out 15 questions covering erectile function, orgasmic function, sexual desire and satisfaction, and overall satisfaction (445). Even though this instrument is sensitive, highly reliable and also very well available, it was not selected for this trial as it only focuses on erectile functions.

4.2.5.2.4 Urolife BPH QoL-9-questionnaire

A simple, reliable instrument for the measurement of SDys related to BPH is the subscale for ‘patient’s perceived sexual life’ of the Urolife BPH Quality of Life 9-questionnaire (Figure 21). The total score consists of nine questions covering quality of life items, the subscore on SDys consists of three questions covering sexual desire, satisfaction with erections, and satisfaction with sex life which have to be answered on a 10 cm visual analogue scale (446). The score ranges from 0 to 300 or from 0 to 30. The Urolife BPH QoL-9 ‘patient’s perceived sexual life’ subscale is recommended for the evaluation of SDys in BPH (447), easy to apply, and validated patient data from a large trial with 2289 men with BPH are available (448). Due to its validity and easy application, I decided to use this instrument in this pilot trial with saw palmetto. In the following, this ‘patient’s perceived sexual life’ subscale will be abbreviated as ‘Urolife BPH QoL-9 sex’.

---

Andy Suter
Figure 21: Urolife BPH QoL9-subscale ‘patient’s perceived sexual life’ (from (446)). Patients have to mark the intensity of the corresponding item.

<table>
<thead>
<tr>
<th>Currently your sexual desire is</th>
<th>You are satisfied with your erections</th>
<th>You are satisfied with your sex life</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRONG</td>
<td>VERY SATISFIED</td>
<td>FREQUENTLY</td>
</tr>
</tbody>
</table>

WEAK NOT SATISFIED AT ALL RARELY

4.2.5.2 brief Male Sexual Function Inventory (bSFI)

The other questionnaire chosen for this study to assess efficacy was the brief Male Sexual Function Inventory (bSFI). It consists of two questions on sexual drive, three on erections, two on ejaculations, three on problems in each area, and one on overall satisfaction (Figure 22). The instrument is easy to apply, well understandable and takes about 10-15 minutes per patient to fill out alone.
### Figure 22: The brief Sexual Function Inventory bSFI questionnaire (4)

<table>
<thead>
<tr>
<th></th>
<th>Sexual Drive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Let's define sexual drive as a feeling that may include wanting to have a</td>
</tr>
<tr>
<td></td>
<td>sexual experience (masturbation or intercourse), thinking about having sex,</td>
</tr>
<tr>
<td></td>
<td>or feeling frustrated because of lack of sex.</td>
</tr>
<tr>
<td></td>
<td><strong>1. During the past 30 days, on how many days have you felt sexual drive?</strong></td>
</tr>
<tr>
<td></td>
<td>None at all</td>
</tr>
<tr>
<td></td>
<td>Only a few days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>2. During the past 30 days, how would you rate your level of sexual drive?</strong></td>
</tr>
<tr>
<td></td>
<td>None at all</td>
</tr>
<tr>
<td></td>
<td>Only a few days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Erections</strong></td>
</tr>
<tr>
<td></td>
<td>Over the past 30 days, how often have you had partial or full sexual erections when you were sexually stimulated in any way?</td>
</tr>
<tr>
<td></td>
<td>None at all</td>
</tr>
<tr>
<td></td>
<td>Only a few days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Over the past 30 days, when you had erections, how often were they firm enough to have sexual intercourse?</td>
</tr>
<tr>
<td></td>
<td>Did not get erections at all</td>
</tr>
<tr>
<td></td>
<td>Only a few days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>5. How much difficulty did you have getting an erection during the past 30 days?</strong></td>
</tr>
<tr>
<td></td>
<td>Have had no sexual stimulation in past month</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ejaculation</strong></td>
</tr>
<tr>
<td></td>
<td>In the past 30 days, how much difficulty have you had ejaculating when you have been sexually stimulated?</td>
</tr>
<tr>
<td></td>
<td>Did not climax</td>
</tr>
<tr>
<td></td>
<td>Only a few days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>7. In the past 30 days, how much did you consider the amount of semen you ejaculate to be a problem?</strong></td>
</tr>
<tr>
<td></td>
<td>Big problem</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Problem Assessment</strong></td>
</tr>
<tr>
<td></td>
<td>In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?</td>
</tr>
<tr>
<td></td>
<td>Very dissatisfied</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Overall satisfaction</strong></td>
</tr>
<tr>
<td></td>
<td>In the past 30 days, how satisfied have you been with your sex life?</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4: Clinical pilot study

It is a thoroughly validated instrument which evolved in the validation process from a 41-item questionnaire to a score with 11 questions (4).

An advantage of using the bSFI in this pilot trial is that it was already used in two large epidemiological studies. O’Leary and his colleagues tested 2’115 men aged 40 to 79 years (449) and a survey investigated in Norway 1185 men between 20 to 79 years (450) both with the bSFI and thus good epidemiological data for comparison is available.

Two questionnaires, the bSFI and the Urolife BPH QoL-9 sex were used instead of only one to achieve a better soundness of changes in SDys. No validated German version was available for the Urolife BPH QoL-9 sex - and the bSFI questionnaire, and thus they were first translated to German by two independent translators. From these two translated versions, one German version was compiled, which was then re-translated to English by two other translators, to be compared to the original version. The German version was then corrected and used by a German speaking doctor in his daily practice. Based on his experiences, further corrections were made and final versions of the German scores completed.

4.2.6 Assessment of adverse and serious adverse events

An adverse event is defined as any untoward medical occurrence in a patient and does not need to have a causal relationship to the treatment (451). Any occurring adverse event needed to be documented on a special form in the case record form where the following items were noted: Nature of the adverse event, seriousness, date of onset, severity (light, medium, severe), relationship to treatment, measures taken, outcome, end of the adverse event, and if a concomitant medication had been given for treatment of the adverse event.

A serious adverse event is any adverse event which is lethal, life threatening, leads to hospitalisation or prolongs a hospitalisation, causes continuous damages, as well as any malignant deformation or congenital anomaly (451).

Serious adverse events had to be reported within one workday on a special form by fax to A.Vogel Bioforce AG and the responsible ethical committee.
4.2.7 Assessed parameters

Changes in BPH symptoms were evaluated using the IPSS, SDys with the bSFI and the Urolife BPH QoL-9 sex questionnaire. At end of the treatment, global assessment of efficacy by patient and investigator was given on a four point scale (very good, good, moderate, or unchanged). Additionally, it was examined if the patient observed the best effect of the treatment on libido, erections or both and about the patients' daily routines. Patients were asked the practice and policy questions if they would take the medication again, how important it was for them to use a herbal treatment, and whether they would prefer a herbal remedy over a synthetic compound. Investigators were addressed if they would use the test medication again and were asked to provide reasons if they answered affirmatively.

Safety parameters included the occurrence of adverse events and the global assessment of safety by patient and investigator at the end of the treatment as very good, good, moderate, or poor.

4.2.8 Quality Standards and patient's safety

The study was carried out according to the provisions of Good Clinical Practice GCP (452) which is a legally binding law for Switzerland written down in the regulations for clinical trials, the 'Verordnung für klinische Studien, VKlin' (453) and the ethical obligations of the Declaration of Helsinki were also respected (454).

The trial was approved by the cantonal ethical committees of the cantons St. Gallen on the 13th of May 2009, from Zurich and Grisons on the 30th of June 2009, from Zug on the 12th of August 2009, and from Berne on the 27th of August. The Swiss regulatory authority Swissmedic notified the study on the 6th of August 2009, the trial is registered in the international clinical trial registry ClinicalTrials.gov, identifier number NCT01021267. The School of Pharmacy Research Ethics Working Group was informed about the trial on the 16th of July 2009, they confirmed the acceptance of the information on the 5th of August 2009.
Each study participant was covered by an insurance (Gerling, Policy Nr. 01050561-14042) against any potential harmful event, which could have taken place throughout the whole study. The whole trial was insured for the sum of 10 million Swiss francs and one single patient for personal harm up to 1 million Swiss francs.

Furthermore, A.Vogel Bioforce guaranteed that damages which would exceed the sum of 1 million per patient would be covered by the company itself and its liability insurance.

The study could be terminated at any time by a single patient without giving details or reasons why.

During the trial I visited each physician thrice for monitoring of the data quality and to assure the study procedure was carried out as outlined in the study protocol.

4.2.9 Statistical analysis

All variables measured in the study, were described descriptively using Excel and SAS Version 9.2. For continuous variables, the following descriptive statistics were calculated: mean, standard deviation, number non-missing, median, 25th percentile, 75th percentile, minimum, and maximum. For categorical or binary variables, absolute and relative frequencies were displayed.

For the outcome measures IPSS, bSFI and Urolife BPH QoL-9 sex within group comparisons of changes from visit 1 to visit 2, from visit 1 to visit 3 and from visit 2 to visit 3 were performed using the Wilcoxon test for paired differences. Correlation of changes between IPSS and bSFI, between IPSS and Urolife BPH QoL-9 sex and between bSFI and Urolife BPH QoL-9 sex were analysed calculating Pearson’s coefficient of correlation.

All statistical analyses were checked for correctness by Peter Klein from the d.s.h. statistical services GmbH, Rohrbach, Germany.

An outline on the study procedure for every patient is given in Table 13.
Table 13: Study procedure for a patient

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 (day -7)</th>
<th>Visit 2 (day 0)</th>
<th>Visit 3 (day 56±5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient information and informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check of inclusion and exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation of diagnostic criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation of concomitant therapies</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation of concomitant medication</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filling out of IPSS</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Filling out of bSFI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Filling out of Urolife BPH QoL-9 sex</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Handing out of study medication</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of efficacy by investigator and patient</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assessment of tolerability by investigator and patient</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Documentation of adverse events</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questions for practice</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Return of test medication</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimbursement for travel costs and study participation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Run in phase

Treatment phase
4.3 Results

4.3.1 Patients and centres

Eighty two patients were included in the trial between June 24th 2009 and October 29th 2010. This was the period from inclusion of the first patient until final visit of the last study participant. Only six of the ten study centres recruited participants, whereas centre 7, a practice specialised in complementary medicine in the centre of Zurich recruited the majority of the patients (Figure 23). The baseline characteristics of the patients from this one centre did not differ significantly from those form the other centres.

Figure 23: Number of patients per study centre, the blue bars comprise the intention to treat- (n=84), the red bars the per protocol population which was used for the efficacy analysis (n=69)

The patient population was separated for the analysis in three sub-populations. The safety population which was used for safety analysis comprised all patients who were included and treated once, the intention to treat (ITT) - population those patients who had additionally at least one efficacy assessment, and in the Per Protocol (PP)-population were all patients which completed the study without one major protocol violation which was defined as use of less than 80% or more than 120% of the study
medication, treatment duration less than 51 days or longer than 63 days, and violation of an exclusion or inclusion criterion. The safety and the ITT population were identical with the totally recruited 84 patients.

Thirteen patients had at least one major protocol deviation and were excluded from the PP population which was used for final analysis with 69 patients. Deviations included one patient with IPSS <7 at inclusion, one with sexual drive component of bSFI >5 at inclusion, four patients with disallowed concomitant medication, and seven patients who did not return to the participating practice after the first visit. Reasons for discontinuation of treatment included one instance of the death of a patient's wife, two adverse events (nausea that was seen as related to the study medication and an unrelated transient ischemic attack), and in four cases patients did not show up at all to the follow-up visits.

The demographic parameters of the ITT- and the PP-population were comparable thus to take the PP as the population for efficacy analysis was justified (Table 14).
Chapter 4: Clinical pilot study

Table 14: Demographic characteristics of the Intention to Treat and the Per Protocol population

<table>
<thead>
<tr>
<th></th>
<th>Intention to Treat population</th>
<th>Per Protocol population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>82</td>
<td>69</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>56.6 ± 11.4 years</td>
<td>57.3 ± 11.1 years</td>
</tr>
<tr>
<td>Age (median)</td>
<td>60.0 years</td>
<td>60.0 years</td>
</tr>
<tr>
<td>Body weight (mean ± SD)</td>
<td>79.5 ± 12.5 kg</td>
<td>80.3 ± 13.0 kg</td>
</tr>
<tr>
<td>Systolic blood pressure (mean ± SD)</td>
<td>132.5 ± 14.1 mmHg</td>
<td>132.5 ± 14.8 mmHg</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean ± SD)</td>
<td>84.9 ± 8.4 mmHg</td>
<td>84.3 ± 8.3 mmHg</td>
</tr>
<tr>
<td>Heart rate (mean ± SD)</td>
<td>71.8 ± 11.5 bpm</td>
<td>71.4 ± 11.2 bpm</td>
</tr>
<tr>
<td>IPSS at inclusion</td>
<td>14.4 ± 4.9</td>
<td>14.6 ± 4.9</td>
</tr>
<tr>
<td>Total bSFI at inclusion</td>
<td>22.2 ± 7.3</td>
<td>22.0 ± 7.7</td>
</tr>
<tr>
<td>Total Urolife BPH QoL-9 sex at inclusion</td>
<td>139.7 ± 50.6</td>
<td>138.1 ± 47.9</td>
</tr>
<tr>
<td>Age distribution (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 21-30 years</td>
<td>1 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Age 31-40 years</td>
<td>6 (7.3%)</td>
<td>5 (7.2%)</td>
</tr>
<tr>
<td>Age 41-50 years</td>
<td>19 (23.2%)</td>
<td>16 (23.2%)</td>
</tr>
<tr>
<td>Age 51-60 years</td>
<td>21 (25.6%)</td>
<td>19 (27.5%)</td>
</tr>
<tr>
<td>Age 61-70 years</td>
<td>28 (34.1%)</td>
<td>22 (31.9%)</td>
</tr>
<tr>
<td>Age 71-80 years</td>
<td>7 (8.5%)</td>
<td>7 (10.1%)</td>
</tr>
</tbody>
</table>

Twenty seven of all patients were treated with a concomitant medication at baseline visit, none took a PDE-5-inhibitor. Only six participants changed the medication during the treatment period, in all other patients the concomitant treatment remained stable.

Compliance during the treatment period was assessed as good when 80-120% of the test medication was taken; 78.6% of the patients fulfilled this criterion, only 7.1% of the participants took less than 80% of the medication.
4.3.2 Efficacy

For all efficacy parameters there was no statistically significant difference between the first and the second visit showing that the symptoms were stable in the treatment free run-in week. In the following only efficacy data from the treatment phase, means from visit 2 to visit 3 will be shown.

4.3.2.1 International Prostate Symptom Score IPSS

The IPSS was reduced by 51%, from 14.4 ± 4.7 to 6.9 ± 5.2, after 8 weeks of treatment (P < 0.0001) (Figure 24).

Figure 24: Change of International Prostate Symptom Score IPSS between the start and end of treatment (Per Protocol population, n = 69; P < 0.0001)

A score between 0-7 is defined as mild, 8-19 as moderate, and 20-35 as severe BPH symptoms. At the beginning of the treatment, 18.8% of all patients had severe and 78.3% had moderate symptoms; by the final visit, this shifted to 63.8% patients with mild, 31.9% with moderate, and only 4.3% with severe symptoms.

Looking at the single items contributing to the score, they were all significantly improved to the same extent except for nycturia which had the lowest relative change.
The average nycturia score changed from $1.7 \pm 1.1$ to $1.0 \pm 0.8$, the obstructive sub score from $8.1 \pm 3.9$ to $3.7 \pm 3.7$, and the irritative sub score from $6.3 \pm 2.6$ to $3.2 \pm 2.3$. Figure 25 shows the relative change of all single IPSS items and the sub scores (Figure 25).

**Figure 25**: Relative changes of the single IPSS items and the subscores from visit 2 to visit 3 (Per Protocol population, n=69). All changes were statistically significant ($p<0.05$).
4.3.2.2 Brief Sexual Function Inventory (bSFI)

The total bSFI score improved from $22.4 \pm 7.2$ to $31.4 \pm 9.2$ ($P < 0.0001$) (Figure 26).

**Figure 26:** Improvement of brief Sexual Function Inventory (bSFI) at start and end of therapy. (Per Protocol population, $n = 69$; $P < 0.0001$)

The single item scores for sexual drive, erectile function, ejaculatory function, problem assessment, and sexual satisfaction were each also significantly improved ($P < 0.0001$) (Table 15).

**Table 15:** Single item scores of the bSFI and Urolife BPH QoL-9 sex at the start and end of treatment ($n = 69$)

<table>
<thead>
<tr>
<th>Score item with range (min-max)</th>
<th>Start of treatment day 0</th>
<th>End of treatment day 56</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bSFI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual drive (0-8)</td>
<td>$2.0 \pm 0.8$</td>
<td>$2.9 \pm 0.9$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Erectile function (0-12)</td>
<td>$6.2 \pm 3.0$</td>
<td>$8.5 \pm 3.5$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Ejaculatory function (0-8)</td>
<td>$5.0 \pm 2.0$</td>
<td>$6.3 \pm 2.4$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Sexual problem assessment (0-12)</td>
<td>$5.8 \pm 2.4$</td>
<td>$9.2 \pm 3.0$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Sexual satisfaction (0-4)</td>
<td>$2.0 \pm 0.8$</td>
<td>$2.9 \pm 0.9$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td><strong>Urolife BPH QoL-9 sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual drive (0-100)</td>
<td>$48.7 \pm 20.6$</td>
<td>$66.1 \pm 20.0$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Erections (0-100)</td>
<td>$45.0 \pm 21.0$</td>
<td>$65.2 \pm 24.2$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Sexual satisfaction (0-100)</td>
<td>$43.6 \pm 19.7$</td>
<td>$63.7 \pm 22.4$</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

* Wilcoxon signed rank test

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The biggest relative improvements in single questions were seen in the problem assessment domain, where “getting and keeping an erection” improved by 64%, and “having problems with lack of drive” and “ejaculation” each increased by 54%. “Feeling sexual drive within the last 30 days” progressed by 47% and “having an erection firm enough to have sexual intercourse” was scored as 42% better, which, in absolute values, is a change from below “fairly often” to “usually” (Figure 27).

**Figure 27:** Single item scores of the bSFI at the start and end of treatment, normalised to a scale of 0-10 (0 = worst state, 10 = best) (PP population, n = 69)

There was a centre effect, as mean values of the centre with the most patients exhibited a significant improvement, whereas the other 15 patients pooled together from the other centres only exhibited a trend (\(P = 0.12\)). Of these 15 patients, eight saw an improvement, four no change, and three a worsening of their state, whereas the vast majority of the patients from the single centre experienced at least some improvement of their SDys.
4.3.2.3 Urolife BPH QoL-9 sex

The results were first published incorrectly in the Phytotherapy Research as the value of 0 was rated as the most severe symptom and 100 as being symptom free (455) but were corrected with an erratum.

The Urolife BPH QoL-9 sex total score saw an improvement from $137.3 \pm 47.9$ to $195.0 \pm 56.3$ ($P < 0.0001$) (Figure 28).

Contrarily to the bSFI, the improvements in Urolife BPH QoL-9 sex were significant at all centres. All three single questions were also statistically significantly improved, as detailed in Table 14.

Figure 29 shows the relative changes from begin to end of treatment in both scores for SDys with the single sub scores (Figure 29).
Figure 29: Relative improvements of the bSFI and Urolife QoL-9 sex total scores and single items between begin and end of treatment (PP-population, n=69)
4.3.2.4 Global assessment of efficacy

The majority of the patients rated the efficacy as very good (22%) or good (54%) and only 15% saw a small effect. The investigators assessed efficacy more favourably, reporting 38% of the cases as being very good, 44% good, and only 7% patients with unchanged condition (Figure 30).

Figure 30: Assessment of efficacy at end of treatment by patient and investigator for the PP-population (n=69)

When asked on what parameters the study medication had the best effect, 8% of the patients indicated erectile function, 26% libido, and 66% erectile function and libido together.

4.3.3 Acceptance and practice and policy questions

Of the total 82 patients, 62 patients would take the capsules again (data are missing from six patients) and in 91% of all cases the investigators would use the medication again.

For 61% of the patients, it was very important that the medication was of herbal origin and 97% of them would, given the same efficacy and safety, prefer a herbal to a synthetic drug. Investigators stated that the most important reason to apply this saw...
palmetto preparation was the good safety assessed in 95% of all cases, followed by the efficacy observed in 93% of patients.

### 4.3.4 Safety

Five patients reported six adverse events, including nausea, eructation, and acid regurgitation, all of which were mild in nature and seen as related to the study medication, and two incidents of a transient ischemic attack in the same patient and a mild pruritus, which were not related to the study medication. From the total 82 patients, data from six patients were missing on the safety assessment; from the remaining patients, 89.5% rated tolerability as very good and 6.6% as good. Similarly, investigators regarded tolerability in 90.8% of the cases as very good and 5.3% as good (Figure 31).

**Figure 31:** Assessment of tolerability at end of treatment by patient and investigator for the safety population (n=82), values from six patients are missing.
4.3.5 Subgroup analyses

The mean total bSFI improved significantly in centre 7, the general practice recruiting
the majority of study participants, but not in the average in all the other study centres.
Therefore, sub analyses were carried out to assess if the patient population of centre 7
was different than that of all the other centres.

Baseline characteristics for age, body weight, blood pressure, heart rate, as well as for
initial IPSS, total bSFI, and total Urolife QoL-9 sex score were not significantly different
between the 54 patients from centre 7 compared to the other 15 patients. The IPSS
decreased in participants from centre 7 in the average by 8.43 points, in all the other
centres by 4.33 points. The total bSFI improved in almost all patients in centre 7 (98.1%)
and in 53.3% of all other study participants, but a big part of these patients (40%)
experienced already an improvement in the treatment free run in—phase. Thus when
compared the total bSFI between visit 1 and visit 3, for 73.3% of these patients an
improvement was observed. Also the administration of co-medication was not different
between the study participants from centre 7 compared to all the other patients.

The main difference was that centre 7 was a well known practice in Zurich specialised
on complementary medicine and it was easy for the physician to recruit patients. The
other investigators reported that they barely found patients who were eager to
participate in the trial.

Because of the small patient numbers per centre, no distinct pattern or parameters
could be elucidated why some of them showed not the same improvement in the bSFI
than those from centre 7.

Additional subgroup analyses were performed for all patients by using age, symptom
severity, and concomitant medication as co-factors for efficacy.

They showed that patients with a higher IPSS at inclusion (IPSS 20-35) exhibited better
improvements in their bSFI (P = 0.029) and in their Urolife QoL-9 sex (P = 0.031) values
than did patients with lower IPSS (8-19). Comparing younger patients (21-50 years) to
older patients (51-80 years) did not reveal a significant difference regarding changes of
IPSS, bSFI, and Urolife QoL-9 sex, nor did concomitant medication have an influence on
these parameters.

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4.3.6 Correlation analysis of changes and relationship between bSFI and Urolife QoL-9 sex score

In cooperation with the statistician Peter Klein, I carried out correlation analyses to assess if changes in IPSS, bSFI, and Urolife QoL-9 sex were associated. Reason was to see firstly, if the known influence of BPH symptoms on SDys was linearly related and secondly, if for an assessment of total SDys symptoms rather the easier to fill out Urolife QoL-9 sex score than the bSFI could be used.

There was a negative correlation between changes from visit 2 to visit 3 in the IPSS score and the bSFI (Pearson's rho = -0.366; P = 0.002) (Figure 32) and between changes in the IPSS and the Urolife QoL-9 sex (Pearson's rho = -0.365; P = 0.002) (Figure 33), indicating that less urinary problems were associated with better assessment of sexual function. Both correlations were statistically significant but of rather moderate extent.

Correlation between change in IPSS and changes in bSFI - Per-Protocol population
Furthermore, there was a more pronounced positive correlation between the bSFI and Urolife QoL-9 sex, showing that both questionnaires were valid for evaluating SDys and consequently assessed changes to the same degree (Pearson’s rho = 0.607; P < 0.0001) (Figure 34)
A further regression analyses of the subdomains of the bSFI and Urolife QoL-9 sex based of actual scores showed that the erection sub scores of both questionnaires were correlated best at visit 3 (Pearson's rho = 0.806; P < 0.0001). A good correlation is given with a Pearson's rho of > 0.7 \[456].

The sexual drive subscale of the bSFI and Urolife QoL-9 sex score (Pearson's rho = 0.645; P < 0.0001) and the Urolife satisfaction and the bSFI satisfaction subscale (Pearson's rho = 0.657; P < 0.0001) were thus comparatively weaker correlated compared to the total score and the erection sub scores, showing a rather moderate but still significant correlation.

The Urolife QoL-9 sex satisfaction question was less prominently correlated to the bSFI problem assessment sub score (Pearson's rho = 0.559; P < 0.0001).

An analysis using the Spearman coefficient which is used in non-normally distributed data yielded about the same results as with the Pearson's coefficient.

Summarised, the analysis showed a good correlation of BPH symptoms and SDys measured either with the bSFI or the Urolife QoL-9 sex score. The two total scores for SDys correlated well and also the sub scores for erection, sexual drive, and satisfaction.
4.4 Discussion

In this pilot trial we wanted to assess if a saw palmetto berry preparation had an influence on both, prostate symptoms and SDys. We first examined the improvement in BPH symptoms as measured with the IPSS, which is the standard instrument to quantify severity of BPH symptoms (99). We saw a greater than 50% reduction, indicating a good treatment response that was in the range observed for saw palmetto treatments in other trials on BPH and larger than the effect of placebo. A survey of seven clinical trials for a lipophilic saw palmetto preparation with a total of 2555 patients described an average treatment duration of 300 days and a mean initial IPSS value of 14.72. At the end of the treatment, IPSS was reduced on average by 31.2% (457). In two other clinical trials, 320mg lipophilic saw palmetto berry extract was used daily and, after 6 months, the IPSS was reduced by 26.3% (433) and 37% (160) with respective reductions under placebo of 13.9% and 13.6%.

Secondly and more importantly, we assessed whether the treatment had a positive influence on concomitant SDys.

To determine this, it was important to confirm at inclusion that the patients in our trial definitely suffered from SDys; all patients here had obvious SDys, based on comparisons of the initial values from the bSFI and the Urolife QoL-9 sex in our trial with epidemiological data.

O’Leary (2003) observed an average total bSFI score of 27.7 in a population of 1883, >50-year-old men in the United States (449), whereas in our study the same age group had a lower initial value of 20.1. In another study the patients with ages of 36.9 ± 12.0 years displayed an average total bSFI of 33.5 ± 2.2 (458) compared to the total initial bSFI of 26.3 ± 6.6 observed in our 21-50-year-old patients. A large study of 2829 LUTS patients with an average age of 65.9 years evaluated Urolife QoL-9 scores and found an for the Urolife QoL-9 sex an initial total value of 8.8 ± 0.1 (scale 0-30) (448), while in our study an initial score of 130.0 ± 47.0 (scale 0-300) was recorded for the 51-80 year patient group.
Saw palmetto showed a significant improvement of SDys in this study population. Both scores for SDys changed significantly, the bSFI by 41% and the Urolife QoL-9 sex by 42.0%.

Looking at the sub scores “sexual drive” and “erectile function”, almost the same degree of improvement was seen for both scores, with 35.3% and 37% in the bSFI and 35.7% and 44.9% in the Urolife QoL-9 sex, respectively. The major difference between these two scores is caused by the more weighted problem assessment domain of the bSFI. It has been shown that both questionnaires are equally sensitive in assessing sexual dysfunctions, which was also substantiated by the correlation analysis. Interestingly, we observed that it was almost impossible for patients to fill out the bSFI without a doctor’s help, whereas the Urolife QoL-9 sex was quite easy for patients to fill out alone.

In summary, we have shown for the first time that a saw palmetto intervention in patients with BPH and SDys had a beneficial influence on both BPH symptoms and on SDys.

Our efficacy results are of further importance when considering the other available options for simultaneous treatment of LUTS and SDys. It is currently debated whether alpha blockers or phosphodiesterase (PDE) inhibitors may be beneficial for treating symptoms of both disorders. Experimental models showed that α1-adrenergic agents may improve erectile dysfunctions by influencing the balance between contraction and relaxation of the corpus cavernosum smooth muscle, of which, relaxation leads to an erection (459). On the other hand, experimental data also indicates that NO synthase and NO could play important roles in tissue from the urethra, corpus cavernosum, prostate, vas deferens, and bladder neck (460). Reduced concentrations of NOS/NO in the prostate and bladder increase smooth muscle tone and may improve prostatic cell proliferation (461), indicating that PDE-5-inhibitors, which increase the NO concentration, may have positive effects on LUTS.
Initial clinical trials were carried out with alpha blockers or PDE-5-inhibitors (462). Clinical data with alpha blockers, however, showed a good treatment effect on BPH symptoms but only a small positive influence on SDys. In a clinical trial where patients with moderate to severe BPH symptoms took 10mg alfuzosin for six months, the IPSS decreased from 18.93 to 9.59 points and the Male Sexual Health Questionnaire MSHQ ejaculation sub score improved from 23.09 to 21.54; this was statistically significant, but the clinical relevance remains doubtful with an improvement only of about 7%. The overall number of patients with moderate to severe erectile dysfunctions decreased from 35% to 22% (434).

These results were not confirmed in another trial where patients with BPH symptoms took 10mg alfuzosin daily for 12 weeks. Results of this trial showed that IPSS decreased significantly from 17.92 to 12.07, but the MSHQ ejaculatory subdomain worsened significantly from 24.9 to 27.14 and subdomains for erection and satisfaction did not change significantly (463).

In a large open trial with 839 enrolled patients suffering from LUTS caused by BPH, 10mg alfuzosin was taken daily for two years. The initial IPSS of 15.5 was reduced by 7 points, while the total initial bSFI value of 21.5 improved only slightly during the treatment period, leading to the assessment by the authors that the treatment at least “did not have any deleterious effect on sexual functions” (435).

A further open clinical trial with 10mg alfuzosin showed, besides a significant improvement of the IPSS after 1 year of treatment, a significant improvement of the bother score of the Danish Prostatic Symptom Score questionnaire for sexual dysfunction (DAN-PSSsex) (464) while a study comparing tamsulosin/solifenacin either alone or in combination in patients with LUTS also saw improved IPSS, but observed no significant changes in the IIEF (465).

The IPSS reductions of about 6 to 7 points found in these studies with alpha-blockers were similar to those observed in placebo-controlled trials (466, 467). This is in line with the trials of Debruyne (2004) and Zlotta (2005), which showed similar IPSS reductions following treatment with a saw palmetto preparation and tamsulosin (468, 469).

It also remains doubtful whether PDE-5 inhibitors are a good treatment for both LUTS and SDys together. Clinical data for PDE-5 inhibitors showed a good improvement on
erectile dysfunctions, but a small effect on BPH symptoms.
McVary (2007) saw a significant decrease in the IPSS following 12 weeks of treatment with 100mg sildenafil, with an IPSS change of −6.3 vs. −1.9 with placebo, as well as a significant improvement of the IIEF erectile function domain (470).
In the trial of Roehrborn et al. (2008), the application of different dosages of tadalafil demonstrated that an increased dosage correlated with increased IPSS improvement, from +3.9 at 2.5mg to +5.2 at 20mg, with a dose of 5mg showing the best benefit/risk ratio. After a treatment period of 12 weeks, improvement was also seen in the IIEF erectile function subdomain (471).
Vardenafil (20mg) taken twice daily for 8 weeks improved the IPSS by 5.9 points, compared to placebo with 3.6 points; significant changes were also seen in the IIEF-ED, and the Urolife QoL-9 sex improved by 62.6% compared to 17.2% under placebo (472).
While IPSS was improved in these trials, interestingly, changes in flow rates were never reported.
In total, clinical data for PDE-5-inhibitors showed a moderate improvement in LUTS from 2.3 to 4.4 IPSS-points compared to placebo even though sildenafil and vardenafil were used at the highest applicable daily dosage, meanwhile the SDys improved in all studies significantly.
One solution discussed in the literature for concomitant reduction of BPH symptoms and ED is the combination of an alpha blocker with a PDE-5-inhibitor. Data from three such clinical studies are presently available.
One small trial investigated alfuzosin, sildenafil, or the combination on LUTS and erectile dysfunctions. After 12 weeks of treatment, initial values of IPSS, which were between 16.9 and 17.8, were reduced significantly in all treatment groups with the largest reduction (24.1%) in the combination group. The IIEF erectile function score was significantly improved by the combination and sildenafil, but not in the alfuzosin group (473).
Another combination trial with sildenafil or tamsulosin showed comparable results, with the largest IPSS improvement observed with the combination (~40.1%), followed by tamsulosin (~36.2%), and sildenafil (~28.2%); the IIEF improved significantly with sildenafil and the combination but not with tamsulosin (474).
In a further trial, 100mg udenafil was added to a stable alpha-blocking therapy in patients with BPH and erectile dysfunction for 8 weeks. The IPSS was reduced by 2.8 points and the IIEF-5 improved by more than 5 points, indicating that a combination or add-on therapy of udenafil may be beneficial (475).

PDE-5-inhibitors are expensive treatments; therefore, a cost-benefit assessment is warranted for a further extensive PDE-prescription. In the USA, a single dose of 25mg sildenafil costs about 8 times as much as an alpha-blocking agent like 1mg doxazosin (476) or 30 times more than 0.4mg tamsulosin in Germany (477), whereas the cost for a daily dosage of Prostasan® is in the lower range of an alpha blocker. These differences in price, in addition to the only moderate efficacy, make it doubtful if PDE-5-inhibitors should be advocated as a standard treatments for BPH symptoms.

When looking at safety and tolerability, our data was in accordance with previous findings and indicated that saw palmetto was very well tolerated, in contrast to the standard treatments for LUTS. A major problem for patients taking an alpha blocker and/or a 5-alpha-reductase inhibitor is the occurrence of sexual adverse effects that cause many men to discontinue treatment (478).

Study data show that 2-16% of all patients under alpha reductase inhibitor therapy experience erectile dysfunctions, decreased libido, and decreased volume of ejaculate (twice the frequency seen with placebo), whereas alpha-blocking agents, particularly tamsulosin, have been frequently linked with ejaculatory disorders in around 10% of all patients (479).

In daily practice, the incidence rates may even be higher than in clinical trials. In a large epidemiological study carried out with urologists and internal medicine physicians in the United States, doctors estimated that 18-27% of the patients taking an alpha-blocking medication suffer from ejaculatory disorders and 16-22% of men taking a 5-alpha-reductase-inhibitor suffer from erectile dysfunctions (480). Nevertheless, the latest American Urology Association guideline for treatment of BPH symptoms also advocates using a combination of alpha-blockers and 5-alpha-reductase inhibitors (197), a protocol designed to achieve better efficacy, but without fully considering the additive side effect rates of these two drugs as shown in combination trials (461).
This trial has some limitations; it was designed as an uncontrolled pilot trial to elucidate if an effect of a saw palmetto treatment could be observed. Consequently, the size of the placebo effect can only be estimated.

A review on the placebo effect in studies with alpha blockers and 5-alpha-reductase inhibitors in BPH found a reduction in LUTS under placebo ranging from 9-34% (481). Considering this effect size, that the reductions in IPSS seen in our trial were similar to those of other controlled saw palmetto trials it can be assumed that our Sabal treatment was probably efficacious in reducing BPH symptoms.

To assess the placebo effect in reducing SDys in this trial is more difficult and no clear statement can be made as our observed improvement of SDys was about 40%. A review on treatments for erectile dysfunction showed an average placebo effect when looking at improvement of erectile function in nine clinical trials of 28.0% (482), another review taking the intercourse success rate as main measure found a placebo effect of 31.4% as mean from 19 sildenafil trials, 32% from twelve tadalafil studies, and 35.1% from eleven vardenafil trials (483).

Furthermore, there was a strong centre effect in our trial, as one centre recruited substantially more patients than the others and these other centres did have fewer responders than the main centre. Subgroup analysis did not unveil any significant differences in patient characteristics between these centres; however, these analyses were limited by the low number of patients in the other five centres together. Nevertheless, a strong influence by the treating physician on the outcome of SDys could not be confirmed with the data available as there was a positive correlation between the bSFI which was filled out by the investigator and the Urolife sex QoL-9 score which was completed by patients. Further, during the treatment-free run in period the values for SDys and IPSS remained in the majority stable.

Nevertheless, the results of this uncontrolled pilot trial showed that the applied saw palmetto treatment exerted a good benefit/risk ratio in reducing BPH symptoms and at least not negatively affecting SDys at the same time. When considering also the low treatment costs, the very good acceptance and compliance by the patients it can be nonetheless assumed that this trial showed promising results for the effectiveness, which describes the degree of a beneficial effect in a real world clinical settings (484) of saw palmetto in treating BPH symptoms and concomitant SDys.
Based on our findings here, a further placebo-controlled clinical trial with a more balanced patient distribution in the centres would be the next step to prove the efficacy.

Conclusions

This is the first trial ever to observe that a saw palmetto treatment could have a positive effect in reducing BPH symptoms and in concomitant SDys. The applied medication was very well tolerated, safe, highly accepted and the compliance was very good. Further, the cost of daily treatment with saw palmetto is much cheaper than with many other medications, for example, in Switzerland the cost would be 0.75 Swiss francs for saw palmetto vs. 22.30 Swiss francs for 100mg sildenafil (485).

The results from our pilot trial let assume that due to the positive benefit/risk ratio of saw palmetto in treating BPH symptoms and at least not deteriorating SDys, there is a good chance for a good effectiveness of this treatment.

Based on these promising results, a further, larger placebo-controlled clinical trial should be carried out to confirm the findings and answer questions on the efficacy of saw palmetto in treating BPH symptoms and SDys.
Chapter 5

*General discussion and conclusion*
Chapter 5: General discussion and conclusion

5.1 General discussion

In the last 150 years saw palmetto has made a fascinating journey as a medical plant: Starting with the first use by the Indians of Florida, then discovered by white settlers and made popular within 20 years in the United States, soon after in Europe to become today's world favourite herbal treatment for BPH with a turnover of an estimated 700 million dollars (163) which is equivalent to the worldwide annual combined sales of the 5-alpha-reductase inhibitor top brands Proscar® (486) and Avodart® (487).

This thesis followed important aspects of this path and gained new data on the past, present and future of saw palmetto as a medical therapy.

In terms of the past the aim was to show who first made medical use of saw palmetto among the U.S. American physicians and how the plant became popular in the United States and later in Germany.

I identified the first written record of saw palmetto as a medical treatment in 1877 by J.B. Read of Savannah, Georgia (208). One can speculate that his description of the use of the plant was lead by commercial interests as Dr. Read was to become president of the Georgia Medical Society (210) and a large manufacturer of medical products, the A.A. Solomons Drug Co. was situated in his hometown (488). It was the time of the so called 'Gilded Age' in the United States, an exciting era of economic growth - also for venturers in the medical field and quacks. This is well documented in the 1880's, for example, in case of Echinacea - made popular in the U.S.A. also as a product called 'Meyer's Blood Purifier'. Its producer, H.C.F. Meyer proposed to a medical board to prove the efficacy of his product by letting himself bite by a rattlesnake and then take the 'Blood Purifier' as a treatment (489).

But saw palmetto was more than quackery - it proved to be a good remedy which is demonstrated by the broad acceptance and use firstly among the eclectic physicians, followed soon by homeopathic doctors. A comprehensive collection of various sources documenting the wide spread use of the plant indicate that the first experiences with
Sabal were gathered in respiratory tract infections (208) but soon after in genito-urinary problems and as a sexual stimulant (253). The important medical role of eclectic medicine in this period contributed to the plant becoming a popular therapy. The 'gold standards' of available therapies for BPH symptoms in the second half 19th century like catheterisations or use of mercury, iodine, and bromine were generally harmful. Consequently, saw palmetto could fill a gap as a safe and also efficacious new therapy which proved to be best for prostatic problems.

To show how saw palmetto was introduced as a medical treatment in Europe, I chose Germany as a model. In this country mainly the homeopaths were the first to use saw palmetto and they had strong ties to the American homeopathic society (265). Soon afterwards the pharmacists, too and then food scientists and chemists became interested in the plant and until the beginning of the Second World War the species must have been known and also used at least by a certain group of practitioners in Germany.

Further botanico-historical studies especially in archives need to focus on

- How the plant became popular in Germany,
- Who were its main promoters and
- Which were the main brands being used.

Nevertheless, this is at the time the most comprehensive medico-historical evaluation of the first use on saw palmetto in the U.S.A. and Germany from publicly available sources.

Regarding the present, the largest phytochemical analysis so far of 46 products from nine different countries containing Sabal was carried out. The advantage of saw palmetto is that in clinical trials 320mg berry extract with 70-95% fatty acids proved to be efficacious and safe in treating BPH symptoms demonstrating that the fatty acids are most probably one of the main active constituent of saw palmetto preparations (17,
Like this a good reference standard is given to measure the product quality of saw palmetto preparations.

There was an unexpectedly large difference in the amount of fatty acids per daily dose among saw palmetto mono preparations: The highest dosed product contained 177 times more fatty acids than the lowest dosed. When compared to the proposed dosage of the monographs of 320mg extract (17, 40, 146, 147), unregistered Sabal preparations contained in the majority either too low or too high daily amounts of fatty acids and these were further often wrongly declared, casting serious doubts on the usefulness of these products as therapeutic agents, especially since extensive preclinical and clinical research with more than 90 publicly available clinical trials provided sound evidence for this dose range (151). The analysis also showed that on average registered products contained an amount of 320mg lipophilic saw palmetto extract and the declarations were correct. The capsule sizes of unregistered preparations were in average also bigger than those of registered products, indicating that manufacturers wanted to profit from the fact that patients regard larger capsules as more efficacious than smaller ones (490).

Additionally, the ethanolic mono-extracts showed a characteristic pattern in their composition of nine fatty acids and, consequently, a saw palmetto extract can be distinguished easily from other herbal extracts containing fatty acids. Based on this study the proposed amount of 20% lauric acid for a saw palmetto extract proposed by the European Pharmacopoeia (336) may not be sufficient to characterise the quality of a Sabal extract; in the future minimum concentrations of oleic or myristic acids should be recommended as well.

Even though fatty acids are an important marker, further investigations should focus also on other active constituents as well. This could be phytosterols like β-sitosterol, campesterol or stigmasterol which showed to have a positive effect on mechanisms associated with the BPH pathology (385, 387, 388). These compounds were also shown to be efficacious in improving BPH symptoms (127). However, they had to be taken in dosages at least 60 times higher than generally found in saw palmetto mono preparations (127, 340).
To assess the characteristics of the different test samples, we used a different method than just to determine a further marker substance. For the first time a metabolomic approach to characterise saw palmetto preparations using proton-NMR was carried out in the MSc-thesis of Anthony Booker (341). His results emphasise that in the future this could become the method of choice for a characterisation of saw palmetto products. It is fast and reliable, straightforward to set up a library of products and their characteristics and with PCA a good statistical method is available to analyse the different preparations. With the applied clustering, preparations which are similar in their characteristics could be grouped together and outliers can well be identified.

In general, this phytochemical analysis showed that what is sold on the markets under the label ‘saw palmetto’ varies widely in its amount of active constituents highlighting that the registration of herbal medicinal products would be the best measure for quality assurance on the markets.

The last part of my thesis addressed the future of saw palmetto with a clinical pilot trial in patients with BPH and concomitant SDys. I stated in the discussion of the historical part that being a BPH patient at the end of the 19th century was a miserable thing. At the begin of the 21st century, the situation looks brighter for a patient but it is far from being shiny.

The disease is better understood but why it evolves is still unclear; the latest hypothesis that BPH could be caused by a venous insufficiency in the testicular veins (97) still needs to be substantiated. There are only two classes of medication available for treatment of BPH symptoms, alpha-blockers and 5-alpha-reductase inhibitors but both cause frequently side effects like ejaculatory disorders (426) or erectile problems (428). The last treatment option is surgery and the golden standard, TURP is a surgical method which is about hundred years old (175) and also causes a lot of side effects (139).

It is also known today that a BPH patient is at a greater risk of experiencing SDys. Large epidemiological studies carried out about 10 years ago corrected the existing paradigm that SDys in the elderly male population were simply age related. The results of these
trials showed that BPH is besides age the most important factor causing SDys - which could be worsened significantly with the mentioned therapy options to treat BPH.

Therefore, additional treatment solutions are intensively sought which are efficacious and safe in treating BPH and SDys together (411).

Saw palmetto with its clinically proven efficacy in BPH and the traditional use as a therapy for SDys was predestined to be a good treatment for these disorders. Our clinical pilot trial which was designed to be a pragmatic study (491) showed a tendency that after a treatment duration of eight weeks, saw palmetto could reduce BPH symptoms and at the same time improve SDys.

Our results are of considerable interest in particular in the context of improved compliance, good acceptance, the low treatment costs of the saw palmetto treatment, and the good benefit/risk ratio for one patient. Consequently, a good effectiveness of saw palmetto in treating BPH symptoms and concomitant SDys can be assumed.

Nevertheless, the study has several limitations and its level of evidence is II-b according to the rating in Evidence Based Medicine where level I stands for a well designed randomised clinical trial and level III are case reports or opinions from expert authorities (492). There was no placebo control involved in our study and the amount of the placebo effect could only be estimated. Further, a strong centre effect was noted as one centre recruited the majority of the patients and since this study was designed as a pilot study to generate hypotheses for a further controlled study, the sample size was also rather small with 69 analysable patients.

To confirm the promising findings from our pilot trial, next a placebo controlled study needs to be carried out. The results from our trial can be taken to estimate the effect size of the saw palmetto treatment and the needed sample size.

Probably even better results could be obtained when combining Sabal with another plant which proved to be efficacious in SDys like Panax ginseng where a review on six placebo controlled trials reported efficacy in treating ED (493) or maca (Lepidium meyenii) which in two placebo controlled studies improved SDys (494). Existing combinations of saw palmetto with an additional herbal extract were mainly developed.
to improve uroflow or BPH symptoms like with *Urtica dioica* (150) but none to improve concomitant SDys.

A further topic of interest relates to the mechanisms underlying these effects. It could be that in our trial the reduction of BPH symptoms leads to the improvement of SDys or that saw palmetto itself has aphrodisiac properties. A trial with BPH-free patients suffering from SDys could answer this question.

In summary, our trial gave interesting hints that saw palmetto has also a positive effect on concomitant SDys. Given, this the plant has now even more the potential to become the first line treatment for mild to moderate BPH symptoms.

### 5.2 Final conclusion

Saw palmetto is one of the best known and investigated herbal treatments worldwide. This thesis contributes new historical, analytical and clinical knowledge on the plant. Overall, good quality products which are manufactured in accordance with the existing monographs on saw palmetto have a bright future – they could become a well tolerated and cost effective therapeutic option for patients suffering from mild to moderate BPH symptoms with concomitant SDys. More clinical research and maybe a combination with another plant which is efficacious in improving SDys is warranted to secure saw palmetto its place as a more widely recognised treatment for BPH and other urogenital conditions.
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7 Appendix

7.1 Appendix 1

Data on reference samples for analytic investigations including sample number, country of origin, brand name, producer, galenic form, tablet or capsule weight, amount of saw palmetto per unit, daily dosage, drug extractant ratio DER, active constituents, and batch numbers.
<table>
<thead>
<tr>
<th>Sample nr. (SP)</th>
<th>Country</th>
<th>Brand name</th>
<th>Producer</th>
<th>Regulatory status (R) @Food supplement (FS)</th>
<th>Table or capsule</th>
<th>Tablet or capsule weight [mg]</th>
<th>Amount of saw palmetto per unit [mg] as given on package</th>
<th>Daily dosage (units/d)</th>
<th>DER and extractant of saw palmetto extract</th>
<th>active constituents</th>
<th>Batch Nr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAN</td>
<td>Prostate Perform</td>
<td>New Roots Herbal</td>
<td>R combi soft gel capsule</td>
<td>1800</td>
<td>160</td>
<td>2x1: 4:1 (95% oil extract)</td>
<td></td>
<td></td>
<td>sterols and sterolins, SP extract, SP, rye flower pollen, vit E, PS, pau d'arco, Zn, lyc, Se, borage oil, olive oil, pygeum, vit B6, l-alanine, l-glycine, l-glutamic acid</td>
<td>691</td>
</tr>
<tr>
<td>7</td>
<td>UK</td>
<td>Saw Palmetto Berry</td>
<td>Viridian</td>
<td>FS combi hard capsule</td>
<td>450</td>
<td>150 mg SP extract, 132 mg SP berry powder</td>
<td>1x1 For extract: 45% 50% free fatty acids</td>
<td></td>
<td></td>
<td>SP extract, SP powder, bilberry extract, alfalfa, spirulina</td>
<td>492411</td>
</tr>
<tr>
<td>8</td>
<td>ESP</td>
<td>Sereprostat</td>
<td>Robapharm ESP</td>
<td>FS mono tablet</td>
<td>450</td>
<td>80</td>
<td>4x1 --</td>
<td></td>
<td></td>
<td>SP</td>
<td>C04</td>
</tr>
<tr>
<td>11</td>
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<td>Saw Palmetto</td>
<td>Holland&amp;Barrett</td>
<td>FS mono hard capsule</td>
<td>450</td>
<td>450</td>
<td>2x2 --</td>
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<td></td>
<td>SP</td>
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<td>Permixon</td>
<td>Pierre Favre SA</td>
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<td>410</td>
<td>160</td>
<td>2x1 6-12 1, Hexane</td>
<td></td>
<td></td>
<td>SP</td>
<td>D01</td>
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<tr>
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<td>Saw Palmetto Berries</td>
<td>Natural Factors</td>
<td>R mono hard capsule</td>
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<td>500</td>
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<td></td>
<td>SP</td>
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</tr>
<tr>
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<td>Solgar</td>
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<td>300</td>
<td>1-3x1 --</td>
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<td></td>
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<td>400</td>
<td>120</td>
<td>1-3x1 45% fatty acids</td>
<td></td>
<td></td>
<td>SP, Pyg, urt root, rice bran</td>
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<td>CJ Nutra</td>
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<td>750</td>
<td>500</td>
<td>1x1 --</td>
<td></td>
<td></td>
<td>SP, Zn, PS</td>
<td>128152A</td>
</tr>
<tr>
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<td>333.5</td>
<td>2x1 --</td>
<td></td>
<td></td>
<td>vit D, Zn, Se, Cu, SP, Cal-gluCarate, lyc</td>
<td>128152A</td>
</tr>
<tr>
<td>18</td>
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<td>Chung Wae Pharma Corporation</td>
<td>Chung Wae Pharma</td>
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<td>500</td>
<td>1x1 --</td>
<td></td>
<td></td>
<td>SP, Zn, soybean oil, tomato extract powder</td>
<td></td>
</tr>
<tr>
<td>Sample nr. (SP)</td>
<td>Country</td>
<td>Brand name</td>
<td>Producer</td>
<td>Regulatory status</td>
<td>mono or combination</td>
<td>Tablet or capsule</td>
<td>Tablet or capsule weight [mg]</td>
<td>Amount of saw palmetto per unit [mg] as given on package</td>
<td>Daily dosage (units/d)</td>
<td>DER and extractant of saw palmetto extract</td>
<td>active constituents</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>------------</td>
<td>----------</td>
<td>------------------</td>
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<td>---------------------------------------------------------</td>
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<td>19</td>
<td>CAN</td>
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<td>Prairie Naturals</td>
<td>R</td>
<td>combi</td>
<td>soft gel capsule</td>
<td>1362</td>
<td>80</td>
<td>1-2x2</td>
<td>--</td>
<td>SP, Co, Zn, SP, pyg, lyc, rosemary</td>
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<tr>
<td>20</td>
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<td>Quality Supplements and Vitamins Inc.</td>
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<td>soft gel capsule</td>
<td>1800</td>
<td>160</td>
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<tr>
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<td>Bional</td>
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<td>combi</td>
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<td>1400</td>
<td>160</td>
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<td>Dietéticos Intersa S.A.</td>
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<td>Nature's aid</td>
<td>FS</td>
<td>combi</td>
<td>tablet</td>
<td>1200</td>
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<td>1:10. 72mg fatty acids per tab!</td>
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<td>Bloem Natuurprodukte n Winschoten bv</td>
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<td>hard capsule</td>
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<td>40</td>
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<td>500</td>
<td>320</td>
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<td>10-14:3:1, ethanol 90% m/m</td>
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<td>500</td>
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<td>--</td>
<td>SP</td>
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<td>Max Zeller AG (Schwabe Pharma AG)</td>
<td>R</td>
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<td>soft gel capsule</td>
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<td>SabCaps</td>
<td>Vifor SA</td>
<td>R</td>
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<td>320</td>
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<td>9-11:1, ethanol 96% V/V</td>
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Andy Suter | 217
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<th>Producer</th>
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<th>Registered Food supplement (FS)</th>
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<th>Tablet or capsule</th>
<th>Tablet or capsule weight [mg]</th>
<th>Amount of saw palmetto per unit [mg] as given on package</th>
<th>Daily dosage (units/d)</th>
<th>DER and extractant of saw palmetto extract</th>
<th>active constituents</th>
<th>Batch Nr.</th>
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<td>Chong Kun Dang Health</td>
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<td>mono</td>
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<td>500</td>
<td>320</td>
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<td>--</td>
<td>SP</td>
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<td>FIN</td>
<td>Curbisal</td>
<td>Pharbio</td>
<td>R</td>
<td>mono</td>
<td>soft gel capsule</td>
<td>480</td>
<td>320</td>
<td>1x1</td>
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<td>soft gel capsule</td>
<td>600</td>
<td>160</td>
<td>1x2</td>
<td>Standardized to 85-95% fatty acids</td>
<td>SP</td>
<td>1214706 0039</td>
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<td>A. Vogel Bioforce AG</td>
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<td>soft gel capsule</td>
<td>485</td>
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<td>Dr. Dünnen AG</td>
<td>R</td>
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<td>soft gel capsule</td>
<td>260</td>
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<td>SP</td>
<td>34426</td>
<td></td>
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<td>NL</td>
<td>Prostaat</td>
<td>Phital</td>
<td>FS</td>
<td>combi</td>
<td>tablet</td>
<td>1450</td>
<td>100</td>
<td>2x1</td>
<td>--</td>
<td>SP</td>
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<td>Schwabe Pharma AG</td>
<td>R</td>
<td>combi</td>
<td>soft gel capsule</td>
<td>675</td>
<td>160</td>
<td>2x1</td>
<td>10-14:3:1, ethanol 90% m/m</td>
<td>SP, urt</td>
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<td>41</td>
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<td>Prostalife</td>
<td>Bloem Natuurprodukte n Winschoten bv</td>
<td>FS</td>
<td>combi</td>
<td>hard capsule</td>
<td>550</td>
<td>320</td>
<td>2-3x1</td>
<td>4:1</td>
<td>SP, urt root, Epimedium, Muro puama, b-sit, Se, Zn, vit B6, vit E, lyc</td>
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<td>Sample nr. (SP)</td>
<td>Country</td>
<td>Brand name</td>
<td>Producer</td>
<td>Regulatory status</td>
<td>Registered (FS)</td>
<td>mono or combination</td>
<td>Tablet or capsule</td>
<td>Tablet or capsule weight [mg]</td>
<td>Amount of saw palmetto per unit [mg] as given on package</td>
<td>Daily dosage (units/d)</td>
<td>DER and extractant of saw palmetto extract</td>
<td>active constituents</td>
<td>Batch Nr.</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------</td>
<td>-----------------</td>
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<tr>
<td>42 NL</td>
<td>Prosta Totaal</td>
<td>Distributie care bv</td>
<td>FS combi tablet</td>
<td>1450</td>
<td>100</td>
<td>1-2x1</td>
<td>--</td>
<td>[mg]</td>
<td>--</td>
<td>--</td>
<td>[mg]</td>
<td>lyc, Pyg, phytosterols, urt, SP, provit A, vit A, vit E, B1, vit B2, vit B3, vit B5, vit B6, vit B8, vit B11, vit B12, vit C, vit D3, vit K, choline, inositol, paba, lutein, b-sit, Ca, Cr, Fe, I, Na, Cu, Mg, Mn, Se, Mo, Se, Si, Zn, grape seed, ginseng, ginkgo biloba, green tea</td>
<td>08818E</td>
</tr>
<tr>
<td>43 NL</td>
<td>Prostalan Forte</td>
<td>VSM</td>
<td>FS combi soft gel capsule</td>
<td>666</td>
<td>160</td>
<td>2x1</td>
<td>--</td>
<td>[mg]</td>
<td>--</td>
<td>--</td>
<td>[mg]</td>
<td>SP, urt, saturated fatty acids</td>
<td>71221</td>
</tr>
<tr>
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<td>Bional</td>
<td>FS combi soft gel capsule</td>
<td>1400</td>
<td>2.5</td>
<td>1-3x1</td>
<td>--</td>
<td>[mg]</td>
<td>--</td>
<td>--</td>
<td>[mg]</td>
<td>SP, PS oil, urt, echinacea pallida, b-sit, Mg, vit E, Zn</td>
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<tr>
<td>45 CAN</td>
<td>Saw Palmetto</td>
<td>Homeocan</td>
<td>R mono hard capsule</td>
<td>350</td>
<td>350</td>
<td>04. Jun</td>
<td>--</td>
<td>[mg]</td>
<td>12 :1, standardised to 25% fatty acids</td>
<td>--</td>
<td>[mg]</td>
<td>SP</td>
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<td>Health Aid</td>
<td>FS combi soft gel capsule</td>
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<td>1x1</td>
<td>12 :1</td>
<td>[mg]</td>
<td>--</td>
<td>--</td>
<td>[mg]</td>
<td>SP, Pyg, plant sterol complex, soy phospholipids (soy lecithin), lipase</td>
<td>710</td>
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<tr>
<td>47 USA</td>
<td>Saw Palmetto &amp; Pygeum Extract</td>
<td>Country Life</td>
<td>FS combi soft gel capsule</td>
<td>600</td>
<td>160</td>
<td>2x1</td>
<td>9 :1, standardised to 45% fatty acids=72mg/cap</td>
<td>[mg]</td>
<td>--</td>
<td>--</td>
<td>[mg]</td>
<td>SP, Pyg, plant sterol complex, soy phospholipids (soy lecithin), lipase</td>
<td>104996A</td>
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<td>48 CAN</td>
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<td>Preferred Nutrition</td>
<td>R combi soft gel capsule</td>
<td>1800</td>
<td>80</td>
<td>2-4x1</td>
<td>85% fatty acids</td>
<td>[mg]</td>
<td>--</td>
<td>--</td>
<td>[mg]</td>
<td>b-sit, PS oil, flower pollen extract, SP, urt, Pyg, Zn, hydrazane root, lyc, Cu</td>
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<tr>
<td>49 USA</td>
<td>ProstActive</td>
<td>Nature’s Way (Schwabe Pharma Ag)</td>
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<td>480</td>
<td>320</td>
<td>1x1</td>
<td>12.01</td>
<td>[mg]</td>
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<td>--</td>
<td>[mg]</td>
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<td>Prostate SLX</td>
<td>New Chapter Inc.</td>
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<td>750</td>
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<td>--</td>
<td>[mg]</td>
<td>SP, Se, probiotic nutrients, green tea, PS</td>
<td>40503009 A</td>
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</tbody>
</table>

**Appendix**

**Sample nr. (SP):** Identification number for each sample.

**Country:** Geographical location of the sample.

**Brand name:** Name of the product.

**Producer:** Manufacturer of the product.

**Regulatory status:** Status of the regulatory body concerning the product.

**Registered (FS):** Information regarding the registration of the product.

**mono or combination:** Type of product (mono or combination).

**Tablet or capsule:** Form of the product.

**Tablet or capsule weight [mg]:** Weight of the tablet or capsule.

**Amount of saw palmetto per unit [mg] as given on package:** Amount of saw palmetto per unit as indicated on the package.

**Daily dosage (units/d):** Daily dosage given in units per day.

**DER and extractant of saw palmetto extract:** Derivatives and extractant of saw palmetto extract.

**active constituents:** Constituents present in the active part of the product.

**Batch Nr.:** Batch number for the product.
<table>
<thead>
<tr>
<th>Sample nr. (SP)</th>
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<th>Brand name</th>
<th>Producer</th>
<th>Regulatory status Registered (R) Food supplement (FS)</th>
<th>mono or combination</th>
<th>Tablet or capsule</th>
<th>Tablet or capsule weight [mg]</th>
<th>Amount of saw palmetto per unit [mg] as given on package</th>
<th>Daily dosage (units/d)</th>
<th>DER and extractant of saw palmetto extract</th>
<th>active constituents</th>
<th>Batch Nr.</th>
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<td>Enzymatic Therapy Inc.</td>
<td>FS combi soft gel capsule</td>
<td>555</td>
<td>80</td>
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<td>Standardised to 85-95% fatty acids</td>
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<td>52</td>
<td>USA</td>
<td>Saw Palmetto &amp; Pygeum</td>
<td>Nature’s Way</td>
<td>FS combi soft gel capsule</td>
<td>850</td>
<td>350</td>
<td>1x1</td>
<td>Standardised to 85-95% fatty acids</td>
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<td>53</td>
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<td>Saw Palmetto Berry Extract</td>
<td>Solaray</td>
<td>FS mono soft gel capsule</td>
<td>570</td>
<td>160</td>
<td>1x1-2</td>
<td>85% fatty acids and sterols</td>
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<td>Saw Palmetto Extract</td>
<td>Source Naturals</td>
<td>FS mono soft gel capsule</td>
<td>700</td>
<td>320</td>
<td>1x2</td>
<td>85-95% fatty acids and sterols</td>
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<td>Prosta - Fort</td>
<td>GSN Compania General Suplementos Nutricionales</td>
<td>FS combi tablet</td>
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<td>Country Life</td>
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<td></td>
<td>2-04</td>
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</table>

Abbreviations: SP = saw palmetto extract, PS = pumpkin Seed extract, Pyg = *Pygeum africanum* extract, Urt = *Urtica dioica* (stinging nettle), b-sit = beta-sitosterol, lyc = lycopene
7.2 Appendix 2

Total fatty acid content per capsule or tablet of each tested preparation and of the single fatty acids lauric acid, capric acid, caprylic acid, myristic acid, palmitic acid, linolenic acid, oleic/linoleic acid and stearic acid
<table>
<thead>
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<th>Mono or combination</th>
<th>Brand name</th>
<th>Producer</th>
<th>Country</th>
<th>SP Nr.</th>
<th>Total fatty acid [mg/tablet or capsule]</th>
<th>Lauric acid [mg/tablet or capsule]</th>
<th>Caprylic acid [mg/tablet or capsule]</th>
<th>Capric acid [mg/tablet or capsule]</th>
<th>Myristic acid [mg/tablet or capsule]</th>
<th>Palmitic acid [mg/tablet or capsule]</th>
<th>Linolenic acid [mg/tablet or capsule]</th>
<th>Oleic+Linoleic acid [mg/tablet or capsule]</th>
<th>Stearic acid [mg/tablet or capsule]</th>
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<td>Source Naturals Inc.</td>
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<td>39.15</td>
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<td>212.96</td>
<td>11.27</td>
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<td>Curbisal</td>
<td>Pharbio</td>
<td>Finland</td>
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<td>92.94</td>
<td>6</td>
<td>8.61</td>
<td>34</td>
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<td>89.6</td>
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<td>Chong Kun Dang Health</td>
<td>Korea</td>
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<td>8.21</td>
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<td>25.25</td>
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<td>Switzerland</td>
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7.3 Appendix 3

Chromatograms of GC analytic of each investigated preparation from chapter 2
SP22  Biprostat, Dietéticos Intersa S.A., Spain

SP12  Permixon, Pierre Fabre Iberica S.A., Spain

SP47: Saw Palmetto, Homeocan, Canada

SP13  Saw Palmetto Berries, Natural Factors, Canada
Appendix

SP11  Saw Palmetto, Holland & Barret, UK

SP15  Saw Palmetto & Pygeum Bark, Higher Nature, UK

SP7   Saw Palmetto Berry, Viridian, UK

SP14  Saw Palmetto Berries, Solgar Vitamin and Herb, UK

Andy Suter  228
SP41  Prostalife, Bloem Natuurprodukten Winschoten bv, Netherland

SP24  ProstaFleur Extra Forte, Bloem Natuurprodukten Winschoten bv, Netherland

SP17  Prostate Health, Schiff Nutrition Group, USA

SP47  Saw Palmetto & Pygeum Extract, Country Life, USA
SP55  Prosta – Fort, GSN Compañía General Suplementos Nutricionales, Spain

SP8  Sereprostat, Robapharm España S.A., Spain

SP57  Spasmo – Urgenin, Madaus, Spain
SP23  Saw Palmetto Complex, Natures Aid Ltd. UK

SP42  Prostaat, Phital, Netherland

SP38  Prostaat, Phital, Netherland

SP56  Prosta - Max, Country Life, USA
SP19  Prost – Force, Prairie Naturals, Canada

SP1  Prostate Perform, New Roots Herbal, Canada

SP37  Saw Palmetto, Swiss Herbal Remedies Ltd, Canada
SP48  Saw Palmetto & Pygeum, Preferred Nutrition, Canada

SP20  Life Extension, Quality Supplements and Vitamins Inc., USA

SP49  ProstActive, Nature’s Way, USA

SP50  Prostate SLX, New Chapter Inc., USA
Appendix

SP51 Prostate Advantage, Enzymatic Therapy Inc., USA

SP52 Saw Palmetto & Pygeum, Nature's Way, USA

SP53 Saw Palmetto Barry Extract, Solaray, USA

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**SP34**  Saw Palmetto Extract, Now Foods, USA

**SP54**  Saw Palmetto Extract, Source Naturals Inc., USA

**SP33**  Curbisal, Pharbio, Finland

**SP43**  Prostalan Forte, VSM, Netherlands
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SP44 Prostavit, Bional, Netherland

SP21 Prostavit Forte, Bional, Netherland

SP46 Prostavital, Health Aid, UK

SP16 Sawpalmetto Combination Product 1 (HFS), CJ Nutra, Korea
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SP18  Saw palmetto Combination Product 2 (HFS), Chung Wae Pharma Corporation, Korea

SP29  Sawpalmetto Mono Product 1 (HFS), CJ Nutra, Korea

SP32  Sawpalmetto Mono Product 2 (HFS), Chong Kun Dang Health, Korea

SP35  Prostasan, Bioforce AG, Switzerland

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SP30 Prosta Urgenin, Zeller, Switzerland

SP31 SabCaps, Vifor, Switzerland

SP27 Prostagutt Uno, Schwabe, Switzerland

SP40 Prostagutt F, Schwabe, Switzerland

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SP36  Prostadyn, Dr. Dünner, Switzerland

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7.4 Publications

Publications

Suter A, Sailer R, Riedi E, Heinrich M. Improving BPH symptoms and sexual dysfunctions with a saw palmetto preparation? Results from a pilot trial. Phytother Res. DOI: 10.1002/ptr.4696, Published online, 23rd of April 2012

Poster presentations


Talks