available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

A Critical Analysis of Permixon™ in the Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Enlargement

Carmen Maccagnano [a], *Andrea Salonia* [a], *Alberto Briganti* [a], *Pierre Teillac* [b], *Claude Schulman* [c], *Francesco Montorsi* [a,*], *Patrizio Rigatti* [a]

[a] *Department of Urology, Universita' Vita Salute San Raffaele, Milan, Italy*
[b] *Department of Urology, CHU Saint-Louis, Paris, France*
[c] *Department of Urology, Erasme University, Brussels, Belgium*

Article info

Keywords:
Benign prostatic hyperplasia
Benign prostatic obstruction
Lower urinary tract symptoms
Permixon™
Serenoa repens

Abstract

Objectives: The lipidosterolic extract of *Serenoa repens* (Permixon™) is commonly used to treat lower urinary tract symptoms related to benign prostatic enlargement. Pertinent peer-reviewed literature was critically analysed with the aim of clarifying the role of Permixon™ in view of recent basic science and clinical data.

Methods: MEDLINE and Cochrane Library searches were used to assess articles published between 1995 and 2005. The key words ''*Serenoa repens*,'' ''Saw palmetto,'' ''Permixon™,'' ''benign prostatic hyperplasia,'' ''lower urinary tract symptoms,'' ''chronic prostatitis,'' and ''prostate cancer'' were used.

Results: The chemical structure of Permixon™, its efficacy and tolerability, and the comparative studies between Permixon™ and inhibitors of both 5-α-reductase and α-blockers were considered and discussed. The basic rationale behind the therapeutic effects of Permixon™ is sound. Efficacy and safety of the drug are clearly shown. Comparative studies showed similar results between Permixon™, α-blockers, and finasteride in terms of efficacy. Also the tolerability profile of Permixon™ has been shown to be excellent.

Conclusions: Although some methodologic limitations hampered the positive results shown in the early studies on *Serenoa repens* in the treatment of lower urinary tract symptoms due to benign prostatic enlargement, recent sound research clearly revealed the positive role of Permixon™.

* Corresponding author. Department of Urology, Universita' Vita Salute San Raffaele, Via Olgettina 60, 20132 Milan, Italy. Tel. +39 02 26437286; Fax: +39 02 26437298.
E-mail address: montorsi.francesco@hsr.it (F. Montorsi).

1. Introduction

Since the 1990s, phytotherapy, being the use of plants and plant extracts (''herbal products'') for the treatment of many medical conditions, has become an increasingly common form of alternative therapy used in Europe, Asia, and the United States [1–4]. Prevalence rates are as high as 50% throughout

1569-9056/$ – see front matter doi:10.1016/j.eursup.2006.02.006

the world [5]. This has happened for many reasons, but mainly it is due to the fact that there is an easier access to these agents attributable to the expansion of health food stores and vitamin shops and due to the development of Internet commerce [6]. Patients have shown a general dissatisfaction with conventional treatments whilst, instead, phytotherapeutic agents often have a good tolerability, a low cost, and a high level of acceptance by the patient [7].

A survey in 1997 estimated that 12.1% of the adults in the United States had used a herbal medicine in the previous 12 mo, resulting in $5.1 billion out-of-pocket payments [8].

De Smet reported that, among those who had used herbal medicine, 15.1% had seen an alternative medicine practitioner, with a total of 10.5 million office visits, 19.8% of which had been completely or partially covered by insurance [1]. Nevertheless, it is difficult to assess precisely the production, distribution, and use of herbal preparations in the United States, due to the lack of standardisation of these products, especially since the US Food and Drug Administration (FDA) categorised them as ''food additives.'' Phytotherapeutic agents are commonly used in urology, especially in the treatment of benign prostatic hyperplasia (BPH). Among many different compounds, the most popular is an extract from the berry of the American dwarf palm tree (*Sabal serrulata*), called the Saw palmetto (*Serenoa repens* [SR]) [6]. This plant is common in swampy areas of the West Indies (Hill), Florida, and other areas of the south-eastern United States (North Carolina, Alabama, and Texas). The fruit is a dark purple-black berry, which grows in clusters and ripens from October to December. The ripe, partially dried berries, or drupes are the source of the extract, which have been used since the 1800s to treat a variety of prostatic conditions [9]; Saw palmetto was listed as an official drug in the United States Pharmacopoeia from 1906 to 1917. It entered the national formulary in 1926 and was eliminated only around 1950 because of a failure to detect an active principle in the herb. It therefore received no further attention since the arrival of modern synthesized pharmaceuticals [10].

2. Permixon™ chemical structure

The commercial name of SR is Permixon™ (Pierre Fabre Médicament, Castres, France) and it is a lipidosterolic hexane extract of the *Sabal serrulata*, consisting of 80% free (e.g., 94 g/100 g extract) and 7% esterified fatty acids, as well as small amounts of sterols (β-sitosterol, campesterol, stigmasterol, cycloartenol), and a minimum percentage of polyprenic compounds, arabinose, glucose, galactose, uronic acid, and flavonoids (Table 1).

Table 1 – Chemical composition of Permixon™

Components	Percentage (%)
Free fatty acids	86.7
Oleic	40
Lauric	32
Myristic	13
Palmitic	10
Linoleic	5
Fatty acids methyl and ethyl	4.5
Triglycerides	1.2
Long-chain esters	1.1

2.1. *Pharmacodynamic properties*

SR knowledge is based on the results of in vitro and in vivo animal and human studies. However, the exact mechanism of action is unknown because plant extracts are made of different chemical molecules and, therefore, they may singularly or in synergy display a wide spectrum of pharmacologic activities. In the past 5 yr, several excellent and comprehensive reviews have appeared in the literature along with the results of various clinical studies on the use of SR extract [10].

Mainly, Permixon™ is selective for prostate cells, as demonstrated by Bayne et al., who found damage of the intracellular membrane of these cells following treatment with the drug; the ultimate effect is apoptosis of prostatic cells [11]. Non–prostate-derived cells, that is, breast, skin, epididymis, testis, and kidney, do not appear to be susceptible to Permixon™. Only skin fibroblasts demonstrated a slight increase in apoptotic index after the treatment [11].

Several mechanisms of action are described for Permixon™ and are reported below.

2.1.1. *Noncompetitive inhibition of 5-α-reductase*

One of the most debated mechanisms of action of SR is a non-competitive inhibition of 5-α-reductase [12–16]. Testosterone, the androgen secreted by the testes, is the chief circulating androgen in the human prostate and skin, and it acts as a precursor of androgen action. The active hormone is dihydrotestosterone (DHT), which results from the reduction of the 4–5 double bond of testosterone by a membrane-bound enzyme, 5-α-reductase. This explains the considerably high DHT concentration in the prostate compared with plasma levels [12,17].

DHT is a critical factor for the growth of the prostate and the development of BPH; several drugs

have been developed to reduce the activity of androgens on target cells by inhibiting the action of 5-α-reductase isoenzymes.

In dogs and humans two isoenzymes of 5-α-reductase have been identified (type 1 and type 2) and they are both overexpressed in BPH tissue [12]. They are coded by two different genes [18], display a maximal activity at different pH values (neutral/basic for type 1, acidic for type 2), and they have different biochemical characteristics and selectivity towards various inhibitors [19–21]. The activity of 5-α-reductase, which is a nuclear membrane-associated enzyme, depends on fatty acids, which are important components of the membranes [22]. The two types of 5-α-reductase isoenzymes seem to be very sensitive to the composition of their molecular environment because accessibility of the enzyme to its cofactor depends on the conformational state of the protein, the latter depending on the composition of the membrane [23]. Many authors suggested that SR acts, at least partly, due to modulatory effects by its lipid components on the enzyme environment [14,21,23–25]. It has been shown that phospholipids and cholesterol represent, respectively, two thirds and one third of total lipids in BPH homogenate. The main fatty acids were palmitic (C16:0), stearic (C18:0), linoleic (C18:2), and arachidonic (C20:4). Furthermore, there were significant differences in fatty acid composition of phospholipids between epithelium and stroma. In the epithelium, the amount of oleic acid was significantly higher than in stroma, whereas the opposite was true for the arachidonic acid, with an age-dependent alteration (desaturation) of the fatty composition in BPH.

The lipidosterolic extract of SR inhibits in vitro DHT formation in rat prostate, in human foreskin, and in stromal and epithelial cells of human BPH either separated [26] or cocultured [27]. Furthermore, in an ex vivo study, Di Silverio and colleagues showed inhibition of the conversion of testosterone in DHT in patients with BPH treated for 3 mo with Permixon™ (320 mg/d); 50% reduction of prostate concentration of DHT was observed [28].

Two other studies showed that Permixon™ intake was associated with prostatic epithelium contraction and a significant decrease in tissue levels of DHT [29,30]. Also Veltri et al. [31], in a pharmaceutical study model (which used a randomisation of patients in a double-blind, placebo-controlled trial), showed that after 6 mo of treatment with SR (106 mg × 3 = 418 mg, no pure extract), the DNA chromatin structure and organisation in prostate epithelial cells were altered.

Raynaud et al. showed that SR was a non-competitive inhibitor of both type 1 isoenzyme a type 2 5-α-reductase [12] and they explained that the discrepancies found by different authors [22,32] were due to different experimental conditions and to a selectivity for fatty acids. In fact, only specific aliphatic unsaturated fatty acids have been shown to inhibit 5-α-reductase activity [12,16].

SR inhibits the 5-α-reductase activity of the prostate without interfering with secretion of prostate-specific antigen (PSA) because it does not affect the transcription of the PSA gene, both in vitro [27] and in vivo [33,34]. The results of these studies agree with clinical trial data in the Bayne et al. study, which demonstrated no significant effect on PSA level in patients with BPH receiving the drug [27]. However, these result are in conflict with the data of Sultan et al. [35], where a supraphysiologic concentration of Permixon™ was used. In this study, inhibition of the androgen receptors was reported. Ravenna et al. [25] confirmed this observation and showed that an anti-androgenic effect could be obtained using concentrations of Permixon™, higher than those used in Bayne et al. study [27].

2.1.2. *Inhibition of DHT binding to the cytosolic androgen receptor in prostatic cells*

Dèlos et al. [26] and Carilla et al. [36] have shown that Permixon™ inhibits DHT by binding itself to the cytosolic androgen receptor in prostatic cells. In vitro studies have demonstrated that Permixon™ leads to competitive inhibition of radiolabeled DHT by binding to its receptor in rat cytosolic and human skin fibroblasts receptors [14,15].

2.1.3. *Inhibition of the nuclear oestrogen receptors in prostatic tissue*

Paubert-Braquet et al. have described that SR was able to inhibit the nuclear oestrogen receptors in prostatic tissue [37,38]. This has become evident also in studies by Iehle and Van Coppenolle where the authors used samples from patients receiving placebo or the herbal agent for 3 mo before open prostatectomy [16,39].

2.1.4. *Anti-inflammatory effects of Permixon™ in the prostate*

Several authors showed an anti-inflammatory effect in the prostate by inhibiting the enzymes responsible for the synthesis of prostaglandins and leukotrienes [13,14,38], mediated by neutrophils [15,16].

Moreover, Vela-Navarrete et al. found a significant reduction of interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), which are two important inflammatory markers in BPH tissue [40]. Also, correlated to the anti-inflammatory effects, there

is an antiedematous effect of SR on prostatic tissue in animal models [14,15].

2.1.5. *Action of growth factors on prostatic tissue*

Although the precise role of growth factors (GFs) in the human prostate has not yet been completely elucidated, evidence indicates that some of these peptides may act independently or in synergy with androgens and other cell mediators to induce BPH. GFs receptors have been demonstrated in the prostate [41–43].

Epidermal Growth Factor (EGF) is highly expressed in BPH tissue and the receptors have been located along the basal cell layer of the epithelium. EGF is also a strong mitogen for the primary cultures of human prostate epithelial cells. Also, Fibroblast Growth Factor (FGF), with EGF, induces an increased prostatic cell proliferation, ranging from 30% to 200% of the baseline value [41].

Transforming Growth Factor-α (TGF-α), which is a member of EGF family, has been found in large concentrations in BPH, but our knowledge about its importance in prostate physiology has not yet been elucidated.

Many in vitro studies demonstrated an inhibition of FGF- and EGF-induced prostatic epithelial proliferation by SR [10,14,15,28,38,41–43]. The effects are dose-dependent and are particularly evident in the glandular epithelium. Di Silverio et al. found a reduction of EGF concentrations in human BPH after 3 mo of treatment [28].

2.1.6. *Apoptosis*

Vela-Navarrete et al. [44] tested the effect of SR on molecular mechanisms associated with apoptosis, such as the Bax/Bcl-2 expression ratio and caspase-3 activity in prostatic tissue of men with BPH treated for 3 mo before surgery. The Bax/Bcl-2 ratio is an apoptotic index and they found that it was significantly enhanced in SR-treated patients compared with untreated patients. Caspase-3 is primarily responsible for the cleavage of Poly-Adenosine diphosphate-Ribose Polymerase (PARP). The authors found that the level of the intact 116-kD PARP form was significantly decreased in the prostatic tissue of SR-treated patients compared with that observed in the control group, suggesting that treated patients had increased caspase-3 activity in the prostate.

Wadsworth et al. tested the hypothesis that SR induces apoptosis in prostate epithelial cells by inhibiting the Insulin-like Growth Factor-1 (IGF-1) signalling pathway and inducing the cleavage of PARP [45].

2.1.7. *Modulation of prolactin-induced prostatic growth by receptor signal transduction*

The growth of the prostate gland depends mainly on androgens. Other hormones such as prolactin (PRL) also modulate prostate development by receptor signal transduction [14,39,46]. Van Coppenolle et al. analysed and compared the effects of SR and finasteride in an in vivo model of rat prostate hyperplasia induced by hyperprolactinaemia; they demonstrated for the first time the anti-PRL activity of SR (dose of 320 mg/kg) [39]. This was based on the fact that in men testosterone levels decrease with age, whereas PRL concentrations increase [47,48] and it is becoming increasingly clear that PRL is involved in prostate growth [49,50]. It has been suggested that PRL acts in synergy with androgens, either by enhancing the testosterone effect [51] or by increasing the number of cytosolic and nuclear androgen receptors [52].

The mechanism by which SR affects the PRL action on prostate cells is unknown. SR may inhibit PRL transduction or modify the activity of PRL receptors, as shown by Vacher et al. [46], resulting in reduced K^+ channel conductance and a reduction in the activity of protein kinase C (PKC).

Therefore, PRL may regulate prostate growth in an autocrine-paracrine loop, but it has not yet been taken into account in hormonotherapy for prostate diseases.

2.2. *Pharmacokinetics*

There are very limited data on the pharmacokinetic properties of SR because the drug is a complex mixture of different compounds. The active substance of Permixon™ shows an important trophism for prostatic tissue, both in animals and men. In fact, the tissue distribution of the lipidosterolic extract of SR was evaluated in rats with experimentally induced fibromuscular proliferation after oral administration of the drug, supplemented with ^{14}C-labeled oleic or lauric acid or β-sitosterol. Uptake of radioactivity was much higher in the prostate gland than in the liver or genitourinary tissue [53].

Chevalier et al. [53] evaluated drug pharmacokinetics in 24 male volunteers after oral administration of Permixon™ 160 mg, supplemented with labeled lauric or myristic acid. Permixon™ reached the peak concentration 3 h after intake.

In another study with 12 young male volunteers (mean age, 24 yr) De Bernardi et al. analysed the plasma concentration of one of the components of SR (second component, retention time 26.4 min on High-Performance Liquid Chromatography assay) after single-dose administration of 320 mg during

fasting. A mean peak plasma drug concentration of 2.6 mg/l was achieved 1.5 h after oral administration, the mean value of the area under the concentration versus time curve was 8.2 mg/l/h and the elimination half-life was 1.9 h [54].

3. Efficacy in patients with benign prostatic enlargement

Benign prostatic enlargement (BPE) due to BPH is a common condition throughout the world, and its incidence is increasing in old men; approximately 50% of men aged 60 yr and 90% aged 85 yr are affected by this condition, which results from excessive proliferation of both glandular and stromal tissues in the prostate. Indeed, symptoms are mainly caused by the growth of the prostate gland, which leads to a periurethral adenoma, which compresses the urethra and obstructs urine flow [55]. Another main cause of symptoms is an increased tone of the bladder neck and prostate smooth cells, which is regulated by α_1-adrenergic receptors. Thus, the main groups of drugs used for the treatment of BPH are α_1-receptor blockers (alfuzosin, doxazosin, tamsulosin, terazosin) or 5-α-reductase inhibitors (dutasteride and finasteride).

Several phytotherapeutic compounds are currently available for BPH, most of them derived from eight plant sources. Many of them have a significant placebo effect [56,57]. The most widely used plant extract is SR, which appears to have been more rigorously investigated, both clinically and scientifically, than any other extract [10]. Nevertheless, although SR was used to treat BPH from the late 1800s, it was not until the 1980s that the first clinical trials testing its efficacy in men were published. It is important to note that the first studies were often limited by the small numbers of patients studied and a treatment interval of only 1–3 mo [58].

The efficacy of SR has been evaluated, especially in an attempt to treat lower urinary tract symptoms. It is also important to consider the high degree of comorbidity between lower urinary tract symptoms and sexual dysfunction and, in the ultimate analysis, the patient's global quality of life [59,60].

3.1. *Permixon™ and lower urinary tract symptoms*

The efficacy of Permixon™ as a treatment for lower urinary tract symptoms (LUTS) associated with BPH has been described in several studies [56,61,62]. Evaluation of efficacy in BPH is based on reducing LUTS, increasing peak urinary flow rates in urine flow studies [63], determining postvoiding residue, and assessing the benefits in voiding using the International Prostate Symptom Score (IPSS).

In a study performed in rats, Oki et al. [64] examined SR effects on the micturition reflex and on autonomic receptors in the lower urinary tract. They demonstrated that SR significantly alleviated urodynamic symptoms in hyperactive rat bladders by increasing bladder capacity and subsequently prolonging the micturition interval. These data may support the clinical efficacy of SR for the treatment of LUTS.

On the other hand, in 1998, Gerber et al. [65] found no improvement in urodynamic parameters and they obtained the same data in a double-blind, placebo-controlled study, performed in 2004, in which they randomised 85 patients who were to receive either a placebo or SR for 6 mo [66]. They demonstrated an improvement of the symptoms' score, but no statistically significant change in urinary flow rate. Debruyne et al. [67] found similar results in another study performed in the same year. They randomised men with LUTS due to BPH to receive either SR or placebo, and after 4 mo of follow-up no significant beneficial effect of SR was found in the IPSS or peak urinary flow rate. However, the initial IPSS was significantly less in the Permixon™ group, leading the authors to conclude that the IPSS improvement was directly related to the initial severity of LUTS.

Both Descotes et al. [68] and Stepanov et al. [69] demonstrated clinical efficacy of Permixon™ in improving urinary frequency and urinary flow. In the latter study, the authors [69] examined two regimens of the drug in 100 men with BPH. Both the once-daily dose of 320 mg and the twice-daily dose of 160 mg Permixon™ reduced the IPSS value, with similar results. Quality-of-life scores and urinary flow improved after a month and were stable for the 3-mo duration of the trial.

Wilt et al. [70] conducted a meta-analysis of 2939 men treated with SR. They analysed the results of 18 trials and concluded that men treated with SR had an improvement of 1.9 ml/s in mean peak urinary flow rate and a mean decrease of 1.4 points in the symptoms' score, compared with controls. However, the mean duration of all studies was about 9 wk, and many trials did not include a placebo arm or did not include the use of SR together with other herbal medicaments.

In 2004, Boyle et al. published another meta-analysis about 2589 patients. Eleven randomised clinical trials and two open-label trials were considered. Peak urinary flow rate and nocturia were the two common end-points. The authors showed that the average $\pm$ SE placebo effect on the peak

urinary flow rate was an increase of 0.51 ± 0.51 ml/s. The estimated effect of Permixon™ was a further increase of 2.20 ± 0.51 ml/s ($p < 0.001$). Placebo was associated with a reduction in the mean number $\pm$ SE of nocturnal urinations of 0.69 ± 0.15. A further reduction of 0.50 ± 0.01 episodes of urination ($p < 0.001$) occurred that was attributable to Permixon™ [13].

3.2. *Permixon™ and sexual function*

In recent years quality-of-life issues, including sexual function, have received increased attention from patients affected by BPE. In a study with the aim of determining which aspects of quality of life were considered as most important in patients being treated for BPH, sexual activity and satisfaction with sexual relationships were considered of utmost importance by patients [71].

In an European multicentre trial of 1098 patients randomised to take either Permixon™ or finasteride for 6 mo, patients receiving Permixon™ showed a lower incidence of sexual dysfunction compared to those treated with finasteride [61].

Zlotta et al. [72] used the MSF-4 in a study comparing Permixon™, tamsulosin, and finasteride to analyse the sexual function of 2511 patients with LUTS due to BPH. At 6 mo, as compared to pretreatment data, there was a slight increase in sexual disorders in patients treated with tamsulosin (+0.3) and finasteride (+0.8), whereas sexual function slightly improved with Permixon™ therapy (−0.2). Ejaculation disorders were the most frequently reported side-effects after tamsulosin or finasteride.

4. Tolerability

The safety of SR has always been considered good [56,61]. In reviewing the literature, Gerber and Fitzpatrick pointed out good patient compliance and tolerability in Permixon™ trials, with serious adverse events being extremely uncommon and unrelated to the drug [66]. Moreover, it has been shown that side-effects occurred in similar numbers of patients receiving either Permixon™ or placebo [15,67].

In a large European study, Permixon™ caused no changes in standard blood tests and no change in serum PSA levels during 6 mo of treatment. Among 1098 patients with BPH in that study, the general safety profile of Saw palmetto compared favourably with that of finasteride [61].

The most common adverse events reported in clinical trials have been minor gastrointestinal complaints, such as nausea and abdominal pain, which were resolved by taking the drug in association with meals [15]. Similar results were obtained in a 1-mo placebo-controlled study of 176 patients [67].

Adverse events were reported by 3.9% of the men treated with SR compared with 1.1.% receiving placebo, and only one patient receiving active treatment interrupted therapy due to poor tolerability. In the largest clinical trial comparing SR with finasteride, 5 mg once daily, no statistically significant difference was demonstrated in the incidence of adverse events between treatment groups [61]. Among men randomised to receive 6 mo of therapy with SR, 551 were evaluable for tolerability compared with 542 receiving finasteride. The adverse events reported by at least 1% of the patients in either treatment group were decreased libido, impotence, urinary retention, dysuria, hypertension, headache, influenza-like symptoms, abdominal pain, back pain, nausea, constipation, and diarrhea. Gastrointestinal complaints were the most frequently reported category of adverse events in both therapies and occurred more frequently with finasteride.

5. Comparative studies

At the present time, a number of medical therapies are available to relieve symptoms of BPH including 5-α-reductase inhibitors, α-adrenergic receptor blockers, and phytotherapeutic agents. Comparisons between Permixon™ and these alternative treatments have shown similar levels of clinical efficacy.

5.1. *5-α-reductase inhibitors: finasteride*

Finasteride is a specific inhibitor of 5-α-reductase. The inhibition of this enzyme causes a significant reduction of intraprostatic DHT levels by lowering the conversion of testosterone to DHT, resulting in a decrease of prostate volume seen in men treated with finasteride.

Unlike other 5-α-reductase inhibitors, SR blocks the 5-α-reductase activity of epithelial cells without interfering with their capacity to secrete PSA [11,33,34]. This contrasts with the synthetic 5-α-reductase inhibitors, which down-regulate PSA gene expression and secretion within the cell by directly inhibiting the binding of the activated α-reductase to the hormone response element (HRE) of the PSA gene promoter [73]. Thus, finasteride and other similar inhibitors have a dual effect on androgen action in the prostate: indirectly through inhibition of 5-α-reductase activity, thereby reducing the

availability of the more potent ligand DHT, and directly through interference with DNA binding by the α-reductase.

Although the mechanism responsible for the down-regulation of PSA after treatment with finasteride has been established, no one has been able to explain why SR suppresses prostate growth without interfering with PSA production by the epithelial cells of the gland.

In a randomised, multicentre, double-blind clinical trial conducted by Sökeland [74], involving 453 patients in the early stages of BPH, patients received a fixed combination of SR and *Urtica dioica*, or finasteride The patients assessed had valid ultrasonographic measurements and baseline prostate volumes of either <40 ml or >40 ml. The mean maximum urinary flow (the main outcome variable) increased (from baseline values) after 24 wk by 1.9 ml/s with the combination SR-*Urtica dioica* and by 2.4 ml/s with finasteride. There were no statistically significant group differences. The subgroups with small prostates showed similar improvements and this was also seen in patients with large prostates. There were improvements in the IPSS in both treatment groups, with no statistically significant differences. The subgroup analysis showed slightly better results for voiding symptoms in the patients with prostates of >40 ml, but there were also improvements in the subgroup of smaller prostates. The safety analysis showed that more patients in the finasteride group reported adverse events.

The finding of finasteride effects being unrelated to baseline prostate volumes as reported in Sokeland's study are in contrast with those by Boyle et al. [73] and Lepor et al. [75]. In these articles the authors support the hypothesis that the efficacy of treatment with finasteride may be predicted by the baseline prostate volumes of the patient.

In the study by Carraro et al., which compared the effects of Saw palmetto and finasteride, the two compounds were found to have nearly equal effects, causing parallel and statistically significant decreases in symptom scores and increases in maximal flow rates [61].

5.2. *α-Adrenergic receptor blockers*

5.2.1. *Tamsulosin*

Debruyne et al. [67] reported on a 1-yr, two arms head-to-head comparison of Permixon™ 320 mg/d and tamsulosin 0.4 mg/d with the aim of assessed the equivalence between the two products. Of note, no placebo arm was included in this study. Eight hundred and eleven men with symptomatic BPH (IPSS ≥ 10) were recruited in 11 European countries. At 12 mo, IPSS decreased by 4.4 in each group and no differences were observed in either irritative or obstructive symptoms' improvements. The increase in maximum flow was similar in both treatment groups (1.8 ml/s Permixon™, 1.9 ml/s tamsulosin). PSA remained stable while prostate volume decreased slightly in Permixon™-treated patients. The two compounds were well tolerated; however, ejaculation disorders occurred more frequently in the tamsulosin group. The same authors also reported on a subset of patients included in the same study showing an IPSS >19 (i.e., severely symptomatic) [76]. In this patient subgroup at 12 mo, total IPSS decreased by 7.8 with Permixon™ and 5.8 with tamsulosin ($p = 0.051$). The irritative symptoms improved significantly more ($p = 0.049$) with Permixon™ (−2.9 versus −1.9 with tamsulosin). The superiority of Permixon™ in reducing irritative symptoms appeared as soon as month 3 and was maintained up to month 12. Safety profiles between tamsulosin and Permixon™ were also fairly similar as 8.2% and 7.7% of tamsulosin- and Permixon™-treated patients experienced at least one adverse event leading to definitive interruption of treatment.

Thus, the antiandrogenic, antiproliferative, and anti-inflammatory complementary activities of SR could constitute an advantage over α-blockers to treat severe symptomatic BPH where both obstruction and irritation are involved. Nevertheless, this trial lacked a placebo arm, so it is not possible to prove the individual efficacy of either Permixon™ or tamsulosin, but it demonstrates equivalence between the two drugs.

5.2.2. *Alfuzosin*

In a comparative trial of Permixon™ to alfuzosin, 63 patients with BPH, who did not respond to placebo, were randomised to receive either 160 mg Permixon™ twice a day or 2.5 mg alfuzosin three times a day. Again, the symptoms' score improved significantly from baseline, with no significant differences between treatment groups [77].

6. Other targets of Permixon™

Permixon™ has also been used in the treatment of other conditions, such as prostate cancer and chronic prostatitis.

6.1. *Prostate cancer*

Evidence indicates that alternative medicine is used by a significant proportion of North American men

with prostate cancer [78–80]. The reported rates of complementary and alternative medicine (CAM) use among American men diagnosed have ranged from 18% to 43%. Boon and colleagues [81] reported an elevated prevalence of the use of CAM (almost 30%) in men diagnosed with prostate cancer in Ontario, Canada, in addition to conventional medical treatments. The three characteristics highly associated with CAM use were support group attendance, disease status, and beliefs about the efficacy and adverse effects of CAM.

Many authors have tried to identify the molecular pathways that might mediate the action of these compounds in the human prostate [25,82]. Goldmann et al. [83] investigated the role of SR in prostate cancer by comparing the growth of prostatic cancer cell lines in the presence and absence of SR. The data collected suggested that the drug inhibits the growth of a normal prostatic-derived cell line and prostatic carcinoma cell lines. The results may suggest an ''operating mechanism'' involving growth inhibition via expression of Bcl-2 and prevention of prostate carcinoma development through the inhibition of expression of cyclooxygenase 2 (COX-2).

Therefore, the best advantage of SR is the inhibition of the 5-α-reductase activity of the prostate without interfering with PSA secretion [34]. Because PSA is the main serum marker for the diagnosis and progression of prostate cancer, it is imperative that any treatment should not interfere with its production.

6.2. *Chronic prostatitis*

Given the overlap of LUTS between BPH and chronic prostatitis, phytotherapeutic agents either alone, or in combination in ''prostatic health'' formulations, have also been recommended for men with prostatitis [7], because the etiology and pathophysiology remain to be defined. Among reported effects of saw palmetto is involution of the prostatitic epithelium in men with BPH. Other effects include the antiandrogenic action and the inhibition of α_1-adrenergic receptors and the antioxidant effect to specific inhibition of cytokines such as IL-8 [15,32].

Kaplan et al. designed a prospective 1-yr trial using saw palmetto versus finasteride to assess their efficacy in the treatment of category III prostatitis/chronic pelvic pain syndrome (CP/CPPS). They found that CP/CPPS treated with SR had no appreciable long-term improvement [84]. In a poster presented at the 2001 American Urological Association meeting Volpe et al. compared therapy with SR or finasteride in CPPS for 1 yr [85]. Although there was some improvement seen in the finasteride group, there was no improvement in the saw palmetto group.

7. Conclusion

Both subjective and objective measurements of the benefits of Permixon™ have been described in several studies, but they still remain underrecognised. The short-term duration of early trials with SR (which could have led to underestimation of the efficacy of SR), the lack of a control group in many studies, and the different composition and consistency of formulas in all brands of SR (and related to this, different clinical profiles and unknown interaction with other drugs) have certainly hampered the results of early studies.

Nevertheless, high levels of patient tolerance and safety, together with easy use and clinical efficacy, indicate that Permixon™ could be considered as a valid alternative in BPH treatment, especially to preserve sexual function and a good quality of life in complex cases. Therefore, the drug appears to be as effective as α-blockers and 5-α-reductase inhibitors while showing a more favourable tolerability and safety profile.

References

[1] De Smet PAGM. Herbal remedies. New Engl J Med 2002; 347:2046–56.
[2] Weinrich SP, Hudson Priest J, Moyad MA, Weinrich MC. Intake of selected nutritional supplements by African-American men. Urology 2004;64:1094–7.
[3] Moyad MA. The prevalence and effectiveness of complementary and alternative medicine: what has been learned and it may be telling us about our patient, ourselves and conventional and medical treatment. Semin Urol Oncol 2001;19:257–69.
[4] Eisenberg DM, Kessler DC, Foster C, et al. Unconventional medicine in the United States: prevalence, costs, and pattern of use. N Engl J Med 1993;328:246–52.
[5] MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. Lancet 1996;347: 569–73.
[6] Fagelman E, Lowe FC. Herbal medicine in the treatment of benign prostatic hyperplasia (BPH). Urol Clin North Am 2002;29:23–9.
[7] Shoskes DA. Phytotherapy in chronic prostatitis. Urology 2002;60:35–7.
[8] Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine used in the United States, 1990–1997: results of a follow-up national survey. JAMA 1998;280: 1569–75.

[9] Murray MT, Pizzorno J. Encyclopaedia of natural medicine. Seattle, WA: John Bastyr University Publishing; 1994
[10] Buck AC. Is there a scientific basis for the therapeutic effects of *Serenoa repens* in benign prostatic hyperplasia? Mechanism of action. J Urol 2004;172:1792–9.
[11] Bayne CW, Ross M, Donnelly F, Habib FK. The selectivity and specificity of lipido-sterolic extract of *Serenoa repens* (Permixon™) on the prostate. J Urol 2000;164:876–81.
[12] Raynaud J-P, Cousse H, Martin P-M. Inhibition of type 1 and type 2 5-alpha-reductase activity free fatty acids, active ingredients of Permixon™. J Steroid Biochem Mol Biol 2002;82:233–9.
[13] Boyle P, Robertson C, Lowe F, Roehrborn C. Update meta-analysis of clinical trials of *Serenoa repens* extract in the treatment of symptomatic benign prostatic hyperplasia. BJU Int 2004;93:751–6.
[14] Gerber GS. Saw palmetto for the treatment of men with lower urinary tract symptoms. J Urol 2004;163:1408–12.
[15] Plosker GL, Brogden RX. *Serenoa repens* (Permixon™). A review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. Drugs Aging 1996;9:379–85.
[16] Iehlé C, Delos S, Guirou O, et al. Human prostatic steroid 5-alpha-reductase isoforms—a comparative study of selective inhibitors. J Steroid Biochem Mol Biol 1995;54: 273–9.
[17] Krieg M, Nass R, Tunn S. Effect of aging on endogenous level of 5-alpha-dihydrotestosterone, testosterone, estradiol and estrone in epithelium and stroma of normal and hyperplastic human prostate. J Clin Endocrinol Metab 1993;77:375–81.
[18] Anderson S, Rissell DW. Structural and biochemical properties of cloned and expressed human and rat steroid 5-alpha-reductase. Proc Natl Acad Sci USA 1990;87: 3640–4.
[19] Jenkins EP, Andersson S, Imperato Mc-Ginley J, Wilson JD, Russell DW. Genetic and pharmacological evidence for more than one steroid 5-alpha-reductase. J Clin Invest 1992;89:293–300.
[20] Thigpen AE, Silver RI, Guileyardo JM, Casey LM, McConnell JD, Russell DW. Tissue distribution and ontogeny of steroid 5-alpha-reductase isozyme expression. J Clin Invest 1993;92:903–10.
[21] Span PN, Benraad ThJ, Sweep AGH, et al. Kinetic analysis of steroid 5-alpha reductase activity at neutral pH in benign prostatic hyperplastic tissue: evidence for type I isozyme activity in the human prostate. J Steroid Biochem Mol Biol 1996;57:103–8.
[22] Liang T, Liao S. Inhibition of steroid 5-alpha-reductase by specific aliphatic unsaturated fatty acids. Biochem J 1992;285:557–62.
[23] Ielhé C, Radvanyi F, Gil Diez de Medina S, et al. Differences in steroid 5-alpha-reductase isoenzymes expression between normal and pathological human prostate tissue. J Steroid Biochem Metab 1999;68:189–95.
[24] Délos S, Iehlè C, Carsol J-L, et al. Inhibition of human prostatic testosterone metabolism by a lipido-sterol extract of *Serenoa repens* (Permixon™). J Urol 1996;155: 572A (abstract no. 1046).
[25] Ravenna L, di Silverio F, Russo M, et al. Effect of lipidosterolic extract of *Serenoa repens* (Permixon™) in human prostatic cell lines. Prostate 1996;29:219–30.
[26] Dèlos S, Carsol J-L, Ghazarossian E, Raynaud J-P, Martin PM. Testosterone metabolism in primary culture of human prostate epithelial cells and fibroblasts. J Steroid Biochem Metab 1995;55:375–83.
[27] Bayne CW, Donnelly F, Ross M, Habib FK. *Serenoa repens* (Permixon™): a 5-α-reductase types I and II inhibitor. New evidence in a co-cultured model for BPH. Prostate 1999;40:232–41.
[28] Di Silverio F, Monti S, Sciarra A, et al. Effects of long term treatment with *Serenoa repens* (Permixon™) on the concentrations and regional distribution of androgens and epidermal growth-factor in benign prostatic hyperplasia. Prostate 1998;37:77–83.
[29] Marks LS, Partin AW, Epstein JI, et al. Effects of a saw palmetto herbal blend in a symptomatic benign prostatic hyperplasia. J Urol 2000;163:1451–6.
[30] Marks LS, Hess DL, Dorey FJ, et al. Tissue effect of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic androgens. Urology 2001;57: 999–1005.
[31] Veltri RW, Marks LS, Craig Miller M, et al. Saw palmetto alters nuclear measurement reflecting DNA content in men with symptomatic BPH: evidence for a possible molecular mechanism. Urology 2002;60:618–22.
[32] Weisser H, Tunn S, Behnke B, et al. Effects of the *Sabal serrulata* extracts IDS 89 and its subfractions on 5-alpha-reductase activity in human benign prostatic hyperplasia. Prostate 1996;28:300–6.
[33] Dreikorn K, Lowe F, Borkowski A, et al. Other medical therapies. In: Chatelain C, Denis L, Foo KT, Khuory S, McConnell J, editors. Benign prostatic hyperplasia. Plymouth, United Kingdom: Health Publications; 2001 . p. 481–511.
[34] Habib FK, Ross M, Ho CKH, Lyons V, Chapman K. *Serenoa repens* (Permixon™) inhibits the 5-alpha-reductase activity of human prostate cancer cell lines without interfering with PSA expression. Int J Cancer 2005;114: 190–4.
[35] Sultan C, Twerraza A, Devillier C, et al. Inhibition of androgen metabolism and binding by a lipidosterolic extract of *Serenoa repens* B in human foreskin fibroblasts. J Steroid Biochem 1984;20:515–9.
[36] Carilla E, Briley M, Fauran F, et al. Binding of Permixon™ a new treatment for benign prostatic hyperplasia, to the cytosolic androgen receptor in rat prostate. J Steroid Biochem 1984;20:521–3.
[37] Paubert-Braquet M, Richarson FO, Servent-Saez N, et al. Effect of the *Serenoa repens* extract (Permixon™) on estradiol/testosterone-induce experimental prostate enlargement in the rat. Pharmacol Res 1996;34:171–9.
[38] Paubert-Braquet M, Cousse H, Raynaud JP, et al. Effect of the lipidosterolic extract of *Serenoa repens* (Permixon™) on the ionophore A23187-stimulated production of leukotriene B4 (LTB-4) from human polymorphonuclear neutrophils. Prostaglandins Leukot Essent Fatty Acids 1997; 57:299–304.

[39] Van Coppenolle F, Le Bourhuis X, Carpentier F, et al. Pharmacological effects of the lipidosterolic extract of *Serenoa repens* (Permixon™) on rat prostate hyperplasia induced by hyperprolactinemia: comparison with finasteride. Prostate 2000;43:49–58.

[40] Vela-Navarrete R, Garcia-Cardoso J, Barat JV, Manzarbeitia A, Lopez-Farre A. BPH and inflammation: pharmacological effects of Permixon™ on histological and molecular inflammatory markers. Result of a double blind pilot clinical assay. Eur Urol 2003;44:549–55.

[41] Paubert-Braquet M, Cousse H, Raynaud J-P, Mencia-Huerta JM, Braquet P. Effect of the lipidosterolic extract of *Serenoa repens* (Permixon™) and its major components on basic fibroblast growth factor-induced proliferation of cultures of human prostate biopsies. Eur Urol 1998;33: 340–7.

[42] Maddy SQ, Chisholm GD, Hawkins RA, Habib FK. Localization of epidermal growth factor receptors I the human prostate by biochemical and immunocytochemical methods. J Endocrinol 1987;113:147–53.

[43] Ibrahim GK, Kerns B-J, MacDonald JA, et al. Differential immunoreactivity of epidermal growth factor receptor in benign, dysplastic and malignant prostatic tissue. J Urol 1993;149:170–3.

[44] Vela-Navarrete R, Scribano-Burgos M, Lopez Farré A, Garcìa-Cardoso J, Manzarbeitia F, Carrasco C. *Serenoa repens* treatment modifies Bax/Bcl-2 index expression and caspase-3 activity in prostatic tissue from patients with benign prostatic hyperplasia. J Urol 2005;173:507–10.

[45] Wadsworth T, Carroll JM, Mallinson RA, Roberts CT, Roselli CE. Saw palmetto extract suppresses insulin-like growth factor-I signalling and induces stress-activated protein kinase/c-Jun N-terminal kinase phosphorylation in human prostate epithelial cells. Endocrinology 2004; 145:3205–14.

[46] Vacher P, Prevaeskaya N, Skyrma R, et al. The liposterolic extract from *Serenoa repens* interferes with prolactin receptor signal transduction. J Biomed Sci 1995;2:357–65.

[47] Davidson JM, Chen JJ, Crapo L, Gray GD, Greenleaf WJ, Catania JA. Hormonal changes and sexual function in aging men. J Clin Endocrinol Metab 1983;57:71–7.

[48] Nankin HR, Calkins JH. Decreased bioavailable testosterone in aging normal and impotent men. J Clin Endocrinol Metab 1986;63:1418–20.

[49] Costello LC, Franklin RB. Effects of the prolactin on the prostate. Prostate 1994;24:162–6.

[50] Wennbo H, Kindblom J, Isaksson OGP, Tornell J. Transgenic mice overexpressing the prolactin gene develop dramatic enlargement of the prostate gland. Endocrinology 1997;138:4410–5.

[51] Nevalainen MT, Valve EM, Ingleton PM, Nurmi I, Martikainen PM, Harkonen PL. Prolactin and prolactin receptors are expressed and functioning in human prostate. J Clin Invest 1997;99:618–27.

[52] Farnsworth WE. Prolactin effect in the permeability of human benign hyperplasic prostate to testosterone. Prostate 1988;12:221–9.

[53] Chevalier G, Bernard P, Cousse H, Bengone T. Distribution study of radioactivity in rats after oral administration of the lipido/sterolic extract of *Serenoa repens* (Permixon™) supplemented with [I-14C]lauric acid, [I-14C]oleic acid or [4-14C]β-sitosterol. Eur J Drug Metab Pharamacokinet 1997 Jan–Mar;22:73–83.

[54] De Bernardi di Valserra M, Tripodi AS, Contos S, et al. *Serenoa repens* capsules: a bioequivalence study. Acta Toxicol Ther 1994;15:21–39.

[55] Geller J, Kirschenbaum A, Lepor H. Therapeutic controversies: clinical treatment of benign prostatic hyperplasia. J Clin Endocrinol Metab 1995;80:745–8.

[56] Marks LS, Tyler VE. Saw palmetto extract: newest (and oldest) treatment alternative for men with benign prostatic hyperplasia. Urology 1999;53:457–61.

[57] Nickel JC. Placebo therapy of benign prostatic hyperplasia: a 25-month study (Canadian PROSPECT study group). Br J Urol 1998;81:383–7.

[58] Gerber GS, Zagaja GP, Bales GT, Chodak GW, Contreras BA. Saw palmetto (*Serenoa repens*) in men with lower urinary tract symptoms: effects on urodynamic parameters and voiding symptoms. Urology 1998;51:1003–7.

[59] Frankel SJ, Donovan JL, Peters TI, et al. Sexual dysfunction in men with lower urinary tract symptoms. J Clin Epidemiol 1998;51:677–85.

[60] Pytel YA, Lotpakin N, Gorilovsky L, Vinarov A, Sivkov A, Raynaud JP. Long-term clinical and biological effects of the lipidosterolic extract of *Serenoa repens* in patients with benign prostatic hyperplasia. Adv Ther 2002;19:297–306.

[61] Carraro JC, Raynaud J-P, Koch G, et al. Comparison of phytotherapy (Permixon™) with finasteride in the treatment of benign prostatic hyperplasia: a randomized international study of 1098 patients. Prostate 1996;29:231–40.

[62] Lowe FC, Kuj JC. Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. Urology 1996;48: 12–20.

[63] Oesterling JE. Benign prostatic hyperplasia. Medical and minimally invasive treatment options. N Engl J Med 1995; 332:9–19.

[64] Oki T, Suzuki M, Nishioka Y, Yasuda A, Umegaki K, Yamada S. Effects of saw palmetto extract on micturition reflex of rats and its autonomic receptor binding activity. J Urol 2005;173:1395–9.

[65] Gerber GS, Kuznetsov D, Johson BC, Burstein JD. Randomized, double blind, placebo controlled trial of saw palmetto in men with lower urinary tract symptoms. Urology 1998;58:960–4.

[66] Gerber GS, Fitzpatrick JM. The role of lipidosterolic extract of *Serenoa repens* in the management of lower urinary tract symptoms associated with benign prostatic hyperplasia. BJU Int 2004;94:338–44.

[67] Debruyne F, Koch G, Boyle P, et al. Comparison of a phytotherapeutic agent (Permixon™) with an alpha-blocker (tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomised international study. Eur Urol 2002;41:497–506.

[68] Descotes JL, Rambeaud JJ, Desejaseaux P, Faure G. Placebo-controlled evaluation of the efficacy and tolerability of Permixon™ in benign prostatic hyperplasia after exclusion of placebo responders. Clin Drug Invest 1995; 9:291–7.

[69] Stepanov VN, Siniakova LA, Sarrazin B, Raynaud JP. Efficacy and tolerability of the lipidosterolic extract of *Serenoa repens* (Permixon™) in benign prostatic hyperplasia: a double blind comparison of two dosage regimens. Adv Ther 1999;16:231–41.

[70] Wilt TJ, Idìshani A, Starck G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for the treatment of benign prostatic hyperplasia: a systematic review. JAMA 1998; 280:1604–9.

[71] Kassabian VS. Sexual function in patients treated for benign prostatic hyperplasia. Lancet 2003;361:60–2.

[72] Zlotta AR, Teillac P, Raynaud J-P, Schulamn CC. Evaluation of male function in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) treated with a phytotherapeutic agent (Permixon™), tamsulosin or finasteride. Eur Urol 2005;48:269–76.

[73] Boyle P, Goul AL, Roehrborn CG. Prostate volume predicts outcome of treatment of BPH with finasteride: meta-analysis of randomised clinical trials. Urology 1996;48:398–405.

[74] Sökeland J. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostatic volume and therapeutic outcome. BJU Int 2000;86:439–42.

[75] Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. N Engl J Med 1996;335:533–9.

[76] Debruyne F, Boyle P, Calais Da Silva F, et al. Evaluation of the clinical benefit of Permixon™ and tamsulosin in severe BPH patients: PERMAL study subset analysis. Eur Urol 2004;45:773–9.

[77] Grasso M, Montesano A, Buonaguidi A, et al. Comparative effects of alfuzosin versus *Serenoa repens* in the treatment of benign prostatic hyperplasia. Arch Esp Urol 1995;48:97–103.

[78] Nam RK, Fleshner N, Rakovitch E, et al. Prevalence and patterns of the use of complementary therapies among prostate cancer patients: an epidemiologic analysis. J Urol 1999:1521–4.

[79] Kao GD, Devine P. Use of complementary health practices by prostate carcinoma patient undergoing radiation therapy. Cancer 2000;88:615–9.

[80] Wilkinson S, Gomella LG, Smith JA, et al. Attitudes and use of complementary medicines in men with prostate cancer. J Urol 2002;168:2505–9.

[81] Boon H, Westlake K, Stewart M, et al. Use of complementary/alternative medicine by men diagnosed with prostate cancer: prevalence and characteristics. Urology 2003;62:849–53.

[82] Bonham M, Arnold H, Montgomery B, Nelson PS. Molecular effects of the herbal compound PC-SPES: identification of activity pathways in prostate carcinoma. Cancer Res 2002;62:3920–4.

[83] Goldmann WH, Sharma AL, Currier SJ, Johston PD, Rana A, Sharma PC. Saw palmetto berry extract inhibits cell growth and Cox–2 expression in prostatic cancer cells. Cell Biol Int 2001;25:1117–24.

[84] Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. J Urol 2004;171:284–8.

[85] Volpe MA, Cabelin M, Te AE, et al. A prospective trial using saw palmetto versus finasteride in the treatment of chronic nonbacterial prostatitis (CP). J Urol 2001;165:27–8.