

3 months of treatment with SPE, the patients showed an improvement in their International Prostate Symptom Score (IPSS). Also, significant decreases in the levels of interleukin-1 β (IL-1 β) and tumor necrosis factor (TNF)- α were observed after the SPE treatment. Thus, SPE was shown to exert an anti-inflammatory effect.

Anti-proliferative effects

Maintenance of a constant number of cells is one of the basic functions of homeostasis. In normal adult prostate, the delicate balance between apoptosis and proliferation is well regulated and these indices are low. In contrast, in a prostate with BPH this equilibrium may not be maintained^[37-40]. Kyprianou *et al*^[37] showed a statistically significant elevation in TGF- β , a negative growth factor able to induce apoptosis under physiological conditions, in the epithelial cells of BPH tissue compared with the normal prostate and a statistically significant increase in the intensity of immunoreactivity for bcl-2 and the number of positive epithelial cells in BPH specimens relative to normal prostate. Claus *et al*^[41] also indicated stromal growth in BPH due to cell proliferation in the absence of apoptosis. Vacherot *et al*^[40] revealed that proliferation exceeded apoptosis in the stroma and epithelium of human BPH tissues. Although the rate of apoptosis did not differ between normal prostate and BPH tissue, the proliferative index was significantly higher in BPH tissue than in normal prostate in both the stroma and the epithelium. Furthermore, comparisons of the proliferative indices and apoptotic indices between the BPH tissues after 3 months of SPE (Permixon®) administration and those without SPE administration showed that in both the stroma and the epithelium, the proliferative index showed a significant decrease in SPE-treated BPH tissue relative to untreated tissue and the apoptotic index showed a significant increase in the SPE-treated BPH tissue.

Vacher *et al*^[42] showed that SPE reduced the basal activity of K⁺ channels and of protein kinase C in Chinese hamster ovary cells and that pretreatment with SPE abolished the effects of prolactin. Furthermore, it was demonstrated that SPE (Permixon®) inhibited the effects of prolactin and androgens on prostate growth in the rat lateral prostate^[23]. Thus, SPE might block prolactin-induced prostate growth by inhibiting several steps of prolactin receptor signal transduction.

Effects on pharmacological receptors in the lower urinary tract

In vitro effects

Goepel *et al*^[13] have shown that SPE displaced an

α_1 -adrenoceptor radioligand to bind to human prostatic and cloned human α_1 -adrenoceptors in a noncompetitive manner and concomitantly suppressed the agonist-induced formation of [³H]-inositol phosphate. We evaluated the *in vitro* and *in vivo* binding of SPE to autonomic receptors in the lower urinary tract^[14, 18, 19]. The *in vitro* experiment has shown that SPE inhibited the specific binding of [³H]prazosin (α_1 -adrenoceptor), [³H]N-methylscopolamine (muscarinic receptor) and (+)-[³H]PN 200-110 (1,4-dihydropyridine receptors), but not [³H] $\alpha\beta$ -MeATP (purinergic receptor), in the prostate, bladder and other tissues of rats in a concentration-dependent manner. Our recent study has shown that SPE competitively inhibited specific binding of [³H]prazosin and [³H]N-methylscopolamine in human prostate and bladder (Yamada *et al.*, unpublished data). Thus, it is suggested that SPE binds to α_1 -adrenergic, muscarinic and 1,4-dihydropyridine receptors, but not to purinergic receptors^[14, 18, 19]. Based on IC₅₀ values (Table 2), the binding activity of SPE for muscarinic receptors was shown to be 2-4 times greater than that for α_1 -adrenergic and 1,4-dihydropyridine receptors. The affinity of SPE for these receptors was comparable to the *in vitro* pharmacological potency of this extract (eg, inhibition of 5 α -reductase (IC₅₀: 71 μ g/mL), anti-inflammatory effect (IC₅₀ of cyclooxygenase and 5-lipoxygenase: 28.1 and 18.0 μ g/mL, respectively) and anti-androgenic effect (IC₅₀: 1004 μ g/mL))^[34, 43] reported previously. Furthermore, Scatchard analysis has revealed that SPE caused a significant decrease in the maximal number of binding sites (B_{max} values) of [³H]prazosin, [³H]NMS and (+)-[³H]PN 200-110 in the prostate or bladder of rats (45%, 45% and 33%, respectively)^[18, 19]. Therefore, it could be presumed that SPE binds non-competitively to α_1 -adrenergic, muscarinic and 1,4-dihydropyridine receptors in rat tissues. Such insurmountable antagonism by SPE was previously

Table 2. IC₅₀ values for *in vitro* inhibition by SPE of specific binding of [³H]prazosin, [³H]NMS, and (+)-[³H]PN 200-110 in rat tissues.

Radioligands	IC ₅₀ values (μ g/mL) (Mean \pm SE, n=4-9)
Specific [³ H]prazosin binding	
Prostate	169 \pm 24
Spleen	188 \pm 47
Specific [³ H]NMS binding	
Bladder	40.0 \pm 4.1
Submaxillary gland	52.3 \pm 4.4
Specific (+)-[³ H]PN 200-110 binding	
Bladder	97.3 \pm 17.1

noted in human prostatic and cloned α_1 -adrenoceptors^[13].

Vanilloids exert their activity through the transient receptor potential vanilloid subtype 1 (TRPV1), a nonselective cation channel. TRPV1 has been shown to be located in urinary bladder epithelial cells^[44]. The urothelial TRPV1 may play a role in concert with TRPV1 nerve fibers^[45]. Thus, TRPV1 may play a significant role in the pathophysiology of bladder disease. Our recent study has also shown that SPE significantly inhibits the capsaicin-induced Ca^{2+} influx in HEK293VR11 cells expressing TRPV1 receptors^[46]. Furthermore, SPE inhibited specific binding of [³H]resiniferatoxin in HEK293VR11 cells in a concentration-dependent manner. Thus, it is assumed that SPE inhibits the activation of TRPV1 in the bladder.

In vivo effects

Suzuki *et al*^[18,19] examined the effects of oral administration of SPE on autonomic receptors in rats. Repeated oral administration of SPE (SABALSELECTTM) for 4 weeks produced a significant decrease of muscarinic receptor (specific [³H]NMS binding) sites in the rat bladder and submaxillary gland^[18,19]. Notably, such a reduction in the number of [³H]NMS binding sites was observed at relatively low doses (0.6, 6 mg·kg⁻¹·day⁻¹) of SPE in the bladder and only at a high dose (60 mg·kg⁻¹·day⁻¹) in the submaxillary gland^[19]. On the other hand, a significant enhancement of α_1 -adrenoceptor (specific [³H]prazosin binding) sites was observed in rat prostate after repeated treatment with the low dose (6 mg·kg⁻¹·day⁻¹) of SPE, but not in the submaxillary gland, spleen and heart. The *in vitro* experiment showed that SPE exhibited little tissue selectivity in the binding of each receptor. These data suggest that SPE administered orally specifically affects muscarinic and α_1 -adrenoceptors in the lower urinary tract. Although there is no clear explanation for such selectivity, the most plausible reason may be the preferential distribution of receptor-binding constituents in the lower urinary tract after the systemic administration of SPE. SPE contains a complex mixture of free fatty acids and their esters, small quantities of phytosterols (eg, β -sitosterol), aliphatic alcohols and various polyphenolic compounds^[47]. A systemic distribution study in rats administered [¹⁴C]oleic acid or [¹⁴C]sitosterol-supplemented SPE has shown that these components are accumulated to a greater extent in the prostate than in other tissues^[48]. Because the prostate is particularly rich in free fatty acids, it would be expected that greater amounts of lipophilic substances accumulate in the prostate than in other tissues.

Repeated administration of SPE (100, 320 mg/kg) for 30 days inhibited prostatic hyperplasia induced by sulpiride

in rats^[23] and repeated administration of SPE (50 mg/kg) for 60 days also inhibited prostate hyperplasia induced by testosterone^[10]. Our previous study has shown that repeated treatment with testosterone for 4 weeks resulted in significantly increased (1.7–1.8 times) prostate weight in rats^[18]. However, repeated oral administration of SPE (6, 60 mg·kg⁻¹·day⁻¹) failed to significantly decrease tissue weight in any region of hypertrophied prostates of rats induced by the testosterone treatment. The reason why our data could not reproduce previous results might be the lower dosage and shorter treatment period. In agreement with the observation by Suzuki *et al*^[18], Rhodes *et al*^[49] noted that even high doses (180, 1800 mg/day) of SPE had no effect on prostatic hyperplasia in rats induced by testosterone treatment. The dosages (6 or 60 mg/kg) were comparable (320 mg/day) or 10 times higher than the dosage used for the treatment for BPH in humans.

Repeated treatment with testosterone in rats brought about a significant (62%) increase in prostatic α_1 -adrenoceptor receptor sites. Such enhancement of prostatic α_1 -adrenoceptor density in testosterone-treated rats was alleviated by the concomitant administration of SPE (SABALSELECTTM, 6 mg/kg)^[18]. Thus, oral administration of SPE has been suggested to attenuate up-regulation of α_1 -adrenoceptors in rat prostate induced by testosterone. It may be concluded that SPE at a clinically relevant dose exerts a direct effect on the pharmacological receptors in the lower urinary tract, thereby improving urinary dysfunction in patients with BPH and overactive bladders.

Effects on hepatic drug-metabolizing enzymes and blood biochemical values

Although the usage of medical herbs has grown quickly as a complementary and alternative medicine, scientific knowledge of the efficacy and safety of herbs is still lacking. Furthermore, the potential for interactions between herbs and drugs should be a concern because all herbs contain a large number of constituents^[50–53]. The proposed interactions would affect the pharmacokinetics and pharmacodynamics of drugs: absorption in the small intestine, metabolism in the intestine and liver, distribution to target organs, transport across cell membranes, and binding to specific receptors. Among these interactions, induction and inhibition of hepatic drug-metabolizing enzymes by herbal medicines or dietary compounds have been investigated. Suzuki *et al*^[18] have shown that repeated oral administration of SPE in rats had little significant influence on the content and activities of hepatic drug-metabolizing enzymes. Markowitz *et al*^[54] reported that SPE (320 mg/day for 14 days) for the treat-

ment of lower urinary tract symptoms suggestive of BPH did not alter plasma concentrations of probe drugs for cytochrome P-450 (CYP)2D6 and CYP3A4 activity in normal volunteers. Therefore, it is unlikely that SPE at generally recommended doses alters the disposition of co-administered drugs. Also, repeated oral administration of SPE in rats had little effect on blood biochemical parameters, except for a slight increase in the albumin value, suggestive of relative safety even with long-term intake^[16].

Clinical trials

Clinical trials conducted with SPE in men with BPH are summarized in Table 3^[15-57]. There have been more than 11

placebo-controlled trials^[8, 17, 58-66] and 4 active-controlled trials^[11, 15, 67, 68].

Placebo-controlled trials

As shown in Table 3, all placebo-controlled trials were conducted with SPE (320 mg/day) and placebo. Most of them were reported in the 1980s; the patient number was usually limited and the evaluation period was relatively short. More recently, two new and relatively large-scale placebo-controlled trials were conducted. One was reported by Willetts *et al*^[17] and the other by Bent *et al*^[8]. A double-blind placebo-controlled trial was held in Australia from January 1999 to March 2000^[17]. One hundred men with symptomatic BPH, aged <80 years with a maximal urinary flow rate of 5–15 mL/s, were included

Table 3. Effect of SPE on IPSS, peak urinary flow rate (Q_{max}) and mean values of urinary frequency (nocturia) in men with BPH in clinical trials.

Study	Group	Dose	Duration	IPSS		Q_{max}		Nocturia	
				n	change	n	change	n	change
Placebo-controlled study									
Bent S <i>et al</i> [8]	SPE	160*2	12m	112	-0.68#	112	0.42		
	Placebo	Placebo		113	-0.72#	113	-0.01		
Willetts KE <i>et al</i> [17]	SPE	160*2	12m			46	1.5		
	Placebo	Placebo				47	4.4		
Gerber GS <i>et al</i> [58]	SPE	160*2	6m	41	-4.4	41	1.0		
	Placebo	Placebo		44	-2.2	44	1.4		
Marks LS <i>et al</i> [59]	SPE (blend)	106*3	6m	21	-2.24	21	1.27		
	Placebo	Placebo		23	-1.39	23	0.09		
Descotes JL <i>et al</i> [60]	SPE	160*2	1m			82	3.42	82	-0.67
	Placebo	Placebo				94	1.06	94	-0.32
Reece SH <i>et al</i> [61]	SPE	160*2	3m			33	2.35	33	-1.0
	Placebo	Placebo				37	2.3	37	-1.0
Cukier J <i>et al</i> [62]	SPE	2*80*2	2–3m					43	-1.1
	Placebo	Placebo						47	-0.5
Tasca A <i>et al</i> [63]	SPE	160*2	3m			14	3.3	14	-2.6
	Placebo	Placebo				13	0.6	13	-1.2
Champault G <i>et al</i> [64]	SPE	2*80*2	1m			46	2.7	47	-1.4
	Placebo	Placebo				39	0.25	41	-0.5
Boccafroschi C <i>et al</i> [65]	SPE	160*2	2m			11	4.13	11	-2.2
	Placebo	Placebo				11	1.96	11	-1.0
Emili E <i>et al</i> [66]	SPE	160*2	1m			15	3.37	15	-1.6
	Placebo	Placebo				15	0.2	15	-0.4
Active-controlled study									
Debruyne F <i>et al</i> [16]	SPE	320*1	12m	350	-4.4		1.79		
	Tamsulosin	0.4*1		354	-4.4		1.89		
Carraro JC <i>et al</i> [11]	SPE	160*2	6m	464	-5.8		2.68	464	-0.74
	Finasteride	5		477	-6.2		3.26	477	-0.69
Grasso M <i>et al</i> [67]	SPE	160*2	0.75m			31	2.8	32	-1.0
	Alfuzosin	7.5				32	4.7	31	-0.9
Adriazora SM <i>et al</i> [68]	SPE	160*2	3m			20	1.5	20	-0.2
	Prazosin					22	0.47	22	-0.4

#: AUASI: American Urological Association Symptom Index

in the trial and were randomized to a group receiving SPE (160 mg twice a day) or placebo. The treatment period was 12 weeks. The primary outcomes were changes in IPSS, maximal urinary flow rate, and the Rosen International Index of Erectile Function (IIEF). The IPSS score decreased over time in both treatment groups; however, there was no significant difference after 12 weeks of treatment between the groups. There were no significant differences between the two treatment groups in the quality of life (QOL) score, the maximal urinary flow rate, and the IIEF score. On the other hand, each treatment group showed a significant improvement between week 0 and week 12. This trial was double-blind placebo-controlled, with high compliance and a low withdrawal rate; therefore, it could be regarded as a well-controlled trial. However, some of the results were unexpected, especially for the IPSS score and urine flow rates. The authors considered that it might be ascribable to a low IPSS at baseline, a small number of patients, and a relatively short trial period.

The other clinical trial was held in the United States from July 2001 to May 2004^[8]. It was a double-blind placebo-controlled trial lasting 14 months (2 months screening, 12 months treatment). Two hundred twenty-five men aged >49 years, with a maximum urinary flow rate of <15 mL/s, were randomly assigned to receive SPE (160 mg twice a day) or placebo. The primary outcomes were changes in the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate. Secondary outcomes were changes in prostate size, residual urinary volume after voiding, QOL, laboratory values, and the rate of reported adverse effects^[8]. No significant differences between the SPE and placebo groups were observed in the change in AUASI scores (mean difference: 0.04 point), maximal urinary flow rate (mean difference: 0.43 mL/s), prostate size, residual volume after voiding, QOL or serum prostate-specific antigen (PSA) levels during the one-year trial. The incidence of side effects was similar in the two groups. During the single-blind, placebo run-in period, there was a small but significant decrease in the AUASI score. Bent *et al*^[8] considered the discrepancy between their results and results from previous trials and questioned the adequacy of blinding, whether certain attributes of participants were taken into account, and specification of the SPE preparations of the previous trials.

Active-controlled trials

Four active-controlled trials have been conducted with SPE in men with BPH (Table 3). Just as the placebo-controlled trials, half of the trials enrolled very limited numbers of patients and had very short evaluation periods. Two active-controlled trials recruited enough patients and had relatively long treatment periods (6 and 12 months).

One of these studies was a 6-month, double-blind, randomized trial that compared the effects of SPE (160 mg twice daily, Permixon®) with that of a 5 α -reductase inhibitor (5 mg finasteride) in 1,098 men with moderate BPH using IPSS as the primary outcome^[11]. Both SPE and finasteride decreased the IPSS (-37% and -39%, respectively), improved QOL (by 38 and 41%) and increased peak urinary flow rate (+25% and +30%). Prostate volume (-18%) and serum PSA levels (-41%) were markedly decreased by finasteride. On the other hand, SPE improved symptoms with little effect on prostate volume and no change in PSA levels. SPE fared better than finasteride in a sexual function questionnaire and resulted in fewer complaints of decreased libido and impotence. Both treatments relieved the symptoms of BPH in about two thirds of the patients but, unlike finasteride, SPE had little effect on so-called androgen-dependent parameters. This suggests that other pathways are also involved in the symptomatology of BPH.

The other trial was a comparison of SPE (Permixon®) with tamsulosin^[6]. Eight hundred eleven men with symptomatic BPH were recruited and 704 patients were randomized to receive either tamsulosin (0.4 mg/d) or SPE (320 mg/d). At 12 months, IPSS decreased by 4.4% in each group and no differences were observed in either irritative or obstructive symptom improvements. The increase in maximal urinary flow rate was similar in both treatment groups. The mean prostate volume decreased by 0.99 mL in the SPE group, whereas it increased by 0.22 mL in the tamsulosin group. Prostate-specific antigen (PSA) remained stable, whereas prostate volume decreased slightly in SPE-treated patients. The tamsulosin group showed no significant changes in total PSA. The two compounds were well tolerated; however, evacuation disorders occurred more frequently in the tamsulosin group. This trial demonstrated that SPE and tamsulosin were equivalent in the medical treatment of lower urinary tract symptoms in men with BPH during and up to 12 months of therapy.

Debruyne *et al*^[69] conducted a subset analysis of the trial mentioned above. One hundred twenty-four patients with severe LUTS (IPSS>19) were stratified: 59 and 65 patients had been randomized to the tamsulosin and SPE groups, respectively. At 12 months, total IPSS decreased by 7.8% with SPE and 5.8% with tamsulosin; the irritative symptoms improved significantly more with SPE. The superiority of SPE in reducing irritative symptoms appeared only 3 months into treatment and was maintained up to month 12. Further analyses were conducted with the most severely symptomatic patients. In this subgroup, the between-group difference was maximal as soon as month 3 and was maintained up to

month 12 for both irritative and obstructive IPSS. For the irritative symptoms, the difference between groups was statistically significant over this period. Although the number of patients decreased, the between-group difference was still statistically significant over this period for the irritative symptoms.

Adverse effects of SPE are rare and usually mild. They include constipation, decreased libido, diarrhea, headache, hypertension, nausea, urine retention and pancreatitis^[3, 70]. In all randomized clinical trials in the meta-analysis^[3], withdrawal rates (a rough indicator of patient acceptance) were 9.1% for SPE, 11.2% for finasteride and 7.0% for placebo. No herb-drug interactions have been described^[54, 71]. However, in high throughput screening, SPE showed potent inhibition of the metabolic activity of CYP3A4, 2D6, and 2C9^[72].

Conclusions

BPH and associated LUTS are common disorders in aging men. Plant extracts are widely used in the treatment of BPH and related LUTS. In fact, SPE has been widely used as a therapeutic remedy for BPH in Europe. In the United States and Japan, SPE is not a prescribed medication; however, it has received attention from patients with BPH.

It is suggested that SPE has various pharmacological mechanisms (eg, inhibition of 5 α -reductase, anti-androgenic effects, anti-proliferative effects, anti-inflammatory effects and anti-edema effects). In addition, SPE may have α_1 -adrenoceptor inhibitory properties. In addition to the α_1 -adrenoceptor binding, we found significant binding to the muscarinic and 1,4-dihydropyridine receptors as novel mechanisms of pharmacological action of SPE in the lower urinary tract (Figure 2). Also, there is a possibility that SPE affects vanilloid receptor activity in the bladder. Anticholinergic agents are widely used for the treatment of OAB; therefore, inhibition of muscarinic receptors could be a novel pharmacological effect of SPE on the lower urinary tract for relief of irritative and obstructive symptoms of dysuria in BPH and LUTS. It is unlikely that the usefulness of SPE is limited by notable interactions with coadministered drugs or serious adverse events. Thus, this review may significantly contribute to the further understanding of the pharmacological effects of SPE in the treatment of patients with BPH and LUTS.

The constituents of different preparations of SPE differed markedly. The efficacy of SPE likely depends on the ingredients. Hence, it would be ideal to identify the active ingredients and to establish the optimal preparation in terms of efficacy and safety, or it should be recognized that the effi-

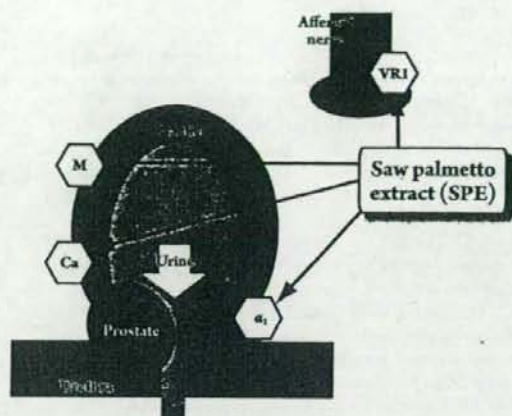


Figure 2. Proposed binding activities of saw palmetto extract (SPE) for pharmacological receptors in the lower urinary tract (bladder and prostate). M: muscarinic receptor, VR1: vanilloid receptor, Ca: 1,4-dihydropyridine receptor, α_1 : α_1 -adrenoceptor.

cacy and the safety of SPE could differ according to brand.

Considering that recent clinical trials, which were relatively large and well-controlled, did not demonstrate the superiority of SPE to placebo, the clinical potency of SPE has been questioned. However, the facts that several clinical studies showed the superiority of SPE over placebo and its comparability to prescribed medications and that many patients appear to reap benefits from SPE should be considered. Hence, it is anticipated that some suitably designed clinical studies (adequacy of blinding, treatment period, patient numbers, patient characteristics, etc.) will be conducted and we could ascertain the real potential of SPE for patients with BPH.

Abbreviations

- SPE: saw palmetto extract
- BPH: benign prostatic hyperplasia
- LUTS: lower urinary tract symptoms
- DSHEA: Dietary Supplement Health and Education Act
- DHT: dihydrotestosterone
- IPSS: International Prostate Symptom Score
- TRPV1: transient receptor potential vanilloid subtype 1
- CYP: cytochrome P-450
- IIEF: International Index of Erectile Function
- QOL: quality of life
- AUASI: American Urological Association Symptom Index
- PSA: prostate-specific antigen

References

- Roehrborn CG, Rosen RC. Medical therapy options for aging men with benign prostatic hyperplasia: focus on alfuzosin 10 mg once daily. *Clin Interv Aging* 2008; 3: 511-24.
- Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N Engl J Med* 1996; 335: 533-9.
- Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw palmetto, and Kava. *Ann Intern Med* 2002; 136: 42-53.
- Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *Jama* 1998; 280: 1604-9.
- Lowe FC, Ku JC. Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. *Urology* 1996; 48: 12-20.
- Koch E. Extracts from fruits of saw palmetto (*Sabal serrulata*) and roots of stinging nettle (*Urtica dioica*): viable alternatives in the medical treatment of benign prostatic hyperplasia and associated lower urinary tracts symptoms. *Planta Med* 2001; 67: 489-500.
- McNaughton-Collins M, Barry MJ. Managing patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Am J Med* 2005; 118: 1331-9.
- Bent S, Kane C, Shinohara K, Neuhaus J, Hudes ES, Goldberg H, et al. Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; 354: 557-66.
- Sultan C, Terraza A, Devillier C, Carilla E, Briley M, Loire C, et al. Inhibition of androgen metabolism and binding by a liposterolic extract of "Serenoa repens B" in human foreskin fibroblasts. *J Steroid Biochem* 1984; 20: 515-9.
- Paubert-Braquet M, Richardson FO, Servent-Saez N, Gordon WC, Monge MC, Bazan NG, et al. Effect of Serenoa repens extract (Permixon) on estradiol/testosterone-induced experimental prostate enlargement in the rat. *Pharmacol Res* 1996; 34: 171-9.
- Carraro JC, Raynaud JP, Koch G, Chisholm GD, Di Silverio F, Teillac P, et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostatic hyperplasia: a randomized international study of 1 098 patients. *Prostate* 1996; 29: 231-40; discussion 241-32.
- 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.
- Goepel M, Hecker U, Kregel S, Rubben H, Michel MC. Saw palmetto extracts potently and noncompetitively inhibit human alpha-1-adrenoceptors *in vitro*. *Prostate* 1999; 38: 208-15.
- 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.
- Andersson KE. LUTS treatment: future treatment options. *Neurourol Urodyn* 2007; 26: 934-47.
- Debruyne F, Koch G, Boyle P, Da Silva FC, Gillenwater JG, Hamdy FC, et al. Comparison of a phytotherapeutic agent (Permixon) with an alpha-blocker (Tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomized international study. *Eur Urol* 2002; 41: 497-506; discussion 506-497.
- Willettts KE, Clements MS, Champion S, Ehsman S, Eden JA. Serenoa repens extract for benign prostate hyperplasia: a randomized controlled trial. *BJU Int* 2003; 92: 267-70.
- Suzuki M, Oki T, Maruyama S, Takagi Y, Umegaki K, Nishioka Y, et al. Pharmacological effects of Saw Palmetto Extract on urodynamic functions and autonomic receptors in lower urinary tract of rats. *Jpn Neurogenic Bladder Soc* 2005; 16: 191-201.
- Suzuki M, Oki T, Sugiyama T, Umegaki K, Uchida S, Yamada S. Muscarinic and alpha 1-adrenergic receptor binding characteristics of saw palmetto extract in rat lower urinary tract. *Urology* 2007; 69: 1216-20.
- Habib FK, Wyllie MG. Not all brands are created equal: a comparison of selected components of different brands of Serenoa repens extract. *Prostate Cancer Prostatic Dis* 2004; 7: 195-200.
- Marks LS, Tyler VE. Saw palmetto extract: newest (and oldest) treatment alternative for men with symptomatic benign prostatic hyperplasia. *Urology* 1999; 53: 457-61.
- Levin RM, Das AK. A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. *Urol Res* 2000; 28: 201-9.
- Van Coppenolle F, Le Bourhis X, Carpentier F, Delaby G, Cousse H, Raynaud JP, 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.
- Steers WD. 5alpha-reductase activity in the prostate. *Urology* 2001; 58: 17-24; discussion 24.
- Delos S, Iehle C, Martin PM, Raynaud JP. Inhibition of the activity of 'basic' 5 alpha-reductase (type 1) detected in DU 145 cells and expressed in insect cells. *J Steroid Biochem Mol Biol* 1994; 48: 347-52.
- Di Silverio F, Monti S, Sciarra A, Varasano PA, Martini C, Lanzara S, 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.
- Iehle C, Delos S, Guirou O, Tate R, Raynaud JP, Martin PM. Human prostatic steroid 5 alpha-reductase isoforms — a comparative study of selective inhibitors. *J Steroid Biochem Mol Biol* 1995; 54: 273-9.
- Weisser H, Tunn S, Behnke B, Krieg M. Effects of the sabal serrulata extract IDS 89 and its subfractions on 5 alpha-reductase activity in human benign prostatic hyperplasia. *Prostate* 1996; 28: 300-6.
- Palin MF, Faguy M, LeHoux JG, Pelletier G. Inhibitory effects of Serenoa repens on the kinetic of pig prostatic microsomal 5alpha-reductase activity. *Endocrine* 1998; 9: 65-9.
- Raynaud JP, Cousse H, Martin PM. Inhibition of type 1 and type 2 5alpha-reductase activity by free fatty acids, active ingredients of Permixon. *J Steroid Biochem Mol Biol* 2002; 82: 233-9.
- Carilla E, Briley M, Fauran F, Sultan C, Duvilliers C. Binding of Permixon, a new treatment for prostatic benign hyperplasia, to the cytosolic androgen receptor in the rat prostate. *J Steroid Biochem* 1984; 20: 521-3.
- Mahapokai W, van den Ingh TS, van Mil F, van Garderen E, Schalken JA, Mol JA, et al. Immune response in hormonally-induced prostatic hyperplasia in the dog. *Vet Immunol Immunopathol* 2001; 78: 297-303.

- 33 Steiner G, Gessl A, Kramer G, Schollhammer A, Forster O, Marberger M. Phenotype and function of peripheral and prostatic lymphocytes in patients with benign prostatic hyperplasia. *J Urol* 1994; 151: 480-4.
- 34 Breu W, Hagenlocher M, Redl K, Tittel G, Stadler F, Wagner H. Anti-inflammatory activity of sabal fruit extracts prepared with supercritical carbon dioxide. *In vitro* antagonists of cyclooxygenase and 5-lipoxygenase metabolism. *Arzneimittelforschung* 1992; 42: 547-51.
- 35 Paubert-Braquet M, Mencia Huerta JM, Cousse H, Braquet P. Effect of the lipidic lipidosterolic extract of *Serenoa repens* (Permixon) on the ionophore A23187-stimulated production of leukotriene B₄ (LTB₄) from human polymorphonuclear neutrophils. *Prostaglandins Leukot Essent Fatty Acids* 1997; 57: 299-304.
- 36 Vela Navarrete R, Garcia Cardoso JV, Barat A, Manzarbeitia F, Lopez Farre A. BPH and inflammation: pharmacological effects of Permixon on histological and molecular inflammatory markers. Results of a double blind pilot clinical assay. *Eur Urol* 2003; 44: 549-55.
- 37 Kyprianou N, Tu H, Jacobs SC. Apoptotic versus proliferative activities in human benign prostatic hyperplasia. *Hum Pathol* 1996; 27: 668-75.
- 38 Cardillo M, Berchem G, Tarkington MA, Krajewski S, Krajewski M, Reed JC, *et al*. Resistance to apoptosis and up regulation of Bcl-2 in benign prostatic hyperplasia after androgen deprivation. *J Urol* 1997; 158: 212-6.
- 39 Colombel M, Vacherot F, Diez SG, Fontaine E, Buttyan R, Chopin D. Zonal variation of apoptosis and proliferation in the normal prostate and in benign prostatic hyperplasia. *Br J Urol* 1998; 82: 380-5.
- 40 Vacherot F, Azzouz M, Gil-Diez-De-Medina S, Colombel M, De La Taille A, Lefrere Belda MA, *et al*. Induction of apoptosis and inhibition of cell proliferation by the lipidic-sterolic extract of *Serenoa repens* (LSEsR, Permixon) in benign prostatic hyperplasia. *Prostate* 2000; 45: 259-66.
- 41 Claus S, Berges R, Senge T, Schulze H. Cell kinetic in epithelium and stroma of benign prostatic hyperplasia. *J Urol* 1997; 158: 217-21.
- 42 Vacher P, Prevarskaya N, Skryma R, Audy MC, Vacher AM, Odessa MF, *et al*. The Lipidosterolic Extract from *Serenoa repens* Interferes with Prolactin Receptor Signal Transduction. *J Biomed Sci* 1995; 2: 357-65.
- 43 Koch E. Pharmakologie und Wirkmechanismus von Extrakten aus Sabalfrüchten (*Sabal fructus*), Brennesselwurzeln (*Urtica radix*) und Kürbissamen (*Cucurbitae peponis semen*) bei der Behandlung der benignen Prostatahyperplasie. *Phytopharmaka in Forschung und klinischer Anwendung* 1995.
- 44 Birder LA, Kanai AJ, de Groat WC, Kiss S, Nealen ML, Burke NE, *et al*. Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. *Proc Natl Acad Sci USA* 2001; 98: 13396-401.
- 45 Apostolidis A, Brady CM, Yianguo Y, Davis J, Fowler CJ, Anand P. Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and effect of intravesical resiniferatoxin. *Urology* 2005; 65: 400-5.
- 46 Ito Y, Kageyama A, Iwasaki Y, Watanabe T, Yamada S. Effects of propiverine and oxybutynin to treat overactive bladder, on vanilloid receptor (transient receptor potential vanilloid subtype 1: TRPV1). *Jpn Neurogenic Bladder Soc in press*.
- 47 Plosker GL, Brogden RN. *Serenoa repens* (Permixon). A review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging* 1996; 9: 379-95.
- 48 Chevalier G, Benard P, Cousse H, Bengone T. Distribution study of radioactivity in rats after oral administration of the lipidic/sterolic extract of *Serenoa repens* (Permixon) supplemented with [¹⁻¹⁴C]-lauric acid, [¹⁻¹⁴C]-oleic acid or [⁴⁻¹⁴C]-beta-sitosterol. *Eur J Drug Metab Pharmacokinet* 1997; 22: 73-83.
- 49 Rhodes L, Primka RL, Berman C, Vergult G, Gabriel M, Pierre-Malice M, *et al*. Comparison of finasteride (Proscar), a 5 alpha reductase inhibitor, and various commercial plant extracts in *in vitro* and *in vivo* 5 alpha reductase inhibition. *Prostate* 1993; 22: 43-51.
- 50 Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 2001; 61: 2163-75.
- 51 Williamson EM. Synergy and other interactions in phyto-medicines. *Phytotherapy* 2001; 8: 401-9.
- 52 Sugiyama T, Kubota Y, Shinozuka K, Yamada S, Wu J, Umegaki K. Ginkgo biloba extract modifies hypoglycemic action of tolbutamide via hepatic cytochrome P450 mediated mechanism in aged rats. *Life Sci* 2004; 75: 1113-22.
- 53 Uchida S, Yamada H, Li XD, Maruyama S, Ohmori Y, Oki T, *et al*. Effects of Ginkgo biloba extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. *J Clin Pharmacol* 2006; 46: 1290-8.
- 54 Markowitz JS, Donovan JL, Devane CL, Taylor RM, Ruan Y, Wang JS, *et al*. Multiple doses of saw palmetto (*Serenoa repens*) did not alter cytochrome P450 2D6 and 3A4 activity in normal volunteers. *Clin Pharmacol Ther* 2003; 74: 536-42.
- 55 Boyle P, Robertson C, Lowe F, Roehrborn C. Meta-analysis of clinical trials of permixon in the treatment of symptomatic benign prostatic hyperplasia. *Urology* 2000; 55: 533-9.
- 56 Boyle P, Robertson C, Lowe F, Roehrborn C. Updated meta-analysis of clinical trials of *Serenoa repens* extract in the treatment of symptomatic benign prostatic hyperplasia. *BJU international* 2004; 93: 751-6.
- 57 Gerber GS, Fitzpatrick JM. The role of a lipidic-sterolic extract of *Serenoa repens* in the management of lower urinary tract symptoms associated with benign prostatic hyperplasia. *BJU international* 2004; 94: 338-44.
- 58 Gerber GS, Kuznetsov D, Johnson BC, Burstein JD. Randomized, double-blind, placebo-controlled trial of saw palmetto in men with lower urinary tract symptoms. *Urology* 2001; 58: 960-4; discussion 964-5.
- 59 Marks LS, Partin AW, Epstein JI, Tyler VE, Simon I, Macairan ML, *et al*. Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia. *J Urol* 2000; 163: 1451-6.
- 60 Descotes JL, Rambeaud JJ, Deschaseaux P, Faure G. Placebo-controlled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clin Drug Investig* 1995; 9: 291-7.
- 61 Reece SH, Memon A, Smart CJ, Dewbury K. The value of permixon in benign prostatic hypertrophy. *Br J Urol* 1986; 58: 36-40.
- 62 Cukier J, Ducasso J, Le Guillou M, Leriche A, Lobel B, Toubol J.

- Permixon versus placebo; resultats d'une 'etude multicentrique. Comptes rendus de thérapeutique et de pharmacologie clinique 1985; 4: 15-21.
- 63 Tasca A, Barulli M, Cavazzana A, Zattoni F, Artibani W, Pagano F. Treatment of obstructive symptomatology caused by prostatic adenoma with an extract of *Serenoa repens*. Double-blind clinical study vs placebo. *Minerva Urol Nefrol* 1985; 37: 87-91
- 64 Champault G, Patel JC, Bonnard AM. A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. *Br J Clin Pharmacol* 1984; 18: 461-2.
- 65 Boccafoschi C, Annoscia S. Comparison of *Serenoa repens* extract and placebo in controlled clinical trial in patients with prostatic adenomatosis. *Urologia* 1983; 50: 1-14
- 66 Emili E, Cingo M, Petrone U. Risultati Clinici su un nuovo farmaco nella terapia dell'ipertrofia della prostata (Permixon®). *Urologia* 1983; 50: 1042-9.
- 67 Grasso M, Montesano A, Buonaguidi A, Castelli M, Lania C, Rigatti P, *et al*. Comparative effects of alfuzosin versus *Serenoa repens* in the treatment of symptomatic benign prostatic hyperplasia. *Arch Esp Urol* 1995; 48: 97-103.
- 68 Adiazola Semino M, Lozano Ortega JL, Garcia Cobo E, Tejada Banez E, Romero Rodriguez F. Symptomatic treatment of benign hypertrophy of the prostate. Comparative study of prazosin and *Serenoa repens*. *Arch Esp Urol* 1992; 45: 211-3.
- 69 Debruyne F, Boyle P, Calais Da Silva F, Gillenwater JG, Hamdy FC, Perrin P, *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.
- 70 Jibrin I, Erinle A, Saidi A, Aliyu ZY. Saw palmetto-induced pancreatitis. *South Med J* 2006; 99: 611-2.
- 71 Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Carrier J, *et al*. *In vivo* assessment of botanical supplementation on human cytochrome P450 phenotypes: Citrus aurantium, Echinacea purpurea, milk thistle, and saw palmetto. *Clin Pharmacol Ther* 2004; 76: 428-40.
- 72 Yale SH, Glurich I. Analysis of the inhibitory potential of Ginkgo biloba, Echinacea purpurea, and *Serenoa repens* on the metabolic activity of cytochrome P450 3A4, 2D6, and 2C9. *J Altern Complement Med* 2005; 11: 433-9.