Invited review

Pharmacological effects of saw palmetto extract in the lower urinary tract

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Saw palmetto extract (SPE), an extract from the ripe berries of the American dwarf palm, has been widely used as a therapeutic remedy for urinary dysfunction due to benign prostatic hyperplasia (BPH) in Europe. Numerous mechanisms of action have been proposed for SPE, including the inhibition of 5α-reductase. Today, α_1-adrenoceptor antagonists and muscarinic cholinoceptor antagonists are commonly used in the treatment of men with voiding symptoms secondary to BPH. The improvement of voiding symptoms in patients taking SPE may arise from its binding to pharmacologically relevant receptors in the lower urinary tract, such as α_1-adrenoceptors, muscarinic cholinoceptors, 1,4-dihyropyridine receptors and vanilloid receptors. Furthermore, oral administration of SPE has been shown to attenuate the up-regulation of α_1-adrenoceptors in the rat prostate induced by testosterone. Thus, SPE at clinically relevant doses may exert a direct effect on the pharmacological receptors in the lower urinary tract, thereby improving urinary dysfunction in patients with BPH and an overactive bladder. SPE does not have interactions with co-administered drugs or serious adverse events in blood biochemical parameters, suggestive of its relative safety, even with long-term intake. Clinical trials (placebo-controlled and active-controlled trials) of SPE conducted in men with BPH were also reviewed. This review should contribute to the understanding of the pharmacological effects of SPE in the treatment of patients with BPH and associated lower urinary tract symptoms (LUTS).

Keywords: saw palmetto extract; pharmacological effects; lower urinary tract receptors

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Introduction

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) are very common disorders in aging men. The prevalence of histopathologic BPH is age dependent, with initial development usually occurring after 40 years of age[1]. By 60 years of age, its prevalence is greater than 50% and by age 85, the prevalence is as high as 90%. Similar to histological evidence, the prevalence of bothersome symptoms also increases with age. The two main forms of internationally accepted medical treatment for BPH are inhibitors of 5α-reductase, such as finasteride and α_1-adrenoceptor antagonists, with the latter being more effective[2]. In addition to these medications, the ripe berries of the American dwarf palm (*Serenoa repens*, saw palmetto) have been traditionally used to treat genitourinary problems; to enhance sperm production, breast size, or libido; and as a mild diuretic[3]. In many European countries, phytotherapeutic agents, including saw palmetto, are very popular. Phytotherapeutic agents represent nearly half of the medications dispensed for the treatment of BPH in Italy, compared with 5% for α-blockers and 5% for 5α-reductase inhibitors[4]. In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate lower urinary tract symptoms and represents more than 90% of all drugs prescribed for the treatment of BPH[4–6]. Saw palmetto is a dwarf palm tree of the family *Arecaceae* and is indigenous to the southeastern parts of the United States. Saw palmetto berries have traditionally been used by American Indians to cure genitourinary disturbances, relieve mucous membrane irritations, increase testicular function, or increase breast size[5, 6]. In the United

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States, the use of phytotherapy for LUTS has grown rapidly, and approximately 2.5 million men used saw palmetto extract (SPE), although a guideline panel did not recommend phytotherapy as a treatment for BPH[7, 8]. In Japan, SPE is not a prescribed medication; however, it has been receiving increasing attention recently among patients with BPH.

The mechanisms of pharmacological action of SPE were not fully understood, although numerous proposals have been made, including inhibition of 5α-reductase, anti-androgenic effects, anti-proliferative effects, anti-inflammatory effects and anti-edema effects[6]. However, most of these pharmacological effects were observed at relatively high concentrations or large doses of SPE[9, 10], and it is uncertain whether the reported modes of action of SPE are therapeutically relevant[11, 12]. As described above, α_1-adrenoceptor antagonists are commonly used in the treatment of men with voiding symptoms (urinary obstruction, pollakiuria and urinary incontinence) secondary to BPH. Goepel *et al*[13] have shown that SPE might have α_1-adrenoceptor inhibitory properties. SPE significantly affects pharmacological receptors, such as the α_1-adrenoceptor and the muscarinic receptor in the lower urinary tract, to relieve the irritative and obstructive symptoms of dysuria due to BPH and LUTS[14]. In addition to traditionally used medications, like α_1-adrenoceptor antagonists, antimuscarinics, 5α-reductase inhibitors, and phytotherapy, several new therapeutic agents, such as selective β_3-adrenoceptor agonists, are potentially useful for treating LUTS suggestive of BPH, particularly for storage symptoms secondary to outflow obstruction[15]. Thus, the effects of SPE on these receptors in the lower urinary tract might be pharmacologically relevant.

To date, more than 11 placebo-controlled trials and 4 active-controlled trials with SPE in men with BPH have been conducted. Most of these were reported in the 1980s. Patient numbers were usually limited and the evaluation periods were relatively short, so it would be difficult to evaluate the effect of SPE and ascertain the efficacy of SPE in BPH patients. However, some placebo-controlled studies and comparisons to α_1-blockers have recently been conducted with relatively long-term treatments and sufficient numbers of patients[8, 16, 17].

Herbal products, including SPE, are often used with other prescription medications, and most patients with BPH are aged men. Elderly individuals frequently take dietary supplements with prescription drugs, and such a tendency will continue to increase in the near future. In such cases, a major concern is adverse events caused by a large excess intake or interactions between dietary supplements and drugs. Thus, the safety, as well as the efficacy, of these natural products and of their active ingredients remains to be analyzed at a scientific level. This review introduces newly revealed pharmacological actions of SPE, as well as some well-known mechanisms of action of SPE, and also summarizes clinical trials of SPE in comparison with currently used medicines.

Chemical composition

SABALSELECT™, manufactured by Indena SpA. (Milano, Italy), was used for the animal experiments[14, 18, 19]. Indena SpA. explains the extraction of saw palmetto in the brochure as follows: the fruits of *S repens* are extracted with supercritical CO_2. This extractive procedure, conducted at 45 °C/220 bar, directly produces a pharmacological product (SABALSELECT™), which can be used without further purification. Table 1 shows the chemical composition of SABALSELECT™. It consists of fatty acids, alcohols and sterols (Brochure of Sabalselect™: Indena SpA). Habib and Wyllie[20] reported that the contents of different brands of SPE were markedly different; for example, free fatty acids ranged from 40.7% to 80.7% (mean %), methyl and ethyl esters from 1.5% to 16.7% (mean %), and glycerides from 6.8% to 52.2% (mean %). In the United States, herbal products are regulated under the Dietary Supplement Health and Education Act (DSHEA); however, approval for launching products onto the market is not required except in cases of a new dietary ingredient. Therefore, herbal products that existed before October 15, 1994, can remain with different ingredients[21]. Levin and Das[22] issued a warning that each

Table 1. Chemical composition of SPE (Brochure of Sabalselect™: Indena SpA. http://www.indena.it/pdf/sabalselect.pdf).

Fatty acids	Content (%)	Fatty alcohols and sterols	Content (%)
Total fatty acids	93.5	Fatty alcohols	0.20
		Hexacosanol	0.017
Saturated	59.8	Octacosanol	0.146
Caproic acid	1.5	Tetracosanol	0.004
Caprylic acid	2.3	Triacontanol	0.003
Capric acid	2.5		
Lauric acid	30.2	Sterols	0.32
Myristic acid	12.0	Campesterol	0.07
Palmitic acid	9.5	Stigmasterol	0.03
Stearic acid	1.8	β-Sitosterol	0.22
Unsaturated	33.7		
Oleic acid	28.5		
Linoleic acid	4.6		
Linolenic acid	0.6		

preparation must be considered individually because of differences in extraction techniques, preparation of products, composition, and biological activities.

Pharmacological properties

BPH causes dysuria and residual urine *via* a mechanical stoppage due to hypertrophy of prostatic tissue and *via* a functional stoppage caused by α_1-adrenoceptor hypertonia of prostatic smooth muscle. Previous studies have demonstrated that SPE had a number of pharmacological effects: 1) an anti-androgenic effect — inhibition of 5α-reductase I and II and inhibition of binding of dihydrotestosterone (DHT) to the cytosolic androgen receptors, 2) an anti-inflammatory effect, 3) an anti-proliferative effect, (Figure 1), and 4) significant binding of pharmacological receptors existing in the lower urinary tract.

Anti-androgenic effects

The development and growth of the prostate gland depend on androgen stimulation[23, 24]. DHT is one of several factors regulating this development and growth[24, 25] and is converted from testosterone by 5α-reductase. This enzyme has two isoforms (5α-reductase 1 and 2)[25]. The respective roles of these 5α-reductases in BPH development have not yet been elucidated[26]. SPE inhibited both isozymes in a noncompetitive manner[27–29], whereas finasteride inhibited only 5α-reductase 2 in a competitive manner[25]. Among the many components of SPE, lauric acid and linoleic acid showed inhibition of both isozymes, oleic acid was active only against 5α-reductase 1 and myristic acid was active only against 5α-reductase 2. However, palmitic acid, stearic acid, esterified fatty acids, sterols, and alcohols were inactive against both[30].

Di Silverio *et al*[26] reported a significant decrease in DHT and increase in testosterone in the periurethral region of prostate tissue from BPH patients receiving Permixon® (320 mg/day) for 3 months and thus suggested that SPE could inhibit 5α-reductase in the human prostate *in vivo*. Sultan *et al*[9] investigated the interaction of SPE with the intercellular androgen-receptor complex. SPE inhibited [^{3}H]dihydrotestosterone from binding to its receptor. The affinity of SPE was higher for cytosol receptors than for nuclear receptors. Competitive interference with the binding of [^{3}H]methyltrienolone to cytosolic androgen receptors was also shown in rat prostate cells [31].

Anti-inflammatory effects

Inflammation was frequently observed in hormonally induced hypertrophied prostates of dogs[32] and in a study of human BPH[33]. Mahapokai *et al*[32] concluded that the development of hyperplasia preceded inflammatory infiltration. An anti-inflammatory effect was indicated as one of the mechanisms of action of SPE. In fact, it is plausible that SPE affects several inflammatory mediators. SPE showed anti-inflammatory and anti-edematous effects *in vivo*[34]. The production of 5-lipoxygenase metabolites was inhibited by SPE (Permixon®) at a concentration of 5 μg/mL[35]. Breu *et al*[34] demonstrated that acid lipophilic compounds of SPE inhibited the biosynthesis of cyclooxygenase and 5-lipoxygenase metabolites with the same intensity as SPE.

Vela Navarrete *et al*[36] conducted a multicenter open pilot clinical study to make a comparison between a control group and an SPE (Permixon®) group in BPH patients. After 3 months of treatment with SPE, the patients showed an

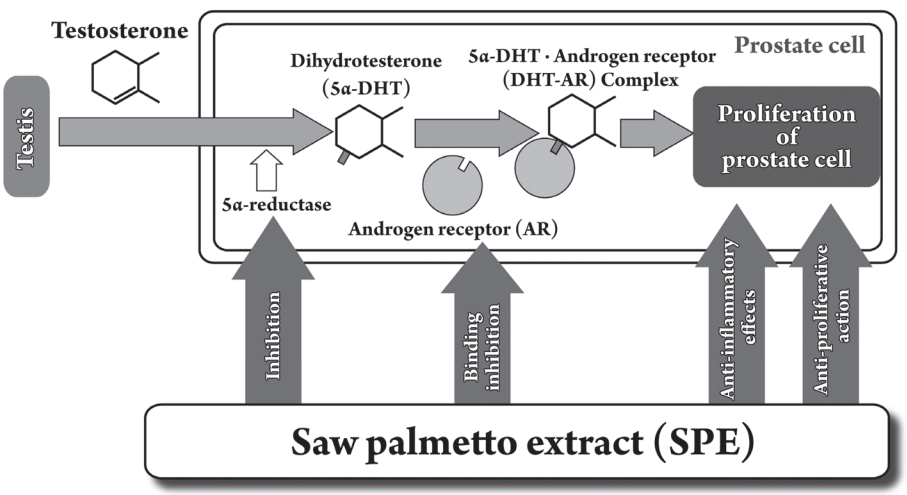

Figure 1. Mechanisms of pharmacological action of saw palmetto extract (SPE). They include antiandrogenic effects, such as inhibition of 5α-reductase I and II and inhibition of binding of dihydrotestosterone (DHT) to the cytosolic androgen receptors, anti-proliferative effects and anti-inflammatory effects.

improvement in their International Prostate Symptom Score (IPSS). Also, significant decreases in the levels of interleukin-1β (IL-1β) 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 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 [^{3}H]-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 [^{3}H]prasozin (α_1-adreceptor), [^{3}H]N-methylscopolamine (NMS, muscarinic receptor) and (+)-[^{3}H]PN 200-110 (1,4-dihydropyridine receptors), but not [^{3}H]αβ-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 [^{3}H]prasozin and [^{3}H]NMS 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 IC_{50} 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 5α-reductase (IC_{50}: 71 μg/mL), anti-inflammatory effect (IC_{50} of cyclooxygenase and 5-lipoxygenase: 28.1 and 18.0 μg/mL, respectively), and anti-androgenic effect (IC_{50}: 1004 μg/mL)][34, 43] reported previously. Furthermore, Scatchard analysis has revealed that SPE caused a significant decrease in the maximal number of binding sites (Bmax values) of [^{3}H]prazosin, [^{3}H]NMS and (+)-[^{3}H]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

Table 2. IC_{50} values for *in vitro* inhibition by SPE of specific binding of [^{3}H]prazosin, [^{3}H]NMS, and (+)-[^{3}H]PN 200–110 in rat tissues.

Radioligands	IC_{50} values (μg/mL) (Mean±SEM, *n*=4–9)
Specific [^{3}H]prazosin binding	
Prostate	169±24
Spleen	188±47
Specific [^{3}H]NMS binding	
Bladder	40.0±4.1
Submaxillary gland	52.3±4.4
Specific (+)-[^{3}H]PN 200-110 binding	
Bladder	97.3 ±17.1

by SPE was previously 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 inhibited the capsaicin-induced Ca^{2+} influx in HEK293VR11 cells expressing TRPV1 receptors[46]. Furthermore, SPE inhibited specific binding of [^{3}H]resineferatoxin 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 (SABALSELECT^{TM}) for 4 weeks produced a significant decrease of muscarinic receptor (specific [^{3}H]NMS binding) sites in the rat bladder and submaxillary gland[18, 19]. Notably, such a reduction in the number of [^{3}H]NMS binding sites was observed at relatively low doses (0.6, 6 mg·kg^{-1}·d^{-1}) of SPE in the bladder and only at a high dose (60 mg·kg^{-1}·d^{-1}) in the submaxillary gland[19]. On the other hand, a significant enhancement of α_1-adrenoceptor (specific [^{3}H]prazosin binding) sites was observed in rat prostate after repeated treatment with the low dose (6 mg·kg^{-1}·d^{-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 polyprenic compounds[47]. A systemic distribution study in rats administered [^{14}C]oleic acid or [^{14}C]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 and 60 mg·kg^{-1}·d^{-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 induced 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 (SABALSELECT^{TM}, 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 (OAB).

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 treatment 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[18].

Clinical trials

Clinical trials conducted with SPE in men with BPH are summarized in Table 3[55–57]. 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 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

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 *et al*[8]	SPE	160*2	12m	112	-0.68#	112	0.42		
	Placebo	Placebo		113	-0.72#	113	-0.01		
Willetts KE *et al*[17]	SPE	160*2	12m			46	1.5		
	Placebo	Placebo				47	4.4		
Gerber GS *et al*[58]	SPE	160*2	6m	41	-4.4	41	1.0		
	Placebo	Placebo		44	-2.2	44	1.4		
Marks LS *et al*[59]	SPE (blend)	106*3	6m	21	-2.24	21	1.27		
	Placebo	Placebo		23	-1.39	23	0.09		
Descotes JL *et al*[60]	SPE	160*2	1m			82	3.42	82	-0.67
	Placebo	Placebo				94	1.06	94	-0.32
Reece SH *et al*[61]	SPE	160*2	3m			33	2.35	33	-1.0
	Placebo	Placebo				37	2.3	37	-1.0
Cukier J *et al*[62]	SPE	2*80*2	2–3m					43	-1.1
	Placebo	Placebo						47	-0.5
Tasca A *et al*[63]	SPE	160*2	3m			14	3.3	14	-2.6
	Placebo	Placebo				13	0.6	13	-1.2
Champault G *et al*[64]	SPE	2*80*2	1m			46	2.7	47	-1.4
	Placebo	Placebo				39	0.25	41	-0.5
Boccafoschi C *et al*[65]	SPE	160*2	2m			11	4.13	11	-2.2
	Placebo	Placebo				11	1.96	11	-1.0
Emili E *et al*[66]	SPE	160*2	1m			15	3.37	15	-1.6
	Placebo	Placebo				15	0.2	15	-0.4
Active-controlled study									
Debruyne F *et al*[16]	SPE	320*1	12m	350	-4.4		1.79		
	Tamsulosin	0.4*1		354	-4.4		1.89		
Carraro JC *et al*[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 *et al*[67]	SPE	160*2	0.75m			31	2.8	32	-1.0
	Alfuzosin	7.5				32	4.7	31	-0.9
Adriazola Semino *et al*[68]	SPE	160*2	3m			20	1.5	20	-0.2
	Prazosin					22	0.47	22	-0.4

#: AUASI: American Urological Association Symptom Index

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 5α-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[16]. Eight hundred and 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. 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 LUTS 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 were 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 5α-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 efficacy 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.

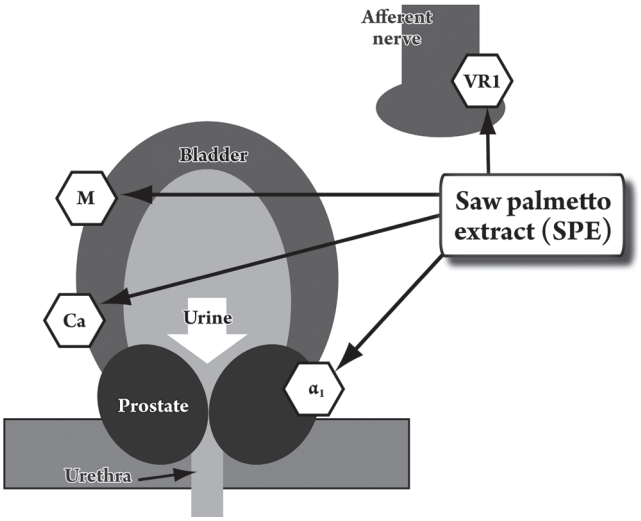

Figure 2. Proposed binding activities of saw palmetto extract (SPE) for pharmacological receptors in the lower urinary tract (bladder and prostate). M: muscarinic receptor, VR1: vanilloid receptor, Ca: 1,4-dihydropyridine receptor, α_1: α_1-adrenoceptor.

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