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Serenoa repens: The Scientific Basis for the Treatment of Benign Prostatic Hyperplasia

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Article info

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Abstract

Context: Medical therapies derived from natural sources have been used for centuries. Many are as effective as synthetic medications. The use of plant-derived medications for benign prostatic hyperplasia (BPH) is no exception. In particular, extracts of *Serenoa repens* (SrE), the fruit of the American dwarf palm, are widely available, and their use is rising throughout the world.
Objective: The underlying basis for SrE popularity stems from its safety and tolerability profile. However, despite its extensive use, its mechanism of action has not been definitely clarified. In this paper, we analyse the scientific basis for SrE efficacy in the treatment of BPH and explore the mechanisms by which its effects are induced.
Evidence acquisition: This literature review focuses on the actions of the lipidosterolic SrE on a host of targets. Several cellular and molecular techniques have been used to characterise the biologic pathways that may mediate these actions. Morphologic studies have been carried out to identify the changes of prostate ultrastructure and to determine modifications that may shed light on the mechanisms underlying SrE efficacy.
Evidence synthesis: Selectivity of the action of SrE for the prostate has been demonstrated. There are several morphologic changes, and these are accompanied by an increase in the apoptotic index of the gland, along with inhibition of the activity of the 5α-reductase isoenzymes. The drug also acts on a number of other biologic systems and shows a capacity to moderate the androgenic, apoptotic, and inflammatory pathways of the cell. These pathways have been implicated in the hyperplastic process.
Conclusions: The interaction between prostate cells and SrE is manifest at several levels of the gland's biological spectrum and results in antiandrogenic, anti-inflammatory, and proapoptotic effects. These effects may account for the beneficial response triggered in some patients with BPH treated with SrE.

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1. Introduction

Medical therapies derived from natural sources have been used for centuries. Many of them are as effective as synthetic medications. The use of plant-derived medications for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) is no exception. In particular, extracts of the fruit of the American dwarf palm

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(*Serenoa repens*, saw palmetto) are widely available, and their uses in the treatment of patients with BPH are rising throughout the world [1].

The underlying basis for the popularity of *Serenoa repens* extracts (SrE) stems from their safety, clinical efficacy, and tolerability profile [2]. However, despite their extensive use, the mechanism of action of SrE has not been entirely elucidated. In the present report, we analyse the scientific basis for the efficacy of this drug in the treatment of prostate diseases and explore the mechanisms by which *Serenoa repens* may induce its clinical benefits.

Although there is a plethora of SrE brands in the market place, these brands differ significantly in the ratios of their constituent components [3]. We describe the action of one of these brands, Permixon, a lipidosterolic extract commercialised by Pierre Fabre Médicament (Castres, France). This product has been subjected to greater scientific scrutiny and is associated with more clinical trials and pharmacologic analyses than any other preparation of SrE.

So far we have been unable to identify the nature of the putative ingredients in SrE responsible for the beneficial effects of the drug in vivo. A number of earlier studies have identified possible constituent candidates [4], but these remain tentative pending further research. This review investigates the effects that these components may exert on the biological behaviour of the prostate. In addition, we discuss whether the effects are instigated by single components within the drug or are triggered by the combined action of the constituent ingredients acting in a synergistic fashion.

2. Evidence acquisition

A wide range of cellular and molecular techniques have been used to establish the mode of action of SrE. Initially, immortalised cell lines from prostate cancer were employed as a model for testing the drug, but they were subsequently replaced by a coculture system of BPH. Other experiments included testing of an in vivo rat model, as well as analysis of prostate tissue from men with BPH treated for 3 mo with the drug before surgery. The models were subjected to a host of techniques, including immunohistochemistry, flow cytometry, transfection, phase contrast microscopy, proliferative studies, apoptosis analysis, measurement of functional enzyme activities, western blot analysis, and assessment of a wide range of peptides and growth factors at both the protein and DNA levels [5–15]. The outcome of these experimental approaches is detailed in the following sections of this review.

3. Evidence synthesis

3.1. *Organ specificity of Serenoa repens*

Our understanding of the cellular and molecular basis of prostate diseases has progressed substantially over the last few years. In that time, a number of new therapeutics targets have been identified and several mechanistic pathways involved in the pathogenesis of BPH have been elucidated. It is now apparent that no single mechanism is entirely responsible for the induction of BPH. Indeed, the underlying process is cumulative, involving androgenic stimulation, oxidative stress, and inflammatory agents, to name a few. Therefore, no single treatment could deliver the desired response and a rationale for combination therapy may well hold the key to an ultimate cure. Interestingly, clinical trials such as the Medical Therapy of Prostatic Symptoms (MTOPS) study have already showed the benefit of such an approach [16] and have lent support for a possible role for combination therapy in the treatment of men with LUTS.

The present generation of medical treatments including α-blockers and 5α-reductase (5-α-R) inhibitors are essentially monotherapies. Additionally, they all exhibit a variety of side-effects forcing many patients to consider alternatives such as the use of plant-derived medication. On the whole, phytotherapeutic drugs demonstrate remarkably benign side-effects and are virtually free of deleterious effects on sexual function [17]. *Serenoa repens*, with its complex mixture of free and esterified long chain fatty acids, polyprenes, and phytosterols, is no exception. This composition of several ingredients confers to the drug a capacity to exhibit several pharmacodynamic properties, which, in turn, induce a wide range of mechanisms of action. Therefore, the effect of SrE may be comparable to combination therapy as each of the different SrE ingredients may act in an additive or synergistic fashion.

One of the more enduring challenges facing phytotherapeutic drugs concerns the specificity and selectivity of their actions. This issue has been addressed at length by the manufacturers of SrE. Exploratory investigations were carried out to ensure that their product met the necessary criteria. Initially, in vitro studies were performed on a host of cells obtained from a variety of human tissues, including prostate, epididymis, testis, kidney, skin, and breast. The cells were used either directly or separated into their constituent stroma and epithelial components and propagated in primary cultures in the presence and absence of increasing concentrations of SrE [5]. Following treatment, morphologic and dynamic studies were undertaken to establish the impact of the drug on the structure and function of the cells. Electron microscopy revealed significantly extensive structural changes to prostate cells following exposure to SrE when compared with untreated control cells. The changes included the accumulation of lipid droplets within the cytoplasm, damage to the nuclear membrane, and disruption of the organelles (Fig. 1) [5]. In addition, SrE induced the polarisation of the nucleus and condensation of the chromatin (Fig. 1), these all being the hallmarks of programmed cell death. In contrast, treatment of non-prostate-derived cells (eg, breast, kidney, testis) with SrE showed no damage to the nuclear membrane, no cytoplasmic lipid accumulation, and no organelle disruption (data not shown) [5]. Together, these results highlight the SrE action specificity for prostate cells [5]. This organ selectivity is further supported by pharmacokinetic studies in rats administered SrE. In these studies, the drug had been

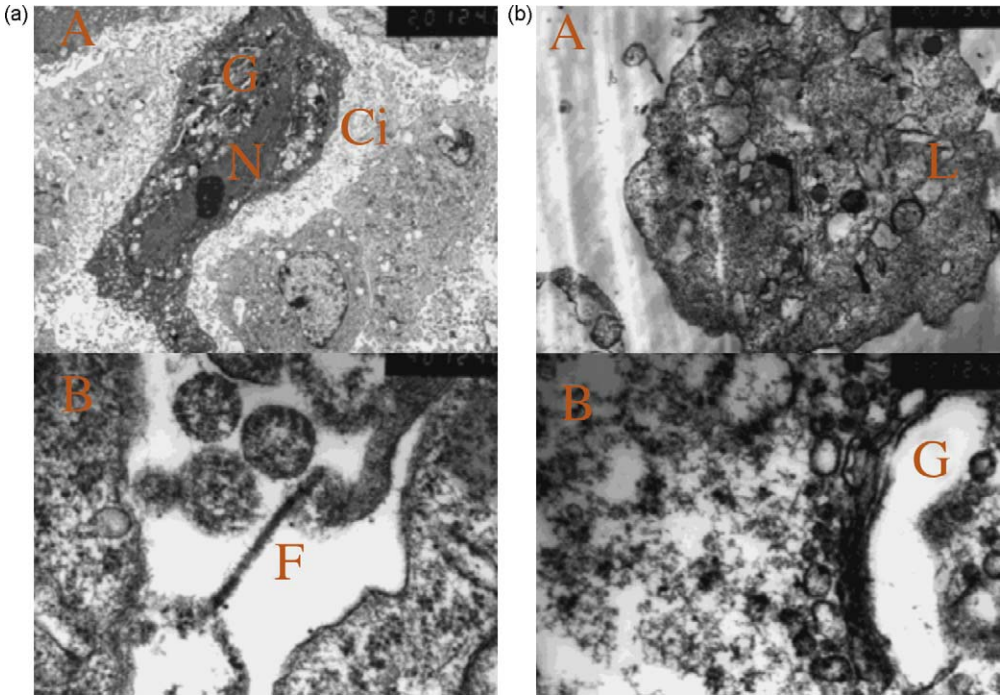

Fig. 1 – (a) Electron micrographs of untreated cocultured fibroblast cells. Micrograph A (×3888) shows characteristic elongated nuclei (N), high levels of Golgi apparatus (G), and cilia. Micrograph B (×86 400) shows a collagen fibril (F) produced by the cocultured fibroblast cells. (b) Electron micrographs of *Serenoa repens* extract (SrE)–treated (10 μg/ml) cocultured fibroblast cells. Micrograph A (×15 984) shows general disruption of the cell cytoplasm and accumulation of lipids (L) in the cell. Micrograph B shows damage to the Golgi apparatus (G) in a fibroblast cell treated with SrE [5].

supplemented with radiolabelled free fatty acids. All animals displayed a significant radioactivity uptake in the prostate compared with brain, seminal vesicles, and epididymis [6].

The morphologic changes described above are exclusively associated with the prostate and are coupled to the capacity of the gland to accumulate large drug concentrations. These structural alterations may affect the physicochemical characteristics of the organ and induce new responses. In the next section of this review, attempts are made to describe some of the pathways targeted by SrE. The mixed composition of this agent may lead to a unique capacity for the drug to act at multiple levels of the biological spectrum and therefore trigger a variety of responses at both the cellular and molecular levels.

3.2. *Antiandrogenic activities of Serenoa repens*

Growth of the prostate, maintenance of its structural pattern, and integrity of its function depend on a continuous supply of androgens. Androgens are derived predominantly from the testis. Testosterone, the main circulating androgen, is converted to dihydrotestosterone (DHT) by the intracellular Δ 4, 3-ketosteroid, 5α reductase isoenzymes. These enzymes are located on the prostate nuclear membrane for both the stroma and epithelium [7]. DHT drives its action on the prostate by binding to a specific receptor. DHT binding triggers the expression of a wide array of hormone-responsive genes. Regulation of these genes has been widely investigated by blocking DHT synthesis through the inhibition of types I and II 5-α-R isoenzymes using synthetic inhibitors of 5-α-R [18]. Controlling enzyme activity is even of greater importance considering the fact that the expression of 5-α-R type II is significantly elevated in hyperplastic prostate tissue [8,19].

Synthetic drugs are not unique in their capacity to inhibit 5-α-R. There is now ample evidence demonstrating that phytotherapeutic agents are also effective inhibitors. Di Silverio et al have reported that phytotherapy contributes to a significant reduction in prostate DHT concentrations following 3 mo of treatment [9]. In the case of SrE, both forms of the enzyme are inhibited [8]. This ensures greater control of the 5-α-R activity in the gland (Fig. 2) [5]. Furthermore, and this confirms the specificity and selectivity of SrE, 5-α-R activity is not inhibited after treatment with the plant extract in cells of nonprostate origin (Fig. 3) [13]. However, in contrast to other 5-α-R inhibitors (5-α-RIs), SrE induces its effects without interfering with the cellular capacity of the prostate to secrete prostate-specific antigen (PSA) in vitro [10] and in vivo [20]. Therefore, SrE offers a major therapeutic advantage over other 5-α-R inhibitors because continuous measurement of PSA levels for prostate cancer screening and for monitoring tumour progression can be carried out in tandem with SrE therapy.

Whilst the mechanism(s) responsible for the down-regulation of PSA following finasteride treatment has been established [21,22], no one has been able to explain why SrE, an equally effective 5-α-RI, suppresses prostate growth without interfering with PSA production by the epithelial cells. We have previously reported that SrE disrupts the

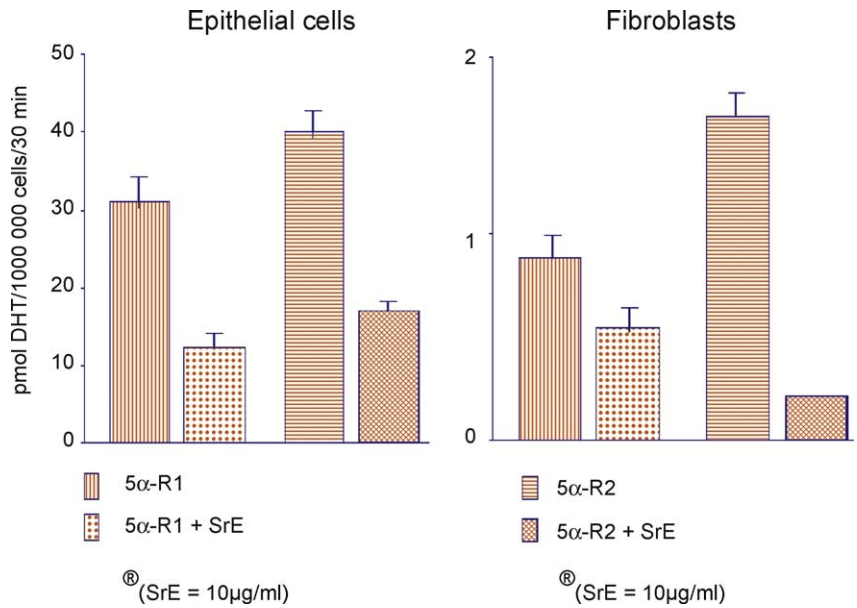

Fig. 2 – Effect of a 5-d treatment with *Serenoa repens* extract (SrE) (10 μg/ml) on the activity of 5α-reductase types I (5α-R1) and II (5α-R2) in cocultured epithelial and fibroblast cells. Each data set is the result of three separate experiments. Results are expressed as means plus or minus standard error of the mean [5].
DHT = dihydrotestosterone.

intracellular membranes of prostate epithelial and fibroblast cells, including the nuclear membrane [5]. In contrast, the physiologic activities of 5-α-R in human prostate depend on its nuclear localisation [23,24]. Therefore, disruption of the enzyme microenvironment by SrE may lead to an inactivation of the isoenzymes. These observations suggest a novel approach for enzyme inhibition by a drug (noncompetitive) without disruption of the mechanism enhancing the androgen responsive genes. This accounts for the inability of SrE to interfere with the expression of PSA.

SrE antiandrogenic activities are not merely confined to 5-α-R inhibition in the prostate. Several studies have demonstrated that SrE may also act on different stages in the androgen pathway. SrE may inhibit DHT binding to its receptor together with a consequent downregulation of the androgen receptors [11]. However, because suprapharmacologic concentrations of the drug were used in early studies [25], one can argue that these effects would not be manifested at more physiologic levels. These data have not been reproduced consistently, suggesting that the effects of

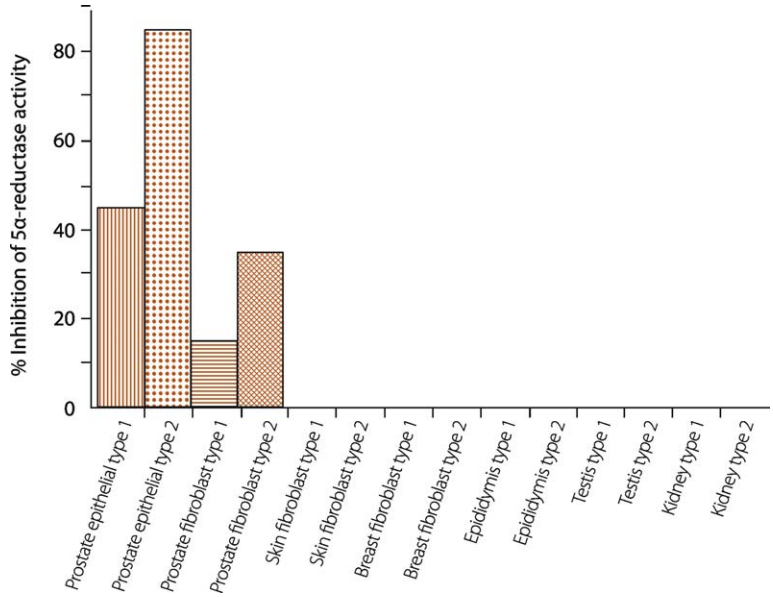

Fig. 3 – Effect of a 2-d treatment with *Serenoa repens* extract (10 μg/ml) on the activity of 5α-reductase types I and II in primary cultured cells from prostate, skin, breast, epididymis, testes, and kidney [13].

SrE may be linked to the unusually high concentrations of SrE employed.

3.3. Anti-inflammatory properties of Serenoa repens

Inflammatory cells such as macrophages and lymphocytes are known to infiltrate the prostate and their appearance can be related to a concomitant inflammatory reaction in BPH [26–29]. They secrete growth factors, including fibroblast growth factor (FGF) and cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) [30,31]. These potent chemotactic agents, along with their receptors, are present in high concentrations in BPH [31]. Furthermore, growth factors are involved in the synthesis of proinflammatory molecules such as cyclo-oxygenase 2 (COX-2) [32], which is responsible for the production of prostaglandins from arachidonic acid. Whilst these pathways moderate the inflammatory process, recent reports suggest that addition of SrE to prostate cells inhibits the production of many of these chemotactic agents [33]. This would account, in part, for the beneficial effect of SrE in BPH patients [1]. SrE anti-inflammatory effects are further supported by the results of a study performed in a small group of patients undergoing transurethral resection of the prostate or open prostatectomy who randomly received placebo or a 3-wk therapy with SrE [12]. Patients' specimens in the active group contained lower B-lymphocyte count as well as lower levels of TNF-α and interleukin B compared with the placebo group [12]. These data were confirmed by other authors [27,30] and are consistent with the reported anti-inflammatory properties of SrE.

3.4. The proapoptotic characteristics of Serenoa repens

The literature is replete with information supporting that the onset of hyperplasia in the prostate is accompanied by a reduction in programmed cell death [34]. Therefore, any attempts to reverse this phenomenon may provide some strategy for overcoming the symptoms associated with BPH. Several studies have recently tested this hypothesis. Treatment of prostate cells with SrE induced distinct morphologic changes, including polarisation of the nucleus and condensation of the chromatin [5]. These alterations are established hallmarks for the induction of apoptosis. These changes consistently were associated with a marked increase in the apoptotic index [13]. By contrast, morphologic signs of apoptosis were not found in cells of nonprostatic origin treated with SrE in parallel studies [13].

Further investigations were extended to an ex vivo setting whereby cell proliferation and cell death were quantified in tissues obtained from organ donors and from patients with BPH treated or untreated with SrE for 3 mo [14]. The study showed that SrE therapy reversed the apoptosis/proliferation pattern described in BPH. There was a 5.5- and 8.8-fold increase in the apoptotic/proliferative index ratio for the epithelium and stroma, respectively. Likewise, the corresponding proliferative index in the two cell types following treatment with SrE was found to be reduced by a factor of 7.7 and 4.9, respectively, when compared with specimens obtained from untreated patients [14].

Along the lines of the aforementioned studies, molecular markers associated with the apoptotic process were assessed [15]. The markers assessed were Bax and Bcl-2, proteins of the Bcl-2 family with proapoptotic and antiapoptotic properties, respectively. The activity of caspase-3, a protein effector in the apoptotic cascade, was also measured. The Bax/Bcl-2 ratio and caspase-3 activity were significantly increased in prostatic tissue after a 3-mo treatment regimen with SrE compared with the untreated control group [15]. Again, these results highlight the proapoptotic influence of SrE on the prostate.

3.5. Are all brands of Serenoa repens equal?

There are >100 varieties of *Serenoa repens* on the market today. However, only the lipidosterolic extract has been subjected to any worthwhile degree of laboratory and clinical investigations to ascertain its efficacy and possible mechanisms of action.

Plant extracts are a composite of several different chemical molecules. These molecules act in a single or synergistic fashion and therefore display a wide spectrum of pharmacologic activities. Recently, we evaluated the composition of 14 SrE brands [3]. The extracts were analysed for their free fatty acids (FFA), methyl and ethyl esters, long chain esters, and glyceride concentrations (Fig. 4). The analyses revealed significant differences between brands in spite of their common origin. The mean proportion of FFA ranged from 40.7% to 80.7%. Methyl and ethyl ester content varied between 1.5% and 16.7%, while long-chain ester ranged from 0.7% to 1.4%. Glyceride concentrations were between 6.8% and 52.2% (Fig. 4) [3].

Furthermore, the potency of these extracts appeared to be significantly different and showed intrabatch variation

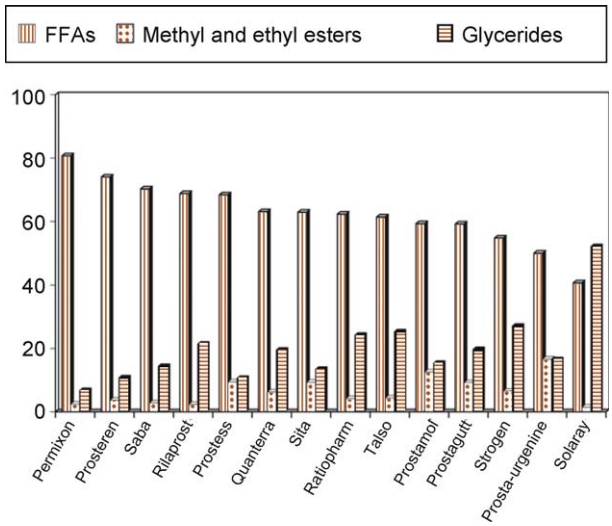

Fig. 4 – Visual representation of the content of 14 brands of SrE, as determined by analysis [3].
FFA = free fatty acids.

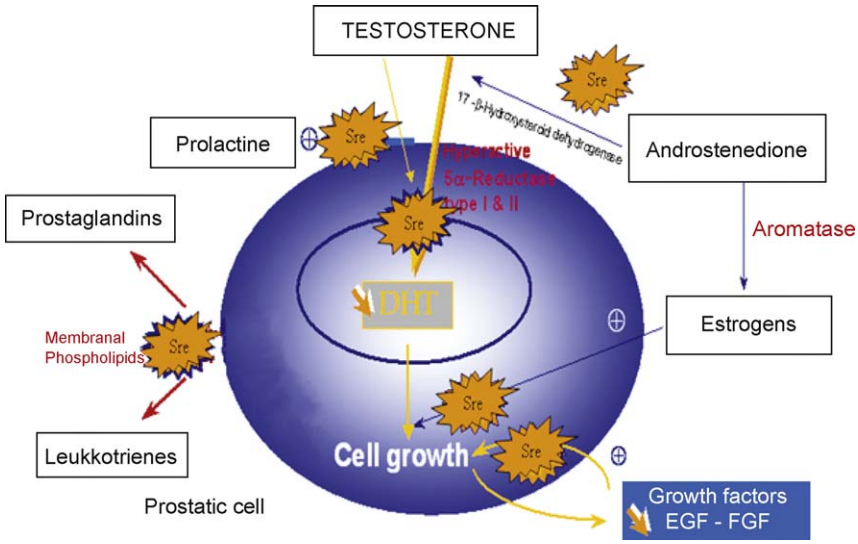

Fig. 5 – Schematic diagram showing some of the *Serenoa repens* extract (SrE) targets at the level of the prostate cell. DHT = dihydrotestosterone; EGF = epidermal growth factor; FGF = fibroblast growth factor.

with respect to their ability to inhibit the two isoforms of 5-α-R [35]. The differences in content and potency between the various brands suggest that plant-derived pharmaceuticals should be analysed separately and considered as distinct entities. Extracts with demonstrated pharmacologic activities and proven clinical efficacy should only be considered for the treatment of patients with BPH.

4. Conclusions

Experimental and clinical evidence suggest a crucial role for SrE as an alternative therapy for the relief of LUTS due to BPH. SrE, with its various ingredients, shows a wide range of biologic activities within the prostate and demonstrates a specificity and selectivity for this organ. The main properties of SrE are its antiandrogenic, proapoptotic, and anti-inflammatory effects, as well as its capacity to intercept each of these distinct pathways (Fig. 5). Although the mechanisms underlying the action of SrE constituent components (ie, additive or synergistic) have not been elucidated, SrE has all the hallmarks of a "combination therapy." Moreover, this drug does not induce many of the side-effects known to be associated with the use of synthetic pharmaceuticals. This confers to SrE many advantages over other competing therapies and might account for its reported superior clinical efficacy.

Conflicts of interest

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