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# Serenoa Repens, Lycopene and Selenium: A Triple Therapeutic Approach to Manage Benign Prostatic Hyperplasia

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**Abstract:** Benign prostatic hyperplasia (BPH) is a major health concern that is likely to have an increasing impact in line with the gradual aging of the population. BPH is characterized by smooth muscle and epithelial proliferation primarily within the prostatic transition zone that can cause a variety of problems for patients, the most frequent are the lower urinary tract symptoms. BPH is thought to involve in disruption of dihydrotestosterone (DHT)-supported homeostasis between cell proliferation and cell death, and, as a result, proliferative processes predominate and apoptotic processes are inhibited. Phytotherapeutic supplements, mainly based on Saw Palmetto-derived *Serenoa Repens (*SeR*)*, are numerous and used frequently. *Serenoa Repens* reduces inflammation and decreases *in vivo* the androgenic support to prostatic cell growth. Furthermore, SeR stimulates the apoptotic machinery; however, data supporting efficacy is limited, making treatment recommendations difficult. Besides SeR, selenium (Se), an essential trace element mainly functioning through selenoproteins and able to promote an optimal antioxidant/oxidant balance, and lycopene (Ly), a dietary carotenoid synthesized by plants, fruits, and microorganisms with a strong antioxidant activity, has been shown to exert beneficial effects in prostate disease. SeR is frequently associated with Ly and Se, in order to increase its therapeutic activity in benign prostatic hyperplasia (BPH). It has been shown that the Ly-Se-SeR association has a greater and enhanced anti-inflammatory activity that might be of particular interest in the treatment of BPH. The Ly-Se-SeR association is also more effective than SeR alone in reducing prostate weight and hyperplasia, in augmenting the pro-apoptotic Bax and caspase-9 and blunting the anti-apoptotic Bcl-2 mRNA. In addition, Ly-Se-SeR more efficiently suppresses the EGF and Vascular Endothelial Growth Factor (VEGF) expressions in hyperplastic prostates. Therefore, SeR particularly when combined with Se and Ly may have a greater potential for the management of benign prostate hyperplasia.

**Keywords:** Apoptosis, BPH, cytokines.

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common proliferative diseases affecting the elderly male [1]. BPH is characterized by smooth muscle and epithelial proliferation primarily within the prostatic transition zone that can cause a variety of problems for patients, the most frequent are the lower urinary tract symptoms (LUTS) [1]. Despite the enormous burden of BPH on public health, the pathogenesis of BPH is not completely understood [2]. Age-related systemic/local hormonal and vascular changes appear to represent the predominant mechanism. However, an emerging body of evidence suggests that inflammation may play a key role in the development and progression of BPH [2, 3]. Inflammation may contribute to tissue injury, and cytokines produced by inflammatory cells may serve to drive local growth factor production and angiogenesis [4]. As a consequence, the development of an inflammatory cascade has also suggested to have a role in prostate cancer. In addition, the development of abnormal prostate growth is thought to involve in disruption of dihydrotestosterone (DHT)-supported homeostasis between cell proliferation and cell death, and, as a result, proliferative processes predominate and apoptotic processes are inhibited [5, 6]. The key role of DHT in the development of BPH prompted the development of 5-alpha reductase inhibitors as a treatment for BPH, and potentially, for the prevention of prostate cancer [5]. Several large trials have shown the efficacy of alpha-receptor blocking medications when used alone and/or in combination with 5-alpha reductase inhibitors in BPH [7]. In addition, none of the data has demonstrated the benefit of anti-muscarinic medications in specific populations who suffer from bladder outlet obstruction causing storage urinary symptoms [8]. However, these therapeutic strategies are not free from side effects on sexuality and blood pressure regulation [9] and, as a direct consequence, it is difficult to identify an effective therapy without side effects.

## SERENOA REPENS

Phytotherapeutic agents, including the ripe berries of the American dwarf palm (*Serenoa Repens*, saw palmetto) have

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been proposed for the treatment of genitourinary disorders; to increase sperm production and breast size; and to enhance diuresis [10]. In several European countries phytotherapeutic compounds are largely used. There are about half of the medications for the treatment of BPH in Italy, compared with 5% of α-blockers and 5% of 5α reductase inhibitors [11-13]. Phytotherapy has an important role in the treatment of mild to moderate lower urinary tract in Germany and Austria where it represents the 90% of all anti-BPH drugs [11-13]. *Serenoa Repens* was very popular among the American Indians and they used it to manage genitourinary disturbances and enhance testicular function and breast size [11-13]. In the Unites States, the clinical therapy with phytotherapeutic agents has largely increased and *Serenoa Repens* is used by roughly 2.5 million men affected by LUTS [14, 15]. In Japan the use of *Serenoa Repens* among patients with BPH has grown rapidly. The mechanisms underlying the pharmacological effects of *Serenoa Repens* (SeR) in BPH are still far from being fully identified. (Table **1**) summarizes the effects of SeR on prostate. It has been proposed that SeR may inhibit 5α-reductase and may have anti-androgenic effects, anti-proliferative effects anti-inflamma tory effects and anti-edema activity [15]. Interestingly, these effects are obtained with high doses [16, 17] of SeR and therefore it has been questioned whether these effects have a therapeutic relevance [18, 19]. Agents blocking the $\alpha_1$ adrenergic receptors represent an important therapeutic strategy in the management of patient with pollakiuria, urinary incontinence and obstruction due to BPH. Interestingly, it has been demonstrated that SeR may exert anti- $\alpha_1$ adrenergic receptors activity [20]. SeR interacts with the $\alpha_1$ adrenergic and muscarinic receptors localized in the lower urinary apparatus, and blunts the obstructive symptoms following BPH [21]. Prostate growth and development is primed by androgen stimulation [22-24] and DHT plays an important role in both phenomena [25] and is produced from testosterone by 5α-reductase. This enzyme presents two isoforms 5α-reductase 1 and 2 [25]. The importance of these two isoforms in BPH has not been fully clarified [26]. It has been reported that SeR blocked both isoforms in a non competitive fashion [27, 28], while finasteride was shown to inhibit 5α-reductase in a non competitive manner. Inflammation has been frequently reported in both experimental and human BPH [29-31] and an anti-inflammatory effect has been proposed for SeR: More specifically, it is possible that SeR interferes with several inflammatory mediators. In fact SeR has both anti-inflammatory and anti-oedematous activity *in vivo* [31]. Furthermore, it blunts 5-lipooxygenase metabolites at a concentration of 5 μg/ml [32]. Breu *et al.* [31] showed also that SeR reduces the production of cyclooxygenase and 5-lipoxygenase metabolites. A recent paper of Latil *et al.* showed that an hexanic lipidosterolic extract of *Serenoa Repens* may inhibit monocyte chemoattractant protein-1/Chemokine (C-C) motif ligand 2 (MCP-1/CCL/2) which stimulates monocyte recruitment and activation during inflammation. This observation provides new insights into the anti-inflammatory mechanism of *Serenoa Repens* [33]. Apoptosis has a key role in maintaining a constant number of cells and represents a protection mechanism against several diseases and in the development of cancer. Changes in the balance between cell proliferation and programmed cell death leads to an increase in prostate size. A significant increase in Transforming Growth Factor-ß (TGF-ß), a negative cytokine that stimulates the apoptotic machinery, in the epithelial cells of BPH specimens compared with the normal prostate tissue and a concomitant increase in bcl-2 immunostaining has been shown [34]. Proliferation exceeding apoptosis has been shown in the stroma and in the prostate epithelium in patients with BPH [35]. Indeed, treatment with an extract of SeR caused a significant reduction in the proliferative index and a rise in the apoptotic index in the BPH specimens [35]. Moreover, hexanic lipidosterolic extract of SeR administration results in complex changes in cell membrane organization and fluidity of prostate cancer cells that have progressed to hormone-independent status [36]. Regarding the latter, it has been shown that the decrease in omega 6 content appears to be responsible for the prolonged and more consistent increase in the apoptosis rate and inhibition of proliferation following treatment with the extract of SeR [36] A systematic review of the literature regarding the clinical efficacy of SeR has been performed by Tacklind *et al.* [37]. Despite enormous amount of experimental and clinical research done on SeR, there is no clear evidence for a therapeutic efficacy in BPH associated with its use [37]. An updated Cochrane systematic review confirmed that SeR therapy did not improve urinary flow measures or prostate size in men with LUTS consistent with BPH even after making the usual dose double and triple [38]. This is likely due to the fact that much of the available research presents important methodological bias, including short duration of the trials and lack of an active control. Furthermore, the clinical studies have been performed with several SeR formulations that may differ in the constituents and in the pharmaceutical formulation.

## SELENIUM

Selenium (Se) is a trace mineral needed in the diet on a daily basis [39, 40]. Plant foods are the major dietary sources of Se and the concentration of Se in diet depends on the soil Se concentrations, the types and amounts of food consumed and other factors which regulate Se uptake. Highest food sources of Se include brazilian nuts, fish, whole grains, wheat germ, soybean and sunflower seeds. Se generally occurs in foods as selenomethionine, the organic Se analog of methionine may have antioxidant and anti-inflammatory effects [41, 42]. In human body, the highest concentrations of selenium are in the liver, kidneys and thyroid gland. Se is usually integrated into proteins to form selenoproteins as glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases which are involved in several biological functions in animals and humans.

Recent research on Se deficiency focused on animal diseases related to low soil concentrations of Se and insufficient amounts of Se in the forage plants. Human Se deficiency is rare but may occur in some countries where soil concentration of Se is low [43]. However, there is evidence that Se deficiency may contribute to the development of heart disease, hypothyroidism, and a weakening of the immune system [44, 45]. Se deficiency has also been described in people who received total parenteral nutrition [46, 47].

**Table 1. Effects of Serenoa Repens, Lycopene and Selenium Either Alone Or in Association, on Prostate Gland**

| Targets on Prostate | Serenoa Repens | Selenium | Lycopene | Serenoa Repens, Lycopene, Selenium Association |
|---|---|---|---|---|
| $\alpha_1$ adrenergic receptors | Blockade of $\alpha_1$ receptors [20] | - | - | Possible effect due to Serenoa Repens |
| Muscarinic receptors | Anti-muscarinic activity [21] | - | - | Possible effect due to Serenoa Repens - |
| 5α reductase | Enzyme Inhibition [27, 28] | - | Inhibition of 5α reductase signalling [68] | Inhibition of enzyme plus 5α reductase signalling |
| Oxidative stress | Antioxidant activity [31] | Antioxidant activity [41-42] | Antioxidant activity [55-57] | Increased antioxidant activity [79] |
| Inflammation | Antiinflammatory effects [32-33] | Antiinflammatory activity [42] | Antiinflammatory effects [55-57] | Increased reduction of inflammation [79-80] |
| Cell proliferation | Inhibition [34-35] | Inhibition [48-50] | Inhibition [61-62] | Enhanced anti-proliferative effects [79-80] |
| Apoptosis | Stimulation [34-35] | Stimulation [48-50] | Stimulation [61-62] | Augmented pro-apoptotic activity [79-80] |

Experimental evidence suggests that Se supplementation can reduce the incidence of many types of cancer when non-toxic doses are provided to the diet of rodent species by inhibiting cell proliferation and stimulating apoptosis [48, 49]. (Table **1**) describes the effects of Se on prostate. In humans, it has been shown that taking a daily supplement containing 200 micrograms of Se could reduce the risk of developing prostate, lung, and colorectal cancer [50]. Furthermore, the researchers of Harvard's Health Professionals Follow-up Study [51] analyzed human toenail clippings for Se concentration. After six years they found that the men with the highest Se levels at the start of the study had a lower incidence of advanced prostate cancer. The SU.VI.MAX study also reported interesting data on a large population of adults who had taken either a placebo or a combination of vitamin E, vitamin C, beta carotene, Se, and zinc [52]. After more than 7 years of follow-up, among men with normal prostate-specific antigen who had taken the antioxidant supplement, there was a significant reduction in the rate of prostate cancer although the exact role of Se is unclear in order to explain these effects.

Indeed, selenoproteins are likely implicated in the protective effects of Se against prostate cancer [53]. Moreover, Se metabolites such as methylselenol formed from gamma-glutamyl-selenomethyl-selenocysteine and selenomethyl-selenocysteine components, identified in certain plants and Se-enriched yeast, might also have anti-cancer effects [53]. Finally, recent data indicate that the beneficial effects of dietary Se in combination with isothiocyanates could be attributed to epigenetic and antioxidant effects. Indeed, the impact of aberrant DNA methylation in addition to modulation of key selenoenzymes, such as gastrointestinal glutathione peroxidase-2 and thioredoxin reductase-1, may be crucial in the cancer chemoprevention [54].

## LYCOPENE

Lycopene, a nonprovitamin A carotenoid, is the red pigment of tomatoes and known as a potent antioxidant [55, 56]. Lycopene is considered to be the major active component in tomatoes [57] and is twice as effective as β–carotene and 10-fold more active than α-tocopherol as an antioxidant and anti-inflammatory compound [55]. Lycopene is known to accumulate in the prostate gland in high concentrations [58] and is found in human semen [59]. The mechanisms by which lycopene is sequestered into prostatic tissue and released into semen and the prostatic interstitial space, remain under investigation. An interesting study suggested that the packaging of lycopene into exosomes (the *in vitro* analogs of prostasomes) for export resulted in reduced degradation of this carotenoid, and therefore maximized the effectiveness of delivery to the sites of action [60]. The abundance of lycopene in prostatic tissue is indirectly implicated in the chemoprevention of pathologies, which may likely to affect the prostate gland in the ageing male, such as slowing the progression of BPH and reducing the risk of developing prostatic cancer. In BPH, these actions are thought to be mediated through various mechanisms including inhibition of cell growth in normal prostatic epithelial cells [61] and induction of apoptosis in hyperplastic prostatic tissue [62]. Several mechanisms of action are implicated in the ability of lycopene to prevent the development and progression of prostate cancer, including reduction of oxidative DNA damage in prostatic tissue [62], initiating upregulation of gap-junction proteins (e.g. Connexin 43) to enable improved intercellular communications [63] and a reduction of local androgen signalling [64]. Ford and coworkers also showed that testosterone levels in CMO-I knockout mice are dependent on the interaction of the expression of carotenoid cleavage enzymes and the dietary levels of lycopene and, therefore, an enhanced production of lycopenoids in tissue may potentially

reduce prostate cancer risk [65]. Table **1** condensates the effects of lycopene on prostate.

Evidence from case–control and cohort studies suggests that high levels of dietary lycopene intake are associated with a lower risk of prostate cancer (including limiting tumor growth) and cell proliferation (benefiting BPH) [66, 67]. The underlying mechanism may be inhibition of 5-α reductase and interleukin-6 signaling, as demonstrated in benign prostate tissue of rats [68]. In 2007, the World Cancer Research Fund reported that a high fruit and vegetable intake may be beneficial in reducing the risk of cancer, including lycopene for prostate cancer [69]. A number of evidences indicate that lycopene exhibits multiple biological functions, such as antioxidant activity [70], antimetastasis [71-73], antiangiogenesis [71], anti-inflammatory ability [74] and anticancer [75-78]. The evidence for the role of lycopene as a chemopreventive agent in prostate cancer arises mainly from epidemiological studies. Several of these are observational prospective studies that show a degree of correlation between the level of tomato or lycopene intake and the relative risk reduction. The largest of these, the Health Professionals Follow-Up Study (47 894 men) showed a strong inverse relationship between the risk of developing prostate cancer and increased consumption of a tomato-enriched diet [78].

## SERENOA REPENS, SELENIUM, LYCOPENE

SeR is frequently combined with other essential trace element Se and the carotenoid lycopene in the effort to increase its therapeutic activity in BPH (Table **1**). It has been recently demonstrated in a bladder outlet obstruction experimental model, that a combination of Selenium (Se), *Serenoa Repens* (SeR) and Lycopene (Ly) is more effective than SeR alone in reducing prostate inflammatory response, growth factor expression, oxidative stress and histological features [79]. These effects have been confirmed in more relevant experimental model. Testosterone administration in rats is a suitable model to investigate BPH. Prostate enlargement induced by testosterone has been used to assess the effects of potential treatments for BPH, since it reproduces adequately, although not fully, the major features of human BPH, including functional and histological changes, supporting the theory that testosterone actually produces prostate hyperplasia. Accordingly, recent paper suggested a prominent growth of prostate following testosterone administration and a consequent increase in its weight, with the typical histological features of BPH [80]. The combined treatment with Se-Ly-SeR was more effective than SeR alone in preventing BPH and inhibited growth by 83%, suggesting that Selenium and Lycopene at pharmacological doses further increase *Serenoa Repens* efficacy in BPH. Prostate growth inhibition by Se-Ly-SeR was likely stimulated via both a caspase-dependent signal, through caspase-9, and an independent mechanism involving the pro-apoptotic Bax and the anti-apoptotic Bcl-2 gene. It was also demonstrated that Bcl-2 staining was intensified within the area of chronic inflammatory infiltrate in radical prostatectomy specimens [81]. This potential concomitant decrease in inflammation, that parallels the increase in apoptotic activity in BPH tissue, is also supported by previous findings in the bladder-obstruction model, in which a significant reduction of inflammatory infiltrate and tumor necrosis factor-α, an important BPH inflammatory marker [79] confirming the anti-inflammatory role of Se-Ly-SeR combination has been observed. Growth factors and cytokines, released by inflammatory cells play a significant role in the regulation and growth of normal, hyperplastic and malignant prostatic epithelium. Moreover, prostatic cells themselves are able to secrete inflammatory mediators and, finally, stimulate their own growth. It has been demonstrated that, during testosterone-induced prostate growth, there is an over-expression of the Epidermal Growth Factor (EGF) that was prevented by treatment with Se-Ly-SeR combination. As a matter of fact, EGF plays a critical role during tumorigenesis of the prostate gland [82] activating intracellular-signaling cascades leading, in turn, to activation of downstream pathways, cell proliferation, migration, adhesion, antiapoptosis, angiogenesis, and metastasis [83]. EGF and its receptor EGFR are frequently over-expressed in prostate cancer, which is associated with a more aggressive clinical outcome [84]. Moreover, inhibition of EGFR has been shown to result in a marked decrease in Bcl-2 and a marked increase in the expression of Bax [85]. Among other growth factors involved in BPH and cancer development, a primary role is also played by VEGF that stimulates neovascularization. VEGF is often called vascular permeability factor, since it enhances vascular leakage, an effect that contributes significantly to tumor development and metastasis [86]. Indeed, VEGF has been observed in BPH stromal cells [87], as well as in prostate cancer epithelial cells [87], where it plays a significant role in tumor growth, inducing angiogenesis. Very recently, VEGF has been indicated as possible therapeutic target to reduce prostate growth [87]. The apoptosis machinery is a promising target for the drug treatment of benign prostatic hyperplasia (BPH). Inhibitor of apoptosis proteins (IAPs) modulates apoptosis by direct inhibition of caspases [88]. The effects of SeR, Se and Ly, alone or in association, on the expression of four IAPs proteins cIAP1, cIAP2, NAIP and survivin were investigated by our research group in rats with experimental testosterone dependent BPH (unpublished observations) [89]. Prostate harvested from vehicle treated BPH animals showed unchanged expression of cIAP-1 and cIAP-2 and increased expression of NAIP and survivin when compared with prostate from sham animals. Immunofluorescence studies confirmed the enhanced expression of NAIP and survivin with a characteristic pattern of cellular localization. Isolated administration of SeR, Se or Ly reduced NAIP and survivin expression and augmented caspases-3. The effects of Ly were greater than those of either SeR or Se, and the association of three compounds showed the highest efficacy in reawakening apoptosis in experimental BPH. However, the SeR-Se-Ly association was also the most effective in reducing prostate weight and hyperplasia. Therefore, these observations suggest that the increasing efficacy of the association might be a direct consequence of a more pronounced ability of this combination of reawakening the apoptosis program and identify the inhibition of NAIP and survivin the molecular mechanism by which this task is accomplished [89]. Furthermore among the three compounds, Ly appears to give the major contribution in maximizing the effects of SeR-Se-Ly which induced activation of the programmed cell death. In fact, the tomato derived compound causes a higher inhibitory effect on IAPs than Se and *SeR*. The efficacy and safety of *Serenoa repens* plus selenium and lycopene (Pro-

fluss) versus S. repens alone were evaluated in patients suffering from category IIIa chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [90]. One hundred and two patients with IIIa CP/CPPS were enrolled and randomized into two groups, each to receive SeR alone or in combination for 8 weeks. Evaluation was based on results of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), IPSS, maximum peak flow rate (MPFR), and PSA measurements at baseline and at weeks 4 and 8, at the end of the treatment. The primary endpoint was a >50% reduction in NIH-CPSI score. Secondary endpoints evaluated were MPFR, IPSS, PSA and white blood cell count. Mean NIH-CPSI score decreased significantly in both groups. A decrease was observed in the total score from 27.45 to 13.27 in the combination group (-51.64%) and from 27.76 to 20.62 in the SeR alone group 2 (-26.06%). IPSS improved significantly ($p < 0.001$) in both arms, but more in the group treated with the combination. PSA and white blood cell count were reduced significantly only in group treated with the association. The MPFR improved more in patients administered with SeR-Se-Ly. Therefore, none of the patients withdrew from the study. Therefore this study confirmed that SeR-Se-Ly association is safe and well tolerated and it improves symptoms associated with IIIa CP/CPPS [90].

## CONCLUSIONS

Phytotherapeutic supplements mainly based on saw palmetto derived SeR are numerous and used frequently. However, data supporting efficacy is limited, making treatment recommendation difficult. SeR is frequently associated with selenium and lycopene to maximize the therapeutic efficacy. An experimental study has confirmed that Ly gives the major contribution in heightening the effects of SeR-Se-Ly in BPH. It has been reported that the SeR-Se-Ly association has greater and enhanced anti-inflammatory activity. In addition, the SeR-Se-Ly combination more efficiently inhibits prostate enlargement by inhibiting growth factors expression and inducing cell programmed death. The enhanced stimulating effect of the association on apoptotic machinery is likely due to higher inhibition of the inhibitory apoptosis proteins (IAPs).

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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