

Efficacy and tolerability of *Serenoa repens* extract (Prostagood®) in patients with lower urinary tract symptoms due to symptomatic benign prostatic hyperplasia

Semptomatik benign prostat hiperplazisine bağlı alt idrar yolları semptomları bulunan hastalarda *Serenoa repens* ekstresinin (Prostagood®) etkililiği ve tolerabilitesi

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Abstract

Objective: The aim of this study was to investigate the efficacy and safety of *Serenoa repens* extract (Prostagood®) in the treatment of lower urinary tract (LUT) symptoms due to benign prostatic hyperplasia (BPH).

Materials and methods: A prospective, open-labelled, multicenter study was designed including 106 patients (mean age 59.2±7.1) with LUT symptoms due to BPH [mean International Prostate Symptom Score (I-PSS) 18.5±5.0]. Following a 2 week run-in period of no treatment, patients received Prostagood® (160 mg *Serenoa repens* extract/softgel twice daily) for 12 weeks.

Results: *Serenoa repens* extract treatment caused a significant improvement in the I-PSS score (12.1±6.7 vs. 18.4±4.9, p<0.001), the SF-36 score (74.1±15.9 vs. 76.9±13.4, p=0.021), and the life quality index score of the I-PSS (median 3 vs. 4, p<0.001). Maximum urine flow (Q_{max}) increased significantly from 9.7±3.0 mL/sec to 10.9±4.4 mL/sec (p=0.003) with treatment, while no significant change was observed in the urine flow (Q_{mean}) (4.8±1.7 mL/sec vs. 5.1±1.9 mL/sec, p=0.178), micturition volume and duration (273.1±138.5 mL vs. 282.4±144.3 mL, p=0.424 and 65.4±34.5 sec vs. 67.4±38.2 sec, p=0.580 respectively), peak flow time (13.3±15.6 sec vs. 14.4±15.4 sec, p=0.447), prostate volume (36.9±16.9 mL vs. 38.8±19.0 mL, p=0.173) and postvoid residual urine volume (63.3±38.0 mL vs. 71.3±59.3 mL, p=0.141). There was no differences in prostate specific antigen (PSA) between baseline and end of study (2.2±2.2 ng/dL vs. 2.1±2.2 ng/dL, p=0.545).

Conclusion: *Serenoa repens* extract decreases LUT symptoms due to BPH, and improves patients' quality of life. It is efficacious according to some of the uroflowmetric parameters and it is well tolerated.

Key words: Benign prostatic hyperplasia; *serenoa repens*; urinary tract.

Özet

Amaç: Bu çalışmanın amacı, benign prostat hiperplazisine (BPH) bağlı olarak alt idrar yolları (AİY) semptomları tedavisiinde *Serenoa repens* ekstresinin (Prostagood®) etkililiğini ve güvenliliğini araştırmaktır.

Gereç ve yöntem: BPH'ye [ortalama International Prostate Symptom Score (I-PSS) 18.5±5.0] bağlı olarak AİY semptomları bulunan toplam 106 hastanın (yaş ortalaması 59.2±7.1) alındığı prospektif, açık-etiketli, çok merkezli bir çalışma tasarlanmıştır. İki haftalık bir arınma dönemi sonrası hastalara 12 hafta süreyle Prostagood® (160 mg *Serenoa repens* ekstresi/jel, günde 2 kez) verilmiştir.

Bulgular: *Serenoa repens* ekstresi tedavisi I-PSS skurunda (12.1±6.7 ve 18.4±4.9, p<0.001), SF-36 puanında (74.1±15.9 ve 76.9±13.4, p=0.021) ve I-PSS'deki yaşam kalitesi indeks puanında (ortanca 3 ve 4, p<0.001) anlamlı düzelme sağlamıştır. Tedavi ile maksimum idrar akımı (Q_{max}) anlamlı olarak 9.7±3.0 mL/sn'den 10.9±4.4 mL/sn'ye (p=0.003) yükselirken, idrar akımında (Q_{mean}) (5.1±1.9 mL/sn vs. 4.8±1.7 mL/sn, p=0.178), miktürisyon hacminde ve süresinde (282.4±144.3 mL vs. 273.1±138.5 mL, p=0.424 ve 67.4±38.2 sn vs. 65.4±34.5 sn, p=0.580), doruk akım süresinde (14.4±15.4 sn vs. 13.3±15.6 sn, p=0.447), prostat hacminde (38.8±19.0 mL vs. 36.9±16.9 mL, p=0.173) ve post-void rezidüel idrar hacminde (71.3±59.3 mL vs. 63.3±38.0 mL, p=0.141) anlamlı bir değişiklik gözlenmemiştir. Çalışmanın başlangıcındaki ve sonundaki prostat spesifik antijen (PSA) düzeyleri arasında herhangi bir farklılık saptanmamıştır (2.2±2.2 ng/dL vs. 2.1±2.2 ng/dL, p=0.545).

Sonuç: *Serenoa repens* ekstresi BPH'ye bağlı AİY semptomlarını azaltır ve hastanın yaşam kalitesini artırır. Bu ilaç bazı üroflowmetrik parametrelere göre etkilidir ve iyi tolere edilmektedir.

Anahtar sözcükler: Benign prostat hiperplazisi; idrar yolu; *serenoa repens*.

Symptomatic benign prostatic hyperplasia (BPH) is one of the most common medical conditions in older men, affecting one in two males over the age of 50 years in Europe.^[1] BPH is often associated with bothersome lower urinary tract (LUT) symptoms, manifested as voiding disturbance, prostatic enlargement, and urodynamic obstruction^[2] that reduce quality of life, impede normal daily activities, and interfere with sleep patterns.^[1-3] The etiology of BPH has not yet been completely clarified, but the sex hormones, androgens, and estrogens seem to play a significant role in the development of BPH.^[4] The symptoms of BPH seem to originate from two obstructive mechanisms; a mechanical obstruction of the urethra caused by the overgrowth of the prostatic epithelium, and a dynamic obstruction due to excess sympathetic tone in the prostate and bladder neck.^[3]

Treatment goals are mainly symptomatic and aim at relieving irritative and obstructive symptoms such as urgency, nocturia, weak stream, intermittency, and incomplete emptying. Treatment options include lifestyle modification, minimally invasive and surgical therapies, and pharmaceutical and phytotherapeutic treatments. The latter are used extensively in Europe, while physicians in the U.S. rely mainly on surgery and pharmacotherapy due to lack of convincing evidence for phytotherapy, raising the estimated number of prostatectomies to 300,000 per year.^[4-6]

Pharmaceutical treatment of BPH symptoms employs either 5- α reductase and type 5 phosphodiesterase inhibitors or α_1 adrenergic receptor antagonists to counteract the androgen-dependent growth of the prostate gland.^[7,8] Often a combination of treatments is used, combining an α_1 -antagonist with a 5- α reductase inhibitor or with an anticholinergic agent.^[9] The activity of testosterone in the prostate gland is increased by dehydrotestosterone, by the 1 and 2 types of the 5- α reductase isoenzymes, hence inhibition of the enzymatic activity of these enzymes is a rational therapeutic treatment. Five- α reductase inhibitors block the reduction of testosterone to 5- α dehydrotestosterone, which stimulates prostatic hyperplasia; α_1 adrenergic antagonists relax the smooth muscle in the prostate epithelium and relieve dynamic obstruction. Though routinely used in everyday practice, both 5- α reductase inhibitors and α_1 -antagonists have compliance issues in some patients. Some α_1 -antagonists are reported to cause postural hypotension and dizziness because of their

vasodilatory effects, which may be critical in aging men and cause falls; while 5- α reductase inhibitors are known to lead to sexual dysfunction.^[10,11] Compliance issues are leading physicians to look into other options.

The use of plant extracts in treating BPH symptoms is common in various European countries and is gaining support in the Western hemisphere. The most widely used compound is the extract of the dried ripe fruit from the American dwarf saw palmetto plant named *Serenoa repens*/*Serenoa serrulata* (also known by its botanical name *Sabal serrulata*).^[12] The medicinal value of *Serenoa repens* for relief of prostate gland swelling has been reported in medical literature since the 1800s.^[13] The mechanism of the action of *Serenoa repens* is thought to depend on alteration of cholesterol metabolism, anti-estrogenic, anti-androgenic, and anti-inflammatory effects, and a decrease in the available sex hormone-binding globulin.^[14-18]

There is accumulating evidence that *Serenoa repens* extract may arrest cell growth and promote apoptosis of androgen-dependent prostate cancer cells.^[19] Additionally it is shown to affect apoptosis molecular markers such as caspase-3 activity and Bax-toBcl-2 expression ratio.^[20] Furthermore, inflammatory biomarkers such as TNF- α and IL-1b are lower in patients treated with a lipidosterolic extract of *Serenoa repens*.^[21] These findings along with the concomitant observation of reduced prostatic interstitial B lymphocytes and significantly improved clinical status, suggest a pharmacological effect of *Serenoa repens* on benign prostatic hyperplasia.

Recent original investigations and meta-analysis of clinical trials report significant improvement in urodynamic variables such as peak flow rate, nocturia, and reduction in the I-PSS scale following *Serenoa repens* extract administration.^[22,23]

The present study was designed to investigate the therapeutic efficacy and safety of the *Serenoa repens* plant extract (Prostagood®) in terms of improvement in both subjective and objective/urodynamic parameters in men with LUT symptoms due to BPH.

Materials and methods

Study design

A total of 106 patients were included in this prospective, open-label, single-arm, non-comparative

multicenter study. Patients received Prostagood® softgels 160 mg twice a day. Prostagood® is a phytopharmaceutical consisting of standardized extract of *Serenoa repens* WS 1473 (licensed by Dr. Willmar Schwabe GmbH&Co. KG, Germany to Abdi Ibrahim Pharmaceuticals in Turkey). No other pharmacological or surgical treatment or other non-drug interventions for the treatment of LUT symptoms due to BPH was allowed during the study. A run-in period of 2 weeks was employed, during which patients did not receive any treatment for LUT symptoms. The run-in period was followed by a 12-week treatment phase, in which all subjects received the same treatment. Patients were followed for a total of 14 weeks. Each patient was scheduled to undergo 5 site visits. Patient eligibility was evaluated at screening visit, and all eligible patients underwent a 2-week run-in period and returned to the study center for the baseline visit evaluation. Treatment with Prostagood® commenced at visit 2 and continued until week 12. Three additional visits were performed during the 12-week treatment period, with a time interval of 4 weeks. Subjective scales for the evaluation of prostate symptoms and quality of life parameters were conducted at each visit, along with measurements of urodynamic parameters. Digital rectal examination and SF-36 questionnaire were applied at screening, baseline, and at the end of treatment visits, while prostate specific antigen (PSA) measurement and blood samples for laboratory safety examinations were conducted at screening and at end of treatment visits.

The study was approved by both local and central ethics committees. Written informed consent was obtained prior to inclusion of patients in the study and involvement in any study related procedures.

Patients

Patients were screened for inclusion in the study if they were 45 years or older and were diagnosed with symptomatic BPH without surgical indication or other acute or emergency BPH treatment, and presented with an I-PSS (International Prostate Symptom Score) >10 [quality of life (QoL) question of the I-PSS >2]. Other inclusion criteria included maximum urinary flow rate (Q_{max}) <15 mL/sec and maximal residual volume <150 mL.

Patients were excluded from the study if they had received previous treatment with 5- α reductase inhibitors, if they had undergone any surgical procedure or pharmaceutical treatment, or were diagnosed with any associated disease likely to affect detrusor/bladder sphincter function. Patients were also excluded from the study if they were diagnosed with active or recurrent urinary tract infections, acute or chronic prostatitis, chronic heart failure, prostate cancer, bladder cancer, interstitial cystitis, upper tract stone disease, or required an indwelling catheter or intermittent catheterization.

Assessments

Questionnaires used in this study to record objective parameters on health status and quality of life included: I-PSS a screening tool consisting of 7 symptom-related questions and 1 QoL question, which is used to rapidly diagnose and track the symptoms of BPH. The I-PSS is a self-administered questionnaire and can be used in various settings and on multiple occasions to compare the progression of symptoms and their severity over time. Clinical Global Impression–Severity (CGI-S) is a tool for global evaluation of severity of disease by the

Table 1. Total International Prostate Symptom Score (I-PSS; scale 0-35) in visits 2 and 5

	Mean±SD	Median
Visit 2	18.4±4.9	18
Visit 5	12.0±6.7*	11

SD: Standard deviation; * $p < 0.001$, Wilcoxon signed rank test.

Table 2. Descriptive statistics for urodynamic measurements and post-void residual urine in visits 2 and 5

	Visit 2 Mean±SD	Visit 5 Mean±SD	p^*
Q_{max} (mL/sec)	9.7±3.0	10.9±4.4	0.003
Q_{mean} (mL/sec)	4.8±1.7	5.0±1.9	0.178
Micturition volume (mL)	273.0±138.5	282.4±144.2	0.424
Micturition time (sec)	65.4±34.5	67.4±38.2	0.580
Peak flow time (sec)	13.3±15.6	14.4±15.4	0.447
Prostate volume (mL)	36.9±16.9	38.8±19.0	0.173
Residual urine volume (mL)	63.3±37.9	71.3±59.3	0.141

SD: Standard deviation; *Wilcoxon signed rank test.

physician. The severity of disease is assessed using a 7-grade scale ranging from 1 (normal, no disease) to 7 (extremely severe disease). Clinical Global Impression–Improvement (CGI-I), is a tool for global evaluation of the level of improvement or exacerbation of symptoms of disease. The scale ranges from 1 (very much improved) to 7 (very much worse/exacerbated). Brief Male Sexual Function Inventory (BMSFI) is an 11-item questionnaire that includes questions relating to sexual drive, erection, ejaculation, and overall satisfaction.^[24] Urodynamic measurements included maximum and mean urinary flow (Q_{max} , Q_{mean}), flow increase rate, micturition volume, micturition duration, time to peak flow rate, post-void residual urine volume, and prostate size. Blood samples for hematological and biochemical parameters, and the evaluation of PSA were also collected

Statistical analysis

Efficacy analysis was conducted with data of 106 patients, and all missing values were replaced by the last observation carried forward method. The primary efficacy endpoint was the change of I-PSS total score between baseline and week 12.

I-PSS and secondary efficacy endpoints were analyzed using a Wilcoxon signed rank test to measure the following: changes in the I-PSS at visit 5 compared to baseline, changes in the BMSFI score at visit 5 compared to baseline, evaluation of satisfaction by patient, and changes in QoL of I-PSS at visit 5 compared to baseline.

Differences in means were evaluated by two-tailed paired t-tests. The following secondary efficacy endpoints were evaluated: change in the uroflowmetry, prostate size, residual urine, and quality of life index (SF-36) compared to baseline.

Results

Efficacy

I-PSS

Following 12 weeks of Prostagood® treatment, I-PSS showed significant improvement (18.4 ± 4.9 vs. 12.0 ± 6.7 , $p < 0.001$), with 86 (81.3%) of 106 patients showing decreased I-PSS total score at visit 5 compared to baseline visit (Table 1).

CGI

At visit 5, CGI scores indicated that 73.6% of patients felt their conditions were improved. This rate represents the sum of patients reporting “fairly improved” or “very much improved.”

Q_{max} and urodynamic parameters

After 12 weeks of Prostagood® treatment, Q_{max} increased significantly (9.7 ± 3.0 mL/sec vs. 10.9 ± 4.4 mL/sec, $p = 0.003$). No other significant changes were observed in the other urodynamic parameters measured (Table 2).

SF-36 and QoL

There was a significant improvement in average SF-36 total score (74.1 ± 15.9 to 76.1 ± 13.4 , $p = 0.021$, Table 3) and the QoL questions of I-PSS scale. Seventy-two of 106 patients showed improved QoL; 4 patients worsened; and 30 had no change (Fig. 1).

PSA

PSA was not significantly different from baseline after 12 weeks of Prostagood® treatment (2.2 ± 2.2 ng/mL vs. 2.1 ± 2.2 ng/mL at baseline and end of study, respectively, $p = 0.545$).

Prostate volume

There was no difference in prostate size between baseline and end of study visit (36.9 ± 16.9 mL vs.

Table 3. SF-36 score and overall satisfaction by patient in visits 2 and 5

	Mean $\pm$ SD	Median	p^*
SF-36 Score (scale: 1-100)			0.021
Visit 2	74.1 $\pm$ 15.9	78	
Visit 5	76.9 $\pm$ 13.4	80	
Overall Satisfaction (scale: 0-4)			0.487
Visit 2	2.1 $\pm$ 1.2	2	
Visit 5	2.0 $\pm$ 1.2	2	

SD: Standard deviation; *Wilcoxon signed rank test.

38.8±19.0 mL at baseline and end of study, respectively, $p=0.173$).

Residual urine volume

There were no differences in postvoid residual urine volumes between baseline and end of study visit (63.3±38.0 mL vs. 71.3±59.3 mL at baseline and end of study, respectively, $p=0.141$).

Safety

Of 106 patients who were randomized and received at least one dose of the study medication, 25 reported 34 different adverse events (AE). Three AE were defined as serious. During the study, only one patient had to discontinue treatment because of AE (epigastric pain and erectile dysfunction); only the epigastric pain was considered to be possibly related to the study drug.

Detailed analysis of safety data showed that the administration of the study medication was safe, causing a minimum number of AE, without posing any significant threats to patients. Safety analysis is summarized in Table 4.

Discussion

The present study aimed at investigating the efficacy and safety of *Serenoa repens* extract (Prostagood®),

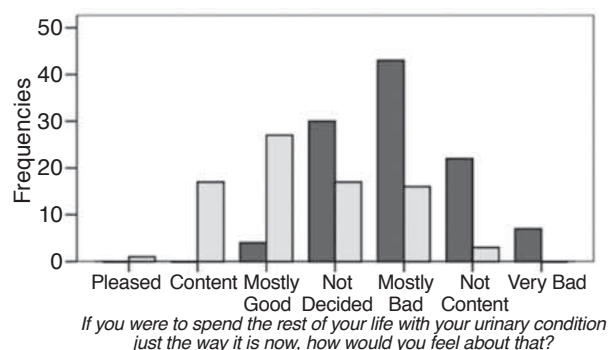


Figure 1

Differences in frequencies of QoL index score before and after 12 weeks of *Serenoa repens* extract treatment. Dark bars, baseline visit; light bars, visit 5. Totally 67.9% of patients had decreased score at visit 5 compared to baseline visit ($p<0.001$).

administered for 12 weeks in a group of patients presenting with LUT symptoms due to BPH. At the end of the study the majority of patients (a percentage close to 90%) had significant improvement of severity of LUT symptoms from baseline visit, as defined by the use of I-PSS. The I-PSS questionnaire is considered as the benchmark for the evaluation of LUT symptoms, and its change from baseline was defined as the primary efficacy endpoint.

The use of *Serenoa repens* extract for a 12-week period led to a significant improvement in patients' mean SF-36 scores and mean I-PSS QoL index values. This improvement in both quality scales is strong evidence that the subjective improvement in symptoms was noted by the patients as a significant progress in their quality of life.

The comparison of uroflowmetric and ultrasound measurements demonstrated that the Q_{max} was significantly increased. In addition to the significant increase in Q_{max} , there was a trend for improvement in many uroflowmetric parameters (such as micturition volume and time, and maximum urine flow), although not significant. Follow-up of outcomes for a longer period of treatment may be needed to detect possible further improvement.

There are numerous randomized, double-blind studies that present evidence regarding the beneficial effects of *Serenoa repens* extract on LUT symptoms due to BPH.^[10,23,25-35] Previous research has suggested that clinically meaningful change in symptoms of BPH requires a change of at least 3 points.^[33] We report a change of 6.4 points in the I-PSS scale, which suggests that this improvement is of significant clinical value. In most previous studies, a summary

Table 4. Summary of drug-related adverse events (AE)

	n	%
<i>Number of patients with at least one drug-related AE</i>	15	
<i>Mild</i>		
Constipation	1	6.67%
Diarrhea	1	6.67%
Dyspepsia	1	6.67%
Dysuria	1	6.67%
Influenza	1	6.67%
Hearing problems	1	6.67%
Nausea	2	13.33%
Painless macroscopic hematuria	1	6.67%
Vertigo	2	13.33%
<i>Moderate</i>		
Dysuria	1	6.67%
Epistaxis	1	6.67%
Epigastric Pain	1	6.67%
Headache	1	6.67%

estimate showed that *Serenoa repens* extract increased peak urinary flow rate by 1.86 mL per second more than placebo.

A study that compared *Serenoa repens* extract and tamsulosin, an α_1 adrenergic receptor antagonist, showed that *Serenoa repens* extract was superior to tamsulosin in reducing LUT symptoms after a 12 months of double-blind treatment, while the first beneficial results in Q_{max} were observed as early as 12 weeks.^[36] Another recent study carried out in a group of Turkish patients by Hizli and Uygur reported similar efficacy but higher tolerability with *Serenoa repens* extract in the treatment of LUT symptoms due to BPH.^[10]

Adverse drug reactions and safety of pharmaceutical products is receiving increased attention from both clinicians and investigators. In some instances, adverse reactions may cause discontinuation of treatment; in other instances, adverse reactions need to be treated, increasing health expenditure. In daily practice, this may leave the patient untreated or undertreated. Five- α reductase inhibitors may occasionally cause sexual dysfunction, which is considered quite shameful in some societies.^[37] This can cause more doctor visits, complaining patients, changes in medication, and more operations. Alpha-1 blockers may cause postural hypotension, which can result in falls in aging men.^[38] Treating consequences of falls also consumes much time and expense from the health system.^[39] Another concern with 5- α reductase inhibitors is alteration of blood PSA levels and reduced likelihood of a diagnosis of prostatitis. Any effect on PSA, which is one of the most valuable markers of prostate carcinoma will delay diagnosis and early treatment, also leading to increased costs in later stages.^[40] Though it may require longer time to observe than in the current study, we saw no significant changes in PSA levels with *Serenoa repens* extract.

In terms of safety endpoints, *Serenoa repens* extract demonstrated a very mild and well-tolerated profile throughout the study. Of 106 patients in the study, there were a total of 34 AEs reported. Three of the cases were defined as serious, and these serious AEs were not considered as related to the study drug. Throughout the study, only one patient had to discontinue treatment due to AE (epigastric pain and erectile dysfunction); and only epigastric pain was considered related to the study drug.

We conclude that the use of *Serenoa repens* extract may improve patients' LUT symptoms secondary to BPH, and enhances self-appraisal of quality of life. Moreover, during the study, it seems to be efficacious in improving certain uroflowmetric parameters with an acceptable safety profile.

Conflict of interest

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