Measuring the efficacy of Serenoa repens (USPlus) extract with mobile uroflowmetry

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WINOGRAD J, LAMA J, CODELIA-ANJUM A, BHOJANI N, ELTERMAN DS, ZORN KC, MARGOLIS E, BRAHMBHATT J, GONZALIEZ R, CHUGHTAI B. Measuring the efficacy of Serenoa repens (USPlus) extract with mobile uroflowmetry. *Can J Urol* 2024;31(6):12053-12059.

Introduction: *Benign prostatic hyperplasia (BPH) is a prevalent condition affecting a significant portion of the male population, leading to secondary lower urinary tract symptoms (LUTS). Alternative therapies such as phytotherapy using Lipidosterolic extract of Serenoa repens (LSESR USPlus) are commonly used. However, the efficacy of LSESr remains controversial due to conflicting data. We sought to determine the effect of a standardized USP-verified Saw Palmetto extract on male LUTS secondary to BPH.*

Materials and methods: *In this prospective single-arm trial, we investigated the efficacy of a standardized USP-verified Saw Palmetto extract in treating male LUTS secondary to BPH. We utilized the ProudP mobile application for home uroflowmetry and symptom assessment.*

Results: *Results from 46 patients using 320 mg daily of USP-verified Saw Palmetto extract revealed significant improvements in IPSS and QoL scores at 12 weeks compared to baseline, particularly in patients with moderate symptoms. Uroflowmetry parameters also improved with increased flow rates, primarily in patients with mild symptoms.*

Conclusion: *Our findings support the efficacy of USP-verified Saw Palmetto extract in alleviating LUTS in men with BPH. Further studies are warranted in larger, diverse cohorts over longer follow up periods.*

Key Words: phytotherapy, BPH, LUTS, mobile uroflowmetry

Introduction

Benign prostatic hyperplasia (BPH) is a prevalent problem, with nearly 50% of males experiencing BPH by their fourth decade of life.[1,2] Of these men, more than half will experience lower urinary tract symptoms (LUTS).[3] The current American Urological Association guidelines recommend alpha-adrenergic antagonists (alpha-blockers), 5 alpha-reductase inhibitors (5-ARIs), phosphodiesterase 5 inhibitors (PDE5), and anticholinergic medications to treat LUTS secondary to BPH.[4] Many patients do not want to start a lifetime of medications and would like to pursue a more natural route.

One driving factor in the decision for patients to pursue a more naturally derived treatments is the greater perceived health benefits and safety of these products, as well as a combination of social and cultural influences. Clinical evidence was rarely

Accepted for publication November 2024

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Acknowledgement
This study received funding from Valensa International

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mentioned by consumers as a consideration in their decision.[5] A popular LUTS nutraceutical involves the use of a Lipidosterolic extract of *Serenoa repens* (LSESR USPlus). Given the popularity of natural treatments, evaluation of their safety and efficacy of this treatment is important for understanding and building a therapeutic alliance with patients who may be interested in a natural treatment for their LUTS.

LSESr derived from the dwarf American palm tree (*Serenoa repens*), has demonstrated anti-inflammatory properties and potentially reverses the apoptosis/proliferation ratio seen in BPH related prostate inflammation.[6-9] LSESr has inhibitory effects against certain pro-inflammatory cytokines, further developing its use for BPH-associated inflammation symptoms.[10] The use of *Serenoa repens* extracts has become increasingly popular, with many countries reportedly using it as a first-line therapy in patients with BPH.[11-13] Despite its potential efficacy, the existing body of research on LSESr's impact in treating LUTS has conflicting data.[4]

Challenges in evaluating these effects lie in the conventional methods of assessment, which often entail cumbersome uroflowmetry measurements. Our primary objective is to measure the effect of a standardized USP-verified Saw Palmetto extract on male LUTS secondary to BPH.

Materials and methods

Forty-five patients were recruited from February 2023 to January 2024 experiencing LUTS secondary to BPH who used a standardized USP-verified Saw Palmetto extract, which is extracted via an ultra-high pressure, supercritical CO_2 extraction with ≥ 80% fatty acids (USPlus, Valensa International, Eustis, Fl). Using ProudP (www.proudP.com, Soundable Health Inc., San Francisco, CA, USA), the mean voided volume, voiding time and maximum flow rate were measured at baseline, as well as 6 weeks and 12 weeks after starting a daily 320 mg LSESr-USPlus treatment. ProudP is validated for use as an acoustic measure of uroflowmetry parameters.[12,13] The validation study of ProudP showed that the sound-based voided volume estimation algorithm accurately estimates voided volumes and uroflowmetry.

Validated questionnaires including the International Prostate Symptom Score, Male Sexual Health Questionnaire – Ejaculatory Dysfunction (MSHQ-EjD), and Chronic Prostatitis Symptom Index (CPSI) were used to track symptom changes.

The inclusion criteria included to be between 40 and 99 years old, and able to independently operate a smartphone. Exclusion criteria include individuals unable to follow written instructions without assistance, recent urinary catheterization within the past month, LUTS from another medical condition besides BPH, sex reassignment surgery within the past 2 years, and the inability to stand and urinate independently. This study is IRB approved (IRB #20-226657).

The change in International Prostate Symptom Score (IPSS) and Quality of Life (QoL), as well as changes in the voiding and storage subscores, at 6 and 12 weeks after starting LSESr treatment, were evaluated. The median, interquartile range (IQR), z-score, p-value and effect size at baseline, 6 weeks, and 12 weeks were reported. All changes were analyzed with patient-matched signed-rank Wilcoxon analysis, averaging trials when multiple were present at a single timepoint. Python version 3.13 with SciPy version 1.14 was used for statistical analysis with a p value < 0.05 indicating significance.

Results

Forty-five men with a mean age of 55 years (range 40-76) were included. Our population study was largely healthy with no significant comorbidities, Table 1. Five patients were on alpha blockers at the time of the study, 2 were on a 5-alpha reductase inhibitor (5ARI), and 6 were on a phosphodiesterase 5 inhibitor (PDE5I), with 2 patients on multiple of these medications. No patients reported changes in dosing regimens. Additionally, 4 patients were on antiplatelet medication, 9 had hyperlipidemia, and 2 had erectile dysfunction. No adverse events were reported.

A priori study power was calculated. Using a two-tailed test with a normal parent distribution, an alpha of 0.05, and an effect size of d = 0.5, for a power of 80%, a sample size of 35 was found, which suggests this study is adequately powered to capture moderate changes.

TABLE 1. **Patient demographics for 45 patients**

Patient characteristics	
Age: mean (SD) [range]	55 (10) [40, 76]
Alpha blockers (%)	5 (11)
5-ARIs (%)	2 (4)
PDE5-I (%)	6 (13)
Anti-platelet	4 (9)
Erectile dysfunction (%)	2 (4)
Hyperlipidemia (%)	9 (20)

Significant decreases in the IPSS and QoL, Table 2, at 12 weeks, going from a median of 6.5 (IQR: 3, 10) to 5 (IQR: 3, 8, p = 0.03), and 2 (IQR 1, 3) to 2 (IQR: 1, 2, p = 0.003) respectively were measured. These reductions may be driven by the reduction in the voiding subscore from 4 (IQR: 2, 5) to 3 (IQR: 1, 4, p = 0.03) at 12 weeks. When these same changes were analyzed excluding those on alpha blockers, 5ARIs, or PDE5Is, a similar decrease in IPSS from 6 to 5 was found, but without statistical significance (p = 0.06), implying the stable dose of BPH meds did not change the improvement in LUTS.

When looking at patients with a baseline moderate IPSS score (8 to 19), a significant decrease in IPSS and QoL was measured from medians of 10 (IQR: 10, 12) to 7 (IQR: 5, 8.3, p = 0.005), and 3 (IQR: 2, 4) to 2 (IQR: 2, 3, p = 0.003), respectively. Looking further, significant changes in both the voiding and storage subscores at 12 weeks were seen, from an initial voiding subscore median of 6 (IQR: 4.5, 6) to 2 (IQR: 2, 3, p = 0.02), and

TABLE 2. **Changes in IPSS and QoL, along with voiding and storage for all patients at baseline, 6 weeks, and 12 weeks of LSESr-USPlus treatment. Median with interquartile range (IQR), Wilcoxon statistic, z statistic, p value, and Cohen's d is given for all comparisons. Comparisons are further stratified by all patients, those with baseline mild IPSS (0-7), and those with baseline moderate IPSS (8-19). Data is shown both including and excluding patients on alpha blockers, 5 alpha reductase inhibitors (5ARIs), or phosphodiesterase 5 inhibitors (PDE5I). Bold values indicate change from baseline was statistically significant**

Score		All patients (n = 45)					Baseline mild symptoms (IPSS: 0-7) (n = 25)				
	Time	**Median (IQR)**	**W***	**z**	**p**	**d****	**Median (IQR)**	**W***	**z**	**p**	**d****
IPSS	Baseline	6.5 (3.0, 10)					3.0 (1.0, 5)				
	Week 6	5.3 (2.9, 8.3)	209	0.21	0.63	0.05	3.0 (1.0, 5.5)	60.5	0.68	0.70	0.23
	Week 12	**5.0 (3.0, 8.0)**	**313**	**1.78**	**0.034**	**0.25**	3.3 (2.0, 5.5)	122	1.28	0.62	0.35
QoL	Baseline	2.0 (1.0, 3.0)					1.0 (1.0, 2.0)				
	Week 6	2.0 (1.0, 2.0)	179	0.47	0.81	0.13	1.5 (0.25, 2.0)	21	0.43	0.86	0.13
	Week 12	**2.0 (1.0, 2.0)**	**91**	**3.13**	**0.003**	**0.42**	1.0 (1.0, 2.0)	47	0.32	0.72	0.07
Voiding subscore	Baseline	2.5 (1.0, 5.8)					1.0 (0, 2.0)				
	Week 6	2.0 (0.9, 5.0)	91.5	0.03	0.81	0.03	1.0 (0, 2.0)	29	1.07	0.43	0.35
	Week 12	2.0 (1.0, 4.0)	104	0.25	0.15	0.25	1.5 (1.0, 1.3)	29.5	1.62	0.15	0.44
Storage subscore	Baseline	4.0 (2.0, 5.0)					2.0 (0, 4.0)				
	Week 6	3.0 (1.3, 3.0)	81	0.28	0.74	0.06	2.0 (0.25, 2.9)	33	0.19	0.64	0.06
	Week 12	**3.0 (1.0, 4.0)**	**136.5**	**1.46**	**0.025**	**0.20**	2.0 (1.0, 3.0)	99	0.71	0.82	0.18
		Baseline moderate symptoms (IPSS: 8-19) (n = 19)									
IPSS	Baseline	10 (10, 12)									
	Week 6	6.5 (5.4, 9.9)	19	1.81	0.13	0.73					
	Week 12	**7.0 (5.0, 8.3)**	**27**	**3.47**	**0.005**	**0.86**					
QoL	Baseline	3.0 (2.0, 4.0)									
	Week 6	2.0 (2.0, 3.0)	7	1.20	0.23	0.51					
	Week 12	**2.0 (2.0, 3.0)**	**6**	**3.73**	**0.003**	**0.74**					
Voiding subscore	Baseline	6.0 (4.5, 6)									
	Week 6	3.5 (2, 5.5)	18	1.39	0.18	0.63					
	Week 12	**2.0 (1.5, 4.5)**	**37**	**2.83**	**0.018**	**0.75**					
Storage subscore	Baseline	5.0 (4.0, 6.0)									
	Week 6	3.0 (3.0, 5.3)	15	1.78	0.10	0.58					
	Week 12	**4.0 (3.0, 5.0)**	**18**	**3.02**	**0.016**	**0.68**					

*Wilcoxon statistic; **Cohen's d

TABLE 3. **Maximum flow rate, average flow rate, voided volume, and voiding time for all patients and stratified by baseline IPSS score at baseline, 6 and 12 weeks of LSESr-USPlus treatment. Wilcoxon statistic, z statistics, p value, and Cohen's d is given for all comparisons. Comparisons are further stratified by all patients, those with baseline mild IPSS, and those with baseline moderate IPSS. Data is shown both including and excluding patients on alpha blockers and 5ARI. Data is shown both including and excluding patients on alpha blockers and 5ARI. Bold values indicate change from baseline was statistically significant**

Uroflowmetry parameter		All patients (n = 45)					Baseline mild symptoms (IPSS: 0-7) (n = 25)				
	Time	Median (IQR)	W*	z	p	d**	Median (IQR)	W*	z	p	d**
Maximum flow rate mL/s	Baseline	18.4 (14.6, 22.5)					21.5 (17.3, 25.3)				
	Week 6	19.4 (14.3, 22.2)	409	0.01	0.86	< 0.01	21.6 (19.7, 24.6)	81	0.31	0.87	0.04
	Week 12	20.2 (14.6, 23.9)	238.5	1.57	0.08	0.14	**23.9 (21.2, 26.0)**	**37**	**2.54**	**0.01**	**0.39**
Average flow rate mL/s	Baseline	12.9 (9.0, 15.7)					14.5 (11.3, 16.8)				
	Week 6	13.6 (9.4, 15)	367	0.56	0.41	0.05	14.2 (13.6, 16.3)	70	0.85	0.523	0.12
	Week 12	**13.3 (9.2, 16.4)**	**337**	**1.97**	**0.03**	**0.15**	**16.4 (13.4, 17.3)**	**21**	**3.17**	**0.001**	**0.40**
Voided volume (mL)	Baseline	260 (213, 302)					289 (226, 362)				
	Week 6	269 (212, 351)	430	0.39	1	0.05	328 (243, 393)	71	0.96	0.55	0.20
	Week 12	257 (226, 339)	427	1.20	0.22	0.18	279 (246, 375)	74	0.93	0.26	.23
Voiding time (sec)	Baseline	24.5 (17.3, 31.3)					23.8 (16.4, 30.7)				
	Week 6	22.6 (18.6, 30.4)	405	0.34	0.75	< 0.01	22.1 (17.6, 29.5)	80	0.59	0.83	0.12
	Week 12	26.3 (18.1, 32.6)	424	0.82	0.21	0.1	18.8 (16.1, 26.6)	94	0.57	0.70	0.10

Uroflowmetry parameter		Baseline moderate symptoms (IPSS: 8-19) (n = 19)				
	Time	Median (IQR)	W*	z	p	d**
Maximum flow rate mL/s	Baseline	19.1 (17.4, 21.5)				
	Week 6	18.1 (15.5, 21.6)	32	0.63	0.38	0.14
	Week 12	18.7 (12.6, 21)	31	1.21	0.19	0.22
Average flow rate mL/s	Baseline	12.9 (10.7, 15.1)				
	Week 6	11.0 (10.5, 15)	38	0.65	0.64	0.13
	Week 12	12.3 (9.2, 14.8)	33	0.99	0.24	0.24
Voided volume (mL)	Baseline	266 (219, 360)				
	Week 6	270 (211, 360)	32	0.76	0.38	0.13
	Week 12	254 (201, 400)	45	0.30	0.67	0.07
Voiding time (sec)	Baseline	22.1 (18.4, 39.1)				
	Week 6	20.2 (19.2, 33.9)	32	0.29	0.38	0.04
	Week 12	24.5 (19.3, 38.2)	32	0.19	0.22	0.04

*Wilcoxon statistic; **Cohen's d

an initial storage subscore median of 5 (IQR: 4, 6) to 4 (IQR: 3, 5, p = 0.02) at 12 weeks respectively. All these changes had an effect size of 0.68 or greater, indicating a large magnitude of change.

A significant change in average flow rate, Table 3, from 12.9 (IQR: 9,15.7) to 13.3 (IQR: 9.2, 16.4, p = 0.03) mL/s from baseline to 12 weeks was seen. However, the low effect size of 0.15 suggests that our study may not be adequately powered for this magnitude change. When these same changes were analyzed excluding those on alpha blockers, 5ARIs, or PDE5Is, a similar change in average flow rate

from 13.4 (IQR: 11.3, 16.3) to 14.2 (IQR: 12.2, 16.6) mL/s was found but this change was not statistically significant (p = 0.07).

When looking at patients with a baseline mild IPSS score (0 to 7), significant increases in the maximum flow rate from 21.5 (IQR: 17.3, 25.3) to 23.9 (IQR: 21.2, 26, p = 0.01) mL/s at 12 weeks and in the average flow rate from 14.5 (IQR: 11.3, 16.8) to 16.4 (IQR: 13.4, 17.3, p = 0.001) mL/s at 12 weeks was seen. When these same changes were analyzed excluding those on alpha blockers, 5ARIs, or PDE5Is, similar statistically significant changes in the maximum flow rate of 22.3 (IQR: 17.3, 25.4) to 23.9 (IQR: 20.9, 26.2, p = 0.01) mL/s and in the average flow rate of 15.0 (IQR: 11.3, 16.8) to 16.5 (IQR: 13.1, 17.5, p = 0.01) mL/s were seen. No other significant changes in uroflowmetry parameters was seen.

Discussion

Patients taking LSESr had significant decreases in baseline IPSS from a median of 6.5 to 5 (p = 0.03) at 12-week follow up for all patients with LUTS symptoms, correlating with a significant decrease in the storage subscore in all patients from a median baseline of 4 to 3 at the 12-week follow up (p = 0.003). These findings are consistent with previous studies evaluating the efficacy of Lipidosterolic Extract of *Serenoa repens* in LUTS treatment. Our report of a reduction in IPSS of 1 is consistent with the average median symptom improvement found across nearly 1681 patients in 9 randomized controlled trials highlighted in the Cochrane review of Lipidosterolic Extract of *Serenoa repens* efficacy in BPH.[16] Our findings also suggest LSESr may be a useful medication for patients already on LUTS pharmacotherapy. Glémain et al and Ryu et al studied the efficacy of Lipidosterolic Extract of *Serenoa repens* in combination with tamsulosin, an alpha-1 inhibitor, and found similar enhanced decreases in IPSS compared to tamsulosin alone.[17,18] Comparing hexane extracted Lipidosterolic Extract of *Serenoa repens* (HSESr), which has a similar fatty acid signature to the compound used in this study, versus finasteride, a 5-alpha reductase inhibitor, Carraro et al demonstrated similar improvements in IPSS (-5.8 with HSESr vs. -6.2 with finasteride; p = 0.17) and IPSS-QoL (-1.5 vs. -1.4, respectively; p = 0.14) in patients with moderate-to-severe LUTS.[19] In addition, the use of *Serenoa repens* to traditional LUTS medications did not come with an increased incidence of side effects; none of the patients in our study reported new or worsened adverse events after beginning LSESr. In this sense, LSESr is a safe, appealing add-on medication for patients interested in nutraceutical LUTS treatment.

A statistically significant decrease in the average flow rate from 12.9 (IQR: 9, 15.7) to 13.3 (IQR: 9.2, 16.4) mL/s from baseline to 12 weeks was found. These findings are consistent with previous literature that reported significantly increased peak flow rates from baseline of +1.19 mL/s vs. -0.49 mL/s at 4 weeks (p = 0.01) and +4.09 mL/s vs. +0.93 mL/s at 24 weeks (p = 0.0008) in BPH-LUTS patients using *Serenoa repens* extracts compared to placebo.[20] Focusing on patients with only mild BPH-LUTS symptoms, Djavan et al compared outcomes of *Serenoa repens* extract use vs. placebo and reported similar significant improvements in IPSS (-1 vs. +0.3), QoL (-0.4 vs. -0.2), and Qmax (+1.8 mL/s vs. -1 mL/s) at 2-year follow up.[21]

Our findings of decreased IPSS and QoL scores in patients with moderate baseline IPSS were statistically significant and had sufficient effect size to be reliably captured in this study. This may be due to the fact that patients with baseline mild IPSS may have unfavorable anatomy for medical management, perhaps due to a large middle lobe or a high bladder neck. Our finding of increased *Serenoa repens* efficacy with higher IPSS scores is consistent with prior research from Strum et al, who reported greater improvement in IPSS in patients taking Lipidosterolic with more severe (20 < IPSS < 35) compared to moderate symptoms (8 < IPSS < 19).[22] This trend may be attributed to the varying purported mechanisms of action for Lipidosterolic Extract of *Serenoa repens* in BPH, which range from pro-apoptotic and anti-proliferative properties to detrusor and prostate relaxation.[8,23] Accordingly, different mechanisms may predominate in varying prostates, such as heightened anti-proliferative and anti-inflammatory action in patients with more severe LUTS, as seen in our moderate IPSS patients reporting greater reductions in voiding and storage subscores compared to the mild group. Further evaluation of the clinical mechanisms of LSESr action in vivo is needed to better predict how it will impact different patients.

No significant changes in sexual health using the Male Sexual Health Questionnaire-Ejaculatory Dysfunction (MSHQ-EjD) scale nor prostatitis symptoms using the Chronic Prostatitis Symptom Index (CPSI) at both 6- and 12-week follow up for all patients was found, Table 4. This is consistent with previous studies that found no change in sexual function in patients using Lipidosterolic Extract of *Serenoa repens* compared to placebo and tamsulosin.[24]

The current study does have limitations to note. Firstly, the small sample size and relatively short patient

TABLE 4. **Prostate symptom scores, including the MSHQ-EjD in 4a and the CPSI in 4b, at baseline, 6 weeks, and 12 weeks after starting LSESr-USPlus**

a)			
MSHQ-EjD	**Median**	**W***	**p**
Baseline	12		
Week 6	13	12.5	0.9375
Week 12	13	9	0.7389
b)			
CPSI	**Median**	**W***	**p**
Baseline	4		
Week 6	6.5	15.5	0.2324
Week 12	1.5	9	0.398

*Wilcoxon statistic

follow up of up to 12 weeks may have implications in study outcomes. However, similar studies measuring the effects of *Serenoa repens* have reported statistically significant improvements in BPH outcomes within the same study period.[25-27] Additionally, patients were not advised to discontinue concomitant medications for BPH to see their effects when taken with *Serenoa repens*. The change in QoL scores for all patients, as well as IPSS and QoL scores for baseline moderate patients was observed for both inclusion and exclusion of these drugs. Neither prostate volume nor median lobe size were reported in our patient cohort. Lastly, the precise preparation of *Serenoa repens* extract utilized in this study may limit generalizability of safety and efficacy data.

Extract quality may be a limiting factor producing heterogeneity across studies.[28] *Serenoa repens* have shown high variability in activity. The present study with LSESr of 80% fatty acids in patients with moderate symptoms and validates benefits of LSESr use even in mild IPSS patients. Strengths of the present study include validation of the efficacy of ProudP use in seamlessly measuring uroflowmetry parameters in BPH patients using *Serenoa repens*, as patient outcomes paralleled or exceeded previous reports. To the best of our knowledge, this is also the first study that stratified according to BPH symptom severity, mild versus moderate, and analyzed the outcomes of *Serenoa repens* between these two cohorts.

Conclusion

A standardized USP-verified Saw Palmetto extract shows some promise in reducing LUTS and improving uroflowmetry parameters, especially in patients with baseline moderate symptoms. Modest symptomatic improvements in IPSS and QoL scores across all patients with LUTS at 12 weeks, with decreases in both storage and voiding subscores, were observed. Patients with baseline moderate symptoms were found to have greater improvements in IPSS and QoL after 12 weeks compared to those with baseline mild symptoms, without change in sexual function. Further research should investigate these effects in a larger, diverse patient cohort over a longer duration.

Disclosure

Bilal Chughtai is a consultant for Olympus, Boston Scientific, FEMSelect, ARMs, Prodeon Medical, Sumitomo, Zenflow, and Teleflex. He is an advisor for Promaxo, Bright Uro, COSM, and Soundable. Dean Elterman is a consultant for Olympus, Boston Scientific, and Procept BioRobotics. Kevin C. Zorn is a consultant and proctor for Boston Scientific, Procept BioRobotics, and investigator for Zenflow. Naeem Bhojani is a consultant for Olympus, Boston Scientific, and Procept BioRobotics. Ricardo Gonzalez is a consultant for Boston Scientific and Procept BioRobotics. The other authors declare that they have no known competing interests. □

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