Scientific Research Publishing

Food and Nutrition Sciences, 2026, 17(3), 297-313
https://www.scirp.org/journal/fns
ISSN Online: 2157-9458
ISSN Print: 2157-944X

Efficacy and Safety of a Proprietary Free Fatty Acid Rich Saw Palmetto Extract (USPlus® PRO) for Lower Urinary Tract Symptoms in Males: A Randomized, Double-Blind, Placebo-Controlled Trial

Amanda Rao[1*], Leigh Vinocur[2], Janice Pellow[1], David Briskey[1]

[1]RDC Clinical, Brisbane, Australia
[2]GameDay Men's Health Clinic, Owings Mills, Maryland, USA
Email: *amanda@rdcglobal.com.au

How to cite this paper: Rao, A., Vinocur, L., Pellow, J. and Briskey, D. (2026) Efficacy and Safety of a Proprietary Free Fatty Acid Rich Saw Palmetto Extract (USPlus® PRO) for Lower Urinary Tract Symptoms in Males: A Randomized, Double-Blind, Placebo-Controlled Trial. *Food and Nutrition Sciences*, **17**, 297-313.
https://doi.org/10.4236/fns.2026.173021

Received: January 13, 2026
Accepted: February 28, 2026
Published: March 3, 2026

Abstract

Background: Lower urinary tract symptoms (LUTS) affect most men aged 50+ and can significantly impair quality of life. Saw palmetto extracts have been evaluated for LUTS with mixed results, likely due to differing extraction quality, dosing, and study design. This study aimed to evaluate the efficacy and safety of USPlus PRO saw palmetto extract on LUTS in males. **Methods:** This randomized, placebo-controlled trial enrolled 80 males aged 45 - 80 years with LUTS. Participants were randomized 1:1 to two daily 160 mg USPlus PRO soft gels (providing 240 mg free fatty acids) or matched placebo for 12 weeks. Primary outcomes included changes in International Prostate Symptom Score (IPSS) and urinary frequency. Secondary outcomes included Brief Sexual Function Inventory (BSFI), quality of life, liver function, and safety. **Results:** Data from 62 participants were analyzed (USPlus PRO n = 30; Placebo n = 32). At Week 12, a statistically significant between group difference in IPSS total score was observed ($p = 0.047$). A clinically meaningful IPSS response (≥25% reduction) was evident in the USPlus PRO group by week 4. At week 12, statistically significant improvements were observed in the USPlus PRO group for the IPSS voiding subscore (IPSS-V) ($p = 0.027$), incomplete emptying ($p = 0.002$), weak stream ($p = 0.026$), BSFI total scores ($p = 0.041$), and erection domain scores ($p = 0.039$). Safety outcomes were comparable between groups. **Conclusions:** USPlus PRO saw palmetto extract provided significant, clinically meaningful improvements in LUTS, notably voiding symptoms, incomplete emptying, and weak stream over 12 weeks. Furthermore,

significant improvements in sexual function were found. USPlus PRO demonstrated a favorable safety profile and may be a beneficial treatment option for LUTS (Clinical Trial ID NCT06266000).

Keywords

Serenoa repens, Saw Palmetto, Lower Urinary Tract Symptoms, Randomized Controlled Trial, Free Fatty Acids, USPlus PRO, USPlus, LUTS, Urinary Health, Male Sexual Health

1. Introduction

Male lower urinary tract symptoms (LUTS) are defined by the International Continence Society (ICS) as patient-reported complaints grouped into storage (e.g. urgency, frequency, nocturia), voiding (e.g. hesitancy, slow stream, intermittency), and post-micturition symptoms. Modern ICS terminology treats LUTS as a symptom construct independent of etiology, distinct from specific diagnoses such as benign prostatic hyperplasia (BPH) [1]. LUTS is often associated with BPH, a histologic condition with prostatic enlargement and possible bladder outlet obstruction. BPH is a frequent cause of male LUTS, but the relationship between LUTS and BPH is non-deterministic: not all men with BPH develop bothersome LUTS, and many men with LUTS do not have BPH as the primary driver [2].

Epidemiologically, LUTS are common and increase with age in men. Population studies from the United States (U.S.) and Europe estimate that 15% - 60% of men older than 40 years of age report LUTS [3], increasing up to 70% in men aged > 80 years [4]. Importantly, LUTS are present even in younger cohorts. In the BACH survey, approximately 8% of men aged 30 - 39 years reported LUTS [5]. A recently published study observed that LUTS related to BPH affects nearly 38.1 million men in the U.S., that is about one-fourth of the male population in the U.S. [6]. The quality of life (QoL) burden for LUTS is substantial. Nocturia and other LUTS impair sleep quality, daytime function, and work productivity, with decrements in health status that scale with symptom frequency/urgency and severity [7].

Symptoms commonly associated with LUTS include increased urinary frequency, nocturia, weak urinary stream, hesitancy, incomplete emptying, and urgency, and they are commonly captured with validated instruments such as the International Prostate Symptom Score (IPSS). The IPSS is a validated 7-item symptom index plus a single QoL item, categorizing symptoms as mild (0 - 7), moderate (8 - 19), or severe (20 - 35). The IPSS enables standardized baseline characterization and response assessment in clinical research and practice [8].

Given the prevalence, impact, and severity of LUTS, a broad range of therapeutic approaches, including behavioral interventions, pharmacotherapy, and surgery

have been used in clinical settings. In fact, management of male LUTS has been stepwise and mechanism-guided: lifestyle/behavioral measures and watchful waiting are most commonly advised by physicians for mild disease. As disease severity increases, management escalates to mechanism-directed pharmacotherapy, including α1-blockers, and 5-α-reductase inhibitors such as finasteride when prostatic enlargement is present, and phosphodiesterase-5 inhibitors used alone or in combination. Refractory LUTS are treated with minimally invasive surgical interventions, however these options are not free from side effects, especially with long-term use. One of the consequences of using finasteride that has the attention of consumers is Post Finasteride Syndrome (PFS) [9], which is characterized by persistent and distressing symptoms of sexual dysfunction, such as erectile dysfunction and decreased libido, as well as neuropsychiatric symptoms. There is also growing concern about the possibility that long term use of certain drugs like finasteride and dutasteride might lead to permanent adverse events such as cognitive impairment among the elderly population [10]. As a result, many patients seek well-tolerated, non-prescription interventions to manage mild to moderate symptoms [11].

Herbal medicines have a long history of use for managing urinary symptoms as described under LUTS, and several randomized trials have investigated lipidosterolic extracts (LSESr) of *Serenoa repens* (saw palmetto) [12]. Meta-analyses and systematic reviews have reported heterogeneous results: some studies indicate modest benefits while others report effects indistinguishable from placebo [13]. A key contributor to this heterogeneity is variability in extract preparation (use of solvent extracted berries), standardization (fatty acid or sterol content), and dosing [13] [14].

Solvent and Supercritical CO_2 extraction methods can enrich saw palmetto's lipid fraction, increasing the fatty acids content of the extracted oil. However, potency is often driven less by totals than by fine chemistry; thus, efficacy is best interpreted in the context of composition of free versus esterified fatty acids, chain-length and unsaturation patterns, rather than aggregate lipidosterolic content [14]. A wide variance in extraction precision contributes to a wide variance in the resulting oil and is a factor in the inconsistent clinical findings on saw palmetto extract for addressing LUTS.

USPlus PRO was developed as a next-generation LSESr with predefined targets for Free Fatty Acids enrichment and distribution, the free-to-ester ratio, sterol speciation, and oxidative markers. This specification is mechanism-led: it emphasizes functionally active constituents rather than bulk lipid enrichment, defining USPlus PRO by its free-fatty-acid profile based on their documented 5α-reductase inhibition, biologically aligned with LUTS pathophysiology. The present study was designed to evaluate the clinical efficacy and safety of a proprietary free fatty acids-enriched saw palmetto product (USPlus PRO) compared with placebo in males with mild to severe LUTS.

2. Materials and Methods

2.1. Trial Design and Setting

A 12-week randomized, double-blind, placebo-controlled, parallel-group trial conducted at a single site (RDC Clinical) in Brisbane, Australia. The trial protocol, case report forms, and statistical analysis plan were prepared prior to study start. Enrollment occurred from March 2024 to March 2025.

2.2. Participants

Eligibility criteria included males aged 45 to 80 years with symptomatic LUTS as defined by an IPSS ≥ 8 and who were generally healthy. The exclusion criteria included having a serious or unstable illness (e.g. uncontrolled diabetes mellitus, uncontrolled psychiatric disorder); use of a drug/natural therapy for LUTS/urological symptoms within the previous 30 days; a urinary infection in the previous 30 days; chronic urinary infections or diagnosed with chronic prostatitis, chronic persistent local pathology (e.g. interstitial cystitis, bladder stones), cancer (including prostate cancer) or genital anatomical deformities; urogenital surgery in the last 6 months; bladder biopsy and/or cystoscopy within the previous 30 days; use of anticoagulation therapy; history of spinal cord injury; abnormal secondary sexual characteristics; active smokers and/or nicotine or drug abuse, chronic alcohol use (>14 alcoholic drinks/week); known allergy to any ingredient in the active or placebo formula; participated in any other clinical trial in the previous month; or having any condition which in the opinion of the investigator makes the participant unsuitable for inclusion.

2.3. Interventions

The active investigational product, USPlus PRO, contains a standardized *Serenoa repens* (saw palmetto) extract with a proprietary free fatty acid composition. USPlus PRO was manufactured using mature saw palmetto berries, which were processed using cryogenic milling to conserve the natural composition of fatty acids. These berries, rich in fatty acids, were further extracted using proprietary processing and extraction using DeepExtract supercritical CO_2 technology, yielding enriched free fatty acid composition. Participants randomized to the active arm consumed two soft gels of USPlus PRO daily (160 mg each), providing a total daily dose of 240 mg of the free fatty acid blend. The placebo arm received matched for appearance and containing palm oil. Study products were supplied in labeled containers, with accountability and returned product reconciliation conducted at each visit.

2.4. Randomization and Blinding

Randomization was performed in a 1:1 ratio using a computer-generated random allocation sequence (www.sealedenvelope.com) prepared by an independent person (Figure 1). Allocation codes were maintained by the sponsor's designated unblinded pharmacist/service and were not accessible to site personnel, investiga-

tors, or participants unless medically required. Study staff, participants, and outcome assessors were blinded to treatment allocation until database lock.

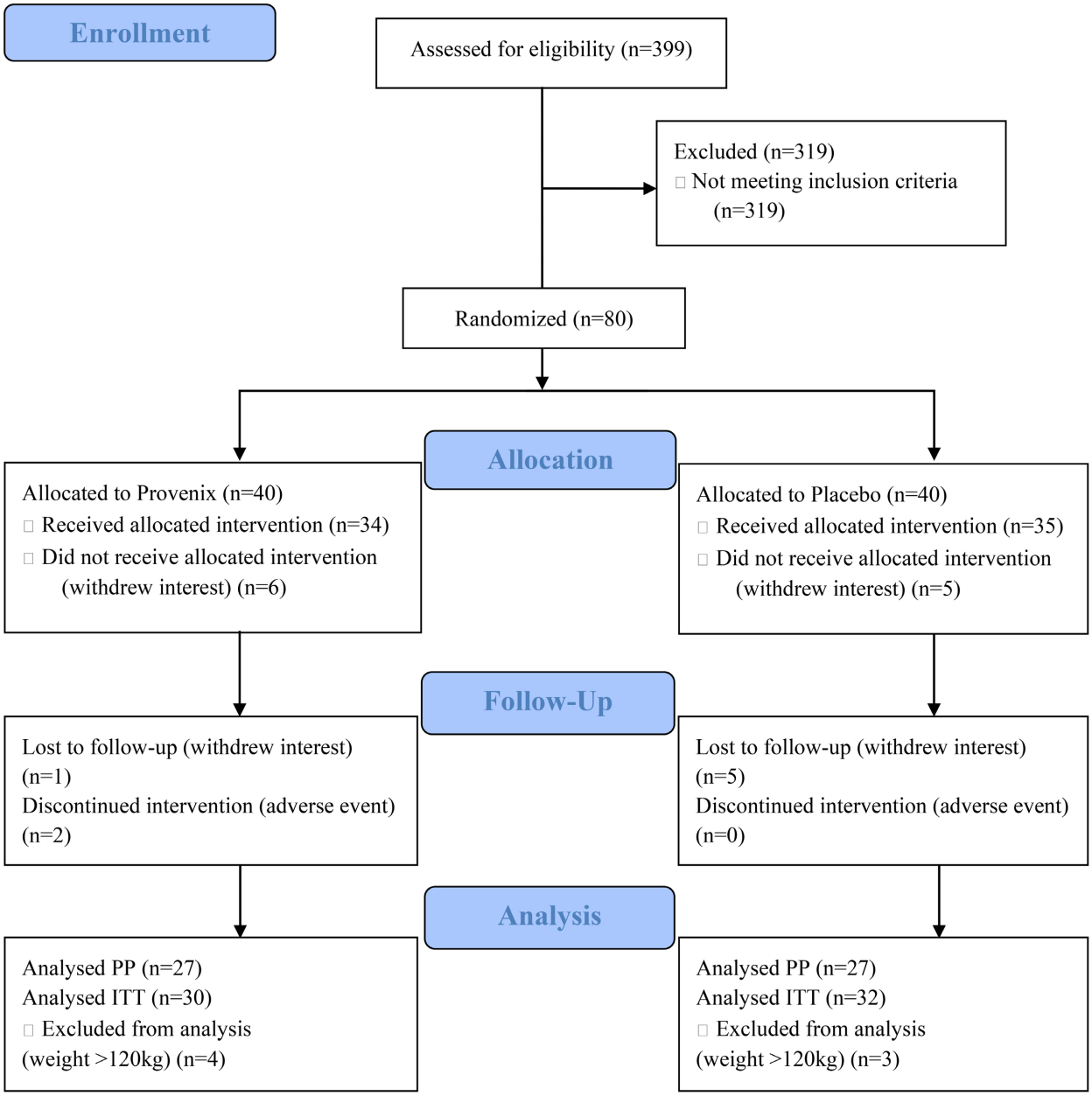

Figure 1. CONSORT flow diagram of the study. CONSORT (Consolidated, Standards of Reporting Trials), ITT (intention-to-treat), PP (per protocol).

2.5. Outcomes and Assessments

Primary endpoints included the change from baseline to Week 12 in total IPSS and mean daily urinary frequency as recorded in a 7-day voiding diary. The IPSS is a validated 7-item questionnaire with scores ranging from 0 (no symptoms) to 35 (severe symptoms) and includes storage (IPSS-S) and voiding (IPSS-V) subscores. A ≥25% reduction in IPSS score and ≥2-point reduction on either subscore

was prespecified as a clinically meaningful change [15]. Secondary endpoints included the Brief Sexual Function Inventory (BSFI) assessing erectile function, ejaculation, sexual drive and overall satisfaction, the International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms Module (ICIQ-MLUTS), safety biomarkers [Electrolytes and liver function tests (E/LFTs) included: sodium, potassium, chloride, bicarbonate, urea, creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, albumin, and total protein], vital signs, and adverse event monitoring. Assessments were performed at screening, baseline (Day 0), Week 4, Week 8, and Week 12 (end of treatment).

2.6. Statistical Analysis

Efficacy analyses was conducted on the modified intention-to-treat (mITT) population (participants with at least one post-baseline assessment and weighing ≤ 120 kg) as per the Standard Analysis Plan. For outcomes measured across visits, a repeated measures analysis of covariance (RMCOVA) was conducted as a sensitivity analysis, including treatment, visit, and treatment × visit as factors, with the baseline value of the outcome included as a covariate. Binary outcomes (e.g. proportion achieving ≥25% reduction in IPSS) were compared using chi-square tests or Fisher's exact tests as appropriate, and risk differences with 95% confidence intervals were reported. Missing data were handled using Mixed Model for Repeated Measures (MMRM; assuming missing at random) for primary repeated-measures analyses. All tests were two-sided with $\alpha = 0.05$. Statistical analyses were performed using JASP 19.2.

2.7. Ethics and Trial Registration

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocol was approved by Bellberry Ltd ethics committee (HREC 2023-06-669). Written informed consent was obtained from all participants prior to any study procedures. The trial was registered at Clinicaltrial.org with Clinical Trial ID NCT062660003.

3. Results

3.1. Participant Disposition and Baseline Characteristics

Eighty eligible males were randomized to USPlus PRO (n = 40) or placebo (n = 40). Eleven withdrew before dosing and six discontinued after initiation (placebo n = 5; USPlus PRO n = 1), including two USPlus PRO participants due to adverse events (abdominal pain and blepharitis). The intention-to-treat (ITT) analysis included 62 participants (USPlus PRO n = 30; placebo n = 32). After a pre-specified upper body-weight limit of 120 kg was applied, seven participants (USPlus PRO n = 4; placebo n = 3) were excluded from the modified ITT population. Baseline characteristics did not differ significantly between groups (**Table 1**).

Table 1. Baseline demographic and anthropometric characteristics.

Parameter	Placebo (n = 32)	USPlus PRO (n = 30)
Age, years (mean ± SD)	63.6 ± 8.8	59.1 ± 7.4
Weight, kg (mean ± SD)	88.1 ± 12.1	85.0 ± 11.0
Height, m (mean ± SD)	1.70 ± 0.07	1.70 ± 0.07
BMI, kg/m^2 (mean ± SD)	28.9 ± 3.2	26.7 ± 2.9

3.2. Primary Efficacy Outcomes

3.2.1. Change in Total IPSS

Both groups showed improvements in IPSS scores over the 12 weeks (Table 2). Within the USPlus PRO group, IPSS symptom reduction was evident at Week 4 and continued through Week 8 and Week 12. Repeated-measures ANOVA with Time as the within-subject factor showed significant decreases from baseline at each visit (Week 4: mean difference −4.2 ± 4.9, $p < 0.001$; Week 8: −5.7 ± 5.4, $p < 0.001$; Week 12: −6.4 ± 4.9, $p < 0.001$).

Table 2. Total IPSS scores for all visits.

	Placebo				USPlus PRO			
	Week				Week			
Visit	0	4	8	12	0	4	8	12
IPSS Score	14.81 ± 4.26	12.00 ± 5.84	10.52 ± 5.34	10.96 ± 5.66	16.40 ± 4.59	12.13 ± 4.97	10.7 ± 4.94	10.00 ± 5.23
T-Test		$p = 0.004$	$p < 0.001$	$p < 0.001$		$p < 0.001$	$p < 0.001$	$p < 0.001$
▲IPSS from baseline		−3.19 ± 5.30[a]	−4.63 ± 5.45[b]	−3.84 ± 5.00[b]		−4.27 ± 4.96[b]	−6.07 ± 5.41[b]	−6.40 ± 4.90[b,c]

T-test values presented are relative to baseline within group. [a]Statistical significance from baseline ($p < 0.005$), [b]Statistical significance from baseline ($p < 0.001$), [c]Statistical significance compared to placebo ($p < 0.05$).

The mean overall reduction in IPSS Score by end of the clinical trial at the 12th week corresponded to a 38.5% decrease from baseline in the USPlus PRO group (Figure 2).

At 12 weeks, the USPlus PRO group had a statistically significant reduction in total IPSS compared to the placebo group (mean change −6.4 ± 4.9 vs −3.8 ± 5.0; $p = 0.047$). Clinically meaningful improvement was evident as early as Week 4 in the USPlus PRO group, and by Week 12, improvement was observed in 80.0% of participants receiving USPlus PRO compared with 53.1% in the placebo group (between-group $p = 0.025$; Table 3).

Table 3. Participants achieving a clinically meaningful response by week 12.

Groups	Responders IPSS	
	Non-Responders	Responders
USPlus PRO	6 (20.0%)	24[a] (80.0%)
Placebo	15 (46.8%)	17 (53.1%)

[a]Statistical significance compared to placebo.

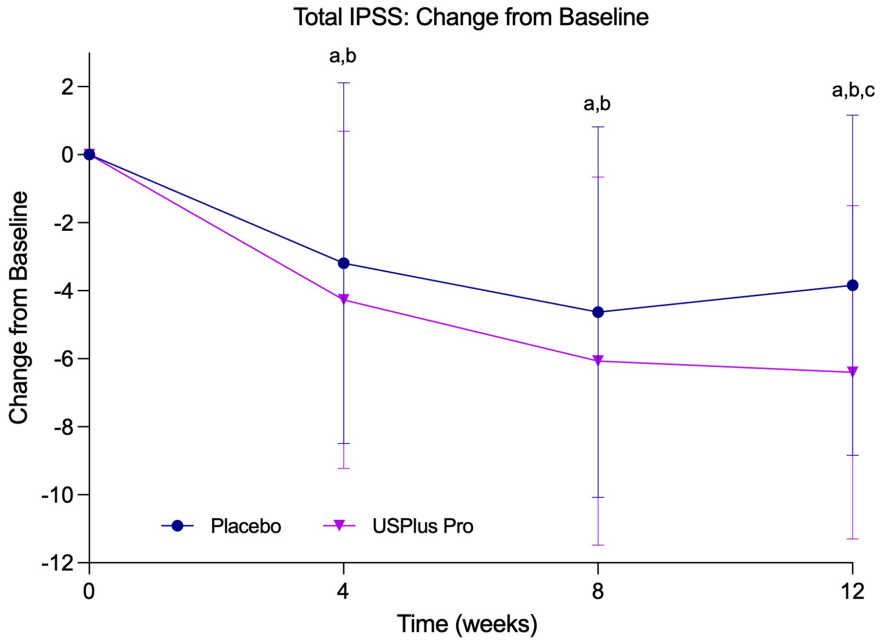

Figure 2. Total IPSS Score change from baseline. [a]Significantly different to baseline for placebo, [b]Significantly different to baseline for USPlus PRO, [c]Significantly different to placebo.

Among participants with severe LUTS (baseline IPSS 20 - 35), 90% demonstrated an improvement sufficient to reclassify them into the moderate severity category (IPSS 8 - 19), with a mean reduction in IPSS of 8.4 points.

1) IPSS Subscore

IPSS-V (Voiding Subscore) and IPSS-S (Storage Subscore)

At Week 12, both groups demonstrated clinically meaningful improvements in IPSS-V scores, with mean reductions of −2.2 ± 3.2 in the placebo group and −4.1 ± 3.3 in the USPlus PRO group. The between-group difference was statistically significant in favour of USPlus PRO (p = 0.027). Improvements were also observed in IPSS-S scores in both treatment arms, with a greater mean reduction in the USPlus PRO group (placebo −1.75 ± 2.4; USPlus PRO −2.20 ± 2.9); however, the between-group comparison did not reach statistical significance at Week 12 (p = 0.450; Table 4).

Table 4. Change in IPSS-V and IPSS-S sub-scores.

	Placebo				USPlus PRO			
Visits	Baseline	12 weeks	▲Change	p-value	Baseline	12 weeks	▲Change	p-value
IPSS-V	6.8 ± 3.5	4.5 ± 3.2	−2.2 ± 3.2	<0.001	8.1 ± 3.5	4.0 ± 2.6	−4.1 ± 3.3[a]	<0.001
IPSS-S	8.0 ± 2.3	6.2 ± 3.1	−1.75 ± 2.4	<0.001	8.2 ± 3.1	6.0 ± 3.4	−2.2 ± 2.9	<0.001

[a]Statistically significant compared to Placebo.

2) Individual IPSS Domains

The results of the individual IPSS domains are presented in Figure 3. Two domains (Incomplete Emptying and Weak Stream) showed clear separation from

placebo, while others trended favorably without crossing significance thresholds by the end of the trial.

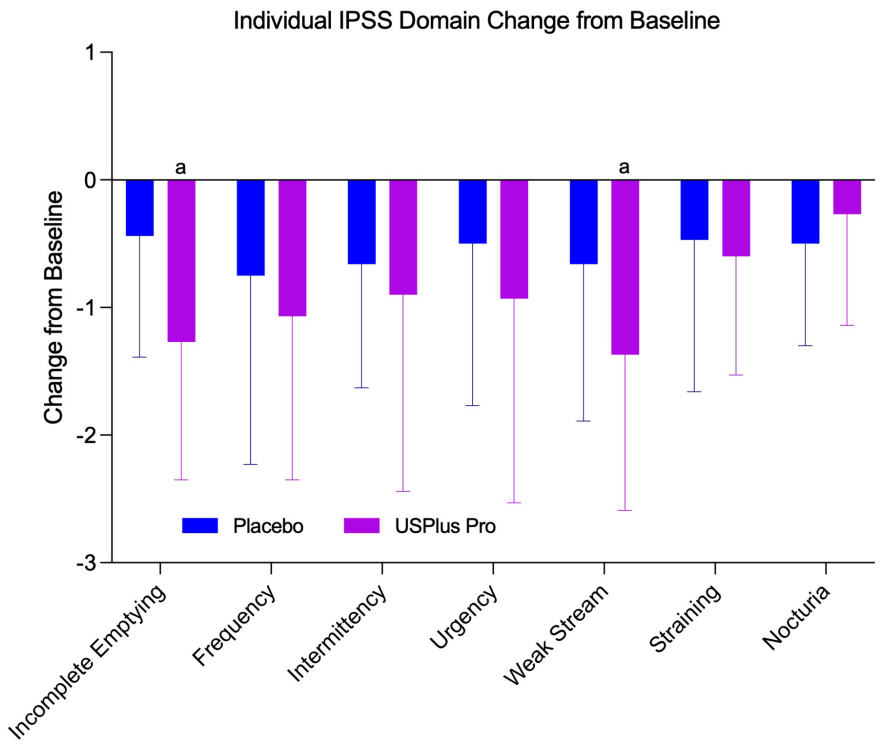

Figure 3: Individual IPSS domain change from baseline. [a]Statistically significant compared to placebo.

Incomplete emptying

At Week 12, a statistically significant reduction in incomplete emptying was observed in the USPlus PRO group compared with placebo when analysed as change from baseline (between-group Δ = −0.82; USPlus PRO −1.26 ± 1.08 vs placebo −0.44 ± 0.94; p = 0.002) representing approximately a 2.9-fold greater improvement with USPlus PRO.

Weak stream

At week 12, a statistically significant difference in change from baseline for weak stream symptom score was observed between groups, with a greater reduction in the USPlus PRO group compared with placebo (between-group Δ = −0.71; USPlus PRO −1.37 ± 1.21 vs placebo −0.66 ± 1.23; p = 0.026) representing approximately a 2.1-fold greater improvement with USPlus PRO.

Other IPSS items

There were no statistically significant differences found between the groups for the other IPSS domains: frequency (p = 0.373), intermittency (p = 0.456), urgency (p = 0.240), straining (p = 0.632) and nocturia (p = 0.276).

3.2.2. Voiding Diary

The results for the voiding diary showed no significant difference between groups.

3.3. Secondary Outcomes

3.3.1. Brief Sexual Function Inventory (BSFI) Questionnaire

Baseline BSFI total scores were comparable between groups (USPlus PRO 30.3 ± 9.4 vs placebo 27.1 ± 11.2). At Week 12, a statistically significant between-group difference was observed for the BSFI total score in favour of the USPlus PRO group (USPlus PRO 32.8 ± 8.4 vs placebo 27.6 ± 9.5; p = 0.041), as well as for the erections domain (USPlus PRO 8.6 ± 2.6 vs placebo 6.5 ± 3.6; p = 0.039) (Table 5).

Table 5. BSFI scores.

	Placebo		USPlus PRO		
Visits	Baseline	12 weeks	Baseline	12 weeks	p-value
Sexual Drive Score	4.9 ± 1.7	4.8 ± 1.6	5.3 ± 1.9	5.7 ± 1.9	0.115
Erection Score	6.7 ± 3.6	6.5 ± 3.6	7.7 ± 3.3	8.6 ± 2.6	0.039[a]
Ejaculation Score	6.0 ± 2.3	6.0 ± 2.3	6.6 ± 1.2	6.8 ± 1.4	0.115
Problem Assessment Score	7.3 ± 4.2	7.8 ± 3.9	8.3 ± 3.4	9.2 ± 3.1	0.073
Overall Satisfaction Score	1.9 ± 1.3	2.3 ± 1.0	2.3 ± 1.1	2.4 ± 1.1	0.277
Total BSFI Score	27.1 ± 11.2	27.6 ± 9.5	30.3 ± 9.4	32.8 ± 8.4	0.041[a]

[a]Statistically significant compared to placebo.

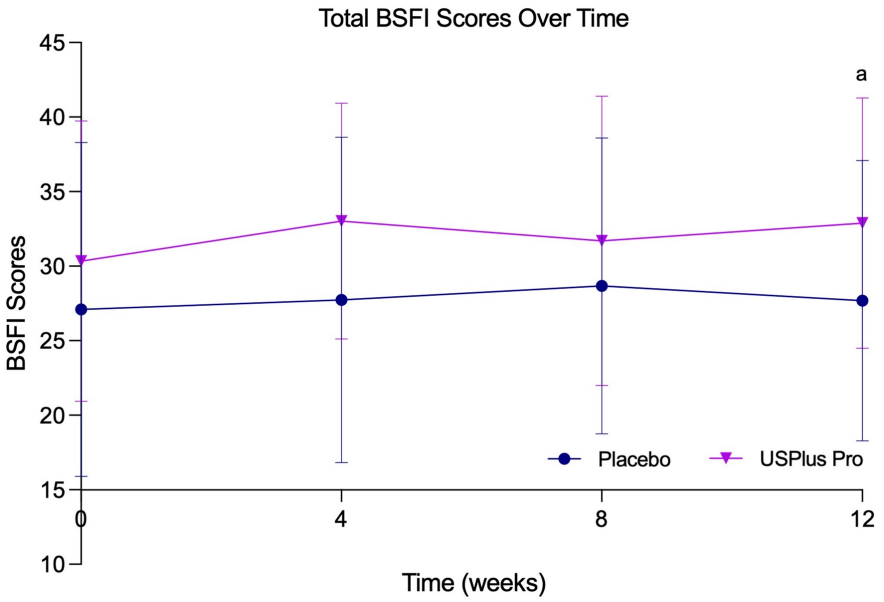

Figure 4. Total BSFI scores over time. [a]Statistically significant compared to placebo.

Among participants aged ≥ 50 years (placebo n = 29; USPlus PRO n = 25), a statistically significant between-group difference in total BSFI score was observed at Week 12 (USPlus PRO 34.30 ± 6.50 vs placebo 26.83 ± 9.39; p = 0.005). Statistically significant between-group differences were also observed across all BSFI domains, including sexual drive (p = 0.018), erections (p = 0.016), ejaculation (p

= 0.041), problem assessment (p = 0.029), and overall satisfaction (p = 0.046). The change-from-baseline in the BSFI total score was 3.85 times higher in the USPlus PRO group (3.51) compared with placebo (0.91) (Figure 4).

3.3.2. Incontinence and Incomplete Emptying (ICIQ-MLUTS)

A statistically significant between-group difference in change from baseline for ICIQ incontinence score was observed at Week 12 (USPlus PRO −1.13 ± 1.7 vs placebo −0.65 ± 1.4; p = 0.020), with a 30.5% reduction in symptoms observed within the USPlus PRO group over time (p < 0.002) (Table 6). A statistically significant between-group difference was also observed for daytime urinary frequency (p = 0.049). In participants aged ≥ 50 years, a clinically meaningful response (≥2-point improvement) in incontinence score was observed in 36.0% of those receiving USPlus PRO compared with 13.7% receiving placebo (p = 0.050).

Table 6. ICIQ-MLUTS baseline values and change at Week 12.

Mean ± SD	USPlus PRO			Placebo			▲in score p-value
	Baseline	Week 12	▲in score	Baseline	Week 12	▲in score	
Voiding subscore	7.2 ± 4.0	5.2 ± 3.7	−2.2 ± 2.8	7.5 ± 4.3	5.7 ± 3.9	−1.7 ± 2.8	0.617
Voiding QOL	15.7 ± 11.7	10.9 ± 10.5	−5.2 ± 10.5	17.2 ± 13.1	12.1 ± 10.9	−5.1 ± 9.8	0.692
Incontinence subscore	3.7 ± 2.3	2.4 ± 1.4	−1.1 ± 1.7	4.4 ± 2.7	3.8 ± 2.8	−0.6 ± 1.4	0.02[a]
Incontinence QOL	15.3 ± 12.1	9.4 ± 9.5	−5.3 ± 10.7	19.3 ± 16.1	15.1 ± 14.5	−4.1 ± 6.7	0.08
Frequency day	1.6 ± 1.2	1.0 ± 1.1	−0.5 ± 0.7	1.0 ± 0.92	0.9 ± 0.7	−0.1 ± 0.6	0.049
Frequency night	2.1 ± 1.1	1.93 ± 1.0	−0.1 ± 0.6	2.1 ± 1.2	1.6 ± 1.0	−0.5 ± 0.7	0.09

[a] Statistically significant compared to placebo.

3.3.3. Safety

No statistically significant between-group differences were observed for safety biomarkers or vital signs. USPlus PRO was well tolerated. A total of nine adverse events were reported during the study (placebo n = 3; USPlus PRO n = 6), all of which were classified as mild to moderate in severity. Two adverse events—one in each group—were assessed as possibly related to the study product and were gastrointestinal in nature. Vital signs, electrolytes, and liver function parameters remained within normal reference ranges at the end of the study.

4. Discussion

This study aimed to evaluate the efficacy and safety of USPlus PRO saw palmetto extract in males experiencing LUTS. USPlus PRO is a proprietary Deepextract® supercritical CO_2 *Serenoa repens* berry extract enriched with free fatty acids. Its production and specification differ from other saw palmetto extracts and commodity products in three key ways: These include: (1) controlled berry processing combined with a high-efficiency supercritical CO_2 extraction method (DeepExtract) that selectively yields a higher proportion of free fatty acids while avoiding

solvent residues; (2) analytical specification and batch control anchored to a multi-analyte lipid fingerprint, including free fatty acids and fatty-acid ratios; and (3) a hybrid, risk-based quality control framework linking chemical fingerprinting with functional potency and archival traceability. These features create a reproducible chemotype that is analytically and functionally distinct from generic ethanol, hexane or whole-oil and sterol-enriched products. The previously published data on a first generation LSESr extract, USPlus® (Valensa International) confirms that well-characterized lipidosterolic preparations, when standardized to an appropriate lipid profile, deliver reproducible symptom relief in men with mild to moderate LUTS [16]. Insights from the USPlus® clinical program informed a deliberate pivot: USPlus PRO was defined by free fatty acids rather than sterol-centric markers, standardized accordingly, and subsequently evaluated clinically. The present trial evaluated whether these analytical and manufacturing specifications were associated with clinical outcomes distinct from those reported in prior studies of saw palmetto extracts, including USPlus®.

In this randomized, double-blind, placebo-controlled trial, USPlus PRO (320 mg/day containing 240 mg of FFAs) demonstrated statistically significant superiority against placebo in improving LUTS as measured by the IPSS, with a mean within-arm IPSS total score reduction of −6.40 at 12 weeks compared to −3.8 in the placebo group ($p = 0.047$). Only the USPlus PRO group showed clinically meaningful lowering of >25% in IPSS symptom score in the study at 4 weeks. At Week 12, the between-group difference corresponded to a 61% greater reduction in IPSS total score in the USPlus PRO group compared with placebo. At Week 12, 80% of participants in the USPlus PRO group demonstrated a clinically meaningful reduction in total IPSS score ($p < 0.05$). Among participants with severe baseline symptoms (IPSS 20 - 35), 90% improved sufficiently to reclassify to the moderate severity category (IPSS 8 - 19). The sizeable reduction in total IPSS was observed along with improvements in the voiding domain, notably incomplete emptying and weak stream.

Participants in the USPlus PRO group demonstrated a larger mean improvement in bladder emptying symptoms compared with placebo (USPlus PRO: −1.26 vs placebo: −0.44, $p = 0.002$), representing approximately a threefold greater reduction. Similar patterns were observed (USPlus PRO: −1.37 vs Placebo: −0.66, $p = 0.026$). Consistent with these findings, The IPSS-V voiding sub-score, decreased nearly two-fold more with USPlus PRO than placebo (-4.1 ± 3.3 vs -2.2 ± 3.2, $p = 0.027$).

Improvement in voiding symptoms played a significant role in producing a reduction of the IPSS score, which mirrors the clinical signature typically produced by tamsulosin, an α1-adrenergic antagonist (α-blocker). α-Blockers have shown to rapidly reduce outlet resistance and improve urinary flow by lowering smooth-muscle tone. In an earlier double-blind, randomized 12-month study (PERMAL), Permixon, an LSESr extract was compared against an α-blocker Tamsulosin in the treatment of severe LUTS associated with BPH. The results showed that Permixon

320 mg/day produced comparable clinical benefits to Tamsulosin, as shown in IPSS scores. By end of the trial, Tamsulosin produced a −5.8 reduction in the total IPSS score, while Permixon reduced the score by −7.8 [17]. In the current study, USPlus PRO, a second-generation LSESr, similarly improved IPSS scores and demonstrated an earlier onset of benefit with a clinically meaningful IPSS reduction by Day 28; these improvements were sustained through the full study duration with total reduction of −6.4 from baseline ($p < 0.001$). Further studies comparing the effects of USPlus PRO to Permixon and Tamsulosin need to be conducted to further enhance understanding of its effects.

Other IPSS subdomains namely storage, also showed improvement in those taking USPlus PRO compared to placebo, but they did not reach statistical significance. However, the consistent pattern of numerical improvements across multiple subdomains supports clinical relevance of the treatment.

Sexual function was assessed with the BSFI. During the trial, USPlus PRO was shown to improve sexual function as evidenced by its effects on the total BSFI scores, as well as improve participants' perception of erectile function. These benefits address two interconnected quality-of-life concerns prevalent in men with prostatic enlargement and may potentially enhance treatment satisfaction compared with therapies targeting urinary symptoms alone [18].

In a prespecified subgroup analysis of participants aged ≥ 50 years, statistically significant between-group differences were observed across all BSFI domains at the final visit, namely sexual desire, arousal/erection, orgasm/ejaculation, and satisfaction, indicating a broader improvement in sexual function in the age range where decline is typically observed.

Age-related sexual dysfunction is multifactorial, with declines in endothelial nitric-oxide signaling and smooth-muscle responsiveness contributing to impaired cGMP-mediated vasodilation. Ingredients with phosphodiesterase-5 (PDE5) inhibitory activity can potentiate cGMP signaling and improve erectile physiology [19]. In a previously published study, lipidosterolic saw palmetto extract has been reported to exhibit in vitro PDE5-inhibitory effects [20], suggesting a plausible mechanism for the effects of saw palmetto on the male reproductive system. In the current study, the broader BSFI benefits observed in men aged ≥ 50 years, together with improvements in lower urinary tract symptoms (e.g. reduced nocturia and pelvic discomfort), are biologically consistent with the proposed mechanism. However, as this study did not measure PDE5 activity or cGMP levels, direct mechanistic links cannot be established. The subgroup analysis remains exploratory and warrants confirmation in trials powered a-priori for sexual-function endpoints in older men.

USPlus PRO's bioactive free fatty acids enriched profile and prior studies on LSESr lipidosterolic extracts of *Serenoa repens* supports the possibility of 5α-reductase inhibition combined with anti-inflammatory activity as the most likely mechanistic explanation for the clinical findings in the current study. This interpretation is supported by the product chemotype, the timing of symptomatic im-

provement (statistically significant improvements compared to baseline by Day 28 and progressive benefit through Day 84), and the favorable sexual-function signals as recorded in BSFI scores. To our knowledge this is the first randomized, double-blind, placebo-controlled study of a CO_2-extracted *Serenoa repens* reproduce results within the range reported for α-blockers in prior studies, [17], while also showing statistical improvement in sexual function score, especially in age group of 50+ male adults.

Meta-analysis of randomized trials of saw palmetto extracts show mixed results in terms of clinical benefits, mainly due to variability in extraction method, chemistry of the active fraction, dosing, and study design, which can explain much of the heterogeneity across studies [21]. The current trial adds to the literature of correctly standardized saw palmetto berries extract, by evaluating a CO_2 extract with defined manufacturing controls in a rigorously conducted randomized setting. The observed effects on sexual function (BSFI) are of particular interest because prior research has reported variable sexual safety signals for other agents used to treat LUTS. For example, selective 5α-reductase-II inhibitors like Finasteride, Dutasteride may adversely affect sexual function [22]. In contrast, USPlus PRO showed improvement in sexual domains as evident from BSFI questionnaire, suggesting a potential beneficial effects that merit further mechanistic studies as potential PDE5 inhibitor.

The safety profile of USPlus PRO in this 12-week study was favorable, with no SAEs attributed to the product and mild, self-limited adverse events being the most common findings. Liver function tests and other routine safety assessments did not reveal clinically meaningful changes. Nonetheless, larger and longer trials are necessary to fully characterize safety, particularly for rare events and in populations with comorbid conditions.

These findings suggest that USPlus PRO, a proprietary free fatty acid enriched *Serenoa repens* extract may represent a tolerable, non-prescription option for men with mild to severe LUTS, particularly those whose chief complaints are in the voiding domain. Future research should include larger, multicenter trials with longer follow-up time periods (≥6 - 12 months), dose-finding studies, and comparative effectiveness research versus guideline-recommended pharmacotherapies (alpha-blockers, 5α-reductase inhibitors). Mechanistic studies exploring anti-inflammatory effects, androgen metabolism, and direct bladder/prostate tissue effects would help clarify the biological basis for observed clinical effects.

5. Conclusion

In conclusion, this 12-week randomized controlled trial demonstrated that USPlus PRO, a proprietary Free Fatty Acid based extract from *Serenoa repens* berries, provided improvements that exceeded clinically meaningful thresholds for LUTS in males, measured by change in IPSS and voiding symptoms. Further significant improvements in measures of sexual function compared with placebo were observed over 12 weeks, with a favorable safety profile. These results support the

beneficial effects of USPlus PRO for managing LUTS, supporting men's urinary performance and sexual function.

Authors' Contributions

AR—Conceptualization, Methodology, Investigation, Visualization, Analysis, Supervision, Writing-Review & Editing.

LV—Writing-original draft.

JP—Writing-Review & Editing.

DB—Conceptualization, Methodology, Supervision, Writing-Review & Editing.

Consent for Publication

All participants provided written informed consent prior to their inclusion in the study and for the publication of their data.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Funding

The study was financially supported by Valensa International.

Conflicts of Interest

Dr Leigh Vinocur has served as a consultant to Valensa, who sponsored the clinical trial reported in this manuscript. The consultancy relationship did not influence the study design, data collection, analysis, or interpretation. All other authors report no conflicts of interest.

References

[1] Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U., *et al.* (2003) The Standardisation of Terminology in Lower Urinary Tract Function: Report from the Standardisation Sub-Committee of the International Continence Society. *Urology*, **61**, 37-49. https://doi.org/10.1016/s0090-4295(02)02243-4

[2] Roehrborn, C.G. (2005) Benign Prostatic Hyperplasia: An Overview. *Reviews in Urology*, **7**, S3-S14.

[3] Parsons, J.K., Bergstrom, J., Silberstein, J. and Barrett-Connor, E. (2008) Prevalence and Characteristics of Lower Urinary Tract Symptoms in Men Aged ≥ 80 Years and Older. *Urology*, **72**, 318-321. https://doi.org/10.1016/j.urology.2008.03.057

[4] Launer, B.M., McVary, K.T., Ricke, W.A. and Lloyd, G.L. (2020) The Rising Worldwide Impact of Benign Prostatic Hyperplasia. *BJU International*, **127**, 722-728. https://doi.org/10.1111/bju.15286

[5] Kupelian, V. (2006) Prevalence of Lower Urinary Tract Symptoms and Effect on Quality of Life in a Racially and Ethnically Diverse Random Sample. *Archives of Internal Medicine*, **166**, Article No. 2381. https://doi.org/10.1001/archinte.166.21.2381

[6] Arnold, M.J., Gaillardetz, A. and Ohiokpehai, J. (2023) Benign Prostatic Hyperplasia: Rapid Evidence Review. *American Family Physician*, **107**, 613-622.

[7] Shao, I.H., Wu, C.C., Hsu, H.S., Chang, S.C., Wang, H.H., *et al.* (2016) The Effect of Nocturia on Sleep Quality and Daytime Function in Patients with Lower Urinary Tract Symptoms: A Cross-Sectional Study. *Clinical Interventions in Aging*, **11**, 879-885. https://doi.org/10.2147/cia.s104634

[8] Gewanter, R.M., Sandhu, J.S., Tin, A.L., Gross, J.P., Mazzarella, K., Urban, J., *et al.* (2023) Assessment of Patients with Prostate Cancer and Their Understanding of the International Prostate Symptom Score Questionnaire. *Advances in Radiation Oncology*, **8**, Article ID: 101200. https://doi.org/10.1016/j.adro.2023.101200

[9] Pereira, A.F.J.R. and Coelho, T.O.d.A. (2020) Post-Finasteride Syndrome. *Anais Brasileiros de Dermatologia*, **95**, 271-277. https://doi.org/10.1016/j.abd.2020.02.001

[10] Abreu-Mendes, P., Silva, J. and Cruz, F. (2020) Pharmacology of the Lower Urinary Tract: Update on LUTS Treatment. *Therapeutic Advances in Urology*, **12**, 1-16. https://doi.org/10.1177/1756287220922425

[11] Michel, M.C., Miller, K., Schneider, T., Ude, C. and Oelke, M. (2025) Characteristics of Men Using Non-Prescription Medicines to Treat Their Lower Urinary Tract Symptoms. *World Journal of Urology*, **43**, Article No. 283. https://doi.org/10.1007/s00345-025-05560-1

[12] Strum, S. (2021) *Serenoa repens* (Saw Palmetto) for Lower Urinary Tract Symptoms (LUTS): The Evidence for Efficacy and Safety of Lipidosterolic Extracts. Part II. *Uro*, **1**, 139-154. https://doi.org/10.3390/uro1030016

[13] Franco, J.V.A., Trivisonno, L.F., Sgarbossa, N., Alvez, G.A., Fieiras, C., Escobar Liquitay, C.M., *et al.* (2024) *Serenoa repens* for the Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Enlargement: An Updated Cochrane Review. *The World Journal of Men's Health*, **42**, 518-530. https://doi.org/10.5534/wjmh.230222

[14] De Monte, C., Carradori, S., Granese, A., Di Pierro, G.B., Leonardo, C. and De Nunzio, C. (2014) Modern Extraction Techniques and Their Impact on the Pharmacological Profile of *Serenoa repens* Extracts for the Treatment of Lower Urinary Tract Symptoms. *BMC Urology*, **14**, Article No. 63. https://doi.org/10.1186/1471-2490-14-63

[15] D'Agate, S., Wilson, T., Adalig, B., Manyak, M., Palacios-Moreno, J.M., Chavan, C., *et al.* (2019) Impact of Disease Progression on Individual IPSS Trajectories and Consequences of Immediate versus Delayed Start of Treatment in Patients with Moderate or Severe LUTS Associated with BPH. *World Journal of Urology*, **38**, 463-472. https://doi.org/10.1007/s00345-019-02783-x

[16] Winograd, J., Lama, J., Codelia-Anjum, A., Bhojani, N., Elterman, D.S., Zorn, K.C., *et al.* (2024) Measuring the Efficacy of *Serenoa repens* (USPlus) Extract with Mobile Uroflowmetry. *The Canadian Journal of Urology*, **31**, 12053-12059.

[17] Debruyne, F., Boyle, P., Calais Da Silva, F., Gillenwater, J.G., Hamdy, F.C., Perrin, P., *et al.* (2004) Evaluation of the Clinical Benefit of Permixon and Tamsulosin in Severe BPH Patients—Permal Study Subset Analysis. *European Urology*, **45**, 773-780. https://doi.org/10.1016/j.eururo.2004.01.015

[18] Braun, M.H., Sommer, F., Haupt, G., Mathers, M.J., Reifenrath, B. and Engelmann, U.H. (2003) Lower Urinary Tract Symptoms and Erectile Dysfunction: Co-Morbidity or Typical "Aging Male" Symptoms? Results of the "Cologne Male Survey". *European Urology*, **44**, 588-594. https://doi.org/10.1016/s0302-2838(03)00358-0

[19] Corbin, J.D. (2004) Mechanisms of Action of PDE5 Inhibition in Erectile Dysfunc-

tion. *International Journal of Impotence Research*, **16**, S4-S7.
https://doi.org/10.1038/sj.ijir.3901205

[20] Yang, S., Chen, C., Li, Y., Ren, Z., Zhang, Y., Wu, G., *et al.* (2013) Saw Palmetto Extract Enhances Erectile Responses by Inhibition of Phosphodiesterase 5 Activity and Increase in Inducible Nitric Oxide Synthase Messenger Ribonucleic Acid Expression in Rat and Rabbit Corpus Cavernosum. *Urology*, **81**, 1380.e7-1380.e13.
https://doi.org/10.1016/j.urology.2012.12.062

[21] Chughtai, B., Bhojani, N., Zorn, K.C. and Elterman, D. (2023) Variability of Commercial Saw Palmetto-Based Supplements for the Management of Benign Prostatic Hyperplasia/lower Urinary Tract Symptoms. *JU Open Plus*, **1**, e00037.
https://doi.org/10.1097/ju9.0000000000000040

[22] Irwig, M.S. and Kolukula, S. (2011) Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss. *The Journal of Sexual Medicine*, **8**, 1747-1753.
https://doi.org/10.1111/j.1743-6109.2011.02255.x