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Clinical effect of phytosterol-enriched saw palmetto extract on urinary function in healthy middle-aged and older males: a double-blind, placebo-controlled randomized comparative study

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ABSTRACT

Background: Saw palmetto extract (SPE) is one of the most widely used supplements for benign prostatic hyperplasia (BPH) due to its pharmacological effects. β-sitosterol-enriched saw palmetto oil (VISPO™) contains more than 3% β-sitosterol and 85% total fatty acids and has been shown to improve symptoms in patients with BPH. Lower urinary tract symptoms (LUTS) require primary preventive measures in countries with accelerated population aging, including Japan. VISPO™ is expected to be effective against the early symptoms of LUTS. However, the effect of VISPO™ on urinary function in healthy individuals has not been elucidated.

Objective: This clinical study evaluated the efficacy and tolerability of VISPO™ in the management of urinary complaints among healthy middle-aged and older men who did not require treatment.

Methods: We conducted a randomized, double-blind, placebo-controlled trial that included 54 male participants who were assigned to consume VISPO™ or placebo (olive oil) capsules for 12 weeks. Biometric data, uroflowmetry results, and salivary hormone levels were assessed at weeks 1 and 12. Urinary function and quality of life were assessed at weeks 1, 4, 8, and 12 using the International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), Core Lower Urinary Tract Symptom Score (CLSS), and WHOQOL-26.

Results: Two-way analysis of variance revealed that IPSS and OABSS were significantly lower in the VISPO™ group that in the placebo group. However, there were no significant differences in urine volume, urinary flow rate, or salivary hormone levels. In addition, no participants reported adverse effects (diarrhea, abdominal pain, etc.).

Conclusion: The results of the present study, which is the first randomized controlled trial of VISPO™ conducted among healthy participants, demonstrate the effectiveness of VISPO™ in the management of lower urinary tract complaints that do not require treatment.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry (UMIN000046386).

Keywords: saw palmetto, VISPO™, β-sitosterol, fatty acids, healthy subjects, primary preventive, IPSS, OABSS, lower urinary tract symptoms (LUTS)

INTRODUCTION

Lower urinary tract dysfunction (dysuria) is classified into urinary output disorders and urine storage disorders, presenting with various lower urinary tract symptoms (LUTS) including nocturia [1]. Cross-sectional studies conducted in various countries have revealed that many individuals in the general population exhibit moderate-to-severe LUTS (international prostate symptom score [IPSS] of 8 points or more), and that LUTS are influenced by factors such as region and race [2-5]. A representative large-scale epidemiological study of LUTS known as the EPIC study was conducted in five countries (Canada, Germany, Italy, Sweden, and the United Kingdom) in 2005, involving 19,165 men and women aged 18 and over. The authors reported that the prevalence rates for storage symptoms, micturition symptoms, and post-micturition symptoms were 51.3%, 25.7%, and 16.9% for men, while they were 59.2%, 19.5%, and 14.2% for

women, respectively. Prevalence rates for storage and post-micturition symptoms were relatively higher in male participants, among whom the prevalence of LUTS was correlated with age, especially in those aged 60 years and older. Among both men and women, the most frequent symptom was nocturia (≥1 time), which was observed in 48.6% of men and 54.5% of women, followed by urinary urgency (overactive bladder: OAB), which was observed in 10.8% of men and 12.8% of women. In men, OAB tends to be complicated with multiple LUTS [6].

Researchers have also noted that male LUTS are associated with benign prostatic hyperplasia (BPH), erectile dysfunction, neurological problems [7], lifestyle-related diseases such as heart disease, diabetes, hypertension, dyslipidemia, obesity (increased body mass index: BMI) and depression, as well as lifestyle habits such as drinking, smoking, and exercise [8-10]. For example, a 3-year follow-up cohort study of 547 men aged 45 years and older concluded that exacerbation of LUTS was associated with heavy smoking, low physical activity, and a high-protein diet [11].

Serenoa repens, commonly known as the American dwarf saw palmetto plant, contains bioactive compounds, including phytosterols, fatty acids, and their ethyl esters, which have been identified as beneficial against cardiovascular risk factors [12]. These compounds are derived from the plant's dried fruits [13]. Saw palmetto extract (SPE) is one of the most widely used supplements for BPH. Its pharmacological effects include inhibition of 5α-reductase, inhibition of dihydrotestosterone (DHT) binding to androgen receptors, and effects at estrogen receptors in prostate tissue [14].

In a recent 8-week randomized controlled trial (RCT) with Japanese men aged 40 years or older, who reported being awakened by urination more than once during the night, the SPE group demonstrated a significant reduction in IPSS compared to the placebo group. This indicates a noteworthy improvement in addressing urination problems [15]. In addition, a recent 12-week RCT of SPE involving Japanese women aged 50 and over who reported urinary symptoms but did not require treatment at the discretion of a physician reported improvements in the Overactive Bladder Symptom Score (OABSS) and Core Lower Urinary Tract Symptom Score (CLSS), while demonstrating the safety of SPE treatment [16]. Other studies have confirmed that SPE free fatty acids bind to muscarinic receptors, leading to contraction of smooth muscle in the bladder/prostate and promoting urination [17]. SPE has also been shown to inhibit vanilloid receptors on the bladder afferent nerves, which transmit sensory information signaling the need to urinate [18].

β-sitosterol is one of plant sterols with chemical structures similar to that of cholesterol, which exhibit analgesic, anti-hyperglycemic and skin hydrating roles [19]. β-sitosterol enriched saw palmetto oil (VISPO^{TM}) contains more than 3% β-sitosterol and 85% total fatty acids, while conventional SPE oil contains 0.2–0.3% β-sitosterol in addition to fatty acids. A previous study demonstrated improved treatment efficacy when model rats with testosterone-induced BPH were treated with β-sitosterol-enriched VISPO rather than conventional SPE oil [20]. VISPO™ has also been shown to improve symptoms in human patients with BPH, significantly increasing maximum and mean urinary flow rates ($p < 0.001$) as well as serum free testosterone levels [21]. LUTS, which has been indicated to have a negative impact on the quality of life (QOL) of older individuals, requires primary preventive measures in countries with accelerated aging of the population, including Japan.

Therefore, the development of food products that act effectively against early stages of LUTS is an important effort to benefit public health in these countries. The new definition of the term functional food (FF) was recently proposed by the Functional Food Center (FFC) as follows: "Natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [22]. FFC also proposes a 16-step process for creating FF, including setting FF goals and determining related bioactive compounds [23]. VISPO™ is expected to be effective against the early symptoms of LUTS, as it has been shown to be effective in BPH animal studies and clinical trials compared to SPE. However, to the best of our knowledge, the effect of VISPO™ on urinary function in healthy individuals has not been studied.

To update the VISPO evidence base, we conducted the present clinical study to evaluate the efficacy and tolerability of a standardized VISPO™ in the management of urinary complaints in healthy middle-aged and older men who do not require treatment.

METHODS

Investigational product: The investigational product was a standardized SPE containing 3% β-sitosterol (VISPO™, Vidya Herbs, Indo). VISPO™ was prepared in-house from berries (Florida, USA) using the supercritical fluid extraction method. The higher percentage of β-sitosterol in VISPO™ was achieved via column chromatography, and β-sitosterol content was quantified via liquid chromatography/mass spectrometry [21]. Each capsule contained 200 mg of extract. Placebo capsules consisted of the organic edible olive oil (Nunez de Prado. C.B., Spain) only.

Ethical considerations: This clinical trial was approved by the ethical committee of the Teikyo Heisei University (reference no. 2021-046) and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000046386). Informed consent was obtained from each participant in accordance with the provisions outlined in the Declaration of Helsinki.

Participants: Overall, 54 participants were recruited and divided into the following two groups: a VISPO™ group (mean age, 52.74±5.76 y) and a placebo group (mean age 51.19±3.72 y) (Figure 1). The inclusion criteria were as follows: (a) male sex, (b) age ≥ 40 but ≤ 65 years, (c) consent to participate in the study; (d) no participation in other experiments within 3 months; (e) presence of symptoms related to urination that did not require medical treatment based on the discretion of the investigator; (f) IPSS score of 7 points or less; (g) OABSS score of 5 points or less. The exclusion criteria were as follows: (a) outpatient care or use of medication for an underlying disease, (b) alimentary allergy, (c) poor physical condition during the test period. Individuals deemed unsuitable for inclusion by the investigator were also excluded.

Experimental design: In the present randomized, double-blind, placebo-controlled trial, participants were randomly assigned to the VISPO™ or placebo group. Participants received oral doses of 200 mg capsules twice daily (after breakfast and dinner) for 12 weeks. Throughout the study period, participants were instructed to maintain a daily diary recording their intake

of the assigned substance, any adverse events observed, and any medication used. Participants were also instructed to maintain their usual lifestyle habits (e.g., diet, alcohol intake, and exercise) as much as possible.

Measurements of body composition/blood pressure, uroflowmetry, and saliva sample collection were performed at weeks 1 and 12. Participants were asked to refrain from consuming alcohol the day before measurement and to refrain from caffeinated drinks (e.g., coffee or tea) on the day of measurement. They were also instructed to fast for 2 h before measurements to limit carbohydrate intake.

Evaluations of urinary function and QOL were performed at weeks 1, 4, 8, and 12.

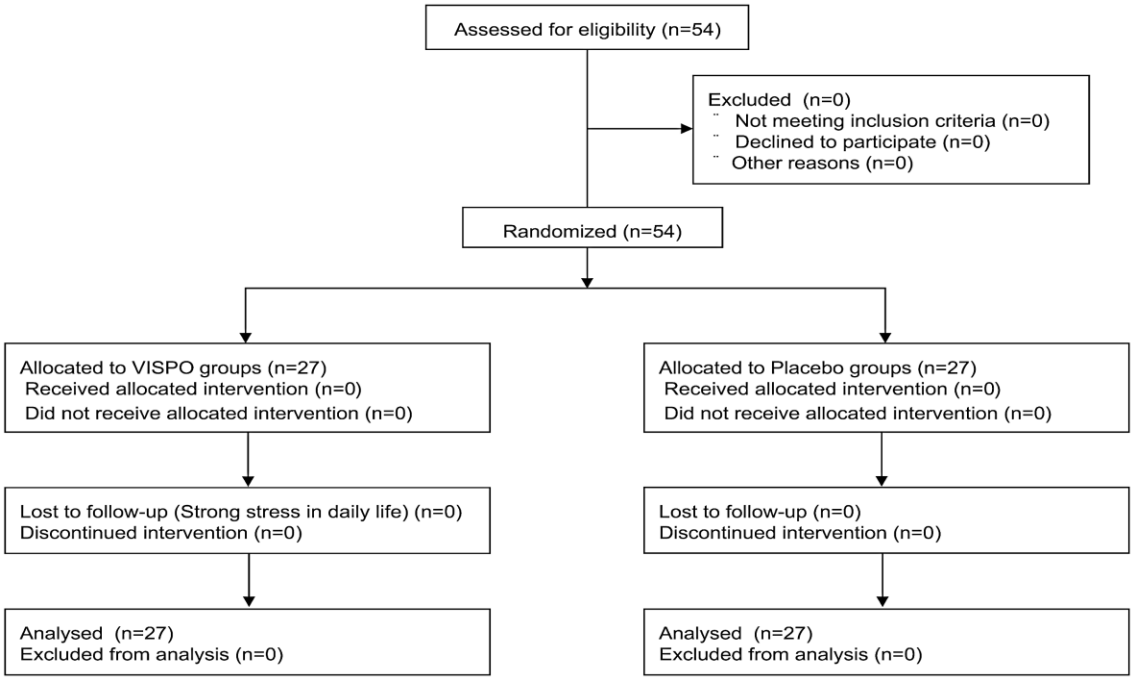

Figure 1. Study flow chart: VISPO™: saw palmetto extract containing 3% β-sitosterol.

Outcomes: Body composition and blood pressure were recorded using a BC-760 system (TANITA Corporation, Tokyo, Japan) and an HEM-6310F system (OMRON Corporation, Kyoto, Japan), respectively.

Urinary function was assessed based on the following:

IPSS: The IPSS is based on answers to seven questions concerning urinary symptoms (incomplete emptying, daytime frequency, intermittency, urgency, slow stream, straining and nocturia) and one question concerning QOL. Each response is assigned a score ranging from 0 to 5 points, with total scores ranging from 0 to 35 points (asymptomatic to very symptomatic).

OABSS: The OABSS is based on questions related to four symptoms (daytime frequency, nocturia, urgency, and urge incontinence), and the total score is obtained as the sum of the four symptom scores. The total score ranges from 0 to 15.

CLSS: The CLSS evaluates 10 LUTS. Scores are derived from five questions concerning storage (daytime

frequency, nocturia, urgency, urgency incontinence and stress incontinence), three questions concerning voiding symptoms (slow stream, straining and incomplete emptying), and two questions concerning lower urinary tract pain (bladder pain and urethral pain). Each item is scored on a 4-point scale, from "0" (no symptoms) to "3" (terrible), with the total score ranging from 0 to 30 points.

QOL: We evaluated QOL using the Word Health Organization Quality of Life 26 (WHOQOL-26(, a self-reported survey that consists of 26 questions regarding quality of life, divided into the following four domains: physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items). Overall QOL is rated on a five-point scale (very poor, poor, neither poor nor good, good, and very good). Higher scores indicate better QOL.

Uroflowmetry: The amount of urination, maximum urine flow rate, and average urine flow rate were recorded using *Freeflow*® (GM-100; GEO System Corporation, Kanagawa, Japan).

Salivary hormone levels: Saliva was collected by Salivette (Sarstedt, Inc., Nuembrecht, Germany). Each participant chewed an absorbent cotton swab for 2 min, which was then placed back into the Salivette. The Salivette was then centrifuged at 3,500 rpm for 10 min. Saliva samples were kept at -80˚C until analysis. Salivary cortisol levels were quantified using a Cortisol EIA kit (Salimetrics LLC, State College, PA), in accordance with the manufacturer's instructions. Salivary testosterone levels were measured by a laboratory testing service (Filgen Inc., Aichi, Japan).

Adverse effects: Common events (upper respiratory tract infection, back pain, rash, diarrhea, gout, gastroesophageal reflux disease, abdominal pain, joint pain or swelling, trauma and cough) and other symptoms were evaluated.

Statistical analysis: All data are expressed as the mean ± standard deviation (mean ± SD). Nonparametric tests were performed when a significant difference was observed in Levene's test. Participant characteristics were analyzed using the Mann-Whitney tests with two between-group factors. Urinary function, uroflowmetry results, QOL, and saliva data were analyzed using two-way analyses of variance (ANOVA) with two between-group factors and time factors. Tukey's Honest significant difference post hoc test was used for multiple comparisons. The significance level for all statistical analyses was set at $p < 0.05$. and IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA) was used to perform all statistical analyses.

RESULTS

Participant characteristics: There were no significant baseline differences between the two groups in any participant characteristics, including age, BMI, body weight, body fat percentage, fatty acid level, lean body mass, muscle mass, body water content, body water percentage, estimated bone mass, and basal metabolic rate (Table 1).

Urinary function: As illustrated in Figure 2, the two-way ANOVA indicated that IPSS significantly differed between the intervention periods (0 w vs 8 w: $p < 0.01$, 0 w vs 12 w: $p < 0.01$). Further, significant differences were found in IPSS between the placebo and VISPO™ groups ($p < 0.01$). As shown in Figure 3, two-way ANOVA revealed that OABSS also significantly differed between intervention periods (0 w vs 12 w: $p < 0.01$) and between the placebo and VISPO groups ($p < 0.05$). As shown in Figure 4, two-way ANOVA revealed that CLSS significantly differed between intervention periods (0 w vs 4 w: $p < 0.05$, 0 w vs 8 w: $p < 0.01$, 0 w vs 12 w: $p < 0.01$), although no significant differences were observed between groups ($p > 0.05$).

Table 1. Background characteristics of the VISPO and placebo groups.

	VISPO™	Placebo	p value
Age (years)	52.74 ± 5.76	51.19 ± 3.72	n.s.
BMI (kg/m²)	23.33 ± 2.59	23.65 ± 4.39	n.s.
Body weight (kg)	68.80 ± 7.53	68.54 ± 12.38	n.s.
Body fat percentage (%)	22.45 ± 4.32	20.89 ± 5.38	n.s.
Fatty acid level (kg)	15.67 ± 4.36	14.88 ± 6.53	n.s.
Lean body mass (kg)	53.13 ± 4.26	53.66 ± 6.36	n.s.
Muscle mass (kg)	50.38 ± 4.05	50.87 ± 6.05	n.s.
Body water content (kg)	34.40 ± 3.80	35.91 ± 5.66	n.s.
Body water percentage (%)	50.14 ± 4.17	52.73 ± 4.07	n.s.
Estimated bone mass (kg)	2.76 ± 0.22	2.79 ± 0.32	n.s.
Basal metabolic rate (kcal)	1456.56 ± 130.45	1473.30 ± 200.23	n.s.

BMI: body mass index. VISPO™: saw palmetto extract containing 3% β-sitosterol.

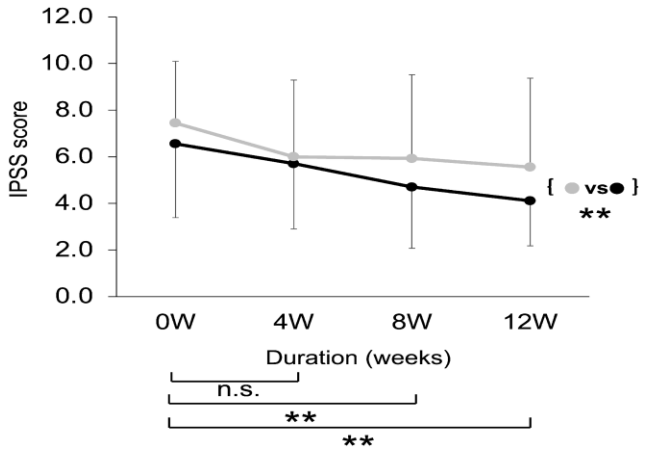

Figure 2. IPSS results.

IPSS results at 0–12 weeks in the VISPO™ group (black circles) and placebo group (gray circles). Data are presented as the mean ± SD. The IPSS data were analyzed using a two-way ANOVA with between-group and time factors. Tukey's Honest significant difference post hoc test was used for multiple comparisons (*: $p<0.05$, **: $p<0.01$). IPSS: International Prostate Symptom Score; n.s, not significant; SD, standard deviation; VISPO™: saw palmetto extract containing 3% β-sitosterol; W, weeks.

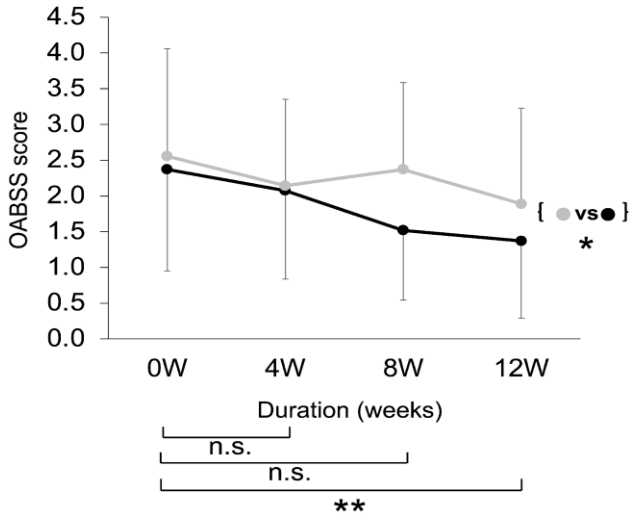

Figure 3. OABSS results

OABSS results at 0–12 weeks in the VISPO™ group (black circles) and placebo group (gray circles). Data are presented as the mean ± SD. The OABSS data were analyzed using a two-way ANOVA with between-group and time factors. Tukey's honest significant difference post hoc test was used for multiple comparisons (*: p<0.05, **: p<0.01). n.s, not significant; OABSS: Overactive Bladder Symptom Score; SD, standard deviation; VISPO™: saw palmetto extract containing 3% β-sitosterol; W, weeks.

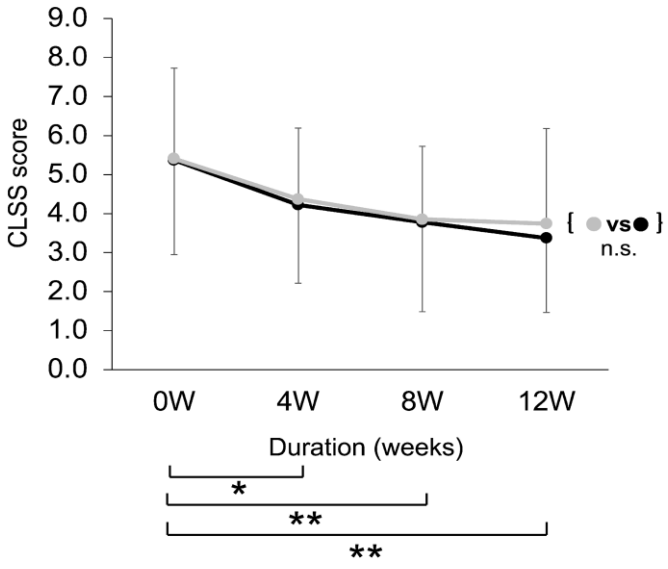

Figure 4. CLSS results

CLSS results at 0–12 weeks in the VISPO™ group (black circles) and placebo group (gray circles). Data are presented as the mean ± SD. The CLSS data were analyzed using a two-way ANOVA with between-group and time factors. Tukey's Honest significant difference post hoc test was used for multiple comparisons (*: p<0.05, **: p<0.01). CLSS: Core Lower Urinary Tract Symptom Score; n.s, not significant; SD, standard deviation; VISPO™: saw palmetto extract containing 3% β-sitosterol; W, weeks.

Table 2. WHOQOL-26 Results

	Groups	0W	4W	8W	12W	p value
Physical	Placebo	3.77 ± 0.43	3.69 ± 0.49	3.73 ± 0.42	3.74 ± 0.45	n.s.
	VISPO™	3.83 ± 0.37	3.77 ± 0.49	3.84 ± 0.61	3.82 ± 0.52	
Psychological	Placebo	3.56 ± 0.55	3.55 ± 0.59	3.56 ± 0.65	3.49 ± 0.56	n.s.
	VISPO™	3.57 ± 0.56	3.56 ± 0.66	3.62 ± 0.70	3.59 ± 0.62	
Social	Placebo	3.31 ± 0.53	3.17 ± 0.58	3.16 ± 0.58	3.20 ± 0.61	n.s.
	VISPO™	3.20 ± 0.55	3.23 ± 0.59	3.22 ± 0.58	3.32 ± 0.47	
Environmental	Placebo	3.49 ± 0.42	3.49 ± 0.51	3.52 ± 0.55	3.43 ± 0.42	n.s.
	VISPO™	3.55 ± 0.37	3.52 ± 0.51	3.59 ± 0.55	3.62 ± 0.51	
Total	Placebo	3.13 ± 0.56	3.13 ± 0.53	3.11 ± 0.59	3.14 ± 0.49	n.s.
	VISPO™	3.11 ± 0.53	3.24 ± 0.56	3.26 ± 0.71	3.28 ± 0.67	

Measurements of the WHOQOL-26 for 0-12 week in the VISPO™ group and the placebo group. Data are presented as mean ± SD. The WHOQOL-26 data were analyzed using a two-way ANOVA. SD, standard deviation; VISPO™: saw palmetto extract containing 3% β-sitosterol; WHOQOL-26, World Health Organization Quality of Life 26.

Table 3. Uroflowmetry and salivary hormone results in each group

	Groups	0W	12W	p value
Amount of urination (ml)	Placebo	174.94 ± 100.11	184.08 ± 137.85	n.s.
	VISPO™	190.63 ± 108.10	202.04 ± 131.86	
Maximum urinary flow rate (ml/s)	Placebo	13.63 ± 4.98	15.16 ± 8.25	n.s.
	VISPO™	16.65 ± 9.64	16.42 ± 11.01	
Average urinary flow rate (ml/s)	Placebo	7.73 ± 2.83	8.74 ± 4.49	n.s.
	VISPO™	8.46 ± 4.31	9.04 ± 5.84	
Salivary cortisol (μg/dl)	Placebo	0.12 ± 0.08	0.16 ± 0.09	n.s.
	VISPO™	0.12 ± 0.06	0.15 ± 0.09	
Salivary testosterone (pg/dl)	Placebo	179.28 ± 48.10	165.63 ± 40.21	n.s.
	VISPO™	169.27 ± 39.23	158.11 ± 43.72	
Salivary DHEA-S (pg/dl)	Placebo	928.83 ± 718.59	953.87 ± 673.21	n.s.
	VISPO™	1107.23 ± 962.74	1170.31 ± 1113.87	

Uroflowmetry and salivary hormone results for 0–12 weeks in the VISPO™ and placebo groups. Data are presented as mean ± SD. The data were analyzed using a two-way ANOVA. DHEA-S: dehydroepiandrosterone sulfate; n.s, not significant; VISPO™: saw palmetto extract containing 3% β-sitosterol; W, weeks.

QOL: There were no significant differences in scores for physical health, psychological health, social relationships, environmental health, or total scores between intervention periods or groups (Table 2).

Uroflowmetry and salivary hormone levels: No significant differences in the amount of urination, maximum urine flow rate, or average urine flow rate were observed between intervention periods or groups. No significant differences in salivary cortisol or testosterone levels were observed between intervention periods or groups (Table 3).

Adverse effects: No participants in either group reported common events (upper respiratory tract infection, back pain, rash, diarrhea, gout, gastroesophageal reflux disease, abdominal pain, joint pain and swelling, trauma, cough) or other symptoms.

DISCUSSION

In this study, we investigated the usefulness of VISPO™ in a 12-week RCT of healthy middle-aged and older men with urinary complaints who did not require treatment based on the investigator's discretion. Our results indicated that VISPO™ significantly decreased IPSS and OABSS scores.

The effectiveness of VISPO™ has been verified in RCTs of patients with BPH, and its effects on IPSS, residual urine volume, and prostate specific antigen have been confirmed [21]. Furthermore, the results of this study suggest that VISPO™ can improve or reduce the severity of mild urinary symptoms in healthy participants as well as those with BPH. However, we observed no significant changes in CLSS score and various indices related to LUTS mechanisms or risk factors (WHOQOL-26, uroflowmetry, salivary hormone). CLSS, beyond assessing urinary and urine storage symptoms as covered by the IPSS and OABSS, incorporates inquiries concerning pain in the bladder and urethra. It serves as a comprehensive tool for evaluating chronic pelvic pain syndrome (chronic prostatitis) and interstitial cystitis (urinary tract infection). It was developed in Japan as a questionnaire that makes evaluating conditions, such as urinary tract infections, easy. A total of 10 questions are comprehensively structured to allow for accurate differentiation, particularly at the first consultation [24]. Compared with the IPSS and OABSS, which evaluate the state of urination and urine collection, the CLSS is suitable for evaluating pathological conditions that require treatment, such as inflammation and infection. Because the LUTS of this study's participants did not require treatment, the effect of VISPO™ may not have affected the CLSS. Furthermore, the fact that the survey items were scored on a 4-point scale for the CLSS, 6 points for the IPSS, and 3–6 points for the OABSS may have influenced the CLSS results.

Conventional SPE is mainly composed of 90% free fatty acids (saturated and unsaturated fatty acids), higher alcohols, and sterols [25, 26]. Since free fatty acids such as oleic acid and lauric acid contained in SPE bind to muscarinic receptors, α1-adrenergic receptors, and 1,4-dihydropyridine calcium channel antagonist receptors (among others), the pharmacological effect of SPE is believed to be due to the free fatty acids contained in SPE [27, 28]. The free fatty acid content of VISPO™ is 85% or more, which is similar to that of conventional SPE, as determined via component analysis using a gas chromatograph-mass spectrometer (GC-MS). The percentage of free fatty acids is as follows: 2.25% caproic acid, 5.73% caprylic acid, 1.28% capric acid, 31.75% lauric acid, 9.38% myristic acid, 5.14% palmitic acid, 0.04% palmitoleic acid, 0.72% stearic acid (saturated fatty acids), 32.54% oleic acid, 2.01% linoleic acid (unsaturated fatty acids) (Vidya Herbs, unpublished data). Therefore, given that free fatty acids such as oleic acid, lauric acid, linoleic

acid, myristic acid, and palmitic acid contained in VISPO™ also bind to muscarinic receptors and α1-adrenergic receptors, they may suppress abnormal contraction of the bladder, prostate, and urethral smooth muscle. These mechanisms may explain the improvements in IPSS and OABSS among participants of the present study.

The olive oil (Nunez de Prado, Spain) used as the placebo in the current study also contains free fatty acids, as follows: lauric acid < 0.01%, myristic acid 0.02%, palmitic acid 12.83%, palmitoleic acid 1.24%, stearic acid 3.82%, oleic acid 73.38%, linoleic acid 6.98%, alpha-linolenic acid 0.71% (Nunez de Prado survey data). Although this form of olive oil contains 70% or more of oleic acid, like ordinary olive oil, it contains only about 0.01-0.02% of lauric acid and myristic acid. Therefore, the inability of lauric acid and myristic acid in olive oil to bind to muscarinic and α1-adrenergic receptors may explain the failure of olive oil to improve IPSS and OABSS when compared with VISPO™.

To date, relatively few controlled trials have examined the efficacy of plant sterol supplements in men with BPH symptoms. A 6-month study of 200 men with BPH found that β-sitosterol at 60 mg/day improved symptom scores, increased peak flow, and decreased postvoid residual volume when compared with placebo [29]. Furthermore, in their follow-up study, the authors reported that 38 patients who continued treatment with β-sitosterol maintained improvement for up to 18 months [30]. Similarly, in a 6-month study of 177 men with BPH symptoms, β-sitosterol at 130 mg/day was more effective than placebo in improving symptom scores, maximal urine flow, and postvoid residual urine volume [31]. A systematic review reported that β-sitosterol extract increased maximal urine flow by 3.9 ml/s on average and decreased postvoid residual urine volume by 29 ml on average [32]. Given these findings, it can be inferred that relatively low doses of β-sitosterol may improve LUTS associated with BPH, although the need for further research has been emphasized in previous studies as well [33].

VISPO™, which was used as the test supplement in the current study, comprised SPE enriched with β-sitosterol to 3%. However, in contrast to results reported in previous studies, this supplement did not improve maximum urine volume or residual urine volume.

To the best of our knowledge, no studies have reported severe adverse effects of SPE, and its safety has been confirmed in several reports [34, 35]. Similarly, we observed no adverse effects in the current study (upper respiratory tract infection, back pain, rash, diarrhea, gout, gastroesophageal reflux disease, abdominal pain, joint pain and swelling, trauma, cough), verifying the safety of VISPO™, in accordance with findings in previous rat and human studies [18, 19].

When LUTS are mild and uncomplicated, or when the patient does not desire treatment, aggressive treatment is contraindicated [36]. However, in a 4-year study of mildly symptomatic patients with an IPSS score of <8, exacerbation of symptoms occurred in 31%, while acute urinary retention occurred in 4.9% [37]. In Europe, SPE is approved for the treatment of LUTS in individuals with mild-to-moderate BPH [38]. Efforts to prevent exacerbation of mild LUTS are considered an urgent issue in Japan as well. We hope that the scientific evidence presented herein will contribute to the promotion of VISPO™ supplementation for urinary symptoms in the future.

This study is the first RCT to assess the use of VISPO™ in healthy participants. Our results demonstrate the efficacy of VISPO™ as a food supplement for effectively managing subclinical LUTS. The limitations of this study are as follows: As there was no follow-up period in this study, the sustainability of the interventions is unknown; The mechanism of action is

unknown, as no significant differences were found in the objective assessment. Therefore, the study protocols and timing of measurements should be considered in the future; In the study by Sudeep et al., the dose of VISPO™ was 500 mg × 2/day [19], whereas in this study, it was 200 mg × 2/day; this difference may have influenced the results; Olive oil, which contains fatty acids, was used as a placebo test product and may have affected IPSS and OABSS.

CONCLUSIONS

Our findings, indicating that VISPO™ diminishes the occurrence of untreated urinary-related symptoms, propose potential measures to enhance the quality of life (QOL) for middle-aged and older adults, particularly in countries experiencing rapid population aging.

Abbreviations: ANOVA: Analysis of variance, BPH: Benign prostatic hyperplasia, CLSS: Core Lower Urinary Tract Symptom Score, IPSS: International Prostate Symptom Score, LUTS: Lower urinary tract symptoms, OABSS: Overactive Bladder Symptom Score, QOL: Quality of life, SPE: Saw palmetto extract; WHOQOL-26, World Health Organization Quality of Life 26

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