Original Article - Lower Urinary Tract Dysfunction

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SHPro® (mixture of *Angelica gigas* and *Astragalus membranaceus*) in men with lower urinary tract symptoms: A randomized, double-blind, placebo-controlled clinical trial

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Purpose: A preclinical trial confirmed that *Angelica gigas* and *Astragalus membranaceus* had a curative effect on benign prostatic hyperplasia (BPH). Therefore, this study aimed to investigate the effects of this compound in patients with BPH symptoms.

Materials and Methods: Subjects were divided into the treatment and control groups. They underwent four visits, and medication was initiated from the 2nd visit onwards, with a total of 12 weeks of intake. The endpoints were the International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF), prostate-specific antigen level, testosterone, dihydrotestosterone, maximal urinary flow rate, residual urine volume, and subjective evaluation improvement. Safety tests included clinical pathology tests and checking for adverse reactions.

Results: A total of 39 patients from the treatment group and 45 from the control group were included in the efficacy analysis. After 12 weeks, a significant improvement was seen in IPSS total score (p=0.0219) and incomplete emptying score (p=0.0007). Furthermore, there were statistically significant improvements in the IIEF total score, erectile function, sexual desire, intercourse satisfaction, and overall satisfaction in the treatment group. The subjective improvement evaluation also showed a significant improvement (p=0.0143). Ten cases of mild adverse events were reported, including gastrointestinal problems, skeletal pain, dermatitis, and others. However, no severe adverse reactions were observed, and it was unlikely that these were related to the test product.

Conclusions: After taking the trial product (SHPro®) for 12 weeks, the total and incomplete emptying IPSS improved, as did the IIEF, which indicated subjective improvements. And its safety was confirmed.

Keywords: Clinical trial; Dihydrotestosterone; Pharmacologic effects; Safety; SHPro®

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INTRODUCTION

The global aging phenomenon is particularly rapid in Korea. Benign prostatic hyperplasia (BPH) is accompanied by urinary symptoms and bladder outlet obstruction, and its prevalence increases with age. As the Korean population continues to age, BPH is becoming a significant health problem [1,2].

BPH is associated with androgen levels. Testosterone is converted to dihydrotestosterone (DHT) by 5-alpha reductase. DHT binds to the androgen receptor (AR) in the prostate epithelium and stroma, facilitating tissue growth and cellular proliferation, which in turn cause prostate enlargement [3,4]. Treatment modalities include medications, minimally invasive procedures, and surgical interventions [5,6]. Surgeries involve removal of prostatic tissue and are considered when conservative care or medication are ineffective [7,8]. Alpha blockers act on the prostatic stroma, relaxing smooth muscles, and thereby inducing symptom improvement. 5-alpha reductase inhibitors prevent the conversion of testosterone to DHT, thereby inhibiting prostate enlargement [9,10]. Although antimuscarinics and anti-androgen agents are also used, they may take a long time to show effects and can lead to sexual dysfunction, voiding difficulty, and urinary retention as side effects [11].

Currently, BPH medications focus not only on improving lower urinary tract symptoms (LUTS) but also on reducing side effects such as sexual dysfunction and minimizing the risk of surgery [5]. Owing to the various side effects of BPH medications, there is a sustained demand for new products and an increasing interest in natural substances and health products that have proven to be safe and effective.

Natural substances such as *Angelica gigas* and *Astragalus membranaceus* have been reported in previous studies to have a positive impact on prostate health. *A. gigas* contains decursin and decursinol angelate, which are known for their antioxidant, antibacterial, and memory-enhancing properties. *In vitro* studies from patent data on *A. gigas* extract revealed its efficacy in inhibiting the expression of prostate-specific antigen (PSA), AR, and 5-alpha reductase [12,13]. The roots of *A. membranaceus* contain vanillic acid. A rat animal study showed that vanillic acid reduced the size of the prostate and decreased the expression of AR and markers of hyperplastic cells, such as cytokeratin and alpha smooth muscle actin [14].

Using these natural extracts, BPH medication with proven safety and efficacy has been devised. In this study, a comparative analysis was conducted between complex compound containing extracts of *A. gigas* and *A. membranaceus*, along with other components, and a control product.

MATERIALS AND METHODS

This clinical trial was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (approval number: 2021-2782-020). Informed consent was obtained from all participants upon enrollment.

1. Test supplements

The test products administered to the subjects were provided by the National Institute of Horticultural and Herbal Science, Rural Development Administration (Eumseong, Chungbuk, Republic of Korea). The trial product in this study was manufactured using ethanol extraction of *A. gigas* and hot water extraction of *A. membranaceus*, concentrating them, mixing them at ratio of 2:1, and then spray-drying the mixture to obtain the extract powder (SHPro®). Each tablet contained 300 mg of each trial product. The placebo product was prepared using microcrystalline cellulose and had the same appearance, aroma, and weight as the trial product. Similar to SHPro®, it was to be taken in a dose of 600 mg (2 tablets) per day. The trial and placebo products were provided by SUHEUNG Co., Ltd.

2. Subjects

The subjects were males aged between 40 and 75 years with prostate symptoms, specifically those with an International Prostate Symptom Score (IPSS) ranging from 8 to 19. Subjects meeting the following criteria were excluded: those who underwent treatment for severe diseases, blood PSA >4.0 ng/mL, maximum urinary flow rate (UFR) <5 mL/s, diagnosed with prostate/bladder cancer, history of urogenital surgery or invasive procedures, thyroid disease, and recent medication for BPH within 4 weeks prior to the start of the study.

3. Design overview

This clinical trial was designed as a randomized, double blind, placebo-controlled parallel trial. Subjects were recruited from Yonsei University Severance Hospital and Hallym University Dongtan Sacred Heart Hospital. A total of 100 subjects were selected and divided into control and treatment groups in a ratio of 1:1. The participants took the test product once daily in two doses for 12 weeks (Fig. 1).

Subjects assessed as eligible were randomized into the treatment or control groups using block randomization. The random allocation table was generated by sequentially applying random number permutations produced by the ran-

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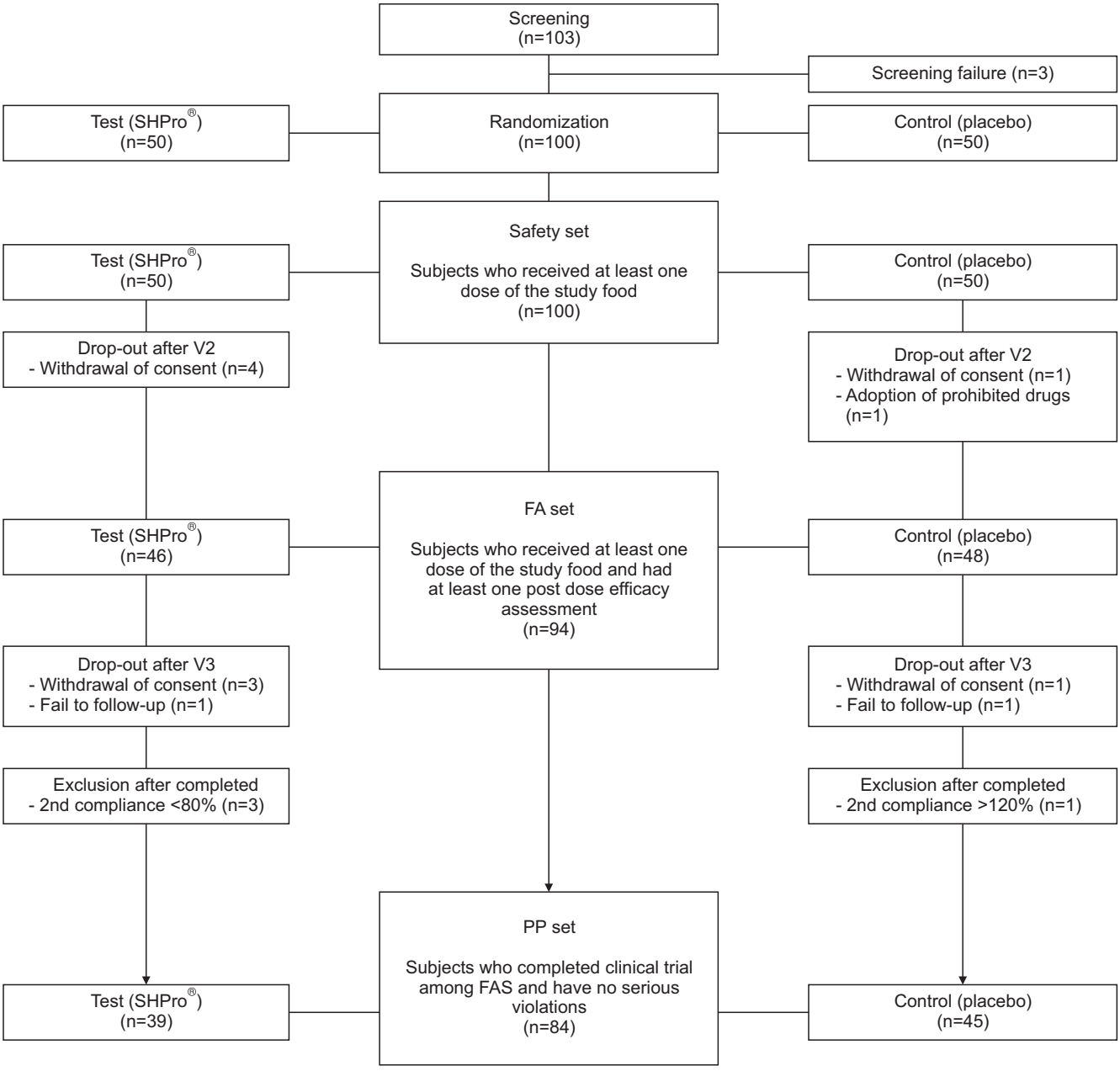

Fig. 1. Flow diagram of the clinical trial. FA, full analysis; PP set, per protocol set; FAS, full analysis set.

domization program in SAS system, starting from subject number 1. This process was conducted by a contract research organization. Investigational product (IP) labeling was performed in accordance with a random allocation table and applied to the products. Each IP label included a randomization number and a unique code.

Double blinding was maintained by the principal investigator, who securely managed the unique allocation codes for each group in a sealed condition. The participants received the test products according to their assigned randomization numbers while remaining blinded to their group allocation.

The participants received a total of four visits, with medication intake commencing at the second visit. Surveys and examinations were conducted during each visit. The first visit was on the screening day and the second visit occurred within 2 weeks. The third and fourth visits occurred 6 weeks and 12 weeks later, respectively. During the first visit, written consent was obtained, medical history was gathered, demographic and lifestyle surveys were conducted, and clinical pathology tests were performed to assess individual patient characteristics. The IPSS was assessed at each visit. Blood tests for PSA, testosterone, DHT, maximal UFR, and residual urine volume were checked at the 1st, 3rd, and 4th visits. The International Index of Erectile Function (IIEF)

was assessed at the 2nd, 3rd, and 4th visits. Side effects, patient compliance, and subjective improvements evaluation were assessed at 3rd and 4th visits.

The sample size calculation was based on a previous study by Noguchi et al. [15], which showed significant results regarding IPSS. Each group included 37 participants. Considering a dropout rate of 25%, the sample size for each group was calculated to be 50, totaling 100 individuals.

The primary endpoint was the change in IPSS, and the differences in improvement were evaluated within and between clusters. The secondary endpoints included changes in the blood levels of PSA, testosterone, and DHT; maximal UFR; residual urine volume; IIEF; and subjective improvement evaluation. Testosterone levels were evaluated as total and free testosterone and DHT levels. Total and free testosterone levels were analyzed in blood collected before 12 pm. DHT was collected as a 5 mL serum sample, stored frozen, and analyzed by an external laboratory. Residual urine volume was checked using ultrasonography. The IIEF was assessed for symptom scores in each domain and total scores. Subjective improvement evaluation was assessed using a scale of five levels.

The safety evaluations included adverse events (AEs), clinical pathology tests, and vital signs. Clinical pathology tests included complete blood count and chemistry tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), electrolyte, blood urea nitrogen (BUN), and creatinine, along with urinalysis.

4. Statistical analysis

The SAS system version 9.4 (SAS Institute) was used for statistical analysis. Comparisons within groups for IPSS, PSA, testosterone, DHT, maximal UFR, residual urine volume, IIEF, and clinical pathology test results were conducted using paired t-tests, while intergroup changes were assessed using either a two-sample t-test or the Wilcoxon rank sum test. Urinalysis results were divided into normal and abnormal categories, and intragroup comparisons were conducted using McNemar's test. AEs were analyzed using either the chi-squared test or Fisher's exact test.

RESULTS

1. Subjects

A total of 103 participants were recruited during the first visit. After excluding 3 participants, 100 were enrolled and randomized into two groups, control and treatment, each comprising 50 individuals. Among these, 42 subjects from the treatment group and 46 patients from the control group completed the study. Among them, 39 subjects from the treatment group and 45 from the control group were suitable for efficacy analysis at the end (PP set). There were no significant differences in subject characteristics between the two groups (Table 1).

2. Primary endpoints

The baseline IPSS total score assessed at the 2nd visit were 13.33±4.05 for the treatment group and 12.04±3.74 for the control group (Table 2). At the 3rd visit, the change in IPSS total score was a decrease of 3.21±4.60 ($p<0.0001$) in the treatment group, showing significant within-group difference, and a decrease of 1.27±4.23 ($p=0.0507$) in the control group. There was no statistically significant difference between the two groups ($p=0.0944$). At the 4th visit, however, the changes in the IPSS total score were a decrease of 3.41±4.55 ($p<0.0001$) in the treatment group and 1.36±3.50 ($p=0.0127$) in the control group, showing a statistically significant difference between groups ($p=0.0219$) (Table 2, Fig. 2).

Moreover, at both the 3rd and 4th visits, the changes in the IPSS incomplete emptying score showed statistically significant differences between the two groups ($p=0.0004$ at 3rd visit and $p=0.0007$ at 4th visit) (Table 2, Fig. 3).

At the 3rd visit, the change in the nocturia component of the IPSS showed a decrease of 0.56±1.05 ($p=0.0017$) in the treatment group, indicating statistically significant difference ($p=0.0394$) compared to the control group. Similarly, the change in the quality of life section at the 3rd visit, the treatment group showed a decrease of 0.87±1.13 ($p<0.0001$), also demonstrating a significant difference ($p=0.0452$) compared to the control group.

3. Secondary endpoints

The IIEF is a reliable questionnaire for evaluating and monitoring male erection function [16]. After 12 weeks, the changes in the IIEF total score were an increase of 6.15±15.64 ($p=0.0187$) in the treatment group and a decrease of 2.58±21.60 ($p=0.4277$) in the control group, indicating statistically significant difference ($p=0.0354$) (Table 3, Fig. 4). Furthermore, in the changes in IIEF erectile function score, the treatment group showed an increase of 2.97±7.16 ($p=0.0134$) while the control group showed a decrease of 1.40±10.36 ($p=0.3695$), demonstrating statistically significant difference. The other IIEF scores also showed significant differences (Table 3, Fig. 5).

The changes in the levels of PSA, total testosterone, free testosterone, DHT, maximal UFR, and residual urine volume did not show a statistically significant difference between the two groups at the 3rd and 4th visits (Table 4).

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Table 1. Baseline clinical characteristics between the test group and placebo group

Characteristic	Treatment (n=39)	Control (n=45)	p-value
Sex			-
Male	39 (100.0)	45 (100.0)	
Female	0 (0.0)	0 (0.0)	
Age (y)	56.69±10.76	58.42±10.65	0.4621[a]
Weight (kg)	71.99±8.15	71.82±10.54	0.9352[a]
Height (cm)	170.27±5.28	169.90±6.11	0.7637[a]
Marital status			
Married or living as married	38 (97.4)	44 (97.8)	>0.9999[b]
Separated, divorced, or widowed	0 (0.0)	0 (0.0)	
Others	1 (2.6)	1 (2.2)	
Drinking status			
No	10 (25.6)	13 (28.9)	0.7392[c]
Yes	29 (74.4)	32 (71.1)	
Smoking status			
Never smoke	22 (56.4)	27 (60.0)	0.9286[b]
Quit (≥1 y)	9 (23.1)	9 (20.0)	
Quit (<1 y)	0 (0.0)	1 (2.2)	
Current smoker	8 (20.5)	8 (17.8)	
Exercise status			
Never	11 (28.2)	9 (20.0)	0.8217[b]
1–2 times/wk	16 (41.0)	17 (37.8)	
3–4 times/wk	8 (20.5)	11 (24.4)	
5–6 times/wk	3 (7.7)	5 (11.1)	
Everyday	1 (2.6)	3 (6.7)	

Values are presented as number (%) or mean±standard deviation.
[a]:p-value for two-sample t-test. [b]:p-value for Fisher's exact test. [c]:p-value for chi-square test.

The mean scores of subjective improvement evaluation were 2.31±0.52 for the treatment group and 2.58±0.62 for the control group at the 4th visit, demonstrating statistically significant difference between the two groups (p=0.0143) (Table 5).

4. Safety test outcomes

A safety test analysis was conducted on participants who had consumed the product at least once after randomization (safety set).

In the treatment group, a total of 3 subjects (6.0%) experienced 3 cases of mild AEs, including skin disorders such as dermatitis and rash, as well as abdominal pain. In the control group, 5 subjects (10.0%) experienced 7 cases of mild AEs, including gastrointestinal problems, skeletal pain, and vitreous disorders. There were no statistically significant differences between the two groups, and there were no dropouts due to AEs.

In the clinical pathophysiology test, AST, ALT, and LDL-cholesterol levels increased compared to baseline, and there were statistically significant differences between the two groups (p=0.0036, p<0.0001, and p=0.0086). There was a statistically significant difference in urinalysis protein levels between the two groups (p=0.0286). Vital signs were normal in both groups and there were no significant differences.

DISCUSSION

As age increases, the incidence of BPH increases, causing various LUTS. With an aging population, its significance is becoming more pronounced.

In the preclinical trial, it has been proven that SHPro® has effects on histological improvement of prostate tissue and on reduction of protein and factors related to BPH.

In the study by Park et al. [17], it was confirmed that SHPro® inhibits the activity of 5-alpha reductase. This effect reduces the conversion of testosterone to DHT, thereby reducing its binding to 5-alpha reductase. Additionally, it suppresses AR expression. These actions inhibit the proliferation of prostate cells. This antiproliferative effect was attributed to the ability of SHPro® to induce apoptosis. Sub G1 phase increased and the expression of pro-PARP, pro-

Table 2. Changes in the parameters of the International Prostate Symptom Score (IPSS) after 6 or 12 weeks supplementation

		Treatment (n=39)	Control (n=45)	p-value
6 weeks	IPSS incomplete emptying			
	Baseline	2.31±1.03	1.58±0.87	0.0004[a]
	6 weeks	1.36±0.87	1.51±1.29	
	Changes from baseline	-0.95±0.89	-0.07±1.10	
	p-value	<0.0001	0.6851	
	IPSS nocturia			
	Baseline	1.95±1.15	1.49±0.94	0.0394[a]
	6 weeks	1.38±1.14	1.40±0.86	
	Changes from baseline	-0.56±1.05	-0.09±1.00	
	p-value	0.0017	0.5524	
	IPSS quality of life			
	Baseline	3.36±1.06	3.22±1.13	0.0452[a]
	6 weeks	2.49±1.39	2.80±1.20	
	Changes from baseline	-0.87±1.13	-0.42±1.23	
	p-value	<0.0001	0.0265	
	IPSS total score			
	Baseline	13.33±4.05	12.04±3.74	0.0944[a]
	6 weeks	10.13±5.18	10.78±5.49	
	Changes from baseline	-3.21±4.60	-1.27±4.23	
	p-value	<0.0001	0.0507	
12 weeks	IPSS incomplete emptying			
	Baseline	2.31±1.03	1.58±0.87	0.0007[a]
	12 weeks	1.46±1.02	1.73±1.45	
	Changes from baseline	-0.85±1.06	0.16±1.33	
	p-value	<0.0001	0.4371	
	IPSS nocturia			
	Baseline	1.95±1.15	1.49±0.94	0.1651[a]
	12 weeks	1.46±1.14	1.33±0.83	
	Changes from baseline	-0.49±0.94	-0.16±0.88	
	p-value	0.0026	0.2410	
	IPSS quality of life			
	Baseline	3.36±1.06	3.22±1.13	0.0514[a]
	12 weeks	2.38±1.31	2.78±1.28	
	Changes from baseline	-0.97±1.31	-0.44±1.18	
	p-value	<0.0001	0.0151	
	IPSS total score			
	Baseline	13.33±4.05	12.04±3.74	0.0219[b]
	12 weeks	9.92±5.42	10.69±5.56	
	Changes from baseline	-3.41±4.55	-1.36±3.50	
	p-value	<0.0001	0.0127	

Values are presented as mean±standard deviation.
[a]:p-value for Wilcoxon rank-sum test. [b]:p-value for two-sample t-test.

caspase 3, FOXO3a, AR, and PSA in BPH cells decreased. An increase in reactive oxygen species (ROS) production was also observed, suggesting that the antiproliferative effect was attributed to the activation of PARP and caspase 3 by ROS and the subsequent suppression of FOXO3a/AR/PSA signaling [12,17]. Therefore, to confirm the efficacy and the safety of the SHPro® in real-world patients, this clinical trial was conducted.

The efficacy and validity of IPSS for BPH follow-up were verified [18,19]. In this study, we analyzed changes in

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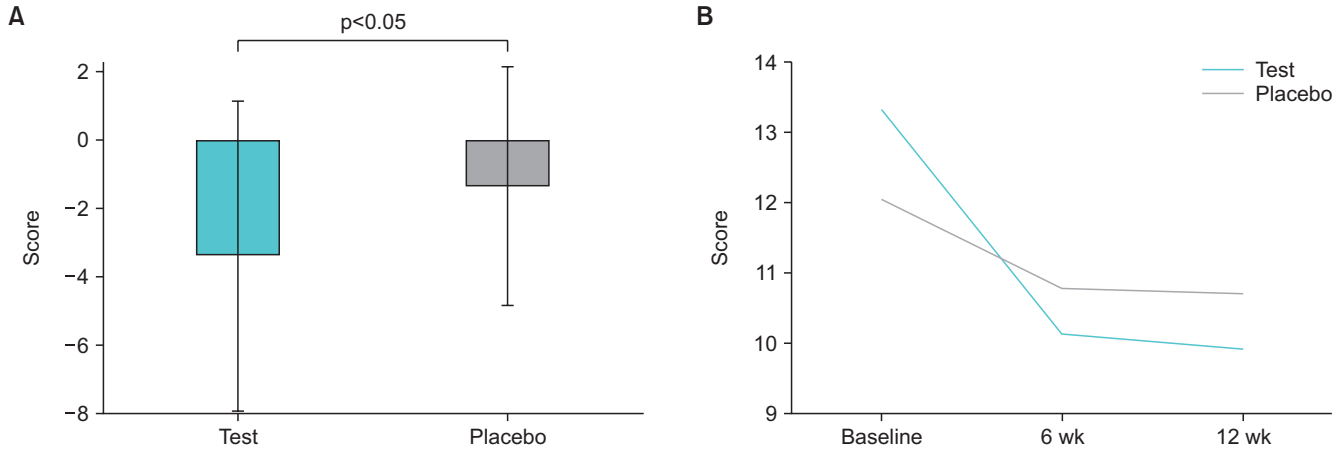

Fig. 2. Changes in IPSS total score after 12 weeks supplementation. (A) Mean±SD in changes from baseline. (B) Mean±SD in scores. IPSS, International Prostate Symptom Score; SD, standard deviation.

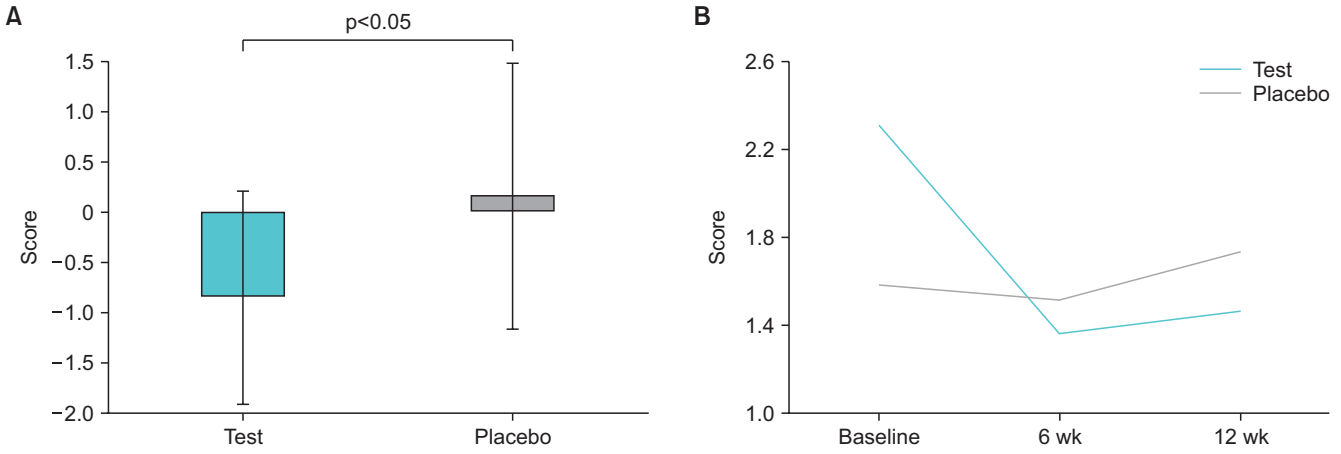

Fig. 3. Changes in IPSS incomplete emptying score after 12 weeks supplementation. (A) Mean±SD in changes from baseline. (B) Mean±SD in scores. IPSS, International Prostate Symptom Score; SD, standard deviation.

both the IPSS total score and the scores of specific categories. After 6 weeks, statistically significant improvements in nocturia, incomplete emptying, and quality of life index were observed in the treatment group. After 12 weeks of intake, statistically significant improvements were observed in the total score and incomplete emptying score of the IPSS compared to the control group (Table 2).

The subjective improvement evaluation assessed the improvement in symptoms compared with the 1st visit. A score of 1 indicated a significant improvement, 2 indicated a moderate improvement, 3 indicated no change, 4 indicated a moderate worsening, and 5 indicated a significant worsening. After 12 weeks, the treatment group had a mean of 2.31±0.52, showing statistically significant improvement compared to the control group (p=0.0143), which had a mean of 2.58±0.62 (Table 5).

Symptom improvement is the most common objective of BPH treatment. This suggests that subjective symptoms are important indicators [18]. Our study clearly confirmed a significant improvement in the participants' subjective assessments and symptom improvement in the IPSS results. Furthermore, Jeh et al. [20] reported that incomplete emptying was the most bothersome BPH symptom among Koreans, and our study indicated improvement. Therefore, it is evident that the trial products improved BPH symptoms. These results were presumed to be due to the inhibition of 5-alpha reductase action, suppression of AR, and the antiproliferative effect of the trial product on prostate cells, as confirmed in a previous study.

We also observed that the trial product had a positive effect on erectile function. Statistically significant improvements were observed in the IIEF total score (Fig. 4), erectile function, sexual desire, intercourse satisfaction, and overall satisfaction in the treatment group (Table 3, Fig. 5).

The exact mechanisms through which SHPro® affects erectile function have not yet been clearly defined. Although

Table 3. Changes in the parameters of the International Index of Erectile Function (IIEF) after 12 weeks supplementation

		Treatment (n=39)	Control (n=45)	p-value
12 weeks	IIEF total score			
	Baseline	33.54±19.04	32.80±19.93	0.0354[a]
	12 weeks	39.69±21.04	30.22±21.34	
	Changes from baseline	6.15±15.64	-2.58±21.60	
	p-value	0.0187	0.4277	
	IIEF erection function			
	Baseline	13.87±8.95	13.71±9.65	0.0257[a]
	12 weeks	16.85±10.24	12.31±10.24	
	Changes from baseline	2.97±7.16	-1.40±10.36	
	p-value	0.0134	0.3695	
	IIEF orgasmic function			
	Baseline	4.33±3.23	4.22±3.66	0.0417[b]
	12 weeks	5.23±3.73	3.62±3.95	
	Changes from baseline	0.90±3.18	-0.60±4.32	
	p-value	0.0858	0.3565	
	IIEF intercourse satisfaction			
	Baseline	5.08±3.81	4.71±3.86	0.0459[c]
	12 weeks	6.03±4.16	4.20±4.19	
	Changes from baseline	0.95±3.58	-0.51±4.45	
	p-value	0.1065	0.4456	
	IIEF overall satisfaction			
	Baseline	5.26±2.15	5.04±2.33	0.0476[b]
	12 weeks	6.23±2.05	5.27±2.21	
	Changes from baseline	0.97±1.80	0.22±2.41	
	p-value	0.0017	0.5396	

Values are presented as mean±standard deviation.
[a]:p-value for two-sample t-test. [b]:p-value for Wilcoxon rank-sum test. [c]:p-value for GLM (generalized linear model)-adjusted baseline.

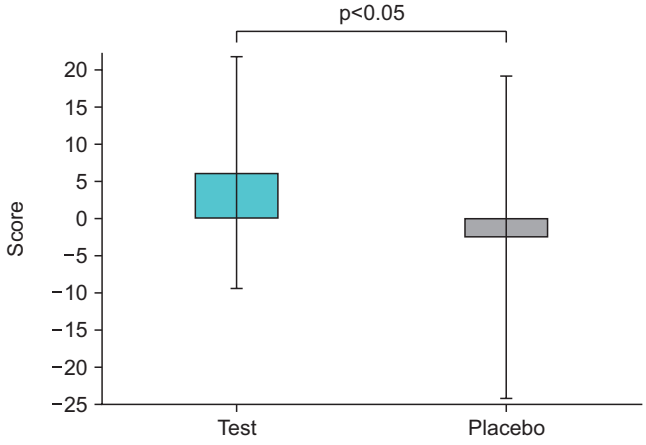

Fig. 4. Changes in IIEF total score after 12 weeks supplementation. Mean±SD in changes from baseline. IIEF, International Index of Erectile Function; SD, standard deviation.

this study cannot prove clear mechanisms, it is possible to hypothesize based on the effects of *A. gigas* on vascularity.

Various factors that impair arterial blood circulation are associated with erectile dysfunction [21,22]. *A. gigas* has been shown to improve blood circulation through antiplatelet aggregation, inhibit vascular smooth muscle cell proliferation, and demonstrate effectiveness in improving atherosclerosis [23,24]. The cavernous smooth muscle is important in the erectile process. In the flaccid state, it is contracted. However, when stimulation is administered, nitric oxide (NO) is released from the cavernous nerves and induces relaxation of the cavernous smooth muscle following dilation of the arteries [25]. NO reduces bioavailability in the corpus cavernosum owing to ROS, and in the case of 5-alph reductase inhibitors, this effect leads to erectile dysfunction [8]. In contrast, *A. gigas* decreases NADPH oxidase expression, leading to reduced ROS synthesis [26]. In addition, *A. gigas* positively affects NO synthesis by acting on endothelial NO synthases. Therefore, it can be assumed that the mechanisms of increasing NO production and enhancing its bioavailability may lead to the improvement of erectile function. The explanations thus far are hypothetical mechanisms based on preclinical data and *in vitro* studies, and do not fully explain the underlying mechanisms.

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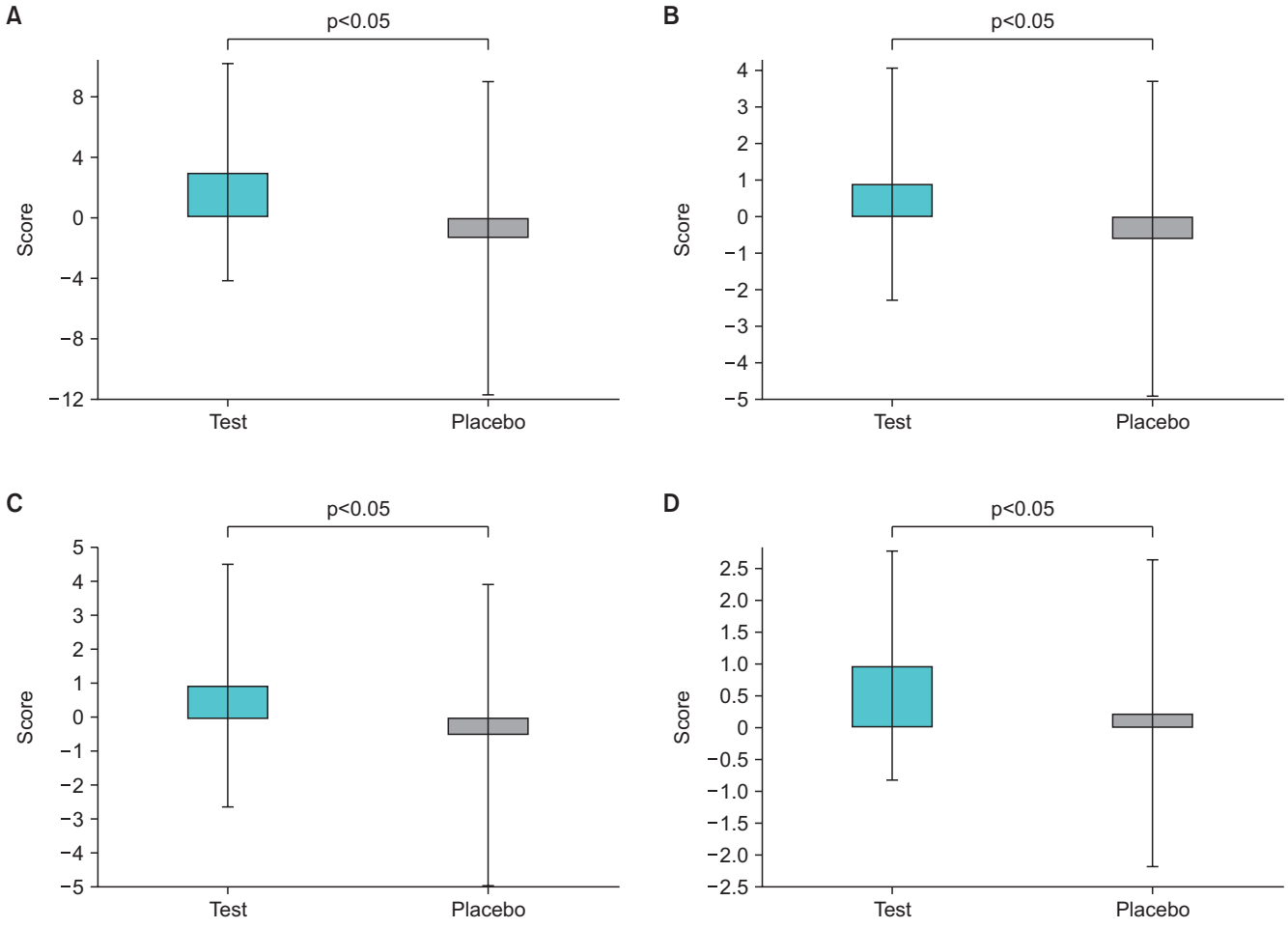

Fig. 5. Changes in IIEF several scores after 12 weeks supplementation. (A) IIEF erection function. (B) IIEF orgasmic function. (C) IIEF intercourse satisfaction. (D) IIEF overall satisfaction. Mean±SD in changes from baseline. IIEF, International Index of Erectile Function; SD, standard deviation.

It was revealed that there is suppressive effect on the expression of PSA and DHT in vanillic acid [27] and the compound extract of SHPro® [17]. However, no significant differences were observed in this study.

In all subjects, AEs were reported in 10 cases: 3 in the treatment group and 7 in the control group. All of these were mild cases, and it was confirmed that they were not related to the products.

The results of the pathophysiological tests indicated an increase in AST, ALT, and LDL cholesterol levels. However, all levels remained within the normal reference ranges. According to U.S. Food and Drug Administration guidelines, mild elevations in AST and ALT levels less than three times the upper limit of the reference range are not considered hepatotoxic [28]. In the treatment group, four patients shifted from normal to abnormal proteinuria, four from abnormal to normal, and four remained abnormal. This was found to be statistically significant compared to that in the control group. However, considering that there was no difference compared to baseline within the treatment group ($p>0.999$) and that no abnormalities were observed in other results, such as BUN and creatinine, we regarded this as temporarily observed proteinuria. Therefore, we considered these changes clinically insignificant.

Considering that there were no severe adverse reactions, no reported AEs were highly related to the products, and there were no clinically significant findings in the clinical pathology tests, the safety of the test products was confirmed.

CONCLUSIONS

Through this trial, it was confirmed that SHPro®, which has been shown to inhibit the expression of proteins, factors, PSA, ARs, and 5-alpha reductase related to BPH, can significantly improve the symptoms related to the prostate in actual patients. Improvement in erectile function was also evident. Furthermore, the safety of the test products was confirmed. Admittedly, our study presented the findings after 12 weeks of treatment. However, the efficacy and

Table 4. Changes in the parameters of the secondary endpoints after 12 weeks supplementation

		Treatment (n=39)	Control (n=45)	p-value
PSA				
	Baseline	1.13±0.82	1.19±1.31	0.5598[a]
	12 weeks	1.20±0.94	1.19±1.21	
	Changes from baseline	0.07±0.35	-0.00±0.26	
	p-value	0.1907	0.9353	
Total testosterone				
	Baseline	265.89±279.35	263.06±283.42	0.7625[a]
	12 weeks	258.01±275.21	256.24±287.34	
	Changes from baseline	-5.96±116.12	1.24±68.37	
	p-value	0.7536	0.9045	
Free testosterone				
	Baseline	7.84±2.39	8.25±2.51	0.5843[a]
	12 weeks	8.66±3.65	8.83±4.13	
	Changes from baseline	0.82±3.56	0.58±3.51	
	p-value	0.1589	0.2773	
DHT				
	Baseline	327.51±111.80	337.11±108.40	0.7707[b]
	12 weeks	342.87±114.17	357.26±108.62	
	Changes from baseline	15.36±74.53	20.15±75.16	
	p-value	0.2059	0.0790	
Maximum urinary flow rate				
	Baseline	16.75±8.64	5.04±2.33	0.2014[b]
	12 weeks	15.56±8.27	5.27±2.21	
	Changes from baseline	-1.19±6.89	0.22±2.41	
	p-value	0.2878	0.5396	
Residual urine				
	Baseline	7.46±16.63	14.24±5.93	0.7508[a]
	12 weeks	13.56±49.93	14.99±7.68	
	Changes from baseline	6.10±42.82	0.75±6.89	
	p-value	0.3791	0.4682	

Values are presented as mean±standard deviation.
PSA, prostate-specific antigen; DHT, dihydrotestosterone.
[a]:p-value for Wilcoxon rank-sum test. [b]:p-value for two-sample t-test.

Table 5. Subjective improvement evaluation after 6 or 12 weeks supplementation

	Treatment (n=39)	Control (n=45)	p-value
Subjective improvement evaluation			
6 weeks	2.23±0.58	2.64±0.71	0.0033[a]
12 weeks	2.31±0.52	2.58±0.62	0.0143[a]

Values are presented as mean±standard deviation.
[a]:p-value for Wilcoxon rank sum test.

safety of prolonged use beyond this period have not yet been evaluated. While traditional medicinal herbs are generally believed to carry toxicities such as hepatotoxicity, we have research report of the 90-day repeated-dose toxicity. This suggests that no observed adverse effects level is expected at doses greater than 2,000 mg/kg·bw/day [29]. Previous studies have shown that *A. gigas* and *A. membranaceus* reduce AST, ALT, and LDL cholesterol levels. Considering this, it is more likely that the observed results were due to non-specific causes or interactions between SHPro® and other medications [24,30].

However, given the need for continuous and long-term medication, this does not constitute direct evidence. Therefore, long-term cohort studies that include continued safety monitoring, with particular attention paid to liver enzymes and LDL cholesterol, are necessary to further evaluate safety and efficacy.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

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