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Research Article

Cervi Parvum Cornu complex for men with lower urinary tract symptoms: a multicenter, randomized, double-blind, placebo-controlled trial

Dongho Shin [a], Byung Il Yoon [a], Soomin Kim [c], JunJie Piao [c], Kyung-Hwa Jeon [d], Youngjoo Kwon [d], Sang-Hyuck Park [e], Young Tae Koo [f], Jin-Soo Kim [f], Dong Sup Lee [b], U-Syn Ha [b], Sae Woong Kim [b, c, g], Hoon Jang [b, **], Woong Jin Bae [b, c, *]

[a] *Department of Urology, College of Medicine, Catholic Kwandong University, Incheon, Korea*
[b] *Department of Urology, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[c] *Catholic Integrative Medicine Research Institute, The Catholic University of Korea, Seoul, Korea*
[d] *College of Pharmacy, Ewha Womans University, Seoul, Korea*
[e] *Institute of Cannabis Research, Colorado State University Pueblo, Pueblo, CO, USA*
[f] *Kwang Dong Pharmaceutical Co, Ltd., Seoul, Korea*
[g] *Green Medicine Co., Ltd, Pusan, Korea*

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ABSTRACT

Background: To evaluate the efficacy and safety of *Cervi Parvum Cornu*, Angelicae Gigantis Radix and Glycyrrhizae Radix complex (CAG) in men with moderate lower urinary tract symptoms (LUTS).
Materials and methods: From November 2020 to January 2022, participants with International Prostate Symptom Score (IPSS) of 12–19 in two centers were recruited and randomize into three groups: a CAG 500 mg/day group (CAG 500), a CAG 1000 mg/day group (CAG 1000), and a placebo group (PG). They were treated for 12 weeks. The primary endpoint was change of IPSS at the end of study from baseline. Secondary end points included change of prostate specific antigen (PSA), testosterone, dihydrotestosterone (DHT), maximum urinary flow rate (Q max), post-void residual volume (PVR), International Index of Erectile Function (IIEF), and drug safety.
Results: A total of 103 patients were able to finish the study according to the study protocol. Total IPSS and sub-scores (residual urine sensation, frequency, weak stream, hesistancy, nocturia, and quality of life) in CAG 500 and CAG 1000 were significantly improved at the 12th week compared to those of the PG. Changes of serum PSA, DHT, and testosterone levels at the 12th week from baseline did not show significant differences among the three groups. Q max and PVR changes did not show significant differences among the three groups either. Total IIEF and sub-scores (erectile function, orgasmic function, sexual desire, intercourse satisfaction) in CAG 1000 were significantly improved at 12th week compared to those in PG. No significant adverse events were found.
Conclusions: CAG is well tolerated in patients with moderate LUTS. Treatment with CAG for 12 weeks has a therapeutic effect on moderate LUTS.

1. Introduction

The incidence of lower urinary tract symptoms (LUTS) in men is increasing worldwide with an aging population.[1] The risk of LUTS is known to increase by 10% every decade after the age of 40.[2] Men with LUTS have a very poor quality of life and an increase of medical expenses. Treatment for LUTS includes behavioral therapy, medications, and surgery. Alpha-blocker is a representative drug used for treating LUTS.[3,4] However, it is difficult to administer an alpha-

* Corresponding author. Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Korea.
** Corresponding author. Department of Urology, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 64, Daeheung-ro, Jung-gu, Daejeon 34943, Korea.
E-mail addresses: urjan@gmail.com (H. Jang), bwoong@catholic.ac.kr (W.J. Bae).

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blocker to elderly male patients due to its side effects such as orthostatic hypotension, dizziness, and headache. Therefore, various phytotherapy with few side effects are being studied worldwide.[5,6]

Cervi Parvum Cornu is a young horn of *Cervus elaphus* (red deer) that is densely haired and not ossified. It is known to have antioxidative activity[7] and anti-inflammatory effects.[8] It is a medicinal ingredient that has been spotlighted as a health functional food and herbal medication in Asian culture. It is also being actively studied as a traditional medication with pharmacopunctures.[9] According to a previous Chinese study, it has treatment effects on impotence and incontinence.[10]

Angelicae Gigas Nakai is the dried root of *Angelicae*, a perennial herb belonging to the *Apiaceae* family. Its pharmacological effects such as vasodilation in the cardiovascular system, neuroprotection against Glutamate toxicity in the nervous system, and inhibition of inflammation by TNF-α and NO pathways have been reported.[11]

Glycyrrhizae Uralensis Fischer is the root and main stem of *Glycyrrhiza*. It is a common oriental medicine prescribed with the highest frequency in Korea, China, and Japan. It is known to possess anti-pain, anti-inflammatory, and antipyretic effects. It can also attenuate prostate enlargement.[12]

A previous in vitro and in vivo experiment has shown that mRNA expression level of Bax protein in prostate tissue and Bax/Bcl2 ratio are significantly increased in a group treated with CAG (*Cervi Parvum Cornu, Angelicae gigas Nakai,* and *Glycyrrhizae Uralensis Fischer*) complex compared to those in the placebo group and that the CAG complex could reduce prostate epithelial cell thickening and enlarge lumen, showing its potential for LUTS treatment due to benign prostate hyperplasia (BPH).[13]

The objective of this prospective, multicenter, randomized, double-blind clinical trial was to investigate the efficacy and safety of CAG complex treatment for men with LUTS.

2. Materials and methods

2.1. CAG complex

Cervi Parvum Cornu, Angelica gigas Nakai and *Glycyrrhiza uralensis Fischer* mixed (1:3:1) and put through an extraction process using 50% ethanol at twice. The concentrated complex was then spraying dry to make a CAG complex, which was encapsulated to make it easier for patients to take. The placebo capsule had cellulose at the same weight, shape, and color. Investigational products were labeled and coded for blinding following Good Clinical Practice standards. Both capsules were provided by Kwang Dong Pharmaceutical in Seoul, Korea. The product was manufactured according to Korean Traditional Medicine Standardization Project guidelines on pharmacopuncture.[14] In order to apply the validated efficacy dose from animal experiment[13] to humans, the Human Equivalent Dose conversion factor (rat 0.16) recommended by the FDA was applied. As a result, the optimal effective dosage of 200 mg/kg was converted to 1,920 mg when applied to an adult weighing 60 kg. In order to explore the effective dosage, the intake levels in this human trial were set at 500 and 1,000 mg per day.

2.2. Study design and participants

This multicenter, double-blind, randomized placebo-controlled trial was conducted in two medical centers (Seoul St. Mary's hospital of Korea, St. Vincent's Hospital of Korea) from November 2020 to January 2022. With variability based on a previous study,[15] a power of 80%, a significance level of 5%, and a dropout rate of 25%, the minimum target number of subjects to be recruit for each group was determined to be 40. Patients who visited the outpatient clinic with moderate LUTS (IPSS 12–19) who met the inclusion criteria (Table 1) were enrolled. All enrolled participants were allocated randomly to three groups (a CAG 500 mg/day group, CAG 500; a CAG 1000 mg/day group, CAG 1000; and a placebo group, PG) at a 1:1:1 ratio and treated for 12 weeks. Patients visited the clinic four times (at screening, 0-week, 6th week, and 12th week) (Fig. 1). A total of 122 volunteers were recruited in the screening stage. Participants answered the International Prostate Symptom Scores (IPSS) questionnaires and International Index of Erectile Function-5 (IIEF-5) at screening, 6th, and 12th week. Maximum urinary flow rate (Q max) and post-void residual volume (PVR) were checked at screening, 6th and 12th week. Prostate specific antigen (PSA), testosterone and dihydrotestosterone (DHT) were checked at screening and 12th week. For blinding, all patients, study site personnel, and the sponsor were blinded to group assignments.

2.3. Outcome measures

The primary endpoint was change in IPSS score over the treatment period for CAG 500, CAG 1000, and PG. Secondary endpoints were changes in PSA, testosterone, DHT, Qmax, and PVR according to the treatment period of each group. Changes in IIEF-5 were also evaluated to confirm male sexual function. Safety was assessed according to adverse events. Hematology, biochemistry, urinalysis, vital signs were also observed or performed.

2.4. Statistical analysis

All statistical analyses were performed using SAS® Version 9.4 (SAS Institute, Cary, NC, USA). Two sample t-test or Wilcoxon rank sum test were used to evaluate primary and secondary outcomes. Safety assessment was evaluated using analysis of variance (ANOVA). Data were considered significant at *P*-value less than 0.05. *P*-values for generalized linear model, compared between groups were adjusted by age, body mass index (BMI) and exercise.

3. Results

3.1. Baseline characteristics

Of 122 participants, a total of 103 were able to complete the examination according to the protocol (CAG 500: 36; CAG 1000: 33;

Table 1
Inclusion and exclusion criteria

Inclusion	Exclusion
• Patients with LUTS aged 40–75 y. • IPSS 12–19.	• Concurrent acute or chronic cardia-cerebrovascular, immune, respiratory, liver, kidney, urinary, nervous, musculature, mental, infectious and hematologic disease. • Tumor in treatment. • PSA ≥4.0 ng/mL. • Q max <5 mL/s. • PVR >150 mL. • History of prostate invasive therapy. • Uncontrolled diabetes. • Thyroid disorder. • Taking BPH drug or health food within 4 wk. • Participating other trials within 12 wk. • Allergic to CAG. • Others who were unfitted for this trial.

IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PSA, prostate specific antigen; PVR, post-void residual volume; Q max, maximum urinary flow rate.

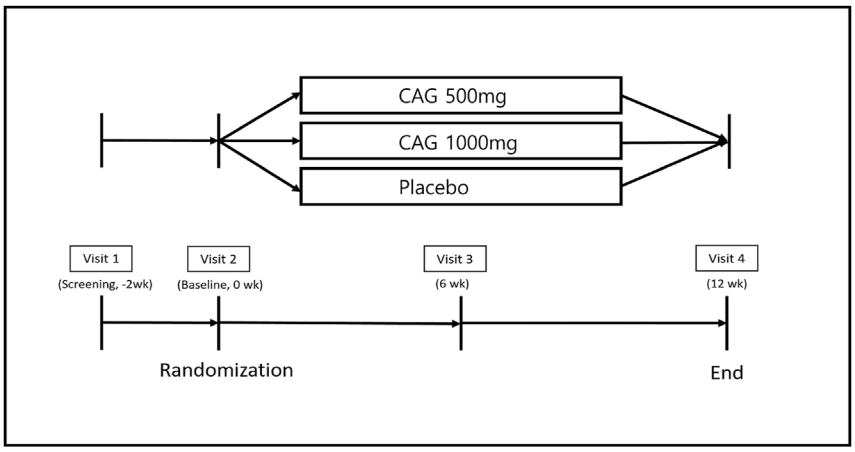

Fig. 1. Study design. Visit 1: screening, Visit 2: randomization, Visit 3: 6th week of treatment, Visit 4: 12th week of treatment. Participants were randomized 1:1:1 into 3 groups. At 6th and 12th week, efficacy and safety assessments were assessed.

PG: 34.) The mean age was 62.64 ± 8.15 years for all subjects. It was 62.81 ± 8.64 years for CAG 500, 62.55 ± 8.16 years for CAG 1000, and 62.56 ± 7.84 years for PG, showing no significant difference between groups ($P = 0.9708$). The mean BMI of total enrolled participants was 25.2 kg/m^2, without significant difference between the groups ($P = 0.6501$). The CONSORT diagram is shown in Supplementary 1.

3.2. International Prostate Symptom scores

Table 2 shows percentage changes in IPSS total and subscores of each groups. IPSS total score for CAG 500 showed a significant improvement compared to that for PG at both the 6th week ($P = 0.0068$) and the 12th week ($P < 0.0001$). IPSS total score for CAG 1000 also showed a significant improvement compared to that for PG at 6th ($P = 0.0189$) and 12th week ($P < 0.0001$). IPSS subscores for CAG 500 showed significant improvement compared to those for PG in subscores of frequency ($P = 0.0134$) and straining ($P = 0.0283$) at 6th week. At the 12th week, residual urine sensation ($P = 0.0226$), frequency ($P = 0.0004$), urgency ($P = 0.0251$), weak stream ($P = 0.0012$), straining ($P = 0.0027$), nocturia ($P = 0.0019$), and quality of life ($P = 0.0004$) showed significant improvement compared to PG. IPSS subscores for CAG 1000 showed significant improvement compared to those for PG in subscores of frequency ($P = 0.044$) and weak stream ($P = 0.0437$) at 6th week. At 12th week, residual urine sensation ($P = 0.0005$), frequency ($P < 0.0001$), weak stream ($P = 0.0001$), straining ($P = 0.0004$), nocturia ($P = 0.0014$), and quality of life ($P = 0.0002$) showed significant improvement compared to PG.

Fig. 2 shows changes in IPSS scores by IPSS total score, IPSS voiding subscore (sum of residual urine sensation, intermittency, weak stream and straining subscores), IPSS storage subscore (sum of frequency, urgency and nocturia subscores) and quality of life subscore. In terms of changes in the voiding subscore, CAG 500 showed significant improvement compared to placebo at 6th week ($P = 0.0116$) and 12th week ($P = 0.0102$), while CAG 1000

Table 2
Percentage changes of IPSS and IPSS subscores compared with placebo

		CAG 500 $N = 36$	P (vs placebo)	CAG 1000 $N = 33$	P (vs placebo)	Placebo $N = 34$
Total IPSS	Δ6th wk	−37.6	0.0068	−39.4	0.0189	−18.3
	Δ12th wk	−44.9	<0.0001	−51.0	<0.0001	−9.47
Residual urine sensation	Δ6th wk	−30.5	0.1019	−30.1	0.1191	−5.12
	Δ12th wk	−29.0	0.0226	−43.3	0.0005	−16.0
Frequency	Δ6th wk	−23.4	0.0134	−26.0	0.0440	−8.11
	Δ12th wk	−40.3	0.0004	−41.3	<0.0001	−5.79
Intermittency	Δ6th wk	−26.0	0.1875	−22.5	0.5855	−11.0
	Δ12th wk	−18.7	0.2244	−30.9	0.1196	−5.19
Urgency	Δ6th wk	−22.0	0.2404	−22.5	0.4994	−14.7
	Δ12th wk	−33.7	0.0251	−23.8	0.4327	−14.7
Weak stream	Δ6th wk	−24.6	0.1468	−32.3	0.0437	−15.0
	Δ12th wk	−31.1	0.0012	−37.1	0.0001	−6.55
Straining	Δ6th wk	−32.0	0.0283	−29.0	0.0888	−11.6
	Δ12th wk	−37.9	0.0027	−46.0	0.0004	−7.20
Nocturia	Δ6th wk	−16.0	0.3804	−22.3	0.1740	−7.92
	Δ12th wk	−26.2	0.0019	−23.9	0.0014	−3.00
Quality of life	Δ6th wk	−26.4	0.0632	−21.8	0.2601	−13.2
	Δ12th wk	−28.8	0.0004	−33.7	0.0002	−9.23

Δ: median values for percentage (%) of score changes from baseline.
P-value: generalized linear model adjusted for age, BMI and exercise compared with placebo group.

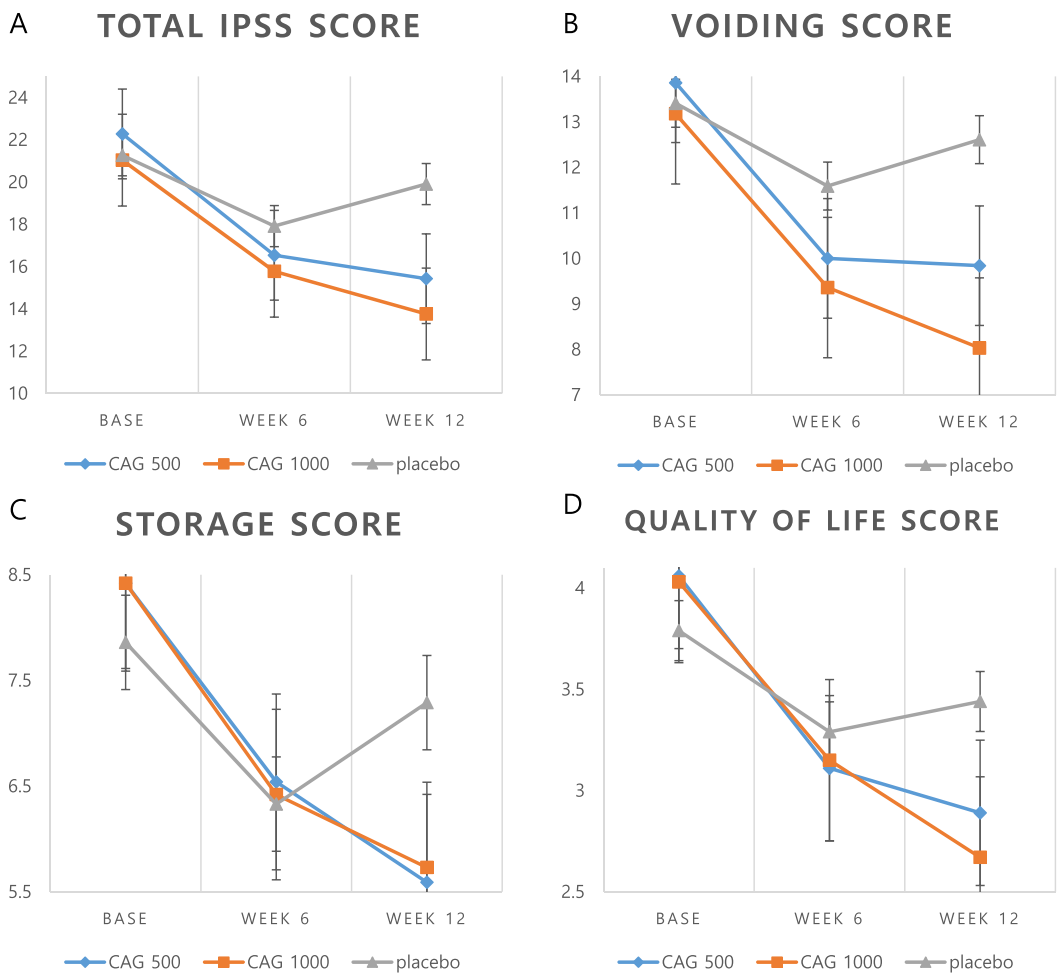

Fig. 2. Changes in International Prostate Symptom Score (IPSS) of each group. A) Total IPSS score, B) IPSS voiding subscore, C) IPSS storage subscore, D) Quality of life subscore. Data are presented as median and interquartile ranges.

demonstrated significant improvement at 6th week (P = 0.0209) and 12th week (P = 0.0044). Regarding changes in the storage subscore, CAG500 exhibited significant improvement compared to placebo at 12th week (P = 0.0090), and CAG 1000 showed significant improvement at 12th weeks as well (P = 0.014).

3.3. *Serum PSA, testosterone, and dihydrotestosterone*

Changes in serum PSA, testosterone (total and free), and dihydrotestosterone levels are summarized in Table 3. There was no statistically significant difference in serum PSA, testosterone (total and free), or dihydrotestosterone level among the three groups, which means that CAG can be safely taken without affecting serum PSA and testosterone.

3.4. *Maximum urinary flow rate (Q max) and post-void residual volume (PVR)*

Changes in Q max and PVR are summarized in Table 3. There was no statistically significant difference in Q max or PVR among the three groups.

3.5. *International Index of Erectile Function-5 (IIEF-5)*

Changes in IIEF-5 are summarized in Supplementary table 1. Changes in IIEF total score showed a statistically significant difference between CAG 1000 and PG (P = 0.0010) after 12 weeks of treatment. Changes of erectile function (IIEF-5 sub-score) showed a statistically significant difference between CAG 1000 and PG (P = 0.0005) after 12 weeks of treatment. Changes of orgasmic function (IIEF-5 subscore) showed a statistically significant difference between CAG 1000 and PG (P = 0.0018) at 12 weeks after treatment. Changes in sexual desire (IIEF-5 sub-score) showed a statistically significant difference between CAG 1000 and PG (P = 0.0365) at both 6th and 12th week after treatment. Changes of intercourse satisfaction (IIEF-5) also showed a statistically significant difference between CAG 1000 and PG (P = 0.0015) at 12 weeks after treatment.

3.6. *Safety assessment*

Safety evaluation was conducted with a safety set analysis. After being randomly assigned to three groups, 40 subjects in CAG 500, 41 in CAG 1000, and 41 in the placebo group were included in the analysis as subjects who were treated at least once. Acknowledged adverse events that are related with the investigational products were 2 cases of dyspepsia in CAG 500, 1 case of constipation and 2 cases of penile discomfort in CAG 1000. Thus, a total of 5 (4.1%) cases of adverse events occurred among all participants including those in the placebo group. All adverse events resolved spontaneously with a conservative therapy.

Table 3
Changes in serum PSA, testosterone (total and free), dihydrotestosterone levels, Qmax and PVR of each group

		CAG 500 $N = 36$	CAG 1000 $N = 33$	Placebo $N = 34$
PSA (ng/mL)	Baseline	1.05 ± 0.74	1.51 ± 2.29	1.49 ± 1.13
	12th week	1.13 ± 0.79	1.29 ± 1.18	1.59 ± 1.26
Total testosterone (ng/mL)	Baseline	4.22 ± 1.37	4.35 ± 1.94	4.20 ± 1.38
	12th week	3.86 ± 1.11	4.23 ± 1.50	4.08 ± 1.36
Free testosterone (pg/mL)	Baseline	7.42 ± 1.88	7.41 ± 2.10	7.10 ± 2.32
	12th week	7.57 ± 2.07	7.67 ± 2.43	7.52 ± 2.31
DHT (ng/mL)	Baseline	378.46 ± 174.35	409.26 ± 174.22	362.22 ± 185.50
	12th week	338.30 ± 127.80	361.55 ± 138.80	372.09 ± 232.67
Q max (mL/sec)	Baseline	13.41 ± 6.93	14.59 ± 7.64	12.36 ± 5.64
	12th week	13.71 ± 7.89	15.59 ± 8.42	13.47 ± 6.23
PVR (mL)	Baseline	20.17 ± 22.63	23.61 ± 28.81	24.00 ± 29.83
	12th week	26.42 ± 33.76	24.24 ± 26.36	27.65 ± 38.22

Data are presented as mean ± standard deviation. DHT, dihydrotestosterone; PVR, post-void residual volume; Q max, maximum urinary flow rate.

4. Discussion

Deer antler has been used as a valuable drug in Eastern cultures such as China, Japan, and Korea for its pharmacological effects on immune system enhancement, anti-fatigue, tissue regeneration, and sexual function improvement.[16] Recently, it has also been used in Australia, New Zealand, and Canada. The global medicinal market for deer antlers is growing rapidly to meet the demand.[17] In a recent animal study, the mRNA expression of Bax protein and the Bax/Bcl2 ratio in the prostate tissue were significantly increased in the *Cervi Parvum Cornu complex* treatment group used in this study than in the BPH group, suggesting the possible use of *Cervi Parvum Cornu complex* as a treatment for LUTS caused by BPH.[13]

Since the 1980s, the efficacy of alpha blocker in the treatment of LUTS and BPH has been confirmed through systematic reviews and meta-analysis.[18,19] However, side effects such as retrograde ejaculation and hypotension could occur.[20] In the case of CAG used in this study, total IPSS improved by 6–7 points without ejaculatory dysfunction or blood pressure change, not inferior to alpha blocker which showed improvement by 4–7 points.[21] Additionally, CAG can be used relatively safely in patients with cardiovascular disease since its side effects are at the level of indigestion and constipation, which can be improved with conservative treatment.

5 alpha reductase inhibitors can be used for LUTS caused by benign prostatic hyperplasia. It can reduce prostate volume, decrease incidence of complications such as acute urinary retention, and lower the risk of surgical treatment.[19] However, its side effects such as erectile dysfunction and decreased libido have been reported.[22] On the other hand, CAG could improve total IIEF, erectile function, sexual desire, and intercourse satisfaction score based on results of the present study without causing any changes in serum testosterone when it was administered for 12 weeks. In addition, as shown in Fig. 2, it was shown that as the duration of CAG administration lengthened, not only the IPSS total score but also the subscores of voiding, storage, and quality of life demonstrated significant improvements compared to the placebo group. Furthermore, a greater improvement was observed in the IPSS total score, voiding subscore, and quality of life subscore in the higher dosage group.

A previous study has confirmed the mechanism and effect of CAG used in this clinical trial through *in vitro* and *in vivo* experiments.[13] Cell experiments proved that CAG could decrease the proliferation of human prostatic hyperplasia epithelial cells significantly. On the other hand, in animal experiments, prostatic hyperplasia could be suppressed by increased Bax protein mRNA expression level and Bax/Bcl-2 ratio in prostate tissues induced by CAG.

Gangliosides as components of *Cervi parvum cornu* have various functions. They can act as receptors and various biological substances, contributing to the expression of immune cell functions. Accordingly, the possibility of their application for treating prostate cancer,[23] melanoma,[24] and diabetic nephropathy[25] has been suggested, and related research is being actively conducted. According to Nicolae et al., titers of anti-GDA1a and antiGQ1b (ganglioside antibodies) were higher in patients with BPH than in controls.[26] Therefore, it can be inferred that *Cervi parnum cornu* used in this study may be effective for treating LUTS caused by BPH.

A limitation of this study was that transrectal-ultrasonography of prostate or urodynamic study were not included in test items in consideration of patients' discomfort. Also, since the study period was relatively short (12 weeks), large scale and long-term follow-up studies are needed in the future. In this study, we could not find significant difference in Qmax or PVR. There are studies showing positive effect of phytotherapies on the subjective IPSS, but no improvement in the objective uroflowmetry.[27] However, considering that IPSS scores were improved, possibility of improvement in Qmax and PVR can be seen if CAG is administered with a longer period in a future study. To the best of our knowledge, this study is the first clinical trial conducted on *Cervi Parvum Cornu* for treating male LUTS.

Lastly, CAG significantly improved IPSS and IIEF subscores at 12 weeks when the intake of CAG was higher and longer. Therefore, if a study is conducted with a longer period in the future, better results can be expected in several IPSS subscores and IIEF subscores, Qmax, and PVR, which did not show significant improvement in this study.

5. Conclusion

CAG is a safe and effective treatment for LUTS without causing side effects such as orthostatic hypotension, dizziness, tachycardia, and headache that can occur with an alpha blocker. It did not cause erectile dysfunction or decrease libido that could occur with 5-ARI.

Author contribution

Conceptualization: DSL, SWK, USH, WJB. Data curation: DS. Formal analysis: SK, JP. Funding acquisition: SWK. Investigation: YTK, JSK. Methodology: DS. Project administration: DSL, USH. Resources: YTK, JSK. Supervision: BIY, KHJ, DSL, SWK, USH, WJB.

Validation: DS. Visualization: SHP. Writing – original draft: DS. Writing – review & editing: All authors.

Ethics statement

This trial was approved by the Institutional Review Board (IRB) of Catholic University of Korea (IRB no. XC20HDDE0083). It was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Good Clinical Practice Guidelines.

Also, the study was approved by the Clinical Research Information Service of South Korea (CRIS No: KCT0007449).

Conflicts of interest

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2023.09.002.

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