Original Article - Lower Urinary Tract Dysfunction

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Quisqualis indica extract for men with lower urinary tract symptoms: A randomized, double-blind, placebo-controlled trial

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Purpose: To evaluate the efficacy and safety of *Quisqualis indica* in men with moderate lower urinary tract symptoms (LUTS).

Materials and Methods: A total of 135 subjects with International Prostate Symptom Score (IPSS) of 8–19 were randomized in 2 centers from June 2018 to April 2019. Patients were assigned into one of the three groups: a low-dose group (LG, 1,000 mg *Q. indica*), a high-dose group (HG, 2,000 mg *Q. indica*) or a placebo group (PG). The primary endpoint was the change of IPSS at the end of treatment from baseline. Secondary end points included the changes of prostate specific antigen, testosterone, dihydrotestosterone, maximum urinary flow rate (Qmax), postvoid residual volume (PVR) and International Index of Erectile Function-5 (IIEF-5), with drug safety.

Results: 113 patients were able to finish the study. Compared to the PG, total IPSS in the LG and the HG was significantly improved at 6 weeks and 12 weeks. For IPSS subscores, LG showed improvements in all except for urgency and quality of life at 6 weeks. HG showed improvements in incomplete emptying and frequency at 6 weeks and 12 weeks along with improvements in intermittency, straining, and quality of life at 12 weeks. For IIEF-5 subscores, orgasmic function and overall satisfaction improved in HG when compared to PG at 12 weeks. Lastly, increase of Qmax and decrease of PVR was observed at 6 weeks in LG.

Conclusions: 12-week treatment with *Q. indica* has a therapeutic effect and is well tolerated in patients with LUTS.

Keywords: Dihydrotestosterone; Pharmacologic effects; Plant extract; Safety

INTRODUCTION

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS), which represents one of the most prevalent disorders in aging men with an incidence of over 2,000 per 100,000, is a considerable quality of life (QoL) issue [1,2]. The last guideline on the management of LUTS secondary to BPH recommended certain pharmacotherapies to pa-

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tients who are unwilling to undergo an invasive treatment. As first-line oral medications, 5α-reductase inhibitors (5-ARIs) and α-blockers have shown great advantages [3,4]. However, they still have some limitations in terms of poor response and/or side effects [5].

To date, various plant extracts—such as permixon [6], pollen extract [7], Prelox [8], saw palmetto [9], etc.—have already been mentioned in urological studies, and several of them have been evaluated to be suitable in clinical trials. Because of their significant effects, plant extracts have been used to improve LUTS and reduce the risk of progression, even though their roles as single agents have thus far appeared to be limited [10]. As plant extracts are becoming increasingly accepted by patients and urologists, the safety and efficacy of plant extracts in clinical use are becoming even more important.

Quisqualis indica, which is known as a complex formulation consisting of Chinese honeysuckle or Rangoon creeper, has been shown to induce cytotoxicity and apoptosis *in vitro* study [11]. More recently, the extract of *Q. indica* has been identified as a compound consisting of trans-linalool oxide, methyl benzoate, 2,2,6-trimethyl-6-vinyl-tetrahydropyran-3-one, 2,2,6-trimethyl-6-vinyl-tetrahydropyran-3-ol, (E,E)-α-farnesene, and quinoline-4-carbonitrile; quinoline-4-carbonitrile has proven effects as a potential anti-inflammatory and antioxidant agent [12]. Moreover, in a pharmacological study, researchers have proven that *Q. indica* reduced size and ameliorated LUTS in a BPH rat through anti-proliferative and pro-apoptotic activities [13]. However, there has yet to be a clinical trial investigating the efficiency of *Q. indica* for LUTS.

In this study, we presented 12-week results from a randomized, double-blind, placebo-controlled trial. The main objective of this study was to assess the efficiency of different amounts of *Q. indica* (1,000 mg/2,000 mg per day) for men with moderate LUTS (International Prostate Symptom Scores [IPSS] 8–19). This study also evaluated safety and supplementary efficacy outcomes.

MATERIALS AND METHODS

1. *Q. indica*

The seeds of a *Q. indica* were obtained from a local herbal market in Ansan of Korea, then deposited at the herbarium of the HUONS Research Center (Voucher no. HU033/SKJA150427, Ansan, Korea). The dried seeds of *Q. indica* were homogenized to a fine powder and extracted by reflux with 50 kg/500 L of 70% ethanol at 80°C for 6 hours. This extract was mixed with maltodextrin 1:1 and the final product was manufactured as described in the previous described process [14]. In a previous preclinical experiment [13,14], when *Q. indica* extract powder was orally administered at 75 and 150 mg/kg, LUTS secondary to BPH was shown to be improved. Therefore, the *Q. indica* dose in this study was calculated in terms of a Human Equivalent Dose (mg/kg)=Animal dose (mg/kg) multiplied by (Animal correction factor [Km]/Human Km). Low dose group: 75 mg/kg (animal dose)×6 (Animal Km)/37 (Human Km)=12.16 mg/kg; 12.16 mg/kg×70 kg (adult male)=851.2 mg/day, estimated to be 1,000 mg/70 kg/day. High dose group: 150 mg/kg (animal dose)×6 (Animal Km)/37 (Human Km)=24.32 mg/kg; 24.32 mg/kg×70 kg (adult male)=1,702.4 mg/kg, estimated to be 2,000 mg/kg/day [15].

2. Study design and participants

This double-blind, randomized, placebo-controlled trial (Protocol no. HOS_HU-033) was conducted from June 2018 to

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
• Patients who understood the purpose of this study, wanted to participate this trial by his own decision and signed the written informed consent	• Concurrent acute or chronic cardia-cerebrovascular, immune, respiratory, liver, kidney, urinary, nervous, musculature, mental, infectious and hematologic disease
• Patients with lower urinary tract symptoms aged 40–75 y	• Tumor
• International Prostate Symptom Score 8–19	• Prostate specific antigen ≥4.0 ng/mL
	• Maximum urinary flow rate ≤5 mL/s
	• Postvoid residual volume ≥150 mL
	• History of prostate invasive therapy
	• Concurrent diabetes
	• Thyroid disorder
	• Taking benign prostatic hyperplasia drug or health food within 4 wk
	• Participating other trials within 12 wk
	• Allergic to *Quisqualis indica*
	• Others who were unfitted for this trial

April 2019 at two study sites in Korea. Patients with moderate LUTS (IPSS 8–19) who met the inclusion criteria (Table 1) were enrolled before treatment as outpatients. Randomization and double blinding were carried out in each study site by a randomization sequence. Patients visited the outpatient center a total of four times: at screening, and at 0, 6th, and 12th weeks (Fig. 1). At screening, 135 patients were collectively recruited from two study sites in Korea. At baseline, the eligible patients were randomized 1:1:1 into a low-dose group (LG, 1000 mg *Q. indica* per day), a high-dose group (HG, 2,000 mg *Q. indica* per day), and a placebo group (PG) for 12 weeks. At the 6th week, participants came to the outpatient center and a mid-test was administered. At the 12th week, all participants took part in final tests. IPSS and International Index of Erectile Function-5 (IIEF-5) questionnaires were completed at 0, 6, and 12 weeks. Meanwhile, prostate specific antigen (PSA), testosterone, dihydrotestosterone (DHT), maximum urinary flow rate (Qmax), postvoid residual volume

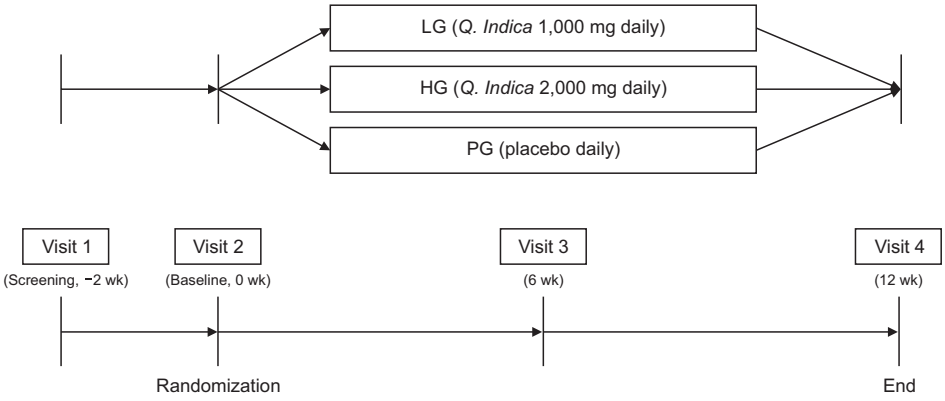

Fig. 1. Study design. Patients came to outpatient (visit 1) at 2 weeks and written informed consents were obtained from participants who were involved this trial. Then participants were randomized 1:1:1 into 3 groups. At baseline, participants were received different treatment according to their group for 12 weeks. At 6 and 12 weeks, efficacy and safety assessments were assessed. LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group.

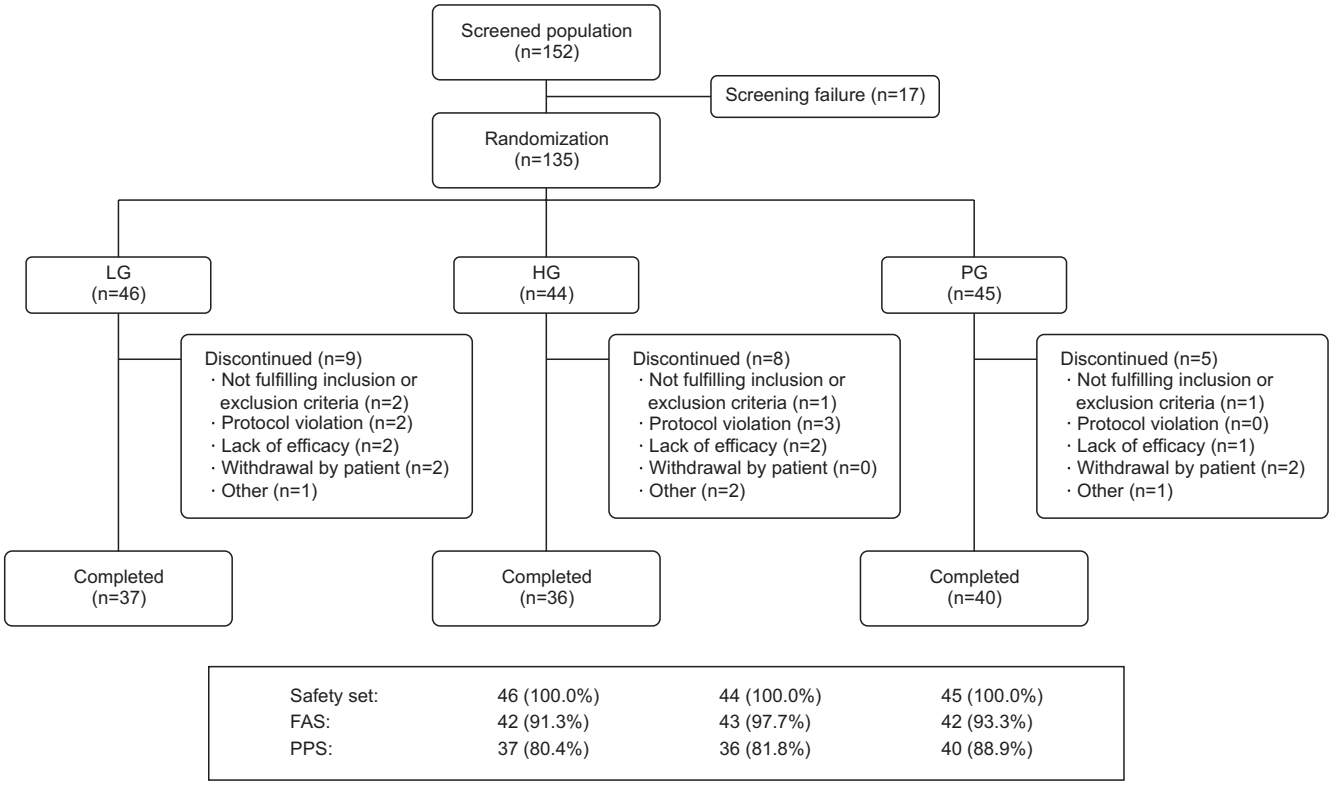

Fig. 2. Patient disposition. LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group; FAS, full analysis set; PPS, per protocol set.

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(PVR), and IIEF-5 were also tested at 0, 6th, and 12th weeks.

This trial was approved by the Institutional Review Board (IRB) of the Catholic University of Korea (IRB no. KC18HODE0126) and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practice Guidelines. All participants provided written informed consent.

3. Efficacy and safety assessments

The primary endpoint was the change in total IPSS scores (sum of answers to questions 1–7) at the end of treatment compared to baseline. All participants completed IPSS questionnaires at the 0th, 6th, and 12th weeks to compare the results before and after treatment among the three groups. Secondary end points included the changes in the

Table 2. Demographic and baseline characteristics

Variable	LG (n=37)	HG (n=36)	PG (n=40)
Age (y)	59.14±9.24	60.17±9.14	61.38±8.94
Height (cm)	167.98±6.56	169.15±4.85	169.27±5.62
Married	36 (97.30)	34 (94.44)	40 (100.00)
Smoking			
Non	13 (35.14)	6 (16.67)	13 (32.50)
Ex-smoker	15 (40.54)	25 (69.44)	18 (45.00)
Smoker	9 (24.32)	5 (13.89)	9 (22.50)
Exercise ≥60 min			
Non	8 (21.62)	7 (19.44)	7 (17.50)
1–3/wk	5 (13.51)	7 (19.44)	10 (25.00)
≥4/wk	24 (64.86)	22 (61.11)	23 (57.50)
Comorbidities (NP [%], ND)			
Blood and lymphatic system disorders	0 (0.00), 0	0 (0.00), 0	1 (2.50), 1
Cardiac disorders	4 (10.81), 4	1 (2.78), 1	3 (7.50), 4
Endocrine disorders	0 (0.00), 0	0 (0.00), 0	1 (2.50), 1
Eye disorders	1 (2.70), 1	0 (0.00), 0	1 (2.50), 3
Gastrointestinal disorders	3 (8.11), 4	0 (0.00), 0	2 (5.00), 2
Congenital, familial, and genetic disorders	1 (2.70), 1	0 (0.00), 0	0 (0.00), 0
Ear and labyrinth disorders	1 (2.70), 1	0 (0.00), 0	0 (0.00), 0
Metabolism and nutrition disorders	8 (21.62), 10	5 (13.89), 6	11 (27.50), 12
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (2.70), 1	0 (0.00), 0	0 (0.00), 0
Musculoskeletal and connective tissue disorders	0 (0.00), 0	1 (2.78), 1	0 (0.00), 0
Nervous system disorders	0 (0.00), 0	1 (2.78), 1	0 (0.00), 0
Psychiatric disorders	2 (5.41), 2	0 (0.00), 0	1 (2.50), 1
Renal and urinary disorders	2 (5.41), 2	2 (5.56), 2	1 (2.50), 2
Reproductive system and breast disorders	11 (29.73), 11	9 (25.00), 9	15 (37.50), 16
Respiratory, thoracic, and mediastinal disorders	0 (0.00), 0	0 (0.00), 0	1 (2.50), 1
Skin and subcutaneous tissue disorders	2 (5.41), 3	1 (2.78), 1	0 (0.00), 0
Vascular disorders	8 (21.62), 10	9 (25.00), 10	7 (17.50), 7
Total	25 (67.57), 50	18 (50.00), 31	27 (67.50), 50
History of previous surgery (NP [%], NS)	3 (8.11), 3	1 (2.78), 1	1 (2.50), 1
Previous medications prior to screening within 30 days (NP [%], NM)			
Alimentary tract and metabolism	7 (18.92), 12	4 (11.11), 6	6 (15.00), 8
Antiinfectives for systemic use	1 (2.70), 1	0 (0.00), 0	0 (0.00), 0
Blood and blood forming organs	5 (13.51), 6	1 (2.78), 1	6 (15.00), 6
Cardiovascular system	12 (32.43), 22	9 (25.00), 17	10 (25.00), 19
Nervous system	4 (10.81), 5	1 (2.78), 3	1 (2.50), 2
Respiratory system	0 (0.00), 0	0 (0.00), 0	1 (1.30), 1
Total	17 (45.95), 46	10 (27.78), 27	13 (32.50), 36

Data are presented as mean±standard deviation or number (%).
LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group; NP, number of patients; ND, number of disorder; NS, number of surgeries; NM, number of medications.

Table 3. Changes in total IPSS scores of each group

Total IPSS	LG (n=37)	HG (n=36)	PG (n=40)	p-value	
				LG vs. PG	HG vs. PG
Baseline	13.51±2.87	13.31±2.54	14.18±2.96	0.290	0.153
6 wk	8.95±4.99	11.36±5.87	14.48±5.56	<0.001*	0.048*
ΔBaseline	-4.57±5.52	-1.94±5.47	0.30±5.32		
p-value	<0.001*	0.005*	0.723		
12 wk	6.81±4.94	9.56±5.46	14.25±6.98	<0.001*	0.007*
ΔBaseline	-6.70±5.58	-3.75±5.07	0.08±6.79		
p-value	<0.001*	<0.001*	0.945		

Data are presented as mean±standard deviation.
IPSS, International Prostate Symptom Score; LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group; ΔBaseline, difference from baseline.
*Statistically significant p<0.05.

subscores of IPSS for each question as well as changes in PSA, testosterone, DHT, Qmax, PVR, and IIEF-5, which were measured at the 0th, 6th, and 12th weeks. Safety was assessed according to adverse events (AEs). Hematology, biochemistry, urinalysis, and vital signs were also observed.

4. Statistical analysis

Thirty-six patients per group provided 80% power to demonstrate the superiority of *Q. indica* (1,000 mg or 2,000 mg) over placebo with a two-sided significance level of 5%. The ratio of LG, HG, and PG was 1:1:1. The number of subjects was calculated using the previous study [16] results of the mean difference of the IPSS after the test of the test group/control group was 6.9 and the standard deviation was 5.2. Considering a dropout rate of 20%, 135 patients were recruited into this trial. Full analysis set (FAS) was used for efficacy analysis and safety set (all patients who received at least one doses) was used for safety analysis. The paired t-test or the Wilcoxon signed rank test was used to compare continuous type data. For comparison between groups, a two-sample t-test or Wilcoxon rank sum test was performed depending on whether distribution was satisfied, and significance values were presented. Urinalysis data were analyzed by McNemar test. AEs were analyzed by chi-squared test or Fisher's exact test for participants who were randomized at visit 2 and treated accordingly. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). This study presents data in the form of mean±standard deviation or proportions for continuous or categorical variables. All statistical assessments were two-sided, and p<0.05 was considered to be statistically significant.

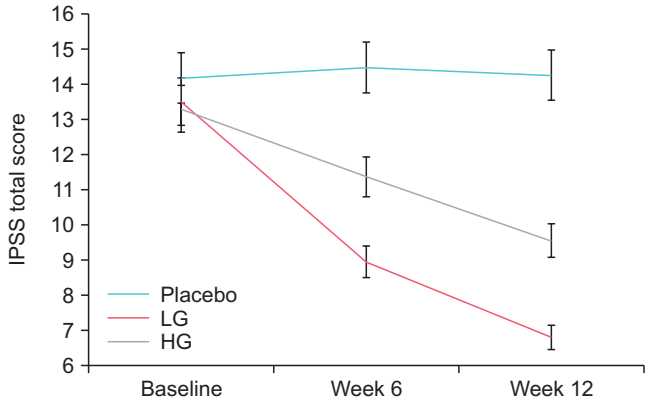

Fig. 3. Changes in International Prostate Symptom Score (IPSS) total scores of each group. LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day).

RESULTS

1. Demographics

Initially, 135 patients were enrolled in the trial, and these patients were randomized into LG (n=46), HG (n=44), and PG (n=45) (Fig. 2). The demographic and baseline characteristics were similar in concomitant medications across the treatment groups (Table 2). Ultimately, 113 patients were able to complete the study, with LG (n=37), HG (n=36), and PG (n=40).

2. Efficacy of *Q. indica*

Compared to PG, the total IPSS scores in LG and HG were significantly improved (Table 3 and Fig. 3). From baseline to the 12th week, total IPSS gradually decreased in LG and HG. These results suggest that *Q. indica* was beneficial in continuously moderating LUTS, while the patients were under medication. In other words, *Q. indica* remained effective as a long-term medication. Total IPSS decreased 4.57±5.52 points at the 6th week and 6.70±5.58 points at the 12th week

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in LG, along with decreases of 1.94±5.47 points at the 6th week and 3.75±5.07 points at the 12th week in HG. Meanwhile, there were increases of 0.30±5.32 points at the 6th week and of 0.08±6.79 points at the 12th week in PG. Comparisons of the mean changes in IPSS from baseline to the 6th and 12th weeks indicated that the variation was related to compliance rather than dose. The intake compliance at the end of the study was 96.83%±5.07% in LG, 94.42%±5.87% in HG and 96.71%±5.28% in placebo. There was no statistically significant difference between LG and placebo, but there was a significant difference between HG and placebo (p=0.017).

Table 4 lists the changes in IPSS subscores. In LG, symptoms were significantly improved in all subscores except for straining. In HG, incomplete emptying and frequency were significantly improved at 6 and 12 weeks, while straining and QoL were improved at 12 weeks. When compared to placebo, LG showed significant improvements in symptoms in all subscores except for urgency and QoL at 6 weeks. Compared to placebo, HG showed improvements in incomplete emptying and frequency at 6 and 12 weeks along with improvements in intermittency, straining, and QoL at 12 weeks.

Table 4. IPSS subscores changes in of each group

IPSS sub score	LG (n=37)	HG (n=36)	PG (n=40)	p-value	
				LG vs. PG	HG vs. PG
Incomplete emptying					
Baseline	2.22±0.98	2.11±1.01	2.38±1.23	0.559	0.246
6 wk	1.41±1.01	1.67±1.17	2.35±1.27	<0.001*	0.031*
12 wk	0.97±0.96	1.39±0.96	2.18±1.52	<0.001*	0.017*
Frequency					
Baseline	2.05±1.10	2.00±0.96	1.98±1.17	0.779	0.832
6 wk	1.27±0.96	1.47±1.11	1.98±1.39	<0.001*	0.025*
12 wk	1.08±1.01	1.31±1.01	2.25±1.33	<0.001*	<0.001*
Intermittency					
Baseline	2.00±1.03	1.56±0.91	1.85±1.12	0.668	0.204
6 wk	1.14±1.08	1.56±1.32	2.18±1.34	<0.001*	0.102
12 wk	0.76±0.96	1.17±1.08	2.03±1.40	<0.001*	0.010*
Urgency					
Baseline	1.73±1.10	1.25±1.05	1.33±1.12	0.145	0.693
6 wk	1.30±1.15	1.19±1.26	1.28±1.22	0.474	0.841
12 wk	1.03±1.07	0.97±0.97	1.50±1.43	0.016*	0.070
Weak stream					
Baseline	2.70±1.05	2.94±1.17	3.15±1.21	0.086	0.797
6 wk	1.78±1.20	2.36±1.50	2.93±1.31	<0.001*	0.120
12 wk	1.32±1.13	2.06±1.37	2.60±1.30	<0.001*	0.109
Straining					
Baseline	1.24±1.26	1.81±1.06	1.90±1.08	0.012*	0.719
6 wk	0.89±1.02	1.56±1.08	2.00±1.34	0.002*	0.103
12 wk	0.62±0.89	1.31±1.21	1.98±1.37	<0.001*	0.027*
Nocturia					
Baseline	1.57±0.93	1.64±0.80	1.60±0.84	0.691	0.836
6 wk	1.16±0.83	1.56±1.00	1.78±1.12	0.004*	0.272
12 wk	1.03±1.09	1.36±1.05	1.73±1.04	0.002*	0.068
Quality of life					
Baseline	3.51±1.07	3.36±0.99	3.75±1.06	0.562	0.064
6 wk	2.70±1.13	3.06±1.15	3.28±1.34	0.085	0.818
12 wk	2.41±1.32	2.53±1.30	3.35±1.19	0.002*	0.023*

Data are presented as mean±standard deviation.
IPSS, International Prostate Symptom Score; LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group.
*Statistically significant p<0.05.

Other secondary efficacy variables were influenced by *Q. indica* treatment (Table 5). *Q. indica* showed no effect on PSA. In LG, total testosterone was decreased by *Q. indica* in a manner similar to placebo. Free testosterone was affected by *Q. indica* (p<0.001 in LG, p<0.001 in HG) and placebo (p<0.001) at 6 weeks, but at 12 weeks, low-dose *Q. indica* showed no effect on free testosterone. Placebo reduced DHT at 6 weeks and 12 weeks, but the results showed that this effect weakened with time. At 6 weeks, high-dose *Q. indica* decreased DHT as well (p=0.026), but it was not statistically significant at 12 weeks. Qmax increased in LG by 4.17±10.19 from the baseline at 6 weeks (p=0.017). Lastly, PVR decreased from 26.17±28.90 to 16.68±17.80 at 6 weeks in LG (p=0.004).

Meanwhile, to explore the effect of *Q. indica* on erectile function, all subjects were asked to complete IIEF-5 questionnaires at baseline, 6 weeks, and 12 weeks. In the total score of IIEF-5 (Table 6), there was a decrease of 0.62±18.98 points in LG, an increase of 3.03±19.07 points in HG. and a decrease of 0.88±19.79 points in the placebo group at the end of the study; there were no statistically significant differences among these values. However, subscores of orgasmic function and overall satisfaction, showed significant improvements in HG when compared to PG (p=0.047, 0.020) at 12 weeks.

3. Safety of *Q. indica*

In total, there were two AEs patients in LG, three in HG, and two in PG. No statistically significant difference was observed in the proportion of patients with any AEs (Table 7). No serious or fatal AEs were recorded in this trial, and none of the AEs patients discontinued medication. In the whole treatment period, two drug-related AEs occurred out of seven AEs in total. Dyspepsia as one of the drug-related AEs was observed in LG and HG (one case each), but there was no statistical significance among each group. Changes in hematology, blood biochemistry, urinalysis, and vital signs were minor and not considered to be clinically relevant.

Table 5. Patients' outcomes after 12-wk treatment

Outcome	LG (n=37)	HG (n=36)	PG (n=40)	p-value	
				LG vs. PG	HG vs. PG
Prostate specific antigen (ng/mL)					
Baseline	1.50±1.79	1.30±0.93	1.34±0.96	0.968	0.897
6 wk	1.54±1.44	1.26±0.94	1.29±0.79	0.291	0.979
12 wk	1.32±0.97	1.57±1.77	1.57±1.77	0.614	0.827
Total testosterone (ng/mL)					
Baseline	4.92±2.01	4.64±2.21	5.89±2.84	0.127	0.024*
6 wk	4.21±2.01	4.05±1.67	4.80±2.26	0.362	0.280
12 wk	5.08±2.41	4.48±2.06	5.34±2.66	0.233	0.333
Free testosterone (pg/mL)					
Baseline	9.77±3.44	9.53±3.34	10.69±4.03	0.285	0.178
6 wk	8.15±2.46	7.75±2.48	8.82±3.18	0.653	0.865
12 wk	9.39±3.50	8.41±2.56	9.79±3.48	0.341	0.996
Dihydrotestosterone (ng/mL)					
Baseline	523.08±384.47	454.52±238.27	556.94±324.18	0.740	0.180
6 wk	479.72±381.28	391.47±186.52	454.28±231.24	0.146	0.381
12 wk	558.09±448.51	412.28±153.20	507.04±238.73	0.090	0.699
Qmax (mL/s)					
Baseline	12.29±4.94	12.51±5.86	12.15±4.44	0.895	0.795
6 wk	16.46±8.28	15.02±5.94	14.68±7.45	0.419	0.993
12 wk	15.48±9.04	12.82±5.77	14.01±6.08	0.484	0.306
Postvoid residual volume (mL)					
Baseline	26.17±28.90	28.67±28.15	23.08±26.13	0.934	0.337
6 wk	16.68±17.80	22.14±20.01	21.58±31.04	0.183	0.653
12 wk	1.32±0.97	20.22±24.36	40.10±71.64	0.241	0.062

Data are presented as mean±standard deviation.
LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group; Qmax, maximum urinary flow rate.
*Statistically significant p<0.05.

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Table 6. IIEF-5 outcomes of each group

Outcome	LG (n=37)	HG (n=36)	PG (n=40)	p-value	
				LG vs. PG	HG vs. PG
Total score					
Baseline	35.57±19.95	39.36±19.29	33.50±17.84	0.646	0.199
6 wk	37.65±20.81	39.89±20.45	34.25±19.87	0.405	0.708
12 wk	34.95±20.86	42.39±20.09	32.63±18.99	0.721	0.240
Erectile function					
Baseline	14.43±9.79	16.89±9.80	13.25±8.70	0.646	0.077
6 wk	15.32±10.17	17.11±9.92	13.85±9.72	0.584	0.617
12 wk	14.22±10.47	17.56±10.05	12.78±9.18	0.757	0.137
Intercourse satisfaction					
Baseline	4.70±4.00	5.50±3.58	4.58±3.88	0.967	0.321
6 wk	5.35±4.32	5.81±3.92	4.98±4.29	0.705	0.782
12 wk	4.81±4.37	6.36±4.02	4.93±4.21	0.821	0.268
Orgasmic function					
Baseline	5.03±3.87	5.28±3.72	4.35±3.61	0.346	0.200
6 wk	4.86±3.94	5.36±3.89	4.30±3.73	0.832	0.492
12 wk	4.51±3.88	5.89±3.62	4.00±3.48	0.796	0.047*
Sexual desire					
Baseline	5.84±1.97	6.03±1.87	5.85±1.75	0.912	0.932
6 wk	6.24±1.66	6.11±2.00	5.63±1.89	0.094	0.317
12 wk	5.81±1.70	6.25±1.75	5.65±1.81	0.668	0.151
Overall satisfaction					
Baseline	5.57±2.13	5.67±1.91	5.48±1.87	0.819	0.646
6 wk	5.86±1.99	5.50±2.06	5.50±1.97	0.420	0.852
12 wk	5.59±2.17	6.33±1.88	5.28±1.97	0.523	0.020*

Data are presented as mean±standard deviation.
IIEF-5, International Index of Erectile Function-5; LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group.
*Statistically significant p<0.05.

Table 7. Proportion of patients with AEs (Safety Set)

Variable	LG (n=46)	HG (n=44)	PG (n=45)	Total (n=135)
All AEs	2 (4.35)	3 (6.82)	2 (4.44)	7 (5.19)
Dyspepsia	1 (2.17)	1 (2.27)	0 (0.00)	2 (1.48)
Headache	0 (0.00)	1 (2.27)	0 (0.00)	1 (0.74)
Hematospermia	1 (2.17)	0 (0.00)	0 (0.00)	1 (0.74)
Laryngitis	0 (0.00)	0 (0.00)	1 (2.22)	1 (0.74)
Nasopharyngitis	0 (0.00)	1 (2.27)	0 (0.00)	1 (0.74)
Epistaxis	0 (0.00)	0 (0.00)	1 (2.22)	1 (0.74)
Drug-related AEs	1 (2.17)	1 (2.27)	0 (0.00)	4 (2.96)

Data are presented as number (%).
AE, adverse event; LG, low-dose group (1,000 mg *Quisqualis indica* per day); HG, high-dose group (2,000 mg *Q. indica* per day); PG, placebo group.

DISCUSSION

To our knowledge, this is the first randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of *Q. indica* for patients with moderate LUTS. In this study, we demonstrated that *Q. indica* was a safe and therapeutic medication. Compared to placebo, IPSS was significantly improved under *Q. indica* treatment. Although not all secondary efficacy variables were ameliorated in treatment groups, total testosterone, free testosterone, DHT, Qmax, and PVR showed significant improvements during the therapy. These results prove that *Q. indica* is a promising and novel treatment that is effective for moderate LUTS.

As a progressive disease, BPH is characterized by the pathological proliferation of epithelial and stromal cells of the prostate [17], which affects QoL with incomplete bladder emptying, bladder obstruction, bloody urination, and frequent urination [18]. PSA and prostate volume are recognized as evaluation indicators of BPH [19]. Drugs such as 5-ARIs and α-blockers have been recommended to patients with bothersome, moderate to severe LUTS secondary to BPH [2,3]. Plant extracts, which are generally considered to be an alternative treatment, have begun to be used to im-

prove LUTS secondary to BPH [20,21]. Although the mechanism of this is still under study. It is hard to accurately define the correlation between biological activities and the efficacy of plant extracts. Therefore, there is a need for more studies and clinical trials to contribute to the exploration of plant extracts.

IPSS, which is a widely recognized indicator of LUTS, was found to be decreased by *Q. indica* with time. However, the secondary end points changed in a variable manner in our study. Therefore, the mechanism of *Q. indica* requires further investigation. One study showed that *Q. indica* improved BPH in a rat model through anti-proliferative and pro-apoptotic activities [14]. In this clinical trial, we proved that *Q. indica* also facilitated the improvement of LUTS. However, the mechanism behind *Q. indica* remains undefined.

There is a widespread consensus that DHT plays a key role in the development of prostate, which contributes to pathologic prostate growth in the adult prostate [22]. DHT converted from testosterone disrupts homeostasis of the prostate by promoting proliferation and inhibiting apoptosis [23]. In other words, DHT increases hyperplasia of prostatic stromal and epithelial cells and decreases apoptosis of prostatic stromal cells, thus resulting in enlargement of the prostate. There is a kind of consensus that 5-ARIs improves LUTS secondary to BPH by inhibiting 5α-reductase converting testosterone to DHT [24]. *Q. indica* has been shown to improve LUTS by decreasing prostatic DHT in a rat model [14]. In this study, DHT was detected in participants at baseline, at the 6th week, and at the 12th week. We found that DHT decreased -63.59±159.98 in HG at the 6th week. Meanwhile, there was no significant difference in HG at the 12th week. Curiously, DHT decreased 97.02±178.74 ($p<0.001$) at the 6th week and 47.21±130.50 ($p=0.049$) at the 12th week in PG, but DHT decreased 43.36±130.91 ($p=0.070$) at the 6th week and even increased 35.02±273.88 ($p=0.568$) at the 12th week in LG. For the reason for DHT decrease in the placebo, we found a change in PG in terms of free testosterone from baseline to the 12th week, which resembled the DHT change from baseline to 12th week. Moreover, in LG, the change in free testosterone from baseline to the 12th week was similar to the change in DHT from baseline to the 12th week. According to DHT converted from testosterone, one hypothesis was that *Q. indica* decreased DHT by reducing free testosterone. Certainly, there is a need for more research to support this hypothesis.

In a recent study, *Q. indica* was proven to be a potential treatment of BPH, which showed antagonist effects on α1A- and α1D-adrenergic receptors and inhibitory effects on the protein expressions of androgen receptor and estrogen receptor alpha [25]. Moreover, another rodent animal experiment demonstrated that *Q. indica* can be beneficial for LUTS secondary to BPH by inhibiting 5α-reductase and consequently decreasing prostate and releasing urinary pressure [13]. These basic studies have supported the efficiency of *Q. indica* as an alternative medicine, but the mechanism still needs to be explored.

In recent years, phosphodiesterase 5 inhibitors (PDE5Is) have been recognized as a safe and effective drug that improves both LUTS and erectile dysfunction (ED), particularly among ED patients with LUTS secondary to BPH [26,27]. Although clinical studies are being developed, there is still controversy as to whether treating ED patients with LUTS with PDE5I is a meaningful treatment [28] or a meaningless treatment [29]. Herbal medicines that are effective for ED are recently being studied [30]; as for *Q. indica*, we wanted to explore its therapeutic effect on ED patients with LUTS. Therefore, IIEF-5 was detected as one of the secondary efficacy variables in this study and used to assess the effect of *Q. indica* on erectile function through IIEF-5 questionnaires. The total score of IIEF-5 did not show a significant improvement, but the subscores of orgasmic function and overall satisfaction in HG were improved significantly when compared to PG.

The safety detection showed that both low and high doses of *Q. indica* did not result in more drug-related AEs compared to placebo.

There are some limitations to our study. First, we chose 1,000 mg per day and 2,000 mg per day to be standard doses rather than using individualized doses based on weight, which might have resulted in systemic error. Second, this study was focused on the difference between *Q. indica* and placebo. Therefore, we omitted a comparison of the differences between LG and HG. Thirdly, change in prostate size as an important evaluation indicator was absent from the results due to poor compliance. Also, a 12 weeks of treatment period is too short to represent the whole therapeutic process and the fact that only 113 out of 135 applicants were able to successfully complete the study can also be seen as a limitation of this study.

CONCLUSIONS

We demonstrated that orally taking *Q. indica* at 1,000 mg or 2,000 mg per day for 12 weeks therapeutically improved moderate LUTS. These results provide evidence showing that *Q. indica* is a safe and well tolerated treatment for patients with moderate LUTS.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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