Efficacy and Safety of *Serenoa repens* Extract Among Patients with Benign Prostatic Hyperplasia in China: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

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OBJECTIVE To evaluate the efficacy and safety of *Serenoa repens* among patients with benign prostatic hyperplasia (lower urinary tract symptoms/benign prostatic hyperplasia [LUTS/BPH]) in China.

METHODS We conducted a double blind, placebo-controlled study of 354 patients with LUTS/BPH from 19 institutions, to evaluate the efficacy and safety of *Serenoa repens*. Participants were randomly assigned (1:1) into the *Serenoa repens* extract (320 mg) or placebo groups for 24 weeks. Primary efficacy parameters were changes in International Prostate Symptom Score and peak urinary flow from baseline to each assessment. Secondary efficacy parameters included improvement of storage symptom and voiding symptom scores, prostate volume, urinary frequency, and total prostate-specific antigen level. Other parameters assessed were quality of life score, a four−item male sexual function questionnaire score, and International Index of Erectile Function score across the consecutive double-blind visits.

RESULTS Statistically significant improvement in the peak urinary flow, International Prostate Symptom Score, scores of storage symptoms and voiding symptoms, quality of life score, four−item male sexual function questionnaire score, and International Index of Erectile Function score were observed in the *Serenoa repens* extract group compared with those in the placebo group ($P < .05$). Two (1.18%) of 169 patients in the placebo group and 3 (1.89) of 159 patients in the *Serenoa repens* extract group experienced 1 or more adverse events.

CONCLUSION The *Serenoa repens* extract was effective, safe, well-tolerated, and clinically and statistically superior to placebo in the target LUTS/BPH population. UROLOGY 129: 172−179, 2019.

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Benign prostatic hyperplasia (BPH), the most common benign neoplasm in men, can often result in lower urinary tract symptoms (LUTS) or benign prostatic obstruction-related complications, which drive patients to seek treatment.[1] LUTS associated with BPH (LUTS/BPH) causes concern and impairs the quality of life (QoL).[2] Moreover, some treatment options can have a negative impact on the sexual and erectile function.[3]

The efficacy and safety of phytotherapy agents, like *Serenoa repens* (also known as the saw palmetto), have been assessed in numerous studies. In vitro, the *Serenoa repens* extract has demonstrated anti-inflammatory, antiandrogenic, and estrogenic effects along with decrease in sexual hormone binding globulin; inhibition of 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors, and vanilloid receptors; and neutralization of free radicals.[4,5]

However, no specific recommendations have been made regarding the guidelines because of product heterogeneity and limited regulatory framework.[6] In addition, a few large-scale, multicenter, randomized controlled trials are concentrated in the Chinese population. Thus, this prospective study aims to provide insight into the efficacy and safety of *Serenoa repens* among patients with LUTS/BPH in China.

PATIENTS AND METHODS

Study Design

This clinical trial (ChiCTR-TRC-13003575) was conducted as a multicenter, randomized, parallel-design, double-blind comparison between 2 treatment groups: *Serenoa repens* extract 320 mg/day and placebo. Five visits were planned for each participant suffering from LUTS/BPH: the selection visit (baseline), first assessment visit (Week 2), second assessment visit (Week 4), third assessment visit (Week 12), and end-of-study visit (Week 24).

At the selection visit, the participants were screened for eligibility based on a complete medical and medication history, a detailed history of storage and voiding symptoms using the International Prostate Symptom Score (IPSS)[7] and medical therapy, complete physical examination, and laboratory examination.

After a 2-week wash-out period, participants who satisfied all the inclusion and exclusion criteria were randomly assigned to receive daily *Serenoa repens* extract 320 mg (160 mg BID soft capsule) provided from TAD Pharma GmbH or placebo 160 mg BID soft capsule. The double-blind treatment and follow-up phase lasted a total of 24 weeks. During the study period, α-adrenergic blockers, 5 α-reductase inhibitors, Chinese patent drug, and herbal medicine for BPH were forbidden. Study enrollment began in March 2014, and the study was completed in June 2016.

Study Participants

The study complied with the principles of the Declaration of Helsinki, and was approved by the institutional review board of all participating institutions. Patients were required to understand and sign the consent form and understand and fill in the questionnaires.

Inclusion Criteria. Married men between 50 and 70 years diagnosed with LUTS based on urological symptoms (urinary frequency, urinary urgency, dysuresia, and nocturia), clinically diagnosed with BPH and IPSS of 19 or lower were included in the study. The participants should have had stable relationships at least in the last 6 months. Moreover, participants on α-adrenergic blockers, 5 α-reductase inhibitors, Chinese patent drug, and herbal medicine for BPH willing to withdraw the drug for 2 weeks under the supervision of researchers were included in the study.

Exclusion Criteria. Patients were excluded if they were refractory to medical treatment, had BPH complications, an IPSS of 20-35, suspected or confirmed prostatic cancer, neurogenic bladder dysfunction, urethral stricture, congenital or anatomic abnormality of the genital organ, and a history of surgery or trauma that would affect the evaluation of the efficacy of the drug. Diabetes mellitus, severe cardiovascular disease, sexually transmitted disease, malignant tumor, peptic ulcer, hemorrhagic disease, mental diseases, acrasia, alcohol dependence, and drug abuse were also exclusion criteria. Patients on drugs affecting the bladder or sexual function, those with insufficiency of liver or kidney (aspartate transaminase or alanine transaminase more than 1.5 times the upper limit of normal, creatinine more than the upper limit of normal, and with clinical significance), and those with a history of allergic reactions to the study drug or similar drugs were not eligible to participate in the study. Patients who participated in other clinical trials in the past 3 months were excluded. In addition, anyone deemed unsuitable to participate in the study by the researchers were excluded.

Study Variables

Evaluation of the efficacy was based on the symptomatic and urodynamic improvements. The primary efficacy parameters were the changes in IPSS and peak urinary flow from baseline to those at each assessment. Secondary efficacy parameters included improvement of scores of storage and voiding symptoms, prostate volume, urinary frequency, and total prostate-specific antigen level. Other parameters assessed were QoL score,[7] MSF-4 score, a four−item male sexual function questionnaire,[8] and International Index of Erectile Function score[9] across the consecutive double-blind visits. Safety was assessed primarily based on adverse event profiles.

Statistical Analysis

Descriptive data are shown as numbers and percentages. Continuous data are reported as arithmetic mean ± SD analyses were carried out using modified intent-to-treat samples. Total cohort comparison of baseline characteristics was performed, and a subset analysis was carried out in which the patients were categorized by their baseline IPSS scores as low (IPSS of 1-7) and moderate (IPSS of 8-19). Statistical analysis was performed using Chi-square test for categorical variables and a 1-way analysis of variance for continuous variables. Since there were only a small number of patients with a IPSS of 1-7, for the purposes of analysis in this study, they were not included in further efficacy and safety analysis. Changes of outcome over time were assessed within groups as well as between the 2 groups using parametric (Student t test) or nonparametric (Mann-Whitney U) tests as appropriate. $P < .05$ was considered statistically significant. SPSS version 22.0 (IBM, New York, NY, USA) was used for the statistical analysis.

RESULTS

Patient Demographics

A total of 19 institutions participated in the study, and 354 patients were recruited, of which 325 met the criteria for inclusion in the intent-to-treat population (Supplementary Fig. 1). Twenty-six patients were lost to follow-up from the first visit, whereas 3 patients included in the placebo group violated the protocol.

Of the patients who were randomized in the 2 groups, 51.1% (166 of 325) were in the placebo group (12 patients with a baseline IPSS of 1-7 and 154 patients with a baseline IPSS of 8-19) and 48.9% (159 of 325) were in the *Serenoa repens* treatment group (9 patients with a baseline IPSS of 1-7 and 150 patients with a baseline IPSS of 8-19). Table 1 shows the characteristics of the study population at baseline.

Efficacy

Primary Efficacy Parameters. A significant improvement in peak urinary flow was found in the *Serenoa repens* treatment group (Fig. 1A). The peak urinary flow in the *Serenoa repens* treatment group increased after 2 weeks (12.44 ± 6.40 mL/s vs 11.34 ± 6.48 mL/s, $P = .0349$), and a statistically significant improvement in peak flow was first observed after 4 weeks when compared with that in the placebo group (1.19 ± 5.13 mL/s vs −0.49 ± 5.50 mL/s, $P = .0106$). After 24 weeks, the increase in the peak urinary flow in the *Serenoa repens* treatment group was higher than that in the placebo group (4.09 ± 7.55 mL/s vs 0.93 ± 7.46, $P = .0008$), and was 4.6-fold higher than that after 2 weeks (Table 2).

Changes in IPSS demonstrated that both groups had an obvious improvement in IPSS across the consecutive visits, and that the *Serenoa repens* has a rapid onset of action, as shown in Figure 1B. A statistically significant decrease of IPSS was first observed in the *Serenoa repens* treatment group after 2 weeks (1.83 ± 3.45 vs 0.94 ± 3.26, $P = .0211$), and then the changes in IPSS became relatively slowly. Additionally, the change in IPSS from baseline to end point (visit after 24 weeks) was statistically greater in the *Serenoa repens* treatment group (4.39 ± 4.38 vs. 1.62 ± 3.92, $P < .001$), which was 2.4-fold higher than that after 2 weeks (Table 2).

Secondary Efficacy Parameters. There was an overall trend for storage and voiding symptom scores to progressively improve across the consecutive double-blind visits (Fig. 1C and D); however, improvement was greater among the patients treated with the *Serenoa repens* over the entire double-blind treatment period. Larger changes in scores of storage symptoms and voiding symptoms were observed in the *Serenoa repens* treatment group after 24 weeks (1.82 ± 2.25 vs 0.58 ± 1.99, $P < .0001$; 1.99 ± 2.12 vs 0.65 ± 1.95, $P < .001$), which were 3.43-fold and 3.55-fold higher, respectively, than those after 2 weeks (Table 3). Change from baseline of post void residue was consistent with voiding symptoms score findings. At the end point, change in the

Table 1. Patient characteristics at baseline (intent-to-treat [ITT] analysis)

Variable	Placebo			*Serenoa repens*		
	IPSS 0-7 (n = 12)	IPSS 8-19 (n = 154)	Total (n = 166)	IPSS 0-7 (n = 9)	IPSS 8-19 (n = 150)	Total (n = 159)
Age (years, mean±s.d.)	60.17 ± 5.11	60.33 ± 6.03	60.32 ± 5.96	60.11 ± 5.06	61.55 ± 5.22	61.47 ± 5.20
Weight (kg, mean±s.d.)	69.21 ± 10.19	70.96 ± 12.51	70.84 ± 12.34	69.44 ± 7.51	70.14 ± 8.39	70.10 ± 8.32
Height (cm, mean±s.d.)	169.42 ± 4.25	169.99 ± 5.18	169.95 ± 5.11	169.22 ± 5.02	170.15 ± 4.93	170.09 ± 4.93
Comorbidity, n(%)						
Cardiac and cerebrovascular diseases (including hypertension)	2 (16.67)	16 (10.39)	18 (10.84)	1 (11.11)	16 (10.67)	17 (10.69)
Respiratory diseases	0 (0)	3 (1.95)	3 (1.81)	0 (0)	1 (0.67)	1 (0.63)
Digestive diseases	1 (8.33)	7 (4.55)	8 (4.82)	0 (0)	5 (3.33)	5 (3.14)
Other urologic diseases	2 (16.67)	7 (4.55)	9 (5.42)	2 (22.22)	6 (4.00)	8 (5.03)
Neurological diseases	0 (0)	1 (0.65)	1 (0.60)	0 (0)	0 (0)	0 (0)
Locomotor disorders	1 (8.33)	2 (1.30)	3 (1.81)	0 (0)	2 (1.33)	2 (1.26)
Others	0 (0)	2 (1.30)	2 (1.20)	0 (0)	2 (1.33)	2 (1.26)
Previous operation, n(%)	3 (25.00)	14 (9.09)	17 (10.24)	2 (22.22)	13 (8.67)	15 (9.43)
New BPH cases, n(%)	7 (58.33)	85 (57.05)	92 (57.14)	7 (100.00)	78 (52.70)	85 (54.84)
Previous medical therapy*, n(%)	3 (27.27)	26 (19.40)	29 (20.0)	0 (0)	32 (23.36)	32 (22.38)
Prostate volume (mL, mean±s.d.)	28.27 ± 15.29	37.70 ± 25.72	37.30 ± 25.40	28.39 ± 15.27	37.54 ± 19.84	37.01 ± 19.68
Post void residue (mL, mean±s.d.)	7.27 ± 10.81	23.60 ± 31.98	22.48 ± 31.25	12.22 ± 14.26	27.18 ± 33.26	26.28 ± 32.60
Peak urinary flow (mL/s, mean±s.d.)	14.84 ± 4.75	13.45 ± 7.02	13.55 ± 6.88	9.83 ± 3.13**	11.34 ± 6.48**	11.26 ± 6.36**
Urinary frequency (mean±s.d.)	1.33 ± 0.89	2.44 ± 0.98	2.36 ± 1.02	1.89 ± 1.17	2.45 ± 1.11	2.42 ± 1.12
IPSS total score (mean±s.d.)	5.58 ± 1.68	15.02 ± 3.36	14.34 ± 4.08	6.11 ± 0.93	14.91 ± 3.39	14.42 ± 3.88
Score of storage symptoms (mean±s.d.)	2.83 ± 1.27	6.53 ± 1.97	6.26 ± 2.15	3.22 ± 1.20	6.27 ± 2.11	6.10 ± 2.19
Score of voiding symptoms (mean±s.d.)	2.75 ± 1.48	8.49 ± 2.63	8.08 ± 2.96	2.89 ± 0.93	8.64 ± 2.51	8.31 ± 2.79
QoL (mean±s.d.)	2.50 ± 1.09	4.03 ± 1.00	3.92 ± 1.08	2.78 ± 1.09	4.01 ± 0.88	3.94 ± 0.94
MSF-4 (mean±s.d.)	8.75 ± 3.25	11.94 ± 3.60	11.70 ± 3.66	10.78 ± 4.21	12.09 ± 3.97	12.01 ± 3.98
IIEF (mean±s.d.)	45.08 ± 16.04	33.88 ± 15.35	34.69 ± 15.63	43.11 ± 21.55	31.39 ± 15.97	32.06 ± 16.47
t-PSA (ng/mL, mean±s.d.)	1.65 ± 2.28	2.18 ± 2.63	2.14 ± 2.60	2.27 ± 4.00	2.41 ± 4.97	2.41 ± 4.91
f-PSA (ng/mL, mean±s.d.)	0.44 ± 0.52	0.62 ± 0.60	0.61 ± 0.60	0.46 ± 0.68	0.60 ± 0.58	0.60 ± 0.58

BPH, benign prostatic hyperplasia; f/t PSA, ratio of free to total prostate-specific antigen; IIEF-5, International Index of Erectile Function 5 items; IPSS, International Prostate Symptom Score; MSF-4, Male Sexual Function 4 items; QoL, Quality of Life score; s.d., standard deviation; t-PSA, total prostate-specific antigen.
* With same missing data.
** Statistically significant, experimental group compared with the control group ($P < .05$).

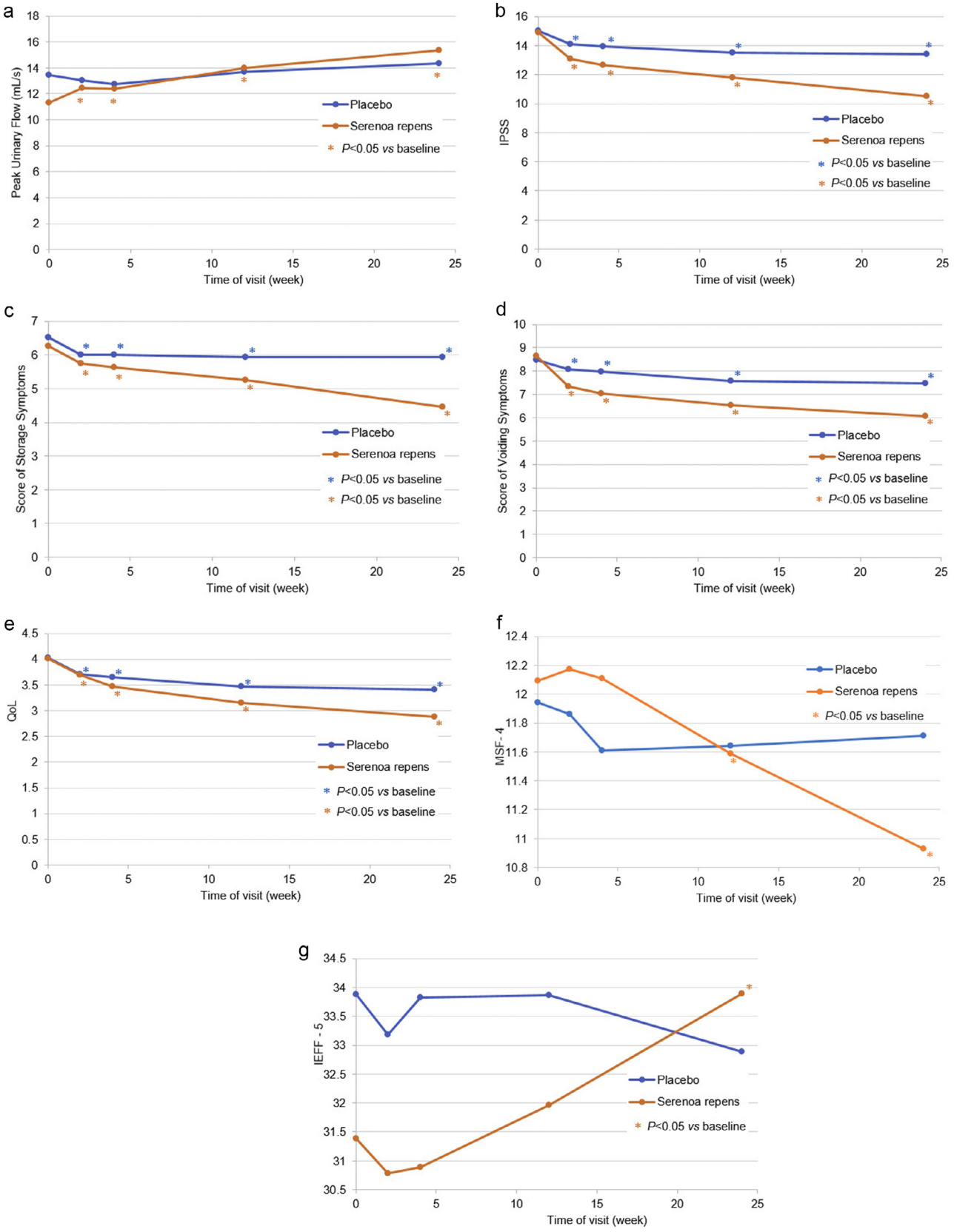

Figure 1. (**A**) Peak urinary flow from baseline by visit; (**B**) International Prostate Symptom Score (IPSS) from baseline by visit. (**C**) Score of storage symptom from baseline by visit; (**D**) Score of voiding symptom from baseline by visit; (**E**) Quality of life (QoL) score from baseline by visit; (**F**) Male Sexual Function 4 items (MSF-4) score from baseline by visit; (**G**) International Index of Erectile Function 5 (IIEF-5) score from baseline by visit. (Color version available online.)

Table 2. Variables changes in primary efficacy parameters after treatment for IPSS 8-19 patients (ITT analysis)

	Placebo (n = 154)	*Serenoa repens* (n = 150)	*P* value
Δ Peak urinary flow			
V1-V0 (mL/s, mean±s.d.)	−0.14 ± 5.53	0.89 ± 4.91	.1046
V2-V0 (mL/s, mean±s.d.)	−0.49 ± 5.50	1.19 ± 5.13	.0106
V3-V0 (mL/s, mean±s.d.)	0.35 ± 6.00	2.77 ± 6.64	.0026
V4-V0 (mL/s, mean±s.d.)	0.93 ± 7.46	4.09 ± 7.55	.0008
ΔIPSS total score			
V0-V1 (mean±s.d.)	0.94 ± 3.26	1.83 ± 3.45	.0211
V0-V2 (mean±s.d.)	1.06 ± 3.58	2.25 ± 3.71	.0048
V0-V3 (mean±s.d.)	1.51 ± 3.57	3.13 ± 4.24	.0003
V0-V4 (mean±s.d.)	1.62 ± 3.92	4.39 ± 4.38	<.0001

IPSS, International Prostate Symptom Score; s.d., standard deviation; V0, initial screening time; V1, visit after 2 weeks; V2, visit after 4 weeks; V3, visit after 12 weeks; V4, visit after 24 weeks.

Serenoa repens treatment group was significantly greater than that observed in the placebo group (11.90 ± 36.81 mL vs −1.74 ± 37.17 mL, $P = .0019$, Table 3). Nevertheless, there was no obvious improvement in prostate volume, urinary frequency, and total prostate-specific antigen level compared with the baseline, and no difference in changes in these parameters was seen between the 2 groups.

Quality of Life. There was a positive change in QoL score among patients in both groups (Fig. 1E). However, the patients treated with the *Serenoa repens* had lower QoL score than those treated with placebo after 12 weeks (3.15 ± 1.11 vs 3.47 ± 1.19, $P = .0231$). Additionally, change in QoL score after 24 weeks were significantly greater in the *Serenoa repens* treatment group (1.11 ± 1.27 vs 0.64 ± 0.99, $P = .0010$).

Table 3. Variables changes in secondary efficacy parameters after treatment for IPSS 8-19 patients (ITT analysis)

	Placebo (n = 154)	*Serenoa repens* (n = 150)	*P* value
Prostate volume			
V0-V4 (mL, mean±s.d.)	0.31 ± 11.40	0.77 ± 9.38	.7453
Post void residue			
V0-V4 (mL, mean±s.d.)	−1.74 ± 37.17	11.90 ± 36.81	.0019
Urinary frequency			
V0-V1 (mean±s.d.)	−0.17 ± 0.72	0	.4973
V0-V2 (mean±s.d.)	0.08 ± 0.79	−0.22 ± 0.67	.3623
V0-V3 (mean±s.d.)	0.08 ± 1.00	−0.22 ± 0.67	.4370
V0-V4 (mean±s.d.)	0 ± 0.85	0.11 ± 0.33	.7167
Score of storage symptoms			
V0-V1 (mean±s.d.)	0.51 ± 1.76	0.53 ± 1.96	.9242
V0-V2 (mean±s.d.)	0.53 ± 1.90	0.65 ± 2.02	.5719
V0-V3 (mean±s.d.)	0.59 ± 1.99	1.03 ± 2.26	.0737
V0-V4 (mean±s.d.)	0.58 ± 1.99	1.82 ± 2.25	<.0001
Score of voiding symptoms			
V0-V1 (mean±s.d.)	0.50 ± 1.68	0.56 ± 1.80	.7493
V0-V2 (mean±s.d.)	0.58 ± 1.85	0.72 ± 1.87	.5170
V0-V3 (mean±s.d.)	0.66 ± 1.92	1.10 ± 2.19	.0821
V0-V4 (mean±s.d.)	0.65 ± 1.95	1.99 ± 2.12	<.001
QoL			
V0-V1 (mean±s.d.)	0.32 ± 0.71	0.31 ± 0.84	.8993
V0-V2 (mean±s.d.)	0.40 ± 0.81	0.57 ± 0.92	.0948
V0-V3 (mean±s.d.)	0.59 ± 0.94	0.84 ± 1.09	.0403
V0-V4 (mean±s.d.)	0.64 ± 0.99	1.11 ± 1.27	.0010
MSF-4			
V0-V1 (mean±s.d.)	0.07 ± 1.84	−0.09 ± 1.86	.4561
V0-V2 (mean±s.d.)	0.32 ± 2.25	−0.02 ± 2.30	.1881
V0-V3 (mean±s.d.)	0.30 ± 2.74	0.49 ± 3.03	.5574
V0-V4 (mean±s.d.)	0.23 ± 2.69	1.15 ± 3.47	.0096
IIEF			
V0-V1 (mean±s.d.)	0.73 ± 7.00	0.61 ± 5.01	.8656
V0-V2 (mean±s.d.)	0.18 ± 8.08	0.25 ± 8.11	.9378
V0-V3 (mean±s.d.)	−0.10 ± 8.52	−0.67 ± 8.83	.5836
V0-V4 (mean±s.d.)	0.88 ± 9.72	−2.61 ± 11.22	.0068
t-PSA			
V0-V4 (ng/mL, mean±s.d.)	0.01 ± 2.29	−0.24 ± 1.36	.2890

IIEF-5, International Index of Erectile Function 5 items; MSF-4, Male Sexual Function 4 items; QoL, Quality of Life score; s.d., standard deviation; t-PSA, total prostate-specific antigen; V0, initial screening time; V1, visit after 2 weeks; V2, visit after 4 weeks; V3, visit after 12 weeks; V4, visit after 24 weeks. *, Statistically significant, experimental group compared with the control group ($P < .05$).

Male Sexual and Erectile Function. The male sexual function and erectile function improved significantly after 12 weeks (11.59 ± 4.03 vs 12.09 ± 3.97, $P = .0479$) and 24 weeks (33.89 ± 17.13 vs 31.39 ± 15.97, $P = .0086$), respectively, among patients in the *Serenoa repens* treatment group, but no significant improvement was found among those in the placebo group (Fig. 1F and G). Besides, the *Serenoa repens* treated patients had a statistically greater improvement after 24 weeks for MSF-4 score and International Index of Erectile Function score (1.15 ± 3.47 vs 0.23 ± 2.69, $P = .0096$; 2.61 ± 11.22 vs −0.88 ± 9.72, $P = .0068$, respectively).

Safety

Overall, 2 (1.18%) of 169 patients in the placebo group and 3 (1.89%) of 159 patients in the *Serenoa repens* treatment group experienced 1 or more adverse events. No one experienced serious adverse events, and no deaths occurred during the study.

One patient in the placebo group experienced mild somnolence, constipation, inhibited sexual desire, and erectile dysfunction. Another patient caught a cold. Two patients in the *Serenoa repens* treatment group experienced mild stomach discomfort and poor appetite during the double-blind treatment period. Besides, 1 *Serenoa repens* treated patient experienced a mild cough, which might be not related to the treatment.

DISCUSSION

This 24-week, randomized, double-blind, direct comparative study evaluated the efficacy and safety of *Serenoa repens* in a large cohort of patients with LUTS/BPH. The results show that the *Serenoa repens*, with no initial dose titration, significantly improved symptoms of storage and voiding and QoL, and this was consistent with The Quality of Life in Benign Prostatic Hyperplasia (QUALIPROST) study.[10]

Nevertheless, earlier studies have suggested that the extract of *Serenoa repens* appears to be no more effective than placebo.[11,12] It is important to note that the general conclusions about the *Serenoa repens* can mask the fact that the extracts produced by different companies do not necessarily have the same biological or clinical effects, and that the latter appears to be dependent on the extraction procedure. Thus, the results obtained by using 1 brand cannot be extrapolated to another. Several meta-analyses suggest that the *Serenoa repens* was not superior to finasteride or tamsulosin for IPSS.[13,14] Recently, short-term studies have pointed out that the combination of *Serenoa repens* with tamsulosin was shown to be more effective than tamsulosin monotherapy in reducing storage symptoms.[15,16]

It is commonly believed that hormonal alterations, metabolic syndrome, inflammation, and tissue remodeling in the aging prostate contribute to the development of BPH.[17] The inflammatory pattern in BPH is based on the cytokine secretion from the inflammatory cell, and hypoxia due to the increased oxygen demand by cell proliferation. The stimuli lead to tissue damage, inflammatory response, and the chronic process of wound healing, resulting in prostate enlargement.[18] In a mouse model of prostate hyperplasia, *Serenoa repens* exerted potent anti-inflammatory properties on the whole prostate, while antiandrogenic effects were lobe-specific, which was confirmed by the global down-regulation of prostate proinflammatory cytokine profile, with significant reduction of CCR7, CXCL6, IL-6, and IL-17 expression.[19]

Although no improvement was found in prostate volume and urinary frequency, the symptoms of storage and voiding, the QoL, and especially the peak urinary flow, which is worse in the *Serenoa repens* treatment group, actually improved significantly, which validated that the *Serenoa repens* has α1-adrenoceptor-inhibitory properties.[20] Some reviews suggest that the monotherapy of *Serenoa repens*, with the quality varied across different *Serenoa repens* extracts, might not be superior to placebo in treating LUTS/BPH.[21,22] However, a recent published systemic review and meta-analysis showed that another specific commercial drug of *Serenoa repens* (Permixon Pierre Fabre Médicament, Castres, France) improved peak urinary flow compared with placebo and had a similar efficacy to tamsulosin and short-term 5-ARI in relieving LUTS.[23] In our study, although the IPSS, including scores of storage symptoms and voiding symptoms, and QoL also improved in the placebo group, the placebo effect was quite weak thus the improvements were not greater than those in the *Serenoa repens* treatment group and the objective parameter—peak urinary flow did not improve in the placebo group. According to an earlier publication, tamsulosin, the most frequently prescribed α-adrenergic blocker, improved the peak urinary flow at 5-7 weeks after the first dose, and then reached a plateau.[24] It is interesting to note that things are different for *Serenoa repens*, as the improvement tend to be bigger over time. It was our hypothesis that the combination of the rapid onset of α1-adrenoceptor-inhibitory properties and the chronic anti-inflammatory activity would contribute to this continuous improvement process. Further studies are needed to validate the mechanism of action.

Overall, the treatment with *Serenoa repens* was well-tolerated. Few treatment-emergent adverse events occurred during the study, which were contradictory to those with the standard medications for the treatment of LUTS/BPH, including alpha-adrenergic blockers and 5 α-reductase inhibitors, as they were associated with a negative effect on sexual function.[25] In our study, treatment with the *Serenoa repens* for 6 months significantly improved male sexual and erectile function, which was in line with the IDIProst Gold Study.[26] Yang et al found that the *Serenoa repens* relaxed corpora cavernosa and thus increased the penile response to stimulation in rat and rabbit models, which may result from higher cyclic guanosine monophosphate levels produced by increasing messenger ribonucleic acid expression for inducible nitric oxide synthase, as well as by suppressing phosphodiesterase-5 activity in the smooth muscles of the corpus cavernosum.[27] Another hypothesis is that the improvement in sexual function would result from improvement in the urinary function itself, since LUTS was also demonstrated to

be an independent risk factor for erectile dysfunction in previous published studies.[28]

However, the present study had some limitations. Patients with IPSS over 19 were not recruited in this study. Further studies are needed to evaluate the efficacy of the *Serenoa repens* among patients with severe symptoms and to assess whether it can delay the surgical intervention. The relatively short follow-up period could also be considered a limitation when studying a chronic disease. Nevertheless, the duration of the study was consistent with the QUALIPROST study,[10] and some studies used even shorter duration.[29,30]

Despite the limitations, we believe that this study has significant clinical implications. To the best of our knowledge, this is the first large-scale population-based prospective, randomized, double-blind study in China, to evaluate the efficacy of phytotherapy not only on urinary symptoms and QoL, but also on male sexual and erectile function. Since α-adrenergic blockers or 5 α-reductase inhibitors have more side effects, such as sexual and erectile dysfunction, hypotension (only in α-adrenergic blocker), and alteration of the prostate-specific antigen level (only in 5 α-reductase inhibitors), treatment with *Serenoa repens* might provide a better treatment option with a favorable benefit-to-risk ratio.

In conclusion, the *Serenoa repens* extract was effective, safe, well-tolerated, and clinically and statistically superior to placebo in the target LUTS/BPH population, resulting in improved LUTS, QoL, and male sexual and erectile function over the time with few side effects.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.02.030.

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