J Chin Med Assoc

ORIGINAL ARTICLE

Efficacy evaluation of Chinese herbal medicine, VGH-BPH1, for patients with benign prostatic hyperplasia: A randomized, double-blind, placebo-controlled, and crossover study

Diem Ngoc Hong Tran[a], Hsin-Fu Yeh[a,b], William J. Huang[c,d], Pei-Wen Wu[e], Ying-Ju Liao[a], Shinn-Jang Hwang[d,f], Yen-Ying Kung[a,g], Jen-Lin Yang[d,g], Ta-Peng Wu[g], Chung-Hua Hsu[a,h,*], Fang-Pey Chen[a,g,*]

[a]Institute of Traditional Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [b]Department of Family Medicine, St. Martin De Porres Hospital, Chiayi, Taiwan, ROC; [c]Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [e]Tian-Yun Chinese Medicine Clinic, Taoyuan, Taiwan, ROC; [f]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [g]Center for Traditional Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [h]Division of Chinese Internal Medicine, Linsen Chinese Medicine and Kunming Branch, Taipei City Hospital, Taipei, Taiwan, ROC

Abstract

Background: Benign prostatic hyperplasia (BPH) can affect quality of life and cause various complications. Previous studies have suggested that Chinese herbal medicine can alleviate symptoms in patients with BPH. This study aimed to investigate whether the Chinese herbal medicine prescription VGH-BPH1 can alleviate BPH symptoms when used as an add-on treatment.

Methods: In this crossover, randomized, double-blind, placebo-controlled trial, patients with BPH were randomly segregated into two groups: group A received VGH-BPH1, and group B received a placebo for 8 weeks. Subsequently, after a 2-week wash-out period, the two groups were switched to the opposite treatment for another 8 weeks. The International Prostate Symptoms Score and Aging Male Symptoms Score were adopted as the primary outcomes to assess improvement in BPH and patient quality of life. The secondary outcomes were the International Index of Erectile Function, Constitution Chinese Medicine Questionnaire, uroflowmetry results, and postvoid residual urine volume.

Results: VGH-BPH1 treatment significantly decreased the International Prostate Symptoms Score total score ($p = 0.027$); however, no significant difference was observed between the treatment and placebo groups. The Aging Male Symptoms Score "joint pain and muscular ache" score in the VGH-BPH1 group was significantly lower than that of the placebo group ($p = 0.022$). The "physical exhaustion" score also exhibited a decreasing trend when both groups were compared ($p = 0.057$).

Conclusion: Although VGH-BPH1 treatment did not outperform the placebo in terms of improving BPH symptoms, it resulted in improvement in several quality of life indicators when relative to the placebo. Future research using a larger sample size with appropriate amendments to the protocol should be conducted to further investigate the effects of VGH-BPH1.

Keywords: Benign prostatic hyperplasia; Chinese herbal medicine; Crossover, Double-blind; Placebo-controlled; Randomized trial

1. INTRODUCTION

Benign prostate hyperplasia (BPH) is a disease in which the prostate gland increases in size non-malignantly. BPH is common in adult men. Specifically, men >50 years of age have a 40% chance of developing BPH; men >80 years of age have an incidence rate of >90%.[1] BPH can cause lower urinary tract symptoms (LUTS), which can be classified into voiding symptoms and storage symptoms.[2] Voiding symptoms include hesitancy, intermittency, weak stream, terminal dribbling, and urinary retention, whereas storage symptoms include high urinary frequency, urgency, and nocturia. In addition, BPH affects patient quality of life[3] and can lead to several complications, such as a thick bladder wall and the presence of kidney stones.[4]

Treatments include lifestyle modification; pharmacotherapy, involving, for example, 5-alpha reductase inhibitors and alpha-adrenergic blockers; dietary supplements; and surgery. However, studies have reported that conventional medications may cause a loss of libido, erectile dysfunction, and other side effects[5,6]; therefore, patients with BPH tend to seek out alternative treatments. Several in vitro and in vivo studies have indicated that Chinese herbal medicine (CHM) potentially alleviates LUTS in patients with BPH.[7–9] A meta-analysis suggested that CHM improves the quality of life and prostate volume of patients relative to Western

Address correspondence. Dr. Fang-Pey Chen, Institute of Traditional Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: fpchen@vghtpe.gov.tw (F.-P. Chen); Dr. Chung-Hua Hsu, Division of Chinese Internal Medicine, Linsen Chinese Medicine and Kunming Branch, Taipei City Hospital, 100, Kunming Street, Taipei 108, Taiwan, ROC. E-mail address: owlherbs@yahoo.com.tw (C.-H. Hsu).

Conflicts of interest: Dr. William J. Huang and Dr. Shin-Jang Hwang, editorial board members at Journal of the Chinese Medical Association, have no roles in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 639-646.

Received August 5, 2021; accepted November 3, 2021.

doi: 10.1097/JCMA.0000000000000717.

medicine; however, the number of clinical studies analyzed was small and the quality of their methodology was low.[10]

From a traditional Chinese medicine (TCM) perspective, one syndrome can appear in various diseases, and, by way of contrast, one disease can have different TCM syndromes. Through the process of "syndrome differentiation," TCM physicians choose specific herbs and herbal formulae for treatment. However, because each formula and single herb has various effects and targets, TCM physicians usually prescribe several formulae and single herbs together to increase the efficacy of treatment for different patients or different conditions in each patient. For that reason, we conducted a retrospective study using Taiwan's National Health Insurance Research Database (NHIRD) to determine what formulae and herbs were most commonly used to treat BPH. The results revealed that Taiwan's top three most commonly prescribed formulae for BPH were *Ji-Sheng-Shen-Qi-Wan* (14.9%), *Ba-Wei-Di-Huang-Wan* (6.5%), and *Sang-Piao-Xiao-San* (4.0%); whereas *Fu-Pen-Zi* (4.1%) was the most frequent single herb used for BPH, followed by *Yi-Zhi-Ren* (3.8%), *Che-Qian-Zi* (3.6%), *Wu-Yao* (2.4%), *Tao-Ren* (2.2%), *Du-Zhong* (2.1%), *Huang-Qi* (1.9%), and *Huang-Bo* (1.9%). After the plan of the proposed study was discussed with several highly experienced TCM physicians and after a literature review, specific dosages of two formulae and seven single herbs were chosen to form a prescription for BPH. The prescription was named VGH-BPH0 and comprised *Ji-Sheng-Shen-Qi-Wan* (濟生腎氣丸) 2.5 g, *Sang-Piao-Xiao-San* (桑螵蛸散) 1.0 g, *Wu-Yao* (烏藥) 0.3 g, *Yi-Zhi-Ren* (益智仁) 0.3 g, *Dan-Shen* (丹參) 0.3 g, *Yin-Yang-Huo* (淫羊藿) 0.3 g, *Fu-Pen-Zi* (覆盆子) 0.1 g, *Zhi-Mu* (知母) 0.1 g, and *Huang-Bo* (黃柏) 0.1 g.

The herbs and formulae used in this prescription all have documented effects. Several studies have demonstrated that *Ji-Sheng-Shen-Qi-Wan* attenuates symptoms related to BPH and LUTS.[11,12] *Sang-Piao-Xiao-San* was reported to exert beneficial effects in patients with LUTS.[13] *Wu-Yao* and *Yi-Zhi-Ren* are the main components of *Suo-Quan-Wan,* which was demonstrated to improve bladder function in rats.[14] The herb *Fu-Pen-Zi* is frequently prescribed as a tonic for the treatment of kidney deficiency, enuresis, impotence, spermatorrhea, among other diseases. *Fu-Pen-Zi* was reported to have antioxidant properties[15] and anti-inflammatory effects.[16] According to TCM theory, "long-term illness involves blood stasis"; therefore, experienced TCM physicians believe that a prescription should include herbs for promoting blood circulation and removing blood stasis. Ancient Chinese medicine texts have recommended *Dan-Shen* as a principal blood-activating drug; thus, it was selected as one of the single herbs in this prescription. Many studies have been conducted on *Dan-Shen*, including a component analysis of the herb,[17] a study of its anticardiovascular disease activity,[18] a study of its anti-inflammatory activity, and an investigation of its antioxidant mechanisms.[19] Furthermore, an observational study from multiple countries in Asia demonstrated that as many as 80% of Asian men suffering from BPH accompanied by LUTS exhibited differing degrees of sexual dysfunction.[20] In TCM, *Yin-Yang-Huo* is the preferred herb for male sexual dysfunction. In agreement with this, a research report has indicated that *Yin-Yang-Huo* extract is able to improve erectile function in mice.[21] Last but not least, a prescription called *Zi-Shen-Wan* (滋腎丸), which includes *Huang-Bo*, *Zhi-Mu*, and *Rou-Gui*, has been used to treat difficulty in urination. A modern study has shown that this formula is able to decrease prostate volume in a BPH rat model.[22]

A pilot study investigating the effect of VGH-BPH0 was performed in 2018.[23] A total of 20 patients with BPH was recruited, and 19 of them finished the study. The participants took VGH-BPH0 for 8 weeks. The results revealed that VGH-BPH0 improved voiding symptoms. Furthermore, posttreatment total International Prostate Symptoms Score (IPSS) and IPSS voiding subscore significantly decreased relative to their baseline values. Postvoiding residual urine exhibited a descending trend at $p = 0.07$.

The present study tweaked the VGH-BPH0 formula to produce the VGH-BPH1 formula. Specifically, we changed the dosages of *Zhi-Mu* and *Huang-Bo* slightly from 0.1 to 0.25 g in the expectation that this would help patients urinate more easily. After tweaking the formula, we performed a crossover, randomized, double-blind, placebo-controlled trial to investigate whether VGH-BPH1 can improve the symptoms of BPH. We hypothesized that VGH-BPH1 would decrease LUTS in patients with BPH, improve patient quality of life, and ameliorate patients' uroflowmetry indices.

2. METHODS

2.1. Participants

Patients with BPH were recruited from the outpatient clinic of the Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan. The inclusion criteria for participants consisted of the following: (1) male patients who have been diagnosed as having BPH by a urologist and had been treated with a conventional first-line Western medicine for more than 3 months, (2) patients who had moderate to severe BPH (IPSS > 12 points), and (3) participants who gave their consent to participate.

A prospective participant was excluded if they met any one of the following exclusion criteria: (1) use during the study of any other CHMs or alternative medicines (including drugs and acupuncture) for more than 1 month; (2) the presence of syphilis, gonorrhea, or any other sexually transmitted disease or urinary tract infection; (3) a prior history of urinary tract stones, prostate cancer, bladder cancer, or acute/chronic renal failure; (4) congenital abnormalities, such as bladder neck fibrosis, interstitial cystitis, or urethral stricture; (5) a history of genital trauma or surgery that affected the muscle or nervous system; (6) upper urinary tract obstruction, renal edema, and similar conditions that affected renal function; and (7) the inability to sign a consent form or communicate with the researchers.

2.2. Study design

This trial was a randomized, double-blind, placebo-controlled, crossover study conducted from January 2019 to December 2019 at Taipei Veterans General Hospital, Taipei, Taiwan. The protocol was approved by the Institutional Review Board of the hospital and registered at ClincalTrials.gov (NCT03829904).

The participants were randomly segregated into groups A and B. The first period of the study lasted 8 weeks, during which group A took VGH-BPH1 daily, whereas group B took a placebo. After 8 weeks, the treatment was stopped for 2 weeks. Thereafter, group A was changed to the placebo group, whereas group B was changed to the VGH-BPH1 group, and the two groups received their respective treatments for another 8 weeks. Participants were instructed to maintain their Western-medicine treatment during the study period. All patients gave their written informed consent and were free to withdraw from the study at any time.

2.3. Randomization and blinding

An independent biostatistician created a random allocation list by using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA.) through block randomization with a block size of four. Subsequently, the list was sealed in an envelope and sent to the pharmaceutical company for the preparation of VGH-BPH1 and the placebo. Both the participants and investigators were blinded to the randomization until the study was completed.

2.4. Sample size

The number of participants needed in this crossover study was estimated by using a quantitative measurement: we set a significance level of 0.05%, used a two-tailed test, set the power to 0.8, and calculated the difference of the standard deviation before versus after treatment for the same patient. If the sample size was set to identify improvement before and after treatment by 50%, it was estimated that this study's sample size needed to be at least 34 persons. Anticipating a dropout rate of at most 20%, the sample size was estimated to need to be 40 participants.

2.5. Preparation of VGH-BPH1 and the placebo

The experimental prescription and placebo were prepared by Ko Da Pharmaceutical Co, Ltd (Taoyuan, Taiwan). The experimental group's VGH-BPH1 components (Table 1) were mixed and formed into 5.3 g of concentrated granules. The control group's placebo comprised cornstarch, caramel coloring, and 1 of 100 of the VGH-BHP1 mixture; the VGH-BHP1 mixture was added to maintain the CHM taste. The same excipient (corn starch) and caramel were used for granulation for both groups, and the excipients were appropriately tinted to make the test drug and placebo have the same appearance, color, aroma, and taste; this was done to ensure the double-blind nature of the study. The participants were asked to consume one package (5.3 g) of the placebo or drug after a meal, three times a day for 8 weeks during each of the two stages of the study. The packages were provided to the participants by a research assistant who was blinded to the contents of the packages.

2.6. Outcome measurements

The IPSS and Aging Male Symptoms Score (AMS) were assessed at baseline and at 8, 10, and 18 weeks and were used as the primary outcomes. The IPSS was used to identify improvement in LUTS, and it consisted of seven questions with scores ranging from 0 to 5, which had meanings from "not at all" to "almost always" in increasing numerical order. The AMS scale was used to measure the participants' quality of life. This questionnaire comprises 17 items that examine general well-being, sleep problems, mental illness (anxiety, depressive mood).

The secondary outcomes comprised the international index of erectile function (IIEF), Constitution in Chinese Medicine Questionnaire (CCMQ), uroflowmetry results, and postvoid residual urine volume. They were assessed at baseline and at weeks 8, 10, and 18. The IIEF is a 5-item questionnaire that is used to evaluate male sexual function. The CCMQ comprises 60 items that categorize patients into nine types of TCM body constitution. These are gentleness (平和質), Blood stasis (血瘀質), Yang deficiency (陽虛質), Yin deficiency (陰虛質), Qi deficiency (氣虛質), Phlegm Dampness (痰濕質), Dampness Heat (濕熱質), Qi depression (氣鬱質), and special diathesis (特稟質). Uroflowmetry evaluates the function of a patient's bladder and urethra during urination and allows for an assessment of the contraction function of the patient's bladder detrusor and for a determination of whether stenosis or obstruction is present in the bladder neck or urethra outlet. Postvoid residual urine volume was determined as the amount of urine left in the bladder after urination in an ultrasound image; this was conducted before and after treatment.

2.7. Statistical analysis

All the data were analyzed using STATA (version 15, StataCorp, Texas, USA). An intention-to-treat analysis was adopted to decrease noncompliance bias. Missing data were handled by the last observation carried forward approach. The carry-over effect in this crossover study was measured by the sum of the IPSS total score after each stage and tested by the independent *t*-test; the results were nonsignificant ($p = 0.378$). Therefore, the final results were evaluated as two-sequence pooled data. The

Table 1

Components of VGH-BPH1 prescription used

Formulae/single herbs	Formulae/single herbs	Scientific name	Dose (g)	
Ji-Sheng-Shen-Qi-Wan	*Shu-Di-Huang* (Rehmanniae radix preparata)	*Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. & C.A. Mey., Scrophulariacae	0.58	2.5
	Fu-Ling (Poria)	*Poria cocos* (Schw.) Wolf., Polyporaceae	0.44	
	Shan-Yao (Dioscoreae Rhizoma)	*Dioscorea persimilis* Prain & Burkill, Dioscoreaceae	0.30	
	Shan-Zhu-Yu (Corni Fructus)	*Cornus officinalis* Siebold & Zucc., Cornaceae	0.30	
	Mu-Dan-Pi (Moutan Cortex)	*Paeonia suffruticosa* Andrews, Paeoniaceae	0.22	
	Ze-Xie (Alismatis Rhizoma)	*Alisma plantago aquatica L.*, Alismaceae	0.22	
	Niu-Xi (Achyranthis Bidentatae Radix)	*Achyranthes bidentata* Blume, Amaranthaceae	0.15	
	Che-Qian-Zi (Plantaginis Semen)	*Plantago major* L., Plantaginaceae	0.15	
	Fu-Zi (Aconiti Radix lateralis praeparata)	*Aconitum carmichaelii* Debeaux, Ranunculaceae	0.07	
	Rou-Gui (Cinnamomi Cortex)	*Cinnamomum cassia* (L.) J.Presl, Lauraceae	0.07	
Sang-Piao-Xiao-San	*Sang-Piao-Xiao* (Ootheca Mantidis)	Ootheca Mantidis	0.125	1.0
	Long-Gu (Os Dracois)	Fossilia Ossis Mastodi	0.125	
	Gui-Ban (Plastrum Testudinis)	Clemmys chinensis Tortoise, Testudinidae	0.125	
	Ren-Shen (Ginseng Radix)	*Panax ginseng* C.A.Mey., Araliaceae	0.125	
	Dang-Gui (Angelicae Sinensis Radix)	*Angelica sinensis* (Oliv.) Diels, Apiaceae	0.125	
	Yuan-Zhi (Polygalae Radix)	*Polygala tenuifolia* Willd., Polygalaceae	0.125	
	Shi-Chang-Pu (Acori Tatarinowii Rhizoma)	*Acorus gramineus* Soland, Acoraceae	0.125	
	Fu-Shen (Scierotium Pararadicis Poriae Cocos)	*Poria cocos* (Schw.) Wolf., Polyporaceae	0.125	
Wu-Yao	Linderae Radix	*Lindera myrrha* (Lour.) Merr., Lauraceae	0.3	
Yi-Zhi-Ren	Alpiniae Oxyphyllae Fructus	*Alpinia oxyphylla* Miq., Zingiberaceae	0.3	
Dan-Shen	Salviae Miltiorrhizae Radix	Salvia miltiorrhiza Bunge, Lamiaceae	0.3	
Yin-Yang-Huo	Epimedii Herba	*Epimedium brevicornum* Maxim, Berberidaceae	0.3	
Fu-Pen-Zi	Rubi Fructus	*Rubus chingii* Hu, Rosaceae	0.1	
Huang-Bo	Phellodendri Cortex	*Phellodendron chinense* C.K.Schneid., Rutaceae	0.25	
Zhi-Mu	Anemarrhenae Rhizoma	*Anemarrhena asphodeloides* Bunge, Asparagaceae	0.25	

independent *t*-test or the Mann-Whitney *U* test was employed to examine differences between the groups. The paired *t*-test or the Wilcoxon sign-rank test was utilized to examine differences between participants within groups. Changes in body constitution were analyzed by McNemar's test. Statistical significance was indicated if $p < 0.05$.

3. RESULTS

3.1. Study flow and demographics

In total, 23 participants were recruited and signed informed consent forms between January 2019 and August 2019. The recruitment ceased in August because the expiration date of VGH-BPH1 and the placebo were on January 2020. Among these participants, 11 and 12 were assigned to groups A and B, respectively. During stage 1, five patients left the study for various reasons including going abroad, taking too many medications, having gastric flux, and having skin problems. Therefore 18 participants completed this study (Fig. 1). Based on the study design and use of intention-to-treat analysis, all collected data from 23 participants were analyzed in the report.

The characteristics of all the participants at baseline are presented in Table 2. The mean age for group A was 67.4 years (VGH-BPH1 as the first procedure), and the mean age for group B was 69.2 years (placebo as the first procedure). In terms of the CCMQ, 22 participants (95.65%) could be classified as having at least one body constitution type. Among them, 43.48% were classified as being of the gentleness type. In total, 21.74% of participants were classified as having more than one body constitution type. No significant differences were observed in the demographic characteristics or primary and secondary outcome measures at baseline between these two groups.

3.2. Primary outcome measures

The IPSS total score and score of each item did not significantly differ between the VGH-BPH1 group and the placebo group. In the placebo group, the symptoms of "incomplete emptying,"

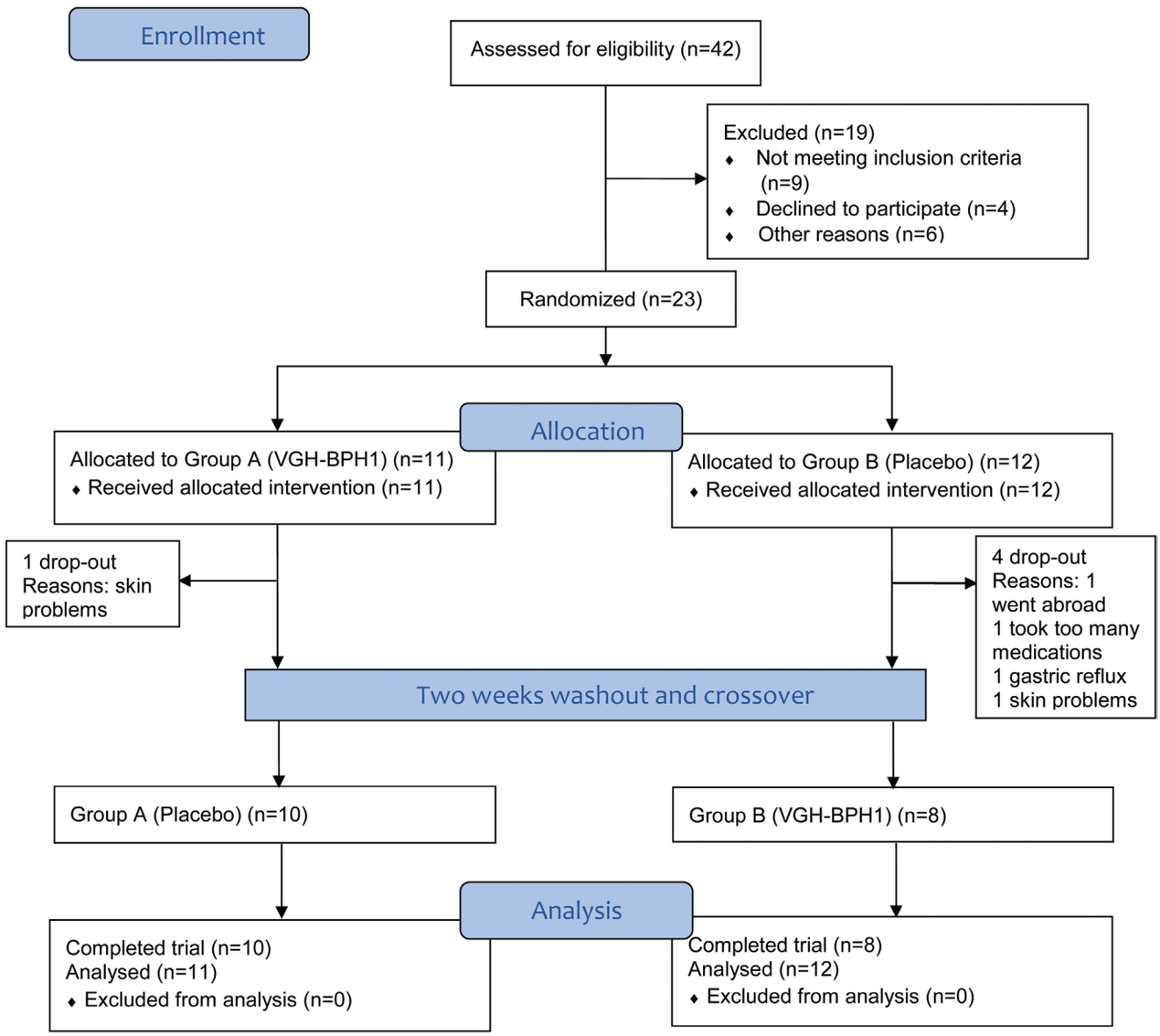

Fig. 1 Study flow chart.

Table 2

Demographic characteristics of participants

Characteristics		Group A (n = 11) Mean (SD)	Group B (n = 12) Mean (SD)
Age, y		67.36 (7.51)	69.17 (7.33)
IPSS total baseline		19.73 (3.90)	22.75 (5.36)
AMS total score baseline		39.73 (9.23)	37.33 (8.87)
IIEF total score baseline*		14.56 (4.39)	14.0 (4.78)
Q max baseline (mL/s)		14.14 (7.56)	15.06 (9.09)
PVR baseline (mL)		65.91 (136.81)	45.67 (38.74)
CCMQ	Gentleness constitution	5	5
	Yang deficiency	1	1
	Yin deficiency	3	1
	Qi deficiency	4	4
	Phlegm dampness	2	3
	Dampness heat	1	1
	Blood stasis	0	1
	Special diathesis constitution	2	2
	Qi depression	1	1
	No	0	1

*Group A (n = 9); group B (n = 8).
AMS = Aging Male Symptoms Score; CMCQ = Constitution in Chinese Medicine Questionnaire; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptoms Score; PVR = postvoid residual urine volume.

"intermittency," and "nocturia" were significantly decreased after 8 weeks ($p = 0.0002$, $p = 0.031$, and $p = 0.042$, respectively), whereas the "frequency" symptom was significantly decreased in VGH-BPH1 group ($p = 0.03$). In addition, the "nocturia" symptom of the VGH-BPH1 group could be seem to have a descending trend (from 2.26 ± 0.96 to 2.04 ± 0.97; $p = 0.057$). The baseline and posttreatment IPSS total scores significantly differed in the VGH-BPH1 and placebo groups. The VGH-BPH1 group showed a significant difference in the IPSS storage symptoms subscore (frequency, urgency, and nocturia) between baseline and posttreatment. By contrast, the posttreatment voiding symptoms subscore (incomplete emptying, intermittency, weak stream, and straining) was lower than the baseline in the placebo group. However, no significant change in subscores between the two groups was observed (Table 3).

In terms of the AMS score, VGH-BPH1 exerted a significantly greater effect in ameliorating the "joint pain and muscular ache" symptom relative to the placebo ($p = 0.022$). The symptom of "physical exhaustion" improved over time in the VGH-BPH1 group from 1.87 ± 0.69 to 1.56 ± 0.59 ($p = 0.005$), and the posttreatment score for this symptom had a borderline significant difference between the two groups ($p = 0.057$). In the placebo group, the "decrease in ability to perform sexually" symptom was lower than that in the VGH-BPH1 group ($p = 0.017$). Furthermore, within-group comparison revealed that VGH-BPH1 significantly decreased the "feeling burnt out" symptom ($p = 0.016$), whereas the placebo resulted in a significant decrease in the following symptoms: "sweating" ($p = 0.016$), "irritability" ($p = 0.016$), "nervousness" ($p = 0.008$), and "decrease muscular strength" ($p = 0.022$), but the differences were not statistically significant when the two groups were compared. Both groups significantly differed in the posttreatment AMS total score. However, no significant change in the AMS total score was observed between the two groups (Table 4).

3.3. Secondary outcome measures

A total of 17 participants filled in the IIEF questionnaire. The other six participants indicated they were not sexually active. The results revealed no significant changes between the treatment and placebo groups. Similarly, CCMQ, uroflowmetry, and postvoid residual urine results did not significantly differ between the treatment and placebo groups (Supplementary Tables 1 and 2, http://links.lww.com/JCMA/A141).

Table 3

IPSS before and after 8 weeks of treatment with VGH-BPH1 or placebo

	VGH-BPH1 (n = 23)		Placebo (n = 23)		
	Mean (SD)	*p*	Mean (SD)	*p*	*p*
Incomplete emptying					
Baseline	2.56 (1.64)	0.866	3.17 (1.50)	**0.0002*** **	0.133
After treatment	2.61 (1.53)		2.26 (1.48)		
Frequency					
Baseline	3.43 (1.37)	**0.030***	3.43 (1.31)	0.056	1.00
After treatment	2.91 (1.31)		2.91 (1.56)		
Intermittency					
Baseline	3.17 (1.47)	0.260	3.48 (1.24)	**0.031***	0.170
After treatment	2.96 (1.52)		3.17 (1.43)		
Urgency					
Baseline	2.52 (1.41)	0.405	2.61 (1.34)	0.628	0.213
After treatment	2.35 (1.43)		2.52 (1.50)		
Weak stream					
Baseline	3.30 (1.10)	0.170	3.00 (1.24)	0.185	0.149
After treatment	3.09 (1.34)		2.61 (1.40)		
Straining					
Baseline	2.09 (1.41)	0.307	2.30 (1.14)	0.095	0.840
After treatment	1.87 (1.25)		1.91 (1.38)		
Nocturia					
Baseline	2.26 (0.96)	0.057	2.30 (0.87)	**0.042***	0.426
After treatment	2.04 (0.97)		2.13 (0.97)		
IPSS total score					
Baseline	19.35 (6.10)	**0.027***	20.30 (5.83)	**0.011***	0.708
After treatment	17.83 (6.33)		17.52 (7.06)		
Voiding symptoms					
Baseline	11.13 (4.01)	0.242	11.96 (3.79)	**0.008****	0.348
After treatment	10.52 (4.39)		9.96 (4.47)		
Storage symptoms					
Baseline	8.22 (2.83)	**0.010***	8.35 (2.79)	0.095	0.503
After treatment	7.30 (2.70)		7.56 (3.20)		

IPSS = International Prostate Symptoms Score; SD = standard deviation.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

4. DISCUSSION

This is the first randomized, double-blind, placebo-controlled crossover trial to investigate the effect of VGH-BPH1 as an add-on treatment for patients with BPH. A review in 2016 reported that BPH was likely to decrease quality of life of individuals with this disease.[3] LUTS was also reported to be associated with sexual dysfunction.[24] Although drugs or surgical interventions are used to improve LUTS and sexual dysfunction, 5% to 6% of patients still experience various side effects after treatment, including delayed ejaculation, erectile difficulties, headaches, dizziness, nausea, urinary tract infection, and bleeding.[20] This study aimed to evaluate whether an add-on treatment involving a CHM prescription might yield improvements for patients with BPH. Therefore, this study included patients with BPH who were being treated with conventional, Western medications and they were asked to continue taking these Western medications throughout the trial.

In the ancient TCM literature, BPH symptoms were classified as "Long Bi" (癃閉), which can be divided to the following types of syndromes: Kidney Yang deficiency, dampness and heat in bladder, heat obstructing the lungs, liver Qi stagnation, blood stasis, and insufficient middle Qi. Two previous studies targeting TCM syndromes related to BPH reported that Kidney Yang

Table 4

AMS before and after 8 weeks of treatment with VGH-BPH1 or placebo

	VGH-BPH1 (n = 23)		Placebo (n = 23)		
	Mean (SD)	*p*	Mean (SD)	*p*	*p*
General well-being					
Baseline	2.26 (0.75)	0.134	2.22 (0.79)	0.575	0.575
After treatment	2.04 (0.77)		2.13 (0.76)		
Joint pain and muscular ache					
Baseline	1.87 (0.76)	0.056	1.91 (0.85)	0.492	**0.022***
After treatment	1.61 (0.66)		1.83 (0.83)		
Sweating					
Baseline	1.56 (0.66)	0.426	1.61 (0.72)	**0.016***	0.257
After treatment	1.48 (0.73)		1.30 (0.56)		
Sleep problems					
Baseline	2.17 (0.98)	0.103	2.09 (1.08)	0.665	0.714
After treatment	2.00 (1.04)		2.04 (1.06)		
Need for sleep					
Baseline	2.30 (0.97)	0.377	2.35 (0.83)	0.083	0.714
After treatment	2.17 (0.83)		2.22 (0.90)		
Irritability					
Baseline	1.87 (0.76)	0.103	1.96 (0.76)	**0.016***	0.575
After treatment	1.69 (0.76)		1.65 (0.77)		
Nervousness					
Baseline	1.78 (0.60)	0.135	1.83 (0.58)	**0.008****	0.328
After treatment	1.56 (0.59)		1.48 (0.59)		
Anxiety					
Baseline	1.78 (0.73)	0.328	1.87 (0.81)	0.103	0.714
After treatment	1.65 (0.71)		1.69 (0.76)		
Physical exhaustion					
Baseline	1.87 (0.69)	**0.008****	1.91 (0.79)	0.185	0.057
After treatment	1.56 (0.59)		1.78 (0.67)		
Decrease muscular strength					
Baseline	2.13 (1.01)	0.096	2.13 (0.92)	**0.022***	1.00
After treatment	1.91 (0.79)		1.91 (0.79)		
Depressive mood					
Baseline	1.73 (0.81)	0.266	1.95 (0.82)	0.057	0.185
After treatment	1.61 (0.72)		1.73 (0.75)		
Passed your peak					
Baseline	2.22 (0.90)	0.295	2.26 (0.81)	0.377	0.492
After treatment	2.04 (0.88)		2.13 (0.87)		
Feeling burnt out					
Baseline	2.09 (0.79)	**0.016***	1.83 (0.78)	0.539	0.714
After treatment	1.78 (0.73)		1.74 (0.75)		
Decrease in beard growth					
Baseline	2.30 (0.93)	0.714	2.09 (1.00)	0.824	0.233
After treatment	2.26 (1.05)		2.04 (0.88)		
Decrease in ability to perform sexually					
Baseline	3.17 (1.23)	0.539	3.13 (1.06)	0.057	**0.017***
After treatment	3.26 (1.18)		2.91 (1.12)		
Decrease in the number of morning erections					
Baseline	3.43 (1.16)	0.426	3.35 (0.98)	0.45	0.109
After treatment	3.52 (1.12)		3.22 (1.28)		
Decrease in sexual desire					
Baseline	3.30 (1.10)	0.665	3.00 (0.95)	1.00	0.056
After treatment	3.26 (1.01)		3.00 (1.09)		
Total score					
Baseline	37.87 (9.87)	**0.018***	37.48 (8.15)	**0.018***	0.506
After treatment	35.43 (8.61)		34.83 (9.10)		

AMS = Aging Male Symptoms Score; SD = standard deviation.
*$p < 0.05$; **$p < 0.01$.

deficiency was the most common syndrome, followed by Kidney Yin deficiency and then Blood stasis.[25,26]

TCM treatment is based on the theory of syndrome differentiation, whereby specific herbal formulae are selected for the treatment of specific syndromes. Therefore, most of the components of VGH-BPH1 are used to treat Kidney Yang deficiency, the most common BPH syndrome. These include *Ji-Sheng-Shen-Qi-Wan*, *Yi-Zhi-Ren*, *Wu-Yao*, *Yin-Yang-Huo*, and *Fu-Pen-Zi*. *Ji-Sheng-Shen-Qi-Wan* was first described during the Southern Song Dynasty (AD 1127–1279). It is intended to nourish the Kidneys, assist the Yang, and dilute the swelling of the water. It is also used to treat edema and unfavorable urine caused by insufficient Kidney Yang. Experimental studies have revealed that *Ji-Sheng-Shen-Qi-Wan* is able to suppress bladder contraction and enhance bladder capacity.[27,28] In terms of human clinical trials, Hiroshi et al conducted two clinical trials in 2015 and 2016 that investigated whether this formula was able to ameliorate LUTS.[11,12] The results indicated that *Ji-Sheng-Shen-Qi-Wan* was a safe and effective treatment for patients with LUTS. Analysis results obtained from the NHIRD also indicated that this formula is the most common formula used to treat patients with dementia with difficultly voiding.[29] Therefore, *Ji-Sheng-Shen-Qi-Wan* was chosen as the basis for the mixture used in this study.

Yi-Zhi-Ren, in combination with *Wu-Yao*, is part of the formula for *Suo-Quan-Wan*, which is used to address Kidney Yang deficiency, the induction of frequent urination, and the problem of nocturnal enuresis. *Suo-Quan-Wan* was reported to improve bladder control, bladder capacity, and contraction ability in an aging rat model.[30] *Yin-Yang-Huo* and *Fu-Pen-Zi* were demonstrated to be efficacious in treating Kidney Yang deficiency associated with impotence, infertility, and urinary frequency. In vitro studies have reported that both single herbs exert antioxidant effects[15,31] and anti-inflammatory effects.[16,32]

Previously, a single-arm pilot study was conducted to investigate the effect of VGH-BPH0.[23] In that study, VGH-BPH0 resulted in a significant improvement in IPSS total score, voiding symptoms subscore, and the severity of the symptom of "incomplete emptying" symptom; furthermore, the frequency symptom exhibited a descending trend with a value of $p = 0.06$. Among the 19 participants in that study, 9 participants had Yang deficiency syndrome. In this crossover study, VGH-BPH1 did not improve the voiding symptoms subscore or the "incomplete emptying" symptom. Instead, a decrease in storage symptoms sub-score and the "frequency" symptom was observed. However, these changes did not differ significantly from the changes in the placebo group. Regarding TCM body constitution, only two patients with Kidney Yang deficiency were recruited at baseline in this study, which could explain why VGH-BPH1 exhibited a reduced effect compared with a previous study. In future clinical trials, Kidney Yang deficiency syndrome should be considered as one of the inclusion criteria.

Although VGH-BPH1 did not significantly improve IPSS relative to the placebo, it was able to attenuate some of the symptoms from the AMS scale better than the placebo, such as "Joint pain and muscular ache" and "Physical exhaustion". According to TCM theory, the kidneys are where essence (精) is stored, which can be understood as a form of life energy.[33] As a human being grows older, TCM claims that essence decreases, which causes symptoms such as fatigue or weakness, as well as mild joints aches and pains. Therefore, the reason for the improvement in some symptoms from the AMS after treatment with VGH-BPH1 could be because most of the formulae and the single herbs that make up VGH-BPH1 are tonic herbs that have been used to tonify the kidneys, as well as increase essence, for centuries.

In this study, the placebo group exhibited improvements in LUTS and several quality of life indicators. Many previous studies have detailed the placebo effect. Current evidence suggests that the therapeutic benefits associated with the placebo effect are that it does not change the pathophysiology of the disease but rather changes the symptoms.[34,35] A review of the placebo effect in the pharmacological treatment of patients with LUTS demonstrated that patients treated with a placebo exhibited a 9%–34% decrease in symptom scores compared with a 22%–45% decrease in patients receiving the drug.[36]

Overall, this study has good design quality. First, the constituents of VGH-BPH1 were selected based on the results of an analysis of NHIRD data, a literature review, and consultations with experienced TCM physicians. Second, a pilot single-armed trial was conducted to verify the effects of VGH-BPH0; and a small change was made to enhance the effectiveness of the prescription.

Our study had several limitations. First, the small sample size made it difficult to confirm the efficacy of the prescription. A larger study with sufficient power is needed. Second, the short duration of the study might not have allowed sufficient time for the CHM treatment to have an effect. Previous clinical trials exploring the effects of *Ji-Sheng-Shen-Qi-Wan* were longer (at 12 weeks) than the present study.[11,12] Furthermore, a systematic review exploring the efficacy of CHM for BPH noted that most studies were conducted for >8 weeks.[10] Future studies should treat patients for at least 12 weeks. Third, as mentioned, an insufficient number of BPH patients with appropriate TCM syndrome were included in the study. Adjustment to the inclusion criteria per the preceding suggestions would be helpful. Finally, participant dropout reduced the ability of this study to detect significant changes in symptoms, which would allow the mixtures effects to be clearly identified. An increase in the size of the study would reduce this effect.

In conclusion, this study was the first randomized, double-blind, placebo-controlled crossover study to evaluate the efficacy of a CHM prescription as an add-on medication for BPH. Although the results revealed that VGH-BPH1 did not produce a significantly better effect than the placebo in improving LUTS, this prescription resulted in improved patient quality of life. Future research with appropriate amendments to the study protocol should be conducted to investigate the potentially beneficial effects of VGH-BPH1.

ACKNOWLEDGMENTS

This research was supported by a grant from Taiwan's Ministry of Science and Technology (MOST 106-2320-B-010-007). We would like to express our gratitude to Prof. Fun-Jou Chen, Doctor Yi-Hsiu Huang, and Doctor Tzu-Chun Wei for their support of the research project. We wish to acknowledge the help in recruitment process provided by Jiun-An Chen. We would also like to thank Prof. Ralph Kirby for English editing.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A141.

REFERENCES

1. Nickel JC. The overlapping lower urinary tract symptoms of benign prostatic hyperplasia and prostatitis. *Curr Opin Urol* 2006;**16**:5–10.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al; Standardisation Sub-Committee of the International Continence Society. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003;**61**:37–49.
3. Pinto JD, He HG, Chan SW, Wang W. Health-related quality of life and psychological well-being in men with benign prostatic hyperplasia: an integrative review. *Jpn J Nurs Sci* 2016;**13**:309–23.
4. Skinder D, Zacharia I, Studin J, Covino J. Benign prostatic hyperplasia: a clinical review. *JAAPA* 2016;**29**:19–23.
5. Barqawi AB, Myers JB, O'Donnell C, Crawford ED. The effect of alpha-blocker and 5alpha-reductase inhibitor intake on sexual health in men with lower urinary tract symptoms. *BJU Int* 2007;**100**:853–7.
6. Corona G, Tirabassi G, Santi D, Maseroli E, Gacci M, Dicuio M, et al. Sexual dysfunction in subjects treated with inhibitors of 5α-reductase for benign prostatic hyperplasia: a comprehensive review and meta-analysis. *Andrology* 2017;**5**:671–8.
7. Park E, Lee MY, Jeon WY, Seo CS, You S, Shin HK. Paljung-San, a traditional herbal medicine, attenuates benign prostatic hyperplasia in vitro and in vivo. *J Ethnopharmacol* 2018;**218**:109–15.
8. Park E, Lee MY, Seo CS, Jeon WY, Shin HK. Yongdamsagan-tang, a traditional herbal formula, inhibits cell growth through the suppression of proliferation and inflammation in benign prostatic hyperplasia epithelial-1 cells. *J Ethnopharmacol* 2017;**209**:230–5.
9. Noguchi M, Kakuma T, Tomiyasu K, Yamada A, Itoh K, Konishi F, et al. Randomized clinical trial of an ethanol extract of Ganoderma lucidum in men with lower urinary tract symptoms. *Asian J Androl* 2008;**10**:777–85.
10. Ma CH, Lin WL, Lui SL, Cai XY, Wong VT, Ziea E, et al. Efficacy and safety of Chinese herbal medicine for benign prostatic hyperplasia: systematic review of randomized controlled trials. *Asian J Androl* 2013;**15**:471–82.
11. Yagi H, Sato R, Nishio K, Arai G, Soh S, Okada H. Clinical efficacy and tolerability of two Japanese traditional herbal medicines, Hachimi-jiogan and Gosha-jinki-gan, for lower urinary tract symptoms with cold sensitivity. *J Tradit Complement Med* 2015;**5**:258–61.
12. Yagi H, Nishio K, Sato R, Arai G, Soh S, Okada H. Clinical efficacy and tolerability of Gosha-jinki-gan, a Japanese traditional herbal medicine, for nocturia. *J Tradit Complement Med* 2016;**6**:126–9.
13. Lin H, Chiang HH, Chiang MC, Chuang CH. Assessment of Bu-Zhong-Yi-Qi-Tang and Sang-Piao-Xiao-San for overactive bladder in clinical efficacy. *J Integrated Chinese and Western Med* 2003; P77–P82.
14. Lai H, Tan B, Liang Z, Yan Q, Lian Q, Wu Q, et al. Effect of the Chinese traditional prescription Suo Quan Wan on TRPV1 expression in the bladder of rats with bladder outlet obstruction. *BMC Complement Altern Med* 2015;**15**:424.
15. Zhang TT, Yang L, Jiang JG. Bioactive comparison of main components from unripe fruits of Rubus Chingii Hu and identification of the effective component. *Food Funct* 2015;**6**:2205–14.
16. Zhang TT, Wang M, Yang L, Jiang JG, Zhao JW, Zhu W. Flavonoid glycosides from Rubus chingii Hu fruits display anti-inflammatory activity through suppressing MAPKs activation in macrophages. *J Funct Foods* 2015;**18**: 235–43.
17. Ge FH, Ma XP, Ma JF, Bi CQ, Chen TL, Zhang XD, et al. Qualitative and Quantitative Characterization of Monosaccharide Components of Salvia miltiorrhiza, Liguspyragine Hydrochloride, and Glucose Injection. *J Anal Methods Chem* 2017;**2017**:9245620.
18. Chen F, Li L, Tian DD. Salvia miltiorrhiza Roots against Cardiovascular Disease: Consideration of Herb-Drug Interactions. *Biomed Res Int* 2017;**2017**:9868694.
19. Bonesi M, Loizzo MR, Acquaviva R, Malfa GA, Aiello F, Tundis R. Anti-inflammatory and Antioxidant Agents from Salvia Genus (Lamiaceae): An Assessment of the Current State of Knowledge. *Antiinflamm Antiallergy Agents Med Chem* 2017;**16**:70–86.
20. Li MK, Garcia L, Patron N, Moh LC, Sundram M, Leungwattanakij S, et al. An Asian multinational prospective observational registry of patients with benign prostatic hyperplasia, with a focus on comorbidities, lower urinary tract symptoms and sexual function. *BJU Int* 2008;**101**:197–202.
21. Chen KK, Chiu JH. Effect of Epimedium brevicornum Maxim extract on elicitation of penile erection in the rat. *Urology* 2006;**67**:631–5.
22. Sun H, Li TJ, Sun LN, Qiu Y, Huang BB, Yi B, et al. Inhibitory effect of traditional Chinese medicine Zi-Shen Pill on benign prostatic hyperplasia in rats. *J Ethnopharmacol* 2008;**115**:203–8.
23. Yeh HF, Li TF, Tsai CH, Wu PW, Huang YH, Huang WJ, et al. The effects of a Chinese herbal medicine (VGHBPH0) on patients with benign prostatic hyperplasia: a pilot study. *J Chin Med Assoc* 2020;**83**:967–71.
24. De Nunzio C, Roehrborn CG, Andersson KE, McVary KT. Erectile Dysfunction and Lower Urinary Tract Symptoms. *Eur Urol Focus* 2017;**3**:352–63.
25. Zhang CH, Chen TB, Qin GZ, Ding SL, Li YF. [Correlation between traditional Chinese medicine syndrome differentiation and urodynamic

parameters in benign prostate hyperplasia]. *Zhonghua Nan Ke Xue* 2007;**13**:185–98.
26. Zhang C, Li Y, Qin G, Chen T, Zhang F, Ding S, et al. Study on the TCM syndrome distribution of 540 patients with benign prostate hyperplasia. *J Tradit Chin Med* 2012;**53**: 45–7.
27. Gotoh A, Goto K, Sengoku A, Shirakawa T, Akao Y, Fujisawa M, et al. Inhibition mechanism of Gosha-jinki-gan on the micturition reflex in rats. *J Pharmacol Sci* 2004;**96**:115–23.
28. Nishijima S, Sugaya K, Miyazato M, Ogawa Y. Effect of Gosha-jinki-gan, a blended herbal medicine, on bladder activity in rats. *J Urol* 2007;**177**:762–5.
29. Lin SK, Lin PH, Hsu RJ, Chuang HC, Liu JM. Traditional Chinese medicine therapy reduces the catheter indwelling risk in dementia patients with difficult voiding symptoms. *J Ethnopharmacol* 2017;**203**:120–6.
30. Xu YF, Liang ZJ, Kuang ZJ, Chen JJ, Wu J, Lu XE, et al. Effect of Suo Quan Wan on the bladder function of aging rats based on the β-adrenoceptor. *Exp Ther Med* 2017;**13**:3424–32.
31. Zhao Y, Hou Y, Tang G, Cai E, Liu S, Yang H, et al. Optimization of ultrasonic extraction of phenolic compounds from epimedium brevicornum maxim using response surface methodology and evaluation of its antioxidant activities in vitro. *J Anal Methods Chem* 2014;**2014**: 864654.
32. Yan N, Wen DS, Zhao YR, Xu SJ. Epimedium sagittatum inhibits TLR4/MD-2 mediated NF-κB signaling pathway with anti-inflammatory activity. *BMC Complement Altern Med* 2018;**18**:303.
33. Wang XQ, Zou XR, Zhang YC. From "kidneys govern bones" to chronic kidney disease, diabetes mellitus, and metabolic bone disorder: a crosstalk between traditional Chinese medicine and modern science. *Evid Based Complement Alternat Med* 2016;**2016**: 4370263.
34. Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med* 2009;**52**:518–39.
35. Morral A, Urrutia G, Bonfill X. Placebo effect and therapeutic context: a challenge in clinical research. *Med Clin (Barc)* 2017;**149**: 26–31.
36. van Leeuwen JH, Castro R, Busse M, Bemelmans BL. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. *Eur Urol* 2006;**50**:440–52.