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ORIGINAL ARTICLE

Effects of Korean ginseng berry extract on sexual function in men with erectile dysfunction: a multicenter, placebo-controlled, double-blind clinical study

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Ginseng is beneficial for many aspects of human physiology, including sexual function. In this study, we have evaluated the efficacy and safety of an extract of ginseng berry, which has a ginsenoside profile distinct from other parts of the plant, on sexual function in men with erectile dysfunction. In all, 119 men with mild-to-moderate ED participated in a multicenter, randomized, double-blind, parallel, placebo-controlled clinical study. They were administered 4 tablets of either standardized Korean ginseng berry (SKGB, 350 mg ginseng berry extract per tablet), or placebo, daily, for 8 weeks. Efficacy was assessed with the International Index of Erectile Function (IIEF)-15 and premature ejaculation diagnostic tool (PEDT) at the end of the 4th and 8th week. We observed that the total and each of the individual domain scores of IIEF-15 increased from 40.95 ± 7.05 to 46.19 ± 12.69 significantly in the SKGB by the 8th week ($P < 0.05$). The erectile function domain of IIEF changed slightly from 17.17 ± 2.57 to 18.59 ± 5.99 in the SKGB group by the 8th week ($P < 0.05$). In addition, PEDT scores significantly improved from 9.14 ± 4.57 to 7.97 ± 4.4 and 7.53 ± 4.26 in the SKGB group after 4 and 8 weeks of treatment ($P < 0.05$). Safety markers including hormone and lipid in the blood were assessed at the end of the 4th and 8th week and they remained unchanged. Oral administration of the SKGB extract improved all domains of sexual function. It can be used as an alternative medicine to improve sexual life in men with sexual dysfunction.

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INTRODUCTION

Sexual dysfunction has a severe impact on the quality of life of affected individuals. Two main symptoms of sexual dysfunction are ED and premature ejaculation (PE). Some studies report that approximately more than half of the male population has some degree of ED[1] and one-third of the global male population, across all age groups, has some degree of PE.[2] To treat these symptoms, drugs such as PDE5 inhibitors and selective serotonin reuptake inhibitors are commonly used. However, these substances can produce negative side effects, including headache, gastrointestinal disorder, muscle pain and blurred vision, and may have dangerous interactions with other medications.[3,4]

To avoid the risks of potential side effects associated with drugs, people often turn to dietary supplements or phytotherapy. *Panax ginseng* is particularly common and widely used in oriental countries, because of its property of boosting the immune system, as well as providing vigor and enhancing sexual activity.[5] It contains medicinal ingredients, including saponin, polysaccharide, polyacetylene, phenols, gomisin, acidic peptide and carbohyderate.[6] The major active components are ginsenosides, a class of steroid glycosides and triterpene saponins naturally occurring in the root, leaf and berry.[7,8] Each part of the plant has a distinct ginsenoside profile; thus, different parts probably have different pharmacological activities.[7,9]

Ginsenosides have been shown to enhance nitric oxide (NO) production in cultured porcine endothelial cells,[10] rat ventricular myocytes,[11] rat thoracic aorta[12] and guinea-pig cardiomyocytes,[13] by inducing NO synthase (NOS) activity. More recently, ginsenoside Rg1, which is abundantly present in ginseng berry, was also reported to improve male copulation behavior via the NO/cGMP pathway.[14] Based on the above findings, we hypothesized that ginseng berry ameliorates sexual function via the NO/endothelial NOS pathway and enhances male sexual health.

This study was carried out to evaluate the effects of standardized ginseng berry extract on erectile function, ejaculation and other aspects of sexual function, in men with ED.

MATERIALS AND METHODS

Preparation of SKGB

Freshly harvested 4-year-old Korean ginseng berry (*P. ginseng* CA Meyer) cultivated in Chungbuk province of South Korea were used. The seeds were separated, and the pulp and juice were dried. The dried ginseng berries were refluxed with 70% ethanol for 10 h. The extract was filtered and evaporated under vacuum at 45 °C to obtain standardized Korean ginseng berry extract (SKGB). The concentration of seven major ginsenosides in SKGB was analyzed by high-performance liquid chromatography and the analysis results are shown in Figure 1.

Each 700 mg SKGB tablet consisted of 350 mg of standardized ginseng berry extract. The content of ginsenoside-Re in standardized ginseng berry extract was maintained at 10%. SKGB tablets also contain excipients and coating materials, such as hydroxypropyl methylcellulose and microcrystalline cellulose. Placebo tablets are made of microcrystalline cellulose, and they also contain excipients and coating materials. SKGB and placebo

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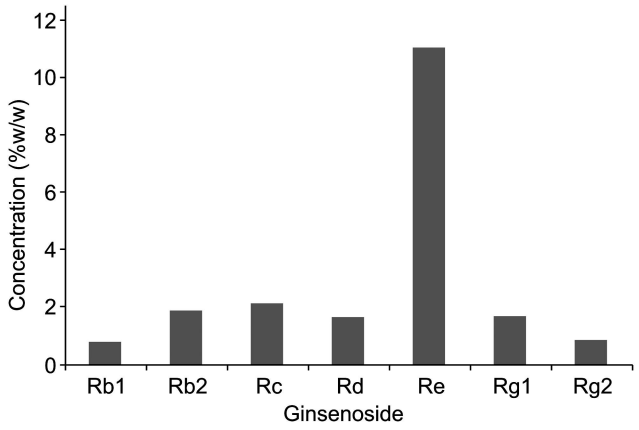

Figure 1. Percentage weight of the seven ginsenosides in the SKGB group obtained by high-performance liquid chromatography analysis. Rb1, ginsenoside-Rb1; Rb2, ginsenoside-Rb2; Rc, ginsenoside-Rc; Rd, ginsenoside-Rd; Re, ginsenoside-Re; Rg1, ginsenoside-Rg1; Rg2, ginsenoside-Rg2.

tablets were identical in appearance. All process was controlled under good manufacturing practice condition, which is managed by Korea Food and Drug Administration. After the tablet production, we checked the content of ginsenoside-Re, especially in the final SKGB tablets. During the trials, four tablets (two tablets at a single time after breakfast and dinner) of SKGB or placebo were given daily for 8 weeks.

Subjects

In this study, 119 men with mild-to-moderate ED were recruited between May 2010 and January 2011. Selected participants were screened using the International Index of Erectile Function (IIEF)-5 scores, and were found to fall within a range of 13–21; they were thereby assessed as having mild-to-moderate ED. They had suffered from ED for a period of 3 or more months, and their ages were between 20 and 70 years. All the participants were married and agreed to make at least four attempts a month at sexual intercourse with their spouse.

Exclusion criteria were as follows: (i) ED caused by endocrine system diseases; ED patients suffering from hypogonadism, which can be treated by testosterone; (ii) prostate disease or cancer; (iii) severe penile pathology: patients with peyronie's disease who cannot have sexual intercourse; (iv) stroke, myocardial infarction, unstable angina within the previous 6 months; (v) liver, kidney and nerve system diseases; (vi) intake of 5-α-reductase inhibitor within the previous 2 weeks; (vii) intake of PDE-5 inhibitors or self-injection with vasodilators for ED treatment within the previous 2 weeks; (viii) intake of ginseng or red ginseng within the previous 2 weeks; (ix) uncontrolled hypertension (over 170/100 mm Hg); (x) uncontrolled hyperglycemia (over 180 mg dl^{-1} on an empty stomach); (xi) alcohol or drug abuse; and (xii) participation in other clinical tests within the previous 3 months.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital of Yonsei University College of Medicine and Mokdong Hospital of Ewha Womans University College of Medicine. Written consent was obtained from all subjects after they were provided a detailed description of the experimental procedures and informed that they could withdraw from the study at any time.

Study design

This was a multicenter, randomized, double-blind, parallel, placebo-controlled study that lasted for 8 weeks. The first visit was for the purpose of screening, following which, the participants were randomly assigned to one of the two 8-week long treatment arms by using a computerized method of random list generation (Figure 2): (1) SKGB group, which received four tablets of SKGB daily, and (2) Placebo group, which received placebo tablets. All participants, investigators, pharmacists and study personnel were blinded to treatment allocation. Baseline parameters, cholesterol levels and hormonal status, including total testosterone and prolactin, were measured at the beginning and the end of the study (8 weeks). Clinical information and trial data were collected during individual interviews (0, 4 and 8 weeks), conducted by a well-trained interviewer.

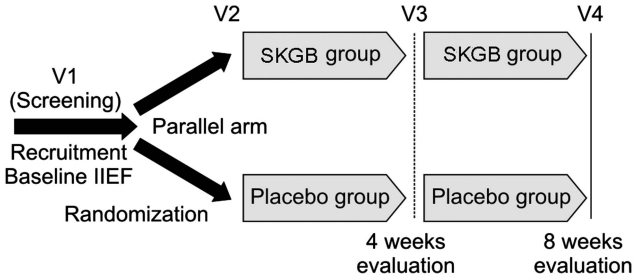

Figure 2. Design of the study. The schematic depicts the course of the randomized, placebo-controlled trial. V1–V4 denotes the hospital visit of the participants; V1, initial screening and recruitment of subjects; V2, assignment of subjects to either the SKGB or Placebo group; V3 and V4, evaluation of efficacy parameters and safety markers at 4 and 8 weeks.

All participants underwent a thorough medical history review and a physical examination. The primary efficacy measure was the score of the erectile function domain of IIEF-15 at 4 and 8 weeks of treatment. The secondary outcomes were other remaining domains of IIEF-15 (intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction) and the PE diagnostic tool (PEDT). The outcome measurements used the Korean version of IIEF and PEDT in this study that were verified for its reliability and validity.[15,16]

All men underwent a physical and clinical laboratory examination (blood chemistry and microscopic urine analysis); their vital signs (pulse and blood pressure) were measured and an electrocardiogram was also obtained for safety evaluation. All populations were asked to report potential side effects related to the treatment. Every 4 weeks, all parameters were compared within groups, as well as between the SKGB and the Placebo group.

Statistical analysis

Statistical analyses were performed using the SPSS software (version 12.0.1.; SPSS Inc., Chicago, IL, USA). A value of $P<0.05$ was considered to indicate a significant difference in demographic characteristics, effectiveness and safety measurements. The primary and secondary efficacy outcomes were evaluated using Wilcoxon's signed-rank test, which was used for within-group comparisons and analysis of covariance with the baseline as covariate between groups. The hematological parameters, blood chemistry, hormone levels and lipid levels in the blood as well as vital sign measurements followed a normal distribution and were evaluated by the *t*-test between groups and paired *t*-test within groups. The comorbid conditions were evaluated by the χ^2 test between groups. All the data were represented as mean ± s.d.

RESULTS

Study population

Of the total 119 subjects, one subject from the SKGB group was excluded because he wished to discontinue the study. Thus, 118 subjects comprising the intent-to-treat group (SKGB: $N=59$; Placebo: $N=59$) completed the entire evaluation, including the IIEF-15 and PEDT questionnaires in the 8-week study. The SKGB and Placebo groups were similar with respect to age, demographic characteristics and medical history (Table 1).

Erectile function

The erectile function domain of IIEF-15 scores at 0, 4 and 8 weeks, using intent-to-treat set analysis, is depicted in Table 2. The SKGB group showed slight improvement with statistical significance after 8 weeks of treatment, as shown by within-group analysis ($P=0.046$ vs 0.487 in the Placebo group).

Table 1. Baseline characteristics

	Double-blind treatment		
	SKGB (N = *59*)	*Placebo* (N = *59*)	P-*value*
Age (years), mean ± s.d.	57.49 ± 7.94	57.32 ± 8.41	0.911*
Min, max	31, 69	32, 69	
IIEF-5, mean ± s.d.	14.36 ± 1.86	14.59 ± 1.79	0.497*
Min, max	13, 21	13, 20	
ED duration (in years), mean ± s.d.	4.67 ± 5.19	4.31 ± 5.12	0.708*
Min, max	0.25, 25	0.25, 30	
Comorbid conditions,[a] n *(%)*			
Cardiovascular disorders	17 (34.00)	23 (40.35)	1.000**
Gastrointestinal disorders	2 (4.00)	3 (5.26)	1.000**
Genitourinary disorders	14 (28.00)	12 (21.05)	1.000**

Abbreviations: ED, erectile dysfunction; IIEF, International Index of Erectile Function; SKGB, standardized Korean ginseng berry. **P*-value by *t*-test. ***P*-value by χ^2 test. [a]Conditions other than those of the exclusion criteria.

Table 2. Changes in the IIEF-15 score at 4 and 8 weeks of treatment

Mean ± s.d.	*Baseline*	*4 Weeks*	P-*value*[a]	*8 Weeks*	P *value*[a]
Erectile function domain					
SKGB (*N* = 59)	17.17 ± 2.57	17.73 ± 4.72	0.450	18.59 ± 5.99	0.046
Placebo (*N* = 59)	17.56 ± 2.89	16.29 ± 5.33	0.074	18.00 ± 5.12	0.487
P-value[b]		0.065		0.501	
Intercourse satisfaction domain					
SKGB (*N* = 59)	7.10 ± 1.88	7.90 ± 2.52	0.013	8.02 ± 2.74	0.005
Placebo (*N* = 59)	7.68 ± 1.70	7.22 ± 2.56	0.217	8.08 ± 2.25	0.216
P-value[b]		0.026		0.902	
Orgasmic function domain					
SKGB (*N* = 59)	5.58 ± 1.71	6.24 ± 2.10	0.020	6.46 ± 2.34	0.002
Placebo (*N* = 59)	6.27 ± 2.07	6.07 ± 2.24	0.644	6.61 ± 2.17	0.284
P-value[b]		0.167		0.719	
Sexual desire domain					
SKGB (*N* = 59)	5.86 ± 1.61	6.54 ± 1.59	0.001	6.73 ± 1.54	0.001
Placebo (*N* = 59)	6.47 ± 1.49	6.32 ± 1.57	0.360	6.71 ± 1.64	0.265
P-value[b]		0.050		0.266	
Overall satisfaction domain					
SKGB (*N* = 59)	5.24 ± 1.38	5.85 ± 1.57	0.006	6.39 ± 1.59	0.001
Placebo (*N* = 59)	5.42 ± 1.68	5.76 ± 1.85	0.268	6.15 ± 1.71	0.012
P-value[b]		0.603		0.342	
Total IIEF-15 score					
SKGB (*N* = 59)	40.95 ± 7.05	44.25 ± 10.74	0.011	46.19 ± 12.69	0.002
Placebo (*N* = 59)	43.39 ± 7.20	41.63 ± 11.55	0.205	45.61 ± 10.81	0.134
P-value[b]		0.04		0.55	

Abbreviations: ANCOVA, analysis of covariance; IIEF, International Index of Erectile function; SKGB, standardized Korean ginseng berry.
The values represent mean ± s.d. [a]*Within-group comparison*: *P*-value by Wilcoxon's signed-rank test. [b]*Between-group comparison*: *P*-value by ANCOVA test.

Other sexual functions

(a) *IIEF-15 score*: The IIEF-15 scores during the 8-week treatment period are also shown in Table 2. Both within- and intergroup analysis indicate a significant increase in the total IIEF-15 scores after 4 and 8 weeks of treatment ($P<0.05$). The four remaining domains other than erectile function were also analyzed: intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction. All of these domains showed significant improvement during the treatment period in the SKGB group ($P<0.05$) but not in the Placebo group ($P>0.05$), except overall satisfaction domain ($P=0.012$). Intergroup analysis revealed a significant increase in total and intercourse satisfaction domain scores only, at 4 weeks of treatment ($P=0.040$ and 0.026, respectively).

(b) *Ejaculatory function*: The comparisons of PEDT values of the groups at 4 and 8 weeks of treatment are shown in Table 3. The PEDT score improved in the SKBG group from 9.14 to 7.97 and 7.53 at 4 and 8 weeks, respectively. Both inter- and within-group analysis revealed statistically significant differences ($P<0.05$).

Hormonal and safety evaluation

The beneficial effect of SKGB on sexual function is not related to hormonal or cholesterol levels in the blood, as no changes were

Table 3. Comparisons of PEDT scores of the SKGB and placebo groups before and after treatment

Mean ± s.d.	*Baseline*	*4 Weeks*	P-*value*[a]	*8 Weeks*	P-*value*[a]
SKGB ($N = 59$)	9.14 ± 4.57	7.97 ± 4.45	0.004	7.53 ± 4.26	0.001
Placebo ($N = 59$)	10.46 ± 4.79	10.31 ± 4.88	0.753	9.66 ± 4.57	0.177
P-value[b]		0.019		0.017	

Abbreviations: ANCOVA, analysis of covariance; PEDT, premature ejaculation diagnostic tool; SKGB, standardized Korean ginseng berry.
The values represent mean ± s.d. [a]*Within-group comparison*: *P*-value by Wilcoxon's signed-rank test. [b]*Between-group comparison*: *P*-value by ANCOVA test.

Table 4. Analysis of cholesterol and hormone levels in the blood of SKGB and placebo group patients before and after treatment

Mean ± s.d.	*Baseline*	*8 Weeks*	P-*value*[a]
Total cholesterol (mg dl^{-1})			
SKGB ($N = 59$)	192.66 ± 37.09	191.58 ± 31.32	0.763
Placebo ($N = 59$)	187.34 ± 33.11	184.02 ± 40.62	0.419
P-value[b]		0.682	
HDL-cholesterol (mg dl^{-1})			
SKGB ($N = 59$)	45.81 ± 10.07	46.95 ± 9.32	0.264
Placebo ($N = 59$)	48.75 ± 12.70	49.42 ± 12.85	0.454
P-value[b]		0.735	
LDL-cholesterol (mg dl^{-1})			
SKGB ($N = 59$)	113.76 ± 31.72	117.12 ± 28.70	0.305
Placebo ($N = 59$)	113.39 ± 29.93	113.03 ± 28.21	0.854
P-value[b]		0.327	
Testosterone (ng ml^{-1})			
SKGB ($N = 59$)	500.53 ± 189.58	499.32 ± 168.00	0.937
Placebo ($N = 59$)	482.05 ± 171.83	469.57 ± 154.02	0.523
P-value[b]		0.649	
Prolactin (ng ml^{-1})			
SKGB ($N = 59$)	7.12 ± 4.26	9.25 ± 11.35	0.142
Placebo ($N = 59$)	6.39 ± 4.84	6.69 ± 5.11	0.642
P-value[b]		0.252	

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SKGB, standardized Korean ginseng berry.
The values represent mean ± s.d. [a]*Within-group comparison*: *P*-value by paired *t*-test. [b]*Between-group comparison*: *P*-value by *t*-test.

observed in these factors in the serum of treated patients (Table 4). Furthermore, assessment of safety markers, including blood chemistry, urinalysis and vital signs of participants, showed no significant difference after the treatment period.

Although one case of mild gastrointestinal symptom was reported during 0–4 weeks in the Placebo group, no patient experienced any critical side effects that would have prevented them from completing the clinical trial.

DISCUSSION

Human sexuality is very complex, and with multiple factors affecting sexual desire, function, orgasm and overall satisfaction. Sexual dysfunction can result from aging or physical disorders affecting the NO pathway.[17–19] Various treatment options are available, including the use of medication, phytotherapy, behavioral therapy, psychiatric consultation and surgery. Despite the successful advent of PDE5 inhibitors for ED and selective serotonin reuptake inhibitors for PE, a large number of patients with mild ED are reluctant to use medication or surgery and prefer phytotherapy.[20]

Among the complementary medicines or dietary supplements that can improve sexual function, ginseng appears to be one of the most attractive options. Ginseng has been used in Asian countries to promote several health aspects, including sexual function, rarely having any adverse effects.[21] Several studies have described the clinical efficacy of ginseng and its extract for treatment of ED.[20,22] However, Jang *et al.*[23] reported that out of 28 published articles on the effect of ginseng on the treatment of ED, only 7 articles satisfied their strict criteria of being double-blind, placebo-controlled trials.[23] The meta-analysis showed that ginseng improved sexual performance. More recently, Shamloul[24] reported that these seven studies did not consider the nature of the placebo used. Moreover, some of these studies did not describe baseline comparison of ED symptoms or obtain appropriate ethical approval.[20–24] The clinical trial described herein was designed as a multicenter, randomized, double-blind, placebo-controlled study, addressing both the efficacy and safety of SKGB extract in men with mild-to-moderate ED.

In our study, we have used ginseng berry, which is most abundant in ginsenoside, to treat male individuals with ED. A number of other clinical studies show that ginseng improves sexual function; however, neither did they mention the method of extract preparation nor did they quantify the components of the experimental product.[24–26] Standardization of herb or plant extracts is important for comparing herbal therapy with conventional medicine and to ensure the delivery of the correct dose in a consistent manner. Our study is the first clinical trial that investigates the effect of a standardized and characterized ginseng berry extract on sexual function. Standardization of ginseng berry extract makes our study more reliable and reproducible.

We report that the SKGB-treated group showed improvement in all domains of sexual function. Clinical observation of patients after the 8-week treatment indicates that SKGB has a positive effect on their sexual life.

Ginseng has been used to treat ED and its efficacy has been shown in several studies.[20,22,25–27] Because ginseng is not a drug that can treat severe ED, we enrolled mild-to-moderate ED patients only. We found that SKGB group showed improvement after 8 weeks of treatment by within-group analysis. A 1.5-point change could be considered clinically dubious for recommending SKGB as a drug; however, it could be useful if used as a supplement. According to a recent review article, the PDE5-I (that is, Tadalafil) could improve erectile function by four points. And the minimal clinically important differences in the EF domain were 2, 5 and 7 for patients with mild, moderate and severe baseline ED, respectively.[28] We checked the number of patients who experienced more than four-point change in IIEF-EF domain and found that 22 (37%) men from the SKGB group and 17 men (28%) from the Placebo group showed this improvement. As our clinical test included the patients with mild-to-moderate ED, 1.5-point change in the SKGB group could mean that SKGB can be useful as a supplement rather than as a drug. SKGB exhibited an improvement that was comparable with well-known supplements, such as Lepidium Meyenii (Maca) and Pyconogenol, that have similar or high IIEF-5 score (1.6 and 1.1, respectively).[29,30] Further,

we did not observe any adverse effects during clinical test contrary to other supplements such as yohimbine.[31]

A run-in phase (period) is very useful to screen potential subjects for adherence and placebo response. Although we tried to screen out the subjects with inclusion/exclusion criteria as well as detailed interviews, we did not have a run-in phase in this clinical trial. In the future study, the inclusion of a run-in phase needs to be considered so that we could achieve more significant results on a highly selected group of patients.

Ginseng has several potential healing properties and pharmacological activities.[26] Ginsenosides, the principle molecular ingredients of ginseng, can induce activation of large-conductance K (Ca) channels in smooth muscles.[32] Ginseng enhances the NO synthesis in the endothelium and acts as an antioxidant, having a protective effect.[33,34] Ginsenosides activate endothelial NOS to release NO and inhibit calcium accumulation, thereby preventing NO-induced calcium channel blockade.[35] In a previous report, the ginseng saponin ginsenoside was shown to effectively improve libido and sexual potency via the NO/cGMP pathway.[14] Thus, the beneficial effects of SKGB may be mediated by endothelium-derived NO.

Ginseng has also been described to have a role in rat brain synaptosomes, inhibiting the uptake of dopamine, serotonin, glutamate, noradrenalin and *r*-aminobutyric acid, in a concentration-dependent manner.[36] Other clinical studies, indicating favorable effects of ginseng on the psychomotor performance of healthy volunteers receiving ginseng, support this mechanism of action.[37] The central effects of ginseng are probably responsible for improving sexual desire and the intercourse satisfaction scores presented in this study. However, in overall satisfaction, Placebo group also showed significant improvement ($P = 0.012$), even though it was not as significant as in the SKGB group ($P = 0.001$). Therefore, we would like to acknowledge that placebo effect might also be displayed in this kind of measurement.

To our knowledge, this is the first clinical study to evaluate the effects of ginseng extract throughout the ejaculation process in men with ED. PE is the most common male sexual complaint as well as the most prevalent ejaculatory disorder. According to a published report, PE has a prevalence of 16–38% in the male population.[38] The PEDT was developed to systematically apply the DSM-IV-TR criteria in the diagnosis of PE.[15,39] PEDT assesses important factors, including control over ejaculation, frequency of PE, minimum sexual stimulation, stress or bother to the patient and partner. This tool has been proven to be highly effective in detecting and following up the patients with PE in several geographical areas, such as Korea, Turkey, the United States and Germany.[15] In our study, the PEDT scores significantly improved within the SKGB group during the treatment and in comparison to the Placebo group. Although the underlying pathophysiology of PE is not well understood, possible mechanisms of the SKGB-induced improvement of ejaculatory function could involve increased NO synthesis and reduced sympathetic tone and smooth muscle dilation in the vas deferens and seminal vesicles, which could in turn oppose sympathetic vasoconstriction and delay ejaculation. In addition, reduced performance anxiety, because of better erection, and downregulation of the erectile threshold to a lower level of arousal could also account for the observed positive effects of SKGB.[40] Our results strongly support that the SKGB might be effective in men with PE and can help improve the quality of their sexual life. However, we would like to specify that this study did not aim at curing patients with PE because our patients were enrolled based on their erectile function only.

Reports of side effects of ginseng are scarce and those that exist report mild effects. Reported adverse effects are headache, insomnia, gastric problem and constipation.[20,25,26] No single adverse event pertaining to SKGB was noted in this study. Also, we did not find any change in blood chemistry, hormone and lipid profile throughout the study. However, a long-term study spanning more than a year might be required for confirming the safety profile.

In conclusion, Korean ginseng berry treatment was both efficacious and well tolerated in men with mild-to-moderate ED, who were dissatisfied with their sexual health. We therefore believe that SKGB is a safe method for improving overall sexual function and satisfaction in patients suffering from mild-to-moderate ED.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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