



Efficacy and Safety of Ginseng Berry Extract (SIRTBERRY™) in Treating Andropause Symptoms: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Purpose: This study aimed to evaluate the efficacy and safety of ginseng berry extract (GBE) (SIRTBERRY™) in treating andropause symptoms in aging men.

Materials and Methods: In this randomized, double-blind, placebo-controlled trial, 116 men with andropause symptoms were assigned to receive either 700 mg/day GBE or placebo for 8 weeks. The primary efficacy variables included changes in the aging male symptoms (AMS) scale and improvement rate as per the androgen deficiency in aging male (ADAM) questionnaire, from the baseline. Secondary efficacy measurements included changes in the total and free testosterone levels, serum lipid levels, International Index of Erectile Function (IIEF) scores, International Prostate Symptom Score (IPSS), and various hormonal and metabolic markers.

Results: The GBE group exhibited significant improvements in AMS scores, ADAM improvement rates, and IIEF scores compared to the placebo group. Specifically, the GBE group showed a 70% improvement in ADAM scores versus a 47.83% improvement in the placebo group ($p=0.0376$), and a greater reduction in AMS scores ($p=0.0205$). Significant enhancements were observed in erectile function, with the IIEF scores improved more in the GBE group ($p=0.0334$), particularly in the erectile function domain ($p=0.0290$). No serious adverse event was reported, and the safety profile of GBE was found to be comparable to that of placebo.

Conclusions: GBE significantly improved andropause symptoms, including sexual function, and demonstrated a favorable safety profile, suggesting its potential as a safe and effective alternative treatment for testosterone deficiency syndrome. Further research regarding its long-term benefits and applicability to broader populations is warranted.

Keywords: Andropause; Libido; Panax; Randomized controlled trial; Testosterone

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INTRODUCTION

Andropause, also referred to as male menopause or late-onset hypogonadism, signifies a natural decline in testosterone levels in aging men, leading to various clinical symptoms such as reduced libido, energy, muscle mass, and other aging-related conditions, along with increased body fat [1]. Prevalence data indicate that andropause symptoms escalate with age, affecting approximately 30% of men in their 50s and up to 50% of men in their 80s, significantly impacting their quality of life [2]. Diagnosis involves a multifaceted approach that combines clinical symptoms with biochemical markers, particularly low serum testosterone levels [2]. Testosterone replacement therapy (TRT) is the main treatment for andropause and is designed to relieve symptoms and normalize testosterone levels; however, it involves risks such as cardiovascular problems and potential worsening of prostate cancer, requiring close monitoring and tailored dosing [3].

Recent studies have highlighted natural alternative therapies for andropause with promising outcomes and minimal side effects, offering effective options to bypass TRT and its associated risks [4]. Dietary supplements, such as unripe black raspberry extract [5], *Trigonella foenum-graecum* seed extract [6], *Eurycoma longifolia* root extract [7], omega-3 fatty acids [8], and *Quisqualis indica* extract [9], effectively manage the symptoms of andropause and aging in men, enhancing urinary function, testosterone levels, overall quality of life, metabolic parameters, and cardiovascular health.

Ginseng, known as *Panax ginseng*, is a perennial plant from Korea that is traditionally valued for its

roots but is now equally valued for its berries, which contain unique ginsenosides with potent medicinal properties, particularly in improving metabolic health and managing andropause symptoms. Ginseng berry extract (GBE) is extensively studied for its efficacy in treating a range of conditions, through various *in-vitro*, *in-vivo*, and clinical trials, targeting neurological [10], immunological [11], muscular health [12], and glycemic control issues [13]. Recent research on Korean GBE has shown its potential benefits in terms of men's health, including improved testosterone production by upregulating key steroidogenic enzymes [14], enhanced erectile function by boosting intracavernosal pressure [15], and significant improvements in sexual function scores, particularly in mild-to-moderate erectile dysfunction [16]. Research on GBE for andropause is extremely limited, and clinical evidence of its efficacy is still lacking, hence emphasizing the need for further investigation [17]. Our trial aimed to assess the benefits of GBE in men with andropause symptoms by administering daily supplements and monitoring health changes. The aim of this study was to confirm the potential of GBE as a therapeutic supplement for age-related metabolic and hormonal disorders in men.

MATERIALS AND METHODS

1. Study design and intervention

This was a double-blind, randomized, placebo-controlled trial. Participants underwent initial evaluations, including demographic and medical assessments. After meeting the inclusion criteria, they were randomly assigned to receive either 700 mg/day of GBE or placebo

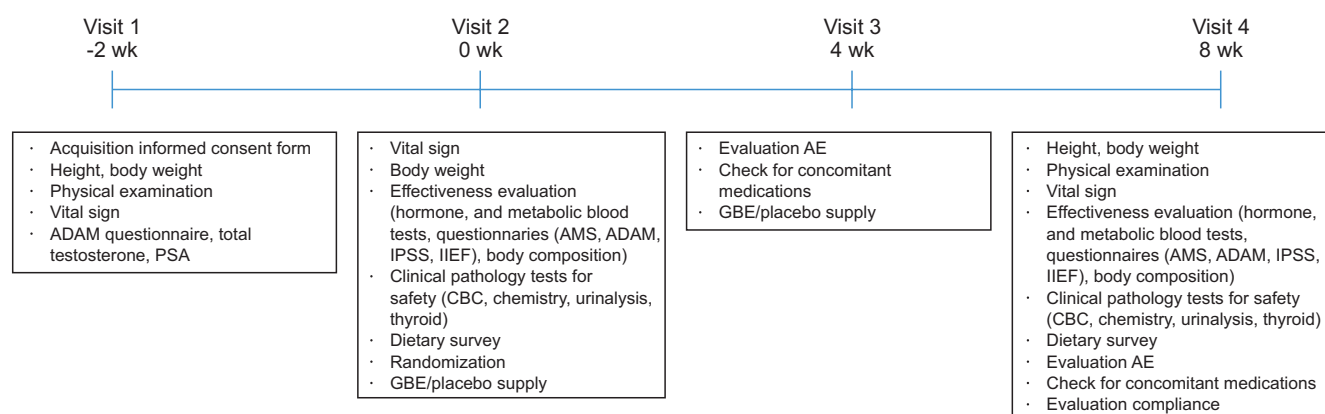


Fig. 1. Overview of the study design. ADAM: androgen deficiency in aging males, PSA: prostate-specific antigen, AMS: aging male symptoms, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, CBC: complete blood count, GBE: ginseng berry extract, AE: adverse event.

for eight weeks. Follow-ups were conducted at four and eight weeks to monitor adverse events (AEs), assess compliance, and collect vital signs and laboratory data (Fig. 1). The participants were prohibited from using specific medications and supplements during the study.

2. Ethics statement

The study protocol was approved by the Institutional Review Board of the Chung-Ang University Hospital (No. 1971-001-378) and was registered with the Clinical Research Information Service (CRIS Identifier: KCT0005471). It adhered to the Korean Good Clinical Practice Guidelines and the Declaration of Helsinki. All participants provided written informed consent before enrollment.

3. Participants

We recruited 116 participants at the Chung-Ang University Hospital (Seoul, Korea). The study included men aged 40 years or older with andropause symptoms, specifically those who responded "yes" to decreased libido (item 1) or erection quality (item 7) on the androgen deficiency in the aging male (ADAM) questionnaire. Participants were excluded if they had: (1) used hormonal agents, including plant extracts, within one month prior to screening; (2) used erectile dysfunction medications within one month prior to screening; (3) prostate-specific antigen (PSA) levels over 4 ng/mL; (4) a diagnosis of prostate cancer; (5) a body mass index >40 kg/m²; (6) a history of myocardial infarction, heart failure, stroke, or angina within six months prior; (7) severe mental illnesses; (8) endocrine disorders affecting weight; (9) uncontrolled hypertension; (10) used insulin or hypoglycemic agents within three months prior to screening; (11) liver enzyme levels exceeding three times the upper limit of normal; (12) creatinine levels exceeding twice the upper limit of normal; (13) used appetite suppressants, oral steroids, or thyroid hormone agents within three months prior to screening; (14) psychogenic andropause disorders; (15) a history of alcoholism or substance abuse; (16) an allergic reaction to ginseng; (17) participated in another clinical trial within one month prior or planned to during the study; or (18) been deemed inappropriate for participation by the investigator.

4. Investigational drugs

GBE capsules (700 mg/capsule) and placebos were

provided by Holistic Bio (Seongnam, Korea). GBE was prepared in water using *Panax ginseng* berries that had been de-seeded. The extract was spray-dried into a powder and standardized to contain 5% Ginsenoside Re [18]. During the study, the participants took two capsules daily for eight weeks. The placebo capsules were identical to the GBE capsules in shape, color, and taste.

5. Outcome measures

The primary efficacy variables were changes in the ADAM [19] improvement rate and the aging male symptoms (AMS) score with respect to baseline [20]. Secondary efficacy variables included changes in individual items of the ADAM questionnaire, serum levels of total testosterone and free testosterone, sex hormone-binding globulin (SHBG), and albumin, as well as lipid profile markers, such as total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol from the baseline. Additional secondary measures included changes in the International Prostate Symptom Score (IPSS) [21], the International Index of Erectile Function (IIEF) domain and total scores [22], and the serum levels of luteinizing hormone, follicle-stimulating hormone, dehydroepiandrosterone sulfate, insulin-like growth factor 1, estradiol, fasting blood sugar, insulin, and insulin-resistance markers. Physical measurements such as blood pressure, anthropometric measurements, and body composition were also assessed. Safety assessments included monitoring for AEs, conducting laboratory tests (hematology, biochemical tests, and urinalysis), measuring pulse rates, and evaluating serum PSA levels.

6. Statistical analysis

Data were analyzed using SAS version 9.4 (SAS Institute). The efficacy and baseline analysis sets included participants who adhered to the protocol and received treatment for more than 80% of the study period. Safety data were evaluated using a safety set. This set consisted of subjects who consumed GBE at least once after randomization. Participants were block-randomized to the GBE or placebo group using a computer-generated randomization scheme by SAS software. Baseline characteristics and post-intervention differences between the two groups were analyzed using two-sample t-tests or Wilcoxon rank-sum tests for continuous data, and chi-square or Fisher's exact test for categorical data. Within-group differences were

assessed using paired t-tests or Wilcoxon signed-rank tests. If the Shapiro-Wilk test indicated non-normality, the Wilcoxon test was used for comparison. Further analyses were planned using a generalized linear model (GLM) with covariates, but was not performed since there was no significant baseline difference. Data are presented as mean±standard deviation, median, minimum, maximum, or as proportion (%). The significance level was set at 0.05 for the efficacy, demographic, nutritional, and safety data analyses, using two-sided tests.

RESULTS

A total of 116 subjects were enrolled and randomized into the GBE and placebo groups at a ratio of 1:1. The full analysis (FA) set included 109 participants who met all the criteria and completed at least one efficacy evaluation. Seven participants were excluded from

the FA set owing to dropout or selection criteria violations. The per-protocol set included 86 participants who completed the trial without major compliance issues; 40 were from the GBE group and 46 from the placebo group, after excluding those with compliance violations or other protocol deviations (Fig. 2).

1. Baseline characteristics

Table 1 shows that the GBE groups had no significant difference in baseline characteristics, including demographics, clinical tests, lifestyle factors, and questionnaire scores.

2. Primary efficacy outcome

In this 8-week clinical study, the primary outcomes were the improvement rates on the ADAM questionnaire and total score on the AMS scale. The GBE group exhibited a significantly higher ADAM improvement rate of 70.00% (n=28) than the placebo group with

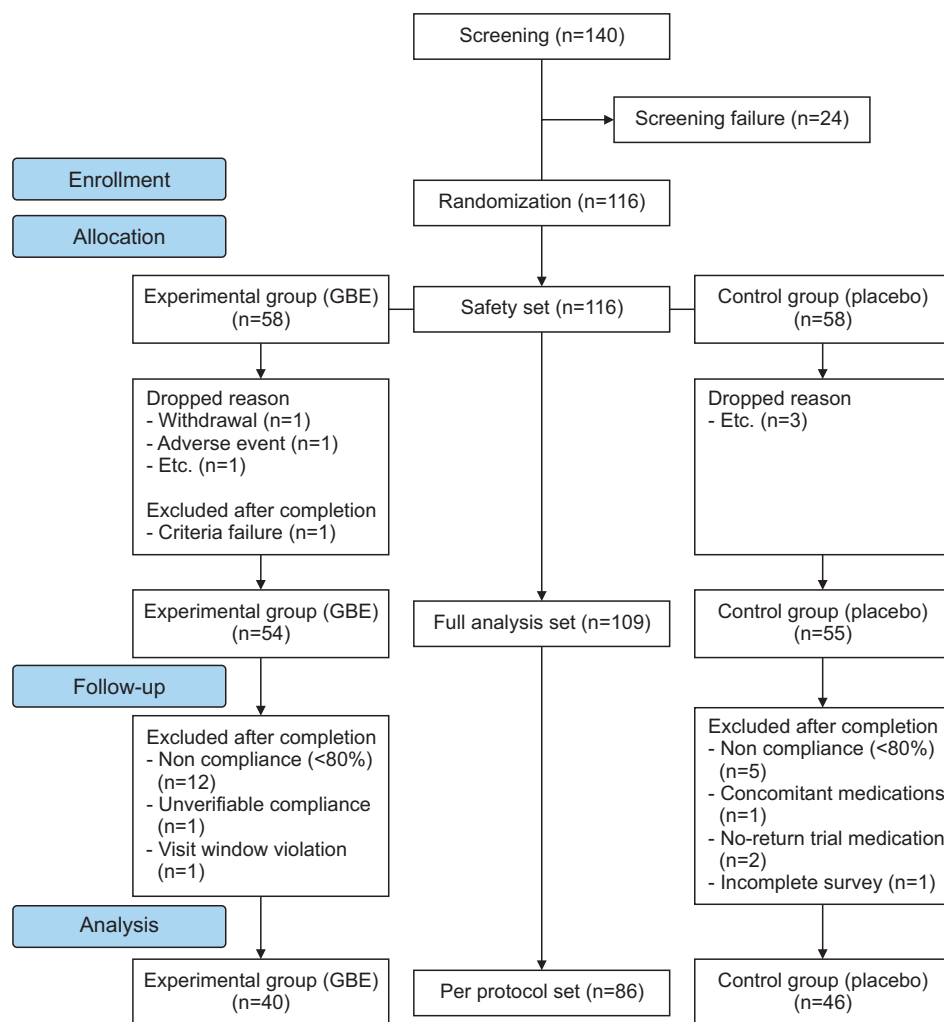


Fig. 2. Flowchart of participant status and analysis. GBE: ginseng berry extract.

Table 1. Demographic and baseline characteristics of the study population

Variable	GBE (n=40)	Placebo (n=46)	p-value
Demographic			
Age (y)	55.95±8.11	56.50±9.69	0.7780
Height(cm)	171.15±5.88	169.90±6.68	0.3618
Body weight (kg)	73.15±8.81	75.84±13.77	0.7454
No exercise status	3 (7.50)	12 (26.09)	0.1316
Non-smoker	14 (35.00)	23 (50.00)	0.1478
Non-drinker	13 (32.50)	10 (21.74)	0.7621
No perceived stress level	2 (5.00)	4 (8.70)	0.7687
Efficacy			
ADAM total	6.85±1.76	6.59±2.41	0.7593
AMS scale	50.40±11.98	50.09±10.81	0.8989
TT (ng/mL)	4.67±1.17	4.41±1.44	0.3741
FT (pg/mL)	8.04±2.22	7.78±2.27	0.9344
SHBG (nmol/L)	40.95±14.83	36.92±13.97	0.1984
Albumin (g/dL)	4.45±0.20	4.46±0.20	0.6705
TC (mg/dL)	193.75±31.71	197.09±44.11	0.6855
TG (mg/dL)	140.88±78.07	180.43±119.33	0.2140
HDL-C (mg/dL)	52.95±10.12	54.11±11.35	0.7848
LDL-C (mg/dL)	119.73±24.24	121.20±33.47	0.8145
IPSS	14.65±7.47	14.02±6.37	0.6748
IIEF total	26.53±16.96	28.96±15.27	0.4802
LH (mIU/mL)	3.70±1.77	3.64±2.14	0.7487
FSH (mIU/mL)	8.94±5.81	10.00±7.11	0.4410
DHEA-S (μg/dL)	204.10±76.65	205.19±122.96	0.5502
IGF-1 (ng/mL)	4,392.32±2,281.98	4,645.98±3,127.31	0.9138
E2 (pg/mL)	35.87±8.80	35.90±10.68	0.9891
FBS (mg/dL)	100.73±11.31	104.00±16.86	0.5214
Insulin (mU/L)	7.29±5.53	11.02±13.49	0.1222
HOMA-IR	1.89±1.75	3.08±4.93	0.0889
QUICKI	0.36±0.04	0.35±0.04	0.1117
HOMA-β	69.88±42.35	94.53±73.22	0.2141
SBP (mmHg)	126.85±13.05	132.35±13.11	0.0553
DBP (mmHg)	77.08±9.08	79.43±10.78	0.2794
Waist circumference (cm)	97.30±5.51	98.41±7.71	0.4393
Hip circumference (cm)	88.33±7.73	91.11±10.35	0.1664
Ginseng-related food	4.25±6.50	5.33±7.51	1.0000
Safety			
Number	58	58	
Pulse	77.41±10.84	75.95±11.19	0.3531
PSA (ng/mL)	0.87±0.57	1.00±0.73	0.2718

Categorical variables are shown as numbers (percentages), and continuous variables are displayed as mean±standard deviation.

GBE: ginseng berry extract, ADAM: androgen deficiency in aging male, AMS: aging male symptoms, TT: total testosterone, FT: free testosterone, SHBG: sex hormone-binding globulin, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, LH: luteinizing hormone, FSH: follicle-stimulating hormone, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, E2: estradiol, FBS: fasting blood sugar, HOMA-IR: homeostatic model assessment for insulin resistance, QUICKI: quantitative insulin sensitivity check index, HOMA-β: homeostatic model assessment beta, SBP: systolic blood pressure, DBP: diastolic blood pressure, PSA: prostate-specific antigen.

p-values were calculated using an independent two-sample t-test (calculated *via* Wilcoxon rank-sum test for non-parametric tests) for continuous variables and the chi-square or Fisher's exact test for categorical variables.

47.83% (n=22) (p=0.0376). The GBE group showed a larger decrease in the total score of AMS (-12.73±15.53) than the placebo group (-6.37±14.12), which was statistically significant (p=0.0205) (Table 2).

3. Secondary efficacy outcome

Improvement rates in specific ADAM questionnaire items showed more significant changes in the GBE

group, particularly in the item related to decreased sexual desire, where 70% of the GBE group reported improvements compared to 47.83% in the placebo group (p=0.0444).

The GBE group demonstrated a notable decrease in the IPSS for difficulty in initiation (-0.63±0.98) than the placebo group (-0.07±1.00) (p=0.0311). However, the total improvement in IPSS was greater in the GBE

Table 2. Change in efficacy-related parameters, with respect to baseline, after 8 weeks

Variable	GBE (n=40)	Placebo (n=46)	p-value
ADAM improvement rate, % (n/total)	70.00 (n=28/40)	47.83 (n=22/46)	0.0376
AMS scale total	-12.73±15.53	-6.37±14.12	0.0205
ADAM total	-3.83±2.92	-2.50±3.14	0.0468
IIEF total	11.73±17.34	4.35±16.02	0.0334
IIEF (erectile function)	5.28±8.16	1.54±7.61	0.0290
IIEF (overall sexual satisfaction)	1.80±2.17	0.87±1.98	0.0411
IPSS (difficulty in initiation)	-0.63±0.98	-0.07±1.00	0.0311
IPSS total	-4.68±6.40	-2.24±5.57	0.2295
TT (ng/mL)	-0.04±0.73	-0.10±0.77	0.7387
FT (pg/mL)	0.06±1.76	-0.20±1.92	0.2567
SHBG (nmol/L)	0.08±5.64	-1.90±6.85	0.1161
Albumin (g/dL)	-0.01±0.21	0.02±0.18	0.5772
TC (mg/dL)	-0.43±15.81	-5.35±22.68	0.6524
TG (mg/dL)	13.70±50.80	-18.20±88.45	0.0990
HDL-C (mg/dL)	0.53±6.18	0.00±6.02	0.6912
LDL-C (mg/dL)	-2.20±10.88	-4.37±14.47	0.7127
LH (mIU/mL)	-0.12±1.15	0.16±0.96	0.2265
FSH (mIU/mL)	0.05±1.30	0.17±1.30	0.7884
DHEA-S (µg/dL)	-6.92±25.90	-7.88±30.16	0.6808
IGF-1 (ng/mL)	-249.57±1296.76	382.63±2918.11	0.2173
E2 (pg/mL)	2.42±7.89	0.07±8.18	0.1799
FBS (mg/dL)	2.88±21.49	0.85±10.31	0.6180
Insulin (mU/L)	3.72±24.29	-1.11±9.95	0.7324
HOMA-IR	2.40±15.16	-0.45±3.97	0.9413
QUICKI	0.00±0.03	-0.00±0.03	0.8495
HOMA-β	3.93±31.95	-2.58±46.38	0.7520
SBP (mmHg)	-0.68±11.71	-1.11±9.76	0.8519
DBP (mmHg)	-1.03±10.26	0.20±8.66	0.5512
Waist circumference (cm)	-0.80±1.87	-0.39±1.47	0.2093
Hip circumference (cm)	-0.40±1.60	-0.07±1.12	0.8776
Weight (kg)	-0.14±1.63	0.09±1.27	0.4716

Categorical variables are presented as numbers (percentages), and continuous variables are presented as the mean±standard deviation.

GBE: ginseng berry extract, ADAM: androgen deficiency in aging male, AMS: aging male symptoms, IIEF: International Index of Erectile Function, IPSS: International Prostate Symptom Score, TT: total testosterone, FT: free testosterone, SHBG: sex hormone-binding globulin, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, LH: luteinizing hormone, FSH: follicle-stimulating hormone, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, E2: estradiol, FBS: fasting blood sugar, HOMA-IR: homeostatic model assessment for insulin resistance, QUICKI: quantitative insulin sensitivity check index, HOMA-β: homeostatic model assessment beta, SBP: systolic blood pressure, DBP: diastolic blood pressure, PSA: prostate-specific antigen.

p-values were calculated using an independent two-sample t-test (calculated *via* Wilcoxon rank-sum test for non-parametric tests) for continuous variables and the chi-square or Fisher's exact test for categorical variables.

group (-4.68 ± 6.40) than in the placebo group (-2.24 ± 5.57), although not statistically significant ($p=0.2295$).

The total IIEF score improvement was greater in the GBE group (11.73 ± 17.34) than in the placebo group (4.35 ± 16.02) ($p=0.0334$). Specifically, the erectile function domain improved significantly in the GBE group (5.28 ± 8.16) than in the placebo group (1.54 ± 7.61) ($p=0.0290$). Overall sexual satisfaction also improved more in the GBE group (1.80 ± 2.17) than in the placebo group (0.87 ± 1.98) ($p=0.0411$).

The total score of the additional analysis conducted on ADAM also reflected more substantial reductions in the GBE group (-3.83 ± 2.92) than in the placebo group (-2.50 ± 3.14) ($p=0.0468$) (Table 2).

Significant improvements were noted in the GBE group across the psychological, somatic, and sexual categories of AMS. Specific improvements included reductions in nervousness ($p=0.0326$), anxiety ($p=0.0031$), and exhaustion ($p=0.0315$); increased muscular strength ($p=0.0362$); and better sexual health indicators, such as beard growth ($p=0.0497$), sexual performance ($p=0.0012$), and libido ($p=0.0321$) (Table 3).

This study found no statistically significant difference between the groups in terms of serum hormone levels, lipid profiles, metabolic tests, or anthropometric measurements, including body composition. The chang-

es from baseline, after 8 weeks, for the individual items of the andropause-related questionnaires (ADAM, IIEF, and IPSS) are detailed in Appendix 1.

4. Safety

The safety evaluation included 116 participants (58 each in the GBE group and the control group). The GBE group reported five AEs (anal skin tags, hemorrhoids, nasopharyngitis, prostatic specific antigen increased, and urticaria) in four participants (6.90%), whereas the placebo group reported two AEs (abdominal discomfort and calculus urinary) in two participants (3.45%), none being serious. One participant discontinued treatment due to a non-product-related AE (hemorrhoid). All AEs were resolved without complications. Safety-related laboratory tests at eight weeks showed statistically significant differences in eosinophil counts, aspartate aminotransferase, and blood urea nitrogen levels; however, none was deemed clinically significant. No other significant laboratory difference was observed between the groups.

5. Supplementary efficacy assessment

Participants avoided regular ginseng-related foods during the intervention, with no significant difference in ginseng intake between the GBE and placebo groups

Table 3. Change in the individual items of AMS scale, with respect to baseline, after 8 weeks

Category	Symptom	GBE (n=40)	Placebo (n=46)	p-value
Somatic	Decline in general well-being	-0.68 ± 1.00	-0.37 ± 1.10	0.1177
	Joint pain and muscular ache	-0.63 ± 1.05	-0.43 ± 1.15	0.2439
	Excessive sweating	-0.43 ± 1.15	-0.39 ± 1.32	0.7418
	Sleep problems	-0.70 ± 1.30	-0.43 ± 1.29	0.2284
	Increased need for sleep, often feeling tired	-0.58 ± 1.17	-0.35 ± 1.20	0.4196
	Decrease in muscular strength	-0.93 ± 1.14	-0.50 ± 1.07	0.0362
Psycho	Irritability	-0.48 ± 1.09	-0.35 ± 1.20	0.5794
	Nervousness	-0.75 ± 1.24	-0.28 ± 0.98	0.0326
	Anxiety	-0.78 ± 1.00	-0.15 ± 1.05	0.0031
	Physical exhaustion/lacking vitality	-0.80 ± 1.09	-0.30 ± 1.24	0.0315
	Depressive mood	-0.73 ± 1.09	-0.28 ± 1.15	0.0632
	Feeling burnt out, having hit rock-bottom	-0.63 ± 1.35	-0.28 ± 1.17	0.2746
Sexual	Feeling that you have passed your peak	-0.85 ± 1.21	-0.59 ± 0.93	0.4322
	Decrease in beard growth	-0.63 ± 1.10	-0.24 ± 1.02	0.0497
	Decrease in ability/frequency to perform sexually	-1.20 ± 1.36	-0.37 ± 1.24	0.0012
	Decrease in the number of morning erections	-1.00 ± 1.24	-0.57 ± 1.33	0.0687
	Decrease in sexual desire/libido	-0.98 ± 1.21	-0.48 ± 1.19	0.0321

Values are presented as mean $\pm$ standard deviation.

AMS: aging male symptoms, GBE: ginseng berry extract.

Comparison between groups: p-value for the two-sample t-test (T) or Wilcoxon rank-sum test (W).

at visits two and four. The compliance rates were high at 98.15% for GBE and 95.73% for placebo, with no significant difference ($p=0.0511$). No significant difference in concurrent medication use was observed between the groups.

DISCUSSION

Andropause, which is often under-recognized compared to female menopause, involves a gradual decline in testosterone levels, leading to symptoms such as fatigue, low libido, mood changes, and health issues as men age. Despite the challenges in defining the threshold for testosterone decline, early diagnosis and treatment are crucial due to the significant impact of andropause on mental health and well-being [1-4].

Recent research on dietary supplements for male health has emphasized the potential of natural ingredients, such as zinc, ginseng, amino acids, and herbal extracts, to improve testosterone levels and sexual function through hormonal regulation and antioxidant properties [5-9]. However, despite promising findings, more rigorous clinical trials on their efficacy and safety profiles are still required, underscoring the trend toward evidence-based formulations in the supplement industry [23].

Ginseng berries, sourced from *Panax ginseng*, are recognized globally and listed as viable food ingredients by regulatory bodies in South Korea, China, Japan, Canada, the EU, and the USA. Research indicates that GBE, enriched with ginsenosides, manages andropause symptoms effectively, surpassing traditional ginseng root uses [24]. It enhances libido, sexual performance, testosterone levels, energy, mood stability, and hormonal balance in aging men [14]. Studies have confirmed its effectiveness in addressing metabolic and hormonal disorders [25], including decreased libido [15-17] and muscle mass [12], while enhancing insulin sensitivity [26]. The comprehensive approach, safety, and natural supplementation status of GBE position it as a safer alternative to TRT.

The benefits of GBE have been validated through detailed questionnaires and biochemical assessments, especially questionnaires allowing for individualized treatment approaches based on andropause symptoms and their severity over time [27]. The AMS scale measures symptom severity from androgen deficiency and categorizes the symptoms into psychological, somatic,

and sexual, with research showing a 15-point average improvement after testosterone treatment [19,20]. In comparison, our study found a reduction of 12.73 ± 15.53 points in AMS scores with GBE, still significant and comparable to testosterone treatment in symptom alleviation. Analysis of data from the GBE study revealed significant improvements across these categories. The GBE group experienced remarkable reductions in psychological symptoms such as nervousness, anxiety, and physical exhaustion, with clear statistical significance. With regard to somatic symptoms, a notable increase in muscle strength was observed. Improvements in beard growth, sexual performance, and libido were significant, indicating the potential efficacy of GBE in enhancing the overall quality of life of aging males by addressing various andropause-related symptoms. Increase in the IIEF score by 5.28 ± 8.16 points in the GBE group exceeded the clinically significant MCID of 4 for the erectile function domain [28]. Similarly, decrease in the IPSS total symptom score by 4.68 ± 6.40 points in the GBE group, despite having no statistical difference from placebo, surpassed the clinical significance with an MCID of 3 [29]. Additionally, the total ADAM score showed statistically significant improvements than in placebo ($p < 0.0468$) [19]. GBE treated andropause symptoms effectively, highlighting its positive effect on testosterone deficiency symptoms and broader benefits for the well-being of aging men without the need for laboratory tests [27].

This study confirmed the safety of GBE in improving the quality of life of men with andropause, showing minimal adverse effects, no serious event, and no significant difference in hematological or biochemical tests compared to placebo, supporting its use as a safe TRT alternative. Historical and modern safety data confirmed the safety of GBE, with animal studies showing a No observed adverse effect level of 500 mg/kg/day and human trials affirming safety at doses of 1,000 to 1,400 mg daily [13,16]. The long history of use of ginseng berries in Asia and its consumption in Korea and Hong Kong since 2014 with no reported side effects further support its global safety as a supplement and food ingredient in diverse regulatory environments.

The participants adhered to regular diets and avoided ginseng-related products to enable an unbiased assessment of GBE functionality during the study. Dietary surveys monitored food intake, established the GBE effects, and provided insights into nutritional

interactions for tailored recommendations, thereby minimizing confounding variables and improving its relevance [30].

Despite the observed improvements in questionnaire-based clinical parameters, no significant changes were detected in serum testosterone levels. This discrepancy may result from the inherent variability of testosterone levels, which fluctuate due to individual differences and measurement timing, making statistical significance difficult to achieve. Previous research supports the lack of correlation between testosterone levels and questionnaire-based outcomes such as ADAM and AMS [31].

An alternative explanation for the observed improvements is the potential role of mitochondrial function. Animal studies demonstrated that ginseng berry administration positively affects mitochondrial function, which plays a key role in energy production and cellular health [32]. This aligns with recent research trends focusing on mitochondrial activity as a potential mechanism for alleviating andropause symptoms. However, the exact mechanism remains unclear, and further studies incorporating biomarker analyses and mechanistic investigations are necessary to clarify these pathways.

Additionally, this study had a relatively small sample size, a short duration, and was limited to middle-aged Korean men, which may restrict the generalizability of the findings. Future research should involve larger, long-term studies with higher dosages and more diverse populations to validate the clinical relevance of GBE's effects and explore the mitochondrial hypothesis further. Despite these limitations, this study provides valuable evidence supporting the efficacy and safety of GBE as a potential alternative to TRT for managing andropause symptoms.

CONCLUSIONS

This study demonstrated the efficacy and safety of GBE. However, its findings are limited by its relatively short duration, small sample size, and demographic focus (middle-aged Korean men). This reduces its broader applicability. Future research should include extended studies with diverse populations to assess the long-term effects of GBE and its applicability to broader demographics, providing comprehensive insights. Additionally, exploring the combined or synergistic effects

of GBE and other treatments could enhance its application in managing andropause symptoms, thereby ensuring a more comprehensive treatment approach.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: JWK, SCM, SJL. Data curation: JWK, SCM. Formal analysis: JWK, SYP. Funding acquisition: SJL. Investigation: SYP, SJL. Methodology: SYP, SJL, IH. Project administration: JWK. Sources: JWK, SCM, SJL. Software: SYP, IH. Supervision: SJL. Validation: JWK, SCM, SYP. Visualization: SYP, IH. Writing – original draft: YSL, SYP, IH, JWK. Writing – review & editing: JWK, SYP.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article (and its supplementary files).

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Appendix 1. Changes in the individual items of andropause-related questionnaire, with respect to baseline, after 8 weeks

Changes in the individual items of androgen deficiency in aging males (ADAM) questionnaire (yes to no) from baseline to 8 weeks

Symptom	GBE(n=40)	Placebo(n=46)	p-value
Do you have a decrease in libido (sex drive)	28 (70.00)	22 (47.83)	
Do you have lack of energy	20 (50.00)	17 (36.96)	
Do you have a decrease in strength and/or endurance	18 (45.00)	17 (36.96)	
Have you lost height	12 (30.00)	9 (19.57)	
Have you noticed a decreased "enjoyment of life"	16 (40.00)	12 (26.09)	
Are you sad and/or grumpy	12 (30.00)	10 (21.74)	
Are your erections less strong	19 (47.50)	15 (32.61)	
Have you noticed a recent deterioration in your ability to play sports	17 (42.50)	12 (26.09)	
Are you falling asleep after dinner	5 (12.50)	8 (17.39)	
Has there been deterioration in your work performance	20 (50.00)	13 (28.26)	

Values are presented as number (%).

GBE: ginseng berry extract.

Comparison between groups: p-value for the two-sample t-test (T) or Wilcoxon rank-sum test (W).

Changes in the individual items of International Index of Erectile Function (IIEF) scores from baseline to 8 weeks

Symptom	GBE (n=40)	Placebo (n=46)	p-value
Erectile function	5.28±8.16	1.54±7.61	
Orgasmic function	1.23±3.29	0.61±3.21	
Sexual desire	1.15±2.14	0.57±1.78	
Intercourse satisfaction	2.28±3.23	0.76±3.92	
Overall satisfaction	1.80±2.17	0.87±1.98	

Values are presented as mean±standard deviation.

GBE: ginseng berry extract.

Comparison between groups: p-value for the two-sample t-test (T) or Wilcoxon rank-sum test (W).

Changes in the individual items of International Prostatism Symptom Score (IPSS) from baseline to 8 weeks

Symptom	GBE(n=40)	Placebo(n=46)	p-value
Incomplete emptying	-0.85±1.35	-0.59±1.29	
Frequency	-0.50±1.15	-0.15±1.28	
Intermittency	-0.73±1.18	-0.37±1.20	
Urgency	-0.60±1.35	-0.09±1.17	
Weak stream	-0.75±1.28	-0.52±1.31	
Straining	-0.63±0.98	-0.07±1.00	
Nocturia	-0.63±1.17	-0.46±1.13	

Values are presented as mean±standard deviation.

GBE: ginseng berry extract.

Comparison between groups: p-value for the two-sample t-test (T) or Wilcoxon rank-sum test (W).