

Original Research



Low-molecular-weight whey protein hydrolysate and ginseng berry extract enhance muscle strength and physical performance in Korean older adults: a randomized controlled trial

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ABSTRACT

BACKGROUND/OBJECTIVES: Sarcopenia can be prevented or mitigated through appropriate nutrition supplementation combined with exercise. We assessed the effects of 12-week supplementation with a mixture of low-molecular-weight whey protein hydrolysate (LMWPH) and ginseng berry extract (GBE), combined with resistance exercises, on muscle strength and physical performance in healthy Korean adults aged 60 yrs or older.

SUBJECTS/METHODS: This randomized, double-blind, placebo-controlled trial enrolled 100 participants aged 60 yrs or older, who were assigned to either the LMWPH-GBE group (5,000 mg/d, including LMWPH-GBE 4,500 mg) or placebo group. Participants performed lower-extremity strengthening exercises for 30–60 min at least 3 days per week. Handgrip strength, knee extensor muscle strength, muscle power and physical performance using short physical performance battery (SPPB), body composition, including appendicular skeletal muscle mass, skeletal muscle mass index, body mass index, fat mass and percentage, were assessed using dual energy absorptiometry.

RESULTS: The LMWPH-GBE group showed significant improvements in right-handgrip strength (0.53 ± 2.82 kg, $P = 0.027$) and total SPPB scores (0.18 ± 0.45 points, $P = 0.049$) compared with the placebo (-0.83 ± 2.86 kg and -0.05 ± 0.61 points, respectively). Additionally, the LMWPH-GBE group demonstrated improvements in the SPPB subscale compared with the placebo, with the 4-m gait speed changed by 0.26 ± 0.37 m/s (placebo: -0.02 ± 0.31 m/s, $P < 0.001$) and repeated chair stand time changed by -2.30 ± 1.78 s (placebo: -0.06 ± 1.60 s, $P < 0.001$). Knee extensor strength, muscle power, and muscle mass did not significantly differ between groups, likely because both groups performed lower-extremity strengthening exercises over 12 weeks.

CONCLUSION: Twelve weeks of LMWPH-GBE supplementation improved physical performance and muscle strength, particularly right-handgrip strength, in older adults. Low-dose protein (LMWPH) and botanical extract (GBE) supplementation shows potential as a practical dietary intervention for older individuals who may not tolerate higher protein doses.

Keywords: Whey protein; phytochemical; muscle strength; sarcopenia; dietary supplements

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Conflict of Interest

The authors declares no potential conflicts of interests.

Author Contributions

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INTRODUCTION

Sarcopenia is a geriatric syndrome involving a gradual decrease in skeletal muscle mass, strength, and physical performance during aging [1,2]. This condition affects approximately 4–45% of older individuals in Korea [3] and is associated with increased risks of frailty, falls, and chronic diseases. Despite its growing prevalence, there are currently no approved drugs for the prevention or treatment of sarcopenia, emphasizing the importance of non-pharmacological approaches including protein and nutritional supplementation, along with resistance strength training [4].

Dietary protein, which is essential for muscle protein synthesis (MPS), provides the amino acids required to build and maintain skeletal muscle. In older adults, insufficient protein intake can lead to slowing of MPS, promoting muscle breakdown and accelerating muscle loss [5]. High-quality proteins with a high biological value (BV), such as whey protein (BV = 104), are particularly effective in supporting MPS compared to plant proteins with lower BV, like soy (BV = 74) and casein (BV = 77) [6]. Hydrolyzed whey protein (WPH), produced through enzymatic hydrolysis, contains bioactive peptides with additional benefits including antioxidant and anti-inflammatory properties and small peptides that are rapidly absorbed and induce anabolism of skeletal muscle protein [7,8]. Particularly, low-molecular-weight WPH (LMWPH), comprised of peptides under 500 Da, has high bioavailability, enabling quick absorption and activation of the mTORC1 pathway, a key regulator of MPS [9]. This rapid absorption is particularly beneficial for older adults with anabolic resistance, where the efficiency of MPS declines despite adequate dietary protein intake [10]. Additionally, bioactive peptides in LMWPH exhibit anti-inflammatory and antioxidant properties, helping to counteract the chronic inflammation and oxidative stress commonly associated with sarcopenia [11].

Recent studies suggested that plant-derived compounds such as botanical extracts and phytochemicals can play a supportive role in muscle health [12–14]. Although they cannot replace adequate protein intake, resistance training, and proper rest, these compounds contribute to an optimal environment for muscle maintenance by reducing oxidative stress, decreasing inflammation, and enhancing MPS [15]. Several studies have investigated the potential of these compounds to support muscle health, including curcumin (found in *Curcuma longa*, turmeric), resveratrol, quercetin, epicatechin, ursolic acid, creatine, and ginseng berry extract (GBE) [13,16–21].

Panax ginseng contains bioactive ginsenosides with pharmacological effects, including anti-inflammatory, antihyperglycemic, and muscle-regenerative properties [22,23]. Although studies of the effects of ginseng on sarcopenia are still in experimental stages, several studies have suggested that ginseng extract helps maintain muscle function and promotes muscle recovery and growth [21,24,25]. GBE has a higher ginsenoside content than does the root extract [26] and can enhance muscle-related factors such as grip strength, muscle mass, and muscle fiber cross-sectional area while reducing body fat and obesity-related factors according to animal studies [27]. GBE activates the PI3K/Akt/mTOR pathway to promote MPS and inhibit protein degradation while lowering inflammatory cytokines and improving insulin sensitivity [28]. Building on this evidence, Han *et al.* [29] investigated the effects of LMWPH combined with GBE (LMWPH-GBE) and found that the combination was more effective in enhancing muscle strength and mass than were the individual effects in a mouse model. They reported that LMWPH and GBE exhibited a synergistic effect to increase

strength and muscle mass. Based on these results, we evaluated the effects of 12-week supplementation with LMWPH-GBE on muscle strength and physical performance in healthy Korean adults aged over 60 yrs.

SUBJECTS AND METHODS

Subjects and study design

From February to July 2022, healthy adults aged 60 yrs or over were recruited. The study was conducted at Chung-Ang University Hospital, Seoul, Korea. This study was approved by the Ethics Committee of the Institutional Review Board of Chung-Ang University Hospital in November 2021 (No. 2110-032-481) and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

This was a single-center, randomized, double-blind, placebo-controlled trial. After screening assessment, all participants who were registered based on the inclusion criteria were assigned a number according to block randomization and allocated to either the LMWPH-GBE supplemented treatment group or placebo group at a 1:1 ratio. The identities of all participants and investigators remained unknown until statistical analysis was completed.

Healthy adults aged 60 yrs or over were recruited. Participants with body mass index (BMI) of 18.5–30 kg/m² and with < 110% of the standard skeletal muscle mass as measured using the body composition analyzer InBody S10 (BioSpace, Inc., Cerritos, CA, USA) volunteered to participate in the study. Participants with the following conditions were excluded: participated in clinical trials, involved in diet and exercise programs in the last 3 mon; creatinine concentration ≥ 1.4 mg/dL; 2+ or greater proteinuria; aspartate aminotransferase or alanine aminotransferase concentration levels 1.5-fold higher than the upper limit; diabetes (diagnosed clinically or based on a fasting glucose concentration > 126 mg/dL); uncontrolled hypertension or notable cardiac disease, such as angina or myocardial infarction; intake of medications for psychiatric disease; intake of any protein supplement within the past 3 mon; received other research medications within the last 8 weeks; currently adjusting their diet for the purpose of disease management; a history of gastrectomy; hypersensitivity to the test food or its ingredients; normally consumed more than 140 g/week of alcohol; asthma or obstruction pulmonary disease, restrictive pulmonary disease; musculoskeletal disorders that made exercise difficult; or an allergic reaction to dairy protein and ginseng.

The sample size was determined using G*Power 3.1.9.7 to ensure sufficient power to detect differences in muscle strength. The calculation was guided by findings from a previous study [30] involving *Schisandra chinensis* extract, which measured knee extensor muscle strength using an isokinetic dynamometer at an angular velocity of 60°/s. In the prior study, the mean difference in muscle strength between groups was 3.2 N·m, with a pooled standard deviation of 4.6 N·m. For this study, the expected mean difference was conservatively adjusted to 2.9 N·m while retaining the same standard deviation, resulting in an effect size of 0.63. Power analysis was performed with the following inputs: a 2-tailed significance level (α) of 0.05, power ($1 - \beta$) of 0.80, and calculated effect size ($d = 0.63$). The results indicated that 80 participants (40 per group) were required to achieve adequate statistical power. To account for a potential dropout rate of 20%, the recruitment target was increased to 100 participants.

The participants visited the hospital at 6 weeks (± 8 d) and 12 weeks (± 8 d) after intervention initiation. Muscle strength and power, handgrip strength, body composition, and physical performance were measured and blood tests were performed. International Physical Activity Questionnaires were conducted at baseline and 12 week (± 8 d) to monitor changes in physical activity. The quality of life (QoL) (European Quality of Life 5 Dimensions 3 Level Version [EQ-5D-3L]) and nutritional status were assessed at each visit. Nutritional assessments were conducted via the 24-h recall method. CAN-Pro version 4.0 (Aided Nutritional Analysis Program for Professionals 4.0; Korean Nutrition Society, Seoul, Korea) was used to assess nutritional intake.

Intervention

The participants were assigned to 2 groups: those receiving LMWPH-GBE supplementation (5,000 mg/d, LMWPH-GBE 4,500 mg, and grain flavor 500 mg) or placebo (5,000 mg/d, cornstarch 4,500 mg, and grain flavor 500 mg). The mixtures were orally administered 2,500 mg twice daily (30 min after breakfast and lunch) for 12 weeks. An intake compliance $\geq 80\%$ was required for therapeutic efficacy and was verified by participants filling out their daily intake log. In addition, all participants were asked to perform body weight-based lower extremity strengthening exercises for 30–60 min/d for at least 3 d per week during the trial period and record their daily workout. The LMWPH-GBE supplement was provided by Maeil Health Nutrition Co., Ltd. (Pyeongtaek, Korea). Based on a previous study [28], an 8:1 mixture of LMWPH and GBE at a dose of 1,100 mg/kg/d for 8 weeks showed a positive impact on muscle function in 10-mon-old male C57BL/6J mice without affecting their body weight and food intake. Therefore, the daily intake for human application was calculated as 4,500 mg/d by applying a conversion coefficient (mouse-human 0.08) using the body surface area of humans and mice. The LMWPH-GBE mixture used in animal and human tests was produced using the same process.

Outcomes

Handgrip strength

The grip strength of both hands was measured using a digital dynamometer (TKK-5401 Grip-D; Takei Scientific Instrument Co., Ltd., Tokyo, Japan) after the participants were seated in a chair with their arms at a 90° angle. Each side was measured 3 times, and the maximum value was calculated.

Knee extensor muscle strength and muscle power

The knee extensor muscle strength and knee joint muscle power (extensors and flexors) of the participants were assessed at an angular velocity of 60°/s using Biodex System Pro 4 (Biodex Medical Systems, Inc., Shirley, NY, USA) isokinetic dynamometers at baseline and after 12 weeks of treatment. The participants were asked to perform extension and flexion 5 times; the peak torque value during extension was taken as muscle strength, and the average value of the 5 repetitions was considered muscle power.

Body composition and muscle mass

Body composition was measured using dual-energy X-ray absorptiometry (DEXA, Hologic, Inc., Marlborough, MA, USA) and bioelectrical impedance analysis (InBody S10; BioSpace, Inc.). Appendicular skeletal mass (ASM, normalized by height, ASM (kg)/height² (m²)) and percentage of body fat (total and trunk) were measured using DEXA. BMI (kg/m²), fat mass, skeletal muscle mass (kg), ASM (adopted normalized by weight, ASM (kg)/weight (kg) $\times$ 100) and skeletal muscle mass index (SMMI, skeletal muscle mass (kg)/height² (m²)) were assessed using bioelectrical impedance analysis.

Physical performance

A short physical performance battery (SPPB) was used to measure physical performance. SPPB involved a 4-m gait speed at a regular pace, 5-time sit-to-stand test, and 10 s balance test with the feet positioned side-by-side, semi-tandem, and in full tandem. The 4-m gait speed and 5-time sit-to-stand time were measured and scored. Each test was rated on a scale from 0 to 4 points, with the scores combined to give a total ranging from 0 to 12 and higher scores reflecting better functional performance.

Laboratory tests

Laboratory tests were performed to evaluate the efficacy and safety of LMWPH-GBE supplementation. Samples were collected after at least 8 h of fasting to assess changes in factors related to muscle strength (creatinine, protein, albumin, and prealbumin) and safety during the 12-week treatment period. Factors for safety evaluation included complete blood count (hemoglobin, white blood cell, platelets), glucose, aspartate aminotransferase, alanine aminotransferase, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglyceride, total cholesterol, Na, K, Cl, gamma glutamyl transferase, total bilirubin, lactate dehydrogenase, free fatty acid, total protein, creatinine kinase, albumin, prealbumin, insulin, and creatinine levels.

Statistical analysis

Statistical analyses were conducted using SPSS version 24 software (SPSS, Inc., Chicago, IL, USA). For continuous variables, independent *t*-test was used to compare the general characteristics (baseline) and changes after 12 weeks between the LMWPH-GBE (treatment group) and placebo groups. Chi-square test was applied for categorical variables, whereas paired *t*-test was used to compare baseline and 12-week data between the 2 groups. The level of significance was set at $P < 0.05$.

RESULTS

Baseline characteristics of participants

In total, 106 participants were screened, 100 of whom were enrolled in the study. Twelve participants were excluded because of withdrawal or violation of the study protocol (**Fig. 1**). After exclusions, 88 participants were included in the final analysis. The mean age of the participants was 67.99 ± 5.09 yrs (LMWPH-GBE group 67.70 ± 4.81 yrs, placebo group 68.27 ± 5.40 yrs, $P = 0.604$), and 67.0% ($n = 59$) of participants were female. There were no significant differences in baseline characteristics, including sex ratio, age, weight, height, daily energy intake, and physical activity level, between the placebo and LMWPH-GBE groups. Of the participants, 95.5% ($n = 84$) used their right side as the dominant limb (**Table 1**).

Effects of intervention on muscle strength and muscle power

Table 2 shows the effects of LMWPH-GBE intake on muscle strength (handgrip strength and knee extensor muscle strength) and power. At baseline, handgrip strength for all participants was 17.4–41.9 kg for males and 11.8–26.6 kg for females in the left hand and 17.9–46.1 kg for males and 14.2–31.3 kg for females in the right hand. After 12 weeks, the right-handgrip strength of the LMWPH-GBE group was significantly greater than that of the placebo group ($P = 0.027$). Additionally, in the LMWPH-GBE group, left-handgrip strength increased significantly after 12 weeks compared to that at baseline ($P = 0.047$). However, isokinetic evaluation (i.e., isokinetic strength of the knee extensor muscle and knee joint muscle power) did not differ between the groups.

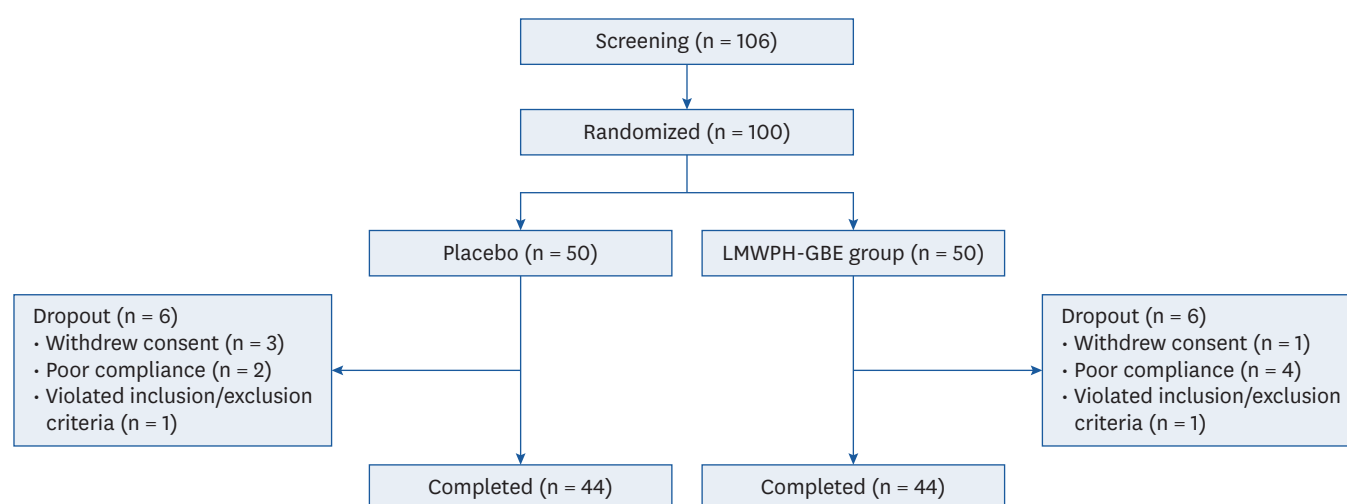


Fig. 1. Flow chart of the study participants.
LMWPH, low-molecular-weight whey protein hydrolysate; GBE, ginseng berry extract.

Table 1. Baseline characteristics of the participants

Variables	Placebo (n = 44)	LMWPH-GBE group (n = 44)	P-value ¹⁾
Sex			0.496
Female	28 (63.6)	31 (70.5)	
Male	16 (36.4)	13 (29.5)	
Age (yrs)	68.27 ± 5.40	67.70 ± 4.81	0.604 ²⁾
Weight (kg)	62.19 ± 8.57	61.29 ± 8.14	0.614 ²⁾
Height (cm)	159.10 ± 6.63	159.36 ± 7.56	0.867 ²⁾
Alcohol	18 (40.9)	14 (31.8)	0.375
Smoker	1 (2.3)	0 (0.0)	0.315
Energy intake (kcal/d) ³⁾	1,627.6 ± 560.4	1,439.4 ± 514.7	0.104 ²⁾
IPAQ	2,069.7 ± 1,784.0	1,871.0 ± 1,537.5	0.577 ²⁾
Dominant side of the limb			0.306
Right	41 (93.2)	43 (97.7)	
Left	3 (6.8)	1 (2.3)	

Values are shown as the mean ± SD or number (%).

LMWPH, low-molecular-weight whey protein hydrolysate; GBE, ginseng berry extract; IPAQ, international physical activity questionnaire.

¹⁾P-values were derived using χ^2 test; ²⁾P-values were derived using independent t-test; ³⁾Energy intake was measured using 24-h recall tasks.

Table 2. Effects of LMWPH-GBE supplementation on muscle strength and power

Variables	Placebo (n = 44)				LMWPH-GBE group (n = 44)				P-value ²⁾
	Baseline	12 weeks	Diff.	P-value ¹⁾	Baseline	12 weeks	Diff.	P-value ¹⁾	
Grip strength (kg)									
Left	23.65 ± 7.38	23.53 ± 6.55	-0.12 ± 2.87	0.782	22.89 ± 7.00	23.74 ± 7.57	0.85 ± 2.75	0.047	0.110
Right	25.33 ± 7.46	24.50 ± 7.19	-0.83 ± 2.86	0.059	24.06 ± 8.16	24.59 ± 7.10	0.53 ± 2.82	0.219	0.027
Knee extensor muscle strength (N·m)									
Left	86.38 ± 33.54	91.05 ± 33.47	4.67 ± 12.79	0.020	86.74 ± 26.80	90.21 ± 27.88	3.47 ± 14.54	0.120	0.683
Right	88.46 ± 31.74	90.25 ± 32.50	1.78 ± 12.45	0.347	88.92 ± 24.79	90.70 ± 25.54	1.78 ± 11.79	0.323	0.998
Knee extension muscle power (W)									
Left	49.18 ± 16.59	51.62 ± 16.91	2.44 ± 8.00	0.050	48.94 ± 16.43	54.12 ± 18.14	5.18 ± 8.18	< 0.001	0.116
Right	51.41 ± 15.97	54.42 ± 18.29	3.01 ± 6.78	0.005	52.00 ± 14.87	56.84 ± 17.42	4.85 ± 9.71	0.002	0.306
Knee flexion muscle power (W)									
Left	19.29 ± 9.12	19.96 ± 9.96	0.67 ± 5.66	0.436	18.76 ± 10.63	21.19 ± 9.85	2.43 ± 6.33	0.014	0.172
Right	20.06 ± 10.01	20.73 ± 10.55	0.66 ± 5.16	0.398	19.86 ± 9.58	21.19 ± 10.09	1.33 ± 6.05	0.151	0.578

Values are shown as the mean ± standard deviation.

LMWPH, low-molecular-weight whey protein hydrolysate; GBE, ginseng berry extract.

¹⁾P-values were derived using paired t-test; ²⁾P-values were derived using independent t-test.

Effects of intervention on muscle mass and body composition

Differences in body composition, including muscle mass, between baseline and after 12 weeks were measured using DEXA and bioelectrical impedance analysis (**Table 3**). Skeletal muscle mass and SMMI/height² in the LMWPH-GBE group increased significantly after 12 weeks compared with those at baseline (skeletal muscle mass, $P = 0.045$; SMMI/height²: $P = 0.044$). In contrast, the placebo group showed no significant differences between baseline and at 12 weeks. Fat mass decreased significantly in the LMWPH-GBE group ($P = 0.003$), whereas total fat (%) and trunk fat (%) significantly increased in the placebo group (total fat, $P = 0.045$; trunk fat, $P = 0.019$). The 2 groups showed no significant differences in any of the other indicators.

Effects of intervention on physical performance, laboratory tests, and QoL

At baseline, all participants had an SPPB score of at least 10. After 12 weeks, the LMWPH-GBE group showed significant improvement in the total SPPB score and subscale times (i.e., 4 m walking speed and repeated chair stand time) compared to the placebo group ($P < 0.05$), as shown in **Table 4**.

There were no differences in any blood parameters related to muscle strength between groups, except for a significant decrease in protein levels in the placebo group after 12 weeks of intervention ($P = 0.023$). The results of the EQ-5D-3L, a quality-of-life evaluation tool, showed no significant difference between the 2 groups; a significant increase was observed only in the LMWPH-GBE group ($P = 0.005$).

Table 3. Effects of LMWPH-GBE supplementation on body composition and muscle mass

Variables	Placebo (n = 44)				LMWPH-GBE group (n = 44)				P-value ²⁾
	Baseline	12 weeks	Diff.	P-value ¹⁾	Baseline	12 weeks	Diff.	P-value ¹⁾	
Skeletal muscle mass (kg)	22.55 ± 4.21	22.65 ± 4.30	0.09 ± 0.51	0.230	22.42 ± 4.22	22.56 ± 4.24	0.14 ± 0.46	0.045	0.629
ASM/height ² (kg/m ²)	5.85 ± 0.94	5.77 ± 0.93	-0.08 ± 0.19	0.007	5.81 ± 0.84	5.75 ± 0.86	-0.06 ± 0.24	0.090	0.668
ASM/weight × 100 (%)	27.53 ± 3.27	27.81 ± 3.34	0.28 ± 0.69	0.011	27.73 ± 3.46	28.21 ± 3.48	0.48 ± 0.64	< 0.001	0.164
SMMI (kg/m ²)	8.84 ± 1.00	8.87 ± 1.03	0.03 ± 0.19	0.245	8.75 ± 0.98	8.81 ± 0.97	0.06 ± 0.18	0.044	0.586
BMI (kg/m ²)	24.53 ± 2.68	24.53 ± 2.59	0.00 ± 0.50	0.976	24.07 ± 2.35	24.01 ± 2.37	-0.07 ± 0.43	0.318	0.526
Fat mass (kg)	20.61 ± 5.79	20.41 ± 5.67	-0.20 ± 1.11	0.251	19.97 ± 4.81	19.50 ± 4.62	-0.47 ± 0.98	0.003	0.222
Total fat (%)	37.29 ± 6.38	37.64 ± 6.04	0.36 ± 1.14	0.045	37.17 ± 5.15	37.30 ± 5.52	0.14 ± 1.44	0.532	0.428
Trunk fat (%)	38.04 ± 6.31	38.63 ± 5.99	0.59 ± 1.60	0.019	38.61 ± 5.02	38.83 ± 5.45	0.21 ± 2.07	0.497	0.347

Values are shown as the mean ± standard deviation.

LMWPH, low-molecular-weight whey protein hydrolysate; GBE, ginseng berry extract; ASM, appendicular skeletal muscle mass; SMMI, skeletal muscle mass index; BMI, body mass index.

¹⁾P-values were derived using paired t-test; ²⁾P-values were derived using independent t-test.

Table 4. Effects of LMWPH-GBE supplementation on physical performance, laboratory tests, and quality of life

Variables	Placebo (n = 44)				LMWPH-GBE group (n = 44)				P-value ²⁾
	Baseline	12 weeks	Diff.	P-value ¹⁾	Baseline	12 weeks	Diff.	P-value ¹⁾	
SPPB, total score	11.82 ± 0.50	11.77 ± 0.57	-0.05 ± 0.61	0.623	11.82 ± 0.45	12.00 ± 0.00	0.18 ± 0.45	0.010	0.049
4 m gait speed (m/sec)	1.35 ± 0.29	1.33 ± 0.26	-0.02 ± 0.31	0.718	1.34 ± 0.25	1.61 ± 0.31	0.26 ± 0.37	< 0.001	< 0.001
Repeated chair stand time (s)	8.71 ± 1.84	8.65 ± 1.98	-0.06 ± 1.60	0.815	9.01 ± 2.09	6.71 ± 1.59	-2.30 ± 1.78	< 0.001	< 0.001
Creatinine (mg/dL)	0.74 ± 0.14	0.72 ± 0.16	-0.02 ± 0.08	0.155	0.74 ± 0.18	0.74 ± 0.18	-0.01 ± 0.08	0.646	0.529
Protein (g/dL)	7.20 ± 0.39	7.10 ± 0.34	-0.09 ± 0.26	0.023	7.13 ± 0.36	7.11 ± 0.41	-0.02 ± 0.25	0.585	0.196
Albumin (g/dL)	4.40 ± 0.21	4.35 ± 0.21	-0.05 ± 0.16	0.057	4.34 ± 0.25	4.30 ± 0.27	-0.04 ± 0.14	0.051	0.831
Prealbumin (mg/dL)	27.03 ± 4.59	27.55 ± 3.97	0.53 ± 2.49	0.168	27.21 ± 4.03	28.01 ± 4.97	0.80 ± 3.15	0.101	0.659
EQ-5D	0.939 ± 0.140	0.975 ± 0.040	0.037 ± 0.150	0.104	0.962 ± 0.060	0.985 ± 0.030	0.023 ± 0.050	0.005	0.567

Values are shown as the mean ± standard deviation.

LMWPH, low-molecular-weight whey protein hydrolysate; GBE, ginseng berry extract; SPPB, short physical performance battery; EQ-5D, European Quality of Life 5 Dimensions.

¹⁾P-values were derived using paired t-test; ²⁾P-values were derived using independent t-test.

Safety and adverse effects

Blood analysis for safety monitoring revealed a significant difference in the change in gamma glutamyl transferase between groups, but the level was within the normal range (female: 9–41 IU/L, male: 13–64 IU/L). Other safety parameters showed no significant differences between groups. No abnormal findings were observed in the individual results (**Table 5**). A total of 23 adverse events (AEs) were reported in 19 patients during the 12-week study period. However, there was no significant difference in the number of participants experiencing AEs between groups (data not shown). The reported AEs resolved, and there were no dropouts among participants due to AEs. Additionally, no serious AEs were reported.

DISCUSSION

Several previous studies demonstrated that LMWPH affects sarcopenia, but only a few have reported the effect of GBE on muscle or sarcopenia in mouse models [27,28]. However, the effect of the LMWPH-GBE mixture on muscle mass and sarcopenia in humans has not been reported. In addition, most studies of WPH in older adults used doses of 20–35 g/d [31–33]. However, consuming such large amounts of protein may be challenging for older individuals with impaired digestive function. Therefore, we investigated the positive effects of low-dose protein combined with GBE on muscle strength and physical performance.

The results of handgrip strength and SPPB tests revealed that daily administration of LMWPH-GBE for 12 weeks improved physical performance in physically active adults aged 60 yrs or older. However, LMWPH-GBE supplementation had no significant effect on muscle mass or knee extensor muscle strength of the lower extremities. During the 12-week study, 23 AEs were reported in 19 participants. The reported AEs were mild symptoms unrelated

Table 5. Changes in laboratory values for safety during 12-week study period

Variables	Reference	Placebo (n = 50)			LMWPH-GBE group (n = 50)			P-value ²⁾
		Baseline	12 weeks	P-value ¹⁾	Baseline	12 weeks	P-value ¹⁾	
RBC (10 ¹² /L)	F: 3.7–5.0, M: 4.3–5.6	4.54 ± 0.45	4.47 ± 0.41	0.007	4.58 ± 0.39	4.51 ± 0.38	0.007	0.940
Hb (g/dL)	F: 11–15, M: 13–17	13.62 ± 1.24	13.48 ± 1.16	0.037	13.62 ± 1.05	13.57 ± 0.96	0.416	0.352
WBC (10 ⁹ /L)	3.5–10	5.67 ± 1.26	5.56 ± 1.21	0.492	5.61 ± 1.24	5.32 ± 1.21	0.004	0.301
Hct (%)	F: 34–44, M: 40–50	42.09 ± 3.56	41.84 ± 3.25	0.245	42.06 ± 3.06	41.85 ± 2.69	0.282	0.913
Platelet (10 ⁹ /L)	140–400	244.38 ± 50.03	232.64 ± 52.71	0.007	235.86 ± 46.89	224.62 ± 46.54	< 0.001	0.920
Glucose (mg/dL)	74–107	99.14 ± 11.31	103.18 ± 13.54	0.004	98.80 ± 8.63	100.80 ± 10.93	0.031	0.209
Insulin (mU/L)	3–25	4.24 ± 2.08	4.92 ± 4.59	0.216	4.74 ± 2.35	4.86 ± 2.44	0.645	0.347
CK (IU/L)	0–190	111.72 ± 55.19	116.24 ± 66.40	0.602	112.44 ± 50.03	118.86 ± 60.60	0.345	0.862
Total bilirubin (mg/dL)	0.1–1.3	0.82 ± 0.32	0.78 ± 0.22	0.089	0.77 ± 0.19	0.76 ± 0.20	0.394	0.481
Na (mEq/L)	137–145	141.32 ± 2.09	142.42 ± 1.51	< 0.001	141.74 ± 1.74	142.48 ± 1.72	0.013	0.364
K (mEq/L)	3.5–5.3	4.36 ± 0.35	4.44 ± 0.30	0.061	4.31 ± 0.31	4.37 ± 0.28	0.134	0.806
Cl (mEq/L)	99–108	103.94 ± 2.11	105.38 ± 1.75	< 0.001	104.10 ± 2.02	105.30 ± 2.15	< 0.001	0.561
AST (IU/L)	0–34	25.04 ± 5.82	24.58 ± 5.09	0.449	27.08 ± 7.70	25.56 ± 5.87	0.147	0.377
ALT (IU/L)	0–40	22.34 ± 11.20	22.12 ± 10.02	0.848	23.50 ± 10.75	21.46 ± 6.82	0.140	0.308
GGT (IU/L)	F: 9–41, M: 13–64	25.82 ± 14.57	26.76 ± 17.53	0.388	21.48 ± 12.31	19.60 ± 8.51	0.039	0.046
LDL (mg/dL)	54–159	111.08 ± 33.88	108.58 ± 37.08	0.393	114.62 ± 33.40	110.08 ± 30.01	0.191	0.650
HDL (mg/dL)	40–88	57.12 ± 14.20	57.66 ± 11.97	0.602	56.78 ± 12.34	56.72 ± 12.17	0.943	0.652
Total cholesterol (mg/dL)	132–239	195.40 ± 36.82	191.62 ± 39.29	0.262	199.54 ± 35.75	193.80 ± 31.13	0.165	0.710
Triglyceride (mg/dL)	44–199	99.00 ± 48.59	102.74 ± 50.37	0.460	103.44 ± 51.28	111.02 ± 96.65	0.424	0.719
FFA (uEq/L)	172–586	536.46 ± 193.50	457.10 ± 192.30	0.025	485.68 ± 134.13	488.54 ± 181.15	0.913	0.059

Values are shown as the mean ± standard deviation.

LMWPH, low-molecular-weight whey protein hydrolysate; GBE, ginseng berry extract; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; Hct, hematocrit; CK, creatine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; LDL, low density lipoprotein; HDL, high density lipoprotein; FFA, free fatty acid.

¹⁾P-values were derived using paired t-test; ²⁾P-values were derived using independent t-test.

or unlikely to be associated with LMWPH-GBE supplementation. There was no significant difference in the number of participants experiencing AEs between the LMWPH-GBE and placebo groups.

The mechanism underlying the effects of LMWPH-GBE on muscle strength, function, and mass was identified by Han *et al.* [28]. In that study, administering the LMWPH-GBE mixture to aged mice resulted in a dose-dependent increase in handgrip strength and muscle mass, elevated anti-inflammatory cytokines, and an increase in mitochondria, which are crucial for energy production in skeletal muscles and in determining muscle function and strength. In addition, the LMWPH-GBE mixture increased activation of the PI3K/Akt pathway and gene expression of muscle regeneration-related factors as well as decreased myostatin, which interferes with MPS and regeneration. Based on these results, consumption of the LMWPH-GBE mixture may lead to effects similar to those of exercise. In another study, Han *et al.* [29] found that LMWPH and GBE had synergistic effects on muscle mass; GBE was more effective for protein synthesis, whereas LMWPH tended to be slightly more effective for protein degradation.

Specifically, the LMWPH and GBE mixture activated MPS through the PI3K/Akt/mTORc1 pathway and inhibited muscle protein degradation by inhibiting ubiquitin-proteasome system and autophagy-lysosome systems. These effects result in increased levels of total muscle protein, thereby increasing muscle mass and strength.

We found that LMWPH-GBE increased muscle strength, particularly right handgrip strength. This right-hand-specific increase is likely attributed to the lower prevalence of left-handedness, which occurs in only 8–15% of individuals [34]. Only 4.5% of our participants were left-handed. An imbalance in muscle function, including muscle strength, coordination, and accuracy, between the dominant and non-dominant sides is associated with variations in the muscle cell count and size. Typically, the strength difference between the 2 sides range from 5% to 10% [35]. Our results showed that after consuming the LMWPH-GBE mixture for a short period of 12 weeks, the muscle strength of the dominant side increased by more than that of the non-dominant side, which is likely attributed to frequent use of the dominant side in daily life or effects of exercise. However, no significant differences were observed in knee extensor muscle strength or muscle power between groups. Although muscle power showed greater improvement in the intervention group than in the placebo group, both groups exhibited improvements, with no significant difference between the 2 groups. Vechin *et al.* [36] reported that when older adults performed low-intensity resistance training with blood flow restriction for 12 weeks, their muscle strength and mass increased without additional supplements, such as protein, indicating that resistance exercise improves muscle strength and mass. In this study, the participants were instructed to perform body weight-based lower extremity strengthening exercises for 30 min to 1 h 3 times per week. Considering the results of previous studies regarding exercise, the overall increase in knee extensor muscle strength and muscle power in the experimental and placebo groups in the present study is likely attributable to the effects of exercise rather than to taking LMWPH-GBE.

Notably, the total SPPB score and changes in subscale scores improved in the experimental group after 12 weeks of treatment with the LMWPH-GBE mixture. The SPPB was previously established as a reliable indicator of mobility limitations and mortality [37], and recent evidence has shown that muscle strength has a greater impact on physical performance than on muscle mass in older adults [38]. Particularly, Stevens *et al.* [39] established a relationship between the SPPB total score and its subscales with handgrip strength, and

Legrand *et al.* [40] suggested that low physical performance assessed by the SPPB in older adults was associated with low handgrip strength. Therefore, in this study, the improvement in SPPB performance may have been influenced by improvements in muscle strength (grip strength and knee extensor muscles). Handgrip strength and physical performance (SPPB), which are both key diagnostic criteria for sarcopenia, showed significant improvement in the experimental group compared to those in the placebo group. Thus, consuming the LMWPH-GBE mixture for 12 weeks or longer may prevent or improve the decline in physical performance due to aging to some extent.

Improvements in handgrip strength and physical performance (SPPB) by consuming the LMWPH-GBE mixture can also affect the QoL of older adults. The QoL of older adults consists of 3 important factors: mood (psychological factor), the capability to perform basic daily activities required for living (physical factor), and the ability to live independently (social factor) [41]. Therefore, disability and declining physical freedom or psychological health are major factors that reduce QoL. Lower handgrip strength and balance ability in older adults are associated with lower QoL, which is associated with higher morbidity [42]. Specifically, balance is among the most important requirements in everyday life. When balance becomes compromised, the risk of falling increases, potentially leading to a fear of falling, reduced mobility, disability, and social isolation, all of which can negatively impact the overall health and QoL of older adults [43]. These results suggest that QoL becomes more important with age. Although the older adults in the study did not show a significant decline in QoL, the experimental group showed an increased QoL, suggesting that improvements in handgrip strength and physical performance after consuming the experimental food for 12 weeks also influenced QoL.

In contrast to previous experimental animal studies showing that LMWPH-GBE supplementation may increase muscle mass and strength, the results of this study showed that LMWPH-GBE supplementation did not affect muscle mass or body fat-related indicators despite an increase in handgrip strength (muscle strength) and physical performance. However, previous studies [44-46] showed inconsistent results regarding the relationship among muscle mass, muscle function decline, and muscle strength; thus, we assumed that an increase in muscle strength and function is not necessarily accompanied by an increase in muscle mass. As reported in previous studies of the effects of exercise, exercise initially increases the efficiency of the nervous system, which can first increase muscle strength and then lead to hypertrophy or an increase in muscle mass. However, the increase in muscle mass in older adults may be both slower and lower than that in younger age groups. The findings of these previous studies align with those of the current study. In addition, in within-group comparison, the experimental group showed slight improvements in some outcomes related to muscle mass and body composition. It may be difficult to detect changes following consumption of an experimental food for a short period. Therefore, consuming experimental food for a longer period may positively affect body composition changes, such as by increasing muscle mass and decreasing body fat. Furthermore, previous animal studies showed that LMWPH-GBE has a dose-dependent effect on muscle mass and muscle strength. The participants in the present study were older adults over the age of 60 yrs who had difficulty gaining muscle mass. Thus, further studies are required to validate the effects of higher doses of the LMWPH-GBE mixture and to investigate its application in younger participants to confirm its efficacy in enhancing muscle mass and improving body composition. This study had several limitations, including being conducted at a single medical institution. Furthermore, participants reported nutrient intake using the

24-h recall method, which may not accurately reflect their usual dietary habits. In addition, the 12-week study period was too short to observe long-term changes in muscle mass or body composition. Despite these limitations, the results of this study remain valuable. To the best of our knowledge, this is the first clinical study conducted as a randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of LMWPH-GBE supplementation in older adults. Furthermore, we demonstrated the positive effects of the LMWPH-GBE mixture on muscle strength and physical performance.

Twelve weeks of LMWPH-GBE mixture supplementation improved physical performance and muscle strength in older adults. Although higher doses of protein supplements are typically recommended, achieving this level of intake can be challenging for older adults with reduced digestive function. Notably, we demonstrated that even low doses of protein (LMWPH) combined with GBE supplementation enhanced both physical performance and muscle strength.

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