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Research article

Influence of *Panax ginseng* on obesity and gut microbiota in obese middle-aged Korean women

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ABSTRACT

Background: Gut microbiota is regarded as one of the major factors involved in the control of body weight. The antiobesity effects of ginseng and its main constituents have been demonstrated, but the effects on gut microbiota are still unknown.
Methods: To investigate the effect of ginseng on gut microbiota, 10 obese middle-aged Korean women took *Panax ginseng* extracts for 8 wk and assessment of body composition parameters, metabolic bio-markers, and gut microbiota composition was performed using 16S rRNA gene-based pyrosequencing at baseline and at 8 wk. Significant changes were observed in body weight and body mass index; however, slight changes were observed in gut microbiota. We divided the participants into two groups, the effective and the ineffective weight loss groups, depending on weight loss effect, in order to determine whether the antiobesity effect was influenced by the composition of gut microbiota, and the composition of gut microbiota was compared between the two groups.
Results: Prior to ginseng intake, significant differences of gut microbiota were observed between both at phyla and genera and the gut microbiota of the effective and ineffective weight loss groups was segregated on a principal coordinate analysis plot.
Conclusion: Results of this study indicate that ginseng exerted a weight loss effect and slight effects on gut microbiota in all participants. In addition, its antiobesity effects differed depending on the composition of gut microbiota prior to ginseng intake.

1. Introduction

Ginseng (the root of *Panax ginseng* Meyer, Araliaceae) has been used in herbal medicine as a general tonic for the promotion of health in Asian countries, including Korea, China, and Japan for 1,000 years [1]. The pharmacological properties of ginseng are attributed to ginsenosides, also referred to as steroid saponins, which are found in extracts of ginseng [2]. The pharmacological effects of ginseng extracts and ginsenosides have been reported to show various biological activities in inflammation, immunology, and cancer [3—5]. The effects of ginseng on obesity and metabolic disease, such as hypertension, diabetes, and hyperlipidemia, have also been reported [6—10].

Obesity is a serious health problem that has become prevalent in developed countries in recent years and is a risk factor for metabolic disease [11]. Recent studies have demonstrated a link between diet-induced obesity and changes in the gut microbial ecology, resulting in an increased capacity of the distal gut microbiota to promote host adiposity [12,13]. Animal and human studies have revealed a remarkable microbial influence on host metabolism, energy utilization and storage, and metabolic disease [14—16]. Gut microbiota is regarded as one of the major etiological factors involved in the control of body weight, so that drugs or components that help to maintain balance in the composition of the gut microbiota can increase the antiobesity effect [17,18].

Although the antiobesity effects of ginseng have been reported, whether or not it has an effect on the gut microbiota is still unknown. Other studies on ginseng-related gut microbiota have reported that metabolic activity of ginsenoside Rb1 to compound K (a metabolite of ginseng saponin) is variable between individuals,

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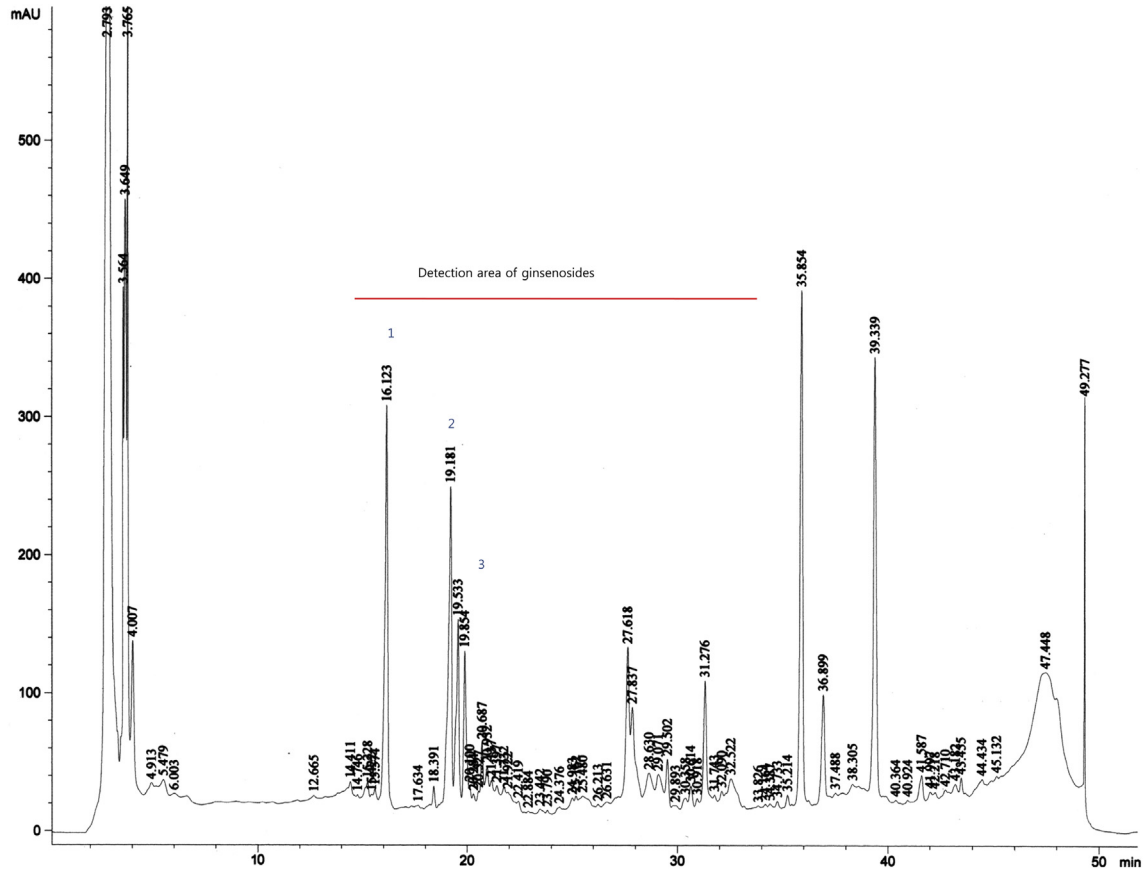E-mail address: kimklar@dongguk.ac.kr (H. Kim).

Fig. 1. High performance liquid chromatography analysis of *Panax ginseng* extracts. Peaks: (1) Rg1; (2) Rf; and (3) Rc.

depending on the composition of gut microbiota in particular [19,20].

Therefore, this study was conducted to assess the effects of ginseng on obesity and gut microbiota using pyrosequencing based on the 16S rRNA gene. In addition, the difference of its antiobesity effects depending on gut microbiota composition was also investigated.

2. Materials and methods

2.1. Study participants and design

This study was approved by the Institutional Review Board of Dongguk University Ilsan Hospital (Gyeonggi-do, Korea; approval no. 2012-SR-25). Participants were recruited by advertisements in the local newspaper or by posters in the hospital. For qualification, participants should be obese [body mass index (BMI) $\geq$25 kg/m^2] and female aged 40–60 yr. They must have been weight-stable within $\pm$10% during the past 6 mo, and free from antibiotics, probiotics, or any drugs that could impact their weight for the past

3 mo. Participants with weight-influencing diseases, including hyper/hypothyroidism, heart diseases, psychogenic diseases, or other chronic systemic diseases were excluded. Smokers or pregnant women confirmed by a positive hCG screening test were also excluded. Nineteen participants were recruited, and 10 of them completed the study. The participants were asked not to change their exercise or diet habits during the 8-wk clinical trial. During the study, participants who failed to take <80% of the required dose of medicine, retracted their consents due to inconvenience (personal choices), or refused to have communication with members of the research staff were dropped from the study.

2.2. Herbal preparation

Panax ginseng extracts were manufactured and provided by Korea Medicine Biofermentation Co., Ltd (Andong, Korea).

Table 1
Progress of Analysis in the Course of the Study

	Blood analysis	Stool analysis	BP	BW	WC	Body composition analysis
Visit 1 (wk 0)	O	O	O	O	O	O
Visit 2 (wk 2)			O	O	O	O
Visit 3 (wk 4)			O	O	O	O
Visit 4 (wk 6)			O	O	O	O
Visit 5 (wk 8)	O	O	O	O	O	O

BP, blood pressure; BW, body weight; WC, waist circumference.

Table 2
Changes of Anthropometric and Biochemical Measurement

Parameters	Prior to	After	p
Age	50.40 ± 4.95		
BW (kg)	71.39 ± 4.95	70.33 ± 5.38	0.042*
BMI (kg/m^2)	28.35 ± 2.00	27.87 ± 1.97	0.031*
WC (cm)	94.08 ± 7.12	92.50 ± 7.08	0.058
Body fat percentage (%)	37.89 ± 4.27	37.24 ± 5.21	0.544
TC (mg/dL)	209.90 ± 27.23	211.00 ± 27.30	0.821
TG (mg/dL)	136.50 ± 67.48	139.20 ± 53.07	0.841
HDL (mg/dL)	56.80 ± 14.54	56.20 ± 13.81	0.853
Glucose (mg/dL)	108.10 ± 13.30	113.60 ± 13.15	0.100

Data are presented as mean ± SD.
* $p < 0.05$.
BMI, body mass index; BW, body weight; HDL, high-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Table 3
Summary of Estimated Diversities Obtained from Pyrosequences

Sample		Analyzed reads	Normalized reads	Observed OTUs	Estimated OTUs (Chao1)	Shannon diversity	Good's coverage
Prior to	1	1,866	1,866	336	1,728.13	3.67	0.86
	2	2,923	2,000	340	3,087.25	3.20	0.85
	3	2,753	2,000	243	1,743.23	2.96	0.90
	4	5,354	2,000	246	1,103.37	3.68	0.91
	5	4,863	2,000	350	1,988.45	3.89	0.87
	6	2,485	2,000	227	595.88	3.63	0.93
	7	3,320	2,000	179	485.71	3.01	0.94
	8	3,334	2,000	213	717.79	3.38	0.93
	9	4,503	2,000	427	3,647.56	4.32	0.83
	10	5,070	2,000	218	784.25	3.37	0.92
After	1	2,056	2,000	372	1,440.03	4.14	0.87
	2	2,262	2,000	343	2,893.88	3.38	0.85
	3	2,953	2,000	244	1,544.20	2.96	0.90
	4	4,922	2,000	297	1,394.29	3.49	0.89
	5	5,137	2,000	522	3,800.79	4.65	0.79
	6	4,345	2,000	415	1,555.36	4.21	0.85
	7	3,209	2,000	229	913.00	3.65	0.92
	8	2,417	2,000	96	255.00	2.59	0.97
	9	3,510	2,000	159	366.83	3.29	0.96
	10	6,329	2,000	163	649.77	2.47	0.94

OTU, operational taxonomic unit.

Quantities of the freeze-dried granulated extracts weighing 4 g each were packed in paper medicine pockets. The medicines were distributed to the participants per 2 wk at every visit. The participants were asked to take one packet two times/d. The herbal medicines were distributed to the participants by the administrative pharmacist in the dispensary of the hospital.

2.3. Ginsenosides analysis

Ginsenosides were determined using high performance liquid chromatography (HP 1050, AGILENT, Santa Clara, CA, USA), the analytical column was an Ultrasphere ODS (C18, 5 μm, 4.6 mm × 250 mm, Shiseido, Tokyo, Japan). The two mobile phases
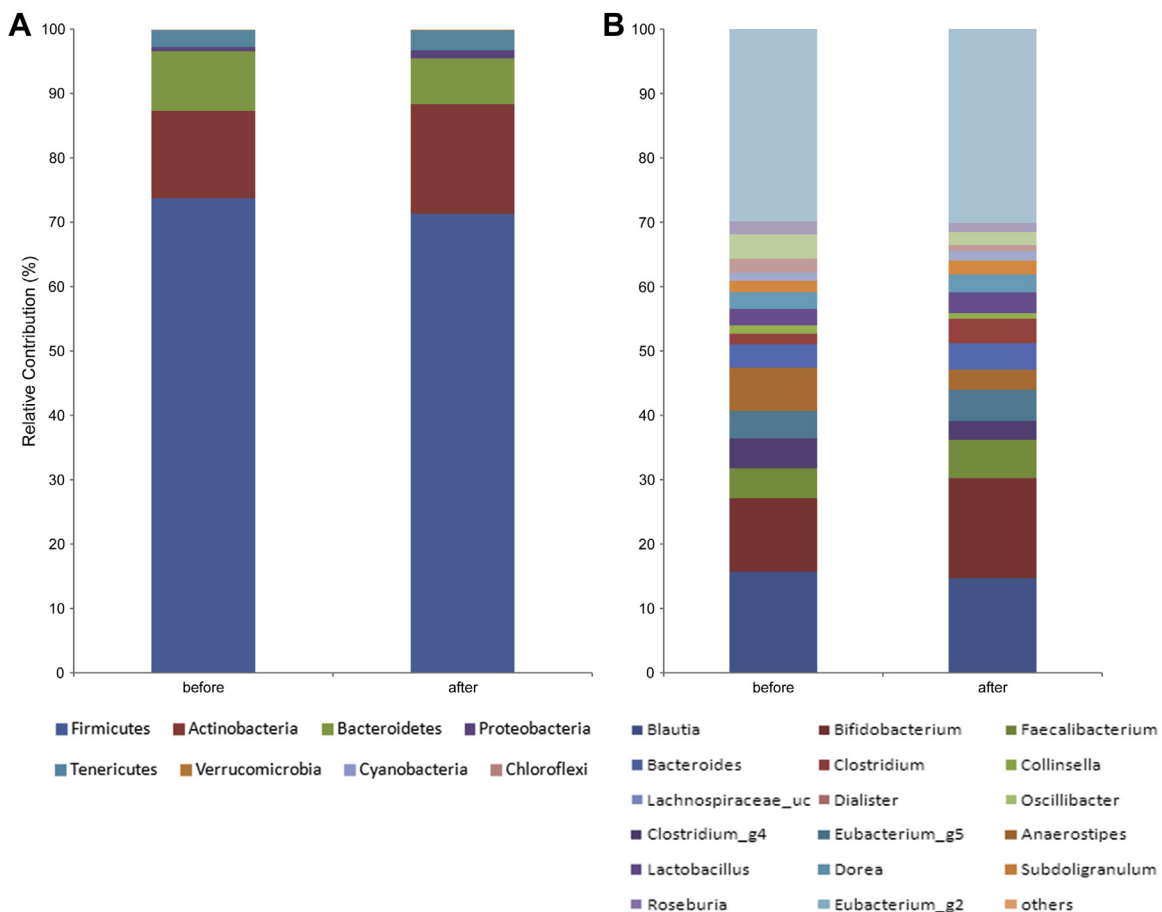

Fig. 2. The phylum and genus composition of fecal bacteria were compared between prior to and after treatment in a total of 10 participants. The relative abundance of dominant phyla identified from pyrosequencing data is shown. (A) Phylum composition of fecal bacteria. (B) Genus composition.
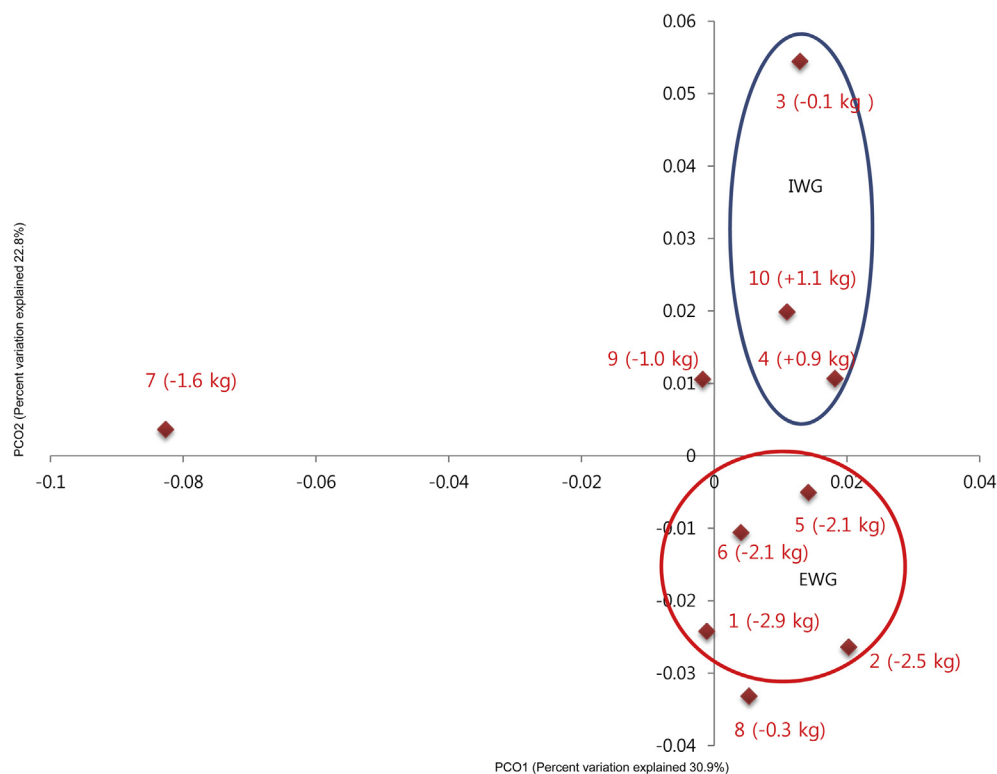
Fig. 3. Principal coordinate analysis (PCoA) plot in a total of 10 participants. The plot shows the clustering pattern depending degree of weight loss. The participants' number and body weight change are shown. EWG, effective weight loss group; IWG, ineffective weight loss group.

were water (Samchun Chemical, Gyeonggi, Korea) and acetonitrile (Samchun Chemical, Gyeonggi, Korea). The flow rate was set at 0.4 mL/min and wavelength was 203 nm. Seventeen saponins (Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2S, Rg2R, Rg3S, Rg3R, Rh1, Rh2S, Rh2R, C-K, F1, F2; Sigma—Aldrich, St Louis, MO, USA) were used as standards for this purpose. Rg1, Rf, and Rc were the main contents, the retention time of Rg1 was 16.12 min, that of Rf was 19.18 min, and that of Rc was 19.53 min. The concentration of Rg1 was 3.73%, that of Rf was 3.57%, and that of Rc was 1.87% (Fig. 1).

2.4. Assessment

Progress of analytical measurements in the study is shown in Table 1.The participants were asked to visit every 2nd wk. Blood pressure, body weight, waist circumference, and body composition were measured at every visit, and blood analysis and stool analysis were checked on the 1st visit day (wk 0) and last day (wk 8).

2.5. Physical examination and anthropometry

Blood pressure and heart rate were measured using an automatic digital sphygmomanometer. Wearing a hospital gown, body weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively. Waist circumference was measured three times according to the World Health Organization method [21] by the same observer.

2.6. Body composition analysis

Body composition was measured at every visit using the bioelectrical impedance analysis method (InBody 3.0; Biospace, Seoul, Korea). This device measures impedance through eight tactile electrodes placed on palms, thumbs, heels, and soles. Each

participant stood upright, stepping onto the foot electrodes and loosely gripping the pipe-shaped hand electrodes with arms held vertically. Lean body mass, body mass index, and percent fat were measured and recorded.

2.7. Blood chemistry

Blood tests including fasting glucose, high-density lipoprotein-cholesterol, triglyceride, and total cholesterol were performed prior to the start of the experiment and 8 wk later. At baseline, participants with high fasting blood glucose (>140 mg/dL) or possible liver problems (aspartate aminotransferase or alanine aminotransferase >100 IU/L) were excluded.

2.8. Pyrosequencing

The participants were asked to bring their stool samples on the 1st visit day (wk 0) and last day (wk 8) in the stool-sampling

Table 4
Comparison of General Characteristics Between the Effective Weight Loss Group (EWG) and Ineffective Weight Loss Group (IWG) at Baseline

Parameters	EWG	IWG	p
Age (y)	53.25 ± 5.06	49.25 ± 4.65	0.182
BW (kg)	71.65 ± 4.55	74.57 ± 3.49	0.200
BMI (kg/m²)	28.83 ± 2.83	28.57 ± 0.95	0.887
TC (mg/dL)	207.75 ± 18.66	209.67 ± 33.84	0.926
TG (mg/dL)	111.75 ± 55.99	187.00 ± 67.51	0.199
HDL (mg/dL)	53.25 ± 5.31	62.33 ± 26.27	0.612
Glucose (mg/dL)	100.25 ± 16.62	108.00 ± 6.92	0.446

Data are presented as mean ± SD.
BMI, body mass index; BW, body weight; HDL, high-density lipoprotein -cholesterol; TC, total cholesterol; TG, triglyceride.

container. The fresh human stools were collected and immediately stored at −70°C. Genomic DNA were extracted from fecal samples of participants using a Fast DNA SPIN extraction kit (MP Bio-medicals, Santa Ana, CA, USA), and fragments of the 16S rRNA gene (V1−V3) were amplified from the extracted DNA. The amplifications were performed according to previous reports using a

barcoded fusion primer [22,23] using a C1000 Touch thermal cycler (Bio-Rad, Hercules, CA, USA). The amplified products were visual-ized on 2% agarose gel electrophoresis using the Gel Doc system (Bio-Rad). Amplicons were purified using the QIA quick PCR puri-fication kit (Qiagen, Valencia, CA, USA) and quantified using the PicoGreen dsDNA Assay kit (Invitrogen, Carlsbad, CA, USA).
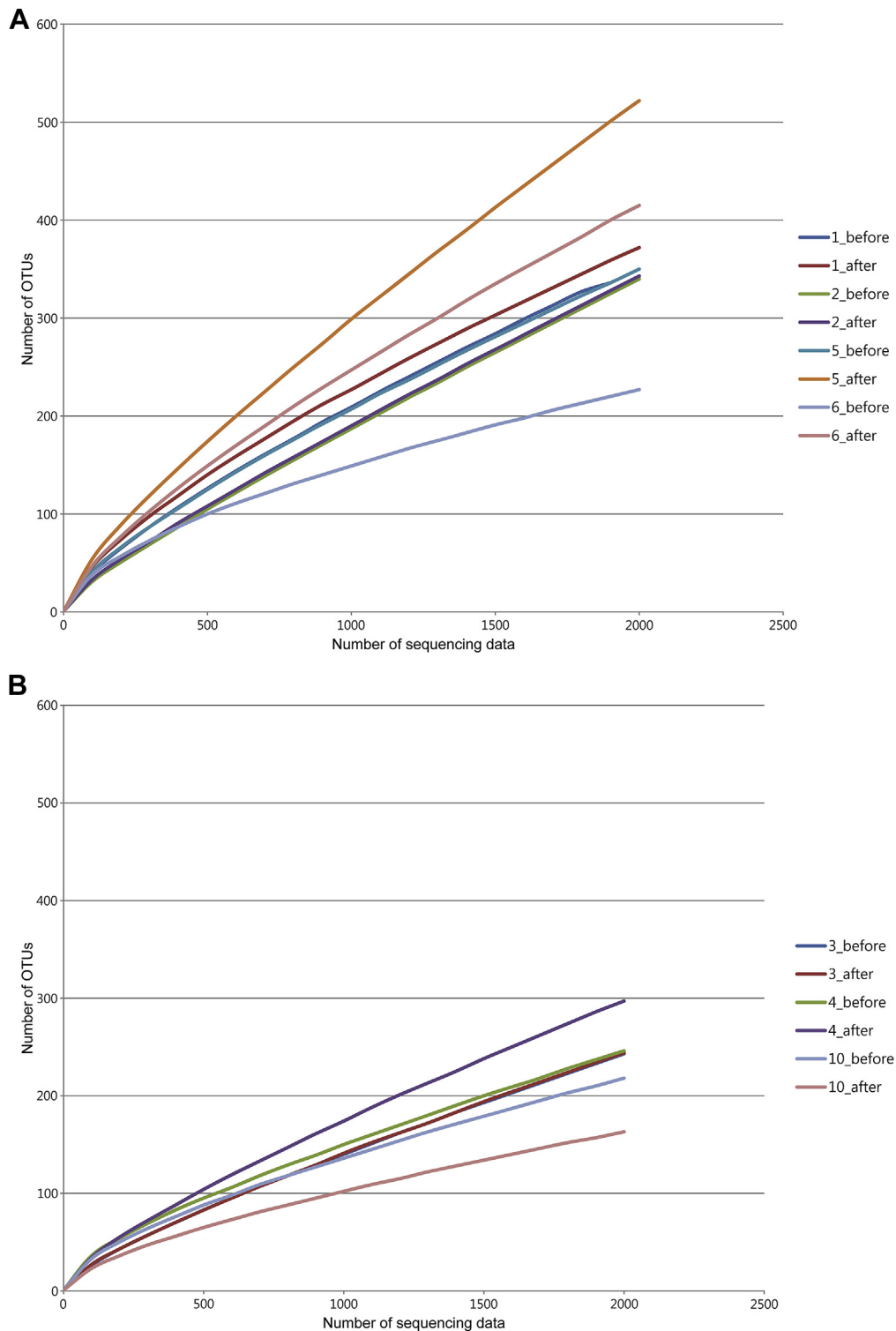

Fig. 4. Rarefaction curves of (A) effective weight loss group (EWG) and (B) ineffective weight loss group (IWG) samples were compared. The rarefaction curves were obtained after obtaining a normalized read size in each sample.

Equimolar concentrations of each amplicon from different samples were pooled and purified using the AMPure bead kit (Agencourt Bioscience, Beverly, MA, USA) and then amplified on sequencing beads by emulsion PCR. Sequencing reactions were performed using a Roche/454 GS Junior system (454 Life Sciences, Branford, CT, USA) following the manufacturer's instructions.

2.9. Sequence data analysis

Obtained sequences were sorted according to their unique barcode in the demultiplexing step, and low quality reads (average quality score <25 or read length <300 bp) were removed for further analysis. Primer sequences were trimmed by pairwise sequence alignment and the hmm-search program of the HMMER 3.0 package [24]. To modify sequencing errors, representative sequences in clusters of trimmed sequences were chosen for taxonomy identification. Each read was characterized by their taxonomic positions according to the highest pairwise similarity among the top five BLASTN hits against the EzTaxon-e database [25]. Chimera sequences were removed by UCHIME [26]. Various read numbers in samples were normalized by random subsampling, and the diversity indices were calculated using the mothur program [27]. Pyrosequencing reads obtained from this study are available in the European Molecular Biology Laboratory Sequence Read Archive database under study number PRJEB4531 [28].

2.10. Statistical analysis

Results are presented as mean ± standard deviation. Comparison of prior to and after treatment was performed using paired *t* test and Wilcoxon signed-rank test and the two groups divided according to weight loss effect were compared using the Mann−Whitney *U* test. Values of $p < 0.05$ were considered statistically significant. All analyses were performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results and discussion

3.1. Anthropometric and biochemical changes

Differences of gut microbial communities are related to gender and age [29,30], therefore we limited our inclusion criteria to a specific gender and the participants were middle-aged (40−59 yr) women. A total of 10 participants completed the trial; their general characteristics are shown in Table 2. Age was 50.40 ± 4.95 yr and body weight and BMI were 71.39 ± 4.95 kg and 28.35 ± 2.00 kg/m², respectively.

After ginseng intake, significant decreases were observed in weight and BMI, with difference of −1.06 ± 1.41 kg and −0.48 ± 0.59 kg/m², respectively. However, no significant decrease was observed in waist circumference, body fat percentage, high-density lipoprotein-cholesterol, triglyceride, total cholesterol, and glucose. In contrast to this result, the effects of ginseng, ginsenosides, or compound K on antiobesity have been reported as lowering cholesterol and controlling blood glucose via inhibition of lipid accumulation in adipocyte and increase of phosphorylation of insulin receptor substrate-1, Akt, membranous glucose transporter 4 in muscle [7−9]. However, there was no significant effect on obesity related parameters in this study. No effects of ginseng on these parameters were reported in randomized controlled studies for healthy obese participants during 12 wk, [31,32]. A longer duration of taking ginseng might be needed to confirm significant effects for human beings. Different bacterial ginsenoside-hydrolyzing effects between humans and experimental mice [33] and

individual difference of metabolic ability to ginseng could be a reason for this result.

3.2. Analysis of gut microbiota

We performed pyrosequencing for analysis of the gut microbiota of prior to and after in ginseng treated participants. Bacterial richness and diversity obtained from pyrosequencing after normalization of reads number are shown in Table 3. A total of 73,611 sequences were obtained and analyzed, and the normalized read number of each sample for comparison of diversity indices was 2,000. Good's coverage of samples was over 80%, except for the after treatment sample of Participant 5. Increased Shannon diversity indices were detected in the after treatment sample compared to the prior to treatment sample for Participants 1, 2, 5, 6, and 7, whereas deceased indices were detected for samples of Participants 4, 8, 9, and 10.

Predominant phyla in average community compositions were Firmicutes, Actinobacteria, and Bacteroidetes, and no significant change in phylum level was observed between prior to and after. Selected genera having over 1% proportion of median value were compared. The main dominants were changed after ginseng intake; those prior to intake were genera of *Blautia*, *Bifidobacterium*, and *Anaerostipes* whereas those after intake were *Bifidobacterium*, *Blautia*, and *Faecalibacterium*, in order of abundance (Fig. 2). Significant change was observed only in the relative abundance of *Anaerostipes*; prior to was 6.70 ± 3.35%, and after was 3.11 ± 3.24% (data not shown).

3.3. Comparison of gut microbiota between the effective and ineffective weight loss groups

To express the pharmacological actions of ginseng saponins, it is presumed that ginsenosides, the main constituent of ginseng, must be metabolized by human intestinal microbes after being taken orally [34]. The ginsenoside Rb1 in orally administered ginseng is metabolized to compound K by gut microbiota prior to its absorption into the blood. Beta-glucosidase, produced by intestinal

Table 5
Comparison of Gut Microbiota Between the EWG and IWG at Baseline

	Gut microbiota (%)	EWG (%)	IWG (%)	*p*
Phylum	Firmicutes	84.25 ± 10.33	68.44 ± 5.20	0.034*
	Actinobacteria	7.29 ± 7.21	28.46 ± 6.81	0.034*
	Bacteroidetes	3.42 ± 2.74	1.48 ± 1.71	0.480
	Proteobacteria	0.07 ± 0.06	1.54 ± 1.73	0.034*
	Tenericutes	4.86 ± 4.90	0.01 ± 0.01	0.142
	Verrucomicrobia	0.13 ± 0.27	0.07 ± 0.08	0.172
Genus	*Blautia*	23.78 ± 23.80	14.06 ± 8.61	0.724
	Bifidobacterium	5.75 ± 5.40	25.43 ± 9.74	0.034*
	Faecalibacterium	3.49 ± 3.82	7.13 ± 3.42	0.289
	Clostridium_g4	3.97 ± 3.26	3.86 ± 5.84	1.000
	Eubacterium_g5	12.99 ± 7.60	4.20 ± 3.96	0.480
	Anaerostipes	12.99 ± 7.60	1.87 ± 1,48	0.157
	Bacteroides	1.87 ± 1.48	1.00 ± 1.48	0.289
	Clostridium	1.09 ± 1.03	1.80 ± 2.73	0.724
	Collinsella	1.01 ± 1.80	2.38 ± 4.13	1.000
	Lactobacillus	0.51 ± 0.63	7.08 ± 12.73	0.724
	Dorea	4.08 ± 4.73	1.74 ± 1.26	0.480
	Subdoligranulum	1.49 ± 1.50	1.40 ± 1.42	0.858
	Lachnospiraceae_uc	1.57 ± 1.01	1.29 ± 0.54	0.480
	Dialister	8.32 ± 15.90	0.10 ± 0.09	0.714
	Oscillibacter	2.53 ± 2.34	1.17 ± 1.14	0.212
	Roseburia	2.53 ± 2.34	1.17 ± 1.14	0.289
	Escherichia	0.00 ± 0.00	0.89 ± 0.57	0.019*
	Clostridium_g23	0.00 ± 0.00	0.17 ± 0.21	0.019*

Data are presented as mean ± SD.
* *p* < 0.05.

microbiota, plays an important role in the pharmacological actions of ginsenoside and the components of ginseng; it is the representative ginsenoside-transforming enzyme. This enzyme activity of gut microbiota varies significantly between individuals, so that the metabolizing activities of ginsenoside Rb1inindividuals are significantly different [19]. People with different levels of ginsenoside Rb1 degradation to compound K had different gut microbiota [20].
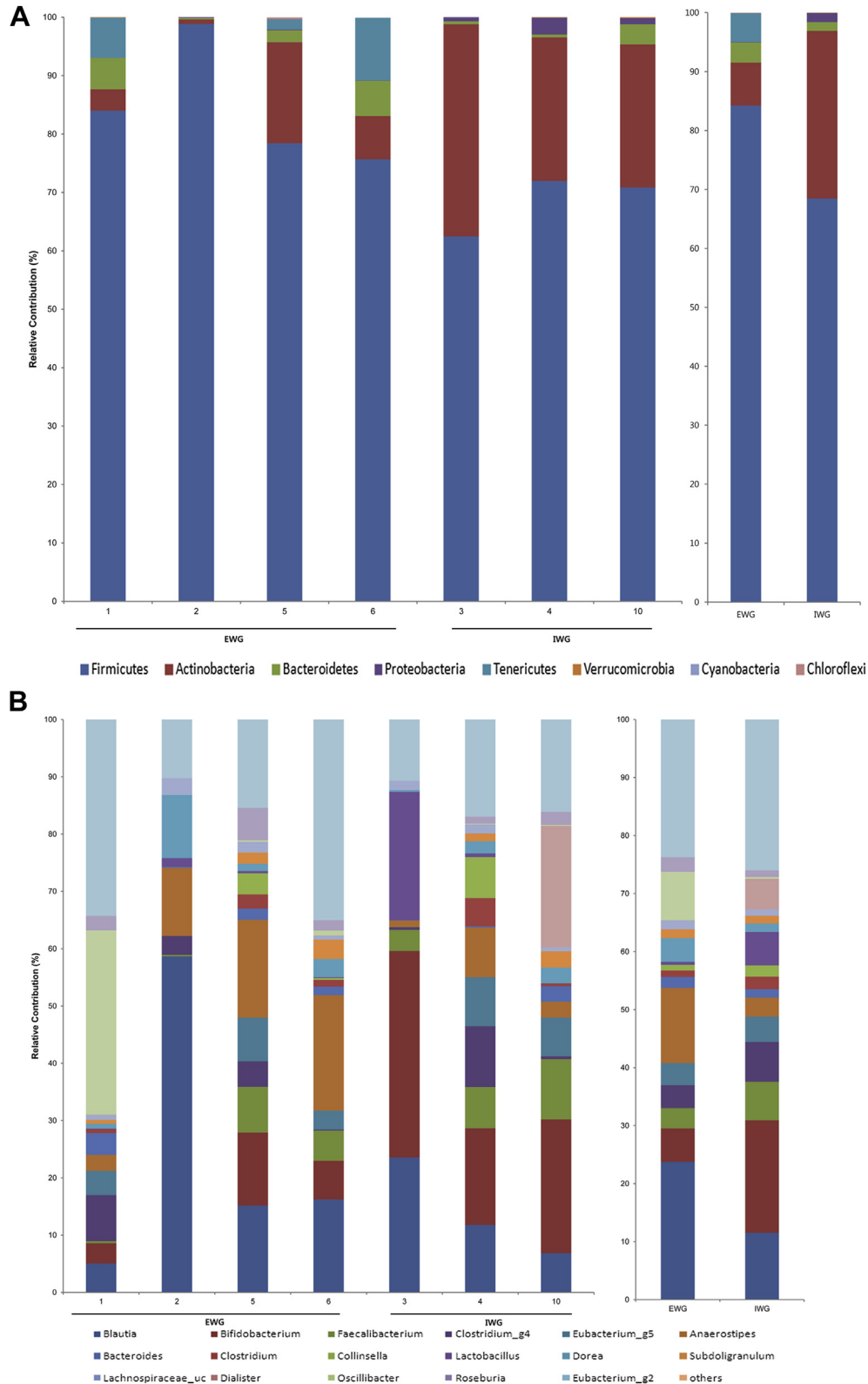

Fig. 5. The phylum and genus compositions of fecal bacteria were compared between prior to and after treatment in the effective weight loss group (EWG) and ineffective weight loss group (IWG). The relative abundance of dominant phyla identified from pyrosequencing data is shown (individual samples are on the left panels and pooled samples are on the right panels). (A) Phylum composition of fecal bacteria prior to ginseng intake. (B) Genus prior to intake. (C) Phylum after intake. (D) Genus after intake.
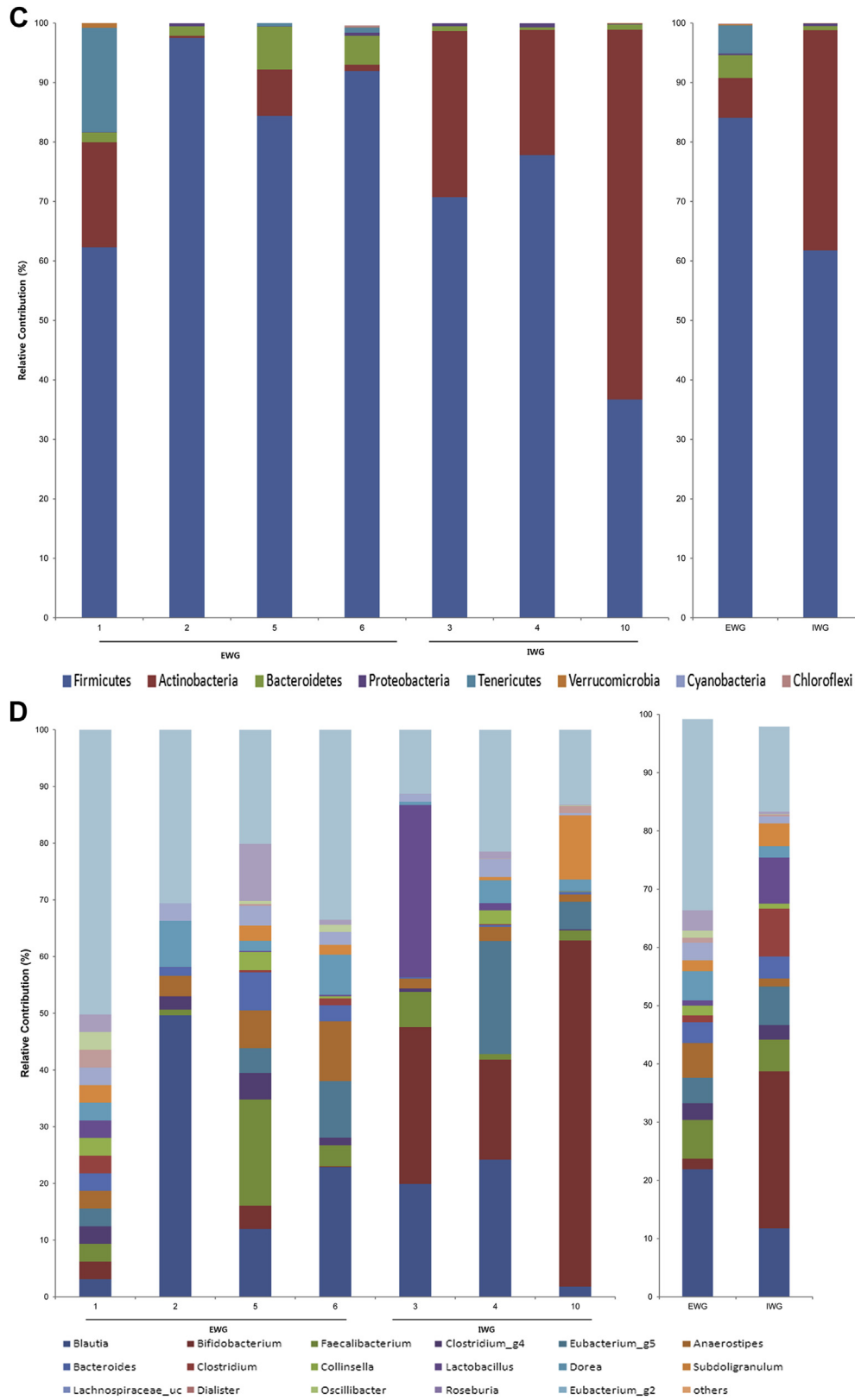
Fig. 5. (*continued*).

To investigate whether the antiobesity effect of ginseng might be influenced by the composition of gut microbiota, we analyzed bacterial communities of all participants at the baseline using principal coordinate analysis (PCoA). In the PCoA plot, gut microbiota of each member was clustered according to the degree of weight loss (Fig. 3). The groups were designated as: the effective weight loss group (EWG; Participants 1, 2, 5, and 6; weight change, -2.4 ± 0.38 kg); and ineffective weight loss group (IWG; Participants 3, 4, and 10; weight

Table 6
Changes of Gut Microbiota Between Effective Weight Loss Group (EWG) and Ineffective Weight Loss Group (IWG) Samples After Ginseng Intake

	Gut microbiota (%)	EWG (%)	IWG (%)	p
Phylum	Firmicutes	−0.20 ± 16.06	−6.69 ± 23.82	0.724
	Actinobacteria	−0.57 ± 10.43	8.59 ± 25.34	0.724
	Bacteroidetes	0.41 ± 3.77	−0.77 ± 1.57	0.724
	Proteobacteria	0.21 ± 0.25	−1.21 ± 1.01	0.034*
	Tenericutes	−0.12 ± 8.42	0.01 ± 0.01	0.714
	Verrucomicrobia	0.19 ± 0.36	−0.03 ± 0.28	0.067
Genus	*Blautia*	−1.88 ± 6.48	1.25 ± 9.70	1.000
	Bifidobacterium	−0.36 ± 10.11	10.00 ± 24.39	0.289
	Faecalibacterium	2.52 ± 5.55	−4.14 ± 5.94	0.157
	Clostridium_g4	−0.02 ± 0.93	−1.10 ± 2.69	0.480
	Eubacterium_g5	1.03 ± 4.11	3.16 ± 7.19	0.724
	Anaerostipes	−7.03 ± 4.95	2.36 ± 3.46	0.157
	Bacteroides	1.18 ± 3.02	−0.64 ± 1.36	0.157
	Clostridium	−0.43 ± 1.20	−1.75 ± 2.64	0.289
	Collinsella	−0.12 ± 0.26	−1.55 ± 2.75	0.593
	Lactobacillus	−0.32 ± 0.71	2.88 ± 4.45	0.289
	Dorea	0.38 ± 2.76	0.47 ± 1.34	0.480
	Subdoligranulum	−0.23 ± 1.00	2.57 ± 5.14	0.858
	Lachnospiraceae_uc	0.80 ± 0.94	0.34 ± 1.09	0.289
	Dialister	0.10 ± 0.17	−6.64 ± 11.54	0.372
	Oscillibacter	−6.21 ± 12.86	−0.05 ± 0.47	0.372
	Roseburia	0.29 ± 2.88	−0.07 ± 1.25	0.480

Data are presented as mean ± SD.
* *p* < 0.05.

change, 0.63 ± 0.64 kg). Although there was no significant difference in general characteristics such as age and obesity related parameters (Table 4), different gut microbiota was observed between groups. The rarefaction curves showed the difference of gut microbiota between the two groups (Fig. 4). The richness of bacterial communities obtained from EWG was relatively higher than that of IWG. Phyla of Firmicutes, Actinobacteria, Tenericutes, and Bacteroidetes were predominant in EWG samples of prior to ginseng intakes, whereas Firmicutes, Actinobacteria, and Proteobacteria were dominant in IWG samples (Table 5, Fig. 5A). Relative abundances of Actinobacteria and Proteobacteria in EWG were lower than those in IWG, whereas phyla of Tenericutes, Bacteroidetes, and Firmicutes were more abundant in the EWG than IWG. Furthermore the relative abundances of Firmicutes, Actinobacteria and Proteobacteria were significantly different between both groups. These results partly correspond with the earlier one. Samples with fecal activity potently metabolizing ginsenoside Rb1 to compound K had lower levels of Proteobacteria and higher levels of Tenericutes and Bacteriodetes than in samples with fecal activity non-metabolizing ginsenoside Rb1 to compound K [20]. For detailed microbial composition, we analyzed the composition of genera, it had also noteworthy differences between groups (Table 5, Fig. 5B). The three predominant genera in EWG were *Blautia*, *Anaerostipes*, and *Oscillibacter*, whereas those in IWG were *Bifidobacterium*, *Blautia*, and *Clostridium_g4*. The relative abundances of *Anaerostipes* and *Eubacterium_g5* were increased in EWG, whereas that of *Lactobacillus* was increased in IWG. Furthermore, the relative abundance of *Bifidobacterium*, *Escherichia*, and *Clostridium_g23* in EWG were significantly lower than those in IWG. However, the genera that had significant differences between the groups (*Clostridiales_uc_g, Oscillibacter, Ruminococcus, Holdemania*, and *Sutterella*) were not consistent with a previous study [20]. Individual variations of gut microbiota [35] can generate these different results, so it is not easy to compare directly between the two limited sample sized studies.

The antiobesity effect of ginseng could work differently depending on gut microbiota composition as explained above. We also wanted to know whether ginseng could make changes of gut
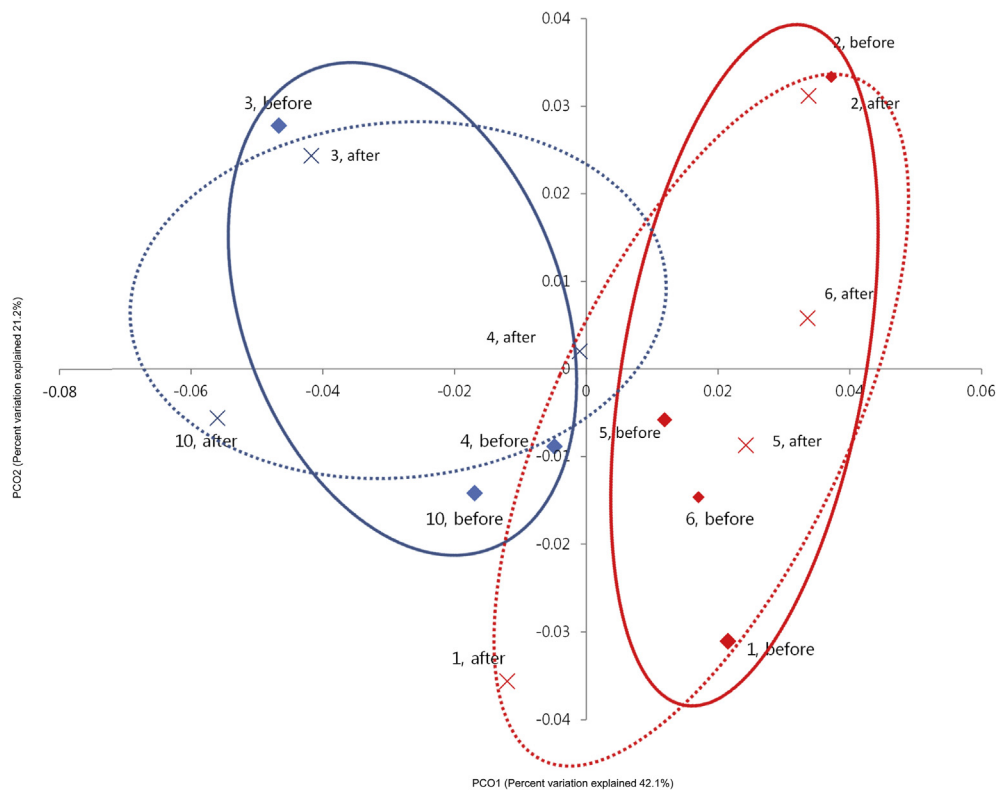

Fig. 6. Principal coordinate analysis plot. The plot shows the clustering pattern between the effective weight loss group (EWG) and ineffective weight loss group (IWG) based on weighted pairwise Fast UniFrac analysis. ◆, the community of EWG in the prior to ginseng intake; ✕, that of EWG in the after ginseng intake, ◆, that of IWG in the prior to ginseng intake; ✕, that of IWG in the after ginseng intake. Unbroken circles indicate grouping of the communities in the prior to ginseng intake and broken circles indicate that in the after ginseng intake.

microbial composition. Therefore, we investigated changes of microbial composition after ginseng intake. Each group showed changes in microbial composition; the three main dominant genera of EWG were changed to *Blautia*, *Faecalibacterium*, and *Anaerostipes*, and those of IWG were changed to *Bifidobacterium*, *Blautia*, and *Clostridium* at the genus level (Fig. 5C and D). However, neither group showed statistically significant changes at the phylum or genus level (data not shown). In addition, we compared the changes of gut microbiota after ginseng treatment between the two groups; only the relative composition of Proteobacteria had significant change (Table 6).

The comparisons of bacterial communities between prior to and after ginseng intake in both groups were analyzed by PCoA plot (Fig. 6). Prior to ginseng intake, bacterial communities were segregated depending on weight loss effect, but there was no remarkable change of bacterial communities in both groups after ginseng intake. This indicates that the influence of ginseng intakes on bacterial community was not considerable, however the compositions of gut bacteria could determine whether weight loss is effective or not.

Ginseng exerted a weight loss effect and slight effects on gut microbiota in all participants. It is an important result that its antiobesity effects differed depending on the composition of gut microbiota prior to ginseng intake. The biotransformation activity from ginsenoside-Rb1 to compound K was significantly different among individuals [36], and intestinal bacterial metabolism of ginseng is dependent on the composition of gut microbiota [19,20]. Therefore, a single ginsenoside or a ginseng extract may lead to different effects among participants [33]. However, we did not analyze the biotransformation activity ginsenoside to compound K, for example, so supplemental studies are necessary to confirm the metabolism of ginseng by gut microbiota for antiobesity.

There were other limitations in this study including: no controlled study, a limited number of participants, and a limited study period. Therefore, the present study can be considered explorative research, which can motivate a full-scaled one. However, it was the first trial to assess the effects of ginseng on obesity and gut microbiota as well different weight loss effects depending on the composition of gut microbiota.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

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