Enhanced production of compound K in fermented ginseng extracts by *Lactobacillus brevis*

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Abstract The purpose of this study is to establish the best condition and microorganism for preparation of fermented ginseng including rich compound K. When raw ginseng parts were incubated with various microorganisms, there was an increase in compound K at 5 days in all samples fermented by *Lactobacillus brevis* (*L. brevis*) and *Lactobacillus plantarum*, isolated from kimchi. Especially, ginseng fine roots fermented with *L. brevis* (FR-B) included higher levels of compound K, total phenolic compounds, and antioxidant activities compared with other products. Conclusively, these results indicate that the optimum condition for providing rich compound K product in fermented ginseng is ginseng fine roots are fermented with *L. brevis* for 5 days. Additionally, with FR-B there was greater improvement in physiochemical properties than with other products. Such information may be helpful for the manufacture of fermented ginseng including rich compound K as well as for understanding the biological features of fermented ginseng.

Keywords Antioxidant activity · Compound K · Ginseng fermentation · *Lactobacillus brevis* · Total phenolic compounds

Abbreviations

FR-B	Fine root fermented with <i>L. brevis</i>
FR-P	Fine root fermented with <i>L. plantarum</i>
MR-B	Main root fermented with <i>L. brevis</i>
MR-P	Main root fermented with <i>L. plantarum</i>
RB-B	Root bark fermented with <i>L. brevis</i>
RB-P	Root bark fermented with <i>L. plantarum</i>

Introduction

Ginseng (*Panax ginseng*) has been used as a component in traditional medicine in East Asia, and it has received worldwide attention as a constituent of functional food. Ginseng is known to possess various bioactive activities such as anti-cancer (Hofseth and Wargovich, 2007), anti-inflammation (Hofseth and Wargovich, 2007), and anti-obesity (Yin et al., 2008). Such effects of ginseng are closely associated with ginsenosides, active compounds of ginseng (Dai et al., 2017). Especially, red ginseng, which is a processed form of ginseng, shows more potent bioactive actions than ginseng because it is richer in ginsenosides (Shibata, 2001).

Fermentation for herbal medicines using microorganisms has been reported to improve the beneficial effects of the herbal medicines such as anti-allergy (Yoo et al., 2016), anti-cancer (Kim et al., 2015), anti-colitis (Kim et al., 2017), and neuroprotection (Park et al., 2016) because the microorganisms can convert glycosides to aglycones and/or produce their metabolites (Yoo et al., 2016). In addition, compound K, a bioactive ginsenoside, is converted from

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ginsenoside Rb1 and ginsenoside Rb2 by intestinal microflora (Akao et al., 1998); and it exerts various bioactivities such as anti-arteriosclerosis (Park et al., 2013), anti-cancer (Shibata, 2001), and neuroprotection (Oh and Kim, 2016). Recently, there have reports on fermentation of red ginseng and ginseng fruit by various microorganisms (Bae et al., 2004; Bai and Ganzle, 2015; Lee et al., 2015; Li et al., 2016; Park et al., 2017). Nonetheless, details of the process of raw ginseng fermentation and the best microorganism for the fermentation remain unknown.

In this study, to optimize a preparation method for fermented ginseng, we investigated the effects of various microorganisms such as *Lactobacillus brevis* [*L. brevis*, which is found in kimchi (Park and Oh, 2007)], *Lactobacillus plantarum* (*L. plantarum*), *Saccharomyces cerevisiae* (*S. cerevisiae*), *Monascus purpureus* (*M. purpureus*), Yoflex, and *Bifidobacterium* on ginseng fermentation in a time-dependent manner. Further, we evaluated the effects of *L. brevis* and *L. plantarum*, which were selected for preparation of fermented ginseng including rich compound K, on fine root, main root, and root bark of ginseng. To examine the change of physiochemical properties of ginseng, we determined total phenolic compound contents and antioxidant activities in products of non-fermented and fermented ginseng. In addition, to compare the ginsenoside contents in the products, we analyzed the contents of ginsenoside Rb1, ginsenoside Rg1, and compound K using a high-performance liquid chromatography (HPLC) system. Herein, we found that *L. brevis* was the best microorganism for the fermentation of ginseng including rich compound K and optimized the fermentation condition for the preparation of fermented ginseng from raw ginseng. Furthermore, we found that fine roots fermented with *L. brevis* (FR-B) showed high levels of compound K, total phenolic compounds, and antioxidant activities compared with the other products. These results may provide novel information for the manufacture of fermented ginseng and the application of FR-B as a functional food, and they may be helpful for understanding the biological features of fermented ginseng.

Materials and methods

Materials

Fine root, main root, root bark, and whole dried ginseng were purchased from Wooshin Co., Ltd (Geumsan-gun, Korea). *L. brevis* (KCTC 3498), *L. plantarum* (KCTC 3103), *S. cerevisiae* (KCTC 7904), and *M. purpureus* (KCTC 6121) were obtained from the Korean Collection for Type Cultures (Jeongeup, Korea). Yoflex and *Bifidobacterium* (BB-12) were procured from Chr. Hansen A/S (Hoersholm, Denmark). 2,2'-diphenyl-1-picrylhydrazyl

(DPPH), 2,2'-azinobis (2-ethyl benzothiazoline-6-sulfonate (ABTS), ferric-reducing antioxidant power (FRAP), and all other chemicals were purchased from Sigma-Aldrich (St Louis, MO, USA). All other chemicals were of analytical grade.

Sample preparation

Extraction of ginseng parts

Extracts of fine root, main root, root bark, and whole dried ginseng (100 g) were prepared by extraction with 70% ethanol (1 L) at 75 °C for 24 h, repeated 3 times, and then all the supernatant was collected. The supernatant was concentrated under vacuum at 40 °C using a rotary evaporator (MG-2100, Buchi, Flawil, Switzerland). The residues were collected when the weight of each residue reached about 25 g.

Fermentation for extracts of ginseng

The 2.5 g extracts were diluted with 50 mL of distilled water containing 7% α -herbzyme, and then the mixture was sterilized at 95 °C for 10 min. The sterilized solution was adjusted to pH 6.5 with 1 N NaOH, inoculated with microorganisms including *L. brevis* (1×10^5 – 10^7 CFU/mL), and then incubated at 37 °C for 3, 5, or 7 days. The fermented solution was centrifuged ($1900 \times g$, 4 °C) for 20 min, and then the supernatant was concentrated using a rotary evaporator.

Determination of total phenolic compounds

The amounts of total phenolic compounds in non-fermented and fermented ginseng extracts were determined in accordance with methods described previously (Yoo et al., 2014). Briefly, the solution (0.33 mL) was mixed with 2.5 mL of distilled water and then incubated with 0.16 mL of Folin–Ciocalteu reagent for 5 min. The above solution was further incubated for 30 min in darkness after treatment with 10% sodium bicarbonate solution (0.3 mL). Then absorbance at 760 nm was measured using a microplate reader (DU650, Beckman Coulter, Inc., Brea, CA, USA). A standard curve was prepared to express the results as caffeic acid equivalents.

Antioxidant activity assays

DPPH scavenging activity assay

DPPH radical scavenging activity was measured in accordance with the method reported previously (Birasuren et al., 2013). Briefly, various concentrations (0–10 mg/mL)

of samples dissolved in methanol (200 μ L) were mixed with 0.1 mM DPPH solution (4 mL) and then incubated for 30 min in the darkness. Absorbance at 517 nm was determined using a micro-plate reader.

Hydroxyl radical scavenging activity assay

Hydroxyl radical scavenging activity was determined in accordance with the method reported previously (Birasuren et al., 2013). Absorbance of the final mixture at 532 nm was measured using a micro-plate reader.

FRAP assay

FRAP assay was determined in accordance with the method reported previously (Birasuren et al., 2013). Absorbance of the final solution at 593 nm was measured using a micro-plate reader.

ABTS radical scavenging activity assay

ABTS radical scavenging activity assay was determined in accordance with the protocol reported previously (Birasuren et al., 2013). Absorbance of the mixture at 734 nm was measured using a micro-plate reader.

High-performance liquid chromatography analysis

To quantitate ginsenoside Rb1, ginsenoside Rg1, and compound K in all samples, HPLC analysis was performed using a HPLC system equipped with a 515 HPLC pump, 717 plus autosampler, and 2996 photodiode array detector (Waters Co., Milford, MA, USA) with a C₁₈ column (4.6 $\times$ 250 mm, 5 μ m; Sigma-Aldrich, St Louis, MO, USA). The ginsenosides were eluted in a gradient system composed of solvent A (deionized water) and solvent B (acetonitrile). The gradient was 20-20-32-50-65-90-90-20% of solvent B at the gradient time t_G = 0-10-40-55-70-71-80-81-90 min, respectively. The column oven temperature was 40 °C, and the flow rate was 1.2 mL/min. An injection volume of 20 μ L was applied. The UV/Vis detector was set at the wavelength range of 203 nm. The standards of ginsenoside Rb1, ginsenoside Rg1, and compound K as well as the samples (200 mg/mL) were dissolved and diluted in 50% methanol. All the sample solutions were used after filtering with a syringe filter (0.45 μ m). Calibration curves constructed using linear least-squares regression were linear over the concentration range of the standards used. The relative standard deviation of the measured concentrations was used to assess the precision. A comparison of the mean measured concentration versus the corresponding nominal concentration was used to assess the accuracy. Data acquisition was

performed using Empower 3 Chromatography Data Software (Waters Co., Milford, MA, USA).

Statistical analysis

The experimental results were listed as mean $\pm$ SD for all the experiments. One-way ANOVA was used for multiple comparisons (GraphPad Prism version 5.03 for Windows, San Diego, CA, USA). The Dunnett test was applied for significant variations between the non-fermented or fermented groups. Differences at the $*p < 0.05$ and $**p < 0.01$ levels were considered statistically significant.

Results and discussion

Effects of microorganisms on the fermentation of ginseng: comparison of ginsenoside contents

First, we investigated the effects of microorganisms such as *L. brevis*, *L. plantarum*, and *S. cerevisiae* on bioconversion of ginsenosides in whole ginseng extract because intestinal microflora are able to convert ginsenosides to compound K (Akao et al., 1998). When whole ginseng extract was fermented by *L. brevis*, *L. plantarum*, *S. cerevisiae*, *M. purpureus*, Yoflex, and *Bifidobacterium* for 3 days or 5 days, the level of compound K was rapidly elevated in the extracts of ginseng fermented by *L. brevis* [Fig. 1(A)] and *L. plantarum* [Fig. 1(B)] during the experimental period. In contrast, the levels of ginsenoside Rb1 and ginsenoside Rg1 were gently decreased in the period [Fig. 1(A, B)]. Meanwhile, the other microorganisms showed reduced levels of all the ginsenosides in ginseng extract during the experimental period [Fig. 1(C–F)]. These results suggest that the microorganisms can deglycosylate ginsenoside Rb1, ginsenoside Rg1, and compound K and that *L. brevis* and *L. plantarum* have lower abilities for compound K degradation than the other microorganisms. In support of this, it has been reported that the bioconversive activities of microorganisms are different when they convert ginsenosides (Park et al., 2017). In addition, microorganisms can deglycosylate and disintegrate ginsenosides (Odani et al., 1983). Collectively, *L. brevis* and *L. plantarum* are suitable microorganisms for preparation of fermented ginseng including rich compound K.

Effects of *L. brevis* and *L. plantarum* on the fermentation of ginseng parts: comparison of ginsenoside contents

Because we found that *L. brevis* and *L. plantarum* could convert ginsenosides to compound K, we further examined the effects of them on fermentation for fine root, main root,

Fig. 1 Effects of fermentation on ginsenoside contents in ginseng extracts. Ginseng extract was fermented by *L. brevis*, *L. plantarum*, *S. cerevisiae*, *M. purpureus*, *Yoflex*, or *Bifidobacterium* for 3 or 5 days.

and root bark of ginseng. Fine root is generally known to have a richer ginsenoside content than main root and root bark (Oh et al., 2014). Moreover, fine root is a by-product in the preparation of red ginseng because red ginseng is made from main root alone in Korea. When the amounts of ginsenosides in non-fermented fine root, main root, and root bark were analyzed using a HPLC system, fine root included higher levels of ginsenoside Rb1 and ginsenoside Rg1 than main root and root bark, but none of the samples contained compound K (Fig. 2). In contrast, when the extracts of fine root, main root, and root bark were fermented by *L. brevis* or *L. plantarum* in a time-dependent manner, the amounts of ginsenoside Rb1 and ginsenoside Rg1 in all the samples were decreased in proportion to

The ginsenoside contents in the samples were analyzed as described in “Materials and methods”. **A** *L. brevis*; **B** *L. plantarum*; **C** *S. cerevisiae*; **D** *M. purpureus*; **E** *Yoflex*; **F** *Bifidobacterium*

fermentation time (Fig. 2). In addition, the amounts of compound K in fine root, main root, and root bark were decreased at 7 days after being elevated until 5 days (Fig. 2). The reason for the decrement of compound K at 7 days may be that the microorganisms can deglycosylate and disintegrate ginsenosides (Odani et al., 1983). The levels of compound K in all samples fermented by *L. brevis* were higher than those fermented by *L. plantarum* at the same fermentation time (Fig. 2). Especially, FR-B showed the highest level of compound K in comparison with main root fermented with *L. brevis* (MR-B) and root bark fermented with *L. brevis* (RB-B) [Fig. 2(A, C, E)]. These findings indicate that *L. brevis* is the best microorganism for preparation of fermented ginseng containing rich

Fig. 2 Fermentation of fine root, main root, and root bark of ginseng by *L. brevis* and *L. plantarum*. The extracts of fine root, main root, and root bark were fermented by *L. brevis* or *L. plantarum* for 3, 5, or

7 days. The ginsenoside contents in the samples were analyzed as described in “Materials and methods”. A, B fine root; C, D main root; E, F root bark

compound K, and the optimum condition for preparation of the best fermented ginseng is that using fine root fermented by *L. brevis* for 5 days.

Effects of fermentation by *L. brevis* and *L. plantarum* on physiochemical properties of ginseng parts: comparison of antioxidant activity and total phenol contents

Next, we were interested in the physiochemical properties of fermented ginseng by *L. brevis* and *L. plantarum*. Occasionally, the fermentation by microorganisms leads to improvement in the levels of total phenolic compounds and antioxidant activity (Liu et al., 2017). When fine root, main

root, and root bark were fermented by *L. brevis* and *L. plantarum*, the antioxidant activities of all the fermented samples were significantly elevated (Table 1). In addition, the antioxidant activities of FR-B, MR-B, and RB-B were better than those of fine root fermented with *L. plantarum* (FR-P), main root fermented with *L. plantarum* (MR-P), and root bark fermented with *L. plantarum* (RB-P), respectively. Consistent with the compound K levels in FR-B, MR-B, and RB-B, the antioxidant activities of FR-B were significantly better than those of MR-B and RB-B. Furthermore, the amounts of total phenolic compounds in all the fermented samples were increased, and the ginseng fermentation by *L. brevis* also led to a greater increase in the total phenolic compounds than that by *L. plantarum*

Table 1 Antioxidant activities of ginseng parts fermented by *L. brevis* and *L. plantarum*

Sample	Scavenging activity assays			
	DPPH (%)	Hydroxyl radical (%)	FRAP (mg/mL)	ABTS (%)
FR	28.86 ± 0.39**	25.00 ± 0.44**	0.130 ± 0.005**	21.98 ± 0.18**
FR-B	53.74 ± 0.19	46.80 ± 0.39	0.228 ± 0.003	52.49 ± 0.52
FR-P	51.68 ± 0.25**	43.10 ± 0.58**	0.215 ± 0.003*	49.37 ± 0.12**
MR	23.45 ± 0.01**	21.04 ± 0.53**	0.080 ± 0.003**	14.60 ± 0.58**
MR-B	44.89 ± 0.84##	38.22 ± 0.73##	0.198 ± 0.002##	39.47 ± 0.65##
MR-P	43.28 ± 0.53*	36.95 ± 0.15*	0.184 ± 0.004**	37.26 ± 0.25**
RB	22.75 ± 0.42**	15.24 ± 0.54**	0.071 ± 0.004**	9.77 ± 0.76**
RB-B	37.04 ± 0.92##	30.81 ± 0.77##	0.161 ± 0.005##	26.55 ± 0.52##
RB-P	29.83 ± 0.46**	27.86 ± 0.60**	0.154 ± 0.003	23.86 ± 0.16**

The data are expressed as the mean ± SD values of three determinations

FR, fine root; MR, main root; RB root bark

* $p < 0.05$ and ** $p < 0.01$ versus FR-B, MR-B, or RB-B group; ## $p < 0.01$ versus FR-B group

Table 2 Composition of total phenolic compounds in ginseng parts fermented by *L. brevis* and *L. plantarum*

Species	FR	MR	RB
<i>L. brevis</i>	1.83 ± 0.01**	1.60 ± 0.09**	1.57 ± 0.06**
<i>L. plantarum</i>	2.70 ± 0.01	2.32 ± 0.01##	2.08 ± 0.05##
<i>L. plantarum</i>	2.65 ± 0.01**	2.26 ± 0.01	1.78 ± 0.04**

The data are expressed as the mean ± SD values of three determinations

Unit: mg/g dry weight; FR, fine root; MR, main root; RB, root bark

** $p < 0.01$ versus FR-B, MR-B, or RB-B group; ## $p < 0.01$ versus FR-B group

(Table 2). Moreover, the level of total phenolic compounds in FR-B was significantly higher than that in MR-B and RB-B (Table 2). These results suggest that the fermentation by microorganisms also improves the levels of antioxidant activities and total phenolic compounds in ginseng parts. Especially, FR-B showed higher levels of antioxidant activities and total phenolic compounds compared with the other fermented ginseng parts. Taken together, the results show that the FR fermentation by *L. brevis* elevates compound K as well as the physiochemical properties in ginseng. This information may be useful as an indicator for elevation of the quality of fermented ginseng. In addition, the regulation of fermentation time is very important for the preparation of high quality fermented ginseng product.

In summary, this study established the optimum condition for preparation of fermented ginseng including rich compound K, and it demonstrated that *L. brevis* is the best microorganism for such preparation. In addition, it confirmed that the bioconversion of *L. brevis* is closely associated with changes of the physiochemical properties such

as ginsenoside contents, antioxidant activities, and total phenolic compounds in ginseng parts. The improvements of compound K, antioxidant activities, and total phenolic compounds in FR-B may provide further information for the application of FR-B as a functional food for therapy and prevention of various diseases. Furthermore, the established fermentation condition can be applicable to the manufacture of FR-B possessing high levels of compound K, antioxidant activities, and total phenolic compounds.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Human and animal rights This article does not contain any studies performed by any of the authors with human participants or animals.

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