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Increased antioxidative and nitric oxide scavenging activity of ginseng marc fermented by *Pediococcus acidilactici* KCCM11614P

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Abstract This study aimed to improve the antioxidant and nitric oxide scavenging activities of ginseng marc fermented by *Pediococcus acidilactici,* thereby creating a biofunctional resource with improved anti-inflammatory capability. *P. acidilactici* was inoculated in 1% ginseng marc extract; cell viability, pH, and total titratable acidity were measured. Total phenolic and flavonoid contents were measured using Folin–Ciocalteu reagent and colorimetric method. Ferric reducing antioxidant power (FRAP), β-carotene, and sodium nitroprusside (SNP) assays were used to evaluate functionality. Polyphenols and flavonoids totaled 33.7 ± 0.4 and 10.0 ± 0.4 mg/g of solid, respectively, at 24 h fermentation. *P. acidilactici* had 40 nM β-galactosidase and 20 nM β-glucosidase activities. Antioxidative activities increased up to 34.5 and 10.2%, respectively, as measured via FRAP and β-carotene assays. Anti-inflammatory activity of the fermented extract—as measured via SNP assay—increased 342%, suggesting that ginseng marc fermented by *P. acidilactici* could be used in food or pharmaceutical industries.

Keywords Ginseng marc · Fermentation · *Pediococcus acidilactici* · Antioxidative activity · Nitric oxide scavenging · Flavonoid

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Introduction

Korean ginseng, *Panax ginseng* Meyer, is widely consumed as a functional food because it has a good safety profile and exhibits pharmaceutical effects. As the demand for ginseng has increased, the amount of ginseng marc has also increased [1]. Ginseng marc, a byproduct of the extraction of ginseng, contains biologically active compounds such as polyphenols and ginsenoside, but ginseng marc has traditionally been discarded [2]. Various polyphenols such as gallic acid, protocatechuic acid, vanillic acid, caffeic acid, coumaric acid, kaempferol, and quercetin were found in ginseng marc. Both in vitro and in vivo experiments have shown that these natural polyphenols and flavonoids exhibit antioxidant and anti-inflammatory properties [3]. However, many bioconversion techniques have recently been used to increase biofunctional activities by using fungi or bacteria such as lactic acid bacteria (LAB) [4].

LAB derived from traditional foods are undergoing studies to screen for probiotic properties or to study their application to raw materials for fermentation [5]. Among LAB, *Pediococcus acidilactici* is found in fermented vegetables, in meat, and in dairy products. *P. acidilactici* is known as a probiotic that has shown promising results in animal and human experiments [6]. Some LAB have known to produce β-glucosidase during fermentation [7]. The β-glucosidase enzymes are important factors in ginseng fermentation because these enzymes are capable of decomposing glycoside to a aglycone and sugars [8]. Increases in glucosidase or galactosidase result in increases in the quantities of minor ginsenosides. Accordingly, functionality related to polyphenols is enhanced [9].

Fermented milk is widely consumed all over the world because of its nutritional quality and sensory properties

[10, 11]. Milk products are fortified with minerals, vitamins, or herbal extracts [12, 13] to improve functional properties. In recent decades, several study of probiotic fermented milk have concentrated on assessment of anti-inflammatory properties [14], allergic processes [15], and modulating the immune response [16].

During the process of inflammation, NO, pro-inflammatory, and prostaglandin were produced by inducible NO synthase and cyclooxygenase-2 (COX-2) [17]. In particular, several compounds such as NO, iron, and reactive oxygen species (ROS) are recognized as inducing factors of human diseases such as Alzheimer's, Parkinson's, chronic kidney disease, coronary heart disease, insulin-dependent diabetes mellitus (IDDM), myocardial infarction, and mutagenic activity [18]. Moreover, NO has been known to play a key role in the central nervous, cardiovascular, and immune systems [12].

Therefore, the aim of this study was to evaluate whether fermenting ginseng marc with *P. acidilactici* increases the antioxidative and anti-inflammatory activities such that it has practical application as a functional food or in the pharmaceutical industry.

Materials and methods

Microorganism

Pediococcus acidilactici was isolated from kimchi and identified as KCCM 11614P by the Korean Culture Center of Microorganisms (Seoul, Korea). The strain was cultured and activated in Man Rogosa Sharpe (MRS) broth at 37 °C for 24 h.

Chemicals

MRS broth was purchased from Difco Laboratories (Detroit, MI, USA). Aluminum nitrate; ammonium thiocyanate; β-carotene; ferric chloride; kaempferol; linoleic acid; phosphoric acid; potassium acetate; potassium ferricyanide; quercetin; (SNP); sulfanilamide; 2,4,6-tripyridyl-s-triazine (TPTZ); and Tween 80 were purchased from Sigma–Aldrich Company (St. Louis, MO, USA). Acetonitrile, chloroform, ethanol (95%), and methanol were obtained from J.T. Baker (Austin, TX, USA).

Preparation of ginseng marc fermentation

Panax ginseng marc was obtained from Ginseng Research Institute of Il Hwa Co., Ltd., (Guri-si, Gyeonggi-do, Korea). Ginseng marc was extracted three times with 70% ethanol and filtered with a 0.45-μm membrane filter. Ethanol extract were concentrated a vacuum evaporator (EYELA N-1000 V, Tokyo, Japan). Crude extracts were freeze dried and stored at −20 °C until used.

An initial cell number was adjusted to approximately 6.3 log colony-forming units (CFU)/mL. The fermentation medium comprised 4 g ginseng marc and 400 mL distilled water. During fermentation, cultured samples were taken at 0, 8, 16, and 24 h for various tests. To estimate the viable cell number, 100 μL of serially diluted fermented extract was plated on MRS agar plates, and single colonies were counted. TTA beyond pH 8.2 was determined via titration with 0.1 M sodium hydroxide (NaOH). TTA was calculated as the percentage of lactic acid as follows [19]:

$$\text{Total titratable acidity} = \text{volume of } 0.1\,\text{M NaOH} \times 0.009 \times 100/\text{weight of the sample.}$$

Determination of total phenolics and flavonoids contents

The total phenolics content (TPC) was determined by the Folin–Ciocalteu method [19]. Each fermented extract (100 μL) was mixed with 2% sodium carbonate (2 mL) for 5 min and Folin–Ciocalteu's reagent was then added. The mixture was allowed to stand at 25 °C for 30 min. Absorbencies were then measured at 750 nm with a spectrophotometer (Optizen, Mecasys, Korea), and TPC was expressed as gallic acid equivalents (mg GAE/g of solid).

The total flavonoid content (TFC) was determined by the colorimetric aluminum chloride method [19]. A 0.5 mL quantity of fermented extract was sequentially mixed with 1.5 mL of 95% ethanol, 0.1 mL of 10% aluminum nitrate in 1 M potassium acetate, and 2.8 mL of distilled water. The absorbance of the mixture after incubation at 25 °C for 30 min was measured at 415 nm. TFC was expressed as kaempferol equivalents (mg kaempferol/g of solid).

Enzymatic activities

The enzymatic activity of *P. acidilactici* KCCM 11614P was evaluated using the API ZYM kit (Biomerieux Inc., Marcy l'Etoile, France). The subcultured strains of 10^7 CFU/mL of strain were suspended in sterile saline (0.85% NaCl) and inoculated in each cupule at 37 °C for 4 h. ZYM-A and ZYM-B reagents were then added and the solutions observed for color change. Enzyme activities produced by the *P. acidilactici* strain during culturing were expressed as 0, 5, 10, 20, or 40 nM, as indicated in the API ZYM kit [20].

Determination of antioxidative activity

Ferric reducing antioxidant power assay

The FRAP of the fermented extract was determined by the method of Xiao et al. [21]. The FRAP reagent contained 2.5 mL TPTZ, 10 mM in 40 mM HCl, 2.5 mL iron chloride ($FeCl_3$, 20 mM), and 25 mL acetate buffer (300 mM, pH 3.6). A 100 μL sample was added to 1.9 mL FRAP reagent at 37 °C for 30 min, and the absorbance was measured spectrophotometrically at 593 nm. Ferrous sulfate ($FeSO_2$) was used for the standard curve.

β-Carotene/linoleic acid bleaching assay

The method of Terpinc et al. [22] was used to determine the antioxidant activity using β-carotene/linoleic acid. A 10 mL β-carotene reagent in chloroform (0.2 mg/mL) was mixed with 44 μL linoleic acid and 200 μL Tween 80. After evaporation of the reagent, 200 mL distilled water was added. A 4.5 mL aliquot of emulsion was added to the 0.5 mL sample and was measured at 470 nm. This reaction was performed at 50 °C for a 2 h interval. The β-carotene/linoleic acid bleaching was calculated as follows:

$$\text{Bleaching activity}\,(\%) = (A_{\text{control}}/A_{\text{sample}}) \times 100$$

where $A_{control}$ and A_{sample} were absorbance of control and sample, respectively.

Ferric thiocyanate assay

The antioxidant activity was determined by the method of Su et al. using ferrous reducing power [23]. A 100 μL of sample was mixed with 200 μL distilled water, 200 μL linoleic acid, and 400 μL of potassium phosphate buffer (40 mM, pH 7). The mixture was incubated at 37 °C in the dark and absorbance at 500 nm was measured at 24 h intervals. The inhibition of lipid oxidation was calculated as follows:

$$\text{Inhibition of peroxidation}\,(\%) = [1 - (A_{\text{control}}/A_{\text{sample}}) \times 100]$$

where $A_{control}$ and A_{sample} were absorbance of control and sample, respectively.

Preparation of fermented milk

A ginseng marc extract (1%, w/v), skimmed milk powder (4%), and pectin (0.1%, w/v) were mixed in city milk (Seoul Milk Co., Seoul, Korea), and pasteurized at 85 °C for 10 min. After cooling, 1% *P. acidilactici* KCCM 11614P (initial cell number: 6.3 log CFU/mL) was inoculated into ginseng marc milk base at 40 °C in a water bath for 24 h.

NO scavenging activity

The NO scavenging activity was determined by the SNP assay [24]. A 10 mM SNP and sample were incubated at 37 °C for 24 h. We than added 100 μL Griess reagent to 100 μL reaction mixture, and measured absorbance at 540 nm. The NO scavenging activity was calculated as follows:

$$\text{NO scavenging}\,(\%) = [(N_c - N_s/N_c)] \times 100$$

where N_c is the nitrite concentration of the control, and N_s the nitrite concentration of the sample.

Statistical analysis

All experiments were carried out in triplicate, and standard deviation values are presented. Linear regression analysis was used for total phenolic and flavonoid contents. One-way analysis of variance (ANOVA) was used to determine significant differences between samples in SNP assay using SPSS Statistics version 19 (SPSS Inc., Chicago, IL, USA).

Results and discussion

Effect of fermentation on viable cell, pH, and TTA

A viable cell number of ginseng marc extract fermented with *P. acidilactici* for 12 h increased from 6.3 to 7.5 log CFU/mL for 24 h (Fig. 1A). The pH of the fermented ginseng marc broth decreased from 6.5 to 4.8, and TTA increased from 0.25 to 0.42% (Fig. 1B). The TTA of milk supplemented with red ginseng extract increased from 0.10 ± 0.01 to 0.22 ± 0.01%, which can be attributed to factors in the media that promote bioconversion [11]. For example, in the case of fermented ginseng wine, studies have shown that lactic acid content increased up to 8% with LAB-induced fermentation [20].

Effect of fermentation on total polyphenol and flavonoid content

TPC and TFC of fermented ginseng marc extract as a function of fermentation time are shown in Table 1. The regression equations of total phenol and flavonoid contents are as follows (x = absorbance of sample):

$$\text{Total phenolic content} = 423.5x + 15.442\,(R^2 = 0.99827)$$

$$\text{Total flavonoid content} = 0.0053x - 0.0073\,(R^2 = 0.99961)$$

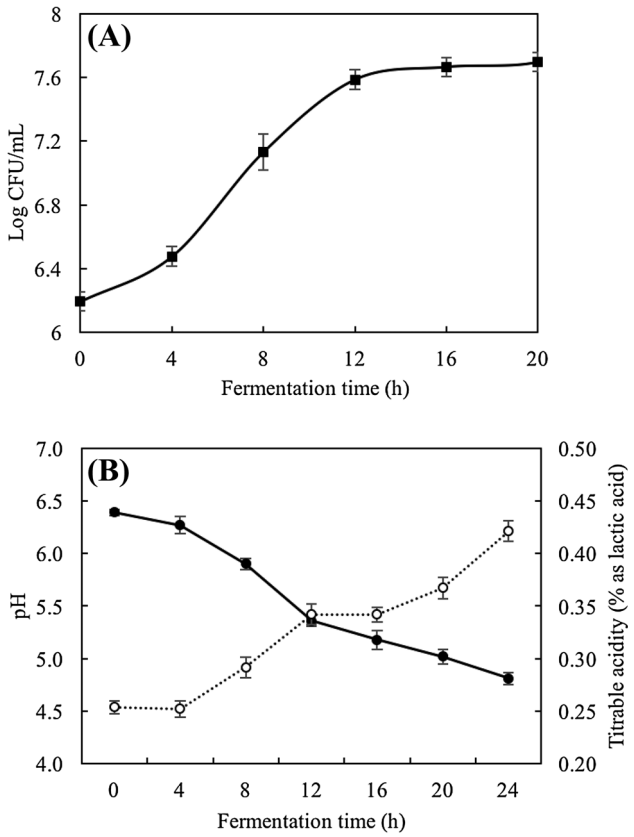

Fig. 1 Microbiological and chemical change of ginseng marc fermentation by *P. acidilactici* KCCM11614P. (**A**) Cell growth, (**B**) pH (solid line) and total titratable acidity (dashed line); TTA was calculated as the percentage of lactic acid

Compared with the control (not fermented) ginseng marc extract, the fermented ginseng marc extract had higher TPC and TFC. The TPC of fermented ginseng marc extract increased to 25.4 to 30.0%, and the highest TPC was 33.7 ± 0.4 mg GAE/g of solid at 24 h of fermentation. Park et al. [19] found that the TPC of magnolia increased to 11.2 to 14.9% using *P. acidilactici* fermentation and fermented extract showed antioxidant and anticancer effect. Additionally, the TPC of ginseng seed [7] increased to 27.7 to 39.2% when fermented with *Pediococcus pentosaceus*.

Kaempferol is a standard substance used to measure flavonoid content because it is known to exist in ginseng root and leaves [25]. This study showed that flavonoids such as the kaempferol in ginseng marc extract might be slightly increased to 11.5 to 34.4% during fermentation.

Enzymatic activity of *P. acidilactici* KCCM 11614P

The API ZYM kit is used for detection of 20 types of enzymatic activity. The enzyme β-glucosidase is among those that decomposes phenolic glycoside to phenolic acid [4]. Since phenolic compounds have a positive correlation with antioxidants [24, 26], fermentation by microorganisms producing β-glucosidase could improve antioxidant activity.

The β-glucosidase activity of *P. acidilactici* was 20 nM of hydrolyzed substrate (Table 2). Other researchers reported that *P. acidilactici* isolated from *inziangsang*, a traditional fermented vegetable product in India, had 20 nM of β-glucosidase activity, and *P. pentosaceus* isolated from traditional fermented rice noodles had β-glucosidase activity of 30 nM [27]. Tamang et al. [20] found that *P. pentosaceus* isolated from *gundruk,* which is a lactic-fermented vegetable product processed manly in Nepal, referred to positive reaction of β-glucosidase. The β-galactosidase displayed a minimum high activity at 40 nM in *P. acidilactici*. Kim [28] showed β-galactosidase producing microorganisms was able to used for ginseng bioconversion. Theriault et al. [29] reported that phenolic compound from maple syrup with β-galactosidase showed antioxidant, antiradical, and antimutagenic properties. However, β-glucuronidase, which is one of the factors in developing colorectal cancer, was not detected in this study [30].

Effect of fermented ginseng marc on antioxidant activity

FRAP assays were performed to evaluate the reducing power of the ferric-tripyridyltriazine complex to a ferrous-tripyridyltriazine complex. The FRAP values of fermented

Table 1 Total phenolic and flavonoid contents of ginseng marc fermented with *P. acidilactici* KCCM11614P

Fermentation time (h)	Solid content (mg/mL)	Total phenolic content (mg GAE/g of solid)	Total flavonoid content (mg kaempferol/g of solid)
0	9.0 ± 0.2^{a}	26.4 ± 0.4^{d}	9.3 ± 0.3^{c}
8	8.2 ± 0.1^{b}	27.9 ± 1.2^{c}	11.4 ± 0.7^{a}
16	7.7 ± 0.2^{c}	29.8 ± 0.9^{b}	10.4 ± 1.8^{b}
24	7.3 ± 0.1^{d}	33.7 ± 0.4^{a}	10.0 ± 0.4^{bc}

Values are mean ± SD of triplicate experiments. Different letters in same column indicate significant differences as determined by Duncan's multiple range tests ($p < 0.05$)

Table 2 Enzyme activity of *P. acidilactici* KCCM11614P using the API ZYM kit

Enzyme	Activity[1]	Enzyme	Activity[1]
Control	0	Acid phosphatase	≥40
Alkaline phosphatase	0	Naphthol-AS-BI-phosphohydrolase	≥20
Esterase	0	α-Galactosidase	0
Esterase lipase	0	β-Galactosidase	≥40
Lipase	≥10	β-Glucuronidase	0
Leucine arylamidase	≥30	α-Glucosidase	0
Valine arylamidase	≥30	β-Glucosidase	≥20
Cystine arylamidase	≥40	N-Acetyl-β-glucosaminidase	0
Trypsin	≥40	α-Mannosidase	0
α-Chymotrypsin	0	α-Fucosidase	0

[1] 0, no enzyme activity; 5, 10, 20, 30, ≥40 indicates nM of hydrolyzed substrate after 4 h of incubation at 37 °C

ginseng marc extract increased from 362.3 ± 4.3 to 487.3 ± 13.2 mM $FeSO_4$ eq (Table 3), as β-glucosidase breaks glycoside down to phenolic compounds. Researchers have evaluated the antioxidative activities of American, Asian, and Siberian ginseng roots through FRAP activity [31]. Moreover, the FRAP value was reported to increase over control both in red ginseng marc fermented by *Bacillus subtilis* [32] and in chickpeas fermented by *Cordyceps militaris* [21].

β-Carotene/linoleic acid bleaching assays were performed to evaluate the inhibition of lipid oxidation. Inhibition of β-carotene oxidation of fermented ginseng marc increased from 59.6 ± 0.1 to 65.7 ± 0.8% (Table 3). Lee et al. [33] reported that the leaf, stem, and root of *Panax ginseng* exhibited inhibition of linoleic acid oxidation. Park et al. [34] showed that kaempferol (flavonols with 3-hydroxyl) had high lipoxygenase inhibition activity rather than glycosidic substituents and showed scavenging activity of oxygen species by terminating radical chaing reactions.

FTC assays were performed to evaluate the inhibition of lipid peroxidation using ammonium thiocyanate. The antioxidant activity of fermented ginseng extract using the FRAP and β-carotene bleaching assays was higher than that for the non-fermented ginseng marc extract. In the FTC assay, the antioxidant activity of non-fermentation ginseng marc extract was slightly higher than that of the fermented samples (Table 3). During fermentation, TFC having inhibition activity of peroxidation might be decreased. Researchers have reported that the TPC of rabbit-eye blueberry juice prior to fermentation was higher than that of the fermented skin, whereas the antioxidant activity of juice prior to fermentation—as determined by FTC assay—was lower than that of fermented skin [23].

The effect of fermented milk added ginseng marc extract on NO scavenging activity

Milk was prepared to examine the applicability of ginseng marc and *P. acidilactici* on food industry and the amount of NO was measured to confirm functionality of fermented milk added ginseng marc extract. NO plays a role in inflammation because it increases vascular permeability and induces toxic oxidative responses [3]. The NO generated from SNP reacts with superoxide (O_2^-) to form $ONOO^-$, which are known to induce inflammation [24]. Therefore, we performed the SNP assay to evaluate NO concentration. The NO scavenging of non-fermented and fermented milk added ginseng marc extract for 24 h was 6.4 and 28.3%, respectively (Fig. 2). Phenolic acid and

Table 3 Effect of fermentation time on antioxidant activity of ginseng marc fermented by *P. acidilactici* KCCM11614P

Fermentation time (h)	FRAP assay (mM FeSO4 eq)	Inhibition of β-carotene oxidation (%)	Inhibition of peroxidation (%)
0	362.3 ± 4.3^{a}	59.6 ± 0.1^{a}	56.0 ± 0.9^{b}
8	450.0 ± 2.9^{b}	63.2 ± 0.3^{b}	54.6 ± 0.6^{ab}
16	469.5 ± 9.2^{c}	64.1 ± 0.6^{c}	51.8 ± 2.2^{a}
24	487.3 ± 13.2^{d}	65.7 ± 0.8^{c}	50.0 ± 1.9^{a}

Values are mean ± SD of triplicate experiments. Different letters in same column indicate significant differences as determined by Duncan's multiple range tests ($p < 0.05$)

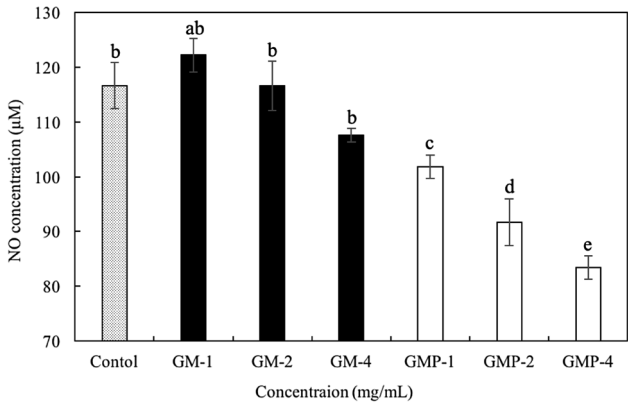

Fig. 2 Nitric oxide (NO) concentration of non-fermented (GM) and 24 h-fermented ginseng marc milk (GMP) using SNP assay. NO concentration of control was calculated using distilled water instead of ginseng milk. Different letters showed significant differences between samples ($p < 0.05$)

flavonoid were able to remove reactive nitrogen intermediates and increase phenolics levels in ginseng marc through LAB fermentation [35]. Several studies showed that plant foods such as ginseng, grape, and longan contain high levels of phenolics and flavonoids, which inhibit NO synthesis in both in vitro and in vivo experiments [36]. In particular, kaempferol, a major flavonoid compound in ginseng, has been reported to suppress proinflammatory cytokines (interleukin-6 [IL-6], IL-8, interleukin-1 receptor-associated kinase [IRAK1], and IRAK4) [15, 37].

This study aimed to enhance the antioxidant and anti-inflammatory activities of ginseng marc using fermentation. During a 24 h fermentation, *P. acidilactici* was successfully grown in ginseng marc extract. TPC and TFC of the fermented ginseng marc increased, and β-glucosidase activity was detected in *P. acidilactici* KCCM 11614P. Our results demonstrate that enhanced antioxidant and anti-inflammatory activities of the fermented ginseng marc resulted in increased production of phenolic compounds by β-glucosidase produced by *P. acidilactici* KCCM 11614P. Ginseng marc as by product in ginseng processing has relatively low bioactivity but this study suggests that using fermentation to improve the antioxidant and NO scavenging activities of ginseng marc is a viable method for increasing its use as a biofunctional resource in the food and pharmaceutical industries. In addition, *P. acidilactici* KCCM 11614P reveal that fermentability of herb or other by-products from agriculture and applicability to dairy products as an additional starter.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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