

Article

Antioxidant and Cytoprotective Effects of Fermented *Panax ginseng* Berry and Root Extracts

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Abstract

The roots of *Panax ginseng* are well known for their bioactive properties, while its berries have recently attracted attention for their pharmacological potential. This study investigated whether fermentation with *Lactiplantibacillus plantarum* enhances the antioxidant properties of ginseng roots and berries and their protective effects against oxidative stress in vitro. Fermentation significantly increased total polyphenol, flavonoid, and saponin contents and promoted the conversion of major ginsenosides (ginsenoside Rg1, ginsenoside Rb1, and ginsenoside Rb2), which are relatively less bioavailable, into minor ginsenosides (ginsenoside Rh1, ginsenoside Rg2, and ginsenoside Rg3) with enhanced biological activity and bioavailability. Fermented extracts exhibited higher radical-scavenging activities in 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and ferric reducing antioxidant power (FRAP) assays than non-fermented extracts. In tert-butyl hydroperoxide (t-BHP)-stimulated Chang liver cells, fermented extracts reduced intracellular reactive oxygen species (ROS) generation, inhibited lipid peroxidation, restored the reduced glutathione/oxidized glutathione (GSH/GSSG) ratio, and enhanced antioxidant enzyme activities, including superoxide dismutase (SOD) and catalase (CAT). These results demonstrate that *L. plantarum*-mediated fermentation effectively enhances the antioxidant and cytoprotective potential of ginseng roots and berries, supporting their application as functional food ingredients.

Keywords: *Panax ginseng*; ginseng berry; *Lactiplantibacillus plantarum*; antioxidant activity; oxidative stress; fermentation

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1. Introduction

Reactive oxygen species (ROS) are inevitably generated during normal cellular metabolism. At moderate levels, ROS play essential roles in antimicrobial defense and intracellular signaling; however, excessive accumulation leads to oxidative stress, resulting in lipid peroxidation, protein modification, DNA damage, and mitochondrial dysfunction [1]. Such oxidative damage is closely associated with the onset and progression of chronic disorders, including cardiovascular disease, diabetes, neurodegenerative diseases, cancer, and aging [2]. To maintain redox homeostasis, the human body relies on endogenous antioxidant defense systems, such as catalase (CAT), glutathione peroxidase, and superoxide dismutase (SOD). Nevertheless, when oxidative stress exceeds the capacity of these systems, the intake of exogenous antioxidants derived from plant-based foods becomes increasingly important [3].

Fermentation has long been utilized to improve food preservation and sensory quality and has recently gained attention as an effective strategy to enhance the bioavailability and functionality of phytochemicals [4]. In particular, fermentation with lactic acid bacteria enhances the antioxidant capacity and physiological efficacy of plant-derived materials by facilitating the biotransformation of complex compounds into more bioavailable low-molecular-weight metabolites through enzymatic deglycosylation and the release of bound phenolic compounds [5,6].

Panax ginseng C.A. Meyer is a well-recognized medicinal plant containing a wide range of bioactive constituents, including ginsenosides, phenolic compounds, and polysaccharides, which have been associated with antioxidant, anti-inflammatory, and neuroprotective effects [7,8]. While the pharmacological properties of ginseng roots have been extensively investigated, ginseng berries have received comparatively less attention despite their high ginsenoside content. Ginseng berries are particularly rich in ginsenosides, especially ginsenoside Re, as well as vitamins and minerals, and have been reported to exert beneficial effects on blood glucose regulation and antioxidant-related physiological functions, including skin health [9,10]. However, ginseng berries exhibit high respiration rates and rapid postharvest quality deterioration, leading to moisture loss, discoloration, and microbial decay during storage, which severely limits their shelf life and industrial utilization despite their biological potential [11].

In the present study, ginseng roots and berries were fermented with *Lactiplantibacillus plantarum* to enhance their antioxidant potential. Although several studies have investigated the antioxidant properties of ginseng extracts or the fermentation of ginseng materials, most have focused primarily on chemical antioxidant activity or fermentation process optimization. In contrast, the present study provides a comparative evaluation of ginseng berries and roots fermented with *Lactiplantibacillus plantarum* and further examines their cytoprotective effects using a cellular oxidative stress model. This integrated approach provides new insights into the functional potential of fermented ginseng materials.

2. Materials and Methods

2.1. Materials

Commercial-grade ginseng roots and berries of *Panax ginseng* C.A. Meyer were purchased from Daegu Yangnyeongsi Market (Daegu, Republic of Korea). *L. plantarum* KCTC 3108 was obtained from the Korean Collection for Type Cultures (KCTC, Jeongeup, Republic of Korea) and maintained in de Man, Rogosa, and Sharpe (MRS) broth (Difco, Sparks, MD, USA). Unless otherwise specified, analytical-grade chemicals, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), dimethyl sulfoxide (DMSO), L-ascorbic acid, Folin–Ciocalteu reagent, gallic acid, quercetin, sulfanilic acid, α -naphthylamine, glacial acetic acid, sodium nitrite (NaNO_2), sodium carbonate (Na_2CO_3), aluminum nitrate, potassium acetate, 2,4,6-tripyridyl-s-triazine (TPTZ), ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), sodium acetate, hydrochloric acid (HCl), phosphate and acetic acid buffers, ethanol, and high-performance liquid chromatography (HPLC)-grade acetonitrile, were purchased from Sigma-Aldrich (St. Louis, MO, USA). Cell culture reagents, including Dulbecco's Modified Eagle's Medium (DMEM, high glucose; HyClone, Logan, UT, USA), fetal bovine serum (FBS), penicillin–streptomycin, trypsin–ethylenediaminetetraacetic acid (trypsin–EDTA), and phosphate-buffered saline (PBS), were obtained from Gibco (Waltham, MA, USA). Thiobarbituric acid reactive substances (TBARS; malondialdehyde, MDA), reduced and oxidized glutathione (GSH/GSSG), and JC-1 dye (5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide) assay kits were also purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Preparation of Extracts

Four types of samples were prepared in this study: non-fermented ginseng berry ethanol extract (EGB), fermented ginseng berry ethanol extract (FEGB), non-fermented ginseng root ethanol extract (EGR), and fermented ginseng root ethanol extract (FEGR). The lactic acid bacterium used for fermentation was *Lactiplantibacillus plantarum* KCTC 3108, which was precultured in MRS broth at 37 °C prior to use. Ginseng berries and roots were washed and dried at 35 °C under light-protected conditions until no further change in weight was observed. The dried samples were then mechanically disrupted using a variable-speed laboratory blender (Blender 7011S, B-type, 1 L, SUS container; Waring, Torrington, CT, USA). To minimize interference from indigenous and environmental microorganisms during fermentation, the dried samples were sterilized by high-pressure steam at 121 °C for 15 min prior to fermentation. The sterilized samples were mixed with distilled water at a ratio of 1:10 (*w/v*) to prepare a slurry, and the initial pH of the slurry was adjusted to 6.5 using 0.1 N HCl prior to fermentation. Subsequently, 1 mL of a bacterial suspension (1.0×10^7 CFU/mL) was inoculated per 100 g of sample slurry. Fermentation was carried out at 37 °C for 48 h without agitation. After fermentation, the samples were extracted with 70% (*v/v*) ethanol at a solid-to-solvent ratio of 1:10 (*w/v*) by refluxing at 70 °C for 1 h. The extracts were filtered through No. 2 filter paper (Advantec Toyo Kaisha, Tokyo, Japan), concentrated under reduced pressure, lyophilized, and stored at −18 °C until further analysis. The sterilization, lactic acid fermentation, and ethanol extraction conditions applied in this study were established based on previous studies on the fermentation of ginseng and plant-based substrates and the analysis of functional components such as ginsenosides and polyphenols [5,7].

2.3. Determination of Total Polyphenol, Total Flavonoid, and Crude Saponin Contents

Total polyphenol content (TPC) was determined using the Folin–Ciocalteu method [12]. Each extract (1 mL) was mixed with distilled water and 0.2 N Folin–Ciocalteu reagent, followed by the addition of 7.5% (*w/v*) sodium carbonate (Na_2CO_3) after 8 min. After incubation for 2 h in the dark, absorbance was measured at 750 nm using a UV–visible spectrophotometer (UV-1800, Shimadzu Corp., Kyoto, Japan). Results were expressed as milligrams of gallic acid equivalents per gram of extract (mg GAE/g) based on a gallic acid standard curve. R^2 value of the calibration curve for total polyphenol content was 0.9986.

Total flavonoid content (TFC) was measured according to Moreno et al. [13]. Briefly, 0.5 mL of extract was mixed with 1 mL of 10% (*w/v*) aluminum nitrate, 0.1 mL of 1 M potassium acetate, and 4.3 mL of 80% (*v/v*) ethanol, followed by incubation in the dark for 40 min. Absorbance was recorded at 510 nm, and results were expressed as milligrams of quercetin equivalents per gram of extract (mg QE/g). R^2 value of the calibration curve for total flavonoid content was 0.9985.

Crude saponin content was determined using the vanillin–perchloric acid colorimetric method [14]. Each extract (100 mg) was dissolved in 80% (*v/v*) ethanol, sonicated for 30 min using an ultrasonic bath (SD-100H, Seongdong Ultrasonic Co., Seoul, Republic of Korea), and centrifuged at $3000 \times g$ for 10 min (1580R, Labogene, Lynge, Denmark). The supernatant (1 mL) was reacted with vanillin–ethanol solution and perchloric acid, heated at 60 °C for 15 min, cooled to room temperature, and absorbance was measured at 544 nm. Crude saponin content was calculated using a ginsenoside standard curve and expressed as milligrams of ginsenoside equivalents per gram of extract (mg GE/g).

2.4. HPLC Analysis of Ginsenosides

Ginsenosides (Rg1, Re, Rf, Rb1, Rc, Rb2, and Rd) were quantified using a high-performance liquid chromatography (HPLC) system (Prominence, Shimadzu Corp., Kyoto,

Japan) equipped with a C18 reversed-phase column (5 μm , 250 $\times$ 4.6 mm; Phenomenex, Torrance, CA, USA). Extracts were dissolved in distilled water, filtered through a 0.45 μm membrane filter (Millipore, Billerica, MA, USA), and separated using a water–acetonitrile gradient. The flow rate was set at 0.8 mL/min, and the column temperature was maintained at 40 °C. The injection volume was 10 μL , and ginsenosides were detected at 203 nm using a UV detector (SPD-20A, Shimadzu Corp., Kyoto, Japan). Data acquisition and analysis were performed using Class-VP software (version 6.14; Shimadzu Corp., Kyoto, Japan).

2.5. Antioxidant Assays

2.5.1. DPPH Radical Scavenging Activity

DPPH radical scavenging activity was evaluated according to Blois [15]. Extracts (1 mL) were mixed with 2 mL of 7.5×10^{-5} M DPPH solution in ethanol, incubated at 37 °C for 30 min in the dark, and absorbance was measured at 517 nm using a UV–visible spectrophotometer (UV-1800, Shimadzu Corp., Kyoto, Japan). L-Ascorbic acid was used as a positive control. DPPH radical scavenging activity was expressed as percentage inhibition (%) relative to the control.

2.5.2. ABTS Radical Scavenging Activity

ABTS radical scavenging activity was determined following Re et al. [16]. $\text{ABTS}^{\bullet+}$ was generated by reacting 7 mM ABTS with 2.45 mM potassium persulfate and incubating the mixture in the dark at 30 °C for 12 h. The solution was diluted to an absorbance of 0.70 ± 0.02 at 734 nm. Each extract (40 μL) was added to 4 mL of $\text{ABTS}^{\bullet+}$ solution, and absorbance was measured at 734 nm after 1 min. ABTS radical scavenging activity was expressed as percentage inhibition (%).

2.5.3. Ferric Reducing Antioxidant Power (FRAP)

FRAP was measured according to Benzie and Strain [17]. Samples (0.5 mL) were mixed with 3.5 mL of freshly prepared FRAP reagent, incubated at 37 °C for 5 min, and absorbance was measured at 593 nm. FRAP values were expressed as micromoles of FeSO_4 equivalents per gram of extract ($\mu\text{mol FeSO}_4 \text{ eq/g extract}$).

2.5.4. Nitrite Scavenging Activity

Nitrite scavenging activity was evaluated according to Gray and Dugan [18]. Extracts were reacted with sodium nitrite under acidic conditions, treated with Griess reagent, and absorbance was measured at 520 nm. Nitrite scavenging activity was expressed as percentage inhibition (%) relative to the control.

2.6. Antioxidant Enzyme Activities

2.6.1. SOD-like Activity

SOD-like activity was determined by monitoring the auto-oxidation of pyrogallol at 420 nm according to Marklund and Marklund [19]. SOD-like activity was expressed as percentage inhibition (%).

2.6.2. CAT Activity

CAT activity was measured according to Aebi [20]. The decomposition of hydrogen peroxide was monitored at 240 nm using a UV–visible spectrophotometer (UV-1800, Shimadzu Corp., Kyoto, Japan). CAT activity was expressed as units per milligram of protein (U/mg protein).

2.7. Cell-Based Assays

2.7.1. Cell Viability Assay

Cell viability was evaluated using the MTT assay to determine the non-cytotoxic concentration range of the extracts. Human Chang liver cells were obtained from the Korean Cell Line Bank (KCLB, Seoul, Republic of Korea; Accession No. 21472) and cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum and 1% penicillin–streptomycin at 37 °C in a humidified atmosphere containing 5% CO₂. Cells (1×10^4 cells/well) were seeded in 96-well plates and treated with the extracts at concentrations of 50–400 µg/mL for 24 h. After treatment, MTT solution was added and incubated for 4 h to allow the formation of formazan crystals. The crystals were dissolved in a solution containing 10% sodium dodecyl sulfate and 50% dimethyl sulfoxide, and absorbance was measured at 570 nm using a microplate reader (VersaMax, Molecular Devices, San Jose, CA, USA).

2.7.2. Intracellular ROS Measurement

For the evaluation of cellular antioxidant and protective effects, oxidative stress was induced using tert-butyl hydroperoxide (t-BHP). Intracellular reactive oxygen species (ROS) levels were measured using the 2',7'-dichlorofluorescein diacetate (DCF-DA) assay. Cells were pretreated with the extracts for 2 h, loaded with DCF-DA (e.g., 20 µM) for 30 min, and subsequently exposed to t-BHP (80 µM) for 1 h. Fluorescence intensity was recorded at excitation and emission wavelengths of 485 and 538 nm, respectively, using a multimode plate reader (Spark 10M, Tecan Group Ltd., Männedorf, Switzerland).

2.7.3. Lipid Peroxidation (TBARS) Assay

Lipid peroxidation was assessed using the thiobarbituric acid reactive substances (TBARS) assay following t-BHP exposure. Treated cell lysates (100 µL) were mixed with 0.67% thiobarbituric acid containing 10% trichloroacetic acid and 1% butylated hydroxytoluene, heated at 95 °C for 45 min, cooled, and centrifuged at $3000 \times g$ for 10 min. The absorbance of the supernatant was measured at 532 nm, and malondialdehyde (MDA) levels were calculated using a 1,1,3,3-tetramethoxypropane standard curve. For data presentation, lipid peroxidation was expressed as an inhibition percentage relative to the t-BHP-treated control according to the following equation:

$$\text{Inhibition (\%)} = [1 - (\text{MDA}_{\text{sample}}/\text{MDA}_{\text{t-BHP control}})] \times 100 \quad (1)$$

2.7.4. Glutathione (GSH/GSSG) Ratio

Intracellular glutathione status was evaluated by determining the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG) after t-BHP treatment. Cells were deproteinized with 5% metaphosphoric acid, centrifuged, and analyzed using an enzymatic cycling method. Reduced glutathione levels were calculated as total glutathione minus twice the oxidized glutathione concentration and normalized to protein content.

2.7.5. Mitochondrial Membrane Potential ($\Delta\Psi_m$)

Mitochondrial membrane potential ($\Delta\Psi_m$) was assessed using the JC-1 dye assay following t-BHP-induced oxidative stress. Cells were incubated with JC-1 (2 µM) for 25 min at 37 °C in the dark, washed with phosphate-buffered saline, and analyzed for fluorescence at excitation/emission wavelengths of 485/535 nm for the monomer form (green fluorescence) and 530/590 nm for the aggregate form (red fluorescence). $\Delta\Psi_m$ was expressed as the ratio of red to green fluorescence, with higher ratios indicating improved mitochondrial membrane potential. This parameter was consistently used for subsequent statistical and correlation analyses.

2.8. Statistical Analysis

All data are expressed as the mean $\pm$ standard deviation (SD) of at least three independent experiments ($n = 3$). Statistical differences among groups were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test with SPSS software (version 25.0; IBM Corp., Armonk, NY, USA), and differences were considered statistically significant at $p < 0.05$. Pearson's correlation coefficients were calculated to evaluate the relationships between antioxidant indices (total polyphenol content, total flavonoid content, DPPH, ABTS, FRAP, and nitrite scavenging activity) and functional parameters (reactive oxygen species inhibition, lipid peroxidation, glutathione ratio, mitochondrial membrane potential, and CAT and superoxide dismutase activities). For correlation analysis, mitochondrial membrane potential was expressed as the JC-1 red/green fluorescence ratio. Correlation analyses and heatmap visualizations were performed using Python (version 3.9) with the pandas, NumPy, and Matplotlib libraries.

3. Results

3.1. Total Polyphenol, Total Flavonoid, and Crude Saponin Contents

Fermentation significantly increased total polyphenol, total flavonoid, and crude saponin contents in both ginseng berries and roots (Table 1). The enhancement effects were more pronounced in ginseng roots than in ginseng berries. Among all samples, fermented ginseng root extract exhibited the highest levels of total polyphenols and flavonoids. Crude saponin content also showed a clear increasing trend following fermentation in both ginseng berries and roots.

Table 1. Total polyphenols, total flavonoids, and crude saponin contents of fermented and non-fermented ginseng root and berry extracts.

Sample	Total Polyphenols (mg GAE/g)	Total Flavonoids (mg QE/g)	Crude Saponin (%)
EGB	46.40 $\pm$ 5.27 ^c	11.73 $\pm$ 0.63 ^d	4.10 $\pm$ 0.15 ^d
FEGB	52.32 $\pm$ 1.13 ^c	13.21 $\pm$ 0.47 ^c	4.65 $\pm$ 0.12 ^c
EGR	58.69 $\pm$ 2.88 ^b	15.64 $\pm$ 0.60 ^b	5.25 $\pm$ 0.18 ^b
FEGR	62.70 $\pm$ 0.62 ^a	19.09 $\pm$ 0.64 ^a	6.05 $\pm$ 0.14 ^a

EGB and FEGB indicate ethanol extracts of non-fermented and fermented ginseng berries, respectively, while EGR and FEGR indicate ethanol extracts of non-fermented and fermented ginseng roots, respectively. Total polyphenol content is expressed as mg gallic acid equivalent (GAE)/g of sample, and total flavonoid content is expressed as mg quercetin equivalent (QE)/g of sample. Values are expressed as mean $\pm$ standard deviation ($n = 3$). Different superscript lowercase letters within the same column indicate significant differences ($p < 0.05$) according to Duncan's multiple range test.

3.2. Ginsenoside Profiles Determined by HPLC

The ginsenoside profiles of EGB, FEGB, EGR, and FEGR were analyzed using high-performance liquid chromatography (HPLC), and the results are presented in Table 2. Non-fermented ginseng root extracts contained relatively high levels of ginsenosides Rg1, Re, Rb2, Rc, Rb3, and Rb1. Fermentation of ginseng berries resulted in increased levels of ginsenosides Rh1, Rg2, Rg3, Rf, Re, Rd, Rc, and Rb3 compared to non-fermented ginseng berry extracts. Similarly, fermented ginseng root extracts showed increased contents of ginsenosides Rg2, Rf, and Re relative to non-fermented ginseng root extracts. Compared with non-fermented samples, fermented extracts exhibited decreased levels of high-molecular-weight ginsenosides such as Rb1 and Rb2, while low-molecular-weight ginsenosides, including Rh1 and Rg3, were increased.

Table 2. Percentage weight (% *w/w*) of ginsenosides in ginseng berry extract, fermented ginseng berry extract, ginseng root extract, and fermented ginseng root extract.

Sample	Rh2	Rh1	Rg2	Rg3	Rg1	Rf	Re	Rd	Rb2	Rc	Rb3	Rb1	Total
EGB	N.D.	N.D.	0.02	N.D.	0.48	0.11	0.42	0.21	0.48	0.32	0.05	0.13	2.22
FEGB	N.D.	0.06	0.11	0.10	0.33	0.17	0.56	0.28	0.26	0.59	0.09	0.04	2.59
EGR	N.D.	N.D.	0.08	N.D.	0.60	0.21	0.72	0.30	0.83	1.02	0.13	1.82	5.71
FEGR	N.D.	N.D.	0.10	0.35	0.50	0.27	0.97	0.30	0.70	0.92	0.12	1.61	5.84

EGB and FEGB indicate ethanol extracts of non-fermented and fermented ginseng berries, respectively, while EGR and FEGR indicate ethanol extracts of non-fermented and fermented ginseng roots, respectively. Ginsenoside contents are expressed as percentage weight (% *w/w*) relative to the dry weight of each ethanol extract. N.D. indicates not detected. Total indicates the sum of all detected ginsenosides in each sample.

3.3. Antioxidant Activities

3.3.1. DPPH Radical Scavenging Activity

All samples exhibited a clear concentration-dependent increase in DPPH radical scavenging activity (Figure 1A). Fermentation consistently enhanced DPPH scavenging activity compared to non-fermented extracts, with a more pronounced effect observed in ginseng root extracts. This enhancement is consistent with the increased levels of antioxidant constituents observed following fermentation.

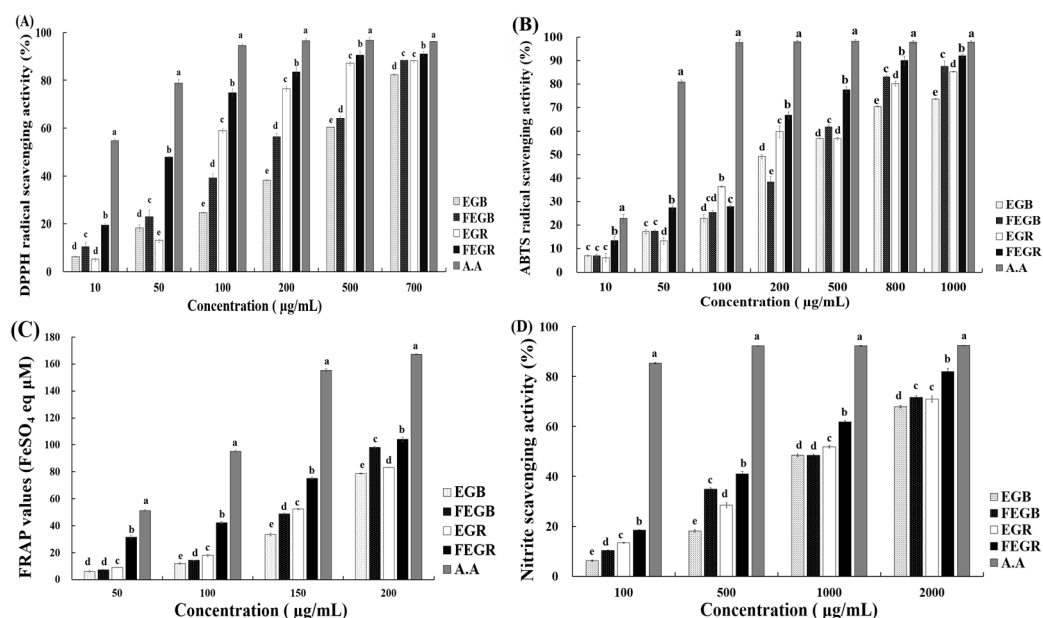


Figure 1. Antioxidant activities of ginseng berry and ginseng root extracts and their fermented counterparts. (A) DPPH radical scavenging activity, (B) ABTS radical scavenging activity, (C) ferric reducing antioxidant power (FRAP), and (D) nitrite scavenging activity. EGB and FEGB indicate ethanol extracts of non-fermented and fermented ginseng berries, respectively, while EGR and FEGR indicate ethanol extracts of non-fermented and fermented ginseng roots, respectively. A.A indicates ascorbic acid, which was used as a positive control. Different lowercase letters (a–e) indicate significant differences among different samples at the same concentration according to Duncan's multiple range test ($p < 0.05$).

3.3.2. ABTS Radical Scavenging Activity

ABTS radical scavenging activity also increased in a concentration-dependent manner for all samples (Figure 1B). Fermented extracts showed higher ABTS radical scavenging activities than non-fermented extracts at equivalent concentrations. Among the samples, FEGR exhibited the highest ABTS radical scavenging activity across the tested concentration range.

3.3.3. FRAP

FRAP values increased in a concentration-dependent manner in all samples (Figure 1C). Fermented extracts consistently exhibited higher reducing power than their non-fermented counterparts across the tested concentration range. Among the samples, FEGR showed the highest FRAP values at all concentrations, followed by EGR, FEGB, and EGB. The differences between fermented and non-fermented extracts became more pronounced at concentrations of 200–700 µg/mL.

3.3.4. Nitrite Scavenging Activity

Nitrite scavenging activity increased with increasing concentration in all samples (Figure 1D). Fermented extracts showed significantly higher nitrite scavenging activities than non-fermented extracts at equivalent concentrations ($p < 0.05$). Notably, the differences between fermented and non-fermented extracts became more pronounced at higher concentrations (≥ 500 µg/mL). Among the samples, FEGR tended to exhibit higher nitrite scavenging activity than the other extracts across the tested concentration range.

3.4. Antioxidant Enzyme Activities

3.4.1. SOD-like Activity

SOD-like activity of EGB, FEGB, EGR, and FEGR at concentrations of 50–300 µg/mL are presented in Table 3. SOD-like activity increased in a concentration-dependent manner in all samples, with fermented extracts exhibiting significantly higher activities than non-fermented extracts ($p < 0.05$). Among the tested samples, fermented ginseng root extract exhibited the strongest SOD-like activity, while EGR consistently showed higher activity than EGB among the non-fermented extracts.

Table 3. Superoxide dismutase (SOD)-like activity of fermented and non-fermented ginseng root and berry extracts at different concentrations.

Sample	SOD-like Activity (% Inhibition)			
	50	100	200	300
EGB	20.45 ± 0.84 ^{bC}	35.64 ± 1.85 ^{cB}	48.83 ± 2.72 ^{dA}	59.00 ± 4.58 ^{dA}
FEGB	21.05 ± 0.66 ^{aC}	38.45 ± 0.32 ^{bB}	49.43 ± 3.37 ^{cA}	67.77 ± 0.59 ^{bA}
EGR	19.46 ± 0.88 ^{cC}	33.52 ± 2.52 ^{dB}	49.44 ± 1.91 ^{bA}	61.73 ± 0.68 ^{cA}
FEGR	18.61 ± 0.17 ^{dD}	39.56 ± 0.07 ^{aC}	52.04 ± 1.51 ^{aB}	70.47 ± 4.72 ^{aA}

EGB, ginseng berry ethanol extract; FEGB, fermented ginseng berry ethanol extract; EGR, ginseng root ethanol extract; FEGR, fermented ginseng root ethanol extract. Values are expressed as the mean ± standard deviation (SD) ($n = 3$). Means with different lowercase letters (a–d) within the same column (between samples) and uppercase letters (A–D) within the same row (between concentrations) are significantly different according to Duncan's multiple range test ($p < 0.05$).

3.4.2. CAT Activity

CAT activities of EGB, FEGB, EGR, and FEGR at concentrations of 50–300 µg/mL are shown in Table 4. CAT activity significantly increased with increasing concentration in all samples ($p < 0.05$). Fermentation significantly enhanced CAT activity compared to the corresponding non-fermented extracts across the tested concentration range. Among the samples, fermented ginseng root extract exhibited the highest CAT activity, indicating a stronger fermentation-associated enhancement in ginseng roots than in berries.

Table 4. Catalase (CAT) activity of fermented and non-fermented ginseng root and berry extracts at different concentrations.

Sample	CAT Activity (U/mg Protein)			
	50	100	200	300
EGB	5.05 ± 0.59 ^{dC}	3.98 ± 0.93 ^{dC}	10.12 ± 0.61 ^{dB}	9.80 ± 2.29 ^{dA}
FEGB	9.95 ± 0.36 ^{bC}	10.93 ± 0.07 ^{bC}	16.19 ± 0.23 ^{bB}	17.89 ± 0.59 ^{bA}
EGR	6.52 ± 0.69 ^{cC}	7.57 ± 0.41 ^{cC}	12.29 ± 0.83 ^{cB}	23.57 ± 0.51 ^{aA}
FEGR	12.21 ± 0.91 ^{aD}	18.81 ± 0.75 ^{aC}	23.47 ± 0.27 ^{aB}	26.14 ± 0.09 ^{aA}

EGB, ginseng berry ethanol extract; FEGB, fermented ginseng berry ethanol extract; EGR, ginseng root ethanol extract; FEGR, fermented ginseng root ethanol extract. Values are expressed as the mean ± standard deviation (SD) ($n = 3$). Means with different lowercase letters (a–d) within the same column (between samples) and uppercase letters (A–D) within the same row (between concentrations) are significantly different according to Duncan's multiple range test ($p < 0.05$).

3.5. Cell-Based Assays

3.5.1. Cell Viability

Cell viability was initially evaluated at concentrations up to 400 µg/mL to assess potential cytotoxicity (Figure 2A). Although cell viability was measured across the full concentration range, the viability of Chang liver cells treated with both fermented and non-fermented ginseng root and berry extracts remained above 80% at concentrations up to 300 µg/mL. Therefore, concentrations ≤ 300 µg/mL, which satisfied the cell viability criterion, were selected for subsequent cell-based oxidative stress-related assays.

3.5.2. Inhibition of Intracellular ROS Generation

All extracts suppressed intracellular ROS generation in a *t*-BHP-induced oxidative stress model in a concentration-dependent manner (Figure 2B). Fermented extracts exhibited greater inhibitory effects on ROS generation than non-fermented extracts. At 300 µg/mL, fermented extracts, particularly FEGR, exhibited the strongest inhibitory effects on intracellular ROS generation.

3.5.3. Inhibition of Lipid Peroxidation

Lipid peroxidation was inhibited by all extracts in a concentration-dependent manner (Figure 2C). Fermented extracts exhibited stronger inhibitory effects than their non-fermented counterparts across the tested concentration range. Among the samples, fermented ginseng root extract showed the most pronounced inhibition of lipid peroxidation, indicating enhanced cytoprotective efficacy following fermentation.

3.5.4. GSH/GSSG Ratio

The intracellular redox status of *t*-BHP-stimulated Chang liver cells was evaluated based on the GSH/GSSG ratio (Figure 2D). All extract-treated groups exhibited higher GSH/GSSG ratios than the control, and the ratio increased in a concentration-dependent manner. Among the non-fermented samples, ginseng root extract consistently showed higher GSH/GSSG ratios than ginseng berry extract. Fermented extracts exhibited greater effects than non-fermented extracts, with fermented ginseng root extract showing the highest GSH/GSSG ratio at 300 µg/mL, followed by fermented ginseng berry extract, non-fermented ginseng root extract, and non-fermented ginseng berry extract.

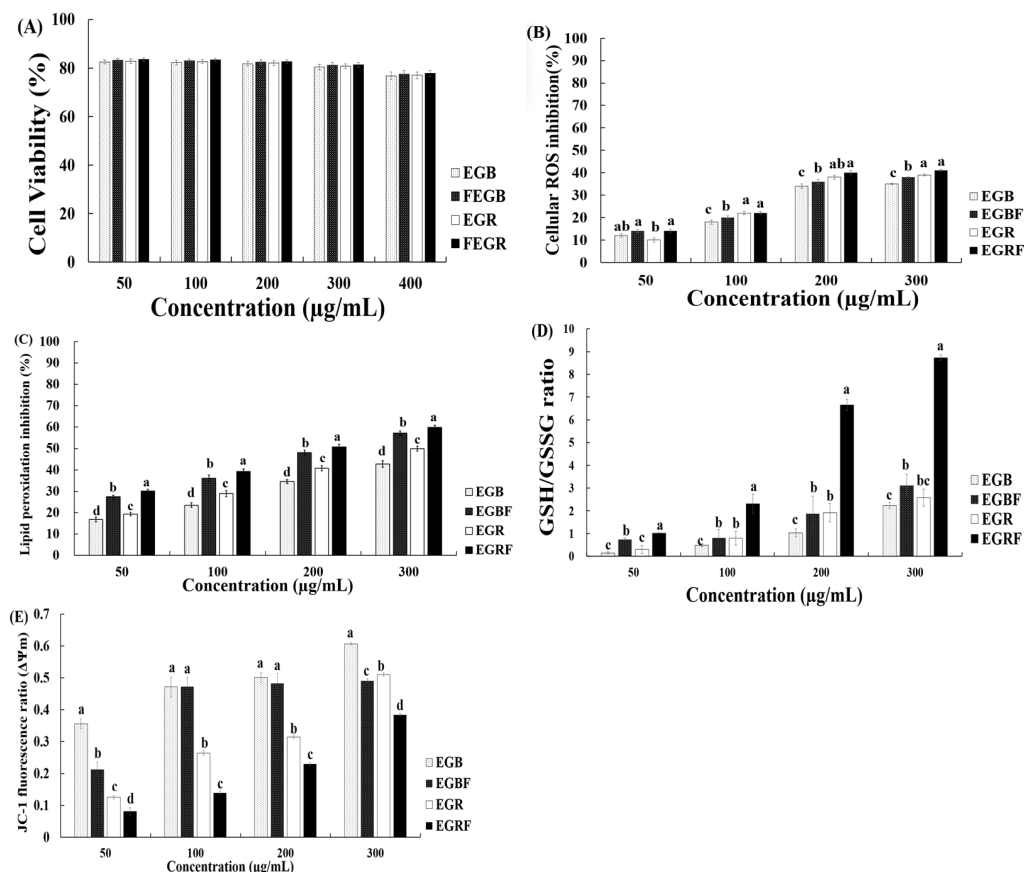


Figure 2. Effects of ginseng berry and root extracts before and after fermentation on oxidative stress and mitochondrial function in Chang liver cells. (A) Cell viability, (B) cellular ROS inhibition, (C) lipid peroxidation inhibition, (D) GSH/GSSG ratio, and (E) mitochondrial membrane potential ($\Delta\Psi_m$) at concentrations of 50–300 $\mu\text{g/mL}$. EGB and FEGB indicate ethanol extracts of non-fermented and fermented ginseng berries, respectively, while EGR and FEGR indicate ethanol extracts of non-fermented and fermented ginseng roots, respectively. Data are presented as mean $\pm$ SD ($n = 3$). Different lowercase letters (a–d) indicate significant differences among different samples at the same concentration according to Duncan's multiple range test ($p < 0.05$).

3.5.5. Mitochondrial Membrane Potential ($\Delta\Psi_m$)

Mitochondrial membrane potential ($\Delta\Psi_m$) was evaluated using the JC-1 assay in *t*-BHP-challenged Chang liver cells (Figure 2E). Pretreatment with all extracts increased the JC-1 red/green fluorescence ratio in a concentration-dependent manner, indicating attenuation of *t*-BHP-induced mitochondrial depolarization. Notably, higher extract concentrations, particularly at 300 $\mu\text{g/mL}$, tended to show the greatest improvement in $\Delta\Psi_m$, suggesting enhanced preservation of mitochondrial membrane potential under oxidative stress. The attenuation of intracellular ROS generation by fermented ginseng extracts was accompanied by the preservation of mitochondrial membrane potential ($\Delta\Psi_m$) and the restoration of glutathione redox balance. These findings suggest that the cytoprotective effects of fermented extracts are closely associated with the maintenance of mitochondrial integrity, which in turn contributes to improved cellular redox homeostasis.

3.6. Correlation Analysis Between Antioxidant and Functional Indices

Correlation analysis further supported that fermentation-enhanced antioxidant components were associated with improved cellular protective outcomes; however, the strength of these associations varied depending on the antioxidant assay, reflecting differences in reaction mechanisms and measurement principles. TPC/TFC showed relatively strong

positive correlations with functional indices related to cellular redox regulation, including lipid peroxidation inhibition (LPO) and glutathione redox status (GSH/GSSG), suggesting that increased phenolic constituents may contribute to enhanced redox buffering capacity. ABTS radical scavenging activity and nitrite scavenging activity, which represent chemical antioxidant indices, also exhibited relatively strong correlations with cellular protective parameters, including mitochondrial membrane potential ($\Delta\Psi_m$). This relationship indicates that fermentation-induced enhancement of antioxidant capacity is associated with improved cellular redox homeostasis and cytoprotection. In contrast, DPPH and FRAP displayed weaker or inconsistent correlations with several functional indices, which may be attributable to the distinct characteristics of these assays (e.g., DPPH is based on a stable organic radical under relatively hydrophobic conditions, whereas FRAP primarily reflects reducing power rather than radical scavenging). Moreover, the strong inter-relationships among antioxidant enzyme activities (CAT and SOD), glutathione homeostasis, and mitochondrial function ($\Delta\Psi_m$) further suggest that enzymatic and non-enzymatic antioxidant systems act coordinately to mitigate oxidative stress and maintain cellular function.

4. Discussion

The changes in antioxidant composition observed after lactic acid fermentation of ginseng berries and roots can be attributed to microbial enzymatic activities that promote the release and transformation of bioactive compounds. In the present study, fermentation increased total polyphenol content by approximately 13% in ginseng berries and 7% in ginseng roots, while total flavonoid content increased from 11.73 to 13.21 mg QE/g in ginseng berries and from 15.64 to 19.09 mg QE/g in ginseng roots. The increases in total polyphenol and flavonoid contents following fermentation are likely associated with the hydrolysis of complex phenolic conjugates and the liberation of bound phenolics by microbial enzymes such as β -glucosidase [21]. This interpretation is consistent with previous studies demonstrating that microbial biotransformation enhances the bioavailability of phytochemicals through enzymatic deglycosylation and structural modification [22]. Recent evidence further supports lactic acid bacterial fermentation as a biotransformation strategy that improves phenolic bioavailability via deglycosylation, depolymerization, and conversion to low-molecular-weight derivatives [23–25].

Similar enhancements in phenolic availability and antioxidant activity following lactic acid fermentation have been reported in various plant-derived substrates. Fermentation-mediated enzymatic hydrolysis has been shown to increase electron-donating capacity and radical scavenging activity, particularly through the modification of phenolic profiles [26,27]. Mechanistically, such shifts are frequently attributed to microbial- and acid-driven release of bound phenolics and enzyme-assisted remodeling of phenolic structures during fermentation. Importantly, these fermentation-driven improvements in antioxidant potential have been consistently observed across diverse botanical matrices, regardless of the specific plant origin or tissue type. In this context, Song et al. [28] reported that lactic acid fermentation significantly enhanced the antioxidant and anti-inflammatory activities of seaweed extracts, supporting the notion that fermentation-induced phenolic transformation represents a broadly applicable mechanism for strengthening antioxidant capacity.

These compositional changes were closely reflected in the enhanced antioxidant activities measured by DPPH, ABTS, and FRAP assays in the present study. Notably, increases in TPC and TFC plausibly contributed to improved intracellular redox homeostasis, as phenolic enrichment is directly associated with electron donation and radical quenching capacity [29]. In this context, ABTS scavenging activity (reflecting both hydrophilic and lipophilic radical quenching) can be linked to reduced intracellular ROS and improved mitochondrial membrane potential, whereas FRAP (reducing power), reflecting

enhanced electron-donating capacity, is more closely associated with reinforcement of endogenous antioxidant defenses such as CAT and SOD-like activities [30]. Fermented ginseng extracts consistently exhibited higher radical scavenging and reducing capacities than their non-fermented counterparts, indicating that fermentation not only increases the extractable amount of antioxidant compounds but also improves their functional efficacy. The enhanced electron-donating ability observed in fermented samples suggests that fermentation-induced low-molecular-weight antioxidants play a critical role in reinforcing overall antioxidant capacity.

Alterations in ginsenoside profiles further support the functional significance of fermentation. In this study, fermentation resulted in a decrease in high-molecular-weight ginsenosides such as Rg1, Rb1, and Rb2, accompanied by an increase in low-molecular-weight ginsenosides including Rh1, Rg2, and Rg3. This conversion is known to occur through microbial deglycosylation processes and is particularly important because low-molecular-weight ginsenosides exhibit higher bioavailability and biological activity than their parent compounds [7]. Therefore, lactic acid fermentation appears to induce not only quantitative but also qualitative improvements in ginseng saponins, thereby enhancing their functional potential.

At the cellular level, ginseng extracts effectively suppressed intracellular reactive oxygen species (ROS) generation, reduced lipid peroxidation, improved the GSH/GSSG ratio, and enhanced mitochondrial membrane potential. These findings indicate that fermentation-enhanced ginseng extracts contribute to the regulation of intracellular redox homeostasis and mitochondrial function. The simultaneous improvement in glutathione redox balance and mitochondrial membrane potential suggests coordinated modulation of multiple components of the cellular antioxidant defense system, consistent with previous observations reported for fermented ginseng materials [7]. In addition, fermented plant extracts have been shown to exert cytoprotective effects by attenuating oxidative damage and reinforcing endogenous antioxidant defense systems, supporting microbial fermentation as an effective strategy for improving cellular resilience against oxidative stress [22,29].

Importantly, the cell-based analyses in the present study were conducted to evaluate whether fermentation-induced compositional changes translate into biologically meaningful cellular protection. The concurrent attenuation of intracellular ROS generation, lipid peroxidation, disruption of glutathione redox balance, and mitochondrial dysfunction suggests that fermentation-enhanced ginseng extracts modulate interconnected oxidative stress-related pathways rather than a single antioxidant endpoint. Compared with previous studies on fermented ginseng materials that primarily focused on fermentation process optimization or chemical antioxidant activity [10,11], the present study provides a comparative evaluation of ginseng berries and roots and further investigates their cytoprotective effects using cell-based oxidative stress models. Correlation analysis further demonstrated that fermentation-enhanced antioxidant components were associated with improved cellular protective effects (Figure 3). As shown in Figure 3A, total polyphenol content (TPC) and total flavonoid content (TFC) were positively correlated with chemical antioxidant activities, including DPPH, ABTS, FRAP, and nitrite scavenging activity. In addition, functional cellular parameters such as lipid peroxidation inhibition (LPO), glutathione redox balance (GSH/GSSG), mitochondrial membrane potential ($\Delta\Psi_m$), and antioxidant enzyme activities (CAT and SOD) exhibited close associations with each other (Figure 3B). The integrated correlation analysis (Figure 3C,D) further indicated that fermentation-induced increases in phenolic compounds were closely linked to improved cellular redox homeostasis and cytoprotective responses.

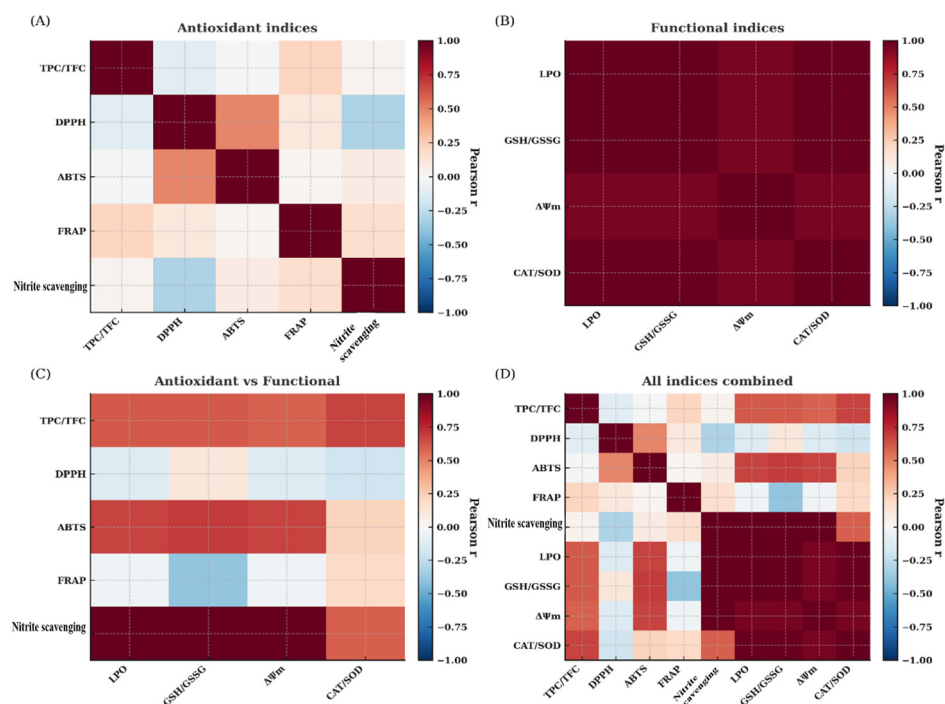


Figure 3. Correlation analysis between antioxidant capacities and cellular protective effects of ginseng extracts. **(A)** Correlations among antioxidant indices (TPC, TFC, DPPH, ABTS, FRAP, and nitrite scavenging activity), **(B)** correlations among functional indices (LPO, GSH/GSSG, $\Delta\Psi_m$, CAT and SOD), **(C)** correlations between antioxidant and functional indices, and **(D)** correlation matrix of all combined indices. The color scale represents Pearson's correlation coefficient (r), with red indicating positive correlations and blue indicating negative correlations.

5. Conclusions

In conclusion, lactic acid fermentation mediated by *Lactiplantibacillus plantarum* effectively enhanced the antioxidant composition of ginseng berries and roots and strengthened their cytoprotective effects against oxidative stress at the cellular level. This fermentation process significantly increased the functional value of ginseng berries, whose industrial utilization has been limited due to insufficient functional characterization, while also further expanding the utilization potential of ginseng roots. Collectively, these findings suggest that lactic acid fermentation represents a promising strategy for the value-added utilization of ginseng resources as functional food ingredients. Future studies should include in vivo evaluations to verify the biological efficacy of fermentation-derived bioactive compounds, along with further investigations into their bioavailability.

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Abbreviations

ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
CAT	catalase
DPPH	2,2-diphenyl-1-picrylhydrazyl
DMEM	Dulbecco's Modified Eagle's Medium
EGB	ethanol extract of non-fermented ginseng berry
EGR	ethanol extract of non-fermented ginseng root
FEGB	ethanol extract of fermented ginseng berry
FEGR	ethanol extract of fermented ginseng root
FRAP	ferric reducing antioxidant power
GAE	gallic acid equivalents
GSH	reduced glutathione
GSSG	oxidized glutathione
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
JC-1	5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide
LPO	lipid peroxidation
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
QE	quercetin equivalents
ROS	reactive oxygen species
SOD	superoxide dismutase
t-BHP	tert-butyl hydroperoxide
TBARS	thiobarbituric acid reactive substances
TFC	total flavonoid content
TPC	total polyphenol content
TPTZ	2,4,6-tripyridyl-s-triazine
$\Delta\Psi_m$	mitochondrial membrane potential

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