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Propionic acid-rich fermented blueberry supernatant improves DSS-induced colitis symptoms by regulating inflammatory pathways

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ABSTRACT

This study investigated the anti-inflammatory effects of a short-chain fatty acid (SCFA)-enriched fermented blueberry supernatant (BBS) and its key component, propionic acid (PropA), in both *in vitro* and *in vivo* models of colitis. High-performance liquid chromatography confirmed the presence of PropA in BBS at a concentration of 1.86 mg/mL. In LPS-stimulated RAW 264.7 macrophages, BBS significantly reduced nitric oxide, monocyte chemoattractant protein-1, and interleukin-6 production in a dose-dependent manner. Western blotting revealed that BBS suppressed the expression of inducible nitric oxide synthase, COX-2, and NF-κB. In a DSS-induced colitis mouse model, BBS administration significantly improved disease indicators, including body weight loss, colon shortening, and spleen enlargement. Moreover, BBS restored serum IgG and colonic IgA levels and reduced systemic and local inflammatory mediators. These findings highlight the potential of SCFA-enriched fermented blueberry as a functional postbiotic food capable of modulating inflammatory responses through NF-κB and COX-2 signaling pathways in colitis.

1. Introduction

Blueberry, often regarded as a "natural health package", are rich in vitamins, including vitamins C, K1, and the B-complex group, as well as minerals such as manganese, copper, potassium, and iron. In addition to these nutrients, blueberries contain trace polyphenols, such as resveratrol and anthocyanins, and organic acids, including citric, malic, quinic, and shikimic acids (Buran et al., 2014; Rashidinejad, 2020; Wood et al., 2019). These bioactive compounds contribute to various health benefits, including cardiovascular protection, anti-inflammatory effects, immune system enhancement, and defense against oxidative stress and chronic diseases (Duan et al., 2022; Norberto et al., 2013; Törrönen et al., 2013; Wood et al., 2019). However, because of their high perishability, fresh blueberries present challenges in storage and preservation, necessitating essential processing to enhance their stability and economic value (Li et al., 2021). Blueberries are commonly processed into commercial products such as wine, juice, vinegar, jams, and dried goods (Nile & Park, 2014). Recently, lactic acid bacteria (LAB)-fermented foods have

Abbreviations: ASA, 5-aminosalicylic acid; COX-2, cyclooxygenase-2; DAI, disease activity index; DMEM, Dulbecco's Modified Eagle Medium; DSS, dextran sulfate sodium; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated kinase; FBS, fetal bovine serum; H&E, hematoxylin and eosin; IBD, inflammatory bowel disease; IgA, immunoglobulin A; IgG, immunoglobulin G; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; IκBα, nuclear factor kappa-light-chain-enhancer of activated B cells inhibitor alpha; JNK, c-Jun N-terminal kinase; LAB, lactic acid bacteria; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MTT, 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide; NC, negative control; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOR, normal control; P/S, penicillin/streptomycin; p38, p38 kinase; PBS, phosphate-buffered saline; PC, positive control; PFBBr, pentafluorobenzyl bromide; PropA, propionic acid; SCFAs, short-chain fatty acids; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha..

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gained considerable attention for their enhanced sensory properties (Şanlier et al., 2019), extended shelf life (Qiao et al., 2022), and ability to generate health-beneficial compounds (Di Cagno et al., 2009; Şanlier et al., 2019). LAB-fermented blueberries have demonstrated antibacterial (Oh et al., 2017) and antioxidant (Zhang et al., 2021) activities as well as anti-obesity and anti-hyperglycemic effects (Chu et al., 2023; Johnson et al., 2016). Despite these promising findings, research on LAB fermentation of blueberries remains limited, and such products have yet to achieve widespread commercial availability (Li et al., 2021).

In 2021, the International Scientific Association of Probiotics and Prebiotics formally defined postbiotics as bioactive compounds, including microbial cells, cellular components, and metabolites, produced by microorganisms during fermentation (Salminen et al., 2021). These compounds have garnered considerable attention owing to their diverse health benefits, such as anti-aging, antioxidant, antibacterial, anti-inflammatory, and antitumor effects, as well as their roles in immune regulation, gut microbiota modulation, and enhancement of epithelial barrier function (Da et al., 2024; Mishra et al., 2024; Zhao et al., 2024). Recent advancements in postbiotic research have aimed to address the limitations of probiotics and integrate postbiotics into early-life nutrition to improve health outcomes (Ayichew et al., 2017; Wegh et al., 2019). Ongoing studies have focused on producing postbiotic metabolites within food matrices and investigating the influence of various food components on their activity and efficacy (Mishra et al., 2024). Short-chain fatty acids (SCFAs), including acetic, propionic, and butyric acids, are well-recognized fermentation products of dietary fiber by gut microbiota (Silva et al., 2020). As a rapidly expanding area of research, studies on SCFAs aim to elucidate their mechanisms of action and therapeutic potential to develop innovative interventions for health improvement. However, despite accumulating evidence supporting their health benefits, research on screening SCFA-producing probiotic strains and developing functional foods enriched with SCFAs remains underdeveloped. Optimizing fermentation processes to enhance SCFA production can yield innovative functional foods with therapeutic applications, particularly for acute colitis.

To date, most studies on blueberries have focused on their polyphenols and antioxidant properties, while the role of microbial fermentation in generating bioactive metabolites has been less explored. In particular, although short-chain fatty acids such as propionic acid are well recognized for their anti-inflammatory functions, little attention has been given to using fermented fruit matrices as a direct source of SCFA-rich postbiotics. Therefore, this study aimed to develop SCFA-enriched fermented blueberry products and evaluate their potential as postbiotic materials to improve gut health. To our knowledge, this is the first study to develop a propionic acid–rich fermented blueberry and to investigate its efficacy in an *in vivo* colitis model. This approach not only provides a new strategy for enhancing the functional value of blueberries but also offers a practical route to generate SCFA-enriched postbiotic ingredients with potential applications in dietary intervention for inflammatory bowel diseases (IBDs).

2. Materials and methods

2.1. Preparation of blueberry supernatant

2.1.1. Bacterial strain

Frozen *Lactiplantibacillus plantarum* HBS01 (KCTC 19214P) stock was thawed and cultivated in two stages: a 12-h seed culture followed by a 12-h pre-culture, both conducted at 37 °C and 80 rpm using a shaking incubator (HB-201S; Hanbaek Scientific Technology, Bucheon, South Korea). The OD600 reached approximately 8.0 during intermediate cultivation, maintaining a viable cell count of approximately 1×10^9 CFU/mL.

2.1.2. Blueberry fermentation

A blueberry base mixture (BB base mix) was prepared by combining the blueberry juice liquid, HBS broth (HBS001; Mediogen, Jecheon, South Korea), and distilled water at a ratio of 50:7:500. The mixture was heat-treated at 90 °C for 10 min, cooled at room temperature, and UV irradiated at a vertical laminar flow (JSCB-900SL; JS Research, Gongju, South Korea) for 30 min. The sterilized BB base mix was diluted 10–20 times with water, and ammonia gas (NH_3) was used to maintain a pH of 6.0. The pH was continuously monitored, and NH_3 was automatically added as needed to ensure a stable fermentation environment. HBS containing dietary fiber and minerals were added to the diluted mix, followed by incubation with *L. plantarum* HBS01 at 5–10 % (*v*/v). Fermentation was conducted at 37 °C and 80 rpm in a shaking incubator. The final fermented product, designated as blueberry supernatant (BBS; 1×), was provided by Human Bioscience (Chungju, South Korea) and was used for subsequent evaluations.

2.2. SCFA analysis using HPLC-ultraviolet analysis

SCFAs were identified and quantified using pentafluorobenzyl bromide (PFBBr) derivatization. Briefly, each sample was dissolved in HPLC-grade water and combined with acetonitrile (2:8 v/v). A 1 mL aliquot of the mixture was reacted with 2 μL of PFBBr (101,052; Sigma-Aldrich, St. Louis, MO, USA) and incubated at 65 °C for 24 h. Sodium propionate (P1880; Sigma-Aldrich) at various concentrations was used to generate a standard calibration curve. The derivatized SCFAs were analyzed using HPLC-ultraviolet (HPLC-UVD) analysis as specified in Supplementary Table S1.

2.3. Anti-inflammatory activity evaluation using lipopolysaccharide-induced RAW 264.7 cells

2.3.1. Cell culture and viability assessment

RAW 264.7 cells (Korean Cell Line Bank; KCLB Seoul, South Korea) were grown in Dulbecco's Modified Eagle Medium (Sigma-Aldrich) supplemented with 10 % fetal bovine serum (Corning, Manassas, VA, USA) and 100 U penicillin/100 μg/mL streptomycin (Welgene, Gyeongsan, South Kore) at 37 °C in a CO_2 incubator (Thermo Fisher Scientific, Waltham, MA, USA). The cells were subcultured every 2–3 d. For viability assessment, cells were seeded in 96-well plates (6×10^5 cells) and incubated for 24 h, followed by treatment with various concentrations of BBS for another 24 h. After removing the culture medium, viable cells were assessed using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (Sigma-Aldrich) assay, as previously described (Kim et al., 2020).

2.3.2. Griess and enzyme-linked immunosorbent assays

The cells were seeded in 96-well plates (6×10^5 cells) and incubated for 24 h. After treatment with BBS for 1 h, the cells were stimulated with 1 μg/mL of *Escherichia coli* lipopolysaccharide (LPS; Sigma-Aldrich) for another 24 h. Cell culture supernatants were collected to measure nitric oxide (NO) production using Griess assays kit (Thermo Fisher Scientific) and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) using enzyme-linked immunosorbent assay (ELISA) kits (Supplementary Table S2).

2.3.3. Western blotting

The cells were seeded in 100-mm dishes (3×10^7 cells) and incubated for 24 h. After BBS treatment (1 h) and LPS stimulation (1 μg/mL, 24 h), the cells were rinsed with phosphate-buffered saline (PBS; Biosesang, Yongin, South Korea) and radioimmunoprecipitation assay buffer. Total proteins were normalized, denatured, separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transferred onto nitrocellulose membranes, analyzed using western blotting, and quantified using ImageJ software (v1.54j; https://imagej.net/ij/) as previously described by Kim et al. (2024). The details of the antibodies are provided in Supplementary Table S3.

2.4. Anti-colitis activity evaluation using dextran sulfate sodium-induced C57/BL mice

2.4.1. Mice and administration schedule

C57BL/6 mice (6 weeks old, 18–20 g, $n = 42$) were obtained from Dooyeol Biotech (Seoul, South Korea) and housed under controlled conditions (temperature: 20–26 °C, humidity: 30–75 %, 12 h light/dark cycle, illuminance: 150–300 Lux, air exchange: 10–15 times/h) at the Chung-Ang University animal facility (Anseong, South Korea). After one week of acclimation, mice were randomly assigned to six groups (seven mice per group) with comparable body weights (21.26–22.04 g) and treated as follows: the normal (NOR) and dextran sulfate sodium (DSS) control groups received saline (200 μL/day), the positive control (PC) group received 5-aminosalicylic acid (ASA, 50 mg/kg/day), the BBS 0.5× and 1× groups received diluted (1:2) BBS and undiluted BBS, respectively, and the propionic acid (PropA) group received propionate (80 μg/kg/day). All treatments were administered by oral gavage once daily for 19 days (200 μL/mouse). From day 10, all groups except the NOR group were provided with 3 % DSS solution *ad libitum* instead of purified water for 9 days to induce colitis.

2.4.2. Assessment of body and spleen weight, colon length, and disease activity index

Body weights were recorded every 2–3 days, and the final measurements were compared across groups. After the experimental period, the mice were anesthetized by CO_2 inhalation, followed by cardiac puncture for blood collection and euthanasia. The spleen was excised and weighed, the colon (cecum to rectum) was dissected, and its length was measured. The disease activity index (DAI) was evaluated based on body weight loss, stool consistency, and fecal blood, as described by Kim et al. (2014). Each parameter was scored on a scale of 0–4, with higher scores indicating greater disease severity, and the total DAI score was calculated by summing all three parameters.

2.4.3. Hematoxylin and eosin staining

Histomorphometric evaluation of colonic tissue was performed using hematoxylin and eosin (H&E) staining as described by Kim et al. (2024). Following euthanasia, descending colon tissues were collected, fixed in 10 % formalin for 24 h, and washed for 12 h. The samples were then paraffin-embedded using an automated tissue processor (Leica Biosystems, Wetzlar, Germany) and sectioned into 3–5 μm slices. Tissue sections were stained with H&E (15086–94-9, Sigma-Aldrich) and histomorphometric analysis was conducted using an automated digital slide scanning system (KFBio, Ningbo, China).

2.4.4. Measurement of biomarkers in serum, luminal fluid, and colonic tissue

After euthanasia, total blood was collected and centrifuged at 3000 ×*g* for 15 min to isolate the serum. Luminal fluid was obtained by finely mincing small intestinal tissue, incubating it overnight in PBS at 4 °C, and centrifuging at 13,000 ×*g* for 10 min. This process was repeated twice for clarity, and the supernatants were collected. Inflammatory cytokines (MCP-1 and IL-6) and immunoglobulins (immunoglobulin G [IgG] and A [IgA]) in the serum and luminal fluid were quantified using commercial ELISA kits, following the manufacturer's instructions (Supplementary Table S2). For colonic tissue analysis, 100 mg of colon tissue was homogenized in 500 μL of lysis buffer using a microtube homogenizer (D1030-E; Benchmark Scientific, Sayreville, NJ, USA). The homogenates were centrifuged at 13,000 ×*g* for 10 min, and the supernatants were collected. Protein concentrations were measured using a bicinchoninic acid protein assay kit (Thermo Fisher Scientific) and normalized. The extracted proteins were analyzed by western blotting to assess intracellular protein expression, as described in Section 2.3.3. The antibody details are listed in Supplementary Table S3.

2.5. Statistical analyses

The results are presented as the mean ± standard deviation (for *in vitro* experiments) or the standard error of the mean (for *in vivo* experiments). Statistical analyses were performed using IBM Statistics (v26; IBM Corp., Armonk, NY, USA). Significant differences were evaluated using a one-way analysis of variance followed by Duncan's post-hoc multiple range. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. SCFA determination

HPLC-UVD analysis with PFBBr derivatization was used to identify the major SCFAs in BBS. The UV chromatograms of blank (distilled water), PropA standard (2.5 mg/mL), and BBS (1×) shared two main peaks (5.0–5.1 and 11.3–11.4 min) and one minor peak (7.6–7.7 min) (Fig. 1), likely artifacts from the derivatization process. After excluding overlapping peaks, both the PropA standard and BBS exhibited a prominent peak at 10.8 min, confirming the presence of PropA in BBS. PropA was selected for anti-inflammatory evaluation to assess its role as a potential bioactive compound in BBS. The final concentration of PropA in 1× BBS was 1.86 mg/mL.

3.2. Anti-inflammatory activities of BBS in LPS-stimulated RAW 264.7 cells

The cytotoxic effects of BBS at various concentrations (0.125× to 1×) on normal RAW 264.7 cells are shown in Fig. 2A. No significant cytotoxic effects were observed across all groups, demonstrating the non-toxic nature of BBS at these concentrations. Based on this finding, 0.5 and 1× were selected for the subsequent evaluation of anti-inflammatory activity. The anti-inflammatory effects of BBS in LPS-stimulated RAW 264.7 cells are shown in Figs. 2B–2D. Compared to the negative control (NC) group (3.0 μM for NO, 0.1 ng/mL for MCP-1, and 0.5 ng/mL for IL-6), LPS stimulation significantly increased the levels of inflammatory mediators (25.1 μM for NO, 6.0 ng/mL for MCP-1, and 12.7 ng/mL for IL-6). However, treatment with dexamethasone (20 μM) as the PC group significantly reduced these levels (4.0 μM for NO, 1.2 ng/mL for MCP-1, and 0.7 ng/mL for IL-6). Compared to the LPS-induced group, BBS treatment significantly decreased the levels of inflammatory mediators in a concentration-dependent manner (12.1–12.1 μM for NO, 4.6–1.4 ng/mL for MCP-1, and 10.6–5.6 ng/mL for IL-6). Furthermore, PropA, a putative active component of BBS, significantly decreased the levels of inflammatory mediators (8.3 μM for NO, 4.4 ng/mL for MCP-1, and 7.8 ng/mL for IL-6).

The intracellular inflammatory signaling mechanisms modulated by BBS were analyzed using immunoblotting. The blotting images (Fig. 3A; original images in supplementary Fig. S2) and quantified levels (Fig. 3B) of NO-related molecules [inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2)] and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling components [p65 and nuclear factor kappa-light-chain-enhancer of activated B cells inhibitor alpha (IκBα)] are presented. The iNOS and COX-2 expression levels were normalized to β-actin, whereas phosphorylated p65 and IκBα were compared to their total forms. LPS stimulation significantly increased iNOS and COX-2 expression levels by 3.7- and 11.1-fold, respectively, compared to the NC group. Co-treatment with BBS significantly reduced these levels by 1.9–2.0 fold (iNOS) and 8.6–4.8 fold (COX-2) at all tested concentrations. PropA treatment significantly decreased iNOS and COX-2 expression by 1.7- and 3.0-fold, respectively. For NF-κB signaling, LPS treatment elevated p65 (1.8-fold; $p < 0.05$) and IκBα (1.4-fold; $p > 0.05$) phosphorylation levels. These phosphorylation levels were significantly reduced in BBS-treated cells to 1.1- (p65) and 0.8-fold (IκBα), specifically at a concentration of 1×. PropA treatment further decreased

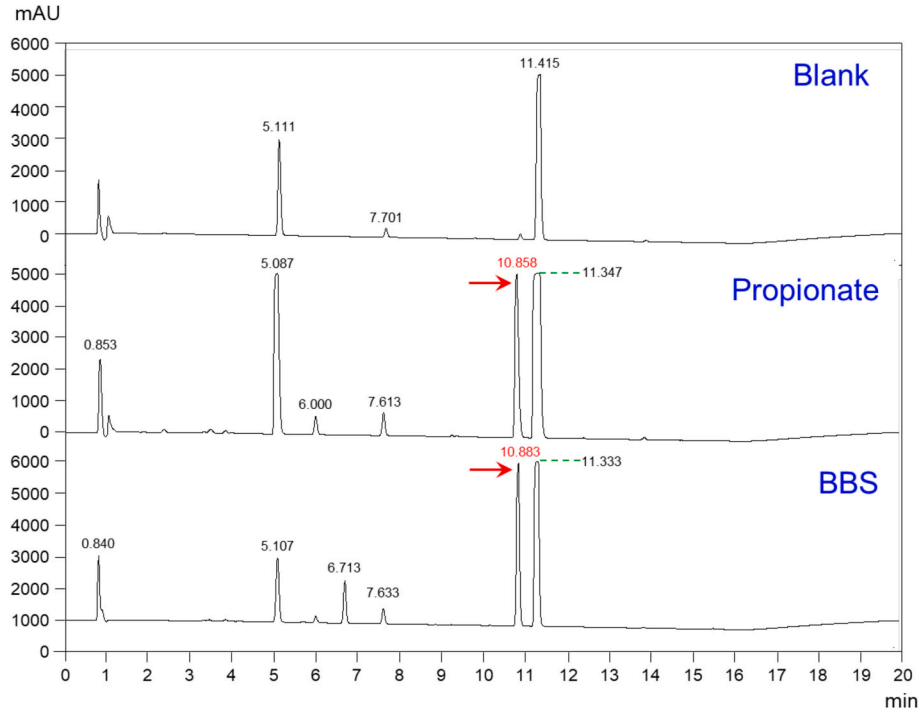

Fig. 1. UV chromatogram of blank, propionic acid (PropA; 2.5 mg/mL), and blueberry supernatant (BBS; 1×) obtained after pentafluorobenzyl bromide (PFBBr) derivatization. Analytical conditions are detailed in Supplementary Table S1.

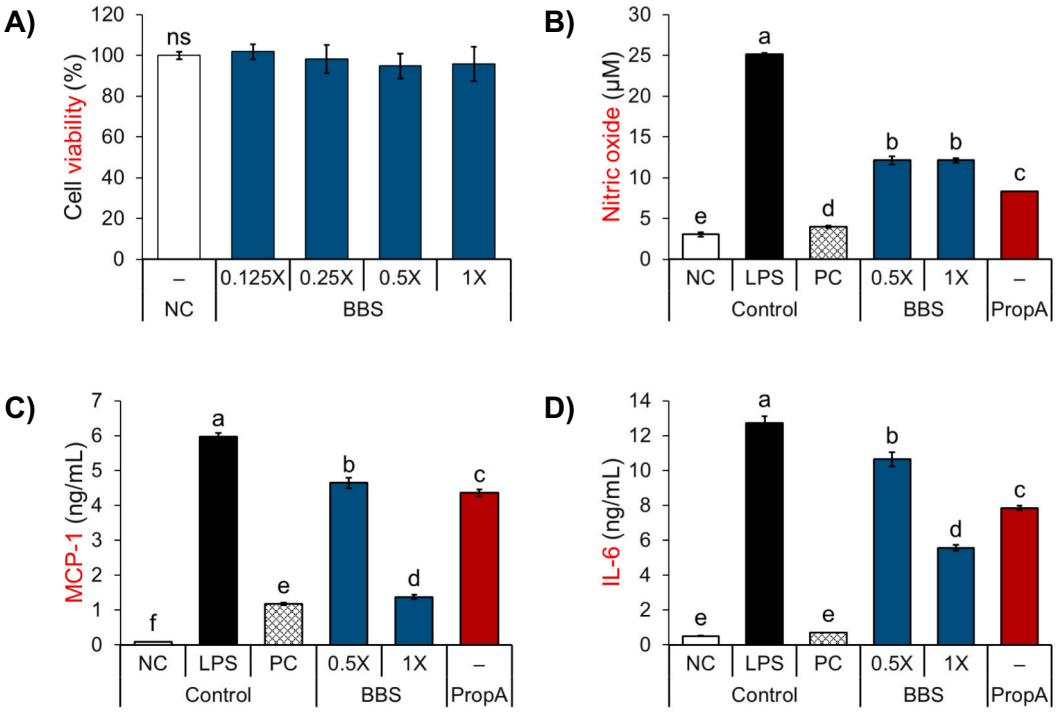

Fig. 2. Effects of BBS and PropA on (A) cell viability and (B—D) pro-inflammatory mediator production in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. Cells were pretreated with samples for 30 min, followed by LPS treatment for 24 h. Serum-free medium [SFM; negative control (NC)] and dexamethasone [20 μg/mL; positive control (PC)] were used as controls. PropA (80 μg/kg/day) was used as a potentially bioactive compound of BBS. Cell viability was assessed using the MTT assay, and pro-inflammatory mediators were measured using the Griess assay and ELISA. Data are presented as the mean ± SD ($n = 3$) of three independent experiments. Means sharing common letters indicates no significant differences ($p < 0.05$, Duncan's test).

phosphorylation levels to 0.3- (p65) and 0.4-fold (IκBα).

The involvement of the mitogen-activated protein kinase (MAPK) signaling pathway was further investigated, focusing on p38 kinase (p38), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK). The blotting images (Fig. 4A; original images in supplementary Fig. S2) and quantified levels (Fig. 4B) of the phosphorylated

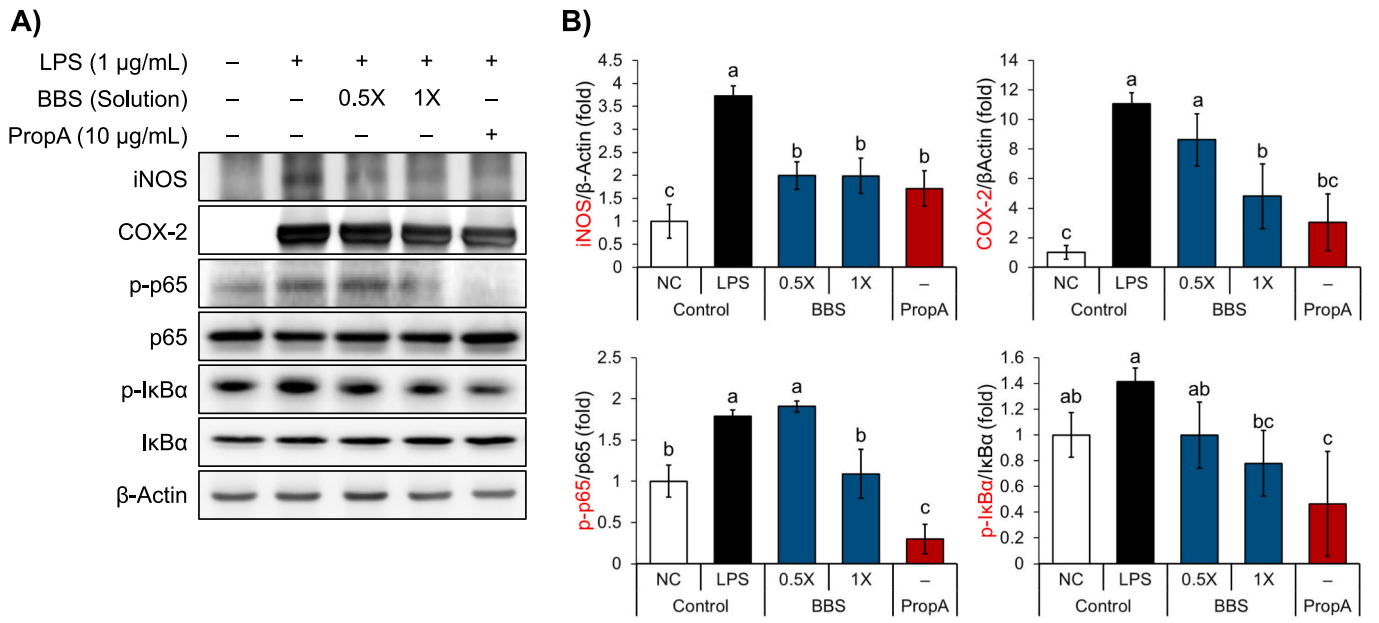

Fig. 3. Effects of BBS and PropA on inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expressions and nuclear factor-κB (NF-κB) signaling activation in LPS-stimulated RAW 264.7 cells. Cells were pretreated with samples for 30 min, followed by LPS treatment for 24 h (iNOS and COX-2) or 20 min [p65 and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα)]. SFM was used as the NC. PropA (80 μg/kg/day) was used as a potentially bioactive compound of BBS. (A) Representative blotting images and (B) relative protein expression normalized to control proteins were analyzed using ImageJ software. Data are presented as the mean ± SD ($n = 3$) of three independent experiments. Means sharing common letters indicates no significant differences ($p < 0.05$, Duncan's test).

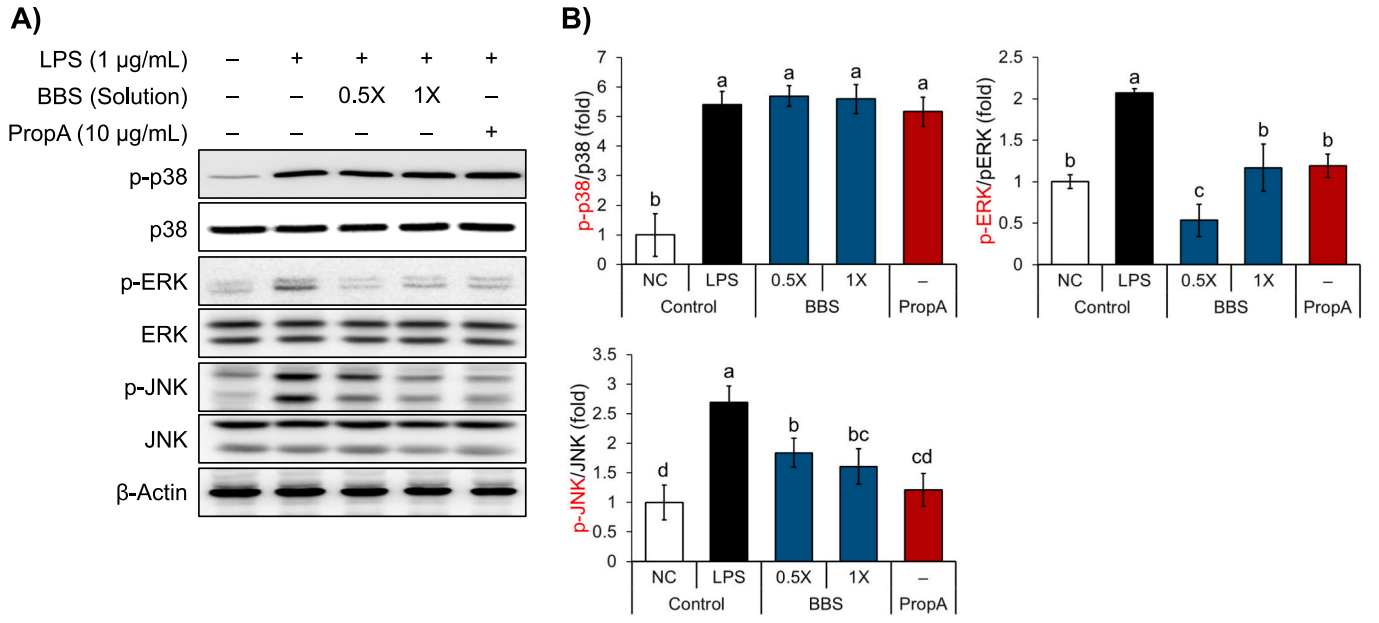

Fig. 4. Effects of BBS and PropA on mitogen-activated protein kinase (MAPK) signaling activation in LPS-stimulated RAW 264.7 cells. Cells were pretreated with samples for 30 min, followed by LPS treatment for 10 min. SFM was used as the NC. PropA (80 μg/kg/day) was used as a potentially bioactive compound of BBS. (A) Representative blotting images and (B) relative protein expression normalized to control proteins were analyzed using ImageJ software. Data are presented as the mean ± SD ($n = 3$) of three independent experiments. Means sharing common letters indicates no significant differences ($p < 0.05$, Duncan's test). ERK, extracellular signal-regulated kinase; JNK, c-JUN N-terminal kinase.

and total forms revealed significant increases in the phosphorylation of all MAPK components upon LPS stimulation (5.4-fold for p-p38, 2.1-fold for p-ERK, and 2.7-fold for p-JNK). Co-treatment with BSS significantly downregulated ERK (0.5–1.2 fold) and JNK (1.8–1.6 fold) phosphorylation compared to that in the LPS group, but did not affect p38 phosphorylation ($p > 0.05$). Similar p-ERK (1.2-fold) and p-JNK (1.2-fold) downregulation were observed in the PropA-treated group.

3.3. Effects of BBS administration on colon length, spleen weight, and DAI in colitis-induced mice

Based on the *in vitro* findings, the mice were orally administered BSS at doses of 0.5× and 1× to produce a DSS-induced colitis mouse model. Body weight declined across all DSS-treated groups starting on day 4, with reductions reaching 21.0–24.0 % compared to the NOR group by

day 9 (Supplementary Fig. S1). The severity of colitis was assessed using the DAI based on body weight loss, stool consistency, and bloody stool (Fig. 5A). The DAI score was significantly elevated in the DSS-administered mice (8.4) compared to that in the NOR group (0.0). Although mice administered ASA (7.4) and 0.5× BBS (7.3) showed a slight reduction in DAI compared to the DSS group, the differences were not significant. In contrast, significant reductions in the DAI were observed in mice dosed with 1× BBS (5.1) and PropA (5.3). The morphology and weight of the spleen are shown in Fig. 5B. Spleen weight was significantly increased in the DSS-administered group (129.8 mg, 44.0 %) compared to the NOR group (90.11 mg). This increase was significantly reduced in the ASA (105.9 mg, 60.2 %), 1× BBS (104.4 mg, 63.9 %), and PropA (105.3 mg, 61.8 %) groups compared to the DSS group. The colon length measurements after euthanasia are shown in Fig. 5C. Colon length was significantly shorter in DSS-treated mice (4.0 cm, 30.3 %) than in NOR mice (5.7 cm). Treatment with ASA (4.6 cm, 33.9 %), 0.5× (4.6 cm, 33.7 %), and 1× BBS (4.5 cm, 29.8 %) significantly mitigated colon shortening, whereas the PropA group (4.0 cm) showed no change in colon length ($p > 0.05$) compared to the DSS group.

3.4. Determination of serum and colonic antibodies and cytokines

Serum IgG, IL-6, and MCP-1 levels were determined using ELISA (Fig. 6A). The DSS-treated group showed significantly lower serum IgG levels (29.3 ng/mL; 52.2 %) than the NOR group (61.3 ng/mL). Although the ASA, 0.5× BSS, and PropA groups showed no significant change in serum IgG levels, the 1× BSS group exhibited a significant increase (33.7 ng/mL; 13.8 %). Serum IL-6 and MCP-1 levels were significantly elevated in the DSS group (218.5 and 295.5 pg/mL, respectively) compared to those in the NOR group (104.8 and 99.6 pg/mL, respectively). ASA administration significantly reduced serum IL-6 (151.0 pg/mL; 59.4 %) and MCP-1 (214.3 pg/mL; 41.4 %) levels. Similarly, the BSS groups showed significant reductions in serum IL-6 and MCP-1 levels (174.5 and 248.9 pg/mL at 0.5× BSS; 174.1 and 206.1 pg/mL at 1× BSS, respectively) compared to those treated with DSS. The PropA group also showed significantly decreased serum IL-6 (193.8 pg/mL; 21.7 %) and MCP-1 (258.6 pg/mL; 18.8 %) levels.

The colonic IgA, IL-6, and MCP-1 levels are shown in Fig. 6B. DSS treatment significantly reduced colonic IgA levels (6.9 μg/mL; 44.6 %) compared to the NOR group (12.5 μg/mL). This reduction was significantly mitigated in the ASA (8.9 μg/mL; 35.5 %), 0.5× BSS (8.6 μg/mL; 29.9 %), and 1× BSS (10.2 μg/mL; 58.5 %) groups; however, this reduction was not significant in the PropA group (8.0 μg/mL). Colonic IL-6 and MCP-1 levels exhibited opposite trends to those of their serum levels. IL-6 and MCP-1 in the colon were significantly reduced in the DSS group (3.5 and 1.9 ng/mL, respectively) compared to those in the NOR group (4.6 and 2.6 ng/mL, respectively). Compared to the DSS group, IL-6 levels were significantly improved in the ASA (3.8 ng/mL, 27.4 %) and 1× BSS (3.7 ng/mL, 24.4 %) groups, whereas MCP-1 levels only showed significant improvement in the PropA group (2.1 ng/mL, 40.3 %).

3.5. Histological observation of the colon tissue

Histological analysis and mucosal thickness measurements of the colon specimens after H&E staining are shown in Fig. 7A. The NOR group exhibited intact colonic wall structures, including normal mucosa and crypts. In contrast, the DSS group showed shortened mucosal layers, thickened mucosa and muscular layers, and severe crypt destruction. The crypt damage and mucosal thickness were partially ameliorated in the ASA-treated group. Notably, although crypt distortion and inflammatory cell infiltration persisted, the significantly shortened mucosal layer observed in the DSS group (116.5 μm) was significantly improved in the 1× BBS (201.7 μm) and PropA (178.3 μm) groups, approaching the levels observed in the NOR group (Fig. 7B). Meanwhile, the clustered dark dots observed at the basal region in the 1× BBS group are

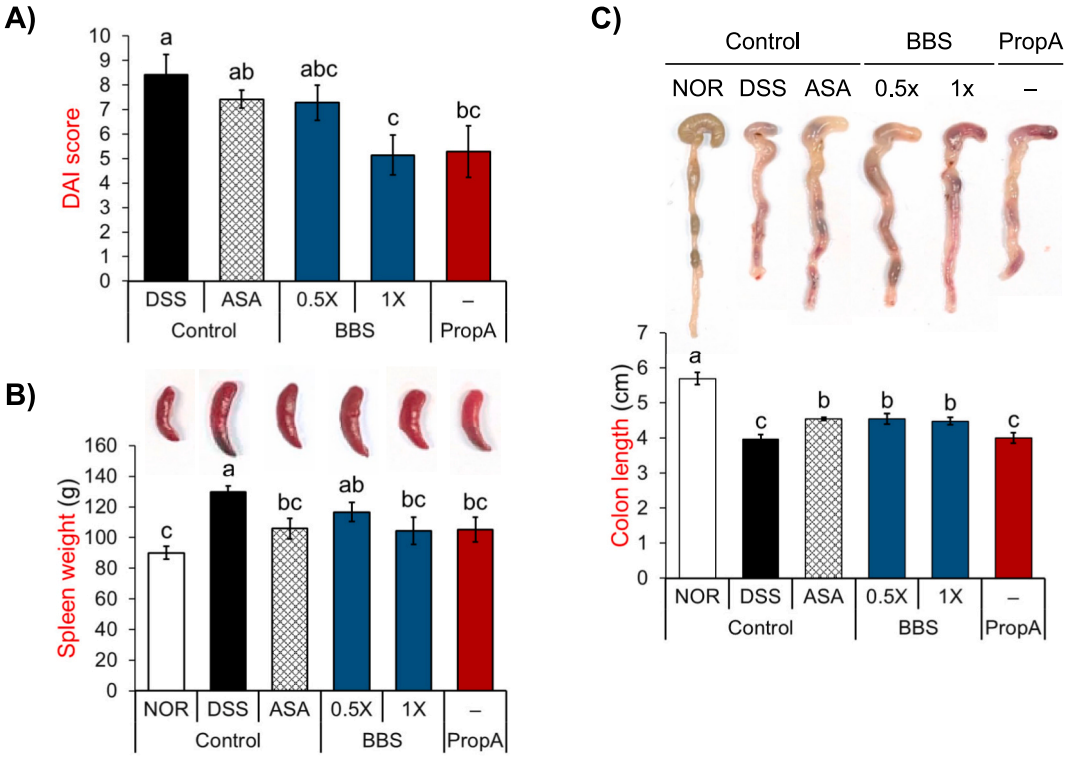

Fig. 5. Effects of BBS and PropA administration on (A) disease activity index (DAI), (B) spleen weight, and (C) colon length in dextran sulfate sodium (DSS)-induced C57BL colitis mice. The DAI score was calculated as described in Section 2.4.2. Groups: NOR (normal control), DSS (vehicle with DSS), 5-aminosalicylic acid (ASA; 50 mg/kg), and PropA (80 μg/kg/day, bioactive compound of BBS). Data are presented as the mean ± standard error of the mean (SEM; $n = 7$). Means with common letters are not significantly different ($p < 0.05$, Duncan's test).

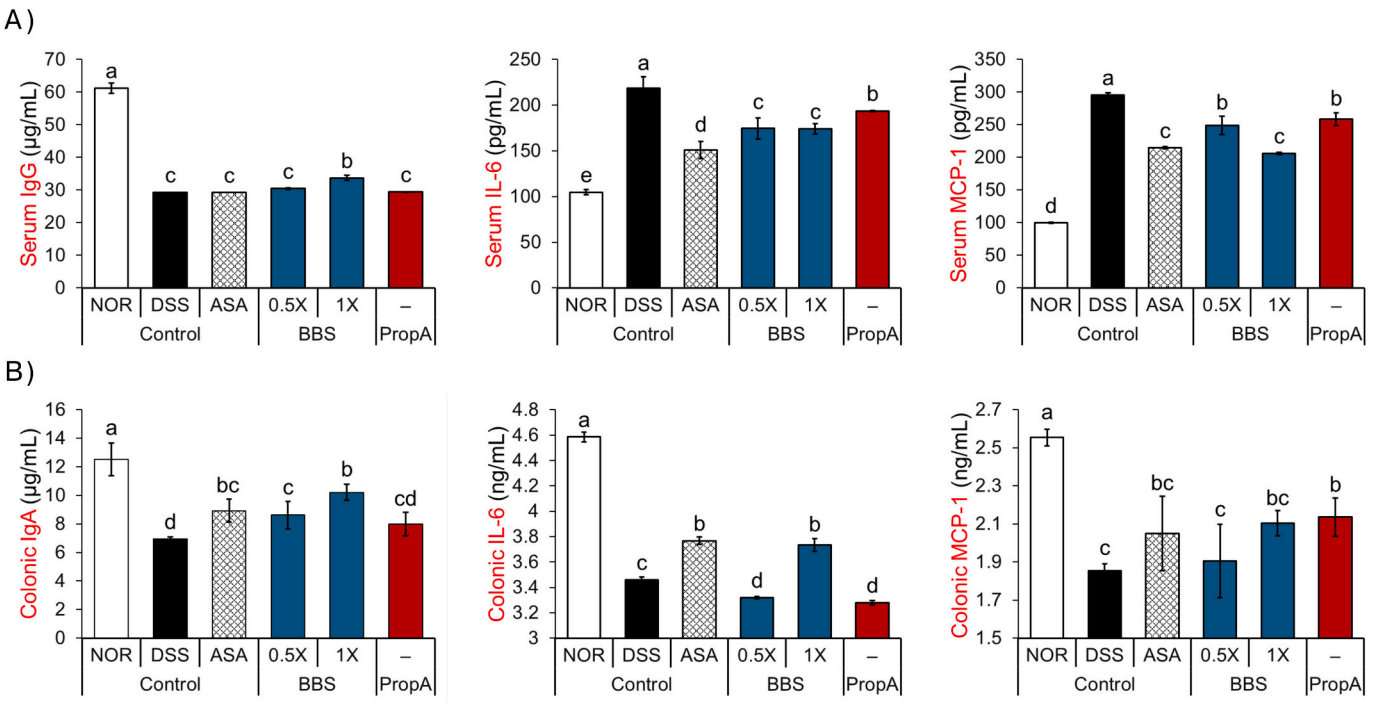

Fig. 6. Effects of BBS and PropA administration on colonic histomorphometry in DSS-induced colitis C57BL mice. (A) Representative hematoxylin and eosin (H&E)-stained colon sections (scale bar = 100 μm). (B) Mucosa thickness measured from H&E images. Groups: NOR (normal control), DSS (vehicle with DSS), ASA (50 mg/kg), and PropA (80 μg/kg/day, bioactive compound of BBS). Data are presented as the mean ± SEM (n = 4). Means with common letters are not significantly different ($p < 0.05$, Duncan's test).

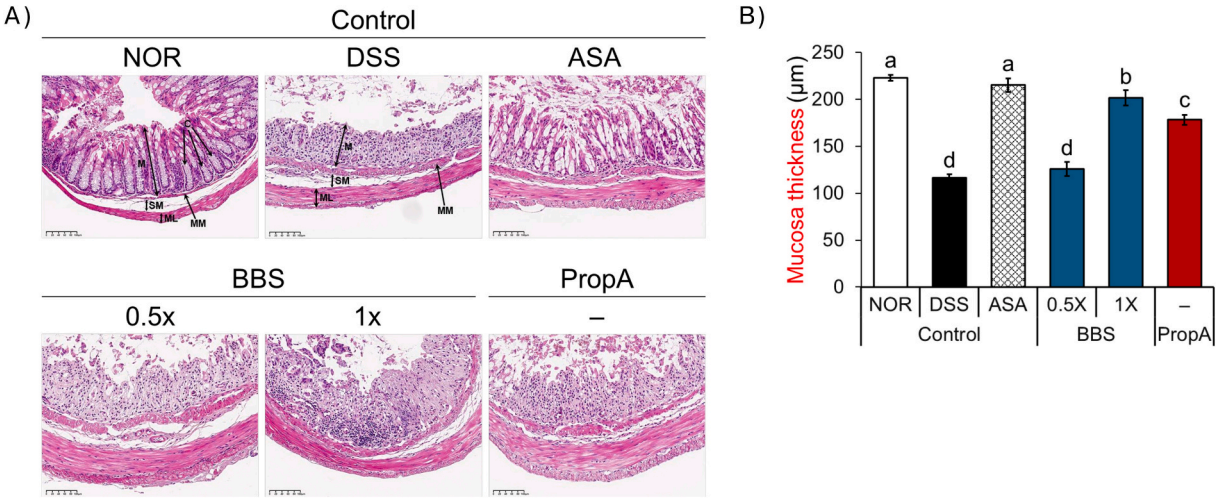

Fig. 7. Effects of BBS and PropA administration on antibody and pro-inflammatory cytokine levels in (A) serum and (B) colonic fluid of DSS-induced colitis C57BL mice. Biomarkers were quantified using respective ELISA kits. Groups: NOR (normal control), DSS (vehicle with DSS), ASA (50 mg/kg), and PropA (80 μg/kg/day, bioactive compound of BBS). Data are presented as the mean ± SEM (n = 3). Means with common letters are not significantly different ($p < 0.05$, Duncan's test).

interpreted as dense nuclear staining or sectioning artifacts, rather than true inflammatory cell infiltration.

3.6. Molecular mechanism underlying BSS-mediated anti-colitis effects

Western blotting was conducted to examine the activation of inflammatory signaling molecules in colon tissue. The blotting images (Fig. 8A; original images in supplementary Fig. S2) and quantified levels (Fig. 8B) of COX-2, p65 (NF-κB), and ERK (MAPK) were provided. COX-2 expression levels were normalized to β-actin, and phosphorylated p65 and IκBα forms were compared to their total forms. DSS treatment significantly upregulated COX-2 expression (2.7-fold) compared to the NOR group (1.0-fold). Although ASA treatment (2.3-fold) did not significantly attenuate this increase, COX-2 levels were significantly reduced in the 0.5× BBS (1.7-fold), 1× BBS (1.6-fold), and PropA (0.9-fold) groups compared to those in the DSS group. Similarly, p65 phosphorylation was significantly elevated in the DSS group (2.8-fold) relative to that in the NOR group (1.0-fold); however, p65 phosphorylation was significantly downregulated by ASA (2.0-fold), 0.5× BBS (1.4-fold), 1× BBS (1.5-fold), and PropA (0.7-fold) administration. For p-ERK, a slight but non-significant increase (1.2-fold) was observed in the DSS group compared to the NOR group (1.0-fold). Notably, p-ERK was significantly downregulated in the PropA group (0.2-fold), whereas the other treatment groups showed insignificant changes.

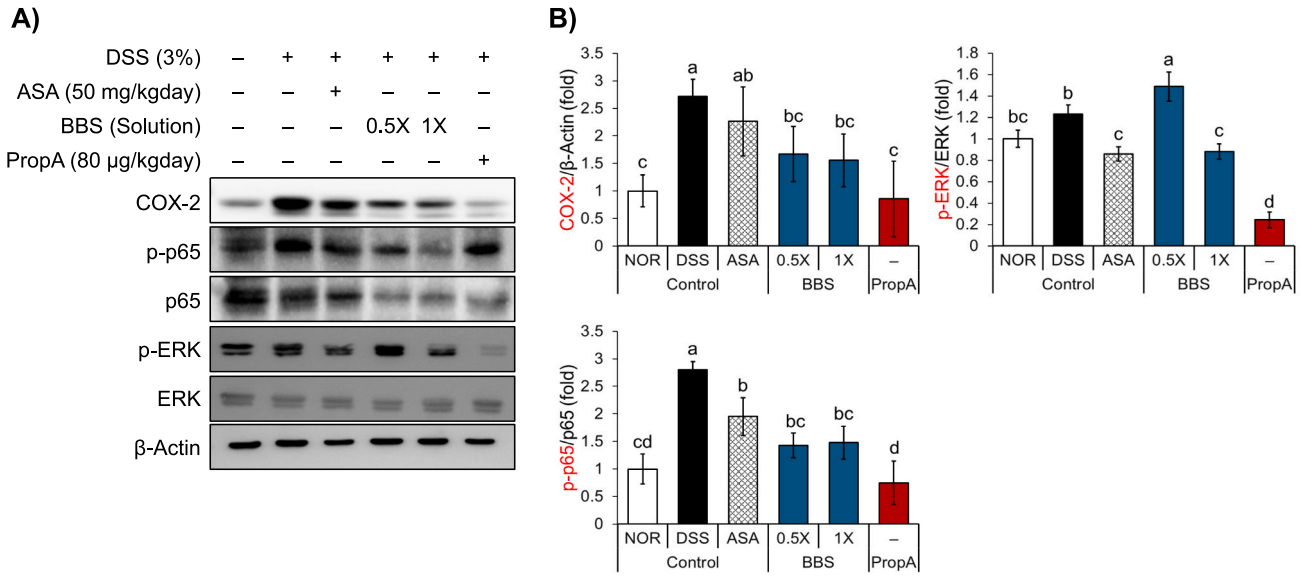

Fig. 8. Effects of BBS and PropA administration on COX-2, p65, and ERK expression in the colon tissue of DSS-induced C57BL mice. (A) Representative blotting images and (B) relative protein expression normalized to control proteins were analyzed using ImageJ software. Groups: NOR (normal control), DSS (vehicle with DSS), ASA (50 mg/kg), and PropA (80 μg/kg/day, bioactive compound of BBS). Data are presented as the mean ± SEM ($n = 3$). Means with common letters are not significantly different ($p < 0.05$, Duncan's test).

4. Discussion

Fresh blueberries and their extracts have previously been reported to ameliorate experimental colitis by reducing oxidative stress, modulating inflammatory cytokines, and improving histological outcomes (Pervin et al., 2016; Wang et al., 2024; Wu et al., 2011). Building on this evidence, our study takes a different approach by examining lactic acid bacteria–fermented blueberries, focusing on propionic acid enrichment as a novel postbiotic strategy to enhance gut health. Meanwhile, recent research has highlighted the importance of SCFAs in gut health, particularly their role in regulating metabolic processes and preventing diseases such as colorectal cancer and IBD (Silva et al., 2020). Thus, this study investigated the potential of SCFA-enriched fermented blueberry products as postbiotic materials to improve gut health. Blueberry fermentation by L. *plantarum* HBS01 significantly enhanced PropA production, which exhibited anti-inflammatory effects *in vitro* and *in vivo*. Notably, SCFA-enriched BBS mitigated inflammatory responses in LPS-stimulated macrophages and improved colitis-associated parameters in mice with DSS-induced colitis.

HPLC-UVD analysis confirmed the presence of PropA as a major SCFA in BBS (Fig. 1). PropA plays a crucial role in maintaining gut homeostasis by modulating immune responses and epithelial integrity (Silva et al., 2020). The enhanced production of PropA in the fermented blueberry product aligns with previous findings that LAB fermentation can generate beneficial postbiotic metabolites (Mishra et al., 2024). Notably, a distinct, unidentified peak at a retention time of 6.713 min was detected in the BBS chromatogram, potentially representing uncommon SCFAs. Given that acetic, propionic, and butyric acids collectively constitute >95 % of total SCFAs in the body (Tian et al., 2020), further structural elucidation is needed to identify and assess the functional relevance of these compounds in gut health. Additionally, we cannot exclude the possibility that other constituents, such as phenolic compounds, may have contributed to the observed effects through synergistic or complementary actions. Further compositional analyses and mechanistic studies will be necessary to clarify the potential contribution. However, selecting PropA as a key bioactive compound aligns with emerging evidence highlighting its role in inhibiting pro-inflammatory pathways and oxidative stress in gut disorders (Zhao et al., 2024).

In vitro analysis revealed that BBS and PropA significantly reduced the levels of LPS-stimulated inflammatory mediators, such as NO, MCP-1, and IL-6 (Fig. 2). These effects were comparable to those of the pharmacological PC, dexamethasone, suggesting that BBS exerts anti-inflammatory effects. Immunoblotting analysis demonstrated that BBS and PropA inhibited the NF-κB pathway by downregulating p65 and IκBα phosphorylation, as well as suppressing iNOS and COX-2 expression (Fig. 3). NF-κB signaling inhibition is a crucial mechanism underlying the anti-inflammatory effects of PropA and aligns with previous research showing that it suppresses LPS-induced intestinal inflammation by targeting the toll-like receptor 4/NF-κB pathway (Yang et al., 2020). Additionally, both BBS and PropA attenuated ERK and JNK phosphorylation in the MAPK pathway (Fig. 4), suggesting broad-spectrum anti-inflammatory effects. However, the selective inhibition of ERK and JNK, without affecting p38 phosphorylation, remains unexplored. To the best of our knowledge, no previous studies have elucidated the underlying mechanisms driving this specificity. Further investigations are required to elucidate the precise molecular mechanisms by which BBS and PropA modulate these signaling pathways.

The efficacy of BBS and PropA *in vitro* was further validated *in vivo* using a DSS-induced acute colitis mouse model. Meanwhile, the highest experimental dose of BBS (1×, containing 1.86 mg/mL PropA) corresponds to approximately 18.6 mg/kg/day in mice, which translates to a human equivalent dose (HED) of ~1.51 mg/kg/day (~90.6 mg/day for a 60 kg adult) using the FDA body surface area conversion. DSS administration for nine days led to a noticeable decrease in body weight across all groups, including those receiving ASA, BBS, and PropA (Supplementary Fig. S1). This outcome was expected as DSS exposure induces toxicity, leading to ulcerative colitis-like conditions characterized by hematochezia, colonic tissue shortening, and progressive weight loss (Kim et al., 2024; Maria-Ferreira et al., 2018). Oral administration of BBS and PropA significantly alleviated DSS-induced colitis symptoms, including spleen enlargement and increased DAI scores (Fig. 5). Interestingly, both treatments significantly improved the colon length, which is a key indicator of the severity of colonic inflammation. Colon length measurements and DAI scores indicated that BBS and PropA mitigated severe bloody diarrhea and attenuated colon shortening; however, they did not prevent persistent weight loss. Notably, a previous study reported elevated endogenous PropA levels in patients with diarrhea-

predominant irritable bowel syndrome, suggesting a potential indirect association between PropA and diarrhea (Tian et al., 2020). To the best of our knowledge, these findings provide the first direct evidence that the exogenous administration of PropA and BBS alleviates diarrhea and protects against colon shortening.

Next, colonic and serum antibody and cytokine levels were measured to explore the DSS-induced systemic inflammatory responses to BBS and PropA administration (Fig. 6). IgG, the predominant antibody isotype in vertebrate plasma, constituting 70–75 % of the total antibody pool (Vidarsson et al., 2014), and reduced systemic IgG levels are strongly associated with IBD (Rai et al., 2015). IgA, the most abundantly secreted antibody in the gut, plays a pivotal role in mucosal immunity, with deficiencies observed in various chronic conditions, including IBD, allergies, autoimmune diseases, and recurrent infections (Nagaishi et al., 2022). While less amounts than IgA, IgG is also presented in the intestinal lumen, where it contributes to intestinal immune system (Castro-Dopico & Clatworthy, 2019, 2020). Antibody assessment results revealed consistent trends across the groups, demonstrating that BBS administration restored antibody-mediated humoral immunity, which was impaired by DSS-induced colitis. In contrast, PropA supplementation did not significantly enhance serum or colonic antibody production, suggesting minimal effects on humoral immunity. Although PropA plays a role in gut health through various mechanisms (He et al., 2023; Xia et al., 2017; Zhou et al., 2021), few studies have explored its direct effect on antibody production. Additionally, the pro-inflammatory cytokines IL-6 and MCP-1 are well-established contributors to the pathogenesis of several inflammatory diseases, including colitis (Rose-John et al., 2023; Shahini & Shahini, 2023; Singh et al., 2021). Notably, IL-6 and MCP-1 levels exhibited inverse patterns in serum and colonic tissue. DSS-induced increases in IL-6 and MCP-1 levels were significantly reduced in the serum after BBS and PropA treatment, whereas their levels in the colon were notably elevated in the treatment groups compared to those in the DSS-stimulated group, where they were significantly diminished. This inverse distribution of cytokines may reflect distinct systemic and localized immune regulatory mechanisms (Sanchez-Munoz et al., 2008; Turner et al., 2014). Although direct studies on this phenomenon remain scarce, differential cytokine levels between serum and colonic tissue under inflammatory conditions are likely influenced by multiple factors, including disparities between systemic and tissue-specific immune responses (Alhendi & Naser, 2023), cytokine sequestration and clearance (Gabay, 2006), localized cytokine regulation (Chen & Sundrud, 2016; Lu et al., 2022), and differential sensitivity to inflammatory signals (Lee et al., 2018).

Histological evaluation confirmed that DSS consumption resulted in severe intestinal epithelial damage (Fig. 7). Treatment with BBS and PropA preserved colonic architecture by mitigating necrosis, edema, crypt damage, and mucosal atrophy, thereby increasing mucosa thickness. DSS-induced epithelial injury is primarily driven by oxidative stress and mitochondrial dysfunction (Araki et al., 2012), along with toll-like receptor/NF-κB/MAPK (Jin et al., 2017; Testro & Visvanathan, 2009) and COX-2/prostaglandin pathways activation (Tanaka et al., 2009). To further elucidate the mechanism underlying these protective effects, the modulation of DSS-induced COX-2 overexpression and NF-κB activation by BBS and PropA was investigated (Fig. 8). PropA derivatives, such as indole-3-propionic acid (Zhuang et al., 2023) and 3-(4-hydroxyphenyl)-propionic acid (Zhang et al., 2023), modulate inflammatory response through COX-2 regulation or NF-κB signaling inhibition. However, to the best of our knowledge, the findings of this study provide the first evidence that BBS and PropA administration significantly suppress COX-2 overexpression and NF-κB activation in colonic tissue, mitigating the severe DSS-induced colitis symptoms.

Although the findings of this study provide valuable insights, further research is required to enhance their industrial applicability. BBS liquid concentrate was directly tested in both *in vitro* and *in vivo* models; however, its precise chemical composition was not quantified. Other constituents of BBS, including SCFAs and phenolic compounds, may also contribute to the observed effects through synergistic or complementary actions. Thus, future studies should incorporate detailed chemical profiling to ensure reproducibility and standardization. SCFAs, particularly PropA, are increasingly recognized as key mediators linking diet, gut microbiota, and host health, with established roles in maintaining intestinal barrier function and reducing inflammation (Peterson et al., 2022). In line with a recent report (Tian et al., 2025), it is plausible that BBS exerts its protective effects not only through direct anti-inflammatory activity of PropA but also by modulating gut microbial composition and metabolite production. Future studies should therefore investigate these microbiota-mediated mechanisms in greater depth. Finally, although BBS is derived from the microbial biotransformation of edible blueberry juice using safety-certified LAB, a comprehensive safety evaluation is essential. This evaluation should assess acute and chronic toxicity, pharmacokinetics, reproductive toxicity, genotoxicity, carcinogenicity, and other relevant pharmacological evaluations to establish its safety for long-term use (Kim et al., 2024).

5. Conclusion

This study demonstrated that BBS, an SCFA-enriched fermented blueberry product, exerts significant anti-inflammatory effects in both cellular and colitis-induced animal models. The presence of PropA in BBS was confirmed through HPLC-UVD analysis, and its bioactivity was validated by suppressing NO, MCP-1, and IL-6, as well as key inflammatory signaling pathways, such as NF-κB and MAPK, in LPS-stimulated macrophages. *In vivo*, BBS alleviated DSS-induced colitis symptoms by reducing DAI scores, preserving colon morphology, and restoring systemic and colonic antibody levels. COX-2 and NF-κB downregulation further supports the anti-inflammatory role of BBS in the colonic tissues. Although these findings provide compelling evidence for the therapeutic potential of BBS as a postbiotic functional food, future studies should focus on optimizing fermentation conditions, detailed metabolite profiling, and clinical trials to confirm its efficacy and safety for human applications.

CRediT authorship contribution statement

Daun Lee: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Seon-Kyung Hwang:** Investigation, Formal analysis. **Sumin Choo:** Validation, Methodology. **Byungdoo Hwang:** Formal analysis, Data curation. **Jun-Hui Song:** Methodology, Investigation. **Soo Ah. Jeong:** Resources, Project administration, Investigation. **Yeong Hwan Jeong:** Resources, Formal analysis. **Myeong Gwan Son:** Resources, Formal analysis. **Gi Hyeon Kim:** Resources, Investigation. **Beong Ou Lim:** Validation, Supervision, Funding acquisition. **Hoon Kim:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Sung-Kwon Moon:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition.

Ethics statement

All animal procedures followed the guidelines of the Institutional Animal Care and Use Committee of Chung-Ang University (approval no. 202401030112) and carried out according to the guidelines of the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: We wish to disclose potential conflicts of interest involving some of the authors. Yeong Hwan Jeong, Myeong Gwan Son, Gi Hyeon Kim, Beong Ou Lim are employed by Human Bioscience Corp., which develops products related to the subject matter of this manuscript. This affiliation may potentially influence their opinions and interpretations of the research findings. However, Human Bioscience Corp. did not have any role in the study design, data collection, analysis, interpretation, or writing of this manuscript. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2025.107013.

Data availability

Data will be made available on request.

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