Prev. Nutr. Food Sci. 2023;28(4):418-426
https://doi.org/10.3746/pnf.2023.28.4.418
ISSN 2287-8602

Wheat Ceramide Powder Mitigates Ultraviolet B-Induced Oxidative Stress and Photoaging by Inhibiting Collagen Proteolysis and Promoting Collagen Synthesis in Hairless Mice

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ABSTRACT: The protective effects of wheat ceramide powder (WC-P) on ultraviolet B (UVB)-induced skin oxidative stress and photoaging in hairless mice were investigated in this study. Moreover, the activities of antioxidant enzymes, inflammation, wrinkle formation-related pathway, and moisturizing capacity were evaluated. Mice were randomly divided into six groups (n=8): normal control (non-UVB irradiation), control (UVB irradiation), L-ascorbic acid [positive control, UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)], WC-P5 (UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw), WC-P20 (UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw), and WC-P40 (UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw). AIN-96G diet and water were supplemented ad libitum, and 100 μL of L-ascorbic acid and WC-P dissolved in water were forcefully administered orally to mice. UVB irradiation resulted in dehydration and wrinkle formation in the dorsal skin of mice. However, WC-P supplementation suppressed. Furthermore, WC-P supplementation enhanced the activites of antioxidant enzymes and expression of transforming growth factor-β receptor I, procollaten C-endopeptideas enhancer protein, hyaluronan synthase, and ceramide synthase 4 and reduced the activation of the inflammation and the c-Jun N-terminal kinase/c-FOS/c-Jun-mediated matrix metalloproteinase pathways. These findings demonstrate that WC-P can protect the skin from UVB-induced oxidative stress, inflammation, and photoaging by inhibiting collagen proteolysis and promoting collagen synthesis, thereby promoting skin health.

Keywords: collagen, ultraviolet ray, skin aging, wheat ceramides

INTRODUCTION

The skin is the most externally exposed organ of the body. It is composed of three main layers: epidermis, dermis, and subcutaneous fat layer. The epidermis forms the outermost layer and plays a crucial role in providing skin structure and protection against environmental damage; it comprises keratinocytes, melanocytes, Langerhans cells, and Merkel cells (Kanitakis, 2002; Baroni et al., 2012). The dermis provides strength and elasticity to the skin and comprises matrix components (Shin et al., 2019). The skin layers protect against ultraviolet (UV) radiation, which causes skin photoaging, characterized by wrinkle formation, dryness, and thinning. Maintaining skin moisture and structural components such as collagen, hyaluronic acid, and ceramides, which moisturize and reinforce the protective skin barrier, can address cutaneous aging, including premature aging caused by UV irradiation (Wlaschek et al., 2001; Shin et al., 2019; Ansary et al., 2021).

UV irradiation causes the excessive production of reactive oxygen species (ROS) in the epidermis. ROS cause oxidative stress, which contributes to the development of various skin diseases. Oxidative stress also triggers inflammatory responses, including the production of pro-inflammatory molecules, and impairs the skin's ability to retain moisture (Dupont et al., 2013; Panich et al., 2016; Nakai and Tsuruta, 2021). In the dermis, UV-induced oxi-

Received 25 September 2023; Revised 20 November 2023; Accepted 20 November 2023; Published online 31 December 2023

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dative stress also stimulates the production of pro-inflammatory cytokines and the degradation of extracellular matrix proteins through matrix metalloproteinases (MMPs), which contribute to wrinkle formation (Freitas-Rodríguez et al., 2017; Gao et al., 2018; Nakai and Tsuruta, 2021). Natural foods have been found to have antioxidant properties that can prevent UV-induced oxidative stress and subsequent photoaging (Ahmed et al., 2020; Tanveer et al., 2023).

Wheat ceramides are a plant-based source of ceramides derived from wheat germ oil that can be used in skincare products or consumed orally as a supplement (Bizot-Foulon et al., 1995; Guillou et al., 2011; Son et al., 2020). Ceramides are natural lipids present in the skin that play a vital role in maintaining the skin's barrier function and preventing moisture loss (Tessema et al., 2017). Several studies have also shown that wheat ceramides may enhance the skin's barrier function, improve moisture retention, and promote overall skin health (Bizot-Foulon et al., 1995; Guillou et al., 2011; Son et al., 2020). In Guillou et al.'s (2011) study, with wheat extract oil treatment increased skin hydration and improved associated clinical signs among women with dry skin. Additionally, Son et al. (2020) demonstrated that wheat extract oil supplementation attenuated ultraviolet B (UVB)-induced wrinkle formation in hairless mice, supporting the potential benefits of wheat ceramides in skincare. To further investigate the physiological effects of wheat ceramide powder (WC-P) and establish its value, this study examined the impact of WC-P on skin oxidative stress, inflammation, wrinkle formation, and moisturization in UVB-induced photoaging using hairless mice. This study aims to provide scientific evidence regarding the positive effects of WC-P on skin health.

MATERIALS AND METHODS

WC-P preparation

The WC-P (Ceramosides®), which is from Seppic S.A., was provided from GREEN STORE, Inc. It is made by extracting hydroalcohol from wheat flour (*Triticum aestivum*) and purifying it with acetone. High-performance liquid chromatography was used to analyze glucosylceramides in WC-P in accordance with Yan's method with modifications (Yan et al., 2015). WC-P was standardized based on glucosylceramides (Fig. 1) and stored in an airtight container at −20°C until further use.

UVB irradiation of hairless mice

Five-week-old male hairless mice (SKH-1) were obtained from Charles River Laboratory and housed under controlled environmental conditions (23±2°C, humidity 50±5%, and a 12/12-h light/dark cycle). They were randomly

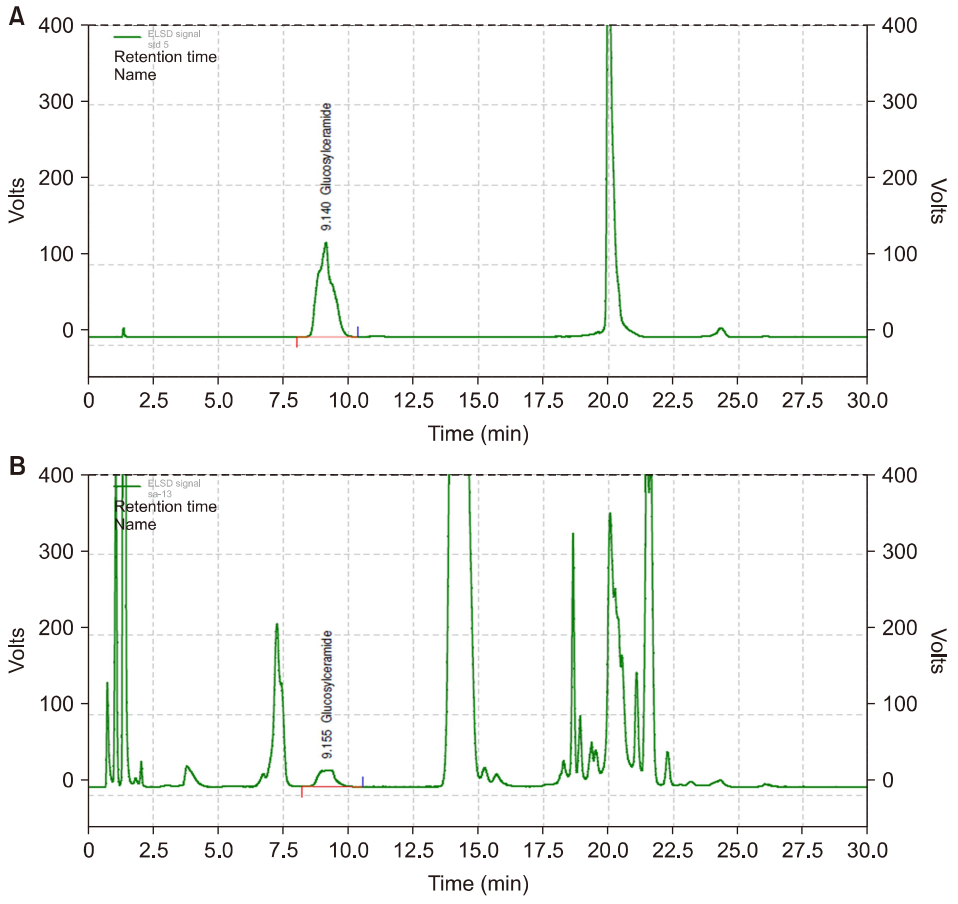

Fig. 1. High-performance liquid chromatography chromatograms. Standard compound (A), and wheat ceramide powder glucosylceramides (B).

divided into six groups (n=8): normal control (NC; non-UVB irradiation), control (C; UVB irradiation), L-ascorbic acid [positive control, PC; UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)], WC-P5 (UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw), WC-P20 (UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw), and WC-P40 (UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw). The mice were supplemented with AIN-93G diet and water ad libitum. About 100 μL of L-ascorbic acid and WC-P dissolved in water were forcefully administered orally to mice. A UVB lamp (Sankyo Denki Co.) was used for UVB radiation of the dorsal skin of mice. The mice received one (150 mJ/cm^2), two (300 mJ/cm^2), three (450 mJ/cm^2), and four (600 mJ/cm^2) minimal erythema doses in the first, second, third, and fourth to eighth weeks, respectively. The Howskin device (Innoinsight, Inc.) was used to assess skin hydration at the eighth week. After isoflurane anesthesia, the mice were sacrificed through cervical dislocation. The study protocol was approved by the Institutional Animal Care and Use Committee of Kyung Hee University (KHGASP-22-617).

Hematoxylin and eosin (H&E) staining

To preserve the cellular structure, skin tissue samples were initially fixed in formalin solution. Afterward, they were embedded in paraffin wax to provide support during sectioning. A microtome was used to cut thin sections of skin tissue. Next, the tissue sections were mounted on glass slides. Subsequently, xylene was used to eliminate paraffin wax from the tissue sections. Thereafter, the tissue sections were rehydrated graded alcohol solutions. Finally, they were stained with H&E.

Measurement of superoxide dismutase, catalase, and glutathione peroxidase activities

Skin tissue samples were collected from mice for analysis. Assay kits from BioVision Inc. were used to measure superoxide dismutase, catalase, and glutathione peroxidase activities. The activities of superoxide dismutase 1, catalase, glutathione peroxidase were measured using a mouse enzyme-linked immunosorbent assay kit, colorimetric/fluorometric assay kit, colorimetric assay kit, respectively. All measurements were performed in accordance with the manufacturer's protocols.

Quantitative real-time polymerase chain reaction (PCR)

The RNeasy Mini Kit (Qiagen) was used to extract total RNA from skin tissues. RNA was quantified using NanoDrop (Quawell Technology). The iScript cDNA Synthesis Kit (Bio-Rad) was used to synthesize complementary DNA (cDNA) using 100 ng of RNA. Real-time PCR (Applied Biosystems) was performed on triplicate samples using 1 μL of cDNA with SYBR Green Master Mix (Thermo Fisher Scientific) for the mRNA assay. cDNA was amplified with 40 cycles of denaturation (95°C for 3 s) and annealing and extension (60°C for 30 s) using the CFX96 Touch Real-Time PCR Detection System (Bio-Rad). Table 1 shows the primer sets used in real-time PCR.

Western blot analysis

A lysis reagent (Sigma-Aldrich) was used to lyse skin tissues. Equal amounts of protein (100 μg/lane) were separated on a 10% Mini-PROTEAN® TGX™ Precast Protein Gel (Bio-Rad). The Trans-Blot® Turbo™ Transfer System (Bio-Rad) was used to perform electrophoretic membrane transfer. Subsequently, the membranes were blocked and incubated with primary antibodies against IκBα, p-IκBα, p65, p-p65, cyclooxygenase-2 (COX-2), c-Jun N-terminal kinase (JNK), p-JNK, c-FOS, p-c-FOS, c-Jun, p-c-Jun, MMP-1, MMP-2, MMP-3, MMP-9, Smad3, p-Smad3, CerS4, and β-actin (Cell Signaling Technology). Next, the membranes were incubated with a secondary antibody (Anti-rabbit IgG HRP-linked Antibody, 1:5,000, Cell Signaling Technology). Then, the resulting protein bands were detected, quantified using CS Analyzer 3.0 (ATTO), and normalized with β-actin as a loading control.

Table 1. Primer sets used in real-time polymerase chain reaction

Gene	Sequence
TNF-α (M)	F 5′-CAC CGT CAG CCG ATT TGC-3′
	R 5′-TTG ACG GCA GAG AGG AGG TT-3′
IL-1β (M)	F 5′-GAT GAT AAC CTG CTG GTG TGT GA-3′
	R 5′-GTT GTT CAT CTC GGA GCC TGT AG-3′
IL-6 (M)	F 5′-CGC TAT GAA GTT CCT CTC TGC AA-3′
	R 5′-CAC CAG CAT CAG TCC CAA GAA-3′
TGF-β RI (M)	F 5′-CAT CCT GAT GGC AAG AGC TAC A-3′
	R 5′-TAG TGG ATG CGG ACG TAA CCA-3′
Collagen Type I (M)	F 5′-GAC CGT TCT ATT CCT CAG TGC AA-3′
	R 5′-CCC GGT GAC ACA CAA AGA CA-3′
PCOLCE (M)	F 5′-TTA CGT GGC AAG TGA GGG TTT-3′
	R 5′-TGT CCA GAT GCA CTT CTT GTT TG-3′
Fibirillin-1 (M)	F 5′-ACA ATT GTT CAC CGA GTC GAT CT-3′
	R 5′-ACT GTA CCT GGG TGT TGC CAT T-3′
HAS1 (M)	F 5′-TCA GGG AGT GGG ATT GTA GGA-3′
	R 5′-AAA TAG CAA CAG GGA GAA AAT GGA-3′
HAS2 (M)	F 5′-AAT ACA CGG CTC GGT CCA AGT-3′
	R 5′-CCA TCG GGT CTG CTG GTT-3′
HAS3 (M)	F 5′-GGC CAT GGG AGC TAA AGT TG-3′
	R 5′-CCA AAT TGA TGT TGA AAC TCT TGA AA-3′
LCB1 (M)	F 5′-AGC GCC TGG CAA AGT TTA TG-3′
	R 5′-GTG GAG AAG CCG TAC GTG TAA AT-3′
DEGS1 (M)	F 5′-CCG GCG CAA GGA GAT CT-3′
	R 5′-TGT GGT CAG GTT TCA TCA AGG A-3′
GAPDH (M)	F 5′-CAT GGC CTT CCG TGT TCC TA-3′
	R 5′-GCG GCA CGT CAG ATC CA-3′

Statistical analysis

Data are presented as the mean±standard deviation. SPSS software (IBM SPSS Statistic 23.0, IBM Corp.) was used to perform statistical analysis. One-way ANOVA was performed, followed by Duncan's multiple range tests. Statistical significance was considered at $P<0.05$.

RESULTS

WC-P protected the skin against UVB irradiation in hairless mice

UVB-irradiated hairless mice (C) exhibited skin wrinkling, irregular skin shape (Fig. 2A), increased wrinkle area (Fig. 2B) and epidermis thickness (Fig. 2C), and reduced skin hydration (Fig. 2D) compared with normal hairless mice (NC). However, dietary supplementation with L-ascorbic acid and WC-P significantly reduced skin wrinkling and significantly increased skin hydration of UVB-irradiated hairless mice ($P<0.05$; Fig. 2). In particular, WC-P were decreased the wrinkle area and epidermis thickness in a dose-dependent manner. These results showed that WC-P protected the skin against wrinkle formation and skin dryness induced by UVB irradiation.

WC-P increased the activities of antioxidant enzymes in UVB-irradiated hairless mice

UVB-irradiated hairless mice exhibited decreased superoxide dismutase, catalase, and glutathione peroxidase activities compared with normal hairless mice. However, dietary supplementation with L-ascorbic acid and WC-P significantly increased the activities of antioxidant enzymes ($P<0.05$; Fig. 3).

WC-P alleviated skin inflammation in UVB-irradiated hairless mice

UVB-irradiated hairless mice exhibited significantly decreased in mRNA expression levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) and protein expression levels of IκBα phosphorylation, p65 phosphorylation, and COX-2 compared with normal hairless mice (Fig. 4). UVB irradiation resulted in a notable reduction in the mRNA expression levels of IL-1β, IL-6, and TNF-α, and a significant decrease in the protein expression levels of IκBα phosphorylation, p65 phosphorylation, and COX-2 in the PC and WC-P groups compared with the C group ($P<0.05$; Fig. 4).

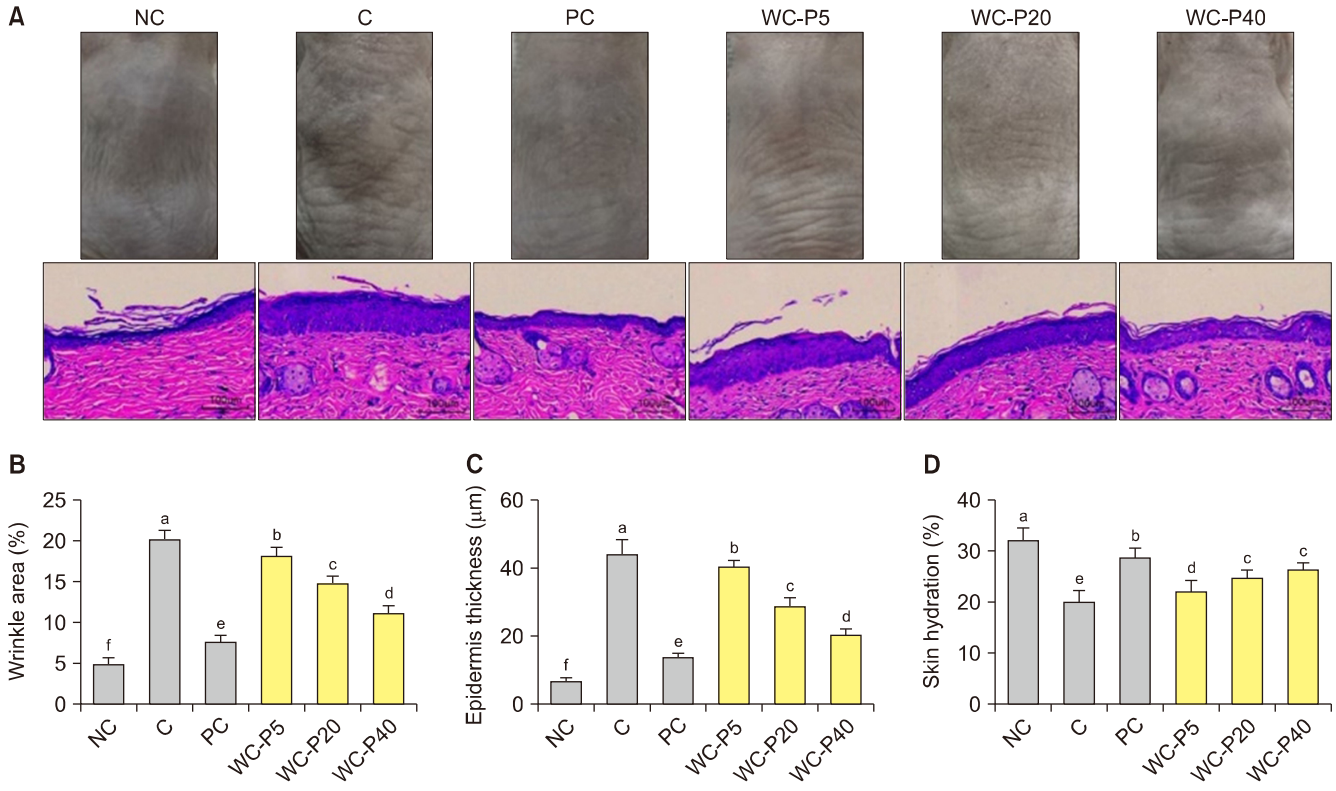

Fig. 2. Effect of wheat ceramide powder (WC-P) on wrinkle formation and skin dryness in ultraviolet B (UVB)-irradiated hairless mice. Morphological and histopathological changes (A), wrinkle area (B), epidermis thickness (C), and skin hydration (D) in the dorsal skin of UVB-irradiated hairless mice. NC, normal control (non-UVB irradiation); C, control (UVB irradiation); PC, positive control [UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)]; WC-P5, UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw; WC-P20, UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw; WC-P40, UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw. Values are presented as the mean±SD. Different letters indicate a significant difference at $P<0.05$ using Duncan's multiple range test.

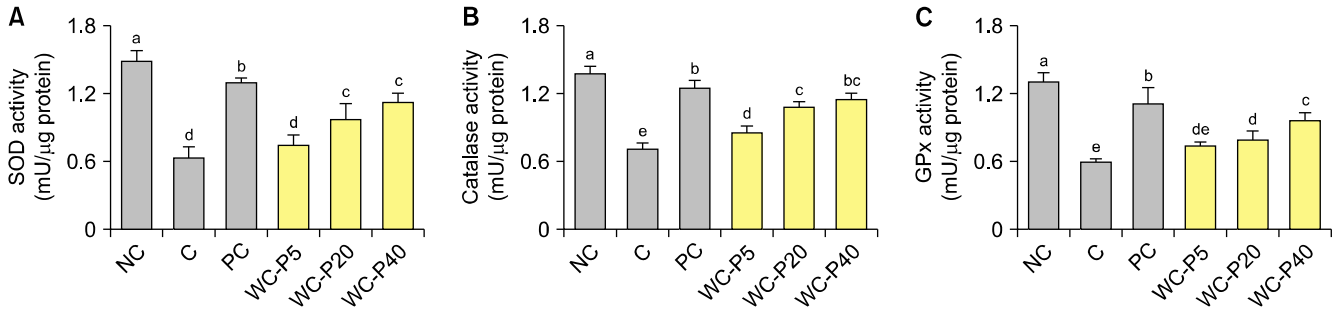

Fig. 3. Effect of WC-P on the activities of superoxide dismutase (A), catalase (B), and glutathione peroxidase (C) in the dorsal skin of UVB-irradiated hairless mice. NC, normal control (non-UVB irradiation); C, control (UVB irradiation); PC, positive control [UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)]; WC-P5, UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw; WC-P20, UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw; WC-P40, UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw. Values are presented as the mean±SD. Different letters indicate a significant difference at $P<0.05$ using Duncan's multiple range test.

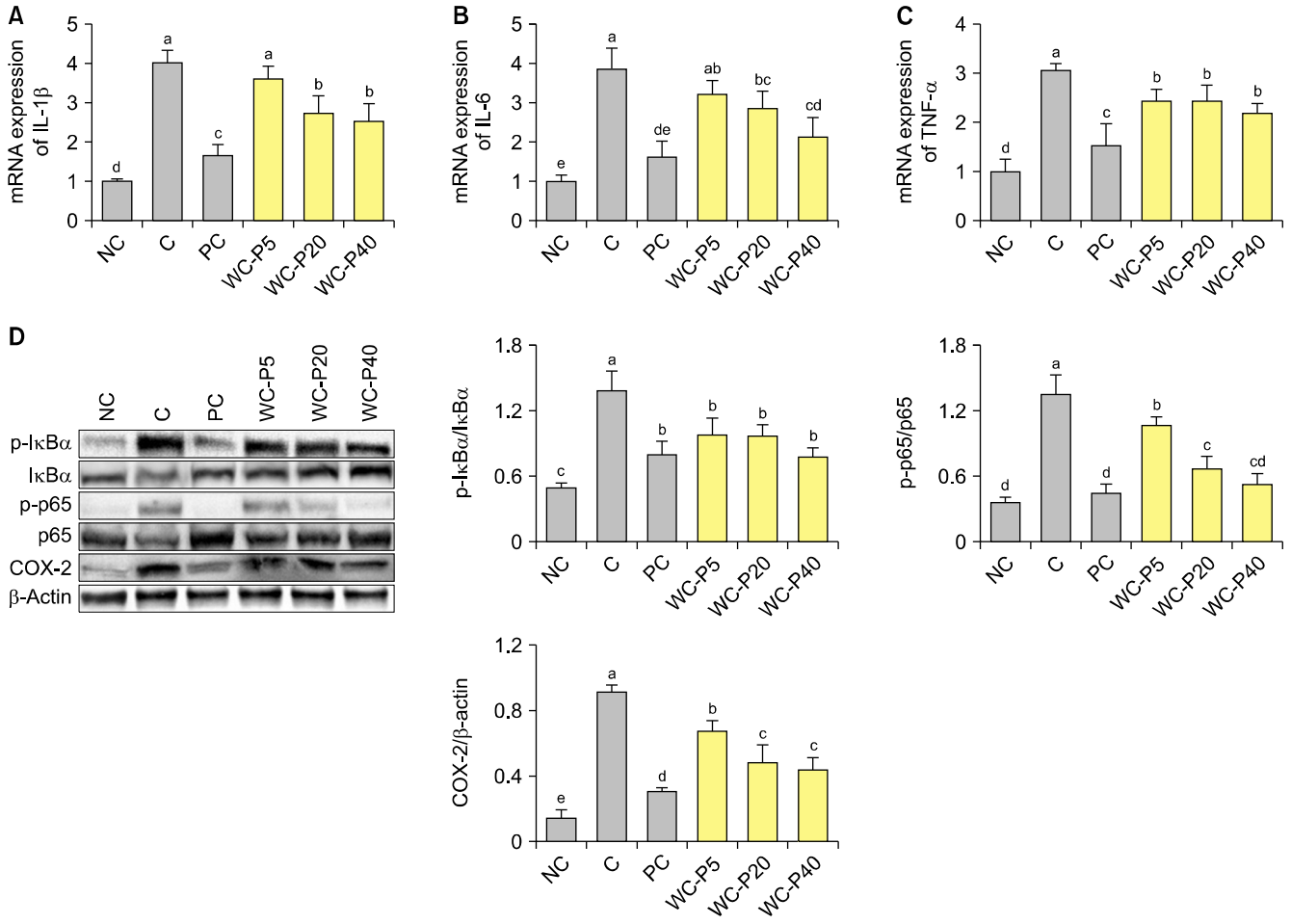

Fig. 4. Effect of wheat ceramide powder (WC-P) on the mRNA expression of IL-1β (A), IL-6 (B), and tumor necrosis factor-α (TNF-α) (C) and protein expression of IκBα phosphorylation, p65 phosphorylation, and cyclooxygenase-2 (COX-2) (D) in the dorsal skin of ultraviolet B (UVB)-irradiated hairless mice. NC, normal control (non-UVB irradiation); C, control (UVB irradiation); PC, positive control [UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)]; WC-P5, UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw; WC-P20, UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw; WC-P40, UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw. Values are presented as the mean±SD. Different letters indicate a significant difference at $P<0.05$ using Duncan's multiple range test.

WC-P suppressed the wrinkle formation pathway by UVB irradiation in hairless mice

The dorsal skin was examined to investigate the molecular mechanism underlying WC-P-mediated wrinkle formation. Compared with normal hairless mice, UVB-irradiated hairless mice showed increased activation of proteins involved in the wrinkle formation pathway and decreased mRNA expression of transforming growth fac-

tor-β receptor I (TGF-β RI), collagen type I, procollagen C-endopeptidase enhancer protein (PCOLCE), and fibrillin-1 involved in extracellular matrix synthesis. However, the PC and WC-P groups exhibited decreased activation of proteins related to the wrinkle formation pathway and significant increased mRNA expression levels of TGF-β RI, collagen type I, PCOLCE, and fibrillin-1 compared with the C group ($P<0.05$; Fig. 5).

WC-P increased the moisturizing capacity in UVB-irradiated hairless mice

UVB-irradiated mice exhibited significantly decreased in mRNA expression of hyaluronan synthase (HAS) 1, HAS2, and HAS3 in the dorsal skin compared with the normal hairless mice. Moreover, the protein expression of ceramide synthase 4 and mRNA expression of serine palmitoyltransferase 1 (LCB1) and delta 4-desaturase (DEGS1) were decreased in the dorsal skin of UVB-irradiated mice compared with normal hairless mice. However, mRNA expression levels of HAS1, HAS2, HAS3, LCB1, and DEGS1 and protein expression levels of ceramide synthase 4 were significantly increased in the PC and WC-P groups than the C group ($P<0.05$; Fig. 6).

DISCUSSION

Chronic exposure to UVB radiation leads to the excessive ROS production, which in turn stimulates transcription factors involved in inflammatory response. The pro-inflammatory cytokines released in response to UVB activate nuclear factor-kappa B (NF-κB), a transcription factor that remains inactive as a p50/p65 heterodimer bound to its inhibitor (IκB), in the cytoplasm. Upon activation, NF-κB is dissociated dissociates from IκB and translocated into the nucleus where it binds to gene promoters and regulates their expression. In addition, pro-inflammatory cytokines can activate the JNK/c-FOS/c-Jun pathway. The activation of NF-κB and the JNK pathway triggers the MMP-induced degradation of extracellular matrix proteins by expressing activator protein 1 in the dermis (Ruszczak, 2003; López-Camarillo et al., 2012). The expression of pro-inflammatory cytokines, phosphorylation of IκBα and p65, and MMP levels were increased in UVB-irradiated skin, indicating skin inflammation and proteolysis. However, the results demonstrated that WC-P supplementation suppressed the expression of inflammatory factors and reduced the activation of NF-κB and the JNK pathway in UVB-irradiated mice. These findings suggest that WC-P supplementation attenuated inflammation and extracellular matrix protein degradation by inhibiting oxidative stress.

Collagen, predominantly collagen type I, constitutes more than 90% of the dermis and serves as the main component of the skin matrix. Thus, collagen degradation represents a crucial driver of wrinkle formation. Collagen type I undergoes depletion in UVB-incued photoaging, resulting in decreased elasticity and subsequent formation of deep wrinkles. UVB exposure inhibits the expression of TGF-β RI, a receptor involved in collagen type I production, leading to collagen degradation and wrinkle formation (Ruszczak, 2003; Choi et al., 2007; Liu et al., 2019; Liarte et al., 2020). However, dietary supplementation with WC-P stimulated the expression of TGF-β RI and PCOLCE, a regulator of collagen fibrillogenesis, in the dorsal skin of UVB-irradiated mice. Therefore, WC-P supplementation plays a significant role in inhibiting collagen proteolysis and promoting collagen synthesis.

UVB irradiation disrupts hyaluronic acid synthesis through hyaluronic acid synthase in keratinocytes, thereby compromising the moisture retention capacity of the epidermis (Dai et al., 2007). Furthermore, UVB-exposed skin exhibits reduced levels of ceramides, which are crucial for maintaining skin barrier function and preventing water loss (Takagi et al., 2004). These changes disrupt skin moisture retention and barrier function, and the inflammatory mediators released from the epidermis activate MMPs through the MAPK signaling pathway, thereby exacerbating collagen degradation in the dermis and contributing to wrinkle formation (López-Camarillo et al., 2012; Dupont et al., 2013; Ansary et al., 2021). The results demonstrated that WC-P supplementation enhances the mRNA expression of hyaluronic acid synthase, ceramide synthase, LCB1, and DEGS1, highlighting its beneficial effects on skin health and barrier function.

Tsuji et al. (2006) demonstrated that dietary glucosylceramide effectively reduced transepidermal water loss and improved the stratum corneum's flexibility in hairless mice with chronic barrier perturbation. Additionally, in their human clinical study, Bizot et al. (2017) found that showed oral administration of wheat glucosylceramides significantly improved skin hydration and decreased wrinkle formation compared with a placebo. Based on the results of these preliminary studies and the present study, WC-P supplementation can inhibit skin water loss and wrinkle formation induced by UVB irradiation. The results also suggest that these effects are mediated by increased collagen synthesis and reduced collagen degradation.

In conclusion, WC-P has anti-inflammatory and antioxidative effects, effectively protecting the skin against UVB-induced photoaging in hairless mice. WC-P treatment increased collagen synthesis and reduced collagen degradation, thereby inhibiting wrinkle formation. These findings suggest that WC-P supplementation may help prevent skin photoaging by inhibiting oxidative stress, inflammation, and collagen degradation and promoting skin moisturization, providing scientific evidence regarding its

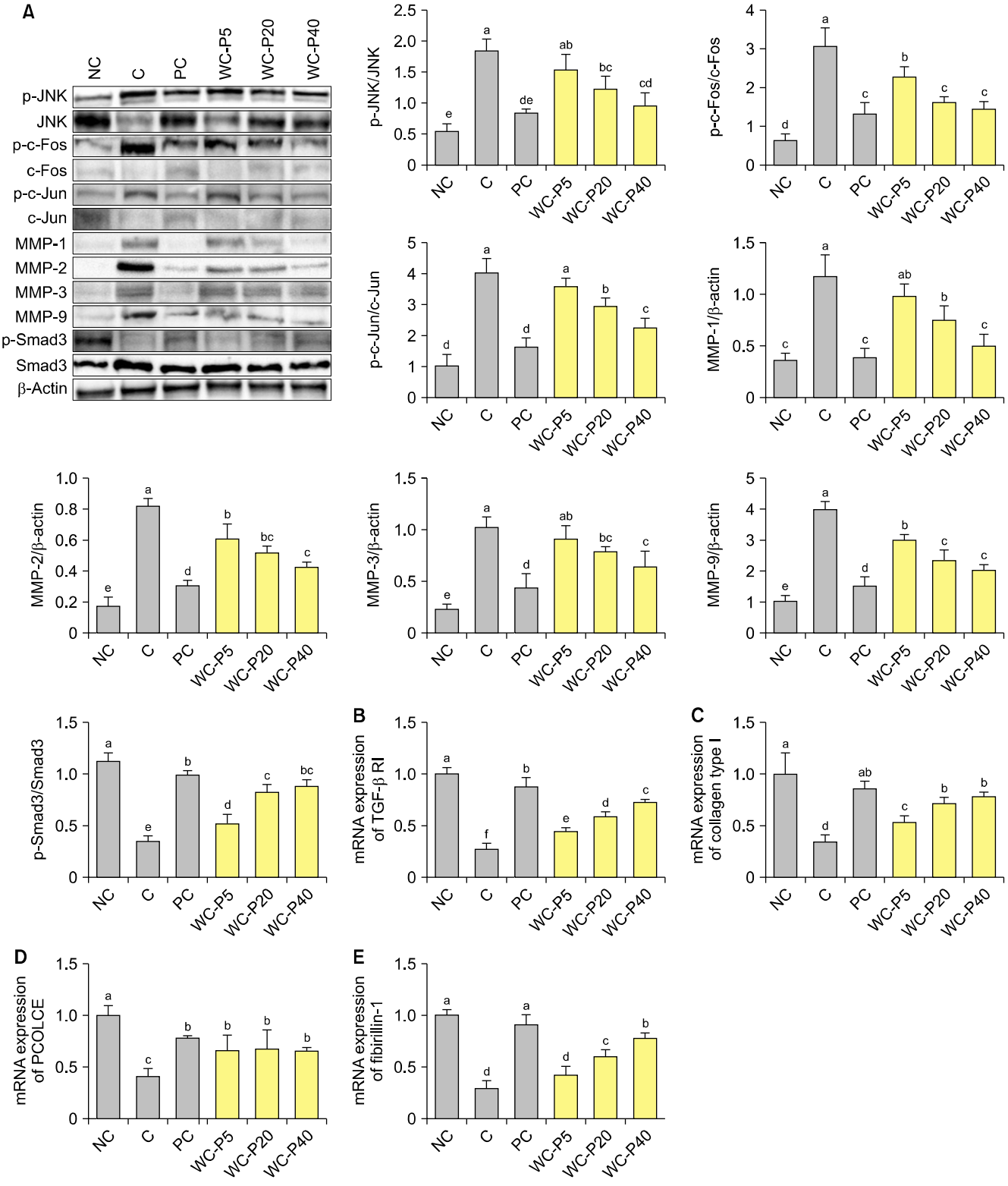

Fig. 5. Effect of wheat ceramide powder (WC-P) on the protein expression of JNK, c-FOS, c-Jun, MMPs, and Smad3 (A) and mRNA expression of TGF-β RI (B), collagen type I (C), PCOLCE (D), and fibrillin-1 (E) in the dorsal skin of ultraviolet B (UVB)-irradiated hairless mice. NC, normal control (non-UVB irradiation); C, control (UVB irradiation); PC, positive control [UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)]; WC-P5, UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw; WC-P20, UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw; WC-P40, UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw. Values are presented as the mean±SD. Different letters indicate a significant difference at $P<0.05$ using Duncan's multiple range test.

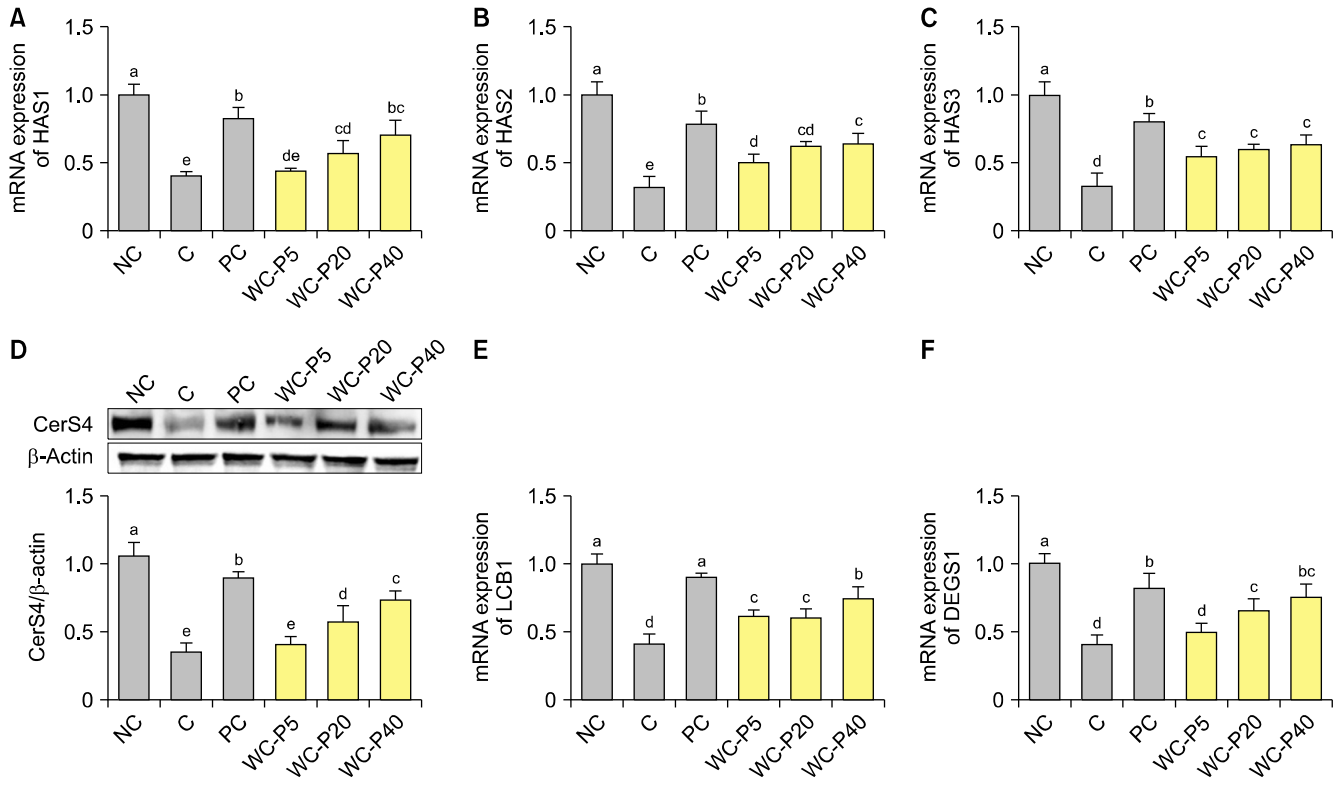

Fig. 6. Effect of wheat ceramide powder (WC-P) on the mRNA expression of hyaluronan synthase (HAS) 1 (A), HAS2 (B), and HAS3 (C), protein expression of CerS4 (D), mRNA expression of serine palmitoyltransferase 1 (LCB1) (E), and delta 4-desaturase (DEGS1) (F) in the dorsal skin of ultraviolet B (UVB)-irradiated hairless mice. NC, normal control (non-UVB irradiation); C, control (UVB irradiation); PC, positive control [UVB irradiation with dietary supplementation of L-ascorbic acid at 100 mg/kg/body weight (bw)]; WC-P5, UVB irradiation with dietary supplementation of WC-P at 5 mg/kg/bw; WC-P20, UVB irradiation with dietary supplementation of WC-P at 20 mg/kg/bw; WC-P40, UVB irradiation with dietary supplementation of WC-P at 40 mg/kg/bw. Values are presented as the mean±SD. Different letters indicate a significant difference at $P<0.05$ using Duncan's multiple range test.

beneficial effects on skin health.

FUNDING

None.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: SHP, JP, JK, JG, OKK, JL. Analysis and interpretation: SHP, JP, ML. Data collection: SHP, JP, ML. Writing the article: SHP, JP, OKK, JL. Critical revision of the article: ML, WJ, OKK, JL. Final approval of the article: all authors. Statistical analysis: SHP, JP. Overall responsibility: OKK, JL.

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