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UVA 조사된 인체피부섬유아세포에서 갯제비쑥에서 분리한 sesamin의 MAPK 경로 조절을 통한 MMP의 발현 억제효과

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Sesamin from *Artemisia littoricola* Attenuates UVA-Induced MMP Expression in Human Dermal Fibroblasts via MAPK Pathway Modulation

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ABSTRACT

Background: Photoaging is predominantly caused by ultraviolet (UV) radiation and is a major contributor to premature skin aging. Photoaging of the skin is characterized by oxidative stress and collagen degradation. Damage to skin extracellular matrix proteins is mainly caused by the upregulation of matrix metalloproteinases (MMPs). Sesamin, a lignan commonly found in sesame seeds, possesses antioxidant, anti-inflammatory, and other beneficial properties, making it a promising compound for skin photoprotection.
Methods and Results: The photoaging amelioration potential of sesamin isolated from *Artemisia littoricola*was investigated using UVA-stimulated human dermal fibroblasts (HDFs). Sesamin significantly reduced intracellular ROS accumulation and attenuated UVA-mediated elevation in secreted MMP-1. Sesamin also suppressed phosphorylation of the terminal mitogen-activated protein kinases (MAPKs), ERK, JNK, and p38. MMP-1 and MMP-3 protein levels were also downregulated, and collagen content was preserved.
Conclusions: These results demonstrate that sesamin protects against UVA-induced damage in HDFs by reducing oxidative stress and inhibiting MAPK-mediated MMP expression. These results indicate that sesamin is a potential natural photoprotective agent with potential applications in skin care. Isolation of sesamin from *A. littoricola*highlights the relevance of medicinal crops as a source of bioactive compounds for cosmeceutical applications.

Key Words: A*rtemisia littoricola*, Human Dermal Fibroblasts, Matrix Metalloproteinases-1, Photoaging, Sesamin

INTRODUCTION

Skin photoaging is a multifactorial process characterized by the excessive degradation of collagen fibers and the consequent remodeling of the extracellular matrix (ECM). These processes lead to wrinkles, loss of elasticity and strength, impaired skin repair and other signs of premature skin aging. Ultraviolet (UV) radiation which penetrates the dermis is the most important environmental factor behind these detrimental changes. Among other types of UV, UVA penetrates deeper into skin and UVA exposure induces the overgeneration of reactive oxygen species (ROS) which in turn activates matrix

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metalloproteinases (MMPs), particularly MMP-1, MMP-3 and MMP-9 enzymes which are responsible for collagen degradation and ECM disruption (Gromkowska-Kępka *et al.*, 2021). The accumulation of ROS is also known to trigger intracellular signaling cascades, including the mitogen-activated protein kinase (MAPK) pathway which enhances MMP expression and contributes to inflammatory responses and detrimental effects (Prasanth *et al.*, 2020).

Given the pivotal role of oxidative stress in photoaging, natural compounds with antioxidant and MMP-inhibitory activities have gained considerable attention as potential photoprotective agents. Plant-derived bioactive compounds, including polyphenols, flavonoids and lignans have been studied for their ability to mitigate UVA-induced damage via antioxidant properties, suggesting a promising strategy for preventing or attenuating photoaging (Calvo *et al*., 2024; Lin *et al*., 2024). Some studies have demonstrated that compounds like caffeic acid phenethyl ester and ferulic acid possess antioxidant properties and can inhibit MMP expression, thereby protecting the skin from UV-induced damage (Staniforth *et al.*, 2012; Shin *et al*., 2019).

Sesamin, a major lignan found in sesame seeds (*Sesamum indicum*) and several other plant species, exhibits a broad spectrum of biological activities including but not limited to antioxidants, anti-inflammatory and anti-cancer effects (Wu *et al*., 2019; Zhang *et al*., 2022). Its antioxidant properties allow it to scavenge ROS, modulate redox sensitive signaling pathways and suppress oxidative damage while its anti-inflammatory activity may reduce the production of pro-inflammatory cytokines associated with skin aging. Previous studies have demonstrated its protective effects in various cell and animal models, but its potential as a photoprotective agent against UVA-induced skin damage remains underexplored.

Sesamin was isolated for the first time from *Artemisia littoricola* in the present study. *A. littoricola* is a medicinal plant and it is known for its diverse bioactive compounds (Kwon and Lee, 2001). The current study focused on the ability of sesamin to attenuate deteriorative effects of UVA exposure via reducing oxidative stress, regulating MMP secretion and controlling key signaling pathways, particularly the MAPK cascade which was aimed at providing mechanistic insights into its potential action mechanism as a natural anti-photoaging agent.

MATERIAL AND METHODS

1. Chemicals and reagents

Sesamin (Fig. 1A) was isolated from *Artemisia littoricola* and identified by comparison of its ^{1}H and ^{13}C NMR data with reported literature (Baures *et al.*, 1992). Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS) and penicillin-streptomycin were purchased from Gibco (Thermo Fisher Scientific, Waltham, MA, USA). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), 2',7'-dichlorofluorescin diacetate (DCFH-DA), and other analytical-grade chemicals were obtained from Sigma-Aldrich (St. Louis, MO, USA). ELISA kits for human MMP-1 were obtained from R&D Systems (Minneapolis, MN, USA). Antibodies against MMP-1, MMP-3, collagen type I, ERK, phospho-ERK, JNK, phospho-JNK, p38, phospho-p38, and β-actin were purchased from Cell Signaling Technology (Danvers, MA, USA). All reagents were of the

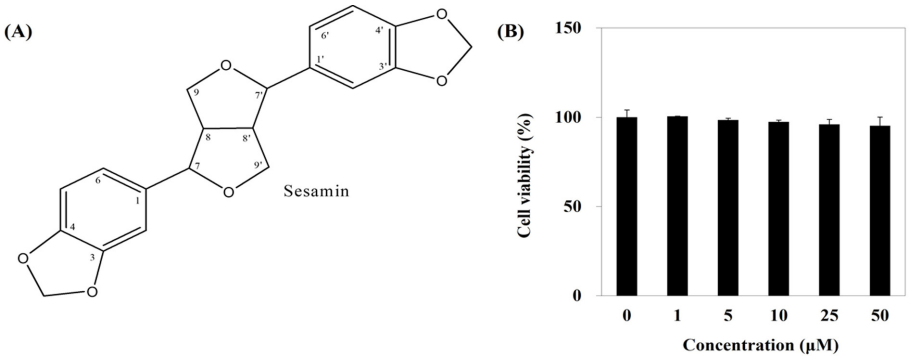

Fig. 1. Sesamin structure and its cytotoxicity profile in HDFs. (A) Chemical structure of sesamin isolated from *A. littoricola* derived from ^{1}H and ^{13}C NMR spectra. Spectra confirm characteristic signals of the lignan framework. (B) Cell viability of HDFs treated with increasing concentrations of sesamin (1–50 μM) for 24 h. No significant cytotoxicity was observed. Values are expressed as mean ± SD (n = 3).

highest commercial grade available.

2. Cell culture

Human dermal fibroblasts (HDFs; ATCC PCS-201-012) were maintained in DMEM supplemented with 10% (v/v) heat-inactivated FBS, 100 U/mL penicillin and 100 μg/mL streptomycin at 37℃ in a humidified atmosphere containing 5% CO_2. Cells were sub-cultured every 23 days using 0.05% trypsin–EDTA and seeded at appropriate densities for each experiment. Cells between passages 5 and 10 were used for all assays.

3. UVA irradiation and sample treatment

For UVA exposure, cells were washed twice with phosphate-buffered saline (PBS, pH 7.4) and covered with a thin layer of PBS to prevent drying. UVA irradiation was performed using a Bio-Sun biological UV–irradiation system (Vilber Lourmat, Marine, France) equipped with 4× 30-Watt 365 nm UVA lamps (T.40L, Vilber Lourmat) at a measured intensity of approximately 6 J/cm^2, as calibrated with a UV radiometer (VLX-3W, Vilber Lourmat). After irradiation, PBS was replaced with serum-free DMEM containing sesamin at the indicated concentrations (1–50 μM) and incubated at 37℃. Non-irradiated and untreated cells served as negative controls.

4. Cell viability assay (MTT)

The cytotoxicity of sesamin was determined using the MTT assay as previously described (Oh *et al*., 2021). HDFs were seeded in 96-well plates at 1×10^4 cells/well and allowed to adhere overnight, and absorbance was measured at 540 nm using a GENios microplate reader (Tecan Austria GmbH, Grodig, Austria). Cells were treated with sesamin (0–50 μM) for 24 h, followed by incubation with MTT (0.5 mg/mL) for 3 h. The formazan crystals formed were dissolved in dimethyl sulfoxide (DMSO) and cell viability was expressed as a percentage of the untreated control.

5. Measurement of intracellular ROS

Intracellular ROS generation was quantified using the DCFH-DA fluorescent probe. After treatment and UVA exposure, cells were incubated with 10 μM DCFH-DA in serum-free medium for 30 min at 37℃. Excess dye was removed by washing with PBS, and fluorescence was measured at excitation/emission wavelengths of 485/530 nm using a microplate reader (GENios, Tecan). Relative ROS levels were calculated as a percentage of the UVA-irradiated control group.

6. Enzyme-linked immunosorbent assay (ELISA)

Secreted MMP-1 levels were determined in cell culture supernatants using a commercial ELISA kit according to the manufacturer's protocol. Briefly, conditioned media were collected, centrifuged at 10,000 × g for 10 min to remove debris and incubated in antibody-coated wells. Absorbance was read at 450 nm, and MMP-1 concentrations were normalized to total protein content and quantified from standard curves according to manufacturer's instructions.

7. Semi-quantitative RT-PCR

Total RNA was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and 2 μg RNA was reverse-transcribed using M-MLV reverse transcriptase (Promega, Madison, WI, USA). PCR amplification was performed using Luna Universal qPCR Mix (New England Biolabs, Ipswich, MA, USA) with specific primers for MMP-1, MMP-3, COL1A1, and β-actin (internal control) under the following conditions: 95℃ for 5 min, followed by 30 cycles of 95℃ for 45 s, 60℃ for 60 s, and 72℃ for 45 s, with a final extension at 72℃ for 5 min in TP800 Thermal Cycler Dice™ Real Time System (Takara Bio, Ohtsu, Japan).

8. Western blot analysis

Cells were lysed in RIPA buffer containing protease and phosphatase inhibitors (Thermo Fisher Scientific). Equal amounts of protein (20 μg) were separated by SDS-PAGE and transferred to nitrocellulose membranes (Millipore, Billerica, MA, USA) using Trans-Blot Turbo (Bio-Rad, Hercules, CA, USA). Membranes were blocked with 5% skim milk in TBS-T (Tris-buffered saline containing 0.1% Tween-20) for 1 h and incubated overnight at 4℃ with primary antibodies (1:1000). After washing, membranes were incubated with HRP-conjugated secondary antibodies (1:5000) for 1 h. Bands were visualized using an ECL detection kit (Thermo Fisher Scientific) and quantified by densitometry using ImageJ. Protein expression levels were normalized to β-actin.

9. Statistical analysis

All experiments were performed in triplicate (n = 3). Data were expressed as mean ± standard deviation (SD). Statistical

analyses were conducted using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Differences were considered statistically significant at $p < 0.05$.

RESULTS

1. Cytotoxicity of sesamin in human dermal fibroblasts

The cytotoxicity of sesamin in human dermal fibroblasts (HDFs) was assessed using the MTT assay following treatment with increasing concentrations of sesamin (0, 1, 5, 10, 25, and 50 μM). Cell viability remained above 90% across all concentrations tested, indicating minimal cytotoxicity under the experimental conditions (Fig. 1B). Notably, treatment with the highest concentration (50 μM) maintained statistically full viability relative to untreated control cells, confirming that sesamin is well-tolerated by HDFs at concentrations used in subsequent experiments.

2. Sesamin reduces UVA-induced intracellular ROS generation

Exposure to UVA irradiation (6 J/cm^2) significantly increased intracellular ROS levels in HDFs which were normalized to 100% for easy comparison. Sesamin treatment at concentrations of 25 μM and 50 μM markedly decreased ROS levels to 82.96% and 75.44%, respectively (Fig. 2A). Lower concentrations of sesamin (5 μM) produced only modest reductions that were not statistically significant. The reductions observed at 25 μM and 50 μM were statistically significant at $p < 0.01$ indicating that sesamin effectively attenuates UVA-induced oxidative stress in HDFs in a dose-dependent manner.

3. Inhibition of UVA-induced MMP-1 secretion by sesamin

MMP-1 secretion, evaluated using ELISA, was significantly elevated upon UVA exposure, increasing from 9.58 ng/ml in untreated controls to 14.68 ng/ml. Treatment with sesamin led to a dose-dependent suppression of MMP-1 levels: 5 μM (13.77 ng/ml), 10 μM (13.14 ng/ml), and 50 μM (9.87 ng/ml) (Fig. 2B). The inhibitory effect at 50 μM was statistically significant ($p < 0.01$), demonstrating that sesamin can effectively counteract UVA-induced MMP-1 overproduction.

4. Modulation of MMP gene expression

Semi-quantitative RT-PCR analysis revealed that UVA irradiation upregulated mRNA levels of MMP-1, MMP-3 and MMP-9 (set as 1.0 in control cells). Treatment with 50 μM sesamin reduced MMP-1 expression to 0.23-fold and MMP-3 to 0.14-fold relative to UVA-only samples (Fig. 3). Although a decrease in MMP-9 expression was observed, it did not reach statistical significance compared to UVA controls. These results suggest that sesamin selectively downregulates MMPs most relevant to ECM degradation during photoaging.

5. Sesamin restores collagen and suppresses MMP protein levels

Western blot analysis confirmed that UVA-induced upregulation of MMP-1 and MMP-3 proteins was significantly reduced

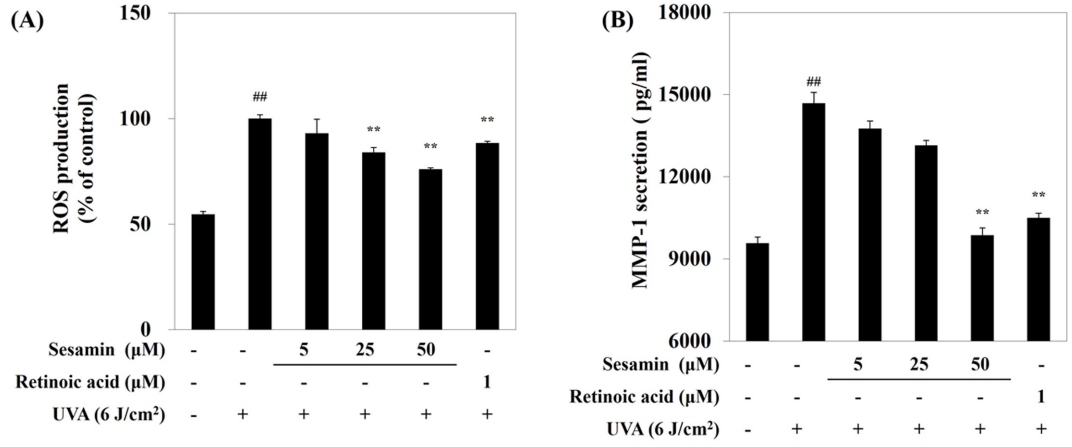

Fig. 2. Sesamin reduces intracellular ROS generation and MMP-1 secretion in UVA-stimulated HDFs. (A) Intracellular ROS levels measured by DCFH-DA fluorescence assay in HDFs exposed to UVA (6 J/cm^2) and treated with sesamin. (B) ELISA quantification of MMP-1 secretion from HDFs following UVA exposure with or without sesamin treatment. Data are shown as mean ± SD (n = 3). $^{\#\#}p < 0.01$ vs. blank group; $^{**}p < 0.01$ vs. UVA-only control.

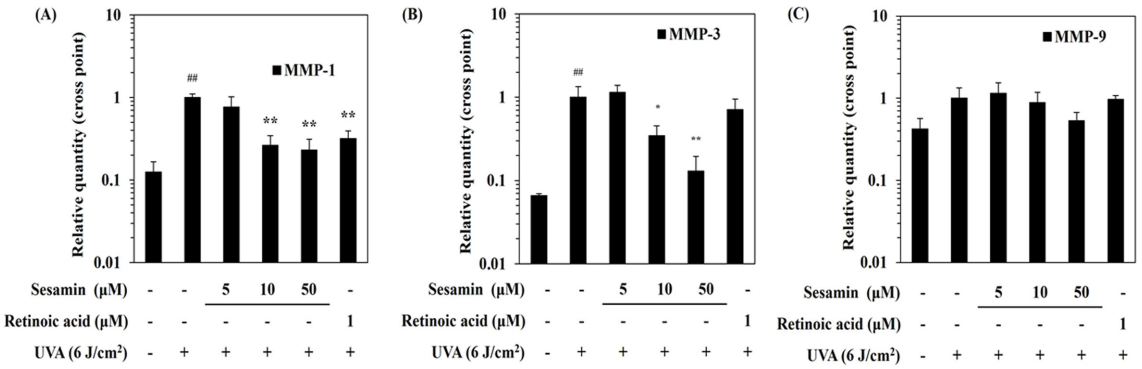

Fig. 3. Sesamin modulates gene expression of MMPs. Relative mRNA expression levels of (A) MMP-1, (B) MMP-3, and (C) MMP-9 in UVA-stimulated HDFs as determined by qRT-PCR. Sesamin reduced MMP gene expression β-actin was used as a loading control. Data are shown as mean ± SD (n = 3). $^{\#}p < 0.05$ vs. blank group; $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. UVA-only control.

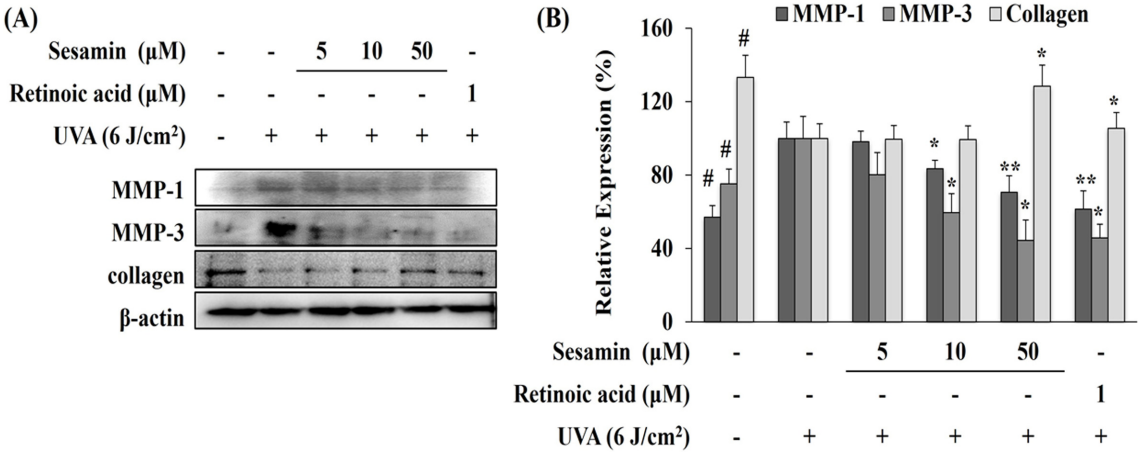

Fig. 4. Sesamin modulates protein expression of MMPs in UVA-stimulated HDFs. (A) Representative Western blot images of MMP-1, MMP-3 and collagen in UVA-stimulated HDFs with or without sesamin treatment. (B) Densitometric quantification of protein expression levels normalized to β-actin. Data are shown as mean ± SD (n = 3). $^{\#}p < 0.05$ vs. blank group; $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. UVA-only control.

following sesamin treatment at 5, 10, and 50 μM (Fig. 4A). Concurrently, collagen I expression, which was suppressed to approximately 82% by UVA irradiation, was partially restored following sesamin treatment. At 50 μM, MMP-1 and MMP-3 protein levels decreased to approximately 42% and 23%, respectively, while collagen I expression recovered to 72% of control levels Fig. 4B. These findings indicate that sesamin protects ECM integrity by suppressing MMP protein expression and preserving collagen content.

6. Inhibition of MAPK signaling by sesamin

UVA irradiation induced phosphorylation of MAPK proteins, including ERK, JNK, and p38, which are key regulators of MMP expression Fig. 5A. Treatment with 50 μM sesamin significantly suppressed phosphorylation levels of ERK, JNK, and p38 by 52%, 49%, and 59%, respectively (Fig. 5B). This result indicates that sesamin's inhibitory effect on MMP expression may be mediated through modulation of MAPK signaling pathways, contributing to its overall photoprotective effect.

DISCUSSION

In this study, sesamin isolated from *A. littoricola* demonstrated a protective effect against UVA-induced damage in human dermal fibroblasts, as assessed by viability, ROS production, MMP-1 release and expression and MAPK pathway modulation. These findings add to the already present body of knowledge on sesamin and on plant-based anti-photoaging agents using *in vitro* dermal fibroblast models.

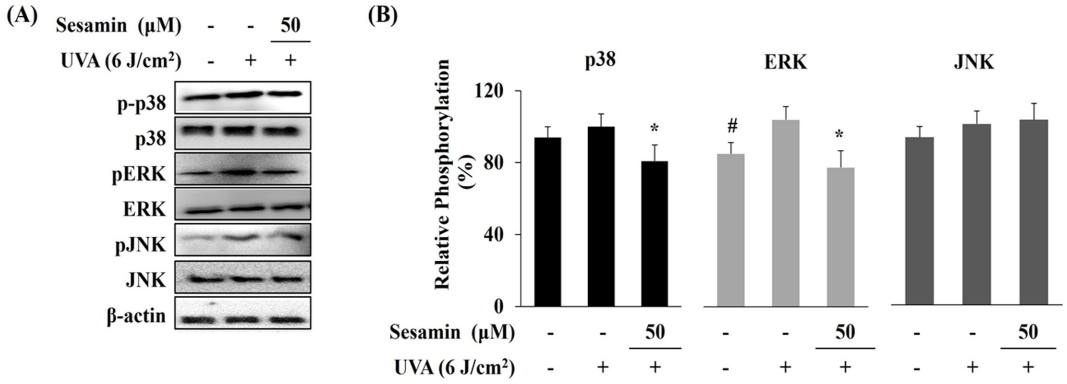

Fig. 5. Sesamin modulates MAPK pathway phosphorylation in UVA-stimulated HDFs. (A) Representative Western blot images of phosphorylated ERK (p-ERK), JNK (p-JNK), and p38 (p-p38) in UVA-stimulated HDFs treated with or without sesamin. (B) Densitometric quantification of MAPK phosphorylation levels normalized to β-actin. Data are presented as mean ± SD (n = 3). #$p < 0.05$ vs. blank control; *$p < 0.05$ vs. UVA-only control.

Current results align with prior reports of sesamin's anti-oxidative effects. For example, sesamin was shown to reduce intracellular ROS after UVB exposure in Hs68 cells, attenuate and enhance TIMP-1 and thereby increasing total collagen content (Lin *et al.*, 2019). In particular, sesamin reduced iNOS and COX-2 expression, inhibited NF-κB translocation, and prevented epidermal hyperplasia and wrinkle formation in hairless mice after chronic UVB exposure.

More recently, a study by Li *et al.* (2024) demonstrated that sesamin attenuated UV-induced keratinocyte injury via reducing MMP-1 and MMP-9 in keratinocytes. The mechanistic motif of MAPK modulation (especially JNK/p38) via suppression of phosphorylation appears consistent with other sesamin reports. Thus, current data reinforces and extends these reports by demonstrating that in dermal ECM-relevant cells, sesamin could suppress UVA-induced MMP-1 expression (both secreted and mRNA), reduce ROS and down-modulate phosphorylated ERK, JNK and p38. This suggests that sesamin's photo-protective effect is present across different skin cell types (keratinocyte, fibroblast) across UV spectra (UVB, UVA).

The present findings strengthen the established photoaging progression in which ultraviolet irradiation elevates intracellular ROS levels, leading to activation of the MAPK family (ERK, JNK, and p38). This canonical signaling pathway is widely accepted as a standard pathway to look into in photoaging research. Accordingly, MAPKs along with their downstream targets MMP-1, MMP-3, and collagen were specifically selected in this study to evaluate the protective mechanism of sesamin against UV-induced skin aging. Hence, this characterized cascade provides the mechanistic basis for interpreting current observations that sesamin modulates MAPK phosphorylation, downregulates MMP expression, and preserves collagen under UVA exposure (Kuo *et al.*, 2020; Prasanth *et al.*, 2020).

By demonstrating that sesamin treatment reduces ROS generation as assessed by DCFH-DA assay and concomitantly reduces the phosphorylation of MAPKs (ERK, JNK and p38), it was shown that sesamin intervened early in this cascade. The downstream reduction of MMP-1 and preservation of collagen type I or prevention of its degradation further suggest that the upstream inhibition of ROS/MAPK has meaningful ECM outcomes.

Previous studies have reported the protective effects of various natural compounds in UV-induced skin damage models. For example, glycoproteins isolated from sesame seeds were shown to inhibit UV-induced MMP-1 expression, suppress MAPK/AKT activation, and reduce wrinkle formation in hairless mice (Baik *et al.*, 2024). Similarly, carnosine was reported to modulate Nrf2-mediated oxidative stress responses and protect the extracellular matrix in UVA-exposed three-dimensional fibroblast spheroids (Aiello *et al.*, 2022). Collectively, these reports highlight the photoprotective capacity of natural compounds, although direct efficacy comparisons with sesamin are beyond the scope of the present study. A distinguishing aspect of the present study is the direct investigation of sesamin under UVA exposure in human dermal fibroblasts, which reflects the predominant form of solar ultraviolet radiation reaching the dermis and therefore enhances the translational relevance of the current results.

On the other hand, the discovery that sesamin can be found in *A. littoricola* and it exhibits anti-photoaging potential provides

important insights into both undervalued crop utilization and skin health applications. These findings underscore the potential of *A. littoricola* as a bioactive-rich species suitable for development into cosmeceutical resources. From a dermatological standpoint, sesamin or sesamin-enriched extracts may serve as promising candidates for topical or nutraceutical interventions aimed at protecting the skin against photoaging.

While the present work has aforementioned strengths, it was limited to an in vitro fibroblast model under controlled UVA exposure, which does not fully capture the complexity of human skin or chronic UV conditions. Although the present findings provide clear mechanistic evidence for the anti-photoaging effects of sesamin in human dermal fibroblasts, further validation using three-dimensional skin-equivalent models and in vivo systems will be required to confirm its translational potential. Further mechanistic analyses and donor-diverse fibroblast models would clarify pathway involvement and biological variability, while formulation and delivery studies will be essential to ensure stability, skin penetration, and safety for practical applications.

In conclusion, this study showed that sesamin from A. littoricola attenuated UVA-induced ROS generation, MAPK activation (ERK, JNK, p38), MMP-1 overexpression and potentially preserves dermal ECM integrity via collagen maintenance. This builds on prior evidence of sesamin's anti-photoaging effect under UVB and adds a UVA/fibroblast dimension, which increases relevance for dermal photoaging. In addition, results support A. littoricola as a functional medicinal crop species with potential for cosmeceutical development. Future studies should include in vivo validation, chronic exposure models, formulation development and mechanistic research. Nevertheless, it was suggested that sesamin's multi-target mechanism on ROS scavenging, MAPK inhibition and MMP rduction offers a favorable profile and merits further development.

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