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Potato Peel Extract Attenuates the Reduction in Type I Collagen in Normal Human Dermal Fibroblast Cells Induced by Oxidative Stress

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Abstract

Oxidative stress contributes to skin aging. Potato peels contain various functional components, and potato peel extract (PPE) promotes type I collagen synthesis in normal human dermal fibroblasts (NHDFs). In this study, we investigated the effects of PPE under oxidative stress conditions. NHDFs were exposed to hydrogen peroxide, followed by treatment with PPE prepared by ethanol extraction of potato peel residues. Exposure to hydrogen peroxide reduced type I collagen secretion in NHDF. However, this reduction was suppressed by the addition of PPE. The expression level of the type I collagen gene, *COL1A2*, showed a tendency to improve with PPE treatment. The promotion of collagen synthesis by PPE appears to involve the TGFBR2, ERK, and Akt signaling pathways. PPE also reduced the increased production of MMP-1 induced by hydrogen peroxide exposure and suppressed the upregulation of AP-1, a transcription factor upstream of MMP-1. While PPE exhibited antioxidant activity at high concentrations, it did not reduce intracellular ROS levels at the concentrations used for cell treatment. These findings suggest that PPE suppresses the reduction in collagen levels under oxidative stress conditions by promoting type I collagen synthesis and modulating MMP-1/AP-1/TIMP-1-related pathways, suggesting decreased collagen breakdown under oxidative stress conditions. PPE may serve as a potential material for maintaining collagen levels.

Keywords: potato peel extract; oxidative stress; type I collagen; MMP-1; TGF-β signaling; skin aging

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1. Introduction

The skin, the largest organ of the human body, acts as a vital barrier against environmental stressors such as ultraviolet (UV) radiation, pollutants, and oxidative damage [1,2]. Beyond its protective role, the skin is essential for maintaining physiological homeostasis and appearance [1]. Skin aging, particularly photoaging caused by chronic UV exposure, results in structural and functional deterioration of the dermal extracellular matrix [3,4], leading to visible changes such as wrinkles, sagging, and loss of elasticity [5,6]. These changes significantly impact perceived age and psychosocial well-being, underscoring the need for effective strategies to prevent or mitigate skin aging [7,8].

The dermis plays a critical role in maintaining skin firmness, elasticity, and moisture retention [9]. Collagen fibers, the most abundant components of the dermis, provide structural support to the skin [9]. Type I collagen accounts for nearly 90% of total collagen and is primarily responsible for the mechanical strength of the skin [10]. In both

intrinsic aging and photoaged skin, collagen fibers are reduced due to decreased collagen synthesis by fibroblasts and increased collagen degradation mediated by matrix metalloproteinase-1 (MMP-1) [11,12]. This imbalance in collagen metabolism is a central driver of skin aging. Among collagen-degrading enzymes, MMP-1 plays an important role in the degradation of type I collagen in human skin and is closely associated with skin aging and photoaging [13,14]. Therefore, MMP-1 was selected in this study as a representative marker related to collagen degradation.

Oxidative stress, driven by reactive oxygen species (ROS) generated from UV exposure and other environmental factors, is recognized as a key driver of skin aging. ROS activate intracellular signaling pathways that upregulate MMP expression and suppress collagen synthesis. Specifically, ROS-mediated activation of transcription factors such as activator protein-1 (AP-1) enhances MMP-1 expression while inhibiting transforming growth factor (TGF)-β signaling, which is essential for collagen production [4,15,16]. Accordingly, plant-derived ingredients with antioxidant and anti-photoaging properties have attracted increasing attention for their potential applications in cosmetic formulations [2].

Potato (*Solanum tuberosum* L.) peels are rich in phenolic compounds such as chlorogenic acid, as well as flavonoids like catechin and rutin [17,18], which have been reported to exhibit antioxidant activity and MMP-1 inhibitory effects [19–21]. As a byproduct of potato processing, potato peel extract (PPE) has garnered significant interest as a sustainable and value-added functional ingredient for cosmetic and skin health applications. Our previous studies demonstrated that PPE promotes type I collagen synthesis in normal human dermal fibroblasts (NHDFs) via TGF-β receptors and the extracellular signal-regulated kinase (ERK)/protein kinase B (Akt) pathway [22].

However, in addition to the decline in collagen synthesis, increased collagen degradation due to elevated MMP-1 levels is also a critical factor in skin aging [10]. Based on the properties of its phenolic constituents [19,23], PPE is hypothesized to not only promote collagen synthesis but also inhibit MMP-1-mediated collagen degradation. Nevertheless, the effects of PPE on MMP-1-mediated collagen degradation, particularly under oxidative stress conditions, remain unclear. Furthermore, it is not fully understood whether PPE can simultaneously regulate both the synthesis and degradation of collagen in a physiologically relevant oxidative stress environment. Although UV irradiation is an important cause of photoaging, H_2O_2 was used in this study because it enables direct evaluation of oxidative stress-induced changes in dermal fibroblasts under in vitro conditions.

Therefore, in this study, we investigated the effects of PPE on type I collagen synthesis and degradation in NHDFs under oxidative stress conditions induced by hydrogen peroxide, a widely used model of ROS-mediated cellular damage. Specifically, by evaluating both collagen production and MMP-1 expression under ROS-induced conditions, we aimed to clarify the dual regulatory role of PPE in collagen metabolism with relevance to its potential application in skin anti-aging strategies.

2. Materials and Methods

2.1. Preparation of PPE

Potato (*Solanum tuberosum* L., cv. Kitahime) peels were collected and dried at 60 °C for one week. The dried peels were extracted with 50% (*v*/*v*) ethanol (30 mg of peel per sample) and incubated at room temperature (22–25 °C) for one week. The extraction period of one week was selected to allow sufficient extraction of a broad range of components from potato peel residues under room temperature conditions. The extract was filtered and concentrated using a centrifugal evaporator (NVC-1100, EYELA, Tokyo, Japan). PPE was stored at −80 °C until use.

2.2. Cell Culture

NHDFs were purchased from Kurabo (Osaka, Japan) and cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma-Aldrich, St. Louis, MO, USA) supplemented with 5% fetal bovine serum (FBS; Biowest, Nuaillé, France) at 37 °C in a humidified atmosphere containing 5% CO_2. For PPE treatment, NHDFs were incubated with PPE at a concentration of 15 μg/mL for 24 h, after which cells and culture supernatants were collected for analysis. The PPE concentration used in this study was selected based on preliminary experiments and previous findings showing collagen-promoting activity of PPE. In addition, a neutral red uptake assay using NHDFs was performed as a preliminary assessment of cell viability, and 15 μg/mL PPE, which maintained cell viability above 90%, was used in the subsequent experiments (Supplementary Figure S1). For pathway inhibition assays, the ERK inhibitor U0126 (10 μM) and the PI3K/Akt inhibitor LY294002 (10 μM) (both from Cell Signaling Technology, Danvers, MA, USA) were used.

2.3. ELISA

NHDFs were detached using 0.25% Trypsin–EDTA (Gibco, Invitrogen, Carlsbad, CA, USA) and seeded into 96-well plates at a density of 2.0×10^4 cells/well. After 24 h, the culture medium was replaced with 300 μM H_2O_2 diluted in HBSS(+) (with Ca^{2+} and Mg^{2+}; Wako, Osaka, Japan), and the cells were incubated for 1 h. Preliminary experiments confirmed that treatment with 300 μM H_2O_2 for 1 h maintained approximately 70% cell viability in NHDFs (Supplementary Figure S2). For the control group, HBSS(+) without H_2O_2 was used. The concentration of H_2O_2 was verified spectrophotometrically at 240 nm using an extinction coefficient of 0.041 $mM^{-1} \cdot cm^{-1}$. After H_2O_2 treatment, the solution was replaced with 0.5% FBS/DMEM containing PPE at a concentration of 15 μg/mL, which was dissolved in 50% (*v*/*v*) ethanol and diluted in culture medium (final ethanol concentration was 1%), and the cells were further incubated for 24 h. Control cells were treated with an equivalent concentration of ethanol (1%). Culture supernatants were collected and analyzed by ELISA. Type I collagen levels were quantified as previously described [17]. MMP-1 levels were quantified using a commercial ELISA kit (Human MMP-1 ELISA Kit, Sigma-Aldrich, RAB0361-1KT). The total protein content was measured using a BCA protein assay kit (Thermo Fisher Scientific, Waltham, MA, USA), and the secretion levels were normalized to the total protein. Intracellular ROS levels were evaluated using DCFH-DA fluorescence after treatment with PPE at concentrations of 10 and 15 μg/mL, as described in Supplementary Figure S3.

2.4. Quantitative PCR (qPCR)

NHDFs were seeded into 96-well plates at a density of 2.0×10^4 cells/well. After 24 h, the culture medium was replaced with 300 μM H_2O_2 diluted in HBSS(+) (with Ca^{2+} and Mg^{2+}; Wako, Osaka, Japan), and the cells were incubated for 1 h. For the control group, HBSS(+) without H_2O_2 was used. The concentration of H_2O_2 was verified spectrophotometrically at 240 nm using an extinction coefficient of 0.041 $mM^{-1} \cdot cm^{-1}$. After H_2O_2 treatment, the solution was replaced with 0.5% FBS/DMEM containing PPE at a concentration of 15 μg/mL, which was dissolved in 50% (*v*/*v*) ethanol and diluted in culture medium (final ethanol concentration was 1%), and the cells were further incubated for 24 h. Control cells were treated with an equivalent concentration of ethanol (1%). Total RNA extraction and cDNA synthesis were performed using the SuperPrep Cell Lysis & RT Kit for qPCR (Toyobo, Osaka, Japan) according to the manufacturer's protocol. qPCR was conducted as previously described [17]. The primer sequences used in this study are listed in Table 1.

Table 1. Target genes and primer sequences used for qPCR.

Gene	Primer Sequence (Sense)	Antisense
COL1A1	GACATGTTCAGCTTTGTGGAC	TTCTGTACGCAGGTGATTGG
COL1A2	GTGAGAGAGGAGTTGTTGGAC	CCTTCAATCCATCCAGACCAT
TGFβR1	GGTCTTGCCCATCTTCACA	GCCAGTCCTAAGTCTGCAAT
TGFβR2	TGACAACCAGAAATCCTGCAT	CTGTCTCTAGTGTTATGTTCTCGTC
AP-1	GACGGACTGTTCTATGACTGC	TGCTCTGTTTCAGGATCTTGG
TIMP-1	CCTTCTGCAATTCCGACCT	GCTTGGAACCCTTTATACATCTTG
GAPDH	AGGGTGGTGGACCTCAT	TGAGTGTGGCAGGGACT

2.5. Statistical Analysis

Data are presented as mean ± SD. Statistical analyses were performed using GraphPad Prism 8.4.3. One-way ANOVA was used to analyze ELISA and qPCR data, followed by Dunnett's test for multiple comparisons. Statistical significance was set at $p < 0.05$, and trend-level significance was defined as $p < 0.10$. All experiments were performed in triplicate.

3. Results

3.1. PPE Suppresses the Reduction in Type I Collagen Under Hydrogen Peroxide Exposure Subsection

In NHDFs exposed to hydrogen peroxide (H_2O_2), the secretion of type I collagen into the culture supernatant was significantly reduced (−/−: 1.74 ± 0.10, +/−: 0.84 ± 0.08) (Figure 1A). However, the addition of potato peel extract (PPE) suppressed the reduction in type I collagen secretion (+/+: 1.62 ± 0.06). Subsequently, the expression levels of type I collagen synthesis-related genes (*COL1A1* and COL1A2) were analyzed. Under H_2O_2 exposure, the addition of PPE showed a tendency to improve the reduced expression of the *COL1A2* gene (*COL1A1*: −/−: 1.00 ± 0.10, +/−: 0.51 ± 0.03, +/+: 0.56 ± 0.06; *COL1A2*: −/−: 1.00 ± 0.12, +/−: 0.19 ± 0.04, +/+: 0.44 ± 0.06) (Figure 1B).

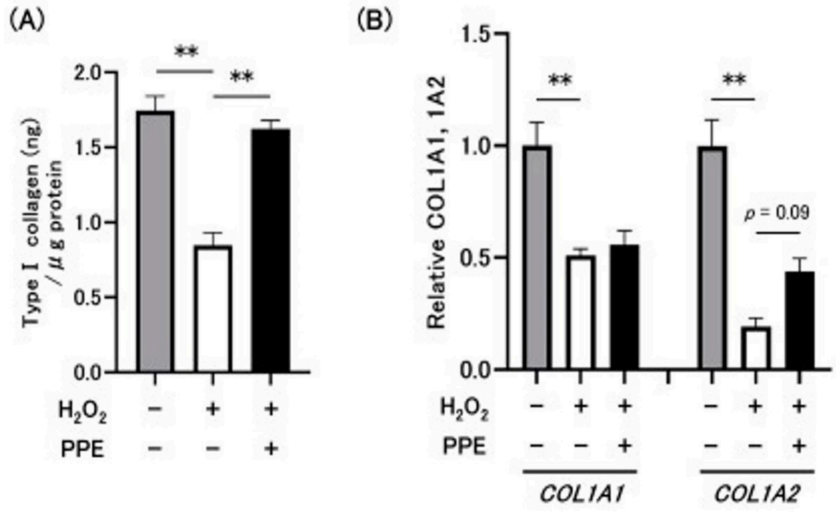


Figure 1. Potato peel extract (PPE) attenuates hydrogen peroxide (H_2O_2)-induced reduction in type I collagen in normal human dermal fibroblasts (NHDFs). (**A**) Type I collagen secretion levels were measured by ELISA. (**B**) Relative mRNA expression levels of *COL1A1* and *COL1A2* were analyzed by quantitative PCR (qPCR). Data are presented as mean ± SD ($n = 3$). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. ** $p < 0.01$. A p-value < 0.10 was considered indicative of a trend toward significance; $p = 0.09$ indicates a trend.

3.2. Possible Involvement of TGFBR2, ERK, and Akt Pathways in PPE-Induced Type I Collagen Synthesis

Our previous studies suggested that PPE promotes type I collagen synthesis through *TGFBR2*-mediated ERK and Akt signaling pathways. First, the expression levels of the *TGFBR1* and *TGFBR2* genes were analyzed. Under H_2O_2 exposure, the addition of PPE improved the reduced expression of the *TGFBR2* gene (*TGFBR1*: −/−: 1.00 ± 0.02, +/−: 0.43 ± 0.04, +/+: 0.48 ± 0.05; *TGFBR2*: −/−: 1.00 ± 0.05, +/−: 0.43 ± 0.01, +/+: 0.55 ± 0.01) (Figure 2A).

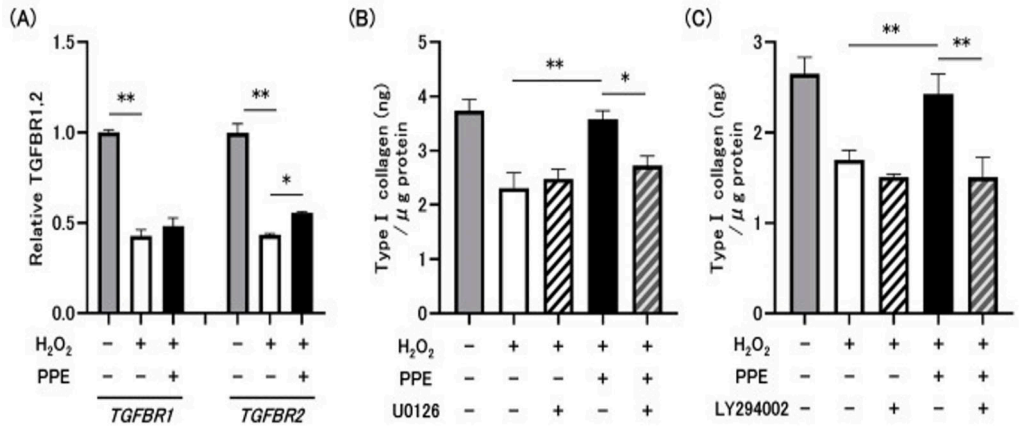


Figure 2. Possible involvement of *TGFBR2*, ERK, and Akt pathways in PPE-induced type I collagen synthesis under oxidative stress conditions. (**A**) Relative mRNA expression levels of *TGFBR1* and *TGFBR2* in NHDFs exposed to H_2O_2 with or without PPE treatment were analyzed by qPCR. (**B**) Type I collagen secretion levels were measured by ELISA in the presence or absence of PPE and the ERK inhibitor U0126. (**C**) Type I collagen secretion levels were measured by ELISA in the presence or absence of PPE and the Akt inhibitor LY294002. Data are presented as mean ± SD ($n = 3$). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. * $p < 0.05$; ** $p < 0.01$.

Next, the involvement of the ERK pathway was investigated using the ERK inhibitor U0126. While the addition of PPE under H_2O_2 exposure restored type I collagen secretion, the addition of the ERK inhibitor abolished the restorative effect of PPE (−/−/−: 3.74 ± 0.20, +/−/−: 2.31 ± 0.28, +/−/+: 2.48 ± 0.17, +/+/−: 3.58 ± 0.16, +/+/+: 2.72 ± 0.18) (Figure 2B). Similarly, the involvement of the Akt pathway was examined using the Akt inhibitor LY294002. Under H_2O_2 exposure, the addition of PPE restored type I collagen secretion, but the addition of the Akt inhibitor abolished the restorative effect of PPE (−/−/−: 2.65 ± 0.18, +/−/−: 1.70 ± 0.10, +/−/+: 1.51 ± 0.03, +/+/−: 2.43 ± 0.22, +/+/+: 1.51 ± 0.22) (Figure 2C).

3.3. PPE Suppresses the Increase in MMP-1 Production Induced by Hydrogen Peroxide Exposure

The amount of type I collagen is maintained by the balance between synthesis and degradation in fibroblasts, with matrix metalloproteinase-1 (MMP-1) being a major factor responsible for collagen degradation. In this study, exposure to hydrogen peroxide (H_2O_2) significantly increased MMP-1 production, but the addition of potato peel extract (PPE) suppressed this increase (−/−: 0.007 ± 0.0003, +/−: 7.80 ± 0.45, +/+: 5.23 ± 0.43) (Figure 3A). It has been suggested that intracellular reactive oxygen species (ROS) are involved in the H_2O_2-induced increase in MMP-1 production. To investigate the antioxidant activity of PPE, assays for H_2O_2 scavenging, superoxide elimination, and intracellular ROS reduction were conducted. While high concentrations of PPE exhibited antioxidant activity, PPE at the concentration used for cell treatment (10 μg/mL) did not significantly affect intracellular ROS reduction (Figure S1).

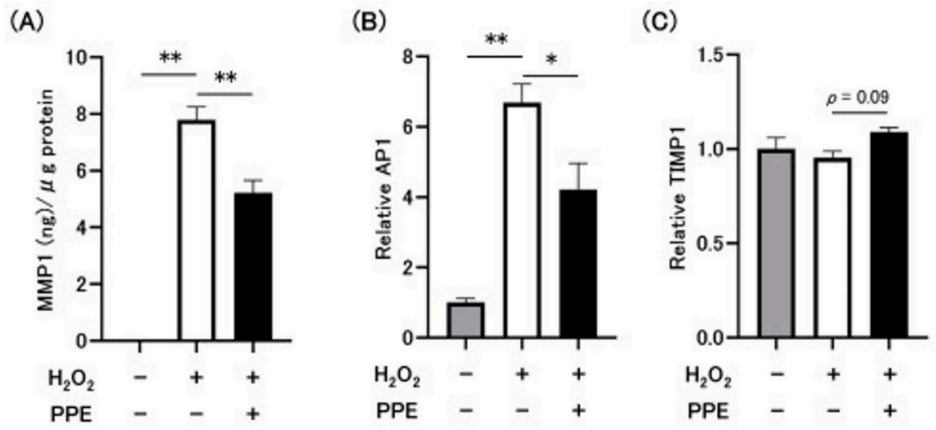


Figure 3. PPE suppresses H_2O_2-induced MMP-1 production and modulates related gene expression. (**A**) MMP-1 secretion levels in NHDFs exposed to hydrogen peroxide (H_2O_2) with or without PPE treatment were measured by ELISA. (**B**) Relative mRNA expression levels of AP-1 were analyzed by quantitative PCR (qPCR). (**C**) Relative mRNA expression levels of TIMP-1 were analyzed by qPCR. Data are presented as mean ± SD (n = 3). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. * $p < 0.05$; ** $p < 0.01$. A p-value < 0.10 was considered indicative of a trend toward significance; $p = 0.09$ indicates a trend.

Next, the expression levels of AP-1, a transcription factor upstream of MMP-1, were analyzed. H_2O_2 exposure significantly increased AP-1 gene expression, but the addition of PPE suppressed this increase (−/−: 1.00 ± 0.12, +/−: 6.69 ± 0.53, and +/+: 4.22 ± 0.74) (Figure 3B). Furthermore, the expression levels of TIMP-1, a gene encoding an inhibitor of MMP-1 activity, showed a tendency to increase with PPE treatment compared to H_2O_2 exposure alone (−/−: 1.00 ± 0.06, +/−: 0.95 ± 0.04, +/+: 1.09 ± 0.02) (Figure 3C).

4. Discussion

In this study, we demonstrated the potential of potato peel extract (PPE) to mitigate the reduction in type I collagen levels in normal human dermal fibroblasts (NHDFs) exposed to hydrogen peroxide (H_2O_2), a widely used oxidative stress model. These results suggest that the effects of PPE may involve, at least in part, promotion of collagen synthesis via the TGFBR2–ERK/Akt pathway and modulation of MMP-1-related pathways associated with collagen degradation.

Transforming growth factor-beta (TGF-β) signaling is a key regulator of extracellular matrix homeostasis, transmitting signals through a heterocomplex composed of type I and type II TGF-β receptors on the cell membrane [24]. TGF-β receptor type II (TGFBR2) is an essential factor that initiates downstream signaling by phosphorylating and activating the type I receptor, thereby serving as the starting point of TGF-β signaling [25]. TGF-β signaling is transmitted not only via the Smad-dependent pathway but also through Smad-independent pathways, including MAP kinase (MAPK), such as ERK and phosphatidylinositol-3-kinase (PI3K)/Akt [25,26]. In aged skin and photoaged skin, the expression of *TGFBR2* decreases, leading to reduced responsiveness to TGF-β and consequently a decline in collagen production capacity [27]. In this study, PPE improved the reduced expression of *TGFBR2* under H_2O_2 exposure, and the collagen synthesis-promoting effect of PPE was abolished by the co-treatment with ERK and Akt inhibitors. These findings suggest that the TGFBR2–ERK/Akt pathway plays a critical role in the effects of PPE, even under oxidative stress conditions. PPE may restore collagen synthesis signaling impaired by oxidative stress, thereby contributing to extracellular matrix maintenance.

The PI3K/Akt and MAPK/ERK signaling pathways are not only involved in the regulation of collagen synthesis but also play important roles in skin aging [6,28]. It has

been reported that these signaling pathways decline in aged and photoaged skin, and their functional impairment contributes to the manifestation of aging phenotypes [29,30]. Oxidative stress is involved in such signal reduction, and the effectiveness of components with antioxidant properties has been widely studied. For example, vitamin C has been reported to increase the expression of type I and type III collagen in human skin [31]. Additionally, chlorogenic acid has a known suppressive effect on photoaging in skin fibroblasts [32]. Previous studies have reported that rutin-containing extracts and catechin-related polyphenols modulate collagen metabolism and extracellular matrix degradation under oxidative stress or photoaging-related conditions [20,21]. In this study, PPE was confirmed to contain vitamin C and chlorogenic acid and ferulic acid, caffeic acid, and protocatechuic acid were also detected under the experimental conditions used in this study (Supplementary Table S1); however, at the concentrations used for cell treatment, these components did not reduce intracellular ROS (Supplementary Figure S3). Despite the lack of direct ROS-scavenging activity, PPE promoted type I collagen synthesis in NHDFs via the activation of the PI3K/Akt and MAPK/ERK signaling pathways under H_2O_2 exposure conditions. These results suggest that PPE may help maintain skin homeostasis under oxidative stress conditions even without directly reducing intracellular ROS levels.

The amount of type I collagen is also influenced by degradation pathways, with MMP-1 being the primary enzyme responsible for collagen degradation [27,33]. In this study, PPE suppressed the increased production of MMP-1 induced by H_2O_2 exposure and inhibited the upregulation of AP-1, a transcription factor upstream of MMP-1 that is regulated by multiple MAPK signaling pathways [28]. Previous studies have reported that certain plant-derived phenolic compounds can suppress MMP expression and extracellular matrix degradation under oxidative stress or photoaging conditions [20,21]. Additionally, TIMP-1, an endogenous inhibitor of MMP activity [34], showed a tendency to increase with PPE treatment. The suppression of AP-1 expression under PPE treatment conditions may contribute to the reduction in MMP-1 levels. These findings suggest that PPE may influence MMP-1-related pathways associated with collagen degradation under oxidative stress conditions, further supporting its potential as an anti-aging agent.

Several limitations of this study should be noted. First, H_2O_2 was used as an oxidative stress model, but further investigations using models such as UV irradiation, which more closely mimic in vivo conditions, are necessary, as UV exposure is a major contributor to photoaging in human skin. Second, this study was limited to fibroblasts, and the phenotypes in epidermal cells should also be examined to better understand skin aging mechanisms. In addition, only a single PPE concentration and exposure time were evaluated in this study, and further studies examining dose–response relationships, time dependence, and cytotoxicity are needed. Additionally, collagen degradation and MMP-1 activity were not directly measured in this study. Therefore, the effects of PPE on collagen degradation were inferred from changes in MMP-1, AP-1, and TIMP-1 expression. Furthermore, while potato peels contain phenolic compounds such as chlorogenic acid and flavonoids like catechin and rutin, which have been reported to exhibit antioxidant activity and MMP-1 inhibitory effects, the specific active components responsible for the observed effects of PPE remain unidentified [18,19]. The presence of unidentified active constituents represents an important area for future research to elucidate the underlying mechanisms of PPE. Several studies have reported skin-related biological activities of potato-derived extracts and their phenolic constituents. For example, topical formulations containing potato peel extracts have been reported to promote wound healing, fibroblast proliferation, and collagen formation in skin models. In addition, antioxidant properties of potato peel phenolics have been suggested to contribute to skin-protective and wound-healing effects under oxidative stress conditions [18,35]. These findings support the potential applicability

of potato-derived materials in cosmetic and skin-care applications. PPE contains relatively hydrophilic compounds, including chlorogenic acid and ferulic acid, suggesting potential applicability in water-based cosmetic formulations such as lotions. However, the present study focused on the biological effects of PPE at the cellular level, and formulation compatibility and stability in cosmetic products were not evaluated. In addition, although dermal fibroblasts are widely used as an in vitro model for evaluating skin aging and collagen metabolism, the actual penetration of PPE-derived components into the dermal layer following topical application was not evaluated in this study. Further studies using skin penetration models and optimized formulations will be necessary to assess the practical applicability of PPE in cosmetic products.

5. Conclusions

This study demonstrated the potential of potato peel extract (PPE) to suppress the reduction in type I collagen levels under oxidative stress conditions through the promotion of collagen synthesis associated with TGFBR2–ERK/Akt-related pathways and the modulation of MMP-1-related pathways associated with collagen degradation (Figure 4). These findings suggest that PPE may serve as a promising material for maintaining collagen metabolism under oxidative stress conditions in an in vitro skin fibroblast model. Future studies focusing on the identification of PPE's active components and investigations using photoaging models are warranted to further elucidate its mechanisms of action.

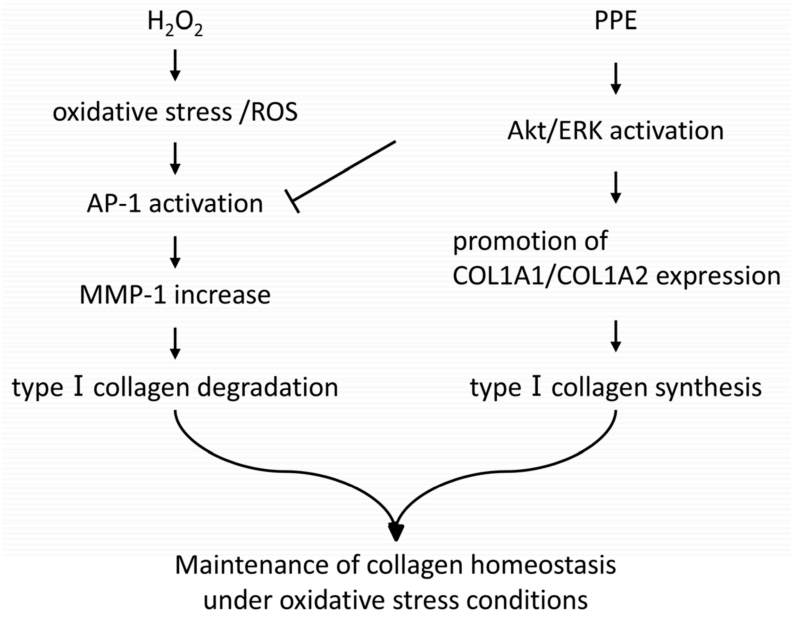


Figure 4. Schematic illustration of the proposed mechanisms by which PPE modulates collagen synthesis- and degradation-related pathways under oxidative stress conditions in NHDFs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cosmetics13030134/s1, Supplementary Figure S1: Cell viability of NHDFs treated with PPE at different concentrations; Supplementary Figure S2: Cell viability of NHDFs following treatment with various concentrations of H_2O_2 for 1 h; Supplementary Figure S3: Antioxidant activity assays of PPE, including H_2O_2 scavenging activity, superoxide elimination activity, and intracellular ROS reduction assay; Supplementary Table S1: Major compounds detected in PPE and estimated concentrations in the culture medium under the experimental conditions used in this study.

Author Contributions: Conceptualization, M.S. and H.M.; investigation, M.S.; data curation, M.S.; visualization, M.S. and H.M.; formal analysis, H.M.; writing—original draft preparation, M.S. and H.M.; writing—review and editing, K.I.; supervision, K.I. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study used commercially available NHDFs purchased from Kurabo (Osaka, Japan), and no human subjects were involved. Therefore, ethical review and approval were not required.

Informed Consent Statement: The study did not involve human subjects; therefore, informed consent was not applicable.

Data Availability Statement: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: Author M.S., H.M., and K.I. were employed by Calbee, Inc. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that this study received funding from Calbee, Inc. The funder had the following involvement with the study: data analysis, interpretation of data, and writing of the manuscript. The funder did not affect the experimental process and results in the study. The funding relationship does not affect the scientific quality of the manuscript.

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