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Unraveling the role of oxidized protein hydrolase in removing glycated and carbonylated proteins in skin

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1. Introduction

Aging is an inevitable and complex physiological process [1]. Visible signs of aging, such as facial wrinkles, sagging, and dullness [2], have long been targeted for prevention and improvement through cosmetics, supplements, and medical aesthetics. Skin aging is accelerated by the accumulation of advanced glycation end products (AGEs) [3] and carbonylated proteins (CPs) [4], which are formed on proteins by combining nonenzymatic glycation [5] and oxidation reactions [6], respectively. Proteins carbonyl-modified by lipid peroxidation-derived aldehydes are classified as advanced lipoxidation end products (ALEs) [7]. Both AGEs and CPs are promoted under an oxidative environment. Although antioxidants have been used to inhibit the formation of AGEs [8], [9] and CPs [7], cosmetic interventions exhibit limited efficacy in removing pre-existing AGEs and CPs from skin.

Oxidized protein hydrolase (OPH) is a serine protease ubiquitously distributed in the cytoplasm of various organisms. It has been identified in animal tissues such as pig liver, rat brain, and human blood [10], where it selectively degrades oxidized and glycated proteins [11]. Analysis of streptozotocin-induced diabetic rats showed that serum OPH activity increased in parallel with elevated blood glucose levels, accompanied by a reduction in carbonyl-modified proteins in blood [12]. Collectively, OPH functions as a bifunctional protease involved in protein quality control, oxidative stress mitigation, and aging process deceleration [13]. Furthermore, OPH-like activity has been detected in the stratum corneum, where it could be involved in the proteolysis of corneum AGEs. This activity declines with age [14], suggesting OPH plays a role in mitigating cutaneous aging phenotypes associated with the accumulation of AGEs and CPs in skin. However, thus far, precise localization and mechanistic understanding of OPH's function in skin remains incomplete. Elucidation of OPH's precise role in cutaneous physiology is essential to establish a therapeutic strategy aimed at intracellular degradation of glycated and carbonylated proteins.

Alteromonas ferment extract (AFE), a bioactive compound derived from fermentation of the marine bacterium *Alteromonas macleodii*, is a complex mixture of polysaccharides, proteins, and other active components [15]. This extract has attracted scientific interest for its potential benefits in skincare, particularly regarding mitigation of pollution-induced skin

damage [16]. In vivo, AFE forms a protective film on the skin that reduces fine particle adhesion and enhances barrier function. In vitro keratinocyte models have revealed that AFE confers protection against ultraviolet-induced lipid peroxidation formation [17], suggesting its significant potential in combating carbonyl reactions.

Here, we systematically investigated the localization characteristics of OPH and its degradation efficacy against AGEs and CPs in skin. We also evaluated the regulatory effects of AFE on OPH expression in vitro, along with its impact on skin conditions including visible aging signs and AGEs fluorescence in vivo. Our findings provide novel insights into molecular mechanisms underlying skin aging and lay theoretical groundwork for anti-aging strategies that enhance endogenous protein clearance systems.

2. Materials and methods

Correlation analysis between AGEs and human skin conditions

Forty-eight Chinese female volunteers aged 20–59 years were recruited with approval from the Scientific Research Ethics Committee. All participants provided informed consent and underwent comprehensive health screening. Measurements were performed on each participant's cheek area; the mean value constituted the final result.

Skin autofluorescence of AGEs (AGEs SAF) was measured using the AGE Reader™, an autofluorescence spectroscopy device. Skin elasticity (R2) was assessed using the Cutometer® MPA 580. Skin yellowness (b* value) was measured using the Skin-Colorimeter CL 400®. The crow's feet wrinkle area was captured using the VISIA-CR imaging system and analyzed with Image-Pro® Plus, Chinese version 7.0.1, for wrinkle area calculation.

Measurement of OPH localization

Human skin tissue samples were obtained from the upper eyelid skin of female patients aged 30–40 years. OPH localization was detected by immunohistochemical (IHC) staining. The primary antibody used was an OPH polyclonal antibody.

Measurement of OPH gene expression

HaCaT (immortalized human keratinocyte) and HSF (immortalized human splenic fibroblast) cells were selected for this study. Cells were cultured for 2 days in high-glucose Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin–streptomycin at 37°C in a 5% CO_2 atmosphere. Total RNA was extracted, and OPH expression levels were measured using reverse transcription (RT)–quantitative polymerase chain reaction (qPCR). Table 1 shows primer sequences used for RT-qPCR.

Table 1. Primer sequences used for RT-qPCR

Gene	Primers (5'-3')
Human-*Gapdh*	F: GGAGCGAGATCCCTCCAAAAT R: GGCTGTTGTCATACTTCTCATGG
Human-*Oph*	F: ATGTCGAGAGTGGCAACATCT R: GCGATTGGTGCAAAAGCG

Measurement of OPH activity

N-acetyl-L-alanine-p-nitroaniline (AAPA) was used as the substrate. HaCaT and HSF cell extracts were mixed with 37.5 mmol/L AAPA (9:1 ratio); the reaction proceeded at 37°C for 1 hour. Changes in reaction solution absorbance were measured at 405 nm. Protein concentrations in cell extracts were determined via bicinchoninic acid. OPH-specific activity was calculated based on the amount of p-nitroaniline generated in the reaction solution.

Measurement of OPH, AGEs, and CPs in OPH knockdown keratinocytes

siRNA-NC and siRNA-OPH were synthesized first. Subconfluent HaCaT cells were transfected with 20 nM siRNA-OPH or siRNA-NC in DMEM using INTERFERin and incubated for 48–72 hours. Cell lysates were collected from each group. OPH-specific activity was measured via procedures described in the measurement of OPH activity above, AGEs and CPs were quantified via enzyme-linked immunosorbent assay kits, following manufacturer protocols.

Evaluation of OPH expression after treatment with 0.1% AFE

AFE (0.1% concentration) was added to subconfluent HaCaT cells in each well, and the cells were cultured for 48 hours. RNA was extracted; this was followed by cDNA synthesis and RT-qPCR. Data were analyzed using the $2^{-\Delta\Delta Ct}$ method, with GAPDH as the internal reference.

Efficacy test with lotion containing 0.1% AFE

This randomized, split-face clinical study involving 33 Chinese female volunteers adhered to the Declaration of Helsinki. The study protocol was approved by the Clinical Research Ethics Committee. Written informed consent was obtained from all participants prior to enrollment. The test product (0.1% AFE) and control product were randomly assigned to the left or right side of the face via computer-generated allocation. Participants applied these products twice daily (morning and evening) for 56 consecutive days. Instrumental assessments were conducted at baseline (W0) and week 8 (W8) on the cheekbone area. AGEs SAF, R2, b* value, and crow's feet wrinkle area were measured via procedures described in the correlation analysis section above.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) of three independent experiments ($n = 3$). All results were statistically analyzed using GraphPad Prism version 9.5.0. For comparisons between two groups, an unpaired two-tailed t-test was used. For multiple group comparisons, one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was utilized. For comparisons involving multiple factors, two-way ANOVA with Bonferroni correction was conducted. The statistical significance threshold was defined as $p < 0.05$ ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$); $^{ns}p \geq 0.05$ indicated no statistically significant difference.

3. Results

Correlation of skin AGEs level with age and skin physiological parameters

A significant positive correlation was observed between skin AGEs autofluorescence (AGEs SAF) and chronological age ($p < 0.01$) (Figure 1a). As age increased, AGEs accumulation in skin also increased, resulting in elevated AGEs SAF.

A significant negative correlation was observed between AGEs SAF and skin elasticity (R2) (Figure 1b), indicating a close relationship between AGEs accumulation and diminished skin mechanical properties. Additionally, skin AGEs SAF showed a significant negative correlation with skin yellowness (b* value) (Figure 1c). Elevated AGEs level corresponded with more yellowish skin tones, supporting the detrimental impact of AGEs accumulation on skin color. Moreover, AGEs SAF exhibited a significant positive correlation with the wrinkle area in the crow's feet region (Figure 1d). Higher AGEs levels were associated with increased wrinkle areas, suggesting that AGEs accumulation is a robust biomarker of skin aging.

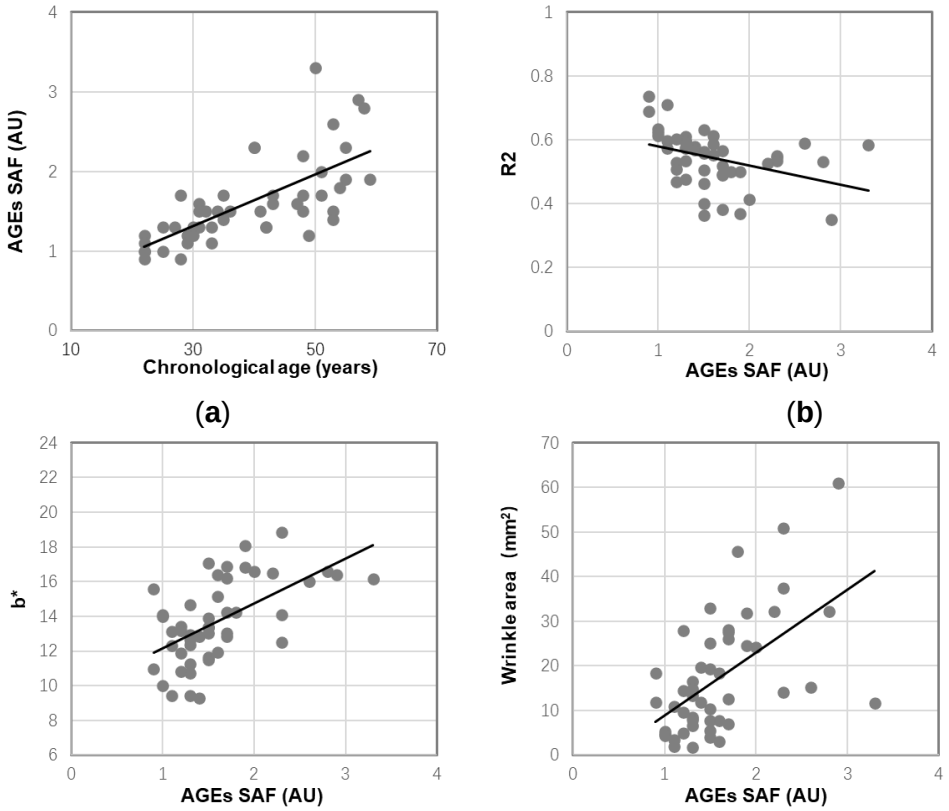
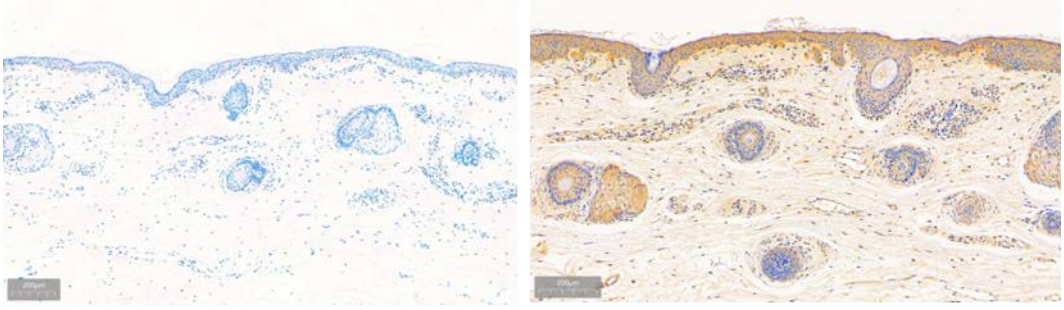


Figure 1. Correlation of AGEs SAF with skin parameters. (a) Chronological age: y = 0.0324x + 0.3377, r = 0.768, $p < 0.01$. (b) Skin elasticity (R2): y = -0.0606x + 0.6403, r = -0.382, $p < 0.01$. (c) Skin yellowness (b*): y = 2.573x + 9.5944, r = 0.579, $p < 0.01$. (d) Crow's feet wrinkle area: y = 14.055x - 5.1181, r = 0.563, $p < 0.01$. Statistical analysis was conducted using Spearman's rank-order correlation coefficient; $n = 48$.

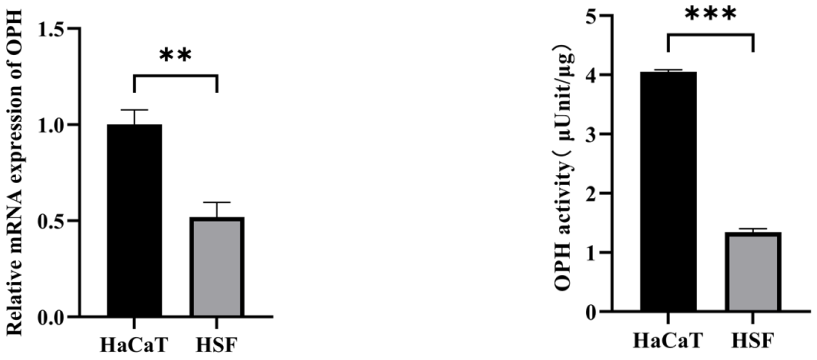
Localization of OPH in skin tissue and OPH gene expression in various skin cells

IHC staining (brownish-yellow coloration) revealed OPH expression in healthy human skin tissue (Figure 2b). Staining intensity differed between the epidermal and dermal layers; the epidermis exhibited darker brown, whereas the dermis displayed lighter brown. The negative control (NC) group—lacking the primary antibody—did not show obvious brown staining, excluding the possibility of false-positive results (Figure 2a).

Subsequently, we evaluated OPH expression and activity in HaCaT cells derived from the epidermis and HSF cells derived from the dermis. The mRNA expression levels of OPH were significantly higher in HaCaT cells than in HSF cells (Figure 2c), indicating more active OPH gene expression in epidermal cells. Furthermore, OPH enzymatic activity was significantly higher in HaCaT cells than in HSF cells (Figure 2d).



(a) (b)



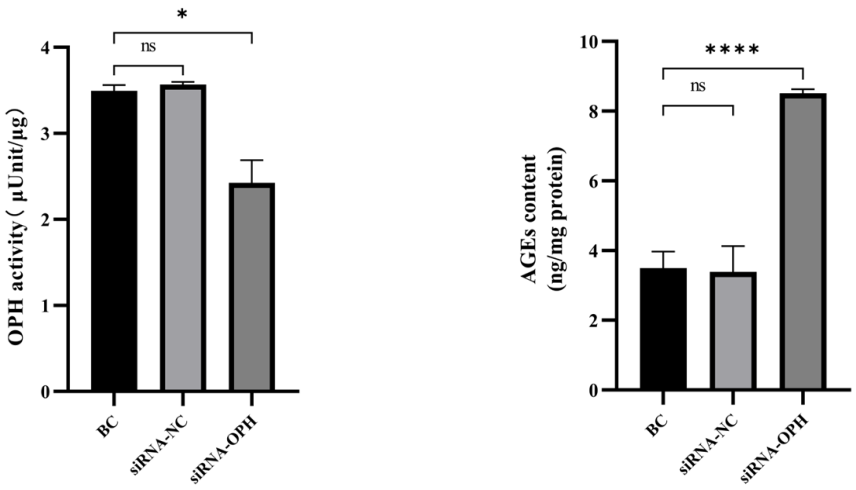
(**c**) (**d**)

Figure 2. Localization and expression of OPH in skin tissue and various skin cell types. (a) NC: IHC staining without OPH polyclonal antibody. (b) IHC staining of human skin tissue. (c) OPH mRNA expression levels in HaCaT and HSF cells. (d) OPH enzymatic activity in HaCaT and HSF cells. ***p* < 0.01, ****p* < 0.001. Results are presented as mean ± SD, *n* = 3.

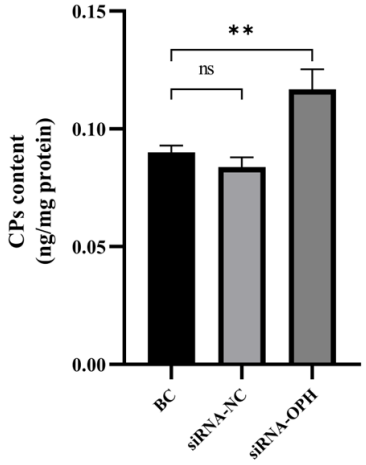
Effect of OPH gene knockdown in HaCaT cells

We evaluated the effect of siRNA on OPH activity in HaCaT cells (Figure 3a). Compared with the blank control group, OPH activity was similar in the siRNA-NC group. However, OPH activity was significantly lower in the siRNA-OPH group than in the blank control group.

As shown in Figure 3b, AGEs content was significantly higher in the siRNA-OPH group than in the blank control group, whereas no significant difference was observed in the siRNA-NC group. Similarly, Figure 3c shows that CPs content was significantly higher in the siRNA-OPH group than in the blank control group. In summary, OPH activity exhibited a positive correlation with OPH gene expression, whereas AGEs and CPs levels showed a negative correlation with OPH gene expression.



(**a**) (**b**)



(**c**)

Figure 3. OPH activity, AGEs content, and CPs content in HaCaT cells. (a) OPH activity in each group. (b) AGEs content in each group. (c) CPs content in each group. BC denotes blank control, $^{ns}p \geq 0.05$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$. Results are presented as mean ± SD, $n = 3$.

Effect of 0.1% AFE on OPH expression

Treatment of HaCaT cells with 0.1% AFE resulted in substantial OPH upregulation relative to the blank control group (Figure 4). Therefore, AFE may promote OPH expression in epidermal cells.

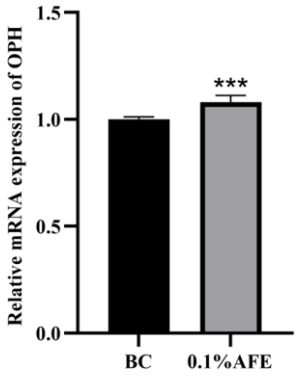


Figure 4. Effect of 0.1% AFE on OPH expression in HaCaT cells. BC denotes blank control, $^{***}p < 0.001$. Results are presented as mean ± SD, $n = 3$.

In vivo effects of 0.1% AFE

The change in AGEs SAF was greater in the 0.1% AFE group than in the control group ($p < 0.001$) (Figure 5a). Skin elasticity (R2) at W8 was also greater in the 0.1% AFE group ($p < 0.001$) (Figure 5b). Notably, the decrease in skin yellowness (b* value) at W8 was greater in the 0.1% AFE group ($p < 0.001$) (Figure 5c). Finally, the crow's feet wrinkle area was smaller in the 0.1% AFE group relative to the control group at W8 ($p < 0.001$) (Figure 5d).

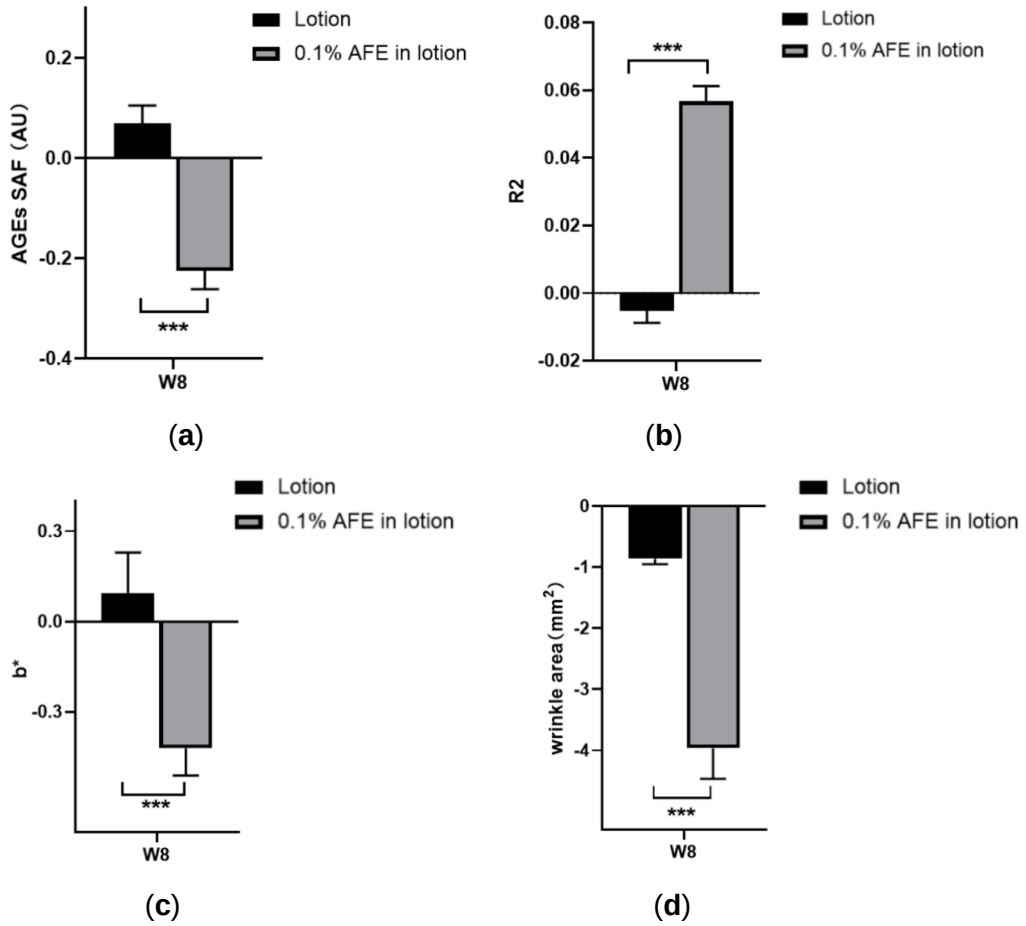


Figure 5. Changes in skin physiological parameters after application of control lotion and 0.1% AFE in lotion between W0 and W8. (a) AGEs SAF. (b) Skin elasticity (R2). (c) Skin yellowness (b* value). (d) Crow's feet wrinkle area. ***$p < 0.001$. Results are presented as mean ± SD, $n = 33$.

4. Discussion

Current strategies to manage age-related accumulation of AGEs and CPs in skin primarily focus on prevention, with limited emphasis on existing AGEs and CPs. Our novel strategy for AGEs and CPs degradation targets intracellular pathways by activating skin OPH.

To assess the role of AGEs accumulation in skin aging, we investigated the relationship of AGEs level with chronological age and key skin physiological parameters. This correlation analysis of 48 Chinese individuals demonstrated that age-dependent accumulation of AGEs in skin contributes to multiple aging phenotypes ($p < 0.01$, Figure 1). Significant negative correlations were observed between AGEs level and both skin elasticity (R2) and crow's feet wrinkle area, consistent with previous studies [18], [19], [20]. These findings reflect crosslinking-induced stiffening of the extracellular matrix, in which AGE-modified collagen and elastin reduce dermal recoil capacity. Concurrently, AGEs level showed a significant positive correlation with skin yellowness (b* value), likely because intracellular AGEs promote oxidative stress and activate inflammatory melanogenesis pathways, which contribute to skin-tone alterations [21]. These findings support the use of AGEs as a unified biomarker of skin aging phenotypes and highlight the importance of AGE-degrading agents for effective skin protection.

Through IHC and RT-qPCR analyses, this pioneering study systematically characterized the localization and expression patterns of OPH in the epidermis and dermis, as well as in various skin cell types. The results indicated significantly higher OPH expression in the

epidermis than in the dermis, with particularly strong expression in the epidermal layer. This localization pattern is consistent with functional demands on the epidermis. High epidermal expression of OPH may be associated with its protection against external oxidative and glycation-induced damage. OPH expression was detected in both HaCaT and HSF cells; higher levels were observed in HaCaTs, supporting its critical role in the epidermis. Elevated epidermal expression of OPH holds considerable physiological relevance because the epidermis is a metabolically active tissue for fatty acid processing, continuously exposed to ultraviolet radiation and air pollutants [22]. Considering OPH's ability to degrade glycated and oxidized proteins in various cell types [11], [23], along with its expression in skin cells (e.g., HaCaTs and HSFs), these findings suggest that OPH plays a vital role in degrading glycated and carbonylated proteins in skin.

This study also confirmed the importance of OPH in degrading AGEs and CPs through siRNA-mediated gene silencing. OPH knockdown in HaCaT cells resulted in significant increases in AGEs and CPs, highlighting the role of OPH in protecting skin cells from glycation and oxidative stress. This observation aligns with previous reports concerning OPH-mediated degradation of oxidatively damaged proteins in human erythrocytes [24]. Although prior studies indicated that OPH in renal fibroblasts degrades CPs only under oxidative stress conditions [23], the present findings suggest that OPH in skin maintains oxidative clearance activity regardless of overt oxidative stress. This continuous activity may reflect the skin's need to respond to persistent environmental exposure and maintain redox homeostasis. With advancing age, levels of AGEs and CPs in skin significantly increase [25], whereas OPH activity gradually declines [14]. Combined with the results of the OPH knockdown experiments described above, these observations suggest that the decline in OPH is a key factor contributing to age-related accumulation of AGEs and CPs in skin. Such findings constitute evidence that OPH functions as an effective intracellular pathway for degrading both glycated and carbonylated proteins, offering a novel therapeutic target for the mitigation of AGE- and CP-associated skin aging. Accordingly, efforts to identify cosmetic ingredients capable of enhancing OPH expression and activity have robust potential for addressing skin aging due to modified proteins.

Building on this rationale, we evaluated the effects of AFE on OPH to clarify its potential anti-glycation and anti-carbonylation activities in skin. Our experimental results showed that 0.1% AFE significantly upregulated OPH gene expression in HaCaT cells ($p < 0.05$). In subsequent in vivo experiments, topical application of a 0.1% AFE-containing lotion for 8 consecutive weeks significantly reduced AGEs SAF. This reduction was accompanied by improvements in skin yellowness, elasticity, and wrinkle area, indicating that AFE may exert anti-glycation effects by enhancing OPH-mediated degradation of AGEs, thus contributing to visible improvements in skin appearance. Despite no direct evidence of CPs reduction in skin, carbonylation reactions are known to impair skin physicochemical properties [26], [27]. Such observations support the hypothesis that AFE improves skin aging by promoting OPH-mediated CPs degradation. These findings offer novel insights into the development of anti-glycation and anti-carbonylation skincare products that regulate OPH expression.

5. Conclusion

Our study confirms that AGEs serve as key biomarkers associated with visible and physiological manifestations of skin aging. OPH plays a critical role in anti-glycation and anti-carbonylation mechanisms, providing new insights into the molecular basis of skin aging and the functional role of OPH in skin health. This pioneering study demonstrated that AFE significantly enhances OPH expression, highlighting potential cosmetic applications of AFE in anti-aging formulations. These findings establish a theoretical foundation for skin protection and rejuvenation strategies centered on OPH and AFE.

6. References

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