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A novel antioxidant tripeptide identified by molecular docking ameliorates photoaging in skin cells

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Abstract

Reactive oxygen species (ROS) has been reported to plays a pivotal role in the skin photoaging, implying that antioxidant strategies could be beneficial in delaying this process of skin aging. Peptides as active ingredients, characterized by high nutritional value, good bioavailability, low or no immune response, have been paid more attention. However, it's still unclear which peptide with antioxidant properties has anti-skin aging ability. In this study, molecular docking was utilized to screen potential antioxidant peptides based on the ligands of 20 amino acids, 400 dipeptides, and 8,000 tripeptides and the receptor of Keap1-Kelch domain which involves in the activation of antioxidant signaling pathway of Nrf2. Combining the antioxidant properties of the amino acid residues such as indole, phenolic hydroxyl, or thiol groups, we screened several potential peptides with antioxidant activity. Subsequently, the activities of these peptides were further validated through *in vitro* assays. The results showed that the peptide Phe-Ala-Trp (FAW (INCI name: Tripeptide-128)) exhibited strong antioxidant activity, which was validated by strong binding interaction with the Keap1-Kelch domain *in silico*, high ABTS radical scavenging capacity, and significantly reducing the ROS level in H_2O_2-induced cells. Moreover, peptide FAW effectively decreased the ROS level and restored the cell viability in human epidermal keratinocytes (HaCaT) and human dermal fibroblasts under condition of UVB and UVA irradiation, respectively. Simultanously, peptide FAW enhanced the expression of Nrf2-Keap1-mediated antioxidant genes (GPX1, GPX4, CAT, SOD2) in UVB-induced HaCaT. Notably, peptide FAW reduced the rate of senescence-associated β-galactosidase staining-positive cells in chronological factor-induced and UVB-induced HaCaT cell. Additionally, peptide FAW upregulated the moisturizing and barrier repair related gene expression including filaggrin (FLG), aquaporin 3 (AQP3), zonula occludens-1 (ZO-1), SIRT1, and type XVII collagen (Col-XVII) in HaCaT, as well as it promoted HaCaT migration function. Collectively, peptide FAW showed the potential for anti-photoaging, moisturization, barrier repair and soothing applications on the skin, and could be considered for further research as a cosmetic ingredient.

Keywords: Anti-aging, Barrier function, Photo-aging, UV damages, UV protective ingredient

1. Introduction

Skin aging is a complex process, which is induced by intrinsic and extrinsic factors. Intrinsic aging is mainly due to genetic and chronological factors, while extrinsic aging, especially photoaging, is significantly affected by environmental factors such as ultraviolet (UV) radiation. UV radiation is a main cause of photoaging. UVA (320–400 nm) reaching the basal and dermal layers, induces ROS, activates the mitogen-activated protein kinase (MAPK) pathway, promotes matrix metalloproteinases (MMPs) expression, and inhibits collagen synthesis or degrades extracellular matrix, leading to wrinkles, laxity, and pigmentation[1]. UVB (280–320 nm), acting on the epidermis, causes immediate damage like erythema and longterm effects such as increased MMPs expression and reduced collagen production [2, 3]. Research also focuses on the immune system's role in photoaging. UV-induced oxidative stress disrupts immune cells like Langerhans cells, weakening the body's defense and promoting skin photoaging [4]. Additionally, air pollutants like particulate matter, polycyclic aromatic hydrocarbons, and heavy metals interact with UV, generating ROS in the skin and accelerating skin aging [5, 6].

The current research focus about countering photoaging is on effective antioxidants. As we known, oxidative stress from excessive ROS during photoaging will disrupts normal cell function. Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway is a key regulator in the cell response to oxidative stress. In this process, the transcription factor Nrf2 can activate antioxidant response element (ARE)-mediated gene expression. In skin cells, Nrf2 activation enhances endogenous antioxidase production, neutralizing ROS and maintaining redox balance, thus protecting against photoaging[7, 8]. Therefore, for ameliorating photoaging, much attention should be focused on the the antioxidant that can activate Nrf2 signaling pathway in addition to simply neutralizing ROS.

Peptides as active ingredients, characterized by high nutritional value, good bioavailability, low or no immune response, have been paid more attention. So far, many peptides with antioxidant activity have been reported. However, it’s still unclear which peptide with antioxidant properties has anti-skin aging ability. On the one hand, cosmetic ingrediants with effective antioxidant activity are important in mitigating skin aging. On the other hand, the moisturizing and barrier repair function are essential for maintaining skin homeostasis. Therefore, for peptide exerting anti-skin aging, one crucial strategy is to explore peptides with antioxidant, moisturizing and barrier repair function.

In this study, molecular docking was utilized to screen potential antioxidant peptides based on the ligands of 20 amino acids, 400 dipeptides, and 8,000 tripeptides and the receptor of Keap1-Kelch domain which involves in the activation of Nrf2 signaling pathway. Simultaneously, potential peptides containing antioxidant groups such as indole, phenolic hydroxyl, or thiol groups, are also considered to be favorable candidates. Subsequently, potential antioxidant peptides were further validated through *in vitro* assays, such as cytotoxicity, antioxidant activity and migration ability, etc. Finally, peptide FAW not only had antioxidant activity, but also showed potential in moisturizing and barrier repair function, which were beneficial to ameliorate skin photoaging and exert skin soothing effect.

2. Materials and Methods

2.1 Molecular docking

20 amino acids, 400 dipeptides, and 8,000 tripeptides were constructed to establish a ligand peptide library. Subsequently, we employed the Autodock Vina program to perform molecular docking studies on the Keap1-Kelch domain according to the methods as described elsewhere

with slight modification[9, 10]. Combining the antioxidant properties of the amino acid residues, we conducted a preliminary structure-activity relationship analysis based on the molecular docking results, and screened several potential peptides with antioxidant activity. Subsequently, the activities of these peptides were further validated through *in vitro* assays, such as cytotoxicity, antioxidant activity and migration ability, etc (data not shown). Finally, peptide Phe-Ala-Trp (FAW) was selected for further investigation.

2.2 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay

Briefly, 5 mL of 7.0 mmol/L ABTS solution was mixed with 0.075 mL of 2.45 mmol/L potassium persulfate solution and left in the dark at room temperature for 16 h. The resulting mixture was diluted 40-45-fold with pH 7.4 phosphate buffer until its absorbance at 734 nm was 0.70 ± 0.02, forming the ABTS radical working solution. For the assay, 10 μL of peptide FAW or Trolox with different concentration were added to 96-well plates, followed by 200 μL of the ABTS working solution. After 6 min incubation at 30℃ in the dark, the absorbance at 734 nm was measured using a plate reader. Trolox was used as the antioxidant positive control, and the results of ABTS radical scavenging activity were expressed as half maximal inhibitory concentration (IC50) .

2.3 Cell culture

The human immortalized keratinocyte cell (HaCaT) used in this study was sourced from the Conservation Genetics CAS Kunming Cell Bank (CHN) and cultured in DMEM medium (Gibco, USA) with 10% fetal bovine serum (FBS, Gibco, USA) in a 37℃, 5% CO_2 incubator. The Human Skin Fibroblast cell (HSF) were obtained from Beijing EallBio Biomedical Technology Co., Ltd and cultured in DMEM/F12 medium (Gibco, USA) with 10% FBS (Gibco, USA) under the same 37℃, 5% CO_2 incubator conditions.

2.4 UV irradiation treatment

HaCaT cells were seeded 3×10^4 cells/cm² in culture plates and incubated in a cell culture incubator for 24 h. Subsequently, they were irradiated with UVB (300 mJ/cm²) emitted by a TL 20W/01 lamp (PHILIPS, Belgium). After irradiation, the cells were further cultured for 24 h. To construct a photoaging model using senescence-associated β-galactosidase (SA-β-Gal) staining, HaCaT cells were exposed to UVB irradiation at a dose of 20 mJ/cm² once a day for three consecutive days, followed by an additional 72 h incubation time. HSF cells were plated at 4.5×10^4 cells/cm² and incubated for 24 h. They were then irradiated with UVA (1500 mJ/cm²) from a TL-K 40W/10R lamp (PHILIPS, Belgium) and cultured for 48 h after irradiation. The intensity of UVA radiation was measured using a UV radiometer (UV-340A, Lutron, Taiwan) before and after each irradiation event.

2.5 Cell viability assay

The cytotoxic effects of peptide FAW, UVB irradiation on HaCaT or UVA irradiation on HSF were determined by using Cell Counting Kit-8 (CCK-8) (Beyotime, Shanghai, China). For CCK-8 assays, HaCaT was seeded on a 96-wells plate and irradiated with or without UVB and treated with peptide FAW at different concentration for 24 h. HSF was seeded on a 96-wells plate and irradiated with or without UVA and treated with peptide FAW at different concentration for 48 h. Cell viability were subsequently assessed using the CCK-8 according to the manufacturer's instructions.

2.6 Flow cytometry assay

ROS level in cell was assessed by using 2′,7′-dichlorofluoresce in diacetate (H_2DCFDA) (Sigma, D6883-50MG) probe. Briefly, the cells were seeded on a 12-well plate. After treatment with UVA/UVB or peptide FAW, H_2DCFDA (10 μmol/L) were diluted in basic medium. For the H_2O_2-induced oxidative stress model, the medium containing H_2DCFDA was kept at 37 ℃ in CO_2 incubator for 45 mins and then loaded for 30 mins with or without H_2O_2 at different concentration. Subsequently, ROS intensity were measured by BD FACSCalibur Flow Cytometer.

2.7 Real-time quantitative polymerase chain reaction analysis

At the end of the treatment, cells were collected. The total RNA was extracted using HiPure Total RNA Mini Kit. 1 μg of the RNA was reverse transcribed to cDNA using a reverse transcription kit. Real-time quantitative polymerase chain reaction (RT-qPCR) was performed using the TB Green™ Premix Ex Taq™ II (Tli RNaseH Plus) in a LightCycler 480 II (Roche) detection system. GAPDH was used as an internal reference. The relative gene expression was calculated using the $2^{-\triangle\triangle Ct}$ method.

2.8 Senescence-associated β-galactosidase activity staining

Aged HaCaT cells were stained using the SA-β-Gal activity staining kit. 72 hours after the last UVB irradiation, the cell culture medium was removed and washed with phosphate-buffered saline (PBS). Then, 100 μL of fixative solution was added, and the cells were fixed at room temperature for 15 minutes. Subsequently, the samples were washed three times with PBS for 3 minutes each time. After removing the PBS, 100 μL of staining solution was added to each well, and the plates were placed in a humidified chamber at 37°C overnight. The morphology and staining of the cells were observed under an optical microscope.

2.9 Cell migration assay

HaCaT cells were seeded in 12-well plates at 3×10^5 cells/well and incubated for 24 h until 90% confluent. A scratch was made in the cell monolayer with a 200 μL pipette tip. After washing with PBS to remove debris, DMEM was added to start the migration assay. Images of the scratch area were taken at 0 h and 24 h using an inverted microscope. The cell migration was quantitated by measuring the recovered scratch area.

2.10 Statistical Analysis

All data were expressed as mean ± standard deviation (SD). The statistical analysis was conducted by using GraphPad Prism version 8.0.2. The significant difference was assessed by unpaired t test or one-way analysis of variance (ANOVA). p-value < 0.05 was considered to be statistically significant.

3. Results

3.1 Peptide FAW showed strong antioxidant activity

Compared with the standard antioxidant peptide GSH, peptide FAW had more negative binding affinity (Figure 1A), showing strong binding interaction with the Keap1-Kelch domain. In addition, peptide FAW had higher ABTS radical scavenging ability than well-known antioxidant Trolox (Figure 1B). We further explore whether peptide FAW has antioxidant capacity in skin cells. As shown in Figure 1C and D, peptide FAW had no significant cytotoxicity in HaCat and HSF among indicated concentrations. The ROS intensity of HaCaT cell treated

with H_2O_2 significantly increased, but it decreased when the HaCaT was treated with peptide FAW (Figure 1E). Similal results were also observed in HSF cell (Figure 1F). These results indicated that peptide FAW showed strong antioxidant activity.

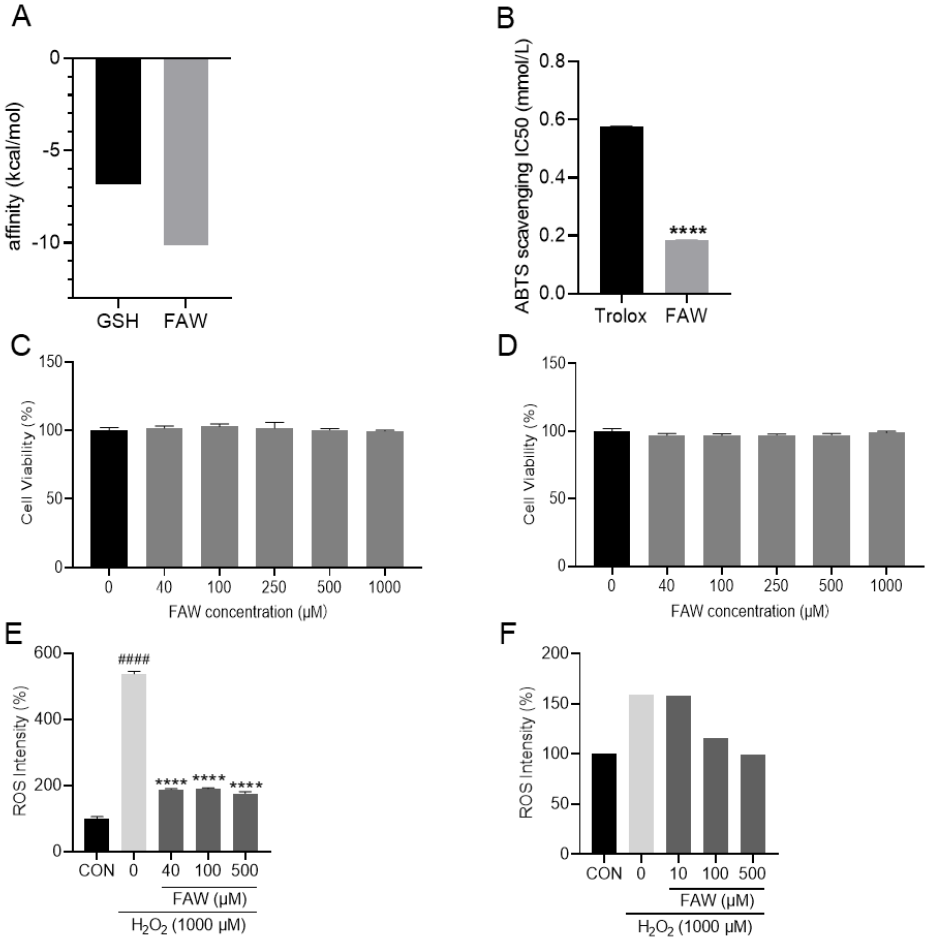

Figure 1. (A) The binding affinity between peptides (GSH and FAW) and Keap1-Kelch domain. (B) The ABTS radical scavenging activity of Trolox and peptide. The cell viability of HaCaT(C) and HSF(D) treated with different peptide FAW concentrations. The ROS intensity in HaCaT (E) and HSF (F) treated with H_2O_2. Compared with CON group, ####P < 0.001. Compared with 0 group, **P < 0.01, ***P < 0.001, ****P < 0.0001.

3.2 Peptide FAW ameliorated the photoaging in UVB/A-induced HaCaT and HSF

Based on the fact that UV irradiation will induce lots of ROS production and impair the cell viability in skin cells, we further investigated the effect of peptide FAW on the ROS level and cell viability in cells under the condition of UV irradiation. As shown in Figure 2A and B, UVB and UVA could increase the intensity of ROS in HaCaT and HSF, respectiviely. However, peptide FAW treatement could reduce the increased ROS level in these cells. In addition, the cell viability of HaCaT and HSF decreased when these cells were irradiated with UVB and UVA, respectively (Figure 2C and D). However, the decreased cell viablitiy in UVB- and UVA-induced cells were restored while these cells were treated with peptide FAW (Figure 2C and D). These results indicated that peptide FAW could ameliorate the photoaging induced by UVB and UVA in skin cells.

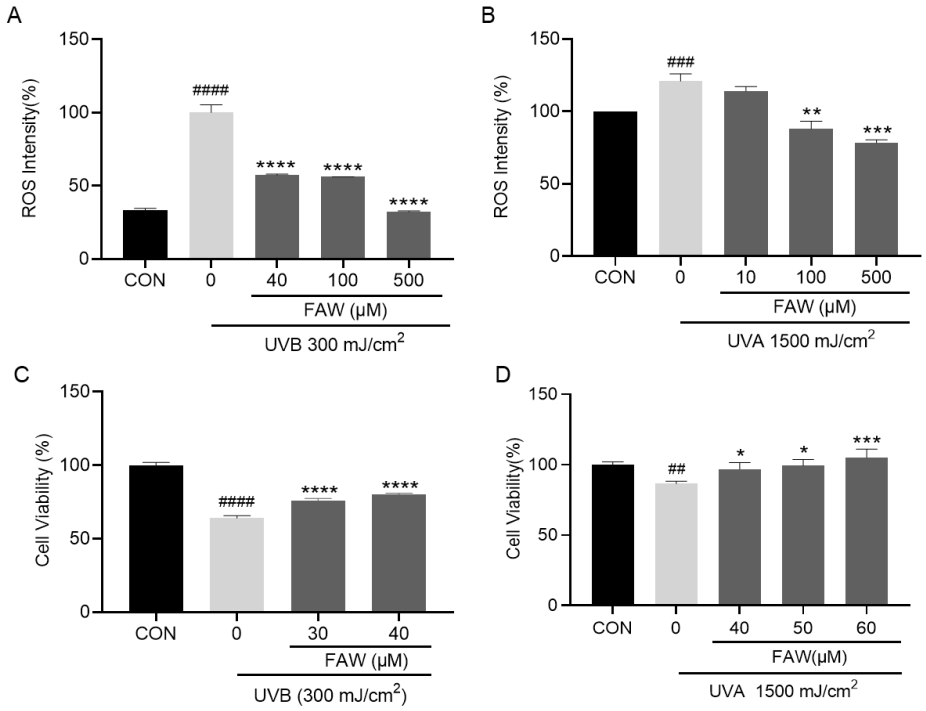

Figure 2. (A) The ROS intensity in HaCaT under UVB irradiation. (B) The ROS intensity in HSF under UVA irradiation. (C) The cell viability of HaCaT under UVB irradiation. (D) The cell viability of HSF under UVA irradiation. Compared with CON group, ##P < 0.01, ###P < 0.001, ####P < 0.0001. Compared with 0 group, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

3.3 Peptide FAW upregulated the expression of antioxidant genes in skin cell

We found that UVB induced the downregulation of antioxidant gene expression in HaCaT cells, which included GPX1, GPX4, CAT and SOD2 (Figure 3A-D). However, peptide FAW

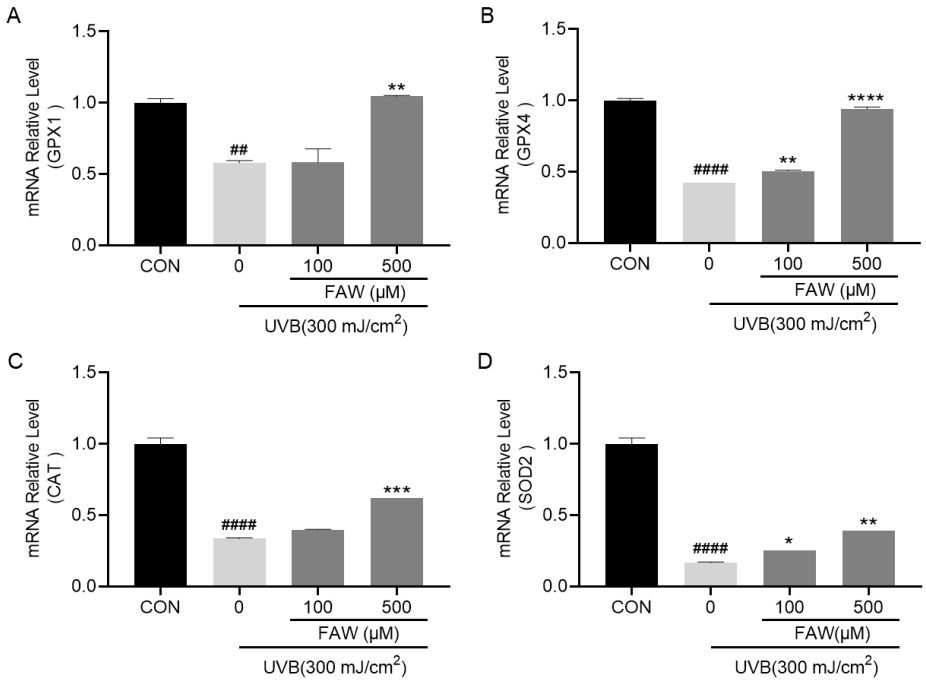

Figure 3. The mRNA level of GPX1 (A), (B) GPX4, (C) CAT and (D) SOD2. Compared with CON group, ##P < 0.01, ####P < 0.0001. Compared with 0 group, *P < 0.05, **P < 0.01,***P < 0.001, ****P < 0.0001.

could restored the mRNA levels of these antioxidase (Figure 3A-D), reflecting the potential of peptide FAW on the improvement of redox balance in UVB-induced skin cell.

3.4 Peptide FAW decreased the positive rate of SA-β-Gal staining in aged cells

To investigate the anti-aging effects of peptie FAW, we established two cellular senescence models: a chronological factor-induced natural aging model and a UVB-induced photoaging model, which mimic the intrinsic and extrinsic aging process, respectively. As shown in Figure 4A and B, compared with Young group, SA-β-Gal staining-positive cells significantly increase in Old group. However, peptide FAW treatment markedly reduced the SA-β-Gal staining-positive rate of Old group cells. Similarly, UVB increased the rate of SA-β-Gal staining-positive cells and peptide FAW treatment alleviated the rate of that (Figure 4C and D). These results demonstrated the anti-aging potential of peptide FAW in skin cells.

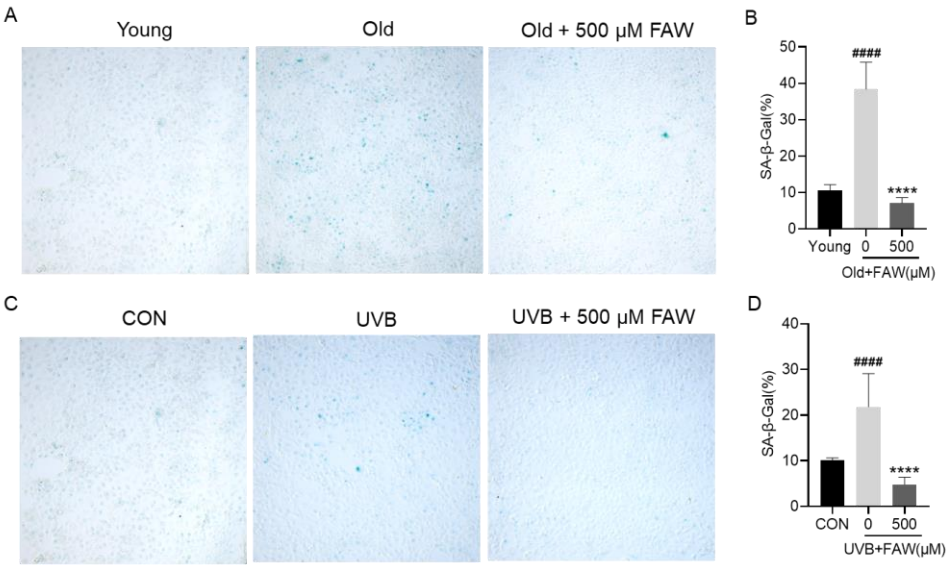

Figure 4. (A) The representative images of the SA-β-Gal staining for Young, Old and Old plus FAW group. and quantitative results of that (B), compared with Young group, ####P < 0.0001, compared with Old group, ****P < 0.0001. (C) The representative images of the SA-β-Gal staining for Con, UVB and UVB plus FAW group, and quantitative results of that (D), compared with CON group, ####*P* < 0.0001, compared with UVB group, ****P < 0.0001.

3.5 Peptide FAW enhanced the gene expression related to moisture and barrier repair function

We next detected the mRNA levels of genes related to the moisture and barrier repair function in HaCaT cell treated with peptide FAW. The results showed that peptide FAW could upregulate gene expression of FLG, AQP3, ZO-1, Col-XVII and SIRT1 (Figure 5A-E), indicating that peptide FAW would play an important role in moisture and barrier repair function.

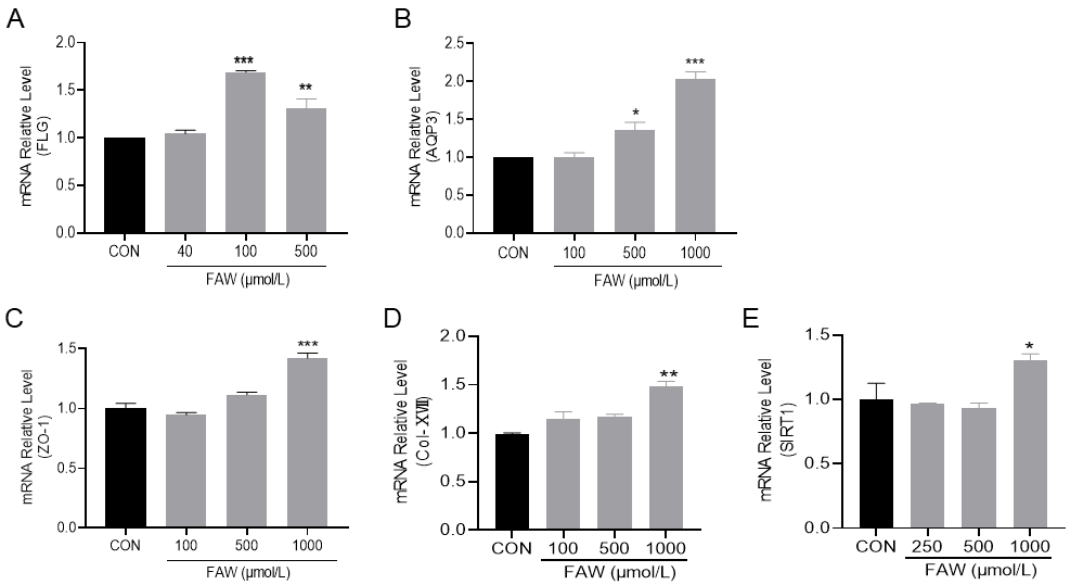

Figure 5. The change of mRNA level of FLG (A), AQP3 (B), ZO-1 (C), Col-XVII (D) and SIRT1 (E) in HaCaT treated with peptide FAW. Compared with CON group, *p < 0.05, **p < 0.01 and *** p < 0.001.

3.6 Peptide FAW promoted the migration ability of HaCaT cells

We further detected the effect of peptide FAW on the barrier repair ability of skin cell through the cell migration assay and found that peptide FAW could promote the migration of HaCaT cells in a concentration-dependent manner (Figure 6A and B), demonstrating that peptide FAW had potential in barrier repair ability in skin.

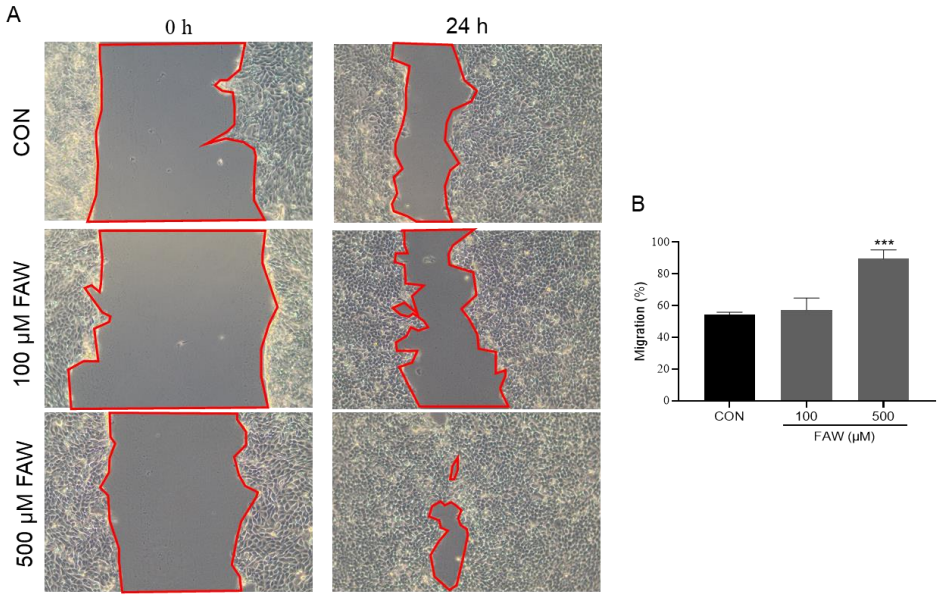

Figure 6. (A) The representative images for the cell migration of HaCaT treated with peptide FAW in different concentration, and quantitative results of that (B). Compared with CON group, ***P < 0.001.

4. Discussion

During the progression of skin aging, photoaging mainly induced by UV irradiation plays an important role in the skin aging. In this process, ROS significantly increases and leads to the

oxidative stress, which will activate the MAPK pathway, promote MMPs expression, and inhibit collagen synthesis or degrade extracellular matrix, leading to skin wrinkles, laxity, and pigmentation. Therefore, antioxidant strategy would be essencial in delaying this process of skin aging. Peptides as active ingredients, characterized by high nutritional value, good bioavailability, low or no immune response, have been paid more attention. In this study, a novel antioxidant tripeptide FAW was found through molecular docking based on the ligands of 20 amino acids, 400 dipeptides, and 8,000 tripeptides and the receptor of Keap1-Kelch domain which involves in the activation of antioxidant signaling pathway of Nrf2, as well as through considering the peptide containing antioxidant groups such as indole, phenolic hydroxyl, or thiol groups, and through subsequent *in vitro* assay.

In the present study, peptide FAW exhibited stronger binding interaction with the Keap1-Kelch domain than standard antioxidant peptide GSH, higher ABTS radical scavenging capacity than well-known antioxidant Trolox, and significantly reduced the ROS intensity in H_2O_2-induced cells, showing strong antioxidant activity *in silico*, as well as in biochemical and cellular levels. As we known, UV radiation triggers oxidative stress through ROS overproduction that overwhelms endogenous antioxidant defenses, which is a key mechanism driving cutaneous aging. Therefore, exerting antioxidant effect following UV irradiation is a critical strategy for skin protection. Herein, UVB and UVA irradiation both induced increased ROS level and lower cell viability in skin cells. However, peptide FAW treatment could effectively decreased the ROS level and restore the cell viability, demonstrating that peptide FAW with effective antioxidant activity was able to exert cellular protection against UV irradiation. Moreover, we also furthe found that peptide FAW could enhance the Nrf2-Keap1-mediated antioxidase gene expression including GPX1, GPX4, CAT and SOD2 in HaCaT under condition of UVB irradiation, which was beneficial to counteract oxidative stress induced by UV irradiation and maintain the redox balance, further achieving the melioration of photoaing. Notably, peptide FAW significantly reduced SA-β-Gal staining-positive rate in chronological factor-induced and UVB-induced HaCaT cell, suggesting its potential in mitigating cellular aging through enhanced oxidative defense mechanisms.

In addition, peptide FAW not only upregulated gene expression of AQP3, FLG and ZO-1, but also enhanced cellular migration capacity in HaCaT cell, demonstrated that peptide FAW could play an important role in the moisturizing and barrier repair function, which was also beneficial for the skin protection. Simultaneously, the upregulation of Col-XVII and SIRT1 gene in HaCaT treated with FAW treatment was also beneficial to maintain skin homeostasis and ameliorate skin aging[11, 12].

Together, these findings indicated that peptide FAW with antioxidant, moisturizing and barrier repair function would act as a novel and multifunctional ingrediant counteracting skin photoaging and exerting soothing effect.

5. Conclusion

In summary, our study found a novel tripeptide FAW that exhibited strong antioxidant activity, which was validated by strong binding interaction with the Keap1-Kelch domain *in silico*, high ABTs radical scavenging capacity in biochemical level, and significantly reducing the ROS intensity in H_2O_2-induced cells. Moreover, peptide FAW exhibited significant anti-photoaging effect in UVB-induced HaCaT and UVA-induced HSF cellular aging model through reducing the excessive ROS production and restoring the cell viability. Simultaneously, peptide FAW markedly enhanced the Nrf2-Keap1-mediated antioxidase gene expression including GPX1, GPX4, CAT and SOD2 in UVB-induced HaCaT cell, as well as significantly reduced SA-β-Gal staining-positive rate in chronological factor-induced and UVB-induced HaCaT cell. In addition, peptide FAW would play an important role in the moisturizing and barrier repair function while it not only upregulated moisturizing and barrier repair related gene expression of AQP3, FLG and ZO-1, but also enhanced cellular migration capacity in HaCaT cell. Peptide FAW might maintain the skin homeostasis and ameliorate skin aging through its ability to upregulate Col-XVII and SIRT1 gene in HaCaT. This study provided insights into the mechanism on the novel

peptide FAW to ameliorate photoaging in skin cell. It is expected that present work can make certain contribution to the development of functional cosmetic ingredient for the improvement of skin aging.

Acknowledgements

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Conflict of Interest Statement

The authors declare no conflict of interest.

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