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ORIGINAL CONTRIBUTION

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Dual functional bioactive-peptide, AIMP1-derived peptide (AdP), for anti-aging

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Summary

Background: Human skin aging is caused by several factors, such as UV irradiation, stress, hormone, and pollution. Wrinkle formation and skin pigmentation are representative features of skin aging. Although EGF and arbutin are used as anti-wrinkle and skin whitening agents, respectively, they have adverse effects on skin. When more cosmeceutical ingredients are added to cosmetic product, adverse effects are also accumulated. For these reasons, multifunctional and safe cosmetic ingredients are in demand. The aim of the present study is to investigate the novel anti-aging agents, AIMP1-derived peptide (AdP, INCI name: sh-oligopeptide-5/sh-oligopeptide SP) for cosmetic products.

Methods: To assess the anti-wrinkle effect of AdP, collagen type I synthesis and fibroblast proliferation were determined on human fibroblasts. The anti-wrinkle effect of AdP was examined by ELISA and cell titer glo assay. To assess the whitening, melanin content and tyrosinase activity were determined on melanocytes. The whitening effect of AdP was examined by melanin measurement and enzyme activity assay. The safety of AdP was determined by cytotoxicity and immunogenicity, CCK-8 and TNF-α ELISA assay, respectively.

Results: AdP treatment induced the collagen type I synthesis and fibroblast proliferation. Also, AdP treatment inhibited melanin synthesis by regulating tyrosinase activity. The anti-aging effect of AdP is more potent than EGF and albutin. AdP did not show adverse effects.

Conclusion: These results show that AdP can be dual functional and safe cosmeceutical agent to prevent skin aging.

KEYWORDS
AIMP1-derived peptide, anti-wrinkle, cosmeceuticals, sh-oligopeptide-5 SP, whitening

1 | INTRODUCTION

Skin aging is a complex biologic process, influenced by a combination of intrinsic (genetics, cellular metabolism, hormones, and metabolic processes) and extrinsic (chronic light exposure, pollution, ionizing radiation, chemicals, and toxins) factors.[1,2] Together, these factors lead to cumulative structural and physiologic alterations and progressive changes in each skin layer, as well as changes in skin appearance. Since intrinsic and extrinsic factors reduce collagen type I synthesis in fibroblasts and induce melanin in melanocytes, skin aging is characterized by wrinkling, roughness, dryness, and pigmented lesions. To inhibit and restore skin aging, a number of peptide-derived cosmeceutical ingredients are being developed.[3,4]

Collagen type I is the main component of skin layers. The amount of collagen is important to sustain the elasticity and strength of the skin.[5,6] In the dermis, UVB exposure has been shown to

stimulate dermal fibroblast production of collagenase. This induces the degeneration of collagen and deposition of altered elastic tissue, which presents as wrinkles.[7,8] Growth factors, which play an important role in biologic processes, have been suggested as therapeutic and cosmetic agents for skin regeneration. Among the many growth factors, epidermal growth factor (EGF) is a single polypeptide, composed of 53 amino acids, which promotes epithelial cell division and proliferation. Fibroblast growth factor-1 (FGF1), also called the acidic fibroblast growth factor, is a member of the FGF family and is known to regulate cellular proliferation and survival. Although these growth factors are considered good agents for the prevention and treatment of skin damage, including wrinkles, their cosmetic application is limited. As high doses of EGF and FGF show side effects on skin, the use of a high dose is prohibited.[9,10]

Melanin synthesis is the major source of skin color and plays an important role in protection against UV-induced dermal irritation; however, over-production of melanin poses not only an esthetic problem, but also a dermatologic issue. Ingredients, such as hydroquinone, ascorbic acid, and retinoic acid, have been used as whitening agents to lighten the skin. Despite their benefits, these whitening agents can cause some harmful side effects, resulting in their limited application.[11,12]

Aminoacyl-tRNA synthetases (ARSs) are responsible for the ligation of specific amino acids to their cognate tRNAs. ARSs carry out a two-step catalytic function: amino acid activation and transfer of the amino acid to the tRNA.[13] In general, ARSs are a family of enzymes, and among them, 9 ARSs compose the multi-synthetases complex (MSC) in higher eukaryotes, with three non-enzymatic factors: aminoacyl-tRNA synthetase complex-interacting multifunctional protein (AIMP)1, AIMP2, and AIMP3.[14] ARSs and AIMPs are essential components of the protein translation machinery. Although AIMP1 is associated with the translational machinery under normal conditions, AIMP1 is released from the MSC upon stress and then secreted into the extracellular space.[13] Secreted AIMP1 has various non-canonical functions, such as the regulation of angiogenesis, wound healing, and stem cell activation.[13]

Interestingly, AIMP1 exhibits wound healing and stem cell activation effects. The secretion of AIMP1 is induced in the wound region and fluids. It may be released from TNF-α-stimulated macrophages and induces fibroblast proliferation and collagen synthesis in an ERK-dependent manner, showing rapid wound healing effects in mice.[15,16] AIMP1 promotes the proliferation of bone-marrow-derived mesenchymal stem cells (BMMSCs) by activating the β-catenin/TCF complex via FGFR2-mediated activation of Akt, leading to an increase in MSCs in peripheral blood.[17]

To develop AIMP1-derived peptides for cosmeceutical ingredients, several deletion fragments of AIMP1 were generated, and their activities toward the target cells were compared. AIMP1 promoted endothelial cell death and caspase-3 activation through its 101-114 amino acid regions, fibroblast proliferation through its 6-46 amino acid regions, and endothelial migration through its 114-192 amino acid regions, as revealed by deletion mapping. Thus, this work revealed that AIMP1 uses different regions for its diverse extracellular activities.[18]

Although an AIMP1-derived peptide (AdP, amino acid region 6-46, sh-oligopeptide 5/sh-oligopeptide 5 SP) induces fibroblast proliferation, it has not been determined whether AdP could be used as cosmeceutical ingredient. To address this question, a comparison of its functional activity with cosmeceutical ingredients was conducted.

2 | MATERIALS AND METHODS

2.1 | Cell culture

Hs68, B16F10, Vero, and RAW264.7 cell lines were purchased from ATCC and cultured in high-glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% streptomycin/penicillin. Cells were cultured at 37°C in a humidified atmosphere at 5% CO_2. Hs68 cells were utilized between the 4th and 7th passages. B16F10, Vero, and RAW 264.7 cells were utilized between the 8th and 12th passages.

2.2 | Preparation of AdP

AdP was synthesized by standard Fmoc-SPPS (solid phase peptide synthesis) protocols on 2-chlorotrityl chloride resin (Merck), and commercially available amino acids. AdP was cleaved from the resin and deprotected side chain protecting group using 95% trifluoroacetic acid (TFA, Sigma-Aldrich), 2.5% water, and 2.5% triisopropylsilane (Sigma-Aldrich) for 1 hr and precipitated with ice-cold ether (Sigma-Aldrich). AdP was purified by the reverse phase HPLC (Shimadzu 10 Avp, Shimadzu) using a C18 column. Elution was carried out with a water-acetonitrile linear gradient (0%-75% (v/v) of acetonitrile) containing 0.1% (v/v) TFA. Molecular weight of the purified AdP was confirmed using MALDI-TOF mass spectrometer (AXIMA-Assurance, Shimadzu). The concentration of dissolved AdP was determined by BCA protein assay kit (Thermo Scientific).

2.3 | Collagen ELISA

Hs68 cells (2×10^4 cells) were seeded at 48-well culture plate. After 12 hours incubation, the culture media was changed as DMEM media, supplemented with 2% FBS and cultured for further 12 hours. Cells were treated with AIMP1-derived Peptide (AdP) and hTGF-β1 5 ng/mL (Sigma) or hEGF (Sigma) for 24 hours. hTGF-β1 and hEGF were used as positive control and comparison ingredient, respectively. The cultured media and cells were harvested. Procollagen type I was analyzed by Procollagen type I ELISA kit (Takara) in accordance to the manufacturer instructions. For comparison with EGF, relative collagen induction was calculated. Collagen induction was normalized by collagen amount of control group.

2.4 | qRT-PCR

Hs68 cells were harvested and washed with PBS. Total RNA of fibroblast was isolated by RNeasy mini kit (Qiagen). Using RNA,

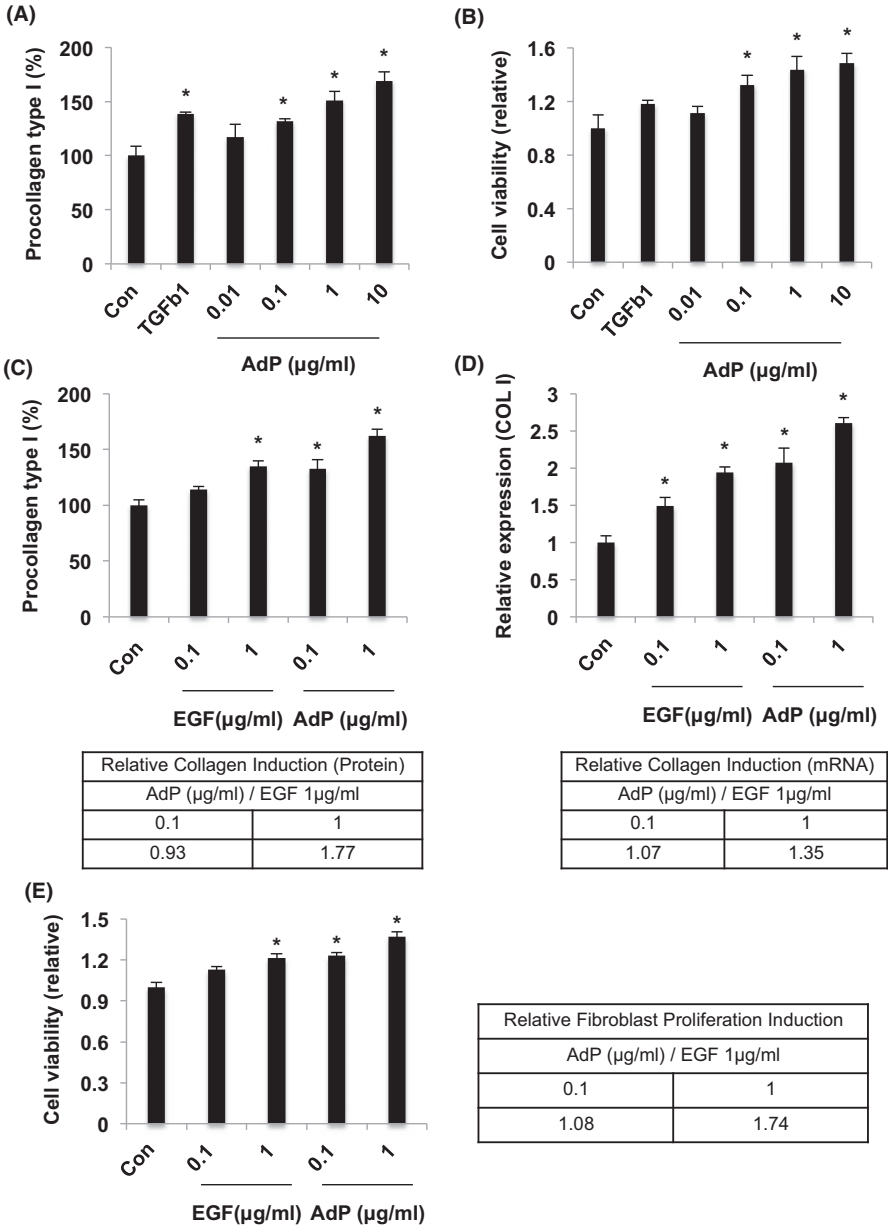
cDNA was synthesized using Maxima first strand cDNA synthesis kit (Thermo Fisher Scientific) according to the manufacturer's instruction. Gene expression was determined by Maxima SYBR Green/ROX qPCR mater mix (Thermo Fisher Scientific) on 7500 real-time PCR system (Applied Biosystems) according to the manufacturer's instruction. The gene expression was normalized with GAPDH.

2.5 | Proliferation assay

Hs68 cells (3×10^3 cells) were seeded into 96-well plate and cultivated. After 12 hours incubation, cells were replaced with serum-starved media and then treated with AdP for 48 hours. Cell proliferation was determined by CellTiter-glo luminescence cell viability assay (Promega) in accordance to the manufacturer instructions. For comparison with EGF, relative fibroblast proliferation induction was calculated. Fibroblast proliferation induction was normalized by fibroblast proliferation of control group.

2.6 | Measurement of melanin

B16F10 cells (6×10^4 cells) were seeded into six-well plate and cultivated. After 12 hours, the medium was replaced with α-MSH (0.5 μmol/L) and AdP contained medium. After 24 hours incubation, cells were harvested. The cell number was determined using C-chip (disposable hemacytometer, INCYTO). Cells (1×10^5 cells) were lysed with 1 N NaOH at 70°C for 1 hours. After centrifugation at 1500 *g* for 5 minutes, supernatant was harvested to measure melanin content. Melanin was determined using microplate



Relative Collagen Induction (Protein)	
AdP (μg/ml) / EGF 1μg/ml	
0.1	1
0.93	1.77

Relative Collagen Induction (mRNA)	
AdP (μg/ml) / EGF 1μg/ml	
0.1	1
1.07	1.35

Relative Fibroblast Proliferation Induction	
AdP (μg/ml) / EGF 1μg/ml	
0.1	1
1.08	1.74

FIGURE 1 AdP stimulates collagen synthesis and fibroblast proliferation. A, Hs68 cells, foreskin fibroblasts, were treated with AdP (0.01, 0.1, 1, 10 μg/mL) and TGF-β1 (5 ng/mL) for 24 h. The amount of collagen type I in fibroblasts was measured by ELISA in cultured media. B, Fibroblasts were treated with TGF-β1 and AdP (0.01, 0.1, 1, 10 μg/mL) for 48 h. Cell proliferation was determined by Celltiter glo assay. C, D. Fibroblasts were treated with AdP and EGF (0.1, 1 μg/mL) for 24 h. The amount of collagen type I, induced by EGF and AdP, was determined by ELISA (C) and qRT-PCR (D) (upper panel). For comparison, relative collagen induction was calculated as described methods (lower panel). E. Fibroblasts were treated with AdP and EGF (0.1, 1 μg/mL) for 48 h. Cell proliferation, induced by EGF and AdP, was determined (left panel). For comparison, relative fibroblast proliferation induction was calculated as described methods (right panel). Error bars indicate the mean ± standard deviation from the average of three independent experiments. *P* value was determined by Student's t test. $^*P < .01$

reader at 490 nm absorbance (Synergy 2, BioTek). For comparison with albutin, relative melanin synthesis inhibition was calculated.

2.7 | Tyrosinase activity assay

B16F10 cells (6×10^4 cells) were seeded into six-well plate and cultivated. After 12 hours, the medium was replaced with α-MSH (Sigma) and AdP contained medium. After 24 hours incubation, cells were harvested. Cells were lysed with 1% Triton X-100 (Sigma) containing PBS buffer. After centrifugation at 13 500 *g* for 20 minutes, supernatant was harvested and protein concentration was determined by BCA assay kit (Thermo Fisher Scientific). To measure tyrosinase activity, 50 μg of protein was incubated with 5 mmol/L L-DOPA at 37°C. Absorbance at 490 nm was measured every 10 minutes for 1 hours using microplate reader (Synergy 2, Biotek).

2.8 | Cytotoxicity assay

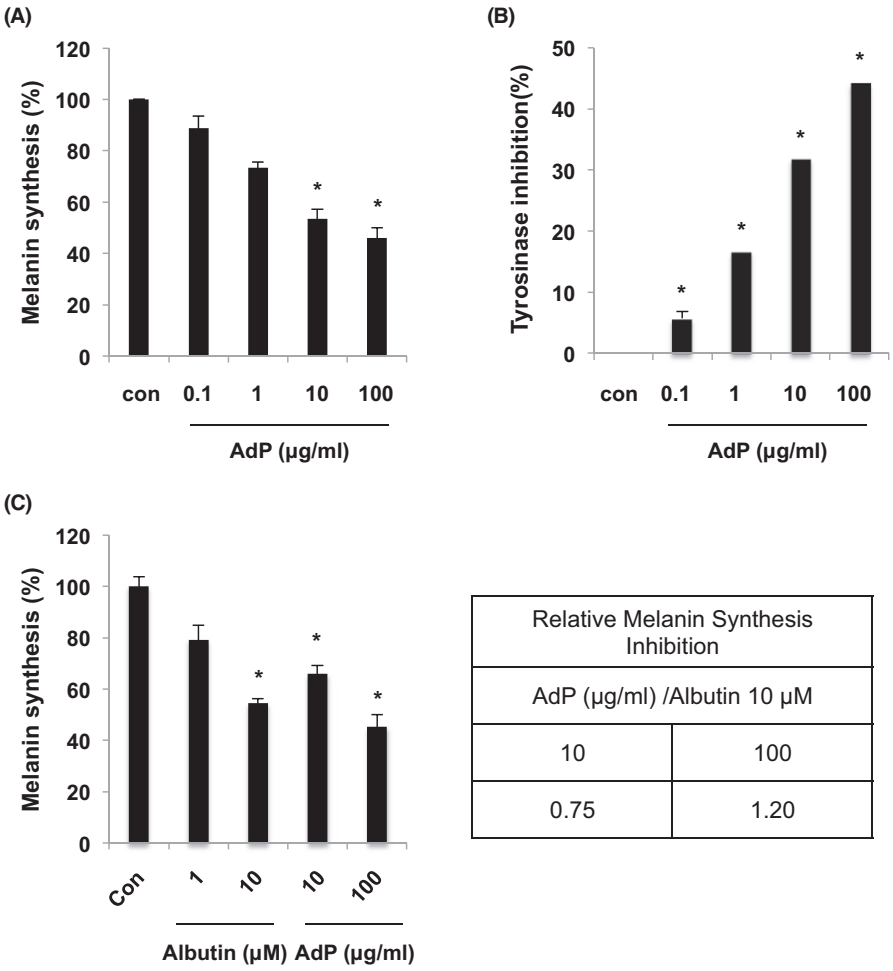
The CCK-8 assay was used to measure cytotoxicity under starved conditions, which are based on the conversion of a water-soluble tetrazolium salt, 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt (WST-8), to a water-soluble formazan dye upon reduction by dehydrogenases in the presence of an electron carrier. Vero cells (3×10^3 cells/well) were grown in 96-well plates for 12 hours and treated with AdP under serum-starved conditions. After 48 hours, the epithelial cells were washed, and the extent of cell growth was assessed using a CCK-8 assay (Dojindo). CCK-8 solution (10 μL) was added to each well, followed by incubation for 2 hours at 37°C. The absorbance at 450 nm was determined by a multiplate reader (Synergy2, Biotek).

2.9 | TNF-α ELISA

RAW264.7 cells (1.5×10^4) were seeded on 24-well plate and treated with 10 ng/mL LPS and AdP. After 6 hours incubation, culture media were harvested and centrifugated for 10 minutes at 850 *g*. TNF-α in supernatants was determined by TNF-α ELISA kit in accordance to the manufacturer instructions.

2.10 | Statistics

Statistical analysis was performed using unpaired two-tailed Student's t test. All results were presented as means ± standard deviation. $P < .01$ was considered statistically significant.



Relative Melanin Synthesis Inhibition	
AdP (μg/ml) /Albutin 10 μM	
10	100
0.75	1.20

FIGURE 2 AdP blocks melanin synthesis by inhibiting tyrosinase activity. A, Melanocytes, B16F10 cells, pre-treated with α-MSH (0.5 μmol/L) for 24 h, were treated with AdP (0.01, 0.1, 1, 10 μg/mL) for 2 days. The amount of melanin was determined as described in methods. B, Melanocytes, pre-treated with α-MSH (0.5 μmol/L) for 24 h, were treated with AdP (0.1, 1, 10, 100 μg/mL) for 24 h. Tyrosinase activity was measured as described in methods. C. Melanocytes, induced by α-MSH (0.5 μmol/L), were treated with AdP (0.1, 1 μg/mL) and albutin (10 μmol/L) for 24 h. The amount of melanin, inhibited by AdP and albutin, was determined (left panel). For comparison, relative melanin synthesis inhibition was calculated as described methods (right panel). Error bars indicate the mean ± standard deviation from the average of three independent experiments. *P* value was determined by Student's *t* test. *$P < .01$

3 | RESULTS

3.1 | Stimulatory effect of AdP on Fibroblast Proliferation and Collagen Type I Synthesis

As elastase 2 can cleave AIMP1 to create a 6- to 46-residue fragment and the N-terminal peptides showed fibroblast activation,[18] the biologic activity of the AIMP1-derived peptide (AdP, residues 6-46) was tested in skin-associated cells. Collagen type I synthesis and fibroblast proliferation are important factors that maintain the elasticity and strength of skin. To address the biologic function of AdP in skin, the effect of AdP on collagen type I synthesis and fibroblast proliferation was examined. Since fibroblasts are an important source of collagen type I synthesis, the induction of collagen type I synthesis was examined in AdP-treated fibroblasts. Collagen type I synthesis increased with AdP treatment in a dose-dependent manner (Figure 1A). AdP treatment also increased the proliferation of fibroblasts in a dose-dependent manner (Figure 1B). For comparison, a representative growth factor, EGF, which is used as a cosmeceutical ingredient, was tested. Collagen type I (Figure 1C and D) synthesis and fibroblast proliferation (Figure 1E) were determined to compare AdP with EGF. AdP, at 0.1 μg/mL, showed similar activity for the induction of collagen type I synthesis and fibroblast proliferation, when compared with EGF at 1 μg/mL. AdP at 1 μg/mL showed 77% and 35%, and 74% more potent activity for collagen type I protein and mRNA induction, respectively, when compared with EGF at 1 μg/mL (Figure 1C and D, lower panel). AdP at 1 μg/mL also showed 74% more potent activity for fibroblast proliferation when compared with EGF at 1 μg/mL (Figure 1E, right panel). Together, these results demonstrated that AdP stimulates collagen type I synthesis and the proliferation of fibroblasts.

3.2 | Inhibitory effect of AdP on Melanin synthesis

Melanin synthesis is an important factor for skin pigmentation. To address the biologic function of AdP in skin pigmentation, the effect of AdP on melanin synthesis was examined. Since melanocytes are an important source of melanin synthesis, the potential for AdP to inhibit melanin synthesis was examined in AdP-treated melanocytes. To activate melanin synthesis, melanocytes were pre-treated with α-MSH (0.5 μmol/L). Melanin synthesis, induced by α-MSH, was

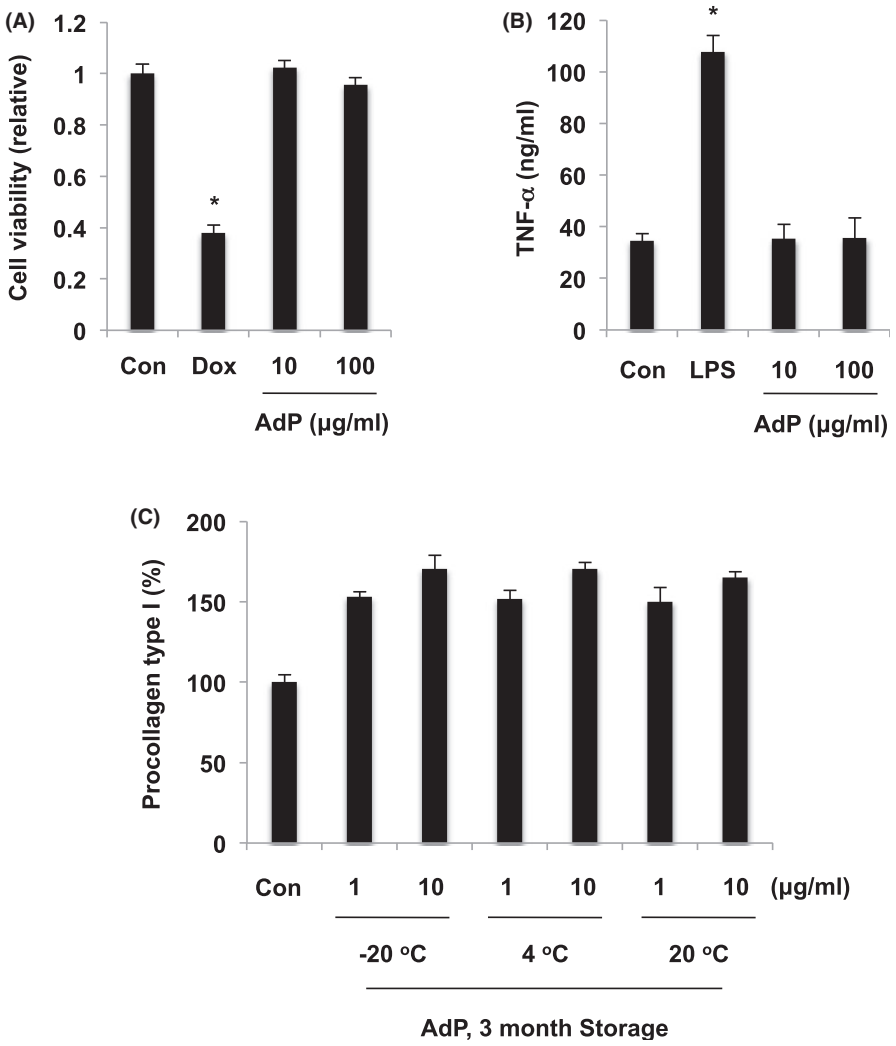


FIGURE 3 AdP shows safety and stability. A, Normal epithelial cells, Vero cells, were incubated with AdP (10, 100 μg/mL) for 48 h. Doxorubicin (50 μg/mL) was used as positive control. After incubation, cytotoxicity was determined by CCK-8 assay. B, Macrophages, RAW264.7 cells, were incubated with AdP (10, 100 μg/mL) for 6 h. LPS (10 ng/mL) was used as positive control. To check TNF-α secretion, media were harvested and centrifuged. TNF-α level was determined in harvested media by ELISA. C, AdP was incubated for 3 months at indicated temperature. Fibroblasts were treated with incubated AdP (1, 10 μg/mL) for 24 h. The amount of collagen type I in fibroblasts was measured by ELISA in cultured media. Error bars indicate the mean ± standard deviation from the average of three independent experiments. *P* value was determined by Student's *t* test. $^*P < .01$

inhibited by AdP treatment in a dose-dependent manner (Figure 2A). To determine the mechanism of the inhibitory effect of AdP on melanin synthesis, a tyrosinase enzyme activity assay was carried out. When AdP was treated with mushroom tyrosinase, tyrosinase enzyme activity decreased in a dose-dependent manner (Figure 2B). For comparison, a representative whitening cosmetic ingredient, albutin, was tested. The inhibitory effects of AdP and albutin on melanin synthesis were compared (Figure 2C, left panel). AdP at 100 μg/mL showed 20% more potent activity for the inhibition of melanin synthesis, compared with 10 μmol/L albutin (Figure 2C, right panel). These results demonstrated that AdP blocks melanin synthesis by inhibiting tyrosinase activity.

3.3 | Characterization of AdP for development as cosmeceutical ingredient

To develop AdP as a cosmeceutical ingredient, the safety of AdP was examined. Since AIMP1 has apoptotic and pro-inflammatory effects, the cytotoxicity and immunogenicity of AdP were tested. Although the apoptotic and pro-inflammatory domains of AIMP were removed in AdP,[14] the cytotoxicity and pro-inflammatory effects of AdP were tested to confirm the safety of AdP. AdP did not show cytotoxic or pro-inflammatory effects (Figure 3A,B). To check the stability of AdP, AdP was incubated for 3 month at −20, 4, and 20°C. After 3-month incubation, fibroblast-inducing activity of AdP was determined by collagen ELISA. Collagen synthesis-inducing activity of AdP was maintained (Figure 3C). The concentration of AdP was also not changed for 3 months (data not shown). These results demonstrated that AdP is a promising candidate as a cosmeceutical ingredient, which shows safety and stability.

4 | DISCUSSION

The most common dermatologic problem is skin aging. Skin aging phenotypes, such as wrinkles and pigmentation, lead to an increase in the demand for anti-aging products in the cosmetic market. Research on skin aging has advanced over the decades to satisfy the demand of the cosmetic market.[15] Although many cosmetic ingredients have been developed and used in cosmetics, the demand for a suitable bioactive ingredient has increased.

A number of pharmaceutical materials with potent biologic activity toward the skin have also been tested for cosmetic products. Among pharmaceutical materials, safe ingredients are recognized as cosmeceuticals and used in cosmetics. Since the usage of cosmetics is not tightly regulated, the safety of cosmeceutical ingredients is the most important factor. For example, peptides, growth factors, and antioxidants are used as cosmeceuticals.[16] EGF is a representative cosmeceutical ingredient and activates fibroblasts to produce collagen. Although EGF has anti-aging activity and anti-wrinkle effects, some have reported adverse activity at a high dose of EGF. High-dose EGF treatment induced melanoma in a mouse model. Therefore, the concentration of EGF in cosmetics is regulated.[19] Nevertheless, cosmeceutical ingredients show more potent biologic activity than classical cosmetic ingredients. Thus, a new, safe cosmeceutical ingredient is needed.

AIMP1 is associated with the multi-aminoacyl-tRNA synthetase complex. When it was discovered, it was identified as a cofactor protein that provides an efficient aminoacyl-tRNA synthesis trafficking channel for translation.[20] Moreover, the level of AIMP1 is increased in wounded skin, and AIMP1 plays a significant role in wound healing,[17] an AIMP1-derived peptide (AdP, amino acid region 6-46, sh-oligopeptide 5/sh-oligoepeptide 5 SP) has the potential to be used as a cosmeceutical. AdP showed more potent activity for promoting fibroblast proliferation and collagen type I synthesis than EGF, a representative cosmeceutical ingredient. AdP also showed an anti-pigmentation effect, inhibiting melanin synthesis through tyrosinase inhibition. Compared with other cosmeceutical ingredients, such as growth factors and peptides with a single activity for anti-aging, AdP is a novel cosmeceutical ingredient that has dual functions with anti-wrinkle and whitening effects. As some materials interact with each other and trigger adverse effects, the use of fewer ingredients is better for multifunctional cosmetic products. Thus, AdP, with its dual functions, is an alternative ingredient that can be used to reduce the number of components in multifunctional cosmetics.

As AIMP1 shows anti-tumorigenic activity,[21] AdP could suppress tumorigenicity, unlike EGF or TGF-β1. Besides the anti-tumorigenic effect of AdP, AdP was also safe in terms of cytotoxicity and immunogenicity. In conclusion, AdP could be beneficial for anti-aging and as a safe cosmeceutical ingredient.

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