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ORIGINAL ARTICLE

Effect of *A. polygama* APEE (Actinidia polygama ethanol extract) or APWE (Actinidia polygama water extract) on wrinkle formation in UVB-irradiated hairless mice

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Abstract

Background: *Actinidia polygama* (silver vine) is considered a medical plant which has been used in oriental medicine. It has been used for the treatment of pain, gout, rheumatoid arthritis, and inflammation. Few studies reported on the effect of *Actinidia polygama* (silver vine) on skin photoaging.

Objective: To evaluate the anti-photoaging effect of the ethanol and water extracts of *A. polygama* (APEE and APWE, respectively) in UVB-irradiated hairless mice.

Methods: SKH-1 hairless mice were exposed to UVB irradiation (30–60 mJ/cm^2), following orally APEE or APWE oral administration for 10 weeks. We examined the effect on winkle improvement by a measuring Fullscope, PRIMOS, Craniometer, and Cutometer. Furthermore, we analyzed histological changes in mouse dorsal skin through hematoxylin and eosin (H&E) and Masson's trichrome (MT) staining. The expression of matrix metalloproteinase (1, 3, and 9) was analyzed by immunoblotting.

Results: Oral administration of APEE or APWE at 100 or 200 mg/kg in UVB-irradiated mice alleviated the symptoms of skin aging, such as wrinkling, epidermal hyperplasia, and water loss. In addition, the APEE or APWE oral administration increased skin elasticity by enhancing the production of type I collagen, elastin, and hyaluronic acid synthase and downregulating matrix metalloproteinase (1, 3, and 9) expression.

Conclusion: Based on results for our study, APEE or APWE could protect the UVB-mediated skin wrinkle and is new target for the developing anti-wrinkle cosmetics.

KEYWORDS
Actinidia polygama, photoaging, wrinkle, skin elasticity

Abbreviations: APEE(E), Actinidia polygama ethanol extract; APWE(W), Actinidia polygama water extract; ECM, extracellular matrix; MED, minimal erythema dose; MMP, matrix metalloproteinases; ROS, reactive oxygen species; UV, ultraviolet.

Yu-jin Kim and Jung Ok Lee contributed equally to the study.

1 | INTRODUCTION

Photoaging due to UV radiation causes dry skin, wrinkles, a decrease in skin tightening, pigmentation, an increase in epidermal thickness, and a decrease in skin moisture.[1,2] UV irradiation decreases procollagen production and results in the breakdown of collagen fibers (the main structural protein that maintains the tension and strength of skin).[3] It is regulated by matrix metalloproteinases (MMPs), a type of collagenase in the skin[4,5] Continuous exposure of skin to UV radiation reduces the elasticity of the dermal layer through physiological changes in the connective tissues, subsequently inducing wrinkle formation.[6]

The roles of various natural compounds have been being investigated in reducing skin damage and wrinkles.[7-9] *Actinidia polygama* (silver vine) has long been used to relieve pain, gout, rheumatoid arthritis, and inflammation.[10,11] In the previous study, *A. polygama* extracts show anti-inflammatory and anti-asthmatic effects by reducing the levels of interleukin (IL)-4, interleukin (IL)-5, interleukin (IL)-13, and immunoglobulin E (IgE) in an ovalbumin-induced allergic airway inflammation mouse model.[12] In addition, Bang et al.[10] demonstrated that the actinidiamide, extracted from *A. polygama*, reduces allergy and inflammation by inhibiting NO production and ß-hexosaminidase release in lipopolysaccharide (LPS)-stimulated RAW264.7 cells and IgE-sensitized RBL-2H3 cells. However, the effects of *A. polygama* against UVB radiation-induced wrinkle have not been investigated. In the present study, we studied the effects of both APEE and APWE on wrinkle formation in UVB-induced hairless mice.

2 | MATERIALS AND METHODS

2.1 | *Actinidia polygama* extracts

To obtain the ethanol extract (APEE) and water extract (APWE) of A. polygama, the dried fruits of silver vine were purchased from Minkyung Corperation (Seoul, Korea) and extracted with a 14-fold of 30% ethanol or water at about 85°C for 6 h. Each extract was filtered and concentrated up to 45% ± 5% of solid contents by vacuum evaporator under 60°C. The concentrates were mixed with dextrin (dextrin 30%: solid content 70% of weight ratio) and powdered using a spray dryer. The dosage of APEE and APWE used in this experiment was calculated as the solid content of these powdered extracts.

2.2 | Animals

Six-week-old SKH-1 hairless female mice were purchased from Saeron Bio, Inc. The mice were acclimatized for a period of seven days in the following conditions: 23 ± 2°C, 55% ± 10% humidity, in a light–dark cycle (12–12 h), with enough water and feed (without antibiotics). All animal experiments were conducted according to the Principles of Laboratory Animal Care of the NIH (National Institutes of Health) and received approval from the Chung-Ang University IACUC (Institutional Animal Care and Use Committee). Before evaluation, animals were anesthetized using zoletil 50 (50 mg/kg) and xylazine (10 mg/kg). In addition, all possible efforts were taken to avoid animal suffering and to minimize the number of animals used at each stage of the study. A total of 48 hairless mice were divided into the following six groups (8 mice in each group): normal (saline), UVB +saline, UVB +E100 (100 mg/kg of APEE), UVB +E200 (200 mg/kg of APEE), UVB +W100 (100 mg/kg of APWE), and UVB +W200 (200 mg/kg of APWE). The extracts or saline (200 µl) were administered orally to the mice six times a week for 10 weeks.

2.3 | UVB irradiation

Induction of photoaging through UVB irradiation using BIO-SPECTRA (Vilber Lourmat) was performed, as described previously.[13] The irradiation doses were increased weekly in increments of 1 minimal erythemal dose (1 MED = 40 mJ/cm^2). The starting dose of UVB radiation was 30 mJ/cm^2 during the first week, and the dose was increased weekly by UVB radiation until reaching 70 mJ/cm^2, which was maintained until 10 weeks. Immediately after each session of UVB irradiation, the extracts or saline (200 µl) were administered orally to the mice six times a week for 10 weeks.

2.4 | Assessment of wrinkle formation and hydration

To determine the severity of wrinkling, each hairless mouse was anesthetized, and its UVB-irradiated dorsal skin was photographed using a computerized hand-held USB camera PT system (Folliscope®; LeadM Corp), as described in a previous report.[14] Wrinkle severity (roughness) was measured using three-dimensional fringe projection (PRIMOSlite®; GFMesstechnik GmbH, Germany)[15] and analyzed using PRIMOS^{lilte} software version 5.8E. A stratum corneum (SC) hydration was assessed using a Corneometer CM820 (Courage+ Khazaka).

2.5 | Assessment of skin elasticity using Cutometer

Skin elasticity on back of mice was measured using Cutometer MPA 580 (Courage & Khazaka Kőln).[16] It generates negative pressure (450 mbar), causing the test area to enter the hole of the probe. Measurements were taken three times (suction time: 2 s; relaxation time: 2 s). The curves of the obtained skin deformation values were analyzed using the Software Cutometer® MPA 580, and a several parameters could be deducted from the U parameters: R2, the overall elasticity of the skin, including creep and creep recovery (Ua/Uf), and R7, the ratio of elastic recovery to the total deformation (Ur/Uf).

2.6 | RNA extraction and real-time PCR

Total RNA was extracted from skin tissue using Tri-RNA reagent (Favorgen Biotech, WAPing-Tung 908, Taiwan). cDNA synthesis was performed using PrimeScriptTM RT Master Mix (Takara). Resulting cDNA was subjected to real-time PCR using CFX96 (Bio-Rad) and qPCR 2 × PreMIX SYBR (Enzynomics). qPCR was performed for 40 cycles (95°C for 10 min; 60°C for 15 s; and 72°C for 30 s), following by the denaturation process at 95°C for 10 min. Expression data were calculated as a cycle threshold (Ct) value using the 2−ΔΔCT quantification method normalized to GAPDH. Oligonucleotides used for real-time PCR were as follows: mouse Col1a1, forward, 5′-GCT CCT CTT AGG GGC CAC T-3′, reverse, 5′-CCA CGT CTC ACC ATT GGG G-3′, mouse MMP1, forward, 5′-AAC TAC ATT TAG GGG AGA GGT GT-3′, reverse, 5′-GCA GCG TCA AGT TTA ACT GGA A-3′, mouse MMP3, forward, 5′-TGG AGA TGC TCA CTT TGA CG-3′, reverse, 5′-GCC TTG GCT GAG TGG TAG AG-3′, mouse MMP9, forward, 5′-TGT CTG GAG ATT CGA CTT GAA GTC-3′, reverse, 5′-TGA GTT CCA GGG CAC ACC A-3′, mouse GAPDH, forward, 5′-AGG TCG GTG TGA ACG GAT TTG-3′, and reverse, 5′-TGT AGA CCA TGT AGT TGA GGT CA-3′.

2.7 | Western blot analysis

The skin tissues were collected and lysed in PRO-PREP (iNtRON), containing a protease inhibitor cocktail (Complete™; Roche). The supernatant was centrifuged for 10 min, followed by the measurement of protein concentration using a BCA protein assay kit (Bio-Rad). Following quantification, equal amounts of protein were resolved on 10% SDS-PAGE gels and electrotransferred to polyvinylidene fluoride membranes (Millipore). After blocking with 5% skim milk in Tris-buffered saline containing 0.5% Tween-20 (TBST), the membranes were probed overnight at 4°C with the following antibodies: anti-MMP1 (ab137332, Abcam), anti-MMP3 (ab52915, Abcam), anti-MMP9 (ab38898, Abcam), and anti-β-actin (sc-47778, Santa Cruz Biotechnology, Inc.). After washing, the membranes were incubated with HRP-conjugated anti-mouse (Vector Labs Inc.) or anti-rabbit (Vector Labs Inc.) secondary antibodies. Immunoreactive signals were detected using enhanced chemiluminescence reagents (EzWestLumi plus; ATTO).

2.8 | Histological analysis

Each tissue block was cut into 5-μm sections and placed on microscope slides. The tissue slides were rehydrated using ethanol after deparaffinization with xylene. Next, the tissues were stained using hematoxylin and eosin (H&E) dye (to observe changes in epidermal thickness) and Masson's trichrome (MT) (for collagen), and examined using optical microscopy (DM750, Leica).

2.9 | Statistical analysis

Data were analyzed using GraphPad Prism version 7.0 (GraphPad Software). Data are expressed as the mean ± standard deviation (SD) of at least three independent experiments. Statistical significance was assessed using one-way ANOVA analysis followed by Tukey's multiple comparisons test. A p-value < 0.05 indicated a statistically significant difference.

3 | RESULTS

3.1 | Oral administration of *A. polygama* extracts reduces UVB-induced wrinkle formation

To determine whether APEE or APWE prevents wrinkle formation in UVB-irradiated hairless mice. The dorsal skin of hairless mice was irradiated with UVB followed by APEE or APWE (100 or 200 mg/kg) orally administration by six times a week for 10 weeks (Figure 1A). An image of wrinkle formation was captured by using Folliscope. These results indicate that wrinkles were well induced by UVB and APEE or APWE treatment decreases the wrinkle formation at 10 weeks (Figure 1B).

3.2 | Oral administration of *A. polygama* extracts suppress UVB-mediated roughness of skin

To analysis detailly the effect of *A. polygama* extracts on the skin roughness, the change of winkle's pattern after oral administration in UVB-induced photoaging mice was confirmed by roughness parameters using PRIMOS^{lite}, which is an optical three-dimensional skin measurement system. Consequently, it was observed that the group with UVB-saline had a deep wrinkle and numerous wrinkles. However, the wrinkles of the group orally administrated with APEE or APWE were found to be like those of the group without UVB irradiation (Figure 2A). The depth of wrinkles was quantitatively improved by the APEE 200 mg/kg (**$p < 0.01$ vs. UVB-saline) or APWE 100 or 200 mg/kg (*$p < 0.05$ vs UVB-saline) administration when comparing Ra (Figure 2B). Taken together, these results suggested that oral administration of APEE or APWE reduces UVB-induced wrinkle formation.

3.3 | Oral administration of *A. polygama* extracts enhances both hydration and elasticity of skin

To deeply evaluate skin barrier function of the APEE or APWE, we measured the value of corneometer to measure the hydration of the epidermis outer layer following APEE or APWE after UVB irradiation. The APEE or APWE recovered the reduced skin hydration compared to that in the UVB-saline group (Figure 3A). A skin elasticity was measured using a Cutometer (R2 and R7). The loss of the skin elasticity was also suppressed in APEE or APWE orally administered

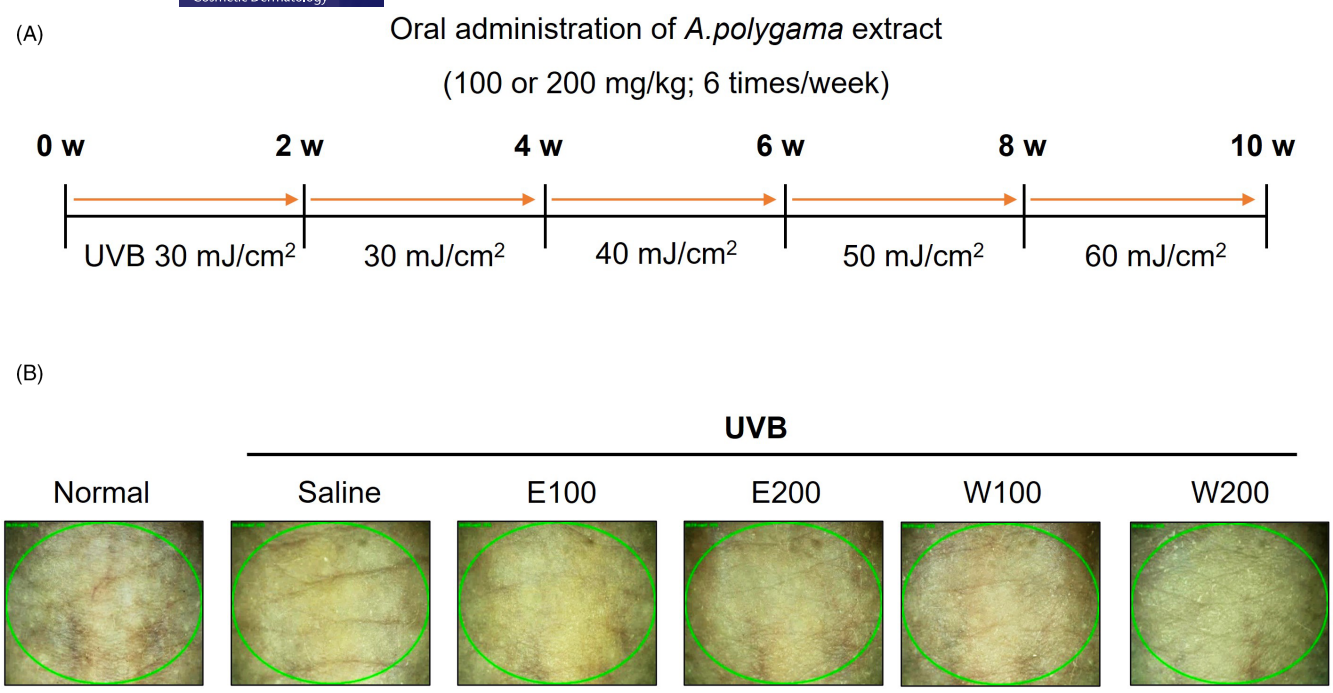

FIGURE 1 Effect of *A. polygama* extracts on UVB-induced wrinkle formation. (A) A schematic diagram of animal experiments. Dorsal skin of hairless mice (eight mice per group) was subjected to UVB irradiation, followed by the administration of APEE or APWE (100 or 200 mg/kg) for 10 weeks. (B) To evaluate changes in dorsal wrinkle formation, images were taken using a folliscope

mice (Figure 3B,C). These results suggest that APEE or APWE treatment could protect photoaging by regulating of the hydration and elasticity of skin.

3.4 | Oral administration of *A. polygama* extracts protects loss of collagen in UVB-irradiated mice

Epidermal hyperplasia is closely related to wrinkle formation.[17] UVB irradiation induced epidermal hyperplasia; however, the UVB irradiation-mediated increase of epidermal thickness was markedly decreased in mice orally administered APEE or APWE (Figure 4A,C). Collagen is the main structural component of connective tissue. The main cause of Winkles formation is to be a reduction in the amount of collagen.[13] To evaluate the effect of APEE or APWE on the collagen expression, we performed Masson's trichrome (MT) staining to identify collagen fibers. In the APEE or APWE groups, collagen level was restored compared to that in the UVB-irradiated group (Figure 4B,D). These results suggested that APEE or APWE could suppress the loss of epidermal thickness and collagen by UVB induction.

3.5 | *A polygama* extracts regulates the expression of collagen, procollagen and MMPs

To analyze deeply the effect of the APEE or APWE on the collagen regulation, we measured the mRNA expression of type I collagen in UVB-irradiated dorsal skin. APEE or APWE oral administration protects UVB-induced collagen type1 down-regulation (Figure 5A). UVB-induced deep wrinkle formation is caused by the degradation of dermal collagen. The main degradation enzymes of the collagen in extracellular matrix (ECM) are matrix metalloproteinases (MMPs).[18] We found that MMP1, MMP3, and MMP9 mRNA and protein expression were increased following UVB irradiation. However, oral administration of APEE or APWE significantly suppressed protein and mRNA expression of MMP1, MMP3, and MMP9 compared to that in the saline-treated group (Figure 5B,C). These results indicate that APEE or APWE inhibited the UVB-induced wrinkle formation by up-regulating of collagen type1 and downregulating MMP1, MMP3, and MMP9 expressions.

4 | DISCUSSION

Ultraviolet irradiation of the skin interferes with the synthesis of collagen by increasing the production of reactive oxygen species (ROS).[19] Additionally, by up-regulating MMPs, it promotes the degradation of the extracellular matrix (ECM) in the dermis.[20,21] The use of antioxidants and anti-inflammatory agents may improve UV-mediated photodamage by up-regulating MMP-1 and MMP-3 expression.[22,23] Previous studies have demonstrated that *A. polygama* extracts or compounds from *A. polygama* exhibit antioxidant and anti-inflammatory activity, which may contribute to anti-photoaging.[10,11,24,25,26,27] The number and depth of the wrinkles formed on the dorsal skin of the mouse after UVB irradiation were confirmed to have increased when

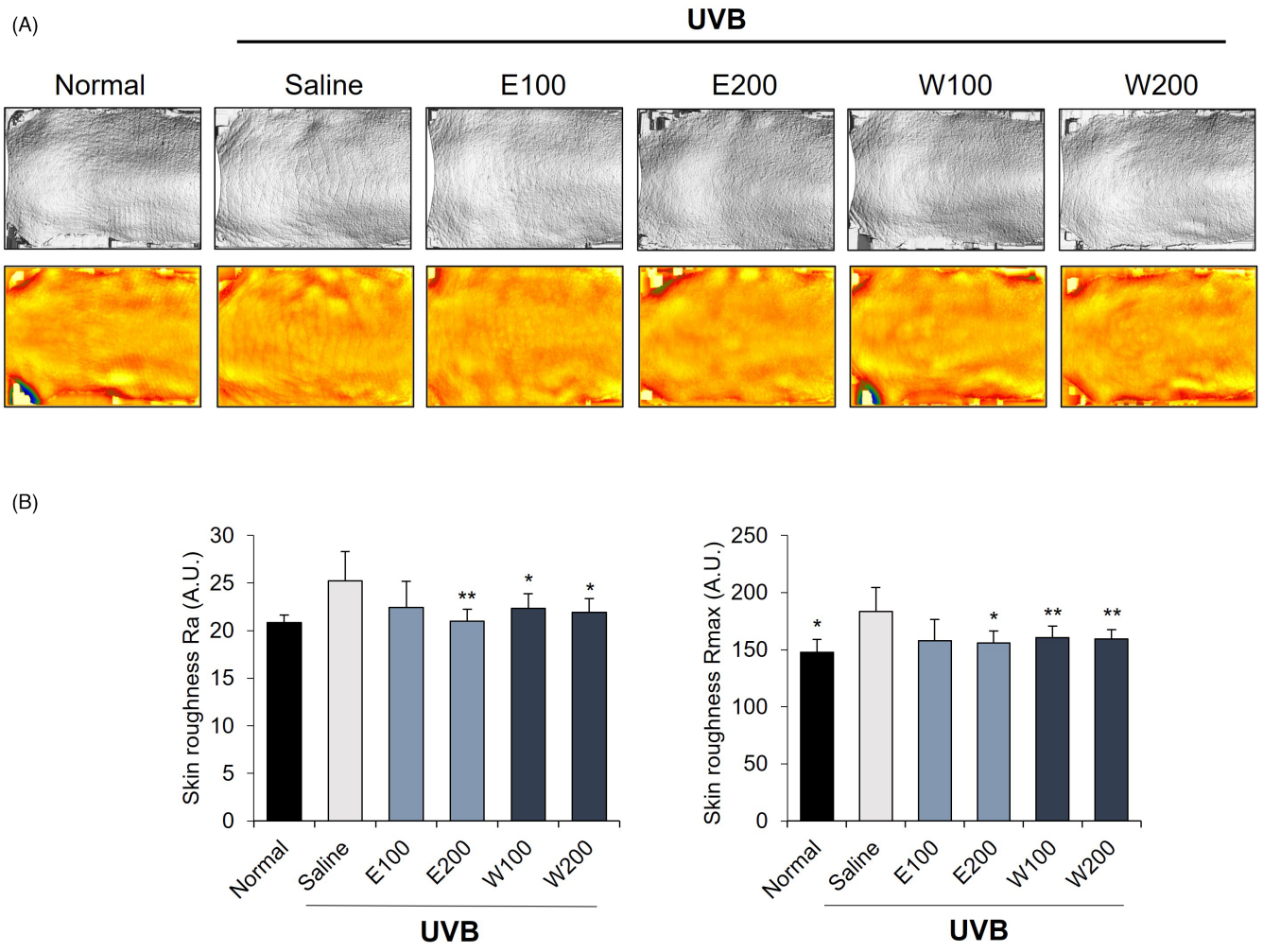

FIGURE 2 Reduction in UVB-induced wrinkle formation after orally administration of *A. polygama* extracts. (A) Optical three-dimensional skin image of dorsal skin of hairless mice using PRIMOS^{lite}. Skin roughness was evaluated after 10 weeks of UVB irradiation. (B) Quantification of wrinkles (roughness) showed that the depth of the wrinkles was reduced by APEE or APWE. Ra: average roughness, Rmax: maximum roughness. All data represent mean ± standard deviation. Significant value was $^{*}p < 0.05$, $^{**}p < 0.01$ versus UVB +saline. E100 or E200; 100 or 200 mg/kg of APEE, W100 or W200; 100 or 200 mg/kg of APWE

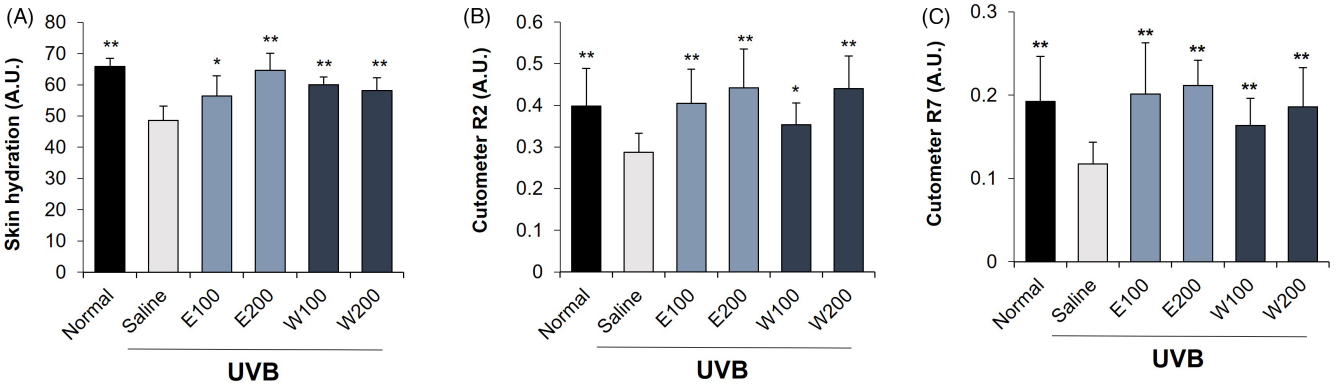

FIGURE 3 Effect of *A. polygama* extracts on both hydration and elasticity of skin. Hairless mice were exposed to UVB (30–60 mJ/cm^2), followed by the administration of APEE or APWE (100 or 200 mg/kg) for 10 weeks. (A) Skin hydration was evaluated using a Corneometer, respectively. The effects of APEE or APWE on (B) gross elasticity (R2) and (C) skin firmness (R7) of skin were measured using a Cutometer. All data represent mean ± standard deviation. Significant value was $^{*}p < 0.05$, $^{**}p < 0.01$ versus UVB + saline. E100 or E200; 100 or 200 mg/kg of APEE, W100 or W200; 100 or 200 mg/kg of APWE

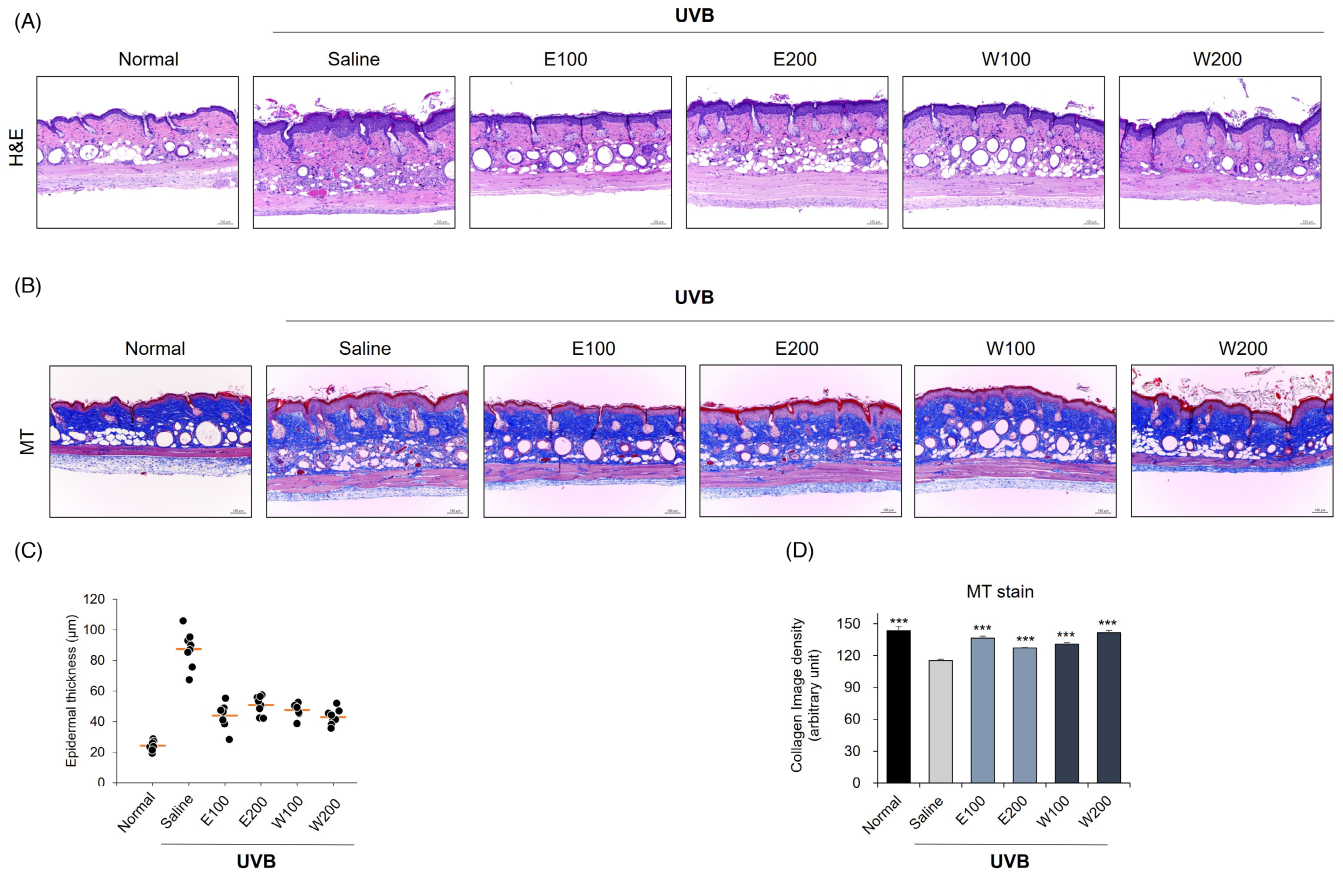

FIGURE 4 Effect of *A. polygama* extracts on epidermal thickness and collagen in UVB-irradiated hairless mice. Hairless mice were exposed to UVB (30–60 mJ/cm^2), followed by the administration of APEE or APWE (100 or 200 mg/kg) for 10 weeks. (A) Skin tissue sections were stained using hematoxylin and eosin (H&E) and (B) Masson trichrome (MT). Scale bar, 100 μm. (C) Epidermal thickness was measured using ImageJ. (D) Collagen fiber was measured using Image J. All data represent mean ± standard deviation. Significant value was $^*p < 0.05$, $^{**}p < 0.01$ versus UVB + saline. E100 or E200; 100 or 200 mg/kg of APEE, W100 or W200; 100 or 200 mg/kg of APWE

compared with those of the non-UVB irradiation group (Figure 1B). We evaluated the degree of wrinkle reduction by oral administration of APEE or APWE for 10 weeks as a parameter of skin roughness using a PRIMOS^{lite}. Using the evaluation results of Rmax and Rt, we quantitatively showed the effects of wrinkle improvement (Figure 2B). We also demonstrated that skin with wrinkling had a significant reduction in elastic measures with cutometer. The elastic properties of the skin in the UV-exposed mice treated with APEE or APWE were significantly repaired in the major measures, R2 and R7, compared with the UV-exposed mice (Figure 3B,C). In addition, APEE or APWE orally administration suppressed the degradation of collagen in the dorsal skin of UVB-irradiated mice (Figure 4B). Furthermore, APEE or APWE inhibits UVB-induced MMP1, MMP3, MMP9 mRNA and protein (Figure 5B,C). In the further study, analysis of the mechanism of the regulation on the collagen and MMPs expression is need.

Several compounds including actinidine, dehydroiridodial, triterpenoids, flavonol triglycosides, and iridoid monoterpene lactones have been isolated from *A. polygama*.[25,26,28,29] Actinidine, a monoterpenoid alkaloid and thiol protease, was first isolated from *A. polygama*. Kissper, produced from actinidin, has been shown to have antioxidant and anti-inflammatory activity in intestinal cells in vitro, and in the ex vivo tissues of patients suffering from Crohn's disease[30] and in the mucosa of patients suffering from celiac disease.[31] In addition, the extracts of Actinidia species containing protein-dissolving enzymes (actinidin) have been shown to be effective in wound healing, diabetic foot ulcers, burns, and pressure ulcers.[32-34] The diacetylated flavonol triglycoside, isolated from *A. polygama*, has been shown to exert antioxidant effects.[26] ROS can be scavenged using antioxidants including polyphenolic compounds and flavonoids.[35,36] UVB-induced ROS generation results in the production of proinflammatory mediators, such as cytokines, NO, and cyclooxygenase (COX)-2, leading to skin inflammation.[37] The increase in the levels of cytokines and NO causes skin inflammation and degradation of the extracellular matrix.[38,39] A previous study reports that APWE suppressed LPS-induced NO production and inducible NO synthase (iNOS) expression.[24] α-Linoleic acid, isolated from *A. polygama*, inhibited the expression of COX-2, iNOS, and tumor necrosis factor-α (TNF- α) by inhibiting the activation of NF-κB and MAPK in LPS-activated Raw264.7 cells.[40] These results support the hypothesis that APEE or APWE have anti-wrinkle effect on UVB-induced wrinkle formation.

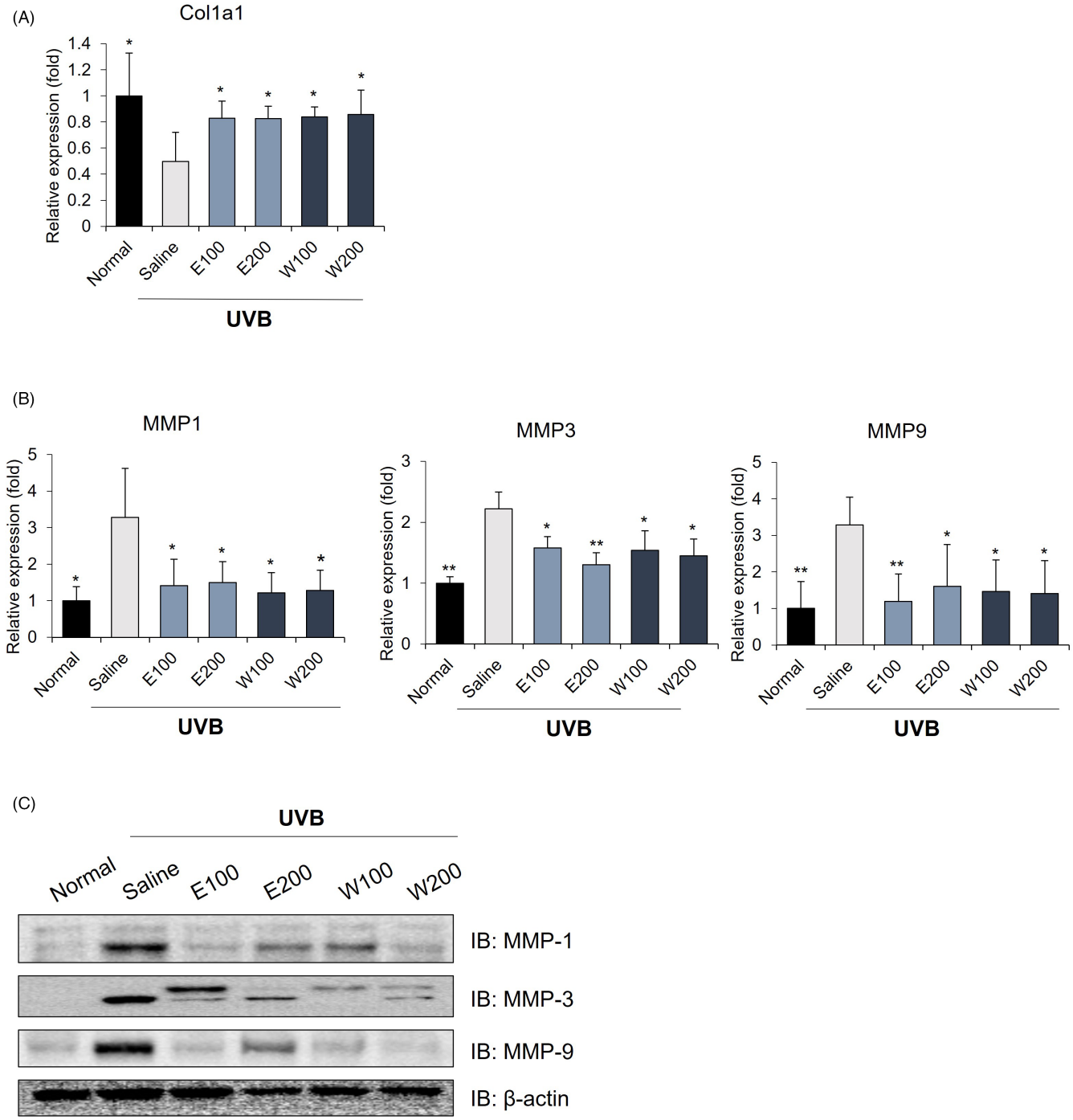

FIGURE 5 Effect of *A. polygama* extracts on procollagen and MMPs expression in UVB-irradiated hairless mice. Hairless mice were exposed to UVB (30–60 mJ/cm^2), followed by the administration of APEE or APWE (100 or 200 mg/kg) for 10 weeks. (A) Transcripts of Col1a1 were quantified using real-time PCR. (B) Transcripts of MMP1, MMP3, and MMP9 were quantified using real-time PCR. (C) Lysates from skins were immunoblotted with anti-MMP1, anti-MMP3, anti-MMP9, and β-actin antibodies. All data represent mean ± standard deviation. Significant value was $^*p < 0.05$, $^{**}p < 0.01$ versus UVB + saline. E100 or E200; 100 or 200 mg/kg of APEE, W100 or W200; 100 or 200 mg/kg of APWE

5 | CONCLUSION

In conclusion, APEE or APWE orally administration protects UVB-induced photoaging. We believe that APEE or APWE is a great therapy material for UVB-induced skin damage.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

B.J.K and J.O.L designed and wrote the manuscript. Y.K, J.N, S.P, and E.L. contributed to the experiment and data analysis. K.Y, S.K, and J.L analyzed the data. All authors have read and agreed to the published version of the manuscript.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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