

The Effects of Apigenin Isolated from Sungkai Leaves (*Peronema canescens* J.) on Skin Collagen Density in Male White Mice (*Mus musculus*) in an Ultraviolet B-Induced Aging Model

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What's Known

- Ultraviolet B (UVB) radiation accelerates skin aging by inducing oxidative stress, elevating malondialdehyde (MDA) levels, and degrading collagen.
- Apigenin, a flavonoid found in many plants, is recognized for its antioxidant and anti-inflammatory effects.

What's New

- This study provided the first empirical evidence of apigenin isolated from Sungkai leaves against UVB-induced oxidative stress and collagen degradation in mice.
- The results demonstrated a dose-dependent antioxidant effect, with 100 mg/Kg BW normalizing MDA levels and preserving collagen density to levels comparable to those in healthy controls.

Abstract

Background: Skin aging is a multifactorial process driven by intrinsic factors and environmental exposure, particularly ultraviolet radiation, which induces oxidative stress and the degradation of dermal collagen. Given the limited evidence regarding apigenin derived from *Peronema canescens*, this study aimed to evaluate its protective effects against oxidative stress and collagen degradation in an ultraviolet B (UVB)-induced skin aging model.

Methods: A true experimental study with a post-test-only control group design was conducted from March to August 2025 in Padang, Indonesia. Twenty-five male white mice (*Mus musculus*) were randomly assigned into five groups (n=5 per group): a negative control, a UVB-exposed positive control, and three UVB-exposed treatment groups receiving apigenin at 25, 50, or 100 mg/Kg body weight (BW) for 30 days. Data were analyzed using SPSS version 27. Normality and homogeneity of variances were assessed using the Shapiro–Wilk and Levene tests, respectively. Malondialdehyde (MDA) levels were analyzed using one-way ANOVA followed by Tukey's *post hoc* test, while collagen density scores were analyzed using the Kruskal–Wallis test followed by Dunn's test with Bonferroni correction.

Results: MDA levels differed significantly among groups ($F[4,20]=61.743$, $P<0.001$). The 100 mg/Kg BW group did not differ significantly from the negative control, indicating the restoration of MDA levels to near-normal values. Collagen density also differed significantly among groups ($P=0.003$), with significant improvement in the 100 mg/Kg BW group compared with the positive control (adjusted $P=0.049$).

Conclusion: Apigenin derived from *P. canescens* exhibited dose-dependent antioxidant and dermoprotective effects in a UVB-induced photoaging model.

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Keywords • Apigenin • Malondialdehyde • Collagen • Skin aging

Introduction

Photoaging is a progressive cutaneous aging process caused predominantly by chronic ultraviolet exposure, with ultraviolet-B (UVB) radiation playing a major role in dermal injury.¹ At the

molecular level, UVB increases the formation of reactive oxygen species (ROS), disrupts redox homeostasis, and damages lipids, proteins, and nucleic acids.² Persistent oxidative stress activates signaling pathways that upregulate the expression of matrix metalloproteinases (MMPs), particularly matrix metalloproteinase 1 (MMP-1), thereby promoting dermal collagen degradation.¹⁻³ These changes contribute to wrinkling, loss of elasticity, and irregular skin texture.³

Collagen constitutes approximately 70-90% of the extracellular matrix of the skin and is a major structural protein supporting tissue strength, elasticity, and repair.⁴ In photoaged skin, collagen synthesis decreases while collagen degradation increases, partly through ROS-mediated proteolytic pathways.⁵ Malondialdehyde (MDA), a stable end product of lipid peroxidation, is commonly used as a marker of oxidative injury and membrane damage.^{6, 7} Therefore, evaluating MDA alongside collagen density provides complementary biochemical and histological information in a UVB-induced aging model.

Sungkai (*Peronema canescens* Jack) is an Indonesian medicinal plant traditionally used to treat bruises and fever, and is increasingly studied because of its phytochemical profile.^{8, 9} Its leaves contain flavonoids, alkaloids, saponins, tannins, steroids, and phenolic compounds, and its ethanolic extracts were shown to have antioxidant activity.⁸⁻¹¹ Anti-inflammatory, antibacterial, antidiabetic, and immunomodulatory activities have also been reported, supporting further investigation of Sungkai-derived compounds for skin protection.^{8, 10, 11}

Apigenin, a naturally occurring flavone found in *P. canescens* leaves, is widely recognized for its antioxidant and photoprotective properties, making it a promising candidate for preventing ultraviolet-induced skin damage.¹²⁻¹⁴ Experimental evidence demonstrated that apigenin could attenuate oxidative stress by reducing reactive oxygen species-mediated lipid peroxidation and enhancing endogenous antioxidant defenses, thereby limiting cellular injury in skin tissues.^{14, 15} At the molecular level, apigenin modulates key signaling pathways involved in photoaging, particularly by inhibiting mitogen-activated protein kinase (MAPK) activation and suppressing activator protein-1 (AP-1), which in turn reduces MMP-1 expression, a critical mediator of collagen degradation in the dermis.¹⁶⁻¹⁸

Although the effects of apigenin on the skin have been studied using other sources, no study to date has investigated apigenin

isolated specifically from Sungkai leaves in a UVB-induced aging model. Therefore, this study aimed to investigate the effects of apigenin isolated from Sungkai leaves on MDA levels and collagen density in the skin of male white mice (*Mus musculus*) subjected to UVB-induced aging. The findings were expected to provide additional scientific validation for the antioxidant properties of apigenin and support the development of phytotherapy strategies aimed at preventing skin aging.

Materials and Methods

Study Design

This study employed a true experimental design with a post-test-only control group, in which each male white mouse (*Mus musculus*) served as an experimental unit. The study was conducted over 6 months (March–August 2025) at multiple facilities, including the Animal House, Immunology and Serology Laboratory, Pharmacology Laboratory, and Quantitative Pharmaceutical Chemistry Laboratory of the Faculty of Pharmacy, Andalas University; The Biochemistry Laboratory of the Faculty of Medicine, Andalas University; and the Pathology and Anatomy Laboratory of the Faculty of Medicine, Baiturrahmah University. All experimental procedures were reviewed and approved by the Ethics Committee of the Faculty of Pharmacy, Andalas University (Approval No. 59/UN16.10.D.KEPK-FF/2025). All efforts were made to minimize animal suffering and reduce the number of animals used.

Tools and Materials

The tools used in this study included an analytical balance (Ohaus, USA), an animal weighing balance (Ohaus, USA), animal cages, beakers (Pyrex, USA), vials, oral gavage needles (Terumo, Japan), a narrowband UV-B lamp PL-S 9W/01/2P, 311 nm (Philips, Netherlands), a centrifuge (Health, China), surgical scissors (OneMed, Indonesia), tweezers (OneMed, Indonesia), forceps (Surrtext, Pakistan), micropipettes (Dragonlab, China), sterile pipette tips (Labnet, USA), a vortex mixer (Gemmy, Taiwan), microtubes (Medcare, China), EDTA tubes (OneMed, Indonesia), a spectrophotometer (Spectronic, USA), a microscope (Olympus CX33, Japan), a microtome, and other standard laboratory equipment.

The materials and reagents used in this study included sodium carboxymethyl cellulose (Na-CMC; Merck, Germany), distilled water (BarataChem, Indonesia), diethyl ether (Merck, Germany), 4% paraformaldehyde (Merck, Germany),

ethanol (Supelco, USA), xylene (Supelco, USA), paraffin wax (Merck, Germany), hematoxylin solution (Merck, Germany), 1% eosin Y solution (Merck, Germany), 1% acid alcohol (Supelco, USA), 0.1% ammonia solution (Merck, Germany), Canada balsam (Loba Chemie, India), 1% ovalbumin (ROFA Laboratory, Indonesia), thiobarbituric acid solution (Merck, Germany), and 15% trichloroacetic acid solution (Merck, Germany).

Animals

A total of 25 male BALB/c white mice (*Mus musculus*), aged 8–10 weeks and weighing 25–35 g, were obtained from a certified local breeding facility. Upon arrival, the animals underwent a 7-day acclimatization period under controlled conditions (temperature 25 ± 2 °C, relative humidity $50 \pm 5\%$, and a 12-hour light/dark cycle) in accordance with standard guidelines for laboratory animal care.¹⁹ All mice were housed in standard plastic cages with bedding material and were provided *ad libitum* access to standard pellet feed and water. Mice that were sick, died, or failed to gain weight during acclimatization were excluded from the study. Only animals showing normal behavior and weight change within $\pm 10\%$ of their initial body weight (BW) were included.

During the 30-day experimental period, the animals were monitored daily for clinical signs of distress, severe infection at the irradiation site, excessive BW loss, and mortality. Mice that developed severe local infection, lost more than 20% of their baseline BW, or died during the study period were excluded from the final analysis. In the present study, no animals met these exclusion criteria after randomization, and all included animals completed the 30-day observation period.

Randomization, Group Allocation, and Blinding

Animals were randomly allocated to five experimental groups (n=5 per group) using a simple randomization method. The groups were as follows:

- **K⁻ (Negative Control):** Healthy mice administered only 0.5% Na-CMC suspension orally for 30 days, without UVB exposure.

- **K⁺ (Positive Control):** UVB-induced aging model mice administered 0.5% Na-CMC suspension orally for 30 days.

P1 (Treatment I): UVB-induced mice were administered 25 mg/Kg BW apigenin suspension orally once daily for 30 days.

P2 (Treatment II): UVB-induced mice were administered 50 mg/Kg BW apigenin suspension orally once daily for 30 days.

P3 (Treatment III): UVB-induced mice were administered 100 mg/Kg BW apigenin suspension orally once daily for 30 days.

Outcome assessments were performed by an investigator blinded to group allocation. The follow-up time for all experimental groups was 30 days.

Preparation and Administration of Apigenin Suspension

The apigenin isolate used in this study was prepared according to a previously published protocol by the authors, involving ethanol extraction, liquid–liquid partitioning (n-hexane and ethyl acetate), and chromatographic purification, with structural confirmation by UV-Vis, FT-IR, ¹H/¹³C NMR, and UPLC–MS/MS (negative ion mode; m/z 268.99).¹³

Apigenin was suspended in 0.5% sodium carboxymethyl cellulose (Na-CMC). To prepare the Na-CMC vehicle, 250 mg of Na-CMC was ground in a mortar, then gradually mixed with 10 mL of hot water while grinding to form a homogeneous gel. The mixture was diluted with distilled water to a final volume of 50 mL. Apigenin isolate was added and homogenized to obtain the required concentrations. The suspensions were administered orally once daily using an oral gavage for 30 consecutive days.

UVB Irradiation Procedure

UVB irradiation was applied to the shaved dorsal skin (2×5 cm) of the mice, which were kept hairless throughout the study. Irradiation was conducted three times per week (Monday, Wednesday, and Friday) using a Philips PL-SW9/01/2P narrowband 311 nm UVB lamp (Philips, Netherlands), positioned approximately 20 cm from the skin surface. The cumulative UVB dose was 840 mJ/cm² with the following schedule:

- Week 1: 50 mJ/cm² for 50 sec
- Week 2: 70 mJ/cm² for 70 sec
- Week 3: 80 mJ/cm² for 80 sec
- Week 4: 80 mJ/cm² for 80 sec

Blood Collection and MDA Assay

At the end of the experimental period, blood samples (1 mL) were collected from the carotid artery under anesthesia. Samples were anticoagulated with ethylenediaminetetraacetic acid (EDTA) and incubated at room temperature for 30 min, then centrifuged to obtain plasma. MDA levels were measured using the thiobarbituric acid reactive substances (TBARS) assay, which quantified the pink MDA–TBA complex spectrophotometrically at 532–535 nm.²⁰

Skin Tissue Collection and Histology

After blood collection, skin samples (2.5 cm×2 mm) were excised from the dorsal area, fixed in 10% formalin, and processed for histological examination. Tissues were embedded in paraffin, sectioned, and stained with hematoxylin-eosin (H&E). Sections were dehydrated through a graded series of alcohols, cleared in xylene, and mounted with a coverslip.

Collagen Density Assessment

Collagen density was evaluated under an Olympus CX33 light microscope (Olympus, Japan) at 40× magnification from three randomly selected fields using an S-shaped observation pattern. Collagen density was scored as follows:²¹

- 0: No collagen fibers
- +1: Low collagen density (25%)
- +2: Moderate collagen density (50%)
- +3: Dense collagen density (75%)
- +4: Very dense collagen density (100%)

Sample Size Justification

The sample size was determined using Federer's formula: $(n-1)(t-1) \geq 15$, where n represents the number of subjects per group and t represents the number of experimental groups. With five groups included in this study ($t=5$), the minimum required sample size per group was calculated as $n \geq 4.75$. Therefore, five animals were allocated to each group ($n=5$) to satisfy the minimum requirement and ensure adequate statistical validity.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY, USA), and figures were prepared using R software (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were presented according to data distribution. MDA levels were expressed as mean±SD, whereas collagen density scores were expressed as median and interquartile range (IQR). Data normality was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated using Levene's test. The MDA levels fulfilled the assumptions of normality and homogeneity. Therefore, comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) *post hoc* test. Collagen density scores did not meet the assumption of normality and were ordinal. Therefore, comparisons among groups were performed using the Kruskal–Wallis test, followed by Dunn's *post hoc* test with Bonferroni adjustment for multiple comparisons. Statistical significance was set at $P < 0.05$.

Results

Malondialdehyde Level Assessment

MDA levels across experimental groups are presented in figure 1. The positive control group exhibited the highest MDA concentration, reflecting severe oxidative damage induced by UVB irradiation, and the negative control group

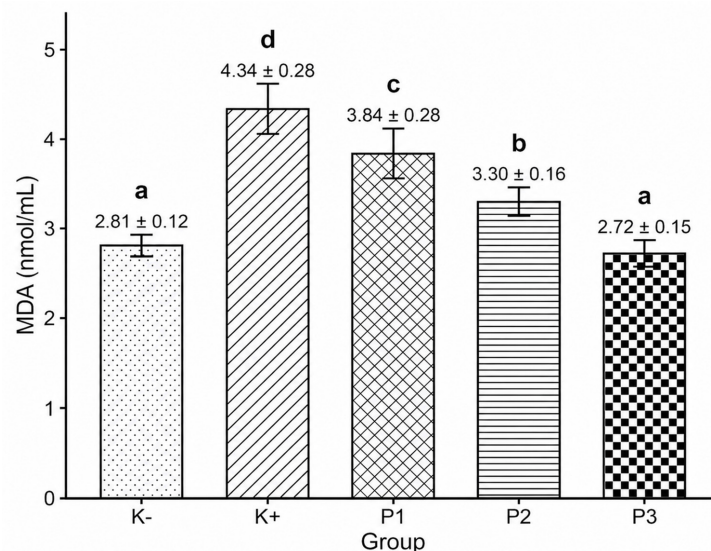


Figure 1: The figure shows the Malondialdehyde (MDA) levels in male white mice administered with apigenin isolated from *Peronema canescens* leaves. Different lowercase letters (a–d) indicate significant differences between groups at $P < 0.05$ based on one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference *post hoc* test. Groups sharing the same letter are not significantly different. K-: Negative control receiving sodium carboxymethyl cellulose without ultraviolet B exposure; K+: Positive control receiving sodium carboxymethyl cellulose with ultraviolet B exposure; P1: Ultraviolet B exposure and apigenin at 25 mg/Kg body weight (BW); P2: Ultraviolet B exposure and apigenin at 50 mg/Kg BW; P3: Ultraviolet B exposure and apigenin at 100 mg/Kg BW.

showed low MDA levels, representing normal physiological conditions.

A dose-dependent reduction in MDA levels was observed in mice treated with apigenin isolate from Sungkai leaves. The 100 mg/Kg BW group exhibited the lowest MDA level, comparable to that of the negative control, suggesting near-complete protection against UVB-induced lipid peroxidation. The 50 mg/Kg BW group showed partial protection, with MDA levels lower than those of the positive control. However, it was still higher than those of both the negative control and the 100 mg/Kg BW group. The 25 mg/Kg BW group exhibited only minimal protection, with MDA levels closer to those of the untreated UVB-exposed mice.

Assumptions of normality and homogeneity of variance were met based on the Shapiro–Wilk and Levene's tests, respectively. The results of ANOVA revealed a significant effect of apigenin treatment on MDA levels ($F[4, 20]=61.743$, $P<0.001$). Subsequent Tukey's HSD *post hoc* analysis identified four distinct subsets (figure 1). The 100 mg/Kg BW group clustered with the negative control, indicating no significant difference between these groups. The 50 mg/Kg and 25 mg/Kg BW groups formed separate subsets, each differing significantly from the negative control and the 100 mg/Kg BW group. The positive control group constituted a distinct subset with the highest MDA levels, which were significantly different from those of all other groups.

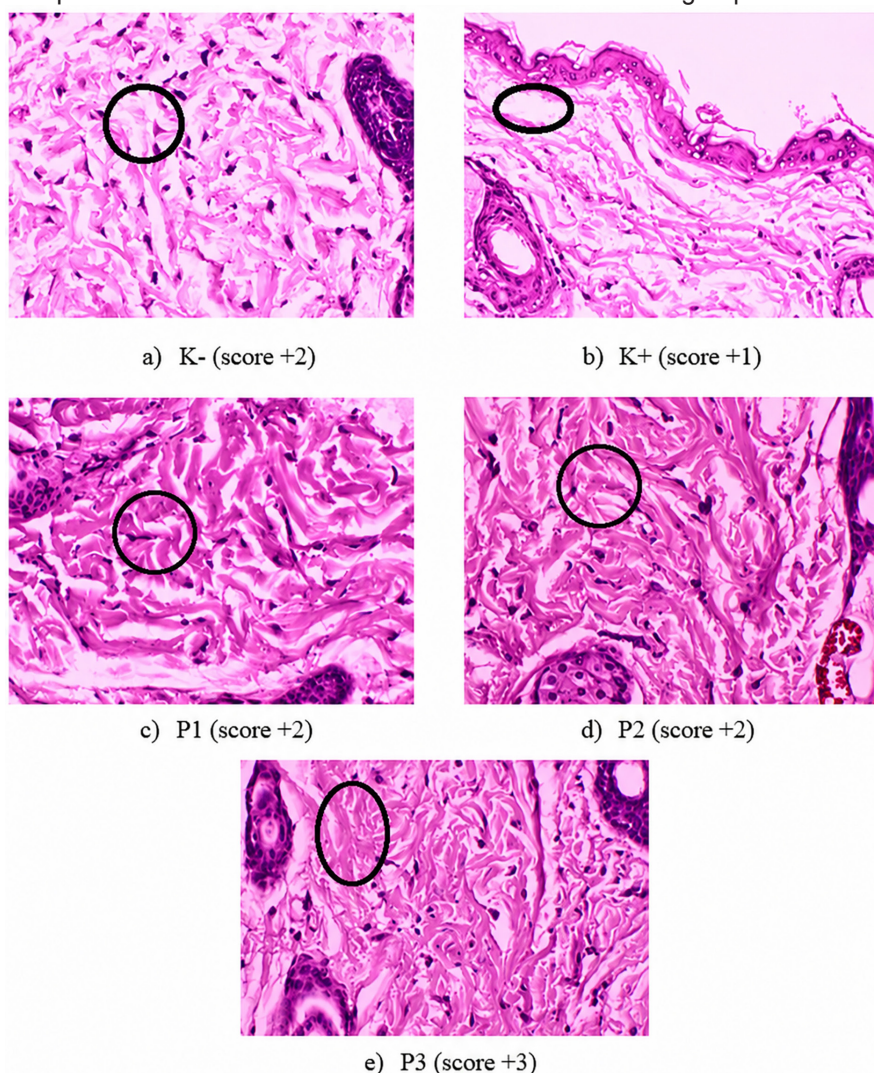


Figure 2: The images show the histopathological assessment of collagen density in the dorsal skin of male white mice (*Mus musculus*) stained with hematoxylin–eosin at 40× magnification. Representative micrographs are shown for the following experimental groups: (a) negative control group, (b) positive control group, (c) P1 group treated with apigenin at 25 mg/Kg BW, (d) P2 group treated with apigenin at 50 mg/Kg BW, and (e) P3 group treated with apigenin at 100 mg/Kg BW. Arrows indicate representative areas used for collagen density evaluation. Loosely arranged and fragmented collagen fibers indicate low collagen density, whereas compact and densely organized collagen bundles indicate high collagen density. Collagen density was semi-quantitatively scored as +1 for low density, +2 for moderate density, and +3 for high density. K⁻: Negative control group receiving sodium carboxymethyl cellulose without ultraviolet B exposure; K⁺: Positive control group receiving sodium carboxymethyl cellulose with ultraviolet B exposure; P1: Ultraviolet B-exposed group treated with apigenin at 25 mg/Kg BW; P2: Ultraviolet B-exposed group treated with apigenin at 50 mg/Kg BW; P3: Ultraviolet B-exposed group treated with apigenin at 100 mg/Kg BW.

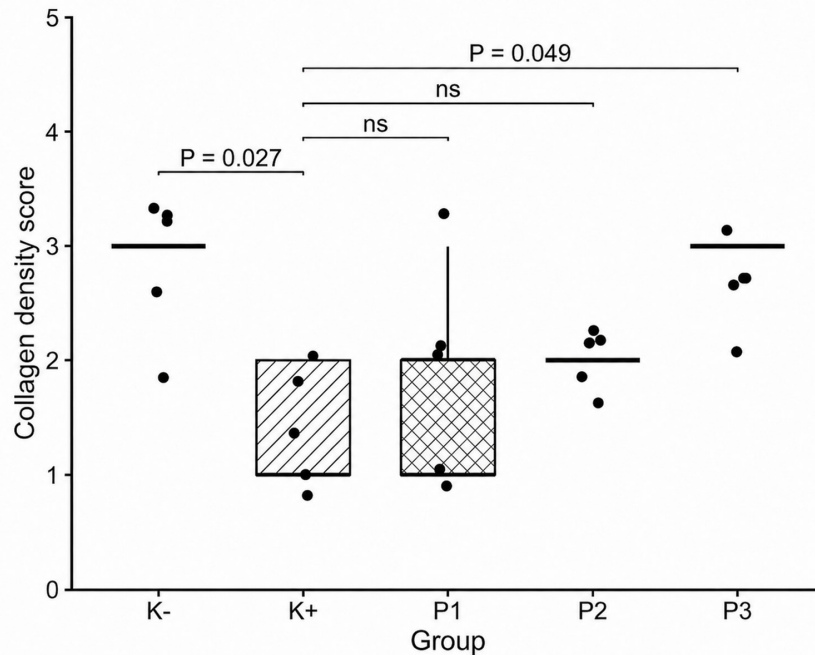


Figure 3: The figure shows the collagen density scores in male white mice across the experimental groups. Data are presented as median and interquartile range ($n=5$ per group), and individual observations are shown as black dots. The boxplots represent the interquartile range, with the horizontal line indicating the median. Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's *post hoc* test with Bonferroni adjustment. Brackets indicate pairwise comparisons between groups. Adjusted P values are shown for statistically significant comparisons, whereas “ns” indicates no statistically significant difference. K⁻: Negative control group receiving sodium carboxymethyl cellulose without ultraviolet B exposure; K⁺: Positive control group receiving sodium carboxymethyl cellulose with ultraviolet B exposure; P1: Ultraviolet B-exposed group treated with apigenin at 25 mg/Kg BW; P2: Ultraviolet B-exposed group treated with apigenin at 50 mg/Kg BW; P3: Ultraviolet B-exposed group treated with apigenin at 100 mg/Kg BW.

Histopathological Assessment of Collagen in Mouse Skin

Figure 2 shows representative histological images of collagen density in mouse skin. The collagen density scores for each group are presented in figure 3 as boxplots with individual data points. Collagen density scores did not meet the assumption of normality, as assessed by the Shapiro–Wilk test, indicating a non-normal data distribution. Therefore, nonparametric tests were applied. Further analysis was conducted using the nonparametric Kruskal–Wallis test. The Kruskal–Wallis test revealed significant differences among the groups ($P=0.003$). Consequently, Dunn's *post hoc* test with Bonferroni adjustment was conducted to determine which groups differed significantly.

Pairwise *post hoc* analysis showed a significant difference between the positive control and the negative control groups (adjusted $P=0.027$) and between the positive control and the 100 mg/Kg BW group (adjusted $P=0.049$). Collagen density was markedly reduced in the positive control due to UVB-induced oxidative stress. In contrast, treatment with apigenin at 100 mg/Kg BW effectively preserved collagen structure, consistent with its antioxidant protective activity (figure 3).

Discussion

Chronic UVB irradiation (840 mJ/cm², 30 days) significantly elevated MDA levels and reduced collagen density in male white mice (*Mus musculus*), confirming the successful induction of the photoaging model. MDA is a validated indicator of cumulative oxidative injury and is closely associated with UVB-induced skin damage.²² At the molecular level, UVB-generated ROS activate the MAPK signaling cascade (ERK, JNK, p38), which induces the transcription factors AP-1 and NF- κ B.² AP-1 subsequently drives the upregulation of MMP-1, the principal collagenase responsible for degrading fibrillar type-I and type-III collagen in the dermis, while NF- κ B amplifies the inflammatory response through COX-2 induction and elevated prostaglandin E₂ (PGE₂) production.^{23, 24} The reduction in collagen density observed in the positive control group was thus mechanistically consistent with this ROS–MAPK–AP-1/NF- κ B–MMP-1 axis, which disrupted collagen homeostasis both transcriptionally and post-translationally in photoaged skin.²⁴

Oral administration of the apigenin isolate from Sungkai (*Peronema canescens* Jack) produced a

dose-dependent reduction in MDA levels, while collagen preservation was most evident at the highest dose. At 100 mg/Kg BW, MDA levels were statistically equivalent to those of the negative control, and collagen density was significantly higher than that of the positive control. The 25 and 50 mg/Kg BW doses reduced MDA levels compared with the positive control. However, the MDA levels in these groups remained higher than those observed in the negative control and the 100 mg/Kg BW group. In contrast, collagen density in the 25 and 50 mg/Kg BW groups did not show a statistically significant improvement compared with the positive control based on Dunn's *post hoc* test with Bonferroni adjustment. The effective dose of 100 mg/Kg BW was consistent with pharmacologically active ranges reported for apigenin in comparable murine models, in which oral doses of 50–200 mg/Kg BW demonstrated significant antioxidant effects, including MDA reduction and glutathione restoration, across multiple organ systems without overt toxicity.^{12, 25, 26} These findings were also consistent with studies demonstrating that apigenin decreased MDA and lipid peroxide concentrations while increased total antioxidant capacity and catalase activity in UV-irradiated and oxidatively damaged murine skin.^{27, 28}

In parallel, apigenin exerts collagen-preserving effects through convergent mechanisms: inhibition of MAPK phosphorylation (ERK, JNK, p38) blocks AP-1–driven MMP-1 transcription, suppression of the NF- κ B pathway reduces COX-2 and iNOS expression, and activation of the Smad2/3 pathway downstream of TGF- β 1 directly stimulates type-I and type-III collagen synthesis in dermal fibroblasts.^{18, 29, 30} However, since collagen density was assessed using an ordinal semi-quantitative score, the observed collagen-preserving effect should be interpreted primarily as a histological improvement that reached statistical significance only at 100 mg/Kg BW. Collectively, the 100 mg/Kg BW dose appeared to represent a pharmacological threshold at which systemic antioxidant capacity is sufficient to overcome the UVB–induced ROS burden and maintain collagen homeostasis.

Several limitations should be acknowledged. First, oxidative stress was assessed solely via MDA levels; the inclusion of antioxidant enzyme activities (SOD, CAT, GPx) and downstream molecular markers (MMP-1 protein, NF- κ B, COX-2) would have provided more direct mechanistic evidence.¹⁶ Second, collagen density was evaluated using a semi-quantitative scoring system based on hematoxylin–eosin staining. While useful for general histopathological assessment, this method is not collagen-specific

and might be susceptible to inter-observer variability. Accordingly, future studies employing quantitative digital morphometry using Masson's trichrome–stained sections would enhance objectivity and reproducibility.³⁰ Third, the small sample size limited the statistical power and generalizability. Additionally, the murine effective dose of 100 mg/Kg BW corresponded to a human-equivalent dose of approximately 8.1 mg/Kg BW (~486 mg for a 60 Kg adult) via allometric scaling. However, the oral route employed here did not reflect cosmeceutical topical applications, where bioavailability and tissue distribution profiles would differ substantially.¹⁶ Collectively, these limitations underscored the need for future investigations incorporating a comprehensive biomarker panel, quantitative histomorphometry, and translational models to validate these findings and advance the development of Sungkai-derived apigenin as a viable photoprotective agent.

Conclusion

Chronic UVB exposure significantly increased MDA levels and reduced collagen density in murine skin, confirming oxidative stress as a central mechanism of photoaging. The apigenin isolate from Sungkai (*P. canescens* Jack.) demonstrated a dose-dependent protective effect, with the 100 mg/Kg BW dose effectively normalizing MDA levels and preserving collagen density to levels comparable to those of the negative control. Lower doses (25 and 50 mg/Kg BW) demonstrated partial yet insufficient protection. These findings indicated that Sungkai-derived apigenin possessed notable antioxidant activity and potential as a natural anti-photoaging agent.

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Authors' Contribution

D.D: Conceptualization, study design, supervision, data interpretation, and reviewing the manuscript; Y.A: Conceptualization, study design, methodology validation, and reviewing the manuscript; H.H: Data gathering, experimental procedures, data analysis, and drafting the manuscript; All authors approved

the submission of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of AI

The authors acknowledge that artificial intelligence-based tools, including ChatGPT (OpenAI, San Francisco, CA, USA) and Grammarly (Grammarly Inc., San Francisco, CA, USA), were used to assist with linguistic refinement and stylistic enhancement of the manuscript. Full responsibility for the content, interpretation, and final editorial decisions remains solely with the authors.

Conflict of Interest: None declared.

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