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The Effect of Apigenin Isolate from Sungkai Leaf (*Peronema canescens*) on Skin Collagen Density and Fibroblast Cell Count as Anti-aging Indicators in D-Galactose-Induced Male White Mice

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ABSTRACT

Skin aging is a degenerative process characterized by increased oxidative stress, decreased collagen density, and reduced number of dermal fibroblasts. This study aimed to evaluate the effect of apigenin isolated from Sungkai leaves (*Peronema canescens* Jack) on malondialdehyde (MDA) levels, collagen density, and the number of skin fibroblast cells of male white mice induced by D-galactose. The study design used a completely randomized post-test-only control group design with five treatment groups, namely negative control, positive control, and administration of apigenin doses of 25, 50, and 100 mg/kg BW. The results showed that administration of apigenin significantly reduced MDA levels (p<0.05), with a dose of 100 mg/kg BW producing the lowest value compared to the negative control. Histopathological analysis also showed a significant increase in collagen density at doses of 50 and 100 mg/kg BW, while evaluation of the number of fibroblasts showed a significant increase at medium and high doses, with a dose of 100 mg/kg BW providing the highest average cell count (21.13). Overall, these findings indicate that the isolated apigenin from Sungkai leaves is able to provide a protective effect against skin aging through an antioxidant mechanism that supports cell membrane stability, maintains collagen density, and increases fibroblast proliferation. Apigenin from *Peronema canescens* has the potential for development as a natural herbal-based anti-aging agent.

Keywords: *Peronema canescens* Jack, Apigenin, Malondialdehyde, Collagen, Fibroblast cell, Anti-aging, D-galactose

Introduction

The skin is the outermost and largest organ in the human body, acting as the primary barrier against various external factors, such as bacteria, chemicals, and sun exposure. Furthermore, it plays a role in temperature regulation, water retention, and cell regeneration, allowing skin condition to reflect an individual's health status [1,2]. As an easily observable organ, changes in the skin are a primary visual indicator of the aging process. Skin aging is defined as a degenerative process characterized by a decline in the skin's physiological function and regenerative capacity, including reduced collagen production and a decrease in the number and function of fibroblasts in the dermis [3,2].

Collagen, which is mainly composed of type I (80–85%) and type III (10–15%) collagen, is the main component of the dermal matrix that determines the texture and elasticity of the skin [4]. During the ageing process, the number of fibroblasts and their proliferative ability decrease, causing a reduction in collagen and elastin production, which results in the skin becoming dry, wrinkled, and losing its elasticity [2.] Fibroblasts themselves play an essential role in maintaining skin homeostasis through the production of extracellular matrix, and can be stimulated by fibroblast growth factor (FGF) to reproduce and increase collagen and elastin synthesis [2,4].

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Skin aging occurs due to a combination of intrinsic (genetic and hormonal) and extrinsic factors (lifestyle, ultraviolet light exposure, pollution, and cigarette smoke). Both factors are closely related to the theory of oxidative stress, which is an imbalance between reactive oxygen species (ROS) and the body's antioxidant defense system. The accumulation of ROS triggers oxidative damage to proteins, lipids, and DNA, which disrupts cellular function and accelerates the aging process [3,5]. One model often used to mimic the aging process in animals is D-galactose induction. High-dose D-galactose administration causes increased ROS, decreased antioxidant enzyme activity (SOD, CAT, GSH-Px), and increased malondialdehyde (MDA), which leads to reduced collagen density, skin elasticity, and fibroblast count [6].

The phenomenon of premature aging is now becoming a growing concern, with surveys showing that around 76% of Indonesian women have experienced symptoms of premature aging, which has an impact on decreasing self-confidence and quality of life [7]. Lifestyle factors, such as excessive sugar consumption, lack of hydration, and UV exposure, contribute to worsening this condition [5]. Therefore, efforts to prevent aging through the use of natural antioxidants are increasingly in demand.

Antioxidants function to neutralize free radicals and maintain skin homeostasis. Various plants rich in polyphenols, particularly flavonoids, are known to possess potent antioxidant activity. One such plant is Sungkai (*Peronema canescens* Jack), a plant from the Verbenaceae family that is widespread in Indonesia and traditionally used as a herbal medicine. Sungkai leaves contain various bioactive compounds, including flavonoids such as apigenin, which have anti-inflammatory, antibacterial, antiviral, and antioxidant activities [8,9].

Apigenin (4′,5,7-trihydroxyflavone) is known as a flavonoid with broad biological activities, including antioxidant, anti-inflammatory, and antiapoptotic [10]. *In vitro* studies have shown that apigenin is able to increase the expression of collagen genes and proteins in human fibroblasts in a dose-responsive manner without causing cytotoxicity

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and does not trigger pathological differentiation of fibroblasts into myofibroblasts [4]. The primary mechanism involves activation of the Smad2/3 pathway of the TGF-*β* pathway, which is vital in regulating extracellular matrix synthesis. Furthermore, *in vivo* studies have reported that apigenin can increase dermal collagen density and skin elasticity, reduce the length of fine wrinkles, and improve skin moisture and barrier function [11,12]. Apigenin is also known to suppress the TGF-*β* pro-fibrotic signaling pathway and inhibit the activation of NF-κB, PI3K-Akt, and MAPK, thus playing a role in preventing tissue damage due to oxidative stress [13].

Although various studies support the potential of apigenin as an anti-aging agent, there is still limited data regarding the effects of administering apigenin isolated from sungkai leaves specifically, primarily through the oral route in animal models with D-galactose-induced skin aging conditions, particularly for collagen density and the number of skin fibroblast cells. Therefore, this study aims to provide scientific evidence regarding the potential of Sungkai leaf apigenin isolate as a natural anti-aging agent. The results of this study are expected to not only enrich the science of phytopharmaceuticals but also support the use of local Indonesian herbal plants in the development of safer, natural, and sustainable therapies and cosmetic products.

Materials and Methods

Materials

Plant Collection and Identification

Leaves of *Peronema canescens* Jack. (sungkai) were collected from Aia Pacah, Padang City, West Sumatera, Indonesia (GPS: −0.8654234, 100.3869164) in October 2024. The plant material was identified and authenticated by Dr. Nurainas at the Herbarium ANDA, Department of Biology, Universitas Andalas, with voucher specimen number 717/K-ID/ANDA/X/2024. The samples were air-dried, ground into a fine powder, and stored in an airtight container until use.

Chemicals and Reagents

D-galactose (Himedia, Indonesia), Hematoxylin and Eosin dye (Pupick Med), Na CMC (Merck, USA), PBS formalin 10% (Leica), alcohol 50% (Brata Med), alcohol 70% (Brata Med), alcohol 90% (Brata Med), absolute ethanol (Brata Med), xylene (Merck), paraffin (Merck), ovalbumin (RPI), Canadian balsam (DPX mountant), standard solution of 1,1,3,3-tetramethoxypropane (TMP), thiobarbituric acid (TBA) solution (Merck), trichloroacetic acid (TCA) solution 5% (Merck), acid alcohol 3% (Indo Reagen), diethyl ether (Merck).

Equipment

Other equipment used in this study include: analytical weighing scales (Ohaus®, USA), animal scales (Ohaus®, USA), waterbaths (Memmert Wnb 22®), staining jars, dehydration tools (Tissue-Tek VIP 5 Jr®), embedding centers (Microm®), embedding cassettes (Macrosette®), timers, rotary microtomes (Leica®, Japan), computers, microscopes (Olympus CX33®, USA), spectrophotometers (Spectronic®, Thermo Scientific, USA), syringes, vortex (IKA®), yellow tip (Onemed®), blue tip (Onemed®), centrifuge, cuvette, and micropipette (Socorex®). Also, various glassware, pipettes, beakers, spatulas, probes (Terumo®), tweezers (Lai Gooi TS®), razor blades (Gillette®), surgical scissors, funnels, vials, glass objects (Onelab®), and cover glass (Onelab®) were used in this experiment.

Isolation of Apigenin

Apigenin was isolated from dried *Peronema canescens* (sungkai) leaves through a multistep extraction, fractionation, and chromatographic purification process. Initially, powdered dried leaves (17 kg) were exhaustively extracted by maceration using 96% ethanol (2:5 w/v) at room temperature for 72 hours, with solvent replacement every 24 hours. The combined ethanolic extracts were concentrated under reduced pressure using a rotary evaporator to obtain a crude extract. The crude extract was subsequently fractionated by liquid–liquid extraction with solvents of increasing polarity, namely *n*-hexane, ethyl acetate, and ethanol. The ethanol-soluble fraction was further purified by vacuum liquid chromatography on silica gel, employing gradient elution with *n*-hexane-ethyl acetate mixtures (100:0 to 0:100) followed by methanol. Based on thin-layer chromatography (TLC) profiles, the resulting fractions were combined into five major fractions.

The fraction exhibiting strong UV-active spots was subjected to radial chromatography on 0.5 mm silica gel plates using *n*-hexane-ethyl acetate solvent systems with varying ratios (6:4, 5:5, 3:7). This purification step yielded a yellow solid (10 g) identified as apigenin. Spectroscopic analyses confirmed that Isolate 1 was apigenin. The UV-Vis spectrum recorded in methanol showed absorption maxima at 210, 267, and 336 nm. FT-IR analysis revealed characteristic bands of hydroxyl groups at 3286 cm^{-1}, carbonyl stretching at 1653 cm^{-1}, aromatic C=C vibrations at 1587-1446 cm^{-1}, and C-O stretching at 1298-1031 cm^{-1}. Structural elucidation was further supported by ^{1}H- and ^{13}C-NMR spectra in DMSO-d_6 (500/125 MHz), which were consistent with a flavonoid framework and corroborated by HMBC and COSY correlations.

Experimental Animals and Ethical Clearance

Male BALB/c mice (25–35 g, 25 mice) were purchased from Pondok Tikus Padang and fed with standard mouse feed with access to distilled water (Andeska laboratory). Ethical approval for the study was obtained from the Ethics Committee of the Faculty of Pharmacy, Andalas University, with approval number 60/UN16.10.D.KEPK-FF/2025. The study was a post-test-only control group with a completely randomized design method with five replications per treatment.

Preparation of Test Animals

The animals used were 25 male white mice, 6 weeks old, weighing 25-35 grams, and had never been treated with drugs. The test animals were first acclimatized for 7 days at the Animal House of the Faculty of Pharmacy, Andalas University, at room temperature (25 ± 2°C). The mice were allowed 12 hours of dark and 12 hours of light and received food and water *ad libitum*. Mice that were sick, died, or did not gain weight during acclimatization were excluded.

Preparation of Apigenin Suspension from Sungkai Leaves

Apigenin extracted from sungkai leaves was prepared as a suspension in a 0.5% Na CMC solution. 250 mg of Na CMC was weighed and sprinkled over 10 mL of hot water in a mortar and pestle, and allowed to stand for 15 minutes. The mixture was then ground until homogeneous. Afterward, distilled water was added step-wise until a volume of 50 mL was reached. The isolated apigenin was then dissolved in the Na CMC solution according to the specified concentration, resulting in a ready-to-use apigenin suspension.

Preparation of Induction Compound (D-galactose)

D-galactose (5 g) was weighed and mixed with 100 mL of distilled water, and stirred until completely dissolved, to give an induction dose of 500 mg/kg BW.

Administration of Suspension of Sungkai Leaf Apigenin

Twenty-five male white mice were divided into five groups (n = 5). The negative control (K−) consisted of healthy mice receiving Na-CMC suspension for 6 weeks, while the positive control (K+) consisted of D-galactose-induced aging mice receiving 0.5% Na-CMC and D-galactose (500 mg/kg BW) orally for 6 weeks. Treatment groups P1, P2, and P3 received apigenin at doses of 25, 50, and 100 mg/kg BW, respectively, in the morning, followed by oral D-galactose (500 mg/kg BW) in the afternoon for 6 weeks.

Serum Collection and MDA Level Measurement

Blood was drawn using the intracardial method, in which 1 mL of blood was collected in a microtube and left for 30 minutes. The blood sample was then centrifuged for 30 minutes at 3000 rpm to separate the serum from other blood components. The serum obtained was then used to measure malondialdehyde (MDA) levels using the Thiobarbituric Acid Reactive Substances (TBARS) method. This method works based on the reaction of MDA with thiobarbituric acid (TBA) to form a pink complex (MDA–TBA_2 adduct) which can be measured spectrophotometrically at a wavelength of 532–535 nm.[14]

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Preparation of Skin Sample

Skin tissue was taken from the back area of the mouse, shaved to a length of approximately 1-1.5 cm^2 with a thickness of approximately 3 mm, covering the hypodermis layer. The skin organ was placed in a tube containing a 10% PBS formalin solution for approximately 18-24 hours to maintain the tissue structure. Then, dehydration was performed, where the biopsy excision was placed in a graded alcohol solution. This was followed by the process of clearing with xylol solution, embedding, slicing, fixing, staining with Haematoxylin Eosin, and mounting [15].

Collagen Density Measurement

Collagen density measurements were performed through histopathological analysis using a light microscope (Olympus CX33) and EPview software. Observations were made in three microscopic fields at 40× magnification. Microscopic evaluation was conducted according to a standardized protocol with quantitative scoring criteria as follows: a score of 0 indicated the absence of collagen fibers; a score of +1 represented low collagen density (25%); a score of +2 indicated moderate collagen density (50%); a score of +3 corresponded to dense collagen density (75%); and a score of +4 represented very dense collagen density (100%)[15].

Analysis of The Number of Fibroblast Cells

Fibroblast cell count analysis was performed manually using a light microscope (Olympus CX33) and EPview software at 40x magnification. Each sample was observed in three different fields of view, and the cell counts from each field were averaged to obtain a representative value. This average value was then used as data for statistical analysis using SPSS software to evaluate significant differences in fibroblast cell count between treatment groups.

Statistical analysis

Results were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess data normality, and the Levene test was used for data homogeneity. A one-way ANOVA test was performed, followed by a Tukey post-hoc test using Statistical Product and Service Solution (SPSS) software. Non-parametric statistical analysis was performed using the Kruskal-Wallis test, followed by a Mann-Whitney post-hoc test. Statistical significance was set at $p < 0.05$.

Results and Discussion

The results of the Tukey HSD analysis showed a significant difference in MDA levels between the positive control group (K+) and the treatment groups at doses of 50 mg/kg BW, 100 mg/kg BW, and the negative control (K−) (Table 1). However, the difference between K+ and the 25 mg/kg BW dose was not significant. This indicates that administration of Sungkai leaf isolated apigenin can reduce the increased MDA levels induced by D-galactose. The high MDA levels in the K+ group (3.6740±0.493 nmol/mL) reflect oxidative stress due to the accumulation of free radicals that trigger lipid peroxidation. Conversely, the treatment group showed a significant decrease in MDA levels, particularly at the 100 mg/kg BW dose, which produced the lowest value (2.5800±0.332 nmol/mL), even lower than the negative control (2.8460±0.122 nmol/mL) (Figure 1). The reduction of MDA can be explained by the antioxidant mechanism of apigenin, a natural flavonoid of the flavone group with strong antioxidant potential. Apigenin donates hydrogen atoms from the hydroxyl group to neutralize free radicals while inhibiting the formation of ROS (Reactive Oxygen Species), which play a role in lipid peroxidation.[16] Thus, the higher the dose of apigenin given, the greater the decrease in MDA levels obtained. The consistency of these results was also seen in the homogeneous subsets analysis, where the 100 mg/kg BW, 50 mg/kg BW, and K− dose groups were in the same subset with lower MDA levels, indicating a protective effect of apigenin comparable to normal conditions.

This decrease in MDA levels has direct implications for skin anti-aging mechanisms, particularly in maintaining collagen density and fibroblast count.[17] Increased MDA indicates cell membrane damage caused by free radicals, which impacts collagen degradation and reduces fibroblast proliferation in the dermis. The results showed that apigenin administration improved collagen density, as evidenced by a significant difference between the positive control and the medium (50 mg/kg BW) and high (100 mg/kg BW) doses (Figure 2, Table 2). The absence of a difference between the high dose and the negative control indicates that apigenin at this dose was able to normalize tissue conditions closer to physiological levels. These results are consistent with the study conducted by Zhang et al. (2015), which demonstrated that apigenin administration significantly increased dermal thickness and collagen density in mice compared with the positive control group.[4]

Table 1: Tukey HSD Test for MDA levels in all treatment groups

Means for groups in homogeneous subsets are displayed

a. Uses Harmonic Mean Sample Size = 5.000

Tukey HSD[a]		Subset for alpha = 0,05	
Groups	N	1	2
100 mg/kg BW Dose	5	2.5800	
K-	5	2.8460	
50 mg/kg BW Dose	5	2.9340	
25 mg/kg BW Dose	5	3.1400	3.1400
K+	5		3.6740
Sig.		0.165	0.200

Figure 1: A plot of average MDA levels in all treatment groups (nmol/ml). K+: positive control; P1: apigenin 25 mg/kg BW; P2: apigenin 50 mg/kg BW; P3: apigenin 100 mg/kg BW; K-: negative control

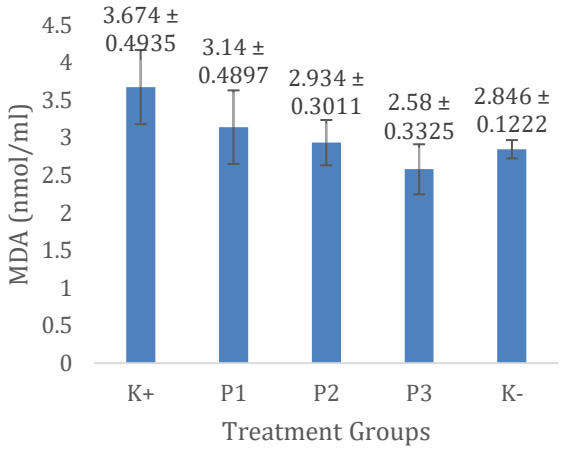

Table 2: Post-Hoc Test (Mann-Whitney Test) for collagen density of mice skin in all treatment groups[18]

Comparison between groups	p-value	Significance (< 0.05)
K+ vs P_1	0.221	Not significant
K+ vs P_2	0.031	Significantly different
K+ vs P_3	0.013	Significantly different
K+ vs K-	0.021	Significantly different
P_1 vs P_2	0.093	Not Significant
P_1 vs P_3	0.018	Significantly different
P_1 vs K-	0.045	Significantly different
P_2 vs P_3	0.077	Not Significant
P_2 vs K-	0.307	Not Significant
P_3 vs K-	0.496	Not Significant

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Furthermore, analysis of fibroblast cell counts showed that apigenin also increased fibroblast cell count in a dose-dependent manner (Figure 3, Table 3). The medium (50 mg/kg BW) and high (100 mg/kg BW) dose groups showed significant differences compared to the positive control, with the high dose producing the highest average cell count (21.13) and the most important difference (p=0.003). Meanwhile, the low dose (25 mg/kg BW) showed no significant difference compared to the control. These findings are in line with the study by Zhang et al. (2015), which reported that apigenin is non-cytotoxic and improved fibroblast function via Smad2/3 pathway activation, rather than by directly stimulating fibroblast proliferation.[4] These findings confirm that administration of Sungkai leaf isolate apigenin, especially at high doses, is effective in suppressing oxidative stress, maintaining collagen density, and increasing fibroblast proliferation, thus potentially providing a protective effect against D-galactose-induced skin aging.

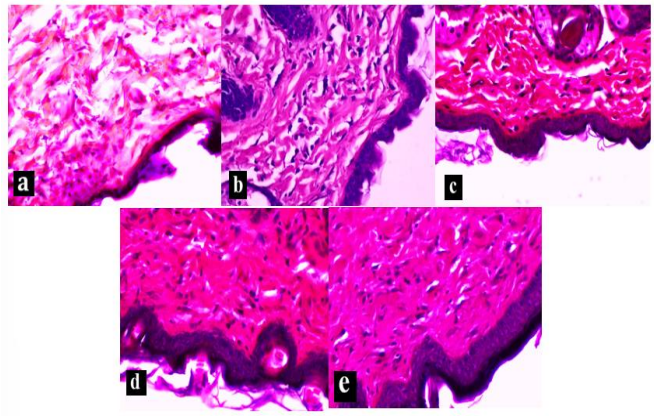

Figure 2: Microscopic image of collagen density of mice skin with Hematoxylin-Eosin staining at 40x magnification. a) Positive control group (induced by D-galactose); b) Group P1 (received apigenin 25mg/kgBW and induced by D-galactose); c) Group P2 (received apigenin 50mg/kgBW and induced by D-galactose); d) Group P3 (received apigenin 100mg/kgBW and induced by D-galactose); e) Group K- (skin tissue of healthy mice).

Table 3: Tukey HSD Test for Measurement of Fibroblast Cells in Mice Skin[19]

		Subset for alpha = 0.05	
Groups	N	1	2
K+	5	11.0666680	
25 mg/kg BW Dose	5	14.8000020	14.8000020
K-	5		18.0666660
50 mg/kg BW Dose	5		19.0666660
100 mg/kg BW Dose	5		21.1333340
Sig.		0.512	0.086

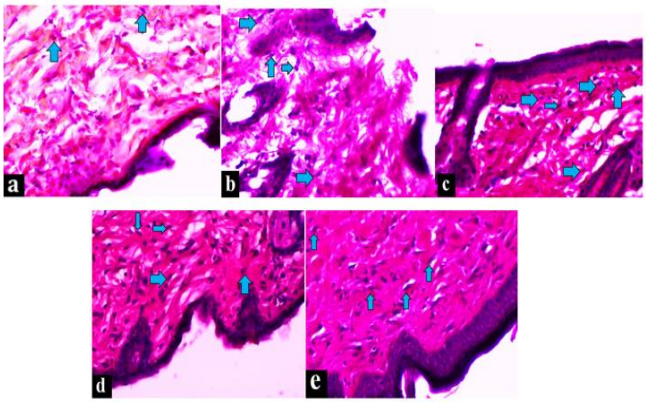

Figure 3: Microscopic image of fibroblast cells (indicated by blue arrows) of mouse skin with Hematoxylin-Eosin staining at 40x magnification. a) Positive control group (induced by D-galactose); b) Group P1 (received apigenin 25 mg/kg BW and induced by D-galactose); c) Group P2 (received apigenin 50 mg/kg BW and induced by D-galactose); d) Group P3 (received apigenin 100 mg/kg BW and induced by D-galactose); e) Group K- (skin tissue of healthy mice).

Conclusion

The results showed that administration of apigenin significantly reduced MDA levels at low extract levels. Histopathological analysis also showed a significant increase in collagen density at low extract, while evaluation of the number of fibroblasts showed a significant increase at medium and high doses. Overall, these findings indicate that the isolated apigenin from Sungkai leaves has the potential to provide a protective effect against skin aging through an antioxidant mechanism that supports cell membrane stability, maintains collagen density, and increases fibroblast proliferation, thus potentially being developed as a natural herbal-based anti-aging agent.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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