TRENDS IN SCIENCES 2025; 22(11): 10144
https://doi.org/10.48048/tis.2025.10144 RESEARCH ARTICLE

Unlocking the Anti-Aging Potential of Apple (*Malus domestica*) Extract: In Vitro Modulation of TIMP-1, Casp-3, and GPX Gene Expression in Fibroblast Cells

Sri Utami[1,*], Qomaryah Romadhiyani Sachrowardi[1], Sonny Pamuji Laksono[1], Nunung Ainur Rahmah[1], Insan Sosiawan Tunru[1], Dewi Nurul Mustaqimah[2], Eko Purwanto[1], Aryenti[1], Susi Endrini[3], Irfan Syarif[1], Kholis Ernawati[1], Wahyu Widowati[4], Dwi Nur Triharsiwi[5], Eksa Adhwa Fadhilah[6], Dhanar Septyawan Hadiprasetyo[5,7], Haidir Syafrullah[8], Said Nafik[9] and Betharie Cendera Arrahmani[10]

[1]*Faculty of Medicine, Universitas YARSI, Central Jakarta, Indonesia*
[2]*Faculty of Dentistry, Universitas YARSI, Central Jakarta, Indonesia*
[3]*Faculty of Medicine, Universitas Abdurrab, Riau, Indonesia*
[4]*Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia*
[5]*Biomolecular and Biomedical Research Center, Aretha Medika Utama, Bandung, Indonesia*
[6]*Biology Study Program, Faculty of Mathematics and Natural Sciences Education, Universitas Pendidikan Indonesia, Bandung, Indonesia*
[7]*Faculty of Pharmacy, Universitas Jenderal Achmad Yani, Cimahi, West Java, Indonesia*
[8]*Nursing Study Program, Sekolah Tinggi Ilmu Kesehatan Dharma Husada Bandung, Bandung, Indonesia*
[9]*Directorate General of Intellectual Property, Ministry of Law and Human Rights Republic of Indonesia, South Jakarta, Indonesia*
[10]*Risk and Regulatory Consulting Pharma and Life Sciences, PricewaterhouseCoopers (PwC) GmbH WPG, Frankfurt, Germany*

([*]Corresponding author's e-mail: uutsuyono@yahoo.com)

Received: 11 March 2025, Revised: 18 April 2025, Accepted: 25 April 2025, Published: 1 August 2025

Abstract

Ultraviolet (UV) exposure accelerates skin aging by inducing oxidative stress, apoptosis, and extracellular matrix degradation. *Malus domestica* (apple) extract (AE) is rich in antioxidants and bioactive compounds that may counteract these effects. This study evaluates the protective effects of AE on fibroblast cells exposed to UV radiation by assessing the expression of Tissue Inhibitor of Metalloproteinase 1 (TIMP-1), Caspase 3 (Casp-3), and Glutathione Peroxidase (GPX). Fibroblast cells were exposed to UV radiation and treated with different concentrations of AE (3.13, 6.25, 12.5 µg/mL). Gene expression levels of TIMP-1, Casp-3, and GPX were analyzed using qRT-PCR. AE significantly increased TIMP-1 and GPX expression while downregulating Casp-3 in a concentration-dependent manner. The highest concentration (12.5 µg/mL) demonstrated the most pronounced protective effects. These results suggest that apple extract enhances extracellular matrix stability, reduces oxidative stress, and inhibits apoptosis in UV-exposed fibroblasts. AE exhibits potent anti-aging properties by modulating key molecular pathways involved in skin damage. This study provides scientific evidence supporting its potential as an active ingredient in skincare formulations for UV protection and skin rejuvenation.

Keywords: Anti-aging, Fibroblast cells, Oxidative stress, UV

Introduction

Aging is known as complex biological process characterized by the progressive decrease in physiological functions and an increased susceptibility to illnesses and death. All living things are impacted by this complex phenomenon, which has multiple causes that include lifestyle, environmental, and genetic factors. Research on the mechanisms of aging and the creation of interventions to support healthy aging is becoming more and more crucial as the world's population ages [1]. Skin is the largest organ in the body and the main defense against environmental stressors, so wrinkles are one of the most obvious indicators of aging. Skin aging is caused by both intrinsic (chronological) and extrinsic (environmental) factors, which alter the dermal and epidermal layers' structure and function [2]. Among other effects, these changes show up as wrinkles, elasticity loss, irregular pigmentation, and a reduced ability to heal wounds. Numerous factors play a role in aging process, such as glycation, oxidative stress, telomere shortening, and changes in hormone levels [3]. Cellularly, aging skin is linked to a reduction in skin cells' ability to proliferate, especially keratinocytes and fibroblasts. The production of collagen and elastin, 2 important proteins that keep skin elastic and structured, is also declining in tandem with this decline [4]. Furthermore, the build-up of advanced glycation end products (AGEs) impairs skin integrity and function by causing the cross-linking of collagen fibers [5].

The genes namely Tissue Inhibitor of Metalloproteinases 1 (TIMP-1), Glutathione Peroxidase (GPX), and Caspase 3 (Casp-3) are important biomarkers in anti-aging research because they contribute in the processes associated with cellular aging, oxidative stress response, and apoptosis. By blocking matrix metalloproteinases (MMPs), which reduce elastin and collagen, TIMP-1 helps to preserve the extracellular matrix (ECM) integrity. The increase in TIMP-1 expression is linked to less ECM degradation, which protects skin elasticity and structural integrity, 2 important components of anti-aging benefits [6]. An essential caspase for execution in the apoptotic pathway is Caspase 3 (Casp-3). Casp-3 activation frequently rises with age, promoting enhanced apoptosis in a variety of tissues. This increases the risk of organ dysfunction and age-related tissue deterioration [7]. Loss of functioning cells can occur from excessive Casp-3 activation, especially in post-mitotic tissues such as cardiomyocytes and neurons. Cellular senescence induction and maintenance have been linked to Casp-3. Senescent cells proliferate with aging and play a role in tissue dysfunction and inflammation. The senescence-associated secretory phenotype (SASP), which is a hallmark of aging and chronic low-grade inflammation, can be induced by Casp-3 activation [8]. Conversely, hydrogen peroxide and organic hydroperoxides are reduced by the vital antioxidant enzyme GPX, which shields cells from oxidative damage. By averting oxidative damage, high GPX activity reduces oxidative stress, a primary cause of cellular aging. By preventing oxidative damage to cellular components, high GPX activity promotes cell survival and function and mitigates oxidative stress, a major contributor to cellular aging [9].

Particularly in relation to skin health, there has been an increase in interest in natural substances that may be able to reverse the effects of aging in recent years. Apples, or *Malus domestica*, have become known as a potentially useful source of bioactive compounds that may have anti-aging effects. Polyphenols, flavonoids, and other phytochemicals that have anti-inflammatory, antioxidant, and photoprotective properties abound in these fruits [10]. Apple extracts (AE), which come from the peel, flesh, and seeds of the fruit, have demonstrated encouraging outcomes in in vitro and in vivo investigations concerning the aging of the skin [11]. Quercetin, chlorogenic acid, and catechin are examples of the polyphenolic compounds found in apples that have been shown to scavenge free radicals and reduce oxidative stress, 2 major factors that contribute to skin aging [12]. Furthermore, it has been discovered that some substances derived from apples inhibit the enzymes known as matrix metalloproteinases (MMPs), which are in charge of reduce elastin and collagen in the skin [13]. Beyond their antioxidant qualities, apple extracts hold great potential in skincare products designed to fight aging. Previous research has demonstrated that substances derived from apples can alter a number of signaling pathways related to skin repair and homeostasis. Procyanidins from apples, have been shown to inhibit melanogenesis and increase collagen biosynthesis, indicating a potential role in

controlling pigmentation and preserving skin structure [14]. Furthermore, previous study have shown that apple extracts can protect against UV-induced damage, which is a significant cause of extrinsic skin aging [15].

This study uniquely combines the investigation of AE's effects on 3 key genes involved in aging processes TIMP-1, GPX, and Casp-3 in human fibroblast cells. The results are more applicable to human skin health and aging when fibroblast cells, a commonly used model for skin aging research, are used [16]. Furthermore, by concentrating on gene expression, the study goes beyond conventional antioxidant assays and provides insights into the molecular mechanisms underlying the anti-aging effects of AE, surpassing conventional assays for antioxidants. This mechanistic strategy is in line with current trends in nutraceutical research, which explore the importance of comprehending the molecular underpinnings of the effects of bioactive compounds [17].

Materials and methods

Preparation of apple fruit extract

Apple extract (AE) is produced by PT FAST Depok, West Java, which is in accordance with Good Manufacturing Practices (GMP) standards with batch number 001.10.23.EBA.01 as stated on the Certificate of Analysis (CoA). The AE was extracted using 70% ethanol and added with lactose [18]. The extracts were stored under 30 °C in a dry place and avoided direct sunlight.

Gene expression test

Briefly 10^6 cells at 80% confluence were exposed to UV light in a 6-well plate for 75 min at 37°C and 5% CO_2. After being exposed to UV light for 4 days and treated with AE at concentrations of 3.13, 6.25, 12.5 µg/mL, cells were harvested using 0.25% trypsin-EDTA (25200072; Gibco, Waltham, MA, USA). Gene expression of TIMP-1, GPX, and Casp-3 was assayed from treated pellet cells. The total RNA isolation process was carried out using the Direct-zol™ RNA Miniprep Plus Kit (Zymo Research, R2073; Zymo Research Corp., Irvine, CA, USA), following the standardized procedure outlined by the manufacturer. RNA concentration and purity can be seen in **Table 1**. To synthesize complementary DNA, the Sensi-FAST cDNA synthesis kit (Meridian, 65053) was used using the protocol from the manufacturer. The expression levels of target genes were quantified using the AriaMx 3000 Real-Time PCR System (Agilent, G8830A; Agilent Technologies, Santa Clara, CA, USA) and the SensiFast™ SYBR® No-ROX reaction mix (Meridian, BIO-98005; Meridian Bioscience, Cincinnati, OH, USA). The procedure was following the manufacturer's protocol. Primer sequence can be seen in **Table 2**, β-Actin was employed as an endogenous control for data normalization [19,20].

Table 1 Concentration and purity of RNA.

Sample	Concentration (ng/µL)	Purity (λ260/λ280 nm)
NC	17.87	2.7743
PC	20.35	2.5643
AE1	19.88	1.9472
AE2	18.89	2.0982
AE3	20.65	2.2813

NC: Negative Control (Normal cell), PC: Positive Control (PC: Cells + UV), AE1 (PC+AE 3.13 µg/mL), AE2 (PC+ AE 6.25 µg/mL, AE3 (PC+AE 12.50 µg/mL)

Table 2 Primer sequence.

Gene symbols	Primer sequence (5' to 3')	Product size (bp)	Cycle	References
TIMP-1	F: GGAGGCAAGTTGAAAAGCGG R: CCACATCAGGCACTCCACAT	150	40	NM_002421.4
Casp-3	F: GCTTGTCGGCATACTGTTTCAG R: AGAACTGGACTGTGGCATTGAG	191	40	NM_001329455.2
GPX	F: CCAAGCTCATCACCTGGTCT R: TCGATGTCAATGGTCTGGAA	127	40	NM_001329455.2
β-actin	R: AGCACAGCCTGGATAGCAACG F: TCATGGCACCACACCTTCTACAATG	167	40	NM_001101.5

Data analysis

Statistical analysis using normality and homogeneity tests. For testing normally distributed and homogeneous data using the One-way ANOVA test and followed by Tukey's post hoc follow-up test while data that are not normally distributed and homogeneous use the Mann Whitney test followed by the Kruskal Wallis post hoc test with a confidence level of 95% ($p < 0.05$).

Results and discussion

The result shows that the UV can reduce the TIMP-1 gene expression compared to the negative control (untreated fibroblast cells), as shown in (**Figure 1**). The treatment of AE following UV exposure increased the TIMP-1 expression. The highest level of TIMP-1 expression was observed at the highest AE concentration (12.5 µg/mL, Treatment V), which was significantly higher than in the positive control group (UV-exposed fibroblasts without AE treatment) and other lower concentration groups. These results suggested that AE exhibited a dose-dependent effect, where the effectiveness of AE in enhanced TIMP-1 expression increased with higher concentrations.

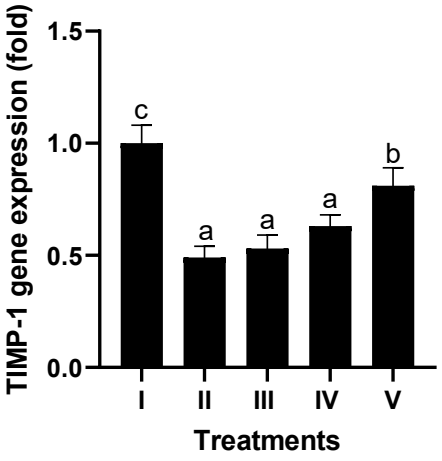

Figure 1 Effect of various concentration of AE on TIMP-1 gene expression.
*Data represented as mean ± standard deviation (SD), tests were conducted in 3 replications. Treatment I: negative control (untreated BJ cells), II: positive control (BJ cells + UV), III: positive control + AE 3.13 µg/mL, IV: positive control + AE 6.25 µg/mL, V positive control + AE 12.5 µg/mL. Different codes (a, b, c) indicate significant differences between treatments based on Tukey post hoc Test.

A dose-dependent effect was suggested by the observation that the increase in TIMP-1 expression increased in direct proportion to the increase in apple AE concentration. TIMP-1 expression peaked at the highest

concentration (12.5 µg/mL), suggesting that AE may be able to modulate the expression of genes linked to skin aging [21]. The potential of AE as an anti-aging agent is indicated by its ability to increase TIMP-1 expression. In order to preserve the structure and suppleness of the skin, TIMP-1 helps to regulate the ratio of extracellular matrix component synthesis to degradation. AE may help prevent the deterioration of collagen and elastin by raising TIMP-1, which may help prevent wrinkles and elasticity loss [22]. Flavonoids, in particular, are abundant in polyphenolic compounds found in AE and are known for anti-inflammatory and antioxidant properties. These substances might have an impact on cellular signaling pathways, such as TIMP-1, that control genes linked to aging. Increased expression of protective genes like TIMP-1 may be a result of apple polyphenols in activating of nuclear factor erythroid 2-related factor 2 (Nrf2) [23]. Previous studies have highlighted the role of apple in activating the Nrf2 pathway and enhancing antioxidant capacity [24]. Apple upregulate protective genes like TIMP-1, helping to inhibit extracellular matrix degradation [25,26]. These findings are consistent with our results, suggesting that the protective effects of AE against UV-induced skin aging may involve Nrf2 activation and the regulation of extracellular matrix-related genes.

The results shows that the UV can increase the Casp-3 gene expression compared to the negative control group (untreated fibroblast cells), as shown in (**Figure 2**). The treatment of AE following UV exposure decreased the Casp-3 expression. The lowest level of Casp-3 gene expression was observed at the highest AE concentration (12.5 µg/mL, Treatment V), which was significantly lower than in the positive control group (UV-exposed fibroblasts without AE treatment) and other lower concentration groups. These results indicated that AE may attenuated UV-induced Casp-3 expression, with its suppressive effect become evident at higher concentrations.

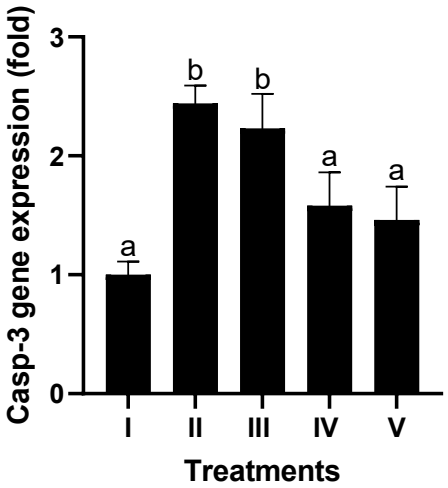

Figure 2 Effect of various concentration of AE on Casp-3 gene expression.
*Data represented as mean ± standard deviation (SD), tests were conducted in 3 replications. Treatment I: negative control (untreated BJ cells), II: positive control (BJ cells + UV), III: positive control + AE 3.13 µg/mL, IV: positive control + AE 6.25 µg/mL, V positive control + AE 12.5 µg/mL. Different codes (a, b) indicate significant differences between treatments based on Tukey post hoc Test.

This study indicates that the expression of Casp-3 mRNA is inhibited by AE. AE was demonstrated a significant reduction in Casp-3 expression when compared to the positive control [21]. A negative dose-dependent relationship was observed, where by a higher concentration of AE resulted in a more significant reduction in Casp-3 expression. This implies that the bioactive elements in AE can control Casp-3 expression in a proportionate way [23]. One important enzyme in the apoptotic (programmed cell death) process is Casp-3. AE may have anti-apoptotic properties, as evidenced by the decrease in Casp-3 expression, which could slow

down the aging process of cells. AE may contribute to the preservation of tissue integrity and cell function by lowering the level of apoptosis, which is significant in the context of anti-aging [22]. Previous studies have shown that apple, rich in phenolic compounds, can modulate apoptosis-related proteins like Casp-3 and reduce apoptotic markers, thereby enhancing cell viability under stress conditions [27,28].

The results shows that the UV can reduce the expression of GPX gene compared to the negative control group (untreated fibroblast cells), as shown in (**Figure 3**). The treatment of AE following UV exposure increased the expression of GPX gene. The highest level of GPX expression is observed at the highest AE concentration (12.5 µg/mL, Treatment V), which higher than in the positive control group (UV-exposed fibroblasts without AE treatment) and other lower concentration groups. These results demonstrated a dose-dependent effect, where higher concentrations of AE led to progressively greater recovery of GPX expression.

There was a greater increase in GPX expression when the concentration of AE increased. This dose-dependent effect indicates that the bioactive components in AE have the capacity to proportionately regulate GPX expression [23]. GPX is a crucial antioxidant enzyme that helps protect cells from oxidative damage and neutralize peroxides. An important factor in the resistance to aging is cellular antioxidant capacity, which may be increased in response to AE, as seen by the increase in GPX expression. AE may help slow down the aging process of cells by improving protection against oxidative stress [22]. Polyphenols, particularly flavonoids like quercetin and catechin, are abundant in AE. These substances may stimulate cellular signaling pathways linked to antioxidant defense in addition to their well-established strong antioxidant activity. Apple polyphenols activate the transcription factor Nrf2, which controls the antioxidant genes expression, potentially mediating the increase in GPX expression [16]. These findings suggest that AE could be useful as active components in skin care products that target aging. To improve skin antioxidant protection and slow down the aging process, topical formulations containing apple extracts at optimal concentrations could be developed [29]. Previous study reported that apple-derived polyphenols enhance antioxidant enzymes like GPX, with a dose-dependent increase that strengthens protection against oxidative stress, supporting the role of apple extract in preventing aging-related damage [30].

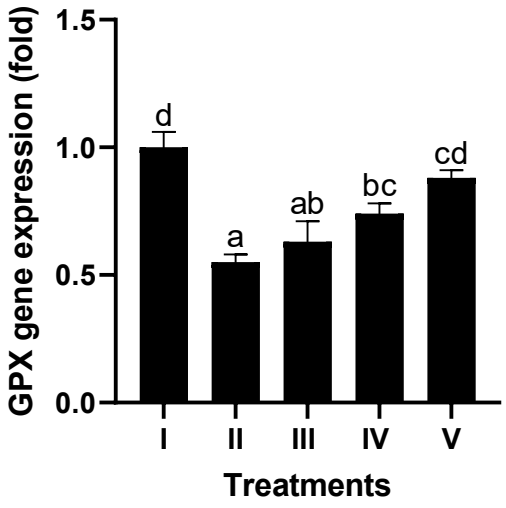

Figure 3 Effect of various concentration of AE on GPX gene expression.

*Data represented as mean ± standard deviation (SD), tests were conducted in 3 replications. Treatment I: negative control (untreated BJ cells), II: positive control (BJ cells + UV), III: positive control + AE 3.13 µg/mL, IV: positive control + AE 6.25 µg/mL, V positive control + AE 12.5 µg/mL. Different codes (a, ab, bc, cd, d) indicate significant differences between treatments based on Tukey post hoc Test.

This study suggests a synergistic anti-aging effect (**Figure 4**) that may be more potent than targeting individual pathways, as it demonstrates the ability of AE to modulate multiple aging-related pathways simultaneously [31]. Studies have shown that TIMP-1, Casp-3, and GPX are interconnected, particularly through mitochondrial apoptosis pathways. TIMP-1 levels can influence Casp-3 activity [32], while GPX regulates oxidative stress, which impacts TIMP-1 expression and apoptosis [33]. Both TIMP-1 and Casp-3 play key roles in apoptotic signaling cascades [34]. Additionally, the examination of dose-dependent responses addresses an important issue that is frequently disregarded in studies on natural products and offers insightful information for possible future uses in cosmeceuticals or nutraceuticals [35]. Moreover, apple extract shows potential as an anti-aging agent by modulating oxidative stress and inflammation markers, similar to the mechanisms of well-established active ingredients such as retinoids and vitamin C, which are commonly used in anti-aging formulations [36,37]. Finally, by providing a scientific foundation for the creation of apple-derived anti-aging products, this study closes the knowledge gap between conventional wisdom about the health benefits of apples and contemporary molecular biology [29].

Exposure to ultraviolet (UV) rays increases reactive oxygen species (ROS), leading to activation of nuclear factor kappa B (NF-κB), Casp-3, and matrix metalloproteinase-1 (MMP-1), while decreasing GPX and TIMP-1. These changes promote apoptosis, reduce antioxidant stress tolerance, and cause collagen degradation, resulting in photoaging. Apple extract containing polyphenols, flavonoids, quercetin, and catechin reduces ROS, inhibits NF-κB and Casp-3, increases GPX and TIMP-1, thereby maintaining collagen structure and enhancing antioxidant stress tolerance, protecting against photoaging.

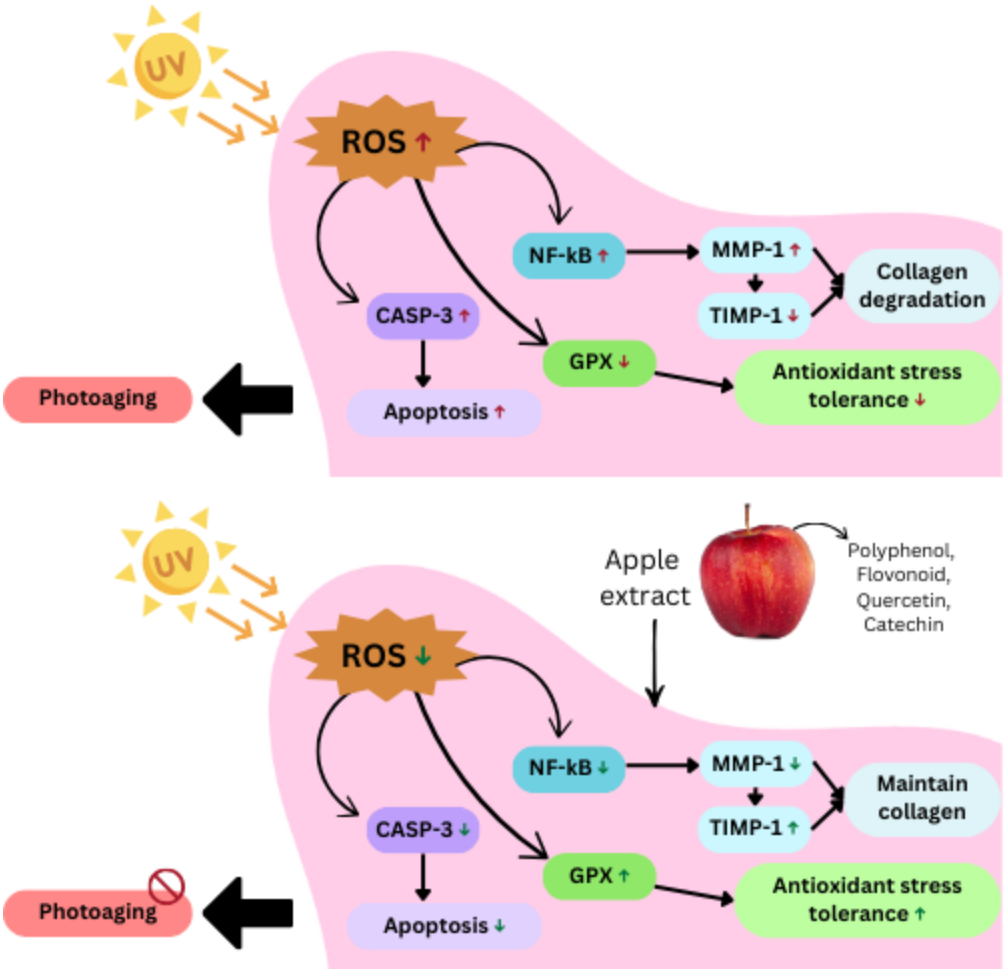

Figure 4 Proposed mechanism of apple extract (AE) as anti-aging agents.

Conclusions

The study demonstrates apple extract as an anti-aging agent by modulating TIMP-1, Casp-3, and GPX genes. The highest concentration of apple extract (12.5 µg/mL) produced the most significant increase in TIMP-1 and GPX expression. Apple extract significantly inhibited Casp-3 expression, these findings suggest that apple extract could be a valuable active ingredient in anti-aging skincare formulations, particularly by improving extracellular matrix regulation and enhancing antioxidant defenses.

Acknowledgements

This research was supported by Universitas YARSI (Hibah Penelitian Internal 2024) which provided funding for this research. This research also supported by Aretha Medika Utama (BBRC), Bandung, Indonesia which provided research methodology and laboratory facilities.

References

[1] C López-Otín, MA Blasco, L Partridge, M Serrano and G Kroemer. The hallmarks of aging. *Cell* 2013; **153(6)**, 1194-1217.

[2] R Ganceviciene, AI Liakou, A Theodoridis, E Makrantonaki and CC Zouboulis. Skin anti-aging strategies. *Dermato-Endocrinology* 2012; **4(3)**, 308-319.

[3] L Rittié and GJ Fisher. Natural and sun-induced aging of human skin. *Cold Spring Harbor Perspectives in Medicine* 2015; **5(1)**, a015370.

[4] F Gruber, C Kremslehner, L Eckhart and E Tschachler. Cell aging and cellular senescence in skin aging - Recent advances in fibroblast and keratinocyte biology. *Experimental Gerontology* 2020; **130(9)**, 110780.

[5] P Gkogkolou and M Böhm. Advanced glycation end products: Key players in skin aging? *Dermato-Endocrinology* 2012; **4(3)**, 259-270.

[6] S Zhu, L Jia, X Wang, T Liu, W Qin, H Ma, Y Lv, J Hu, Q Guo, S Tan, X Yue, Y Yan, T Liu, Y Liu, Q Xia, P Zhang, H Zhang and N Li. Anti-aging formula protects skin from oxidative stress-induced senescence through the inhibition of CXCR2 expression. *Journal of Ethnopharmacology* 2024; **318(B)**, 116996.

[7] LC Hunt, A Upadhyay, JA Jazayeri, EM Tudor and JD White. Caspase-3, myogenic transcription factors and cell cycle inhibitors are regulated by leukemia inhibitory factor to mediate inhibition of myogenic differentiation. *Skeletal Muscle* 2011; **1(1)**, 17.

[8] M Xu, T Pirtskhalava, JN Farr, BM Weigand, AK Palmer, MM Weivoda, CL Inman, MB Ogrodnik, CM Hachfeld, DG Fraser, JL Onken, KO Johnson, GC Verzosa, LGP Langhi, M Weigl, N Giorgadze, NK LeBrasseur, JD Miller, D Jurk, RJ Singh, …, JL Kirkland. Senolytics improve physical function and increase lifespan in old age. *Nature Medicine* 2018; **24(8)**, 1246-1256.

[9] R Brigelius-Flohé and M Maiorino. Glutathione peroxidases. *Biochimica et Biophysica Acta* 2013; **1830(5)**, 3289-3303.

[10] L Calvo-Castro, M Lobo-Vázquez, J Gómez-González, E Arnáez-Serrano, G Zamora-Fallas, K Sánchez-Zúñiga, and C Centeno-Cerdas. Bioactive potential of tropical highland apple (Malus domestica cv. Anna) crude extract: opportunities for food waste revalorization. *Future Journal of Pharmaceutical Sciences.* 2022; **8(1)**, 57.

[11] N Nanashima, H Maeda, A Nakajima, M Nishizuka, T Narumi, J Ichita and K Itoku. Apple pomace extract induces cell proliferation and increases type I collagen and hyaluronan production in human skin fibroblasts *in vitro*. *Plant Foods for Human Nutrition* 2024; **79(3)**, 693-699.

[12] L Orozco-Flores, E Salas, B Rocha-Gutiérrez, M Peralta-Pérez, G González-Sánchez and L Ballinas-Casarrubias. Determination of polyphenolic profile of apple pomace (Malus domestica Golden Delicious variety) by HPLC-MS. *ACS Omega* 2023; **9(1)**, 196-203.

[13] S Balık, T Kaya and R Aslantaş. Fruit quality parameters, sugars, vitamin C, antioxidant activity, organic acids, and phenolic compounds for a new endemic apple variety “Long Apple”. *Horticulturae* 2023; **9(11)**, 1171.

[14] K Bindon, Q Song, S Kassara, L Nicolotti, A Jouin and M Beer. Apple pomace compositional data highlighting the proportional contribution of

polymeric procyanidins. *Molecules* 2023; **28(14)**, 5494.

[15] D Khayatan, M Nilforoushzadeh, H Ashtiani and F Hashemian. Effect of apple (*Malus domestica*) stem cells on UVB-induced damaged skin with anti-inflammatory properties: An *in vivo* study. *Advances in Materials Science and Engineering* 2022; **2022(5)**, 1-13.

[16] HJ Kim, SH Kim and JM Yun. Fisetin inhibits hyperglycemia-induced proinflammatory cytokine production by epigenetic mechanisms. *Evidence-Based Complementary and Alternative Medicine* 2012; **2012(3)**, 639469.

[17] DG Lazaridis, AP Kitsios, AS Koutoulis, O Malisova and IK Karabagias. Fruits, spices and honey phenolic compounds: a comprehensive review on their origin, methods of extraction and beneficial health properties. *Antioxidants* 2024; **13(11)**, 1335.

[18] W Widowati, D Pryandoko, CD Wahyuni, M Marthania, HS Kusuma and T Handayani. Antioxidant properties of soybean (*Glycine max* L.) extract and isoflavone. *In:* Proceedings of the 2021 IEEE International Conference on Health, Instrumentation & Measurement, and Natural Sciences (InHeNce), Medan, Indonesia. 2021, p. 1-6.

[19] W Widowati, DK Jasaputra, P Onggowidjaja, SB Sumitro, MA Widodo, E Afifah, DD Rihibiha, R Rizal, A Amalia, HSW Kusuma, H Murti and I Bachtiar. Effects of conditioned medium of co-culture IL-2 induced NK cells and human Wharton's jelly mesenchymal stem cells (HWJMSCs) on apoptotic gene expression in a breast cancer cell line (MCF-7). *Journal of Mathematical and Fundamental Sciences* 2019; **51(3)**, 205-224.

[20] E Afifah, T Mozef, F Sandra, S Arumwardana, DD Rihibiha, H Nufus, R Rizal, A Amalia, I Bachtiar, H Murti and W Widowati. Induction of matrix metalloproteinases in chondrocytes by interleukin IL-1β as an osteoarthritis model. *Journal of Mathematical and Fundamental Sciences* 2019; **51(2)**, 103-111.

[21] AV Anand David, R Arulmoli and S Parasuraman. Overviews of biological importance of quercetin: A bioactive flavonoid. *Pharmacognosy Reviews* 2016; **10(20)**, 84-89.

[22] G Bjørklund, M Shanaida, R Lysiuk, M Butnariu, M Peana, I Sarac, O Strus, K Smetanina and S Chirumbolo. Natural compounds and products from an anti-aging perspective. *Molecules* 2022; **27(20)**, 7084.

[23] A Francini and L Sebastiani. Phenolic compounds in apple (Malus × domestica Borkh.): compounds characterization and stability during postharvest and after processing. *Antioxidants* 2013; **2(3)**, 181-193.

[24] T Huang, Q Che, X Chen, D Chen, B Yu, J He, H Chen, J He, P Zheng, Y Luo and B Yu. Apple polyphenols improve intestinal antioxidant capacity and barrier function by activating the NRF2/KEAP1 signaling pathway in a pig model. *Journal of Agricultural and Food Chemistry* 2022; **70(24)**, 7576-7585.

[25] Q Ma, J Gao, P Fan, T Yang, Z Zhuang, S Zhang, R Hu, L Cui, B Liang, X Xie, J Liu and J Long. Thinned young apple polyphenols may prevent neuronal apoptosis by up-regulating 5-hydroxymethylcytosine in the cerebral cortex of high-fat diet-induced diabetic mice. *Food & Function* 2023; **14(7)**, 3279-3289.

[26] C Joshi, S Stacy, N Sumien, A Ghorpade and K Borgmann. Astrocyte HIV-1 Tat differentially modulates behavior and brain MMP/TIMP balance during short and prolonged induction in transgenic mice. *Frontiers in Neurology* 2020; **11**, 593188.

[27] L Xiao, T Zhu, S Yang, X Li, B Song, Y Wang, Q Lin and J Cao. Analysis of phenolic components and related biological activities of 35 apple (*Malus pumila Mill*.) cultivars. *Molecules* 2020; **25(18)**, 4153.

[28] W Xia, B Song, T Li and RH Liu. Phytochemical profiles, antioxidant activities, and synergistic antiproliferative effects of blueberry and apple peel extracts. *Journal of the Science of Food and Agriculture* 2023; **104(2)**, 737-745.

[29] AS Ribeiro, M Estanqueiro, MB Oliveira and JMS Lobo. Main benefits and applicability of plant extracts in skin care products. *Cosmetics* 2015; **2(2)**, 48-65.

[30] Z Wu, Q Xu, A Li, L Lv, L Li. Apple polyphenol extract suppresses Clostridioides difficile infection in a mouse model. *Metabolites* 2022; **12(11)**, 1042.

[31] D Li, Y Cui, X Wang, F Liu and X Li. Apple polyphenol extract improves high-fat diet-induced hepatic steatosis by regulating bile acid synthesis and gut microbiota in C57BL/6 male mice. *Journal of Agricultural and Food Chemistry* 2021; **69**(24), 6829-6841.

[32] J Wei, Q Xie, X Liu, C Wan, W Wu, K Fang, Y Yao, P Cheng, D Deng and Z Liu. Identification of the prognostic value of glutathione peroxidases expression levels in acute myeloid leukemia. *Annals of Translational Medicine* 2020; **8(11)**, 678.

[33] M Nazıroğlu. A novel antagonist of TRPM2 and TRPV4 channels: Carvacrol. *Metabolic Brain Disease* 2022; **37(3)**, 711-728.

[34] S Wen, Q Wang, J Jia, X Gong, Y Zhao and G Li. Downregulation of IGFBP7 and TIMP-2 protects kidney cells by regulating cell cycle in sepsis-associated acute kidney injury, Available at: https://doi.org/10.21203/rs.3.rs-2975261/v1, accessed January 2025.

[35] X Yao, Y Mei and W Mao. Quercetin improves mitochondrial function and inflammation in H_2O_2-induced oxidative stress damage in the gastric mucosal epithelial cell by regulating the PI3K/AKT signaling pathway. *Evidence-Based Complementary and Alternative Medicine* 2021; **2021**, 1386078.

[36] KT Mellody, E Bradley, B Mambwe, L Cotterell, O Kiss, P Halai, Z Loftus, M Bell, TW Griffiths, CEM Griffiths and REB Watson. Multifaceted amelioration of cutaneous photoageing by (0.3 %) retinol. *International Journal of Cosmetic Science* 2022; **44(6)**, 625-635.

[37] S Omar, RM El Borolossy, TW El-Said and NA Sabri. Evaluation of the combination effect of rutin and vitamin C supplementation on the oxidative stress and inflammation in hemodialysis patients. *Frontiers in Pharmacology* 2022; **13**, 961590.