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Potential of *Curcuma xanthorrhiza* Extract in Protecting Fibroblast Cells from UV-Induced Aging

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ABSTRACT

The skin serves as the body's first line of defence against environmental exposures, making it vulnerable to tissue damage, especially skin aging, which is characterised by a decrease in integrity and structure. Extrinsic factors contribute significantly to skin aging, with UV exposure as the main contributor. In Indonesia, most women realise the signs of ageing in their mid-twenties. This study aimed to investigate the potential of *Curcuma xanthorrhiza* extract (CXE) as an anti-aging agent by examining its effects on UV-irradiated fibroblast cell viability, MMP-1 gene expression, and collagen content. Cell viability was measured using a cytotoxic assay, MMP-1 expression was measured by RT-PCR, and collagen content was evaluated by ELISA assay. The results showed that CXE significantly increased fibroblast cell viability, with safe concentrations of 12.5; 6.25; 3.13 µg/mL. In addition, CXE administration resulted in a significant decrease in MMP-1 expression and an increase in collagen content in aging cell model, with the best results observed at a concentration of 12.5 µg/mL. These findings suggest that CXE may serve as a natural antioxidant agent to reduce the adverse effects of UV exposure on skin aging, highlighting its potential applications in skin care and dermatological treatments.

Keywords: *Cell viability, collagen, MMP-1, skin aging, turmeric extract.*

INTRODUCTION

Human skin experiences aging as a result of both intrinsic mechanisms by natural, genetically determined biological changes and extrinsic mechanisms that arise from environmental and lifestyle influences. Research has shown that extrinsic determinants account for the vast majority of skin aging, representing approximately 97% of its progression, while intrinsic factors contribute to only about 3% (Nabila et al., 2021). Among these external contributors, exposure to ultraviolet (UV) radiation stands out as the most detrimental. Prolonged UV exposure accelerates the formation of wrinkles and fine lines, induces uneven pigmentation, and compromises skin elasticity through the degradation of structural proteins (Salminen et al., 2022). The World Health Organization (WHO) has estimated that more than 90% of visible aging manifestations on the skin are primarily attributed to chronic exposure to UV radiation. This evidence highlights the profound role of environmental UV stress in the skin-aging process and reinforces the urgent need to develop and implement effective preventive

measures. Such strategies are essential to mitigate UV-induced damage, thereby maintaining the skin's physiological function, structural integrity, and youthful appearance (Boo, 2020).
Ultraviolet radiation possesses the ability to penetrate deep into the layers of the skin, triggering a cascade of molecular and biochemical reactions that accelerate the aging process. One of the primary consequences of UV exposure is the generation of oxidative stress, which activates matrix metalloproteinases (MMPs). A family of enzymes contribute in reducing key extracellular matrix components, such as collagen, which provides structural strength, and elastin, which maintains skin elasticity. The breakdown of these structural proteins compromises skin firmness and elasticity, ultimately contributing to photoaging manifestations such as wrinkles and sagging (Geng et al., 2021). Experimental studies have further revealed that UV irradiation reduces collagen density and significantly upregulates MMP-1 expression in animal models of UV-induced skin aging, reinforcing its destructive effect on dermal integrity (Widowati et al., 2024). In addition, prolonged UV exposure impairs the skin's antioxidant defenses, causing excessive ROS accumulation that induces oxidative stress, triggers inflammation, and accelerates the degradation of structural proteins like collagen and elastin (Tanveer et al., 2023). The elevated oxidative burden disrupts normal cellular homeostasis, promotes molecular damage, and accelerates degenerative processes associated with photoaging. Over time, this chronic oxidative environment not only exacerbates visible aging but also increases the risk of long-term pathological conditions, including the various forms of skin cancer development (Geng et al., 2021).
Natural compound from plants provide an alternative prevention of skin aging with minimal side effects. *Curcuma xanthorrhiza*, also referred to as Javanese turmeric, has long been utilized in traditional medicine and contains essential bioactive compounds, including essential oils, curcumin, flavonoids, alkaloids, phenolics, and steroids (Rahmat et al., 2021). Curcumin and terpenoids are the most abundant phytochemicals found in *C. xanthorrhiza* (Minarni et al., 2023). Previous studies have shown that *C. xanthorrhiza* exhibits antioxidant (Laksmitawati et al., 2022), wound healing (Malau et al., 2024), anti-aging (Wargasetia et al., 2023), hepatoprotective, and neuroprotective properties (Rahmat et al., 2021).
The excessive UV exposure leads to collagen degradation and ECM damage, finding alternative treatments to mitigate these effects is essential. The bioactive metabolites in *C. xanthorrhiza* may serve as promising anti-aging agents. Therefore, this study aims to investigate the *C. xanthorrhiza* extract (CXE) potential in maintaining collagen content, regulating MMP-1 gene expression, and preserving fibroblast cell viability under UV-induced aging conditions.

METHODS

Curcuma xanthorrhiza extraction

The *Curcuma xanthorrhiza* extract (CXE) was obtained through a maceration process carried out by PT. Fathonah Amanah Shidiq Tabligh in Depok, Indonesia. The extraction employed 70% ethanol as the solvent, and all procedures were executed in full accordance with the Good Manufacturing Practice (GMP). Upon the extraction process completion, lactose was added as a carrier agent to facilitate handling and formulation. The final extract was subsequently stored under controlled conditions at 25 ± 2°C to preserve its chemical stability and ensure consistent product quality throughout storage (Widowati et al., 2024b).

Cells culture

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Human dermal fibroblast cells (BJ; ATCC® CRL-2522™) were utilized as an in vitro model to investigate the cellular mechanisms underlying UV-induced aging. The cell line was sourced from Aretha Medika Utama (Bandung, Indonesia) and cultured in culture medium, namely Minimum Essential Medium or MEM from Thermo Fisher Scientific in USA that supplemented with cell-supporting nutrients to promote optimal cell proliferation and maintenance. The cells were maintenanced at 37°C with 5% CO_2 (IH3543; Thermo Fisher Scientific), simulating physiological conditions. After a 24-hour incubation period, cell density and viability were assessed using a Neubauer hemocytometer (Marienfeld, Lauda-Königshofen, Germany) in conjunction with trypan blue exclusion staining from Gibco (15250-100) in Billings, USA. These assessments ensured that an adequate population of viable fibroblast cells was available prior to proceeding with subsequent experimental treatments (Widowati et al., 2024c).

Cells viability assay

Fibroblast cultures were plated into 96-well culture plates, which were purchased from Costar (Washington, USA) with the product code 3596, at a cell density of approximately 1×10^4 cells per well and permitted to adhere in duration of 24 hours at temperature of 37°C. Subsequent to the incubation period, the culture medium underwent a replacement with 90 µL of fresh medium. Following this, 10 µL of *Curcuma xanthorrhiza* extract (CXE) was introduced to attain final concentrations of 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 µg/mL. The samples were then further maintenanced for other 24 hours in identical experimental conditions. Subsequently, A volume of 10 µL of Cell Counting Kit-8 reagent from Elabscience with number of catalogue E-CK-A362 in USA was added to each well of the 96-well culture plates, which had been seeded with fibroblast cells. The plates were subsequently incubated at the temperature of 37°C in duration of 3 hours to allow for the formation of formazan, reflecting cellular metabolic activity. Cell viability was then calculated by determining the absorbance in a microplate reader from Multiskan GO (51119300) in USA at 450 nm, ensuring accurate quantification of living cells for downstream analysis (Widowati et al., 2024b).

Quantification of MMP-1 gene expression

The cells were harvested and tested using qRT-PCR method to determine the levels genes expressions of MMP-1. Total RNA was obtained from the experimental samples through an extraction and purification process conducted with the silica membrane-based RNA purification kit from Zymo Research with Catalog No. R2073 (Irvine, USA), which was specifically designed to ensure efficient recovery of RNA while minimizing potential contaminants. Experiments were performed in compliance with the standard instructions provided by the supplier to maintain sample integrity and reproducibility across assays. The standardized extraction workflow facilitated the recovery of RNA with high purity and structural integrity, ensuring its suitability for downstream molecular applications, including complementary DNA synthesis and quantitative gene expression analysis, while effectively minimizing potential contamination and degradation throughout the process. The synthesis of complementary DNA was conducted utilizing the SensiFAST cDNA synthesis kit (Bioline, BIO-65054), with procedures implemented exactly as described by the manufacturer. The PCR or polymerase chain reaction protocol began with an initial priming step at 25°C in duration of 5 minutes to allow proper primer annealing, followed by a reverse transcription phase conducted at 46°C for 20 minutes to synthesize complementary DNA (cDNA) from the RNA template. These steps were performed following the standardized PCR conditions provided by the supplier to ensure optimal reaction efficiency and high-quality cDNA

generation for subsequent gene expression analysis. This was succeeded by a reverse transcription inactivation step for 1 minute at 95°C, culminating in an optimization phase conducted at 4°C. Subsequently, gene expression analysis of MMP-1 was conducted utilizing the SYBR NO-ROX kit (Bioline, BIO-98005) along with the primer as described by Widowati et al. (2024b). The specific primer sequences employed for gene amplification in this study are detailed in Table 1.

Table 1. Primer sequence

Gene	Primer sequences (5′-3′)	Annealing	Cycle	Reference
β-actin	TCT-GGC-ACC-ACA-CCT-TCT-ACA-ATG AGC-ACA-GCC-TGG-ATA-GCA-ACG	58 ^{0}C	40	NM_001101.5
MMP-1	CTG-AAG-GTG-ATG-AAG-CAG-CC AGT-CCA-AGA-GAA-TGG-CCG-AG	58 ^{0}C	40	NM_001145938.2

Quantification of collagen level

The collagen level in the cell was determined with an ELISA or enzyme-linked immunosorbent assay, Human Collagen Type I Alpha 1 or COL1α1 ELISA Kit from Elabscience with catalogue number of E-EL-H0869 in Houston, USA. Upon completion of the assay, the absorbance of each well was carefully calculated with a Multiskan™ spectrophotometer from Thermo Fisher Scientific in USA at the recommended wavelength. This approach allowed for precise quantification of collagen levels, ensuring reliable and reproducible data for subsequent analysis of extracellular matrix integrity.

Statistical analysis

Data analysis was conducted using SPSS v23.0 from USA. Normality and homogeneity were assessed to select the appropriate test. One-way ANOVA followed by Tukey's HSD was used for parametric data, while Dunnett's T3 or Mann–Whitney U test was applied when assumptions were violated. Results are expressed as mean ± SD (n = 3), with $p < 0.05$ considered significant. Graphs were generated in GraphPad Prism v8.0.2 from USA (Widowati et al., 2024c).

RESULTS

The cell viability results of UV-induced fibroblasts treated with CXE as demonstrated through the visual representation in Figure 1 and the corresponding dataset in Table 2. Experimental evidence suggests that CXE treatment increased cell viability compared to the positive control (II). CXE 3.13, 6.25, and 12.5 µg/mL was selected for further analysis, as these concentrations showed cell viability above 90%. These concentrations were also comparable to the negative control (I), suggesting that CXE effectively protects fibroblast cells from UV-induced damage.

Table 2. Fibroblast Cell Viability

Treatment	Cell Viability (%)	*p*-value
NC (fibroblast cells)	100,00 ± 4,52^{bc}	0.002
PC (UV-induced fibroblasts)	70,41 ± 0,45^{ab}	
100 (PC + CXE 100 µg/mL)	84,29 ± 0,40^{b}	
50 (PC + CXE 50 µg/mL)	88,07 ± 4,07^{b}	
25 (PC + CXE 25 µg/mL)	92,80 ± 1,59^{b}	
12.5 (PC + CXE 12.5 µg/mL)	98,90 ± 12,09^{bc}	
6.25 (PC + CXE 6.25 µg/mL)	112,43 ± 3,46^{b}	
3.13 (PC + CXE 3.13 µg/mL)	116,26 ± 3,88^{c}	

1.56 (PC + CXE 1.56 µg/mL)	120,70 ± 2,00[c]

Numerical data are summarized as mean ± SD, with alphabetic superscripts serving as statistical markers of intergroup variation ($p < 0.05$) within the CXE-induced aging cell.

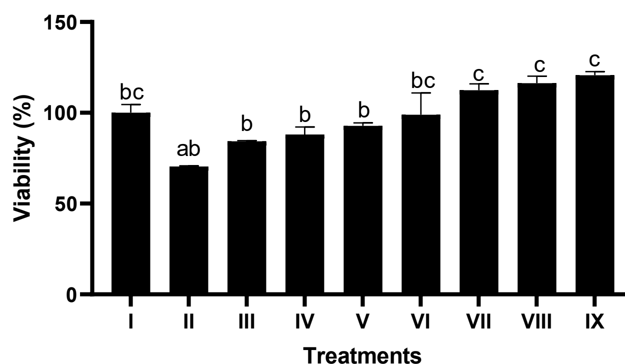

Figure 1. Effect of Various CXE Concentrations on Fibroblast Cell Viability in a UV-Induced Aging Cell Model

Mean ± SD values are shown for each group: untreated control (I), UV-induced control (II), and UV-exposed fibroblasts co-treated with graded CXE concentrations (III–IX; 100–1.56 µg/mL). Statistically significant variations among treatments are indicated by differing superscript annotations ($p < 0.05$, Tukey's HSD).

The influence of different concentrations of CXE on the MMP-1 gene expressions in UV-induced fibroblast cells is presented in Figure 2 and Table 3. Exposure to UV radiation markedly elevated MMP-1 expression benchmarked against the negative control group (I), as reflected in the positive control group (II), which exhibited the highest expression level. Treatment with CXE markedly attenuated MMP-1 expression in a concentration-dependent manner, indicating its potential inhibitory effect on UV-induced extracellular matrix degradation. The lowest MMP-1 expression among the treated groups was observed in cells treated with CXE at 12.5 µg/mL (V), followed by 6.25 µg/mL (IV) and 3.13 µg/mL (III). These findings suggest that CXE treatment can mitigate the UV-induced increase in MMP-1 expression, potentially contributing to the prevention of collagen degradation in aging fibroblast cells.

Table 3. MMP1 Gene Expression

Treatment	MMP1 Gene Expression (fold)	*p*-value
NC (fibroblast cells)	1,00 ± 0,11[a]	
PC (UV-induced fibroblasts)	9,84 ± 0,52[e]	
3.13 (PC + CXE 3.13 µg/mL)	6,89 ± 0,19[d]	0.009
6.25 (PC + CXE 6.25 µg/mL)	3,56 ± 0,55[c]	
12.5 (PC + CXE 12.5 µg/mL)	2,40 ± 0,16[b]	

Numerical data are summarized as mean ± SD, with alphabetic superscripts serving as statistical markers of intergroup variation ($p < 0.05$) within the CXE-induced aging cell.

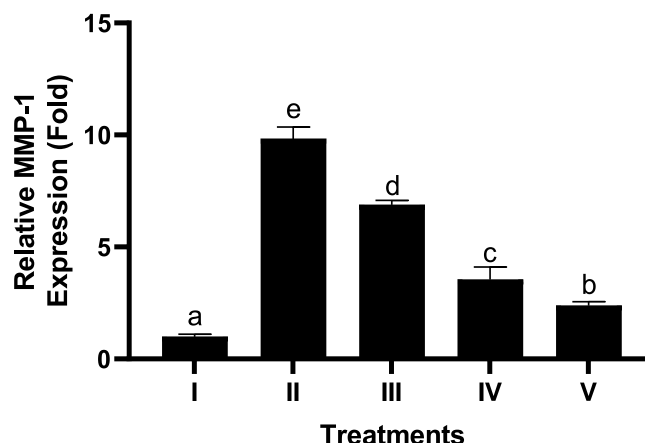

Figure 2. Effect of Various CXE Concentrations on MMP-1 Gene Expression in a UV-Induced Aging Cell Model

Numerical outcomes are conveyed as mean ± SD, capturing responses from untreated fibroblasts (I), UV-challenged controls (II), and CXE-coincubated groups (III–V; 3.13, 6.25, 12.5 μg/mL). Alphabetic superscripts act as statistical markers distinguishing significantly divergent populations ($p < 0.05$, Tukey's HSD criterion).

The impact of different CXE concentrations on collagen levels in UV-induced fibroblast cells is presented in Figure 3 and Table 4. Exposure to UV radiation markedly decreased collagen content benchmarked against the negative control group. In contrast, treatment with CXE at all tested concentrations resulted in a concentration-dependent restoration of collagen levels. The negative control group (I) exhibited the highest collagen concentration, while the positive control group (II) showed the lowest. Among the CXE-treated groups, cells exposed to 12.5 μg/mL CXE (V) demonstrated the greatest improvement in collagen levels relative to the lower concentrations (III and IV). These findings suggest that CXE supplementation can effectively counteract UV-induced collagen degradation in fibroblast cells.

Table 4. Collagen Content

Treatment	Collagen Content (ng/mL)	*p*-value
NC (fibroblast cells)	$16{,}32 \pm 0{,}63^{e}$	
PC (UV-induced fibroblasts)	$5{,}29 \pm 0{,}17^{a}$	
3.13 (PC + CXE 3.13 μg/mL)	$7{,}28 \pm 0{,}70^{b}$	<0.001
6.25 (PC + CXE 6.25 μg/mL)	$8{,}76 \pm 0{,}20^{c}$	
12.5 (PC + CXE 12.5 μg/mL)	$11{,}82 \pm 0{,}32^{d}$	

Numerical data are summarized as mean ± SD, with alphabetic superscripts serving as statistical markers of intergroup variation ($p < 0.05$) within the CXE-induced aging cell.

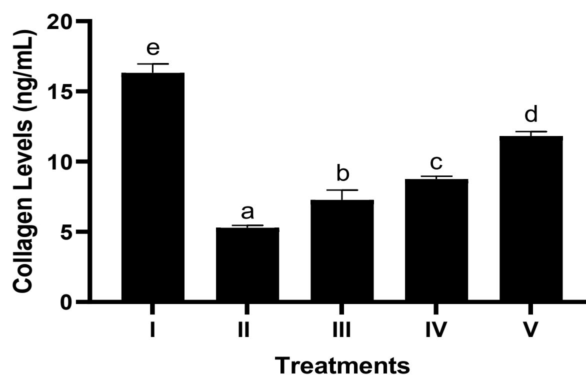

Figure 3. Effect of Various CXE Concentrations on Collagen Content in a UV-Induced Aging Cell Model

Numerical outcomes are conveyed as mean ± SD, capturing responses from untreated fibroblasts (I), UV-challenged controls (II), and CXE-coincubated groups (III–V; 3.13, 6.25, 12.5 µg/mL). Alphabetic superscripts act as statistical markers distinguishing significantly divergent populations ($p < 0.05$, Tukey's HSD criterion).

DISCUSSION

Aging cell models were developed by exposing fibroblast cells to UV radiation. Fibroblasts contribute in anti-aging therapy as their activity and proliferation influence skin regeneration (Zorina et al., 2023). Prolonged UV exposure alters skin structure and composition, leading to oxidative stress (Dai et al., 2021). Oxidative stress develops due to an imbalance between free radical formation and antioxidant defense mechanisms, damaging cells and tissues, accelerating aging (Jo et al., 2020), and disrupting cellular regulation, which may result in mutations and carcinogenesis (Fauziah et al., 2024).

Cell viability is a key indicator in *in vitro* studies, reflecting cellular health. Mechanical and chemical agents influence cell metabolism (Li & Li, 2020). Cytotoxicity testing classifies viability levels: >90% (biocompatible), 60-90% (mild toxicity), 30-59% (moderate toxicity), and <30% (high toxicity) (Sulistyo et al., 2023). Fibroblast viability studies show that plant extracts can enhance cell survival and inhibit collagen degradation under UV exposure (Wasliati et al., 2019).

MMP-1 contributes in UV-induced skin aging (photoaging). UV exposure stimulates fibroblasts to express MMP-1, degrading collagen and leading to wrinkle formation (Murlistyarini & Dani, 2022). Elevated MMP-1 activity is recognized as a major marker of cellular aging and the degradation of skin structure (Lee et al., 2023).

Skin aging is associated with reduced collagen content, affecting skin elasticity. Collagen maintains normal skin structure and promotes fibroblast proliferation, strengthening the extracellular matrix and aiding wound healing (Shiba et al., 2022; Dewi et al., 2024). UV exposure generates reactive oxygen species (ROS), activating activator protein-1 (AP-1), which inhibits collagen synthesis and increases matrix metalloproteinase (MMP) activity, leading to collagen degradation and skin aging (Putri et al., 2023). Antioxidants can mitigate these effects by neutralizing free radicals and maintaining collagen levels (Sunarno & Isdadiyanto, 2010).

Curcuma xanthorrhiza has potential anti-aging properties due to its antioxidant compounds, such as curcumin, which reduce oxidative stress and exhibit radioprotective effects (Kisnanto et al., 2024). Previous studies suggest that *C. xanthorrhiza* inhibits elastase, hyaluronidase,

and tyrosinase activities, marking it as a biologically persuasive contender in the landscape of anti-aging therapeutics (Wargasetia et al., 2023). *C. xanthorrhiza* has been utilized in skincare formulations, particularly in creams aimed at enhancing skin brightness (Nurlinayanti et al., 2019) and gels for wound healing (Malau et al., 2024).

CONCLUSION

Curcuma xanthorrhiza extract significantly enhances the viability of UV-exposed human skin fibroblasts while downregulating MMP-1 gene expression and preserving collagen levels. The extract demonstrates optimal effectiveness at specific concentrations, implying its possible role as an anti-aging agent by mitigating UV-induced cellular damage.

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