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Research Article

The Antiaging Potential of Serum Formulations from *Centella asiatica*, *Curcuma longa*, *Aloe vera*, *Rosa centifolia*, and Salmon DNA on Injured Human Fibroblast Cells

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ABSTRACT

External aging factors such as UV exposure, pollution, and lifestyle choices contribute to skin aging, resulting in deep wrinkles, fine lines, and rough skin, which can lower self-confidence. Plant extracts have been widely studied for their antiaging potential, while Salmon DNA has shown promise in stimulating collagen production. This study explores the formulation of a serum combining *Centella asiatica*, *Curcuma longa*, *Aloe vera*, *Rosa centifolia*, and Salmon DNA for its antiaging effects on injured human fibroblast cells. The serum was formulated using extracts from *C. asiatica*, *C. longa*, *A. vera*, *R. centifolia*, and Salmon DNA. Antioxidant activity was evaluated with the DPPH method, cytotoxicity using the WST-8 assay, and gene expression through qRT-PCR for COL1A1, TGF-β1, HYAL-1, and FGF-2. The serum exhibited weak antioxidant activity (IC_{50} = 373.33 µg/ml) and reduced cell viability at high concentrations. Gene expression analysis revealed increased expression of COL1A1, TGF-β1, and FGF-2, along with reduced HYAL-1 expression in injured BJ cells. The formulated serum shows potential as an antiaging agent, promoting collagen production and reducing hyaluronidase activity.

1. Introduction

Aging is a normal multifactorial pattern that triggers physical alterations in the skin and connective tissue (Widowati *et al*. 2018; Zorina *et al*. 2022). These physiological changes result from intrinsic aging and cumulative extrinsic damage, including exposure to ultraviolet radiation, environmental pollution, and free radicals (Widowati *et al*. 2022). These factors gradually change the shape and function of each layer of the skin, thereby changing the appearance of the skin. In intrinsic aging, the skin undergoes morphological and physiological changes such as dryness, wrinkles, and sagging, and wound healing becomes slower. Extrinsic aging causes deep wrinkles, loss of elasticity, and a rough skin surface (Yusharyahya 2021). Aging is closely related to skin regeneration and skin cell proliferation. Several key genes are important in regulating this mechanism, especially COL1A1, TGF-β1, HYAL-1, and FGF-2.

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COL1A1 is known as the gene encoding the alpha-1 chain of type I collagen, a major structural element of the extracellular matrix (ECM) in the dermis. COL1A1 expression decreases with aging, causing a decrease in collagen production and contributing to skin aging (Iriyama *et al*. 2022). TGF-β1 is a growth factor that governs various cellular processes, such as cell proliferation, differentiation, and ECM production. It plays a crucial role in skin homeostasis, and its dysregulation has been linked with skin aging (Shin *et al*. 2019). HYAL-1 is a hyaluronidase enzyme that degrades hyaluronic acid (HA), a key component of the ECM. Changes in HYAL-1 expression and HA metabolism have been linked to skin aging and various age-related pathologies (Shin *et al*. 2019). FGF-2 is a fibroblast growth factor that promotes cell proliferation, migration, and ECM production. Its expression is important for maintaining skin homeostasis, and its downregulation has been correlated with skin aging (Hatzirodos *et al*. 2019). In this regard, antioxidants also play an important role in skin regeneration by modulating gene expression and creating an environment conducive to tissue regeneration. Antioxidants help neutralize excess reactive oxygen species (ROS), which can interfere with skin regeneration and contribute to skin aging (Fitzmaurice *et al*. 2011).

Natural cosmetics are increasingly in demand because of their positive benefits for skin health and appearance, especially through beauty treatments that utilize natural ingredients from plants and animals. These treatments are considered safer than synthetic chemical products that can cause irritation or side effects, especially for sensitive skin. Amid increasing awareness of the importance of skin health, more and more people are turning to natural cosmetics because they have minimal risk of toxicity and are in line with global trends that are more environmentally friendly. One of the most sought-after cosmetic products is serum products. Serum is a topical cosmetic with a concentrated amount of active ingredients, so it has good potential for effectiveness (Amnuaikit *et al*. 2022).

Salmon DNA is known to help in the formation, repair, and restructuring of tissue, which increases the formation of elastin and collagen (Lee *et al*. 2017; Sato *et al*. 2017; Sveen *et al*. 2023). Salmon DNA also contains vitamins, peptides, and antioxidants in addition to hyaluronic acid. Therefore, salmon DNA can help in skin tissue regeneration (Sato *et al*. 2017). Salmon DNA was used in this study as the main ingredient in the formulation of antiaging serum with the addition of *Centella asiatica*, *Curcuma longa*, *Aloe vera*, and *Rosa centifolia* extracts to increase collagen and elastin synthesis, as well as improve skin structure and elasticity. Phytochemical screening revealed that the extract of *C. asiatica* contained alkaloids, saponins, tannins, phenolics, flavonoids, glycosides, terpenoids, and steroids (Ferdous *et al*. 2017). Meanwhile, turmeric extract (*C. longa*) contains flavonoids, polyphenols, saponins, tannins, glycosides, and secondary metabolites of alkaloids, steroids, terpenoids, and essential oils (Chanda & Ramachandra *et al*. 2019). Phytochemical screening of *A. vera* extract using 96% ethanol solvent showed that the sample contained flavonoids, phenolics, tannins, and saponins (Bista *et al*. 2020). The *R. centifolia* flower petal extract contained alkaloids, carbohydrates, flavonoids, glycosides, saponins, steroids, tannins, triterpenoids, and phenolic compounds (Nimbal *et al*. 2021). Overall, the bioactive components in these extracts are known to stimulate collagen production, promote cell regeneration, and reduce inflammation, so they have the potential as active ingredients in antiaging cosmetics.

Until now, there has been no research that formulates these active ingredients into serum preparations for antiaging, so the formulation and testing of its antiaging potential in vitro was carried out on injured human fibroblast cells as an antiaging model to see its cell regeneration activity. Thus, this study aims to formulate an antiaging serum and test its aging potential by measuring antioxidant parameters with 1,1-diphenyl-2-picrylhydrazyl (DPPH), cytotoxic assay, and measuring the COL1A1, TGF-β1, HYAL-1, and FGF-2 genes expression of in injured human fibroblast cells.

2. Materials and Methods

2.1. Formulation of Serum

The serum product was manufactured at PT. Dizza Karya Utama, which is certified for Good Manufacturing Practices (GMP) by the Indonesian Food and Drug Authority (Indonesian FDA with the certification number PW-S.03.011.44.441.12.22-0457).

The following serum base ingredients contain water as the primary component, Na^2EDTA, Carbomer (Repoly 140), Xanthan Gum (Keltrol CGSFT), Hyaluronic Acid, Glycerin KOH (Potassium Hydroxide), Phenoxyethanol

BMP 800 (Methylpropanediol), Peptide Complex (Natori Peptide Complex), acetyl tetrapeptide-5 (Natori Peptide Complex), Palmitoyl tripeptide-1 (Natori Peptide Complex), Palmitoyl pentapeptide-4 (Natori Peptide Complex), Glycine max polypeptide (Natori Peptide Complex), Saccharomyces polypeptides (Natori Peptide Complex), 1,2-hexanediol (Natori Peptide Complex), d-panthenol (D-Panthenol), Allantoin (Allantoin), Vitamin E (Tocopherol), Glutathione, PEG-40 Hydrogenated Castor Oil (Sabowax), and Perfume (Fragrance).

The active ingredients of the serum can be seen in Table 1.

2.2. DPPH Test for Antioxidant

Serum was tested by DPPH test with serial concentrations, namely 200, 100, 50, 25, 12.5, and 6.25 µg/ml. Serum on various concentrations was added 50 µL to each well of the 96-well plate, then 200 µL DPPH (1,1-diphenyl-2 -picrylhydrazyl) solution (Sigma-Aldrich, D9132) was added to each well. The concentration of DPPH used is 0.077 mmol/L (dissolved in methanol). After that, the plate was incubated in the dark room for 30 minutes at room temperature. After incubation, the absorbance of each well was measured by a microplate reader (MultiskanTM GO Microplate Spectrophotometer, Thermo Scientific) at 517 nm wavelength. The scavenging activity was quantified using this formula (Widowati *et al*. 2018):

$$\text{Scavenging activity (\%)} = (Ac - As)/ Ac \times 100$$

Ac = negative control absorbance (without sample)
As = sample absorbance.

2.3. Cells Viability Assay

The cells used in this study are BJ fibroblast cells obtained from ATCC® CRL-2522. The cells were cultured in medium MEM with supplement complete following the method by Widowati *et al*. (2019). The cells were incubated at 5% CO_2 in 37°C. After cells were confluent around 70-80%, cells were counted by hemocytometer and then cultured at a density of 1 x 10^4 cells/well in a 96-well plate and incubated at 37°C for 24 hours, 5% CO_2. After incubating, the cells medium was replaced by mediums that contained serum with serial concentrations 50, 25, 12.5, 6.25, 3.13, 1.63, and 0.82% with a volume of 100 µL in each well. After 24 hours of incubation, 10 µL WST 8 (Elabscience, E-CK-A362) was added to each well and incubated at 37°C, 5% CO_2 for 3 hours. Absorbance is measured by a spectrophotometer in 450 nm wavelength (Widowati *et al*. 2021; Eder *et al*. 2022).

2.4. COL1A1, TGF-β1, HYAL-1, FGF-2 Genes Expression Assay

Cells were counted by hemocytometer and then cultured at a density of 5 x 10^5 cells/well in a 6-well plate and incubated for 24 hours at 37°C, 5% CO_2. Then, cells were wounded by making a straight line using blue tips (1 ml) in the middle of the well to create an aging model. Culture mediums were replaced by new ones containing serum with serial concentrations (4, 2, and 0.5%) and incubated for 72 hours at 37°C, 5% CO_2. After that, cells were harvested to be tested for gene expression using qRT-PCR. The levels of COL1A1, TGF-β1, HYAL-1, and FGF-2 gene expression were measured from pellet cells. The total RNA isolate applied was the Direct-zol RNA Miniprep Plus Kit (Zymo, R2073), the procedure applied following the protocol from the manufacturer. The concentration and purity of RNA of each sample were measured at 260/280 nm (Table 2). A Sensi-FAST cDNA synthesis kit was used to synthesize the complementary DNA using the manufacturer's protocol. Quantitative gene expression was quantified using AriaMx 3000 Real-Time PCR System (Agilent, G8830A) with primer sequence (Table 3) and Sensi-FAST Syber NO-ROX reaction mixture. The procedure was according to the manufacturer's protocol. Real-time PCR was run for 40 cycles using GAPDH as a reference gene, and the annealing temperatures were 58°C, 59°C, 59°C, and 63°C for COL1A1, TGF-β1, HYAL-1, and FGF-2, respectively (Priyandoko *et al*. 2024).

Table 1. Active ingredients of serum

Ingredients	Percentage
Centella asiatica Extract	0.5-2
Curcuma longa Extract (Turmeric)	0.5-2
Aloe vera extract	0.5-2
Rosa centifolia extract	0.5-2
Salmon DNA	0.5-2
Honey Extract	0.5-2
Niacinamide	4-6

Table 2. Concentration and purity of RNA

Sample	Concentration (ng/µL)	Purity (λ260/λ280) nm
NC	13.60	2.258
PC	10.24	1.345
Serum 4%	8.88	2.345
Serum 2%	10.56	2.154
Serum 0.5%	9.20	2.140

2.5. Statistical Analysis

Data was analyzed using SPSS software 20.0 (SPSS Inc). For normally distributed and homogenous data, one-way ANOVA was used, followed by Tukey HSD post-hoc test. The data's significance level is P-value < 0.05. The data was visualized using GraphPad Prism (version 9.2.0.332), which displays mean±standard deviation in histograms (Widowati *et al*. 2021).

3. Results

3.1. Effect of Formulated Serum on DPPH Scavenging Activity

The antioxidant activity of serum was analyzed using the DPPH method. The results showed the antioxidant activity of the serum. DPPH inhibition is in line with the reduction of serum concentration. The serum showed concentration-dependent antioxidant activity (Figure 1) with a median Inhibitory Concentration (IC_{50}) 373.33 µg/ml (Table 4).

3.2. Effect of Formulated Serum on Fibroblast Cell Viability

The results of the study showed that the serum from the formulation had toxic levels to cells if in high concentrations. This data can be seen in Figure 2A. The higher the concentration of serum given, the lower the cell viability. A serum concentration of 0.82% had exhibited viability similar to the negative control. Inversely proportional to serum on BJ cell inhibition (Figure 2B), the lower the concentration of serum given, the lower the inhibition of cell viability. For further research, the safest concentration was used with viability above 80%.

3.3. Effect of Formulated Serum Toward FGF-2, HYAL-1, COL1A1 and TGFB-1 Gene Expression in Injured-Skin Fibroblast

Based on the results obtained, serum had a regulatory effect on gene expression related to cell regeneration in injured BJ cells. The scratch results on BJ cells can increase the expression of FGF-2 and HYAL-1 genes while decreasing COL1A1 and TGF-β1 (Figure 3). In this case, serum can improve the genes related to regeneration regulation. The results showed that FGF-2 gene expression in BJ cells as an aging cells model treated with serum increased relatively compared to the positive control. The most effective concentration in enhancing FGF-2 gene expression was 0.82%. Serum also decreased HYAL1 gene expression in injured BJ cells. Furthermore, the data showed that serum could increase COL1A1 and TGF-β1 gene expression in aging cells compared to the positive control. The data shown is the average

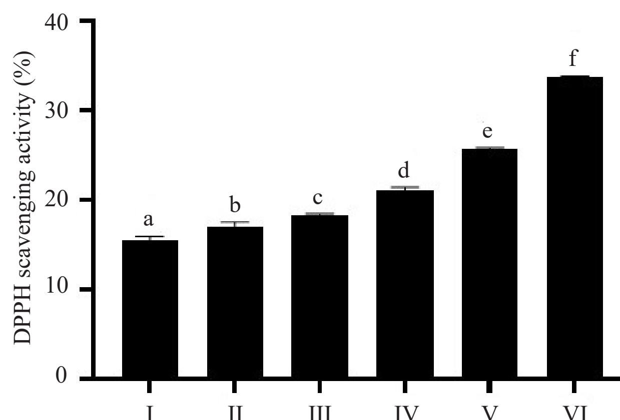

Figure 1. Effect of serum concentrations in DPPH scavenging activity. I: serum 6.25 µg/ml, II: serum 12.5 µg/ml III: serum 25 µg/ml, IV: serum 50 µg/ml, VI: serum 100 µg/ml, VI: serum 200 µg/ml, Data are represented in mean ± standard deviation. The different letters in the graph show significant differences among various serum concentrations based on the Tukey HSD Post Hoc Test P<0.05

Table 4. The antioxidant activity (IC_{50}) values of formulated serum

Assay	Linear Equation	IC_{50} value (µg/ml)
DPPH	y = 0,0914x + 15,878	373.33

Table 3. Primer sequence

Gene symbols	Primer sequence (5' to 3')	Product size (bp)	Annealing (ºC)	Cycle	References
COL1A1	F: GAATTCGGCTTCGACGTTGG R: AGGGGGTTCAGTTTGGGTTG	127	58	40	NM_000088.4
TGF-β1	F: GACTTTTCCCCAGACCTCGG R: ATAGGGGATCTGTGGCAGGT	135	59	40	NM_000660.7
HYAL-1	F: GCCCTTCATCCTGAACGTGA R: AGCTGGATGGAGAAACTGGC	138	59	40	NM_153281.2
FGF-2	F: GAGCCCAGGAGTTCAAGACC R: GAGACCACATGTACACGCCA	93	63	40	NM_002006.6
GAPDH	F: GAAGGTGAAGGTCGGAGTC R: GAAGATGGTGATGGGATTTC	172	58	40	NM_001289745.3

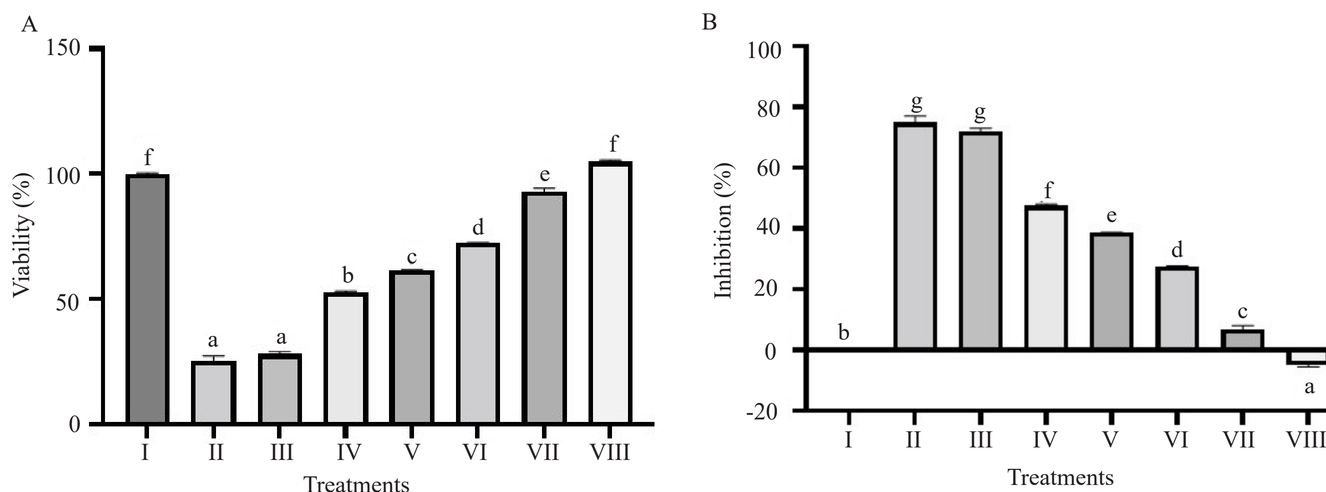

Figure 2. Effect of serum concentrations on the viability of BJ cells as measured based on (A) viability and (B) inhibitory value. I: Negative control II: serum 50 %, III: serum 25 % IV: serum 12.5 %, V: serum 6.25 %, VI: serum 3.13 %, VII: serum 1.63 %, VII: serum 0.82 %, Data are represented in mean ± standard deviation. The different letters in the graph show significant differences among various serum concentrations based on the Tukey HSD Post Hoc Test P<0.05

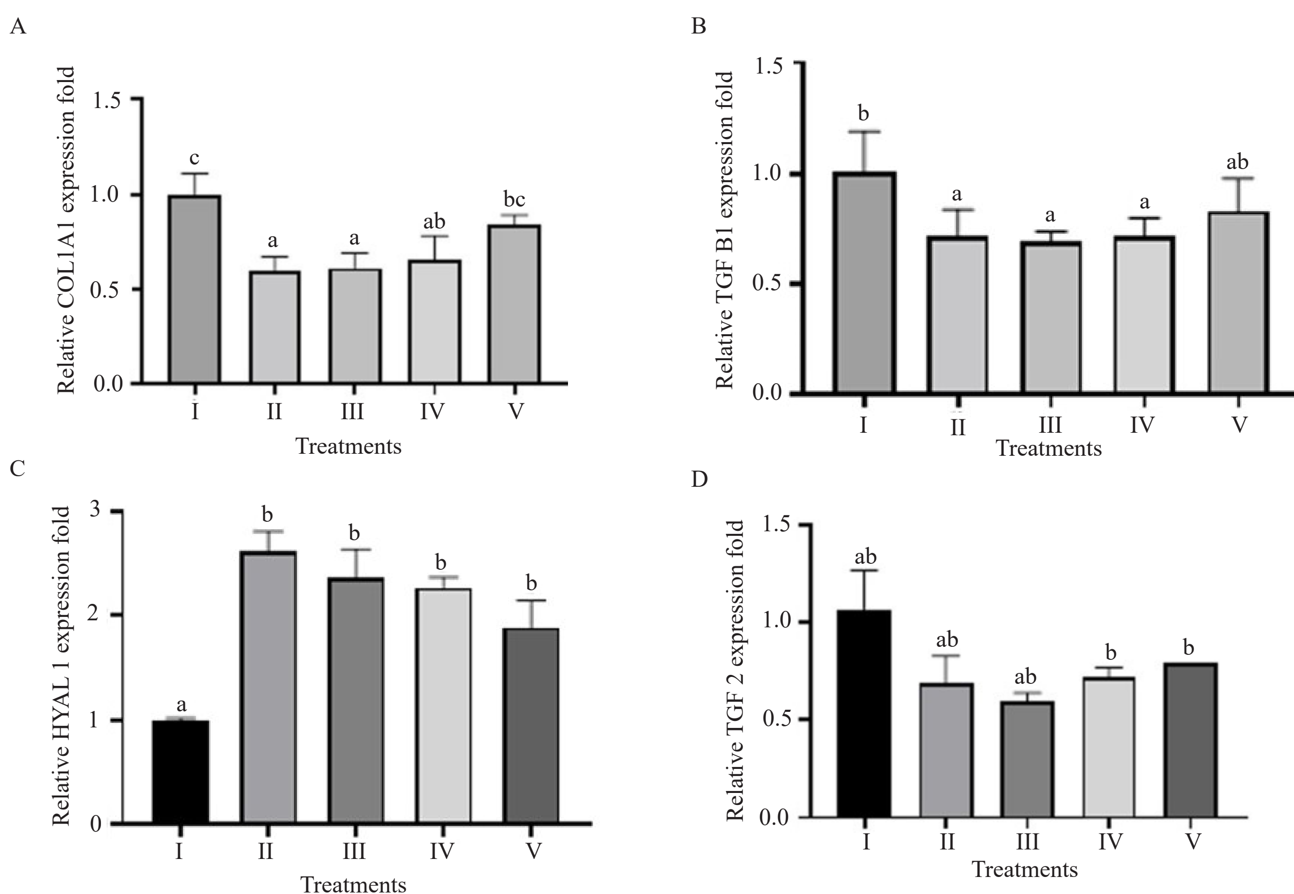

Figure 3. Effect of serum concentrations toward genes expression of (A) COL1A1, (B) TGF-β1, (C) HYAL-1, and (D) FGF-2. I: Negative control II: Positive control, III: Serum concentration 4%, IV: Serum concentration 2%, V: Serum concentration 0.5%, Data are presented in mean ± standard deviation. Different letters in each bar showed significant differences between treatments based on the Tukey HSD Post Hoc Test P<0.05

of three replications where the lower the serum concentration is given, the higher the repair effect.

4. Discussion

Skin aging is a global concern that many women complain about. Preventing skin aging can be achieved by using skincare products with active antiaging ingredients. Serum is a widely used skincare formulation because it contains active ingredients at high concentrations, which allows for faster absorption into the skin, and its low viscosity makes it easy to spread over the skin's surface (Amnuaikit *et al*. 2022). In this study, the serum is formulated with active ingredients that have been proven in many studies to be beneficial for antiaging. *R. centifolia* extract has anti-inflammatory, antibacterial, anti-allergic, and antiaging properties. *C. asiatica* is known to help wound healing and skin inflammation through re-epithelialization and stimulation of collagen synthesis. Its bioactive compounds, including madecassic acid, madecassoside, and asiatic acid, also provide anti-inflammatory, antioxidant, and antimicrobial properties (Yasurin *et al*. 2016). According to Kim *et al*. (2019), turmeric leaf extract contains antioxidant components like phenolic and flavonoid compounds that can scavenge ROS. Turmeric leaf water extract is known to have a high total phenolic content (2.741±0.099 mg GAE/g) and flavonoid content (4.776±0.010 mg QCE/g). In this study, salmon DNA was also added to the serum formulation to support tissue formation, repair, and remodeling, as well as to enhance collagen and elastin synthesis, improving skin manifestations including sagging, loss of firmness, dryness, dullness, and uneven skin tone (Lee *et al*. 2017; Sato *et al*. 2017 Sveen *et al*. 2023).

Antioxidant assay was conducted using the DPPH method to test the activity of the serum's active ingredients. DPPH was used as a free radical source to measure antioxidant activity. The DPPH test results showed that the higher the serum concentration, the greater the DPPH scavenging activity (Figure 1). The antioxidant ability of a compound is classified into several groups. IC_{50} values < 50 µg/ml are 'very strong', IC_{50} values of 50-100 µg/ml are 'strong', IC_{50} values of 101-250 µg/ml are 'medium', IC_{50} values of 250-500 µg/ml are 'weak', and IC_{50} values of more than 500 µg/ml are inactive antioxidants. The serum showed antioxidant activity with IC_{50} 373.33 µg/ml and was classified as a weak antioxidant (Kusumawati *et al*. 2021). These data indicate that the serum has antioxidant activity due to its active ingredients, such as *C. longa* and *C. asiatica*. Based on DPPH, ABTS, H_2O_2, NO, and FRAP tests, *C. longa* extract is known to have high antioxidant activity (Laksmitawati *et al*. 2022). *C. asiatica* extract also exhibits high antioxidant activity in DPPH scavenging tests (Buranasudja *et al*. 2021). *C. asiatica* is known to contain a high amount of flavonoids such as apigenin, catechin, kaempferol, rutin, quercetin, and naringin, making this plant a rich source of antioxidants (Taghizadeh & Jalili 2023). With these active ingredients, the serum provides excellent antioxidant effects.

The cell viability test results show that the serum is safe to use at low concentrations (Figure 2). This can be seen in Figure 2A, where the lower the serum concentration, the higher the cell viability. The serum concentration of 0.82% showed cell viability similar to the negative control. This served as the basis for selecting the concentration for the next study, qRT-PCR.

The effects of serum on FGF-2 gene expression in injured BJ cells showed that FGF2 gene expression increased depending on the concentration applied. Low-concentration serum can increase FGF-2 gene expression more significantly in injured BJ cells. FGF2 is a growth factor that plays an important role in tissue regeneration and repair. It is associated with aging due to its ability to influence cell proliferation, angiogenesis, and differentiation, which can contribute to decreased tissue function with age (Farooq *et al*. 2021). The presence of active ingredients like aloin from *A. vera* may be responsible, as studies have shown that *A. vera* gel extract can increase FGF-2 gene expression (Razi *et al*. 2021).

HYAL-1 is a hyaluronidase enzyme responsible for degrading hyaluronic acid in the skin, and its activity decreases with age, leading to lower hyaluronic acid levels, contributing to the loss of moisture and elasticity, and accelerating signs of aging (Abatangelo *et al*. 2020). Scratch induction increases HYAL-1 gene expression, which can lead to skin aging. The serum significantly reduced HYAL-1 gene expression in injured BJ cells. This may be due to the active ingredients in the serum, as previous studies have shown that *A. vera* extract can modulate HYAL-1 expression in HaCaT cells (Razia *et al*. 2021).

The COL1A1 gene plays a role in collagen synthesis, a key component of the skin's extracellular matrix. Based on the results, the tested serum increased COL1A1 gene

expression compared to the positive control. The serum also enhanced TGF-β1 gene expression compared to the positive control. Several studies have shown that TGF-β1 expression plays an essential role in regulating cell growth and collagen formation (Ansary *et al*. 2021). The proposed mechanism of serum as antiaging can be seen in Figure 4.

The diagram illustrates a proposed mechanism for the antiaging effects of a serum formulation containing active ingredients from *C. asiatica* (asiaticoside), *C. longa* (curcumin), *A. vera* (aloin), *R. centifolia* (quercetin), and salmon DNA. The pathway suggests that these ingredients may influence key aspects of cellular aging, including telomere shortening, oxidative stress, cellular senescence, and chronic inflammation (López-Otín *et al*. 2013). The active compounds appear to modulate several important molecular pathways. For instance, the upregulation of COL1A1 could enhance collagen production, potentially improving skin firmness and elasticity (Quan *et al*. 2010). The increased expression of TGF-β1 may promote collagen synthesis and tissue repair, which are crucial for maintaining skin structure and function (Pakyari *et al*. 2013). Additionally, the stimulation of FGF-2 could boost fibroblast proliferation and tissue regeneration, contributing to skin rejuvenation (Xie *et al*. 2015).

The downregulation of HYAL-1 suggests a potential mechanism for improving skin hydration by reducing hyaluronic acid degradation (Papakonstantinou *et al*. 2012). This multi-faceted approach targeting various aspects of skin aging aligns with the current understanding of the complex nature of the aging process and the need for comprehensive interventions (Ganceviciene *et al*. 2012). The focus on oxidative stress in the pathway is particularly noteworthy, as it is a well-established contributor to skin aging (Rinnerthaler *et al*. 2015). The antioxidant properties of ingredients like curcumin and quercetin may play a significant role in combating oxidative damage and its downstream effects on cellular senescence and inflammation (Boots *et al*. 2008; Altundağ *et al*. 2021). While this mechanism provides a theoretical framework for the antiaging potential of the serum formulation, further experimental validation would be necessary to confirm these pathways in human fibroblasts and skin tissue.

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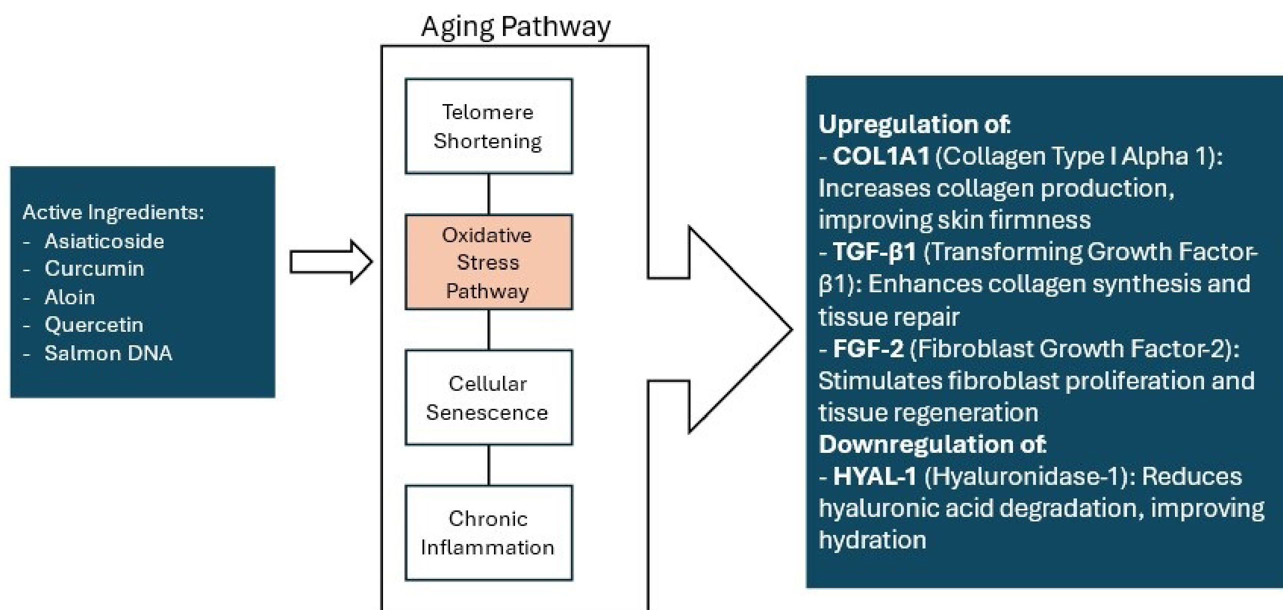

Figure 4. Proposed mechanism formulated serum on aging cell

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