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Wound-Healing Effects of *Centella asiatica* Cream on Fibroblasts and TGF-β1 Expression

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ABSTRACT

Burn injuries represent a major public health concern worldwide, with a disproportionately high burden observed in developing nations. The healing of second-degree burns engages a series of intricate cellular and molecular processes, with Transforming Growth Factor Beta 1 (TGF-β1) playing a crucial role, and fibroblasts stimulate connective tissue formation and assist in re-epithelialization. Pegagan (*Centella asiatica*) has been widely recognized in traditional medicine due to its properties that support wound healing and reduce inflammation. This research aims to evaluate the potential of Pegagan extract cream in modulating TGF-β1 expression and increasing fibroblast density in mice with second-degree burn injuries. Twenty-five male DDY mice were divided into seven groups, including controls, a comparative group treated with silver sulfadiazine, and treatment groups receiving Pegagan cream at three different concentrations (1%, 3%, and 5%). Histological evaluation for assessing fibroblast density was performed using Hematoxylin-Eosin (H&E) staining, while immunohistochemistry (IHC) was used to measure TGF-β1 expression. The results demonstrated that Pegagan cream at concentrations of 1%, 3%, and 5% significantly increased TGF-β1 expression and fibroblast density in burned mice compared to the positive control group. The highest concentration (5%) produced the most pronounced effect, indicating a concentration-dependent response. Cream containing Pegagan promotes wound healing by increasing fibroblast density and TGF-β1 expression.

Keywords: Burn Injury; *Centella asiatica* L.; Fibroblast, TGF-β1

INTRODUCTION

The World Health Organization classifies burn injuries as a critical public health issue due to their high incidence and global burden, with approximately 11 million people suffering from burns and 180,000 deaths occurring annually. Burn injuries are disproportionately more prevalent in countries with low to middle income levels, with Southeast Asia, including Indonesia, being particularly affected. In Indonesia, burn injuries are a common cause of morbidity and mortality, with the 2013 Riskesdas survey revealing a national burn prevalence of 0.7% (Hughes et al., 2021).

Second-degree burns affect both the epidermal and dermal skin layers, making the recovery process particularly complex. This type of wound healing engages multiple molecular and cellular pathways, with Transforming Growth Factor Beta 1 (TGF-β1) serving as a key regulatory factor. TGF-β1 is essential for inducing and regulating fibroblast proliferation and crucial for granulation tissue formation and wound contraction during the healing process (Oryan et al., 2019).

Historically, the treatment of burn wounds has relied heavily on conventional therapies such as topical antibiotics, silver sulfadiazine cream, and various synthetic dressings. While these treatments have been widely used, they come with several limitations. For example, silver sulfadiazine, although effective in preventing bacterial infections, has been associated with delayed wound healing and potential allergic reactions in some patients (Levin et al., 2022). Evidence suggests that silver sulfadiazine is toxic to human keratinocytes and fibroblasts *in vitro*. However, in a porcine wound model, the rate of re-epithelialization improved with silver sulfadiazine treatment. Additionally, silver sulfadiazine appears to inhibit the activity of PMNs in eliminating microorganisms, as well as affecting local lymphocyte function, although its impact on wound healing remains unclear (Mimura et al., 2020).

Currently, silver sulfadiazine is the most widely used topical agent for burn care in the

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United States. While transient leukopenia has been reported in the initial days of use, it is generally not severe and resolves even with ongoing treatment, occurring in only 5% to 15% of patients and showing no correlation with septic episodes. Allergic reactions to the sulfa component in the cream are rare, and very mild skin sensitivities, such as rashes, occur in less than 5% of patients, rarely necessitating the discontinuation of topical therapy (West et al., 2025). Due to the risk of kernicterus associated with sulfonamide therapy, silver sulfadiazine should be avoided in pregnant women, premature infants, and infants under 2 months of age (Mimura et al., 2020).

The past decade has seen a rising trend in the exploration of plant-derived agents for enhancing tissue regeneration, including honey, *Aloe vera*, and propolis, all of which have demonstrated varying degrees of efficacy in promoting tissue regeneration and reducing inflammation. However, each of these natural therapies has its own limitations, such as variability in composition and potency, which can affect their consistency and reliability as therapeutic agents (Atanasov et al., 2021). *Centella asiatica* L. locally known as Pegagan, has been traditionally utilized for treating wounds and managing inflammation. It is rich in several bioactive constituents, particularly triterpenoids such as asiaticoside, which have shown promising effects in promoting tissue repair and modulating inflammatory pathways (Byrne et al., 2018).

Given the significant burn injuries impact on life quality, exploring effective treatments that utilize natural resources is essential. Cream formulations are particularly advantageous as they allow for easy application over large wound areas, maintain moisture, and provide a protective barrier against infection. Additionally, creams ensure sustained release of active compounds, enhancing therapeutic efficacy. Previous studies have demonstrated that cream-based delivery systems improve wound healing outcomes by maintaining an optimal microenvironment (Witkowska et al., 2024).

This study investigates the Pegagan extract cream potential to enhance TGF-β1 expression and increase fibroblast density in mice with second-degree burn wounds. The choice of cream as a delivery vehicle is due to its ease of application on large wound areas and its ability to provide a protective barrier. Creams are usually more easily absorbed by the skin compared to ointments, which can be beneficial for delivering the active ingredients more effectively. Although gels are characterized by high water content and a non-greasy texture, this does not necessarily indicate superior absorption compared with creams. Therefore, creams were selected in this study for their proven efficacy in maintaining an optimal wound healing environment (Radzikowska-Büchner et al., 2023). This study aims to assess the Pegagan cream (CA cream) potential in promoting wound healing in a mouse model of second-degree burns by analysing TGF-β1 expression through immunohistochemistry (IHC) assay and evaluating fibroblast density. Through this investigation, we aim to determine the efficacy of CA cream as a natural treatment in enhancing cellular responses critical to the burn healing process.

MATERIALS AND METHODS

Materials

The tools used were hot plate, shaver, syringe, rotary microtome (Leica RM 2135 BioCut), light microscope (Nikon Eclipse E200), incubator (Memmert ICO50), micropipette (Eppendorf), water bath (Thermo Fisher Precision), and paraffin embedding device (Leica EG1150 H). The materials used were *C. asiatica* L. (CA) extract with Certificate of Analysis (CoA) (batch number 056PW01), 70% Ethanol (Sigma-Aldrich), Maltodextrin (Sigma-Aldrich), CMC-Na (Sigma-Aldrich), Stearic Acid (Sigma-Aldrich), Paraffin Oil (Merck), White Petrolatum (Sigma-Aldrich), Triethanolamine (Sigma-Aldrich), Sorbitan Monostearate (Sigma-Aldrich), Nipagin/Methylparaben (Sigma-Aldrich), 35 male DDY mice, Hematoxylin and Eosin (Thermo Fisher Scientific), 10% Formalin (Sigma-Aldrich), Paraffin for embedding (Leica Biosystems), Entellan (Merck), Antibody TGF-β1 (E-AB-33090, Elabscience), 2-step Plus-Poly-HRP Anti-Mouse/Rabbit IgG Detection System with DAB solution (E-IR-R217, Elabscience), PBS (Sigma-Aldrich), and Polyperoxidase-anti-Mouse/Rabbit IgG (Abcam).

Methods

Preparation of *C. asiatica* extract cream

The extract of *C. asiatica* L. (CA) was prepared from leaves sourced from a local supplier and subjected to drying at ambient temperature (25-30°C). The extraction process was executed by PT Borobudur in compliance with Good Manufacturing Practices, accompanied by a Certificate of Analysis (CoA) (batch number 056PW01). Prior to extraction, the *C. asiatica* leaves were processed using a specialized drying machine, followed by extraction with 70% ethanol as the solvent and the subsequent addition of maltodextrin (Widowati et al., 2024). The resultant extract was employed in the formulation of creams at concentrations of 1, 3, and 5%, each formulation

weighing 50 g, as detailed in Table 1. The specific ingredients incorporated into the CA cream formulations listed in Table I (Utoyo et al., 2025).

Induction of Second-Degree Burn Wounds in Mice

This study was approved by the Ethical Committee of Maranatha Christian University, Bandung, Indonesia (023/KEP/III/2024). A true experimental post-test only control group design was used to evaluate the effects of CA cream on second-degree burn wounds in male DDY mice (*M. musculus*) aged 10-11 weeks and weighing 20-30 g (n=35). Male DDY mice were selected based on their common use in preclinical burn wound studies and consistent physiological responses. Mice were acclimatized for 7 days at 22 (±3°C) and 50-60% humidity, receiving a standard diet with 18% crude protein. Second-degree burns were induced by applying an iron bar plate for 10 minutes to the shaved back of the mice for 5 seconds, with anesthesia administered via intraperitoneal injection of xylazine (10 mg/kg BW) and ketamine (90 mg/kg BW). CA cream was topically applied once daily at concentrations of 1%, 3%, and 5% for 14 days. The treatments group namely, I : Negative Control (NC: no burn induction and no treatment), II: Positive Control (PC: burn induction and no treatment), III: Vehicle Control (VC : PC, treated with base cream), IV: Comparative Control (CC: PC, treated with silver sulfadiazine cream), V: PC, treated with CA cream 1%, VI: PC, treated with CA cream 3%, VII: PC, treated with CA cream 5%. Treatments were applied once daily for 14 days (Witkowska et al., 2024; Utoyo et al., 2025). Upon completion of the treatment period, the mice were humanely euthanized by cervical dislocation, and skin tissue samples from the burn sites were subsequently collected for histological analysis of TGF-β1 expression and fibroblast density, preserved in 10% buffered neutral formalin (Widowati et al., 2022; Utoyo et al., 2025).

Histological Preparation

Histopathological analysis was conducted using Hematoxylin and Eosin (H&E) staining. Skin samples were fixed in 10% formalin for 2-3 days, followed by dehydration in increasing alcohol concentrations for 2 hours and clearing with graded xylene under continuous agitation. The samples were then embedded in liquid paraffin until complete infiltration, reaching 100% concentration at 60°C, and stored at room temperature until paraffin blocks formed. The prepared slides, with paraffin-embedded tissue samples sectioned into 5 μm slices using a rotary microtome (Leica RM 2135 BioCut Rotary Microtome), and subsequently placed onto glass slides then stained using the H&E protocols and the slides were sealed with Entellan and examined under a light microscope (Widowati et al., 2022, 2024).

Measurement of TGF-β1 Expression Using Immunohistochemistry

The immunohistochemical procedure utilized primary antibody TGF-β1 (E-AB-33090) and a 2-step Plus-Poly-HRP Anti-Mouse/Rabbit IgG Detection System with DAB solution (E-IR-R217). Slides were deparaffinized in an incubator at 60°C for 15 minutes, followed by treatment with xylene and graded alcohol for rehydration. After washing with distilled water and PBS, endogenous peroxidase activity was blocked using 3% H_2O_2. The sections were incubated with a Normal Goat Blocking Buffer at 37°C for 30 minutes, followed by an overnight incubation with the primary antibody at room temperature. After PBS washes, a secondary antibody (Polyperoxidase-anti-Mouse/Rabbit IgG) was applied and incubated for 20 minutes. DAB substrate solution was added, incubated in the dark for 15 seconds, and washed with water. Finally, the sections were counterstained with hematoxylin, rinsed, and prepared for analysis (Widowati et al., 2022, 2024).

Data Analysis

Data analysis was performed using SPSS software. Levene's test was used to assess homogeneity, while the Shapiro-Wilk test evaluated data normality. For normally distributed data, One-Way ANOVA was conducted to compare group differences, followed by post hoc tests if significant results were observed ($p < 0.05$). When data were not normally distributed, transformation techniques were applied. If normality was not achieved after transformation, the Kruskal-Wallis test was utilized for further analysis.

RESULTS

Body Weight of Burn-Wound Mice

To evaluate the potential effects of CA cream on body weight recovery in mice with induced burns, a 14-day observation was conducted across multiple treatment groups. Body weight measurements on days 0, 3, 7, 10, and 14 showed no decrease in weight across all groups during the study period. Notably, the administration of CA cream did not appear to impact the body weight of the mice, indicating that

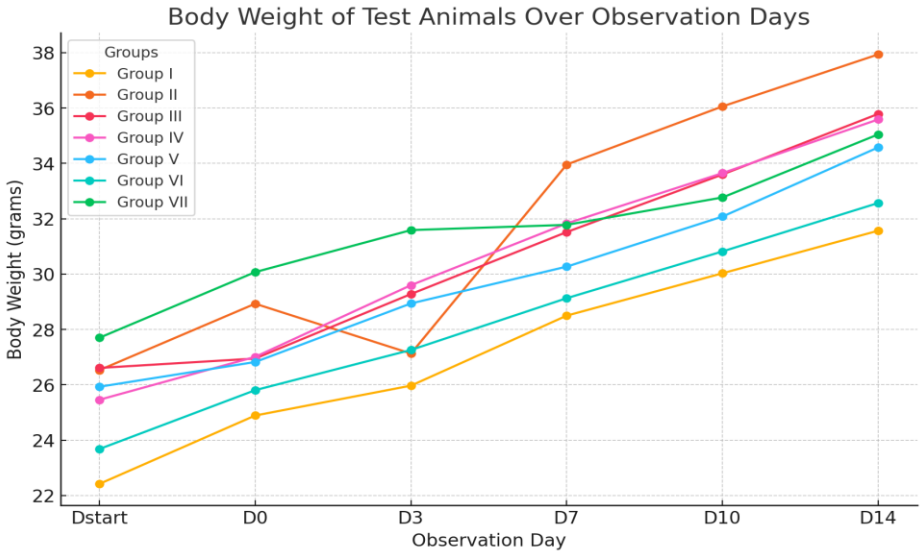

Figure 1. Line diagram of the effect of CA cream on body weight during 14 days in burned mice

(I) unburned, untreated control; (II) burned, untreated; (III) burned, vehicle-treated (cream base only); (IV) burned, treated with silver sulfadiazine; and (V–VII) burned, treated with CA cream at concentrations of 1%, 3%, and 5%, respectively. All groups experienced weight gain over time. The V and VI groups showed moderate increases, with VII group performing the best among the test groups.

Table I. Cream formulation containing various concentrations (1%, 3%, and 5%) of ethanolic extract of *C. asiatica*.

Ingredients	1% CA Cream Formulation (g)	3% CA Cream Formulation (g)	5% CA Cream Formulation (g)
C. asiatica leaf extract	0.5	1.5	2.5
CMC-NA	0.5	0.5	0.5
Stearic acid	5	5	5
Paraffin oil	4	4	4
White petrolatum	3	3	3
Triethanolamine	0.5	0.5	0.5
Sorbitan monostearate	1	1	1
Nipagin	As required	As required	As required
Distilled water	Ad 50	Ad 50	Ad 50

CA cream treatment did not negatively affect general health or cause weight loss in burned mice. The resulting data, displayed in Figure 1.

Fibroblast Density of Burn-Wound Mice

The fibroblast characteristics in Figure 2 are identified by their elongated, spindle-shaped structure in the dermis and between the existing immune cells. The fibroblast count across the groups demonstrates a dose-dependent response to CA cream, with the control group showing minimal healing activity due to the absence of treatment. Group II (PC) and group III (VC) exhibited similar fibroblast density. These data showed that burn induction significantly ($p<0.05$) increased the fibroblast density compared to group I (NC). Group IV, silver sulfadiazine cream showed an increase in fibroblast density higher than PC significantly ($p < 0.05$). Treatment using 1%, 3%, and 5% CA showed an increase in fibroblast density significantly compared to PC ($p < 0.05$). The most effective CA treatment to enhance the fibroblast density in burned mice was 5% CA, this data were comparable with silver sulfadiazine cream.

TGF-β1 Expression of Burn-Wound Mice

The expression of TGF-β1 was quantified by counting the positively stained cells in five high-power fields (HPF) per sample. In the NC group, TGF-β1 expression appeared as dispersed brown staining within the cytoplasm of epidermal cells (Figure 3.I). In contrast, the PC group (burn-induced mice) exhibited intense and widespread

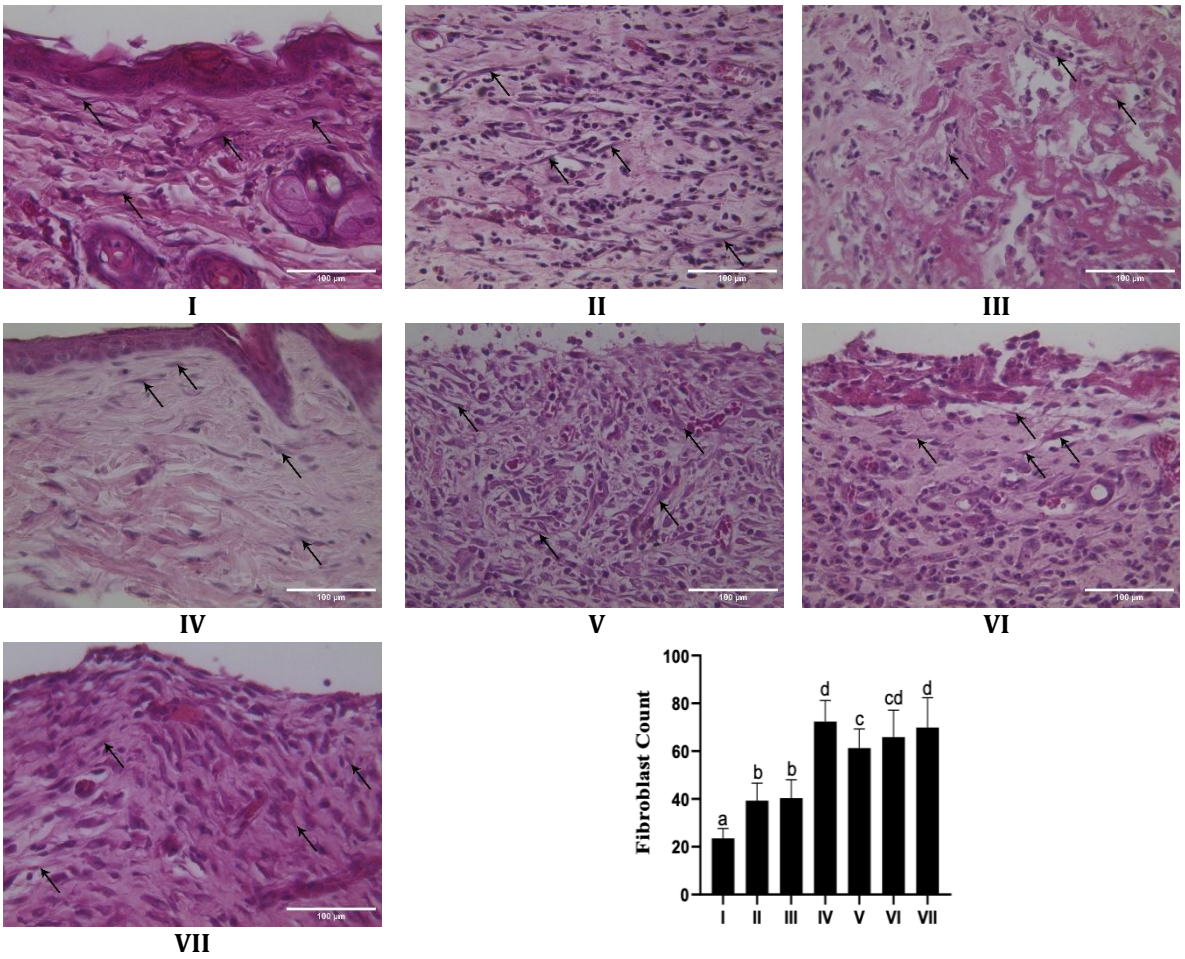

Figure 2. Histological images and bar diagram illustrating the effect of various CA cream concentrations on fibroblast density in burned mice

*Fibroblast cells were observed under 400x magnification with a 100 µm scale bar. The fibroblast density was measured using ImageJ software by assessing color density in the specimens. Counts were taken from five fields of view for each treatment. Black arrows indicate the presence of fibroblast cells.
*The groups were defined as follows: (I) unburned, untreated control as negative control (NC); (II) burned, untreated as positive control (PC); (III) burned, vehicle-treated (cream base only); (IV) burned, treated with silver sulfadiazine; and (V–VII) burned, treated with CA cream at concentrations of 1%, 3%, and 5%, respectively.
*Different letters represent significant differences between treatments based on Mann Whitney post hoc ($p < 0.05$)

cytoplasmic staining, indicating a notably higher level of TGF-β1 expression compared to the NC group. Burn induction significantly increased TGF-β1 ($p < 0.05$) compared to the NC group. Group IV, silver sulfadiazine cream showed an increase TGF-β1 higher than the PC significantly ($p < 0.05$). Treatment using 1%, 3%, and 5% CA showed an increase TGF-β1 and demonstrated a significant improvement over the PC group ($p < 0.05$), indicating treatment efficacy. The most effective CA treatment to enhancing TGF-β1 in burned mice was 5% CA, this data was comparable with silver sulfadiazine cream.

DISCUSSION

In the study, body weight was monitored as an indicator of general health over 14 days post-burn induction and treatment with different concentrations of CA cream. These results align with prior findings that CA and its active compounds do not negatively affect weight or health status in experimental burn models (Sun et al., 2020). TGF-β1 is pivotal in modulating inflammatory responses, promoting collagen synthesis, and facilitating fibroblast proliferation and differentiation. The findings of this study provide valuable insights into the impact of CA

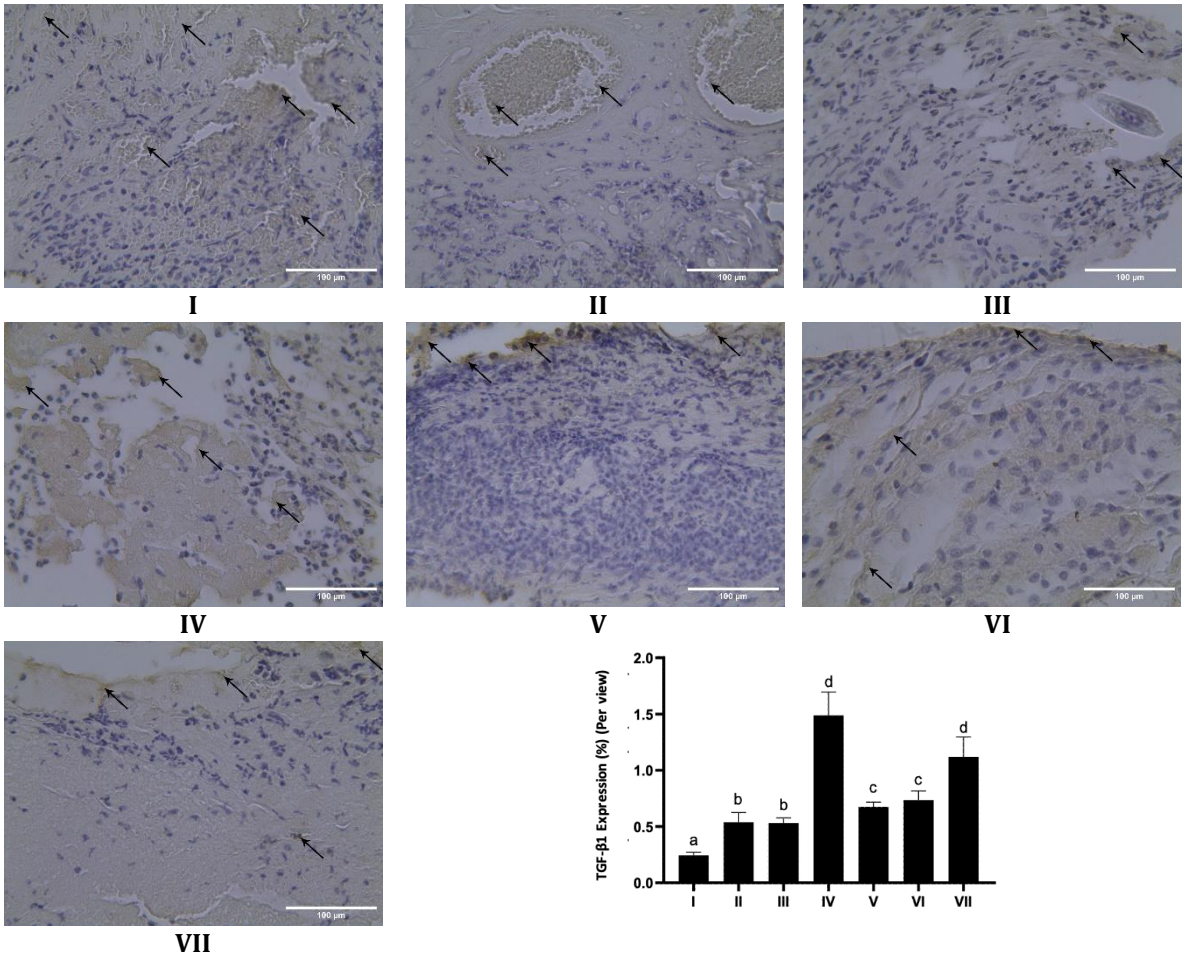

Figure 3. Histological images and bar diagram illustrating the effect of various concentration CA cream toward TGF-β1 expression on burned mice

*Fibroblast cells were observed under 400x magnification with a 100 µm scale bar. The TGF-β1 was measured using ImageJ software by assessing brown, strong cytoplasmic staining. Counts were taken from five fields of view for each treatment. Black arrows indicate the presence of TGF-β1.
*The groups were defined as follows: (I) unburned, untreated control as negative control (NC); (II) burned, untreated as positive control (PC); (III) burned, vehicle-treated (cream base only); (IV) burned, treated with silver sulfadiazine; and (V–VII) burned, treated with CA cream at concentrations of 1%, 3%, and 5%, respectively.
* Different letters represent significant differences between treatments based on Mann Whitney post hoc test ($p < 0.05$)

cream on fibroblast density and TGF-β1 expression during wound healing in second-degree burn wounds in mice. Our results indicate that burn induction significantly enhances fibroblast proliferation, aligning with the natural wound healing process (Wang et al., 2023).

Fibroblasts contribute during the wound healing proliferative phase by producing collagen and the extracellular matrix (ECM), forming granulation tissue, and promoting wound contraction. This phase typically occurs between days 4 to 21 (Cialdai et al., 2022). The complete skin wound healing process under normal conditions generally finishes within 14–21 days (Rodrigues et al., 2019). Both silver sulfadiazine and CA cream treatments further increased fibroblast density, with the 5% CA cream yielding the most significant results. The concentrations of 1%, 3%, and 5% CA cream used in this study were selected based on previous dose-response studies utilizing *Centella asiatica* extracts in topical applications. These studies have shown that such concentration ranges are commonly used to evaluate wound healing efficacy and are considered safe for dermal use. The 5% concentration in our findings demonstrated the

highest fibroblast density and TGF-β1 expression, indicating a dose-dependent effect up to this level (Tanga et al., 2022).

The CA cream also notably elevated TGF-β1 expression. The upregulation of TGF-β1 aligns with CA's known role in wound healing, which involves stimulating growth factors and fibroblast activity essential for tissue regeneration (Radzikowska-Büchner et al., 2023). The active compounds in *C. asiatica*, such as asiaticoside and madecassoside, are key to this effect. However, we acknowledge that the specific phytochemical content of our extract was not analyzed in this study. This limitation was acknowledged, and interpretations were made cautiously based on previously published evidence. These compounds are known to upregulate TGF-β1, a cytokine pivotal in the wound healing cascade.

TGF-β1 has three primary roles in wound healing. TGF-β1 modulates inflammatory responses, which is critical in wound healing as it limits excessive inflammation and promotes a shift from the inflammatory to the proliferative phase. By managing inflammation, TGF-β1 prepares the wound environment for subsequent tissue repair. TGF-β1 directly influences fibroblast activity, encouraging their proliferation and migration to the wound site. This influx of fibroblasts supports the formation of new tissue and matrix components, forming the structural foundation necessary for wound closure. TGF-β1 is essential in promoting collagen synthesis by fibroblasts, a critical component of the ECM that provides tensile strength to the healing tissue. Increased collagen production accelerates the wound healing process, leading to better structural integrity and faster tissue recovery (Wang et al., 2023).

The increase in TGF-β1 and fibroblast density in CA-treated groups supports prior research indicating that CA can promote wound healing by enhancing collagen synthesis, reducing inflammation, and stimulating angiogenesis. These actions facilitate quicker tissue repair and wound closure. Notably, CA's active compounds—asiaticoside and madecassoside—have been found to stimulate fibroblast migration and division, accelerating the wound healing process (Sun et al., 2020).

Further research is warranted to explore additional mechanisms by which CA promotes wound healing, particularly focusing on optimizing CA-based formulations and concentrations (Diniz et al., 2023). Comparing the efficacy of CA-based treatments to conventional therapies will also be essential in determining their potential clinical application. A deeper understanding of these aspects will aid in the development of effective CA-based interventions for burn wound care, ultimately improving patient recovery and clinical outcomes (Skowrońska & Bazylko, 2023).

Moderate concentrations of CA are known to significantly stimulate fibroblast proliferation and collagen synthesis, contributing to tissue repair and structural integrity in the wound site (Lee et al., 2020). Studies have shown that *C. asiatica* promotes the proliferation and migration of fibroblasts, which are essential in the wound healing process. Fibroblasts play a vital role during the proliferative phase of wound healing by synthesizing collagen and ECM, providing structural support to the wound bed, and aiding in wound contraction. Diniz et al., (2023) demonstrated that asiaticoside and madecassoside enhance fibroblast migration, an important step for closing wounds, thus promoting faster tissue regeneration. In addition to directly supporting fibroblast activity, *C. asiatica* possesses strong antioxidant and anti-inflammatory properties that reduce oxidative stress in the wound environment. Excessive free radicals can damage fibroblasts and other cellular components in the wound. The antioxidant effects of *C. asiatica* help reduce reactive oxygen species (ROS), creating a favourable environment for fibroblast activity and matrix synthesis. Lee et al., (2020) highlighted that *C. asiatica* reduces inflammation and supports wound healing by providing antioxidant protection, indirectly enhancing fibroblast function.

In summary, topical application of *C. asiatica* cream at concentrations of 1%, 3%, and 5% significantly enhanced fibroblast density and TGF-β1 expression in experimentally induced second-degree burn wounds in mice, with the 5% formulation showing the most prominent effect. These findings confirm the potential of CA cream in accelerating the wound healing process through stimulation of fibroblast proliferation and TGF-β1–mediated tissue regeneration.

CONCLUSION

Mice were treated with varying *Centella asiatica* cream concentrations (1%, 3%, and 5%) for 14 days following second-degree burn induction. The findings demonstrated that *C. asiatica* cream effectively increased fibroblast density and TGF-β1 expression in burned mice in a dose-dependent manner. The 5% CA cream showed the most significant effect, comparable to silver sulfadiazine. These results confirm the *C. asiatica* cream potential in promoting tissue regeneration during burn wound healing, supporting its use as a natural topical agent.

Further studies are recommended to explore its clinical applications.

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