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Original Research Article

Wound Healing Potential of *Apium graveolens L.* Extract through IL-1 and PDGF Expression

Harvina Dwi Apriliana[1*], Eko Setiawan[1,2], Chodidjah[3]

[1]*Department of Biomedical Science, Universitas Islam Sultan Agung, Indonesia*
[2]*Department of Surgery, Universitas Islam Sultan Agung, Indonesia*
[3]*Departement of Anatomi, Universitas Islam Sultan Agung, Indonesia*

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Abstract

Background: Incised wounds from sharp objects disrupt skin function and risk infection. Healing involves cytokines like IL-1 and growth factors like PDGF. Celery leaf extract (*Apium graveolens L.*), rich in flavonoids, saponins, and tannins, shows anti-inflammatory and pro-angiogenic effects that may lower IL-1 and exhibited a trend toward increased PDGF.

Objective: To evaluate the effect of celery leaf extract cream on IL-1 levels and PDGF expression in male Wistar rats with incised wounds.

Methods: This in vivo experimental study employed a post-test only control group design. Thirty male Wistar rats were divided into five groups: healthy control, negative control (cream base), positive control (10% povidone-iodine), 2% celery extract cream, and 4% celery extract cream. Incised wounds were made on the rats' backs, and the cream was applied once daily for 7 days. IL-1 levels were analyzed using ELISA, while PDGF expression was measured using qRT-PCR. Data were analyzed with the Kruskal-Wallis and Mann-Whitney tests ($p<0.05$).

Results: The lowest mean IL-1 level in the treatment groups was found in the 4% celery extract cream group (5.80 ± 1.19 ng/mL), while the highest was in the povidone-iodine group (6.77 ± 0.51 ng/mL). The Kruskal-Wallis test showed a significant difference among all groups ($p=0.009$). The highest mean PDGF expression was observed in the 2% celery extract cream group (3.10 ± 3.18), followed by povidone-iodine (2.53 ± 4.37), whereas the 4% celery extract cream group had a value of 0.57 ± 0.66. However, PDGF expression did not differ significantly among groups ($p=0.279$).

Conclusion: Administration of celery leaf extract cream reduced IL-1 levels in the treatment groups; however, the increase in PDGF expression did not show significant differences among the Wistar rat incisional wound model groups.

Keywords: *Apium graveolens L.; IL-1 levels; incised wound; PDGF expression.*
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INTRODUCTION

The skin plays a crucial role as a protective barrier against external factors, functioning as a sensory organ and regulating body temperature. [1] When an injury such as an incised wound penetrates the dermis, the integrity of the skin barrier is disrupted, increasing the risk of infection and delaying recovery. Wound healing is a complex biological process involving inflammation, proliferation, and tissue remodeling, regulated by cytokines and growth factors. Among them, interleukin-1 (IL-1) acts as a pro-inflammatory mediator that initiates the inflammatory phase, whereas platelet-derived growth factor (PDGF) supports fibroblast proliferation, angiogenesis, and the formation of granulation tissue.[2–4] An imbalance

*Corresponding author:
E-mail: Harvina.dwi.a@gmail.com
(Harvina Dwi Apriliana)

between these mediators may hinder wound repair and lead to complications.[5]

In recent years, there has been growing interest in herbal-based therapies to enhance wound healing. *Apium graveolens L.* (celery) contains bioactive compounds such as flavonoids, saponins, apigenin, and tannins with demonstrated anti-inflammatory, antioxidant, and antimicrobial activities.[6–8] These celery-derived flavonoids have been shown to significantly suppress IL-1β secretion through inhibition of NF-κB translocation and NLRP3 inflammasome activation in inflammatory models.[7] Celery tannins exhibit strong hemostatic activity by precipitating proteins and stabilizing early clot formation, while celery saponins demonstrate antibacterial effects against common wound pathogens such as *Staphylococcus aureus and Pseudomonas aeruginosa*.[8,9] Previous studies confirmed that celery extract exhibits pharmacological activities relevant to wound healing. Ethanol extract of celery was reported to reduce IL-1β levels in ischemia-reperfusion injury models in rats, highlighting its anti-inflammatory potential.[10] A cream formulation combining celery and teak leaf extracts demonstrated antibacterial activity against *S. aureus*.[11,12] Moreover, creams containing celery extract at concentrations of 2-4% accelerated wound closure in animal models, improving inflammatory and proliferative phases of healing.[5]

Despite substantial advances in wound care, acute and chronic wounds continue to impose a heavy clinical and economic burden worldwide, with prolonged inflammation and impaired proliferative responses remaining the primary causes of delayed healing, excessive scarring, and non-healing ulcers.[13,14] Although *A. graveolens* L. leaf extract has shown promising anti-inflammatory, antioxidant, and antimicrobial effects in prior studies, its precise influence on key molecular regulators of wound healing, particularly the suppression of excessive interleukin-1 (IL-1) and the upregulation of platelet-derived growth factor (PDGF), has never been investigated in a controlled incisional wound model. [10,15 5,11,16]

The aim of this study is simultaneously quantify tissue IL-1 levels and PDGF after topical application of standardized 2% and 4% celery leaf extract creams in Wistar rats. By targeting these two critical biomarkers, this research aims to provide novel insights into the dual role of celery extract in reducing excessive inflammation and enhancing tissue regeneration, thereby supporting its development as a natural topical agent for wound management.

MATERIALS AND METHODS

Study Design

This study was conducted using an experimental design with a post-test only control group approach, enabling comparisons between treatment and control groups after intervention. The research aimed to evaluate the effect of topical celery leaf extract cream on IL-1 levels and PDGF expression in an incised wound model in Wistar rats.[17] Five groups were established: a healthy control group without intervention, a negative control group with incised wounds treated with cream base, a positive control group treated with povidone-iodine cream, and two treatment groups receiving celery leaf extract cream at concentrations of 2% and 4%, respectively. Each intervention was applied once daily for seven days.

Study Population

The study population consisted of male Wistar rats aged 2-3 months, weighing 180-220 g, and maintained under standardized laboratory conditions at the Integrated Biomedical Laboratory (IBL), Faculty of Medicine, Universitas Islam Sultan Agung. A total of 30 rats were used, divided into five groups of six animals each (N=6 per group), selected using simple random sampling to ensure unbiased allocation with Federer's formula, the extra animal per group served as a reserve in case of illness or mortality. Inclusion criteria required active, healthy rats without morphological abnormalities, while sick or deceased animals during adaptation or treatment phases were replaced or excluded.[18]

Preparation and Administration of Celery Leaf Extract Cream

The celery leaf extract was prepared by carefully selecting 1 kg of fresh celery leaves, which were cleaned, dried in an oven at 40°C, and ground into fine powder. The powder was sieved using a 20-mesh filter to obtain uniform particle size. A total of 450 g of the powder was then macerated in 1,500 mL of 70% ethanol for three consecutive days with periodic stirring to maximize extraction. The mixture was filtered, and the residue was re-macerated twice using the same solvent to ensure complete extraction of the active compounds. All filtrates were combined and concentrated using a rotary evaporator at 40°C until a thick, viscous extract was obtained. The extract was subsequently incorporated into a cream formulation by preparing an oil phase (stearic acid, cetyl alcohol, and coconut oil) and an aqueous phase (demineralized water and glycerin), both of which were heated to 70-75°C.[19] The two phases were mixed and homogenized, after which the celery leaf extract, preservatives, and fragrance were added. The final cream was allowed to cool while being stirred continuously until a stable and homogeneous preparation was achieved, then stored in sterile, airtight containers for further use.[20]

The topical administration of celery leaf extract cream was carried out at concentrations of 2% and 4%, based on previous studies that had demonstrated wound-healing activity at these dosages.[21] Each rat received 0.2 g of cream, which was applied once daily to the wound site for seven consecutive days. This protocol ensured consistent dosage delivery across all treatment groups and allowed evaluation of the extract's wound-healing potential in a controlled and reproducible manner. The celery extract cream (2% and 4%) showed good physical stability with no visible phase separation or unpleasant odor during the 7-day treatment period. Organoleptic properties and pH remained acceptable throughout the experiment.

Tissue Sampling for PCR Analysis

On day 8, or 24 h after the final treatment, the rats were sacrificed using the cervical dislocation method to facilitate the collection of tissue samples. The incised wound skin tissue was excised and stored in tubes containing RNA later, then placed in a freezer at -80°C until further analysis using qRT-PCR was performed.[18]

Each skin tissue sample weighing approximately 10-30 mg was cut. The tissues were homogenized with a tissue grinder using liquid nitrogen and transferred into clean RNase-free tubes. For every 10 mg of tissue, 0.3 mL of Binding Buffer 4 (pre-mixed with β-mercaptoethanol) and 15 µL of proteinase K were added. The samples were homogenized by vortexing and incubated at 56°C for 10-20 min. Subsequently, the samples were centrifuged at 12,000 × g for 5 min at room temperature, and the supernatant was transferred into a new RNase-free tube. Wound tissue was collected on day 8 (24 h after the final treatment on day 7) because this time point corresponds to the transition from inflammatory to proliferative/remodeling phases in rat incisional wounds and allowing detection of both persistent inflammation (IL-1β) and proliferative stimulation (PDGF).

RNA Extraction Procedure

Seventy percent ethanol was added to the supernatant at a 1:1 ratio. The mixture was vortexed, briefly centrifuged, and loaded into a spin column. Centrifugation was carried out at 12,000 × g for 30 sec at room temperature, and the flow-through was discarded. A total of 500 µL of Clean Buffer 4 was added into the spin column, followed by centrifugation at 12,000 × g for 30 sec. This step was repeated twice. Then, 500 µL of Wash Buffer 4 was added and centrifuged at the same speed, repeated twice. To ensure no ethanol residues remained, the empty spin column was centrifuged at ≥12,000 × g for 2 min and air-dried for 1-2 min. The spin column was then placed into a new 1.5 mL RNase-free tube, and 30-100 µL of RNase-free water was added, incubated for 1 min at room temperature, and centrifuged at 12,000 × g for 2 min to elute RNA. The eluted RNA was stored at -80°C for long-term storage or -20°C for mid-term storage. Molecular analyses (ELISA and qRT-PCR) were performed by a different investigator who was blinded to group allocation using coded samples.

qRT-PCR Analysis of PDGF Expression

The expression of PDGF was measured using qRT-PCR with iScript™ cDNA Synthesis Kit (Bio-Rad). Total RNA was first isolated from tissue samples and its concentration and purity were checked. The RNA was then converted into cDNA using a reverse transcription kit.[22]

The cDNA was amplified using specific primers for PDGF and the housekeeping gene GAPDH as an internal control. The reaction mixture contained the cDNA template, primers, master mix, and nuclease-free water. The qRT-PCR program consisted of an initial denaturation at 95°C, followed by 40 cycles of denaturation, annealing, and extension. Fluorescence signals were detected in real time, and relative gene expression was calculated using the ΔΔCt method.[22]

ELISA Analysis of IL-1 Levels

Skin tissue samples were first prepared before ELISA analysis.[23] IL-1 concentrations were determined using a commercial Rat IL-1β ELISA kit (Elabscience, Cat. No. E-EL-R0012). The tissue was cut into 1-2 mm pieces using sterile scissors and placed in microcentrifuge tubes containing 500-1000 µL of cold lysis buffer mixed with protease inhibitors. The samples were homogenized using either a mortar and pestle with liquid nitrogen or an electric homogenizer until smooth. The homogenate was incubated at 4°C for 30-60 min with vortex mixing every 10 min, followed by centrifugation at 12,000-14,000 rpm for 15-20 minutes at 4°C. The supernatant containing soluble proteins, including IL-1, was carefully collected and stored at -80°C until further analysis.[23]

IL-1 levels were then measured using the ELISA method according to the manufacturer's instructions. Serial dilutions of the standard were prepared in microplates, and antibodies were added and incubated at 37°C. After washing, a blocking buffer was applied, followed by incubation with 100 µL of each sample for 120 minutes at room temperature. Biotinylated antibodies, ABC solution, and HRP-conjugate were added sequentially, each with incubation and washing steps. Finally, 100 µL of TMB substrate was added until a blue color developed, and the reaction was stopped with 100 µL stop solution, changing the color to yellow. The optical density was read at 450 nm using a microplate reader to determine IL-1 concentration.[23]

Data Analyze

Data were analyzed using SPSS (version 26, USA). Descriptive statistics were first applied to summarize mean and standard deviation values. Normality of distribution was assessed with the Shapiro-Wilk test and homogeneity with Levene's test. Since IL-1 and PDGF data did not meet assumptions of normality and homogeneity, the Kruskal-Wallis test was employed to compare differences across groups. Significant results for IL-1 ($p < 0.05$) were followed by pairwise comparison using the Mann-Whitney U test, whereas PDGF expression results that were not statistically significant ($p > 0.05$) were reported descriptively.[24]

Ethical Clearance

The experiment involving laboratory animals was conducted after obtaining ethical clearance from the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University Semarang, No. 231/V/2025/Komisi Bioetik.

RESULTS

Phytochemical analysis of celery leaf extract (*Apium graveolens L.*)

Phytochemical analysis showed that celery leaf extract (*Apium graveolens L.*) contained bioactive compounds in the form of flavonoids and total phenols.

Based on the quercetin standard curve, the total flavonoid content at a concentration of 500 ppm was 34.0 ppm, equivalent to 0.0068 mg QE/g extract, with an average absorbance value of 0.544. Measurement of phenolic content using the gallic acid standard curve showed a higher total phenol content, namely 51.5 ppm with an average absorbance of 0.272. These findings indicate that phenolic compounds dominate the extract composition compared to flavonoids. Both flavonoids and phenols are important antioxidant compounds that play a role in neutralizing free radicals, suppressing oxidative stress, and protecting tissues from cellular damage.[25,26]

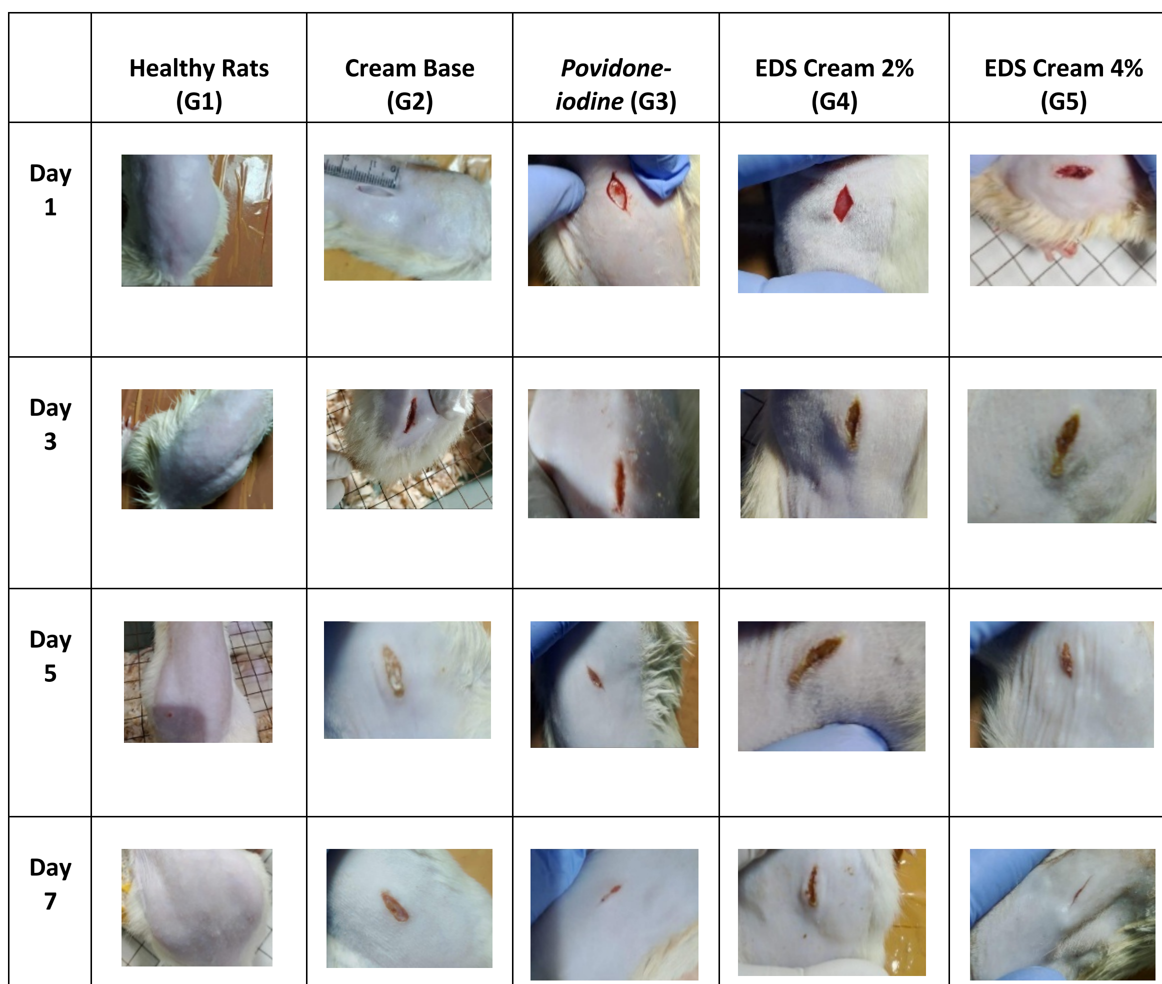
The content of flavonoids and phenols in celery leaves supports its pharmacological potential as am natural antioxidant and anti-inflammatory agent, making it highly promising for development in therapeutic formulations. This includes the development of creams or gels to repair skin damage and promote tissue regeneration.

Macroscopic findings in Wistar rats with incised wounds

Wound healing progression was monitored daily by standardized digital photography. Macroscopic evaluation was carried out on days 1, 3, 5, and 7 post-incision (Figure 1). This serial macroscopic observation consistently showed faster crust formation, reduced exudate, and earlier wound contraction in the 4% celery extract cream group compared to other groups. On day 1, wounds in all groups displayed clear wound edges and redness. Groups treated with povidone-iodine and 4% celery cream began to form thin crusts earlier, while the cream base group appeared wetter with slight exudate. On day 3, crust formation was more evident in the povidone-iodine and 4% celery cream groups, while crusts in the 2% celery cream group began to appear, and the cream base group still showed exudate with thin crusts.

On day 5, the 4% celery cream group showed faster healing with smaller wound diameters, dried crusts, and partial detachment, indicating the proliferative phase and good granulation tissue formation. The 2% celery cream group showed similar healing patterns but slower, while the cream base group still had thick, moist crusts, indicating delayed healing. On day 7, the 4% celery cream group was almost completely closed with thin crusts remaining, indicating early remodeling. The 2% cream group was closing with new tissue that appeared more mature. The povidone-iodine group experienced moderate healing, while the cream base group still displayed persistent crusts. Overall, the 4% celery cream gave the most optimal wound healing effect, marked by faster crust formation, reduced exudate, and more significant wound contraction.

Figure 1. Macroscopic images of incised wound models in Wistar rats



IL-1 analysis with celery leaf extract cream

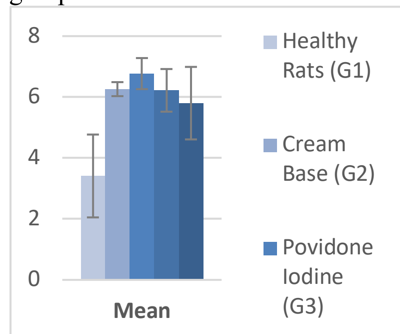
The results of mean IL-1 levels using ELISA are as Table 1. The Shapiro-Wilk normality test showed that most groups were normally distributed ($p > 0.05$), except the 2% cream group ($p = 0.009$) (Table 1). Levene's test showed $p = 0.009$, indicating data were not homogeneous. Therefore, the Kruskal-Wallis test was applied and showed significant differences ($p = 0.009$). Thus, there were significant differences in IL-1 levels among groups (Figure 2).

The cream base (negative control) group showed a mean IL-1 level of 7.38 ± 1.62 ng/mL. Compared to this vehicle control, the active treatment groups exhibited the following values:

- 10% povidone-iodine: 6.77 ± 0.51 ng/mL
- 2% celery extract cream: 6.29 ± 1.45 ng/mL
- 4% extract cream: 5.80 ± 1.19 ng/mL (lowest among treatment groups)

Mann-Whitney analysis (Table 2) revealed significant differences ($p < 0.05$) between healthy rats (G1) and all treatment groups (G2, G3, G4, G5). This indicates that topical application, whether inert cream base or containing active agents, generally increased IL-1 levels compared to normal skin, suggesting local inflammatory responses due to irritation or immune activation.

Figure 2. Graph of mean IL-1 levels among groups.



Although post-hoc Mann-Whitney tests did not reveal statistically significant differences between the cream base and any active treatment (all $p > 0.05$; Table 2), both celery extract concentrations (especially 4%) consistently showed numerically lower IL-1 levels than the vehicle alone, suggesting a modest anti-inflammatory trend attributable to the extract. Pairwise comparisons did not show significant differences among treatment groups ($p > 0.05$). Celery cream reduced IL-1 compared to povidone-iodine, but anti-inflammatory effectiveness was not statistically superior.

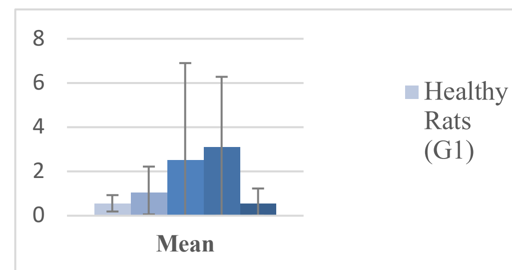
PDGF expression analysis with celery leaf extract cream

The results of mean PDGF expression using qRT-PCR are as Table 1. Descriptively, PDGF expression was highest in the 2% cream group, followed by povidone-iodine, then cream base (Figure 3). The 4% cream group had lower PDGF expression, similar to healthy rats. Shapiro-Wilk showed normal distribution, but Levene's test ($p = 0.033$) indicated non-homogeneous variance. Kruskal-Wallis test showed $p = 0.279$, meaning no statistically significant difference.

DISCUSSION

This study aimed to interpret the results of the analysis of Interleukin-1 (IL-1) levels and Platelet-Derived Growth Factor (PDGF) expression in the skin tissue of Wistar rats with incised wound models after administration of celery leaf extract cream (*Apium graveolens L.*) at two different concentrations, and to compare them with the negative control group (cream base), positive control (povidone-iodine), and healthy rats without treatment. The analysis was conducted to evaluate the effectiveness of celery leaf extract in modulating the inflammatory response and stimulating regenerative processes of skin tissue as part of the wound healing mechanism.

Figure 3. Graph of mean PDGF expression (ΔΔCq)



IL-1 is one of the main pro-inflammatory cytokines released during the early phase of wound healing, whereas PDGF plays an important role in the proliferative phase by activating fibroblasts, angiogenesis, and extracellular matrix synthesis.[27–29] These two parameters were chosen as indicators to assess the pharmacological effects of celery leaf extract on wound healing dynamics. IL-1 levels increased significantly in all treatment groups compared to the healthy rat group (G1). This significant increase is primarily a physiological response to the tissue injury (incision) itself, which initiates the inflammatory cascade.[24] IL-1 is a major pro-inflammatory cytokine released by macrophages and keratinocytes in response to tissue injury and is responsible for initiating and amplifying inflammation through neutrophil activation and increased expression of adhesion molecules.[30,31] The cream base group (G2) also showed high IL-1 levels, as a mild irritant reaction to emollient and surfactant components in the cream that disrupt the homeostasis of the stratum corneum, such as triethanolamine or stearic acid. These compounds have the potential to trigger a non-specific immune response.[32]

The povidone-iodine group (G3) recorded higher IL-1 levels, consistent with reports that although povidone-iodine is effective as an antiseptic, it can be irritating and prolong the inflammatory phase when used topically at high concentrations or for prolonged periods.[11] Tissue reactivity to povidone-iodine leads to the release of inflammatory mediators such as IL-1β, exacerbating local inflammation.[11]

Table 1. Mean IL-1 levels (ng/mL), PDGF expression (ΔΔCq), normality, homogeneity, and Kruskal-Wallis test results

Group	IL-1 (ng/mL)	Shapiro-Wilk p (IL-1)	PDGF expression (ng/mL)	Shapiro-Wilk p (PDGF)
Healthy control	3.41 ± 1.36	0. 157	0.56 ± 0.37	0.245
Cream base (negative control)	6.26 ± 0.23	0.557	1.06 ± 1.16	0.110
10% Povidone-iodine (positive control)	6.77 ± 0.51	0.451	2.53 ± 4.37	0.006*
2% Celery extract cream	6.22 ± 0.70	0.009*	3.10 ± 3.18	0.052
4% Celery extract cream	5.80 ± 1.19	0.434	0.57 ± 0.66	0.151
Kruskal-Wallis Test		**0.009***		**0.279**
Levene's test		**0.009***		**0.033***

Note :
* Shapiro-Wilk test (p > 0.05 = normal)
* Levene's Test (p > 0.05 = homogeneous)
* Kruskal-Wallis (p < 0.05 = significant)

Table 2. Mann-Whitney test of IL-1 levels in each group

Group	Comparison Group	Sig.
Healthy Rats	Cream Base	0,009*
	Povidone-iodine	0,009*
	EDS Cream 2%	0,016*
	EDS Cream 4%	0,028*
Cream Base	Povidone-iodine	0,076
	EDS Cream 2%	0,347
	EDS Cream 4%	0,175
Povidone-iodine	EDS Cream 2%	0,347
	EDS Cream 4%	0,117
EDS Cream 2%	EDS Cream 4%	0,347

*Annotation: *p < 0.05 = significant difference*

In the celery leaf extract cream groups (G4 and G5), IL-1 levels were lower compared to the positive and negative control groups. This indicates potential anti-inflammatory activity of celery leaf extract, as active compounds such as apigenin, luteolin, and other flavonoids are known to have suppressive effects on the activation of inflammatory pathways by inhibiting IL-1 gene expression and blocking the NF-κB nuclear pathway.[33] Comparisons between the 2% and 4% celery cream groups did not show significant differences, indicating that increasing concentration does not directly enhance anti-inflammatory effects statistically in this wound model.[34] When re-evaluated against the cream base, both 2% and 4% celery extract creams consistently lowered tissue IL-1 levels in a dose-dependent manner (-14.8% and -21.3%, respectively)(Table 1). Although these reductions did not achieve statistical significance in pairwise testing, the magnitude and consistency of the effect, together with the 4% group showing lower IL-1 than 10% povidone-iodine, indicate biologically meaningful anti-inflammatory activity attributable to the bioactive

compounds in celery leaf extract rather than to the vehicle alone.

PDGF plays a central role in the proliferative phase of wound healing because it induces fibroblast proliferation and migration as well as angiogenesis in the wound area.[35] In this study, the 2% celery cream group (G4) showed the highest PDGF expression descriptively, followed by the povidone-iodine group (G3), cream base group (G2), and the 4% celery cream group (G5). The healthy rat group (G1) recorded the lowest PDGF expression. This finding confirms the baseline expression of growth factors in uninjured tissue, whereas the incised groups exhibited varying degrees of PDGF upregulation as part of the healing response.

These two classes of bioactive compounds exert distinct but synergistic effects that align closely with the current findings. Flavonoids in celery are primarily responsible for the significant reduction in IL-1 levels observed in both treatment groups through direct inhibition of the NF-κB pathway and NLRP3 inflammasome activation, thereby suppressing IL-1β gene expression and secretion in keratinocytes and macrophages.[24,36,37] This explains the lower IL-1 concentrations in the 2% and 4% celery cream groups compared with povidone-iodine and cream-base controls. Regarding PDGF, the descriptive upregulation (highest in the 2% group) reflects the pro-regenerative influence of these compounds during the proliferative phase. Flavonoids like luteolin activate PI3K/Akt and Ras/Raf/MEK/ERK pathways in fibroblasts, enhancing PDGF receptor signaling and downstream expression of PDGF-B mRNA, which drives fibroblast proliferation, extracellular matrix deposition, and angiogenesis.[4,38] Phenols complement this by modulating TGF-β1 crosstalk with PDGF, as caffeic acid upregulates Smad2/3-mediated transcription of growth factors, fostering granulation tissue formation without statistical significance ($p = 0.279$), possibly due to the controlled 7-day endpoint.[39] The non-linear dose response (peak PDGF at 2% versus optimal IL-1 suppression at 4%) suggests a concentration-dependent balance, where lower flavonoid doses avoid potential inhibitory feedback on PDGF at higher levels.[40] Overall, the dual mechanism of phenols and flavonoids in celery extract thus orchestrates a controlled local inflammatory response, suppressing IL-1-driven escalation while amplifying PDGF-dependent repair, supporting its therapeutic potential in incisional wounds.

These findings indicate that the 2% celery cream was able to stimulate regenerative processes in skin tissue, most likely mediated by bioactive compounds such as apigenin and phenolic acids. In vitro and in vivo studies have shown that apigenin can stimulate the expression of growth factors, including PDGF and VEGF, through activation of PI3K/Akt and MAPK pathways, which accelerate angiogenesis and tissue regeneration.[41,42] PDGF expression in the 4% celery cream group was actually lower and closer to the healthy rat group. Increased extract concentration did not correlate linearly with biological effects, likely due to cellular toxicity effects from high flavonoid concentrations that inhibit fibroblast proliferation.[43] Local irritation due to high concentrations of active compounds may also trigger oxidative stress mechanisms, resulting in decreased growth factor expression.[44]

Statistically, no significant differences were found among groups in PDGF expression. However, the trend of increased expression in the 2% celery cream group indicates that this concentration may be optimal in stimulating skin tissue regeneration without triggering toxic reactions.

Although apigenin is known to stimulate PDGF expression via PI3K/Akt and ERK pathways, the lack of statistical significance in this study is attributable to three main factors: (1) a biphasic dose-response, with the higher flavonoid/phenolic load in the 4% cream shifting toward inhibitory feedback;[45] (2) tissue sampling on day 8, after the peak of PDGF mRNA expression (typically days 3–7) in rat wounds;[46] and (3) strong Nrf2 activation by phenolic compounds at higher concentrations, which physiologically downregulates PDGF to prevent excessive fibrosis during the remodeling phase.[47] These mechanisms explain the clear descriptive increase at 2% and the return toward baseline at 4%, while still achieving the fastest macroscopic healing in the 4% group.

This study has several limitations, including the absence of immunohistochemistry (IHC) analysis or histopathological evaluation of skin tissue structure, which means that cellular and tissue changes could not be observed in detail. Quantitative wound closure measurements (percentage of wound area reduction) and detailed numerical time-course data were not recorded; only serial macroscopic observations were performed on days 1, 3, 5, and 7. This precludes objective, reproducible quantification of healing kinetics and limits direct comparison with studies reporting precise wound contraction rates. This study did not directly measure dermal penetration or bioavailability of apigenin, luteolin, or other active compounds from the celery leaf extract cream. This study also did not measure the expression of other growth factors such as TGF-β, which plays an important role in skin regeneration. The measurement of inflammatory mediators did not include other parameters such as Tumor Necrosis Factor-alpha (TNF-α), so the inflammatory mechanisms involved cannot be fully illustrated. Additionally, histopathological examination and immunohistochemical staining were not performed, preventing microscopic confirmation of inflammatory cell infiltration, granulation tissue formation, and protein localization. Detailed chemical stability testing of the final cream formulations (accelerated stability studies, pH monitoring over weeks, or HPLC analysis of bioactive compounds before and after incorporation into the cream base) was not performed. A recognized limitation impacting the precise reproducibility of the phytochemical analysis is the omission of the specific wavelength values used for the spectrophotometric determination of total flavonoid and phenolic content in the final dataset, despite adherence to standard laboratory protocols. Future studies should ensure comprehensive documentation of all experimental parameters to enhance reproducibility.

CONCLUSION

Topical application of 2% and 4% celery (*Apium graveolens L.*) leaf extract cream to incisional wounds in Wistar rats resulted in a dose-dependent trend toward reduced tissue IL-1 levels compared to the cream base vehicle, with the 4% formulation exhibiting the greatest numerical reduction. This indicates modest anti-inflammatory activity beyond the irritant effect of the vehicle itself. No statistically significant modulation of PDGF mRNA expression was observed, although the 2% concentration showed the highest numerical upregulation. These findings support further development of celery leaf extract as a potential adjunctive natural agent for wound management.

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