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In Vivo Evaluation of Butterfly Pea (*Clitoria ternatea*) Flower Gel on IL-10 and STAT3 Expression in Thermally Induced Skin Burns

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ABSTRACT

Burn injuries caused by thermal exposure trigger oxidative stress and inflammation, largely driven by reactive oxygen species (ROS) and systemic inflammatory response syndrome (SIRS). These mechanisms may disrupt the production of cytokines involved in tissue repair, such as interleukin-10 (IL-10) and signal transducer and activator of transcription 3 (STAT3). Clitoria ternatea L. (butterfly pea) contains potent antioxidant and anti-inflammatory phytochemicals, making it a promising candidate for modulating inflammatory responses and promoting wound healing. This study evaluated the effects of Clitoria ternatea extract gel on IL-10 and STAT3 expression in second-degree burn injuries using a Wistar rat (Rattus norvegicus) model. A post-test only control group design was employed, involving 30 male rats randomly assigned to five groups (G1–G5). Second-degree burns were induced using a 1.8 cm diameter heated metal plate applied to the dorsal skin for 3 seconds after heating for 15 minutes. Treatments with the extract gel were administered topically for seven days. Skin samples were collected 24 hours after the last application and analyzed for IL-10 and STAT3 mRNA expression using qRT-PCR. Data were statistically tested with One-Way ANOVA. The results showed no significant differences in IL-10 expression among all groups. However, STAT3 expression was significantly higher in the groups treated with 5% and 10% Clitoria ternatea extract gel, with the highest observed in the 10% group (6.73 ± 2.94). These findings indicate that while IL-10 remained unaffected, butterfly pea extract gel effectively increased STAT3 expression, suggesting its potential role in modulating regenerative pathways in burn-injured skin.

Key Messages:

- This study highlights the therapeutic potential of Clitoria ternatea gel as a natural, low-toxicity alternative for managing second-degree burn injuries
- The upregulation of STAT3 expression by the extract suggests a promising mechanism for enhancing tissue repair and reducing inflammation in burn wounds.

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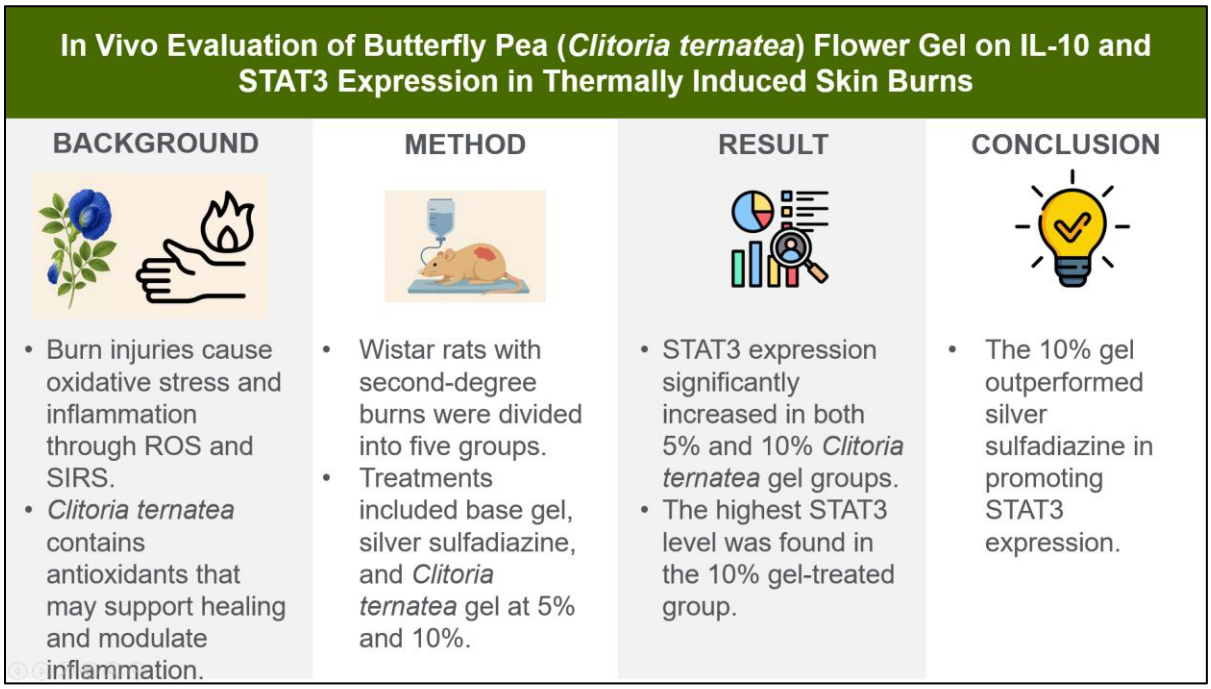
GRAPHICAL ABSTRACT



INTRODUCTION

Burn injuries, particularly those classified as second-degree burns, are known to elicit complex inflammatory responses that can impede the healing process. Such burns damage both the epidermis and portions of the dermis, often resulting in prolonged inflammation, delayed tissue regeneration, and potential scarring (1). The intricate balance of pro-inflammatory and anti-inflammatory cytokines is critical in determining the outcome of wound healing. Interleukin-10 (IL-10), an anti-inflammatory cytokine, plays a central role in suppressing excessive immune responses and promoting tissue repair (2–5). Conversely, while signal transducer and activator of transcription 3 (STAT3) is essential for keratinocyte migration and tissue repair, its persistent overactivation has been implicated in pathways of chronic inflammation and fibrosis, ultimately impairing regeneration (6).

Given these critical roles, increasing attention has been directed toward natural compounds capable of modulating such pathways. Recent studies have highlighted the therapeutic potential of plant-based agents in regulating the wound healing cascade(7). *Clitoria ternatea*, commonly known as butterfly pea, has gained interest due to its antioxidant, anti-inflammatory, and wound-healing properties which are attributed to its rich content of anthocyanins, flavonoids, and ternatin compounds (8–10). Experimental evidence suggests that extracts of *Clitoria ternatea* can accelerate healing in incisional and burn wounds, potentially through modulation of inflammatory mediators such as IL-10 and oxidative enzymes like glutathione peroxidase (8,10–12). Moreover, its capacity to scavenge free radicals and reduce pro-inflammatory mediators indicates a possible role in downregulating detrimental signaling pathways, including STAT3 (13).

Despite these promising findings, limited research has examined the simultaneous effect of *Clitoria ternatea* extract gel on both IL-10 and STAT3 expression in the context of second-degree thermal burns. While individual effects on IL-10 or oxidative stress markers have been documented, comprehensive studies assessing its dual action on anti-inflammatory and profibrotic pathways in vivo remain scarce. Furthermore, few investigations have utilized a dose-comparative topical gel formulation to evaluate its healing efficacy in standardized rat burn models.

Therefore, This study aims to evaluate the effect of *Clitoria ternatea* flower extract gel on IL-10 and STAT3 expression in male Wistar rats with second-degree burns, specifically assessing whether varying concentrations can promote healing by enhancing IL-10 and suppressing STAT3.

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METHODS

The study population comprised healthy male Wistar rats aged 2–3 months, weighing 200–250 g, confirmed by a veterinary health assessment. A total of 30 rats were selected using simple random sampling and allocated equally into five groups (n=6 per group): a normal control group (G1) with no burn and no treatment, a negative control group (G2) with burn and base gel, a positive control group (G3) with burn and silver sulfadiazine cream, and two treatment groups (G4 and G5) receiving 5% and 10% *Clitoria ternatea* gel respectively after burn induction. The sample size was deemed adequate according to WHO standards, which recommend at least five animals per group, with an additional 10% to account for attrition.

The gel formulation was prepared using hydroxypropyl methylcellulose (HPMC) as the base, combined with preservatives (methyl paraben and propyl paraben) dissolved in propylene glycol. *Clitoria ternatea* extract was obtained via maceration of dried flowers using 96% ethanol, followed by filtration and rotary evaporation. Two gel concentrations were prepared: 5% (1 g extract + 19 g base) and 10% (2 g extract + 18 g base), with each formulation totaling 20 g.

Burns were induced by applying a heated metal plate (1.8 cm in diameter, ~100°C) to the shaved and disinfected dorsal skin for 3 seconds under ketamine anesthesia, resulting in second-degree burns characterized by erythema and blistering. Treatments were administered topically for 7 consecutive days. After the final treatment, rats were euthanized using chloroform inhalation for tissue sampling.

Skin tissues (10–30 mg) from the dorsal burn site of male Wistar rats were collected 24 hours after the final treatment following euthanasia with chloroform inhalation to ensure humane termination. The dorsal region was chosen because it provides a consistent and reproducible site for burn induction. The tissues were immediately ground in liquid nitrogen to maintain RNA stability, then lysed with Binding Buffer 4 (0.3 mL per 10 mg tissue) and 12 µL proteinase K, followed by vortexing and incubation at 56°C for 10–20 minutes to optimize protein digestion. The homogenates were centrifuged at 12,000 × g for 5 minutes, and the resulting supernatant was collected in RNase-free tubes. RNA purity and concentration were checked using spectrophotometry, and only samples with adequate purity were used for analysis. Gene expression of IL-10 and STAT3 was measured using quantitative real-time reverse transcription PCR (qRT-PCR) with the PerfectStart Green One-Step qRT-PCR SuperMix, using β-actin as the housekeeping gene to normalize sample variability. PCR was performed with reverse transcription at 50°C for 10 minutes, initial denaturation at 94°C for 30 seconds, followed by 45 cycles of denaturation at 94°C for 5 seconds and annealing/extension at 58°C for 30 seconds, with SYBR Green detection during the annealing/extension step. The relative expression levels of IL-10 and STAT3 were calculated using the ΔΔCt method to determine fold changes in gene expression between groups (14–18).

Data were analyzed using SPSS version 26.0 for Windows. Normality was assessed with the Shapiro-Wilk test, followed by Levene's test for homogeneity. Parametric analysis (One-Way ANOVA) was used when assumptions were met. If data were not normally distributed, non-parametric Kruskal-Wallis tests were employed, with post-hoc Mann-Whitney tests for pairwise comparisons. A significance level of $p<0.05$ was set for all tests.

CODE OF HEALTH ETHICS

This study was conducted following strict ethical standards for the use of experimental animals in biomedical research. The protocol was reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia (Approval Number: 82/II/2025/Komisi Bioetik). All experimental procedures adhered to the Guidelines for the Care and Use of Laboratory Animals issued by the National Research Council (2011) and were designed to minimize animal suffering and ensure humane treatment throughout the study.

RESULTS

The expression of IL-10 was not significantly different across all five groups. As shown in Table 1, mean IL-10 expression did not vary significantly across the groups, with values ranging from 0.97±0.10 (G4) to 1.09±0.16 (G5) (Table 1). Normality of the data was confirmed with Shapiro-Wilk tests ($p>0.05$ for

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all groups), and homogeneity was confirmed with Levene's test (p=0.588). One-way ANOVA revealed no statistically significant difference among the groups (p = 0.822). Although a slight increase in IL-10 expression was observed in the group treated with 10% extract gel, the difference was not statistically meaningful (Figure 1). This suggests that, in the context of acute inflammation following burn injury, the topical application of Clitoria ternatea gel, at either 5% or 10% concentration, did not significantly modulate IL-10 expression within the seven-day treatment window.

Table 1. description of mean IL-10 expression and One-Way ANOVA test

Group	G1	G2	G3	G4	G5	p-value
IL-10 mRNA relative expression						
Mean	1,02	0,99	0,97	0,97	1,09	
SD	±0,24	±0,15	±0,17	±0,10	±0,16	
Shapiro-Wilk	0,766	0,848	0,323	0,530	0,368	
Levene Test						0,588
One Way Anova						0,822

Description:
- Shapiro-Wilk : Normal Distribution (p>0.05)
- Levene Test : Homogen (p>0,05)
- One Way Anova : Significant (p<0,05)

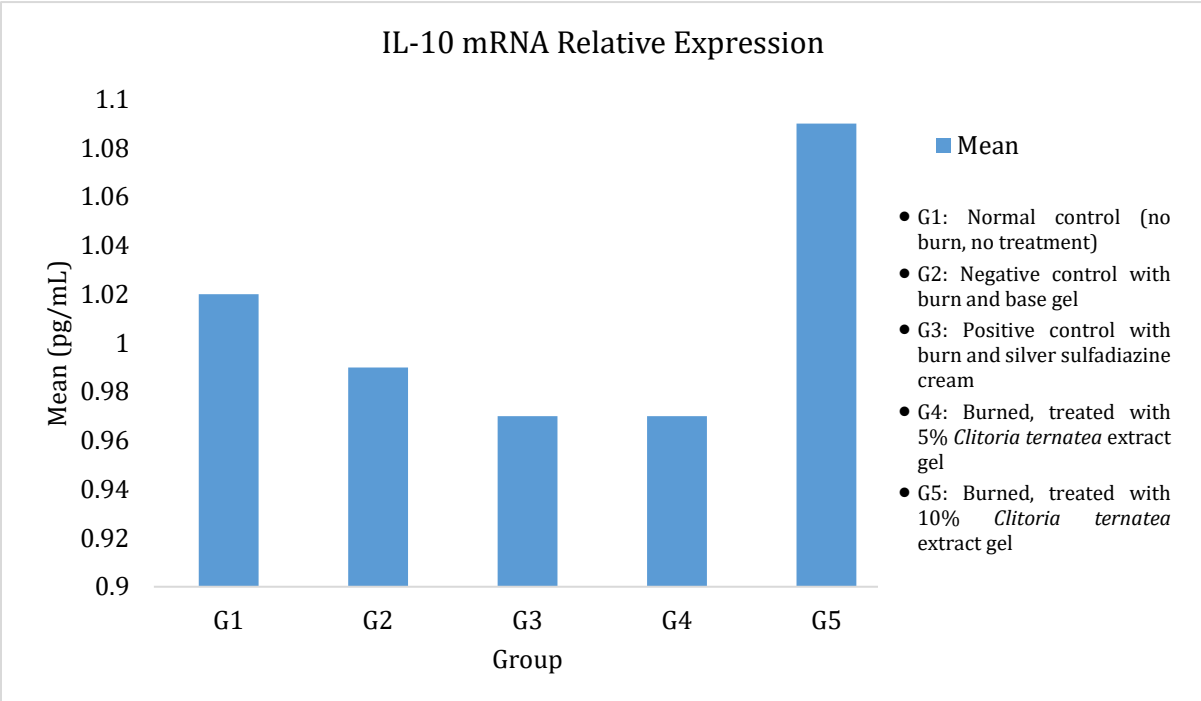

Figure 1. IL-10 mRNA Relative Expression

In contrast, as shown in Table 2, STAT3 expression levels showed a more pronounced and statistically significant response to treatment. The highest expression was observed in the 10% extract group (G5), with a mean of 6.73±2.94, followed by the 5% extract group (G4), at 4.95±2.70. Lower levels were observed in the healthy group (G1) at 2.53±1.36, the placebo group (G2) at 2.14±1.28, and the silver sulfadiazine group (G3) at 1.57±1.20. Shapiro-Wilk tests revealed that G3 and G5 groups were not normally distributed (p<0.05), necessitating the use of non-parametric analysis. Kruskal-Wallis testing revealed significant differences among the groups (p = 0.019).

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Table 2. Description Of Mean STAT3 Expression And Kruskall Wallis Test.

Group	G1	G2	G3	G4	G5	p-value
STAT3 mRNA relative expression						
Mean	2,53	2,14	1,57	4,95	6,73	
SD	±1,36	±1,28	±1,20	±2,70	±2,94	
Shapiro-Wilk	0,309	0,189	0,008	0,330	0,009	
Kruskall Wallis						0,019

Description:
- Shapiro-Wilk : Normal distribution (p>0,05)
- Kruskall Wallis : Significant (p<0,05)

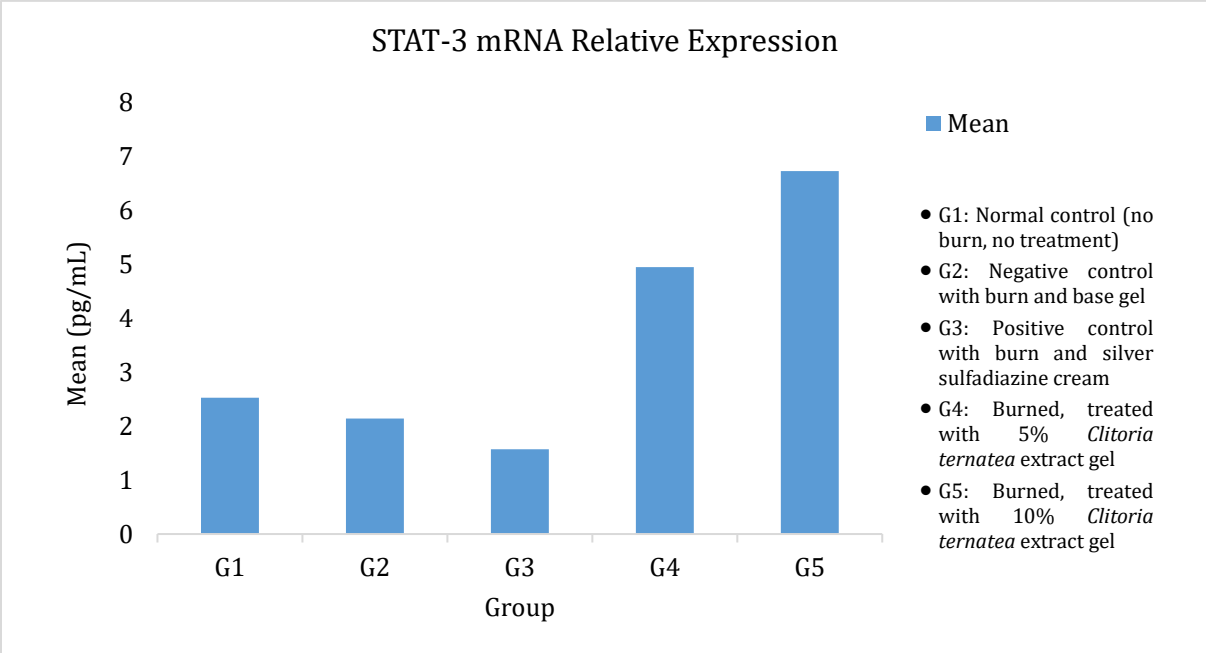

Figure 2. STAT3 mRNA Relative Expression

As shown in **Table 3,** subsequent pairwise comparisons using Mann-Whitney tests demonstrated significant differences between G2 and G5 (p=0.019), G3 and G4 (p=0.017), and G3 and G5 (p=0.004), indicating that both concentrations of *Clitoria ternatea* gel significantly upregulated STAT3 expression compared to the placebo and silver sulfadiazine.

Table 3. STAT3 expression Mann-Whitney test.

Group	Group Comparison	p-value
G1	G4	0,302
	G5	0,122
G2	G1	0,427
	G4	0,068
	G5	0,019
G3	G1	0,176
	G2	0,576
	G4	0,017
	G5	0,004
G4	G5	0,606

DISCUSSION

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that regulates and suppresses the production of proinflammatory cytokines during the recovery phase of tissue injury, thereby reducing

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cytokine-induced damage (2,19). This study aimed to evaluate the effect of topical application of butterfly pea (*Clitoria ternatea*) flower extract gel on IL-10 gene expression in rats with second-degree burn injuries. However, the findings revealed that the administration of both 5% and 10% concentrations of the extract gel did not significantly influence IL-10 expression. This result contradicted the initial hypothesis which posited that *Clitoria ternatea* extract would enhance anti-inflammatory responses through the upregulation of IL-10.

The lack of significant effect on IL-10 expression may be explained by the complexity of molecular mechanisms that govern IL-10 regulation, including intricate feedback loops and the transient nature of cytokine responses in acute injury. It is possible that the seven-day treatment period or the timing of tissue sampling did not capture the optimal window for *Clitoria ternatea's* influence on IL-10 expression in this specific burn model. The lack of significant effect on IL-10 expression may be explained by the complexity of molecular mechanisms that govern IL-10 regulation. These involve a network of transcription factors, cytokines, and signaling pathways such as STAT3 and NF-κB, in addition to epigenetic modifications and genetic polymorphisms (20,21). Furthermore, thermal burn injuries induce systemic responses that can affect various organs, including the adrenal glands, which are integral to stress regulation and immune modulation. Activation of the hypothalamic–pituitary–adrenal (HPA) axis during burn-induced stress leads to sustained cortisol secretion. Although cortisol plays a role in dampening inflammation, chronic elevation may suppress immune function, increase infection susceptibility, and interfere with metabolic homeostasis, insulin sensitivity, and wound healing (1,22).

Thermal injury represents a form of acute trauma that compromises extensive areas of the skin, often exceeding its regenerative capacity (23). Signal transducer and activator of transcription 3 (STAT3) is a cytoplasmic protein that transmits signals to the nucleus and is essential in various biological processes including cell proliferation, migration, and survival (24,25).

These results suggest that both concentrations of *Clitoria ternatea* gel modulated STAT3-related tissue responses to thermal trauma, supporting its role in inflammation control, repair, and tissue regeneration. STAT3 is a crucial mediator in wound healing, particularly in facilitating re-epithelialization and cellular proliferation in injured tissues. However, it is important to emphasize that effective healing requires a balanced STAT3 expression. While transient activation of STAT3 promotes beneficial processes such as keratinocyte migration and angiogenesis, persistent overexpression can lead to chronic inflammation and fibrosis, thereby impairing regeneration (26,27). The greater upregulation observed with the 10% formulation indicates that this concentration may be optimal for promoting regenerative responses in burn wounds. This enhanced activity could be attributed to the presence of bioactive secondary metabolites in *Clitoria ternatea*, such as flavonoids, saponins, tannins, and alkaloids, which are known to exert antioxidant, anti-inflammatory, and pro-healing properties (9,11,13).

Notably, the *Clitoria ternatea* gel was more effective in upregulating STAT3 than silver sulfadiazine, which aligns with previous findings indicating that silver-based topical agents can exert cytotoxic effects on fibroblasts and keratinocytes, thereby impairing the wound healing process (28). Other comparative studies have also shown that silver-containing dressings may delay re-epithelialization and promote scar thickening in burn wounds (29).

Interestingly, no significant difference was observed in baseline IL-10 and STAT3 expression between healthy rats (G1) and burn-injured rats treated with base gel alone (G2). This might be due to the insufficient duration or intensity of burn exposure to elicit a strong inflammatory response, or due to the soothing and hydrating effect of the gel base, which may reduce stress and inflammation at the wound site (30). The gel base may have provided a cooling effect that moderated the systemic stress response and blunted cytokine activity.

Despite these promising outcomes, several limitations must be acknowledged. First, the study duration was limited to seven days, focusing primarily on the inflammatory and early proliferative phases of wound healing. Future studies should include longer observation periods to assess effects on late-phase remodeling and potential scarring. Second, while mRNA expression data are informative, protein-level validation (e.g., ELISA or Western blot) was not performed, potentially limiting the translatability of the results to clinical biomarkers. Second, while mRNA expression data are informative, protein-level

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validation was not performed; however, future studies could apply ELISA by preparing homogenates of burn tissue for protein extraction and quantification, thereby providing complementary evidence to support the gene expression findings. Third, although simple randomization was used, inter-individual variability in immune response among rats might introduce bias. Additionally, the exclusive use of male Wistar rats may limit generalizability, as hormonal differences in females could affect inflammatory responses.

Potential bias may also arise from subjective histological interpretation, even though standardized scoring was applied. While treatment effects appeared dose-dependent, further research with intermediate concentrations could better define the dose-response relationship and potential therapeutic window. Moreover, topical absorption rates and formulation stability of the gel were not assessed, which are critical considerations for future clinical applications.

CONCLUSION

The administration of butterfly pea (Clitoria ternatea) flower extract gel was found to influence STAT3 expression in skin exposed to second-degree burn injuries. Specifically, topical application of the 10% extract gel significantly affected STAT3 expression in Wistar rats subjected to thermal burns. In contrast, the extract gel showed no effect on IL-10 expression in the burned skin. Both the 5% and 10% concentrations of the butterfly pea extract gel, when applied topically, did not alter IL-10 expression levels in Wistar rats with second-degree burns. Future studies are recommended to include protein-level validation, longer observation periods to assess the remodeling and scarring phases, and the use of both male and female subjects to better understand sex-related differences in wound healing responses.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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