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Effect of Butterfly Pea Flower (*Clitoria ternatea* L.) Gel on PDGF and IL-6 Expression in UVB-Exposed Wistar Rats

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Abstract: Ultraviolet-B (UV-B) exposure can trigger inflammation and inhibit skin regeneration by decreasing Platelet-Derived Growth Factor (PDGF) and increasing Interleukin-6 (IL-6). Butterfly Pea (*Clitoria ternatea* L.) is known for its antioxidant and anti-inflammatory properties, but its effectiveness as a topical gel has not been widely studied. This study aims to evaluate the effect of Butterfly Pea (*Clitoria ternatea* L) extract gel on IL-6 and PDGF expression in Wistar rats exposed to UVB. This study is an in vivo experimental study with a post-test-only control group design. A total of 20 Wistar rats (200–250 g) were divided into four groups consisting of 5 rats per group: K1 (healthy control), K2 (gel base + UV-B), K3 (5% *Clitoria ternatea* gel + UV-B), and K4 (10% Clitoria ternatea gel + UV-B). UV-B exposure was carried out for 20 minutes/day (160 mJ/cm²) for 7 days. PDGF and IL-6 expression were analyzed by RT-qPCR. Statistical tests using Shapiro-Wilk, Levene, Kruskal-Wallis for PDGF expression, and One-Way ANOVA for IL-6 expression. Studies have shown that PDGF expression did not show significant differences between groups (p=0.455), with an average expression of K1: 1.39±0.62, K2: 1.39±0.61, K3: 1.66±0.87, and K4: 1.52±1.88. IL-6 expression was also similar (p=0.663), an average of K1: 1.02±0.18, K2: 1.11±0.33, K3: 1.22±0.23, and K4: 1.16±0.26. Conclusion: Administration of *Clitoria ternatea* L. extract gel did not have a significant effect on PDGF and IL-6 expression in the skin of Wistar rats exposed to UVB light. Both 5% and 10% doses showed no significant difference in the expression of the two markers; further studies with larger sample sizes, longer treatment durations, and improved topical delivery systems are needed. are recommended to better evaluate its therapeutic potential.
Keywords: Butterfly pea; *Clitoria ternatea* L; interleukin-6; ultraviolet-B.

INTRODUCTION

Chronic exposure to Ultraviolet B (UVB) radiation leads to increased levels of nitric oxide (NO) and reactive oxysgen species (ROS), which can induce the release of diacylglycerol (DAG) and arachidonic acid, activating protein kinase C-3 (PKC3), thereby triggering the release of proinflammatory cytokines and inhibiting the release of growth factors such as platelet-derived growth factor (PDGF) (Son et al., 2020). PDGF promotes fibroblast proliferation, which plays a key role in collagen synthesis and extracellular matrix (ECM) regeneration. UVB exposure may disrupt this process, making PDGF levels a relevant indicator of tissue damage or repair (Lee & Liu, 2022; Takamura et al., 2021). Butterfly pea flower (*Clitoria ternatea* L) extract is known to exhibit antioxidant, anti-inflammatory, and regenerative properties (Cahyaningsih et al., 2019; Carrillo-Martinez et al., 2024). However, its topical application in gel form for protecting the skin against UVB-induced damage remains underexplored.

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Excessive UVB exposure causes acute inflammatory responses in the skin (Kumar et al., 2015), resulting in structural and functional skin alterations (Gromkowska-Kępka et al., 2021; Z. Xiao et al., 2020), such as shortened and thickened collagen fibers, elastin fiber damage, and altered collagen type composition in the dermis (Li et al., 2022). The most evident clinical manifestation includes erythema or sunburn (T. Xiao et al., 2020). Although topical agents are widely used in cosmetic products for anti-aging treatment, they may cause adverse effects such as irritation, burning, peeling, and dermatitis (Kong R et al., 2016). Butterfly pea extract contains active compounds such as anthocyanins and quercetin, which act as antioxidants and anti-inflammatory agents capable of halting UVB-induced inflammatory processes (Guo et al., 2024; Jayanti et al., 2021; Ritonga et al., 2020). Successfully inhibiting inflammation allows the tissue to transition into the proliferative phase, characterized by the upregulation of growth factors, including PDGF (Evrova & Buschmann, 2017; Gallo-Oller et al., 2020)

Butterfly pea flowers are known to contain several bioactive compounds such as kaempferol, quercetin, and myricetin. Previous studies have shown that aqueous extracts of the flower, leaves, and roots of Butterfly pea possess comparable antioxidant potential. Other findings confirmed that the ethanol extract of Butterfly pea contains secondary metabolites such as flavonoids, saponins, terpenoids, and tannins. The extract demonstrated strong antioxidant activity, classified under the 'strong' category, with an IC50 (Inhibition Concentration 50%) value of 87.86 ppm(T. Xiao et al., 2020). Additional research found that a 5% butterfly pea extract gel could inhibit the increase of MMP-1 levels in UVB-exposed Wistar rat skin (Saritani et al., 2021). The flavonoids in *Clitoria ternatea*, including quercetin, have also been shown to enhance PDGF and suppress IL-6 activity (Zulkefli et al., 2023). Previous studies have demonstrated that *Clitoria ternatea* gel exerted notable photoprotective and regenerative effects under UV-B exposure. For instance, a 5 % gel significantly reduced inflammatory and apoptotic markers TNF-α and caspase-3 in Wistar rats, while the 10 % gel lacked similar efficacy (Ninasara et al., 2025). Another investigation revealed that a 10 % gel markedly increased PDGF and GPx gene expression, supporting collagen preservation (Putri et al., 2022). Other work showed dose-dependent increases in IL-10 and GPx levels in UV-B-exposed rat skin (Asichah et al., 2024). Further, topical application reduced IL-6 and elevated VEGF, demonstrating both anti-inflammatory and angiogenic effects (Adaninggar et al., 2025). The gel has also been found to boost IL-6, EGF expression, and re-epithelialization in incision wound models, and enhance fibroblast proliferation and collagen thickness in UV-B–damaged skin (Adaninggar et al., 2025). However, to date, no studies have simultaneously evaluated PDGF and IL-6 expression in UV-B–exposed Wistar rat skin using topical gel formulations. This research addresses that gap, comparing 5% and 10% gel doses and assessing both PDGF and IL-6 gene expression via RT-qPCR. Therefore, further investigation into the efficacy of butterfly pea extract gel, particularly its effect on IL-6 expression, is warranted.

Based on the aforementioned background, this study aims to assess the efficacy of butterfly pea (*Clitoria ternatea* L.) extract gel on IL-6 and PDGF expression in UVB-exposed Wistar rats.

MATERIALS AND METHODS

This study used an in vivo experimental design using the post-test only control group method. Observations were made after all treatments were completed, with no pre-treatment measurements taken. This approach, while efficient for intervention

assessment, carries the assumption that baseline differences between groups are minimal. The experimental subjects consisted of healthy male Wistar rats (*Rattus norvegicus),* aged between two to three months and weighing 200 to 250 grams. Prior to inclusion, all animals were declared healthy and suitable for experimentation by a veterinarian.

Animals were divided into four groups. The first group (K1) consisted of healthy rats that received no treatment. The second group (K2) received a gel-based formulation and was then exposed to UVB radiation. The third group (K3) was treated topically with a 5% butterfly pea extract gel prior to UVB exposure. The fourth group (K4) received a 10% concentration of the same extract gel and was similarly exposed to UVB radiation. Each group consisted of five Wistar rats. No animals died during the experiment, and all subjects remained in good health until the end of the study.

Gel formulation was prepared using fresh butterfly pea flowers that were washed, dried at 40°C, and powdered. The extraction process was performed by maceration using 70% ethanol over three days. The resulting extract was concentrated using a rotary evaporator and stored under refrigerated conditions. The gel base consisted of hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), propylene glycol, ethanol, methylparaben, propylparaben, and distilled water. Two concentrations were prepared: 5% and 10%, each administered topically at a dose of 0.5 grams once daily for seven consecutive days.

Prior to the treatment, all rats underwent a five-day acclimatization period. Prior to treatment, all rats underwent a five-day acclimatization period. The dorsal fur of each animal was shaved to expose an area of approximately 3 × 4 cm^2 for gel application and UVB exposure. Ultraviolet-B irradiation was delivered using a UV-B lamp (Philips TL 20W/12 RS SLV, Eindhoven, Netherlands) positioned at a fixed distance of 20 cm from the skin. The irradiance was measured using a UV radiometer (UVP UVX Digital Radiometer, calibrated at 312 nm), with an output of approximately 0.18 mW/cm^2. Each rat received a daily exposure of 20 minutes, corresponding to a total dose of 160 mJ/cm^2 per day, for seven consecutive days. This dose was chosen as it is sufficient to induce mild erythema without causing ulceration.

On the eighth day, 24 hours after the final treatment, the rats were euthanized using cervical dislocation. Skin tissue samples were collected from the irradiated area using a 6 mm biopsy punch and immediately preserved in RNA stabilization solution. Samples were stored at −80°C until further analysis. Total RNA was extracted from the skin tissues using a commercial RNA isolation kit. The procedure included tissue homogenization in lysis buffer, enzymatic digestion, ethanol precipitation, and RNA elution in RNase-free water. The purity and concentration of the extracted RNA were assessed prior to gene expression analysis.

Gene expression analysis of PDGF and IL-6 was performed using quantitative real-time reverse transcription PCR (qRT-PCR). Total RNA was extracted from skin tissue samples using the EasyPure® RNA Kit (TransGen Biotech, Cat. No. ER101-01) according to the manufacturer's protocol. RNA concentrations ranged between 20–100 ng/μL as recorded in the laboratory log, with purity confirmed by spectrophotometry (A260/280 ratio 1.8–2.0). RNA integrity was further validated by consistent amplification of the housekeeping gene β-actin across all samples. Gene expression analysis of IL-6 and PDGFB was performed using the TransScript® Green One-Step qRT-PCR SuperMix (TransGen Biotech, Cat. No. AQ211-01; No lot: S10105) with SYBR Green detection. Primers were synthesized by Integrated DNA Technologies (IDT, Singapore), standard desalted, 22 bases in length, and supplied at a 25 nmole scale. The primer sequences were as follows: IL-6 forward 5′-AGA CAG

CCA CTC ACC TCT TCA G-3′ and reverse 5′-TTC TGC CAG TGC CTC TTT GCT G-3′ (IDT Ref. 110793275 and 110793276), PDGFB forward 5′-GAG ATG CTG AGT GAC CAC TCG A-3′ and reverse 5′-GTC ATG TTC AGG TCC AAC TCG G-3′ (IDT Ref. 110793277 and 110793278), with β-actin forward 5′-TCC TCC CTG GAG AAG AGC TA-3′ and reverse 5′-TCA GGA GGA GCA ATG ATC TTG A-3′ used as the housekeeping control. The thermal cycling program consisted of reverse transcription at 50 °C for 10 minutes, initial denaturation at 94 °C for 30 seconds, followed by 45 amplification cycles of 94 °C for 5 seconds and 58 °C for 30 seconds, with fluorescence detection at the annealing/extension step. Melt-curve analysis confirmed the specificity of amplification, showing single sharp peaks without nonspecific products or primer-dimer formation. Relative quantification of IL-6 and PDGFB expression was calculated using the 2^−ΔΔCt method, normalized to β-actin. Amplification plots demonstrated clean exponential kinetics with Cq values clustered between approximately 25 and 32 cycles, and no nonspecific amplification was observed. While standard-curve efficiency was not separately determined in this experiment, the amplification profiles, melt-curve validation, and consistency of housekeeping normalization indicated that the reactions were suitable for ΔΔCt-based relative quantification.

For statistical analysis, descriptive evaluation was first performed. Data normality was assessed using the Shapiro-Wilk test, while homogeneity of variance was evaluated using Levene's test. Depending on the results of these tests, appropriate statistical methods were used to compare gene expression between groups. Non-normally distributed data were analyzed using the Kruskal-Wallis test, while normally distributed data were evaluated using one-way ANOVA

The research was conducted at multiple facilities. Preparation and treatment of the animal models were carried out at the Animal Laboratory of Sultan Agung Islamic University (Unissula), Semarang. qRT-PCR analysis was performed at the CITO Clinical Laboratory in Yogyakarta. The study was conducted over a three-month period from December 2024 to February 2025 with Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University. (Ethical Clearance No. 22/I/2025/Komisi Bioetik) All procedures involving animal handling, treatment, and euthanasia complied with established ethical guidelines.

RESULTS AND DISCUSSION

PDGF Expression Analysis

PDGF expression is presented in Table 1. The healthy rat group (K1) showed PDGF expression of 1.39±0.62, the placebo gel group (K2) had 1.39±0.61, the 5% *Clitoria ternatea* L. gel group (K3) had 1.66±0.87, and the 10% gel group (K4) had 1.52±1.88.

The Shapiro-Wilk test was used to assess the normality of the mean PDGF expression in each group. Results indicated that Group K4 was not normally distributed ($p = 0.002$), suggesting that the data were not normally distributed. Homogeneity of variance was confirmed using Levene's test, which yielded a p-value of 0.150, indicating homogeneity.

A non-parametric comparison between groups was conducted using the Kruskal-Wallis test, resulting in a p-value of 0.455, as shown in Table .1 and Figure 1.

These results suggest that there was no statistically significant difference in PDGF expression among the treatment groups.

Table 1. PDGF Expression Data in Each Treatment Group

Variable	Group				P Value
	K1 Healthy Rats	K2 Plasebo Gel	K3 EBP Gel 5%	K4 EBP GEL 10%	
	Mean ± SD n = 5	Mean ± SD n = 5	Mean ± SD n = 5	Mean ± SD n = 5	
PDGF Expression	1.39±0.62	1.39±0.61	1.66±0.87	1.52±1.88	
Shapiro Wilk	0.471	0.561	0.341	0.002	
Levene's Test					0.150
Kruskal wallis					0.455

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

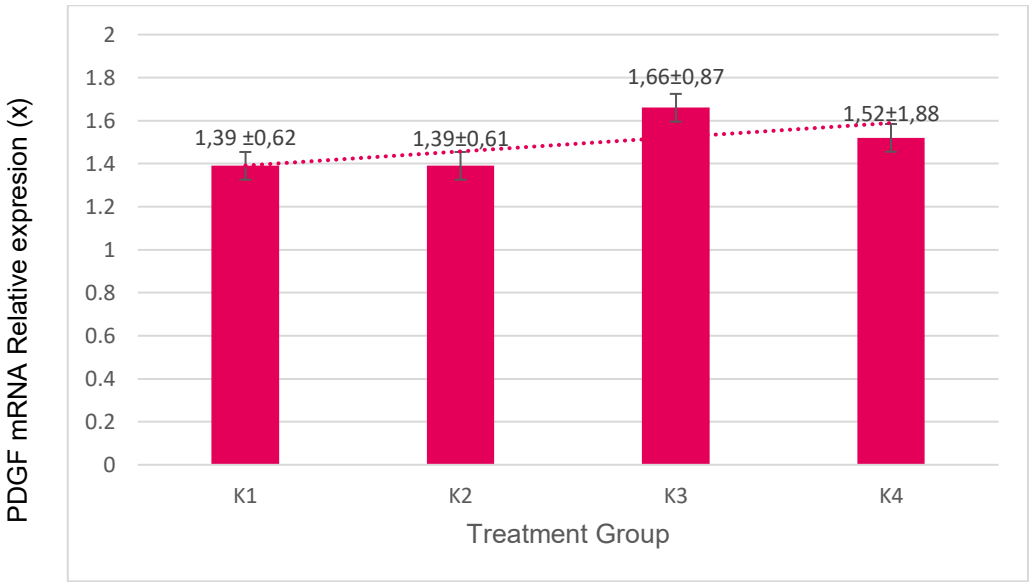

Figure 1. Mean PDGF Expression Graph Across Treatment Groups

Although descriptively, the group receiving 5% *Clitoria ternatea* L. extract gel exhibited higher and more consistent PDGF expression compared to the 10% dose, statistical analysis showed the increase was not significant. The high standard deviation in the 10% group indicated substantial variability in individual responses. This finding aligns with the Shapiro-Wilk test, which revealed a non-normal distribution in the 10% group. While *Clitoria ternatea* L. gel shows potential to enhance PDGF expression, the statistical evidence was insufficient to confirm a significant difference among the treatment groups.

Although descriptively, the 5% *Clitoria ternatea* L. extract gel group showed higher and more consistent PDGF expression compared to other treatments, the

statistical analysis did not confirm a significant difference. This variability can be explained by biological and methodological factors. PDGF signaling is tightly regulated by receptor availability and feedback mechanisms, meaning that once a threshold level is reached, further increases in ligand concentration may not proportionally elevate expression or downstream activity (Wu et al., 2008). This aligns with the concept of a threshold effect, where excessive PDGF may trigger homeostatic control to prevent fibroblast over-proliferation or fibrosis (Hosaka et al., 2013).

Previous studies have demonstrated that PDGF-BB plays a crucial role in wound healing by promoting fibroblast proliferation, angiogenesis, and extracellular matrix deposition (Evrova & Buschmann, 2017). Topical or biomaterial-based delivery of PDGF has been shown to accelerate healing in skin and tendon models (Jian et al., 2022). However, excessive PDGF can have dual effects, including aberrant vascular remodeling and tumor-associated vessel instability, highlighting the importance of maintaining optimal levels (Hosaka et al., 2013).

In the present study, the lack of statistical significance may also be attributed to high inter-individual variability, small sample size, and limitations of gel absorption through the stratum corneum. This issue has been noted in other natural product–based topical studies, where the bioavailability of active compounds limits their efficacy despite promising in vitro effects (Cahyaningsih et al., 2019). Incorporation of penetration enhancers or nanoparticle delivery systems could potentially improve the dermal uptake *of Clitoria ternatea* L. phytochemicals and yield more consistent PDGF upregulation(Jian et al., 2022).

Thus, while the descriptive increase in PDGF expression with 5% extract suggests biological potential, further studies with optimized formulations, larger sample sizes, and controlled delivery systems are needed to validate its therapeutic relevance.

IL-6 Expression Analysis

The results of IL-6 expression analysis are shown in Table 2. The healthy rat group (K1) had IL-6 expression of 1.02±0.18, the placebo gel group (K2) had 1.11±0.33, the 5% extract gel group (K3) showed 1.22±0.23, and the 10% extract gel group (K4) had 1.16±0.26.

Tabel 2. IL-6 Expression Data in Each Treatment Group

Variable	Group				P Value
	K1 Healthy Rats	K2 Plasebo Gel	K3 Gel EBP 5%	K4 Gel EBP 10%	
	Mean ± SD n = 5	Mean ± SD n = 5	Mean ± SD n = 5	Mean ± SD n = 5	
Expression IL-6	1.02±0,18	1.11±0,33	1.22±0.23	1.16±0.26	
Shapiro Wilk	0.123	0.589	0.551	0.711	
Levene's Test					0.507
One One Anova					0.663

Note: Shapiro-Wilk = normal distribution ($p > 0.05$)
Levene's Test = homogeneous ($p > 0.05$)
One-way ANOVA = significant difference ($p < 0.05$)

The Shapiro-Wilk test was used to assess the normality of IL-6 expression data across all groups and showed that all groups followed a normal distribution ($p > 0.05$). The Levene's test indicated data homogeneity with a p-value of 0.507.

A parametric comparison was conducted using One-Way ANOVA, resulting in a p-value of 0.663, as shown in Table 2. This indicates that there was no statistically significant difference in IL-6 expression between the treatment groups.

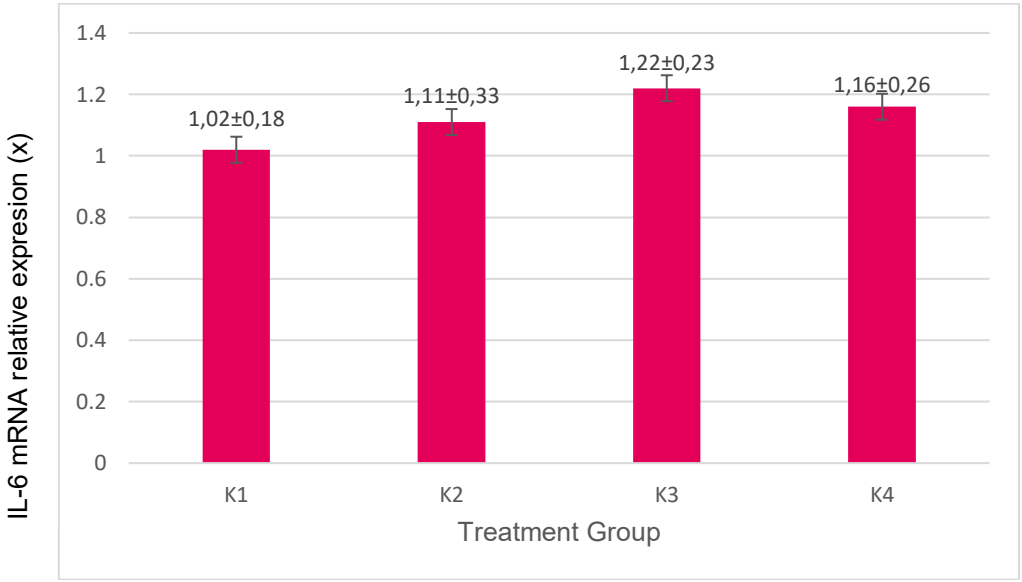

Figure 2. Mean IL-6 Expression Graph Across Treatment Groups

The group treated with 5% *Clitoria ternatea* L. extract gel (K3) showed the highest IL-6 expression, followed by the 10% dose group (K4), the placebo group (K2), and the healthy control group (K1). The increased IL-6 expression in the treatment groups suggests that *Clitoria ternatea* L. extract may influence the early inflammatory response, particularly at the 5% dose, which plays a role in tissue repair. However, the 10% dose did not result in further IL-6 elevation, likely due to threshold mechanisms or anti-inflammatory effects of the extract's bioactive compounds.

The present study found that the 5% *Clitoria ternatea* L. extract gel group showed the highest IL-6 expression, followed by the 10% group, the placebo, and the control. Although the increase was not statistically significant, the descriptive trend suggests that *Clitoria ternatea* extract may modulate the early inflammatory response. IL-6 plays a key modulator of early inflammation and the transition to wound healing by influencing leukocyte dynamics, keratinocyte activation, and fibroblast behavior. Dysregulated IL-6 signaling can lead to either impaired healing or fibrosis (Johnson et al., 2020).

Interestingly, the 10% dose did not further elevate IL-6 expression, which may be explained by threshold mechanisms or by the anti-inflammatory properties of *Clitoria ternatea* bioactive compounds. Anthocyanins and flavonoids present in the extract have been reported to downregulate inflammatory mediators, including IL-6, in various models (Cahyaningsih et al., 2019; Dheeba & Kumar Dheeba B, 2014; Yanti et al., 2020). This aligns with this study's findings that increasing the dose does not necessarily lead to linear increases in IL-6, likely due to negative feedback regulation and the balance between pro- and anti-inflammatory signaling.

Previous studies have shown that UVB exposure induces IL-6 expression as part of the skin's inflammatory response (Narumi et al., 2011). The modulatory effect

of natural antioxidants has been demonstrated in other plant extracts, where treatment reduced excessive IL-6 expression and thereby shortened the inflammatory phase of wound healing (Johnson et al., 2020). These results suggest that *Clitoria ternatea* extract may exert a similar modulatory influence, but the effect was not strong enough to achieve statistical significance under the present experimental conditions.

These findings imply that while *Clitoria ternatea* L. extract has the potential to regulate IL-6 expression and thereby influence the healing process, determining the optimal dose is crucial. Prolonged or excessive IL-6 expression may delay wound closure, whereas balanced modulation could enhance repair. Further studies with larger sample sizes, extended observation periods, and optimized topical formulations (penetration enhancers or nanocarrier delivery) are needed to clarify the therapeutic potential of *Clitoria ternatea* in controlling IL-6–mediated inflammatory responses.

This study has several limitations. First, the treatment duration was relatively short (seven days), which may not fully reflect the long-term effects of *Clitoria ternatea* L. extract gel on wound healing markers. Second, the sample size was limited to five rats per group, which restricts statistical power and may contribute to high inter-individual variability. Third, only two concentrations (5% and 10%) of the extract gel were tested, without exploring a broader dose-response relationship. Additionally, the topical formulation may have had limited skin penetration, reducing the bioavailability of the active compounds. Finally, the study focused solely on PDGF and IL-6 expression; other key mediators of inflammation and tissue repair were not assessed. Future studies with larger sample sizes, extended observation periods, improved delivery systems, and broader biomarker evaluation are recommended to strengthen the evidence.

CONCLUSION

This study demonstrated that topical administration of *Clitoria ternatea* L. extract gel at concentrations of 5% and 10% did not produce a significant effect on PDGF or IL-6 expression in the skin of UVB-exposed Wistar rats. No significant differences were found between the treatment groups and controls for either marker. Nevertheless, the descriptive trends observed suggest a possible modulatory effect of the extract, particularly at the 5% dose. Although these effects were not statistically significant, they indicate potential biological activity of *Clitoria ternatea* L. extract. Future research with larger sample sizes, optimized topical formulations, extended treatment durations, and broader biomarker evaluation is needed to further clarify its therapeutic potential in skin protection and wound healing.

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CONFLICT OF INTEREST

The author declares no conflict of interest related to the publication of this article.

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