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Research article

Activities Analysis of *Uncaria gambir* (*U. gambir*) Ethanol Extract in Vaseline-based Cream to Alleviate Psoriasis in Imiquimod-induced Rats

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Abstract

Psoriasis is commonly treated with topical corticosteroids, but long-term use is associated with safety limitations. *Uncaria gambir*, rich in catechins, exhibits anti-inflammatory and antioxidant properties and may offer a safer topical alternative. This study evaluated the efficacy, early physical stability, systemic safety, and histopathological effects of *U. gambir* cream in an Imiquimod (IMQ)-induced psoriasiform rat model. Male Wistar rats were induced with 5% IMQ and divided into six groups: psoriasis control (K1), betamethasone (K2), vehicle (PCG0), and *U. gambir* cream at 2%, 4.5%, and 7% (PCG2, PCG4.5, PCG7). Psoriasis Area and Severity Index (PASI) scores were assessed on days 5, 8, and 10. Organoleptic stability was observed for 14 days. Blood glucose and nitric oxide (NO) levels were measured, and skin histopathology was evaluated using H&E staining. The results showed that PASI scores were comparable across groups on day 5 ($p=0.396$). Significant reductions were observed on day 8 ($p=0.020$) and day 10 ($p=0.007$), with the greatest improvement in PCG2–PCG4.5 (median PASI ≈1-2), compared with vehicle. All creams remained physically stable. Blood glucose ($p=0.716$) and NO levels ($p=0.611$) showed no significant differences. Histology confirmed reduced epidermal thickness and absence of parakeratosis in PCG2–PCG4.5. In conclusion, *U. gambir* cream at 2-4.5% effectively attenuated psoriatic severity with good physical stability and no detectable systemic effects, supporting its potential as a safe topical therapy.

Keywords: psoriasis; *Uncaria gambi*r; imiquimod; topical formulation; histopathology

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory dermatosis driven by dysregulated innate and adaptive immune responses, particularly activation of the IL-23/IL-17 axis,

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resulting in epidermal hyperproliferation and persistent cutaneous inflammation. Beyond its cutaneous manifestations, psoriasis is frequently associated with systemic inflammation and metabolic comorbidities, contributing to reduced quality of life (Brazzelli et al., 2021). Topical corticosteroids, such as betamethasone, remain first-line therapy; however, long-term use is limited by adverse effects including cutaneous irritation and potential metabolic disturbances (Pagano et al., 1989; Gonzalez et al., 2009; Gisondi et al., 2024).

Given these limitations, there is growing interest in plant-derived anti-inflammatory agents as safer alternatives for chronic inflammatory skin diseases. *Uncaria gambir* Roxb. (*U. gambir*), a catechin-rich medicinal plant traditionally used in Southeast Asia, has demonstrated potent antioxidant and anti-inflammatory properties. Preclinical studies have shown that topical *U. gambir* extracts accelerate wound healing, suppress inflammatory cell infiltration, and promote angiogenesis in burn models (Musdja et al., 2018a). Additional evidence from metabolic and inflammatory models indicates that gambir extracts reduce oxidative stress and pro-inflammatory mediators such as TNF-α and nitric oxide (Permatasari et al., 2022; Armenia et al., 2024).

Despite these promising findings, the effects of *U. gambir* on immune-mediated inflammatory dermatoses, particularly psoriasis, remain insufficiently investigated. The imiquimod (IMQ)-induced psoriasiform model, which reliably recapitulates key pathological features of human psoriasis through Toll-like receptor 7/8 activation, provides a robust platform for therapeutic evaluation (Jabeen et al., 2020). Therefore, this study aimed to assess the anti-psoriatic potential of topical *U. gambir* leaf extract in an IMQ-induced psoriasis model, with evaluation of clinical severity, histopathological changes, and systemic safety indicators.

2. Materials and Methods

2.1 Research design

This study employed a true experimental design using male Wistar rats (10 weeks old; 150-200 g) obtained from a certified laboratory animal supplier and acclimatized for seven days under standard conditions (12 h light/dark cycle, controlled temperature, ad libitum access to food and water). A total of 36 animals were initially allocated (n = 6 per group) and randomly assigned to six experimental groups using simple randomization. The initial group size was determined based on feasibility and consistency with prior exploratory studies using the IMQ-induced psoriasis model, while adhering to the principles of Replacement, Reduction, and Refinement (3R) in animal research.

During the study, two animals in the IMQ-only group (K1) and two in the highest-dose group (PCG7) died, resulting in a final sample size of n = 4 per group; all surviving animals were analyzed (Table 1). No a priori power calculation was performed, which may reduce statistical power and limit detection of small effects; thus, findings should be interpreted as preliminary. Psoriasiform dermatitis was induced by topical 5% IMQ on shaved dorsal skin. Treatments were applied once daily by group allocation. Blood glucose levels were measured using a handheld glucometer, nitric oxide (NO) levels were quantified by the Griess reaction, and dorsal skin tissues were examined histologically using hematoxylin–eosin staining. Histopathological assessments were conducted independently by two assessors and reviewed by a board-certified pathologist. All experimental procedures were approved by the Ethics Committee of Poltekkes Kemenkes Pontianak (Approval No. 015/KEP-PK.PKP/VII/NP/2025).

Table 1. Design of rat experiment

Groups (n=4)	Treatments
K1	IMQ
K2	IMQ + Betamethasone
PCG0	IMQ + Cream 0%
PCG2	IMQ + Cream *U. gambir* 2%
PCG4.5	IMQ + Cream *U. gambir* 4.5%
PCG7	IMQ + Cream *U. gambir* 7%

Notes: IMQ (Imiquimod 5%)

2.2 Extraction and characteristic analysis

2.2.1 Determination analysis

Uncaria gambir leaf material was obtained from local growers in Sungai Mas, Banyuasin, West Sumatra, Indonesia, via an online marketplace. Botanical authentication was performed at the Laboratory of the Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Tanjungpura, Pontianak, Indonesia, by Mukarlina, M.Si., and documented under certificate No. 161/A/LB/FMIPA/UNTAN/2025. A voucher specimen from the authenticated batch was prepared and deposited at FMIPA–Universitas Tanjungpura to ensure traceability and facilitate future reproducibility.

2.2.2 *Uncaria gambir* extraction

Approximately 400 g of dried *U. gambir* leaf powder was extracted with 96% ethanol (2.5 L) using maceration at room temperature for 72 h (three consecutive 24-h cycles) in a sealed container. The extract was filtered every 24 h, and the residual plant material was re-extracted twice with fresh solvent (~1.5 L per cycle). All filtrates (~5 L) were combined and concentrated under reduced pressure at 40-50°C using a rotary evaporator. The concentrate was further thickened in a water bath, dried to constant weight, transferred to amber glass containers, and stored at 4°C under desiccated conditions until use.

2.2.3 Vaseline-based cream preparation

The creams were formulated using a standard oil-in-water emulsification method. The oil phase, consisting of white petrolatum and stearic acid, was heated to approximately 70°C until completely melted and homogeneous, after which *U. gambir* extract was incorporated at the concentrations specified in Table 2. Separately, the aqueous phase was prepared by dissolving methyl paraben (nipagin) in purified water heated to ~70°C, followed by the addition of propylene glycol and triethanolamine (TEA) under continuous mixing. Emulsification was achieved by gradually adding the aqueous phase to the oil phase with constant stirring using a magnetic stirrer for 15 min at ~70°C. The emulsion was manually stirred during cooling to approximately 30°C to obtain a uniform cream, which was aseptically transferred into sterile containers. Stability evaluation in this study was limited to early-stage physical observation, including visual homogeneity, color, odor, and consistency during short-term storage.

Table 2. Cream composition of *U. gambir* extract

Component	F0 (0%)	F1 (2%)	F2 (4.5%)	F3 (7%)
U. gambir extract (g)	0	2.0	4.5	7.0
White petrolatum (g)	8.0	8.0	8.0	8.0
Stearic acid (g)	7.5	7.5	7.5	7.5
Triethanolamine, TEA (g)	0.75	0.75	0.75	0.75
Propylene glycol (g)	4.0	4.0	4.0	4.0
Methyl paraben (nipagin) (g)	0.075	0.075	0.075	0.075
Purified water (mL)	q.s. to 50	q.s. to 50	q.s. to 50	q.s. to 50

Notes: F0 is the placebo base (0% *U. gambir*). “q.s.” indicates quantity sufficient to reach a final batch volume of 50 mL per formulation. All amounts are per 50 mL batch.

2.3 *In vivo* study

2.3.1 Psoriasis induction

Psoriasiform dermatitis was induced by topical application of 5% IMQ cream to the shaved dorsal skin of Wistar rats, a well-established experimental model of psoriasis. Briefly, an approximately 0.5 mg dose of IMQ cream was evenly applied once daily to the exposed dorsal area for five consecutive days. This induction protocol reliably elicited erythema, scaling, and epidermal thickening characteristic of psoriasis-like lesions, thereby providing a consistent platform for subsequent therapeutic evaluation (Badanthadka & D’souza, 2020; Parmar et al., 2021).

2.3.2 PASI analysis

Psoriasis severity was evaluated using a modified Psoriasis Area and Severity Index (PASI), which scores erythema, induration (thickness), and desquamation on a 0–4 ordinal scale (0 = none; 4 = very severe). Scores for each parameter were summed to yield a composite PASI score ranging from 0 to 12 (Manchanda et al., 2023). Assessments were performed on days 5, 8, and 10 by trained and blinded observers under standardized lighting and handling conditions. For descriptive reporting, cumulative PASI scores obtained by numerical summation of ordinal components are presented as mean±SD. However, all inferential analyses were conducted using non-parametric statistical tests appropriate for ordinal data. Topical treatment was initiated after confirmation of psoriasiform lesions on day 5.

2.3.3 Blood glucose analysis

Blood glucose was assessed at the end of the study using a handheld rapid glucometer (Sinocare; Changsha Sinocare Inc., China) on fresh whole blood. Samples were obtained from the periorbital (retro-orbital) sinus using heparinized hematocrit capillary tubes. Prior to blood collection, animals were anesthetized with ketamine (5 mg/kg body weight, intraperitoneal). For each rat, duplicate readings were recorded and averaged to minimize

measurement variability, with the device calibrated according to the manufacturer's instructions.

2.3.4 NO levels analysis

Blood samples (3 mL per rat) were collected from the retro-orbital sinus, allowed to clot, and centrifuged at 5,000 rpm for 15 min to obtain serum (~400 µL). Serum samples were stored at -20°C and thawed only once prior to analysis. NO production was estimated indirectly by quantifying nitrite using the Griess reaction, with absorbance measured at 540 nm on a microplate reader. For each sample, measurements were performed in duplicate to ensure analytical reproducibility, and mean values were used for statistical analysis. Briefly, 50 µL of serum was deproteinized with 10% (w/v) trichloroacetic acid, incubated on ice for 10 min, and centrifuged at 8,000 rpm for 15 min (Green et al., 1982; Miranda et al., 2001; Giustarini et al., 2008).

The clarified supernatant was alkalinized with 0.3 M NaOH, and 30 µL was reacted with equal volumes of Griess reagents A and B in a 96-well plate. After 10 min of incubation at room temperature, absorbance was recorded. Nitrite concentrations were calculated from a sodium nitrite ($NaNO_2$) standard curve (0-100 µM). As this assay detects nitrite only, nitrate-derived NO was not quantified; therefore, measured values represent partial NO metabolites rather than total NOx

2.3.5 Histopathological analysis

On day 10, animals were humanely euthanized by cervical dislocation. Dorsal skin samples were excised, fixed in 10% neutral-buffered formalin for 24-48 h, processed routinely, embedded in paraffin, and sectioned at 4-5 µm. Sections were stained with hematoxylin–eosin (H&E) and examined under a light microscope at 40× magnification using Optilab imaging software. Histopathological evaluation focused on descriptive and quantitative parameters, including epidermal thickness measurements obtained from calibrated digital images using ImageJ (NIH) and qualitative assessment of epidermal architecture (acanthosis, parakeratosis) and inflammatory cell infiltration.

No formal histological scoring system was applied. To minimize observational bias, slide evaluation was performed independently by the primary investigators and two external researchers, followed by blinded review by a board-certified anatomic pathologist from the Department of Anatomical Pathology, Universitas Tanjungpura Hospital. Inter-observer consistency was ensured through consensus discussion, and discrepant interpretations were resolved jointly.

3. Results and Discussion

3.1 Extraction process

Following extraction and solvent removal, *U. gambir* extract was obtained as a viscous, paste-like concentrate with a final yield of approximately 26.8 g. The extract displayed a dark brown–black color, a strong characteristic gambir odor, and a dense consistency with minimal aggregation, indicating acceptable uniformity. These organoleptic characteristics are consistent with enrichment of phenolic compounds during thermal concentration and ethanol evaporation. The increased viscosity and darker coloration observed align with

previous reports of catechin-rich gambir extracts and reflect oxidative and polymerization processes that may occur during ethanolic concentration (Mao et al., 2020).

3.2 Preparation of *U. gambir* vaseline-based cream

The *U. gambir* creams were successfully formulated and demonstrated acceptable organoleptic stability during storage up to 14 days. At baseline (day 0), all formulations exhibited a thick and cohesive consistency, with differences mainly in color and odor. The base cream (F0) was white and odorless, whereas extract-containing formulations (F1-F3) showed hues ranging from greenish-brown to yellowish-brown and a characteristic gambir aroma. After 14 days, mild color darkening was observed in all formulations, particularly in F1 and F2, accompanied by increased odor intensity proportional to extract concentration. Cream consistency remained homogeneous without phase separation, although F3 appeared slightly more viscous and tacky (see Figure 1).

These findings indicate satisfactory early physical stability. Progressive color changes in F1-F2 are consistent with oxidative transformation of catechin-rich polyphenols during storage. Notably, despite its higher extract content, F3 did not exhibit the darkest coloration, likely due to increased viscosity and polyphenol–excipient interactions that altered light scattering and visual appearance. Similar non-linear color behavior has been reported in polyphenol-based topical formulations, where vehicle composition influences apparent color intensity (Getie et al., 2002; Puglia et al., 2017; Draelos, 2018).

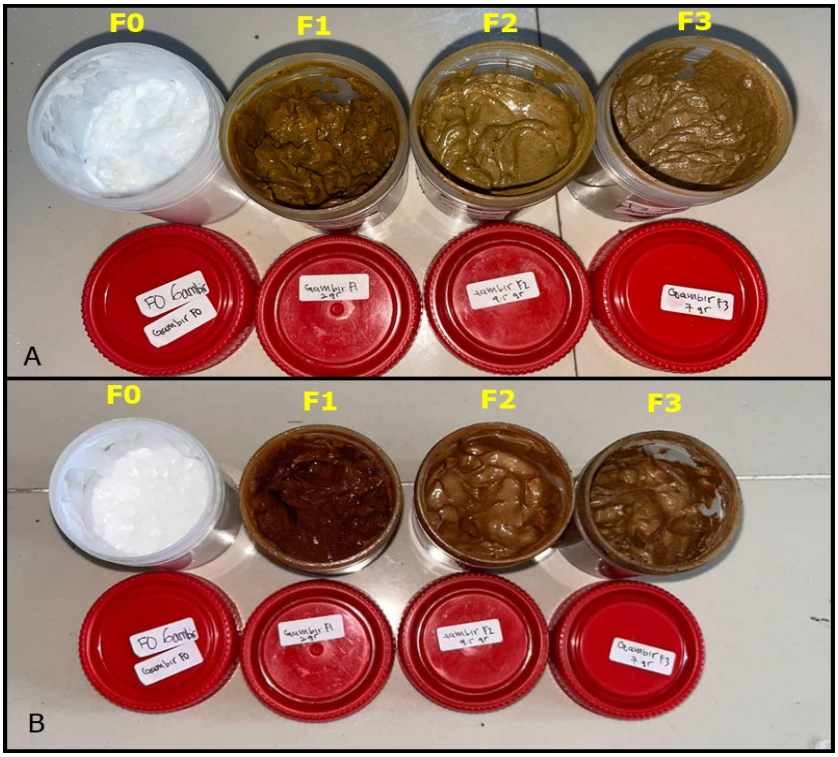

Figure 1. The organoleptic analysis of *U. gambir* cream at (A) 0 day (B) 14 days

3.3 PASI analysis

Kruskal–Wallis analysis of PASI scores revealed no statistically significant differences among groups on day 5 ($p = 0.396$), with median values ranging from 5.00 to 6.00, indicating a homogeneous baseline following IMQ induction. The highest PASI score was observed in the untreated IMQ group (K1; 6.00±0.50), while the lowest scores were recorded in K2 and PCG0 (5.00±0.50-1.00). These findings confirm that psoriasiform dermatitis was consistently established across all experimental groups prior to therapeutic intervention. Macroscopic examination on day 5 corroborated these results, showing comparable erythema, scaling, and epidermal thickening, which are hallmark features of IMQ-induced psoriasis-like inflammation.

Following topical application of IMQ 5%, macroscopic examination of dorsal skin on day 5 revealed comparable erythema, scaling, and epidermal thickening across all experimental groups (Figure 2), confirming uniform induction of psoriasiform dermatitis. As expected for the IMQ paradigm, activation of TLR7 and the IL-23/IL-17 axis drives erythema, epidermal thickening, and scaling, yielding initially comparable lesions (Flutter & Nestle, 2013). Consistently, PASI scores assessed prior to treatment initiation clustered within a narrow range (median 5-6; Table 3), and Kruskal–Wallis analysis showed no significant between-group differences ($p = 0.396$). Although minor numerical variations were observed, these did not reach statistical or clinical relevance and may, in part, reflect limited group size. Collectively, these findings support day-5 measurements as a valid and homogeneous baseline for evaluating subsequent therapeutic effects.

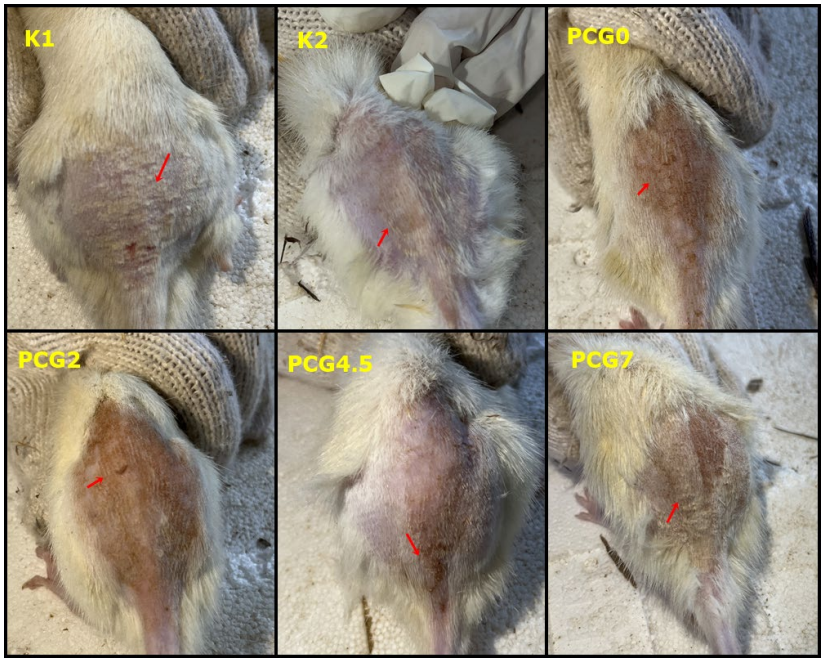

Figure 2. The dorsal skin conditions of all groups on day 5 of observation. All rats show relatively similar levels of erythema, scaling, and thickening, indicating successful induction of psoriasis.

Table 3. Comparative result of psoriasis score development between groups using Kruskall-Walis analysis

Groups (n=4)	Day 5	p-Values	Day 8	p-Values	Day 10	p-Values
K1	6.00±0.50	0.396	6.50±1.41	0.02*	5.00±1.26	0.007*
K2	5.00±0.50		2.00±0.50		2.00±0.50	
PCG0	5.00±1.00		2.50±1.41		3.50±0.96	
PCG2	6.00±0.00		2.50±0.96		1.00±0.82	
PCG4.5	6.00±0.50		3.00±0.50		1.50±0.96	
PCG7	5.50±0.58		2.00±0.00		2.00±0.82	

Notes: The Kruskal-Wallis test showed no significant differences between groups on day 5; however, significant differences were observed between groups on days 8 and 10. Data are presented as median±standard deviation. * indicates statistical significance ($p<0.05$)

By day 8, significant between-group differences emerged ($p = 0.020$), indicating the onset of therapeutic effects in the treatment groups. PASI scores declined most prominently in the *U. gambir* extract cream groups, particularly PCG2 (2.50±0.96) and PCG4.5 (3.00±0.50), whereas the untreated IMQ group maintained higher scores. This temporal response is consistent with the IMQ model, as seen in Figure 3, in which TLR7/8–IL-23–IL-17 axis activation produces rapid lesion development followed by a treatment-responsive phase (Flutter & Nestle, 2013). The greater efficacy at 2-4.5% aligns with prior IMQ studies showing clinical improvement between days 7 and 10 (Zhang et al., 2021). However, interpretation is limited by the short treatment duration and the absence of cytokine profiling (e.g., IL-17, IL-23, TNF-α), precluding direct confirmation of molecular anti-inflammatory mechanisms. Consequently, the observed clinical improvements likely reflect early modulation of inflammatory amplification rather than comprehensive immunological resolution.

The therapeutic effect became more evident by day 10 ($p = 0.007$), with PCG2 and PCG4.5 exhibiting the greatest PASI reductions, as seen in Figure 4, while persistent inflammation was observed in the untreated group. The superior efficacy at intermediate extract concentrations suggests an optimal anti-inflammatory range, potentially related to catechin-rich constituents of *U. gambir.*

These polyphenols, especially (+)-catechin and epicatechin, are known to suppress NF-κB–mediated cytokine production, reduce oxidative stress, and inhibit keratinocyte hyperproliferation—mechanisms directly implicated in IMQ-induced psoriatic pathology (Musdja et al., 2018b). Similar delayed yet sustained improvements have been reported for plant-derived anti-inflammatory agents evaluated in comparable IMQ models (Oswari et al., 2019; Zhang et al., 2021). Consistently, Gupta et al. (2024) reported that topical flavonoids suppress cyclo-oxygenase-2 (COX-2) expression and significantly improve lesion histology between days 7 and 10 of treatment.

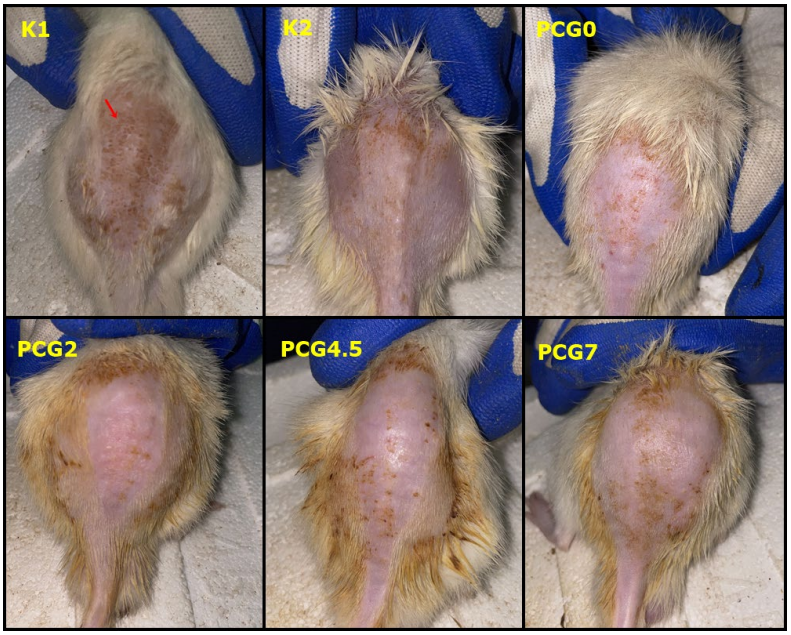

Figure 3. Psoriasis development at day 8. Visual differences begin to appear among the groups. Signs of psoriasis are still present in K1 group (red arrow).

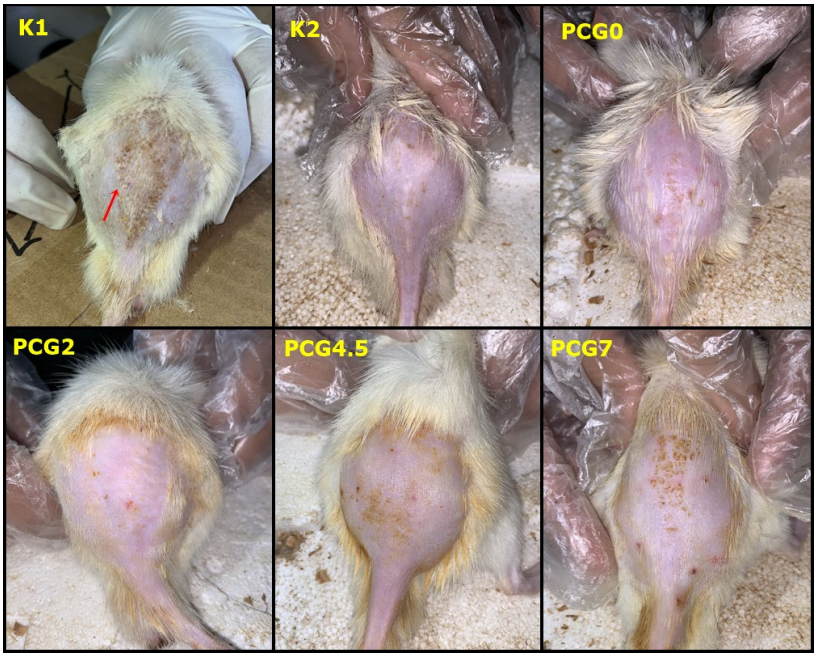

Figure 4. Development of psoriasis in rats at day 10. Notable improvements in skin condition are observed in PCG2 and PCG4.5 groups. Signs of psoriasis are still present in K1 group (red arrow).

The absence of superior efficacy in PCG7, as presented in Figure 5A-C, may be attributed to a non-linear dose–response relationship. At higher concentrations, catechin-rich polyphenols can undergo aggregation, reduced skin penetration, or exert paradoxical pro-oxidant and irritant effects, potentially limiting therapeutic benefit.

Similar bell-shaped responses have been reported for topical polyphenols, where moderate doses optimize anti-inflammatory activity, whereas excessive concentrations diminish biological effectiveness (Katiyar & Elmets, 2001; Galati & O'Brien, 2004). Long-term topical exposure to catechin-rich extracts is generally considered safe; however, excessive or prolonged use may induce local irritation or pro-oxidant effects. Previous studies report dose-dependent oxidative stress at high polyphenol levels, supporting the need for chronic dermal toxicity and irritation studies to confirm long-term safety (Galati & O'Brien, 2004).

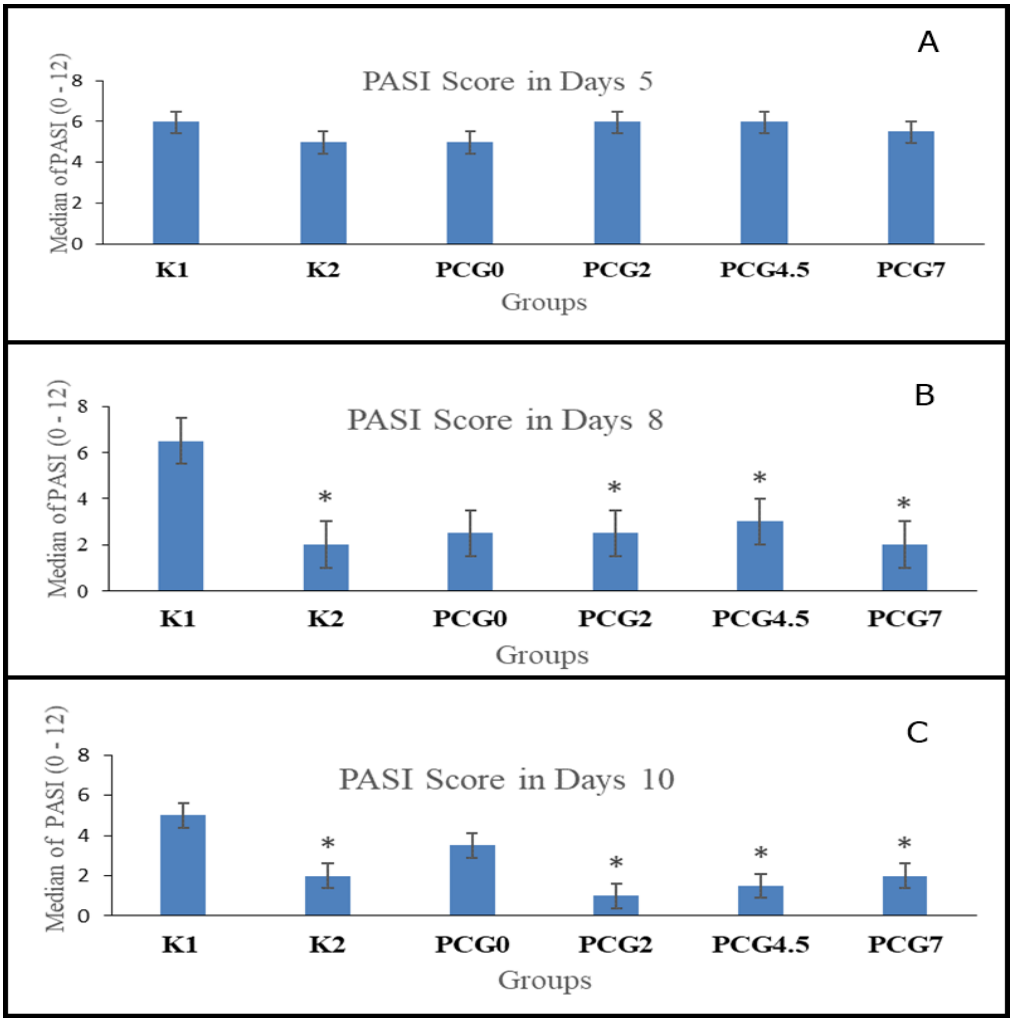

Figure 5. The diagram illustrates the statistical development of PASI scores across different groups from day 5 to day 10, based on Mann-Whitney test.

3.4 Blood glucose analysis

Based on the blood glucose analysis, one-way ANOVA revealed no significant differences among groups (p = 0.716). Mean glucose concentrations across all groups remained within the physiological range, from 86.50±8.70 to 102.50±12.18 mg/dL, indicating preserved systemic glucose homeostasis (Table 4).

The overlap of group means and relatively wide standard deviations, particularly in the betamethasone group (K2), suggests small between-group effect sizes and broad confidence intervals. Given the small sample size (n = 4), these factors limit the precision of intergroup comparisons (Gabros et al., 2025). Importantly, the IMQ-only group (K1) showed glucose values comparable to both the positive control and the *U. gambir*–treated groups, supporting the concept that IMQ primarily induces localized cutaneous inflammation via the TLR7/IL-23/IL-17 axis without systemic metabolic disruption (Li et al., 2021). Furthermore, the absence of glucose alterations in the *U. gambir* groups (PCG2–PCG7) suggests minimal systemic exposure following topical administration, consistent with the intended local action of polyphenol-based topical formulations (Sun et al., 2022).

Table 4. The results of blood glucose analysis using one-way ANOVA

Groups (n=4)	Mean±SD	P-value
K1	94.75±11.70	0.716
K2	99.75±27.10	
PCG0	102.50±12.18	
PCG2	94.75±6.85	
PCG4.5	97.00±10.42	
PCG7	86.50±8.70	

3.5 NO level analysis

The nitrite ($NaNO_2$) calibration curve showed excellent linearity (y = 0.0017x + 0.0475; R^2 = 0.999), supporting the analytical validity of Griess-based nitric oxide (NO) estimation expressed as nitrite. Mean nitrite concentrations varied numerically among groups (K1 ≈ 56, K2 ≈ 49, PCG0 ≈ 66, PCG2 ≈ 40, PCG4.5 ≈ 46, PCG7 ≈ 44 µM); however, one-way ANOVA demonstrated no statistically significant differences (p = 0.611) (Figure 6).

The substantial overlap of group means and error bars suggests small between-group effect sizes with wide confidence intervals, which is expected given the limited sample size (n = 4 per group) and reduces the precision of intergroup comparisons. Methodologically, the Griess assay quantifies nitrite but does not capture nitrate without a reduction step, potentially underestimating total NO metabolites (NOx) (Miranda et al., 2001). In addition, nitrite stability can be influenced by sample processing and storage conditions, affecting analytical sensitivity (Bellavia et al., 2015). Biologically, NO levels in the IMQ-induced psoriasis model are temporally dynamic and not consistently elevated, which may further attenuate detectable differences at single time points (Köhler et al., 2024). Collectively, these factors indicate that nonsignificant findings should be interpreted cautiously, and future studies incorporating total NOx measurement and repeated sampling are warranted.

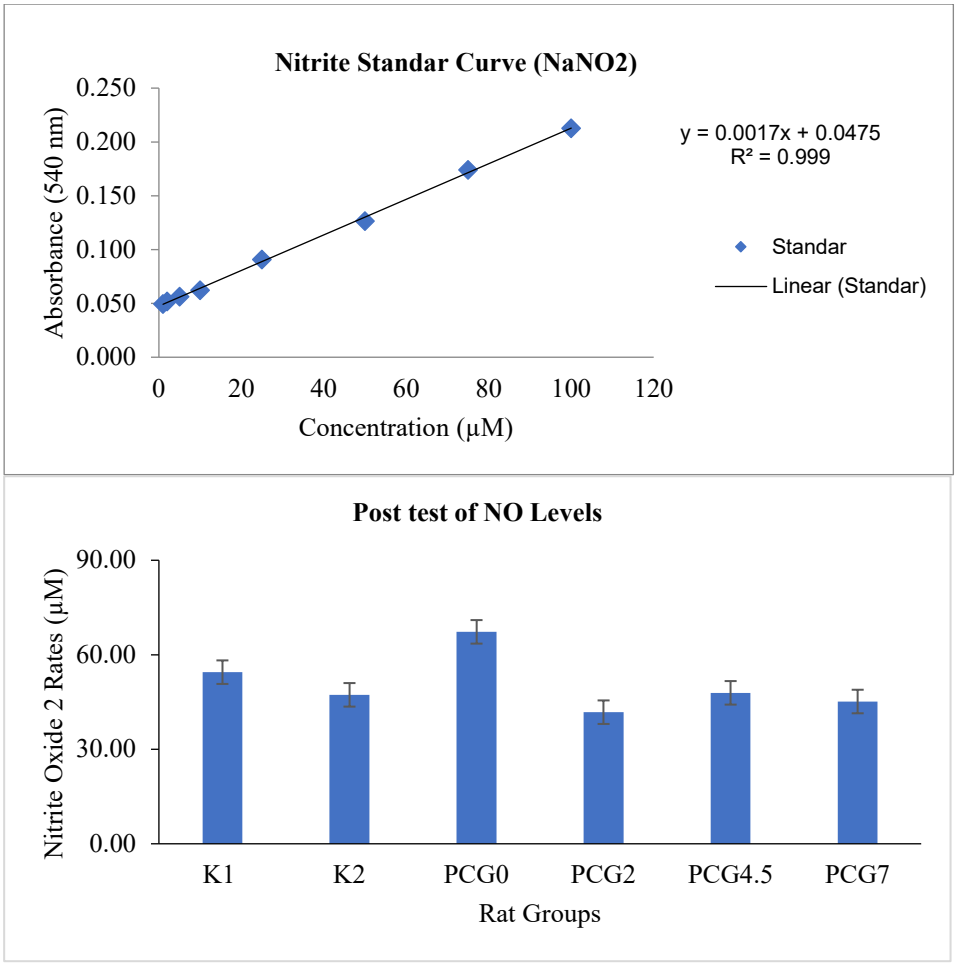

Figure 6. Standard and post test result of NO levels analysis. There is no significant difference between groups based on one-way ANOVA test ($p>0.05$).

3.6 Histopathological analysis

Histopathological analysis revealed clear intergroup differences consistent with IMQ-induced psoriasiform pathology (Figure 7). The negative control (K1) displayed marked acanthosis, a hallmark of IMQ-driven epidermal hyperproliferation mediated through TLR7/IL-23/IL-17 signaling (Zhang et al., 2021). The vehicle group (PCG0) showed persistent hyperplasia with parakeratosis, indicating limited intrinsic anti-inflammatory activity of the base formulation. In contrast, PCG2 and PCG4.5 demonstrated substantial restoration of epidermal architecture with complete resolution of parakeratosis, reflecting effective normalization of keratinocyte differentiation and reduced inflammatory drive.

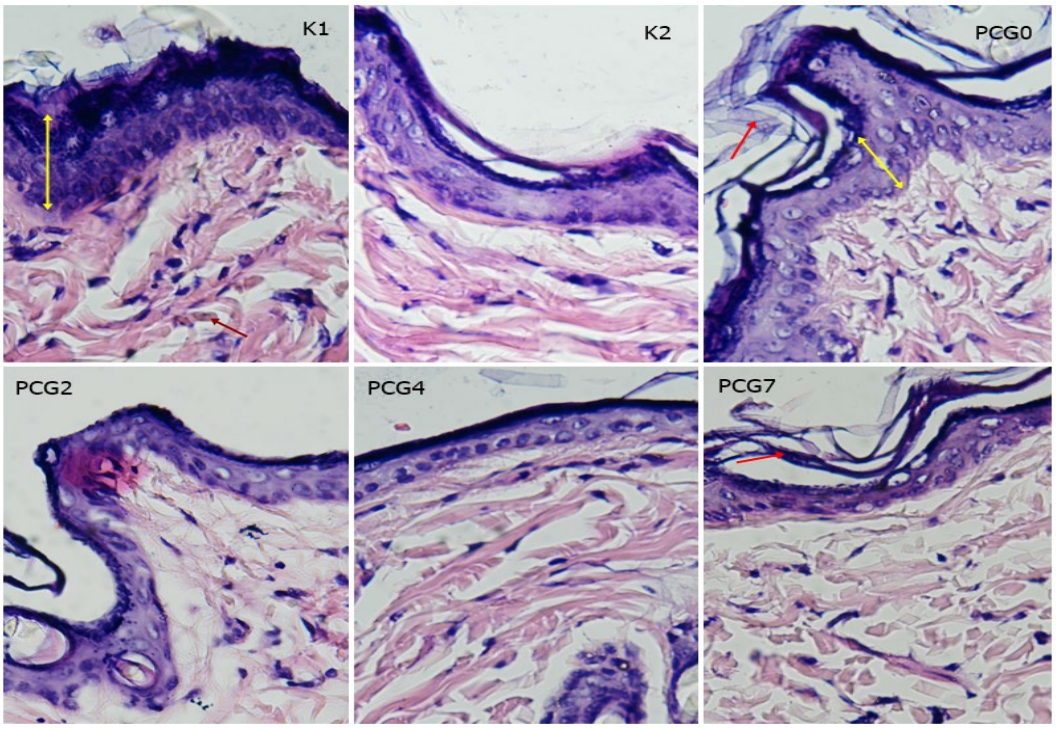

Figure 7. Histopathological examination of dorsal skin revealed marked epidermal hyperplasia in K1, partial improvement in K2, persistent parakeratosis in PCG0, normalization of epidermal architecture in PCG2–PCG4, and reduced hyperplasia with residual parakeratosis in PCG7 (40× magnification)

Although PCG7 produced the greatest reduction in epidermal thickness, residual parakeratosis suggests incomplete terminal differentiation at the highest extract concentration. Similar concentration-dependent histological responses have been reported for polyphenol-based interventions in IMQ models, where optimal efficacy occurs within a moderate dosing range rather than at maximal exposure (Chen et al., 2017; Mihu et al., 2021). It should be noted that these interpretations are based on qualitative morphological observations, as formal quantitative histomorphometric analysis was not performed, representing a limitation of the study and warranting cautious interpretation of treatment-related differences.

4. Conclusions

Topical *U. gambir* creams were successfully formulated and remained physically stable for 14 days. In the IMQ model, mid-dose formulations (2-4.5%) produced significant PASI reductions by days 8-10, accompanied by visible lesion improvement and histological normalization of epidermal structure. Systemic safety was supported by unchanged blood glucose and NO levels. However, the small sample size and short observation period limit statistical power and mechanistic interpretation. Future studies should incorporate larger cohorts, extended treatment durations, and molecular analyses to clarify long-term efficacy and underlying anti-psoriatic mechanisms.

5. Acknowledgements

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6. Authors' Contributions

Khoirul Rista Abidin contributed to the study conception and design, supervised the overall in vivo experimentation, and was responsible for data presentation and analysis. Abdurrafi Maududi Dermawan and Fath Dwisari were involved in the formulation of the *U. gambir* cream. Ariffialdi Nurhidayattulloh contributed to the extraction process. Febrina Siregar assisted in laboratory work related to the cream formulation, while Oktaviria supported the characterization analysis of the formulation. Suchi assisted in the PASI scoring analysis. Hernyati Prasetyaningsih contributed to the implementation of blood glucose analysis. Melly Indriani, Adnan Pramudyo, and Shofia assisted in conducting NO level measurements. Firda Aulia Putri contributed to the histopathological analysis.

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7. Conflicts of Interest

The authors declare no competing financial or personal interests that could have influenced the work reported in this submitted manuscript.

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