

ORIGINAL

## From Leaf to Relief: *Basella alba* Ethanolic Extract Alleviates Psoriasis-Like Skin Inflammation in BALB/c Mice

### De la hoja al alivio: el extracto etanólico de *Basella alba* alivia la inflamación de la piel similar a la psoriasis en ratones BALB/c

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**Cite as:** Oktavriana T, Kariosentono H, Purwanto B, Widyaningsih V. From Leaf to Relief: *Basella alba* Ethanolic Extract Alleviates Psoriasis-Like Skin Inflammation in BALB/c Mice. *Salud, Ciencia y Tecnología*. 2025; 5:2246. <https://doi.org/10.56294/saludcyt20252246>

Submitted: 23-03-2025

Revised: 19-07-2025

Accepted: 18-10-2025

Published: 19-10-2025

Editor: Prof. Dr. William Castillo-González 

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#### ABSTRACT

**Introduction:** psoriasis is a chronic inflammatory skin disorder that can be challenging to manage due to adverse effects linked to long-term treatment. As a result, alternative therapeutic options are being investigated. *Basella alba* exhibits anti-inflammatory and antioxidant activities, indicating its potential as a therapeutic agent for the management of psoriasis.

**Objective:** to investigate the antipsoriatic effect of *Basella alba* as an anti-inflammatory and antioxidant targeting the serum level of Tumor Necrosis Factor (TNF)- $\alpha$ , Malondialdehyde (MDA) and also the severity of psoriasis.

**Method:** psoriasis-like lesions were induced in thirty-six male BALB/c mice using 5 % imiquimod (IMQ) cream. The Balb/c mice were assigned to six groups: G1 (normal control), G2 (psoriasis control, IMQ only), G3 (IMQ + methotrexate 1 mg/kgBW/day), G4 (IMQ + *Basella alba* extract [BAE] 250 mg/kgBW/day), G5 (IMQ + BAE 500 mg/kgBW/day), and G6 (IMQ + BAE 250 mg/kgBW/day plus methotrexate). Serum TNF- $\alpha$ , MDA, and modified PASI scores were measured at baseline and after 14 days of treatment.

**Results:** IMQ application increased TNF- $\alpha$ , MDA, and PASI scores. Treatment with *Basella alba* reduced these markers. The most prominent effects were observed in the combination therapy group, followed by the high-dose extract group. Serum TNF- $\alpha$  levels decreased by 55,8 % in the G6 group and by 51,8 % in the G5 group. Serum MDA levels declined by 85,4 % in the G6 group and by 78,7 % in the G5 group.

**Conclusion:** *Basella alba* extract demonstrated significant anti-psoriatic activity by reducing inflammation and oxidative stress. These findings support its potential use as a monotherapy at 500 mg/kg BW/day or as an adjunct to methotrexate in a lower dose.

**Keywords:** *Basella Alba*; Psoriasis; Imiquimod; Balb/C Mice; TNF-A; MDA.

#### RESUMEN

**Introducción:** la psoriasis es un trastorno inflamatorio crónico de la piel que puede ser difícil de manejar debido a los efectos adversos relacionados con el tratamiento a largo plazo. Como resultado, se están investigando opciones terapéuticas alternativas. *Basella alba* exhibe actividades antiinflamatorias y antioxidantes, lo que indica su potencial como agente terapéutico para el manejo de la psoriasis.

**Objetivo:** investigar el efecto antipsoriásico de *Basella alba* como antiinflamatorio y antioxidante dirigido al nivel sérico de factor de necrosis tumoral (TNF)- $\alpha$ , malondealdehído (MDA) y también a la gravedad de la psoriasis.

**Método:** se indujeron lesiones similares a la psoriasis en treinta y seis ratones machos BALB/c utilizando crema de imiquimod (IMQ) al 5 %. Los ratones Balb/c fueron asignados a seis grupos: G1 (control normal), G2 (control de la psoriasis, IMQ solamente), G3 (IMQ + metotrexato 1 mg/kgBW/día), G4 (IMQ + extracto de *Basella alba* [BAE] 250 mg/kgBW/día), G5 (IMQ + BAE 500 mg/kgBW/día) y G6 (IMQ + BAE 250 mg/kgBW/día más metotrexato). Se midieron las puntuaciones séricas de TNF- $\alpha$ , MDA y PASI modificado al inicio y después de 14 días de tratamiento.

**Resultados:** la aplicación de IMQ aumentó las puntuaciones TNF- $\alpha$ , MDA y PASI. El tratamiento con *Basella alba* redujo estos marcadores. Los efectos más destacados se observaron en el grupo de terapia combinada, seguido por el grupo de extracto de dosis alta. Los niveles séricos de TNF- $\alpha$  disminuyeron en un 55,8 % en el grupo G6 y en un 51,8 % en el grupo G5. Los niveles séricos de MDA disminuyeron en un 85,4 % en el grupo G6 y en un 78,7 % en el grupo G5.

**Conclusión:** el extracto de *Basella alba* demostró una actividad antipsoriásica significativa al reducir la inflamación y el estrés oxidativo. Estos hallazgos apoyan su uso potencial como monoterapia a 500 mg/kg de peso corporal/día o como complemento del metotrexato en una dosis más baja.

**Palabras clave:** *Basella Alba*; Psoriasis; Imiquimod; Ratones Balb/C TNF-A; MDA.

## INTRODUCTION

Psoriasis is a chronic inflammatory disease characterized by recurrent and persistent symptoms over a long period.<sup>(1)</sup> The clinical manifestations of psoriasis include erythematous plaques, silvery-white scales, roughness, and thickness.<sup>(2,3)</sup> According to the most recent Global Burden of Disease Study 2021, approximately 43 million people are living with psoriasis globally.<sup>(4)</sup> The worldwide age-standardized incidence rate of psoriasis is 57,8 new cases per 100 000 people.<sup>(5)</sup> The prevalence of psoriasis is predicted have an increase alongside the effectiveness of treatment and systemic comorbidities.<sup>(6)</sup>

Psoriasis is a complex, multifactorial disease involving genetic predisposition, immune dysregulation, environmental triggers, and lifestyle factors.<sup>(7)</sup> Its pathogenesis is characterized by hyperproliferation and abnormal differentiation of keratinocytes, immune cell infiltration, and increased angiogenesis.<sup>(8)</sup> Central to psoriasis inflammation is the activation of the NF- $\kappa$ B pathway, with downstream cytokines such as IL-23 and IL-17 serving as primary mediators of the inflammatory response.<sup>(9)</sup> Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a key inflammatory biomarker, orchestrating cell proliferation, neovascularization, immune cell migration, and chronicity of the disease.<sup>(10,11)</sup> Oxidative stress, marked by increased reactive oxygen species (ROS) and elevated malondialdehyde (MDA) levels, further contributes to tissue damage and amplifies inflammatory signaling in psoriasis.<sup>(12)</sup>

The advancement of safe and effective alternative or adjunct therapies is essential, since conventional psoriasis treatments continue to encounter challenges, including an increased risk of adverse effects, infections, and drug resistance due to prolonged use.<sup>(13)</sup> Herbal medicine has the potential to be a relatively safe and easily available alternative therapy technique for psoriasis.<sup>(2,13,14)</sup> Several medicinal plants' active substances have been shown to affect the balance of regulatory T cells (Treg) and Th17, proliferation, differentiation, inflammation, and oxidative stress.<sup>(15)</sup> Complementary and alternative medicine, including underexplored plants such as *Basella alba*, has been highlighted for its potential in psoriasis therapy.<sup>(16)</sup>

*Basella alba* originates from Indonesia, naturally growing in the tropical regions of Asia and Africa and is commonly used in traditional medicine to treat a variety of ailments in India and China.<sup>(13,15)</sup> *Basella* sp. is a potential drug due to its secondary metabolic content, including acacetin, rutin, betacyanin, saponins, kaempferol, and ferulic acid. These chemicals possess antioxidant, anti-inflammatory, antiproliferative, and antiangiogenic properties.<sup>(17)</sup> The oral use of *Basella alba* extracts for dermatological conditions and its antioxidant rich profile has already been reviewed in detail.<sup>(18)</sup> Previous studies have shown that *Basella alba* extract has multiple properties, such as antioxidant and anticancer properties,<sup>(19)</sup> diuretic and sedative properties,<sup>(20)</sup> and anti-atherosclerotic properties.<sup>(21)</sup> Previous comprehensive network pharmacology study has identified multiple bioactive compounds in *Basella alba* with predicted anti-psoriatic potential by targeting key inflammatory and oxidative pathways relevant to psoriasis pathogenesis.<sup>(22)</sup>

Although *Basella alba* has demonstrated anti-inflammatory and antioxidant effects relevant to psoriasis, its precise mechanism of action within this context remains insufficiently elucidated. Recent in silico and network pharmacology analyses suggest that bioactive phytochemicals from *Basella alba* may exert antipsoriatic effects by binding to and inhibiting TNF- $\alpha$ , as well as modulating apoptosis, oxidative stress, and key inflammatory pathways.<sup>(22,23)</sup> Evidence from similar studies supports the potential for *Basella alba* to impact immune and redox signaling, but further experimental validation is necessary to substantiate these pathways.<sup>(22,23)</sup> Therefore, this study aims to determine the overall antipsoriatic efficacy of *Basella alba* ethanolic leaf extract, both alone

and in combination with methotrexate, in an established mice model of imiquimod-induced psoriasis. The primary objective is to assess its impact on clinical severity, inflammatory and oxidative stress markers, and histopathology, thereby providing robust preclinical data to support *Basella alba* as a potential adjunct or alternative psoriasis therapy.

## METHOD

### Type of Study

This study was designed as an experimental, non-observational (in vivo, laboratory-based) randomized controlled study to analyze the antipsoriatic and antioxidant efficacy of *Basella alba* ethanolic leaf extract, both individually and in combination with methotrexate, in a mice model of imiquimod-induced psoriasis.

### Universe and Sample

Fresh leaves of *Basella alba* were collected from the cultivation of *Basella alba* plants developed in Dusun II, Gatak, Sukoharjo, Central Java, Indonesia in collaboration with the Agribusiness Vocational School of Universitas Sebelas Maret. The authentication of the *Basella alba* plant was conducted by the Center for Research and Development of Medicinal Plants and Traditional Medicine in Tawangmangu, Karanganyar, Central Java, Indonesia. The test report was identified with the reference TL.02.04/D.XI.5/16536.455/2023 and it belongs to the Basellaceae family, species *Basella alba*, and also known as *Basella oleracea* Alef.

The Pharmacy Centre Laboratory of Universitas Setia Budi, Surakarta, prepared *Basella alba* leaf extract and tested its stability. The leaves were washed, chopped, dried at 40°C, ground into simplicia powder, and sieved through a 40 mesh. The sieved simplicia was weighed and stored in a dry container. Two doses of *Basella alba* ethanolic extract (BAE) test material suspension were prepared. The initial dose (250 mg/kgBW) was administered as a 1-gram solid suspension in a 0,5 % NaCMC solution. The subsequent dose (500 mg/kgBW) was administered as a 2-gram solid suspension in a 0,5 % NaCMC solution. To determine the BAE with a dose of 250 mg/kgBW, the following calculation was performed:  $250 \text{ mg}/1000 \text{ grams/kgBW} = 1 \text{ mg}/4 \text{ grams}$ . Subsequently, 0,5 ml of sterile aquadest was added as a solvent and administered to mice using a probe. Similarly, to calculate the BAE with a dose of 500 mg/kgBW, the following calculation was performed:  $500 \text{ mg}/1000 \text{ grams/kgBW} = 1 \text{ mg}/2 \text{ grams}$ . Subsequently, 0,5 ml of sterile aquadest was added as a solvent and administered to mice using a tube. Meanwhile, the calculation of methotrexate (Ebewe®) dosage is 1 mg/kgBW. A methotrexate tablet preparation of 2,5 mg has an effective dose of 1 mg/kgBW in mice. If a mouse weighs 20-25 grams, its body weight is 0,025 kg. The mouse's stomach holds 0,5 ml, so  $2,5 \text{ mg} \times 0,025 = 0,0625 \text{ mg}/0,5 \text{ ml}$ .

The universe comprised male BALB/c mice (*Mus musculus*), 11 weeks old, weighing  $20 \pm 5 \text{ g}$ , obtained from Universitas Gadjah Mada's animal facility. The mice were fed a commercial diet, water ad libitum and divided into 6 groups of six each. The animals were kept properly in polypropylene cages under standard laboratory conditions (12/12hr light/dark cycle at  $25 \pm 5^\circ\text{C}$ ). This study was conducted at Laboratory of the Centre for Food and Nutrition Studies, House of Experimental Rats CFNS of Universitas Gadjah Mada. After depilating their backs with Veet® depilatory cream, mice were given 62,5 mg of imiquimod (5 %) cream (Aldara®) daily, this caused an inflammatory lesion resembling plaque psoriasis. The reliability of the imiquimod-induced psoriasis mouse model has been confirmed in previous studies.<sup>24</sup> The animal subject divided by randomization into six groups ( $n = 6$  per group): normal control (G1), negative control (IMQ-induced; G2), methotrexate only (G3), BAE at 250 mg/kg BW (G4), BAE at 500 mg/kg BW (G5), and the combination of methotrexate plus 250 mg/kg BW of BAE(G6).

Following group allocation, experimental induction of psoriasis-like skin lesions was performed by applying 62,5 mg of imiquimod cream (5 %) topically to the shaved dorsal area once daily for seven consecutive days, except for the normal control group. On day 8 (pre-test), measurements of serum TNF- $\alpha$  and MDA levels, as well as modified PASI scores, were conducted for all animals. The intervention phase then commenced, with each group receiving its respective oral treatment (methotrexate, BAE, or combination therapy) for 14 days. On day 22 (post-test), TNF- $\alpha$ , MDA, and modified PASI scores were reevaluated, followed by dorsal skin biopsies for histopathological analysis. Figure 1 provides a schematic overview of the experimental timeline, group assignments, induction, interventions, and sampling points, illustrating the workflow from initial induction through intervention to data collection and statistical analysis.

### Variables

The main independent variable in this study was the treatment assignment, consisting of the following groups: IMQ-only (negative control), methotrexate, BAE at 250 mg/kg, BAE at 500 mg/kg, and combination therapy (methotrexate plus BAE 250 mg/kg). The selection of 250 mg/kg and 500 mg/kg doses for BAE was based on several established pharmacological principles and safety considerations.<sup>(25)</sup> The dependent variables included serum TNF- $\alpha$  and MDA levels, the severity of disease as assessed by the modified Psoriasis Area and Severity Index (PASI) score, and histopathological findings of the affected skin.

### Data collection and processing

Blood sampling were conducted twice with a 2-week interval: first on the 8th day after psoriasis appears before treatment, and second on the 22nd day after 14 days of treatment. On the 8th day, modified PASI scores and blood samples were collected from all mice in both control and treatment groups. Blood collection involves holding the mice at the nape and back with the left thumb and forefinger. Using the right hand, hold a glass pipette at a 45-degree angle in the orbital sinus region. Insert the pipette until it penetrates the skin. Tilt the mice to collect the dripping blood in a tube. This method allows repeated collections at 1-week intervals with volumes of around 0,25 ml per mice. Before collection, the mice were anesthetized intramuscularly with ketamine at a dose of 60 mg/kgBW. On the 22nd day, modified PASI scores and blood samples were again collected followed by termination of the animals. Post-treatment blood samples undergo ELISA examination for TNF- $\alpha$  and MDA levels. Commercial ELISA kits for TNF- $\alpha$  and MDA were obtained from Wuhan Fine Biothech Co., Ltd.

The PASI is a modified human grading system derived from the psoriasis area severity index (PASI). It serves as a quantitative indicator of the degree of inflammation during the application process. The PASI comprises three components: thickness, erythema, and scaling, each rated on a scale of 0 to 4. Asymptomatic individuals receive a score of 0, while mild cases are scored 1, moderate cases are scored 2, severe cases are scored 3, and extremely severe cases are scored 4. The sum of these three items constitutes the total PASI score.<sup>(26)</sup>

After PASI scores were recorded, mice were sacrificed by injecting ketamine (100 mg/kgBW). Skin samples (0,5cm  $\times$  0,5cm) were immediately fixed in tissue fixative and stained with H&E. Histopathological examination of the skin tissue was performed at the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Sebelas Maret.

For statistical analysis, the SPSS version 24.0 software was used to analyze the data. The ANOVA test or Brown-Forsythe test was used to compare TNF- $\alpha$  and MDA levels among six mice groups. Mean and standard error of the means (SD) were calculated. An ANOVA and Dunnett's post hoc test with a p-value < 0,05 was assumed to indicate statistical significance. The Shapiro-Wilk test was used to check for data normality. Results are presented graphically as mean and standard deviation, with significance at p < 0,05.

### Ethical Standards

All experimental protocols adhered to the ARRIVE guidelines and the ethical standards for animal research. The procedures were reviewed and approved by the Research Ethics Commission of the Faculty of Veterinary Medicine, Universitas Gadjah Mada (approval number: 132/EC-FKH/int./2024). Efforts were made to minimize animal suffering, reduce animal use, and employ appropriate anesthesia and euthanasia techniques in line with institutional and national regulations.

## RESULTS

### Evaluation of TNF- $\alpha$ Levels in Balb/c Mice Model of Psoriasis

This study measured TNF- $\alpha$  levels in BALB/c mice with psoriasis at two time points: before and after therapy. Based on the measurement results, it was found that 5 % IMQ induction successfully induced psoriasis model mice. The effect of 5 % IMQ induction on TNF- $\alpha$  serum levels in BALB/c mice with psoriasis was analyzed using ANOVA with post hoc LSD. The comparison of each treatment yielded significantly different results, with a p-value of  $\leq 0,001$  (p<0,05). It showed that groups received 5 % IMQ had increased serum TNF- $\alpha$  levels (A) in psoriasis model mice. T). Based on table 1, the impact of BAE on serum TNF- $\alpha$  levels in the psoriasis model of BALB/c mice was evaluated using the Brown-Forsythe test, followed by the Dunnett T3 post hoc test with significant difference results with a p-value of  $\leq 0,001$  (p<0,05). The administration of BAE reduced TNF- $\alpha$  levels with the most significant effect observed at the G6 group followed by the G5 group. The treatment in the G6 group (methotrexate therapy 1 mg/kgBW and BAE 250 mg/kgBW) demonstrated the most significant effect in reducing TNF- $\alpha$ , as its average was closest to the G1 group. These results showed a significant difference with a p-value < 0,05.

Table 1. Comparison of TNF- $\alpha$  levels before and after treatment

| Group | n | TNF- $\alpha$ pre |      | TNF- $\alpha$ post |      | Delta | % Change | p-value |
|-------|---|-------------------|------|--------------------|------|-------|----------|---------|
|       |   | Mean              | SD   | Mean               | SD   |       |          |         |
| G1    | 6 | 5,83              | 0,13 | 5,99               | 0,16 | 0,16  | 2,7 %    | <0,001* |
| G2    | 6 | 14,11             | 0,28 | 14,31              | 0,24 | 0,20  | 1,4 %    | <0,001* |
| G3    | 6 | 14,46             | 0,19 | 7,68               | 0,37 | -6,78 | -46,9 %  | <0,001* |
| G4    | 6 | 14,38             | 0,3  | 8,16               | 0,23 | -6,22 | -43,3 %  | <0,001* |
| G5    | 6 | 14,34             | 0,19 | 6,91               | 0,15 | -7,43 | -51,8 %  | <0,001* |

|    |   |       |      |      |      |       |         |         |
|----|---|-------|------|------|------|-------|---------|---------|
| G6 | 6 | 14,28 | 0,13 | 6,31 | 0,13 | -7,97 | -55,8 % | <0,001* |
|----|---|-------|------|------|------|-------|---------|---------|

**Note:** The significance level is determined by a p-value < 0,05. Symbol \* refers to statistical significance. Abbreviation: SD, standard deviation. G1: normal control; G2: negative control (IMQ 5 %); G3: positive control 0,5 ml methotrexate dose 1 mg/kgBW/day; G4: 250 mg/kgBW of BAE; G5: 500 mg/kgBW of BAE; G6: therapy with methotrexate 1 mg/kgBW and 250 mg/kgBW of BAE

At baseline (A), all groups subjected to 5 % IMQ exposure (G2-G6) exhibited markedly elevated pretest TNF- $\alpha$  serum levels in comparison to the untreated normal control group (G1), confirming successful induction of systemic inflammation characteristic of psoriasis. Post-intervention analysis (B) showed that after treatment, TNF- $\alpha$  levels in groups treated with BAE (G3, G4, G5) and the combination therapy (G6) were significantly reduced compared to the psoriasis model group without intervention (G2). The greatest decrease was observed in the G6 group, indicating a synergistic or additive effect of methotrexate and BAE, as posttest TNF- $\alpha$  concentrations approached those in the healthy control. The higher doses of BAE (G5) were more effective than lower doses (G3, G4), demonstrating a dose-dependent anti-inflammatory response. This result supports the efficacy of BAE, especially in combination with standard therapy, in ameliorating systemic inflammation in the psoriasis mouse model, as evidenced by significant and graded reductions in serum TNF- $\alpha$  levels compared to untreated psoriasis controls.

The paired pretest and posttest analysis of BAE on TNF- $\alpha$  levels in BALB/c mice psoriasis model was conducted using the paired T-test, as the data were normally distributed (Shapiro-Wilk;  $p > 0,05$ ). Statistical results demonstrated a significant downward trend in serum TNF- $\alpha$  concentrations in all treatment groups except the negative control, with particularly marked reductions observed in groups receiving BAE and/or methotrexate therapy. The combination group (G6) had the steepest decrease, nearly matching the levels found in the normal controls (G1), whereas the negative control group (G2) showed minimal change after IMQ exposure alone.

Following treatment, the data indicate that the G6 group exhibited the most significant reduction in TNF- $\alpha$  at -55,8 %, followed by the G5 group at -51,8, confirming substantial anti-inflammatory effects of both BAE and methotrexate, especially when combined. Each intervention group achieved statistical significance ( $p$ -value < 0,05) in reducing TNF- $\alpha$  from pretest to posttest, underscoring the efficacy of the treatments. These findings showed that BAE, alone or in combination, effectively attenuates psoriasis-like skin inflammation in IMQ-induced mice, supporting its role in inhibiting inflammatory cell infiltration and improving disease phenotype.

#### Evaluation of MDA Levels in Balb/c Mice Psoriasis Model

In this study, the MDA levels in the serum of BALB/c mice psoriasis model were assessed twice, before (pretest) and after (posttest) the administration of therapy. The pretest was used to determine the effectiveness of the 5 % IMQ induction on BALB/c mice psoriasis model in increasing MDA levels in the IMQ groups before treatment, except for the normal control group (G1) as a comparison. The effect of 5 % IMQ induction on MDA levels in the serum of BALB/c mice psoriasis model was analysed using the Brown-Forsythe test followed by the Dunnett T3 post hoc test. The group treatments showed significant differences, with a  $p$ -value  $\leq 0,001$  ( $p < 0,05$ ). The IMQ group had increased MDA activity compared to the group without 5 % IMQ induction.

| Table 2. Comparison of MDA levels before and after treatment |   |         |      |          |      |        |          |         |
|--------------------------------------------------------------|---|---------|------|----------|------|--------|----------|---------|
| Group                                                        | n | MDA pre |      | MDA post |      | Delta  | % Change | p-value |
|                                                              |   | Mean    | SD   | Mean     | SD   |        |          |         |
| G1                                                           | 6 | 1,18    | 0,12 | 1,37     | 0,12 | 0,19   | 16,1 %   | <0,001* |
| G2                                                           | 6 | 12,81   | 0,37 | 13,13    | 0,32 | 0,32   | 2,5 %    | <0,001* |
| G3                                                           | 6 | 12,8    | 0,46 | 3,66     | 0,22 | -9,14  | -71,4 %  | <0,001* |
| G4                                                           | 6 | 12,82   | 0,62 | 4,07     | 0,34 | -8,75  | -68,3 %  | <0,001* |
| G5                                                           | 6 | 12,94   | 0,19 | 2,76     | 0,38 | -10,18 | -78,7 %  | <0,001* |
| G6                                                           | 6 | 13,05   | 0,23 | 1,9      | 0,15 | -11,15 | -85,4 %  | <0,001* |

**Note:** The significance level is determined by a p-value < 0,05. Symbol \* refers to statistical significance. Abbreviation: SD, standard deviation; G1: normal control; G2: negative control; G3: positive control 0,5 ml MTX 1 mg/kgBW/day; G4: *Basella alba* extract 250 mg/kgBW; G5: *Basella alba* extract 500 mg/kgBW; G6: therapy with methotrexate 1 mg/kgBW and 250 mg/kgBW of *Basella alba* extract

Based on table 2, the serum MDA levels in BALB/c mice psoriasis models were generally elevated in groups receiving 5 % IMQ induction. IMQ groups showed a significant increase in serum MDA levels in psoriasis model

mice ( $p < 0,05$ ). The development of the psoriasis model mice was successful, as evidenced by the rise in serum MDA levels. There was a reduction in MDA serum level after BAE treatment. It is known that the comparison of each treatment yielded significantly different results simultaneously with a p-value of  $\leq 0,001$  ( $p < 0,05$ ), where it is known that the treatment in the G3 group (methotrexate therapy 1 mg/kg body weight and BAE 250 mg/kg body weight) had the most effect in reducing MDA levels because it had the average closest to the G1 group while the treatment that had the least effect in reducing MDA was the G4 group. Statistical tests showed significant differences in MDA levels before and after therapy for each group ( $p$ -value  $< 0,05$ ). Based on this, the G6 group showed the best results in reducing MDA (-85,4 %), levels, followed by G5 (78,7 %) then G3 (71,4 %). These findings demonstrate that BAE exhibits dose-dependent antioxidant activity in mitigating oxidative stress in IMQ-induced psoriasis, with combination therapy yielding the most robust suppression of lipid peroxidation markers.

According to the description above, the group administered BAE can reduce MDA levels in the serum of psoriasis model mice. *Basella alba* leaf extract reduced MDA levels in IMQ-induced psoriasis-like mice and efficiently modulated the oxidative or antioxidative equilibrium, achieving a more favorable physiological balance. Based on the measurement results, it can be concluded that BAE has a significant effect in reducing MDA levels. The paired pretest and posttest analysis of BAE administration on MDA levels in the serum of BALB/c mice psoriasis model induced by 5 % IMQ demonstrates the therapeutic potential of this natural compound in mitigating oxidative stress.

Following treatment administration, the results demonstrate substantial reductions in MDA levels across all intervention groups, with the combination therapy (G6) achieving the most pronounced decrease from 13,05 to 1,9 nmol/mL, representing an 85,4 % reduction in lipid peroxidation markers. The high-dose BAE group (G5) showed a 78,7 % reduction, while the methotrexate monotherapy group (G3) achieved a 71,4 % decrease, indicating dose-dependent antioxidant efficacy of the plant extract. Notably, the negative control group (G2) maintained persistently elevated MDA levels throughout the study period, confirming sustained oxidative stress in untreated psoriatic inflammation, while the normal control group (G1) remained consistently low, validating the experimental model. These findings underscore the potent antioxidant capacity of BAE in restoring oxidative balance and suggest its therapeutic utility as an adjuvant treatment for inflammatory skin disorders characterized by heightened oxidative stress.

### Modified PASI Score Assessment

In this study, the modified PASI Score assessment of BALB/c mice psoriasis model was assessed twice: before and after therapy. The pretest determined the effectiveness of 5 % IMQ induction on the G2, G3, G4, G5, and G6 groups modified PASI Scores before treatment, except for the normal control group (G1).

The impact of 5 % IMQ induction on modified PASI scores in a BALB/c mice psoriasis model was evaluated using the Kruskal-Wallis test, followed by the post hoc Dunn test. The comparison of each treatment produced significantly different outcomes, with a p-value of  $\leq 0,001$  ( $p < 0,05$ ). The group treated with 5 % IMQ exhibited an increase in the modified PASI score compared to the group without 5 % IMQ induction (G1).

The results show that PASI score of BALB/c mice with a psoriasis model was higher in the group that received 5 % IMQ induction. The subsequent post hoc table offers a restricted perspective on the comparison between each group. It is known that in general, the group given 5 % IMQ induction experienced an increase in PASI scores in the psoriasis model mice.

This is evidenced by the fact that the group induced with the IMQ groups showed a significant difference compared to the group without 5 % IMQ induction with a p-value  $< 0,05$ . Based on the measurement results, it was found that 5 % IMQ induction successfully induced psoriasis model mice. The effect of BAE on PASI score in a psoriasis model was analysed using the Kruskal-Wallis test followed by the post hoc Dunn Test.

Based on table 3, it is known that the group given BAE was able to reduce the PASI score in the psoriasis model mice. The post hoc analysis shows significant differences between the treatment groups and the negative control group (G2) with  $p < 0,05$ . The G6 group showed the best results in reducing PASI scores, followed by G5 and G3. Compared to the normal group G1; the PASI score of G3, G5, and G6 did not show significant differences ( $p > 0,05$ ), indicating that these treatments can achieve normal PASI scores. Therefore, BAE effectively reduces PASI scores, with the G6 group showing the best results.

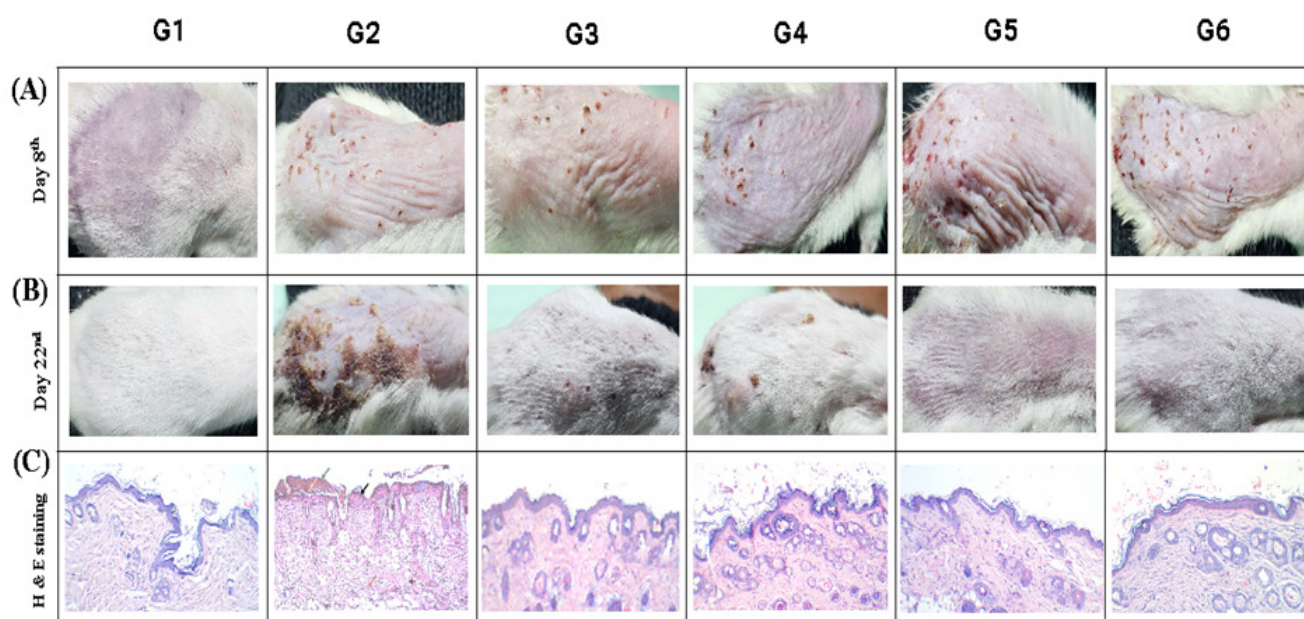
The paired pretest and posttest were analysed using the Wilcoxon rank-sum test due to non-normal data distribution (Shapiro-Wilk;  $p < 0,05$ ). The results show that the G6 group showed the highest reduction in PASI, which was 100,0 %, followed by G5 (-97,8 %) and G3 (-74,6 %), and the least reduction in PASI was in the G2 group (-13,9 %). The statistical test results for each treatment group obtained a p-value  $< 0,05$ , indicating a significant difference in the modified PASI scores before and after treatment in modified PASI scores before and after treatment ( $p$ -value  $> 0,05$ ).

Table 3. Comparison of Modified PASI Score before and after Treatment

| Group | n | PASI pre |      | PASI post |      | Delta | % Change | p-value |
|-------|---|----------|------|-----------|------|-------|----------|---------|
|       |   | Mean     | SD   | Mean      | SD   |       |          |         |
| G1    | 6 | 0,00     | 0,00 | 0,00      | 0,00 | 0,00  | 0,0 %    | 1,000   |
| G2    | 6 | 9,17     | 1,17 | 11,67     | 0,52 | 2,50  | 27,3 %   | 0,027*  |
| G3    | 6 | 9,17     | 2,14 | 2,33      | 2,25 | -6,84 | -74,6 %  | 0,027*  |
| G4    | 6 | 9,67     | 1,63 | 8,33      | 1,63 | -1,34 | -13,9 %  | 0,234   |
| G5    | 6 | 7,67     | 0,82 | 0,17      | 0,41 | -7,50 | -97,8 %  | 0,024*  |
| G6    | 6 | 9,67     | 1,03 | 0,00      | 0,00 | -9,67 | -100,0 % | 0,026*  |

**Note:** The significance level is determined by a p-value < 0,05. Symbol \* refers to statistical significance. Abbreviation: SD, standard deviation; G1: normal control; G2: negative control; G3: positive control 0,5 ml MTX 1 mg/kgBW/day; G4: *Basella alba* extract 250 mg/kgBW; G5: *Basella alba* extract 500 mg/kgBW; G6: therapy with methotrexate 1 mg/kgBW and 250 mg/kgBW of *Basella alba* extract

During our experiments, the skin condition of mice in the control group exhibited no significant alterations, as indicated by the PASI score results, and the PASI score always remained 0. Scales and erythema were observed on the dorsal epidermis of mice in the remaining five groups beginning on the third day. The extent of skin injury progressively worsened as the modeling time was prolonged. The IMQ group exhibited the most severe degree of skin damage and the highest PASI score. The psoriasis symptoms of the mice in the drug administration group were alleviated, and the PASI score was reduced, in comparison to the IMQ groups as shown in figure 1.



**Figure 1.** The clinical representation of psoriasis on the dorsal skin of a mice (A) PASI score assessment on day 8. (B) PASI score assessment on day 22 after 14 days treatment. (C) Histopathological findings of mice tissue sections: hematoxylin-eosin staining (H&E staining). G1: normal control; G2: negative control (IMQ 5 %); G3: positive control 0,5 ml methotrexate dose 1 mg/kgBW/day); G4: 250 mg/kgBW of BAE; G5: 500 mg/kgBW of BAE; G6: therapy with methotrexate 1 mg/kgBW and 250 mg/kgBW of BAE

Overall, these findings demonstrate that topical IMQ application successfully induced psoriasiform skin inflammation, as evidenced by significantly elevated modified PASI scores in the G2 group compared to normal controls. Treatment with BAE, both alone and in combination with methotrexate, effectively ameliorated disease severity, with the greatest improvement observed in G6, whose post-treatment PASI scores returned to baseline levels equivalent to G1. The dose-dependent efficacy of BAE was apparent, as higher extract doses (G5) outperformed lower doses (G4) and methotrexate monotherapy (G3), and the statistical analyses confirmed that G3, G5, and G6 achieved non-inferior PASI outcomes relative to healthy controls ( $p > 0,05$ ). These

collective results underscore the potent therapeutic potential of BAE in modulating psoriatic pathology and restoring skin homeostasis in IMQ-induced BALB/c mice.

## DISCUSSION

Psoriasis remains a major global dermatological burden due to its persistent inflammation and high relapse rates, prompting an ongoing search for novel interventions that offer both safety and efficacy.<sup>(27,28)</sup> The use of botanicals with multitarget bioactivity is of increasing clinical interest, especially those such as *Basella alba*, which is abundant in bioactive flavonoids and phenolic compounds with documented anti-inflammatory and antioxidant effects.<sup>(19,22,29)</sup> This study explored the value of BAE as an adjunct or alternative therapy in an imiquimod-induced mice model of psoriasis, combining in silico predictions of compound-target interactions with in vivo efficacy testing. Notably, treatment with *Basella alba*, particularly when combined with methotrexate, achieved profound reductions in both inflammatory and oxidative markers alongside normalization of clinical skin scores, positioning this extract as a promising candidate for integrated anti-psoriatic strategies.

The effects of ethanolic extract of *Basella alba* on TNF- $\alpha$ , MDA, and PASI scores in BALB/c mice psoriasis models were generally elevated in groups receiving 5 % IMQ induction, consistent with IMQ's activity to modify the immune response. Imiquimod treatment reliably induced psoriasis-like skin inflammation in BALB/c mice, evidenced by marked elevations in TNF- $\alpha$ , MDA, and PASI scores compared to controls, consistent with canonical response profiles for this well-characterized model. These findings are in accordance with previous characterizations of IMQ-induced mice psoriasis, including the histopathological and cytokine changes.<sup>(24)</sup> IMQ stimulates cytokine production, especially interferon, and acts as a synthetic TLR 7/8 agonist, inducing skin inflammation resembling psoriasis through the IL-23/IL-17 pathway, as assessed by histopathology<sup>(26,30)</sup> and also clinical manifestations of modified PASI scores.<sup>(26)</sup>

Building on model validation, the therapeutic efficacy of BAE was demonstrated by significant suppression of both inflammatory and oxidative markers in treated groups. In particular, the combination of methotrexate and BAE 250 mg/kgBW produced a 55,8 % decrease in TNF- $\alpha$  ( $p < 0,001$ ) and an 85,4 % reduction in MDA ( $p < 0,001$ ) compared to negative controls. Such improvements translated to normalized PASI scores, corroborating meaningful clinical benefit in this experimental setting. These observations reflect a therapeutic synergy, where improvements in molecular and clinical parameters occurred concurrently. TNF- $\alpha$  reduction seems linked to improved psoriasis clinical manifestations. In psoriasis, TNF- $\alpha$  mediates the inflammatory cascade, triggering cell growth, neovascularization, apoptosis, and immune cell aggregation at the lesion site.<sup>(10)</sup> The results of this study align with the theory that the increased expression of TLR 7/8 in keratinocytes bound to IMQ will activate the MyD88 adaptor protein,<sup>(31)</sup> leading to the phosphorylation of IRAK4, IRAK1, and TRAF6, and the phosphorylation of I $\kappa$ B in the mitochondria, then activating NF- $\kappa$ B and resulting in the transcription of pro-inflammatory cytokine genes TNF- $\alpha$ , IL-6, and TGF- $\beta$ 1 in the nucleus.<sup>(7)</sup> TNF- $\alpha$  suppresses T-reg cells, prevents the hyperproliferation of pathogenic T cells and IL-17-producing cells, and correlates positively with the increase in PASI scores in psoriasis patients. Therefore, TNF- $\alpha$  can predict psoriasis exacerbation.<sup>(32)</sup>

Our experimental results strongly connect with prior in silico predictions made by our group and others, which identified acacetin, kaempferol, and beta-carotene among *Basella alba*'s most promising anti-psoriatic compounds.<sup>(22)</sup> Docking simulations previously showed these compounds have high affinity for TNF- $\alpha$ , hinting at their direct role in pathway modulation.<sup>(22)</sup> Acacetin and kaempferol, well-recognized for their anti-inflammatory and antioxidant capacities, including inhibition of NF- $\kappa$ B and NLRP3 inflammasome pathways, likely contributed substantially to the anti-psoriatic effects observed in vivo.<sup>(33-35)</sup> Beta-carotene may further enhance these effects via radical scavenging and modulation of nuclear receptor signaling. Beta-carotene is a potent antioxidant with strong peroxyl radical scavenging activity and can modulate nuclear receptor pathways, particularly by influencing retinoid X receptor signaling, thereby contributing to both cellular oxidative balance and gene regulation relevant to psoriatic inflammation.<sup>(36,37)</sup> The observed synergy with methotrexate also supports a cooperative, multi-target pharmacology, as demonstrated by the improved biomarker and PASI outcomes in the combination group.<sup>(38,39)</sup> This current study brings novel insight on an alternative therapy for psoriasis in order to minimize the side effects of conventional therapy. This study has proven consistently that *Basella alba* extract produces effective therapeutic effect on severe psoriasis. It is a potent phytopharmaceutical agent for treating severe psoriasis. It is a promising therapy for psoriatic patient who are intolerant to standard therapy.

## Study Limitations

This study acknowledges several limitations that warrant consideration. It is important to note that this research represents the initial investigation into the effects of oral *Basella alba* formulations on mice with psoriasis. Therefore, further studies are necessary to validate and extend these findings. Additionally, no specific pharmacological experiments were conducted to optimize systemic dosage forms, determine appropriate dosages, or quantitatively assess the active constituents within the *Basella alba* formulations. These factors

are critical for evaluating therapeutic potential and establishing standardized protocols for the use of *Basella alba* in oral therapies. Addressing these limitations in future research will contribute to a deeper understanding of the therapeutic properties of oral *Basella alba* formulations and provide valuable guidance for developing effective, evidence-based treatment strategies for psoriasis.

## CONCLUSIONS

This study provides preclinical evidence supporting the antipsoriatic potential of *Basella alba* ethanolic leaf extract through dual mechanisms involving suppression of systemic inflammation and mitigation of oxidative stress in an imiquimod-induced mice model. The therapeutic efficacy demonstrated by *Basella alba*, particularly when administered at higher doses or combined with conventional methotrexate therapy, suggests its viability as either a standalone botanical intervention or as an adjunctive treatment strategy for inflammatory dermatoses. The observed restoration of clinical severity parameters to physiological baseline underscores the pharmacological relevance of *Basella alba*'s bioactive constituents, which align with traditional ethnomedicinal applications for inflammatory conditions. These findings reinforce the broader potential of plant-derived therapeutics in addressing the limitations of current psoriasis management, including safety concerns and drug resistance associated with prolonged conventional therapy. The multitarget pharmacology of *Basella alba* compounds positions this botanical as a promising candidate for integrated anti-inflammatory and antioxidant therapeutic approaches. Future translational research should focus on isolating and characterizing specific active constituents, establishing comprehensive dose-response relationships, evaluating long-term safety profiles, and conducting controlled human trials to determine clinical applicability and optimal therapeutic protocols for psoriasis and related inflammatory skin disorders.

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## ACKNOWLEDGEMENTS

We sincerely thank all contributors to this manuscript. The authors appreciate the research facilities provided by the Pharmacy Centre Laboratory of Universitas Setia Budi, Surakarta, the Laboratory of the Center for Food and Nutrition Studies, Universitas Gadjah Mada, and the support from the Doctoral Program of Medical Sciences, Universitas Sebelas Maret. We also thank Agribusiness Vocational School of Universitas Sebelas Maret for providing *Basella alba* plants and the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Sebelas Maret.

## FUNDING

None.

## CONFLICTS OF INTEREST

None.

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