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Research article

# Evaluation of clinical severity and histopathological changes on 2,4- dinitrochlorobenzene-induced mouse model of atopic dermatitis treated with *Artocarpus heterophyllus* leaves extract

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## Abstract

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease and one of the most common dermatologic conditions, with a global prevalence of 15-20% in children and 1-10% in adults. It imposes significant psychosocial burdens on affected individuals. This study aimed to investigate the anti-atopic potential of the ethanol extract of jackfruit (*Artocarpus heterophyllus*) leaves in a DNCB-induced mouse model of AD by evaluating the clinical skin scores, ear pinnae thickness, spleen and lymph node weights, epidermal thickness, and mast cell infiltration. Twenty-five mice were randomly assigned to five groups: negative control (AD induction with 1% followed by 0.5% DNCB on the ear pinna), normal control (without induction), treatment group 1 (AD + 100 mg/kg BW extract), treatment group 2 (AD + 200 mg/kg BW extract), and treatment group 3 (AD + 400 mg/kg BW extract). Extracts were administered orally for 15 consecutive days. Clinical severity was evaluated using SCORAD and spleen, lymph node weights and body weights, while histopathological parameters used epidermal and dermal thicknesses and mast cell counts. Data were analyzed using one-way ANOVA followed by Dunnett's post hoc test and Kruskal-Wallis with Dunn's post hoc test. Significant improvements ($p<0.05$) were observed in all treatment groups compared with the negative control, as indicated by reduced SCORAD scores, lower spleen and lymph node weights, thinner epidermis and dermis, and lower mast cell counts. No significant differences ($p>0.05$) were detected among treatment groups. These findings demonstrate that ethanol extract of jackfruit leaves exhibits anti-atopic activity at oral doses ranging from 100 to 400 mg/Kg BW in a DNCB-induced mouse model of AD.

**Keywords**: Atopic dermatitis, *A. heterophylus* leaves extract, DNCB-induced, Skin inflammation

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# INTRODUCTION

Atopic dermatitis (AD), a chronic inflammatory skin disease characterized by pruritus, xerosis, and recurrent eczematous lesions, remains one of the most prevalent dermatological conditions globally, affecting approximately 15-20% of children and 1-10% of adults. Its epidemiological trajectory over recent decades represents a substantial global healthcare challenge (Nutten, 2015). Whereas historical prevalence data from the 1970s-1980s documented rates of approximately 3-5% in developed nations, the current prevalence peak reflects a two- to threefold increase in incidence over a few decades. This temporal pattern suggests the important contribution of gene-environment interactions rather than genetic factors alone. This epidemiological shift temporally coincides with industrialization, dietary modernization, and increased exposure to allergens and irritants. However, despite this critical public health transition, clinical management remains reactive and symptomatic rather than mechanistically targeted (Nutten, 2015; Langan et al., 2020). The disease also imposes substantial non-cutaneous morbidity that extends beyond conventional dermatological descriptions. The pruritus-driven itch-scratch cycle causes chronic sleep fragmentation, averaging 1.5-3.5 hours of sleep loss per night in severe cases, which can independently drive cognitive dysfunction, mood disorders, and occupational disability. This psychosocial burden, documented in the Global Burden of Disease Study 2019, rivals or exceeds that of diabetes and hypertension in terms of quality-of-life metrics, positioning AD not merely as a cosmetic concern but as a systemic inflammatory disease with broad psychosocial consequences (GBD 2019 Diseases and Injuries Collaborators, 2020).

The pathophysiological architecture of AD exemplifies immunological complexity. The disease emerges from the interplay of three major defects: (1) inherent epidermal barrier weakness, including mutations in filaggrin and tight junction proteins; (2) dysregulated innate immunity, characterized by reduced antimicrobial peptide production and impaired interferon responses; and (3) skewed adaptive immunity, characterized by Th2-predominance with elevated interleukin levels (IL-4, IL-5, and IL-13) and increased IgE production. Together, these abnormalities create a perfect environment for allergen penetration, microbial overgrowth, and perpetual inflammation (Weidinger and Novak, 2016).

The predominant immune dysregulation involves Th2-cell hyperactivation, which simultaneously suppresses Th1/Th17 differentiation and promotes B-cell production of high-affinity IgE antibodies. These pathogenic mechanisms trigger a cascade of inflammatory responses. IgE-mediated mast cell degranulation releases histamine (acute pruritus), tryptase (keratinocyte activation), IL-4 and IL-13 (Th2 amplification), and TNF-α (chronic inflammation) (Thomas, 2008). Concomitantly, barrier impairment is exacerbated by Th2-derived cytokines that downregulate filaggrin, loricrin, and involucrin, further compromising the epidermal seal. This process creates the characteristic 'vicious cycle,' in which barrier defects permit allergen and pathogen entry, thereby triggering immune activation that further perpetuates barrier damage (Kobayashi et al., 2015; Nakatsuji et al., 2018).

Experimental animal models have been instrumental in elucidating AD pathophysiology and evaluating potential therapeutic interventions. Among these, the 2,4-dinitrochlorobenzene (DNCB)-induced dermatitis model in mice is widely recognized for reproducing the histopathological and immunological hallmarks of human AD, including epidermal hyperplasia, increased dermal infiltration of immune cells, elevated serum immunoglobulin E (IgE) levels, and enhanced mast cell activation (Riedl et al., 2023; Ye et al., 2025). This model induces a type IV hypersensitivity response that closely mimics the chronic inflammatory environment characteristic of human AD, making it a reliable and reproducible system for the preclinical evaluation of therapeutic agents (Hu and Zhou, 2021). The DNCB model facilitates investigation of the anti-inflammatory and immunomodulatory properties of natural and synthetic compounds under

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controlled conditions and enables a comprehensive assessment of clinical, immunological, and histological parameters.

In recent years, natural products rich in antioxidants and anti-inflammatory phytochemicals have gained considerable attention as promising candidates for AD therapy, particularly as adjunctive or complementary treatments. This growing interest is driven by the limitations of conventional therapeutics, including the potential adverse effects associated with long-term corticosteroid use and the rising health care costs associated with biologic agents. Jackfruit (*A. heterophyllus*) leaves have been reported to contain bioactive compounds, including flavonoids and phenolics, which exhibit potent antioxidant, anti-inflammatory, and immunomodulatory activities (Liu et al., 2020; Moke et al., 2017). These bioactive components play an important role in maintaining physiological balance and have long been used in traditional medicine to treat various skin disorders, infections, and metabolic disturbances (Prakash et al., 2009; Manjare et al., 2020; Murlistyarini and Yuniasih, 2023).

Ethnopharmacological evidence demonstrates that *A. heterophyllus* leaves and other parts of the plant have long been utilized in traditional medicine systems, particularly in Southeast Asian countries, for the treatment of various skin disorders, infections, fever, and metabolic disturbances, reflecting centuries of empirical clinical use (Prakash et al., 2009; Murlistyarini and Yuniasih, 2023). Recent phytochemical characterization has identified over 50 distinct bioactive compounds in *A. heterophyllus* leaf extracts with documented anti-inflammatory and antioxidant potentials (Wei et al., 2005a; Liu et al., 2020). These bioactive constituents comprise various phytochemical classes, including phytosterols, anthraquinones, terpenoids, phenols, glycosides, diterpenes, and flavonoids, with cycloartocarpin, artocarpin, artocarpanone, and cyanomaclurin among the identified compounds, suggesting their potential relevance as therapeutic candidates for AD (Chan et al., 2018; Murlistyarini et al., 2023). However, evaluating the full spectrum of potential adverse effects associated with *A. heterophyllus* leaf extract remains essential prior to clinical translation. *In vivo* subchronic toxicity evaluation of a 70% ethanol leaf extract in Wistar rats revealed no mortality or neurobehavioral alterations. However, high-dose administration (1000 mg/kg) induced a significant, albeit reversible, reduction in body weight, which was attributed to phenolic inhibition of pancreatic lipase (Ardiani et al., 2025; Rupiani et al., 2025). Furthermore, *in vitro* toxicological assays have highlighted notable preparation-dependent adverse outcomes, including significant DNA damage ($p < 0.05$) in human peripheral blood mononuclear cells exposed to ethanol extracts (Noikotr et al., 2018), cytotoxicity in *Allium cepa* root cells at 15–30 mg/mL (da Rocha et al., 2026), and erythrocyte membrane toxicity at 200 µg/mL (De Sousa et al., 2020). Despite this ethnopharmacological precedent and accumulating biochemical evidence, systematic *in vivo* evaluation of the anti-atopic potential remains scarce. Published studies documenting *A. heterophyllus* efficacy in validated disease models are limited, and a comprehensive multi-parameter assessment of both clinical severity and histopathological indices, essential for mechanistic understanding, remains lacking.

Therefore, this study aimed to investigate the anti-atopic potential of the ethanol extract of *A. heterophyllus* leaves in a DNCB-induced mouse model of AD. The therapeutic effects were assessed using clinical scoring based on the SCORAD (Scoring Atopic Dermatitis) index, an internationally recognized and validated tool for assessing AD severity in both murine models and human disease (Oranje et al., 2007). Additional clinical parameters, including pinna thickness and macroscopic skin lesion severity, were also evaluated. Histopathological parameters, including epidermal and dermal thickness, as well as mast cell counts assessed by toluidine blue staining, were comprehensively analyzed. Systemic immune activation was assessed by measuring spleen and lymph node weights as indicators of lymphoid organ hyperplasia. The findings are expected to provide robust scientific evidence supporting the potential use of *A. heterophyllus* leaf extract as a natural therapeutic

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or adjunctive agent for managing atopic dermatitis, particularly in resource-limited settings or as a complement to conventional therapies.

# MATERIALS AND METHODS

## Ethical Approval

This study was conducted under strict compliance with international standards for animal research ethics. The Institutional Animal Care and Use Committee (IACUC) at the Faculty of Veterinary Medicine, Universitas Gadjah Mada, approved all animal-handling procedures under approval number 117/EC-FKH/Int./2024. All procedures adhered to the ARRIVE 2.0 (Animal Research: Reporting of *In Vivo* Experiments) guidelines to ensure transparency and reproducibility of animal research. The committee verified compliance with the 3Rs principles (Replacement, Reduction, and Refinement) throughout the experimental design.

## Extract preparation

The extraction of *A. heterophyllus* leaves in this study was carried out using a maceration method with 70% ethanol as the solvent (Yang et al., 2019). The dried leaves were ground into a fine powder before extraction. The powdered leaves were then macerated three times in 70% ethanol at 25°C for 72 hours with occasional stirring. The resulting extract was filtered through filter paper, and the filtrate was concentrated using a rotary evaporator (0010003324-RV 3, IKA, China) to obtain a thick ethanolic extract.

## Laboratory animals and AD induction

Atopic dermatitis (AD) was experimentally induced in male BALB/c mice aged 4–6 weeks, weighing 20–25 g, using topical application of 2,4-dinitrochlorobenzene (DNCB) (#237329-10G, SIGMA MCLS, USA) on the ear pinna, following previously described methods with minor modifications (Hu and Zhou, 2021; Hwang et al., 2021; Min et al., 2023). The induction procedure consisted of two stages, which are a sensitization phase using 1% DNCB and a challenge phase using 0.5% DNCB.

For each application, 20 µL of the respective DNCB solution was carefully applied to the ear pinnae using a micropipette to ensure uniform coverage and complete contact with the skin. The sensitization phase was performed on days 1, 4, and 7 of the experimental periods. The challenge phase was conducted on days 14, 17, 19, 22, 24, 27, and 29, resulting in 7 DNCB challenges to induce chronic dermatitis-like lesions. Before the induction and treatment phases, all mice underwent a 7-day acclimatization period under standard laboratory conditions (22 ± 2°C, 50–60% relative humidity, and a 12-hour light/dark cycle), with ad libitum access to food and water (Hwang et al., 2021).

A total of 25 mice were randomly assigned into five experimental groups, each consisting of five animals: the normal control (N) group, which was not induced with DNCB and received no treatment; the negative control (AD) group, which was induced with DNCB and administered vehicle orally; and three treatment groups (T1, T2, and T3), which were induced with DNCB and administered ethanol extract of *A. heterophyllus* leaves at doses of 100, 200, and 400 mg/kg body weight (BW), respectively. The extract was administered orally once daily for 15 consecutive days, starting on day 15 and continuing until day 29 of the experimental period. At the end of the experimental day (day 29), all mice were euthanized by an overdose of a ketamine-xylazine cocktail via intramuscular injection.

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## Clinical skin score (dermatitis score) and ear pinna thickness

The clinical score was evaluated at the end of the experimental day using SCORAD. In brief, the overall dermatitis severity score was obtained by summing the individual scores assigned to six clinical signs: redness, swelling, crusting, scratch marks, skin thickening, and dryness. Each sign was scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The SCORAD assessment was performed by a double-blinded observer. Ear pinna thickness of all mice was also measured using a digital caliper (Taffware; Indonesia, YXB series). Measurements were obtained from each ear pinna by the same trained observer, who was blinded to the group assignment (Yang et al., 2019; Min et al., 2023).

## Tissue collection and histopathological analysis

On day 29, the mice were euthanized using an overdose of a ketamine-xylazine cocktail. Tissues were immediately harvested to minimize post-mortem autolytic changes. Spleen and cervical lymph nodes (left and right superficial cervical, mandibular, and submandibular nodes) were carefully isolated using sterile dissection. Tissues were gently blotted with sterile gauze to remove blood and immediately weighed using an analytical balance (Jeon et al., 2021). Skin samples from the challenged ear pinna, including the full thickness of the epidermis and dermis, were immediately fixed in 10% neutral buffered formalin (pH 7.0, buffered with sodium phosphate) for 24 hours at room temperature. Fixed tissues were then processed through a standard automated histology protocol.

Epidermal and dermal thickness were measured using computerized image analysis of hematoxylin and eosin (H&E)-stained sections (ScyTek Laboratories Inc., Utah, USA). Measurements were obtained from five non-overlapping, randomly selected fields of view at 200× magnification per animal to obtain robust mean values. Mast cells were identified using toluidine blue staining (SIGMA-ALDRICH #89640-5G). The total mast cell count per dermis was determined by counting all toluidine blue-positive cells visible in five non-overlapping dermal fields at 200× magnification (approximately 0.25 $mm^2$ per field) per animal. Positive cells were identified by their distinctive appearance, characterized by oval-to-round cell bodies with prominent granular cytoplasm that stained metachromatic (purple-blue). All image capture, measurement, and cell counting were performed by a double-blinded observer to minimize observer-dependent error (Wang et al., 2020).

## Statistical analysis

All data are presented as the mean ± standard deviation (mean ± SD). Data were visualized using GraphPad Prism 10 (GraphPad Software, Inc., La Jolla, CA), with bar graphs used for group comparisons and error bars representing ±SD. One-way analysis of variance (ANOVA) followed by Dunnett's post hoc test was used to evaluate differences in ear pinna thickness, epidermis and dermis thickness, spleen and lymph node weights, and mast cell count. SCORAD data were analyzed using the Kruskal–Wallis test followed by Dunn's post hoc analysis. All statistical tests employed a two-tailed significance level of $p=0.05$. Results with $p<0.05$ were considered statistically significant. In the figures, statistical significance was denoted as follows: *$p<0.05$, **$p<0.01$, ***$p<0.001$, and ****$p<0.0001$.

# RESULTS

## Effect on clinical skin score (SCORAD) and ear pinna thickness

Based on the SCORAD analysis, significant differences were observed among the experimental groups. The negative control group, which was induced

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with DNCB without any treatment, exhibited the highest SCORAD value (5.50 ± 0.55), indicating the most severe clinical manifestation of dermatitis. In contrast, the normal control group, which was not induced with DNCB, showed a score of 0.00 ± 0.00, reflecting the absence of dermatitis symptoms. Table 1 and Figure 1 summarize the effects of *A. heterophyllus* leaf extract on SCORAD values and ear pinnae thickness.

**Table 1** Ear pinna SCORAD and thickness

| Group | Ear Pinna SCORAD (Mean ± SD) | Ear Pinna Thickness (mm) (Mean ± SD) |
|---|---|---|
| **Negative control (AD)** | 5.50 ± 0.55[a] | 0.49 ± 0.05[a] |
| **Normal control (N)** | 0.00 ± 0.00[b] | 0.04 ± 0.01[c] |
| **AD + 100 mg/Kg BW Extract (T1)** | 3,67 ± 0.62[a] | 0.36 ± 0.07[b] |
| **AD + 200 mg/Kg BW Extract (T2)** | 2.00 ± 1.10[b] | 0.27 ± 0.05[b] |
| **AD + 400 mg/Kg BW Extract (T3)** | 1.33 ± 0.52[b] | 0.19 ± 0.02[b] |

Different superscripts ([a, b, c]) across groups indicate a significant difference ($p < 0.05$).

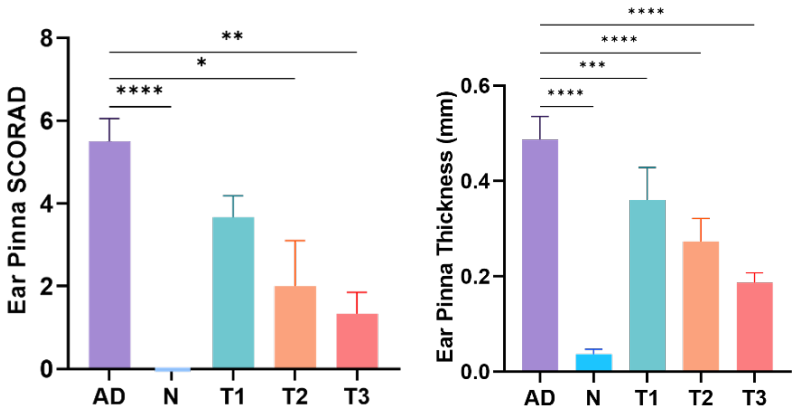



Figure 1 Effect of *A. heterophyllus* leaves extract on ear pinna SCORAD and ear pinna thickness. Values represent the mean ± SD. $p < 0.05$, $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to the negative control group.

Oral administration of *A. Heterophyllus* leaf ethanol extract markedly reduced SCORAD values compared with the negative control. The treatment groups showed a progressive improvement with increasing extract doses, with SCORAD values of 3.67 ± 0.62 in T1 (100 mg/kg BW), 2.00 ± 1.10 in T2 (200 mg/kg BW), and 1.33 ± 0.52 in T3 (400 mg/kg BW). Statistical analysis using the Kruskal–Wallis test followed by Dunn's post hoc test revealed significant differences between all treatment groups and the negative control ($p < 0.05$, $p < 0.01$, and $p < 0.0001$). In contrast, no significant differences were detected among the treatment groups. These findings indicate that *A. heterophyllus* leaf ethanol extract ameliorated the clinical severity of atopic dermatitis in DNCB-induced mice, with the highest dose (400 mg/kg BW) demonstrating the most pronounced improvement.

## Effect on the spleen, lymph node, and body weights

Measurements of spleen and lymph node weights are presented in Table 2, with the corresponding graphical data shown in Figure 2. The results showed that DNCB induction significantly increased spleen and lymph node weights in mice. The AD group had the highest spleen weight (0.5800 ± 0.1986 g), indicating systemic immune activation in response to chronic inflammation induced by DNCB exposure. In contrast, the N group had the lowest spleen weight (0.1848 ± 0.008497 g), consistent with normal physiological conditions in the absence of inflammatory stimuli. Administration of A. *heterophyllus* leaf extract to the treatment

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groups (T1, T2, and T3) significantly reduced spleen weight compared with the AD group, with values of 0.3405 ± 0.09747 grams (T1), 0.3275 ± 0.05118 grams (T2), and 0.3317 ± 0.1114 grams (T3), respectively.

**Table 2** Spleen, lymph node, and body weight

| Group | Spleen weight (gram) (Mean ± SD) | Lymph node weight (gram) (Mean ± SD) | Body weight (gram) (Mean ± SD) |
|---|---|---|---|
| **Negative control (AD)** | 0.58 ± 0.12[a] | 0.52 ± 0.25[a] | 38.25 ± 6.13[a] |
| **Normal control (N)** | 0.18 ± 0.01[b] | 0.08 ± 0.01[c] | 42.00 ± 0.00[a] |
| **AD + 100 mg/Kg BW Extract (T1)** | 0.34 ± 0.10[b] | 0.35 ± 0.11[ab] | 41.17 ± 2.48[a] |
| **AD + 200 mg/Kg BW Extract (T2)** | 0.33 ± 0.05[b] | 0.33 ± 0.07[b] | 37.67 ± 4.55[a] |
| **AD + 400 mg/Kg BW Extract (T3)** | 0.33 ± 0.11[b] | 0.29 ± 0.03[b] | 36.50 ± 5.05[a] |

Different superscripts ([a, b, c]) across groups indicate a significant difference ($p < 0.05$)

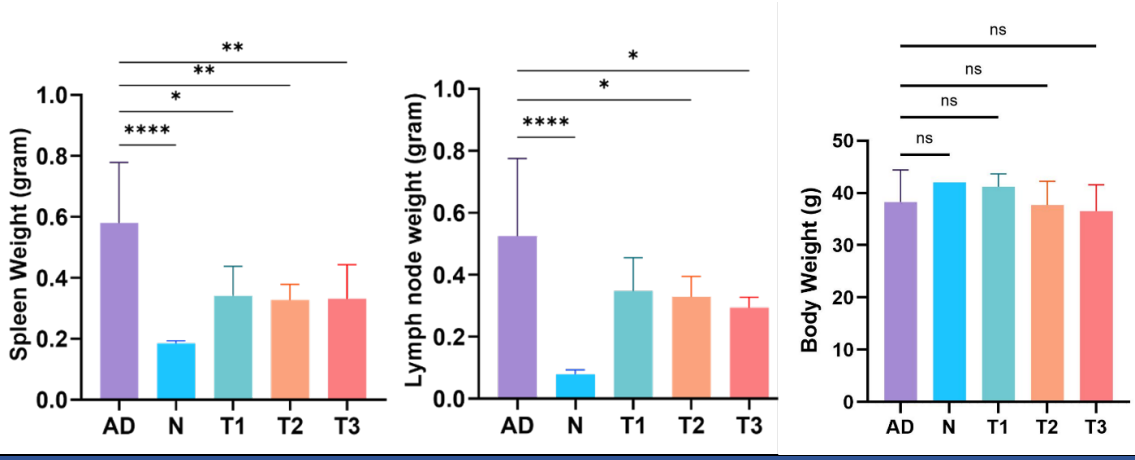



**Figure 2** Effect of *A. heterophyllus* leaves extract on spleen weight and lymph node weight. Values represent the mean ± SD. *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to the negative control group.

This reduction indicates that *A. heterophyllus* leaf extract has the potential to suppress splenic hyperplasia, which typically occurs in systemic inflammatory conditions. Final body weights at the time of organ collection were comparable among the experimental groups, with no significant differences observed (AD = 38.25 ± 6.131 g; N = 42.00 ± 0.000 g; T1 = 41.17 ± 2.483 g; T2 = 37.67 ± 4.546 g; T3 = 36.50 ± 5.050 g; $p > 0.05$). Therefore, differences in spleen and lymph node weights were unlikely to be confounded by differences in final body weight.

A similar pattern was also observed for lymph node weight. The AD group showed the highest value (0.5243 ± 0.2511 grams), indicating strong immune stimulation due to DNCB-induced dermatitis. Meanwhile, the N group had a very low lymph node weight (0.07900 ± 0.01424 g), which is within the normal physiological range. Administration of *A. heterophyllus* leaf extract to the treatment group reduced lymph node weight to 0.3482 ± 0.1065 grams (T1), 0.3287 ± 0.06591 grams (T2), and 0.2943 ± 0.03316 grams (T3). The research graph also shows significant differences between groups, confirming that *A. heterophyllus* leaf extract effectively reduces lymphoid organ enlargement.

## Effect on epidermis and dermis thickness

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The effect of *A. heterophyllus* leaf extract on the epidermis and dermis thickness is presented in Table 3, Figure 3, and Figure 4. Both parameters showed significant differences compared to the negative control group. Mice in the negative control group exhibited the greatest epidermal (67.44 ± 18.69 µm) and dermal (391.5 ± 92.85 µm) thicknesses, indicating marked epidermal hyperplasia and dermal inflammation following DNCB induction. In contrast, the non-induced normal control group showed the lowest epidermal (14.76 ± 2.44 µm) and dermal (79.00 ± 14.00 µm) thicknesses, consistent with normal skin histology.

**Table 3** Ear pinna epidermis and dermis thickness

| Group | Ear Pinna Epidermis thickness (µm) (Mean ± SD) | Ear Pinna Dermis thickness (µm) (Mean ± SD) |
|---|---|---|
| **Negative control (AD)** | 67.44 ± 18.69[a] | 391.50 ± 92.85[a] |
| **Normal control (N)** | 14.76 ± 2.44[c] | 79.00 ± 14.00[c] |
| **AD + 100 mg/Kg BW Extract (T1)** | 25.48 ± 6.51[b] | 184.70 ± 27.33[b] |
| **AD + 200 mg/Kg BW Extract (T2)** | 34.29 ± 6.95[b] | 185.20 ± 31.68[b] |
| **AD + 400 mg/Kg BW Extract (T3)** | 25.39 ± 3.15[b] | 234.20 ± 37.87[b] |

Different superscripts ([a, b, c]) across groups indicate a significant difference ($p < 0.05$)

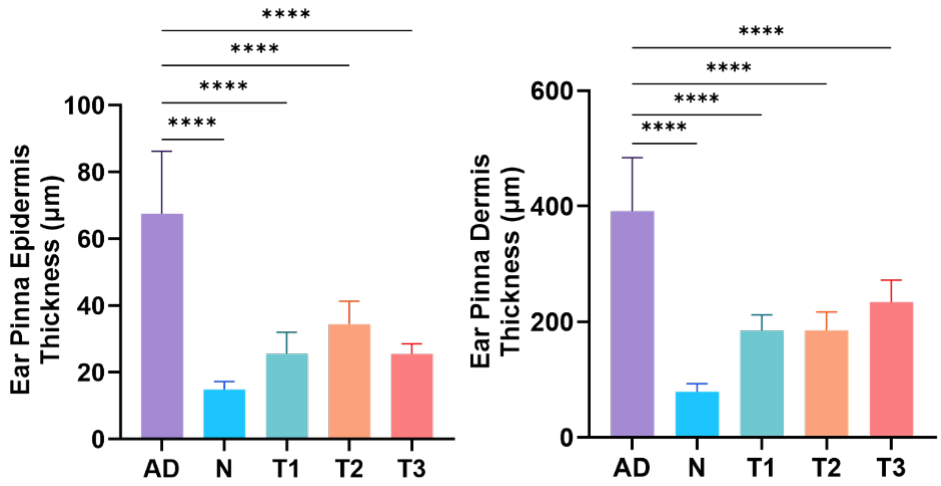



**Figure 3** Effect of *A. heterophyllus* leaves extract on ear pinna epidermis and dermis thickness. Values represent the mean ± SD. *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to the negative control group.

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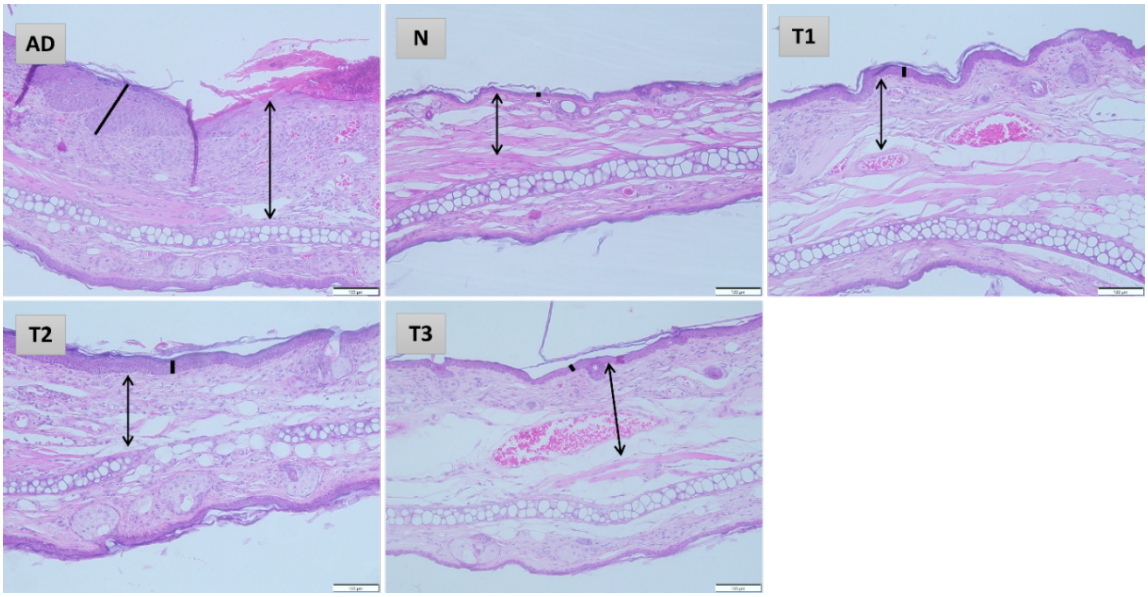



**Figure 4** Histomorphometry of ear pinna epidermis and dermis thickness. (AD) Negative control group; (N) Normal control group; (T1) AD + 100 mg/Kg BW Extract group; (T2) AD + 200 mg/Kg BW Extract group; (T3) AD + 400 mg/Kg BW Extract group. There was an increase in the thickness of the epidermis and dermis in the AD group compared to the N group. The administration of *A. heterophyllus* leaf extract to groups T1, T2, and T3 reduced epidermal and dermal thickness compared with the AD group. The thickness of the epidermis is indicated by a black line; the thickness of the dermis is indicated by a black double-headed arrow (Hematoxylin-Eosin staining, 200x, scale bar = 100 µm).

Treatment with *A. heterophyllus* leaf ethanol extract significantly reduced epidermal and dermal thickness compared with the negative control ($p < 0.0001$). The T1 (100 mg/kg BW), T2 (200 mg/kg BW), and T3 (400 mg/kg BW) groups exhibited epidermal thicknesses of 25.48 ± 6.51 µm, 34.29 ± 6.95 µm, and 25.39 ± 3.15 µm, respectively, and dermal thicknesses of 184.70 ± 27.33 µm, 185.20 ± 31.68 µm, and 234.20 ± 37.87 µm, respectively. Although no significant differences were observed among the treatment groups, all treatment groups showed substantial improvement compared with the negative control. These results suggest that oral administration of *A. heterophyllus* leaf ethanol extract effectively attenuated epidermal hyperplasia and dermal thickening associated with DNCB-induced atopic dermatitis.

## Effect on mast cell count

Quantitative and microscopic evaluations of mast cell infiltration following treatment with *A. heterophyllus* leaf ethanol extract are presented in Table 4, Table 5, Figure 5, and Figure 6. The AD group exhibited the highest mast cell count (45.25 ± 14.15), indicating intense inflammatory infiltration following DNCB induction. In contrast, the normal control group showed the lowest mast cell count (9.90 ± 5.50), reflecting normal skin histology without inflammation.

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**Table 4** Ear pinna mast cell count

| Group | Ear Pinna Mast Cell Count (Mean ± SD) |
|---|---|
| **Negative control (AD)** | 45.25 ± 14.15[a] |
| **Normal control (N)** | 9.90 ± 5.50[c] |
| **AD + 100 mg/Kg BW Extract (T1)** | 24.65 ± 5.97[b] |
| **AD + 200 mg/Kg BW Extract (T2)** | 20.58 ± 6.97[b] |
| **AD + 400 mg/Kg BW Extract (T3)** | 18.18 ± 5.98[b] |

Different superscripts ([a, b, c]) across groups indicate a significant difference ($p < 0.05$)

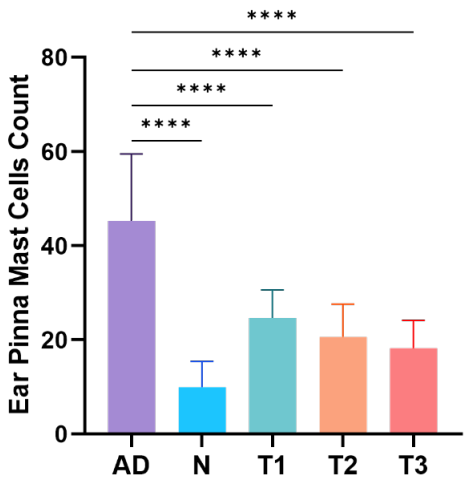



**Figure 5** Effect of *A. heterophyllus* leaves extract on mast cell count. Values represent the mean ± SD. *$p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$, **** $p < 0.0001$ compared to the negative control group.

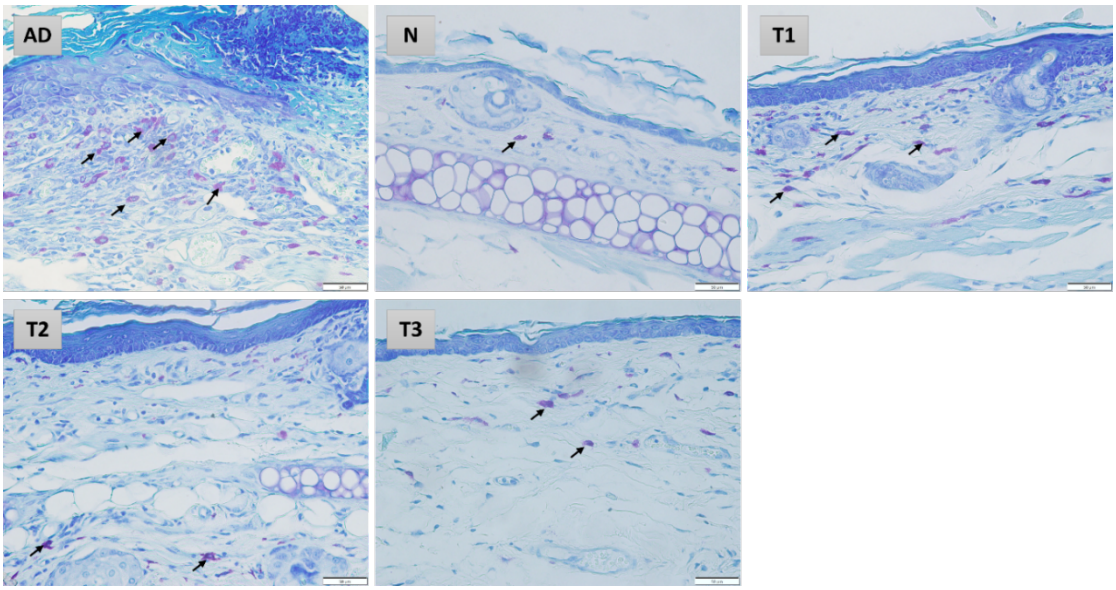



**Figure 6** Photomicrograph of mast cell count. (AD) Negative control group; (N) Normal control group; (T1) AD + 100 mg/Kg BW extract group; (T2) AD + 200 mg/Kg BW extract group; (T3) AD + 400 mg/Kg BW extract group. The highest mast cell count was found in the AD group. A decrease in mast cell count occurred in groups T1, T2, and T3. Mast cells are indicated by black arrows. (Toluidine blue staining, 400x, scale bar = 50 µm).

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Oral administration of *A. heterophyllus* leaf ethanol extract significantly reduced mast cell numbers compared with the negative control ($p < 0.0001$). Mast cell counts in the treatment groups were 24.65 ± 5.97 in T1 (100 mg/kg BW), 20.58 ± 6.97 in T2 (200 mg/kg BW), and 18.18 ± 5.98 in T3 (400 mg/kg BW). All treatment groups showed a marked reduction compared with the negative control. These results indicate that *A. heterophyllus* leaf ethanol extract effectively suppressed mast cell infiltration in DNCB-induced atopic dermatitis, suggesting its potential anti-inflammatory activity in modulating allergic skin responses.

# DISCUSSION

In this study, the ethanol extract of *A. Heterophyllus* leaves significantly improved both clinical and histopathological indices of atopic dermatitis (AD) in a DNCB-induced mouse model. Quantitative assessment revealed a marked reduction in the SCORAD index, a composite measure of AD severity, from 5.50 ± 0.55 in the negative control (AD) group to 3.67 ± 0.62, 2.00 ± 1.10, and 1.33 ± 0.52 in the T1, T2, and T3 treatment groups, respectively, indicating a trend toward greater alleviation of dermatitis symptoms with increasing doses. Histopathological analysis further demonstrated significant reductions in epidermal and dermal thickness in the treated groups. Mast cell counts also decreased following extract administration compared with the untreated AD group.

Collectively, these findings confirm that *A. heterophyll*us leaf extract may ameliorate both macroscopic and microscopic indicators of AD severity. The observed improvements are consistent with the established characteristics of the DNCB-induced AD model, which closely mimics several features of human AD, including epidermal hyperplasia, increased dermal thickness, elevated IgE levels, and enhanced mast cell infiltration (Riedl et al., 2023, 2024). However, the non-linear trend observed in pinna dermal thickness, specifically the shift from 184.7 ± 27.33 µm in T1 and 185.2 ± 31.68 in T2 to 234.2 ± 37.87 µm in T3, requires careful consideration regarding bioflavonoid pharmacodynamics. Plant extracts rich in bioactive flavonoids may display non-linear (biphasic) dose-response relationships. Although lower to moderate concentrations exert anti-inflammatory and antioxidant benefits, higher doses may undergo auto-oxidation, generating reactive oxygen species (ROS) and potentially triggering paradoxical pro-oxidant responses (Chiorcea-Paquim, 2023). This nonlinear pattern highlights the necessity of establishing a strict therapeutic window to ensure that increasing dosage do not exceed optimal concentrations into ranges that might attenuate peak anti-inflammatory efficacy.

The pathophysiology of AD is characterized by epidermal barrier dysfunction, immune dysregulation, particularly T-helper 2 (Th2)-skewed responses, and mast cell activation (Weidinger and Novak, 2016). Impairment of the skin barrier facilitates the penetration of allergens and microbes, thereby triggering local immune activation, mast cell degranulation, and cytokine release. These processes stimulate keratinocyte proliferation and dermal remodeling, resulting in increased epidermal and dermal thickness and elevated mast cell infiltration, features that are consistently observed in DNCB-induced dermatitis models (Riedl et al., 2023). In addition, exposure to DNCB is known to induce severe dermatitis through a type IV hypersensitivity mechanism involving T-cell activation, increased production of proinflammatory cytokines, and recruitment of inflammatory effector cells such as eosinophils and mast cells. Systemic manifestations include splenic and lymph node enlargement driven by the proliferation and activation of peripheral immune cells (Hu and Zhou, 2021). The observed decline in mast cell infiltration may represent an important mechanism responsible to the therapeutic effects of *A. heterophyllus* leaf extract. Mast cells are recognized as key contributors to AD pathogenesis because IgE-mediated activation through FcεRI induces the release of histamine, tryptase, and Th2-

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associated cytokines, including IL-4 and IL-13. These mediators exacerbate pruritus, promote keratinocyte dysfunction, and maintain chronic inflammatory responses. Thus, the reduction in mast cell presence within skin lesions may partially explain the improvements in disease severity and histological architecture recorded in the treated groups.

The results also showed that DNCB induction significantly increased spleen and lymph node weights in mice, indicating strong systemic immune activation in response to chronic inflammation. The AD group exhibited the highest spleen weight (0.5800 ± 0.1986 g), whereas the normal control group (N) showed the lowest spleen weight (0.1848 ± 0.008497 g), reflecting normal physiological conditions without inflammatory stimulation. A similar trend was observed in lymph node weight, with the AD group showing the highest value (0.5243 ± 0.2511 g), while the N group remained within the normal physiological range (0.07900 ± 0.01424 g). These findings are consistent with previous reports demonstrating that DNCB exposure promotes infiltration of mast cells, eosinophils, and inflammatory mediators within skin tissue (Jeon et al., 2021b). Administration of *A. heterophyllus* leaf extract at doses of 100, 200, and 400 mg/kg BW significantly reduced spleen weight, lymph node weight, epidermal and dermal thickness, and mast cell infiltration, indicating that the extract exerts both systemic and local immunomodulatory effects. Treatment with *A. heterophyllus* leaf extract reduced spleen weight to 0.3405 ± 0.09747 g (T1), 0.3275 ± 0.05118 g (T2), and 0.3317 ± 0.1114 g (T3), suggesting suppression of splenic hyperplasia, a common feature of systemic inflammatory responses. Likewise, lymph node weights decreased to 0.35 ± 0.11 g (T1), 0.33 ± 0.07 g (T2), and 0.29 ± 0.03 g (T3), confirming that the extract effectively reduced DNCB-induced enlargement of the lymphoid organs. The attenuation of lymphoid organ enlargement observed in the treated groups may indicate a lower degree of immune stimulation, suggesting that the extract can modulate inflammatory responses beyond the local skin environment. Similar effects have been described for other plant-derived anti-inflammatory compounds, which effectively reduced lymphoid organ hypertrophy and mast cell recruitment in experimental models of DNCB-induced dermatitis (Hong et al., 2020).

The anti-atopic activity observed in this study is explained by the previously reported phytochemical profile of *A. heterophyllus* leaves, which includes flavonoids, phenolics, prenylated chromones, and artocarpin. Studies have demonstrated that flavonoids isolated from *A. heterophyllus* possess anti-inflammatory properties, including inhibition of nitric oxide production and reduced secretion of inflammatory mediators (Wei et al., 2005b). Likewise, artocarpin, norartocarpetin, and other prenylated flavonoids have been reported to suppress ROS-induced activation of the NF-κB and MAPK pathways (Manjare et al., 2020; Yuniarti et al., 2025). Such activity may contribute to decreased oxidative stress–related inflammation and reduced mast cell degranulation through inhibition of ROS-mediated CaMKII activation, a mechanism that is recently recognized as important in allergic skin inflammation. The antioxidant activity of these phytochemicals may also support restoration of epidermal barrier integrity, consequently reducing allergen penetration and downstream immune responses. Furthermore, *A. heterophyllus*-derived phenolic compounds have been shown to modulate immune function by downregulating NF-κB signaling and decreasing the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 (Ranasinghe et al., 2019).

The protective effects of *A. heterophyllus* leaf extract against DNCB-induced dermatitis are likely mediated through multiple interconnected mechanisms, including mitigation of oxidative stress, downregulation of inflammatory signaling pathways, suppression of mast cell activity, modulation of immune responses, and enhancement of epidermal barrier integrity. Consistent with these actions, treated animals exhibited lower SCORAD scores, improved skin histomorphology, reduced mast cell accumulation, and diminished enlargement of lymphoid organs. These findings support the potential of *A. heterophyllus* leaf extract as a natural

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therapeutic option for the atopic dermatitis and allergic contact dermatitis (Moke et al., 2017; Murlistyarini and Yuniasih, 2023). Future research investigating specific molecular targets, cytokine networks, and optimized topical delivery systems will be important for facilitating its future application as a complementary therapy for inflammatory skin disorders.

## CONCLUSIONS

This study demonstrated that *A. heterophyllus* leaf extract significantly alleviated the clinical and histopathological manifestations of atopic dermatitis in a DNCB-induced mouse model. The extract effectively reduced SCORAD scores, ear pinna thickness, spleen and lymph node weights, epidermal and dermal thickness, and mast cell infiltration. However, the absence of a positive control group limits direct comparison of the extract's efficacy with established therapeutic agents. Further studies should incorporate an appropriate positive control, evaluate long-term safety and efficacy, and validate the underlying molecular mechanisms through cytokine profiling and gene expression analysis.

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## CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

**Citra Ayu Pramesti:** Conceptualization (Lead); Methodology (Lead); Supervision (Lead); Formal Analysis (Lead); Writing-Original Draft (Lead).
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**Retno Murwanti:** Resources (Lead); Conceptualization (Supporting); Writing-Review & Editing (Equal); Writing-Original Draft (Supporting).
**Aswin Rafif Khairullah:** Investigation (Supporting); Validation (Supporting).
**Rifaldi:** Investigation (Supporting); Validation (Supporting).
**Pratitis Setyo Wibowo:** Investigation (Lead); Formal Analysis (Supporting); Writing- Original Draft (Supporting).
**Salma Labibah:** Investigation (Supporting); Data Curation (Supporting).
**Muhammad Adnan Fauzi:** Investigation (Supporting); Data Curation (Supporting).
**Oktaviani Nisa Hanafiah:** Investigation (Supporting); Data Curation (Supporting).
**Yashinta Amperawati:** Investigation (Supporting); Data Curation (Supporting).

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