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*Research*

# A comparison of the Hematology Profiles from Preventive and Curative Tests on *Lissachatina fulica* Snail Mucin Cream for Atopic Dermatitis

**Atin Supiyani[1*], Wasmen Manalu[2], Lina Noviyanti Sutardi[3], Mawar Subangkit[4], Andriyanto[5]**

[1]Doctoral Program of Veterinary Biomedical Sciences, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[2]Division of Physiology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[3]Division of Veterinary Pharmacy, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[4]Division of Pathology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[5]Division of Pharmacology and Toxicology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
*Corresponding author: atinbiounj@gmail.com
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## ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Continuous use of topical NSAIDs in AD cases has been shown to cause adverse effects. *Lissachatina fulica* mucin (LFM) cream, a natural alternative, has been used for wound healing and can be used as a preventative or curative agent in AD. The objective of this study is to assess the efficacy of LFM cream, exploring its potential as a preventative and curative measure in AD. A total of 36 male BALB/c mice were divided into three cream dosage groups: 0%, 5%, and 10%. The two treatments were preventive and curative, and the two testing times were 0 and 5 days, with three replicates each. Mice were induced with atopic dermatitis by applying 1% DNCB to a 1x1 cm area on their dorsal area for seven days. The preventive group used LFM cream for seven days before DNCB, while the curative group used it after DNCB. Blood samples were collected on days 0 and 5 of the treatment period and analyzed using a hematology analyzer. The data were analyzed using a two-way ANOVA with GraphPad Prism 10, followed by Tukey's test at a 95% confidence level. The toxicity test confirmed that the LFM cream is non-toxic and safe for topical use. The DNCB compound 1% exhibited four main symptoms of atopic dermatitis: pruritus, erythema, excoriation, and lichenification. LFM cream was highly effective, significantly suppressing AD symptoms, with the ADSI score remaining below 2 ($p<0.05$). Specifically, the curative efficacy was demonstrated by a significant decrease in the ADSI score on day 5 ($p<0.05$). Hematological analysis revealed statistically significant differences ($p<0.05$) in the number of lymphocytes, neutrophils, and thrombocytes across groups. The LFM cream is effective and safe for preventative use and successfully treats acute AD at 5% concentration.

**Keywords:** atopic dermatitis, DNCB, hematology profile, mucin cream, *Lissachatina fulica*

## ABSTRAK

Dermatitis atopik (DA) merupakan penyakit kulit inflamasi kronis. Penggunaan topikal NSAID yang berkelanjutan pada kasus DA diketahui dapat menimbulkan efek samping. Krim lendir dari *Lissachatina fulica* (LFM), sebagai alternatif alami, telah digunakan untuk penyembuhan luka dan berpotensi menjadi agen preventif atau kuratif pada DA. Penelitian ini bertujuan untuk mengevaluasi efektivitas krim LFM sebagai tindakan preventif dan kuratif pada DA. Sebanyak 36 ekor mencit betina BALB/c dibagi menjadi tiga kelompok dosis krim: 0%, 5%, dan 10%. Dengan dua perlakuan, yaitu preventif dan kuratif, serta dua waktu pengujian, yaitu hari ke-0 dan ke-5, masing-masing dilakukan dengan tiga replikasi. DA diinduksi pada mencit dengan mengaplikasikan 1% DNCB pada area seluas 1x1 cm di punggung mereka selama tujuh hari. Kelompok preventif menggunakan krim LFM selama tujuh hari sebelum aplikasi DNCB, sedangkan kelompok kuratif menggunakannya setelah aplikasi DNCB. Sampel darah dikumpulkan pada hari ke-0 dan ke- 5 perlakuan dan dianalisis menggunakan *hematology analyzer*. Data dianalisis menggunakan *two-way* ANOVA dengan GraphPad Prism 10, diikuti uji Tukey dengan tingkat kepercayaan 95%. Uji toksisitas mengonfirmasi bahwa krim LFM tidak toksik dan aman untuk penggunaan topikal. Senyawa DNCB 1% menunjukkan empat gejala utama dermatitis atopik: pruritus, eritema, ekskoriasi, dan likenifikasi. Krim LFM sangat efektif dalam mengurangi gejala DA secara signifikan, dengan skor ADSI tetap di bawah 2 ($p<0.05$). Khususnya, efikasi kuratif ditunjukkan oleh penurunan signifikan dalam skor ADSI pada hari ke-5 ($p<0.05$). Analisis hematologi menunjukkan perbedaan signifikan secara statistik ($p<0.05$) dalam jumlah limfosit, neutrofil, dan trombosit di antara kelompok. Krim LFM efektif dan aman untuk penggunaan preventif serta berhasil mengobati DA akut pada konsentrasi 5%.

**Kata kunci:** dermatitis atopic, DNCB, profil hematologi, krim lendir, *Lissachatina fulica*

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects both children and adults, and its treatment can be challenging. The disease present with cutaneous symptoms during the acute stage, including pruritus, erythema, edema, vesicles, and ulcers. However, in the chronic stage, these symptoms are characterized by the presence of lichenification, a condition characterized by thickened, toughened skin due to increased collagen production (Ariwangsa *et al*., 2019). Atopic dermatitis, a prevalent dermatological condition, has been documented as the fifth most prevalent skin disease in children, with a reported prevalence reported between 10%-20% in pediatric populations. This prevalence decreases notably in adults, ranging from 1% to 3% (Abdi, 2020).

The therapeutic approach for atopic dermatitis necessitates the application of topical medications to mitigate symptoms such as pruritus, reduce inflammation, and enhance the skin barrier's functionality. Current recommendations for the treatment of AD include the utilization of various topical therapies such as emollients, antihistamines, calcineurin inhibitors, glucocorticoids, phototherapy, antimicrobials, and antiseptics (Fishbein *et al*., 2020). However, the efficacy of antihistamines in addressing pruritus remains controversial (Cai *et al*., 2022), and the prolonged use of glucocorticoids is associated with significant adverse effects (Ronchetti *et al*., 2021). The continuous administration of synthetic drug therapies has been associated with an elevated risk of infection, lymphoma, and the development of nonmelanoma skin cancer in AD patients. Consequently, continued research exploring natural ingredients is necessary to overcome these inherent shortcomings of synthetic drugs.

The utilization of natural ingredients derived from animals or products of animal origin as a therapeutic approach is a promising avenue for further exploration. Natural products of animals, such as mucus, are secretions produced by mucus cells as a physiological response to internal and external stimuli. Ethnozoological evidence indicates that the land snail *Lissachatina fulica* has historically been utilized as a medicinal agent for wound healing due to its mucus-producing characteristics. The efficacy of snail mucus as a therapeutic agent for various health concerns has garnered significant attention in recent years. A growing body of research has suggested its potential benefits in treating burns (Ulayya *et al*., 2019), stimulating in vitro lymphocyte proliferation (Harti *et al*., 2018), and inhibiting the proliferation of breast cancer cells (Edison *et al*., 2021). Additionally, studies have demonstrated the effectiveness of snail mucus in the management of gastric ulcers (Petrov *et al*., 2022). These findings highlight the potential of snail mucus as a multifaceted therapeutic agent, warranting further investigation for its therapeutic applications in various medical conditions.

The bioactivity of snail mucus is directly determined by its active contents. Specific active ingredients, such as achasin, have demonstrated antibacterial properties (Noothuan *et al*., 2021). Furthermore, glycosaminoglycans possess anti-inflammatory activity (Nualnisachol *et al*., 2023), and secondary metabolites like alkaloids, flavonoids, and saponins have been identified as anti-inflammatory agents (Anandi *et al*., 2021). The protein content within snail mucus has also been shown to accelerate the healing of various types of wounds and to increase the proliferation of new skin cells (Ulayya *et al*., 2019). Although the utilization of snail mucus as a remedial agent has been extensively documented, its application as a preventative measure in atopic dermatitis remains unreported. As a preliminary measure, it is essential to assess the hematological response to mucin cream as a preventative intervention, given that blood cells constitute the body's primary defense against the infiltration of foreign substances. Accordingly, the present investigation aims to compare the response of blood cells following the application of snail mucin *Lissachatina fulica* in cases of acute atopic dermatitis.

## MATERIALS AND METHODS

### *Ethical Clearance and Research Location*

The research was conducted from May to October 2024. All animal procedures received ethical approval from the Animal Ethics Committee of the School of Veterinary Medicine and Biomedicine (SKHB), IPB University, under approval number 211/KEH/SKE/IV/2024. The research was carried out across three units: the Laboratory Animal Management Unit (UPHL) SKHB for animal husbandry, the Pharmacy Laboratory SKHB to produce snail mucin cream, and the Physiology Laboratory SKHB for hematological examination. The overall research design is illustrated in Figure 1.

### *Research Animal Husbandry*

The research animals used were 36 eight-week-old male BALB/c mice, confirmed to be in good health. The mice were raised in accordance with Per-BPOM 10/2022. They were kept in a plastic cage

(30 x 20 x 15 cm) with a wooden base, provided commercial pellets, and had ad libitum access to water. During the acclimation phase, the mice were administered the dewormer Acepromazine HCl at a dose of 0.1 mg/kg.

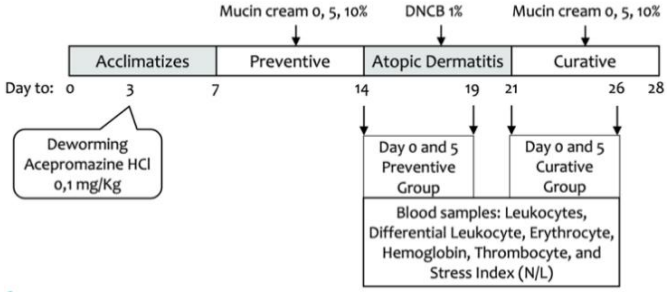


Figure 1. Research design

*Snail Mucin Cream Preparation*

The *Lissachatina fulica* mucin (LFM) extract was incorporated into a cream base. The formulation of the cream base comprises lipophilic ingredients (e.g., acetyl alcohol, paraffin, methylparaben, stearic acid) and hydrophilic ingredients (e.g., propylene glycol, triethanolamine), which were thoroughly dissolved in distilled water. The LFM extract was subsequently added to the cream base at concentrations of 5% and 10%.

*Acute Dermal Toxicity Testing*

The test was conducted prior to the main efficacy study using the fixed-dose method (BPOM, 2022). Mice were treated with 5% or 10% LFM cream for 14 days. Hair was shaved from a 1-by-1-centimeter area on the dorsal side of each mice. The observation of individual toxic symptoms, including irritation, edema, changes in appetite, tremors, changes in body weight, and macroscopic pathological conditions, such as internal organ weight and organ weight relative index, is crucial for a comprehensive assessment of the toxicity of the substance under investigation (BPOM, 2022).

*Atopic Dermatitis Induction and Treatment*

Atopic dermatitis mice were made using a 1% DNCB (2,4-dinitrochlorobenzene) solution on 1x1 cm dorsal skin. Then, a 1-by-1-centimeter cream was applied, and the area was covered with porous gauze and wrapped with an elastic bandage or non-irritating plaster. This procedure was conducted daily for 7 days.

*Scoring Atopic Dermatitis (SCORAD)*

The severity of atopic dermatitis was assessed using the Scoring Atopic Dermatitis (SCORAD) system, calculating the Atopic Dermatitis Severity Index (ADSI) based on symptoms including pruritus, erythema, excoriation, exudation, and lichenification (Silverberg *et al.*, 2020). The calculated scores were categorized as follows:

- 0 – <2 = clear/almost clear
- 2 – <6 = Mild
- 6 – <9 = Moderate
- 9 – 15 = Severe

*Hematological Profile*

Blood samples (0.1 mL) were collected from the caudal vein of the test mice on days 0 and 5 of the treatment phase. The blood samples were placed in microtubes containing EDTA and subsequently homogenized. Blood was calculated for its hematological profile using the Hematology Analyzer.

*Data Analysis*

All quantitative data were expressed as the mean ± Standard Error (SE) and analyzed using GraphPad Prism 10. Data were analyzed using a two-way ANOVA, with a Tukey test performed if there were significant differences, and the confidence level was set at 95%. Atopic dermatitis scores were analyzed descriptively.

## RESULTS

*Acute Dermal Toxicity Test*

The application of LFM cream did not induce any acute toxic symptoms, including irritation, edema, tremors, or anorexia. Macroscopic pathological measurements revealed no statistically significant differences between the treatment groups ($p<0.05$). As shown in Table 1, there is an absence of indications of acute toxicity in the skin when LFM cream was applied. These findings suggest that the LFM cream is safe for topical application.

*Atopic Dermatitis Severity (ADSI) Scores*

The induction of atopic dermatitis in mice using 1% dinitrochlorobenzene (DNCB) successfully resulted in the manifestation of four primary symptoms: pruritus, erythema, excoriation, and lichenification. Furthermore, the ADSI scores in the DNCB control group indicated the development of atopic dermatitis with a score >2 (mild) on days 0 and 5 of the treatment period, as demonstrated in Figure 2.

In the preventive group, the application of LFM cream effectively suppressed the manifestation of AD symptoms, with the ADSI score remaining below 2 on day 5 of treatment ($p<0.05$). Concurrently, the LFM cream also demonstrated efficacy as a curative

agent, resulting in a statistically significant decrease in ADSI score on day 5 (P<0.05).

*Hematological Profile Analysis*

Validation of the reduction of clinical symptoms in the preventive and curative groups is still required through an approach that utilizes a humoral immunity mechanism. The humoral immunity mechanism serves as the initial protective barrier against inflammation within the body. The primary cells responsible for maintaining the humoral immune system are circulating blood cells. Differential profiling of leukocytes following treatment provided a comprehensive representation of the immune response (Figure 3). A statistically significant difference was observed between the treatment groups across several parameters, including the number of leukocytes, eosinophils, lymphocytes, and neutrophils (P<0.05).

The alteration in leukocyte cell count exhibited greater variability in the curative group compared to the preventive group between days 0 and 5 (p<0.05). In the curative group (LFM 5% and 10%), the number of leukocyte cells demonstrated a statistically significant decrease on day 5 (p<0.05). It is hypothesized that the infiltration of certain types of leukocytes into the skin tissue of individuals with atopic dermatitis leads to a decrease in the overall number of circulating leukocytes. Inflammatory skin diseases are characterized by the presence of specific leukocyte subtypes, including monocytes and eosinophils, within the tissue. In addition, monocyte cells in the tissue play a role in phagocytosis to cleanse damaged cells, while eosinophil cells stimulate histamine production in response to allergies and inflammation.

The number of neutrophil cells in the preventive group was significantly higher than the number of neutrophil cells in the curative group (p<0.05).

Despite the development of mild and acute atopic dermatitis, overall hemostatic abnormalities were not substantial, as indicated by the maintenance of blood cell counts and hemoglobin levels within typical ranges. However, a significant difference was observed in the curative group, which showed a 5% increase in the number of erythrocyte cells compared to the cream base. Furthermore, the application of LFM cream enhances the proliferation of new red blood cells, contributing to the body's oxygenation levels. Significant variations were observed in thrombocyte cells, attributable to the effects of preventive and curative administration (p<0.05). In the preventive group, the elevated platelet cell counts on day 5 indicated inflammatory activity in the DNCB-induced area. Consequently, the production of platelet cells was sufficient to suppress/prevent inflammatory reactions.

A comprehensive evaluation of the hematological data revealed that the preventive group exhibited superior outcomes in suppressing inflammatory indicators in comparison with the treatment group. This suggests that the application of LFM cream, when administered prior to DNCB induction, modulates the adaptive immune response more effectively, leading to a significantly lower ADSI score.

Table 1. Body weight and relative organ weight index of mice in the dermal acute toxicity test

| No | Parameter | Cream Base | Mucin 5% | Mucin 10% | Sig. |
|---|---|---|---|---|---|
| 1 | Symptoms of acute dermal toxicity: | | | | |
| | a. Irritation | N. O | N. O | N. O | |
| | b. edema | N. O | N. O | N. O | |
| | c. tremor | N. O | N. O | N. O | |
| | d. anorexia | N. O | N. O | N. O | |
| 2 | Initial Body Weight | 24.31 ± 0.55 | 22.81 ± 2.59 | 27.64 ± 0.86 | 0.242 |
| 3 | Final Body Weight | 25.60 ± 0.10 | 25.66 ± 2.74 | 28.46 ± 1.10 | 0.489 |
| 4 | Weight gain | 1.29 ± 0.45 | 2.85 ± 0.15 | 0.82 ± 0.24 | 0.037* |
| | % weight gain | 5.25 ± 1.97 | 12.58 ± 0.77 | 2.94 ± 0.78 | 0.028* |
| 5 | Liver weight | 1.66 ± 0.00 | 1.45 ± 0.25 | 1.77 ± 0.11 | 0.448 |
| | % liver weight | 6.50 ± 0.00 | 5.60 ± 0.40 | 6.25 ± 0.15 | 0.162 |
| 6 | Kidney weight | 0.40 ± 0.02 | 0.34 ± 0.04 | 0.42 ± 0.04 | 0.364 |
| | % Kidney weight | 1.55 ± 0.05 | 1.30 ± 0.00 | 1.50 ± 0.10 | 0.135 |
| 7 | Spleen weight | 0.20 ± 0.02 | 0.10 ± 0.02 | 0.15 ± 0.03 | 0.128 |
| | % spleen weight | 0.80 ± 0.10 | 0.35 ± 0.05 | 0.50 ± 0.10 | 0.074 |

N. O = Not Occurred; *Significant difference (p<0.05)

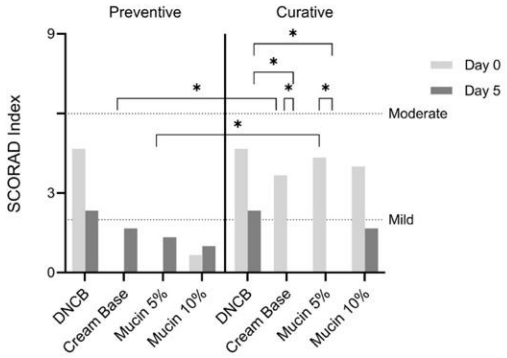


Figure 2. SCORAD Index of atopic dermatitis mice given LFM cream.
*Significant difference from Tukey's test at α<0.05

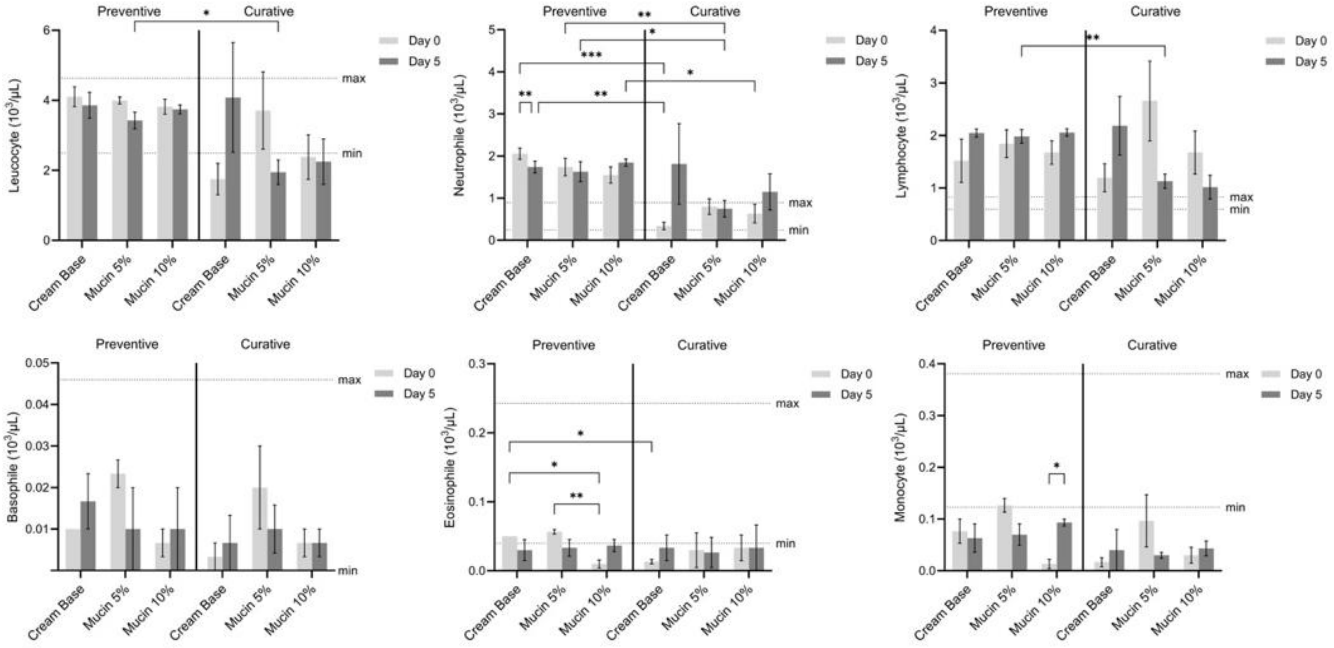


Figure 3. Differential profile of leukocytes of atopic dermatitis mice fed LFM cream. min-max = normal range
* Significant difference from Tukey's test at α<0.05

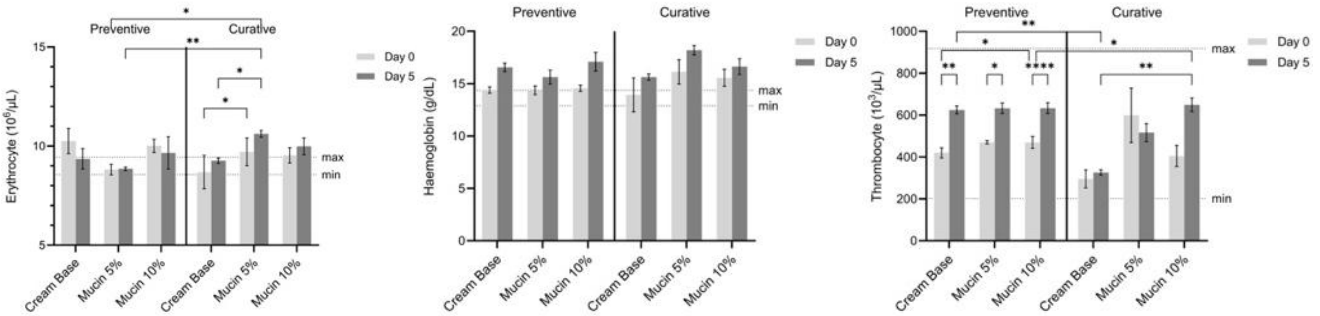


Figure 4. The number of erythrocytes, hemoglobin, and platelets of atopic dermatitis mice given LFM cream. min-max = normal range * Significant difference from Tukey's test at α<0.05.

## DISCUSSION

Atopic dermatitis is an inflammatory skin disease caused by various factors, including genetic factors, impaired skin barrier function, immunological abnormalities, dietary factors, aeroallergens, *Staphylococcus aureus* infection, and stress. In the case of AD, the skin becomes dry due to a mutation of the filaggrin gene (FLG) (Fishbein *et al.*, 2020). This mutation results in the impairment of the skin's barrier function, leading to dehydration, and increased permeability to external allergens. The use of dinitrochlorobenzene (DNCB) in this study exploits its highly irritant properties to chemically compromise and cause damage to the skin barrier and induce AD-like symptoms. The irritant properties of DNCB are

evident in the manifestation of pruritus and erythema, which subsequently lead to the development of excoriation and liquefaction lesions. In this study, the atopic dermatitis model utilizing DNCB resulted in an ADSI score >2, confirming the establishment of a mild to acute condition.

An inflammatory response is the body's typical response to tissue damage or infection. Its primary functions include the removal of cell debris, the localization of pathogenic organisms, and the limitation of infection and tissue damage spread.

The release of abundant thymic stromal lymphopoietin (TSLP) from the damaged epidermis has been shown to trigger an immune response from lymphocyte cells (Hu *et al*., 2020). A notable finding was the elevated number of lymphocyte cells (see Figure 3) observed in all treatment groups on day 0, indicating the significant capacity of DNCB to induce atopic dermatitis. Furthermore, the high response of thrombocyte cells in all groups indicates the body's response to the occurrence of internal bleeding or damage. Thrombocyte cells are responsible for the activation of the blood clotting process, thereby ensuring that the body does not experience significant blood loss.

The initiation of an inflammatory response to DNCB leads to the release of cytokines and chemokines, which serve to protect the body against the spread of infection or uncontrolled tissue damage. However, the duration of the inflammatory process is determined by the resolution phase. The resolution of inflammation is a critical process mediated through a variety of mechanisms, including autophagy, which is responsible for the elimination of damaged cells and organelles (Fullerton & Gilroy, 2016). Extracellular proteoglycan (ECM) compounds have been identified as playing a pivotal role in the function of Damage-associated molecular pattern (DAMPs) (Dwyer & Turnquist, 2021). Proteoglycans found in snail mucus, particularly those comprising elevated concentrations of leucine-hyaluronan binders (i.e., hyaluronan-glycosaminoglycans), are relevant here. These compounds may function as endogenous ligands for Toll-like receptors, which are central to the regulation of innate immunity, with the capacity to activate intracellular inflammasomes and trigger inflammatory responses (Zeng *et al*., 2020).

The active compounds in the mucin of *Lissachatina fulica*, such as achasin and glycosaminoglycan, have been demonstrated to induce the activation of several target proteins like TNF and CCL2. TNF is pivotal in regulating immune cell function and the inflammatory process. Meanwhile, CCL2, a chemokine, functions specifically to recruit monocytes and macrophages to the site of inflammation (Lin *et al*., 2023) and has been shown to trigger inflammation by attracting immune cells, thereby enhancing the inflammatory response. It is hypothesized that the resolution of inflammation in AD will be accelerated by these two pathways.

The findings of the present study confirm that LFM cream is safe for use as both a preventative and a curative topical agent. Crucially, the efficacy of LFM cream was optimal when utilized as a preventive measure, thereby averting the clinical manifestations associated with atopic dermatitis. LFM 5% cream demonstrated high effectiveness in the treatment of atopic dermatitis. The elevated neutrophil count in the preventive group, compared to the curative group, supports the hypothesis that the LFM cream, when administered before DNCB induction, enhances innate immune responses, as evidenced by an augmentation in the number of neutrophils in the bloodstream. The role of neutrophils in the immune system is crucial for phagocytosis and the combat of infections. Concurrently, lymphocyte cells that exhibit an increase in number above normal values due to the local inflammatory process of atopic dermatitis will trigger a specific immune system to activate the formation of antibodies produced by lymphocyte cells. These findings suggest that LFM cream functions as a dual action immunomodulator in both preventative and curative capacities.

A comprehensive understanding of the composition of protein compounds derived from snail mucin is imperative, as this substance has been shown to possess anti-inflammatory and immunomodulatory properties, which are crucial in the management of atopic dermatitis. This research is in progress to ascertain the molecular mechanisms by which protein compounds found in the mucin of the snail *Lissachatina fulica* exert their biological activities.

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*"The authors declare no conflict of interest with any parties involved in this research"*

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