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Research Article

Nanoemulgel containing *Jatropha curcas* leaves extract ameliorated imiquimod-induced psoriasis in BALB/c mice via suppressing TNF-α expression

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ABSTRACT

Psoriasis is chronic inflammatory skin disease arbitrated by the immune system, so the inflammatory response portrays a vital role in the progress and severity of this disease. Unfortunately, conventional psoriasis treatment currently has limitations, including, expensive, has a high risk of side effects and worsening the prognosis of psoriasis if treatment is stopped. Therefore, the development of effective and efficient herbal medicine is desired to treat psoriasis. This research is designed to prove the huge potential of nanoemulgel containing *Jatropha curcas* leaves extract (JCE-NE-gel) as a topical treatment for psoriasis. This study used 24 BALB/c mice induced with 62.5 mg imiquimod cream 5% twice a day for 7 consecutive days. In addition, the effectiveness of JCE-NE-gel as anti-psoriasis was evaluated using PASI scores, epidermis thickness via histopathology and TNF-α expression via immunohistochemistry. The results of *in vivo* studies showed that the 2.5% JCE-NE-gel group was able to improve the physiological appearance of psoriasis skin on the 14th day of the study. It was also able to reduce the PASI score for 66.7% ($p < 0.05$). In addition, histopathological results showed a significant decrease in the epidermis thickness of 2.5% JCE-NE-gel group mice for 78.9% ($p < 0.05$). A decrease in TNF-α expression was also seen in the 2.5% JCE-NE-gel group for 56.9% ($p < 0.05$). This research proves that the nano formulation was able to increase the permeability of *Jatropha curcas* leaves extract into the epidermis and dermis of the skin. This study also proves that nanoemulgel formulation loaded *Jatropha curcas* extract (JCE-NE-gel) could be reflected as a promising treatment for psoriasis disorders via suppressing TNF-α expression.

Keywords:
Jatropha curcas; BALB/C mice; Imiquimod-induced psoriasis model; Nanoemulgel; Topical drug delivery

1. INTRODUCTION

Psoriasis, an autoimmune disease, is a chronic inflammatory skin illness characterized by the presence of erythematous and scaly plaques. The presence of these reddish scaly plaques due to hyperproliferation and abnormal differentiation of keratinocytes[1,2]. The global prevalence of psoriasis is around 2-3% of the world's population[3]. According to the Global Burden of Disease (GBD) in 2019, there were 4,622,594 cases of psoriasis incidents worldwide[4].

In psoriasis, T lymphocytes and pro-inflammatory cytokines play a major role in its pathogenesis[5,6]. One of the pro-inflammatory cytokines involved is Tumor Necrosis Factor Alpha (TNF-α). TNF-α is a cytokine that has pleiotropic effects on various cell types. Several studies have shown that there is an increase in TNF-α expression locally and in serum in psoriasis patients

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So, TNF-α is the target molecule for several biological treatments in psoriasis patients[7].

Currently, there has been significant progress in the management of psoriasis including conventional oral, topical treatments, systemic drugs, new biologic agents and phototherapy. However, these approaches lead to a severe adverse side effects and recurrent relapses. Some conventional treatments (antihistamines) are limited to treating itching symptoms in psoriasis patients or even worsen the prognosis of psoriasis if treatment is stopped[8]. Biologic agents, such as TNF-α and Interleukin-17 (IL-17) inhibitors, effectively treat itching symptoms in psoriasis patients, but some patients cannot obtain these drugs because they are expensive and have a high risk of side effects. Therefore, the development of effective and efficient herbal medicines for psoriasis is still a big challenge.

Jatropha curcas is an herbal plant that is known to be able to treat various skin diseases. Based on the book ASEAN Herbs and Medical Plants, *Jatropha curcas* leaves are used as a traditional treatment for skin diseases in Southeast Asian countries including Thailand and Indonesia. Empirically, *Jatropha curcas* leaves are used as a medicine for skin diseases such as wound healing, ringworm, scabies, and eczema[9]. Several studies have been conducted to demonstrate the anti-inflammatory activity of various parts of the *Jatropha curcas*[10,11]. However, unfortunately, no studies have yet proven the anti-psoriasis activity of this plant.

Jatropha curcas leaves contain various secondary metabolite compounds that can make this plant have various biological activities. Secondary metabolites that can be found in its leaf ethanol extract include alkaloids, steroids, tannins, glycosides, flavonoids, saponins, terpenoids, triterpenoid saponins, coumarins and carotenoids. Analysis of phytoconstituents from *Jatropha curcas* leaves extract using HPLC-MS/MS instruments found 68 compounds including apigenin, vitexin, isovitexin, quercetin, catechins, epicatechins, luteolin, scopoletin, coumarin, naringenin and other compounds[12].

Drug delivery systems with nano formulations are the primary choice for improving solubility, increasing the permeability and drug bioavailability. Nanoparticle-based herbal preparation formulations are one of the most promising efforts to achieve it. Unfortunately, the research regarding nano formulations of plant extracts for psoriasis treatment is still infrequent[13]. In fact, nano formulations of plant extracts have proven to be very effective and efficient as psoriasis therapy. All studies have proven that nano formulations reveal better results in psoriasis recovery compared than the others[14-19]. It verifies that the nano formulations are able to increase bioavailability and enhance drug permeability into the skin.

The appropriate nanoparticle drug delivery system for topical delivery routes, especially in this case is nanoemulgel. Nanoemulgel is a hybrid colloidal system consisting of nano-sized oil-phase droplets dispersed in the water-phase matrix. Nanoemulgel is a combination of nano emulsion and hydrogel systems. As a topical drug delivery system, nanoemulgel portrays as a drug carrier matrix that facilitates the release of drugs across the skin barrier. This system has several advantages including being compatible with the skin, increasing the viscosity of the preparation, increasing the dispersion of the preparation, increasing the adhesive ability of the preparation, prolonging the therapeutic effect and improving skin retention[20].

Therefore, in this study, the optimal formulation of nanoemulgel containing *Jatropha curcas* extract (JCE-NE-gel) from our previous study was tested *in vivo* on imiquimod-induced psoriasis mice.

2. MATERIALS AND METHODS

2.1 Materials

Imiquimod cream 5% (Sichuan Med-Shine Pharmaceutical, China); Veet® hair removal cream; *Jatropha curcas* leaves was obtained from Materia Medika (Indonesia); Ethanol 96%; Ethanol 70%, Carbomer (Carbopol 940), Polysorbate (Tween 80), Sorbitan esters (Span 80), Virgin Coconut Oil, Triethanolamine, Phenoxyethanol, and distilled water were bought from Chemindo Multi Sentosa Ltd (Surabaya, Indonesia).

2.2 Nanoemulgel of *Jatropha curcas* extract (JCE-NE-gel)

Jatropha curcas leaves was extracted using ethanol 70% as solvent by the maceration method. The JCE-NE-gel has been formulated in our previous research using a gel incorporation and nano emulsion method with ultrasonic homogenization. *Jatropha curcas* extract was successfully loaded in the nanoemulgel formulation with pH 6.3; 142.67 nm in size particle; 0,248 for polydispersity index; -23.23 mV in zeta potential; 87.881 cP in viscosity and spread ability at 6.13 cm.

2.3 Animals and ethical statement

In this study, 24 male BALB/C mice were used as experimental animals with a body weight ranging from 18-20 g and aged 6 to 8 weeks, purchased from veterinary house PUSVETMA (Surabaya, Indonesia). This strain has a genetic stability, a unique immune profile, availability of reference data, ease of maintenance, and sensitive to a wide range of pathogens, which is useful for studying the mechanisms of

infectious and immunology diseases including psoriasis. The experimental animals were grouped into six (6) groups with four (4) mice each. All experimental animals were conditioned in a standard environment and provided with sufficient food and drink. The Animal Care and Use Committee (ACUC) of Veterinary Faculty of Airlangga University has accepted all experiment protocols (Protocols No: 2.KEH.126.09.2024).

2.4 Experimental design

2.4.1 Establishment of psoriasis mice model and treatment protocol

The experimental animals were randomly divided into six (6) groups including:

- Normal group (no induction and no treatment)
- Negative group (Imiquimod cream 5% and no treatment)
- Positive group (Imiquimod cream 5% and Desoximetasone® cream)
- A group (Imiquimod cream 5% and nanoemulgel base)
- B group (Imiquimod cream 5% and 2.5% JCE-gel)
- C group (Imiquimod cream 5% and 2.5% JCE-NE-gel).

The induction process began with the experimental animals having their fur cut shortly on the back area with an area of approximately 2 cm x 3 cm using scissors. Then Veet® hair removal cream was applied sufficiently and left for 5 minutes. After that, it was cleaned using dry tissue until all the fur was removed clean. The induction material, Imiquimod cream 5% as much as 62.5 mg was applied twice a day on the exposed skin for 7 consecutive days to induce psoriasis. On the 8^{th} to 14^{th} day of the study, treatment was given according to each group for 7 consecutive days. At the end of the study (on the 15^{th} day), all experimental animals were sacrificed. Then skin lesion samples were taken and collected for further study.

2.4.2 Body weight determination

Body weight was measured for each mouse at day-1, day-4, day-7, day-10 and day-14.

2.4.3 Psoriasis area and severity index (PASI)

The severity of psoriasis skin lesions is assessed using the Psoriasis Area Severity Index (PASI) score. The degree of erythema, scaling and thickening are each assessed on a scale from 0 to 4; 0 for none; 1 for slight; 2 for moderate; 3 for severe; and 4 for very severe. Then, the collective PASI score is summed to indicate the severity of psoriasis on a scale of 0 – 12. The severity of psoriasis can be indicated by the cumulative value of the PASI score as follows: severe psoriasis (PASI >10); moderate psoriasis (PASI 3 – 10) and mild psoriasis (PASI < 3)[21].

2.4.4 Histopathological examinations

The skin tissue that has been obtained is then fixed by soaking it in a 10% formalin solution for ± 48 hours at room temperature. Furthermore, the dehydration process of the skin tissue is carried out by soaking it in an alcohol solution with graded concentrations. The clearing process is the next stage by soaking the tissue in a pure xylol solution. After that, the tissue infiltration process is carried out by soaking the tissue in liquid paraffin.

Then the embedding process or planting of tissue into solid paraffin is carried out. The tissue that has been embedded in solid paraffin is cut 4 µm thick using a microtome. The tissue pieces are attached to the object glass that has previously been smeared with polylysine as an adhesive. Furthermore, the tissue on the object glass is heated in an incubator at a temperature of 56 - 58°C until the paraffin melts.

The final stage is staining which begins with the deparaffination process using xylol then continued with the rehydration process using alcohol. After that, hematoxylin and eosin dyes were given[22]. The thickness of the skin epidermis was measured under a microscope for each mouse, then compared between groups.

2.4.5 Immunohistochemical analysis for TNF-α

The immunohistochemistry procedure begins with immersion of the slide preparation in graded xylol and ethanol solutions. Then the preparation is blocked with 1% Bovine Serum Albumin (BSA) for 30 minutes at room temperature. then incubated overnight with TNF-α primary antibody for 12 hours at 40°C. Then the preparation was incubated with secondary antibodies for 1 hour at room temperature. The slide preparation was dripped with Strep Avidian Horse Radish Peroxidase (SA-HRP). Furthermore, the preparation was dripped with Diamano Benzidine (DAB) chromogen. Staining was done using Mayer Hematoxylin. The preparation was mounted on a glass object and covered with a cover glass. The results of observing TNF-α expression will appear brownish in the endothelial cell cytoplasm[23].

2.4.6 Statistical analysis

Data are expressed as mean ± standard deviation for statistical data analysis. ANOVA test followed by Tukey's test was used to determine statistical differences using SPSS 25.0. The value $p < 0.05$ was considered significant.

3. RESULTS

3.1 Body weight

During the study, the weight of the mice was observed periodically to monitor its condition and health (Figure 1). In the negative group, the weight of the mice was seen to decrease from day-1 to day-14 of the study. This could be due to psoriasis which can interfere with the quality of life of mice, causing stress due to severe itching and loss of appetite. In contrast, group A (nanoemulgel base), group B (2.5% JCE-gel) and group C (2.5% JCE-NE-gel) tend to show weight gain from day-7 to day-14 of the study. The treatment of psoriasis mice reduced the severity of psoriasis so that the mice felt more comfortable and less stressed.

3.2 *In vivo* study of anti-psoriasis

The results of the *in vivo* study of anti-psoriasis activity (Figure 2) showed that the negative group experienced increasing severity of psoriasis skin until day-14 of the study. The positive group that received topical corticosteroids, namely Desoximetasone® cream, showed very good physiological skin improvement. In this group, the mice skin infected with psoriasis on the 7th day of induction gradually disappeared until the mice skin became normal on the 14th day of the study.

Likewise, the groups that received nanoemulgel base treatment (Group A) and 2.5% JCE-gel (Group B) were showing physiological improvements in the skin of mice. This is because there is Virgin Coconut Oil (VCO) in the nanoemulgel base formulation and JCE in the 2.5% JCE-gel formulation. These active ingredients are thought to still have anti-inflammatory activity in psoriasis mice, although not as good as JCE-NE-gel preparation. In fact, in both groups, there were still some mice skins that still suffered from mild psoriasis.

In the group of mice that received 2.5% JCE-NE-gel (Group C), it was also able to improve the physiological skin of mice infected with psoriasis just like the positive group. The skin of mice that were originally infected with psoriasis on the 7th day of induction could return to being clean and smooth after receiving treatment for 7 days. This means that the 2.5% JCE-NE-gel has been able to improve the physiological appearance of the mice skin that were originally infected with psoriasis to be healthy again.

3.3 PASI score

Furthermore, the PASI score was used to assess the severity of psoriasis on the mice skin. The PASI scores on day-7 of induction (after imiquimod induction) and on day-14 of the study (after receiving treatment) were compared statistically to see if there

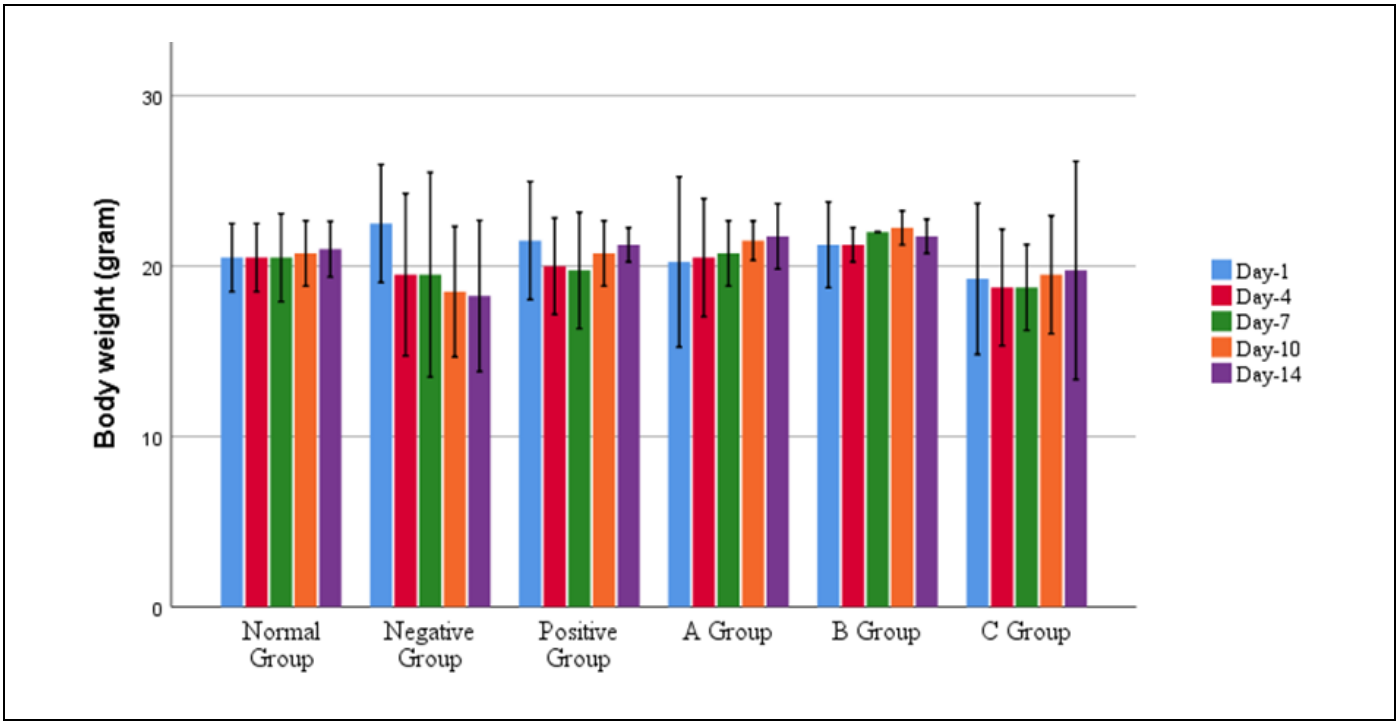

Figure 1. Body weight of mice during study. Normal Group (No induction and No treatment); Negative Group (Imiquimod cream 5% + No treatment); Positive Group (Imiquimod cream 5% + Desoximetasone® cream); Group A (Imiquimod cream 5% + nanoemulgel base); Group B (Imiquimod cream 5% + 2.5% JCE-gel); Group C (Imiquimod cream 5% + 2.5% JCE-NE-gel).

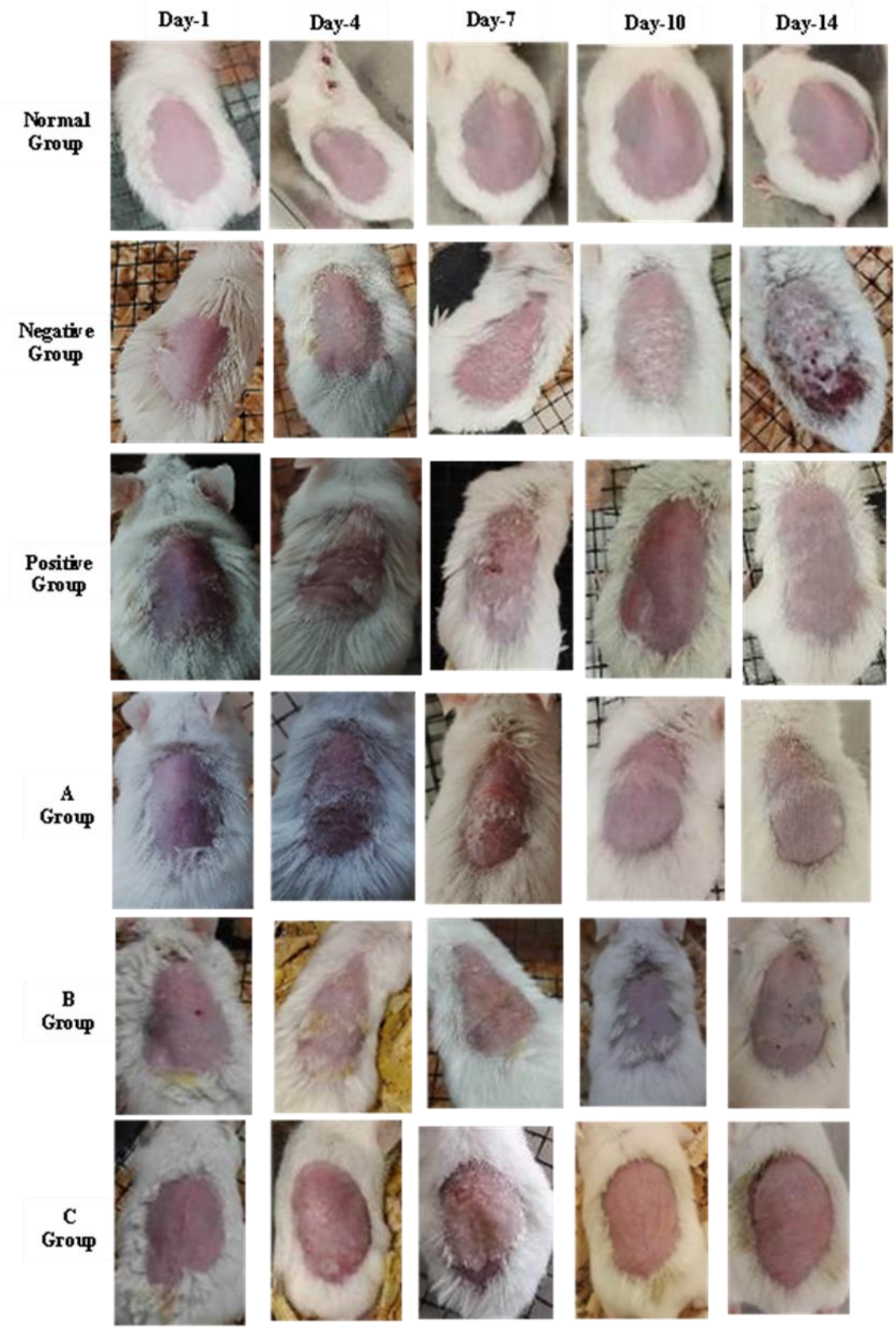

Figure 2. *In vivo* anti-psoriasis study results. Normal Group (No induction and No treatment); Negative Group (Imiquimod cream 5% + No treatment); Positive Group (Imiquimod cream 5% + Desoximetasone® cream); Group A (Imiquimod cream 5% + nanoemulgel base); Group B (Imiquimod cream 5% + 2.5% JCE-gel); Group C (Imiquimod cream 5% + 2.5% JCE-NE-gel).

was a significant difference using the Wilcoxon Test method ($p < 0.05$). The results showed as (Figure 3), that all groups except the normal group had differences in the average PASI score between before and after treatment. The negative group was the only group that experienced an increase in the average PASI score. The negative group initially had a total PASI score of 2.75 on day-7 of induction and then increased to 6.25 on day-14 of the study.

Meanwhile, the positive group, the A group, the B group and the 2.5% JCE-NE-gel group all experienced a significant decrease in PASI scores. The 2.5% JCE-NE-gel preparation was able to reduce the total average PASI score for 66,7% from 3.75 (day-7 of induction) to 1.25 (day-7 of treatment). This means, it can reduce the PASI score as a measure of the psoriasis severity on the mice skin.

3.4 Histopathology analysis

Histopathology was performed to ensure physiological abnormalities in the mice skin infected with psoriasis at the tissue level. Compared to normal mouse skin, the epidermis of mice infected with psoriasis will look thicker due to acanthosis and hyperproliferation of keratinocyte cells in the epidermis. In addition, damaged outer skin barriers, dilated blood vessels and abscesses were also found. In this study, the thickness of the epidermis is one of the parameters to assess the anti-psoriasis activity of the 2.5% JCE-NE-gel. The thickness of the epidermis was measured by measuring the epidermis on histopathology preparations of mouse skin using the ImageJ application (Figure 4).

In the group of normal mice, the average thickness of the epidermis was around 21.32 µm. The positive group also showed an epidermis thickness of around 21.30 µm. Meanwhile, in the negative group, acanthosis was clearly visible due to hyperproliferation of keratinocyte cells so that the epidermis was thicker. The thickness of the epidermis reached an average of 63.58 µm or almost 3 times thicker than normal mice. Likewise, group A (nanoemulgel base) and group B (2.5% JCE-gel) still showed acanthosis in the epidermis with an epidermis thickness of 65.67 µm and 64.86 µm, respectively. This shows that in both groups, the active ingredients only work on the outer skin and cannot penetrate further into the epidermis skin.

Meanwhile, group C (2.5% JCE-NE-gel) showed almost the same epidermis thickness as the normal group and the positive group. The average epidermis thickness reached 13.41 µm. This shows that the JCE-NE-gel system is able to pass through into the epidermis of the skin, so that it can stop hyperproliferation of keratinocytes. The results of statistical analysis using the ANOVA Test also stated that group C had a significant difference in average epidermis thickness compared to the negative group for 78.9% ($p < 0.05$). Thus, the 2.5% JCE-NE-gel preparation can be concluded to reduce the thickness of the epidermis in the skin of psoriasis mice.

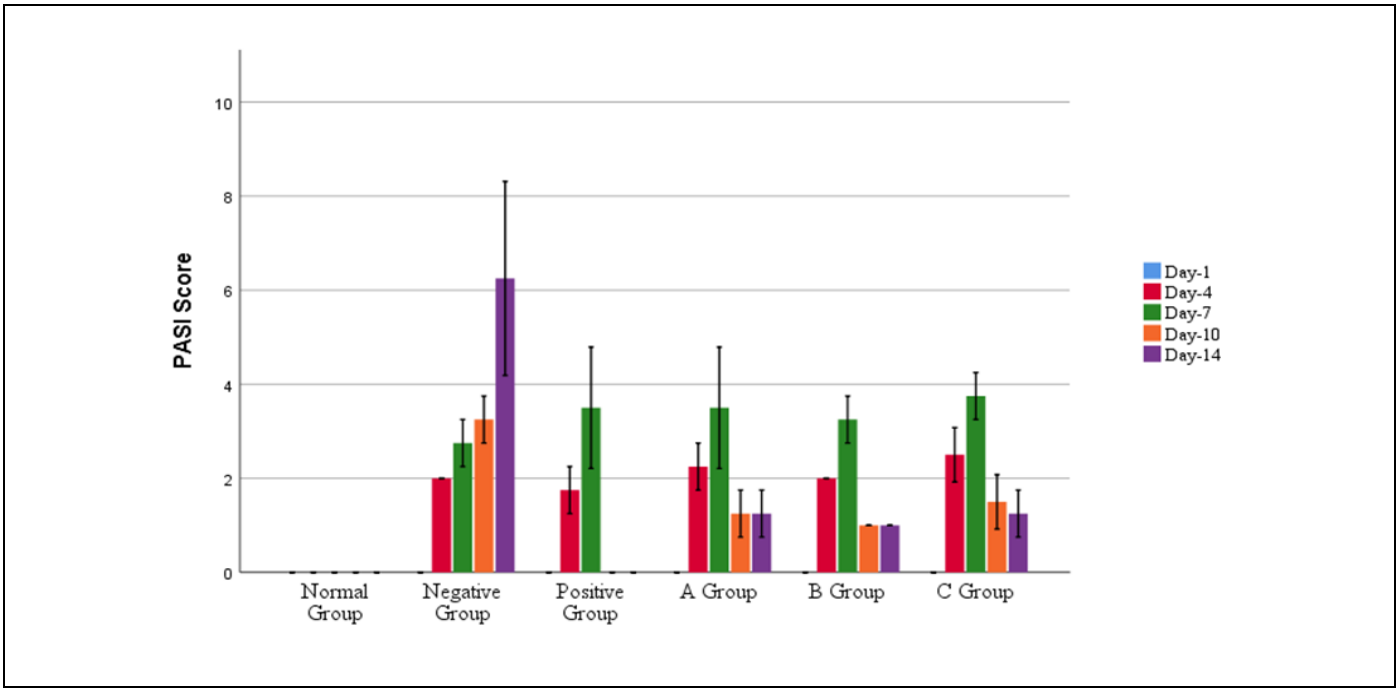

Figure 3. PASI score for psoriasis mice during study. Normal Group (No induction and No treatment); Negative Group (Imiquimod cream 5% + No treatment); Positive Group (Imiquimod cream 5% + Desoximetasone® cream); Group A (Imiquimod cream 5% + nanoemulgel base); Group B (Imiquimod cream 5% + 2.5% JCE-gel); Group C (Imiquimod cream 5% + 2.5% JCE-NE-gel).

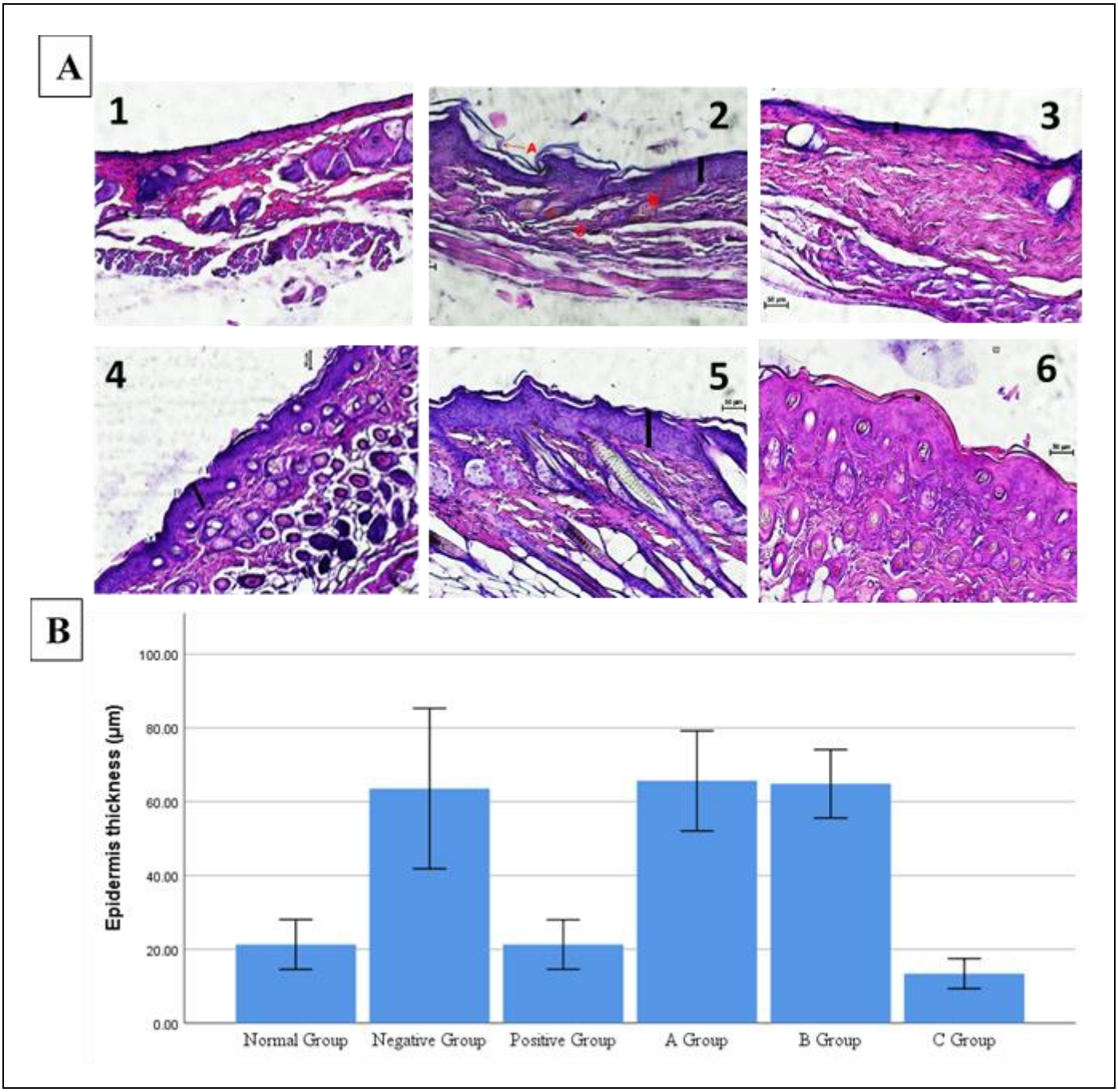

Figure 4. (A) Histopathology of mice skin (100x) and (B) epidermis thickness of psoriasis mice. (1) Normal group (No induction and No treatment); (2) Negative group (Imiquimod cream 5% + No treatment); (3) Positive group (Imiquimod cream 5% + Desoximetasone® cream); (4) A group (Imiquimod cream 5% + nanoemulgel base); (5) B group (Imiquimod cream 5% + 2.5% JCE-gel); (6) C group (Imiquimod cream 5% + 2.5% JCE-NE-gel).

3.5 TNF-α expression by immunohistochemistry

Immunohistochemistry was carried out to prove the anti-psoriasis activity of JCE-NE-gel at the protein level. TNF-α, which is one of the biological indicators in psoriasis patients, is the target protein in this study. Quantification of TNF-α expression was carried out by measuring the color density on immunohistochemical preparations using the ImageJ application (Figure 5). In immunohistochemical preparations, cells expressing TNF-α will be brown and cells that do not express TNF-α will be blue. This color difference is the basis for measuring the percentage of TNF-α expression in the skin of psoriasis mice.

The results of this study revealed that TNF-α expression in the normal group of mice was 16.89%. While in the negative group was 46.59% or almost 3 times higher than normal mice. This is because the inflammation that occurs in psoriasis mice triggers the release of TNF-α in the cytoplasm on a large scale. While in the positive control, TNF-α expression decreased or

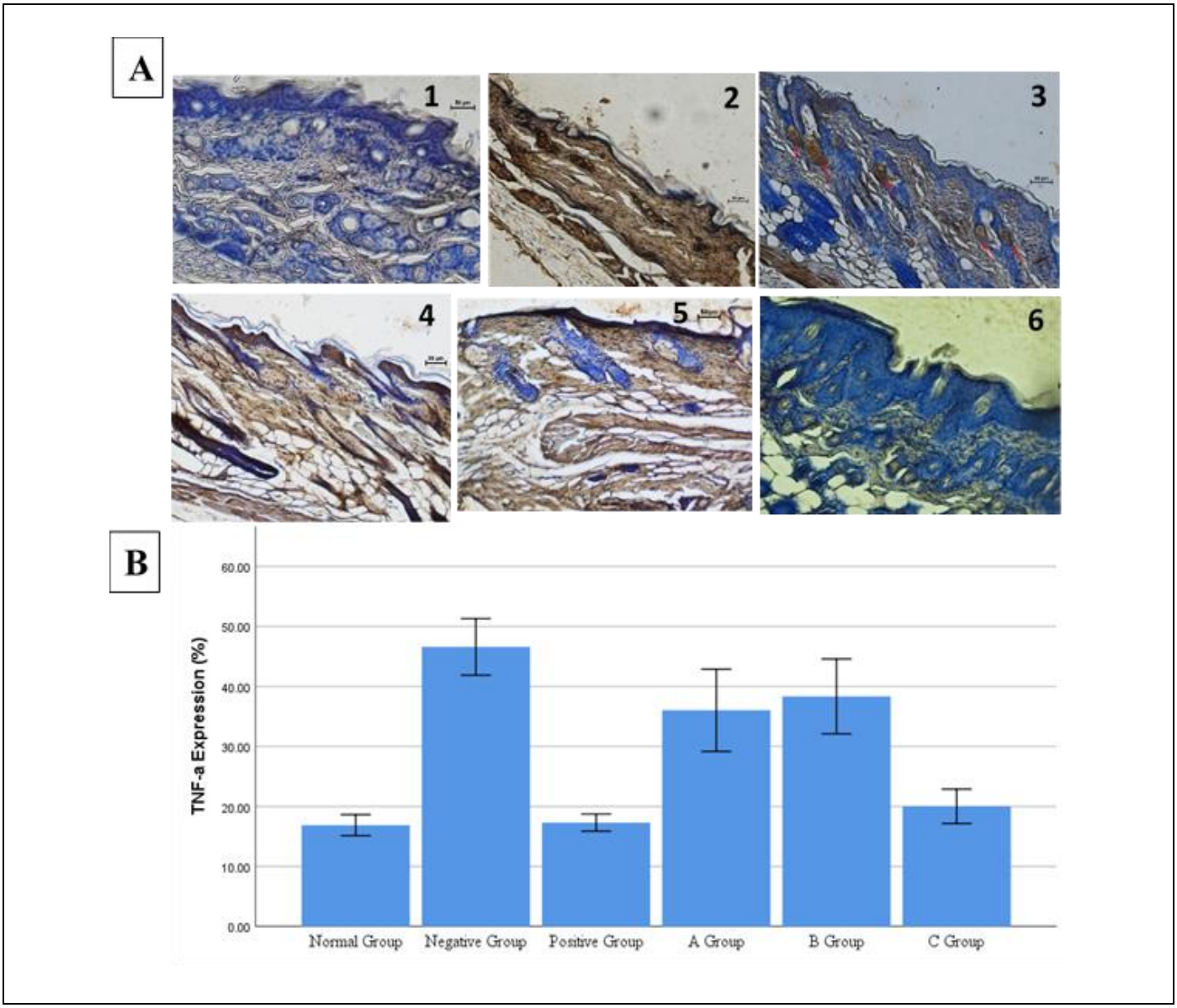

Figure 5. (A) Immunohistochemistry (100x) and (B) percentage of TNF-α expression of psoriasis mice skin. (1) Normal group (No induction and No treatment); (2) Negative group (Imiquimod cream 5% + No treatment); (3) Positive group (Imiquimod cream 5% + Desoximetasone® cream); (4) A group (Imiquimod cream 5% + nanoemulgel base); (5) B group (Imiquimod cream 5% + 2.5% JCE-gel); (6) C group (Imiquimod cream 5% + 2.5% JCE-NE-gel).

was even the same as the normal control with a value of 17.30%. Administration of Desoximetasone® cream was able to reduce inflammation that occurs in psoriasis mice so that TNF-α levels could decrease.

Group A (nanoemulgel base) and group B (2.5% JCE-gel) showed a decrease in TNF-α expression compared to the negative group, but the values were still quite high at 36.03% and 38.34%. These results are in line with the histopathology results which state that these two groups are still not optimal in overcoming psoriasis because the active ingredients are only able to work on the outside of the skin and have not been able to penetrate deep into the skin.

Different result from group C (2.5% JCE-NE-gel) which showed a percentage of TNF-α expression of 20.03% or close to the normal group and the positive group. JCE-NE-gel is able to penetrate into the skin to the dermis, so that the TNF-α protein which is an indicator of inflammation can be suppressed properly. The results of statistical analysis using the ANOVA Test also stated that group C had a significant difference in average TNF-α expression related to the negative group for 56.9% ($p < 0.05$). It means that 2.5% JCE-NE-gel is able to suppress TNF-α expression in the skin of psoriasis mice.

4. DISCUSSION

TNF-α is one of the proinflammatory cytokines that is thought to have a very important role in the immunopathogenesis of psoriasis. TNF-α is a major proinflammatory factor regulated by various factors,

such as lipopolysaccharide, pathogens, IL-1, and immune complexes. Primarily, TNF-α is secreted by macrophages, monocytes, activated T cells and keratinocytes. Increased levels of TNF-α are found in the skin of psoriasis patients[7].

Reducing TNF-α expression is one of the parameters for the success of psoriasis therapy in several studies that have been conducted[24-27]. In psoriasis, TNF-α levels are higher compared to non-lesion skin and normal individual skin. TNF-α levels in lesions and serum of psoriasis patients are directly proportional to the severity of the disease, as assessed by the PASI score. TNF-α activity is in accordance with the histopathological findings of psoriasis which provide a typical picture of keratinocyte hyper-proliferation, angiogenesis, neutrophil and lymphocyte infiltration. This disorder is caused because TNF-α can trigger the expression of adhesion molecules such as Intercellular Adhesion Molecule (ICAM), Vascular Cell Adhesion Molecule (VCAM), Vascular Endothelial Growth Factor (VEGF) expression, synthesis of inflammatory cytokines such as IL-1, IL-6, IL-8 and chemokine synthesis[28].

The four important active compounds contained in *Jatropha curcas* leaves extract as an anti-psoriasis are Apigenin, Vitexin, Quercetin and Catechins. Apigenin, flavonoid, has been shown to have anti-psoriasis activity. Apigenin can improve the skin condition of psoriasis by regulating the transcription of pro-inflammatory cytokines in the TLR4 pathway[29]. Vitexin is also able to reduce neutrophil migration and suppress the expression of pro-inflammatory mediators TNF-α and IL-1β through the p38, ERK1/2 and JNK pathways[30]. Quercetin is able to inhibit inflammation in psoriasis skin through the NF-κB pathway[31].

Catechins have also been shown to be able to treat psoriasis through their ability to suppress the expression of CD11c (+), IL-17A, IL-17F, IL-22, IL-23 and MDA cells in the blood. In addition, catechins are also able to increase CD4(+) T cells, SOD and CAT[32]. Thus, these compounds in *Jatropha curcas* leaves will be an extraordinary potential as an alternative treatment for psoriasis. Thus, in further research, analysis of the expression of pro-inflammatory proteins other than TNF-α such as IL-10, IL-6, NF-κB, CD4(+) and so on can be carried out to determine the specific mechanism of JCE-NE-gel as topical drug for psoriasis.

5. CONCLUSIONS

The results show that nanoemulgel have proven to be suitable carriers for the delivery system of plant extract through the topical route. This nanoemulgel system proved that it could increase the permeability of the active drug to accelerate the healing of psoriasis. This study concludes that 2.5% JCE-NE-gel was able to reduce PASI scores, reduce epidermal thickening, and suppress TNF-α expression in imiquimod-induced psoriasis mice. So, 2.5% JCE-NE-gel could be suggested as a promising treatment for psoriasis disorders. However, analysis of the expression of pro-inflammatory proteins other than TNF-α should be further explored in the future to determine its specific mechanism of anti-psoriasis from JCE-NE-gel.

6. ACKNOWLEDGEMENTS

Author contribution

All authors supported in the conceptualization, methodology, data researching, analyzing, and summarizing. All authors also have read and approved of the final manuscript. Writing-original draft preparation, MANA and JS; Editing and checking the grammar, FNF. Supervision, TE and S.

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Conflict of interest (If any)

None to declare

Ethics approval

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