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The Ameliorating Effect of Swertiamarine against the Imiquimod-Induced Psoriasis-like Inflammation in Mice

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ABSTRACT

Psoriasis is a chronic inflammatory condition affecting the skin and hair. This study evaluates the impact of Swertiamarine on inflammation induced by Imiquimod-induced psoriasis in mice. Swertiamarine ointment was topically administered before Imiquimod application, and mice were divided into five groups for various treatments. The control group received a daily cream application (62.5mg/2cm) on the shaved back along with an oral vehicle dose for 14 days. The Imiquimod group applied a topical vehicle dose one hour before Imiquimod 5% (62.5 mg/2 cm) on the shaved back for 14 consecutive days. The Swertiamarine-treated group applied Swertiamarine topically one hour before Imiquimod 5% (62.5 mg/2 cm) for the same duration. The clobetasol-treated group received clobetasol ointment (62.5mg/2cm) one hour before Imiquimod 5% (62.5 mg/2 cm) for 14 days. The Swertiamarine-only group received topical Swertiamarine doses for 14 days. Results showed a significant reduction in TNF-α, IL-23, IL-17 levels, and improvements in severity index, psoriasis area, skin thickness, spleen index, and decreased gene expression of TNF-α, Nf-KB, IL-1B, IL-17 in the Swertiamarine group compared to the vehicle

group with Imiquimod. In summary, Swertiamarine demonstrated a potent ameliorating effect, surpassing clobetasol in the context of Imiquimod-induced psoriasis-like inflammation in mice.

1. Introduction

Psoriasis is a common chronic skin disorder with a global prevalence of 2-3%. Psoriasis is caused by an immune-mediated inflammatory response. Chemokines and cytokines typically attract immune system cells to the psoriatic skin area. Invading cells and local cell proliferation quickly follow. [1-3] Psoriasis, on the other hand, has been linked to metabolic syndrome and cardiovascular disease are examples of co-morbidities.[4,5] Although research has yet to reveal the precise cause of the condition, environmental factors such as infection, stress, drugs, and trauma have been proposed as possible causes. Psoriasis affects the appearance of the skin, significantly lowering patients' quality of life. There is no complete cure for the disease, despite several short- and longterm treatment options. Initially, the disease was thought to be an autoimmune disease mediated by Th1.[6] However, mounting evidence suggests that the cytokines interleukin (IL)-17, Foxp3 (induced by Th17 or neutrophils, respectively), and Treg cells are to blame for the increased prevalence of psoriatic lesion skin and may play a role in disease progression.[7]

Imiquimod (IMQ) is a potent immune stimulator and Agonist of the toll-like receptor 7/8.IMQ In mice, it causes psoriasis-like skin., that is phenotypically and histologically Dermatitis similar to human psoriasis.[8] Imiquimod-mediated endothelial activation causes an influx of CD8+ T cells, lowering the percentage of tumor Treg cells to normal skin levels. Aside from this recruitment mediated effect, imiquimod reduces Treg cells' ability to suppress T-cell responses.

Swertiamarine is a seco-iridoid glycoside that is mostly found in Enicostemma littorale Blume (E. littorale), has medicinal properties for a variety of diseases.[9] Swertiamarine is a compound with numerous pharmacological properties, including hepatoprotective, analgesic, anti-inflammatory, antiarthritic, antidiabetic, antioxidant, neuroprotective, and gastroprotective properties.[10] Swertiamarine's anticancer activity against various cancer cell lines was recently reported. All of these pharmacological effects appear to regulate a variety of molecular targets, including growth factors, inflammatory cytokines, protein kinases, apoptosis-related proteins, receptors, and enzymes. Swertiamarine also affects the activity of a number of transcription factors, and their signaling pathways are discussed in various pathological conditions.[11] The study evaluated the ameliorating effects of swertaimarin against imiquimod-induced psoriasis in mice.

Swertiamarin is a seco-iridoid glycoside that is mostly present in Enicostemma littorale Blume (E. littorale) and has therapeutic properties that can be applied to a variety of medical conditions.[9] A wide range of pharmacological properties are displayed by swertiamarin, including hepatoprotective, analgesic, anti-inflammatory, antiarthritic, antidiabetic, antioxidant, neuroprotective, and gastroprotective effects.[10] Furthermore, its anticancer potential against several cancer cell lines has been revealed by current research. The regulation of numerous molecular targets, including growth factors, inflammatory cytokines, protein kinases, apoptosisrelated proteins, receptors, and enzymes, is linked to these pharmacological actions. Additionally, swertiamarin affects the activity of a number of transcription factors, and the context of various clinical diseases is examined when considering their role in signaling pathways. [11]

Various extraction methods like static extraction (SE), continuous shaking extraction (CSE), and ultrasonic extraction (USE) were evaluated for increasing recovery percentage of swertiamarin. The quantification was done using reversed phase-ultra flow liquid chromatographic (RP-UFLC) method at 238 nm

(swertiamarin) wavelength. The results revealed that the percentage extraction of swertiamarin from different species of Swertia by SE was more proficient [20].

2. Material and Methods

2.1. Experimental protocol

During approximately 14 days in a row, mice were given Imiquimod cream (Aldara 5%; MEDA Pharma, Germany) topically administered to their shaved back and right ear 15. The mice in the control group were given a vehicle orally. The mice were then divided into the following distinct groups [17].

1. Control group: The control group received treatment consisting of applying a cream base (62.5 mg/2 cm) to their shaved back and 5 mg to their right ear, along with taking a topical vehicle dosage every day for 14 days in a row.

2. Imiquimod group: For a continuous period of fourteen days, the mice were given a daily topical ointment one hour before imiquimod 5% was applied to their shaved back (62.5 mg per 2 cm) and right ear (5 mg).

3. Swertaimarine -treated groups: For two weeks, mice received varying daily topical doses of swertaimarine just before being treated with imiquimod 5% on their shaved back (62.5 mg per square centimeter) and right ear (5 mg).

4. Clobetasol-treated group: In a fourteen-day study, mice were administered Clobetasol (0.05%) topically one hour before applying imiquimod 5% cream to their shaved backs (62.5 mg/2 cm) and right ear (5 mg).

5. Swertaimarine only group: For fourteen days in a row, mice were given a topical dose of swertaimarine every day.

All animals were sacrificed at the end of the experiment, the back area and right ear tissue and blood were collected.

2.1.1 Measurement of Ear Thickness and skin thickness

The ear thickness and skin thickness were measured using digital vernier caliper [17].

2.1.2 Scoring Severity of Skin Inflammation

A clinical PASI-based on scores quantitative evaluation system was used by a dermatologist to assess psoriasis area and severity to determine the degree of inflammation in the back skin. On a range of 0 - 4, erythema, thickness, scaling and were all rated. : 0 = none, 1 = slight, 2 = moderate, 3 = marked, 4 = extremely marked. A lower quality of life and dissatisfaction with one's skin condition were linked to a higher PASI score. Furthermore, improvements in PASI were linked to decreases in general bodily pain in mice. To assess the severity of skin disease, the PASI scale was used. PASI scores range from 0 to 72. The higher the score, the worse the psoriasis. PASI is sensitive to changes in psoriasis severity over time as a result of treatment; However, the PASI score 3 and small skin areas affected by psoriasis are less sensitive. A 50% decrease in PASI score (PASI 50) is considered clinically meaningful improvement [12].

2.1.3 Spleen index estimates

At zero time, all mice were weighed, and the spleen index was computed by dividing (the mice spleen weight in mg by the body weight in gm) [13].

2.1.4 Preparation of serum samples

Blood was collected by the heart puncture and put in the Eppendorf tube and was centrifuged at (3500rpmfor 15 minute) to obtain serum, which was stored at -20 C until the day of analysis.

Serum was utilized for estimation of serum IL-23 level &serum IL-17 level 16.

2.1.5 Preparation of skin tissue homogenate

Blood was collected through a heart puncture, and the animal were euthanized through cervical dislocation. Skin from the back was extracted via incision and was washed with phosphate buffered saline pH (7-7.2). After the skin has been frozen for 24 hours, each

Table 1. Volume and reaction components.	
Component	**Volume**
Total (RNA/MRNA)	4
(dt 18) Anchored Oligo Primer	(0.5μg/1μl) 1μl
Random Primer	(0.1μg/1μl) 1μl
2×EX Reaction Mix	(10μl)
*Easy Scripte*r/RI Enzyme Mix	(1μl)
gDNA Remover	(1μl)
RNase free Water	Up To 20μl

Table 2. Thermal cycler steps [14].			
	Step 1	**Step2**	**Step3**
Temperature	25 Cº	42 Cº	85 Cº
Time	10 minutes	15 minutes	5 seconds
	(N9) Random Primer	(dt 18) Anchored Oligo	Inactivate reverse transcriptase enzyme

0.05 gm of skin was minced in 0.45 ml of phosphate buffer and homogenized separately by tissue homogenizer. The resulting homogenate was centrifuged for 15 minutes at 5000rpm, and the supernatant was collected with a micropipette and stored at -20 C until the day of analysis. TNF-, NF-kB, and other cytokines (IL-17, IL-23) assayed in tissue using skin homogenate.

2.1.6 Polymerase chain reaction

The GENEzolTM TriRNA Pure Kit from Geneiad, India was especially used in the Trizol method to isolate total RNAs. The standard operating procedures were followed when performing reverse transcription PCR (RT-PCR). Table 1 lists the primer pairs that match to

Table 3: Product primer sequences and gene names.	
Gene ID	**Primer sequence (forward/reverse)**
Gap (**Housekeeping)**	Forward gene:**5-CTTTGTCAAGCTCATTTCCTGG-3** **Reverse gene: 5-TCTTGCTCAGTGTCCTTGC-3**
TNF-alpha	Forward gene: 5-TAGCCCACGTCGTAGCAAAC-3 Reverse gene: 5-ACAAGGTACAACCCATCGGC-3
NF-κB	Forward gene: 5-AAGACAAGGAGCAGGACATG-3 Reverse gene: 5-AGCAACATCTTCACATCCC-3
IL-1B	Forward gene: 5-ACGGACCCCAAAAGATGAAG-3 Reverse gene: 5-TTCTCCACAGCCACAATGAG-3
IL-17	Forward gene: 5-TCCAGAATGTGAAGGTCAACC-3 Reverse gene: 5-TATCAGGGTCTTCATTGCGG-3

the expected results. Applied Biosystems provided all of the primers.

2.1.6.1 RNA Purification Protocol

Procedure: Sample Lysis and Homogenization

The samples were prepared at room temperature.

1- Tissue (10-50mg) removed from the animal.

2-Place the tissue in a two-milliliter centrifuge tube with ceramic or stainless-steel beads, then add 700 microliters of GENEzolTM Reagent on top of it. Next, use a Tissue Lyser, Disruptor Genie, or a comparable device to homogenize the material.

3- The homogenized sample was incubated for five minutes at room temperature.

Binding of RNA

1. After centrifuging the samples at 16,000 x g for a minute to remove debrided cells, the supernatant was carefully transferred to a fresh microcentrifuge tube labeled as RNasefree 1.5 mL.

2. Mixture of the sample and absolute ethanol (1:1) ratios was supplemented in GENEzol Reagent.

3. After thoroughly mixing the sample mixture with a vortex, the RB Column was placed in the Collection Tube (two ml).

4. After being transferred to the RB Column, the 700 ml sample mixture was centrifuged at 16,000 x g for one minute.

Washing process of RNA

1. The RB Column was charged with (400ml) of Pre-Wash Buffer and centrifuged 30 secend at (16,000 x g).

2. The RB Column was filled with the 600 ml Wash Buffer, and the procedure was carried out once more.

3. The RB Column was charged with (600ml) of Pre-Wash Buffer, and the process was repeated.

4. drying the column matrix by using centrifuge at (14-16,000 x g) for period of three minutes.

Elution process of RNA

1. The RB Column in its dry condition was placed in a 1.5 ml RNase-free micro-centrifuge tube.

2. Approximately 25 - 50 milliliters of RNase-free Water were gently added to the column matrix's middle region.

3. Duration of three minutes were provided to guarantee that the RNase-free Water was entirely absorbed by the matrix.

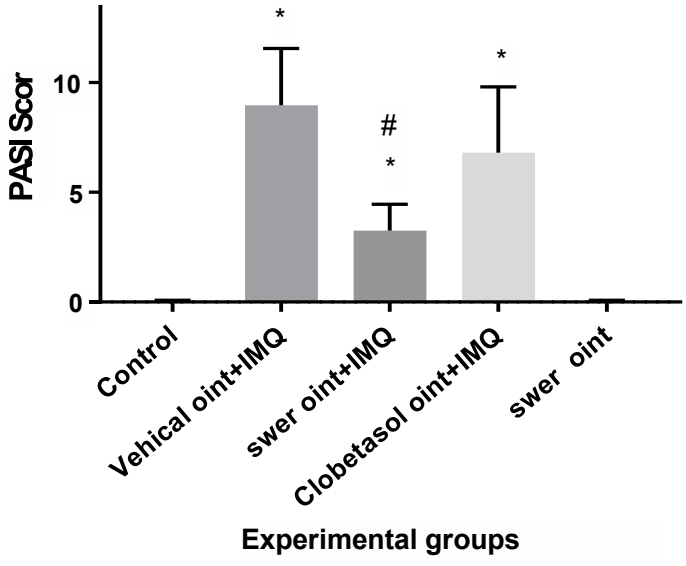

Figure 1. *The psoriasis area and the psoriasis severity index (PASI) in imiquimod induced psoriasis in mice after topical administration of swertaimarine. Each value represents the average of 50 measurments * Distinction from the control group) (P=0. <05). # significant difference from vehicle ointment + IMQ group (P=0.05.)*

4. To complete the elute process, the pure RNA was centrifuged for 60 seconds at (16,000 X g)

2.1.6.2 Remove of gDNA and cDNA synthesis in a single step

To begin cDNA synthesis, the procedure described in the (Easy Script® One-Step gDNA Removal & cDNA Synthesis Super Mix) was utilized. a- First strand cDNA synthesis procedure.

2.2 Histopathological analysis

In this investigation, paraffin sections were produced for histological examination using techniques described by Junqueira et al. (1995) 14 on both the right ear and the back area skin 15.

2.3 Statistical analysis

The unpaired Student t-test, which is used when comparing two distinct subjects, is used to examine the significance of differences in average values. In addition, the analysis employs Microsoft Excel 2016 and the Anova test to compare several independent groups. When the Pvalue goes below 0.05, indicating statistical significance at a 95% confidence level, all of the displayed data is considered significant 15.

3. Results and discussion

3.1 Swertaimarine's topical influence on the PASI score

By comparing the subjects' animal with imiquimod to the control group, the PASI score showed a significant increase. However, the PASI score was dramatically reduced by Swertaimarine as compared to the control group., demonstrating its anti-inflammatory efficacy. Additionally, as seen in Figure 1, the topical administration of Clobetasol resulted in a significant decrease in the PASI score as compared to the IMQ-treated group.

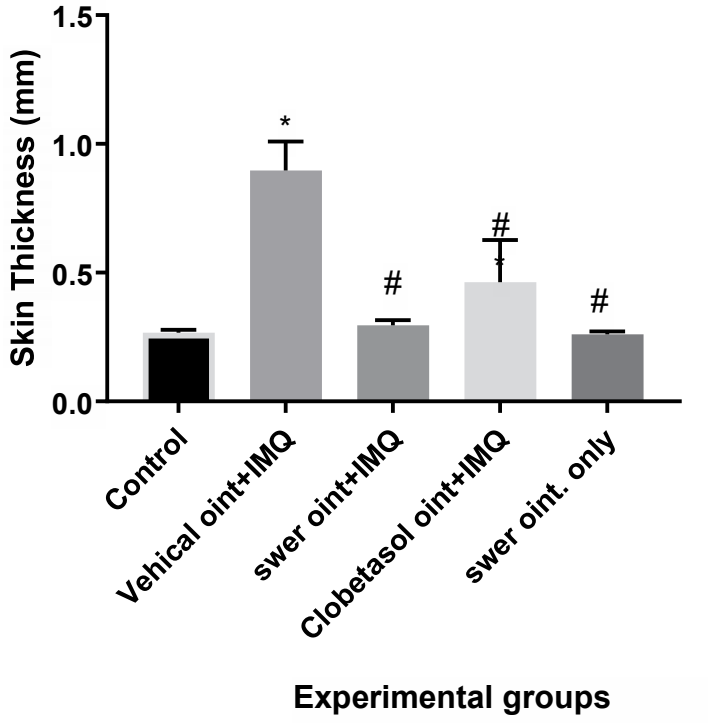

Figure 2. *The effect of topically applied swertaimarine on skin thickness in mice with imiquimod-induced psoriasis. The data include the average of 50 measurments * Distinction from the control group) (P=0. <05). # significant difference from vehicle ointment + IMQ group (P=0.05).*

3.2 Swertaimarine's influence on skin thickness of mice

Figure 2 illustrates a significant comparison of skin thickness between model and control groups. In comparison to the IMQ-treated mice, the administration of Clobetasol and Swertaimarine resulted in a significant reduction in skin thickness. While, in the (swertaimarin ointment) group, skin thickness remained normal.

3.3 Evaluation of the effect of topical swertaimarine application on spleen index in mice with imiquimod-induced psoriasis.

The data shown in Figure 3 indicates that the mice in the IMQ-treated group had a significantly higher spleen index than the mice in the control group. In contrast to the control group, the (swertaimarin ointment + IMQ) group keeps its spleen index within the anticipated range. while the Clobetasol-treated group experiences a significant decrease in spleen index compared to the (Vehicle ointment + IMQ) group.

3.4 The consequence of topically administered swertiamarine on the serum TNF-alfa, IL-17, IL-23 and levels.

The results presented in Figure 4, which represents Groups A and B, demonstrates a significant increase (p-value < 0.05) in the IL-23 and IL-17 levels in the IMQ-treated group relative to the control group. In addition, compared to the model group, the administration of clobetasol significantly decreased the levels of serum IL-23 (p-value < 0.05). Furthermore, when swertaimarine was applied topically, the concentra-

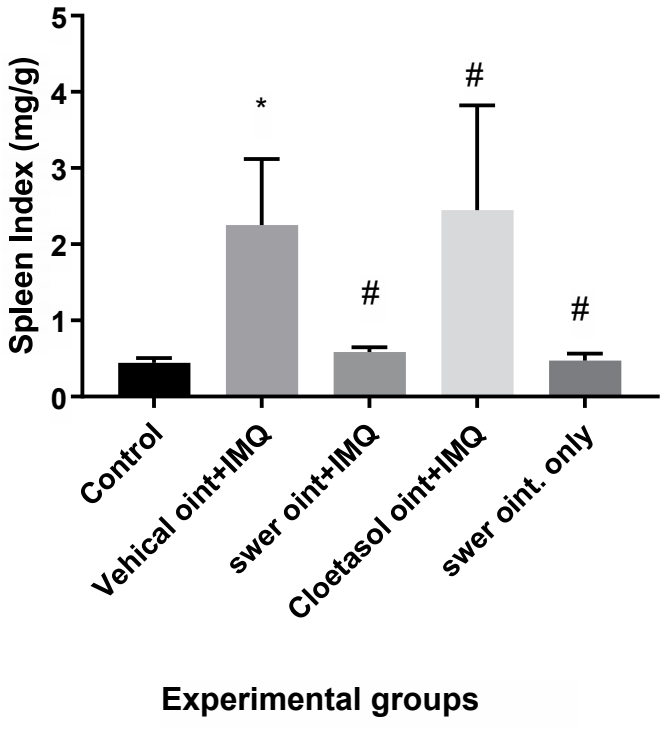

Figure 3. *The Spleen index after topical swertaimarine applied to mice suffering from psoriasis induced by imiquimod. The data include the average of 50 measurments. * Distinction from the control group) (P=0.05). # significant difference from vehicle ointment + IMQ group (P=0.05).*

tion of serum indicators (IL-23 and IL-17) significantly decreased ($p < 0.05$) compared to the (Vehicle + IMQ) cohort. Furthermore, there was a statistically significant ($p < 0.05$) reduction in the effect of swertaimarin ointment on serum

(IL-23 and IL-17) levels as compared to a control group of healthy mice. Figure 4C shows a noteworthy rise in tissue TNF-alpha levels (p 0.05) in the "Vehicle oint + IMQ" group when compared to the normal control group. Furthermore, the "Vehicle oint + IMQ" group showed a substantial reduction in tissue TNF-alpha levels (p 0.05). The "Swertaimarine oint only" group, on the other hand, had considerably lower tissue TNF-alpha levels (p 0.05) than the "Vehicle oint + IMQ" group.

3.5 The influence of topically applying swertaimarine on (A) serum levels of IL-23, (B) IL-17, and (C) TNF- in a mice model of imiquimod-induced psoriasis.

The IL-1B gene expression in mice treated with IMQ is shown in Figure 5A. Comparing Swertaimarine to the model group, there was a substantial decrease in IL-1B expression, suggesting a strong anti-inflammatory impact. Furthermore, the administration of clobetasol and swertaimarine separately revealed a noteworthy inhibition in IL-1B mRNA levels in skin tissue, outperforming that of the control group.

Figure 5B shows that the model mice treated with IMQ had significantly higher levels of TNF-α in their skin than the control group. On the other hand, TNF-α gene expression was considerably lower in the (swer Oint + IMQ) group than in the (Vehicle+IMQ) group.

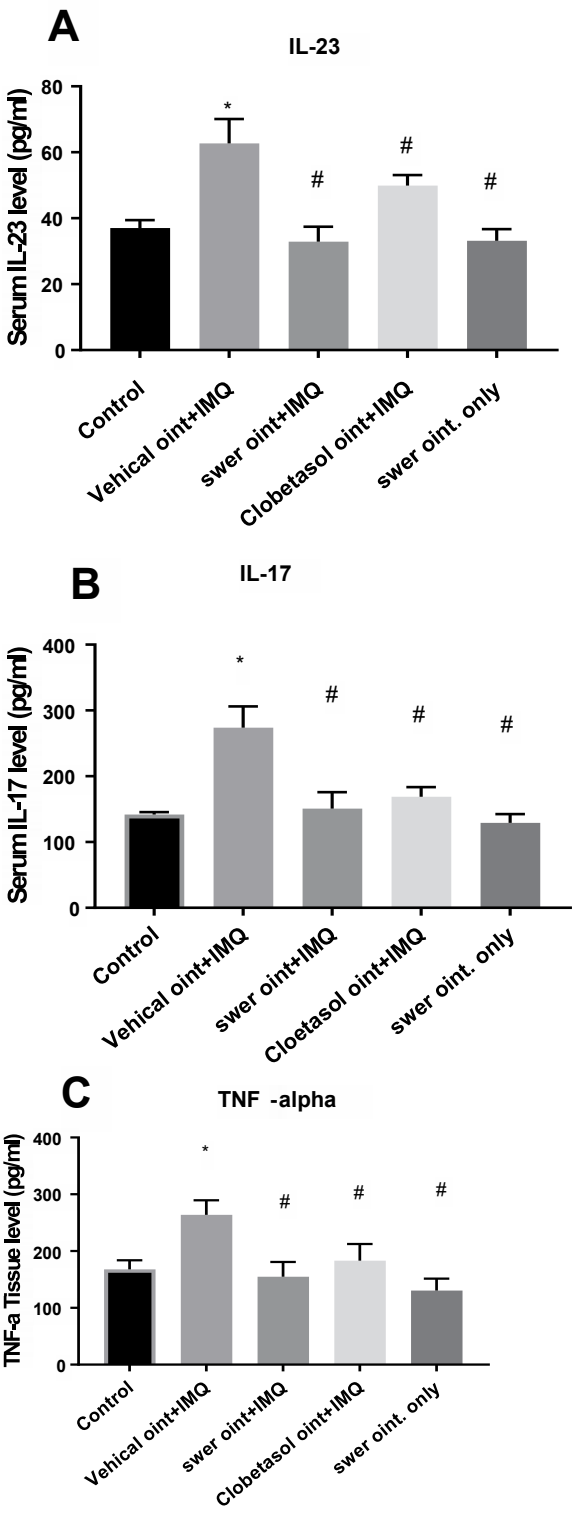

Figure 4. *The consequences of topically applying swertaimarine on (A) serum levels of IL23, (B) IL-17, and (C) TNF- in a mice model of imiquimod-induced psoriasis. The data include the average of 50 measurments * Distinction from the control group) (P=0.05). # significant difference from vehicle oint + IMQ group (P=0.05).*

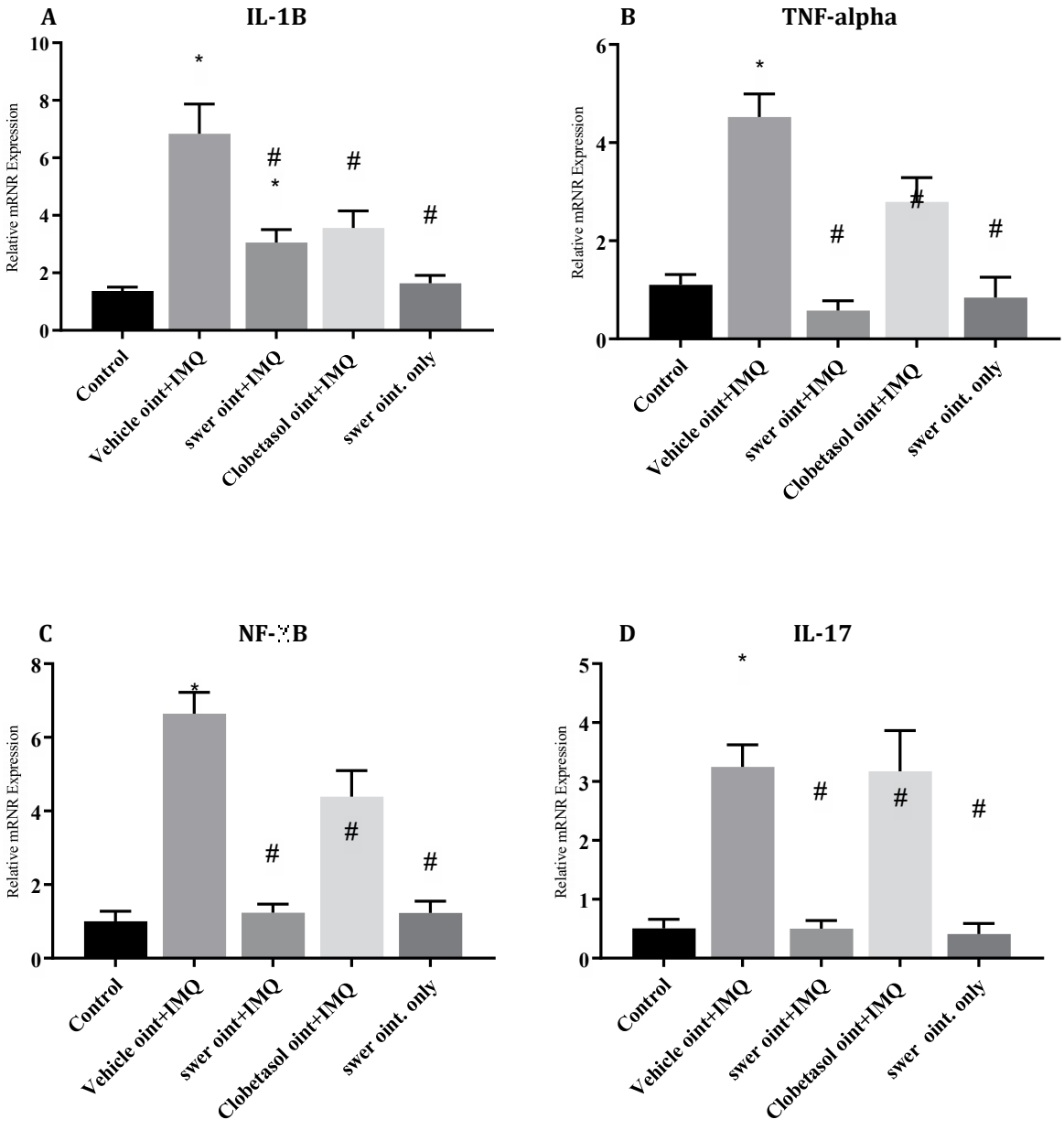

Figure 5*. displayed the influence of swertaimarine topically applying swertaimarine on the gene expression of the (a)IL-1B, (b) TNF-, (c)NF-KB, and (d) IL-17) against imiquimodinduced psoriasis-like inflammation in mice. The data include the average of 50 measurments *Distinction from the control group) (P=0.05). # significant difference from vehicle oint + IMQ group (P=0.05).*

Moreover, there were notable differences in the TNF-α gene expression in the mice from the (Clobetasol oint+IMQ) and (swer oint alone) groups and the TNF-α gene expression in the (Control) group.

As Figure 5C illustrates, topically applied swertaimarine significantly reduces NF-κB mRNA expression

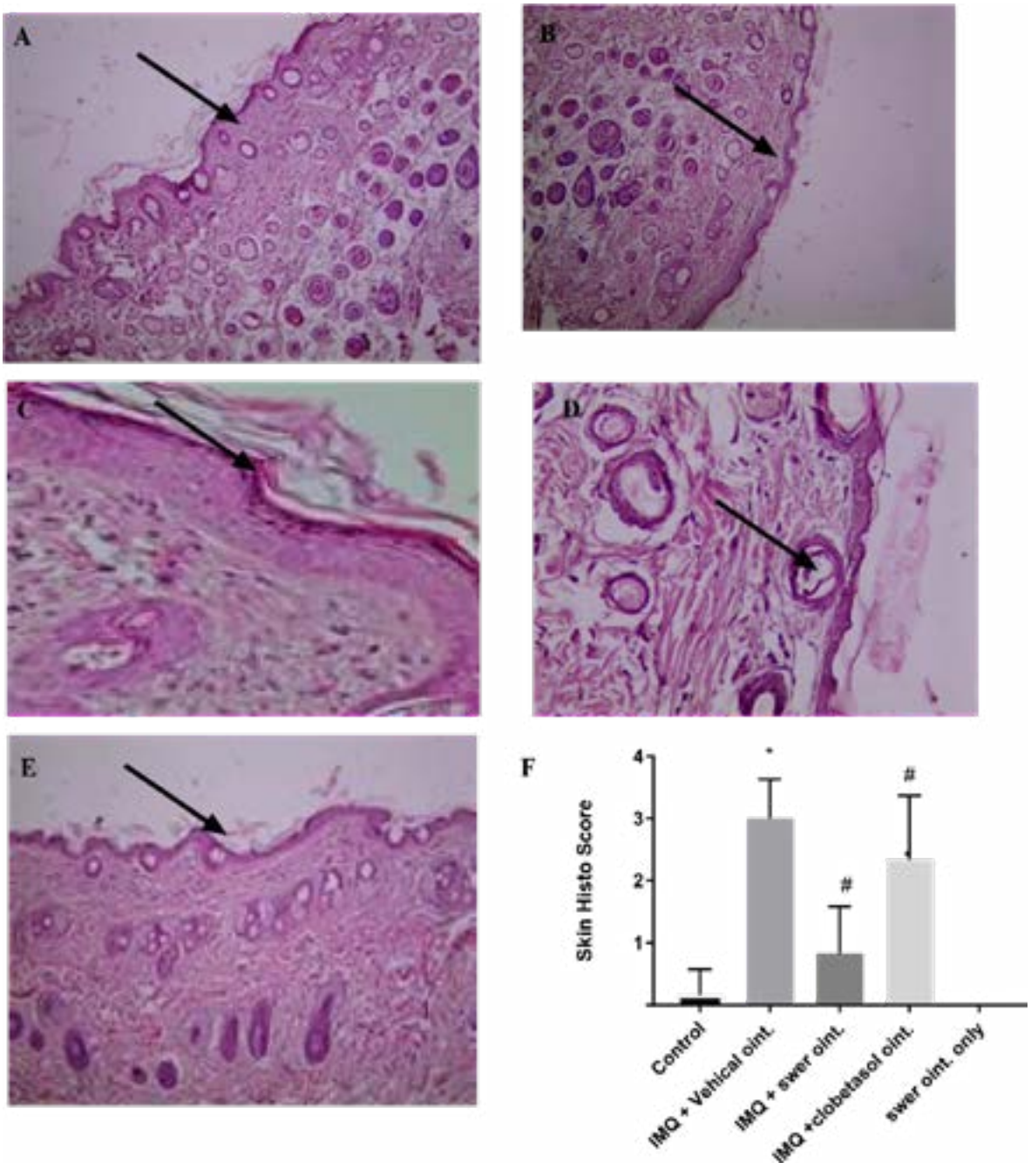

***Figure 6**. The impact of swertaimarine on pathological psoriasis alterations in the back area caused by IMQ. The black arrows indicate the level of thickness of the right ear section's epidermal layer. Analysis of histology scoring A, B, C, D, and E are corresponding to control, vehicle +IMQ, swer ointment +IMQ, Clobetasol ointment+IMQ and swer ointment only groups respectively. F: Each value is the average of 50 measurments * Distinction from the control group) (P=0. <05). # significant difference from vehicle oint + IMQ group (P=0.05)*

in the skin, hence inhibiting the imiquimod-induced inflammatory response. Comparing clobetasol to the model group, there is a noticeable anti-inflammatory effect on NFκB levels.

When compared to the control group, the model group showed a significant increase in IL-17 gene expression in the back skin. While swertaimarine effectively reduced IL-17 gene expression in model mice, similar to Clobetasol's effect on IL-17 levels.

3.6 Impact of swertaimarine topical treatment on histological testing in mice with imiquimod induced psoriasis.

Histological sections showed skin in the normal control group back area had a normal appearance, as shown in Figure 6 A. The histological section of the skin of the back area (vehicle oint + IMQ) showed marked hyperkeratosis and acanthosis (5 cells) of the epidermis with heavy inflammatory cells in the upper dermis, as shown in Figure 6 B. As shown in Figure 6C, pretreatment with swertaimarin resulted in a normal appearance of skin tissues in a back area of the skin.As depicted in figure 6, in mice administered Clobetasol, the dorsal region displayed a thin layer of epidermis, moderate hyperkeratosis, and minor acanthosis, along with a rete ridge with mild infiltration of inflammatory cells.

There have been significant impairments and a reduction in quality of life associated with the chronic inflammatory skin and joint disease psoriasis. In addition, IMQ, a synthetic TLR 7 agonist, is used in the treatment of actinic keratosis, superficial basal cell carcinoma, and vaginal and perianal warts caused by human papillomavirus. In the present work, psoriasis-like skin inflammation has been induced by topical application of IMQ [16]. A clever scoring system was developed to assess the severity of back skin inflammation. Noticeable, when IMQ was administered topically, it exacerbated skin inflammation as shown by thicker skin, as indicated by the considerably higher PASI score for the Vehicle oint+IMQ group than the PASI score for the Control group 17. Furthermore, the PASI score tended to decrease significantly in the (swer oint+IMQ) group compared with the (Vehicle oint+IMQ) group when swertaimarine was given pointing out that swertaimarine showed clear activity as anti-inflammatory. Furthermore, compared to the (Control) group, the daily dose of swertaimarine significantly decreased the serum levels of interleukins (IL17, IL23). This finding demonstrated the anti-inflammatory effect of swertaimarine ointment by lowering interleukin levels, and it was evident in the (swer oint+IMQ) group.

There has also been improvement in the histological features. It was once thought that interleukin 23 (IL-23), a cytokine that promotes the growth of Th17 cells that produce IL-17 and IL-22, was directly responsible for the onset of psoriasis. After receiving swertaimarine treatment, there was a considerable increase in TNF- levels and an abundance of (IL-23) and T-helper 17 cells in the lesional-skin of psoriasis as compared to the control group. Due to swertaimarine's ability to protect against imiquimod-induced inflammation, there has been a decrease in the induction of TNF-alfa in the group that received treatment. This is in line with other earlier research that discovered swertaimarine has anti-inflammatory qualities [17]. TNF-alfa levels were significantly lower in the (swer oint+IMQ) group than in the (vehicle oint+IMQ) group (P-value = 0.05 percent).

Psoriasis and a number of chronic inflammatory diseases have been linked to an overly active immune system, with the TNF, type I IFNs, and the IL-23/IL-17 axis all having significant effects. On the other hand, RT-PCR technical might also identify the expression of the genes for nuclear factor kappa B, interleukin-17, interleukin-1 beta, and tumor necrosis factor-alpha (TNF, IL-17, IL-1B, and NF-Kb) in mRNA. The results of this investigation indicate that there is a substantial positive link between the topically administered swertaimarine and the gene expression of TNF, IL-17, IL-1B, and NF-kB. Specifically, the expression of TNF was much greater in the Vehicle oint+IMQ group than in the Control group. Furthermore, Swertaimarine inhibits proinflammatory cytokines like IL-1B, IL-17, TNF and the NF-Kb gene due to its anti-inflammatory abilities [18]. When compared to the skin section of the back area in the (Vehicle oint+IMQ) group, where IMQ causes symptoms of local psoriasis recognized by inflammation, agglomeration, and scaling of the skin, the histopathological analyzing provid-

ed further support for the anti-inflammatory effects of swertaimarine on psoriasis caused by imiquimod. This section of the skin tissue of the back area in the (swertaimarine oint+IMQ) group appeared normal, which explained the ameliorating effect of swertaimarine. Additionally, dysregulated angiogenesis of cutaneous blood vessels, a neutrophil-rich stratum corneum, and infiltrates of the mononuclear dermal and epidermal layers, T cells, and dendritic cells in plaques have been reported [18]. Additionally, via controlling the TLR4 signaling system, swertaimarine has been demonstrated to lessen inflammation and liver damage brought on by carbon tetrachloride (CCl4) in mice. STM's control over the TLR4/NF-B signaling pathway was at least partially responsible for its suppression of CCl4-induced inflammation [18]. Consistent with this, SM has previously been shown to improve cell inflammatory status and has a high potential as a neurogenic, antioxidant, anti-nociceptive, and TNF suppressor [19,20]. A simple method for the isolation of swertiamarin, a secoiridoid glycoside, from the whole plant of Enicostemma littorale Blume. Methanol extract of defatted plant material when treated with diethyl ether gave a precipitate containing swertiamarin as one of the major components. Swertiamarin was separated from this precipitate by column chromatography over silica gel. The identity of the compound isolated was confirmed through infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), and mass spectra and melting point and co-chromatography with a reference standard on thin-layer chromatography (TLC). The purity of the compound was confirmed from the UV absorption spectrum, NMR, mass, high performance thin layer chromatography (HPTLC), and differential scanning calorimetry [21].

4. Conclusion

In summary, the findings of this study showed that swertaimarine administered to mice produced imiquimod-induced psoriasis ameliorative effects similar to those of clobetasol, but swertaimarine was more efficient than clobetasol in reducing skin thickness, spleen index, PASI, and gene expression. It has been found that swertaimarine able to reduce cytokine production and control inflammation in a mouse model of psoriasis-like inflammation caused by IMQ. However, we think that these novel results provide an optimistic outlook for the earliest phase of swertiamarine's possible therapeutic application. Hence, due to its anti-inflammatory properties, swertaimarine is an intriguing treatment for psoriasis in the future, as evidenced by all the studies that showed a strong ameliorative impact. □

Conflict of Interest

The authors declare that there is no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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