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Evaluation of the Anti-Psoriatic Effect of Topical Dovramilast in an Imiquimod-Induced Psoriasis Mouse Model

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ABSTRACT

Objective: The aim of the study is to determine the pharmacological effect of phosphodiesterase 4 inhibitor (dovramilast) in a psoriasis mice model induced by imiquimod, and to estimate the levels of pro-inflammatory cytokines in skin tissue (IL-17A, IL-23 and TNF-α). Furthermore, histopathological scores for skin tissue were determined.

Methods: Fifty BALB/c male albino mice aged 8 weeks were used in this study. The mice were classified into five groups each group contain ten mice (n=10) as the following, group I (control) contained healthy mice, group II (induction) involve application of imiquimod 5% cream once daily for five consecutive days to produce inflammatory lesions that resemble to plaque psoriasis, group III, IV and V involve application of imiquimod 5% cream then three hours later treatments were applied for five consecutive days were, group III received clobetasol 0.05% ointment, group IV received dovramilast 0.3% ointment and group V utilize combination of formula contain both dovramilast 0.15% with clobetasol 0.025% ointment.

Results: The dovramilast-treated group showed a significant reduction in all inflammatory cytokines (IL-17A, IL-23 and TNF-α) compared to induction ($P<0.05$) and not significantly differ from clobetasol effect. Furthermore, dovramilast/clobetasol combination providing significant reduction in all measured inflammatory cytokines ($P<0.05$) when compared to induction and non-significantly differ from clobetasol-treated group.

Conclusions: Topical dovramilast, alone or in combination with clobetasol, may represent a promising therapeutic strategy for the management of psoriasis

Keywords: Apremilast, inflammation, phosphodiesterase 4, psoriasis.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder affecting approximately 2-3% of the global population. The process of developing psoriasis is complex and includes multiple contributing processes, namely immune cell dysregulation, keratinocyte hyperproliferation, and angiogenesis, which is also a prominent feature [(1)]. The development of psoriasis is related to multiple factors and not restricted to a single cause, including genetic factors, which play a major role in the development of psoriasis. However, nongenetic factors can also be linked to the onset and recurrence of psoriasis in genetically predisposed patients, such as infection, lipid disturbance, hormonal dysregulation, and mental illness [(2)]. Symptoms of psoriasis manifested as cutaneous redness, skin discomfort, pruritus, and bleeding. In addition, the available treatments are considered non-curative. However, it can control psoriasis symptoms and reduce disease flares [(3)]. Current therapeutic options include topical therapies, phototherapy, systemic immune modulators, and biologics. All have the main goal to relieve disease symptoms and improve quality of life. On the other hand, there are several challenges encountered, such as the development of side effects, resistance to treatment, high costs, and variation in response to treatment among patients [(4)].

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Several common oral and topical treatment options can be utilized in psoriasis, such as phosphodiesterase (PDE) 4 inhibitors, Janus kinase (JAK) inhibitors, and oral interleukin (IL)-17 inhibitors [(5)].

Topical corticosteroids are considered the most powerful and effective therapeutic option to manage symptoms of psoriasis. They act by many mechanisms; one of these includes inhibiting the activity of phospholipase A_2 due to their ability to stimulate certain proteins called lipocortins. In addition, corticosteroids affect other mediators that have a role in inflammation, such as prostaglandins and leukotrienes [(6)]. However, there are serious side effects associated with corticosteroid use, especially when utilized for prolonged periods. This includes topical side effects such as skin discoloration, striae, and telangiectasia. Other systemic effects include growth retardation in children, increased risk of cataracts, and rise of intraocular pressure [(7)]. Utilization of phosphodiesterase 4 inhibitors is among the available options to treat psoriasis. Apremilast is considered the first orally administered PDE-4 inhibitor approved by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe plaque psoriasis in 2014 [(8)]. However, apremilast is associated with severe gastrointestinal adverse effects, such as nausea, vomiting, and GI disturbance [(9)]. In patients receiving apremilast for psoriasis or psoriatic arthritis, about 30% discontinued treatment due to intolerance [(10)]. Basically, PDE4 enzymes control the synthesis of many pro-inflammatory and anti-inflammatory cytokines mediated through cyclic adenosine monophosphate (cAMP) [(11)].

PDE4i acts by inhibiting the enzyme PDE4, which is responsible for the hydrolysis of cAMP; therefore, elevating the level of intracellular cAMP leads to reducing the production of inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-17, interferon (IFN)-γ, and IL-23; preventing superoxide proliferation; and suppressing the chemotaxis process. In addition, they can upregulate certain mediators such as IL-10, which is considered a beneficial anti-inflammatory cytokine. Therefore, the PDE4 enzyme is considered a suitable therapeutic target to manage inflammatory diseases, including psoriasis [(12, 13)].

Dovramilast, also known as CC-11050, is classified as a novel potent PDE4i with anti-inflammatory properties and better tolerability. This PDE4i was utilized adjunctively with antibiotics for the management of tuberculosis in mouse and rabbit models infected with pulmonary tuberculosis; the results show that significant improvements in disease stage and enhanced bacillary clearance occur when combined with isoniazid and administered as host-directed therapy [(14)]. In addition, dovramilast reduces the immunopathological response that occurs in tuberculosis and completed phase 2a clinical trials in 2020 as a treatment option for tuberculosis [(15)]. Another study utilizes dovramilast in people living with HIV to manage acute inflammation related to the initiation of antiretroviral therapy (ART), and this condition is known as Immune Reconstitution Inflammatory Syndrome (IRIS). In addition, dovramilast is used for chronic inflammation in patients utilizing ART for a long term and who have suppressed HIV viremia in plasma [(16)]. Lastly, the advantage of utilizing this novel PDE4i topically is associated with a lower incidence of developing systemic side effects that occur with oral PDE4i [(17)].

This study aims to investigate the pharmacological effect of PDE4i (dovramilast) on imiquimod-induced psoriasis in a mice model.

MATERIALS AND METHODS

Drugs and Reagents

The imiquimod cream (5% w/w) was supplied from Glenmark (India). While dovramilast powder was purchased from Bidepharm (China) for animal studies. Clobetasol propionate 0.05% ointment (Promax ointment) ™ was supplied from Jamjoom Pharma Company (Kingdom of Saudi Arabia). Vaseline base (white petrolatum / Aljabal company-Iraq). DMSO (sigma-Aldrich / Germany).

Preparation ointment of Dovramilast 0.3% formula and 0.15%in combination with clobetasol

To prepare a dovramilast ointment of 0.3 w/w% concentration, The exact vehicle composition consisted of dimethyl sulfoxide (DMSO) as a solubilizing agent and white petrolatum (Vaseline) as the primary ointment base. Then weigh 75 mg of dovramilast powder using a sensitive balance, then add a few drops (0.3 ml) of dimethyl sulfoxide (DMSO) solvent to solubilize the drug powder, then mix manually using a stainless-steel spatula. The resulting mixture was geometrically diluted by adding a Vaseline base (white petrolatum) until the required volume of up to 25 gm was reached. On other hand, to prepare 0.15 w/w% of dovramilast in combination with clobetasol, involves the similar steps mentioned above to prepare a 25 g batch of 0.3% dovramilast. Except that this resulting final product is blended with 25 g of commercial clobetasol propionate ointment (0.05%) via

manual spatulation to achieve a homogeneous 50 g mixture containing a final dovramilast concentration of 0.15% w/w [18]. It is important to mention the storage condition, which involves ointments being prepared and stored in tightly sealed containers under refrigerated conditions (2–8 °C) for 5 days.

Experimental Design and Animal Models

The study was an experimental animal study conducted at Al-Nahrain University, College of Pharmacy, Department of Pharmacology, from October 2025 to February 2026. The study protocol was reviewed and approved by the College of Pharmacy at Al-Nahrain University in accordance with the adopted guidelines for experimental animal ethics (ethical approval certificate nah.co.pha.29-B 16/9/2025). The mice were provided from the animal house of the College of Pharmacy at Al-Nahrain University. Fifty BALB/c male albino mice aged 8 weeks were used in this study. They were placed in special polypropylene cages and fed regularly with a pellet diet and free access to water. Before performing the experiment, the mice were allowed to acclimate for 7 days. Then subsequently divide the mice into five groups, and each group contains ten mice. Lastly, two days before the application of any experimental drugs, the back of the mice was shaved using an electronic razor.

Group I was defined as the control group, which included healthy mice. Group II, defined as the induction group, an imiquimod cream 5% (dose equal to 62.5 mg) was topically applied to the shaved dorsal skin of the mice (an area of approximately 2 × 3 cm) using a sterile spatula. The cream was spread with gentle massage into the skin to ensure uniform distribution and optimal absorption. This procedure was performed once daily for five consecutive days to produce a state similar to plaque psoriasis characterized by scaly lesions [19].

Group III, defined as the positive control group, had imiquimod first applied to dorsal skin at 9 A.M.; then, after three hours, a steroid, clobetasol 0.05% ointment, was applied [20]. Group IV received imiquimod cream on the dorsal skin of mice at 9 A.M., and then after three hours, dovramilast 0.3% ointment was applied at 12 P.M. Lastly, group V received dovramilast 0.15% combined with clobetasol ointment, also applied after three hours of imiquimod application at 9 A.M. Figure 1 below illustrates the experimental design.

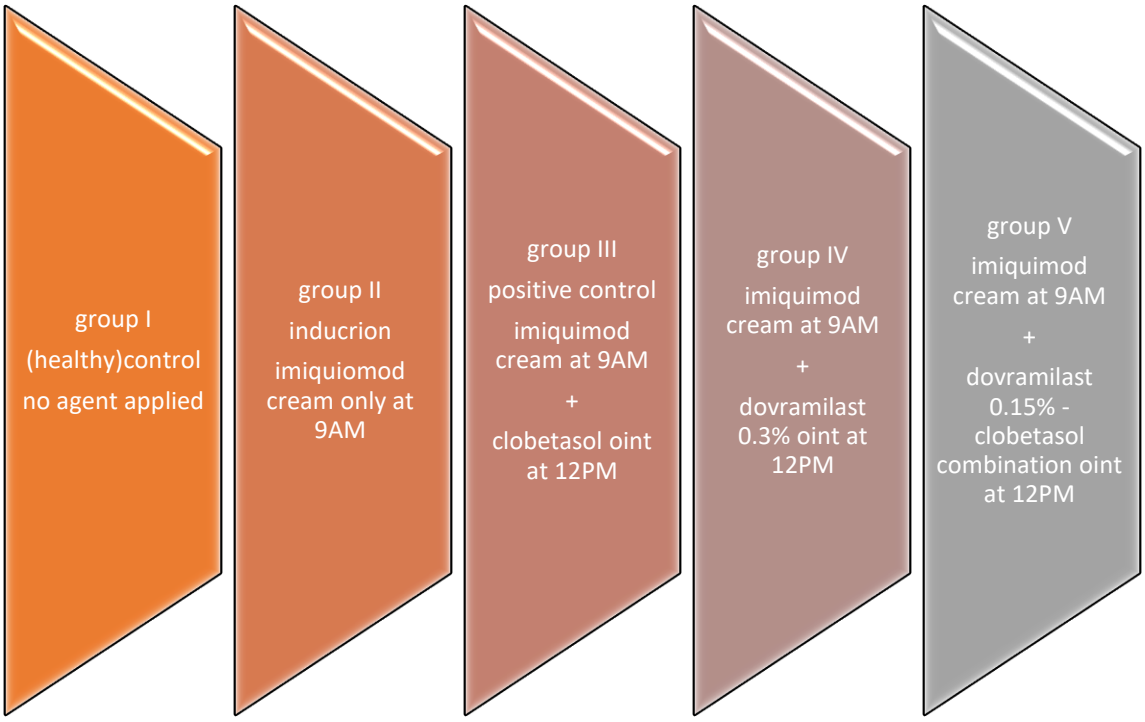

Figure 1. the experimental design of animals

Preparation of Samples

The animal handling and experimental procedures, including the method of sacrifice, were conducted according to ethical standards approved by Al-Nahrain university – college of pharmacy (certification approval number nah.co.pha.29-B 16/9/2025). on day five of the experiment, all mice were sacrificed using intraperitoneal (IP) anesthesia with 80 mg/kg of ketamine and 10 mg/kg of xylazine [21]. Then, by using surgical scissors and tweezers, the skin of the dorsal area can be separated and the extracted skin divided into two parts. The first part was transferred into a plain test tube filled with 10 ml buffered formalin to be used later for immunohistochemistry (IHC) and histopathology procedures [22]. On the other hand, the second part of the skin sample was placed in an Eppendorf tube and stored at -20℃ to conduct an ELISA assay in accordance with the manufacturing kit protocol.

Evaluation of IL-17A and IL-23 in skin sample by using ELISA assay

By performing the sandwich ELISA procedure using special IL-17A and IL-23 ELISA kits designed for mice (Elabscience kit—the catalog number of IL-17A is E-EL-M0047 and for IL-23 is E-EL-M0731-China) to estimate the levels of these inflammatory cytokines in the skin sample by following manufacturer instructions [23].

Immunohistochemical Evaluation

By using the semi-quantitative method that depends on the Immunoreactive Score (IRS) system, the IHC of TNF-α can be determined as originally described by Remmele and Stegner [24]. Furthermore, the level of tumor necrosis factor-alpha (TNF-α) was determined by using a special IHC kit to perform the test. The IRS value was calculated by multiplying the Staining Intensity (SI) score by the Percentage of Positive cells (PP) score to obtain the final score, which represents IRS. The Staining Intensity (SI) was graded as 0 = No staining, 1 = Weak staining, 2 = Moderate staining, and 3 = Strong staining, while the Percentage of Positive cells (PP) was described as 0 (<10% stained cells), 1 (≥10%), 2 (≥25%), 3 (≥50%), and 4 (≥75%). The final score was obtained by multiplying staining intensity by percentage of positive cells (SI × PP), which ranged from 0 to 12 [25]. And this final score is classified as the following: Negative (0–1), Mild (2–3), Moderate (4–8), and strongly positive (9–12), which are essential to use in statistical analysis later [26].

All these procedures of this test were performed by a specialized pathologist in the department of pathology at the College of Medicine, Al-Nahrain University, by following the catalog instructions. The information of the TNF-α IHC kit used (Fine-Test/FNab08821-China).

Histopathology procedure

On the last day of the experiment (day five), the mice were sacrificed by utilization of inhaled chloroform in a glass jar. Then, subsequently, extraction of a skin sample from mice was performed, and the sample was preserved in a plain test tube containing 10% of buffered formalin [27]. Then, to determine the histopathology score of skin samples, a special scoring system was used, which is known as Baker's scoring method. This scoring system is involving each histopathological parameter given a specific value when Munro’s abscess (2), Hyperkeratosis (0.5), Parakeratosis (1), Rete ridges appearance (1.5), Acanthosis (0.5), Lymphocytic infiltrate (mild=0.5, moderate=1, severe=1.5) [28].

Docking Studies

To conduct the docking procedure between the investigated ligand and protein targets, the Genetic Optimization for Ligand Docking (GOLD) Suite (2025 version) program was used. This program provides various beneficial features such as determination of ligand-target pose, the length of bond, hydrogen bond, and other short contacts [29,30].

Preparation of ligands and target

By using the Protein Data Bank (PDB), the crystal structure of targeted proteins can be downloaded. These proteins include phosphodiesterase 4B and phosphodiesterase 4D. the code of each protein obtained in which (PDB code: 1XMU) related to phosphodiesterase 4B enzyme. While (PDB code: 1XOQ) referred to phosphodiesterase 4D enzyme [31,32]. In addition, to obtain the chemical structures of the used ligands, a special program called ChemOffice software (version 20) was used [33]. Furthermore, another software known as BIOVIA Discovery Studio 2021 Client was utilized to convert the chemical structures of ligands obtained by ChemOffice into 3D structures [34].

Molecular docking protocol

The identified two proteins were extracted from the Protein Data Bank (PDB) website, and subsequently the crystal structure of two proteins was prepared, and this was done with the aid of Hermes software in the CCDC GOLD 2025 suite [35]. The next step involves removing water molecules that are not necessary for hydrogen bonding interaction, and this step is performed by using BIOVIA Discovery Studio 2021 client [36]. Then subsequently the reference molecule is removed from the active site of the targeted protein in order to prepare the active site for interaction [37]. Furthermore, 10 Å is the distance selected between the target protein active site and interacting ligands [38]. Finally, the docking process was conducted by using the GOLD 2025 program and a special scoring system utilized called ChemPLP scoring to describe the binding affinity between ligand and target protein [39].

Statistical analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago. Data were presented as mean and standard deviation, and analyzed with Student t-test (for two groups comparison) or analysis of variance (for more than two groups comparison), followed by least significant difference (LSD) as post hoc analysis. A p- value less than 0.05 was considered to indicate a statistically significant difference, while $p<0.01$ was considered as a statically highly significant difference.

RESULTS

Results of Pro-inflammatory cytokines levels in mice skin (IL-17A and IL-23 estimated by ELISA) and (TNF-α score determined by immunohistochemistry).

Table 1 demonstrates that imiquimod induction markedly increased systemic Th17-related cytokines and TNF-α expression compared with healthy mice, confirming successful establishment of a psoriasis-like inflammatory state. IL-17A rose from 220.78±30.37 pg/ml in healthy controls to 864.49±123.57 pg/ml in the induction group, while IL-23 increased from 161.04±12.96 pg/ml to 839.55±103.33 pg/ml, and TNF-α score increased from 0.0±0.0 to 10.44±1.88, with highly significant overall differences among groups ($p<0.001$ for all).

Topical treatment significantly attenuated these inflammatory markers: clobetasol reduced IL-17A and IL-23 to values statistically lower than induction (225.22±38.34 and 195.29±48.05, respectively), while dovramilast also brought IL-17A lower than induction and close to clobetasol levels (269.15±45.72). in addition, IL-23 significantly lower than induction but slightly higher than the clobetasol groups (271.75±70.51).

TNF-α scores were elevated significantly from 0.0±0.0 in healthy group to 10.44±1.88 in induction. Furthermore, reduced by all treatments (2.60±0.44 with clobetasol, 3.0±1.41 with dovramilast, and 2.89±1.05 with the combination), remaining far below induction. The combination of dovramilast with clobetasol produced the greatest suppression of IL-17A (121.42±15.02) and IL-23 to (156.92±27.9) which significantly far below induction and lower than clobetasol or dovramilast alone.

Table 1. Serum level of IL-17A and Il-23 and expression of TNF-α in different groups**,** Different horizontal capital letters indicate significant differences. The capital-letter annotations indicate multiple-comparison results; groups with different letters differ significantly. Groups that are sharing similar letter do no differ significantly. n =10 refer to number of mice utilized in each group.

Variables Mean ± standard deviation	Healthy n = 10	Induction n = 10	Clobetasol n = 10	Dovramilast n = 10	Dovramilast/ Clobetasol n = 10	p-value
IL-17A, pg/ml	220.78±30.37 A	864.49±123.57 B	225.22±38.34 A	269.15±45.72 A	121.42±15.02 C	**<0.001**
IL-23, pg/ml	161.04±12.96 A	839.55±103.33 B	195.29±48.05 A	271.75±70.51 C	156.92±27.9 A	**<0.001**
TNF-α (final score)	0.0±0.0 A	10.44±1.88 B	2.60±0.44 C	3.0±1.41 C	2.89±1.05 C	**<0.001**

Results of Histopathologic scores

Table 2 below illustrate histopathological scores were absent in the healthy group (0.0 ± 0.0), confirming normal epidermal structure and no inflammatory activity. In contrast, imiquimod induction shows the highest severity overall, with increased Munro abscesses (0.8 ± 0.42; B), rete ridge elongation (1.2 ± 0.43; B), and lymphocytic infiltration (1.5 ± 0.28; B), confirming successful induction of prominent pathological changes. Treatment reduces these alterations to varying extents: for Munro abscess and hyperkeratosis, both Clobetasol (0.5 ± 0.2 and 0.32 ± 0.16 respectively) and Dovramilast (0.4 ± 0.0 and 0.31 ± 0.24, respectively) significantly improve outcomes compared with Induction, and the combination group shows the lowest scores among treated groups (0.2 ± 0.2 for Munro abscess and 0.2 ± 0.0 for hyperkeratosis), reaching values statistically comparable to Healthy for these two variables.

For parakeratosis, rete ridge elongation, and acanthosis, all treated groups show significantly lower values than Induction ($p < 0.001$ for each), but their multiple-comparison indicates that the combination group (0.15 ± 0.1, 0.15 ± 0.47, and 0.1 ± 0.05) is statistically closest to Healthy, whereas Dovramilast alone is often intermediate and Clobetasol can overlap with Healthy for some endpoints.

Lymphocytic infiltration shows the clearest separation pattern ($p < 0.001$): Induction is highest (1.5 ± 0.28), Clobetasol reduces it more (0.5 ± 0.0) than Dovramilast (0.6 ± 0.21), and the combination yields the lowest inflammation score (0.32 ± 0.21), indicating an additional anti-inflammatory benefit relative to either monotherapy. Overall, the Dovramilast/Clobetasol combination produces the greatest normalization of epidermal changes and inflammatory infiltration.

Table 2. Expression of histopathologic markers in different groups. The capital-letter annotations indicate multiple-comparison results; groups with different letters differ significantly. Groups that are sharing similar letter do no differ significantly. n =10 refer to number of mice utilized in each group.

Variables Mean ± standard deviation	Healthy n = 10	Induction n = 10	Clobetasol n = 10	Dovramilast n = 10	Dovramilast/ Clobetasol n = 10	p-value
Munro abscess	0.0±0.0 A	0.8±0.42 B	0.5±0.2 C	0.4±0.0 C	0.2±0.2 A	**0.003**
Hyperkeratosis	0.0±0.0 A	0.5±0.0 B	0.32±0.16 C	0.31±0.24 C	0.2±0.0 A	**<0.001**
Parakeratosis	0.0±0.0 A	0.6±0.32 B	0.20±0.16 A	0.32±0.0 C	0.15±0.1 A	**<0.001**
Rete ridge elongation	0.0±0.0 A	1.2±0.43 B	0.2±0.0 A	0.44±0.16 C	0.15±0.47 A	**<0.001**
Acanthosis	0.0±0.0 A	0.5±0.0 B	0.15±0.16 A	0.3±0.0 C	0.1±0.05 A	**<0.001**
Lymphocytic infiltration	0.0±0.0 A	1.5±0.28 B	0.5±0.0 C	0.6±0.21 C	0.32±0.21 D	**<0.001**

Results of histopathological slides

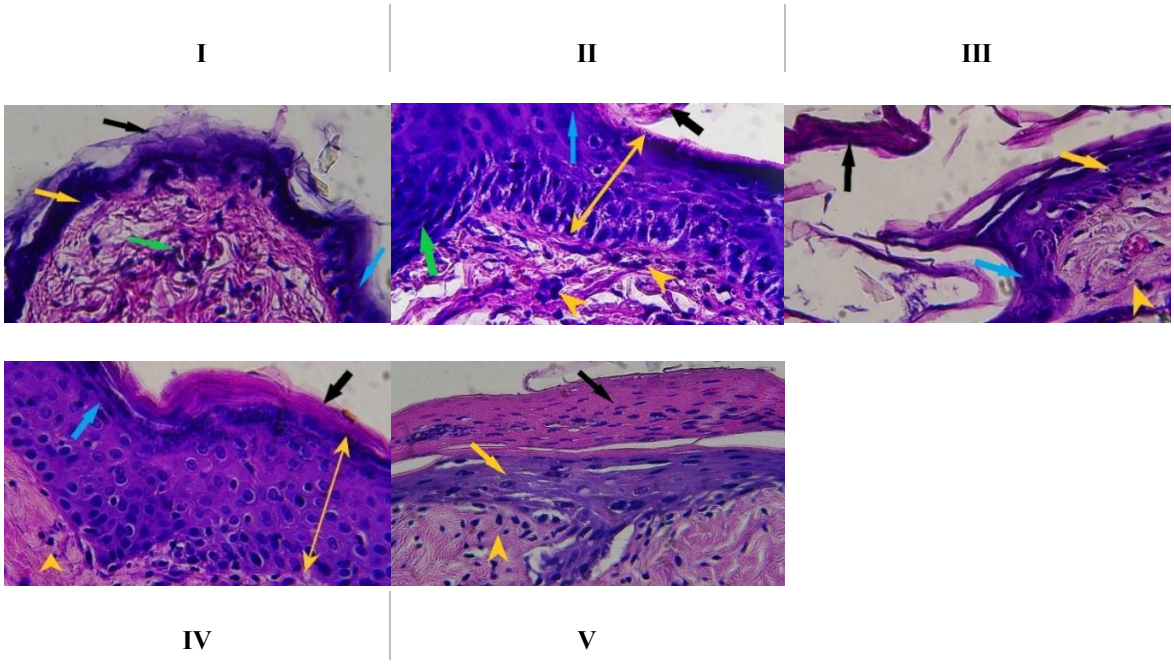

Figure 2. Histopathology mice skin sections**. I:** Healthy group, shows normal Keratinization (Black arrows), normal epidermal layer thickness (Yellow arrow), mature granular layer (Blue arrow), no prominent dermal inflammatory cells infiltration or capillary congestion (green arrows). **II:** induction group show histopathology picture of psoriasis Hyperkeratosis (Black arrow), acanthosis of epidermal layer (Yellow arrows), lack of granular layer (Blue arrow), elongated rete ridges (green arrow), marked dermal inflammatory cells infiltration & capillary congestion (yellow arrow head). **III**: clobetasol group show Hyperkeratosis and Parakeratosis (Black arrow).

Thinning of epidermal layer (Yellow arrows), maturation of granular layer (Blue arrow), mild dermal inflammatory cells infiltration (yellow arrow head). **IV:** dovramilast group show mild acanthosis (Yellow arrows), maturation of granular layer (Blue arrow), dermal inflammatory cells infiltration (yellow arrow head). **V:** dovramilast/clobetasol group show Hyperkeratosis and Parakeratosis (Black arrow). Thinning of the epidermal layer (Yellow arrows), dermal inflammatory cells infiltration (yellow arrow heads). lens power of 40X microscope used.

Results of immunohistochemistry (IHC) slides

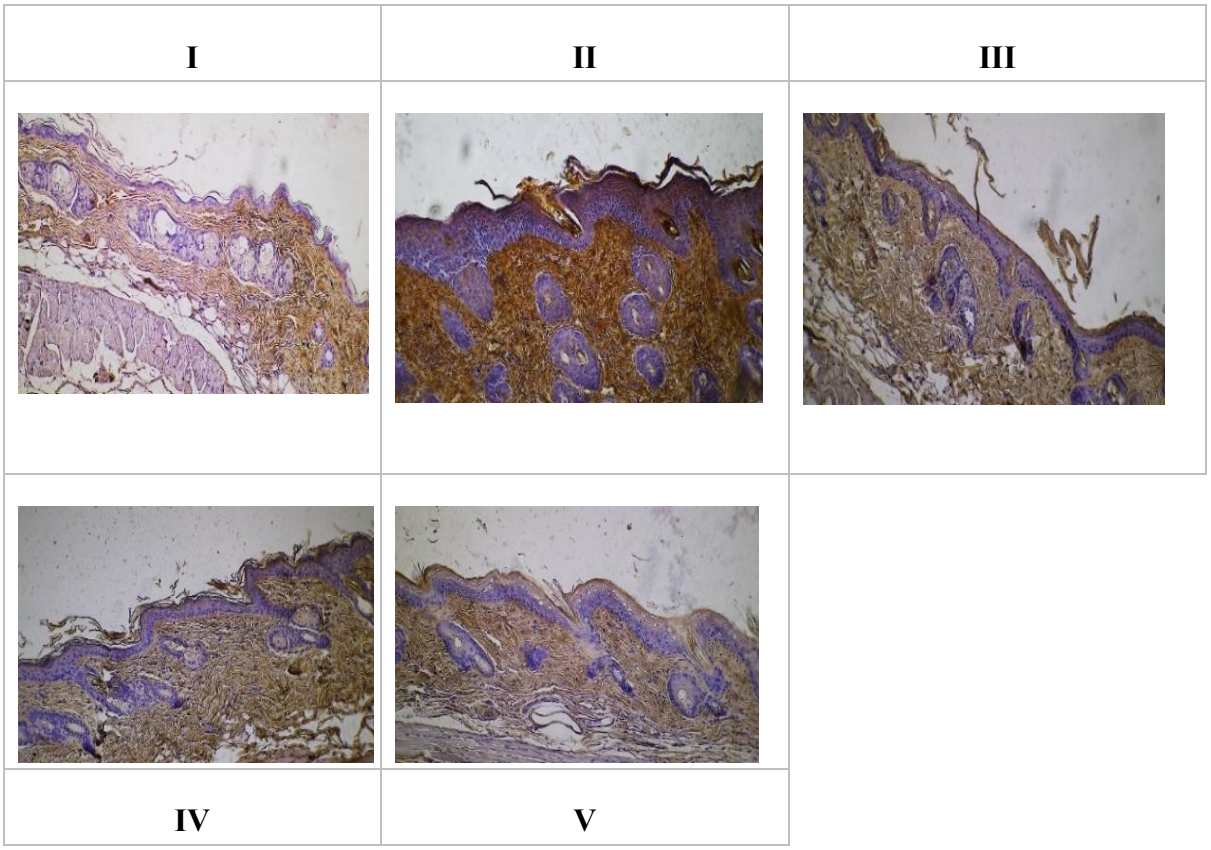

Figure 3. Immunohistochemistry expression of TNF-α in mice skin tissue. **Group I:** Apparently healthy show very weak expression of TNF marker in the cytoplasm of skin epidermal epithelial cells in <5% of the skin tissue. Intensity = 1, Percentage =0. **Group II:** induction group show strong positive expression of TNF marker in the cytoplasm of skin epidermal epithelial cells as brown stain in >75% of the skin tissue. Intensity = 3, Percentage =4. **Group III, IV and V**: clobetasol, dovramilast and dovramilast/clobetasol combination groups respectively show weak positive expression of TNF marker in the cytoplasm of skin epidermal epithelial cells as faint brownish stain in about 50% of the skin tissue. Intensity=1, percentage=2. lens power of 10X microscope used. Samples taken after 5 days.

Molecular docking results

The docking results and multiple interactions that occur between dovramilast and protein targets are illustrated in table 3. Below, dovramilast shows a PLP value equal to 118.94 with the target protein phosphodiesterase 4B (PDB: 1XMU) and a PLP equal to 123.02 with the second target known as phosphodiesterase 4D (PDB: 1XOQ). In addition, roflumilast was used as a reference compound for comparison. In which it's PLP score with

phosphodiesterase 4B (PDB: 1XMU) is equal to 128.23, while with phosphodiesterase 4D (PDB: 1XOQ) it is equal to 123.48 PLP fitness. Table 4 represents the results that occur between roflumilast as a reference molecule and protein targets.

Table 3. show the results and type of interactions obtained from docking of dovramilast with phosphodiesterase 4B and phosphodiesterase 4D targets**.**

compound	target	PLP fitness	interaction
Dovramilast	1XMU Phosphodiesterase 4B	118.94	PHE 414 (Alkyl) PHE 446 (Pi-Pi stacked) ILE 410 (Pi-Sigma) HIS 234 (Pi-Sulfur) H_2O 1 (water • hydrogen bond)
	1XOQ Phosphodiesterase 4D	123.02	MET 357 , PHE 372 , HIS 204 (Alkyl) HIS 160 , MET 273 (Pi-Sulfur) Mg 1002 , Zn 1001 , ASP 201 (Unfavorable Bump)

Table 4. illustrate docking results and binding interactions occur between roflumilast (reference ligand) and phosphodiesterase 4B and phosphodiesterase 4D targets.

compound	target	PLP fitness	interactions
Roflumilast (reference)	1XMU Phosphodiesterase 4B	128.23	Mg 1002 (Pi-Cation) H_2O 8, 1006, 1008, 28 (water hydrogen bond) MET 347, LEU 393, PHE 414, MET 431, MET 411, TYR 403, ILE 410 (alkyl) TYR 233, PHE 446 (Pi-Pi)

			GLN 443 (conventional hydrogen bond) THR 407 (carbon hydrogen bond) ASN 395, TRP 406 (halogen)
	1XOQ Phosphodiesterase 4D	123.48	Mg1002 (Pi-cation) H_2O,1022, 1008 (water hydrogen bond) HIS 160, THR 271, ASP 318, PRO 322, THR 333 (carbon hydrogen bond) MET 273, LEU 319, ILE 336, TYR 329, MET 357 (alkyl) PHE 372 (Pi-Pi stacked) GLN 369 (carbon hydrogen bond) H_2O ,1011 (van der Waals) ASN 321, TRP 332 (halogen)

Furthermore, the 3D pictures of docking analysis were used to illustrate the docking pose more precisely and describe the binding interactions that occur between the utilized ligand (dovramilast) and targeted proteins (PDE4B and PDE4D) in comparison with reference ligand (roflumilast). The figure 4 and figure 5 below describe these interactions.

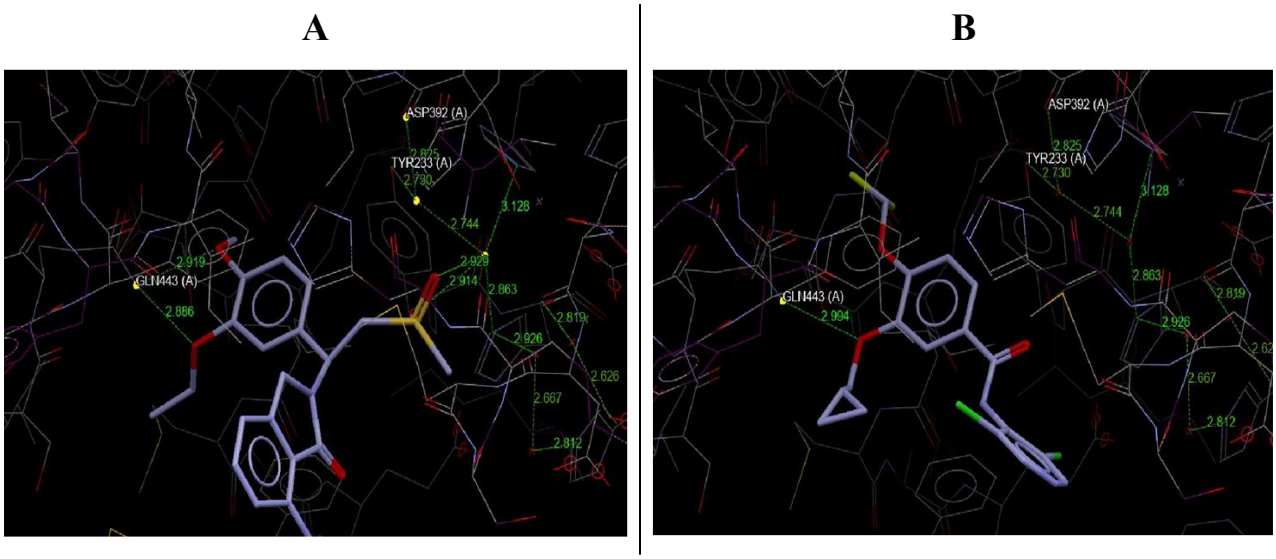

Figure 4. show the 3D pictures of docking process between the utilized ligands and PDE4B enzyme (PDB: 1XMU). A= dovramilast, B= roflumilast.

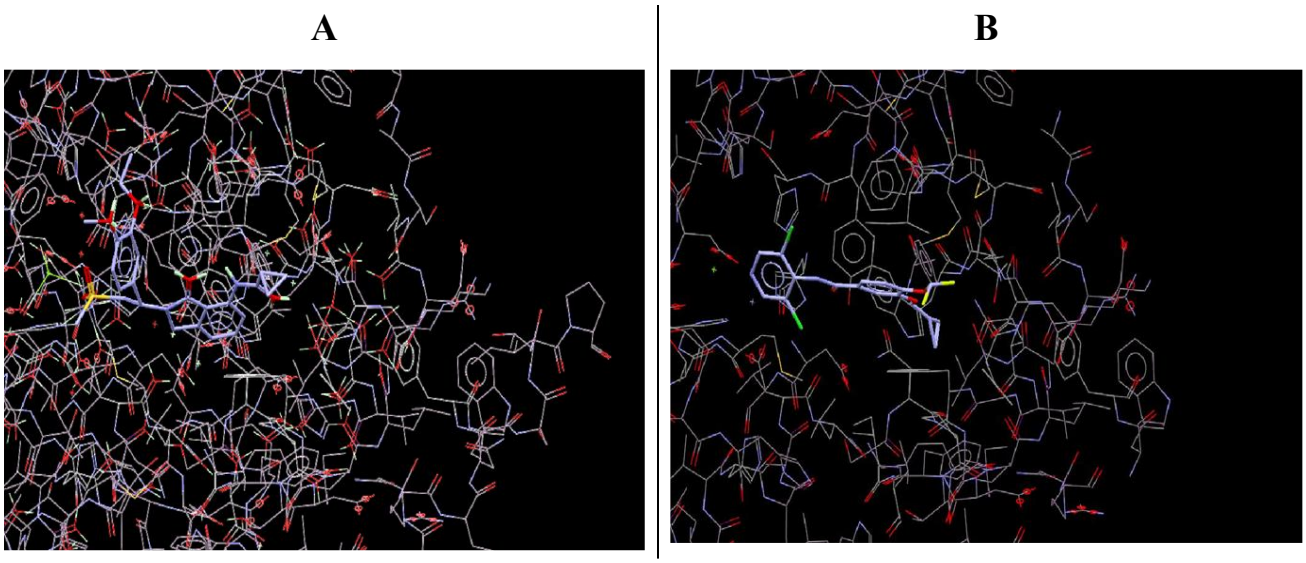

Figure 5. show the 3D pictures of docking process between the utilized ligands and PDE4D enzyme (PDB: 1XOQ). A= dovramilast, B= roflumilast.

DISCUSSION

Psoriasis is a chronic autoimmune disorder that affects the skin and is characterized by erythematous, silver-scaly lesions and associated with various complications such as psoriatic arthritis and cardiovascular events. The main factor associated with development of psoriasis is activation of IL-23/IL-17 axis which play key role in pathogenesis of psoriasis alongside to genetic and environmental factors [(40)]. IL-23, released from many cells, including dendritic cells, macrophages, and keratinocytes, acts to stimulate Th17 cells and other IL-17–producing cells to trigger IL-17A secretion, this process resulting in the development of keratinocyte proliferation with

inflammatory infiltration that contains a mixture of inflammatory cells [41]. So therapeutic suppression of the IL-23/IL-17 axis disrupts this circuit, thereby normalizing keratinocyte proliferation and markedly reducing inflammatory infiltration [42].

In this study, the first finding observed is successful induction of psoriasis like state in skin of mice of induction group which confirmed by significant elevation of all measured inflammatory cytokines namely, IL-17A, IL-23 and TNF-α compared to healthy group. These finding consistent with previous study that confirm the induction of psoriasis performed successfully [43].

Furthermore, the comparison of clobetasol treated group with induction group, show significant reduction in all estimated pro-inflammatory cytokines (IL-17A, IL-23 and TNF-α). This result aligns with previous researches that confirm upon application of clobetasol, a significant reduction in inflammatory marker (IL-17A) was obtained. This interference with IL-17 pathway suggests anti-psoriatic action of clobetasol [44]. Therefore, clobetasol can suppress the IL-23/IL-17A axis in imiquimod induced psoriasis mice model [45].

The dovramilast-treated group showed a significant reduction in all measured pro-inflammatory cytokines (IL-17A, IL-23 and TNF-α) when compared to induction. And providing comparable results to clobetasol for IL-17A and TNF-α. The explanation of this significant finding is related to the mechanism of action of dovramilast as it is considered a class of PDE4 inhibitors, it acts by inhibition PDE4 enzyme. PDE4 serves as a primary regulator of skin inflammation, and its inhibition can diminish pro-inflammatory cytokines in the Th1, Th2, Th22, and Th17 immune pathways. In addition, inhibition of PDE4 may elevate anti-inflammatory cytokines, including IL-10 [46].

Furthermore, Inhibition of PDE4 enzyme result in prevention the hydrolysis of second messenger (cAMP) that led eventually to accumulation and elevation of intracellular cAMP levels which subsequently suppress the transcription process of many pro-inflammatory cytokines [47].

It is important to highlight that activation of the cAMP pathway results in control the pro-inflammatory cytokine production and leukocyte recruitment. As intracellular cAMP levels elevated, the protein kinase A (PKA) became activated. This in turn results in the inhibition of NF-κB, which are important transcription factors that upon activation promote the expression of genes related to inflammatory response and pro-inflammatory cytokine production [48].

In addition, one study utilizes PDE4 inhibitor topically (apremilast gel) in mouse model of imiquimod-induced psoriasis, resulting in significant reduction of many inflammatory markers including of them those that utilized in our current study (IL-17A and IL-23) and this finding consistent with our results. Furthermore, the magnitude of cytokine reduction in our study was comparable to this study that utilized topical apremilast gel [49].

Moreover, other study supports the downregulation of TNF-α level, which is related to the formation of pulmonary granulomas, occurs with dovramilast therapy when used in TB management [50].
In addition, our study utilized PDE4i (dovramilast) topically which offer better tolerability and avoid systemic side effects than oral use of PDE4i such as (apremilast) which associated with severe gastrointestinal adverse effects that may led to treatment discontinuation [51].

Group treated with combination of dovramilast-clobetasol ointment, resulting in considerable improvement in pro-inflammatory cytokines levels that reduced significantly when compared to induction group. while comparison to clobetasol group resulting in comparable finding at level of IL-23 and TNF-α. While IL-17A reduced even less than clobetasol group. The explanation of this interesting results is attributed to additive anti-inflammatory effect that obtained when combined both PDE4 inhibitor and corticosteroid by targeting different, complementary inflammatory pathways. Furthermore, this additive anti-inflammatory action resulting from dovramilast as PDE4 inhibitor that influence cAMP signaling which not affected by corticosteroids alone. There is previous study support this result which involved using of dexamethasone in combination with roflumilast in patients with COPD, resulting in beneficial additive anti-inflammatory effect [52].

For histopathological results, induction group confirm the establishment of psoriasis like state in mice and this proved by observation the histopathological changes that occur in induction group in comparison to healthy among histopathological parameters include (increased thickening of the epidermal layer, hyperkeratosis, parakeratosis, elongation of rete-like ridges and Lymphocytic infiltration) and this finding in our study align all these parameters with previous studies [53].

Clobetasol treated group represent significant improvement in epidermal histopathological features. Therefore, clobetasol considered anti-inflammatory, antiproliferative, antipruritic, and vasoconstrictive which mediate this effect through various mechanisms including (genomic and non-genomic). The genomic pathway include binding of clobetasol to glucocorticoid receptors (GR) and activate it. While non-genomic mode involves the influence of clobetasol on various cells (monocytes, platelets, and T cells) [54]. These actions explain why these histopathological changes reduced in clobetasol-treated group. Our study also consistent with previous study that involve improvement of histopathological features after application of clobetasol in rat induced with psoriasis by imiquimod [55].

For dovramilast treated group, all histopathological features show significant reduction in comparison to induction group suggesting improvement in skin histology. These finding consistent with previous study that utilized another oral PDE4 inhibitor (apremilast) in Patients with Plaque Psoriasis, resulting in significant improvement in skin histopathological results, which parallel with our obtained results [56].

An interesting result obtained when combined PDE4 inhibitor (dovramilast) with corticosteroid (clobetasol), resulting in significant reduction compared to induction and better than dovramilast treated group or clobetasol treated group. These results may be attributed to synergistic action that occur between PDE4 inhibitor and corticosteroid by acting on different pathways, in which dovramilast acting to increase intracellular levels of cAMP by blocking PDE4 enzyme. Therefore, exert their anti-inflammatory action. On other hand clobetasol exert their anti-inflammatory effect by binding to glucocorticoids receptor which subsequently stimulate the production of lipocortins which also known as (phospholipase A2 inhibitory proteins), therefore this produced lipocortins will inhibit phospholipase A2 enzyme and the process of release arachidonic acid from membrane phospholipids will be inhibited. By these steps, the process of prostaglandins and leukotrienes release was prevented. In addition, clobetasol Inhibits cyclooxygenase 2 resulting in suppression of immune cells activations. Clobetasol also exert Antimitotic effect, meaning reduction in scaling and epidermal hyperplasia [57]. Furthermore, the benefit of combination to increase therapeutic effect while reduce the dose of clobetasol required and decrease side effects resulting from long term steroids use.

Molecular Docking Insights

In-silico analysis was performed in this study, represented by molecular docking, to determine the binding pose and interaction affinity between the utilized ligand (Dovramilast) and two types of PDE4 enzymes, namely PDE4B and PDE4D, that are involved in many inflammatory disorders, including psoriasis. Furthermore, comparing the results with the reference ligand (roflumilast) [58,59]. Docking of Dovramilast with PDE4B shows a PLP value equal to 118.94, which is inferior to the PLP score of the reference ligand (roflumilast) against PDE4B, which is equal to 128.23. This is attributed to the reason that roflumilast binding is more stable with the targeted enzyme occurring through hydrophobic interactions with conserved phenylalanine and isoleucine residues [60]. The binding affinity of roflumilast proved by a previous study suggests that the presence of a dialkoxyphenyl group in roflumilast is positioned between the hydrophobic clamp of Phe446 and Ile410 residues. In addition, the difluoromethoxy group present in roflumilast contributes to the interaction in which the fluoride atom interacts with Asn395 while the oxygen atom interacts with Gln443. Lastly, the presence of hydrophobic residues such as Met411, Phe414, Met431, and Phe446 contributes to the stabilization of the cyclopropyl methyl group of roflumilast within the protein target [61].

On the other hand, the docking PLP scores of dovramilast and roflumilast against PDE4D occur close together, which equal 123.02 and 123.48, respectively. In addition, previous studies linked the inhibition of PDE4D, unlike PDE4B, which related to the occurrence of gastrointestinal side effects, mainly emesis, when administered orally. So, in our study, both dovramilast and the reference ligand (roflumilast) show comparable binding scores to the PDE4D target, which means both of them have the same degree of side effects, so topical application can reduce this limitation [62,63,64].

Study limitations

While this study provides valuable insights, it has certain limitations that should be addressed. First, the experiment used an animal model instead of human subjects. Second, the experimental duration was relatively short, limited to five days, meaning a long-term period was required to determine the effects and safety profile. Finally, lack of clinical validation, which means a future need for clinical studies that involve human subjects over extended periods to confirm these preliminary results.

CONCLUSION

This study illustrates that the novel phosphodiesterase 4 inhibitor (PDE4i), dovramilast, has a potential anti-inflammatory effect in the treatment of psoriasis. The topical application of dovramilast ointment (0.3%) to the skin of mice induced with psoriasis by imiquimod cream resulted in significant improvement and attenuation

of skin inflammation, which was proven by reducing the levels of pro-inflammatory cytokines (IL-17A, IL-23, and TNF-α) compared to the induction group and showing a comparable reduction in these markers to clobetasol. Furthermore, using lower doses of a combined regimen of both dovramilast (0.15%) and clobetasol (0.025%) results in maintaining the therapeutic efficacy and reducing levels of inflammatory markers to levels similar to high-dose monotherapies. In addition, histopathological improvement was observed with both dovramilast monotherapy and combination with clobetasol, suggesting its therapeutic potential as an anti-inflammatory. These finding suggest that dovramilast considered a promising treatment option used topically to manage psoriasis. Furthermore, the strategy of using combination drugs in the management of psoriasis highlights its efficacy as a steroid-sparing agent that can provide benefits to reduce corticosteroid-associated side effects while maintaining the therapeutic potential in controlling the IL-23/IL-17 inflammatory pathway.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ETHICS STATEMENTS

The study was conducted with the approval of the Research Ethics Committee at Al-Nahrain university/college of pharmacy (ethical approval certificate number nah.co.pha.29-B, date 16/9/2025) and followed the national regulations for the care and use of animals in research.

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تقييم التأثير المضاد للصدفية لدواء دوفراميلاست الموضعي في نموذج فأر للصدفية المستحثة بالإيميكويمود

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الملخص

الهدف: تهدف هذه الدراسه الى تحديد التأثير الدوائي لمثبط فوسفودايستريز 4 (دوفراميلاست) في نموذج فأر مصاب بالصدفيه المستحثه بواسطة ايميكويمود , وتقدير مستويات السيتوكينات المُحفزة للالتهاب في أنسجة الجلد (IL-17A, IL-23, TNF-α) بالإضافة إلى ذلك، تم تحديد درجات التقييم النسيجي المرضي لأنسجة الجلد.

الأساليب: استُخدم في هذه الدراسة خمسون فأراً ذكراً أبيض من سلالة BALB/c بعمر ثمانية أسابيع. صُنفت الفئران إلى خمس مجموعات كل مجموعه تحتوي عشرة فئران (العدد=10) كما يلي: المجموعة الأولى (الضابطة) تضم فئرانًا سليمة ، والمجموعة الثانية (المحفزة) تتضمن وضع كريم إيميكويمود 5% مرة واحدة يوميًا لمدة خمسة أيام متتالية لإحداث آفات التهابية تُشبه الصدفية اللويحية، والمجموعات الثالثة والرابعة والخامسة تتضمن وضع كريم إيميكويمود 5%، ثم بعد ثلاث ساعات تم تطبيق علاجات أخرى، حيث تلقت المجموعة الثالثة مرهم كلوبيتاسول 0.05%، وتلقت المجموعة الرابعة مرهم دوفراميلاست 0.3%، واستخدمت المجموعة الخامسة تركيبة تحتوي على مرهم دوفراميلاست 0.15% مع مرهم كلوبيتاسول 0.025%.

النتائج: أظهرت المجموعة المعالجة بدوفراميلاست انخفاضًا ملحوظًا في جميع السيتوكينات الالتهابية (IL-17A، IL-23، وTNF-α) مقارنةً بمجموعة التحريض ($P<0.05$)، والتي لم تختلف بشكلٍ ملحوظ عن تأثير الكلوبيتاسول، علاوةً على ذلك، أدى الجمع بين الدوفراميلاست والكلوبيتاسول إلى انخفاضٍ ملحوظ في جميع السيتوكينات الالتهابية المقاسة ($P<0.05$) عند مقارنته بمجموعة التحريض. وأظهرت المقارنة مع الكلوبيتاسول اختلافا غير ملحوظ.

الاستنتاجات: يُعتبر الدوفراميلاست والجمع بين الدوفراميلاست والكلوبيتاسول عاملًا علاجيًا واعدًا، وله دورٌ في إدارة الصدفية في نموذج الفئران المصابة بالصدفية المُستحثة بالإيميكويمود.

الكلمات المفتاحية: أبريميلاست، التهاب، فوسفودايستراز 4، الصدفية.