

Original Research Article

Effect of Apremilast in the treatment and prevention of allergic contact dermatitis in a DPCP-induced rat model

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Abstract

Purpose: To investigate the anti-inflammatory effect of apremilast in diphenylcyclopropenone (DPCP)-induced allergic contact dermatitis model in rats.

Methods: A total of 40 adult male rats were randomly assigned into five groups ($n = 8$). Group 1 was the negative control; group 2 was induced with diphenylcyclopropenone (DPCP) 2 %; groups 3, 4, and 5 were induced with DPCP and treated with apremilast (20 mg/kg), pre-treated with apremilast (20 mg/kg), and dexamethasone (1 mg/kg), respectively. Systemic cytokine levels were quantified after sensitization and challenge phase with DPCP using an enzyme-linked immunosorbent assay (ELISA) kit, and histoarchitecture of the skin was examined using hematoxylin – eosin (H & E) staining.

Results: Induction with DPCP was associated with significant elevation in TNF- α and IL-1 β levels compared to negative control ($p < 0.01$). Apremilast administration, both as treatment and prophylaxis, significantly reduced IL-1 β ($p < 0.01$) and TNF- α ($p < 0.05$). Furthermore, dexamethasone significantly reduced IL-1 β levels only slightly ($p < 0.05$) with no significant effect on TNF- α ($p > 0.05$).

Conclusion: Apremilast administration significantly reduced levels of inflammatory markers compared to dexamethasone.

Keywords: Allergic Contact Dermatitis, Apremilast, Diphenylcyclopropenone (DPCP), TNF- α , IL-1 β

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INTRODUCTION

Allergic contact dermatitis (ACD) is a type 4 delayed-type hypersensitivity reaction arising after direct skin contact with a specific exogenous allergen. It is induced by small reactive chemicals and metal ions acting as haptens such as nickel (Ni²⁺) and chromium (Cr³⁺) [1]. Clinically, ACD manifests as erythema, edema, vesicles and bullae, often accompanied by pruritus, and persistent exposure may lead to chronic lichenification. Pathophysiology of ACD is characterized by complex innate and adaptive immune responses, where TNF- α and IL-1 β play

essential roles as pro-inflammatory mediators. Proinflammatory cytokines produced by keratinocytes and Langerhans cells during the innate immune response play a crucial role in the initiation and maintenance of cutaneous inflammation [2].

Studies using DNCB- and DNFB-induced dermatitis models have reported significant upregulation of these cytokines, which was positively correlated with the extent of cutaneous inflammation [3]. These observations highlight the clinical relevance of suppressing cytokine-driven inflammatory cascades as a therapeutic strategy for allergic contact dermatitis (ACD).

Phosphodiesterase-4 (PDE4) plays a central role in regulating inflammatory responses in the skin by hydrolyzing cyclic adenosine monophosphate (cAMP), a key intracellular messenger involved in anti-inflammatory signaling. Consequently, PDE4 inhibition enhances intracellular cAMP concentrations, activating downstream signaling pathways that modulate gene transcription and ultimately reduce expression and release of pro-inflammatory mediators [4].

Apremilast, an oral selective PDE4 inhibitor, increases intracellular cAMP and modulates cytokine mRNA expression, decreasing proinflammatory cytokines while promoting anti-inflammatory mediators. Apremilast is a recognized systemic PDE4 treatment in dermatology with insufficient data in ACD models. In an earlier study, prophylactic application of difamilast before and during oxazolone exposure mitigated allergic skin inflammation, as reflected by reduced ear swelling and diminished lesional IL-4 expression [5]. Nevertheless, therapeutic and prophylactic use of apremilast in ACD has not been systematically evaluated, thus creating a critical knowledge gap. Despite the widespread use of topical and systemic corticosteroids as first-line agents in allergic contact dermatitis, prolonged use may lead to a wide array of adverse outcomes which may limit long-term therapeutic utility. Local cutaneous complications include epidermal and dermal atrophy, telangiectasia, striae distensae, acneiform eruptions, and impaired barrier integrity predisposing the skin to secondary bacterial, viral, or fungal infections [6].

Systemic absorption, especially with potent corticosteroids applied on extensive areas of skin or under occlusive dressings, may lead to inhibition of the hypothalamic-pituitary-adrenal axis and broader immunosuppression [7]. While immunomodulatory therapies, including cyclosporine, have shown therapeutic benefits in selected conditions, chronic administration may increase the likelihood of complications arising from prolonged immunosuppression [8]. These drawbacks underscore an unmet clinical need for safer, pathway-selective anti-inflammatory agents effective in suppressing disease-related inflammatory responses without inducing steroid-related adverse effects [9]. This study therefore investigated the therapeutic and prophylactic efficacy of apremilast compared to dexamethasone in DPCP-induced ACD rat model, providing preclinical evidence for its potential as a selective immunomodulatory alternative in contact hypersensitivity disorders.

EXPERIMENTAL

Animals

A total of 40 adult male albino rats (200 – 250 g), randomized equally into 5 groups, were used. The animals were kept in the Animal House in the Department of Pharmacology, College of Medicine, University of Babylon, Iraq, and left to acclimatize under standard conditions (25 °C, 12 h light–dark cycle, and relative humidity between 60 – 65 %) with unrestricted access to water and standard feed.

Ethical approval

This was obtained from the Research Ethics Committee, College of Medicine, Babylon University (approval no. 4-39), and conducted in compliance with the guidelines for the care and use of laboratory animals [10].

Grouping and treatments

The rats were randomly allocated to five groups (n = 8 per group). Group 1 was the negative control and received only acetone applied topically (without any sensitizing agent), along with oral normal saline administered via gavage throughout the experimental period. Group 2 was the positive control and was sensitized with 2 % DPCP applied topically on day 8, followed by a challenge dose on day 14 of the experiment at the shaved dorsal skin, and received normal saline only by oral gavage for 15 days. Group 3 received the same DPCP sensitization and challenge protocol as group 2 and apremilast (20 mg/kg orally) was initiated on day 8 and continued once daily until day 14 [11]. Group 4 received apremilast (20 mg/kg orally) once daily for 7 successive days prior to sensitization and continued throughout the period till day 14 (sensitization and challenge with 2 % DPCP were performed on day 8 and day 14, respectively), and the dose was selected based on previous studies [12]. Group 5 was sensitized and challenged with 2 % DPCP as described in Group 2, and received dexamethasone (1 mg/kg orally) via gavage once daily from day 8 to day 14. Dose selection was based on a previously published study [13]. All animals were euthanized on day 15 for sample collection.

Induction of ACD

Allergic contact dermatitis was induced using 2 % diphenylcyclopropenone (DPCP) solution. The selected concentration was based on previously reported human and animal studies of hapten-induced contact dermatitis. A pilot study was

undertaken to establish the optimal conditions for DPCP-induced allergic contact dermatitis (ACD), including concentration selection and scheduling of sensitization and challenge procedures. Diphenylcyclopropenone (2 %) was administered topically to the dorsal skin region of the rats after shaving the backs (application area of 4 cm²). Thereafter, 200 mg DPCP was dissolved in 10 mL acetone to prepare the solution, which was immediately applied using a cotton swab [14]. Sensitization was achieved by topical application of 2 % DPCP on Day 8. Subsequently, a challenge dose was applied on Day 14 at the same site to induce the elicitation phase of contact dermatitis.

Apremilast preparation

Apremilast tablets 30 mg were reduced to fine powder using a clean mortar and pestle and suspended in distilled water immediately before administration by oral gavage.

Sample collection

The animals were anesthetized on day 15 using ketamine (75 mg/kg) and xylazine (10 mg/kg). Thereafter, 2 mL of blood was collected directly from the heart using a 5 mL disposable syringe. Following blood collection, the rats were euthanized.

Evaluation of parameters/indices

Levels of TNF- α

Levels of TNF- α were quantified using commercially available enzyme-

linked immunosorbent assay (ELISA) kits following manufacturer's instructions.

Levels of IL-1 β

Levels of IL-1 β were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits following manufacturer's instructions.

Histopathological evaluation

Skin tissues were obtained from the back of rats and fixed in 10% formalin solution for histopathological examination.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS, version 25.0; SPSS Inc., Chicago, Illinois, USA). Continuous data were expressed as mean $\pm$ standard deviation (SD) and compared using one-way analysis of variance (ANOVA). Dunnett's and Tukey's test procedures were applied for post-hoc analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Serum interleukin-1 β

Levels of IL-1 β significantly increased following induction with 2 % DPCP compared to control group ($p < 0.01$). However, treatment with Apremilast significantly decreased IL-1 β levels compared to group 2 ($p < 0.01$). Treatment with dexamethasone significantly reduced IL-1 β levels compared to group 2 ($p < 0.05$; Figure 1).

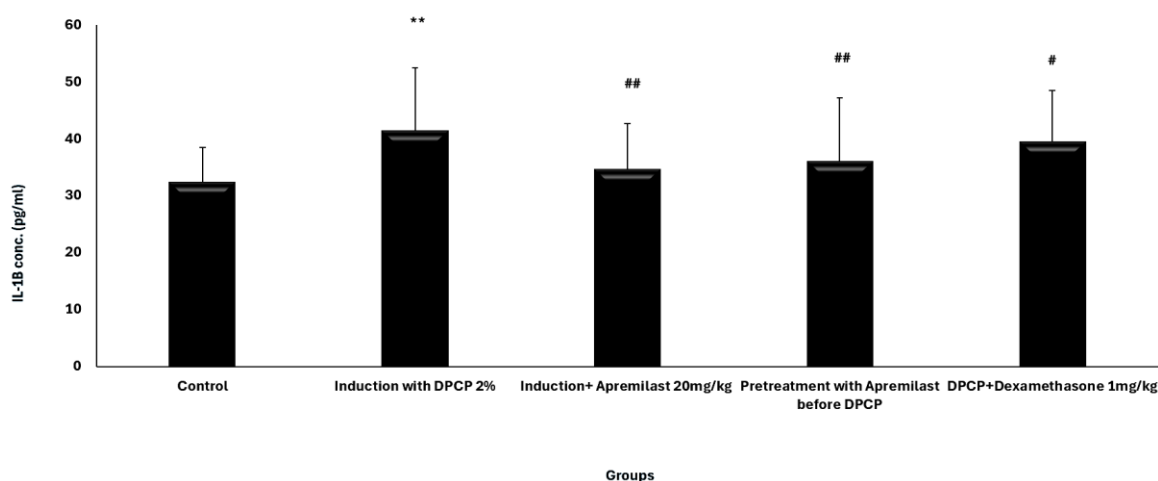


Figure 1: Serum IL-1 β levels. ** $P < 0.01$ compared to control, ## $p < 0.01$ compared to group 2. Group 1 (control), group 2 (2 % DPCP), group 3 (2 % DPCP + apremilast 20 mg/kg), group 4 (2 % DPCP + apremilast 20 mg/kg pretreatment), group 5 (2 % DPCP + dexamethasone 1 mg/kg)

Serum TNF- α

Induction with 2 % DPCP significantly increased TNF- α levels compared with control (** $p < 0.01$). However, treatment with apremilast significantly decreased TNF- α levels compared with group 2 ($p < 0.05$), while dexamethasone did not significantly reduce TNF- α levels compared with group 2 ($p > 0.05$; Figure 2).

Histopathological assessment

Histological examination of skin sections stained with hematoxylin and eosin (H&E) and Masson's

trichrome demonstrated distinct morphological differences among the experimental groups.

Negative control

The skin architecture appeared normal, with a structured epidermis that had uniform thickness. The dermis had a smooth appearance with no signs of inflammation or dermal damage. There were normal distributions of collagen fibers, and associated hair follicles and adnexa were present, indicating normal histological integrity (Figure 3).

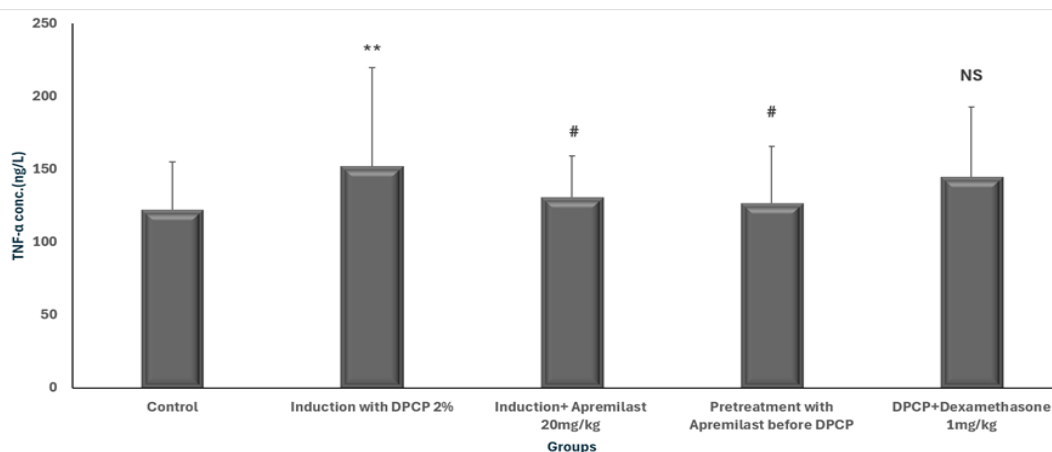


Figure 2: Figure 2: Serum TNF- α levels. ** $P < 0.01$ compared to control, # $p < 0.01$ compared to group 2, NS (not significant). Group 1 (control), group 2 (2 % DPCP), group 3 (2 % DPCP + apremilast 20 mg/kg), group 4 (2 % DPCP + apremilast 20 mg/kg pretreatment), group 5 (2 % DPCP + dexamethasone 1 mg/kg)

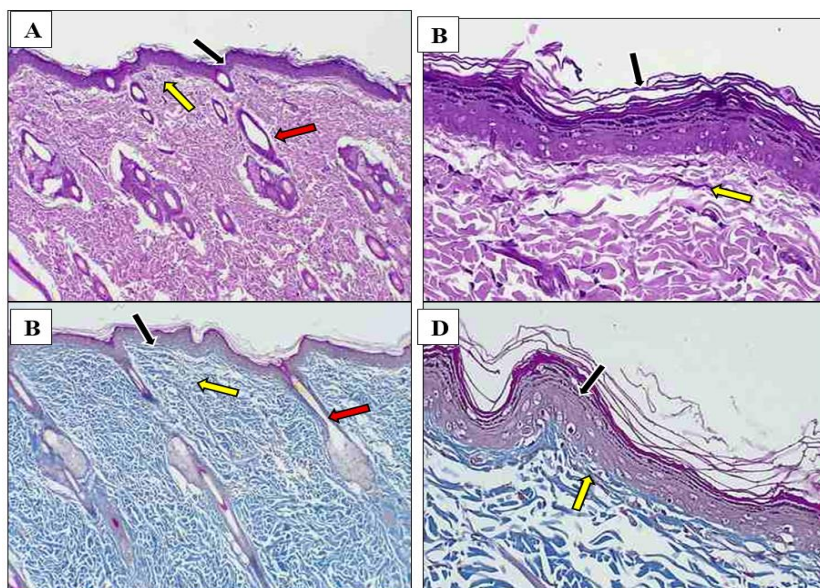


Figure 3: Photomicrograph of skin of negative control group. 1 and 2: Thickness of epidermis (black arrow) is consistently normal with a well-defined stratified structure. The dermal-epidermal junction (yellow arrow) is smooth and distinct, and collagen distribution is proper in the dermis without inflammatory cell infiltration. Hair follicles (marked with red arrow) are also visible. A and B stained with H & E, C and D stained with Masson Trichrome Stain. A and C: 100x, and B and D: 400x

Group 2

Induction with DPCP revealed significant epidermal acanthosis and prominent cytoplasmic vacuolation with 'bird's eye' appearance of keratinocytes. Hydropic degeneration of lower epidermal layers was observed in addition to minimal lymphocytic infiltration in the dermo-epidermal junction and disrupted dermal collagen organization compared to control group.

Group 3

Treatment with Apremilast showed significant improvement close to normal epidermal thickness, with no signs of acanthosis or vacuolation, while only minimal residual clear cells remained. The keratin layer of the epidermis was well maintained, and the dermis appeared dense and filled with organized collagen fibers. Inflammatory cell infiltration was effectively absent.

Group 4

Similarly, group 4 showed preserved skin architecture, with almost normal epidermal thickness, without any signs of acanthosis and vacuolation, and only occasional clear cells with normal nuclear morphology indicating mild hydropic changes. There were no signs of inflammatory cell infiltration, suggesting that

apremilast showed significant protective effects on skin architecture.

Group 5

Treatment with Dexamethasone showed unique patterns of recovery. The epidermis appeared markedly thinned (atrophic) with complete absence of vacuolation. Keratin lamellae were seen superficial to the epidermal surface, forming a stratified but detached stratum corneum. The epidermal surface showed irregular contour. Significantly, inflammatory cells were not present, proving efficient inhibition of the inflammatory response.

DISCUSSION

This study demonstrated that topical sensitization and challenge with diphenylcyclopropenone (DPCP 2 %) triggered significant elevation of inflammatory mediators like TNF- α and IL-1 β , confirming successful establishment of the experimental model and corroborating prior evidence that these cytokines serve as key mediators in hapten-driven cutaneous inflammation [2,9]. Treatment with apremilast significantly decreased these inflammatory cytokines, while pretreatment with apremilast demonstrated a comparable protective effect.

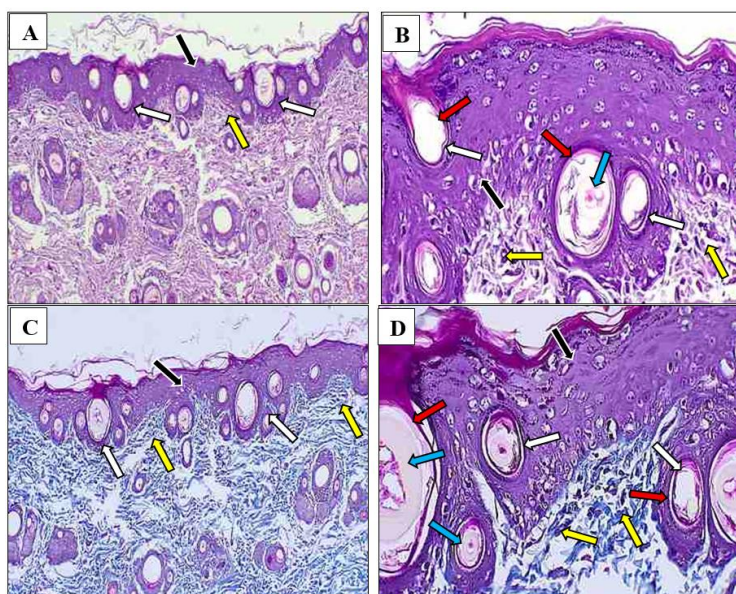


Figure 4: Photomicrograph of skin of group 2. A and B: Prominent epidermal acanthosis (black arrow) was present, along with extensive vacuolation of the cytoplasm (white arrow) and the classic 'bird's eye' pattern (blue arrow), characterized by a condensed central nucleus within a clear space and a dense eosinophilic rim of sequestered tonofilaments (red arrow). The lower epidermis exhibits clear cells with eccentric nuclei, indicative of early hydropic degeneration, along the dermo-epidermal junction. Mild lymphocytic infiltrate (yellow arrow) was identifiable. A and B were stained with H & E, and C and D were stained with Masson Trichrome Stain. A and C: 100x, and B and D: 400x

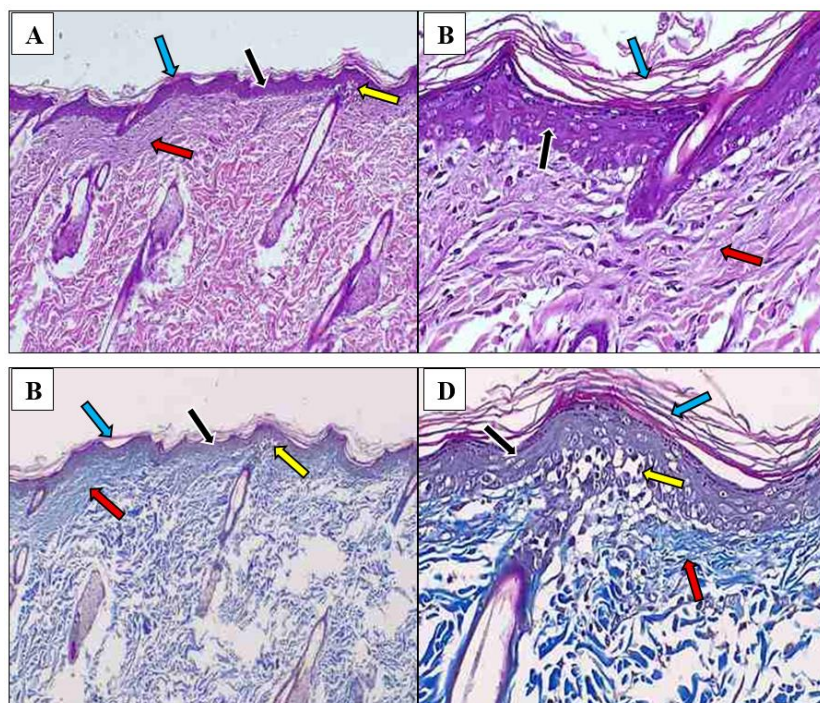


Figure 5: Histoarchitecture of skin of group 3. A and B: No notable acanthosis appears in the epidermis, with a near-normal thickness comparable to group 2, devoid of vacuoles, while exhibiting limited presence of clear cells (yellow arrow) with normal nuclei, indicative of hydropic alterations. A robust keratin layer (blue arrow) persisted on the superficial epidermis, and the dermis appeared dense (red arrow) adjacent to the dermo-epidermal junction, with no significant inflammatory cells. A and B stained with H & E, and C and D stained with Masson Trichrome Stain. A and C: 100x, and B and D: 400x

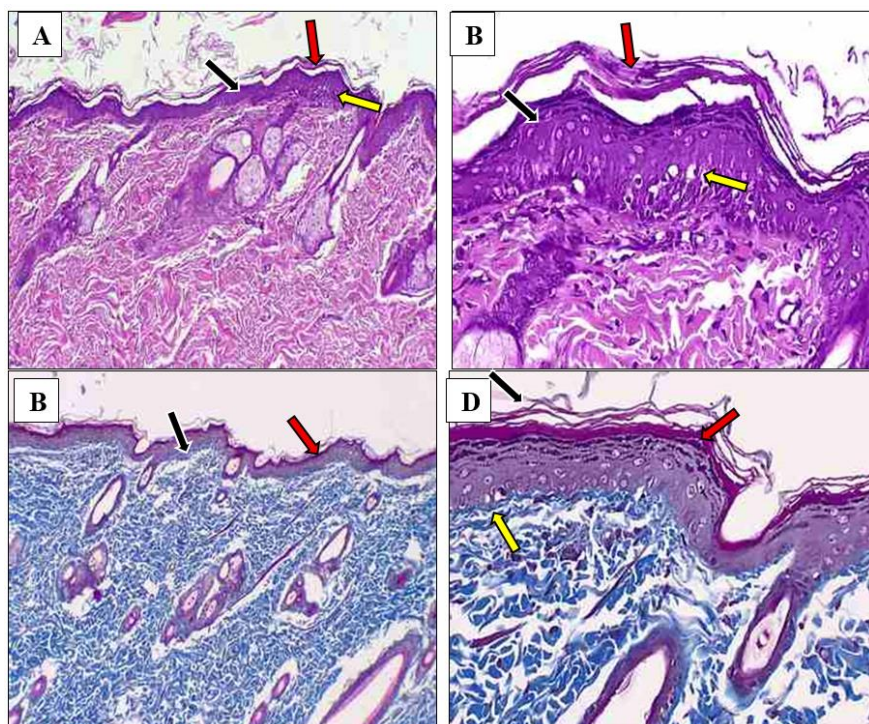


Figure 6: Histomorphology of skin of group 4. A and B: The epidermis (black arrow) demonstrates near-normal thickness without acanthosis compared to group 2, while vacuolization was absent. Scattered clear cells (yellow arrow) with normal nuclei were present, indicating hydropic alteration. The superficial epidermis retained a thick keratin layer (red arrow). No inflammatory cell infiltration was observed, indicating successful suppression. A and B stained with H & E, C and D stained with Masson Trichrome Stain. A and C: 100x, and B and D: 400x

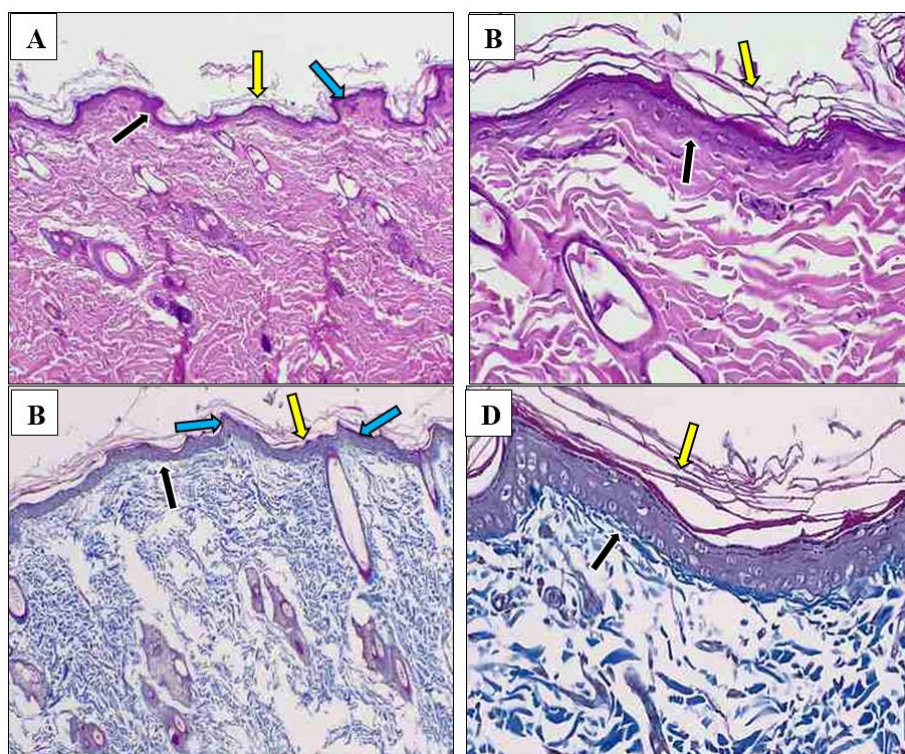


Figure 7: Histoarchitecture of skin of group 5. A and B: The epidermis (black arrow) was present as a markedly attenuated layer with no vacuoles. Multiple lamellae of keratin (yellow arrow) were identified superficial to the epidermal surface, reflecting a stratified yet detached stratum corneum. The superficial epidermal margin exhibited irregular and uneven contour (blue arrow). The complete absence of inflammatory cellular infiltration confirmed successful suppression of inflammatory response. A and B stained with H & E, C and D stained with Masson Trichrome Stain. A and C: 100x, and B and D: 400x

This anti-inflammatory activity results from inhibition of PDE4, thereby increasing cyclic adenosine monophosphate (cAMP) levels, which subsequently down-regulates pro-inflammatory markers such as TNF- α and IL-1 β through PKA-mediated phosphorylation of CREB and inhibition of NF- κ B [15]. These findings are in agreement with previously published studies that demonstrated the anti-inflammatory effects of apremilast in inflammatory conditions, including psoriasis [16]. Similar results have been reported in experimental models of dermatitis, where PDE4 inhibition led to suppression of pro-inflammatory cytokines [17]. Apremilast modulates both innate and adaptive immune systems, indicated by lower TNF- α and IL-1 β levels. Within ACD immunopathological framework (primarily a Th1-driven delayed-type hypersensitivity reaction amplified by IFN- γ), PDE4 inhibition has been shown to attenuate Th1, Th17, and Th2 cytokine axes simultaneously, providing a broader immunoregulatory scope than single-pathway agents [2,18]. The prophylactic apremilast group achieved cytokine levels approaching those of negative control, suggesting that PDE4 pre-sensitization and inhibition may interfere with early sensitization phase by modulating dendritic

cell activation and antigen presentation, in which cAMP-dependent signaling plays a documented regulatory role [5,19]. This is further supported by experimental evidence demonstrating that PDE4 inhibition prior to allergen challenge significantly attenuated immune-mediated skin inflammation in contact sensitization models [5]. Histopathologically, the results were in tandem with the biochemical data, as the DPCP-induced group showed significant epidermal acanthosis, vacuolization, and infiltration of lymphocytes, while both apremilast-treated groups had near-normal epidermal morphology without prominent signs of inflammation. Furthermore, the epidermis was found to be thinned out following treatment with dexamethasone, along with an isolated stratum corneum, indicating steroid-induced skin atrophy, a finding that further differentiated the safety profiles of the two treatment modalities [20]. Also, dexamethasone produced a significant reduction in IL-1 β levels, consistent with the well-established capacity of glucocorticoids to suppress IL-1 β transcription through GR-dependent mechanisms and mRNA destabilization [21]. However, dexamethasone did not significantly reduce TNF- α levels, which may reflect the differential sensitivity of TNF- α to glucocorticoid-mediated suppression. Unlike

some inflammatory mediators, TNF- α transcription is strongly regulated by NF- κ B and AP-1, pathways that may not be completely inhibited by dexamethasone. Moreover, sustained inflammatory signaling may alter the glucocorticoid receptor cofactor profile and consequently diminish its transcriptional regulatory efficacy [22].

Limitations

Although the findings were promising, several limitations exist. The small sample size used in this study may restrict generalizability. Also, the study focused on selected biomarkers (TNF- α and IL-1 β) without profiling broader inflammatory mediators such as IFN- γ , IL-17, IL-4, or chemokines (e.g., CXCL9, CXCL10). The study duration may have been insufficient for complete restoration of normal cytokine levels.

CONCLUSION

Apremilast demonstrates significant anti-inflammatory capability manifested by downregulation of TNF- α and IL-1 β with restoration of normal histoarchitecture. This suggests that apremilast may be beneficial in the management of dermatological hypersensitivity disorders such as allergic contact dermatitis.

DECLARATIONS

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Conflict of interest

The authors declare no conflict of interest

Ethical approval

This was obtained from the Research Ethics Committee, College of Medicine, Babylon University (approval no. 4-39).

Contribution of authors

Ahmed Hyder Al-Mosawi drafted and revised the initial manuscript, provided research resources (animals, equipment, and materials), performed the experiments, contributed to study design, secured financial and logistical support, and approved the final version. Reyadh H. Al-Mosawi developed the study concept and research

framework, established methodological guidelines, supervised the work, and critically reviewed the manuscript with constructive input. We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Use of Artificial Intelligence/large language models

No artificial intelligence (AI)-based system or large language model was used.

Use of research reporting tool

The ARRIVE 2.0 guidelines were used during the preparation and reporting of this animal study.

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