European Journal of Clinical and Experimental Medicine

ONLINE FIRST

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Article type: Original Article

Received: 17 April 2025

Accepted: 10 June 2025

Published online: 16 August 2025

eISSN: 2544-1361

Eur J Clin Exp Med

doi: 10.15584/ejcem.2025.4.7

Ezetimibe mitigates DNCB-induced mouse model of eczematous dermatitis

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ABSTRACT

Introduction and aim. Atopic dermatitis (AD) is a life-long inflammatory dermatosis that features dry, erythematous skin. Ezetimibe is a lipid-lowering agent with enhanced anti-inflammatory and anti-oxidative capacities. This work attempted to evaluate the anti-eczematous action of topically administered ezetimibe in a mouse prototype of 1-chloro-2,4-dinitrobenzene (DNCB)-evoked AD. To our knowledge, this is the first study to investigate the topical use of ezetimibe in an experimental model of AD.

Material and methods. Thirty male Swiss albino mice were randomly allocated into five groups: healthy control, DNCB-induced model, vehicle, tacrolimus (0.1% ointment), and ezetimibe (2% ointment). Treatments were applied daily for 21 days. Clinical severity scores, total and differential leukocyte counts, histopathological changes, immunohistochemical expression of interleukin (IL)-4 and IL-13, and tissue levels of IgE, malondialdehyde (MDA), IL-17, IL-31, transforming growth factor-β (TGF-β), and tumor necrosis factor-α (TNF-α) were assessed.

Results. DNCB increased dermatitis severity (EASI score 9.8±0.7 vs. 0.5±0.1 in controls, $p<0.001$), total leukocytes (14.2±1.6 $\times 10^3$/mL vs. 3.9±0.6 $\times 10^3$/mL, $p<0.001$), and IgE (356±42 ng/mL vs. 92±15 ng/mL, $p<0.001$). Ezetimibe treatment significantly reduced EASI scores (2.1±0.4, $p<0.01$ vs. DNCB), leukocytes (5.9±0.3 $\times 10^3$/mL, $p<0.01$ vs. DNCB), IgE (128±18 ng/mL, $p<0.01$ vs. DNCB), and MDA (2.3±0.4 μmol/L

vs. 5.9±0.7 μmol/L in DNCB, p<0.001). Pro-inflammatory cytokines IL-4, IL-13, IL-17, IL-31, TGF-β, and TNF-α were also markedly decreased (all p<0.05), with effects comparable to tacrolimus.

Conclusion. Topical ezetimibe significantly alleviated DNCB-induced AD-like lesions by reducing histopathological changes, leukocyte infiltration, IgE, oxidative stress, and key inflammatory cytokines. These findings support ezetimibe as a potential adjunctive topical therapy for immune-mediated dermatoses, warranting future clinical evaluation.

Keywords. atopic dermatitis, DNCB, eczema, ezetimibe, inflammatory dermatosis, immune-mediated skin diseases

Introduction

Atopic dermatitis (AD) is a recurring and remitting auto-inflammatory skin disease evoked by the immune system that often begins during the early stages of life. It is often known as eczematous dermatitis and is the most common skin condition that involves a rapid development of itchy patches on the skin.[1-3] Dermatosis is marked by atopic inflammation, lichen formation, itchiness, greater vulnerability to infection, and rashes, frequently followed by acute pruritus.[1,4,5] Inheritance variables, immune disruption, compromised skin barriers, and external stimuli are believed to be among the fundamental reasons.[6] AD collapses beneath the category of atopic ailments that encompass food intolerance, pulmonary asthma, rashes and hay fever, many of which are relevant pathologies associated with elevated immunoglobulin E (IgE) concentrations and diminished filaggrin concentrations.[7,8] Furthermore, AD can occur concurrently with other immune-driven dermatoses, such as psoriasis.[9-13] Furthermore, a possible correlation between ulcerative colitis and AD is shown in the literature study.[14-17] Meanwhile, an immune system mismatch in the Th1/Th2 reactions is a distinguishing prosperity of AD pathogenesis, with higher rates of released cytokines, including interleukin (IL)-4 and IL-13, which drive Th2 replication and B cell IgE liberation[1]. IgE value is a specified indicator of AD intensity, which is corroborated by the efficiency of IgE-focused therapy to reduce AD symptoms among sufferers.[18-20] Tumor necrosis factor (TNF)-α is a significant inflammatory cytokine that modulates immunological responses and cellular division.[21-23] It also facilitates the relocation of NF-κB into keratinocytes, which assists in transcriptional signaling and the liberation of cytokines, particularly IL-6 and IL-8.[24-28] Moreover, IL-17 is a pivotal target for treatment, since it fosters the secretion of TNF-α, exacerbating the effects of atopic inflammation.[8] IL-17 amplification elevates IL-6 and IL-1β concentrations in keratinocytes, which are associated with the pathogenesis of AD.[2,5] Additionally, transforming growth factor (TGF)-β is an anti-inflammatory cytokine that facilitates angiogenesis while simultaneously promoting differentiation and influencing the expansion of keratinocytes; yet, excessive production of TGF-β1 in skin cells induces significant inflammation.[29-31] However, oxidative damage has a role in the etiology of AD. Environmental factors, such as contaminants,

ultraviolet radiation, illness, and mental illness, may elevate reactive oxygen species (ROS) outputs, finally exceeding the protective capacity of the anti-oxidative barrier.[32-36]

Nevertheless, topical medicines, including calcineurin blockers, glucocorticoids, and, lastly, phosphodiesterase 4 (PDE4) antagonists such as crisaborole, are the bedrock of AD management.[37-39] Yet, repeated usage of these medicines might cause an array of unwanted effects. Thus, there is a pressing demand for the identification of innovative and secure methods for treating AD.[40,41] The approval of targeted biologics such as dupilumab, tralokinumab, nemolizumab, baricitinib, upadacitinib, and abrocitinib suggests subsequent best alternatives for controlling moderate to severe forms of AD.[42,43]

Ezetimibe is a lipid-diminishing medication that specifically hinders the cholesterol transporter Niemann-Pick C1-like protein 1 (NPC1L1) in the jejunum brush borders, restricting the digestion of cholesterol in the stomach and bile systems. Ezetimibe was demonstrated to be safe and efficient in decreasing the contents of cholesterol regularly accessible to hepatocytes. As a result of diminished cholesterol supply, the liver raises LDL receptor generation and LDL removal from the circulation.[44-47] Ezetimibe was established to stop atherosclerotic events when combined with statin, making it useful in the treatment of dyslipidemia and related atherosclerotic complications.[48,49] Ezetimibe's impact on many inflammatory indicators was also studied. Ezetimibe was revealed to lower atherosclerotic plaques, limit macrophage accumulations, and prevent liberation of chemotactic cytokines like MCP-1 and TNF-α.[50,51] Other observation demonstrate that combining ezetimibe with simvastatin can effectively alleviate autoimmune alopecia totalis and alopecia universalis, making it a promising treatment option for resistant alopecia areata. [52] This combination also considerably lowered amounts of IL-1β and IL-18 in obese individuals.[53] Beyond that, this medicine exerted protective actions on IL-1β-exacerbated matrix collagen breakdown in murine chondrocytes by modifying NF-κB and Nrf2/HO-1 molecular parameters.[54] In parallel, ezetimibe enhanced endothelial functions and decreased inflammation indicators, disease progression, and aortic stiffening among individuals with rheumatoid arthritis.[55] In comparable vein, ezetimibe shows inhibitory impacts on acetic acid-exacerbated rat prototype of ulcerated colitis by downregulating inflammatory and oxidative indicators, particularly the Akt/NF-κB/STAT3/CXCL10 signaling network.[56]

Aim

Previous studies suggest that ezetimibe possesses anti-inflammatory, antioxidant, and immunomodulatory properties; however, its anti-eczematous efficacy has not been investigated. This study aimed to evaluate, for the first time, the anti-atopic effects of topical ezetimibe in a DNCB-induced murine model of AD, providing novel preclinical evidence for its potential repositioning as a topical therapy in dermatological inflammatory disorders.

Material and methods

Drugs and chemicals

The suppliers of 1-chloro-2,4-dinitrobenzene (DNCB) was the Sigma Aldrich, Germany. Ezetimibe was purchased from Hangzhou Hyper Chemicals Limited. The 0.1% tacrolimus product was supplied by Cleveland Clinic, USA. The extra chemicals utilized in this investigation had been procured from several sources who met specific standards.

Preparation of ezetimibe ointment

2.5 g of white wax (beeswax), 1.25 g of hard paraffin, 2.5 g of lanolin, polyethylene glycol, and a sufficient quantity of soft paraffin were melted together in a saucepan on a hot plate at 70 ºC.[57] 2g of ezetimibe powder was placed to the melted mixture while being continuously stirred.[58,59] The entire mixture was blended while transported on ice to produce 2% ezetimibe ointment.[60-64]

Vehicle components formulation

2.5 g of white wax, 1.25 g of hard paraffin, 2.5 g of lanolin, polyethylene glycol, and an adequate amount of white soft paraffin were combined and heated in a container on a heated surface at 70ºC. The whole solution was constantly agitated and mixed.[65,66]

Study design

This work was licensed by the institutional review board (IRB) of the College of Medicine at Al-Nahrain University (approval no. UNCOMIRB20241037 on 14/10/2021). The experiments were carried out from November 2021 to July 2022. The trial consisted of thirty male Swiss albino-kind mice, with weight about 20 to 30 g and age about 8 to 9 weeks. Mice were placed in a sterile, isolated, and properly designated room with a humidity level of 49±2%. All investigations had been performed in conformity with rules of ethics for the handling of animals.

Animal preparation and sampling

Mice had been randomly separated into 5 different categories of 6 mice each: a healthy untreated control group, an induction non-treated group, a vehicle group, an ezetimibe group, and a tacrolimus group. Following a 14-day acclimation period, mice underwent rigorous hair extraction from their back areas (about 4 cm2) with a precision shaving device. The residual hair strands were subsequently extracted with a depilatory lotion. To develop AD-mimicking skin irritation, DNCB was dispersed in an acetone-based olive oil mixture at a 3:1 proportion and watered down to 0.5 and 1% strengths. Mice developed a sensitivity with 200 µL of 1% DNCB applied to their back skin-folds for 3 straight days, whereas the healthy controls

did not obtain any medications. Mice with AD-like symptoms were treated with 200 µL of 0.5% DNCB locally each other day for 21 days to prevent unexpected resurgence. The vehicle group was given a topical vehicle formulation daily for 21 days, the tacrolimus group obtained tacrolimus 0.1% ointment daily for 21 days, and the ezetimibe group administered ezetimibe 2% ointment product daily for 21 days as indicated in Figure 1. At the completion of the tests, all animals underwent the intraperitoneal analgesic medicines xylazine and ketamine (80 mg/kg). Upon achieving complete anesthesia, the animals were put to death by exsanguinations, which are the optimal means of harvesting and preserving.[67-70] Skin biopsies were subsequently processed to develop tissue homogenates for bio-indicator and histopathology analyses.[71-74]

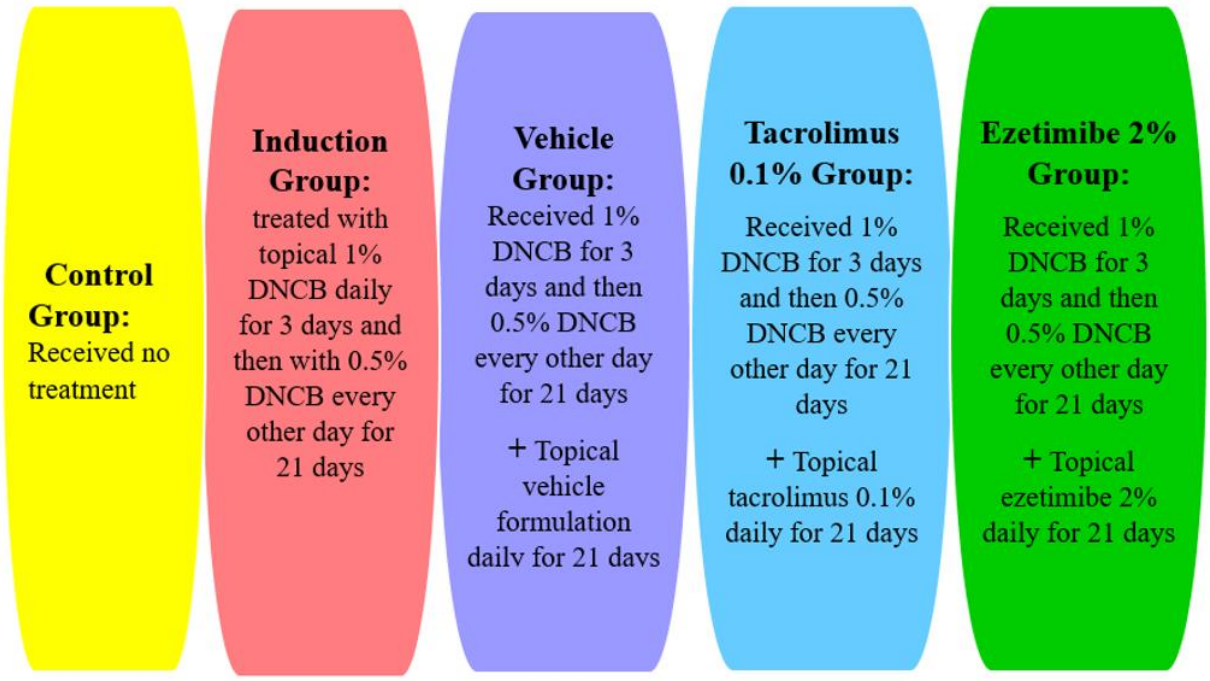

Fig 1. Tabular form of study groups

Measurement of total and differential WBC counts

The complete blood counts involves the overall amount of leukocytes/white blood cells (WBC) alongside the individual percentages for each WBC subgroup, such as neutrophils, lymphocytes, monocytes, and eosinophils. Blood specimens were taken in EDTA-containers and scrutinized with a small 5-part hematologic tester, namely the Mindray BC-5000 version.[75,76] The methodology is based on triangular laser scattering, flow-cytometry, and biochemical dye processing.[77-81]

Estimation of severity grading of AD

The intensity of DNCB-evoked AD-mimicking cutaneous patches was estimated by 4 clinical manifestations: erythema, erosion/excoriation, epidermal thickenings, and lichenification, based on the Eczema Area and Degree Index (EASI) scoring technique.[82] The metrics were evaluated on a scale of 0

(none), 1 (mild), 2 (moderate), and 3 (severe) based on their severity, with total dermatitis levels determined by summing all analyzed data, achieving a highest possible score of 12.[83] The back skin-fold thickening was calculated using a vernier calibrator measuring instrument on the central line of the back skin. [84-86] Dermatitis severity was assessed by two independent raters. Dermatitis scoring and treatment administration were conducted in a blinded fashion to minimize observer bias. The experimenters were unaware of the treatment groups during scoring.

Histopathological estimation

The dorsal skins of mice were obtained from various categories and preserved in 10% neutralizing-buffer formaldehyde employing recognized guidelines.[87-90] Fixed paraffin was then applied to the skin samples. The paraffin-soaked tissues were sliced into slices and prepared for staining with hematoxylin and eosin. The derived specimens were viewed utilizing a light microscopy, and histological changes were documented.[91-95] Histological scoring relied on an amended edition of the scoring system described by Jeong et al., commonly used for DNCB-induced dermatitis models. Parameters encompassed skin thickness/acanthosis, hyperkeratosis, parakeratosis, erosion, inflammatory cell invasion, and edema.[96] The grading mechanisms varied from 0, signifying no irregularity, to 1+, denoting mild irregularity; 2+, representing modest irregularity; and 3+, signifying substantial irregularities.

Immunohistochemistry (IHC) examination

The immunohistochemistry approach was used to assess the severity of AD lesions by determining the scores of IL-4 and IL-13. It is technique for detecting antigens or haptens in biological tissues. The immunohistochemical assessment in this study employs specific antibodies for identifying the protein product of gene expression in the tissues of the investigated animal groups. Following the application of the main antibody (rabbit monoclonal anti-IL-4 and anti-IL-13), the corresponding secondary antibody and a chromogen agent (3,30-diaminobenzidine) are then incorporated into paraffin-fixed segments of the skin tissues.[31,97-99] The skin portions have been treated with hematoxylin. The immunohistochemistry investigation is scored via the following method using semi-quantitative scoring (positive stained cells): "Score 0=no stain; score 1=25%; score 2=26–50%; score 3=51–75%; score 4=67–100%.[30,100,101]

Biochemical marker measurement

Using sandwich enzyme-linked immunosorbent-assays (ELISA), the amounts of IgE, malondialdehyde (MDA), IL-17, IL-31, TGF-β, and TNF-α in mouse skin tissues were determined by the supplier's rules. IgE Invitrogen: catalogue no.: 88-50460-88, sensitivity: 4 ng/mL; MDA Invitrogen: catalogue no.: EEA015, sensitivity: 1.13 μmol/L; IL-17 Sino biological: catalogue no.: KIT51065, sensitivity: 8 pg/mL; IL-31 Invitrogen: catalogue no.: BMS6030, sensitivity: 9.1 pg/mL; TGF-β Invitrogen: catalogue no.: 88-

8350-88, sensitivity: 8 pg/mL; TNF-α Sino biological: catalogue no.: KIT50349, sensitivity: 15.69 pg/mL. To ensure statistical validation, ELISA measurements were done in duplicate. Following a cleansing with washing buffer, the pores were treated with a biotin-based-specific antibody.[102-106] Upon extracting the disengaged biotin-linked antibody, streptavidin/horseradish peroxidases (HRP) were gently transmitted into the wells. Tetramethylbenzidine (TMB) substrate solution was added once all unbound components were eliminated. The amounts of various variables in every experimental group were determined spectro-photometrically by matching their optical density to regular curves. The HRP-combined antibodies and indicators switched to yellow upon the addition of the stop solution The levels of various variables in each experimental group were determined spectro-photometrically by comparing their optical densities to standard curves. Following the addition of the stop solution, the HRP-conjugated antibodies and substrates produced a yellow color, which was measured using an absorbance microplate reader at a wavelength of 450 nm. [107-109]

Statistical analysis

The statistical evaluation was conducted using the program Excel 2013 and the SPSS statistical program edition 24 (IBM, Armonk, NY, USA). The numerical parameters are presented in terms of means with standard deviation (±SD), and the level of significance is estimated at a p value of less than 0.05. Means were contrasted with the t-test for independence and an assessment of variance (ANOVA). Pearson's correlation is adopted to determine linear relationships among the groups under study.[110,111]

Results

Impact of researched agents on observational severity scores

The induction and vehicle groups had significantly elevated observational severity levels than normal controls ($p<0.05$). Also, there was no considerable variance among induction/model and vehicle groups with respect to observational dermatitis levels ($p > 0.05$). Nonetheless, the dermatitis severity ratings got significantly reduced in the tacrolimus and ezetimibe-treated groups when matched with the induction and vehicle groups ($p<0.05$). No noteworthy variances were detected across the tacrolimus and ezetimibe groups with respect to observational dermatitis levels ($p>0.05$) as observed in Figure 2 and Figure 3.

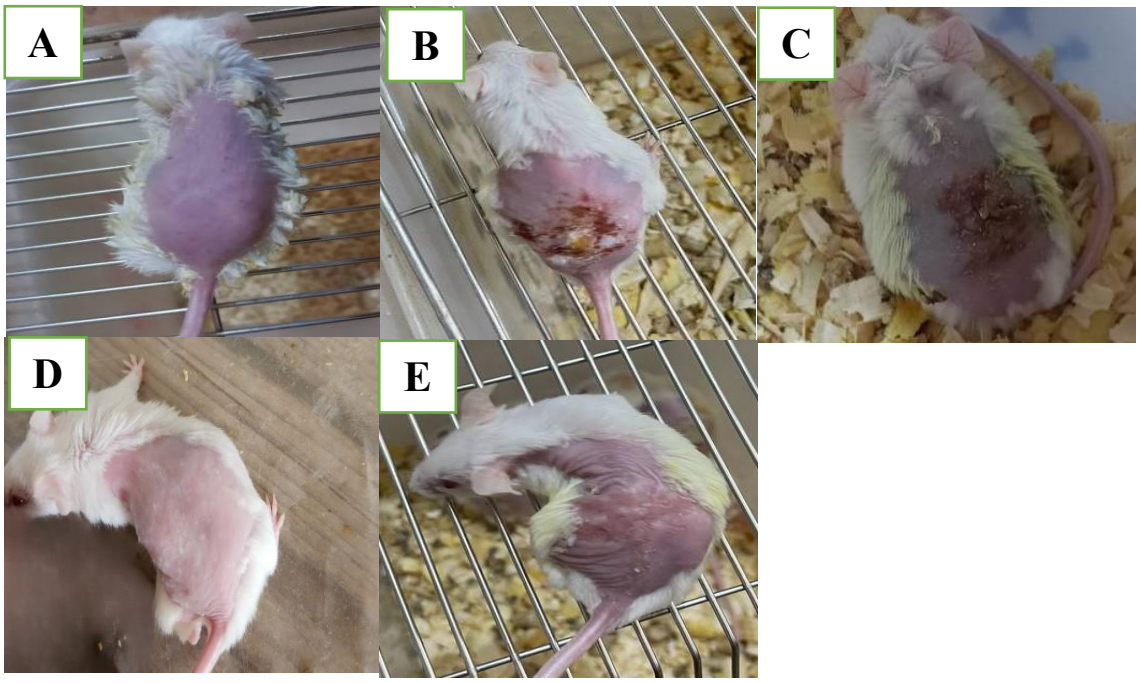

Fig. 2. Images displaying the degree of severity of eczematous lesions in study groups: A – control group, B – induction group, C – vehicle group, D – tacrolimus group, E – ezetimibe

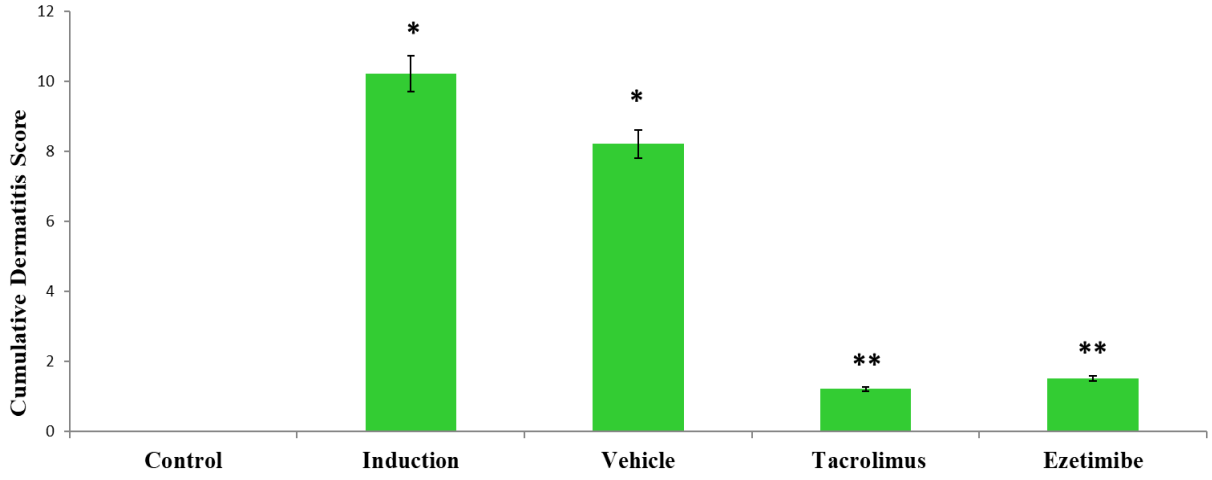

Fig 3. Impact of researched agents on the observational severity scores, data are illustrated as mean±SD; *denote considerable variation ($p<0.05$) vs. control group; # denote considerable variation ($p<0.05$) vs. induction and vehicle groups

Effect of tested agents on total and differential WBC counts

The percentages of total WBC, neutrophils, lymphocytes, monocytes, and eosinophils were substantially increased in induction and vehicle groups as opposed to normal controls ($p<0.05$). Besides, ezetimibe and

tacrolimus groups show considerably diminished counts of total WBC, neutrophils, lymphocytes, monocytes, and eosinophils than induction and vehicle groups as indicated in Table 1.

Table 1. Impact of researched agents on total WBC, neutrophils, lymphocytes, monocytes, and eosinophils counts[a]

	Groups					p
Variables ($x10^3$/mL)	**Control**	**Induction**	**Vehicle**	**Tacrolimus**	**Ezetimibe**	
WBC	3916±558	14180±1856*	14120±1625*	6640±614#	5850±290#	<0.05
Neutrophils	1465±221	4934±1434*	4910±1522*	2880±198#	2519±250#	<0.05
Lymphocyte	2260±638	5940±1086*	5890±982*	3220±580#	2995±442#	<0.05
Monocytes	81±12	1325±352*	1294±416*	543±118#	404±44#	<0.05
Eosinophils	111±28	1939±512*	1888±448*	725±124#	577±93#	<0.05

[a] data were expressed as mean±SD, * – denotes remarkable change ($p<0.05$) contrasted to the control group, # – denotes remarkable change ($p<0.05$) contrasted to the induction and vehicle groups

Effect of tested agents on skin histological abnormalities

The healthy control group has regular skin microstructure; the keratin epidermal layers, dermal uppermost layer, sebaceous glands, and hair proliferating follicles all appear normal, as illustrated in Table 2 and Figure 4. However, the application of DNCB resulted in substantial histopathological changes in the induction group opposed to the healthy untreated controls ($p<0.05$). Those skin changes were recognized by the breakdown of the skin barriers, the presence of clefts, marked hyperkeratosis, marked parakeratosis, increased acanthosis, profound erosion, remarkable edema, profound sloughing, and prominent inflammatory cell infiltration as represented in Table 2 and Figure 4. Except for erosion and extracellular edema, the vehicle group exhibited non-significant histopathological changes as matched to the induction group ($p>0.05$), including increased epidermal thickenings/acanthosis, marked hyperkeratosis, marked parakeratosis, significant erosion, significant edema, and increased inflammatory cell penetration. The

erosion and extracellular edema in the vehicle group were markedly alleviated compared to those seen in the induction. In opposition to the induction and vehicle groups, the tacrolimus 0.1% treated group showed substantially smaller histological aberrations, such as reduced cutaneous thickness, minor hyperkeratosis, minor parakeratosis, slight erosion, slight edema, and reduced inflammatory cell invasion as depicted in Table 2 and Figure 4. Additionally, the histopathological changes were markedly diminished in the ezetimibe group versus the induction group ($p<0.05$), as demonstrated by decreased epidermal thickness, mild hyperkeratosis, mild parakeratosis, mild erosion and reduced inflammatory cell infiltration, as revealed in Table 2 and Figure 4.

Table 2. Effect of tested agents on histopathological scores[a]

Variables	Mean±SD					
	Control	**Induction**	**Vehicle**	**Tacrolimus**	**Ezetimibe**	**p**
Acanthosis	0	3±0.4*	3±0.04*	1±0.05#	1±0.04#	<0.05
Hyperkeratosis	0	3±0.06*	3±0.08*	1±0.2#	2±0.04#	<0.05
Parakeratosis	0	3±0.04*	3±0.18*	0±0.03#	0±0.04#	<0.05
Erosion	0	3±0.05*	1±0.25*	0±0.05#	0±0.04#	<0.05
Inflammatory cell infiltration	0	3±0.1*	3±0.06*	1±0.1#	1±0.04#	<0.05

[a] data are illustrated as mean±SD, * – denote considerable variation ($p<0.05$) vs. control group, # – denote considerable variation ($p<0.05$) vs. induction and vehicle groups

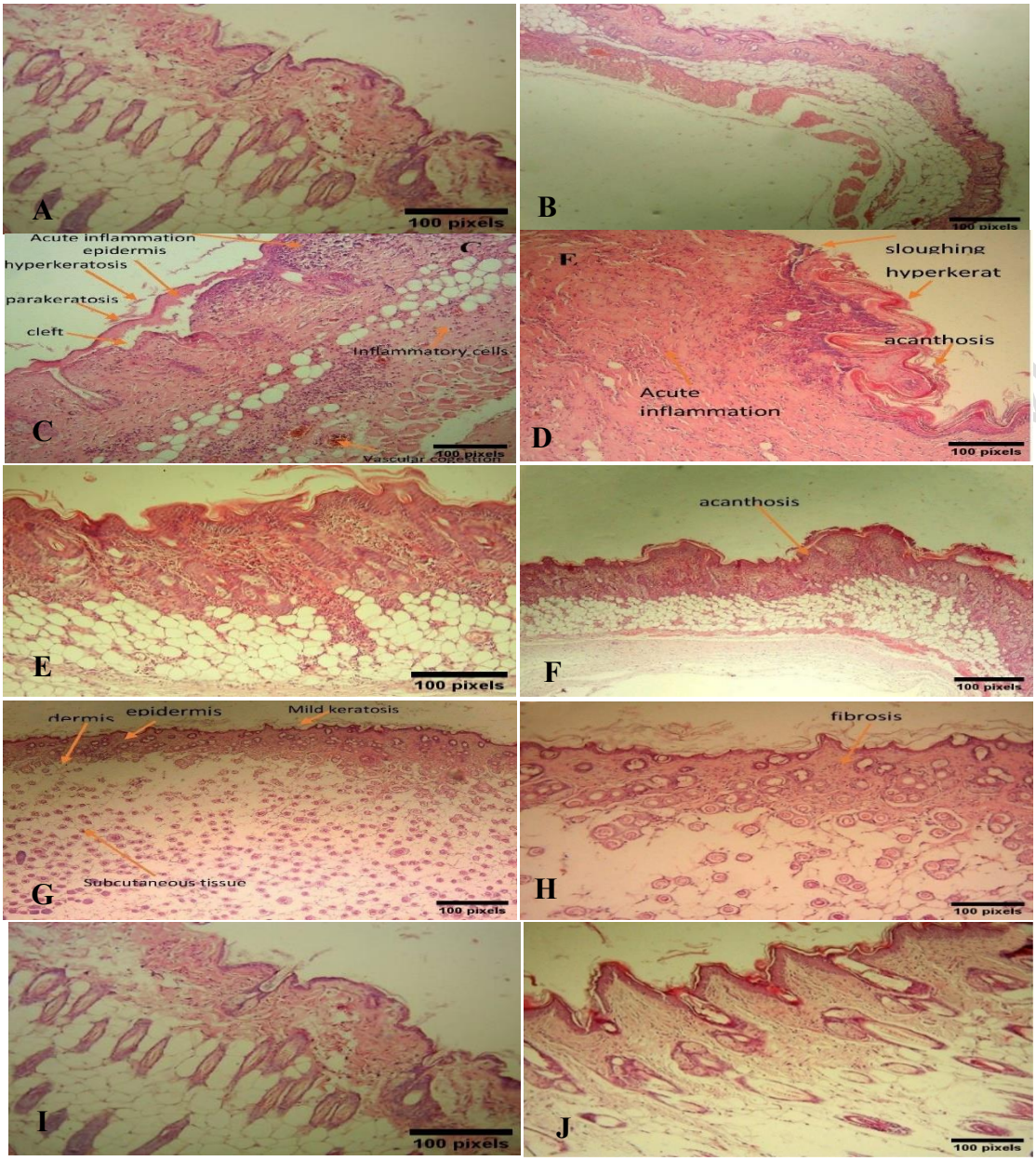

Fig. 4. Effect of studied agents on mouse skin histological alterations: A and B: light microscopy cross-section of mouse skin histopathology for healthy controls (H&E stain=10× and 4×), C and D: light microscopy cross-section of mouse skin histopathology for induction/ model group (H&E stain=10×), E and F: light microscopy cross-section of mouse skin histopathology for vehicle group (H&E stain=10× and 4×), G and H: light microscopy cross-section of mouse skin histopathology for tacrolimus group (H&E stain=10×), I and J: light microscopy cross-section of mouse skin histopathology for ezetimibe group (H&E stain=10×)

Impact of tested agents on skin immunohistochemical levels of IL-4 and IL-13

The immunohistochemistry investigation revealed considerable elevation of IL-4 and IL-13 scores among the model/induction and vehicle groups as opposed to the normal controls ($p<0.05$), but there are no appreciable variations among the induction and vehicle groups ($p>0.05$). The tacrolimus and ezetimibe-treated groups exhibited substantial diminution in IL-4 and IL-13 contents when opposed to the induction and vehicle non-treated groups ($p<0.05$). However, no substantial changes were noted across the tacrolimus and ezetimibe groups in terms of IL-4 and IL-13 scores ($p>0.05$), as clarified in Figure 5 and Figure 6.

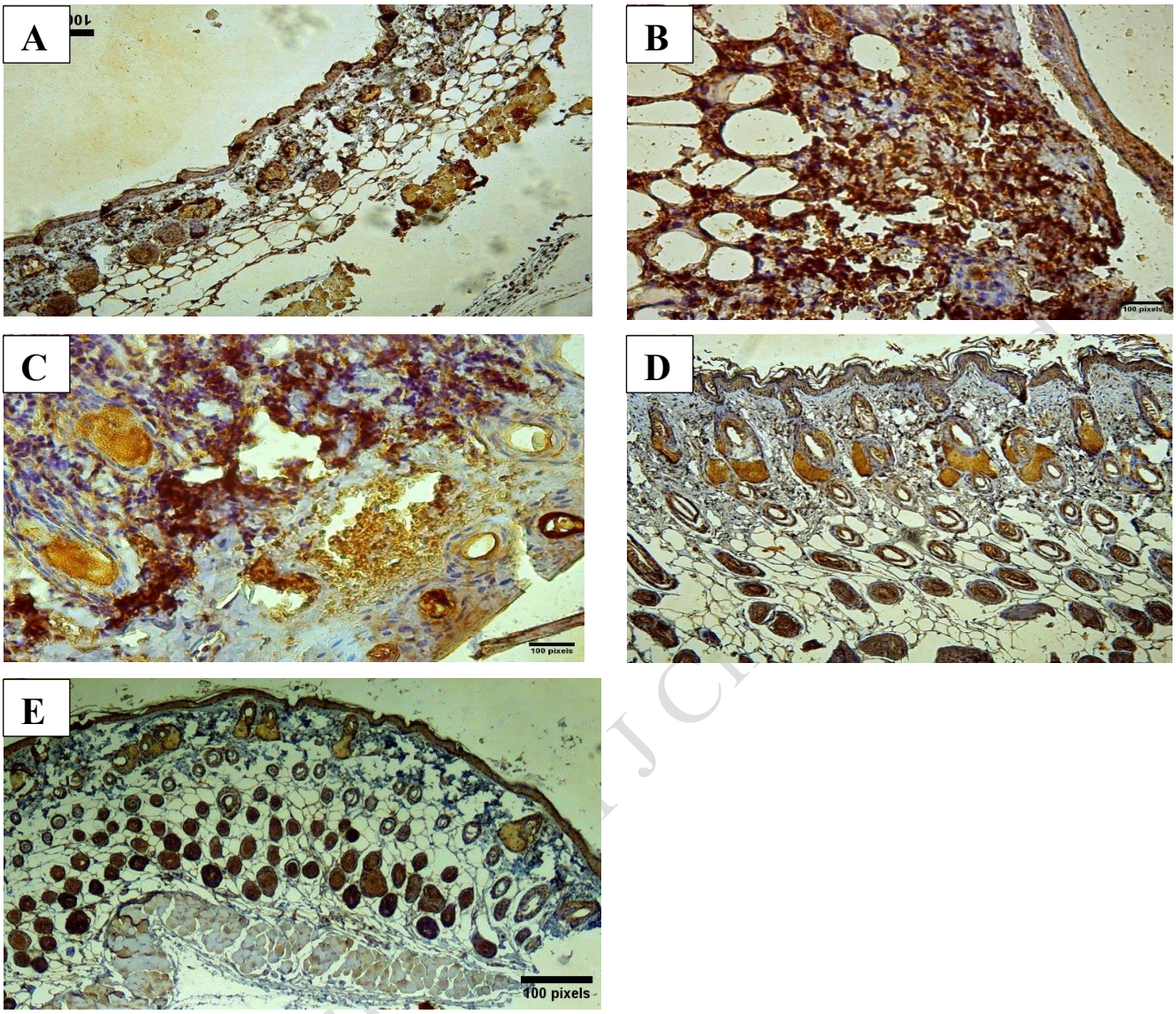

Fig. 5. Impact of studied agents on skin immunohistochemistry scores of IL-4: groups: (scale bar=100 mm), A: microscopic mouse cutaneous slice from the control group illustrating the immunohistochemical levels of IL-4, B: microscopic mouse cutaneous slice from the induction/model group illustrating the immunohistochemical levels of IL-4, C: microscopic mouse skin slice from the vehicle group illustrating the immunohistochemical levels of IL-4, D: microscopic mouse cutaneous slice of the tacrolimus group illustrating the immunohistochemical levels of IL-4, E: microscopic mouse cutaneous slice of the ezetimibe group illustrating the immunohistochemical levels of IL-4

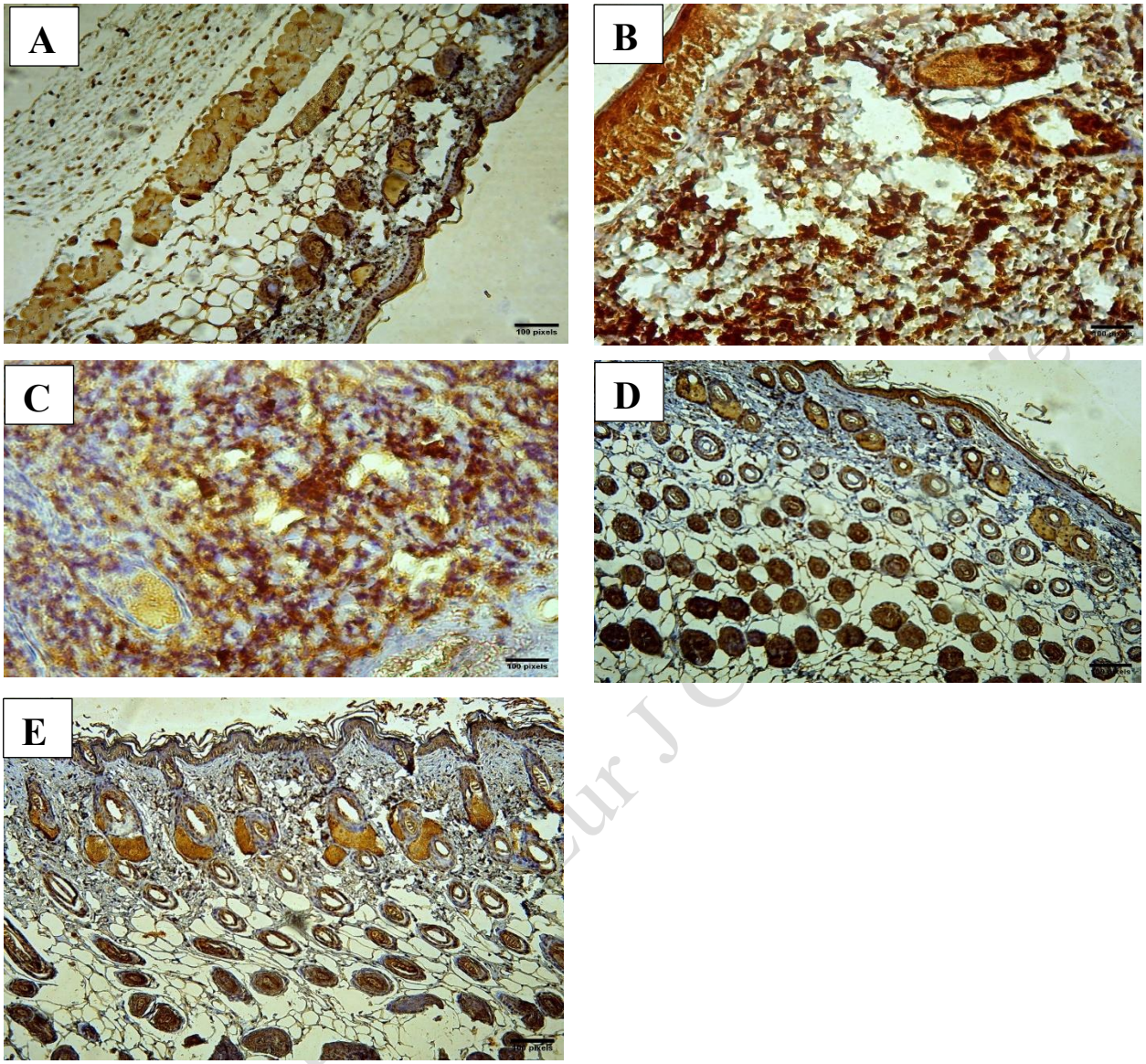

Fig. 6. Impact of studied agents on skin immunohistochemistry scores of IL-13: groups: (scale bar=100 mm), A: microscopic mouse cutaneous slice from the control group illustrating the immunohistochemical levels of IL-13, B: microscopic mouse cutaneous slice of the induction/model group illustrating the immunohistochemical levels of IL-13, C: microscopic mouse cutaneous slice of the vehicle group illustrating the immunohistochemical levels of IL-13, D: microscopic mouse cutaneous slice of the tacrolimus group illustrating the immunohistochemical levels of IL-13, E: microscopic mouse cutaneous slice of the ezetimibe group illustrating the immunohistochemical levels of IL-13

Effect of tested agents on skin tissue levels of IgE and MDA

The outcomes uncovered that the induction/model group exhibited markedly greater mean skin amounts of IgE and MDA as matched to the healthy untreated control group ($p<0.05$). No notable variations were seen in any of the parameters between the induction and vehicle groups. However, the tacrolimus and ezetimibe groups had dramatically lower levels of IgE and MDA relative to the induction and vehicle groups ($p<0.05$). Both the tacrolimus and ezetimibe groups did not vary considerably from one another on any of the parameters ($p>0.05$), as shown in Figure 7.

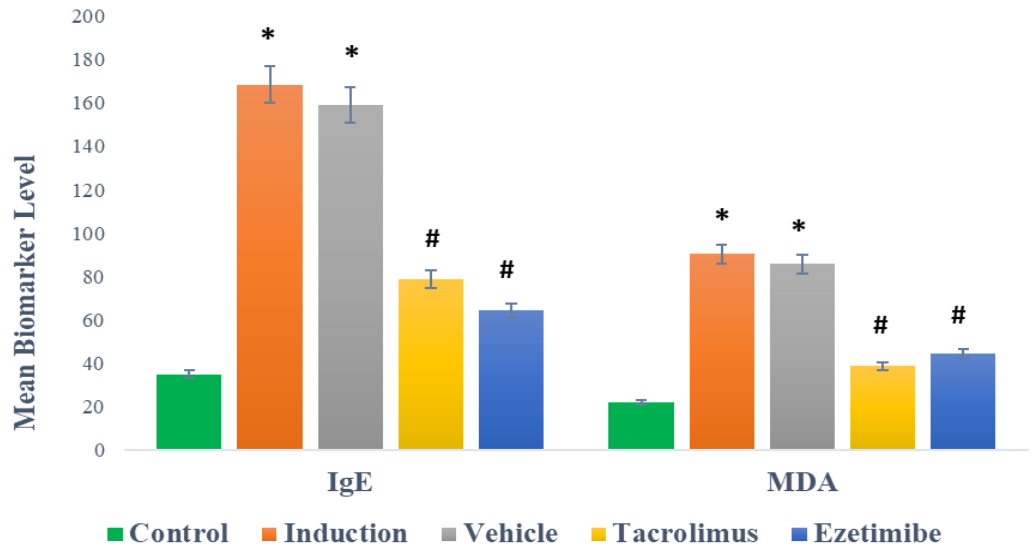

Fig. 7. Impact of tested agents on IgE and MDA (the data expressed as mean±standard deviation; * –implies a statistically marked difference ($p<0.05$) when contrasted to the normal controls, while # – implies a marked variation ($p<0.05$) when contrasted to the model/induction and vehicle groups

Effect of tested agents on skin tissue levels of IL-17, IL-31, TGF-β, and TNF-α

The results demonstrated that the induction group had markedly elevated mean epidermal levels of IL-17, IL-31, TGF-β, and TNF-α in relation to the healthy controls ($p<0.05$). No remarkable variances occurred in all metrics across the model/induction and vehicle groups. Still, the tacrolimus and ezetimibe groups exhibited extensively mitigated amounts of IL-17, IL-31, TGF-β, and TNF-α relative to the induction/model and vehicle groups ($p<0.05$). The tacrolimus and ezetimibe groups exhibited no significant distinctions across all variables ($p>0.05$), as explained in Figure 8.

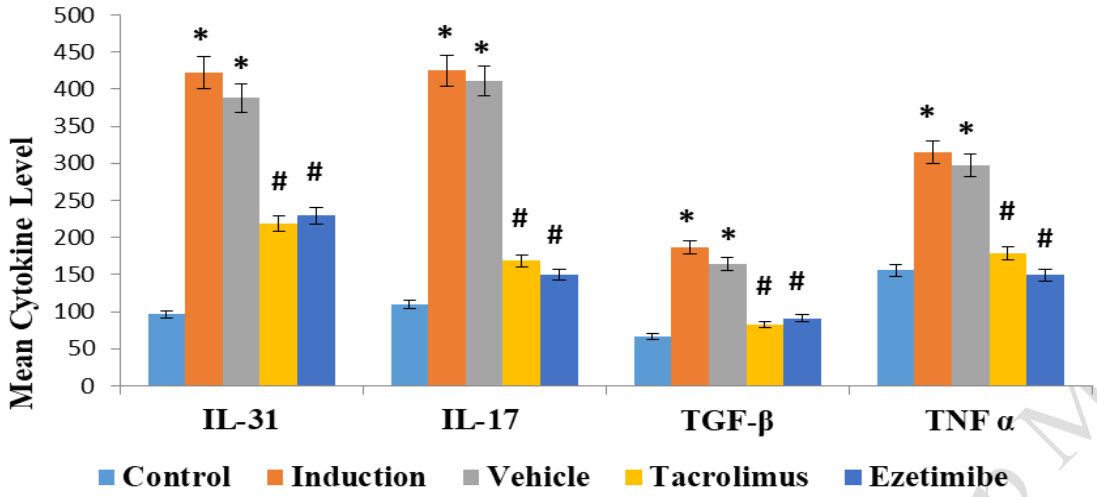

Fig. 8. Effects of tested agents on IL-17, IL-31, TGF-β, and TNF-α, the data expressed in the form of mean ±standard deviation, * – implies a statistically remarkable difference ($p<0.05$) when contrasted to the control group, while # – implies a remarkable variation ($p<0.05$) when contrasted to the model/induction and vehicle groups, IL – interleukin, TGF-β – transforming growth factor-β; TNF-α – tumor necrosis factor-α

Discussion

The novelty of this work lies in demonstrating for the first time that ezetimibe, beyond its systemic lipid-lowering action, exerts strong topical anti-inflammatory and antioxidant effects in a murine model of AD. The mouse prototype of DNCB-aggravated atopic dermatitis was extensively utilized to assess innovative therapies and compounds. The research designs and methodologies are markedly varied, revealing distinct patterns of atopic dermatitis that manifest after sensitization and frequent exposure to DNCB on the back skin.[112] In this work, the disease was induced with 1% DNCB in the sensitization phase and successive administrations of 0.5% DNCB in the challenge stage, resulting in a mild phenotype of eczematous dermatitis.[83] The DNCB-treated skin exhibited a moderate extrinsic subacute atopic dermatitis lesion on day 12 and a mild extrinsic subacute to prolonged phenotype and endotype on day 22, characterized by a predominant Th2 response. Both timepoints demonstrate hallmark features linked with atopic dermatitis, including dorsal skin thickening, hyperkeratosis, parakeratosis, elevated TH1 and TH2 cytokine levels, and alterations in barrier proteins. Elevated mast cell influx in the epidermis and higher plasma IgE levels signify a type I allergic reaction. [83,113]

In this study, administering DNCB to the murine dorsal regions resulted in evident indications of desquamation, erythema, and blisters, along with a notable rise in eczema severity indices. Furthermore, the aggregate populations of WBCs, neutrophils, lymphocytes, monocytes, and eosinophils were strongly elevated, and immunohistochemical testing indicated a large increment in IL-4 and IL-13 values. DNCB

further drastically boosts the amounts of IgE, MDA, IL-17, IL-31, TGF-β, and TNF-α, while histological examination reveals pathological features such as hyperkeratotic changes, dermal thickness, and infiltrating lymphocytes, therefore confirming the AD model. Topical treatment is a popular method of ameliorating clinical manifestations, although it might trigger epidermal thinning and hypersensitivity.[114-116] Tacrolimus is an effective prolonged topical therapy for AD that acts by reducing phosphatase activity in the calcineurin pathway, resulting in decreased T-lymphocyte activation and inflammatory cytokine production. It also improves skin barrier function by stimulating the development and maturation of skin cell. [117-119] Prior research has demonstrated that the anti-atopic benefits of tacrolimus entail the suppression of total and differential leukocytes, IgE activity, oxidative measures notably MDA, and Th1- and Th2-related inflammatory cytokines, notably IL-4, IL-13, IL-17, IL-31, TNF-a, and TGF-β, as well as various molecular signaling cascades.[120-124]

Topical tacrolimus 0.1% yielded an immediate decrement in overall dermatitis scores, inflammation, and pruritus.[117] The most frequent undesirable actions of tacrolimus entail burning irritations at the sites of administration.[125-127] Consequently, developing innovative, efficacious medications for AD is essential.

In the current study, ezetimibe 2% ointment demonstrated a suppressive impact on DNCB-evoked AD-mimicking cutaneous erosions in mice, as evidenced by substantially reduced amounts of inflammatory and oxidative biomarkers, histological alterations, and the dermatitis severity scores. Additionally, a considerable decrement in the numbers of total leukocytes, lymphocytes, monocytes, eosinophils, and neutrophils was observed in comparison to the induction group. These outcomes were similar to those of Suchy et al. who discovered that ezetimibe has direct inhibitory effects on the activation pathways of immune cells, including monocytes and macrophages.[128] Another research indicated that ezetimibe administration yielded in a dose-related decline in both the overall proportion of CD3+CD4+ T cells and the number of $CD3^{+}/CD4^{+}$/CD45RO T memory lymphocytes.[129] Aside from the effect on immune cells, ezetimibe additionally offers other benefits, such as lowering the production of C-reactive protein, an influential inflammatory biomarker.[130] Likewise, topical ezetimibe experienced anti-inflammatory properties, reducing ear edema by 64%.[131] supporting current research that suggests it may be applied to treat inflammatory skin conditions. These favorable effects of ezetimibe could be explained by its ability to downregulate inflammatory mediators, suppress macrophage activation, and regulate the NF-kB, a chain accountable for producing various inflammation-related cytokines. In this context, ezetimibe treatment caused IkB decomposition and thereby suppressed NF-kB translation via the mitogen-activated protein kinases (MAPKs) mechanism. This evidence showed that there might be an opportunity of using ezetimibe to treat and prevent inflammatory disorders.[132] Another proof implies that ezetimibe might exhibit anti-inflammatory features alongside its lipid-lowering impacts, as NF-kB stimulation is influenced by chemotactic cytokines and substances involved in intracellular defense.[53] Moreover, ezetimibe alleviated clinical manifestations of ankylosing spondylitis in animals by suppressing Th17 differentiating-associated

genes like IL-23R and IL-1R and modifying the Th17/Treg cell harmony resulting in a distinct anti-inflammatory impact irrespective of circulatory lipid lowering. The researchers found that ezetimibe dramatically boosted the overall count of Treg cells while decreasing the proportion of Th17 and Th1 lymphocytes. Ezetimibe also markedly decreased IFN-γ, TNF-α, IL-1β, IL-6, and IL-17 concentrations. As a result, ezetimibe modulates T-cell proliferation and pro-inflammatory cytokine release by immune system cells.[133] Similarly, ezetimibe inhibited lymphocytic production of TNF-α, IFN-γ, and IL-2 in hypercholesterolemic individuals in a lipid-unrelated way.[134] Subsequent studies concluded that ezetimibe successfully managed the rat model of ulcerative colitis by alleviating the output of pro-inflammatory measures like TNF-α, IL-1β, and NF-κB alongside oxidative measures like MDA and MPO in colon homogenate.[135-137] Likewise, literatures showed that ezetimibe is effective in treating of alopecia, an immune-related disease featured by T-lymphocyte stimulation, accumulation mast cells and production TNF-a.[138-140] Alopecia sufferers are more likely to acquire other autoimmune disorders, like atopic dermatitis, vitiligo, and skin cancer.[141]

Meanwhile, this work found that ezetimibe remarkably reduced the immunohistochemical expressions of IL-4 and Il-13 in the back cutaneous folds. This outcome concurs with prior research, which indicated that ezetimibe/simvastatin combination contributed to decreased immunohistochemistry expression of chemotactic cytokines among alopecia areata patients.[141] Additional observation revealed that ezetimibe possesses immunomodulatory impacts on antigenic presentation, lymphocytic trafficking, and regulatory T cell function.[142] Ezetimibe was also documented to mitigate inflammatory variables like CRP, monocyte chemoattractant protein-1, IL-1β, IL-6, TNF-α, and pro-oxidant markers.[143-145] In macrophage tests, ezetimibe reduced NF-κB expression and blocked the NLRP3 inflammasome-IL-1β route, resulting in anti-inflammatory activity.[146] Ezetimibe can also attenuate inflammation and oxidative injury induced by caspase-1/IL-1β via the AMP-stimulated protein kinase/NF-E2-relating factor 2 (Nrf2)/thioredoxin-interacting protein (TXNIP) system.[147] In addition, this medication decreases monocyte chemoattractant protein 1-induced recruitment.[148,149] All these outcomes support our hypothesis that ezetimibe could be of an important value in attenuating experimentally-induced model of AD.

Study limitations

Nonetheless, the present investigation encompassed some limitations. Actually, our data exclusively confirmed the inhibitory effect of ezetimibe on a murine male prototype of DNCB-aggravated AD, neglecting the influence of gender-related fluctuations on the experimental results and failing to apply human participants due to the disparities between rodents and humans. Consequently, the effectiveness and security of ezetimibe in the management of AD ought to be assessed in people. Moreover, the further in-depth mechanism by which ezetimibe confers preventive impacts in mice afflicted with AD needs to be elucidated. The issue pertains to implications on other immune-related elements such as the proliferation

of systemic immune receptors (sCD25, sCD30), the atopy patch tests, and the filaggrin genes. Further investigation is necessary to assess the efficacy of the combined use of ezetimibe and tacrolimus.

Conclusion

Topical ezetimibe significantly attenuated DNCB-induced eczematous dermatitis in mice by reducing histopathological alterations, suppressing pro-inflammatory cytokines, and lowering total and differential leukocyte counts. These results provide the first evidence supporting ezetimibe as a potential adjunctive therapy for immune-mediated and inflammatory dermatoses. The findings also highlight a novel therapeutic avenue for drug repurposing of ezetimibe in dermatology, particularly in AD.

Acknowledgements

The research was undertaken during the course of an MSc dissertation at Al-Nahrain University's College of Medicine, namely in the Department of Pharmacology.

Declarations

Funding

The authors completely funded this work.

Author contributions

Conceptualization, A.M.S. and A.R.A.; Methodology, H.R-S.; Software, W.H.A.; Validation, A.R.A., H.R-S. and A.J.H.A.; Formal Analysis, A.M.S.; Investigation, W.H.A.; Resources, A.M.S.; Writing – Original Draft Preparation, H.R-S., A.M.S. and A.R.A.; Writing – Review & Editing, H.R-S.; Visualization, A.R.A., W.H.A. and A.J.H.A; Supervision, A.R.A. and H.R-S.; Project Administration, A.J.H.A.; Funding Acquisition, A.M.S.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The corresponding author may obtain data validating the findings of this research on an adequate request.

Ethics approval

The research proposal has been authorized by the Institutional Review Board (IRB) of AL Nahrain University's College of Medicine (authorization number: 2 on October 14, 2021).

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