



## ANTI-INFLAMMATORY EFFECTS OF FERULIC ACID IN A MOUSE MODEL OF ATOPIC DERMATITIS

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### Summary

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by impaired skin barrier function and predominant Th2-mediated inflammation. Thymic stromal lymphopoietin (TSLP), a cytokine secreted by epidermal keratinocytes, plays a critical role in AD pathogenesis by initiating and amplifying allergic inflammation. Ferulic acid (FA), a natural phenolic compound with potent antioxidant and anti-inflammatory properties, has gained attention as a potential therapeutic agent for AD. This study evaluated the effects of ferulic acid on TSLP expression using immunohistochemical staining in an experimental AD model. Histopathological analysis revealed that ferulic acid treatment significantly reduced epidermal thickness and inflammatory cell infiltration, compared to 2,4-dinitrochlorobenzene (DNCB) group. Furthermore, TSLP immunoreactivity was markedly decreased following ferulic acid administration. In addition, real-time PCR analysis demonstrated that ferulic acid significantly downregulated the mRNA expression levels of pro-inflammatory cytokines TNF- $\alpha$ , IL-4, and IL-13. These findings suggest that ferulic acid modulates TSLP-mediated inflammatory responses and improves histopathological outcomes in AD, highlighting its potential as a supportive treatment option for atopic dermatitis.

**Key words:** atopic dermatitis, ferulic acid, mice, thymic stromal lymphopoietin (TSLP)

### INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease with a complex and multifactorial pathogenesis. It is clinically characterised by pruritus and demonstrates a typical age-related pattern in the distribution of skin lesions (Langan *et al.*, 2020). The underlying mechanisms involve impaired skin barrier function and a predominant type 2 im-

mune response, driven largely by cytokines such as interleukin-4 (IL-4), interleukin-13 (IL-13), and thymic stromal lymphopoietin (TSLP) (Weidinger & Novak, 2016). IL-4, which promotes T cell differentiation, is believed to play a key role in the early stages of AD pathogenesis, whereas IL-13 primarily affects peripheral tissue cells and contributes to the

effector phase of the immune response (Furue *et al.*, 2019). TSLP is a key immune regulator that contributes to the worsening of AD. Primarily produced by keratinocytes, TSLP interacts with various immune cells – including dendritic cells, T cells, and mast cells – to promote a Th2-skewed immune response during AD pathogenesis (Luo *et al.*, 2023).

Ferulic acid (FA) is a natural phenolic compound found in many plants, including rice bran, oats, wheat, and is known for its antioxidant (Zheng *et al.*, 2024), anti-inflammatory (Doss *et al.*, 2016), and photoprotective properties (Lin *et al.*, 2005; Peres *et al.*, 2018). Recent studies have demonstrated that FA exerts protective effects in various inflammatory skin disorders, including UV-induced damage (Pluemsamran *et al.*, 2012) and psoriasis (Lo *et al.*, 2019). In DNCB-induced AD models, FA has been shown to reduce serum IgE levels, attenuate skin inflammation, and inhibit pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ , primarily through the suppression of NF- $\kappa$ B signaling (Zhou *et al.*, 2020). However, its effect on TSLP expression in atopic dermatitis has not yet been fully elucidated.

This study was designed to evaluate the therapeutic potential of ferulic acid in a DNCB-induced murine model of atopic dermatitis, with a specific focus on its ability to modulate TSLP expression at the protein level, as detected by immunohistochemistry. In addition, histopathological evaluation of skin lesions using haematoxylin and eosin (H&E) staining to assess epidermal thickness, dermal inflammation, and tissue architecture, along with toluidine blue staining to visualise and quantify mast cell infiltration in the dermis will be performed. Furthermore, real-time PCR analysis to determine the mRNA expression levels of key pro-

inflammatory cytokines, including TNF- $\alpha$ , IL-4, and IL-13 will be conducted in order to elucidate the molecular mechanisms underlying the anti-inflammatory effects of ferulic acid. It was hypothesised that FA suppresses epidermal TSLP production, thereby improving both clinical and histological outcomes in AD.

## MATERIALS AND METHODS

### *Animals*

Female CD-1 mice (6–8 weeks old, 20–25 g, n=7 per group) were used in this study. All animals were housed under controlled conditions (22 $\pm$ 2 °C, 55 $\pm$ 10% humidity, 12-hour light/dark cycle) with *ad libitum* access to standard pellet feed and water. All experimental procedures were approved by Burdur Mehmet Akif Ersoy University Animal Care and Use Committee (Approval Date: August 06, 2025; Decision No: 1551) and conducted in accordance with relevant guidelines.

### *Induction of atopic dermatitis model and treatment groups*

The atopic dermatitis (AD) model was adapted from the study by Yang *et al.* (2025). The dorsal skin of the mouse was treated with 0.1 mL of a 1% 2,4-dinitrochlorobenzene (DNCB) (Sigma, 237329) solution, prepared in a 4:1 mixture of acetone and olive oil, for three consecutive days (days 0, 1, and 2) to induce sensitisation. Five days following this sensitisation phase, the mice were exposed to a challenge dose of 0.5% DNCB (0.1 mL) on days 7, 9, 11, and 13. Successful model induction was confirmed by visible clinical symptoms such as erythema, thickening, scaling, and scratching behaviour.

Following the induction of atopic dermatitis, the mice were randomly as-

signed to four groups: a negative control group (no DNCB application, no treatment), a positive control group (DNCB application without treatment), a 1% ferulic acid treatment group (DNCB + 1% FA), and a 2% ferulic acid treatment group (DNCB + 2% FA). Ferulic acid (Thermo Fisher, 156360250, purity 99%) was applied in acetone:olive oil in a 4:1 ratio. In the treatment groups, 100 µL of either 1% or 2% ferulic acid solution was applied topically to the affected skin regions from day 7 to day 13.

On day fourteen, all mice were anaesthetised using ketamine (80 mg/kg) and xylazine (10 mg/kg). Skin tissues were harvested and rinsed with phosphate-buffered saline (PBS). Portions of the skin samples were fixed in 10% neutral buffered formalin (NBF) for histopathological examination, while the remaining tissues were stored at -80 °C for reverse transcription-polymerase chain reaction (RT-PCR) analyses.

#### *Histopathological stainings*

Histological evaluation was performed on paraffin-embedded skin sections using haematoxylin and eosin (H&E) and toluidine blue staining methods to assess tissue architecture and inflammatory features. H&E staining was used to evaluate key pathological changes including epidermal thickness, dermal inflammatory cell infiltration. Each parameter was scored semi-quantitatively on a scale from 0 to 3 (0: none, 1: mild, 2: moderate, 3: severe), and a total histological score was obtained by summing the values for each criterion, with a maximum possible score of 6 per sample. Toluidine blue staining was specifically used to identify mast cells within the dermis, which were characterised by their metachromatic purple-stained granules. Mast cells were counted in three

randomly selected fields ( $\times 100$  magnification), and the average number of mast cells per field was calculated for each mouse. All histological evaluations were performed in a blinded manner by two independent observers to ensure objectivity and reproducibility. These stainings allowed for detailed assessment of both structural and immune cell-related changes in the skin tissue following DNCB-induced dermatitis and ferulic acid treatment.

#### *Immunohistochemical stainings*

For immunohistochemical detection of thymic stromal lymphopoietin (TSLP), paraffin-embedded skin sections (4 µm thick) were deparaffinised in xylene and rehydrated through graded alcohols. Antigen retrieval was performed using citrate buffer (pH 6.0) in a microwave oven for 20 minutes. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 minutes. Sections were incubated overnight at 4 °C with a rabbit anti-TSLP primary antibody (Novus, NB110-55234, 1:750 dilution), followed by treatment with an appropriate secondary antibody (Vector Lab, Anti-Rabbit IgG, Peroxidase, MP-7601) and visualisation using a AEC chromogen detection system. Mayer's haematoxylin was used for nuclear counterstaining. Slides were covered with Entellan and examined under a light microscope (Zeiss Axioscope 5, Germany).

#### *Real time-PCR*

Total RNA was extracted from skin tissue samples using the TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. The concentration and purity of RNA were determined spectrophotometrically using a NanoDrop device (Klab Optizen Nano-Q Plus Nanodrop). Complementary DNA (cDNA) was syn-

**Table 1.** Primers used for RT-PCR

Gene	Forward primer sequence (5'-3')	Reverse primer sequence (5'-3')
TNF- $\alpha$	ATCCATCTCTTTGCGGAGGC	GGGGGAGAGGTAGGGATGTT
IL-4	CCAAACGTCCTCACAGCAAC	AGGCATCGAAAAGCCCGAA
IL-13	GCCAAGATCTGTGTCTCTCCC	ATGTGGGGGTCCCGAAGTA
$\beta$ -Actin	AAGGCCAACCGTAAAAAGAT	GTGGTACGACCAGAGGCATAC

thesised from 1  $\mu$ g of total RNA using a reverse transcription kit (VitaScript™ FirstStrand cDNA Synthesis Kit) following the manufacturer's protocol. The reverse transcription reaction was carried out in a thermal cycler under the following conditions: 42 °C for 120 min, 80 °C for 10 min, and 4 °C for 5 min to inactivate the reverse transcriptase enzyme and terminate the reaction.

Real-time PCR (RT-PCR) was performed using a SYBR Green Master Mix (Applied Biosystems, USA) on a StepOnePlus™ Real-Time PCR System (Applied Biosystems, USA). Specific primers for TNF- $\alpha$ , IL-4, and IL-13, as well as the housekeeping gene  $\beta$ -Actin, were designed based on published sequences. Relative gene expression levels were calculated using the  $2^{-\Delta\Delta Ct}$  method, and all data were normalised to  $\beta$ -Actin expression. Genes were demonstrated in Table 1.

#### *Statistical analyses*

Clinical score evaluations for all mouse groups were analysed using repeated measures ANOVA in IBM SPSS Statistics (Version 27.0, IBM Corp., Armonk, NY, USA). Statistical comparisons of histopathological results between groups were conducted using Minitab™ software (version 16.1.1), employing one-way ANOVA followed by Tukey's *post hoc* test.

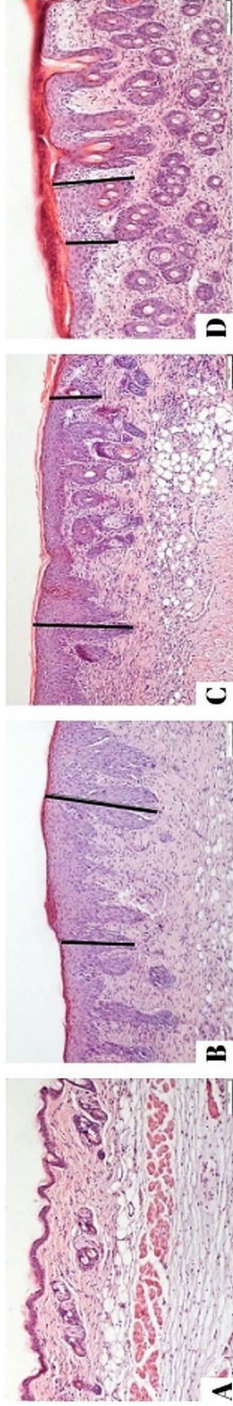
## RESULTS

### *Histopathological findings in mice skin*

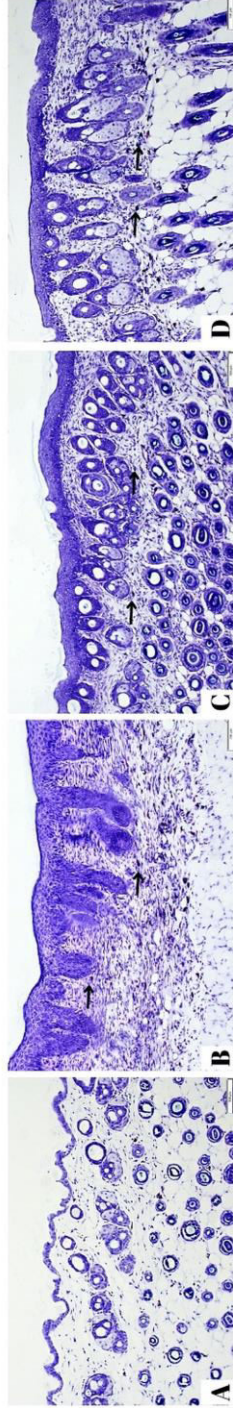
Histological analysis using haematoxylin and eosin (H&E) staining revealed significant epidermal thickness and dense inflammatory cell infiltration in the DNCB-induced atopic dermatitis model group (Fig. 1B) compared to the healthy control group (Fig. 1A). In contrast, ferulic acid-treated groups showed a marked reduction in epidermal thickness. Toluidine blue staining further demonstrated a significant decrease in dermal mast cell infiltration in the ferulic acid-treated groups (Fig. 2C and 2D) compared to the DNCB group (Fig. 2B). These findings indicate that ferulic acid effectively alleviates histopathological damage associated with atopic dermatitis.

In the assessment of epidermal thickness, a marked elevation was detected in the DNCB group (258.94 $\pm$ 29.95  $\mu$ m) when compared to the control group (18.75 $\pm$ 0.52  $\mu$ m) ( $P$ <0.001). Treatment with 1% FA (111.07 $\pm$ 7.86  $\mu$ m) and 2% FA (102.73 $\pm$ 3.86  $\mu$ m) led to a significant reduction in epidermal thickness relative to the DNCB group ( $P$ <0.01). However, there was no statistically significant difference observed between the 1% and 2% FA groups ( $P$ >0.05) (Table 2).

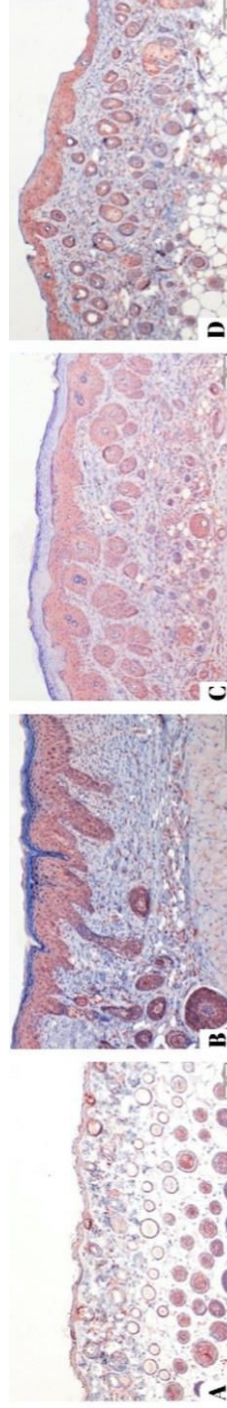
Regarding dermal inflammation, the DNCB group exhibited significantly elevated scores (3.43 $\pm$ 0.20) compared to the



**Fig. 1.** Representative haematoxylin and eosin stained skin sections from control (A), DNCB-induced atopic dermatitis with increased epidermal thickness (B), 1% ferulic acid-treated (C), and 2% ferulic acid-treated (D) groups with increased epidermal thickness (black line). bar = 100 μm.



**Fig. 2.** Toluidine blue staining for mast cell infiltration in dermal tissue. Representative images from control (A), DNCB-treated (B), 1% ferulic acid-treated (C), and 2% ferulic acid-treated (D) groups. Numerous mast cells (purple stained granulated cells, black arrows) are observed in DNCB group, while mast cell numbers are significantly reduced in the FA-treated groups. Scale bar = 100 μm.



**Fig. 3.** Immunohistochemical staining for thymic stromal lymphopoietin (TSLP) expression in mouse skin. TSLP immunoreactivity is prominently increased in the epidermis of the DNCB group (B) compared to the control (A). The 1% (C) and 2% (D) ferulic acid treatment resulted in noticeably reduced TSLP expression. Scale bar = 100 μm.

**Table 2.** Histopathological and immunohistochemical findings for DNCB and FA groups

Groups	Epidermal thickness ( $\mu\text{m}$ )	Dermal inflammation	Number of mast cells
Control	$21.04 \pm 2.10^a$	$0.00 \pm 0.00^a$	$6.86 \pm 0.50^a$
DNCB	$258.94 \pm 29.95^c$	$3.43 \pm 0.20^c$	$28.29 \pm 0.75^c$
1% FA	$111.07 \pm 7.86^b$	$2.14 \pm 0.14^b$	$23.13 \pm 1.71^b$
2% FA	$102.73 \pm 3.86^b$	$2.00 \pm 0.21^b$	$22.85 \pm 0.67^b$

control group ( $0.00 \pm 0.00$ ) ( $P < 0.001$ ). Inflammatory responses in the 1% FA ( $2.14 \pm 0.14$ ) and 2% FA ( $2.00 \pm 0.21$ ) treatment groups were notably lower than those in the DNCB group ( $P < 0.05$ ), though no significant difference was identified between the two FA-treated groups ( $P > 0.05$ ) (Table 2).

Toluidine blue staining revealed a significant increase in mast cell numbers in the DNCB group ( $28.29 \pm 0.75$ ) compared to the control ( $6.86 \pm 0.50$ ) ( $P < 0.001$ ). While no significant difference in mast cell counts was found between the 1% FA ( $23.13 \pm 1.71$ ) and 2% FA ( $22.85 \pm 0.67$ ) groups ( $P > 0.05$ ), both groups demonstrated a statistically significant decrease relative to the DNCB group (1% FA:  $P < 0.05$ ; 2% FA:  $P < 0.001$ ) (Table 2).

#### *TSLP immunohistochemistry in mice skin*

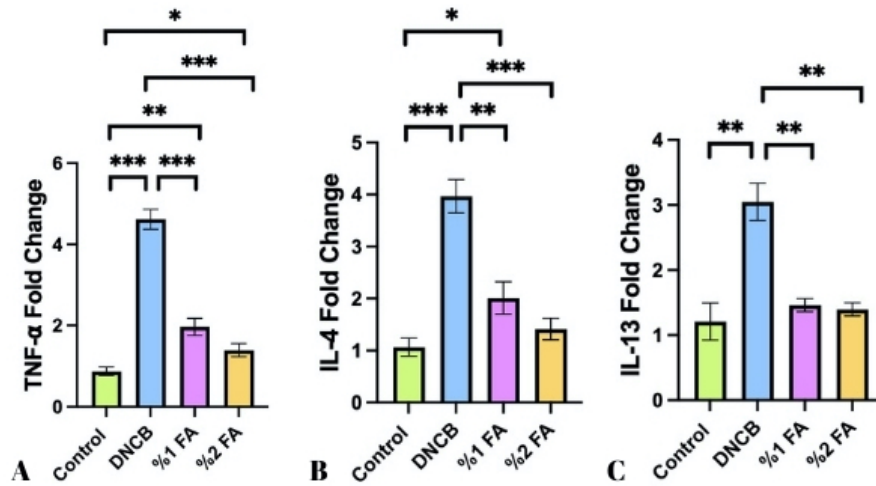
Immunohistochemical staining for thymic stromal lymphopoietin (TSLP) revealed strong immunoreactivity in the epidermis of DNCB-treated mice, particularly in keratinocytes. Treatment with ferulic acid led to a noticeable reduction in TSLP expression, as evidenced by decreased staining intensity and distribution (Fig. 3). The TSLP immunoreactivity in the 1% and 2% FA-treated groups was comparable to that observed in the healthy control group, suggesting that FA may suppress TSLP production in the skin and modulate the associated inflammatory response.

#### *Real-time PCR results*

Real-time PCR analysis revealed a significant upregulation of TNF- $\alpha$  ( $P < 0.001$ ), IL-4 ( $P < 0.001$ ), and IL-13 ( $P < 0.01$ ) mRNA expression levels in the DNCB-treated group compared to healthy controls. Treatment with 2% ferulic acid significantly downregulated TNF- $\alpha$  ( $P < 0.001$ ), IL-4 ( $P < 0.001$ ) and IL-13 ( $P < 0.01$ ), while 1% ferulic acid also resulted in a marked reduction in TNF- $\alpha$  ( $P < 0.001$ ), IL-4 ( $P < 0.01$ ) and IL-13 ( $P < 0.01$ ) mRNA levels, compared to the DNCB group. These findings suggest that FA effectively suppresses inflammatory gene expression. Notably, IL-4 and IL-13 expression levels in the 2% FA-treated group closely approached those of the control group, further supporting the anti-inflammatory potential of FA in the context of atopic dermatitis (Fig. 4).

#### DISCUSSION

This study evaluated and compared the therapeutic effects of 1% and 2% topically administered ferulic acid (FA) on thymic stromal lymphopoietin (TSLP) expression and histopathological changes in a DNCB-induced murine model of atopic dermatitis (AD). Both FA concentrations significantly alleviated AD-like skin lesions, reduced epidermal hyperplasia, and attenuated inflammatory responses at his-



**Fig. 4.** Real-time PCR analysis of inflammatory cytokine mRNA expression in skin tissue. Relative mRNA expression levels of TNF- $\alpha$  (A), IL-4 (B) and IL-13 (C) in control, 2,4-dinitrochlorobenzene (DNCB), and 1% ferulic acid-treated groups (1% FA; 2% FA). All three cytokines were significantly upregulated in the DNCB group and downregulated following FA treatment. Results are normalized to  $\beta$ -Actin expression and presented as fold change relative to control. Data are shown as mean  $\pm$  SD (\* $P$ <0.05, \*\*  $P$ <0.01, \*\*\*  $P$ <0.001).

tological and molecular levels. Histopathological analysis showed a marked reduction in epidermal thickness, dermal inflammatory cell infiltration, and mast cell numbers in FA-treated groups compared to the DNCB control group. These findings were accompanied by the downregulation of Th2-related cytokines, suggesting that FA modulates keratinocyte-derived inflammatory signaling, a key component in the pathogenesis of AD.

Real-time PCR analysis further confirmed these effects, demonstrating that FA significantly reduced the mRNA expression levels of key proinflammatory cytokines such as TNF- $\alpha$ , IL-4, and IL-13—central mediators of the Th1/Th2 immune response (Sin Singer Brugiolo *et al.*, 2017). These cytokines were highly upregulated in DNCB-induced lesions but significantly downregulated in both FA-treated groups, indicating that FA exerts

its immunomodulatory effects by targeting multiple immune axes, not limited to Th2 signalling alone.

Our results agree with existing literature data describing the broad anti-inflammatory effects of FA. For example, Zhou *et al.* (2020) demonstrated that topical FA alleviated AD-like symptoms, reduced scratching behaviour, and decreased serum levels of IL-4, IgE, IL-6, TNF- $\alpha$ , and IL-31 in DNCB-induced BALB/c mice, primarily through NF- $\kappa$ B inhibition. Although TSLP expression was not directly assessed in most dermatological studies, it has been reported in airway inflammation models that FA can downregulate epithelial-derived cytokines such as TSLP, IL-25, and IL-33 (Sin Singer Brugiolo *et al.*, 2017), indicating its potential regulatory effect on alarming cytokines.

Further mechanistic insight is provided by Kim *et al.* (2021), who showed that FA modulates keratinocyte-derived signalling by inhibiting nuclear  $\beta$ -catenin accumulation and activating Nrf2 in wound-induced inflammation. These pathways are intricately linked to skin immune homeostasis and inflammation, supporting the idea that FA regulates both structural and immunologic aspects of the skin barrier. In our model, the modulation of TSLP expression by FA may result from its interaction with upstream regulators such as NF- $\kappa$ B and oxidative stress sensors like Nrf2.

Moreover, FA's strong antioxidant activity adds to its therapeutic value by neutralising reactive oxygen species (ROS) and restoring redox balance, which plays a crucial role in maintaining epidermal barrier integrity and mitigating oxidative stress-induced inflammation (Srinivasan *et al.*, 2007; Zduńska *et al.*, 2018). TSLP, known to be induced by oxidative stress and epithelial damage, is particularly susceptible to such redox modulation (Liu *et al.*, 2025), and its suppression in FA-treated groups may partly reflect this mechanism.

Topical delivery of FA offers pharmacokinetic advantages, allowing for localised high concentrations with minimal systemic exposure, which is especially desirable for chronic inflammatory skin conditions like AD (Lo *et al.*, 2019; Zduńska-Pęciak & Rotsztein, 2020). The therapeutic efficacy observed with both 1% and 2% concentrations suggests that FA may be beneficial even in moderate to severe or treatment-resistant AD.

Despite these promising findings, the study has limitations. The short treatment duration restricts conclusions about long-term effects and recurrence rates. Additionally, although significant downregulation of inflammatory cytokines was ob-

served, further studies are needed to delineate the specific molecular signalling pathways (e.g., NF- $\kappa$ B, MAPK, JAK/STAT) involved in FA-mediated immunomodulation.

## CONCLUSIONS

In summary, this study demonstrates that ferulic acid, when administered topically at concentrations of 1% and 2%, effectively reduces TSLP expression and improves histopathological features in a murine model of atopic dermatitis. Both concentrations exhibited significant anti-inflammatory and immunomodulatory effects. The findings highlight FA's dual antioxidant and suggest that topical ferulic acid, particularly at higher concentrations, is a promising adjunctive therapeutic agent for atopic dermatitis. Selection of concentration may be tailored based on disease severity, lesion extent, and individual response. Further clinical studies are warranted to validate these results in animal and human patients and to establish optimal dosing strategies for effective and safe long-term use.

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