J CLIN PRACT RES

Original Article

Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2026.07056
J Clin Pract Res 2026;48(3):278–287

Loganin Attenuates Psoriasis-Like Inflammation by Regulating the NLRP3 Inflammasome–SIRT1 Axis in Keratinocytes

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ABSTRACT

Objective: The development of psoriasis involves disrupted signaling interactions between immune components and keratinocytes, leading to a chronic autoimmune state characterized by sustained inflammatory responses and epidermal hyperplasia. This study aimed to elucidate the anti-inflammatory potential of loganin (LOG) against the inflammasome–SIRT1 signaling pathway in a $CaCl_2$- and imiquimod (IMQ)-induced cellular model.

Materials and Methods: HaCaT cells were differentiated using $CaCl_2$ and IMQ to establish a psoriasis-like inflammatory model. Cell viability and the IC50 dose of LOG were determined using the MTT assay. Morphological alterations were assessed by hematoxylin and eosin (H&E) staining. Protein expression levels of NLRP3, ASC, and SIRT1 were analyzed using immunofluorescence staining. In addition, IL-1β and TNF-α levels were quantified by enzyme-linked immunosorbent assay (ELISA), while the expression of genes related to the inflammasome, pyroptosis, and apoptosis was measured using qPCR.

Results: Differentiation of HaCaT cells was induced by $CaCl_2$ and IMQ to establish an *in vitro* model of psoriatic inflammation. Following treatment, the MTT assay was used to determine the LOG IC50 dose and overall cell viability. Structural changes were documented using hematoxylin and eosin (H&E) staining. The protein expression status of NLRP3, ASC, and SIRT1 was characterized using immunofluorescence staining. In addition, enzyme-linked immunosorbent assay (ELISA) was used to quantify IL-1β and TNF-α levels, whereas the expression profiles of genes associated with apoptotic and pyroptotic signaling were analyzed by qPCR.

Conclusion: LOG exerts potent anti-psoriatic effects by suppressing NLRP3 inflammasome-mediated pyroptosis and restoring apoptotic competence in hyperproliferative keratinocytes through SIRT1 activation. These findings highlight LOG as a promising translational candidate for targeting keratinocyte-driven inflammation in psoriasis and warrant further preclinical and clinical investigation.

Keywords: Apoptosis, HaCaT, NLRP3 inflammasome, psoriasis, pyroptosis.

Cite this article as:
Çakır M, Açıkgöz E. Loganin Attenuates Psoriasis-Like Inflammation by Regulating the NLRP3 Inflammasome–SIRT1 Axis in Keratinocytes. JClinPractRes2026;48(3):278–287.

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Submitted: 22.01.2026
Revised: 11.05.2026
Accepted: 01.06.2026
Available Online: 30.06.2026

Erciyes University Faculty of Medicine Publications -
Available online at www.jcpres.com

INTRODUCTION

Psoriasis is a chronic, immune-mediated autoimmune dermatological disorder characterized by erythematous plaques, epidermal hyperplasia, abnormal keratinocyte differentiation, and persistent inflammation, affecting approximately 2% of the global population.[1] Epidemiological data from Türkiye indicate a prevalence of approximately 1.18%.[2] Inflammatory mechanisms in psoriasis lead to dysregulated keratinocyte proliferation and impaired differentiation, thereby affecting the phenotypic presentation and therapeutic outcomes of the disease.[3] In addition to its clinical cutaneous symptoms, psoriasis carries a substantial psychosocial and socioeconomic burden, leading to profound impairment in quality of life, emotional distress, and social stigmatization.[4]

Current paradigms recognize keratinocytes not as bystanders but as integral components of the innate immune response in psoriasis.[3,5] The interplay between these cells and Th17-axis cytokines, including IL-17A and IL-22, triggers a cascade of dysregulated proliferation and impaired maturation, sustaining the inflammatory milieu.[5] Key pro-inflammatory cytokines, particularly interleukin-1β (IL-1β), serve as essential orchestrators of the persistent inflammatory environment observed in autoinflammatory skin diseases, including psoriasis. The IL-1β signaling pathway may play a role in cutaneous inflammation and the development of psoriasis by directly regulating cutaneous IL-17-producing cells and stimulating keratinocytes.[6] The inflammasome and pyroptosis pathways are mechanisms that initiate the release of IL-1.[7] Inflammasomes are cytoplasmic multiprotein complexes that function as crucial regulators of innate immune cells.[8] The formation of a functional NLRP3 inflammasome complex requires an initial stimulus that enables the transcriptional upregulation of the NLRP3 receptor and pro-IL-1β precursors. The oligomerization of the inflammasome, triggered by secondary signals, initiates the secretion of pro-inflammatory IL-1β and IL-18 through active caspase-1 (Casp-1).[9] Recent findings have identified an extensive range of molecular pathways and genetic variants that influence inflammasome dynamics, thereby predisposing individuals to the chronic inflammatory environment of psoriasis.[10] Beyond cytokine maturation, Casp-1 activation orchestrates gasdermin D (GSDMD)-mediated pyroptosis, a specialized form of inflammatory cell death. This process facilitates the substantial release of mature IL-1β into the extracellular space, thereby potentiating the sustained inflammatory response.[11] Recent studies have underscored the critical role of GSDMD-driven keratinocyte pyroptosis in the etiology of psoriasis, where it serves as a key link between the immunological microenvironment and the hallmark features of the disease, namely epidermal hyperproliferation and aberrant differentiation.[12]

KEY MESSAGES

- Loganin may attenuate imiquimod-induced keratinocyte inflammation and hyperplasia by modulating the NLRP3–SIRT1 signaling axis.
- Loganin reduced pro-inflammatory cytokine release and attenuated gasdermin D-mediated pyroptotic markers in HaCaT cells.
- By upregulating SIRT1, loganin may promote a shift from inflammatory pyroptosis toward controlled apoptosis, suggesting its potential therapeutic value in psoriasis management.

Loganin (LOG), an iridoid glycoside, is the main active constituent of the medicinal plant Cornus officinalis, especially in traditional Chinese medicine.[13] Accumulating evidence indicates that LOG exhibits anti-inflammatory, antioxidant, and neuroprotective properties.[14] Notably, LOG has been shown to attenuate inflammatory injury in acute kidney failure by modulating the NRF2/HO-1 signaling pathway.[15] In addition, LOG has been reported to ameliorate hepatic steatosis by inhibiting the NLRP3 inflammasome.[16] Furthermore, LOG attenuated high-glucose-induced pyroptosis by suppressing reactive oxygen species (ROS) production and NLRP3 inflammasome activation in the treatment of diabetic peripheral neuropathy.[17] Despite these promising findings, the effects of LOG on keratinocyte biology and NLRP3 inflammasome-associated pyroptosis remain largely unexplored.

Given the emerging role of keratinocyte inflammasome activation in psoriasis, this study aimed to investigate whether LOG exerts anti-psoriatic effects by modulating the NLRP3–SIRT1 axis, suppressing inflammasome-mediated pyroptosis, and restoring apoptotic balance in an *in vitro* psoriasis model induced by imiquimod and $CaCl_2$. By elucidating these molecular mechanisms, the present study seeks to provide translational insight into the potential therapeutic relevance of LOG in keratinocyte-driven psoriatic inflammation.

METHODS

Establishment of an *in Vitro* Psoriasis Model With $CaCl_2$ and IMQ and Cell Viability Assay

In Vitro Psoriasis Induction and Cytotoxicity Assessment

The immortalized human keratinocyte line HaCaT (ATCC, PCS-200-011) was cultured under standard culture conditions (37°C, 5% CO_2) in calcium-depleted Dulbecco's Modified Eagle Medium (DMEM; HyClone #SH3031901). This growth environment was supplemented with 10% calcium-free fetal bovine serum (FBS; Gemini Bio Products, #100–106), 2 mM

L-glutamine, and a 1% antibiotic cocktail. The transition to a psoriasis-mimetic state and subsequent differentiation were performed in accordance with the specialized laboratory framework previously optimized by our research team.[18] To establish the *in vitro* psoriasis model, HaCaT cells were stimulated with 2 mM $CaCl_2$ and 25 µM imiquimod (IMQ). Cell survival was evaluated in the *in vitro* psoriasis model (control), and the cell proliferation assay (MTT) was used to assess the effects of LOG at concentrations ranging from 10 to 160 µM. Drugs were administered at defined doses 24 hours after HaCaT cells were cultured. Cells were incubated with 10 mg/mL MTT solution (Invitrogen, M6494) for 4 hours, and absorbance was measured at 570 nm using a microplate reader (Biobase, China). The MTT assay was performed in six technical replicates per group, and the entire experiment was repeated in three independent biological replicates.

Hematoxylin and Eosin (H&E) Staining

To assess the general morphological characteristics of the cells, H&E staining was performed based on our previous study.[19] Briefly, cells seeded on adhesive coverslips were fixed with 4% paraformaldehyde (PFA) and washed with phosphate-buffered saline (PBS). The cells were then stained with hematoxylin for 1 minute and eosin for 45 seconds at room temperature. Stained cells were visualized and imaged using a light microscope. Morphological evaluation was performed by analyzing at least five random fields per group.

Immunofluorescence (IF) Staining

HaCaT cells were plated on coverslips and treated with LOG under psoriasis-inducing conditions. After incubation, cells were fixed with 4% PFA and permeabilized using 0.25% Triton X-100 for 10 minutes. Subsequently, cells were incubated for 1 hour at room temperature in PBS containing 5% bovine serum albumin (BSA). Cells were then incubated overnight at 4°C in a humidified chamber with the following primary antibodies: anti-NLRP3 (E-AB-65952, Elabscience Biotechnology), anti-ASC (E-AB-63530, Elabscience Biotechnology), and anti-SIRT1 (E-AB-32901, Elabscience Biotechnology). The following day, cells were incubated with FITC-conjugated secondary antibodies, washed, and mounted using DAPI-containing mounting medium. Fluorescent images were captured using an Olympus BX53 fluorescence microscope with a DP74 camera attachment. For quantitative immunofluorescence analysis, five random non-overlapping fields per coverslip were imaged, and mean fluorescence intensity was quantified using ImageJ software (NIH, USA) from at least 50 cells per group.

Enzyme-Linked Immunosorbent Assay (ELISA)

Cell culture supernatants were harvested 48 hours after induction of the psoriasis-like inflammatory condition and subsequently subjected to ELISA analysis. Commercially available ELISA kits specific for interleukin-1β (IL-1β; BioLegend, Cat. No. 437004) and tumor necrosis factor-α (TNF-α; BioLegend, Cat. No. 433915) were used in accordance with the manufacturers' instructions. Absorbance values were measured at 450 nm with wavelength correction at 570 nm, and cytokine concentrations were determined by interpolation from standard curves. Cytokine levels were measured in triplicate for each sample, and the results were validated across three independent biological experiments (n=3).

Quantitative Reverse Transcription Polymerase Chain Reaction (qPCR) Analysis

Cells from the psoriasis model and treatment groups were subjected to trypsinization. The cells were subsequently suspended in 500 µL of TRIzol (Sigma-Aldrich, T9424) and homogenized by sonication. Total RNA was isolated according to the manufacturer's TRIzol protocol. cDNA synthesis was performed using the iScript™ cDNA Synthesis Kit (Bio-Rad, Cytiva, GE27-9261-01). The genes specified in the table were analyzed using SYBR Green staining with the Applied Biosystems StepOnePlus Real-Time PCR System. The expression levels of the tested genes were normalized to basal β-actin mRNA expression. The 2–ΔΔCt method was used to calculate the relative fold change in gene expression among samples. Data are presented as fold change relative to the cell control. All qPCR reactions were performed in triplicate, and gene expression levels were normalized across three independent biological replicates (n=3).

Statistical Analysis

All statistical evaluations and graphical analyses were performed using GraphPad Prism software (version 8.0; GraphPad Software, San Diego, CA, USA). Sample sizes (n) were determined based on preliminary experiments and established protocols in similar *in vitro* models to ensure adequate statistical power. Experimental data are expressed as mean±standard error of the mean (SEM). Comparisons between two independent groups were performed using Student's t-test or the Mann–Whitney U test, depending on data distribution; in these cases, multiple comparison tests were not applied in accordance with statistical requirements. For analyses involving multiple groups, one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to determine significant differences between specific pairs. Differences among multiple experimental groups at a single time point, including qPCR, ELISA, and IF analyses, were determined using one-way ANOVA followed by Tukey's post hoc test. For experiments involving multiple time intervals, including the MTT assay, one-way ANOVA followed by Sidak's post hoc test was used to evaluate the interaction between treatment and time factors.

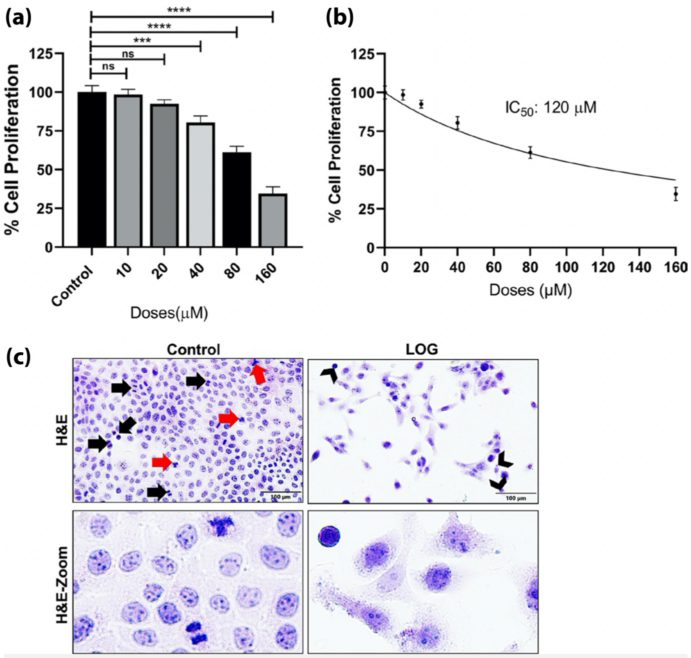

Figure 1. Effects of LOG on cell viability and morphology in IMQ+$CaCl_2$-differentiated HaCaT cells. **(a)** Cell proliferation analysis showing a dose-dependent reduction in HaCaT cell viability following LOG treatment (10–160 µM) compared with control cells after IMQ+$CaCl_2$-induced differentiation. **(b)** Dose–response curve illustrating the inhibitory effect of LOG on HaCaT cell proliferation, with an IC_{50} value of approximately 120 µM. **(c)** H&E-stained cellular images. Black arrows, red arrows, and black arrowheads indicate mitotic figures in proliferating cells, abnormal chromosome segregation, and apoptosis-like cells, respectively. Scale bar: 100 µm. Data are presented as mean±SEM and were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test.

ns: Not significant; ***: $P<0.001$; ****: $P<0.0001$.

RESULTS

LOG Treatment Decreases Cell Number and Induces Morphological Changes

HaCaT cells were differentiated with IMQ and $CaCl_2$ to establish a psoriasis-like inflammatory model, as previously described.[18] Cells were subsequently treated with increasing concentrations of LOG (10–160 µM) to evaluate its effects on keratinocyte viability. LOG induced a dose-dependent reduction in cell proliferation, with no significant effects at low concentrations (10–20 µM) and marked suppression at higher doses (40–160 µM) (Fig. 1a). Dose–response analysis identified an IC_{50} of approximately 120 µM (Fig. 1b). To assess general morphological changes, hematoxylin and eosin staining was performed. IMQ+$CaCl_2$-stimulated keratinocytes exhibited increased cell density, prominent mitotic figures, and abnormal nuclear morphology, consistent with a hyperproliferative phenotype (Fig. 1c). In contrast, LOG-treated cells displayed a marked reduction in cell number, altered nucleus-to-cytoplasm ratios, chromatin condensation, and pyknotic nuclei, indicating the induction of apoptosis-like morphological features.

LOG Modulates the NLRP3 Inflammasome–SIRT1 Axis in Psoriasis-Like Keratinocytes

To determine whether LOG influences the NLRP3 inflammasome–SIRT1 axis, changes in the protein levels of NLRP3, ASC, and SIRT1 were evaluated using IF staining. The obtained images and fluorescence intensity analyses revealed that, compared with the control group, LOG treatment resulted in a significant reduction in the fluorescence intensity of NLRP3 and ASC, whereas SIRT1 expression was significantly increased ($p<0.0001$) (Fig. 2a–c). Quantitative fluorescence analysis confirmed these observations, demonstrating a robust inverse relationship between inflammasome activation markers and SIRT1 expression following LOG treatment.

LOG Suppresses Pro-Inflammatory Cytokine Release in IMQ-Induced Keratinocytes

The secretion of pro-inflammatory cytokines was assessed to evaluate the inflammatory status of keratinocytes. IMQ+$CaCl_2$ stimulation significantly increased the release of TNF-α and IL-1β in HaCaT cells compared with control conditions, confirming the induction of an inflammatory, psoriasis-like phenotype (Fig. 3a, b). Treatment with LOG significantly reduced the release of both cytokines and partially restored cytokine levels to those observed in control cells (Supplementary Table 1a, b). These findings demonstrate that LOG exerts a potent anti-inflammatory effect in this *in vitro* psoriasis model by suppressing key cytokines involved in keratinocyte-derived inflammatory responses.

LOG Attenuates Inflammasome- and Pyroptosis-Related Gene Expression While Modulating Apoptotic Markers

To further characterize the molecular effects of LOG, the expression of genes associated with inflammasome activation, pyroptosis, and apoptosis was analyzed by qRT-PCR. Stimulation with IMQ+$CaCl_2$ significantly upregulated the expression of inflammation-related genes, including GSDM, NLRP3, Casp-1, and IL-1β, compared with healthy control cells, confirming the induction of a psoriasis-like inflammatory phenotype (Fig. 4a–d). LOG treatment significantly downregulated NLRP3 and IL-1β expression and showed a tendency toward decreased GSDM and Casp-1 levels compared with the IMQ+$CaCl_2$ group, indicating

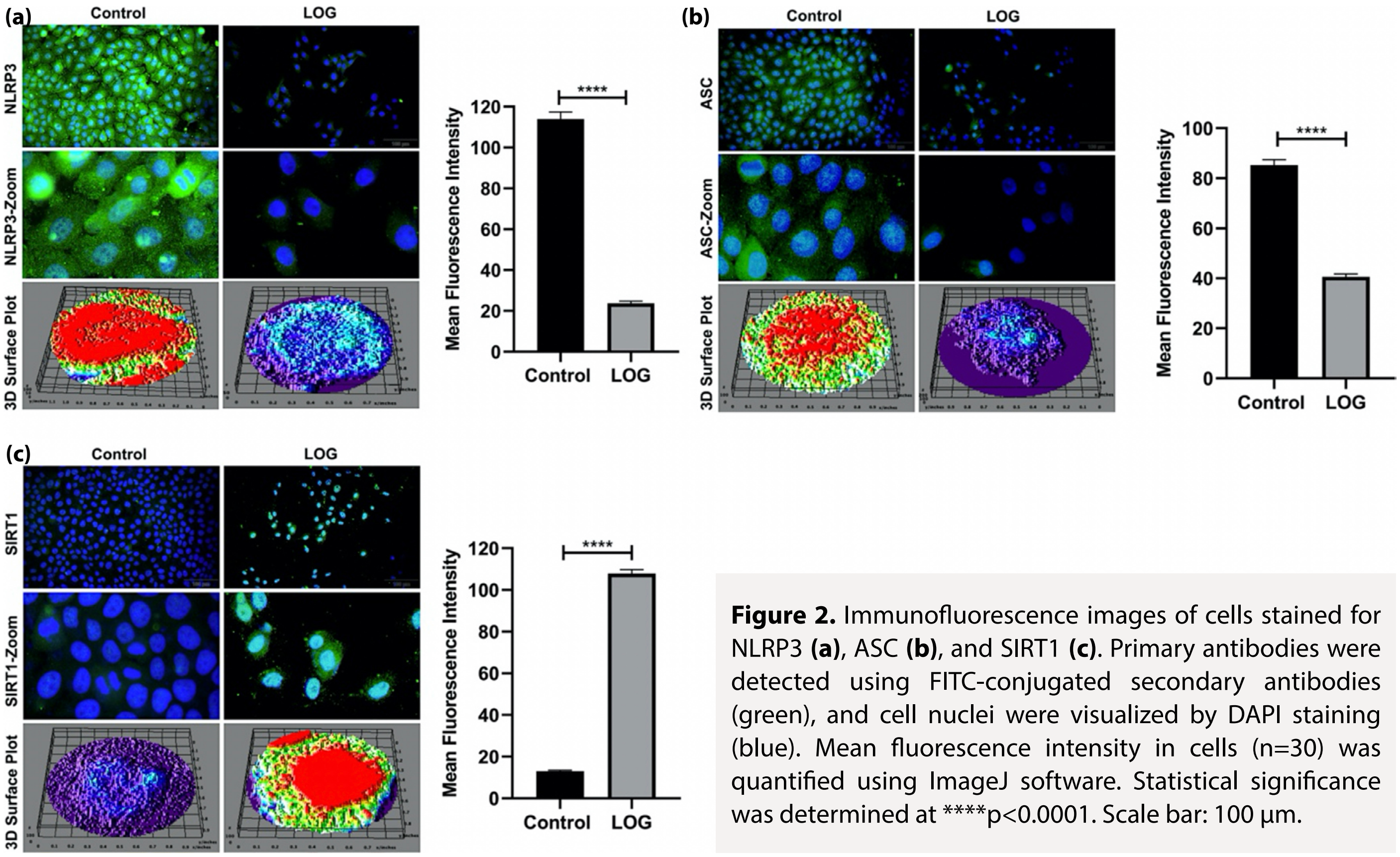

Figure 2. Immunofluorescence images of cells stained for NLRP3 **(a)**, ASC **(b)**, and SIRT1 **(c)**. Primary antibodies were detected using FITC-conjugated secondary antibodies (green), and cell nuclei were visualized by DAPI staining (blue). Mean fluorescence intensity in cells (n=30) was quantified using ImageJ software. Statistical significance was determined at ****p<0.0001. Scale bar: 100 µm.

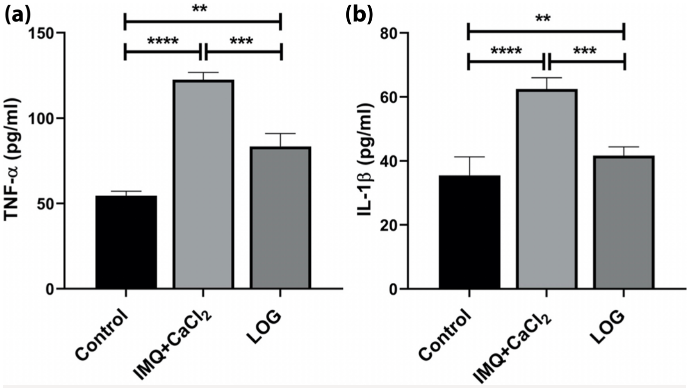

Figure 3. Effects of LOG on pro-inflammatory cytokine secretion in IMQ+$CaCl_2$-differentiated HaCaT cells. HaCaT cells were differentiated using IMQ+$CaCl_2$ and treated with LOG, after which the levels of **(a)** TNF-α and **(b)** IL-1β in culture supernatants were quantified. Data are presented as mean±SEM and were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test.

**: P<0.01; ***: P<0.001; ****: P<0.0001.

attenuation of inflammatory activation (Supplementary Table 2a–c, f). Analysis of apoptosis-related markers revealed that IMQ+$CaCl_2$ alone did not significantly alter BAX expression, whereas LOG treatment significantly increased BAX levels compared with both the control and psoriasis model groups (Fig. 4e; Supplementary Table 2d). In contrast, the expression of the anti-apoptotic gene BCL2 decreased only in the LOG-treated group but remained unchanged in the other groups (Fig. 4f; Supplementary Table 2e). Collectively, these findings demonstrate that LOG attenuates IMQ+$CaCl_2$-induced inflammatory signaling primarily through inhibition of the NLRP3 inflammasome axis, resulting in a selective reduction in associated apoptotic signaling and supporting a protective and anti-inflammatory role for LOG *in vitro*.

DISCUSSION

Psoriasis is a chronic inflammatory skin disorder in which dysregulated keratinocyte proliferation and differentiation are accompanied by persistent activation and accumulation of immune cells within the epidermal and dermal layers.[20] Increasing evidence indicates that keratinocytes are not merely passive targets of immune-mediated injury but actively contribute to the initiation and perpetuation of psoriatic inflammation through cytokine production and innate immune signaling pathways.[21] In this context, targeting keratinocyte-driven inflammatory mechanisms has emerged as a promising therapeutic strategy in psoriasis.

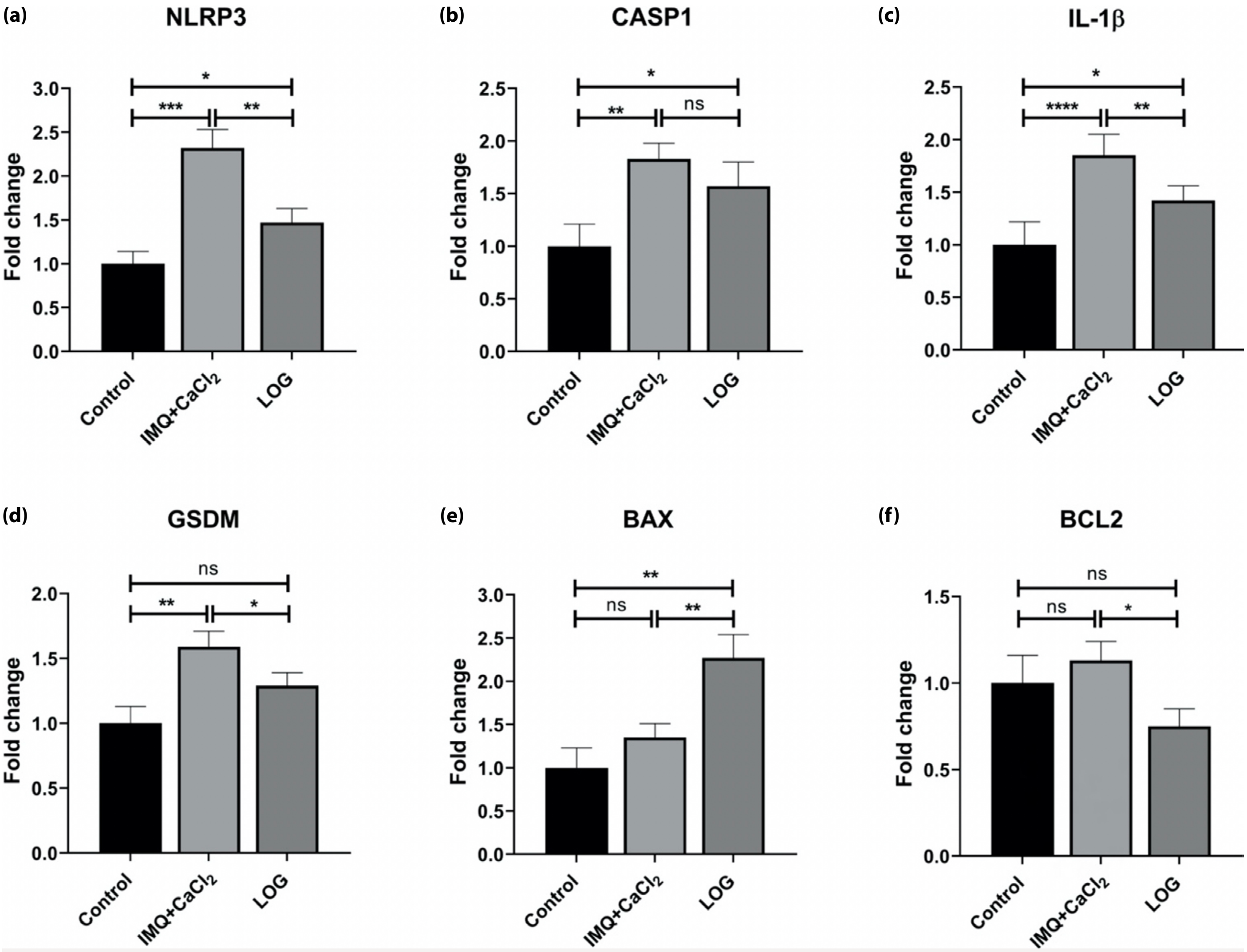

Figure 4. LOG modulates inflammasome- and apoptosis-related gene expression in an IMQ+$CaCl_2$-induced in vitro psoriasis model. Expression levels of **(a)** gasdermin (GSDM), **(b)** NLRP3, **(c)** caspase-1 (CASP1), **(d)** BAX, **(e)** BCL2, and **(f)** IL-1β were assessed in healthy control cells, IMQ+$CaCl_2$-stimulated cells, and LOG-treated cells. IMQ+$CaCl_2$ significantly upregulated inflammasome-associated genes, whereas LOG treatment significantly reduced NLRP3 and IL-1β expression, increased BAX expression, and decreased BCL2 expression. Data are presented as mean±SEM. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test.

ns: Not significant; *: $P<0.05$; **: $P<0.01$; ***: $P<0.001$; ****: $P<0.0001$.

In recent years, *in vitro* psoriasis-like models based on cytokine- and IMQ-stimulated HaCaT keratinocytes have been widely used to reduce animal experimentation and enable the rapid screening of potential therapeutic compounds.[18,22,23] Previous studies have shown that stimulation with 2 mM $CaCl_2$ and 25 µM IMQ induces a pathological hyperproliferative response in HaCaT cells, as evidenced by increased cell viability and proliferation markers such as PCNA.[18,22] In contrast to this uncontrolled proliferation, our findings demonstrate that LOG significantly suppresses keratinocyte proliferation and reverses the inflammation-induced increase in cell viability in the psoriatic *in vitro* model. Although LOG treatment was associated with downregulation of the NLRP3/ASC inflammasome and concomitant upregulation of SIRT1, it is important to note that these changes are correlative. Further mechanistic studies are required to establish a direct causal link between SIRT1 activation and inhibition of the NLRP3/ASC pathway in this context.

Psoriatic keratinocytes are known to exhibit resistance to apoptosis, which contributes to epidermal hyperplasia and disease persistence.[24] In the present study, LOG treatment induced cellular changes consistent with apoptotic cell death, including nuclear condensation and reduced cell density, suggesting that the antiproliferative effect of LOG may be mediated, at least in part, through restoration of apoptosis in keratinocytes. Although the IC_{50} value of LOG is relatively high and may raise concerns regarding cytotoxicity, the selective regulation of inflammatory and apoptotic gene expression, together with apoptosis-specific morphological changes, supports pathway-specific effects rather than nonspecific toxicity. The concentration applied in this study, selected based on preliminary dose–response analyses and relevant *in vitro* literature, suggests that LOG may restore apoptotic balance in psoriatic keratinocytes and contribute to epidermal homeostasis.[25]

The NLRP3 inflammasome is a multiprotein complex composed of a sensor receptor, the ASC adaptor, and pro-caspase-1, and it plays a central role in the pathogenesis of psoriasis.[26] Previous studies have demonstrated that NLRP3 and caspase-1 expression levels are markedly increased in psoriatic lesions compared with healthy skin, contributing to excessive production of bioactive IL-1β and IL-18 and thereby sustaining chronic inflammation.[27,28] NLRP3 activation also promotes the cleavage of gasdermin D (GSDMD), leading to pore formation in the plasma membrane and induction of pyroptotic cell death.[29] In keratinocytes, this process amplifies the inflammatory microenvironment by enhancing IL-17/IL-23 axis activity, which promotes epidermal hyperproliferation and immune cell recruitment.[30]

ASC-mediated assembly of the NLRP3 inflammasome is a critical determinant of inflammatory severity in psoriatic skin, whereas SIRT1 activation negatively regulates this pathway by suppressing inflammasome activation and limiting IL-1β release from keratinocytes.[26,31] LOG treatment effectively suppressed NLRP3 inflammasome activation in the psoriasis-like keratinocyte model while concomitantly increasing SIRT1 expression levels. These changes suggest an inhibitory effect of LOG on inflammasome assembly and pyroptosis-associated signaling in keratinocytes. Moreover, the inverse association between SIRT1 expression and inflammasome components observed in this study supports a regulatory interplay between these pathways, although a direct causal relationship cannot be inferred. Collectively, these findings indicate that LOG modulates pyroptosis-related inflammatory signaling in keratinocytes and may represent a promising candidate for targeting keratinocyte-driven inflammation in psoriasis.

TNF-α and IL-1β form a mutually reinforcing inflammatory loop via the NLRP3 inflammasome, sustaining chronic inflammation and keratinocyte hyperproliferation in psoriasis.[32] TNF-α activates the NF-κB/NLRP3/IL-1β axis, in which mature IL-1β enhances the Th17 response and sustains keratinocyte hyperproliferation. This feedback loop triggers further TNF-α release, driving chronic inflammation and creating a pathological cycle whose central role in disease severity is clinically validated by the efficacy of TNF-α inhibitors.[33] In this study, the increased release of IL-1β and TNF-α in keratinocytes stimulated with IMQ+$CaCl_2$ supports the central role of these cytokines in psoriasis. Keratinocyte-derived TNF-α and IL-1β contribute to the maintenance of the inflammatory response and the persistence of lesions. The observed reduction in both cytokines following LOG treatment suggests a potential role for this compound in modulating psoriasis pathogenesis, likely through suppression of keratinocyte-derived inflammatory responses.

It is now widely recognized that, in the pathogenesis of psoriasis, keratinocytes serve not only as responders to inflammatory signals but also as active effectors of innate immunity.[33] Enhanced NLRP3 inflammasome activation in psoriatic keratinocytes appears to fuel the inflammatory microenvironment through pyroptosis-associated membrane damage and elevated IL-1β release, thereby potentially strengthening the Th17/IL-23 axis and contributing to epidermal hyperplasia and lesion chronicity.[34] In this context, the inhibition of NLRP3 and ASC expression observed following LOG treatment suggests a potential restriction of pyroptosis, which may help disrupt the keratinocyte-driven inflammatory cycle.

Given that keratinocytes in the psoriatic epidermis exhibit characteristic resistance to apoptosis, a crucial factor in hyperproliferation, restoring apoptotic regulation may have therapeutic relevance.[35] In our study, the downregulation of the anti-apoptotic protein Bcl-2, together with increased Bax expression and associated morphological changes, indicates a possible shift in cell death pathways. These results suggest that LOG may favor regulated apoptosis over the more pro-inflammatory pyroptotic pathway, a shift that could be relevant for both limiting inflammatory signaling and enabling the controlled elimination of hyperproliferative cells. Taken together with the observed suppression of NLRP3 inflammasome activity and upregulation of SIRT1 in the *in vitro* model, our findings suggest that LOG may exert both anti-inflammatory and antiproliferative effects in psoriatic keratinocytes under experimental conditions. Although these results are limited to an *in vitro* setting, they indicate that LOG has the potential to modulate key pathways associated with inflammation and keratinocyte hyperproliferation, warranting further investigation in more advanced experimental models of psoriasis.

Notably, GSDMD-mediated pyroptosis has been shown to exacerbate local inflammation by disrupting keratinocyte membrane integrity and promoting the release of pro-inflammatory cytokines, whereas inhibition of this pathway alleviates psoriatic inflammation and clinical manifestations.[36] In this context, the concurrent suppression of multiple pyroptosis-related components by LOG highlights a potential mechanism through which keratinocyte-driven inflammatory circuits may be disrupted in psoriasis.

Previous studies indicate that LOG exerts a broad inhibitory effect on the NLRP3 inflammasome pathway, which plays a pivotal role in psoriatic inflammation, as well as on the associated pyroptotic process.[37] The significant decrease in NLRP3, ASC, caspase-1 (Casp-1), and GSDMD gene expression observed after treatment, along with the suppression of IL-1β and TNF-α release, is consistent with previous studies reporting that these inflammatory mediators are overexpressed in psoriatic lesions and play a key role in disease pathogenesis. Notably, GSDMD-mediated pyroptosis has been shown to exacerbate local inflammation by disrupting keratinocyte membrane integrity and promoting the release of pro-inflammatory cytokines, whereas inhibition of this pathway alleviates psoriatic inflammation and clinical manifestations.[38] In this context, the concurrent suppression of multiple pyroptosis-related components by LOG highlights a potential mechanism through which keratinocyte-driven inflammatory circuits may be disrupted in psoriasis.

From a translational perspective, the ability of LOG to simultaneously suppress inflammatory cytokine release, including IL-1β and TNF-α, and restore apoptotic balance in keratinocytes highlights its therapeutic relevance. Current psoriasis therapies primarily target immune mediators, whereas direct modulation of keratinocyte-intrinsic inflammatory pathways remains relatively underexplored.[39] Our results suggest that LOG may complement existing therapeutic strategies by acting directly at the level of the epidermis, thereby potentially enhancing treatment efficacy and durability. Despite these promising findings, the present study is limited by its reliance on a single *in vitro* model, which cannot fully capture the systemic complexity of psoriasis; therefore, future research involving primary human cells and *in vivo* models is essential to confirm the causal link between SIRT1 and NLRP3 and to validate the clinical potential of LOG.

CONCLUSION

In conclusion, the present study suggests that LOG may exert anti-psoriatic activity in an *in vitro* model by modulating keratinocyte-driven inflammatory mechanisms. LOG was observed to suppress NLRP3 inflammasome activation and downstream pyroptotic signaling while upregulating SIRT1 and supporting the restoration of apoptotic competence in hyperproliferative keratinocytes. This potential dual modulation of inflammatory cell death and apoptosis offers a possible mode of action that addresses key pathological features of psoriasis, such as inflammation and epidermal hyperplasia. By attenuating IL-1β and TNF-α release and potentially shifting keratinocyte fate from inflammatory pyroptosis toward controlled apoptosis, LOG emerges as a noteworthy candidate for further research on psoriasis management. Although further *in vivo* and clinical investigations are essential, these findings provide a preliminary experimental rationale for exploring LOG as a possible keratinocyte-targeted therapeutic strategy in psoriasis.

Ethics Committee Approval: Ethics committee approval was not required for this study.

Informed Consent: The research did not involve human participants, clinical samples, or the use of identifiable human data, and therefore did not require patient consent.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: This study was financially supported by the TUBITAK (The Scientific and Technological Research Council of Türkiye), Project numbers: 123S046 and 123S058.

Use of AI for Writing Assistance: No use of AI-assisted technologies was declared by the authors.

Author Contributions: Concept – MC, EA; Design – MC, EA; Supervision – MC; Resource – MC, EA; Materials – MC, EA; Data Collection and/or Processing – MC, EA; Analysis and/or Interpretation – MC, EA; Literature Review – MC, EA; Writing – MC, EA; Critical Review – MC, EA.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1a. Comparison of TNF-α cytokine levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-68.00	-81.18 to -54.82	*<0.0001*	54.50±1.50	a
Control vs. LOG	-28.90	-42.08 to -15.72	*0.0013*	122.50±2.48	c
IMQ+$CaCl_2$ vs. LOG	39.10	25.92 to 52.28	*0.0002*	83.40±4.39	b

Supplementary Table 1b. Comparison of IL-1β cytokine levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-27.00	-37.55 to -16.45	*0.0006*	35.50±3.35	a
Control vs. LOG	-6.20	-16.75 to 4.35	*0.2467*	62.50±2.02	b
IMQ+$CaCl_2$ vs. LOG	20.80	10.25 to 31.35	*0.0022*	41.70±1.56	a

Data are presented as mean±SEM (n=3). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test. Different letters (a, b, c) indicate statistically significant differences between groups ($p<0.05$). Groups sharing the same letter are not significantly different.

Supplementary Table 2a. Comparison of gasdermin D (GSDMD) gene expression levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-0.5900	-0.8839 to -0.2961	*0.0020*	1.00±0.08	a
Control vs. LOG	-0.2900	-0.5839 to 0.0039	*0.0526*	1.59±0.09	b
IMQ+$CaCl_2$ vs. LOG	0.3000	0.0061 to 0.5939	*0.0463*	1.27±0.05	a

Supplementary Table 2b. Comparison of NLRP3 gene expression levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-1.3200	-1.752 to -0.8878	*0.0002*	1.00±0.08	a
Control vs. LOG	-0.4700	-0.9022 to -0.0378	*0.0361*	2.32±0.12	c
IMQ+$CaCl_2$ vs. LOG	0.8500	0.4178 to 1.282	*0.0023*	1.47±0.09	b

Supplementary Table 2c. Comparison of caspase-1 gene expression levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-0.8300	-1.330 to -0.3300	*0.0054*	1.00±0.12	a
Control vs. LOG	-0.5700	-1.070 to -0.0700	*0.0298*	1.83±0.09	b
IMQ+$CaCl_2$ vs. LOG	0.2600	-0.2400 to 0.7600	*0.3176*	1.57±0.13	b

Supplementary Table 2d. Comparison of BAX gene expression levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-0.3500	-0.9128 to 0.2128	*0.2166*	1.00±0.13	a
Control vs. LOG	-1.2700	-1.833 to -0.7072	*0.0011*	1.35±0.09	a
IMQ+$CaCl_2$ vs. LOG	-0.9200	-1.483 to -0.3572	*0.0058*	2.27±0.16	b

Supplementary Table 2e. Comparison of BCL2 gene expression levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-0.1300	-0.4459 to 0.1859	*0.4637*	1.00±0.10	ab
Control vs. LOG	0.2500	-0.0659 to 0.5659	*0.1119*	1.13±0.08	a
IMQ+$CaCl_2$ vs. LOG	0.3800	0.0641 to 0.6959	*0.0238*	0.75±0.07	b

Supplementary Table 2f. Comparison of IL-1β gene expression levels

Comparison	Mean difference	95% CI of difference	Adjusted p value	Mean±SEM	Significance
Control vs. IMQ+$CaCl_2$	-0.8500	-1.165 to -0.5354	*<0.0001*	1.00±0.13	a
Control vs. LOG	-0.4200	-0.8283 to -0.0118	*0.0431*	1.85±0.12	c
IMQ+$CaCl_2$ vs. LOG	0.4300	0.1154 to 0.7446	*0.0069*	1.42±0.08	b

Data are presented as mean±SEM (n=3). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test. Different letters (a, b, c) indicate statistically significant differences between groups ($p<0.05$). Groups sharing the same letter are not significantly different.