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Lactobacillus-derived extracellular vesicles as postbiotic modulators of redox signalling and cellular senescence in skin homeostasis

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ABSTRACT

The skin acts as a dynamic barrier—combining physical, chemical, and immunological defences—while hosting a diverse microbiome essential for cutaneous homeostasis. Dysbiosis and impaired redox balance are linked to various inflammatory conditions; however, the mechanisms by which microbial signals regulate skin cell senescence remain unclear. This study evaluated the effects of *Lactobacillus*-derived extracellular vesicles (EVs) on human keratinocytes (HaCaTs) and dermal fibroblasts (HDFs) under both physiological and stress-induced premature senescence (SIPS) conditions. SEM analysis confirmed the presence of spherical membrane-bound structures consistent with EV morphology, providing a qualitative characterisation. Functional assays indicate that low concentrations of EVs (1.25–2.5% v/v) increase the metabolic activity of HaCaT cells; however, only the 1.25% v/v concentration significantly promotes early wound closure, whereas the 2.5% v/v concentration induces a decoupling between metabolism and motility. In HDFs, EVs significantly reduced basal intracellular reactive oxygen species (ROS) levels, demonstrating an inherent capacity to modulate redox homeostasis. Furthermore, immunofluorescence analysis revealed that EVs exert cell-specific and context-dependent modulatory effects on the DNA damage response (DDR) and senescence-associated secretory phenotype (SASP). While EVs significantly regulated p21, 53BP1, and MMP-3 expression across both cell types under both basal and SIPS conditions, a specific modulation of COX-2 was observed exclusively in fibroblasts following SIPS induction. These results indicate that *Lactobacillus*-derived EVs support epidermal regeneration and protect dermal cells from molecular senescence by modulating redox-sensitive pathways. Our findings highlight the potential of these vesicles as multifunctional postbiotic regulators—providing a mechanistic basis for future strategies aimed at maintaining skin homeostasis and mitigating cellular ageing.

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1. Introduction

The skin represents the largest organ of the human body and serves as a primary barrier against exogenous threats through the *stratum corneum*, which regulates water loss and pathogen entry [1,2]. Chemical and immunological defences—including antimicrobial peptides and resident immune cells—contribute to maintaining cutaneous homeostasis and modulating immune responses [3–5]. Furthermore, keratinocytes, the extracellular matrix, and human dermal fibroblasts (HDFs) play essential roles in preserving structural integrity and coordinating immune signalling within the skin microenvironment [6–8]. These processes are tightly regulated by cellular metabolic activity and redox homeostasis, which are fundamental for maintaining epidermal barrier integrity and controlling inflammatory signalling [9,10].

Alongside the cellular mechanisms governing cutaneous homeostasis, the skin also hosts a complex and dynamic microbiome that is essential for local immunity and barrier function [11–13]. The cutaneous microbial community is typically dominated by genera such as *Staphylococcus*, *Cutibacterium*, and *Corynebacterium* [12,13], and, in certain niches, *Lactobacillus* species [14]. These beneficial microbes contribute to maintaining physiological pH, modulating inflammation, and protecting against pathogen colonisation—highlighting their potential in probiotic-based dermatological strategies [15,16]. Increasing evidence indicates that these microbes also influence oxidative stress and redox-sensitive pathways within the skin microenvironment [17–19].

In addition to local cutaneous effects, increasing evidence supports the existence of a gut–brain–skin axis, a bidirectional communication network linking intestinal microbiota, neuroendocrine signalling, and skin immune responses [20–22]. Microbial metabolites and systemic mediators derived from the gut microbiota can influence oxidative stress, inflammatory pathways, and epidermal barrier function, thereby contributing to skin homeostasis [20,23].

Disruption of the skin microbial ecosystem, known as dysbiosis, is associated with impaired barrier function and chronic inflammation across multiple dermatological conditions. These include atopic dermatitis, seborrheic dermatitis, contact dermatitis, and irritant dermatitis, where microbial imbalance contributes to immune dysregulation and barrier disruption [13,24–26]. In these diseases, oxidative stress and inflammatory signalling are closely interconnected, often leading to increased production of reactive oxygen species (ROS), activation of DNA damage responses (DDR), and the development of stress-induced premature senescence (SIPS) [27–29]. Senescent cells can further exacerbate inflammation through the release of senescence-associated secretory phenotype (SASP) factors, thereby contributing to tissue dysfunction and impaired regeneration [28].

Among commensal microorganisms, *Lactobacillus* species have attracted particular attention due to their ability to support microbial balance, maintain acidic pH, and modulate immune responses [15,16]. Recent studies suggest that their beneficial effects are mediated not only by live bacteria but also by derived bioactive components, including postbiotics, particularly extracellular vesicles (EVs) [30–33]. These nanoscale vesicles act as carriers of proteins, lipids, and nucleic acids, enabling intercellular communication and modulation of host cellular pathways [34]. In particular, bacterial EVs have been implicated in the regulation of oxidative stress, inflammation, and tissue repair processes [34–37].

Given the central role of redox balance, cellular metabolism, and senescence in maintaining skin homeostasis, investigating the biological activity of microbial-derived EVs represents a promising approach for understanding host–microbe interactions at the molecular level [23,28,29,34,36,37]. Although these mechanisms may be relevant in pathological conditions such as atopic dermatitis (AD), their fundamental effects on skin cells under basal and stress conditions remain incompletely characterised [24,30].

Therefore, the aim of this study was to evaluate the effects of *Lactobacillus*-derived EVs on keratinocytes and dermal fibroblasts, focusing on cellular metabolism, migration, intracellular ROS levels, and the modulation of key markers of the DDR and senescence ($p21_{nuc}$, 53BP1), together with factors of the SASP factors, including MMP-3, and inflammatory mediators (IL-6, COX-2). By investigating these pathways under both physiological and oxidative stress conditions, this work seeks to provide mechanistic insight into the role of microbial EVs in regulating skin homeostasis and redox-associated cellular responses.

2. Methods

2.1. Cell cultures

HaCaT keratinocytes (ATCC) and primary HDFs (Sigma-Aldrich) were cultured in high-glucose Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Cultures were maintained at 37 °C in a humidified incubator with 5% CO_2, and the culture medium was replaced every 48 h. Cells were routinely passaged using trypsin-EDTA in phosphate-buffered saline (PBS) when reaching 70–90% confluence.

For long-term storage, cells were cryopreserved in liquid nitrogen (–196 °C) using a cryopreservation medium consisting of 95% complete culture medium and 5% dimethyl sulfoxide (DMSO). Cells were harvested at approximately 80–90% confluence, resuspended in the cryopreservation medium, and transferred into cryovials. To ensure gradual freezing and preserve cell viability, cryovials were placed in a controlled-rate freezing container (–1 °C/min) at –80 °C for 24 h before transfer to liquid nitrogen storage. For recovery, cryovials were rapidly thawed in a 37 °C water bath and the cell suspension was transferred into pre-warmed complete culture medium. Cells were centrifuged to remove residual DMSO and subsequently reseeded in fresh culture medium under standard culture conditions.

2.2. Lactobacillus extracellular vesicles

Lactobacillus EVs were obtained from a commercial preparation (Natori Exobiome LB, ECOORI PTE LTD, Singapore). The formulation contains 93% *Lactobacillus* EVs, 5% butylene glycol, and 2% 1,2-hexanediol. According to the manufacturer, the stock solution is standardised to a concentration of EVs $\geq 2 \times 10^8$ EVs/mL and has a pH range of 5.0–7.0. EVs are described as nano-sized vesicles approximately 1/20 the size of the parent bacteria—which may potentially facilitate interaction with skin cells. However, independent physicochemical characterisation of EV purity, size distribution, and cargo composition was not performed in this study. The stock solution was diluted in culture medium to obtain experimental concentrations ranging from 2.0×10^4–2.0×10^7 EVs/mL (0.01–10% v/v). This range included and exceeded the manufacturer's recommended dosage (1.0–5.0% v/v) to evaluate potential cytotoxicity. The product was stored in the original sealed container at 10–30 °C, protected from direct light and heat, according to the manufacturer's instructions.

2.3. SEM analysis of Lactobacillus-derived EVs

Lactobacillus-derived EVs were analysed by scanning electron microscopy (SEM) using a Phenom PRO (Generation 5, Thermo Scientific, Netherlands) equipped with a backscattered electron detector (BSD) and a secondary electron detector (SED) at 10 kV–15 kV. Morphology and aggregation were assessed using two sample preparation protocols: lyophilisation and ambient-air drying. Lyophilised samples were observed directly, whereas air-dried samples were sputter-coated with a 4.9 nm layer of gold (EM ACE200, Leica, Germany) to enhance surface conductivity and obtain high-resolution structural details. Representative micrographs were acquired at various magnifications, with at least three independent fields per sample, to confirm structural integrity.

2.4. Metabolic activity assay (MTT assay)

HaCaT and HDF cells were seeded in 96-well plates (10,000 cells/well) and cultured in supplemented high-glucose DMEM until 80–85% confluence. Cells were treated with *Lactobacillus*-derived EVs from 0.01% to 10% v/v for 24 h (HaCaT) or 24–48 h (HDFs); detailed correspondence between volume percentages and particle concentrations is provided in Table S1. Untreated cells served as controls. Prior to the addition of MTT solution (final concentration: 0.5 mg/mL in DMEM), cell monolayers were washed twice with pre-warmed sterile PBS (37 °C) to remove residual serum components. Following a 4-h incubation with MTT, the medium was replaced with 100 μL DMSO per well. Plates were gently agitated on an orbital shaker for 10 min at room temperature (RT) to ensure complete dissolution of formazan crystals. Absorbance was measured at 595 nm using a microplate reader, and all values were normalised to the control group (defined as 100% metabolic activity). All experiments were performed in triplicate.

2.5. Cell migration assay (scratch assay) in HaCaT cells

HaCaT cells were seeded in 6-well plates (5×10^5 cells/well) and cultured until a confluent monolayer was formed. Cells were pretreated with *Lactobacillus*-derived EVs at 2.5×10^6 and 5.0×10^6 EVs/mL (1.25–2.5% v/v) for 24 h. Subsequently, a scratch was created, using a sterile 200 μL pipette tip, and cells were cultured in serum-free DMEM. Wound closure was monitored via time-lapse imaging every 15 min for 24 h, and untreated cells served as controls.

The scratch assay was performed within a controlled environmental chamber maintained at 37 °C and 5% CO_2 to ensure optimal physiological conditions throughout the experiment. The wound closure rate (WCR) was calculated as:

$$\text{WCR } (\%) = \frac{A_0 - A_t}{A_0} \times 100$$

where $A_0$is the initial wound area at 0 h and A_t is the wound area at a specific time point t. Image analysis was performed using the "Wound Healing Tool" macro in ImageJ, allowing consistent measurement of the cell-free area across all replicates to quantify the migration efficiency of HaCaT cells under the influence of *Lactobacillus*-derived EVs. All experiments were performed in triplicate.

2.6. Measurement of intracellular reactive oxygen species (ROS) in HDF cells

HDF cells were seeded in black, clear-bottom 96-well plates at a density of 10,000 cells/well. Cells were exposed to *Lactobacillus*-derived EVs (2.0×10^6 EVs/mL; 1% v/v) for 24 h, with untreated cells serving as controls. After treatment, cell monolayers were washed twice with pre-warmed sterile PBS (37 °C) to remove residual serum components that could interfere with fluorescence measurements. Cells were then incubated with a fluorogenic dihydroethidium (DHE) probe (1:1000 dilution in PBS) for 30 min under strictly controlled dark conditions to prevent light-induced probe oxidation. Fluorescence was measured using a VICTOR Nivo microplate reader (Revvity, USA) at excitation/emission wavelengths of 535/610 nm and expressed in relative fluorescence units (RFU). Raw data were normalised to the untreated control group, defined as 100% relative ROS levels, allowing direct comparison across independent biological replicates. All experiments were performed in triplicate, with each condition assessed in at least three independent wells.

2.7. SIPS model

To induce senescence, HaCaT and HDF cells were exposed to 200 μM hydrogen peroxide (H_2O_2) for 3 h. Following treatment, cells were washed with PBS and cultured in fresh complete medium for 7 days to allow the development of the senescent phenotype. During the post-induction period, the culture medium was replaced every 48 h to maintain adequate nutrient availability and remove metabolic waste products.

2.8. Immunofluorescence analysis

Normal and SIPS-induced cells treated with *Lactobacillus*-derived EVs (1% v/v) for 24 h were fixed with 3.7% formaldehyde and permeabilised with 0.1% Triton X-100 for 30 min. After blocking with 1% bovine serum albumin (BSA) for 30 min at RT, cells were incubated overnight at 4 °C with primary antibodies against p21, 53BP1, MMP-3, IL-6 and COX-2. Primary antibodies and their respective dilution factors were as follows: p21 (rabbit monoclonal, clone R.229.6, 1:800), 53BP1 (rabbit polyclonal, 1:1000), MMP-3 (rabbit polyclonal, 1:400), IL-6 (mouse monoclonal, clone OTI3G9, 1:100), and COX-2 (rabbit polyclonal, 1:100). Texas Red-conjugated goat anti-rabbit IgG or FITC-conjugated goat anti-mouse IgG secondary antibodies were applied at a 1:1000 dilution for 1 h at RT in the dark. Nuclei were counterstained with Hoechst 33342. Fluorescence intensity was quantified using an automated cell analyser and expressed as RFU. Data represent multiple independent experiments. Manufacturer details and catalogue numbers for all antibodies are provided in Table S2.

2.9. Statistical analysis

Data are presented as mean ± SEM from at least three independent experiments. Statistical analyses were performed using GraphPad Prism software (version 8.0.1). One-way ANOVA followed by Dunnett's post hoc test was used for the MTT assay, while a two-way repeated measures ANOVA followed by Sidak's multiple comparisons test was applied to analyse time-lapse data from the scratch assay. ROS and immunofluorescence results were compared using Student's *t*-test. Differences were considered statistically significant at $p < 0.05$.

Manufacturer details and catalogue numbers for all materials used in the study are provided in Table S2.

3. Results

3.1. SEM observation of Lactobacillus-derived EVs

The morphology and aggregation of the *Lactobacillus*-derived EVs were investigated via scanning electron microscopy (SEM) to confirm the presence of spherical membrane-bound structures (Fig. 1). These EVs were obtained from a commercial source, with the manufacturer specifying a size distribution predominantly within the 50–200 nm range.

In lyophilised samples (Fig. 1a–b), the vesicles appeared mostly embedded within a crystalline matrix—likely due to PBS salt residues—which hindered the clear visualisation of individual particles. Conversely, air-dried samples (Fig. 1c–e) revealed a more distinct separation of rounded structures with a heterogeneous size distribution. The observed particles ranged from the sub-micron to the micrometric scale, where majority fell below 200 nm and a significant population of larger, regularly shaped spherical bodies (up to 1–2 μm) displaying well-defined margins and high contrast.

Therefore, individual nanoscale vesicles in the manufacturer-specified 50–200 nm range could be confirmed with SEM only as below 200 nm, without resolving 50 nm limit. Consequently, the smaller structures observed likely represent vesicle clusters and aggregates, rather than isolated extracellular vesicles, which are formed during the dehydration process.

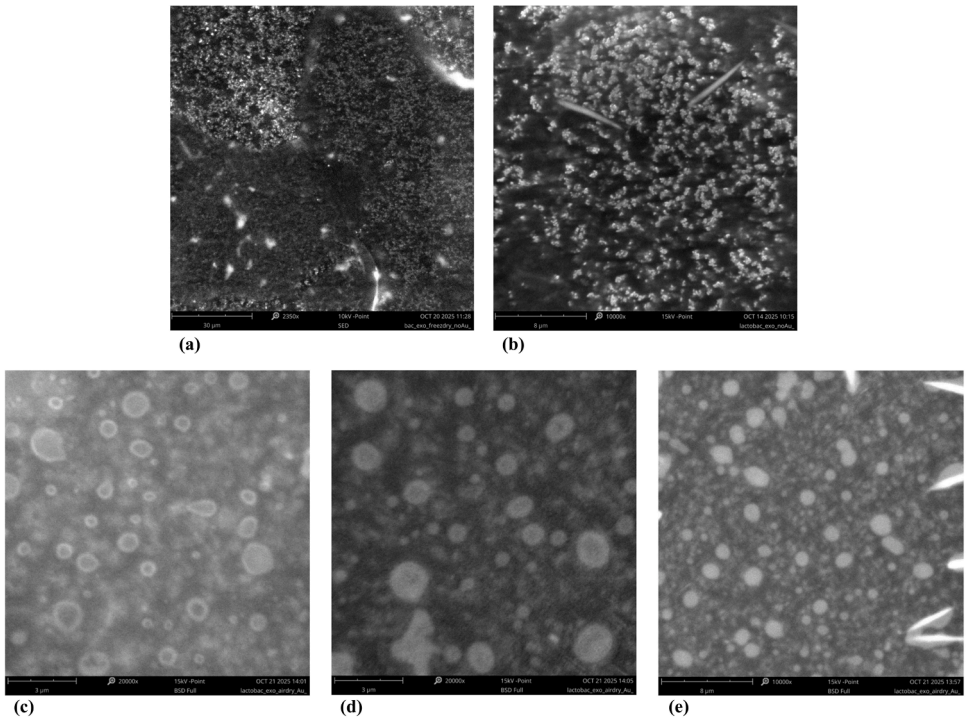

Fig. 1. Scanning electron microscopy (SEM) analysis of *Lactobacillus*-derived EVs. (a–b) Lyophilised samples showing spherical, membrane-like structures embedded within a crystalline matrix, likely due to residual salts. (c–e) Air-dried, gold-coated samples showing rounded structures with a heterogeneous size distribution, including smaller particles and larger vesicle-like structures (up to 1–2 μm) with defined margins. Due to resolution limits, nanoscale vesicles cannot be reliably resolved.

3.2. Effect of Lactobacillus-derived EVs on HaCaT and HDF metabolic activity

MTT assays demonstrated that *Lactobacillus*-derived EVs are well-tolerated within specific concentration ranges (Fig. 2). In HaCaT cells, 24-h exposure to 1.25% and 2.5% v/v significantly enhanced metabolic activity compared with untreated controls ($p < 0.05$; Fig. 2a)—suggesting a dose-dependent stimulatory effect with no cytotoxicity up to 5% v/v (Fig. 2a–b). Conversely, HDFs maintained stable metabolic levels at both 24 and 48 h, with values comparable to controls for all concentrations tested up to 1% v/v ($p > 0.05$; Fig. 2c–d). The highest concentration tested (10% v/v) significantly reduced metabolic activity in both cell lines—dropping below the 80% threshold ($p < 0.0001$; Fig. 2b–d).

3.3. Effect of Lactobacillus-derived EVs on HaCaT cell migration

Scratch assays performed on HaCaT cells revealed a divergent, dose-dependent effect on wound healing (Fig. 3). Treatment with 1.25% v/v EVs significantly accelerated wound closure during the early phase (1–16 h; $p < 0.0001$; Fig. 3a–f CTRL, g–k 1.25% EVs, q - quantification of wound closure), leading to complete closure at 18 h—approximately 4 h earlier than untreated controls. Conversely, the 2.5% v/v concentration—despite its positive impact on metabolic activity—markedly impaired migration from the earliest time points up to 24 h ($p < 0.0001$; Fig. 3a–f CTRL, l–p 2.5% EVs, r - quantification of wound closure). The results indicate that the lower concentration (1.25% v/v) promotes rapid epithelial repair, whereas the higher concentration (2.5% v/v) exerts a persistent inhibitory effect on the migratory response. This apparent discrepancy suggests a functional decoupling between metabolic activity and migratory capacity, indicating that EVs may differentially regulate distinct signalling pathways rather than uniformly enhancing cellular functions.

3.4. Modulation of intracellular ROS levels by Lactobacillus-derived EVs in HDF cells

Intracellular ROS levels were assessed in HDFs following 24-h exposure to 1% v/v EVs. Treatment significantly reduced basal ROS levels compared with untreated controls ($p < 0.05$; Fig. 4)—suggesting that *Lactobacillus*-derived EVs modulate intracellular redox state within the dermal compartment. HDFs were specifically selected for ROS analysis due to their central role in dermal redox homeostasis and the regulation of the extracellular matrix—both of which are critical factors in skin ageing and tissue integrity.

3.5. Modulation of senescence- and inflammation-related markers by Lactobacillus-derived EVs

Immunofluorescence was used to evaluate the impact of EVs at 1% v/v on the expression levels and spatial localisation of key markers of DDR, senescence, and SASP, as well as inflammatory mediators (Figs. 5–7). In HaCaT cells under basal conditions, EV treatment significantly down-regulated $p21_{nuc}$, 53BP1, and MMP-3 ($p < 0.01$; Fig. 6a–c), while IL-6 and COX-2 remained unchanged. Interestingly, in the SIPS model, treatment induced a significant upregulation of $p21_{nuc}$, 53BP1, and MMP-3 ($p < 0.05$; Fig. 6a–c, right panels).

A distinct, context-dependent response was observed in HDF cells. Under basal condition, EV treatment significantly increased $p21_{nuc}$ and 53BP1 expression ($p < 0.001$) while reducing MMP-3 levels ($p < 0.05$; Fig. 7a–c). In the SIPS model, EVs triggered a highly significant increase in 53BP1, MMP-3 expression—whereas $p21_{nuc}$ levels remained effectively unchanged compared with stress-induced controls ($p < 0.001$; Figs. 7b–c, 5d, right panels). Regarding inflammation-related markers, EV treatment selectively induced a significant upregulation of COX-2 in HDF cells under SIPS conditions, while no significant changes were observed in other experimental groups (Fig. 5).

Overall, these results highlight a cell-specific and context-dependent

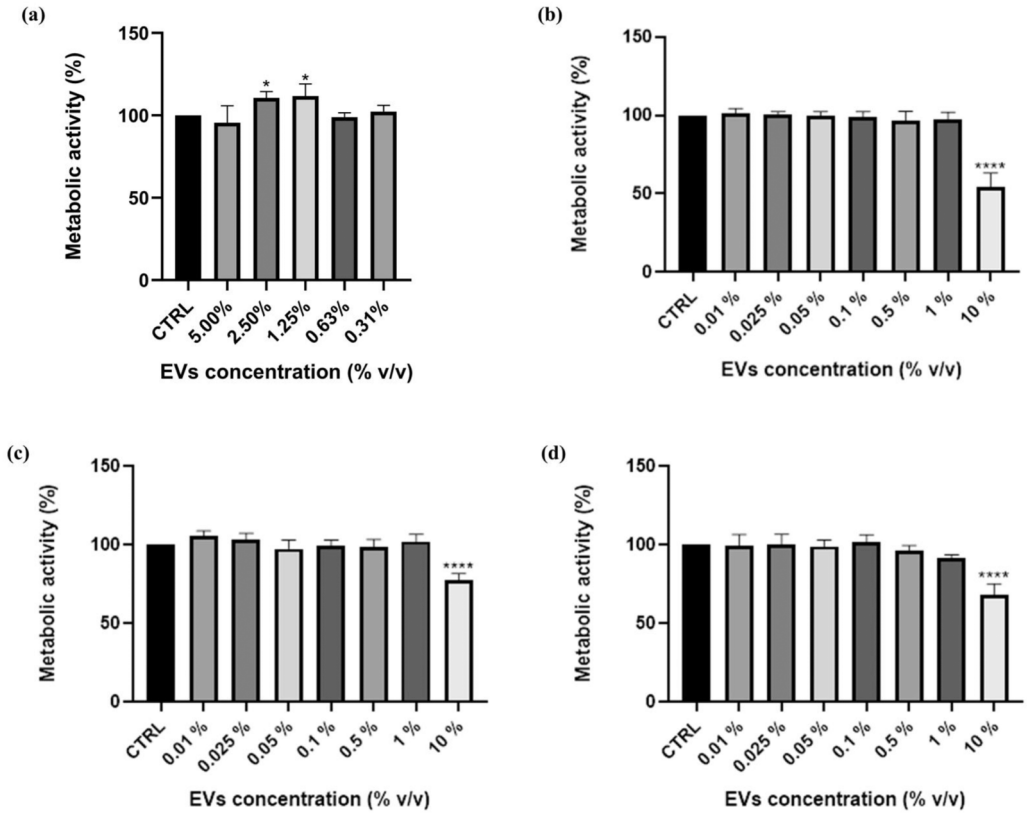

Fig. 2. Impact of *Lactobacillus*-derived EVs on the metabolic activity of HaCaT and HDF cells. (a, b) MTT assay results for HaCaT cells following 24 h exposure. (c, d) MTT assay results for HDF cells following 24 and 48 h exposure, respectively. Cells were treated with EV concentrations ranging from 0.01% to 10% v/v (see Table S1 for detailed concentrations). A dose-dependent response is observed, with increased metabolic activity at lower concentrations in HaCaT cells and reduced viability at 10% v/v in both cell types. Data are expressed as mean ± SEM of three independent experiments ($n = 3$). Statistical significance was determined using one-way ANOVA followed by Dunnett's post hoc test and is indicated relative to untreated controls (*$p < 0.05$, ****$p < 0.0001$).

modulation of the DNA damage response (DDR) and the senescence-associated phenotype (SASP), suggesting that *Lactobacillus*-derived EVs may differentially regulate senescence markers and inflammatory mediators depending on the cell type and the presence of exogenous stress.

4. Discussion

This study investigates the biological activity of *Lactobacillus*-derived EVs as postbiotic mediators capable of modulating key processes involved in skin cell homeostasis [31,34,35]. Overall, our data suggest that EVs may regulate metabolic activity, migration, redox balance, and stress-responsive signalling in keratinocytes and dermal fibroblasts in a dose- and context-dependent manner, rather than inducing uniform cellular activation, independent of a specific disease model [6,7,10].

As a first step in EV characterisation, morphological analysis highlighted the influence of sample preparation on vesicle structure. Lyophilisation preserved vesicle-like structures compatible with extracellular vesicles, in agreement with the generally described EV morphology [38] and with the MISEV2018 guidelines [39], although nanoscale vesicles (50–200 nm) could not be directly resolved under the SEM conditions used. In contrast, air-drying led to the formation of larger aggregates (1–2 μm; Fig. 1c–e), likely reflecting dehydration-induced artefacts as well as intrinsic heterogeneity of Gram-positive bacterial vesicle preparations [40,41]. These structural observations provide a morphological basis for subsequent functional analyses, as vesicle structural features may potentially influence EV–cell interactions and their biological activity [42,43].

Functional assays indicated that *Lactobacillus*-derived EVs are well tolerated in both keratinocytes and dermal fibroblasts within physiological concentrations, suggesting a favourable compatibility profile in skin-relevant *in vitro* systems [31,35]. In keratinocytes, metabolic activity increased at 1.25% and 2.50% (v/v) (Fig. 2a), indicating a concentration-dependent cellular responsiveness to EV exposure [6]. In contrast, a significant reduction in metabolic activity in both cell lines was observed only at the supra-physiological concentration (10% v/v; Fig. 2b–d). Overall, these findings suggest that EVs do not induce evident cytotoxic effects within the physiological range, but rather elicit dose-dependent functional responses that likely reflect modulation of cellular metabolic adaptation rather than cytotoxicity [10]. Given this preserved metabolic responsiveness, we next evaluated whether EVs also influence functional cellular behaviours [41], with particular attention to migration.

Migration assays revealed a biphasic response. *Lactobacillus*-derived EVs significantly enhanced keratinocyte wound closure at 1.25% (v/v), whereas they markedly reduced migration at 2.50% (v/v). This behaviour is consistent with a hormetic-like dose response; however, more importantly, it indicates a functional decoupling between metabolic activity and migratory capacity. Indeed, 1.25% (v/v) is associated with a coordinated increase in metabolic and migratory activity. In contrast, at 2.50% (v/v), metabolic responsiveness is maintained, while migration is inhibited. This suggests that EVs differentially regulate distinct signalling pathways controlling cellular metabolism and cytoskeletal dynamics in a dose-dependent manner [10,41], reflecting pathway-specific sensitivity rather than a uniform cellular response.

Oxidative stress represents a central upstream regulator of cellular senescence, inflammation, and extracellular matrix remodelling in dermal biology [28,29,44]. In this context, EV treatment significantly reduced basal intracellular ROS levels in dermal fibroblasts. Rather than reflecting a direct antioxidant scavenging, this effect suggests modulation of intracellular redox homeostasis, likely mediated by the bioactive

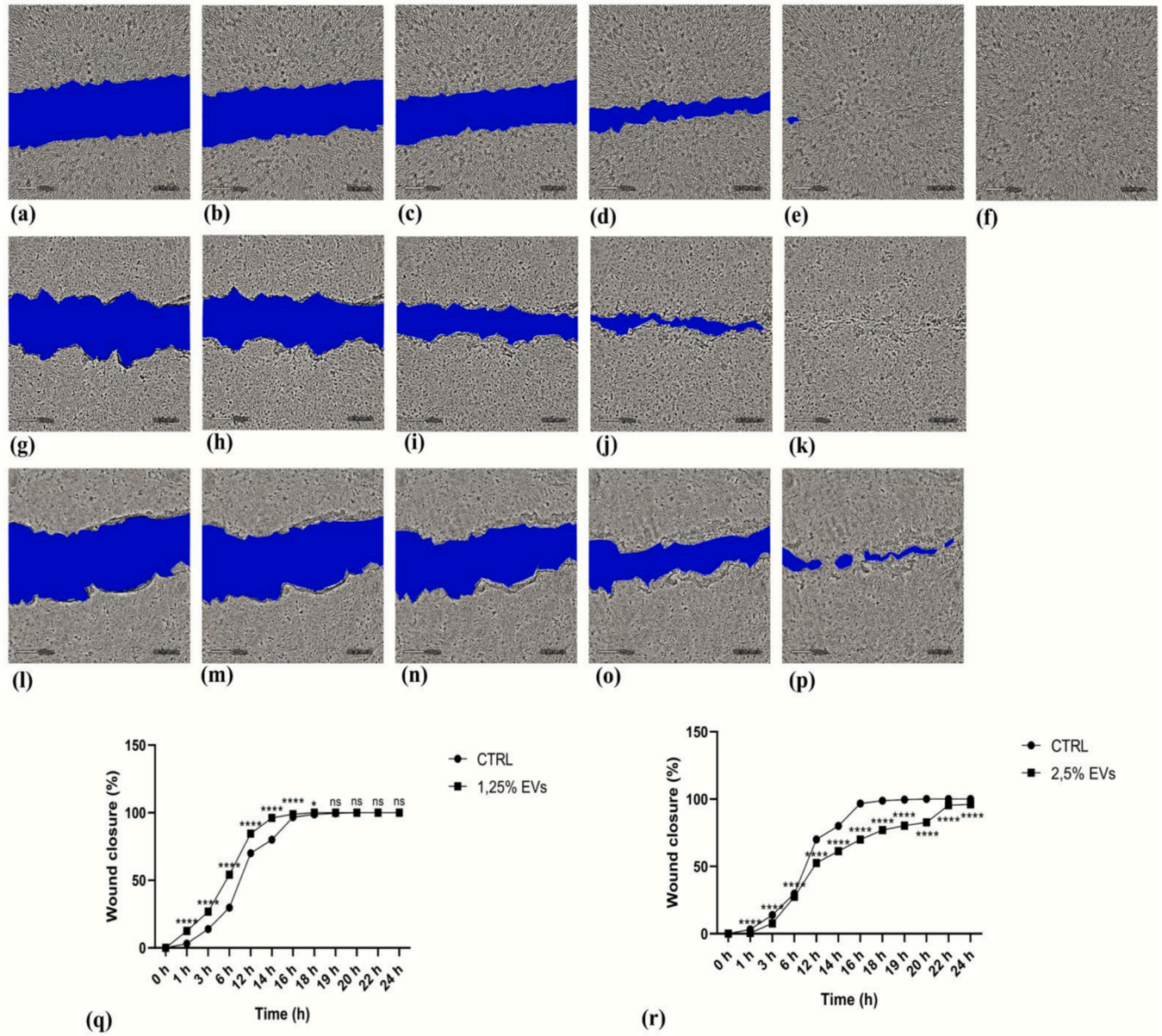

Fig. 3. Impact of *Lactobacillus*-derived EVs on HaCaT cell migration and wound healing dynamics. (a–p) Representative micrographs of the scratch assay, with the wound area highlighted in blue, comparing untreated controls with cells treated with 1.25% or 2.5% v/v EVs at selected time points. (q, r) Quantification of wound closure (%) over 24 h. Differences in wound closure kinetics are observed between treatments, with distinct profiles for 1.25% and 2.5% v/v EVs. Data are expressed as mean ± SEM from three independent experiments (n = 3). Statistical analysis was performed using two-way repeated measures ANOVA followed by Sidak's post hoc test, with significance indicated relative to controls (*$p < 0.05$, ****$p < 0.0001$; ns = not significant).

cargo associated with EVs [28,45,46]. Given the role of ROS as signalling mediators, such variations may influence downstream pathways, including activation of the DNA damage response and inflammatory signalling cascades [28,45], which are tightly interconnected with stress-induced cellular responses.

Accordingly, the observed reduction in basal ROS may represent an early regulatory event linking redox modulation to changes in DNA damage response activation, and to the subsequent modulation of senescence-related markers such as $p21_{nuc}$ and 53BP1, as well as inflammatory mediators including IL-6 and COX-2. This framework supports the tight functional interconnection between oxidative stress, DNA damage, and inflammation, rather than their interpretation as independent biological processes [9,10,29]. Collectively, these interlinked pathways may contribute to the regulation of senescence and extracellular matrix (ECM) remodelling [28,47].

The immunofluorescence analysis demonstrated that EVs regulate key effectors of the DNA damage response, cellular senescence, inflammation, and extracellular matrix remodelling in a cell- and context-dependent manner [42,45,48]. Emerging evidence indicates that EVs are integral components of the senescence-associated secretory phenotype (SASP), contributing to the propagation of pro-inflammatory signals and to the modulation of surrounding cells [49]. This coordinated modulation of DDR effectors and SASP components underscores the potential of *Lactobacillus*-derived EVs to interfere with the establishment and propagation of the senescent state in skin cells. In keratinocytes, EVs modulated $p21_{nuc}$, 53BP1, and MMP-3 under both basal and stress conditions, indicating a coordinated regulation of DNA damage response pathways and matrix remodelling processes [48,50]. The involvement of p21 is consistent with well-established molecular programmes of senescence and stress responses in keratinocytes [28,51]. In parallel, in dermal fibroblasts a distinct and context-dependent pattern emerged involving $p21_{nuc}$, 53BP1, MMP-3, and COX-2 [7,44,

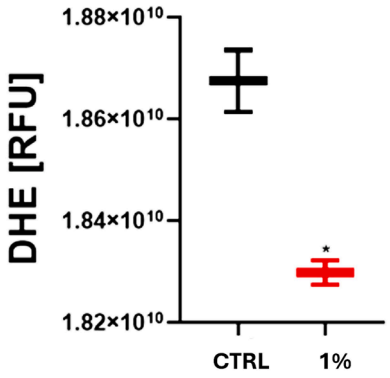

Fig. 4. Modulation of intracellular ROS levels in HDF cells by *Lactobacillus*-derived EVs. Intracellular ROS levels were assessed using the DHE fluorescent probe following 24 h treatment with 1% v/v EVs. A reduction in basal ROS levels is observed compared with untreated controls. Data are expressed as mean relative fluorescence units (RFU) ± SEM of three independent experiments ($n = 3$). Statistical significance was calculated using Student's *t*-test (*$p < 0.05$).

47], suggesting a non-uniform cellular response to the same vesicular stimulus.

This divergence is in line with previous studies demonstrating that fibroblast-derived EVs can modulate keratinocyte behaviour, highlighting the central role of vesicle-mediated intercellular communication in skin homeostasis [52]. Overall, these findings support the concept that EVs act as context-sensitive modulators rather than uniform effectors, in agreement with the role of redox signalling and intercellular crosstalk in driving differential responses between keratinocytes and fibroblasts [9,10,45]. Further studies also support EVs as key mediators of communication between skin cells under both physiological and inflammatory conditions [53].

From a mechanistic perspective, ROS-dependent signalling likely represents an upstream level integrating environmental stress perception with the activation of DNA damage response pathways and inflammatory responses [9,44,45]. Within this framework, EVs act as pleiotropic modulators that coordinate redox balance with cellular stress adaptation programmes [42,45,49], consistent with their ability to transfer bioactive molecules and modulate host signalling networks [42,46].

At the functional level, EVs orchestrate a compartmentalised response: in keratinocytes, they promote migration and metabolic adaptation, whereas in fibroblasts, they support redox homeostasis and matrix integrity [7,52]. The integration of redox regulation, DNA damage response, and matrix remodelling suggests an emergent system-level effect rather than the modulation of isolated pathways [44,47]. Finally, dose-dependent effects indicate that low-to-intermediate concentrations favour adaptive responses, whereas higher concentrations may activate compensatory regulatory mechanisms that limit excessive cellular activation.

5. Biological implications of *Lactobacillus*-derived EVs

Lactobacillus-derived EVs represent bioactive postbiotic mediators capable of modulating interconnected cellular pathways involved in skin barrier-associated functions, redox homeostasis, and tissue remodelling. Their dose- and context-dependent effects, including differential regulation of metabolic and migratory responses, suggest a role in fine-tuning cellular adaptation rather than inducing uniform activation. These findings highlight their relevance in the regulation of fundamental skin cell behaviours, including metabolic adaptation, migration, and stress-responsive signalling. While such properties may be of interest in the context of conditions characterised by altered redox balance and inflammatory signalling, further validation in more physiologically complex and disease-relevant models will be required to fully elucidate their biological and potential applied relevance.

6. Study limitations and future perspectives

This study presents several methodological limitations. SEM analysis provided qualitative morphological insights but does not allow precise nanoscale quantification of vesicle populations [38,39]. In addition, EV

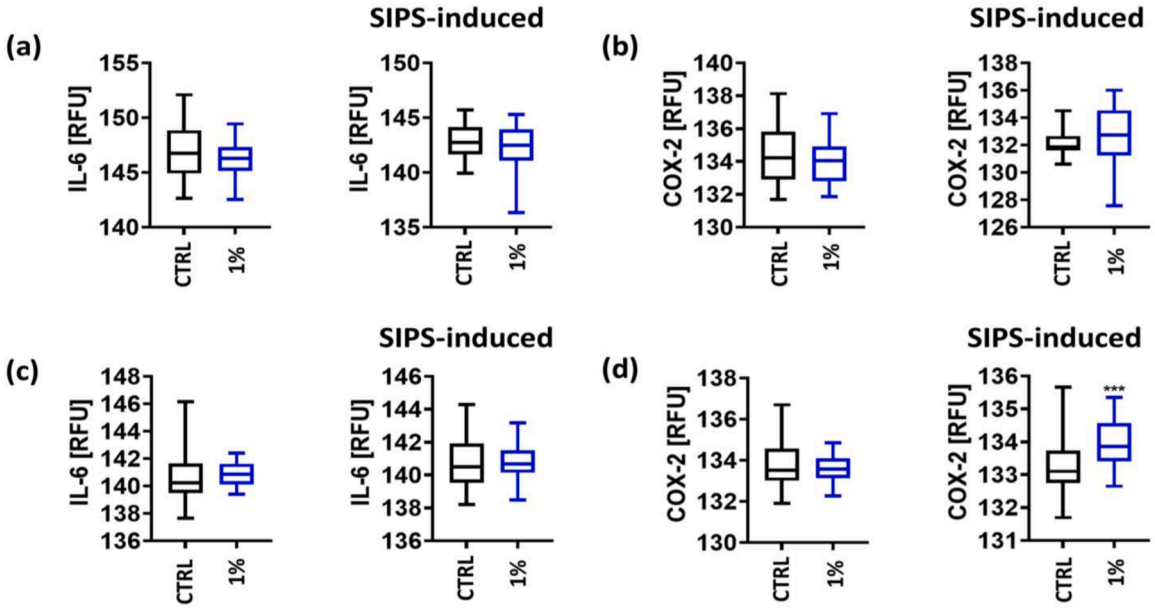

Fig. 5. Modulation of pro-inflammatory markers by *Lactobacillus*-derived EVs in keratinocytes and fibroblasts. (a, b) Immunofluorescence-based quantification of IL-6 and COX-2 expression in HaCaT cells. (c, d) Expression levels of IL-6 and COX-2 in HDF cells. Panels compare basal conditions (left graphs) with SIPS-induced conditions (right graphs) following 24 h treatment with 1% v/v EVs. Changes in marker expression are observed across conditions, including a significant increase in COX-2 levels in HDF cells under SIPS conditions. Data are expressed as mean relative fluorescence units (RFU) ± SEM from three independent experiments ($n = 3$). Statistical analysis—performed using Student's *t*-test—is indicated relative to respective controls (***$p < 0.001$).

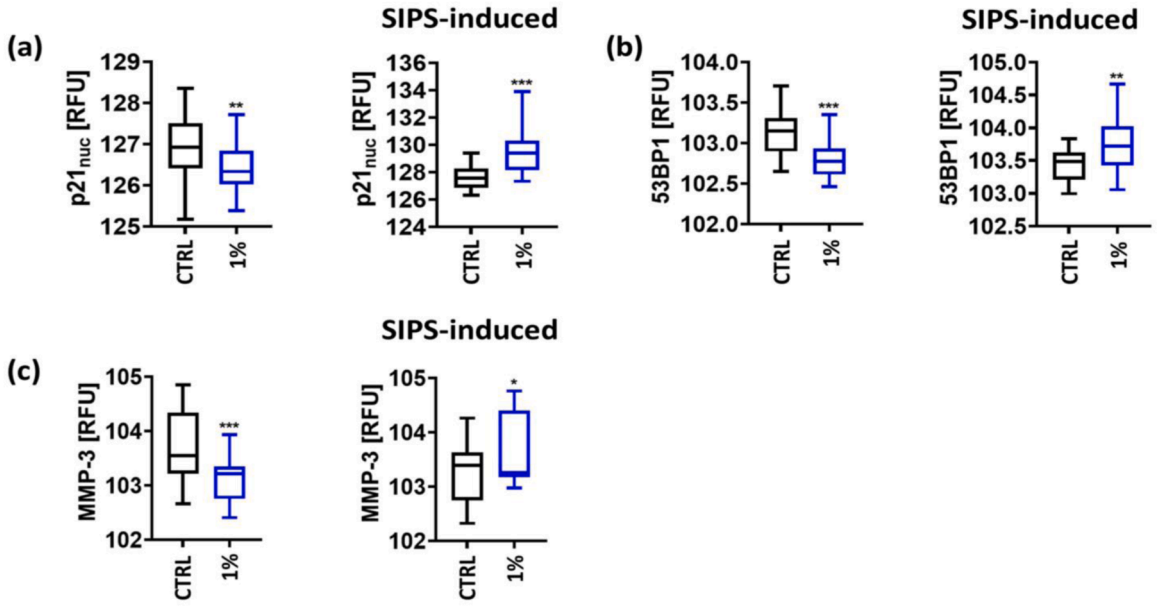

Fig. 6. Modulation of senescence-related markers in HaCaT cells by *Lactobacillus*-derived EVs. Immunofluorescence-based quantification of (a) nuclear p21 ($p21_{nuc}$), (b) 53BP1, and (c) MMP-3 expression in HaCaT cells. Panels compare basal conditions (left graphs) with SIPS-induced conditions (right graphs) following 24 h treatment with 1% v/v EVs. Changes in marker expression are observed under both basal and SIPS conditions. Data are expressed as mean relative fluorescence units (RFU) ± SEM from three independent experiments ($n = 3$). Statistical analysis—performed using Student's *t*-test—is indicated relative to respective controls (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

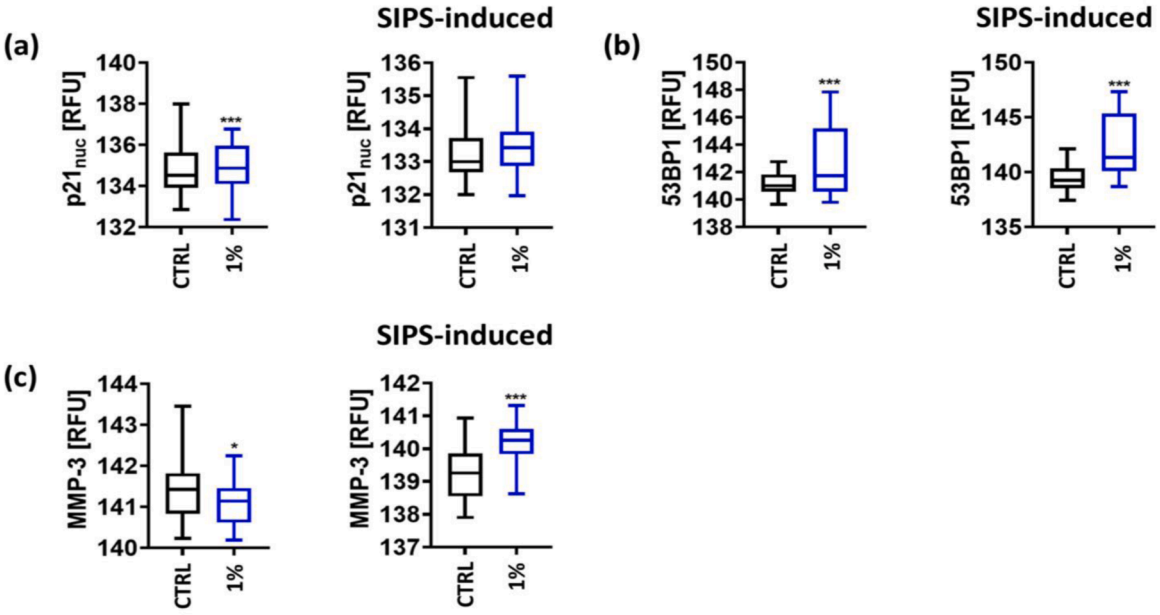

Fig. 7. Modulation of senescence-related markers in HDF cells by *Lactobacillus*-derived EVs. Immunofluorescence-based quantification of (a) nuclear p21 ($p21_{nuc}$), (b) 53BP1, and (c) MMP-3 expression in HDF cells. Panels compare basal conditions (left graphs) with SIPS-induced conditions (right graphs) following 24 h treatment with 1% v/v EVs. Distinct patterns of marker expression are observed between basal and SIPS conditions. Data are expressed as mean relative fluorescence units (RFU) ± SEM from three independent experiments ($n = 3$). Statistical analysis—performed using Student's *t*-test—is indicated relative to respective controls (*$p < 0.05$, ***$p < 0.001$).

cargo was not characterised, limiting mechanistic resolution of the observed effects and warranting further omics-based analyses to identify the bioactive components involved [38,39]. Furthermore, while the preparation is reported to be enriched in EVs, the potential contribution of co-isolated bioactive components cannot be entirely excluded. The use of 2D monoculture systems does not fully recapitulate the complexity of human skin architecture, including multicellular interactions and extracellular matrix organisation [7,8]. Importantly, this study does not evaluate the capacity of EVs to penetrate or traverse the stratum corneum—a critical factor for the translational efficacy of topical treatments. While epidermal barrier dysfunction is a hallmark of conditions like AD, specific studies using reconstructed human epidermis or *ex vivo* skin diffusion assays will be essential to determine the actual rate of EV permeation and uptake.

7. Conclusions

Taken together, *Lactobacillus*-derived EVs act as integrated regulators of skin cell homeostasis by coordinating redox-sensitive signalling, DNA damage responses, inflammatory pathways, and ECM remodelling in a dose- and context-dependent manner. Notably, their differential effects on metabolic activity and cell migration highlight a capacity to fine-tune cellular responses rather than induce uniform activation, while supporting compartment-specific regulation across epidermal and dermal cells. These findings provide a mechanistic basis for future studies exploring their potential as postbiotic mediators in more physiologically relevant models of skin barrier dysfunction and inflammatory skin disorders.

CRediT authorship contribution statement

Magdalena Górska-Ponikowska: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Iwona Rzeszutek:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Investigation. **Krzysztof Cal:** Methodology, Writing – review & editing. **Francesca Rappa:** Writing – review & editing. **Barbara Mikolaszek:** Methodology, Investigation, Writing – review & editing. **Maria Denise Amico:** Visualization, Validation, Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Katarzyna Centkowska:** Methodology, Investigation. **Malgorzata Skowron:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Wioletta Baranska-Rybak:** Writing – review & editing. **Justyna Ruchala:** Writing – review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2026.119457.

Data availability

Data will be made available on request.

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