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Vanillin and Colostrum-Derived Exosome Combination Therapy Against In Vitro UVB Photoaging on HDF-1 Cell Line

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Abstract

Introduction: In vitro studies indicate that Ultraviolet radiation (UVR) causes photoaging in the skin through oxidative stress, collagen destruction, DNA damage, and chronic inflammation. These models play a critical role in the development of anti-aging therapies. The study aimed to investigate the anti-photoaging effects of the combination therapy of vanillin and colostrum-derived exosomes on UVB-irradiated human dermal fibroblast cells.

Materials and Methods: Ultraviolet B (UVB)-exposed human dermal fibroblast cell line (HDF-1) were treated with vanillin (30 μM) and colostrum exosomes (0.1 mg/mL) to assess cell viability and total antioxidant capacity. Matrix metalloproteinase-1 (MMP-1) and procollagen type-1 levels were measured by enzyme-linked ımmunosorbent assay (ELISA), and cell nucleus morphology was examined by 4',6-diamidino-2-phenylindole (DAPI) staining.

Results: Cell viability increased in UVB-irradiated HDF-1 cells in the vanillin and vanillin+exosomes groups. Following UVB exposure, a decrease in procollagen type 1 and antioxidant levels and increased MMP-1 levels were observed in HDF-1 cells. Vanillin+exosome treatment was associated with decreased MMP-1 expression in HDF-1 cells and increased collagen production. Increased antioxidant activity, which UVB suppressed, was observed in the vanillin+exosome group ($p<0.05$). Furthermore, irregular nuclear shapes (signs of apoptosis) were observed in UVB-damaged cells, while near-normal nuclear morphology and a decrease in nuclear fragmentation were observed after vanillin+exosome treatment.

Conclusion: The combination of vanillin and colostrum-derived exosomes showed synergistic effects on skin damage and anti-photoaging by triggering antioxidant activity and increasing collagen synthesis.

Key words: Dermal fibroblast; exosome; photoaging; vanillin; antioxidant capacity.

Introduction

Ultraviolet radiation (UVR) initiates photochemical reactions through electron excitation, leading to energy transfer and/or chemical changes in molecules (1). UVR can cause photoaging, photoimmunosuppression, and photocarcinogenesis, significantly threatening skin health (2, 3). Photoaging is a complex UV-induced process characterized by collagen destruction and oxidative stress (3). Reactive oxygen species (ROS) formed in this process cause lipid peroxidation, DNA damage, protein degradation, and the degradation of collagen and elastin by increasing the production of matrix metalloproteinases (MMPs) (1, 3). In addition, UV in photoaging causes chronic inflammation by activating NF-κB and AP-1 pathways and disrupting cell signaling pathways, which leads to a decrease in collagen synthesis (4). Many organically synthesized agents are commercially available to prevent and ameliorate photoaging (2, 5). However, depending on an individual's constitution, they can cause skin irritation and hypersensitivity-based reactions (2). Therefore, identifying natural, side-effect-free functional therapies prevents skin aging and promotes skin repair. New studies show that exosomes (nanovesicles) may be effective against photoaging (3, 6). Exosomes can stimulate collagen synthesis by containing growth factors such as TGF-β and IGF-1 against photoaging, support cell repair through microRNA (miRNA), and neutralize ROS thanks to their antioxidant content (6). In addition, they can reduce oxidative stress by strengthening endogenous antioxidant defenses by activating the Nrf2 pathway (7). Exosomes can suppress MMP-1 expression and accelerate dermis regeneration by increasing fibroblast proliferation (8). In this way, exosomes are a powerful cellular therapy that protects and heals against UVB. In contrast to animal cell lines, natural biological

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fluids, such as milk, are known as richer exosome sources (9). Colostrum, as a source of exosomes, contains more immune and bioactive factors than mature milk, which is usually produced during breastfeeding (9, 10). It is known that colostrum-derived exosomes can reduce ROS and melanin production and increase collagen production in various skin cell types, which has potential applicability in skin regeneration therapy (9, 11).

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is an aromatic compound produced naturally, synthetically, and widely used in food, cosmetics, and pharmaceutical industries (12). Vanillin has various therapeutic properties, including antioxidant, anti-inflammatory, antimicrobial, neuroprotective, and anticancer effects (12, 13). It can prevent tissue damage by reducing oxidative stress at the wound site and may protect against oxidative stress-related diseases (neurodegeneration, diabetes) (14, 15). Studies have suggested that vanillin suppresses inflammation and increases fibroblast collagen production by activating cell proliferation and the TGF-β signaling pathway (14, 15). Studies have indicated that when vanillin is used with vitamin C, the antioxidant effect is doubled, and its combination with niacinamide reduces inflammation and alleviates rosacea and hyperpigmentation (15). This study aimed to examine the ameliorative effect of the combination therapy of vanillin and colostrum-derived exosomes on UVB-mediated photoaging in human dermal fibroblasts.

Materials and Methods

Cell culture: The Human Dermal Fibroblast (HDF-1) cell line was obtained from stock at the Erciyes University Genome and Stem Cell Center. HDF-1 cells were incubated in Dulbecco's modified Eagle medium (DMEM; Sigma, Aldrich) containing 10 % fetal bovine serum (FBS), 1 % penicillin/streptomycin, 1 % L-glutamine, and high glucose at 37 °C in a 5 % CO_2 incubator.

UVB Irradiation: UVB lamp (Philips) with a wavelength of 302 nm was used for photoaging HDF-1 cells. HDF-1 cells were seeded in 96-well microplates at 5.0×10^5 cells/mL. Before light exposure, HDF-1 cells were washed three times with phosphate-buffered saline (PBS) at pH 7.4. Then, after replacing the culture medium with PBS, UVB irradiation was applied to HDF-1 cells at a dose of 20 mJ/cm^2 (16). The temperature during irradiation was maintained at 37 °C. Cells were incubated in serum-free medium at 37 °C and 5% CO_2 for 24 h, followed by the application of vanillin compound (30 µM) and colostrum exosome (0.1 mg/mL) (17). The groups were determined as control (Cell + medium only), UVB (Cell + UVB), vanillin (UVB + vanillin) and vanillin + exosome (UVB + vanillin + exosome) groups. The experimental setup is shown in Figure 1.

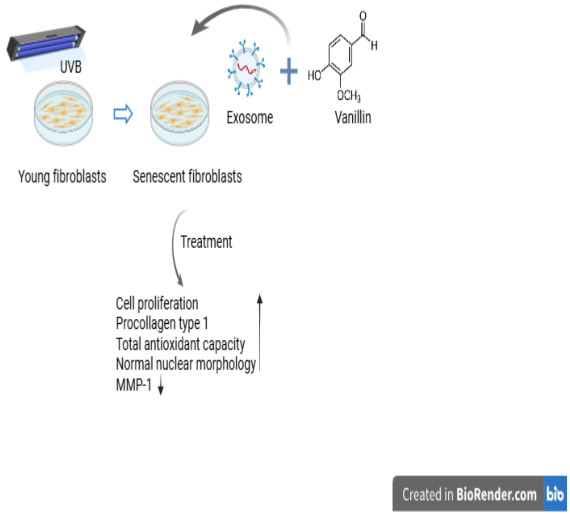


Figure 1: Representative scheme of the study protocol.

Vanillin and exosomes preparation: Vanillin and colostrum exosomes (purasomes nc150+nutri complex; Dermafocus) were purchased commercially. Colostrum exosomes were used at a concentration of 0.1 mg/mL (18). Vanillin dissolved in DMSO, and vanillin+colostrum exosomes were applied to the HDF-1 cell line 24 hours after UVB light exposure (9, 19).

Cell viability analysis: The cell viability analysis was conducted using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) kit (Cayman, San Diego, CA, USA). Dermal fibroblast cells were seeded in 96-well microplates at 1.0×10^5 cells per well. After UVB exposure, a vanillin compound (30 µM) and exosomes were applied at the specified concentration to each well. Only 200 µL of medium was added to the control group. The cells were then incubated for 24 hours. Following incubation, the cells were washed with PBS and incubated with MTT solution for 4 hours. DMSO was added to all groups, and absorbance measurements were performed on a microplate reader (Thermo Scientific Multiskan Go) (20).

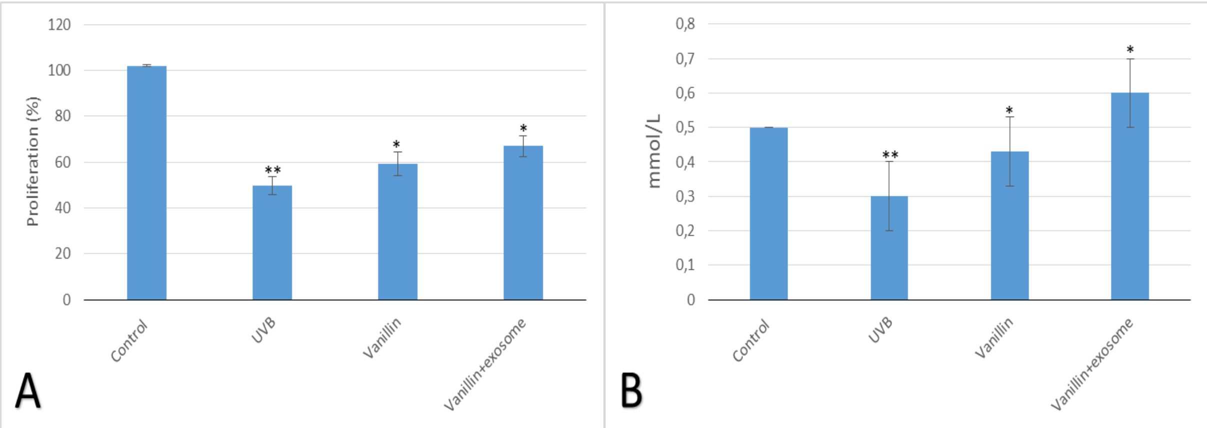


Figure 2: Cell viability (A) and TAC (B) graphs of HDF-1 cells treated with vanillin and vanillin+exosomes after UVB irradiation. Data are shown as Mean±SD. $p<0.05$: *Statistically significant difference was indicated when compared with the *UVB group and **control group.

ELISA analysis: MMP-1 and type 1 procollagen levels were measured by enzyme-linked immunosorbent assay (ELISA). Analysis of MMP-1 (Catalog No: E0916Hu) and type 1 procollagen (Catalog No: E1385Hu) was performed according to the kit instructions. The absorbance of all groups was measured at a wavelength of 450 nm using a microplate reader (Thermo Scientific Multiskan Go) (17).

Total antioxidant capacity (TAC): The TAC kit (Rel Assay, Catalog No: RL0017) was used to determine antioxidant capacity in cells. HDF-1 cells were seeded at 5×10^4 cells/mL in 96-well microplates. TAC was measured in cell lysates obtained after treatment of UVB-irradiated HDF-1 fibroblast cells with vanillin and exosomes (21). The analysis was performed in three (n = 3) replicates by comparing and interpolating with the standard 6-hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylic acid (Trolox) values in the calibration curve.

Fluorescence microscopic valuation: The fluorescent DAPI (4',6-diamidino-2-phenylindole di-hydrochloride; Sigma) staining technique was used to determine the effect of vanillin and exosomes on the nuclear morphology of HDF-1 cells after UVB irradiation. The principle of this fluorescent staining is based on the specific binding of DAPI to the Adenine-Thymine-rich region of living cells. Briefly, HDF-1 cells (2.5×10^3 cells/mL) seeded in 6-well plates were treated with vanillin and exosomes for 24 h at 37 °C in a 5 % CO_2 incubator, followed by 4 % formaldehyde and washing with PBS. DAPI was used to stain the nuclei of treated cells for 10 min at 4 °C under dark conditions, and then the cells were observed under a Nikon Ti inverted fluorescence microscope (22).

Ethical approval: Ethical approval was not required for this study because all experiments utilized established human dermal fibroblast (HDF-1) cell lines and commercially available reagents. The experimental procedures did not involve human participants, patient-derived samples, or animal subjects.

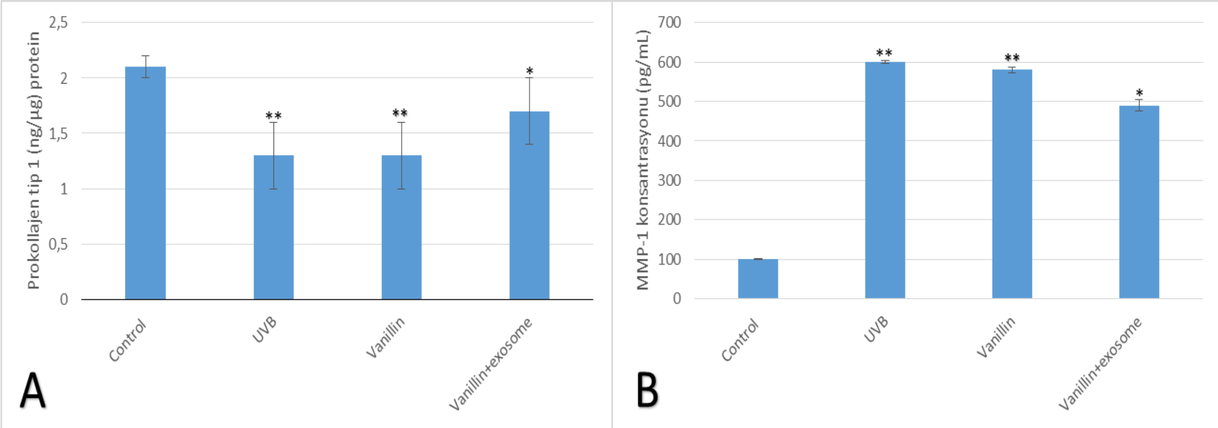
Statistical analysis: Analyses were performed using IBM SPSS Statistics 26.0. One-way analysis of variance (one-way ANOVA) followed by the Dunnett test was used. The Shapiro-Wilk test was employed in MTT, ELISA, and TAC analyses to determine the normal distribution of the groups, and the Levene test was used to assess variance homogeneity. A significance level of $p<0.05$ was considered statistically significant. Results are presented as mean ± SD. In all experiments, each group was repeated 3 times (n=3).

Results

Cell viability: MTT was performed to determine cell viability on the HDF-1 cell line after UVB irradiation of the vanillin compound. We observed significantly higher cell viability in control cells compared to UVB-irradiated cells (Figure 2A) ($p<0.05$). Interestingly, we found that the vanillin+exosome group exhibited higher cell viability compared to the vanillin group in UVB-irradiated HDF-1 cells (Figure 2A) ($p<0.05$), shedding light on the potential of these compounds in cell viability.

Total antioxidant capacity: The antioxidant activity of vanillin and colostrum-derived exosomes on UVB-irradiated HDF-1 cells was assessed using the TAC kit. As shown in Figure 2B, differences in antioxidant activity were observed in the combination group compared to the UVB and vanillin groups ($p<0.05$).

Figure 3: Graph of procollagen type 1 (A) and MMP-1 (B) levels in UVB-irradiated HDF-1 cells treated with vanillin and



vanillin+exosome. $p<0.05$: *Statistically significant difference was indicated when compared with the *UVB group and **control group.

Procollagen type 1 and MMP-1 levels: In our study, we found that UVB induced a decrease in procollagen type 1 levels and an increase in MMP-1 levels in HDF-1 cells (Figures 3A, 3B) ($p<0.05$). Notably, vanillin alone did not significantly affect MMP-1 and procollagen type 1 levels in HDF-1 cells after 24 hours of UVB exposure. However, the combination of vanillin and exosomes was found to be a significant factor, as it increased procollagen type 1 levels and significantly decreased MMP-1 levels (Figures 3A, 3B)($p<0.05$).

Fluorescence microscopic evaluation: DAPI staining was used to assess the severity of DNA damage in HDF-1 cells exposed to UVB. The fluorescence microscopic evaluation revealed a significant difference in nuclear staining between the control group and the UVB-irradiated HDF-1 cells. The latter showed nuclear fragmentation and irregular nuclear morphology, indicating apoptosis. However, the nuclei of fibroblast cells treated with UVB-irradiated combination therapy had normal morphology, and mitotic figures were observed, suggesting a potential therapeutic strategy for UVB-induced DNA damage (Figure 4).

Discussion

UVR reacts with water molecules in the skin, causing oxidative damage to lipids, proteins, and DNA, leading to cell apoptosis and gene mutations (9). Oxidative stress accelerates skin aging by triggering inflammation (23). The appearance of skin wrinkles is caused by many factors, including decreased dermal fibroblast cells and collagen production, the main structural component of the skin (21). In this process, vanillin and exosomes may be an alternative combination therapy in regulating cytokine release, collagen synthesis, and the defense mechanism against oxidative damage. Therefore, our study targeted the healing properties of dermal fibroblasts against UVB irradiation by combining natural compounds and cellular therapy. Vanillin (4-hydroxy-3-methoxybenzaldehyde), a natural phenolic compound, has significant anti-inflammatory, antioxidant, and regenerative properties (13, 14). It has been reported that vanillin at specific concentrations (≤100 µM) is not toxic to human gingival fibroblasts (HGFs) and does not significantly reduce cell viability. At the same time, high doses can cause cell death or inhibit proliferation (13). It has also been suggested that high doses help tissue regeneration by inducing apoptosis in damaged cells (13). The results show that UV-irradiated HDF-1 cells had lower viability compared to control cells (Figure 2A) ($p<0.05$). It was also observed that the vanillin+colostrum exosome group increased cell viability compared to the vanillin group (Figure 2) ($p<0.05$). One study suggested that vanillin at a 10-500 µM concentration showed a >80% survival rate in human fibroblast and keratinocyte cells (24).

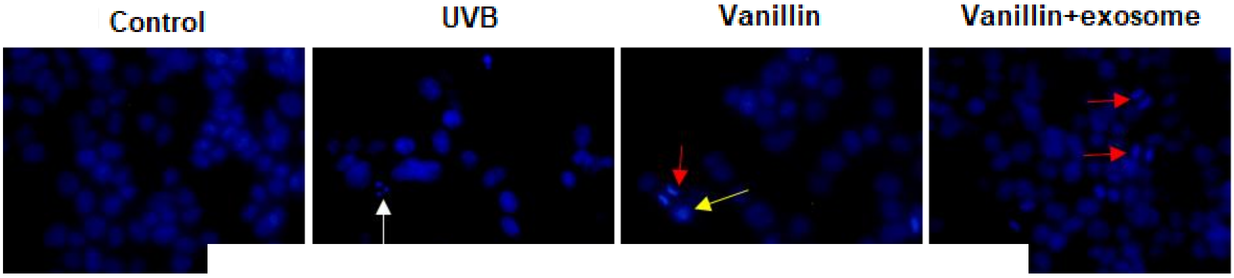


Figure 4: DAPI nuclear staining of HDF-1 cells treated with vanillin, vanillin+colostrum exosomes, and without UVB irradiation (control). The white arrow indicates nuclear fragmentation, the red arrow indicates mitotic figures, and the yellow arrow indicates condensed chromatin. Photographs were taken at 400x magnification.

In our study, vanillin was used at a concentration of 30 µM, and no toxic effects were observed in human fibroblast cells. Furthermore, the vanillin+exosome group demonstrated strong protection against concentration-dependent UVB-induced cellular damage. Studies, particularly with methods such as the MTT test or ATP measurements, have shown increased metabolic activity in exosome-treated cells. Therefore, we concluded that the vanillin + exosome combination treatment we applied in our study is effective in preventing cell damage and is safe and compatible for potential clinical use. Procollagen, the precursor of collagen, is the primary structural protein responsible for skin firmness and elasticity (25). As fibroblasts age due to UVB damage, their ability to produce procollagen decreases, leading to a loss of skin integrity and increased signs of aging (4). In aging skin, MMPs increase, degrading collagen (2). Our study has uncovered a significant finding with practical implications. We observed a robust synergistic effect of vanillin and exosomes, leading to increased procollagen type-1 levels and decreased MMP-1 levels in the combination treatment group (Figures 3A and 3B) ($p<0.05$). This finding suggests a promising avenue for skin repair. It was previously suggested that colostrum exosomes could suppress MMP expression in response to UV-induced aging and damage, while collagen production increased (9,10). Another study reported a positive correlation between antioxidant capacity and MMP-1 inhibition (26). Our study concluded that combining vanillin and exosomes applied to HDF-1 cells could suppress various signaling pathways by neutralizing ROS through its antioxidant effect, thereby reducing MMP-1 levels. This suggests that exosomes derived from bovine colostrum, which possess structural and functional stability, and vanillin exhibit a strong synergistic effect in repairing UV-induced skin aging and damage. Furthermore, the results suggest that this combination may regulate intracellular collagen production and MMP-1 secretion levels, potentially leading to new regenerative treatments for skin aging. Exosomes contain endogenous antioxidants that help scavenge free radicals and reduce oxidative stress in aged or damaged skin cells (9). They may also carry microRNAs (miRNAs) that regulate antioxidant defense pathways (e.g., the Nrf2/ARE pathway) and increase cellular resistance to oxidative damage (27). Thus, colostrum-derived exosomes help prevent lipid peroxidation, DNA damage, and protein degradation in skin cells, key factors in aging and skin damage (6, 7). One study showed that exosomes derived from bovine colostrum exhibited potent antioxidant activity, protecting skin cells from oxidative damage and supporting repair mechanisms (9). Vanillin, with its antioxidant properties, neutralizes superoxide (O_2^-) and hydroxyl radicals (OH) thanks to its phenolic hydroxyl group (–OH), and prevents skin barrier breakdown by inhibiting lipid peroxidation (14, 15). If not mitigated by antioxidants, ROS generated by UV radiation in biological systems can cause cellular damage (1). Our study found that UV radiation suppressed antioxidant levels in HDF cells, while the combination of vanillin and exosomes reversed this effect. Our data suggest that cytoprotective enzymes in exosomes and vanillin regulate oxidative stress in photoaged fibroblasts. This effect may be due to antioxidant molecules in exosomes, repair-promoting microRNAs such as miR-21 and miR-146a, and vanillin's ability to neutralize reactive oxygen species (9, 28). The observed nuclear staining and increased cell proliferation rates support this hypothesis. However, additional evidence is needed to confirm these results. While a certain amount of UV exposure is necessary for humans to synthesize vitamin D in the skin, excessive exposure to UVB, which has various biological effects at wavelengths of 280–320 nm, can damage DNA in dermal fibroblasts (1, 29). Numerous studies have shown that colostrum-derived exosomes, a component of milk, can improve nuclear integrity, reduce oxidative stress, and DNA damage markers (e.g., γ-H2AX) in cells, suggesting that exosomes may play a significant role in maintaining genomic stability and repairing UV-induced damage (9, 30). One study even suggested that HDF exosomes can attenuate genotoxic damage by activating DNA repair proteins (ATM, p53) (3). Another study found that vanillin can cause less condensed chromatin, near-normal nuclear shape, decreased nuclear fragmentation and micronucleus formation, and a significant decrease in γ-H2AX signal in keratinocyte stem cells in response to UVB damage (19). DAPI staining shows that vanillin and exosomes may repair UV-induced damage in HDFs and help maintain normal nuclear morphology (Figure 4). This combination may also improve photo-aged skin by increasing fibroblast viability and function, thereby supporting its cytoprotective effect by reducing nuclear damage (3).

Study limitations: Several limitations of this study should be acknowledged. First, all experiments utilized an in vitro HDF-1 cell model, which may not accurately represent the complex structure and physiological responses of human skin in vivo. Second, although the combined effects of vanillin and colostrum-derived exosomes have been demonstrated, the underlying molecular mechanisms, including specific signaling pathways and miRNA profiles, remain insufficiently characterized. Third, the dose-dependent effects of vanillin have not been fully investigated. Consequently, additional studies employing in vivo models and clinical trials are required to confirm the safety, efficacy, and mechanistic pathways of this combination therapy.

Conclusion

Identifying therapeutic agent targets is crucial for managing UV-induced premature skin aging. Colostrum exosomes, through their antioxidant and proliferative effects, increase the viability of damaged skin cells, suppress apoptotic processes, and promote tissue regeneration. Vanillin, more than just a flavoring, is a multifunctional bioactive molecule with significant therapeutic potential. Indeed, in our study, colostrum exosomes and vanillin contributed to the regeneration of aged skin by stimulating collagen synthesis, inhibiting its degradation, and triggering cellular rejuvenation. This study provides preliminary in vitro data on the combined effects of vanillin and exosomes, suggesting their potential as therapeutic candidates for future in vivo research. Natural therapeutic agents in serum formulations may help prevent or reduce tissue damage and aging by supporting collagen integrity, offering antioxidant protection, and promoting DNA repair. The results support further investigation of vanillin and exosome combinations for dermatological treatments, such as chronic wounds and photoaging, as well as for use in cosmetic products. Future research should focus on human clinical trials and optimizing formulation strategies.

Ethical approval: This study did not require ethical approval as it involved only established cell lines and did not include human or animal subjects.
Conflict of interest: The authors affirm that there are no competing interests to disclose.
Financial support: The research was conducted without any financial support from external institutions.
Author contributions: Conceptualization: BD; Methodology: BD, AK; Formal analysis: BD; Writing-original draft preparation: BD, AK; Supervision: BD. No Artificial Intelligence (AI) tools were used in the writing of this manuscript.

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