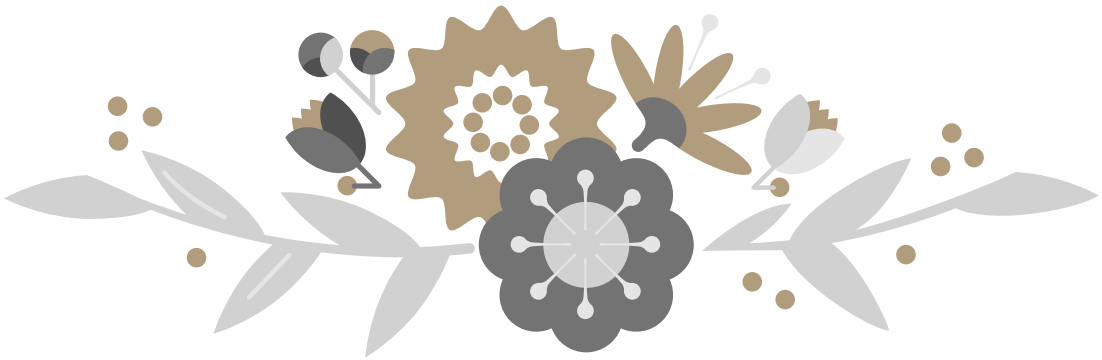

Abstract

ABSTRACT

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Title of the thesis: Skin sensitization mechanism of cinnamaldehyde under ambient UVB exposure based on integrative adverse outcome pathway framework

Allergic contact dermatitis (ACD) and skin sensitization remain critical concerns linked to fragrance allergens such as cinnamaldehyde (CA), a widely used cosmetic compound with inherent high reactivity. This study elucidates the mechanistic basis of UVB-induced augmentation of CA sensitization using integrated physicochemical, cellular, and proteomic approaches. Spectral analysis demonstrated maximal CA absorption at 289 nm within the UVB range. Controlled UVB exposure (0.6 mW/cm², for 1-4 h) induced time-dependent degradation, and trans-to-cis isomerization, confirmed by UHPLC and GC–MS. Molecular docking and a Direct Peptide Reactivity Assay (OECD TG 442C) revealed that CA enhanced binding affinity and depletion of cysteine under UVB, indicating increased electrophilic potential. Non-cytotoxic CA concentrations (0.002%) provoked significant ROS generation ($DCFH_2$-DA), upregulating Nrf2, catalase, MMP-2, and MMP-9, thereby implicating redox signaling and extracellular matrix remodeling in keratinocytes. h-CLAT assays in THP-1 cells revealed elevated CD86 expression (14.2%) and increased secretion of IL-1β, IL-6, and IL-8. ROS scavenging and TLR4 inhibition attenuated these effects, confirming ROS-dependent, TLR4-driven activation of THP-1 cells in response to CA under UVB irradiation. Proteomic profiling of HaCaT cells identified upregulation of mitochondrial and ER-stress proteins, suggesting mitochondrial-ER crosstalk and unfolded protein response activation. Co-culture analyses further demonstrated enhanced MYD88, MAP4K1, STAT5A, and TRAF1 signaling with elevated IL-18 and S100A7 release, indicative of T-cell priming and antigen processing. Further for the validation, the in-vivo study in C57BL/6 mice was performed, where the co-exposure of CA and UVB produced severe erythema, edema, and histopathological lesions consistent with photo-aggravated ACD. Collectively, UVB-induced photoisomerization amplifies CA's electrophilicity, oxidative stress, and immune signaling, delineating a mechanistic framework for photoaugmented ACD and emphasizing the need for photoallergy inclusion in fragrance safety evaluations.