

**TITLE:** EVALUATION OF THE CYTOTOXIC EFFECT AND ANTIMICROBIAL / ANTIBIOFILM ACTION OF CURCUMIN AND CINNAMALDEHYDE HYBRIDS ON ORAL BACTERIA

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**ABSTRACT:**

The anatomical complexity of the root canal system and microbial resistance to chemical-mechanical treatment can lead to persistent or secondary infections in permanent teeth. Many studies have explored the use of phytochemicals seeking for new compounds that exhibit multiples therapeutic properties. Curcumin, a yellow pigment isolated from *Curcuma longa* rhizomes, and cinnamaldehyde, the volatile substance isolated from *Cinnamomum* are broad-spectrum antimicrobial agents, however, they have some limitations, such as color and odor. Molecular hybridization is a strategy that includes the union of structural characteristics of bioactive substances in a single structure, aiming at overcomes the limitations of its prototypes. The objective of the study was to evaluate the cytotoxic effect and antimicrobial /antibiofilm action of curcumin and cinnamaldehyde hybrids on oral bacteria of endodontic interest. Tests were carried out to determine the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of the compounds on *Enterococcus faecalis*, *Streptococcus mutans*, *Lactobacillus casei*, *Actinomyces israelii* and *Fusobacterium nucleatum*. The best antimicrobial compound was evaluated in single and dual-species biofilms in microplate assays by counting of the Colony Forming Units (CFU)/mL. Toxicity was assessed on fibroblasts by the methyltetrazolium assays. In addition, mixed biofilms with the same bacterial species previously selected and multispecies biofilms obtained by human supra and subgingival plaque samples were formed in bovine root dentin and the compounds evaluated by confocal microscopy. Data were statistically evaluated by ANOVA/Tukey ( $p < 0.05$ ). Of the 25 compounds tested, 9 of them had inhibitory effect for at least one of the bacterial species tested with MIC/MBC values ranging from 0.009 to 0.625 mg/mL. The LA11 compound and the chlorhexidine control (CHX) had the best inhibitory effect for all bacterial species tested and were therefore selected for subsequent assays. LA11 showed higher fibroblast compatibility than CHX and had a superior or similar antimicrobial effect compared to CHX, statistically reducing metabolism and bacterial viability in single and dual-species biofilms. For biofilms formed in root dentin, LA11 had a significant effect on mixed biofilms with a reduction of 85.93%, whereas in the multispecies biofilms, the microbial reduction was 33.76%. It is concluded that the hybrid compound LA11 presented cytocompatibility and antimicrobial/antibiofilm effect against oral bacteria related to endodontic treatment.

**Keywords:** Curcumin, Cinnamaldehyde, Antimicrobial activity, Biofilm, Cytotoxicity

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