POTENT ANTIFUNGAL ACTIVITY AND TOXICITY PROFILE OF N-BENZYL- SUBSTITUTED IMIDAZOLIUM SALTS AGAINST CANDIDA SPP. ASSOCIATED WITH ORAL SQUAMOUS CELL CARCINOMA

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INTRODUCTION: Oral candidiasis is a frequent opportunistic infection in patients with oral squamous cell carcinoma (OSCC), driven by local immunosuppression, microbiota dysbiosis, tissue necrosis, and impaired oral hygiene. Beyond secondary colonization, Candida spp. may contribute to tumor progression through inflammation, carcinogenic metabolite production, and immune modulation. However, the clinical effectiveness of conventional azole antifungals has been increasingly compromised by resistance. In this context, N-benzyl- substituted imidazolium salts have emerged as promising antifungal scaffolds. OBJECTIVE: To investigate the antifungal activity and toxicity of *N*-benzyl- substituted imidazolium salts against clinically relevant Candida spp. strains associated with the oral oncologic microenvironment. METHODS: Five *C. albicans* strains and two *Candida tropicalis* strains from the mycology collection were evaluated. Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC) assays were performed according to CLSI protocols, with adaptations. *N*-benzyl-substituted imidazolium salts (C_{16}BnImCl and C_{18}BnImCl) were tested at concentrations ranging from 0.0019 to 1.0 µg/mL, using miconazole, ketoconazole, fluconazole, and amphotericin B as reference drugs. Results were assessed after 24 and 48 hours of incubation at 37 °C. Developmental toxicity was evaluated using the zebrafish embryo toxicity assay (Danio rerio). Embryos were exposed to increasing concentrations of the compounds for 96 hours, and lethality (LC50/EC50) and morphological alterations were assessed. RESULTS: C_{16}BnImCl displayed MIC and MFC values against *Candida albicans* ranging from 0.0019 to 0.125 µg/mL, whereas C_{18}BnImCl showed values between 0.0039 and 0.0625 µg/mL. Against *Candida tropicalis*, C_{16}BnImCl exhibited MIC and MFC values from 0.0625 to 0.125 µg/mL, while C_{18}BnImCl showed values of 0.0312 µg/mL. In contrast, miconazole, ketoconazole, fluconazole, and amphotericin B exhibited MIC and MFC values of 2.0 µg/mL and 1.0 µg/mL, respectively, for both species. Overall, the imidazolium salts demonstrated markedly superior antifungal potency compared with all commercial reference compounds tested. In the zebrafish embryo model, C_{16}BnImCl exhibited concentration-dependent developmental toxicity, with an EC50 of 1.37 µg/mL. Developmental abnormalities were observed at concentrations between 0.37 and 6.25 µg/mL, including caudal deformities, pericardial edema, and delayed larval development. Mortality occurred at concentrations above 6.25 µg/mL. CONCLUSION: *N*-benzyl-substituted imidazolium salts exhibited potent fungicidal activity at substantially lower concentrations than conventional antifungal agents against *C. albicans* and *C. tropicalis*

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