TITLE: KETOCONAZOLE/ CALIX[*N*]ARENES-BASED COMPOUNDS AS ALTERNATIVE ANTIFUNGAL AGAINST *CANDIDA* SPP.

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ABSTRACT:

Ketoconazole (KTZ) has been described as an antifungal agent; however, its bioavailability and therapeutic efficacy are reduced by the low aqueous solubility of the drug. Calix[*n*]arenes are macrocyclic compounds that have desirable structural characteristics to develop new drug alternatives. In order to overcome KTZ reduced water solubility, we used calix[*n*]arenes different as a carrier system. We evaluated some water-soluble KTZ/calix[*n*]arenes-based compounds against *Candida albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. auris* and *C. tropicalis in vitro*, as well as the antifungal activity and safety of these in an *in vivo* larval model of *Galleria mellonella*. The eight calix[*n*]arene-KTZ compounds were evaluated and all showed *in vitro* antifungal activity superior or similar to free KTZ for all *Candida* species tested. The physical mixture and freeze-drying with KTZ and CX6Na (CX6Na/KTZ) was the most active compounds, decreasing KTZ concentrations required for activity against azole-resistant isolates (e.g., *C. auris, C. krusei*). Moreover, CX6Na/KTZ showed no toxic effect on *Galleria mellonella* larvae at 100 mg/Kg. Thereby, *G. mellonella* larvae were infected with *C. albicans* SC 5314 or *C. auris* CBS 12766 and treated with KTZ at 20 mg/Kg or CX6Na/KTZ at 10 mg/Kg or 20 mg/Kg. The treatment of infected larvae was effective at lower or similar dose compared with free KTZ, reducing fungal burden in the tissues and prolonging the larval survival. The use of calix[*n*]arenes is little explored in the development of pharmaceutical formulations with antifungal drugs; here we bring a new possibility in the search for alternatives to treat fungal diseases and understand how this complex improves antifungal efficacy in resistant strains can be an important key to this issue.

Keywords: Drug carrier, imidazole, *Galleria mellonella*, calixarenes.

Development Agency: Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP, grant 2017/19374-9; 2018/12149-2 and 2018/03708-8), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, grant 405556/2018-7) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (CAPES, Finance Code 001).