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Peptides Derived from Palindromic Sequence RWQWRWQWR Exert an Additive Effect with Fluconazole in a Drug-Resistant *C. albicans* Strain.

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Abstract: Antimicrobial resistance is a public health problem, requiring the development of new therapeutic agents. Antimicrobial peptides derived from Bovine Lactoferricin (LfcinB) have exhibited antibacterial and antifungal effects. Lipopeptides and peptides containing non-natural amino acids, derived from LfcinB (21-25) Pal: RWQWRWQWR, were synthesized by SPPS-Fmoc/tBu and characterized by RP-HPLC and MALDI-TOF mass spectrometry. The antimicrobial activity was tested against reference strains *E. coli* ATCC 11775 and 25922, *S. aureus* ATCC 25923, *C. albicans* SC 5314, *C. auris* 435 and 537, as well as against the clinical isolate of *C. albicans* 256 which is resistant to fluconazole. The peptides containing non-natural amino acids exhibited lower minimum inhibitory concentrations (MIC), and minimum fungicidal concentration (MFC) / minimum bactericidal concentration (MBC) values for most of the strains except *C. auris*. The lipopeptides did not show activity at the concentrations evaluated, however, molecules containing amino-isobutyric or lauric acid combined with fluconazole showed an additivity effect against the clinical isolate *C. albicans* (256), finding decreases of two to eight times in the MIC values compared with the MIC of the fluconazole only. The results suggest that these molecules could be candidates to develop combined therapies against strains resistant to fluconazole. All the molecules are synthetically viable and the functionalization with non-natural amino acids is a positive modification to enhance the antimicrobial activity.