**Antimicrobial Peptides: A New Frontier in Antifungal Treatments**

**Objectives:** Expanding the antifungal drug arsenal for treating *Candida* infections is crucial in this era of the rising life expectancy of patients with immunosuppression and comorbidities. Infections caused by *Candida* species are on the rise, including those caused by multidrug-resistant strains or species, and the list of antifungals approved for treating these infections is still limited. Antimicrobial peptides (AMPs), expressed in several organisms and used as first-line defences against microbial infections, have emerged as potential candidates for developing new antifungal therapies, characterized by negligible host toxicity and low resistance rates. Most of the current literature focuses on peptides with antibacterial activity, but there is less information on their antifungal properties. This study explores the antifungal spectrum of two antimicrobial peptides - *Oreoch-1*, isolated from the gills of Nile tilapia (*Oreochromis niloticus*), and *Ranalexin-1G* isolated from the skin of the bullfrog (*Rana catesbeiana*).

**Materials and Methods:** Firstly, we checked in vitro cytotoxicity of the two AMPs through the MTT assay against human and animal cell lines. Secondly, their antifungal spectrum was explored via the broth-microdilution method and time-killing curve analysis. Additionally, the antibiofilm mechanism of action of peptides was also investigated, suggesting that they had a crucial role during the biofilm formation step by inhibiting it.

**Results:** At non-toxic concentrations (25-12.5 μM), the AMPs exerted interesting anti-Candida activity: *Oreoch-1*, showed its minimum inhibitory concentration that inhibits the growth of 90% of tested strains (MIC90) at 25 µM, impairing the growth of both *fluconazole*-resistant (*Candida albicans* ATCC 10231) and sensitive (*Candida albicans* ATCC 90028) strains. Surprisingly, it recorded a MIC90 at 12.5 µM against the clinical isolate. Parallel screening of *Ranalexin-1G* against a *fluconazole*-resistant and sensitive ATCC strain revealed its MIC90 at 12.5 µM against both strains. Furthermore, both peptides showed significant reduction in biofilm formation at MIC concentrations against *fluconazole*-resistant ATCC strain. Time-kill kinetic assay of *Oreoch-1* and *Ranalexin-1G* demonstrated potent, concentration-dependent fungicidal activity against *fluconazole*-resistant ATCC strain at 24h. In contrast, they exploited a fungistatic activity against the *fluconazole*-sensitive ATCC strain. This suggests strain-specific differences in susceptibility, with the *fluconazole*-sensitive ATCC strain potentially requiring higher concentrations for a complete fungicidal effect.

**Conclusions**: These results highlight *Oreoch-1* and *Ranalexin-1G* as promising candidates for combating *C. albicans* infections.