Biofilm Composition in Fungi Fusarium and Development of a Multi-targeted Antifungal Treatment To Inhibit Proliferation

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Fusarium is a genus of fungi that produces biofilms, a collection of microbial cells that confer high antifungal resistance to opportunistic Fusarium pathogens, which cause lethal infections in crop and human populations with a 75% clinical mortality rate. This study first uncovered three critical mechanisms of biofilm formation in four clinically-relevant Fusarium species. Biofilm matrix morphology was visualized through electron microscopy. Abiotic growth conditions and Skn7-deletion mutant analysis reported internal oxidative stress resistance mechanisms. Fluorescence spectroscopy confirmed a biofilm polymeric matrix that consists of polysaccharides, proteins, and extracellular nucleic acids. With these identified targets, computational SB and LBDD analysis optimized a combination antifungal treatment consisting of three compounds to target aforementioned biofilm components: inhibiting cytochrome CYP51 - thus degrading membrane morphology - with Voriconazole, promoting internal resistance disruption using Amphotericin B, and obstructing DNA and protein macromolecular synthesis with 5-Fluorocytosine through TS inhibition. Docking analysis supported binding affinities to targeted pathways and confirmed bioavailability and safety. In-vitro cultures consisting of two-fold antifungal dilutions (128 to 0.125 mg/L) revealed that, across strains, Voriconazole was the most effective antifungal with 60% inhibition efficiency. Amphotericin B displayed 55% efficiency and 5-Fluorocytosine had 40% efficiency. The triple-combination drug treatment exhibited over 90% inhibition efficacy at respective concentrations. This research provides novel insight into the maturation of fungal biofilms and supports the use of a cocktail treatment to combat infections, reducing mortality.