Cyantific Sight: A Novel, Synergistic Approach to Combating Antifungal Resistance Using Naturally Derived Compounds Phycocyanobilin and Curcumin

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Drug-resistant Candida albicans infections are rapidly outpacing current antifungal therapies as mutations in the ERG11 enzyme reduce azole drug efficacy and drive treatment failure. Most antifungals target a single pathway, enabling rapid resistance through mutations. My research investigates a mutation-adaptive and resilient antifungal formulated from naturally derived compounds to lyse C. albicans through simultaneous multi-target disruption. Curcumin (CUR) and Phycocyanobilin (PCB) were selected for their antifungal properties and combined with Beta-cyclodextrin (BCD) to improve solubility and delivery. Using an integrated computational approach, molecular docking and dynamics simulations demonstrated stable, non-competitive binding of CUR and PCB across multiple fungal targets involved in sterol biosynthesis and stress response pathways. PCB showed higher affinity for mutant ERG11 (?G = -9.2 kcal/mol) than Fluconazole (?G = -7.0 kcal/mol), suggesting a resistance-bypassing mechanism. Beyond ERG11 inhibition, PCB targets other survival pathways and proteins involved in vacuolar regulation and apoptotic signaling (VMA1, MCA1, PEP4) enabling multi-protein lysis that disrupts intracellular homeostasis and promotes cell death. QSAR modeling predicted a 206x solubility increase with BCD and identified an optimal therapeutic window of 28–65 µM. Pharmacokinetic modeling revealed a 2.5x synergistic interaction between CUR and PCB. An experimental fluorescence assay showed reduced efflux pump activity and improved intracellular retention, while a disk diffusion assay confirmed significantly larger inhibition zones for the combination. Together, these findings demonstrate a multi-target, mutation-resilient strategy against resistance, providing a foundation for the future.

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