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Network pharmacology, molecular docking-driven, Qbd-Engineered antifungal *in-situ* gel loaded with voriconazole nanostructured lipid carriers

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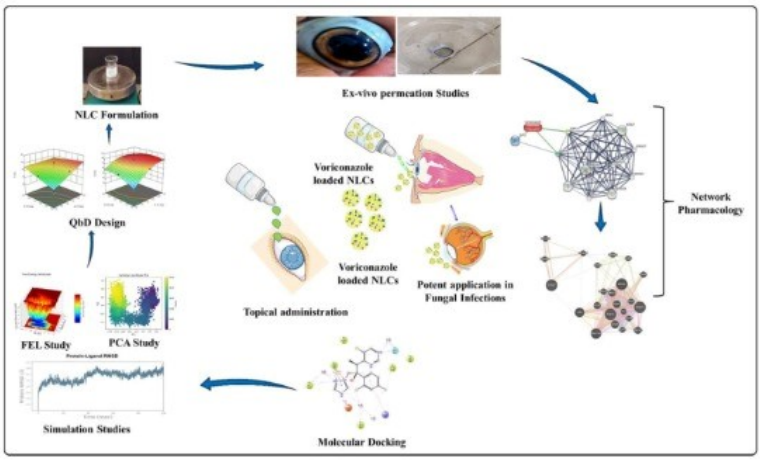
ABSTRACT

Fungal infections (FIs) affect majority of the population, but the current treatments face challenges in terms of their effectiveness. This study focused on specific fungal targets, including dihydrofolate reductase (DHFR), acetohydroxy-acid synthase (AHAS), farnesyltransferase and endoglucanase. The docking studies were conducted with the drug voriconazole (VCZ), comparing it with Fluconazole (FCZ) and Amphotericin B (ATB) against 11 protein data bank (PDB) IDs (IDYR, 3NZB, 6DEQ, 1KS5, 7T0C, 1FY4, 5AJH, 7R79, 6TZ6 and 6IDY). Molecular dynamics (MD) analysis, including RMSD, RMSF, PCA and FEL, confirmed the stability of VCZ. The solubility of VCZ was a problem, so nanostructured lipid carriers (NLCs) were developed to improve ocular penetration. VCF5 was the optimized formulation by using 3^2 full factorial design. VCZF5-NLCs were the best in terms of nanoparticle size (126.6 nm), Zeta potential (33.5 mV), drug content (DC; 97.38 ± 0.210), encapsulation efficiency (EE; 88.01 ± 0.272) and extended drug release. The results of the *ex-vivo* corneal diffusion study indicate that VCZ-NLC-loaded *in-situ* gel (VCZ-NLC-IG3) exhibited DC of 88.25% and drug entrapment (DE) of 74.2%. The results of the zone of inhibition indicated that VCZ-NLC-IG3 had superior efficacy compared to ATB. Network pharmacology showed VCZ interacts with the genes which are responsible for fungus ergosterol biosynthesis, including lanosterol 14-alpha demethylase inhibitors (ERG11), ergosterol biosynthesis protein 5 (ERG5), dimethylallyltransferase 2 (DIT2), ketosynthase (KCN), methylsterol monooxygenase (MSMO1), lamin B receptor (LBR), squalene epoxidase (SQLE), 3-hydroxy-3-methylglutaryl-coenzyme A Reductase (MGCR), 3-hydroxy-3-methylglutaryl-coenzyme A Synthase (HMGCS) and 3-keto-steroid reductase (HSD17B7). In conclusion, the optimized VCZ-loaded NLCs present a promising approach to treat ocular FIs.



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1. Introduction

Fungal infections (FI) are a serious concern among the population due to rising incidence as well as resistance to present drugs available. FI affects more than a billion people throughout the world among them 150 million severe conditions result in 1.7 million deaths yearly (Kainz et al., 2020). This condition may be more severe in Immunocompromised patients or in pandemic conditions that have been observed in the COVID-19 pandemic in the form of black fungus or other FIs in post-Covid patients (Choudhary et al., 2021; Kainz et al., 2020).

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