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Breaking fungal biofilms and multidrug resistance using intelligent ciclopirox-based nanotechnology: Design and experimental validation

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Fungal diseases and especially those linked to biofilms and multidrug resistance (MDR) are a growing health issue around the world, thus leading to the need to develop advanced methods of therapy. The standard antifungal treatment often does not have sufficient efficacy against such multifactorial problems. This study was intended to develop and test an intelligent ciclopirox-based nanoplatform (CPX-NP) that would bypass mechanisms of MDR and interfere with fungal biofilms. CPX-NPs were produced by nanoprecipitation, and nanospheres with the best physicochemical properties (diameter less than 150 nm, low polydispersity, negative zeta potential) were obtained. Their action against MDR fungal isolates was investigated *in vitro*, including the establishment of the minimum inhibitory concentration (MIC), efflux pump inhibition, cytotoxicity tests, and biofilm penetration tests. CPX-NPs could selectively release ciclopirox in the acidic biofilm microenvironment leading to a decrease in MIC to a maximum of eight-fold compared to free ciclopirox. The nanoplatform also exhibited superior biofilm penetration, strong efflux pumping and high therapeutic selectivity index (SI = 100) which are reflective of insignificant cytotoxicity of the human cell. The intelligent CPX-NP platform represents a viable and effective approach to the fight against the MDR fungi infection and biofilm eradication, which will subsequently result in the development of safer and more effective antifungal therapies.

Keywords: Ciclopirox; CPX-NP; extracellular polymeric substance; *Candida albicans*.

Introduction

A systemic destabilisation has taken place in the global health system, characterized by a deliberate yet chronic increase of invasive fungal infections (IFIs). The multidrug-resistant (MDR) fungi have surpassed the importance of bacterial resistance in history and have now reached a critical level that will require world action. WHO published its first Fungal Priority Pathogens List (FPPL) in late 2022 and this was a historic document since it listed fungal threats by their public -health impact and clinical unmet needs (WHO, 2022). Among other prominent examples of the Critical Priority category, were *Candida albicans* and the recently emerged *Candida auris* due to their significant morbidity rates, which can reach above 60% among immunocompromised groups, and to their growing resistance to the few existing antifungal classes, such as the azoles, echinocandins, and polyenes (Bongomin et al., 2017).

The pathogenic burden of these organisms is not only due to their inherent virulence of the pathogen itself but is innate to its ability to assemble complex and organized communities of microorganisms termed biofilms. These biofilms are entrenched in a self-assembled extracellular polymeric substratum (EPS) matrix that forms a strong physical impediment. The EPS matrix restricts the permeability of traditional antifungal agents, entraps the drug molecules, and cells located within it are the so-called persisters that remain metabolically inactive, so they can survive high doses of treatment drugs (Brown et al., 2012). As a result, the biofilm-related infections are infamously hard to eliminate resulting in chronic persistence, device-related issues, and frequent clinical relapses that may bear an immeasurable cost to the healthcare systems across the globe (Ramage et al., 2025).

The problem of antifungal resistance has taken on a local acuity in the Middle East and in Iraq in particular. The occurrence of a remarkably high change in the prevalence of non-albicans *Candida* species and a growing tendency to find MDR phenotypes in clinical isolates have been reported in recent epidemiological surveys in such major urban centres as Baghdad and Basrah (Ghaima et al., 2020; Al-Aameri et al., 2024; Khalaf et al., 2025). Research carried out between 2023 and 2025 in tertiary care hospitals in southern Iraq documents that almost 45% of all isolates of *Candida* in intensive-care units are less susceptible to fluconazole with the general tendency credited to widespread and unregulated consumption of broad-spectrum antibiotics and an increasing proportion of patients possessing underlying comorbidity conditions including diabetes mellitus and oncology (Mohammad et al., 2024).

In addition, environmental and clinical factors in Iraq explained by the high turnover of hospitals, and the lack of diagnostic facilities to identify fungi quickly, have aided the survival of MDR strains (Mohammad et al., 2024). Ample evidence in the literature shows that the need to find new therapeutic approaches that would go beyond conventional drug methods has become a reality in the region. Combining microbiology and modern materials science can no longer be considered a luxury but an essential requirement in solving the particular resistance patterns presented in the Iraqi clinical environment with traditional treatments becoming unsuccessful at an unprecedented pace (Al-Nasrawi et al., 2026).

The existing clinical treatment of MDR fungi infections depends on the use of only a few antifungal agents. Ciclopirox olamine is a synthetic antifungal class (hydroxypyridone) that exhibits a distinct with a multi-targeted mode of action. As opposed to azoles which impair the production of ergosterol or echinocandins, which destroy fungal cell wall, Ciclopirox operates by interfering with metal-dependent enzymatic activities, mitochondrial activity, and energy generation of cells mainly by chelating essential polyvalent cations (Fe^{3+} and Al^{3+}) (Mucha et al., 2024). This extensive activity curbs the chances of the development of traditional resistance measures.

However, this is hindered by the poor aqueous solubility of ciclopirox, its lack of success in penetrating dense biofilm matrix, and its rapid systemic clearance, which significantly impairs its clinical utility. Once the drug is used in a free state, the molecule does not reach therapeutic levels in the deepest layers of the biofilm, and within it, the most resistant cells of the fungus can be found (Denning, 2024). Besides, its efficacy is achieved with high doses that may induce off-target toxicity and local irritation, thus limiting its use in systemic or deep-seated infections. In this regard, a delivery vehicle that can keep the drug molecule safe, increase its penetration, and its release to the