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Article

Unlocking New Strategies: Reversing Fluconazole Resistance in *Candida Species* with Efflux Pump Inhibitors Like Aspirin and Ibuprofen

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Abstract

Background: Inadvertent use of broad-spectrum antibiotics and rise in immunocompromised patients are contributing to increased prevalence of fungal infections. While *Candida albicans* is the most prevalent yeast infection, Non-albicans *Candida* (NAC) are emerging opportunistic pathogens that are more resistant to antifungal agents [1,2]. Thus, we tried to determine candidemia profile and ascertain if efflux pump inhibitors Aspirin and Ibuprofen could elicit reversal of Fluconazole resistance. **Methods:** *Candida* speciation was performed manually and using the VITEK 2 system [3]. Antifungal susceptibility was determined by the broth microdilution method [4,5]. The effect of aspirin and ibuprofen on fluconazole-resistant isolates was also assessed using the broth microdilution method. **Results:** Of 126 *Candida* sp., 15(11.90%) were *Candida albicans* and 111(88.10%) were NAC. *Candida* sp. showed maximum susceptibility to Flucytosine(111/88.10%). 32 isolates were Fluconazole resistant(14 inherently resistant). 16 of 18 remaining isolates that were not inherently but resistant to Fluconazole, concurrent administration of Aspirin or Ibuprofen with Fluconazole caused reversal of resistance, with significant drop in minimum inhibitory concentration($\leq 0.125\mu\text{g}/\text{ml}$), indicating 88.89% conversion rate [6]. **Conclusion:** Emergence of drug-resistant NAC as opportunistic pathogen necessitates species-level identification of isolates to initiate appropriate antifungal as empirical treatment [7]. Common mechanism for azole resistance is reduction of intracellular antifungal concentration by overexpression of efflux pump encoded by CDR1, CDR2, and MDR1 genes [8]. Our study shows concomitant use of efflux pump inhibitors Aspirin and Ibuprofen as suitable therapeutic alternative that may be effective for most *Candida* species that are Fluconazole resistant [9,10].

Keywords: antifungal susceptibility testing; fluconazole resistance; candida efflux pumps; ATP-binding cassette (ABC) transporters; CDR1 and CDR2 overexpression; efflux pump inhibitors (EPIs); aspirin and ibuprofen synergy; reversal of azole resistance

1. Introduction

1.1. Background

Fluconazole, a widely used antifungal agent, has long been a cornerstone in the treatment of *Candida* infections [11]. However, the emergence of Fluconazole-resistant strains poses a significant challenge in clinical management, necessitating innovative approaches to combat antifungal resistance [12]. Fluconazole resistance calls for the need of use of alternative antifungal drugs like Voriconazole, Posaconazole, Ravaconazole, Amphotericin B, and Echinocandins [13]. However, usage of these agents are limited due to high cost or adverse effects associated with these agents [14]. Recent research has shown promising results in reversing Fluconazole resistance by combining this antifungal agent with efflux pump inhibitors (EPIs) such as Aspirin or Ibuprofen [15,16]. This article

explores the role of efflux pumps in mediating Fluconazole resistance, and the potential of EPIs to enhance the efficacy of Fluconazole in combating resistant *Candida* isolates.

1.2. Understanding Fluconazole Resistance and Synergistic Effects of Fluconazole and EPIs

Fluconazole belongs to the azole class of antifungal drugs and acts by inhibiting the synthesis of ergosterol, an essential component of the fungal cell membrane[17]. Resistance to Fluconazole can arise through various mechanisms, including alterations in the target enzyme (lanosterol 14-alpha-demethylase), upregulation of drug efflux pumps, and changes in the fungal cell membrane composition[18]. Among these, overexpression of efflux pumps, particularly ATP-binding cassette (ABC) transporters such as CDR1p and CDR2p in *Candida* species, is a major mechanism of Fluconazole resistance[19].

Efflux pumps play a crucial role in multidrug resistance by actively pumping antifungal agents out of the fungal cell, thereby reducing intracellular drug concentrations. Efflux pump inhibitors (EPIs) are compounds that inhibit the activity of these pumps, restoring intracellular drug levels and enhancing the susceptibility of resistant strains to antifungal agents. While EPIs have been extensively studied in the context of antibacterial resistance, their potential to reverse antifungal resistance is a burgeoning area of research.

Recent studies have demonstrated the synergistic effects of combining Fluconazole with EPIs such as Aspirin or Ibuprofen in reversing Fluconazole resistance in *Candida* species[20,21]. By inhibiting efflux pump activity, EPIs potentiate the antifungal activity of Fluconazole, leading to increased intracellular drug concentrations and improved efficacy against resistant strains[22]. Moreover, the use of EPIs may help overcome cross-resistance to other azole antifungals, thereby expanding the therapeutic options for managing resistant *Candida* infections.

In this study, we aimed to determine whether efflux pump inhibitors such as Aspirin and Ibuprofen could reverse Fluconazole resistance by blocking the efflux of the drug and thereby increasing its intracellular accumulation. This may help in instituting new policies to curb the menace of drug resistance thereby offering novel breakthrough.

2. Materials and Methods

This was an interventional study conducted at a tertiary care hospital in eastern India, involving any culture plate showing pure growth of *Candida* sp. as the study participants. The study duration spanned from October 2021 to June 2023, with blood samples collected and laboratory workup performed from October 2021 to January 2023, followed by data analysis from January 2023 to June 2023. The sampling population comprised Fluconazole-resistant *Candida* species, and the total sample size was 18 *Candida* sp. resistant to Fluconazole, calculated using the Formula for Comparing Paired Proportions. The sampling technique employed was consecutive sampling.

Antifungal Susceptibility Testing of Yeasts by Broth Microdilution was performed for Fluconazole following the M27/A4 protocol of CLSI[23]. The broth microdilution test was performed using sterile, disposable, multiwell microdilution plates (96 U-shaped wells). Antifungal stock solutions were prepared at concentrations of at least 100 times the highest concentration to be tested using Dimethyl sulfoxides (DMSO) as the solvent. The inoculum was prepared by picking five colonies of 1 mm in diameter from a 24-hour-old culture of *Candida* species and suspending them in 5 mL of sterile saline. The resulting suspension was vortexed for 15 seconds, and the turbidity was matched to a 0.5 McFarland standard. This procedure yielded a yeast stock suspension of 1×10^6 to 5×10^6 cells per mL. A working suspension was made by a 1:50 dilution followed by a 1:20 dilution of the stock suspension with RPMI 1640 broth medium, resulting in 5.0×10^2 to 2.5×10^3 cells per mL. The 2x drug concentrations were dispensed into the wells of rows 1 to 10 of the microdilution plates in 100 μ L volumes, with row 1 containing the highest drug concentration and row 10 the lowest drug concentration. Each well of a microdilution tray was inoculated with 100 μ L of the 2x diluted inoculum suspension. The microdilution plates were incubated at 35°C for 24 to 48 hours and observed for the presence or absence of visible growth.

To evaluate the effect of Aspirin or Ibuprofen, 2x drug concentrations of Fluconazole were dispensed into the wells of rows 1 to 10 of the microdilution plates in 100 μ L volumes. Each well of a microdilution tray was inoculated with 100 μ L of the 2x diluted inoculum suspension. Aspirin or Ibuprofen drug solution was dispensed immediately after the addition of the fungal inoculum. The microdilution plates were incubated at 35°C for 24 to 48 hours and observed for the presence or absence of visible growth[24].

3. Results

A total of 126 *Candida* species were isolated from patients with candidemia, out of which 90 were susceptible, 4 susceptible dose dependent, and 32 isolates were resistant to Fluconazole. Figure 1 shows the susceptibility pattern of *Candida* isolates to Fluconazole. Of these 32 isolates, only 18 were included for testing the reversal of resistance when given in combination with Aspirin or Ibuprofen. These 18 isolates comprised 10 *Candida parapsilosis* with a minimum inhibitory concentration (MIC) $\geq 8\mu\text{g}/\text{ml}$, 3 *Candida pelliculosa* with MIC $\geq 4\mu\text{g}/\text{ml}$, 3 *Candida guilliermondii* with MIC $\geq 4\mu\text{g}/\text{ml}$, and 2 *Candida tropicalis* with MIC $\geq 8\mu\text{g}/\text{ml}$. The remaining 14 isolates, comprising 10 *Candida auris*, 3 *Candida glabrata*, and 1 *Candida krusei*, were intrinsically resistant to Fluconazole and were excluded from further resistance reversal testing in combination with Aspirin or Ibuprofen.

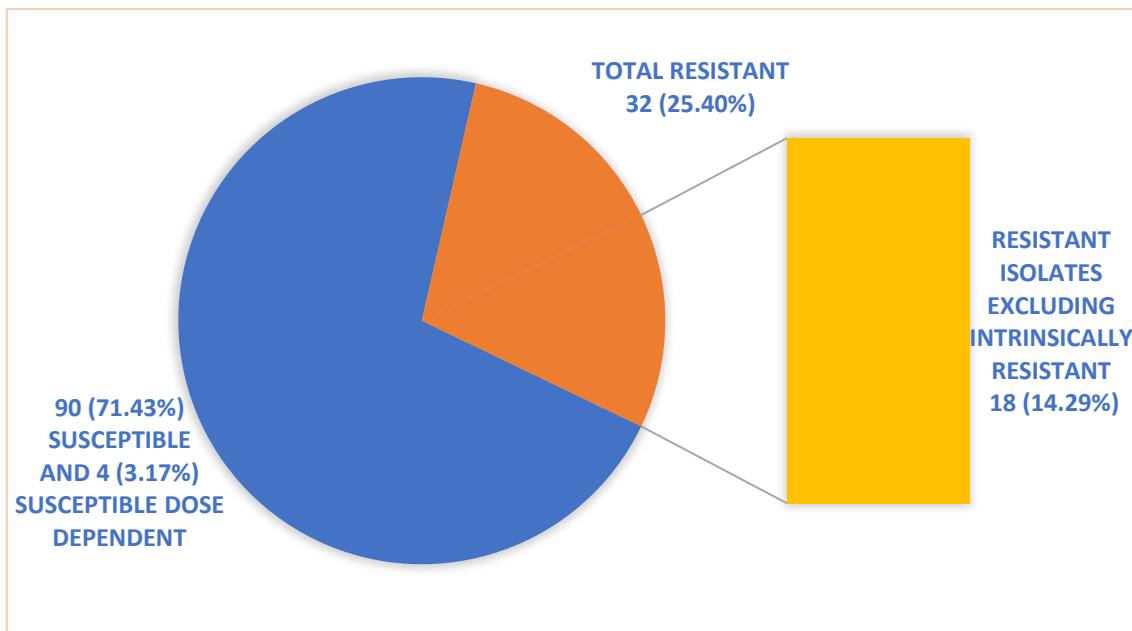


Figure 1. Fluconazole Susceptibility of *Candida* Isolates.

Of the 18 resistant isolates of *Candida* species other than the intrinsically resistant isolates, concurrent use of Aspirin or Ibuprofen with Fluconazole led to the reversal of Fluconazole resistance in 16 isolates (except 1 *Candida parapsilosis* and 1 *Candida pelliculosa*) with a considerable decrease in MIC ($\leq 0.125\mu\text{g}/\text{ml}$), suggesting an 88.89% conversion rate as shown in Table 1. Specifically, the concurrent use of Aspirin or Ibuprofen with Fluconazole led to the reversal of Fluconazole resistance in 9 out of 10 *Candida parapsilosis* (90%), 2 out of 3 *Candida pelliculosa* (66.67%), and all 3 *Candida guilliermondii* (100%) and 2 *Candida tropicalis* (100%) as shown in Table 2. Fluconazole MIC of isolates pre and post intervention with Aspirin or Ibuprofen are shown in Figures 2 and 3.

Table 1. Effect of Aspirin/Ibuprofen on Fluconazole Resistant Clinical Isolates of *Candida* species.

Effect of Aspirin/Ibuprofen	Susceptibility		
	Resistant	Susceptible	Total
Fluconazole without Aspirin/Ibuprofen	18	0	18
Fluconazole with Aspirin/Ibuprofen	2	16	18

Table 2. Species Wise Distribution of Clinical Isolates of *Candida* Demonstrating Reversal of Fluconazole Resistance with Aspirin or Ibuprofen.

Species	Resistant to Fluconazole	Reversal with Aspirin (%)	Reversal with Ibuprofen (%)
<i>Candida parapsilosis</i>	10	9 (90%)	9 (90%)
<i>Candida pelliculosa</i>	3	2 (66.67%)	2 (66.67%)
<i>Candida guilliermondii</i>	3	3 (100%)	3 (100%)
<i>Candida tropicalis</i>	2	2 (100%)	2 (100%)
TOTAL	18	16 (88.89%)	16 (88.89%)



1: *Candida parapsilosis*; 2: *Candida tropicalis*; 3: *Candida pelliculosa*; 4: *Candida guilliermondii*; 5: *Candida glabrata*; 6: *Candida krusei*; 7: *Candida auris*; 8: FLU C - Fluconazole drug control; ASP C: Aspirin drug control; INO C: Inoculum Control; RPMI C: RPMI Control; DMSO C: DMSO Control; FINAL C: Final drug concentration after adding inoculum.

LESS THAN 50% REDUCTION IN TURBIDITY WHEN COMPARED WITH INOCULUM CONTROL SEEN TILL FLUCONAZOLE DRUG CONCENTRATION OF 4 μ g/ml (MIC > 4 μ g/ml).

Figure 2. Fluconazole MIC by Broth Microdilution Method Pre-Intervention.



1: *Candida parapsilosis*; 2: *Candida tropicalis*; 3: *Candida pelliculosa*; 4: *Candida guilliermondii*; 5: *Candida glabrata*; 6: *Candida krusei*; 7: *Candida auris*; 8: FLU C - Fluconazole drug control; ASP C: Aspirin drug control; INO C: Inoculum Control; RPMI C: RPMI Control; DMSO C: DMSO Control; FINAL C: Final drug concentration after adding inoculum.

50% REDUCTION OF TURBIDITY WHEN COMPARED WITH INOCULUM CONTROL SEEN IN ROW 1 AT FLUCONAZOLE DRUG CONCENTRATION 0.125 μ g/ml (MIC= 0.125 μ g/ml); IN ROW 2 AT 0.0625 μ g/ml (MIC= 0.0625 μ g/ml); IN ROW 3 AND 4 AT 0.03125 μ g/ml (MIC= 0.03125 μ g/ml); AND NO REDUCTION IN ROW 5, 6 AND 7 (MIC > 4 μ g/ml) WHEN GIVEN WITH ASPIRIN.

Figure 3. Fluconazole MIC in Combination with Aspirin by Broth Microdilution Method.

4. Discussion

Within the limited antifungal arsenal, the azole antifungals are the most often used class of antifungals to treat *Candida* infections. Due to their low cost, low toxicity, and oral availability, Fluconazole and other azole antifungals are usually preferred over other therapies for diverse *Candida* infections. However, it has been demonstrated that a variety of *Candida species* possess both inherent

and acquired resistance to azole antifungals[25]. As per several studies lower rates of azole resistance (0–5%) are found in *Candida albicans* isolates from candidemic patients. *Candida glabrata* demonstrates intrinsically lower susceptibility to the azole class of antifungals and has the greatest incidence of azole resistance among clinical isolates of *Candida*. Fluconazole resistance in *Candida tropicalis* in the Asia-Pacific region ranges from 0% to 83%. The worldwide incidence of Fluconazole resistance in *Candida parapsilosis* disseminated infections ranges between 2 and 5% . Given that *Candida krusei* demonstrates intrinsic resistance to Fluconazole, it is debatable whether the higher infection rate is a result of prophylactic Fluconazole use or previous therapy

In this study out of 126 isolates of *Candida*, 32 (25.40%) isolates were resistant to Fluconazole of which 14 (11.11%) were inherently resistant. Only 63% of the *Candida parapsilosis* samples in this study were susceptible to Fluconazole, and the remaining 27% were resistant. Also, Fluconazole resistance was noticed in 25% of *Candida guilliermondii*, 16.67% of *Candida pelliculosa* and in 8% of *Candida tropicalis*. This Fluconazole resistance may be caused by a variety of mechanisms, including overexpression of the ERG11 gene, mutations in the genes encoding membrane transport proteins of the ABC transporter (like CDR-1/CDR-2) or the major facilitator superfamilies (like MDR1), changes in sterol biosynthesis, and mutations in the drug target enzyme and sterol 14 alpha-demethylase (14DM). CDR-1 and CDR-2 genes from the ATP-binding cassette superfamily and MDR-1 genes from the major facilitator superfamily are examples of efflux pumps encoded by two carrier gene families.

Since azoles like Fluconazole is one of the most frequently used antifungal medications for the treatment of candidiasis, resistance to the azole group of antifungal medications is a matter for concern. Since Fluconazole is the most popular azole used to treat widespread candidiasis, including candidemia, resistance to it is a serious problem. Despite being effective against most strains of *Candida sp.*, Amphotericin B is not the first-line treatment for candidemia because of its nephro-toxicity. In order to conserve and advance the azole class of antifungals for the treatment of *Candida* infections, it is crucial to explain the causes of such resistance as the frequency of azole resistant *Candida* isolates in the clinical context rises.

In order to deal with treatment failures, several methods have been put forth to make *Candida sp.* more susceptible to Fluconazole, one of which is the combination of Fluconazole with various classes of non-antifungal agents like anti-bacterials, calcineurin inhibitors, heat shock protein 90 inhibitors, calcium homeostasis regulators, and traditional Chinese medicine drugs. The primary mechanisms of these synergistic effects seem to be increasing membrane permeability, decreasing antifungal drug efflux, interfering with intracellular ion homeostasis, inhibiting the activity of proteins and enzymes necessary for fungal survival, and inhibiting the formation of biofilms.

The reversal of Fluconazole resistance with Aspirin and Ibuprofen, as found by us, hints at the likely participation of efflux pumps mediating azole resistance in majority of our isolates, in line with past research revealing Aspirin and Ibuprofen to be a potential efflux pump inhibitor[26]. Similar to our findings, a few other publications have also noted an in-vitro synergistic impact of Ibuprofen and Fluconazole in the pathogenic yeast *Candida*. It was shown that the CDR1, CDR2 and MDR1 efflux pump genes (the former two related to azole cross-resistance, and the third associated with selective resistance to Fluconazole) were overexpressed in resistant isolates that turned susceptible after being exposed to Ibuprofen. In contrast, strains that did not revert showed a substantial increase in the expression of CDR genes and the azole target gene, ERG11. The transmembrane proteins CDR1p and CDR2p are members of the ABC family, ATP-dependent; their substrates are diverse and include unrelated substances including steroids, lipids, and antifungal drugs like azoles, although its specific mode of action is still not well understood. MDR1p is a member of the Major Facilitator protein family, which derives its energy from the proton motive force. As previously mentioned, hypersusceptibility to azoles is conferred by a loss in any one of these genes. Point mutations in the ERG11 gene that change the protein's amino acid sequence reduce the azole's affinity for its molecular target are another resistance mechanism mentioned. One of the most prevalent lipids in fungal cell membranes, ergosterol, is produced by the cytochrome P450 enzyme lanosterol 14a-demethylase, which is encoded by the ERG11 gene. A rise in its expression may also lead to an excess of proteins

that could counteract the effects of the azole concentration and its consequences. Additionally, given the significance of prostaglandins in fungus colonisation, Ibuprofen's inhibitory action on prostaglandin formation may result in additional in-vivo therapeutic benefits[27].

Clinical isolates of *Candida* are becoming resistant to commonly used antifungal Fluconazole. A common mechanism for azole resistance is reduction of intracellular antifungal concentration by overexpression of efflux pump encoded by CDR1, CDR2 and MDR1 genes. In majority of our resistant isolates efflux pumps may contribute to azole resistance, hence we observed Aspirin and Ibuprofen two well-known efflux pump inhibitors can reverse Fluconazole resistance when used concomitantly.

Clinical Implications and Future Directions

The potential of EPIs to reverse Fluconazole resistance holds significant promise for clinical practice, offering a novel strategy to combat antifungal resistance in *Candida* infections. However, further research is needed to optimize EPIs' dosing regimens, evaluate their safety profiles, and elucidate their mechanisms of action in combination with Fluconazole. Additionally, clinical trials are warranted to assess the efficacy of Fluconazole-EPI combinations in treating Fluconazole-resistant *Candida* infections in human subjects.

5. Conclusions

The emergence of Fluconazole-resistant *Candida* strains poses a formidable challenge in clinical management, necessitating innovative approaches to combat antifungal resistance. Efflux pump inhibitors (EPIs), such as Aspirin or Ibuprofen, show promise in reversing Fluconazole resistance by inhibiting the activity of drug efflux pumps. Combining Fluconazole with EPIs represents a novel therapeutic strategy to enhance the efficacy of Fluconazole against resistant *Candida* isolates and warrants further investigation in clinical settings[28]. As our understanding of the interplay between antifungal resistance mechanisms grows, leveraging synergistic drug combinations may pave the way for more effective management of *Candida* infections in the future.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, **Table S1:** Effect of Aspirin/Ibuprofen on Fluconazole Resistant Clinical Isolates of *Candida* species. **Table S2:** Species Wise Distribution of Clinical Isolates of *Candida* Demonstrating Reversal of Fluconazole Resistance with Aspirin or Ibuprofen. **Figure S1:** Fluconazole Susceptibility of *Candida* Isolates. **Figure S2:** Fluconazole MIC by Broth Microdilution Method Pre-Intervention. **Figure S3:** Fluconazole MIC in Combination with Aspirin by Broth Microdilution Method.

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Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ABC	ATP-binding cassette
CDR	Candida drug resistance
CLSI	Clinical and Laboratory Standards Institute
DMSO	Dimethyl sulfoxide
EPI	Efflux pump inhibitor
MIC	Minimum inhibitory concentration
RPMI	Roswell Park Memorial Institute (culture medium)

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