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Overcoming Antifungal Resistance in Oral Candida albicans: Mechanistic Insights and Future Therapeutic Perspectives

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ABSTRACT

Oral candidiasis is a common opportunistic fungal infection most frequently associated with Candida albicans, particularly in immunocompromised individuals and patients with recurrent or persistent oral infection. Although antifungal agents such as polyenes, azoles, echinocandins, and flucytosine remain important in clinical management, their effectiveness may be limited by reduced susceptibility and the emergence of antifungal resistance. This narrative review discusses the mechanisms underlying antifungal resistance in oral *C. albicans* and explores potential mechanism-guided therapeutic strategies. Resistance in *C. albicans* involves multiple interconnected mechanisms, including antifungal target alteration, efflux pump overexpression, ergosterol pathway modification, membrane remodelling, cell wall adaptation, impaired drug metabolism, and adaptive stress-response pathways. In the oral microenvironment, biofilm-associated tolerance further contributes to treatment difficulty by limiting antifungal penetration, protecting fungal cells, and supporting persistent or recurrent infection. Therefore, future strategies should not rely solely on conventional antifungal use but should also consider antifungal susceptibility testing, optimisation of existing therapy, combination therapy, anti-biofilm approaches, alternative antifungal agents, and improved local drug delivery systems. A better understanding of resistance mechanisms and biofilm-associated tolerance may support the development of more targeted and effective therapeutic strategies for oral candidiasis.

Keywords: antifungal agents; antifungal drug resistance; biofilms; candida albicans; oral candidiasis

INTRODUCTION

Oral candidiasis is an opportunistic infection most often caused by Candida albicans and remains one of the most common fungal infections found in the oral cavity, particularly among immunocompromised individuals [1,2]. Under normal conditions, *C. albicans* exists as a commensal microorganism within the oral microbiota [3]. However, disruption of the microbial balance or impairment of host immunity can promote its transition from a commensal organism to an opportunistic pathogen. Oral candidiasis may present in several clinical forms, including pseudomembranous candidiasis, erythematous candidiasis, angular cheilitis, and chronic hyperplastic candidiasis [4].

Oral candidiasis is frequently observed in high-risk populations, particularly individuals with HIV/AIDS, malignancy, and other immunocompromised conditions. However, the clinical concern of oral *C. albicans* infection is not limited to its occurrence in susceptible groups, but also includes its tendency to persist, recur, and become difficult to manage [5]. Reports of decreased susceptibility to commonly used antifungal agents further support this concern. A meta-analysis of HIV patients with oral candidiasis reported azole resistance among Candida spp., with resistance rates ranging from 0.0% to 47.8% for ketoconazole and 4.6% to 56.7% for fluconazole [6]. These findings suggest that antifungal resistance may contribute to treatment failure and recurrent infection, showing the importance of understanding resistance mechanisms in oral *C. albicans.*

The management of oral candidiasis generally relies on antifungal agents from several drug classes, including polyenes, azoles, echinocandins, and flucytosine, although polyenes and azoles remain the most frequently used agents in clinical practice [7]. Despite the importance of these agents in clinical therapy, the emergence of antifungal resistance has created a need for improved control measures and more effective treatment strategies

[8]. In addition, *C. albicans* has been included in the World Health Organization "Fungal Priority Pathogens List", further stressing its clinical relevance and the need for continued treatment development [9].

The development of antifungal resistance in *C. albicans* involves complex mechanisms. These include mutations in antifungal target genes, increased efflux pump activity, alterations in ergosterol biosynthesis, cell wall adaptation, and biofilm-associated tolerance, all of which may reduce susceptibility to available antifungal agents [8]. The complexity of these mechanisms indicates that antifungal resistance not only presents a challenge in clinical practice but also complicates the development of effective alternative therapies. Therefore, a better understanding of antifungal resistance mechanisms in *C. albicans* is essential to optimizing the use of existing antifungal agents and to guide the development of future treatment strategies for oral candidiasis. Thus, this narrative review aims to provide an overview of antifungal resistance in oral C. albicans. It discusses current antifungal drug classes and their mechanisms of action; mechanisms causing antifungal resistance in C. albicans; biofilm-associated tolerance in the oral microenvironment; and mechanism-guided treatment strategies to overcome antifungal resistance.

CURRENT ANTIFUNGAL THERAPIES AND THEIR LIMITATIONS IN ORAL CANDIDIASIS

The management of oral candidiasis involves topical and systemic antifungal agents. The type of agent used is selected according to the severity of infection, host condition, and response to previous therapy. In non-invasive oral candidiasis, topical therapy remains the primary treatment choice due to its local effectiveness, lower cost, and minimal systemic side effects. Commonly used topical antifungal agents are nystatin, miconazole, amphotericin B, and clotrimazole [10]. Nystatin, a membrane-active polyene macrolide, is one of the most frequently prescribed topical antifungal drugs in dental practice and is available in several formulations, including cream, oral pastille, and oral suspension [7]. Systemic antifungal therapy is generally considered for patients who do not respond to topical treatment, have extensive or recurrent infection, or are at higher risk of systemic involvement [11]. Fluconazole, itraconazole, ketoconazole, and other triazoles have been used for oropharyngeal and esophageal candidiasis, particularly in patients with HIV or other immunocompromised conditions [12]. Fluconazole remains widely used because of its favourable safety profile, good efficacy, rapid absorption, high bioavailability, and independence from gastric pH. In cases that are not responsive to fluconazole, alternative systemic agents such as itraconazole and posaconazole may be considered [12,13]. Data from Indonesia also showed that nystatin was the most commonly used antifungal agent, followed by fluconazole and ketoconazole [12].

The main antifungal classes used against Candida include polyenes, azoles, echinocandins, and flucytosine. Polyenes and azoles are among the most frequently used antifungal agents in oral candidiasis, while echinocandins and flucytosine are more commonly associated with systemic or refractory Candida infections [7]. Each antifungal class targets different fungal structures or pathways. Azoles inhibit ergosterol biosynthesis by targeting lanosterol 14-α-demethylase, polyenes disrupt fungal cell membrane integrity by binding to ergosterol, echinocandins inhibit β-1,3-D-glucan synthesis in the fungal cell wall, and flucytosine interferes with fungal DNA and RNA synthesis [14,15]. These different mechanisms of action are summarised in Table 1.

Although antifungal agents remain important in the treatment of oral candidiasis, their clinical effectiveness may be limited by reduced susceptibility and the emergence of antifungal resistance. Resistance to commonly used antifungal agents has been reported among Candida isolates associated with oral candidiasis. A meta-analysis study by Keyvanfar et al reported azole resistance among Candida spp. in HIV patients with oral candidiasis, with resistance rates ranging from 0.0% to 47.8% for ketoconazole and 4.6% to 56.7% for fluconazole [6]. This finding may be related to prolonged or continuous azole exposure, which can increase the proportion of resistant Candida isolates [6,14].

Reduced susceptibility has also been reported in *C. albicans.* Kainthola et al. reported resistance rates of 38% to flucytosine and 26% to fluconazole in *C. albicans* [18]. In addition, Sahu et al. found that only 60% of 35 *C. albicans* isolates were sensitive to nystatin, while 22.86% showed an intermediate response and 17.14% were resistant [19]. Similarly, Yuliana et al. reported that 6.7% of oral *C. albicans* isolates from HIV patients were resistant to nystatin, which was higher than previous reports of 0.8%–4.9% [20]. These findings indicate that current antifungal therapy may be challenged by emerging resistance, supporting the need to understand the mechanisms underlying antifungal resistance in C. albicans.

MECHANISMS DRIVING ANTIFUNGAL RESISTANCE IN CANDIDA ALBICANS

Antifungal resistance in *C. albicans* is a multifactorial process involving genetic, cellular, and adaptive mechanisms that enable fungal cells to survive antifungal exposure. These mechanisms may include alterations in drug targets, increased drug efflux, changes in membrane composition, impaired drug activation, and adaptive changes in cell wall structure [21]. Since each antifungal class targets different fungal structures or metabolic pathways, the mechanisms of resistance in C. albicans may vary according to the antifungal agent involved.

TABLE 1: Antifungal drug classes, representative drugs, and mechanisms of action.

Antifungal class	Representative drugs	Mechanism of action	References
Azoles	Fluconazole, voriconazole, itraconazole, posaconazole, isavuconazole, ketoconazole	Inhibit fungal cytochrome P450-dependent lanosterol 14-α-demethylase, thereby blocking ergosterol biosynthesis. This disruption alters fungal membrane integrity and inhibits fungal growth.	[14,16,17]
Polyenes	Nystatin, amphotericin B	Bind to or extract ergosterol from the fungal cell membrane, leading to membrane disruption, leakage of intracellular components, osmotic imbalance, and fungal cell death.	[14,16]
Echinocandins	Caspofungin, anidulafungin, micafungin	Inhibit β-1,3-D-glucan synthase, thereby disrupting fungal cell wall synthesis and impairing cell wall integrity.	[14,16]
Flucytosine	5-flucytosine	Enters fungal cells through cytosine permease and is converted into 5-fluorouracil. Its metabolites are incorporated into fungal RNA, inhibit protein synthesis, and also inhibit both thymidylate synthetase and DNA synthesis.	[15]

Azole Resistance

Resistance to azoles in *C. albicans* results from several overlapping mechanisms. One major mechanism is the accumulation of mutations in the *ERG11* gene, which encodes lanosterol 14α-demethylase, the primary target of azole drugs. These mutations decrease the affinity of azoles for their target enzyme, consequently reducing therapeutic efficacy [14]. In addition, increased *ERG11* expression may increase the amount of available target enzyme, further contributing to azole resistance [9]. Genomic alterations, such as aneuploidy or the formation of an isochromosome 5L, may similarly contribute to fluconazole resistance by increasing the copy number of *ERG11* and *TAC1*, thereby increasing both drug-target abundance and efflux-related resistance pathways [21]. Resistance may also occur due to increased drug efflux mediated by overexpression of ATP-binding cassette (ABC) and major facilitator superfamily (MFS) transporters. These transporters actively pump azoles out of fungal cells, thereby decreasing intracellular drug concentrations and limiting antifungal activity [14].

In *C. albicans*, increased drug efflux is associated with the upregulation of *CDR1*, *CDR2*, and *MDR1*, which contribute to fluconazole resistance by enhancing multidrug efflux pump activity [22]. Overexpression of these transporters can be promoted by gain-of-function mutations in transcriptional regulator genes, such as *TAC1* and *MRR1*, which increase the expression of resistance-related genes [9]. In addition to target alteration and drug efflux, changes in the ergosterol biosynthesis pathway also contribute to azole resistance. Mutations in the *ERG3* gene, which encodes C5,6-sterol desaturase, can prevent the formation of the toxic product 14α-methyl-3,6-diol and lead to the accumulation of 14α-methylfecosterol. This alternative sterol can maintain cell membrane function, consequently reducing azole efficacy [22].

Polyene Resistance

Resistance to polyenes in *C. albicans* is generally associated with changes in cell membrane composition, particularly reduced ergosterol content, which is the primary target of this antifungal class. This mechanism can result from mutations or loss-of-function changes in ergosterol biosynthesis genes, such as *ERG2*, *ERG3*, *ERG5*, *ERG6*, and *ERG11* [23]. These changes reduce the amount of ergosterol in the fungal cell membrane, thereby decreasing the affinity of polyenes for their target and reducing fungal susceptibility to the drug [9]. However, polyene resistance remains relatively uncommon compared with azole resistance, as alterations in the ergosterol pathway may cause substantial cellular stress and fitness trade-offs on fungal cells [14].

Polyene resistance may also be influenced by more extensive changes in membrane lipid composition, particularly sterols and phospholipids. In addition, increased catalase activity and decreased susceptibility to oxidative damage may help fungal cells withstand the antifungal effects of polyenes. These responses may reduce membrane damage and support fungal survival during polyene exposure [21]. Cellular stress-response pathways, including Hsp90-associated responses, may further support fungal adaptation during polyene exposure and contribute to the emergence of polyene resistance.

Echinocandin Resistance

Resistance to echinocandins in *C. albicans* is primarily associated with mutations in the *FKS* genes, particularly *FKS1*, which encodes a subunit of β-1,3-glucan synthase. This enzyme is the primary target of echinocandins in fungal cell wall synthesis. Mutations, especially in hotspot regions of *FKS1*, can alter the target structure, thereby decreasing the affinity of echinocandins for β-1,3-glucan synthase and reducing the effectiveness of cell wall synthesis inhibition [16,22].

Secondary or acquired resistance to echinocandins has also been associated with point mutations in *FKS1*, which alter the binding capacity of antifungal agents to their target and decrease *Candida* susceptibility to this drug class [9]. In addition to *FKS*-mediated resistance, *C. albicans* may activate compensatory cell wall responses to maintain cell wall integrity when β-1,3-glucan synthesis is inhibited. One proposed adaptive response is increased chitin synthesis, which may strengthen the fungal cell wall and support survival under echinocandin exposure [14].

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Flucytosine Resistance

Although *Candida* species, including *C. albicans*, are generally susceptible to flucytosine, primary flucytosine resistance in *C. albicans* has been reported to occur in approximately 7–8% [15]. Despite its limited role as a first-line therapy for uncomplicated oral candidiasis, its mechanism of resistance is still relevant in the broader context of antifungal resistance in *C. albicans*.

Flucytosine resistance in *C. albicans* may occur through impaired drug uptake or altered intracellular drug metabolism. Flucytosine first enters fungal cells via cytosine permease and is then converted to 5-fluorouracil via the pyrimidine salvage pathway. Its active metabolites can be incorporated into fungal RNA, thereby disrupting protein synthesis, and can also inhibit thymidylate synthetase, leading to impaired DNA synthesis. In *C. albicans*, resistance has been associated with alterations in genes involved in flucytosine uptake and activation, including FCY2, which encodes cytosine permease; FCA1/FCY1, which encodes cytosine deaminase; and FUR1, which encodes uracil phosphoribosyltransferase [24]. Resistance may develop rapidly when flucytosine is used as monotherapy. For this reason, flucytosine is more commonly considered as part of combination therapy for severe or systemic yeast infections rather than as a single agent [15,24].

In addition to drug-specific resistance mechanisms, *C. albicans* can survive antifungal exposure through adaptive stress-response pathways. These responses may include oxidative stress adaptation, cell wall stress responses, and heat shock or calcineurin-related pathways, which help fungal cells maintain cellular homeostasis under antifungal pressure. Hsp90 has been described as an important regulator of antifungal-induced stress responses because it stabilises signalling proteins involved in the calcineurin and PKC-MAPK pathways, consequently contributing to antifungal tolerance and resistance [14]. In *C. albicans*, activation of the calcineurin pathway in response to azole treatment has also been associated with increased antifungal tolerance, allowing fungal cells to survive under otherwise lethal conditions [21].

Overall, antifungal resistance in *C. albicans* involves interconnected mechanisms, including alterations of drug targets, overexpression of efflux pumps, modification of the ergosterol pathway, membrane remodelling, cell wall adaptation, impaired drug metabolism, and activation of stress responses [9]. These mechanisms indicate that resistance is not caused by a single pathway, but by multiple genetic, cellular, and adaptive changes that allow *C. albicans* to survive antifungal exposure. Although some adaptive responses may not always result in stable genetic resistance, they can contribute to antifungal tolerance and fungal persistence during treatment [21]. Understanding these mechanisms provides an important basis for developing mechanism-guided treatment strategies to overcome antifungal resistance in oral candidiasis.

BIOFILM-ASSOCIATED TOLERANCE IN THE ORAL MICROENVIRONMENT

Biofilm formation plays an important role in the persistence and recurrence of oral *C. albicans* infection. In the oral cavity, *C. albicans* can adhere to mucosal surfaces, dentures, dental materials, and other surfaces where it may form structured biofilm [25]. The ability of *C. albicans* to adhere to oral surfaces is influenced by its virulence-related factors, including cell-surface hydrophobicity and extracellular enzyme activity, such as phospholipase, which may support tissue invasion and colonisation [2]. Compared with free-floating *C. albicans* cells in saliva, biofilm-associated *C. albicans* is generally more difficult to eradicate because the fungal cells are protected by an extracellular matrix, altered metabolic activity, and heterogeneous cellular states. [21,26].

The development of *C. albicans* biofilm occurred in several stages, beginning with initial adhesion to oral surfaces, followed by cell proliferation, hyphal formation, maturation of the biofilm structure, and dispersion of fungal cells to new sites. The ability of *C. albicans* to switch from yeast to hyphal forms plays a key role in biofilm architecture and tissue adherence. In the oral microenvironment, this process can be influenced by local factors such as salivary flow, denture use, surface roughness of the involved dental materials, oral hygiene, pH changes, smoking, and host immune status [2,26]. Nutrient availability may also influence biofilm development, as glucose, lactose, protein, and iron have been reported to affect the expression of *C. albicans* biofilm proteins [27].

The decreased susceptibility associated with biofilm formation differs from antifungal resistance caused by genetic mutations. In biofilm-associated tolerance, the extracellular matrix acts as a protective barrier that limits antifungal penetration and reduces drug exposure to *C. albicans* cells. In contrast, genetic resistance usually involves stable changes in fungal genes that alter the antifungal target, reduce drug uptake, or modify drug metabolism [21]. In addition, in mature biofilms, some *C. albicans* cells may become less metabolically active. This condition makes them less affected by antifungal agents that work best against actively growing cells. In addition, some cells may survive antifungal treatment as persister-like cells. These surviving cells can regrow after treatment is stopped,

potentially contributing to biofilm recovery and recurrent infection [28].

Since biofilm formation contributes to the persistence and recurrence of oral *C. albicans* infection, it may be a potential therapeutic target to improve the management of oral candidiasis. Strategies aimed at reducing adhesion, limiting biofilm maturation, or disrupting established biofilm structures may help enhance antifungal effectiveness and reduce recurrent infection [21,26].

MECHANISM-GUIDED THERAPEUTIC STRATEGIES AND FUTURE PERSPECTIVES

Understanding the mechanisms of antifungal resistance in *C. albicans* is important for developing more targeted strategies for oral candidiasis. Since resistance may involve drug-target alterations due to mutations, efflux pump overexpression, changes in the ergosterol pathway, cell wall adaptation, impaired drug metabolism, and biofilm-associated tolerance, treatment should not rely solely on increasing antifungal dosage or switching to another antifungal agent [14,21,28]. Instead, future strategies should also consider the mechanisms that allow *C. albicans* to survive antifungal exposure.

One important approach is the optimisation of existing antifungal therapy. In recurrent or persistent oral candidiasis, treatment should be guided by confirmation of the causative *Candida* species and antifungal susceptibility testing, especially in patients with immunosuppression, repeated antifungal exposure, denture use, or persistent infection. When reduced susceptibility or resistance is detected, antifungal susceptibility testing can help identify alternative agents that may remain effective, thus avoiding unnecessary prolonged exposure to ineffective drugs [29]. These approaches may help reduce selection pressure and improve treatment response in oral *C. albicans* infection [13].

Combination therapy may also be considered as a potential strategy to overcome antifungal resistance. Combining antifungal agents with different mechanisms of action may improve antifungal activity and reduce the possibility of resistance development [30]. In addition, adjunctive compounds that inhibit efflux pumps, interfere with adaptation of the ergosterol pathway, or affect fungal stress-response pathways may enhance the activity of existing antifungal agents [14,21]. Emerging therapeutic targets, such as calcineurin-related signalling, HOG pathway components, and other stress-response regulators, may also provide future opportunities for mechanism-guided antifungal development [30]. These approaches may be useful when *C. albicans* shows reduced susceptibility to commonly used antifungals.

Biofilm-targeted therapy is another important future direction. Oral *C. albicans* biofilms can limit antifungal penetration, protect fungal cells, and support persistent or recurrent infection [28]. Therefore, strategies that reduce adhesion, inhibit biofilm maturation, disrupt extracellular matrix formation, or improve drug penetration into biofilm structures may help improve treatment response. Biofilm-related factors, including adhesins and transcriptional regulators involved in biofilm formation, may also serve as potential therapeutic targets [30]. These approaches may be particularly relevant in denture-associated or recurrent oral candidiasis [26].

Alternative antifungal agents, including natural products and plant-derived compounds, have also gained attention as potential adjunctive or alternative therapies. These agents may act through several mechanisms, such as disrupting fungal cell membranes, inhibiting adhesion and biofilm formation, reducing virulence factors, or affecting oxidative stress responses. Studies on extracts of *Gracilaria verrucosa* and *Tinospora crispa*, for example, suggest that natural compounds may inhibit *C. albicans* virulence factors and biofilm formation [2,26]. In addition, drug discovery approaches such as high-throughput screening, structure-based drug design, synthetic modification of existing molecules, and drug repurposing may support the development of new antifungal candidates [30]. However, further studies are still needed to evaluate their active compounds, effective concentrations, toxicity, formulation stability, and clinical efficacy before they can be recommended for oral candidiasis treatment [7].

Novel drug delivery systems may further improve antifungal therapy in the oral cavity. Local delivery approaches, such as mucoadhesive gels, oral films, nanoparticles, or sustained-release formulations, may increase drug retention at the infected site, improve penetration into biofilms, and reduce systemic side effects [21]. These approaches are relevant for oral candidiasis because saliva flow, mucosal turnover, and denture surfaces can reduce drug contact time and affect therapeutic efficacy.

CONCLUSIONS

Antifungal resistance in oral *Candida albicans* remains a major challenge in managing oral candidiasis, particularly among susceptible patients with recurrent or persistent infection. Current antifungal agents, including polyenes, azoles, echinocandins, and flucytosine, remain important for treatment; however, their effectiveness may be limited by reduced susceptibility and the emergence of resistant *C. albicans* isolates. Resistance in *C. albicans* is driven by multiple mechanisms, including antifungal target alteration, efflux pump overexpression, ergosterol pathway modification, membrane remodelling, cell wall adaptation, impaired drug metabolism, and adaptive stress-response pathways.

In the oral microenvironment, biofilm-associated tolerance further complicates treatment. Biofilms can protect fungal cells from antifungal exposure, limit drug penetration, and support persistent or recurrent infection. Therefore, overcoming antifungal

resistance requires strategies that are guided by the underlying resistance mechanisms, rather than relying solely on conventional antifungal use. Future approaches may include optimisation of existing therapy, antifungal susceptibility testing, combination therapy, anti-biofilm strategies, alternative antifungal agents, and improved local drug delivery systems. A better understanding of resistance mechanisms and biofilm-associated tolerance may support the development of more targeted and effective therapeutic strategies for oral candidiasis.

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