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Candida Auris Features and its Treatment: Global Emergency

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ABSTRACT

Fungal pathogen *Candida auris* was identified in 2009, in Japan. Currently, it is identified in 5 continents, in more than 40 countries. Therefore, it is nowadays defined as critical priority pathogen. The present mini-review describes the resistance to medicines that are currently in use and these drugs' resistance to antimicrobial mechanisms (RAM). Furthermore, therapies and the on-going search for future drugs will also be discussed.

Keywords: *Candida auris,* drug resistance, antifungal, vaccines, silver nanoparticles, violacein

INTRODUCTION

Candida auris was first described in 2009, in Japan (Eix and Nett, 2025). It was identified in India, South Africa, South Korea, and Latin America (Venezuela) in 2013. Since then, *C. auris* infection has spread worldwide. The process to feature the genome sequencing of almost 50 led to four different clades at the all the world. These clades were featured based on their geographic locations, namely: Clade I (South Asian) (Satoh et al., 2009; Ohashi et al., 2023), Clade II (East Asian) (Sekizuka et al., 2019), Clade III (South African) (Price et al., 2021), Clade IV (South American) (Lockhart et al., 2017), Clade V (Iran) (Spruijtenburg et al., 2022), and Clade VI (Singapore) (Suphavilai et al., 2024). They are genetically different and show variations among strains within the same clade; they are differentiated by thousands of single-nucleotide polymorphisms. Each clade has very few unique single nucleotide polymorphisms (SNPs), a fact that points towards clonal expansion in this region. Small differences among these SNPs led to clinically significant phenotypic variations, such as body site tropisms, virulence, host colonization, outbreak potential and fungal resistance (Bhargava et al., 2025).
The Los Angeles Times published a deadly, drug-resistant fungus CDC call for an urgent threat spreading in USA hospitals (World & Nation-2025). The CDC issued a public safety

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announcement declaring *C. auris* as urgent threat in 2023 given its resistance to many antifungal drugs. It spreads fast in healthcare hospitals and causes acute infections that account for high death rates (mortality rate ranging from 30% to 60%). This deadly, drug-resistant fungus attacks sick and old patients and spreads in both hospitals and senior care clinics over the country. It has already killed more than 1 in every 3 infected individuals. *C. auris* was first identified in the U.S. in 2016. There were 52 infection cases descripted all over the country. According to the U.S. CDC and Prevention, the number of cases rose up to 4.514, in 2023. At this same time, as the State of California recorded 1.566 infection cases, and this number is higher than any other recorded by other states (CDC-2023).

The first case in Brazil was reported by the Brazilian Health Surveillance Agency (ANVISA) on December 7, 2020. The fungus was observed in a sample collected from the tip of a catheter used in a patient admitted to an ICU in Bahia State. This case was the first of the initial outbreak recorded in the country. The first outbreak of it accounted for 15 cases and two deaths. Another outbreak was observed in December 2021, also in Bahia State, and it only recorded one case. On January 3, 2022, ANVISA was notified about two *C. auris* cases in Pernambuco State, and it corresponded to the third outbreak in Brazil (ANVISA-2022).

Pernambuco State registered its first *C. auris* case by late 2021. Since then, the state has recorded ten outbreaks and totaled 76 confirmed cases. The fungus was identified in public and private hospitals in the Metropolitan Region of Recife City. Since 2025, Hospital Otávio de Freitas identified four Clinical Intensive Care Unit (ICU) patients with *C. auris*. This health service accounts for an active outbreak of these fungi, although those are all monitored cases (ICU-2025).

Hospital do Servidor Público Estadual de São Paulo confirmed that 15 patients had contact with the super fungus *C. auris* over the first three months of 2025. One of these patients, who was at the age of 74 years, died. However, according to the institution, his death was not caused by this contamination (Hospital-SP-2025).

Candidemia frequency in South America fluctuates from 0.74 to 6.00 per 1000 hospitalizations. Although *C. auris* is currently responsible for a small fraction of these cases, its frequency is expected to keep on increasing (Davi et al., 2025).

CANDIDA AURIS RESISTANCE

Fungus *Candida auris* is the most resistant to antimicrobials (RAM). Therefore, it is of great concern for health authorities. This fungus does not respond to most existing antifungals; in some cases, it resists to all of them. High alerts have significantly increased during the COVID-19 pandemic, and it had also increased the number of long-term hospitalizations over the globe. Consequently, having seriously ill patients spending long times in ICUs taking medicines such as corticosteroids and, in some cases, depending on mechanical ventilation, obviously raised risks for fungal contamination (Nakazato et al., 2021).

C. auris samples have shown high resistance to classical drugs such as antifungals (Chen et al., 2020; Lyman et al., 2023). This fungus recorded minimum inhibitory concentration (MIC) breakpoints at ~32 µg/mL fluconazole, ~2 µg/mL amphotericin B, ~4 µg/mL anidulafungin, ~2 µg/mL caspofungin and ~4 µg/mL micafungin (Eix and Nett, 2025). According to a worldwide analysis, fluconazole reached 91% resistance; amphotericin B, 12%; caspofungin, 0.8%; and anidulafungin, 1.1% (Chen et al., 2020). Assumingly, there were some controversial MIC results recorded during caspofungin and micafungin measurements and it may imply MIC interpretation complications. However, this paradoxical effect does not seem to be correlated to outcomes *in vivo* (Eix and Nett, 2025). Fluconazole resistance is uniformly found among isolates across geographic regions, whereas echinocandins and amphotericin B's MIC can change (Chen et al., 2020; Koleri et al., 2023). Amphotericin B resistance was <5% in the US

Midwestern and Western regions, and it reached approximately 85% in the Mid-Atlantic (Lyman et al., 2023).

It is important observing that *C. auris* infection is caused by strains' spread. Therefore, resistance patterns and considerations must comply with local levels. Qatar, for example, reported 85% resistance to amphotericin B, and this outcome dissociated the relevance of starting first-line treatment with echinocandins to fight this outbreak (Koleri et al., 2023). It is clear that echinocandins are recommended as first-line treatment for patients, whereas MICs flow from local to outbreak. A multi-country analyses also depicted this phenomenon in *C. auris* samples from India, which has shown higher caspofungin resistance rate (23.6%) than other countries (0.2%) (Chen et al., 2020). Although the outcomes recorded for monomicrobial resistance are warring, the certainty of pan-resistant samples resistant to all available drug classes, such as echinocandins, azoles and amphotericin B formulations, is much more concerning (Ostrowsky et al., 2020).

This information allows observing that the resistance to *C. auris* antimicrobials is important to help better understanding the antifungal action of several compounds. This resistance item is mediated by a whole variety of species-specific mechanistic aspects that can be categorized as follows (Figure 1) (Huang et al., 2025).

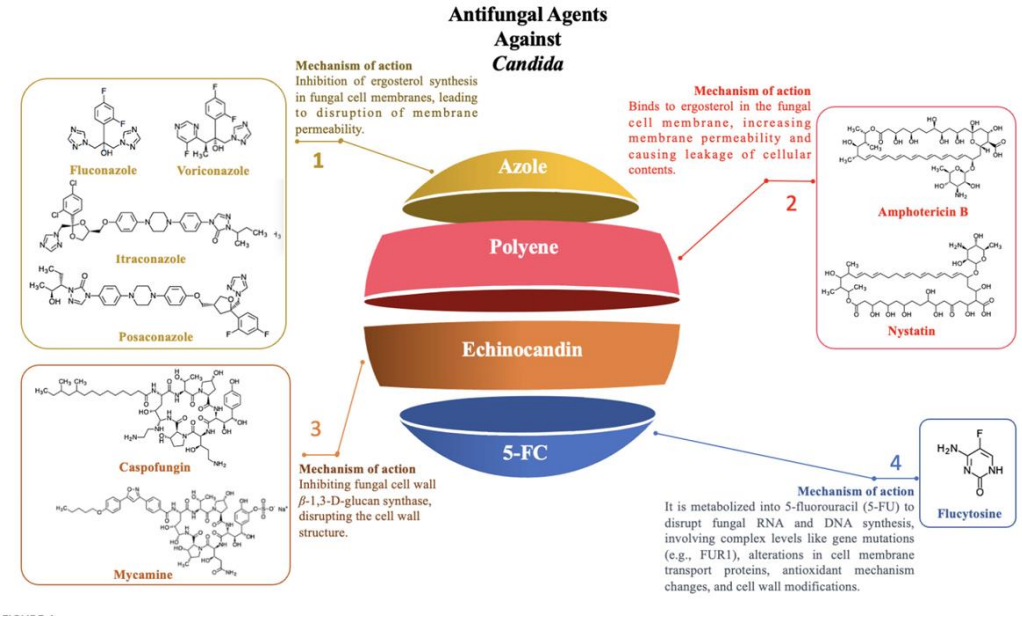

Fig. 1. Antifungal agents against *Candida* (https://biorender.com/) (by permision of Frontier in Microbiology, Ref. Huang et al., 2025. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY)).

SIGNALING THE PATHWAYS AND MECHANISMS THAT RULE ANTIFUNGAL DRUG RESISTANCE IN *CANDIDA AURIS*

The emergence of multidrug-resistant *C. auris* strains makes it extremely important to better understand this pathogen's mechanistic pathways linked to antifungal drug resistance. Fungal species' resistance to azole is firstly related to mutations in the ERG11 gene, since it encodes lanosterol demethylase, which is the very target of azole medicines. Amino acid replacements in ERG11 sequences of clinical *C. auris* strains are related to fluconazole resistance and to its mutation through overexpressed off flux pump CDR1, which rules out azole from cells. Furthermore, CDR1 likely plays a role in *C. albicans* resistance to fluconazole (Fig. 2) (Cha et al., 2025a; Li et al., 2023). As an alternative, the Rpn4 transcription activator plays a role in *C.*

auris fluconazole resistance, since it upregulates efflux pump genes such as CDR1 by reducing this drug's intracellular dose and promoting binding PACE autoregulation in its promoter (Chow et al., 2023).

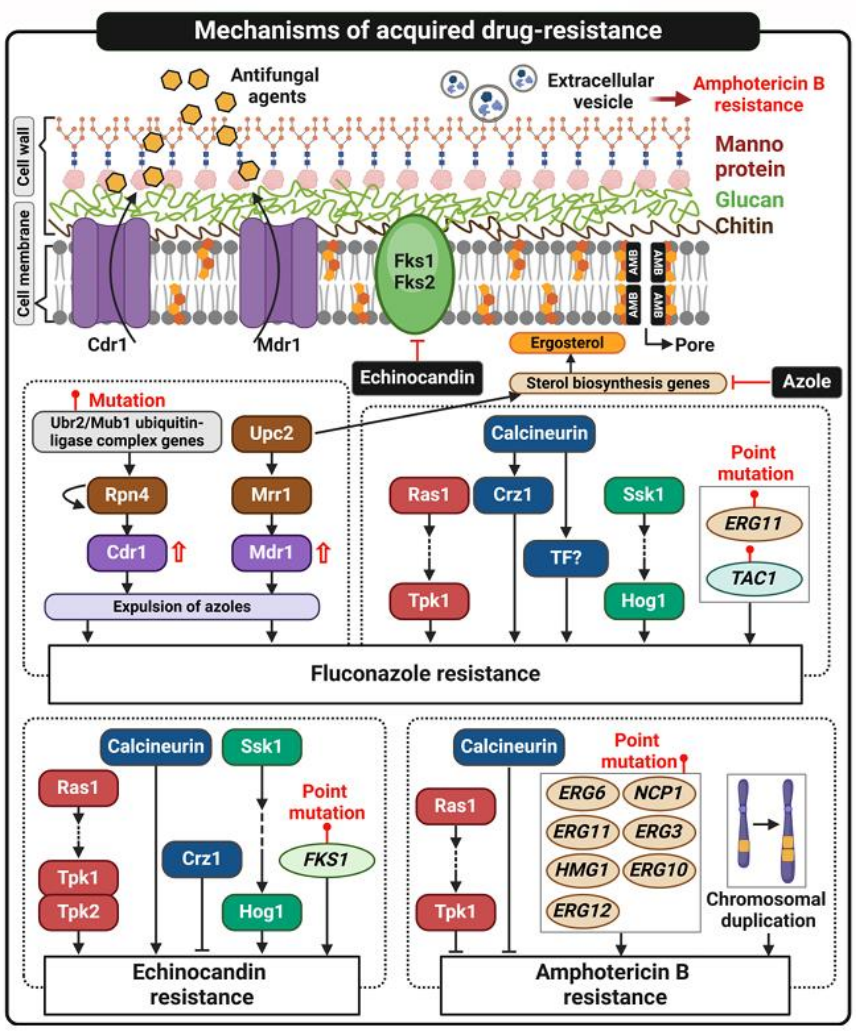

Figure 2. Overview of signaling pathways and mechanisms governing antifungal drug resistance in Candida auris. This figure highlights the primary mechanisms underlying antifungal resistance in C. auris. Azole resistance arises from point mutations in the ERG11 or TAC1 gene and the overexpression of efflux pumps, such as CDR1, which is regulated by transcription factors like Rpn4. Additional contributors include Mrr1 and Upc2, which influence efflux pump expression and ergosterol biosynthesis. Primary signaling pathways, including Ras/cAMP/PKA, calcineurin, and Hog1, also modulate azole resistance. Echinocandin resistance is primarily linked to mutations in FKS1, impairing β-1,3-glucan synthase. Calcineurin signaling plays a complex role in resistance mechanisms; while calcineurin promotes echinocandin resistance, its downstream factor Crz1 represses it, suggesting that additional calcineurin-dependent factors could be involved. Amphotericin B resistance is driven by mutations in sterol biosynthesis genes (e.g., ERG6, ERG11), chromosomal duplications, and extracellular vehicles (EVs). Notably, the Ras/cAMP/PKA and calcineurin pathways inhibit amphotericin B resistance. This figure was created using BioRender (https://biorender.com/). (by permission of American Society for Microbiology. Ref. Cha et al., 2025. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license).

Furthermore, UBR2 and MUB1 stabilize Rpn4 and, consequently, keeps high efflux pump expression levels and increases resistance (Fig. 2) (Chow et al., 2023). Different factors, such as the Mrr1 transcription factor and the Mdr1 drug transporter, also allow *C. auris* resistance to azole. It is so, because this mechanism is not related to ERG11 mutations and CDR1 upregulation (Fig. 2). Factor Upc2 controls the ergosterol biosynthesis pathway, and it allows

resistance to azole by controlling the ERG11 expression and activating the Mrr1/ Mdr1 pathway (Fig. 2) (Li et al., 2022). Like *C. albicans* and *Saccharomyces cerevisiae*, the cAMP/PKA pathway sets *C. auris* multidrug resistance. CYR1 and TPK1 removal affects sensibility to drugs such as fluconazole, besides allowing resistance to amphotericin B; this pattern is not found in the *tpk2*Δ mutant (Kim et al., 2021). Mutants also present altered expression of *genes* required in ergosterol biosynthesis (*ERG11*, *ERG3*, and *ERG6*). It shows that this pathway has remarkable influence on ergosterol generation, which has impact on resistance to amphotericin B. The ras1Δ mutant shows increased sensibility to azole, besides accounting for higher resistance to amphotericin B (Fig. 2) (Kim et al., 2023). Echinocandin resistance is firstly produced by mutations in the *FKS gene*, which encodes β-1,3-glucan synthase (Fig. 2). This synthase stands out for synthesizing β-1,3-glucan, which is a key fungal cell wall component quite relevant for cell shape integrity maintenance, adhesion and interaction with the host. Targeting β-1,3-glucan synthase with echinocandin drugs disrupts cell wall formation and leads to fungal cell death. Overall, echinocandin-resistant *C. auris* samples have hot spot mutations in FKS1 (Fig. 2). These samples present a divided set of 362 differentially expressed *genes*, some of which are demanding for the cell wall function. Furthermore, new non-hot spot mutations downstream hot spot 1 in FKS1 have been featured for contributing to echinocandin resistance. These findings point out a whole diversity of FKS1 mutations that, in their turn, drive *C. auris* resistance to echinocandin (Kordalewska et al., 2023).

The Ras/cAMP/PKA pathway in *C. auris* also imply in resistance to echinocandin because it acts in FKS1 expression or in ras1Δ mutant. Mutants as*1*Δ and *tpk1*Δ *tpk*2Δ are more sensible to caspofungin due to alterations in the FKS1 expression (Fig. 2) (Kim et al., 2021). The cell wall integrity (CWI) signaling pathway is also demanding for resistance to azoles and echinocandins. Echinocandins suppress the β-1,3-glucan synthesis, and it helps chitin synthesis by protein kinase C (PKC)/CWI MAPK, calcineurin and HOG pathways (Costa-de-Oliveira et al., 2020). Mutants with HOG1 and SSK1 deletions in *C. auris* point towards significant sensibility to antifungal medicines and to cell wall stress agents (Fig. 2) (Shivarathri et al., 2020). The calcium calcineurin pathway is essential for *albicans* and *C. auris* resistance to azole and echinocandin (Jia et al., 2012) (Fig. 2). Sensibility increase also happens on CNA1 knockout, which encodes calcineurin, or CNB1's catalytic subunit to azole drugs such as fluconazole, posaconazole and voriconazole. Nevertheless, calcineurin roles in resistance to azole are preserved across different clades, namely: B11220 (AR0381, clade II, isolated in Japan), B11221 (AR0383, clade III, isolated in South Africa) and B11245 (AR0386, clade IV, isolated in Venezuela) (Cha et al., 2025b). CRZ1removalthrough calcineurin downstream transcription also increased sensibility, although to a shorter length. It is important observing that calcineurin is crucial for resistance to echinocandin, whereas *crz1*Δ mutants show strong resistance to echinocandins. This phenotype opposes that found in *cna1*Δ and *cnb1*Δ mutants (Fig. 2) (Cha et al., 2025b). This finding means that other transcription factors may play important role in calcineurin-mediated resistance to echinocandins. Although research on other signaling pathways and components is required to help fully understanding the mechanisms linked to *C. auris* drug resistance, it may differ from those in other fungal types. Amphotericin B is a common antifungal drug used to treat acute fungal infections, mainly when other antifungal drugs are useless due to resistance to them. Its action mechanism regards binding to ergosterol, which is a vital fungal cell membrane component that forms pores capable of causing cell leakage and, ultimately, cell death (Fig. 2). *C. auris* resistance to amphotericin B is operated by four major sterol alteration types depending on sterol biosynthesis *genes* (*ERG6, NCP1, ERG3, ERG11, HMG1, ERG12* and *ERG10*) (Fig. 2). Chromosomal duplications were

observed during resistance evolution, with emphasis on their role in acquired resistance to amphotericin B (Fig. 2) (Carolus et al., 2024). Moreover, extracellular vehicles (EVs) play important role in resistance to amphotericin B (Fig. 2) (Carolus et al., 2024). Interestingly, EVs extracted from resistant azole, but sensible to amphotericin B, have enhanced *C. auris* survival rate in a dose-dependent manner. It increased amphotericin B MIC close to 16-fold. These EVs hold alcohol dehydrogenase 1 and Xog1 (β-1,3 exoglucanase), which may help resistance to drugs (Carolus et al., 2024)). However, EVs-mediated amphotericin B resistance remains unknown and warrant further research. Quantitative proteomic analysis applied to EVs associated with both forward and reverse genetic approaches will probably provide deeper insights into these mechanisms.

CURRENT THERAPIES AND FUTURE OPTIONS

a) Antifungal compounds

Currently, three antifungal medicine classes have been accredited for invasive candidiasis therapy: triazoles (e.g., fluconazole, voriconazole), echinocandins (e.g., caspofungin, anidulafungin, micafungin) and amphotericin B formulations (amphotericin B deoxycholate and liposomal amphotericin B) (Pappas et al., 2016; Eix and Nett, 2025). Given *C. auris* high resistance rates, MIC is often suggested for isolates from patients who require treatment (Bruno et al., 2006). Treatment should be provided to patients with documented invasive infection and to reject colonization cases on nonsterile sites (i.e., skin, respiratory tract) (Bruno et al., 2006). Considering their more adequate sensibility profiles, echinocandins are first-line treatments for the largest number of patients; they should be initiated without sensibility testing (Ong et al., 2019). The murine model has shown that echinocandins disclose powerful activity against *C. auris;* yet, it exceeds 20-fold lower than targets set for other *Candida* species combined to fungal stasis (Lepak et al., 2017). According to these outcomes, *C. auris* strains recording higher MICs are prone to be further effectively treated with echinocandins based on what has been applied to other *Candida* spp, with relatively high MICs. Furthermore, micafungin can be safely prescribed for adults at doses higher than the typical daily 100 mg regimen (Grant et al., 2022). Higher micafungin dosing can work as analysis set for the treatment applied to *C. auris* isolates showing high echinocandin MICs if treatment possibilities are limited. Echinocandin therapy limitations encompass parenteral-only formations, reduced penetration to the central nervous system (CNS), lack of access to resource-limited areas, urine (Chowdhary et al., 2020). Echinocandins also lack penetration to the eye (Pappas et al., 2016). Echinocandins (caspofungin, micafungin, anidulafungin) often prescribed doses usually administered daily. However, a newer formulation (rezafungin) presents high half-life, which allows weekly dosing. It is applied as optional agent for candidemia and invasive candidiasis therapy (Pappas et al., 2016; Lepak et al., 2018). Although echinocandins are the best *C. auris* therapy agents, changes in liposomal amphotericin B can be an option for patients who are not reacting at clinical stages or who have had permanent candidemia for more than 5 days (Bruno et al., 2006). *C. auris* samples presented variable MICs recorded for voriconazole and for other second-generation triazoles (Arendrup et al., 2018). It is recommended to use sensibility to fluconazole as substitute to resistance to triazole (Bruno et al., 2006). Depending of the use made of voriconazole, other second-generation triazoles should be taken into consideration on a case-by-case basis. Flucytosine relevance to treat *C. auris* is not clearly discussed (Eix and Nett, 2025).

Studies carried out in Southern Africa point out that therapy combination to flucytosine can be a short-term strategy to wait for decision made based on sensibility test results (Govender et al., 2019). Flucytosine is often applied as part of an association treatment adopted as invasive candidiasis therapy; it works for refractory infections (i.e., endocarditis, meningitis and

endophthalmitis) (Pappas et al., 2016). Although most *C. auris* outbreak reports regard the population of adult patients, it also has acute effects on patients in neonatal intensive care units, and it can lead to high mortality rates (Kim et al., 2021). The first-line agent suggestion for neonates sensible to *Candida meningitis* is amphotericin B, if one bears in mind its CNS tissue action (Pappas et al., 2016). But unfortunately, this therapy can impair the treatment against *C. auris* due to the group of isolates presenting high MICs values for amphotericin B. Therefore, it is necessary to apply echinocandins within this context (Alvarado-Socarras et al., 2021). Meningitis often prevails among concern with neonates (> 2 months), whereas amphotericin B deoxycholate is the selected antifungal for this group of patients. There has been some suggested dual antifungal therapy due to *C. auris* high resistance level or to more complex mixes, such as amphotericin B, triazoles, echinocandins, and flucytosine combination to likely additive or synergistic action (O'Brien et al., 2020; Caballero et al., 2021, 2023) or primarily indifferent interactions without antagonism (Fakhim et al., 2017; Bidaud et al., 2019). However, the routine use associated treatments is not often recommended for therapy against *C. auris*. This procedure is only used on a case-by-case basis for seriously infected patients, as well as for those with candidemia relapse or persistence (Bruno et al., 2006; Govender et al., 2019). In total, 45% of patients in an outbreak required a second agent due to nonresponse or persistent fungemia during echinocandin monotherapy (Ruiz-Gaitán et al., 2019). Almost all these patients were treated with liposomal amphotericin B (Ruiz-Gaitán et al., 2019). Treatment association can also be considered for infections linked to CNS and/or urine, given echinocandins limited diffusion to these places (Ong et al., 2019). In addition, it is recommended using combined therapy and/or amphotericin B monotherapy in patients who develop *C. auris* candidemia in the echinocandin prophylaxis context (Ashkenazi-Hoffnung and Rosenberg, 2023).

Like azoles, tetrazoles reversibly and competitively suppress Erg11p to consume the fungal membranes of ergosterol and to break membrane integrity. VT-1129, VT-1598 (quilsecondazole) and VT-1161 (oteseconazole) were differentiated as part of a selection of chemicals that account for lower affinity for human Cyp enzymes (Hoekstra et al., 2014; Gu et al., 2024)). VT-1161 shows ~ 1000 folds more selective than the *C. albicans* Cyp51 enzyme relative to the human isoenzyme (Warrilow et al., 2014). VT-1129, VT-1161and VT-1598 have powerful action against a wide range of *Candida* species, including species resistant to azole and echinocandin, at low MICs (Schell et al., 2017a; Break et al., 2018a). VT-1161 records low MIC (0.002 µg/ml) against wild-type, fluconazole-sensitive *C. albicans* (Warrilow et al., 2014). It seems to hold some activity (MIC of 2 µg/ml) against resistance to fluconazole-resistant isolates (Garvey et al., 2015; Schell et al., 2017a; Nishimoto et al., 2019; Monk et al., 2019; Murphy and Bicanic, 2021). The VT-1161 therapy significantly reduced fungal burden in murine vulvovaginal candidiasis (VVC) and invasive candidiasis (IC) models due to *Candida* susceptible and resistant to fluconazole (Garvey et al., 2015; Break et al., 2018b).

VT-1598 accounts for the broadest spectrum of activity against fungal species, including *C. albicans* (Break et al., 2018a) and *C. auris* (MIC 0.03-8 µg/ml) resistant to fluconazole (Wiederhold et al., 2019; Murphy and Bicanic, 2021). It recorded improved efficiency in neutropenic murine fluconazole or caspofungin models. VT-1129 was designed to treat *Cryptococcus*, but it also works well against many *Candida* spp species *in vitro*, including *C. glabrata* and *C. krusei* resistant to azole and echinocandin (Desai et al., 2016; Schell et al., 2017a). Unfortunately, the access to VT-1129 outcomes in *Candida* species is not enough. Nevertheless, the medicine proved by FDA fast tracks orphan drug status to treat *Cryptococus meningitis*. The fact that tetrazole is easily more tolerable is its major advantage given its enhanced fungal Cyp51 specificity (Murphy and Bicanic, 2021).

New antifungal agents have been assessed to treat invasive candidiasis cases induced by *C. auris* (Bhargava et al., 2025).

Ibrexafungerp is an effective antifungal agent against *C. auris*, even in echinocandin–resistant patients. It is effective on samples presenting FKS1 mutations. An open-label study and other clinical trials assessed ibrexafungerp effectiveness to treat infections caused by *C. auris* (Hoenigl et al., 2021; Thompson et al., 2022; El Ayoubi et al., 2024)).

Fosmanogepix is a prodrug of its active component manogepix. It belongs to a new class of antifungal therapies and acts in inhibiting Gwt1. Thus, enzyme is quite important to synthesize glycosylphosphatidylinositol in the cell wall and in the membrane; thus, it changes their integrity and fungal growth (Hoenigl et al., 2021).

b) Vaccines

Vaccines are a crucial strategy to reduce the global impact of drug-resistant *C. auris*. Interestingly, *C. auris* shows a Als3p protein that homologs the *C. albicans* protein which, in its turn, presents important adhesin and invasin skills for host pathogenesis (Phan et al., 2007; Liu et al., 2011). A study showed the most interesting part of many critical Als4112 roles (a conserved adhesin) in *C. auris* colonization and virulence *in vivo*; therefore, it becomes an attractive target for future vaccine production (Zhao et al., 2025). This study also addresses the potential of specific collagen coatings as new strategy to avoid *C. auris* adherence to abiotic surfaces, and it opens a new therapeutic pathway to control *C. auris* spreading in healthcare systems.

The NDV-3A vaccine derived from Als3 protein's N-terminus, and $Al(OH)_3$ was the adjuvant. This vaccine has proven efficient and safe for *Candida* spp in pre-clinical and phase I clinical trials (Spellberg et al., 2006; Edwards et al., 2018). Mice vaccination with NDV-3A generated antibodies against Als3p. They recognized *C. auris*, inhibited its preformed biofilm and increased macrophages' ability to kill the fungus (De Bernardis et al., 2012; Schmidt et al., 2012; Singh et al., 2019). This vaccination led to strong T-cell immunity and preserved immunosuppressed mice from lethal *C. auris* infections. Furthermore, NDV-3A enhanced micafungin efficiency against *C. auris* candidemia reflected on better subsistence rates (Millar et al., 2021; Sahu et al., 2022; John et al., 2023).

b) Probiotics

Researchers are testing many new therapeutic approaches related to genomic investigation success. On the other hand, therapies against *Candida* contamination and biofilm interruption have been assessed as possible options for antifungal drugs capable of suppressing oral *Candida* growth (Contaldo et al., 2023). Therefore, the treatment with probiotics, mainly with strains such as *Lactobacillus* sp. and *Bifidobacterium* sp., can efficiently suppress oral mucosa and skin surface contamination with *Candida* by replacing microbial equilibrium at the infection or contamination areas. Overall, it is a safe therapy option in clinical systems, in the presence of low toxicity (Ricci et al., 2022; Contaldo, 2023; Fusco et al., 2023;).

c) Photodynamic process

Photodynamic therapy uses photosensitizers at specific light wavelength to selectively lysis *Candida* cells. This method provides primacies such as no medicine resistance induction, specific selectivity, and non-toxicity by introducing a new physical approach to treat candidiase (Contaldo et al., 2023). Moreover, biofilm breakdown strategies are linked to methods such as enzymes (like DNase) and metal chelators to break down fungal biofilms associated with *Candida* contamination or infection. This process indirectly suppresses fungal growth, besides being mainly adequate for refractory or recurrent *Candida* contamination or infections cases. It is so, because it provides a new strategy to increase antifungal medicines efficiency and to reduce infection recurrence rates (Contaldo et al., 2023; Contaldo, 2023; Fusco et al., 2023; Chanda et al., 2017). All these approaches and investigation promises open room for new clinical therapy direction aimed at candidiasis contamination or infection, which point out the need for further in-depth research and exploration (Huang et al., 2025).

d) Silver nanoparticles

Silver nanoparticles (AgNP) are efficient materials for biological advantage against *C. auris* (Nakazato et al., 2021; Fayed, 2025). Microwave-assisted AgNP synthesis against *C. auris* has shown suppressor activity at IC50 equals 0.06 µg/mL (biofilm formation) and 0.48 µg/mL (IC50 of preformed biofilms). Wound dressings soaked on AgNPs have suppressed *C. auris* biofilm growth (> 80%, 2.3 up to 0.017 µg/mL) (Lara et al., 2020). The antimicrobial activity of chemically synthesized AgNPs at *C. auris* planktonic and biofilm growth stages has shown MIC values set for AgNPs used against different fungal strains (approximately < 0.5 µg/mL under planktonic conditions) in four different clades. On the other hand, values recorded for biofilm formation suppression reached approximately < 2 µg/mL in all tested strains (Vazquez-Muñoz et al., 2020).

Significant AgNPs antifungal and antibiofilm activity (by chemical reduction) was detected against all isolates. MIC was <6.25 µg/mL, MFC ranged from 6.25 to 12.5 µg/mL in all isolates, and the highest IC50 value was 3.2 µg/mL. Silver nanomaterials could represent a possible antimicrobial agent to prevent *C. auris* infection outbreaks (Aljindan et al., 2022).

AgNPs green synthesized with plant *Trillium* (*govanianum* and *Bergenia ligulata*) extract were used in several *C. auris* clinical strains and showed half maximum growth inhibition (IC50) at 8.02 µg/mL, which inhibited 65% biofilm for extract. The use of DPPH showed more than 90% antioxidant activity. Green synthesized AgNPs showed powerful growth inhibition (IC_{50}) at 4.01 µg/mL, at 87.0% biofilm inhibition. Bandages and catheters coated with Green synthesized AgNPs inhibited *C. auris* growth (Verma et al., 2024).

Chaetoceros spp., *Skeletonema* spp., and *Thalassiosira* spp. were used in AgNPs biosynthesis (Ag-DE/NPs). These AgNPs' antifungal efficacy was assessed against 20 clinical samples. This reference *C. auris* strain showed high resistance to fluconazole. AgNPs synthesized from *Chaetoceros* spp. MIC equals 0.23 µg/mL *C. auris* recorded over 250-fold higher power than fluconazole and presented efficiency like that of amphotericin B. Growth curve analysis and sorbitol supplementation assays pointed out Ag-DE/NPs breakdown fungal cell walls, whereas SEM imaging and ergosterol determination highlighted membrane damage and sterol consumption. These findings underscore the Ag-DE/NP potential, mainly of those synthesized from *Chaetoceros* spp., as promising drug to fight drug-resistant fungal contamination or infections (Jain et al., 2025).

e) Violacein

Large violacein biological outlooks as biocide compound were reported, but some patents on violacein and on its derivatives have described these compounds' effectiveness in fungal management and against insect infections (Durán et al. 2021ab). Numerous violacein applications on fungi were published in the last two decades (Durán et al. 2021b, 2025). Several *Cromobacterium violaceum* strains and supernatants have been causing different antifungal action in *Fusarium* sp., and in other species (Barreto et al. 2008). Sasidharan et al. (2015) screened a new *Chromobacterium* sp. strain - NIIST (MTCC 5522) - in clay mine acidic sediment, and it could produce large amounts of violacein. Just as stated by Sasidharan et al. (2015), violacein in association with other antifungal drugs has high potential to be prescribed against fungal contamination. Interestingly, fabrics (polyamide 66) supplemented with *J. lividum*-derived violacein have shown effective antifungal activity against dermatological fungi such as *Candida krusei*, *C. albicans* and *Candida parapsilosis* (Kanelli et al. 2018). Dike-Ndudim et al. (2021) assessed the antifungal action of violacein in *Aspergillus niger* and *C. albicans*, which are two important human mycosis agents, and included fluconazole as relative standard drug. Fluconazole MICs in *C. albicans* and *A. niger* were 25 µg/mL and 50 µg/mL, respectively. However, violacein had significant inhibition activity in *A. nigers* (875 µg/mL) and *C. albicans* (438 µg/mL), besides showing greater activity against the selected fungi than the standard drug, namely: fluconazole. Arif et al. (2017) assessed *J. lividum* violacein association with AgNPs (from glucose) (vAgNPs). Their outcomes have shown vAgNPs'

increased antifungal activity effectiveness even at high dose of 10 mg and 1 mg, in comparison to that of glucose capped AgNPs, alone. Fungal species presented different susceptibility patterns to vAgNPs, as follows: *A. tamari* > *A. tubingensis* > *F. proliferatum* (Durán et al, 2022).

Functional silk composites (FSC) holding violacein combined to AgNPs integration have shown good synergistic properties such as excellent antimicrobial *C. albicans* activities, due to microbial reduction by 99.85%. FSC not only presented enhanced antimicrobial effects, but also a broader antimicrobial range (Gao et al., 2019).

Filamentous Fungal Human Pathogens (FFHPs), such as *Aspergillus fumigatus*, are growing more resistant to currently available antifungal drugs. Nucleoside diphosphate kinase (Ndk), which is significant for nucleotide biosynthesis and crucial for fungal metabolism, is one possible target. Violacein was assessed for its antifungal effects against *Aspergillus fumigatus* through computational approach against protein Ndk. Molecular docking studies have shown significant interaction with good binding energy between Ndk and violacein. Data have suggested that violacein could potentially breakdown nucleotide metabolism by targeting Ndk, thereby showing antifungal activity. Nevertheless, additional experimental validation is needed to confirm these calculations and to explore the practical use of violacein in antifungal treatments (Sindhu et al., 2024). Therefore, nanotechnology based on violacein is a relevant innovation to enhance the antifungal action of new or already-used compounds and to treat fungal infections.

FINAL REMARKS

Candida auris is an emerging multidrug-resistant yeast that has been causing healthcare-associated and serious infections since its discovery in 2009, in a Japanese patient. It has promptly become an important global health threat. This yeast's emergence is frightening as it shows resistance to azoles, echinocandins and amphotericin B, a fact that may guide to clinical therapy failure in infected patients. South America faces one of most prompt emergencies of it. The number of *C. auris* cases in South America has significantly increased in the last five years, mainly because of the pandemic, due to the severe acute respiratory syndrome virus and to the increase of several pan-resistant strains. In response, new alternative methods have been assessed or authorized to be uses against infections caused by *C. auris*. The main problem lies on *C. auris* resistance to usual medicines. This mini-review pointed out all these problems and recommended future research focused on overcoming this rejection. New drug, vaccine and photodynamic process associations, and new nanomaterials, such as silver nanoparticles and violacein, emerge as promising to rule out these infections.

Author contributions

ND, WJF, GN: Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - original draft, Data, collection and analyses, Formal analysis, supervision of manuscript. Final editing manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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