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The multidrug-resistant *Candida auris, Candida haemulonii* complex and phylogenetic related species: Insights into antifungal resistance mechanisms

Lívia S. Ramos [a], Pedro F. Barbosa [a,b], Carolline M.A. Lorentino [a,b], Joice C. Lima [a,b], Antonio L. Braga [a,b], Raquel V. Lima [a,b], Lucas Giovanini [a,b], Ana Lúcia Casemiro [a,b], Nahyara L.M. Siqueira [a,b], Stefanie C. Costa [c], Célia F. Rodrigues [d], Maryam Roudbary [e,f], Marta H. Branquinha [a,b,g], André L.S. Santos [a,b,g,*]

[a] *Laboratório de Estudos Avançados de Microrganismos Emergentes e Resistentes (LEAMER), Departamento de Microbiologia Geral, Instituto de Microbiologia Paulo de Góes (IMPG), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brasil*
[b] *Programa de Pós-Graduação em Ciências (Microbiologia), Instituto de Microbiologia Paulo de Góes (IMPG), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brasil*
[c] *Laboratório de Resistência Bacteriana, Departamento de Patologia, Universidade Federal do Espírito Santo (UFES), Vitória, Brasil*
[d] *Laboratory for Process Engineering, Environment, Biotechnology and Energy, Faculty of Engineering, University of Porto, Porto, Portugal*
[e] *Sydney Infectious Diseases Institute, University of Sydney, Australia*
[f] *Westmead Hospital, NSW Health, Sydney, Australia*
[g] *Rede Micologia RJ, Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Rio de Janeiro, Brasil*

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ABSTRACT

The rise of multidrug-resistant (MDR) fungal pathogens poses a serious global threat to human health. Of particular concern are *Candida auris*, the *Candida haemulonii* complex (which includes C. *haemulonii sensu stricto, C. duobushaemulonii* and *C. haemulonii* var. *vulnera*), and phylogenetically related species, including *C. pseudohaemulonii* and *C. vulturna*. These emerging, widespread, and opportunistic pathogens have drawn significant attention due to their reduced susceptibility to commonly used antifungal agents, particularly azoles and polyenes, and, in some cases, therapy-induced resistance to echinocandins. Notably, *C. auris* is classified in the critical priority group on the World Health Organization's fungal priority pathogens list, which highlights fungal species capable of causing systemic infections with significant mortality and morbidity risks as well as the challenges posed by their MDR profiles, limited treatment and management options. The mechanisms underlying antifungal resistance within these emerging fungal species is still being explored, but some advances have been achieved in the past few years. In this review, we compile current literature on the distribution of susceptible and resistant clinical strains of *C. auris, C. haemulonii* complex, *C. pseudohaemulonii* and *C. vulturna* across various antifungal classes, including azoles (fluconazole, voriconazole, itraconazole), polyenes (amphotericin B), echinocandins (caspofungin, micafungin, anidulafungin), and pyrimidine analogues (flucytosine). We also outline the main antifungal resistance mechanisms identified in planktonic cells of these yeast species. Finally, we explore the impact of biofilm formation, a classical virulence attribute of fungi, on antifungal resistance, highlighting the resistance mechanisms associated with this complex microbial structure that have been uncovered to date.

* Corresponding author.
E-mail address: andre@micro.ufrj.br (A.L.S. Santos).

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Candida auris, the *Candida haemulonii* complex, and phylogenetically related species: emerging, widespread, and multidrug-resistant fungal pathogens

The emergence and spread of multidrug-resistant (MDR) fungal pathogens present a significant threat to human health, creating substantial challenges for physicians in effectively treating affected patients. The scarcity of therapeutic options in clinical practice further exacerbates the difficulty of managing these fungal infections. In this context, *Candida auris* (*Candidozyma auris*) has emerged as a global threat, spreading through nosocomial transmission in over 50 countries across all six continents, rapidly drawing the attention of health authorities worldwide (Kim et al., 2024). The alarming characteristics of *C. auris* have earned it a place in the critical priority group on the World Health Organization's (WHO) fungal priority pathogens list, which includes fungal species capable of causing invasive infections and exhibiting antifungal resistance (WHO, 2022). For example, *Candida glabrata* (*Nakaseomyces glabratus*) is another emerging MDR fungal pathogen of global concern. This haploid yeast demonstrates reduced susceptibility to fluconazole and has a propensity to develop resistance to echinocandins and, to a lesser extent, amphotericin B (Ostrosky-Zeichner, 2013; Healey et al., 2016; Ahmad et al., 2019). As a result, *C. glabrata* has been categorized within the high-priority group on the WHO fungal priority pathogens list (WHO, 2022).

Candida auris belongs to the *Candida/Clavispora* clade within the *Metschnikowiaceae* family, which includes a diverse group of 45 yeast species isolated from a variety of sources, such as humans, insects, flowers, and seawater (Schutz et al., 2024). The *Candida/Clavispora* clade also includes other important MDR species phylogenetic related to *C. auris*, including the *Candida haemulonii* complex (which typically encompasses *Candida haemulonii sensu stricto* [*Candidozyma haemuli*], *Candida duobushaemulonii* [*Candidozyma duobushaemuli*] and *Candida haemulonii* var. *vulnera* [*Candidozyma haemuli* var. *vulneris*]), *Candida vulturna* (*Candidozyma vulturna*) and *Candida pseudohaemulonii* (*Candidozyma pseudohaemuli*) (Cendejas-Bueno et al., 2012; Sipiczki et al., 2016; Schutz et al., 2024). In fact, *C. auris, C. vulturna* and *C. pseudohaemulonii* are often considered members of the *C. haemulonii* clade (*Candida-auris Candida-haemulonii* clade) due to their phylogenetic similarities (Gómez-Gaviria et al., 2023). It is noteworthy that the nomenclature of these species is still evolving. Recently, the genus *Candidozyma* was proposed to encompass members of the *C. haemulonii* clade within the *Metschnikowiaceae* family (Liu et al., 2024). Many species within the *Candidozyma* genus are clinically significant and exhibit resistance to a range of antifungal drugs, a characteristic that distinguishes them from other genera within the *Metschnikowiaceae* family (Liu et al., 2024). Biochemical methods alone are insufficient for the accurate identification of these emerging yeast species, making the use of molecular techniques essential for reliable detection and classification. In this context, *ITS* gene sequencing is regarded as the gold standard for precise identification, offering a reliable and accurate method for differentiating between closely related yeast species (Satoh et al., 2009; Cendejas-Bueno et al., 2012; Sipiczki et al., 2016). In this regard, *C. auris* was first clinically described in 2009, after being isolated from the external ear canal of a Japanese patient (Satoh et al., 2009). However, pinpointing the exact timeline of its association with humans is challenging, as an isolate of *C. auris* was retrospectively identified in Korea in 1996, where it had previously been misidentified as *C. haemulonii* (Kim et al., 2009).

Following its initial description, *C. auris* was progressively reported in South Korea and India, and later across other continents, including Africa, America, Europe, and Oceania (Garcia-Bustos et al., 2023). Early genetic analyzes identified four major clades of *C. auris*, categorized by their geographical regions: South Asian (Clade I), East Asian (Clade II), African (Clade III), and South American (Clade IV) (Ahmad and Alfouzan, 2021). More recently, the discovery of Clade V in Iranian isolates (Spruijtenburg et al., 2022) and Clade VI in Singapore and Bangladesh (Suphavilai et al., 2024; Khan et al., 2024) expanded the known diversity of this pathogen. Evidence suggests that *C. auris* emerged independently and simultaneously in at least four distinct regions, as the clades differ by tens to hundreds of thousands of single-nucleotide polymorphisms. However, strains within the same clade are highly related and nearly clonal, supporting the idea of localized emergence (Lockhart et al., 2017; Brandt et al., 2023).

Over the years, numerous studies have aimed to clarify the similarities and differences among *C. auris* clades. Of the first four clades described, only Clade II has not been linked to outbreaks of invasive infections, being more commonly associated with ear infections (Welsh et al., 2019; Chow et al., 2020). Molecular epidemiology investigations have shown that *C. auris* outbreaks are typically caused by highly related isolates (Sharma et al., 2016; Rhodes et al., 2018; Chow et al., 2020). However, isolates from different clades have been identified in various countries, including Germany, the United States of America, the United Kingdom, Canada, and Kenya, suggesting multiple introduction events followed by local transmission (Chow et al., 2020). The genome of *C. auris* contains conserved mating and meiosis genes; however, each clade exhibits only one of the two fungal mating types – *MTLa* in isolates from Clades I and IV, and *MTLα* in Clades II and III (Muñoz et al., 2018; Chow et al., 2020). While interclade mating has not been observed, this remains a concern, as clades with opposite mating types exist in different regions. If interclade mating were to occur, it could result in increased genetic diversity, potentially enhancing virulence and antifungal resistance (Chow et al., 2020). Notably, *C. auris* isolates with opposite mating types have been found in a healthcare facility in Kenya, where ongoing transmission is concerning (Chow et al., 2020).

The species *C. haemulonii* was first described in 1962, having been isolated from the gut contents of the fish *Haemulon sciurus* and from the waters of Biscayne Bay during studies on yeast flora in marine material from Miami, Florida (Van Uden and Kolipinski, 1962). The first documented case of human infection caused by *C. haemulonii* was reported in 1984, involving a patient with renal failure. Despite treatment with amphotericin B and flucytosine, the patient succumbed to the *C. haemulonii* infection (Lavarde et al., 1984). Lehman et al. (1993) conducted a study on *C. haemulonii* isolates from various geographic locations and clinical sources, identifying two distinct groups – *C. haemulonii* Group I and Group II – based on isoenzyme profiles, phenotypic characteristics, and DNA reassociation experiments. In 2006, the amphotericin B- and azole-resistant species *C. pseudohaemulonii* was first described. This species, isolated from the blood of a patient in Thailand, exhibited similarities to *C. haemulonii* Groups I and II (Sugita et al., 2006). Subsequently, Cendejas-Bueno et al. (2012) proposed a reclassification of the *C. haemulonii* complex, distinguishing *C. haemulonii sensu stricto* (Group I), *C. duobushaemulonii* (Group II), and *C. haemulonii* var. *vulnera*, based on sequencing of the *ITS* and *D1/D2* regions of ribosomal DNA. In 2016, the dimorphic species *C. vulturna*, isolated from flowers and clinical samples, was identified as phylogenetically related to the *C. haemulonii* species complex (Sipiczki et al., 2016). More recently, in 2023, *C. khanbhai* was described as a member of the *C. haemulonii* species complex. It was isolated from human clinical samples, including nasal swabs and blood, further expanding the known diversity within this complex (Jong et al., 2023).

In addition to their substantial resistance to commonly used antifungal agents, these yeast species possess key virulence factors that are critical for establishing and sustaining infections. These include the expression of surface-associated glycoconjugates that promote adhesion to both biotic and abiotic surfaces, such as medical devices and patient care equipment. They also exhibit the ability to form robust biofilms, undergo phenotypic switching, and produce a diverse array of extracellular bioactive molecules, including hydrolytic enzymes (e.g., proteases, esterases, phospholipases, and phytases), as well as hemolysins and toxins. These virulence attributes collectively play a crucial role in enhancing their pathogenicity (Gómez-Gaviria et al., 2023). Moreover, *C. auris* isolates can be categorized as either aggregative or

non-aggregative, with the aggregation phenomenon also observed in the *C. haemulonii* species complex (Fig. 1). However, the role of this phenotype in virulence is still under investigation (Ramos et al., 2023). Additionally, *C. auris* isolates exhibit remarkable halotolerance and thermotolerance, thriving in salt concentrations of approximately 10 % and at temperatures as high as 42 °C. They also demonstrate significant resistance to desiccation, further enhancing their survival in diverse and challenging environments (Satoh et al., 2009).

Unlike other significant *Candida* species, such as *C. albicans* and *C. glabrata*, which are part of the gastrointestinal microbiota of humans and animals, *C. auris* predominantly colonizes the human skin surface – a warm and salty environment. This unique habitat facilitates its transmissibility between patients and the surrounding environment, contributing to outbreak occurrences (Schutz et al., 2024). Adding to the challenge, *C. auris* can persist in the environment for extended periods, demonstrating resistance to many common disinfectants used in hospital settings. This resilience is particularly pronounced when *C. auris* appears in its aggregative form or as part of wet biofilms, further enhancing its persistence and spread (Omardien and Teska, 2024). For example, *C. auris* frequently colonizes areas such as the axilla, groin, nares, respiratory tract, and urinary tract of hospitalized patients. It has also been shown to persist on reusable axillary temperature probes used on skin surfaces, aligning with higher isolation frequencies of *C. auris* from the axilla compared to other body sites (Cristina et al., 2023).

Candida auris and the *C. haemulonii* species complex are capable of causing infections with diverse clinical manifestations, ranging from superficial to deep-seated infections (Gómez-Gaviria et al., 2023). These species have been isolated from a variety of anatomical sites, including nails, bone, breast, ear, blood, among others (Gómez-Gaviria et al., 2023). A significant concern with these emerging *Candida* species is their resistance to commonly used antifungal agents, which often leads to treatment failures. This resistance is closely linked to increased morbidity and mortality rates, with *C. auris* infections showing mortality rates as high as 72 % in some instances (Ahmad and Alfouzan, 2021). Clinical isolates of these *Candida* species have demonstrated resistance to all major classes of antifungal drugs, including azoles, polyenes, and echinocandins, a topic that will be explored in detail in the following sections.

A comprehensive review of antifungal resistance in *C. auris* and the *C. haemulonii* species complex

This exercise entailed compiling available data on the susceptibility and resistance profiles of *C. auris* and the *C. haemulonii* species complex to antifungal agents across four major drug classes: azoles (fluconazole – FLC, voriconazole – VRC, itraconazole – ITC), polyenes (amphotericin B – AMB), echinocandins (caspofungin – CSF, micafungin – MFG, anidulafungin – ANF), and pyrimidine analogues (flucytosine – 5-FC). The literature search was conducted via the PubMed database (https://pubmed.ncbi.nlm.nih.gov), encompassing peer-reviewed articles published up to July 30, 2024. The term "Candida auris antifungal resistance" was added in the category "title/abstract" in the PubMed database to search the papers that used *C. auris*, and for the species belonging to the *C. haemulonii* complex the following terms were used: "Candida haemulonii antifungal resistance"; "Candida haemulonii var. vulnera antifungal resistance"; "Candida duobushaemulonii antifungal resistance"; "Candida pseudohaemulonii antifungal resistance" and "Candida vulturna antifungal resistance". English-language papers published between 2014 and 2024 that utilized molecular approaches for identifying clinical isolates were analyzed. Each paper was carefully reviewed to select those reporting minimum inhibitory concentration (MIC) values for antifungals from various classes against the *Candida* species included in this study. For interpretation of the resistance profile of *C. auris* against the antifungals, the tentative MIC breakpoints suggested by the Centers for Disease Control and Prevention (CDC, USA) were used as reference: FLC $\geq$ 32 μg/mL; AMB $\geq$ 2 μg/mL; CSF $\geq$ 2 μg/mL; MFG $\geq$ 4 μg/mL; ANF $\geq$ 4 μg/mL. The resistance profile of the *C. haemulonii* species complex was analyzed using the breakpoints recommended by the CDC for *C. auris* (FLC, AMB, CSF, MFG and ANF). For antifungals lacking CDC breakpoints (VRC, ITR and 5-FC), the breakpoints from the CLSI M27S3 protocol for *Candida* spp. were applied to both *C. auris* and the *C. haemulonii* complex, as well as phylogenetically related species (VRC $\geq$ 4 μg/mL; ITC $\geq$ 1 μg/mL; 5-FC $\geq$ 32 μg/mL) (CLSI, 2008).

The results of this literature review offer critical insights into the susceptibility and resistance profiles of *C. auris* clinical isolates to various antifungal agents (Table 1). Overall, resistance to azoles was notably higher than to other antifungal classes. A significant majority of the *C. auris* isolates, approximately 88.4 %, exhibited resistance to FLC. This high level of resistance to FLC is particularly concerning, given its widespread use in the treatment of *Candida* infections (Jangir et al., 2023). Additionally, the prophylactic use of FLC, commonly administered to high-risk patients, may contribute to selective pressure that drives resistance, even though it is not recommended to prevent *C. auris* infections. Similar patterns have been observed in other species, such as *C. glabrata* and *C. parapsilosis*, where prolonged exposure to antifungals has been linked to increased resistance (Trevijano-Contador et al., 2022). It is important to highlight that *C. auris* isolates belonging mainly to Clade I and Clade IV are intrinsically resistant to FLC, while isolates of Clade II exhibit variable susceptibility to this antifungal (Chowdhary et al., 2023). In addition to FLC, considerable resistance was also observed against VRC and ITC, with resistance rates of 51.1 % and 35 %, respectively. Although resistance to these azoles is lower than to FLC, it still poses a challenge for effective treatment of *C. auris* infections (Kim et al., 2024). Regarding polyenes, specifically AMB, 32.6 % of *C. auris* isolates showed resistance to this antifungal. AMB is renowned for its broad-spectrum antifungal activity, including its effectiveness against *Candida* species, and is commonly used in treating severe infections due to its potent fungicidal properties (Jafari et al., 2022). However, the reported resistance in approximately one-third of *C. auris* isolates is concerning, as it could undermine the efficacy of this crucial last-line treatment. Some studies suggest that the high rates of AMB resistance among *C. auris* isolates may be linked to issues with *in vitro* antifungal susceptibility testing methods, which may not accurately reflect the true resistance profiles of the pathogen (Siopi et al., 2023; Asadzadeh et al., 2024). In contrast, echinocandins and 5-FC appear to be more effective against *C. auris*. In this sense, the *C. auris* isolates exhibited relatively low resistance rates to echinocandins, with 8.6 % resistance to CSF, 7.3 % to ANF, and 5.3 % to MFG. This susceptible profile aligns with current literature, which recognizes echinocandin drugs as first-line treatments for invasive *Candida* infections (Pappas et al., 2016). However, when evaluating echinocandins, the Eagle effect, or paradoxical growth effect, should be carefully considered, as it can lead to inconsistent results in antifungal susceptibility testing. This phenomenon occurs when high antifungal concentrations, exceeding the MIC values, result in reduced drug efficacy against the fungus. The Eagle effect has been documented in both *C. auris* and the *C. haemulonii* species complex (Cendejas-Bueno et al., 2012; Kordalewska et al., 2018; Ahmad and Alfouzan, 2021). Similarly to echinocandins, 5-FC demonstrated high efficacy, with only 5 % of *C. auris* isolates showing resistance to this antifungal. However, the use of 5-FC as monotherapy is generally discouraged due to its propensity to rapidly induce resistance, which may lead to treatment failure (Delma et al., 2021). As a result, 5-FC is typically used in combination therapies to minimize this risk. Notably, 51 *C. auris* isolates (0.4 %) were identified as MDR to antifungal agents from three distinct classes. This finding highlights the urgent need for continuous surveillance and a deeper understanding of resistance mechanisms to effectively manage and prevent infections caused by MDR strains (Chowdhary et al., 2014; Chakrabarti et al., 2015; Kathuria et al., 2015; Calvo et al., 2016; Vallabhaneni et al., 2016; Arendrup et al., 2017; Ben-Ami et al., 2017; Fakhim et al., 2017; Larkin et al., 2017; Lockhart et al., 2017; Rudramurthy et al., 2017; Ruiz Gaitán et al., 2017; Berkow and Lockhart, 2018; Chowdhary et al., 2018; Hashemi et al., 2018;

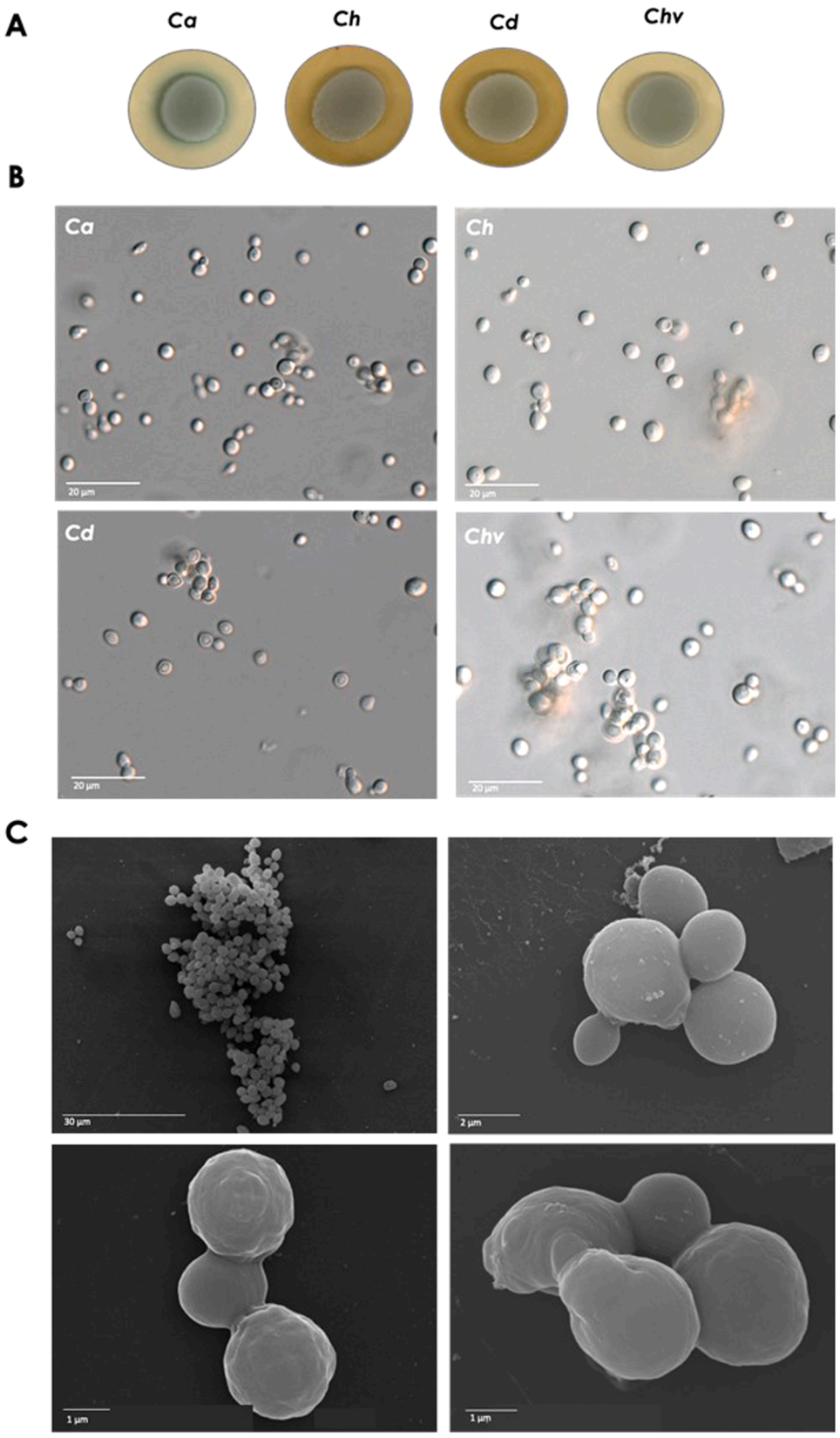

Fig. 1. *Candida auris* and *Candida haemulonii* species complex macromorphology in CHROMagar™ Candida Plus after 48 h at 37 °C (A) and micromorphology evaluated by light microscopy (B) and by scanning electron microscopy (C), in which can be observed homogeneous populations of yeasts with oval shape, composed both by single and aggregated cells. *Ca*, means *C. auris; Ch, C. haemulonii; Cd, C. duobushaemulonii* and *Chv, C. haemulonii* var. *vulnera*.

Table 1
Distribution (%) of susceptible (S) and resistant (R) isolates among 12,216 *C. auris* and 474 *C. haemulonii* species complex clinical isolates against various antifungal agents: A compilation of literature from published papers available until July 30, 2024.

Fungal species	Susceptibility profile*															
	FLC		VRC		ITC		AMB		CSF		MFG		AFN		5-FC	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
C. auris[a]	11.6	88.4	48.9	51.1	65	35	67.4	32.6	91.4	8.6	94.7	5.3	92.7	7.3	95	5
***n* = 10,428**	***n* = 9546**		***n* = 4818**		***n* = 3251**		***n* = 9242**		***n* = 7663**		***n* = 2684**		***n* = 4982**		***n* = 2091**	
C. haemulonii sensu stricto[b]	27.6	72.4	60.1	39.9	43	57	18	82	99	1	95.1	4.9	100	0	37	63
***n* = 261**	***n* = 247**		***n* = 236**		***n* = 112**		***n* = 150**		***n* = 205**		***n* = 62**		***n* = 107**		***n* = 100**	
C. haemulonii var. *vulnera*[c]	3.8	96.2	23.6	76.4	31.3	68.7	53	47	100	0	100	0	100	0	96.4	3.6
***n* = 34**	***n* = 34**		***n* = 34**		***n* = 16**		***n* = 34**		***n* = 19**		***n* = 16**		***n* = 31**		***n* = 28**	
C. duobushaemulonii[d]	55.6	44.4	90.3	9.7	84.8	15.2	56.3	43.7	98.7	1.3	100	0	100	0	100	0
***n* = 138**	***n* = 138**		***n* = 93**		***n* = 79**		***n* = 94**		***n* = 79**		***n* = 77**		***n* = 82**		***n* = 26**	
C. pseudohaemulonii[e]	66.6	33.3	100	0	100	0	37.5	62.5	100	0	100	0	100	0	–	–
***n* = 16**	***n* = 6**		***n* = 6**		***n* = 6**		***n* = 16**		***n* = 6**		***n* = 6**		***n* = 6**		–	
C. vulturna[f]	20	80	20	80	20	80	4	96	4.2	95.8	100	0	100	0	100	0
***n* = 25**	***n* = 25**		***n* = 25**		***n* = 25**		***n* = 25**		***n* = 24**		***n* = 25**		***n* = 24**		***n* = 20**	

*Antifungal susceptibility testing against *C. auris, C. haemulonii* species complex and phylogenetically related species was interpreted according to the tentative MIC breakpoints suggested by CDC for *C. auris*, and for antifungals lacking CDC breakpoints (VRC, ITR and 5-FC), the breakpoints from the CLSI M27S3 protocol for *Candida* spp. were applied to all species; *n*, number of fungal isolates; FLC, fluconazole; VRC, voriconazole; ITC, itraconazole; AMB, amphotericin B; CSF, caspofungin; MFG, micafungin; ANF, anidulafungin; 5-FC, flucytosine; the references used to construct this table were:.

[a] References used for *C. auris*: Chowdhary et al., 2014; Chakrabarti et al., 2015; Kathuria et al., 2015; Calvo et al., 2016; Vallabhaneni et al., 2016; Arendrup et al., 2017; Ben-Ami et al., 2017; Fakhim et al., 2017; Larkin et al., 2017; Lockhart et al., 2017; Rudramurthy et al., 2017; Ruiz Gaitán et al., 2017; Berkow and Lockhart, 2018; Chowdhary et al., 2018; Hashemi et al., 2018; Kordalewska et al., 2018; Pathirana et al., 2018; Rhodes et al., 2018; Tian et al., 2018; Dal Mas et al., 2019; Kwon et al., 2019; Mohammad et al., 2019; Sayeed et al., 2019; Tan et al., 2019; Vatanshenassan et al., 2019; Ahmad et al., 2020; Almaghrabi et al., 2020; Ahsan Sayeed et al., 2020; Chakrabarti et al., 2020; Chow et al., 2020; Chowdhary et al., 2020; Levy et al., 2020; Ninan et al., 2020; O'Brien et al., 2020a, 2020b; Rossoni et al., 2020; Shaban et al., 2020; Shaukat et al., 2020; Wu et al., 2020; Zhu et al., 2020a;; Zhu et al., 2020b; AlJindan et al., 2021; Allaw et al., 2021; Bacchani et al., 2021; Berrio et al., 2021; Bing et al., 2021; Dong et al., 2021; Du et al., 2021; Fuchs et al., 2021; Groot et al., 2021; Hagras et al., 2021; Kamli et al., 2021; Kumar et al., 2021; Li et al., 2021a, 2021b; Maphanga et al., 2021; Naicker et al., 2021; Pandya et al., 2021; Price et al., 2021; Tan et al., 2021; Umamaheshwari et al., 2021; Zhou et al., 2021; Al-Obaid et al., 2022; Burrack et al., 2022; Deshkar et al., 2022; Escandón et al., 2022; Fuchs et al., 2022; González-Durán et al., 2022; Ismail et al., 2022; Jacobs et al., 2022; Jenull et al., 2022; Kilburn et al., 2022; Liu et al., 2022; Maphanga et al., 2022; Narayanan et al., 2022; Prayag et al., 2022; Poester et al., 2022; Rather et al., 2022; Reslan et al., 2022; Rybak et al., 2022; Shahi et al., 2022; Sharma et al., 2022; Shivarathri et al., 2022; Spruijtenburg et al., 2022; Williamson et al., 2022; Zapata-Zapata et al., 2022; Alam et al., 2023; Alvarez-Moreno et al., 2023; Ben Abid et al., 2023; Ceballos-Garzon et al., 2023; de-la-Fuente et al., 2023; Di Vito et al., 2023; Du et al., 2023; Elgammal et al., 2023; Hirayama et al., 2023; John et al., 2023; Katsiari et al., 2023; Kekana et al., 2023; Khodavaisy et al., 2023; Kiyohara et al., 2023; Koleri et al., 2023; Kordalewska et al., 2023; Kurakado et al., 2023; St. Maurice et al., 2023; Mulet et al., 2023; Rasouli Koohi et al., 2023; Shaban et al. 2023; Spettel et al., 2023; Spruijtenburg et al., 2023; Stanciu et al., 2023; Toepfer et al., 2023; Vazquez et al., 2023; Zhu et al., 2023; Ali et al., 2024; Cavallo et al., 2024; Griffith et al., 2024; Hernando-Ortiz et al., 2024; Jaromin et al., 2024; Khan et al., 2024; Misas et al., 2024; Munshi et al., 2024; Osaigbovo et al., 2024; Patwardhan et al., 2024; Politi et al., 2024; Spruijtenburg et al., 2024; Stieber et al., 2024; Thomsen et al., 2024; Tian et al., 2024; Vélez et al., 2024.

[b] References used for *C. haemulonii sensu stricto*: Muro et al., 2012; Shin et al., 2012; Ramos et al., 2015; Silva et al., 2015; Pagani et al., 2016; Ben-Ami et al., 2017; Aslani et al., 2019; Zhang et al., 2019; Gade et al., 2020; Lima et al., 2020; Xiao et al., 2020; Desnos-Ollivier et al., 2021; Moreira et al., 2021; Pharkjaksu et al., 2021; Rodrigues et al., 2021; Li et al., 2022; Ramos et al., 2022; Pagani et al., 2022; Chen et al., 2023; Silva et al., 2023a; Hanifah et al., 2024.

[c] References used for *C. duobushaemulonii*: Ramos et al., 2015; Frías-De-León et al., 2019; Zhang et al., 2019; Gade et al., 2020; Lima et al., 2020; Desnos-Ollivier et al., 2021; Rodrigues et al., 2021; Chen et al., 2022; Ramos et al., 2022.

[d] References used for *C. haemulonii* var. *vulnera*: Ramos et al., 2015; Lima et al., 2020; Rodrigues et al., 2021; Ramos et al., 2022.

[e] References used for *C. pseudohaemulonii*: Shin et al., 2012; Gade et al., 2020.

[f] References used for *C. vulturna*: Gade et al., 2020; Du et al., 2023; Setoguchi et al., 2024.

Kordalewska et al., 2018; Pathirana et al., 2018; Rhodes et al., 2018; Tian et al., 2018; Dal Mas et al., 2019; Kwon et al., 2019; Mohammad et al., 2019; Sayeed et al., 2019; Tan et al., 2019; Vatanshenassan et al., 2019; Ahmad et al., 2020; Almaghrabi et al., 2020; Ahsan Sayeed et al., 2020; Chakrabarti et al., 2020; Chow et al., 2020; Chowdhary et al., 2020; Levy et al., 2020; Ninan et al., 2020; O'Brien et al., 2020a, 2020b; Rossoni et al., 2020; Shaban et al., 2020; Shaukat et al., 2020; Wu et al., 2020; Zhu et al., 2020a;; Zhu et al., 2020b; AlJindan et al., 2021; Allaw et al., 2021; Bacchani et al., 2021; Berrio et al., 2021; Bing et al., 2021; Dong et al., 2021; Du et al., 2021; Fuchs et al., 2021; Groot et al., 2021; Hagras et al., 2021; Kamli et al., 2021; Kumar et al., 2021; Li et al., 2021a, 2021b; Maphanga et al., 2021; Naicker et al., 2021; Pandya et al., 2021; Price et al., 2021; Tan et al., 2021; Umamaheshwari et al., 2021; Zhou et al., 2021; Al-Obaid et al., 2022; Burrack et al., 2022; Deshkar et al., 2022; Escandón et al., 2022; Fuchs et al., 2022; González-Durán et al., 2022; Ismail et al., 2022; Jacobs et al., 2022; Jenull et al., 2022; Kilburn et al., 2022; Liu et al., 2022; Maphanga et al., 2022; Narayanan et al., 2022; Prayag et al., 2022; Poester et al., 2022; Rather et al., 2022; Reslan et al., 2022; Rybak et al., 2022; Shahi et al., 2022; Sharma et al., 2022; Shivarathri et al., 2022; Spruijtenburg et al., 2022; Williamson et al., 2022; Zapata-Zapata et al., 2022; Alam et al., 2023; Alvarez-Moreno et al., 2023; Ben Abid et al., 2023; Ceballos-Garzon et al., 2023; de-la-Fuente et al., 2023; Di Vito et al., 2023; Du et al., 2023; Elgammal et al., 2023; Hirayama et al., 2023; John et al., 2023; Katsiari et al., 2023; Kekana et al., 2023; Khodavaisy et al., 2023; Kiyohara et al., 2023; Koleri et al., 2023; Kordalewska et al., 2023; Kurakado et al., 2023; St. Maurice et al., 2023; Mulet et al., 2023; Rasouli Koohi et al., 2023; Shaban et al. 2023; Spettel et al., 2023; Spruijtenburg et al., 2023; Stanciu et al., 2023; Toepfer et al., 2023; Vazquez et al., 2023; Zhu et al., 2023; Ali et al., 2024; Cavallo et al., 2024; Griffith et al., 2024; Hernando-Ortiz et al., 2024; Jaromin et al., 2024; Khan et al., 2024; Misas et al., 2024; Munshi et al., 2024; Osaigbovo et al., 2024; Patwardhan et al., 2024; Politi et al., 2024; Spruijtenburg et al., 2024; Stieber et al., 2024; Thomsen et al., 2024; Tian et al., 2024; Vélez et al., 2024).

Regarding the *C. haemulonii* species complex, *C. haemulonii sensu stricto* was the most prevalent species in susceptibility tests, followed by *C. duobushaemulonii, C. haemulonii* var. *vulnera, C. vulturna* and *C. pseudohaemulonii* (Table 1). A notably high percentage of azole resistance was observed in *C. haemulonii sensu stricto, C. haemulonii* var. *vulnera* and *C. vulturna*. Specifically, *C. haemulonii sensu stricto* exhibited resistance rates of 72.4 % to FLC and 57 % to ITC, while showing a lower

resistance rate to VRC at 39.9 %. In comparison, *C. haemulonii* var. *vulnera* exhibited extremely high resistance rates to FLC (96.2 %), along with significant resistance to both VRC (76.4 %) and ITC (68.7 %). Similarly, *C. vulturna* displayed resistance rates of 80 % to FLC, VRC, and ITC. In contrast, *C. duobushaemulonii* and *C. pseudohaemulonii* generally exhibited lower azole resistance. Specifically, *C. duobushaemulonii* showed resistance rates of 44.4 % to FLC, 9.7 % to VRC, and 15.2 % to ITC, while *C. pseudohaemulonii* had a 33.3 % resistance rate to FLC and no resistance to either VRC or ITC. For polyenes, specifically AMB, high resistance rates were noted in *C. haemulonii sensu stricto* and *C. vulturna*, with resistance percentages of 82 % and 96 %, respectively. The remaining species within the *C. haemulonii* complex demonstrated similar intermediate resistance patterns to this antifungal agent, with resistance rates ranging from 43.7 % to 62.5 %. In contrast, echinocandins and 5-FC were more effective against isolates of the *C. haemulonii* species complex. CSF, MFG, and ANF demonstrated higher susceptibility rates across all species in this fungal complex, indicating greater effectiveness. Specifically, *C. haemulonii sensu stricto* showed only 1 % resistance to CSF, 4.9 % resistance to MFG, and no resistance to ANF. Similarly, *C. duobushaemulonii* exhibited only 1.3 % resistance to CSF, with no resistance observed to MFG or ANF. *C. pseudohaemulonii, C. vulturna*, and *C. haemulonii* var. *vulnera* showed no resistance to CSF, MFG, or ANF, reinforcing echinocandins as a promising class of antifungals for treating infections caused by these emerging yeast species. Lastly, 5-FC exhibited a substantial resistance rate of 63 % in *C. haemulonii sensu stricto*. Conversely, all other species within the *C. haemulonii* complex showed low resistance rates to 5-FC, with resistance percentages not exceeding 3.6 % (Muro et al., 2012; Shin et al., 2012; Ramos et al., 2015; Silva et al., 2015; Pagani et al., 2016; Ben-Ami et al., 2017; Aslani et al., 2019; Frías-De-León et al., 2019; Zhang et al., 2019; Gade et al., 2020; Lima et al., 2020; Xiao et al., 2020; Desnos-Ollivier et al., 2021; Moreira et al., 2021; Pharkjaksu et al., 2021; Rodrigues et al., 2021; Chen et al., 2022; Li et al., 2022; Ramos et al., 2022; Pagani et al., 2022; Chen et al., 2023; Du et al., 2023; Silva et al., 2023a; Hanifah et al., 2024; Setoguch et al., 2024). This highlights the potential efficacy of echinocandins and 5-FC in managing infections caused by these MDR fungal pathogens.

The current literature underscores the alarming resistance profiles of *C. auris* and species within the *C. haemulonii* complex to the primary antifungal classes used in clinical practice (Fig. 2). This resistance presents significant challenges in the management of infections caused by these emergent pathogens. The following sections provide an in-depth discussion of the antifungal resistance mechanisms associated with the three main classes of antifungal agents – azoles, polyenes, and echinocandins – identified in these fungal species.

Mechanisms of resistance to azoles

Among the principal antifungal agents available in clinical medicine, the azole class is the most extensive and widely used, encompassing prophylactic applications in certain cases. Azoles are synthetic molecules characterized by a heterocyclic ring attached to an aliphatic chain with a phenyl group. These drugs are classified into imidazoles or triazoles based on the number of nitrogen atoms in the azole ring (two for

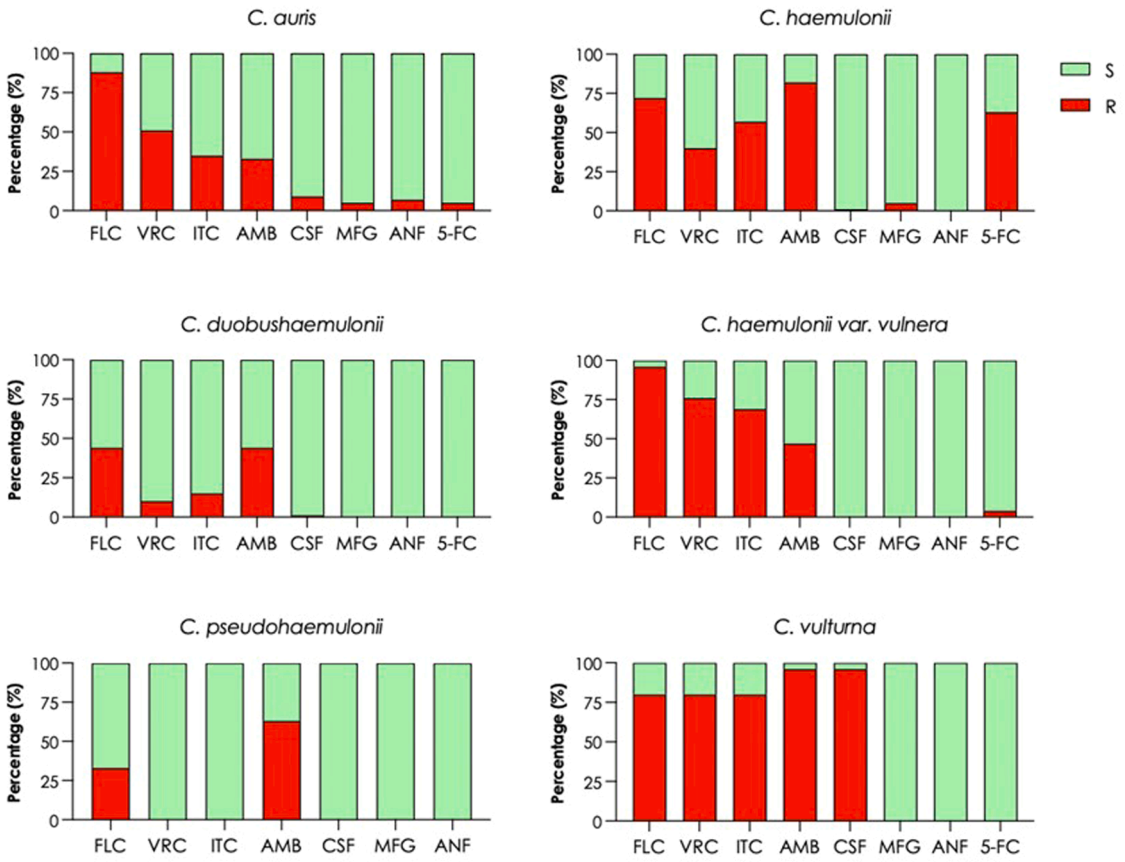

Fig. 2. Distribution of susceptible (S) and resistant (R) strains of *Candida auris* and the *Candida haemulonii* species complex against fluconazole (FLC), voriconazole (VRC), itraconazole (ITC), amphotericin B (AMB), caspofungin (CSF), micafungin (MFG), anidulafungin (ANF) and flucytosine (5-FC) based on the literature review. The search was conducted in PubMed database (https://pubmed.ncbi.nlm.nih.gov) using the terms "Candida auris antifungal resistance"; "Candida haemulonii antifungal resistance"; "Candida haemulonii var. vulnera antifungal resistance"; "Candida duobushaemulonii antifungal resistance"; "Candida pseudohaemulonii antifungal resistance" and "Candida vulturna antifungal resistance" in the category "title/abstract". Papers available in English published from 2014 to 2024, that used molecular approaches for the identification of the clinical isolates were analyzed.

imidazoles and three for triazoles) (Quiles-Melero and García-Rodríguez, 2021). The primary azoles employed in clinical settings include FLC, ITC, VRC, posaconazole and isavuconazole (Pappas et al., 2016). The primary mechanism of action of azoles involves inhibiting lanosterol 14α-demethylase (encoded by the *ERG11* gene in yeasts), thus blocking the biosynthesis of ergosterol, which is a key component of the fungal cell membrane (Perlin et al., 2017; Quiles-Melero and García-Rodríguez, 2021). However, resistance to azole drugs can develop through several mechanisms, enabling fungi to evade their inhibitory effects. These include the overexpression of drug-efflux pumps (mainly those belonging to the ATP-binding cassette (ABC) and major facilitator superfamily (MFS) transporters), mutations in the *ERG11* gene (the target of azoles, reducing azole binding affinity and diminishing their efficacy), and increased *ERG11* gene expression (the aneuploidy or chromosomal rearrangements can lead to overexpression of the *ERG11* gene, counteracting drug effects). Additionally, mutations in other genes involved in ergosterol biosynthesis, such as *ERG3*, can contribute to resistance by bypassing the inhibition of ergosterol biosynthesis. Fungi may also activate stress response pathways, such as the calcineurin signaling pathway or the Hsp90 chaperone system, which enable fungal cells to adapt and survive in the presence of azoles. Moreover, biofilm-associated resistance plays a role, as fungal cells within biofilms exhibit enhanced protection against azoles due to a combination of reduced drug penetration, increased efflux pump activity, and a resilient extracellular matrix (Morio et al., 2010; Zhang et al., 2019; Silva et al., 2020a; Chen et al., 2021).

The primary efflux pumps in the *C. haemulonii* complex are encoded by the genes *ChCDR1, ChCDR2*, and *ChMDR1*, which share a high degree of homology with the corresponding genes *CDR1, CDR2*, and *MDR1* found in *C. albicans* (Silva et al., 2020a). Notably, strains of the *C. haemulonii* complex naturally exhibit significantly higher efflux pump activity compared to other clinically relevant non-*albicans Candida* species (Silva et al., 2020a). Interestingly, the activity of these efflux pumps appears to be constitutive, as their expression and function are unaffected by the presence or absence of azoles (Zhang et al., 2019; Silva et al., 2020a). Furthermore, the use of efflux pump inhibitors has been shown to reduce azole resistance by 4- to over 64-fold, underscoring the critical role of efflux pumps in the azole resistance phenotype (Zhang et al., 2019; Silva et al., 2020a).

In the context of ergosterol biosynthesis, identifying a universal mutation in the *ERG11* gene that consistently leads to resistance across clinical isolates of the *C. haemulonii* complex appears unlikely. Instead, various point mutations collectively contribute to reduced susceptibility to azole compounds (Zhang et al., 2019; Rodrigues et al., 2020; Silva et al., 2020a). For example, a recently reported missense mutation in the *ERG11* gene, specifically A395T, resulting in the amino acid substitution Y132H, increased resistance of a *C. haemulonii* strain by 4-fold to VRC and 8-fold to FLC (Morio et al., 2010; Chen et al., 2021). Additionally, eight mutations identified in *ERG11* in *C. haemulonii* complex isolates by Silva et al. (2020a) have previously been implicated in azole resistance in *C. albicans*. These mutations include F105L, S110A, D116A, K119S, D153E, R267T, A432S, and F487Y. Among these, the K119S substitution was observed exclusively in *C. haemulonii sensu stricto* and *C. haemulonii* var. *vulnera*, whereas R267T and A432S were specific to *C. duobushaemulonii* (Silva et al., 2020a). Notably, the sterol profile of species within the *C. haemulonii* complex closely resembles that of other *Candida* species harboring mutations in *ERG2, ERG3, ERG6*, and *ERG11*, which are associated with cross-resistance to azoles and AMB (Silva et al., 2020a). Furthermore, in *C. vulturna*, a point mutation in the *ERG11* gene resulting in a P135S substitution has been linked to azole resistance (Macedo et al., 2024). These findings emphasize the genetic diversity and complexity of azole resistance mechanisms within the *C. haemulonii* species complex.

In *C. auris*, Byun et al. (2023) reported that isolates exhibiting increased resistance to FLC possessed an elevated number of copies of chromosomes 3 and 5. These chromosomes harbor key genes associated with azole resistance, including *TAC1A, TAC1B, ERG9, ERG11*, and *ERG13*. The amplification of these chromosomal regions likely contributes to the overexpression of these genes, enhancing the resistance phenotype (Byun et al., 2023). Furthermore, Burrack et al. (2022) demonstrated that numerous *C. auris* isolates, whether innately resistant to FLC or having acquired resistance, exhibited heightened expression of genes located on chromosome 5. Remarkably, this increased gene expression could be induced in previously susceptible strains after only three passages in a medium containing FLC. This rapid adaptability highlights the dynamic nature of *C. auris* in developing resistance through transcriptional and chromosomal changes under antifungal pressure (Burrack et al., 2022; Byun et al., 2023).

Ben-Ami et al. (2017) demonstrated that *C. auris* strains exhibit intrinsically and constitutively higher efflux pump activity compared to other non-*albicans Candida* species, contributing significantly to their azole resistance profile. The *MRR1* gene, which encodes the transcription factor Mrr1, plays a crucial role in regulating the expression of the *MDR1* gene. The *MDR1* gene encodes Mdr1-type efflux pumps, which play a critical role in azole resistance in the *Candida* genus. Additionally, Li et al. (2022) identified a specific amino acid substitution, N647T, in the Mrr1 transcription factor. This substitution was shown to enhance azole resistance in *C. auris* by upregulating the expression of the *MDR1* gene, further underscoring the importance of transcriptional regulation and efflux pump activity in the antifungal resistance mechanisms of this pathogen.

The *TAC1* genes encode transcription factors that regulate the expression of *CDR1* and *CDR2* genes, which control efflux pumps associated with azole resistance in the *Candida* genus (Rybak et al., 2020; Carolus et al., 2021; Ben et al., 2023). This regulatory role was confirmed by studies showing that originally resistant *C. auris* strains displayed reduced resistance to FLC following knockout of the *TAC1A* and *TAC1B* genes (Li et al., 2023). Several mutations in the *TAC1B* gene have been linked to azole resistance. Notable mutations include N690S and S19I (Rybak et al., 2019); A640V (Burrack et al., 2022; Byun et al., 2023); V742A, L760S, F214S, and P595L (Byun et al., 2023); Q503E (Hong et al., 2023); and S611P and F214L (Li et al., 2023; Chen et al., 2024). Additional mutations, such as A583S (Chen et al., 2024), and codon deletions (ttc/F15) (Carolus et al., 2021), have also been associated with resistance. Furthermore, mutations in the *CDR1* gene, such as E709D and alterations in *SNQ2*, have been shown to result in higher expression of *CDR1*-type efflux pumps (Ben et al., 2023; Bohner et al., 2023). Variations in amino acids like E709D (Hong et al., 2023; Chen et al., 2024) are also reported to enhance efflux pump activity, further contributing to the resistance phenotype (Ben et al., 2023; Bohner et al., 2023; Hong et al., 2023).

Several mutations in *ERG11* are correlated with increased azole resistance in *C. auris*, such as F444L (Li et al., 2023), Y132F (Chowdhary et al., 2018; Ahmad et al., 2020; Bing et al., 2020; Burrack et al., 2022; Ben et al., 2023; Byun et al., 2023; Hong et al., 2023; Chen et al., 2024), K143R (Chowdhary et al., 2018; Ahmad et al., 2020; Bing et al., 2020; Burrack et al., 2022; Ben et al., 2023; Byun et al., 2023; Casimiro-Ramos et al., 2024), L43H, and Q357K (Byun et al., 2023), T220L (Ceballos-Garzon et al., 2023), T227I (Burrack et al., 2022), F105L, S110A, D116A, K119S, R267T, E291K, A432S, N440V, F487K, D153E, I62V, L282T, and V437T (Chowdhary et al., 2018). Among these mutations, Y132F and K143R amino acid substitutions are notably the most frequently found and commonly associated with azole resistance, with an increase of about 5- to 7-fold in FLC resistance (Chowdhary et al., 2018). However, it was observed that 12 isolates harboring the Y132F mutation remained susceptible to VRC, suggesting that this single mutation is insufficient to confer comprehensive azole resistance (Ahmad et al., 2020; Bing et al., 2020). Li et al. (2023) also observed that *C. auris* strains with the F444L mutation exhibited a 4- to 16-fold increase in MIC for azoles. However, when the *ERG11* gene was inhibited, some resistant strains showed an increase in lanosterol and obtusifoliol sterols, with a prominent presence of the 14-Me-fecosterol metabolite, suggesting the

activation of an alternative sterol biosynthesis pathway (Bohner et al., 2023).

The *UPC2* gene plays a crucial role in the azole resistance of *C. auris* (Byun et al., 2023; Li et al., 2024), as it acts as a key transcription factor regulating both Cdr1 and Mdr1-type efflux pumps. Additionally, *UPC2* gene regulates the transcription of Mrr1, another transcription factor for Mdr1-type pumps, and influences the expression of the *ERG11* gene, which is involved in ergosterol biosynthesis in *C. auris* (Li et al., 2024). Notably, two missense mutations in *UPC2*, A506V and C444Y, have been linked to enhanced azole resistance (Byun et al., 2023). Li et al. (2024) demonstrated that *UPC2* overexpression in *C. auris* led to significantly increased expression of the *MRR1* and *MDR1* genes, which in turn contributed to higher azole resistance. Conversely, deletion of *UPC2* resulted in increased azole susceptibility due to reduced expression of *MRR1* and *MDR1* (Li et al., 2024). This finding suggests that *UPC2* plays a central role in maintaining resistance profiles in *C. auris*, even in strains overexpressing other efflux pump transcription factors such as *TAC1B* and *MRR1*. In the absence of *UPC2*, these strains became more susceptible to azoles (Li et al., 2024). It is also noteworthy that *UPC2* has been shown to regulate *MDR1* expression directly, and more robustly than *MRR1* (Li et al., 2024). Moreover, *C. auris* strains with hyperactivated *UPC2*, even in the absence of *MDR1*, maintained their resistance profiles, likely through the stimulatory effect of *UPC2* on the ergosterol biosynthesis pathway (Li et al., 2024).

Since the *erg3Δ* phenotype had not been previously reported in *C. auris*, Gregor et al. (2023) conducted genetic manipulations to delete the *ERG3* gene in this species, aiming to investigate its role in azole resistance. The resulting mutant *C. auris* strains exhibited azole resistance, akin to *C. glabrata* strains, demonstrating the conserved function of *ERG3* gene in *C. auris*. This observation underscores the essential role of *ERG3* in the production of the toxic sterol 14α-methyl-3,6-diol, as highlighted by Gregor et al. (2023).

Chow et al. (2023) demonstrated that mutation of the E3 ligase *Ubr2* or its adaptor *Mub1* results in high FLC resistance through the stabilization of the transcription activator, Rpn4, leading to elevated levels of Rpn4 in the cell. Through global transcriptome analysis, quantitative PCR, and combinatorial gene deletion, they found that in *ubr2Δ* and *mub1Δ* mutants, the increased cellular levels of Rpn4 contributed to FLC resistance in *C. auris* by upregulating the expression of four efflux pump genes (*SNQ21, SNQ22, MDR1*, and *CDR1*), as well as enhancing efflux activity (Chow et al., 2023). Rpn4 can autoactivate its own expression by binding to a PACE element in its promoter, creating a positive autoregulatory loop. Additionally, Rpn4 can bind to a PACE element in the *CDR1* promoter, thus upregulating *CDR1* expression (Chow et al., 2023). The identification of a mutation in *UBR2* (A316T) in clinical isolates of *C. auris* that confers FLC resistance via the Rpn4-efflux pump axis highlights the clinical significance of this mutation in FLC resistance (Chow et al., 2023).

Finally, it is important to note that *C. auris* strains with acquired resistance to FLC exhibit several altered physiological traits, including reduced mitochondrial activity, diminished catalase enzyme expression (Das et al., 2024), slower growth rates (Bing et al., 2020), and a decrease in chitin content within the cell wall (Ahmad et al., 2020; Bohner et al., 2023). These alterations may contribute to the adaptive mechanisms of *C. auris* in the presence of antifungal agents and could play a role in its overall resistance profile.

Mechanisms of resistance to polyenes

AMB, a cornerstone of the polyene antifungal class, has been widely employed in the treatment of invasive fungal infections for over six decades (Branco et al., 2023; Ahmady et al., 2024). Renowned for its broad-spectrum activity against pathogenic fungi, AMB has become a critical option for managing life-threatening fungal infections, particularly in immunocompromised patients. The classic mechanism of action of AMB involves its specific binding to ergosterol, a key component of the fungal plasma membrane. This interaction integrates AMB into the lipid bilayer, aligning it parallel to the membrane. Once bound, AMB molecules self-assemble to form transmembrane pores, creating channels that allow the uncontrolled leakage of intracellular components, including ions, into the extracellular environment. The resulting ion imbalance disrupts osmotic regulation, leading to the loss of membrane potential and cellular homeostasis. This metabolic collapse ultimately compromises cell integrity, resulting in increased membrane permeability and fungal cell death, often through lysis (Branco et al., 2023). Furthermore, the sterol sponge model has emerged as an additional mechanism of action for AMB. This model suggests that AMB predominantly exists as large, extramembranous aggregates. Rather than primarily forming pores within the membrane, these aggregates physically sequester ergosterol from the lipid bilayers of fungal cells. The depletion of ergosterol disrupts membrane integrity and function, ultimately leading to fungal cell death. This sterol-extraction mechanism highlights an alternative, non-pore-forming pathway by which AMB exerts its antifungal effects (Anderson et al., 2014). Another mechanism through which AMB exerts its antifungal activity is by inducing the accumulation of reactive oxygen species (ROS). This oxidative stress leads to widespread cellular damage, including DNA cleavage, which compromises the integrity of nucleic acids; protein carbonylation, which disrupts protein structure and function; and lipid peroxidation, which destabilizes the phospholipids that form the plasma membrane. These cumulative effects of ROS-driven damage further compromise fungal cell viability and contribute to AMB's potent antifungal efficacy (Ahmady et al., 2024).

Resistance to AMB is relatively rare compared to other antifungal agents. However, several studies have highlighted key mechanisms by which fungi can develop resistance to this classic polyene. The primary mechanism involves alterations in the sterol composition of the fungal plasma membrane, often resulting from mutations or disruptions in the *ERG* genes, such as *ERG1, ERG2, ERG6*, and *ERG11*. These changes reduce the binding affinity of AMB to ergosterol, diminishing its antifungal activity. In addition to sterol alterations, the regulation of oxidative stress responses also plays a significant role in resistance development. By enhancing their ability to mitigate the ROS generated by AMB exposure, fungi can better withstand its damaging effects. This dual mechanism—modifying membrane sterol composition and enhancing oxidative stress defenses—underpins much of the resistance observed to AMB (Carolus et al., 2020).

Studies conducted by Silva et al. (2020b) sought to elucidate the resistance mechanisms in six clinical isolates of the *C. haemulonii* complex and other clinically relevant non-*albicans Candida* species. Initially, plasma membrane permeability was assessed by the incorporation of propidium iodide when fungal cells were cultured in the presence of clinical concentrations of AMB. It was observed that the highest concentration of AMB used (5 mg/L) caused only a slight, but statistically insignificant, increase in fungal plasma membrane permeability. Gas chromatography coupled with mass spectrometry (GC-MS) was used to assess the influence of membrane sterol composition on resistance to AMB. This technique demonstrated that most of the sterols found in AMB-resistant *C. haemulonii* isolates are not ergosterol, but rather intermediates in its synthesis pathway. This finding partially explains the resistance to the drug, as AMB binds to ergosterol to form pores in the membrane. However, the presence of an adequate amount of ergosterol is crucial for effective pore formation and membrane destabilization. The production of ROS was also assessed, and in contrast to other clinically relevant non-*albicans Candida* species, isolates from the *C. haemulonii* species complex showed lower ROS production in the presence of AMB. Building on this finding, experiments were conducted to investigate the antioxidant response by measuring the activity of superoxide dismutase (SOD) and catalase, enzymes responsible for neutralizing ROS within cells. It was demonstrated that AMB-resistant species, including those within the *C. haemulonii* species complex, exhibited higher basal activity of these antioxidant enzymes compared

to AMB-susceptible non-*albicans Candida* species. The assessment of mitochondrial functionality in these *Candida* species was conducted to determine whether mitochondria contribute to resistance to AMB, as this organelle is the primary source of ROS due to the aerobic respiratory process. The results demonstrated that species within the *C. haemulonii* complex exhibit compromised mitochondrial physiology, with reduced dehydrogenase activity and altered mitochondrial membrane potential. In fact, the authors showed that *C. haemulonii* species complex relies primarily on fermentation for energy production, which leads to a reduction in ROS production, contributing to resistance against AMB. Supporting these findings, an analysis of lipid peroxidation was conducted to assess potential damage to lipid membranes following AMB treatment, as lipid peroxidation serves as an indicator of oxidative damage to membranes. The *C. haemulonii* species complex demonstrated a significantly lower rate of lipid peroxidation compared to AMB-susceptible non-*albicans Candida* species, indicating better protection against oxidative membrane damage, which contributes to resistance to the antifungal. The data from this study are pioneering in elucidating the resistance mechanisms of the *C. haemulonii* complex to AMB, offering a deeper understanding of the antifungal resistance mechanisms within this fungal complex (Silva et al., 2020b).

Few studies have investigated the resistance mechanisms of *C. auris* to AMB. Shivarathri et al. (2020) explored the roles of the *SSK1* and *HOG1* genes in AMB resistance by performing gene deletions in three *C. auris* strains. Their results showed that deletion of these genes rendered all three isolates susceptible to AMB. Furthermore, the study examined potential alterations in cell wall structure following the gene deletions. It was observed that the deletion of the *SSK1* and *HOG1* genes led to an increase in plasma membrane permeability across all isolates, thereby enhancing the absorption of AMB and making the cells more susceptible to the antifungal. The *HOG1* gene plays a crucial role in the MAP kinase signaling pathway, which is involved in stress responses, maintaining cell wall integrity, and contributing to resistance against antifungal agents. This study showed that deletion of the *HOG1* gene impaired the stress response following AMB treatment, leading to damage to cell wall integrity and a reduced ability to withstand cellular stresses. As a result, the strains became more susceptible to AMB, suggesting *HOG1* as a potential new target for antifungal treatments. Overall, this study demonstrates the restoration of *C. auris* susceptibility to AMB, providing valuable insights for developing new therapeutic strategies.

Shivarathri et al. (2022) performed transcriptomic analyzes on two *C. auris* resistant isolates and one AMB-sensitive isolate to gain deeper insights into antifungal resistance mechanisms. The analysis revealed that the resistant strains upregulated genes associated with chromatin remodeling, cell adhesion, drug transport, and sterol biosynthesis. To further understand the response of resistant and sensitive strains to AMB, the activation of key signaling proteins Mkc1 and Hog1 was assessed. The results showed that sensitive strains exhibited higher baseline activation of these proteins even before antifungal treatment. After AMB treatment, resistant strains showed enhanced activation of Mkc1, while sensitive strains displayed a reduction in activation. Additionally, the stress profiles related to cell wall integrity were examined, revealing that the sensitive strain was more susceptible to stress agents such as Calcofluor white, caffeine, and Congo red. In contrast, the resistant strains exhibited lower membrane permeability, which hindered AMB penetration and contributed to their enhanced resistance. This study highlights the complex molecular mechanisms underlying *C. auris* resistance to AMB and offers potential targets for therapeutic intervention.

In the study conducted by Ryback et al. (2022), whole-genome sequencing was performed on four *C. auris* isolates recovered from a single patient. Isolate 1, the first sample obtained, was resistant to FLC but susceptible to both AMB and CSF, and the patient was initially treated with CSF and liposomal AMB. One month later, isolate 2 was recovered, showing high resistance to FLC and AMB but remained susceptible to CSF. The patient was treated with CSF; however, after two weeks, isolate 3 was recovered, which was also resistant to both FLC and AMB. At this point, the patient was switched to treatment with liposomal AMB. After ten days, isolate 4 was obtained, exhibiting resistance to FLC and CSF, but regaining susceptibility to AMB. Whole-genome sequencing, comprehensive sterol profiling, and Cas9-mediated genetic manipulations revealed that mutations in the sterol-methyltransferase gene *ERG6* conferred AMB resistance in *C. auris* for the first time. These mutations led to the disruption of ergosterol biosynthesis, the primary target of AMB, thereby nullifying the antifungal's effectiveness. Furthermore, *ERG6* gene mutations were found to be a critical mechanism of AMB resistance in *C. glabrata* as well (Ahmad et al., 2019).

Recently, a clinical *C. auris* isolate obtained from a COVID-19 patient in Qatar exhibited resistance to AMB due to a large deletion in the *ERG3* gene (Ben Abid et al., 2023). Mutations in the *ERG3* gene have also been linked to AMB resistance in other yeast species, including *C. kefyr* and *C. lusitaniae* (Kannan et al., 2019; Asadzadeh et al., 2023). Interestingly, a novel mutation in the *SNG1* gene associated with AMB resistance in *C. auris* clinical isolates was identified by Chen et al. (2024). They discovered a codon insertion mutation (CTT/CTTT|Leu61fs) in *SNG1*, which encodes a subunit of the Pkh/Ypk signaling module. This mutation was linked to a 4- to 8-fold increase in AMB MIC values, suggesting a strong association with AMB resistance. Notably, this mutation was absent in *C. auris* clinical isolates that remained susceptible to AMB (Chen et al., 2024). Sng1, a plasma membrane protein, has been previously implicated in pleiotropic drug resistance mechanisms in *Saccharomyces cerevisiae* (Chen et al., 2024).

Mechanisms of resistance to echinocandins

ANF, CSF, and MFG are antifungal agents from the echinocandin class of large lipopeptides that target and disrupt fungal cell wall biosynthesis. The fungal cell wall is a complex, multi-layered structure in direct contact with the plasma membrane, typically composed of chitin, β-(1,3)-glucan, β-(1,6)-glucan, and mannoproteins, particularly in yeasts. The inner cell wall consists primarily of chitin and β-(1,3)-glucan, while the outer layer is enriched in β-(1,6)-glucan and mannoproteins. Echinocandins inhibit the synthesis of β-(1,3)-glucan by targeting the enzyme β-(1,3)-glucan synthase, which is essential for cell wall integrity. Structural modifications or mutations in this enzyme can reduce the binding affinity between the drug and its target, leading to echinocandin resistance (Fattouh et al., 2024; Yiallouris et al., 2024). Interestingly, *Candida* strains resistant to echinocandins have been shown to increase the production of chitin in their cell walls as a compensatory mechanism, offsetting the loss or reduction of glucan content. This adaptation underscores the dynamic ability of fungal cells to remodel their cell wall architecture in response to antifungal pressure, highlighting the complexity of resistance mechanisms and the challenge of overcoming fungal defenses (Perlin, 2015).

One of the primary mechanisms of resistance to echinocandins is the occurrence of mutations in the *FKS* gene, which encodes the target subunit of β-(1,3)-glucan synthase. These mutations typically arise in specific regions of the *FKS1* and *FKS2* subunits, known as "hot spots" HS1 and HS2, and are characterized by amino acid substitutions that alter enzyme functionality. Chowdhary et al. (2018) observed such mutations in *C. auris* isolates, particularly in the HS1 region of *FKS1*, where a serine-to-phenylalanine substitution (S639F) was frequently associated with echinocandin resistance. Further investigations by Ahmad et al. (2020) and Izume et al. (2024) confirmed that mutations in the S639F region of *FKS1* confer resistance to echinocandins. In an *in vivo* model, mice infected with *C. auris* mutant strains harboring the *FKS1* S639F mutation showed no significant response to CSF treatment, with no reduction in renal fungal load. In contrast, mice infected with a wild-type *FKS1* strain displayed a significant decrease in fungal burden following CSF treatment. These findings underscore the critical role of

the *FKS1* mutation in conferring echinocandin resistance and its impact on treatment outcomes.

In addition to the *FKS1* S639F mutation, Sharma et al. (2022) identified several other mutations in the *FKS1* gene, including F635Y, F635L, and R1354S. Among these, the F635Y and R1354S mutations were found to be associated with increased resistance to CSF in a murine model infected with *C. auris* strains, resulting in significantly higher mortality rates. Similarly, Hirayama et al. (2023) observed that *C. auris* resistance to echinocandins in mice treated with MCF was linked to mutations in *FKS1*, particularly S639Y and R1354H. In the same study, *C. auris* strains treated with CSF showed additional mutations, including S639F, D642Y, R1354Y, and R1354H. These findings underscore the diversity of mutations in the *FKS1* gene that contribute to echinocandin resistance in *C. auris*, suggesting that multiple mutations within this gene play a role in the pathogenicity and treatment resistance of this opportunistic pathogen. *In vivo* evolution of resistance was observed after 19 and 73 days of echinocandin exposure in two patients in Italy, leading to the emergence of the F635Y and S639F mutations in *FKS1*, respectively (Codda et al., 2023). These findings highlighted that echinocandin resistance developed independently in the two patients, suggesting that the duration of drug exposure required for resistance to emerge can vary significantly depending on the individual patient's underlying health conditions and the specific dynamics of the infection (Codda et al., 2023). Similar patterns of resistance evolution have also been reported in *C. tropicalis* (Khan et al., 2018), reinforcing the unpredictable and patient-specific nature of resistance development to antifungal treatments.

Kordalewska et al. (2023) identified a novel mutation in the *FKS1* gene (G2072T) associated with echinocandin resistance in *C. auris*. This mutation results in the substitution of tryptophan (W691L), located outside the traditional "hot spot" regions of the gene. To validate its role in resistance, the researchers introduced this mutation into susceptible *C. auris* strains using the CRISPR/Cas9 system. The results confirmed that the W691L mutation is indeed associated with echinocandin resistance, expanding the understanding of resistance mechanisms beyond the well-characterized hot spots. In a comprehensive investigation, Tian et al. (2024) analyzed the accumulation of mutations in the *FKS1* gene across 29 clinical *C. auris* isolates resistant to echinocandins. The study identified 47 mutated genes, of which 35 exhibited non-synonymous mutations (alterations that change the amino acid sequence) and 12 exhibited synonymous mutations (which do not alter the amino acid sequence). Among the non-synonymous mutations, key genes included *IFF6* (M175I, Y49F), *RBR3* (G1385D, S80F), *NMA111* (L314F, L811H), and *AMN1* (C282Y, S12), with *RBR3* and *IFF6* exhibiting the lowest mutation rates. Notably, protein-protein interactions were identified in 31 of the 35 non-synonymous mutant genes, suggesting that these mutations have functional consequences. The study also highlighted that these mutations were associated with chromosomal remodeling and DNA repair processes, further contributing to the emergence of resistance at critical sites within the *FKS1* gene. This complex interplay between genetic mutations and cellular processes underscores the multifaceted nature of antifungal resistance, offering valuable insights into the mechanisms driving the development of echinocandin resistance in *C. auris*.

Some studies have demonstrated that multiple *FKS* genotypes can be found at different anatomical sites within the same *C. auris*-infected patient, with the potential for translocation from non-invasive sites to the bloodstream. Notably, these *FKS* mutations, rather than the MIC values for echinocandins, are more strongly associated with adverse clinical outcomes in *C. auris*-infected patients (Asadzadeh et al., 2022; Al-Obaid et al., 2022).

Silva et al. (2023b) successfully induced resistance in a clinical isolate of *C. haemulonii* (designated Ch4) through a stepwise escalation of exposure to CSF. Initially, a fungal suspension was exposed to a CSF concentration of 0.125 mg/L, with gradual increases until a final concentration of 4 mg/L was reached. This incremental exposure led to the selection of a resistant *C. haemulonii* population, which also exhibited cross-resistance to other echinocandins, including MFG and ANF. The evolved resistant strain, named Ch4'r, harbored a nucleotide substitution in the *FKS1* gene at position 4061 within the HS2 region. This mutation, which replaced guanine with adenine, resulted in an arginine-to-histidine substitution at position R1354H. Mutations linked to echinocandin resistance have been previously identified in *C. albicans* and other non-*albicans Candida* species, particularly in two critical regions of the *FKS* gene, known as "hot spots" 1 and 2 (HS1 and HS2) (Cowen et al., 2014). In addition to the genetic mutation, Silva et al. (2023b) noted structural adaptations in the resistant *C. haemulonii* strain Ch4'r, including a significantly thicker cell wall and a 2.5-fold increase in chitin content. These modifications likely serve as compensatory mechanisms to mitigate the effects of echinocandins on β-(1,3)-glucan synthase, further enhancing the strain's resistance to this class of antifungal agents.

As described by Lima et al. (2019), fungal cell walls are typically composed of two distinct layers: an internal structural layer, primarily made of chitin and glucan, which provides mechanical support against the osmotic pressure of the cytoplasm, and an external, more heterogeneous layer, which varies across species. This outer layer is primarily composed of mannosylated glycoproteins, with modified *N*- and *O*-linked oligosaccharides. Perlin (2015) further emphasized that *Candida* populations that survive echinocandin exposure often develop tolerance, a phenomenon that is closely linked to an increase in chitin content within the cell wall. This adaptive response likely serves as a compensatory mechanism to offset the disruption of β-(1,3)-glucan synthesis, which is targeted by echinocandins, thereby contributing to the survival and persistence of fungal cells under antifungal stress.

Silva et al. (2023b) found that the CSF-resistant *C. haemulonii* Ch4′r strain was more readily engulfed by macrophages compared to its parental strain. However, the parental strain demonstrated greater resilience to macrophage-mediated killing, with a higher number of viable fungal cells surviving after 24 h of interaction. In an *in vivo Galleria mellonella* model, larvae infected with the CSF-resistant strain exhibited lower mortality rates than those infected with the parental strain, suggesting a potential reduction in virulence associated with resistance. The observed structural adaptations in the resistant strain, including increased chitin content and cell wall thickening, may contribute to this reduced virulence. Additionally, resistance to CSF was linked to a fitness cost. Growth kinetic analysis revealed that the parental strain (Ch4) grew faster and formed more robust biofilms than the resistant strain (Ch4′r). These findings underscore the complex nature of echinocandin resistance, where the genetic and structural adaptations that confer resistance may simultaneously impair fungal virulence and overall fitness, highlighting a trade-off between survival under antifungal stress and pathogenicity.

In the study by Shivarathri et al. (2020), gene deletion experiments were conducted to explore the roles of the response regulators *SSK1* and *HOG1* in antifungal resistance and cell wall integrity in *C. auris*. The *SSK1* gene encodes a two-component response regulator essential for activating signaling pathways in response to environmental stress, while *HOG1* encodes a MAP kinase that is crucial for the osmotic stress response. Deletion of both the *SSK1* and *HOG1* genes restored susceptibility to CSF and AMB in *C. auris* strains, suggesting that these genes play a key role in antifungal resistance. Moreover, strains lacking these genes showed a significant increase in plasma membrane permeability, highlighting that *SSK1* and *HOG1* are vital for maintaining membrane integrity and stability. These findings underscore the importance of *SSK1* and *HOG1* in the resistance mechanisms of *C. auris* and propose them as potential targets for therapeutic intervention in the treatment of drug-resistant infections.

Echinocandin resistance in *C. auris* and the *C. haemulonii* species complex is an intricate, multifactorial process driven by both genetic mutations and phenotypic adaptations. These changes enable the fungi to survive in the presence of echinocandins. Notable genetic mutations,

such as those in the *FKS1* gene, alter the target enzyme, β-(1,3)-glucan synthase, leading to a reduced binding affinity for the drug. Simultaneously, phenotypic changes, such as increased chitin content in the cell wall, serve as compensatory mechanisms to preserve cell wall integrity despite the inhibition of glucan synthesis. This adaptive resilience highlights the need for a thorough understanding of resistance mechanisms. Such insights are crucial for developing effective therapeutic strategies, optimizing antifungal treatment, and designing control measures to combat infections caused by resistant fungal strains.

All of the studies discussed herein mark a significant advancement in our understanding of antifungal resistance in planktonic cells of these emerging *Candida* species. However, further research is essential to gain a more comprehensive understanding of the underlying mechanisms and to develop effective strategies for combating antimicrobial resistance. Continued exploration of resistance pathways, along with innovative therapeutic approaches, is crucial for addressing the growing threat posed by these resistant fungal strains.

Biofilms × antifungal resistance

The antifungal resistance observed in *C. auris* and the *C. haemulonii* species complex is influenced by multiple factors, including point mutations in cellular targets, overexpression of target molecules, and the upregulation of efflux pumps (Cowen et al., 2014; Lee et al., 2021). Additionally, antifungal tolerance can be associated with the phenomenon of phenotypic plasticity, which enables these opportunistic pathogenic fungi to adopt diverse phenotypic traits. This adaptability helps them counteract host defense mechanisms, including through strategies such as cell aggregation and biofilm formation, both of which contribute to their persistence in hostile environments (Szekely et al., 2019; Horton and Nett, 2020; Bing et al., 2024).

Biofilms are structured communities of microbial cells that interact with each other and/or adhere to both biotic and abiotic surfaces, encased in an extracellular polymeric matrix they secrete (Costerton et al., 1995; Ramage et al., 2005; Santos et al., 2015, 2018; Mello et al., 2017, 2020; Nett and Pohl, 2021). These biofilms are capable of forming in both natural and artificial environments, such as medical devices, and are a major cause of chronic and recurrent infections (Donlan, 2002; Ascenzioni et al., 2021; Mendhe et al., 2023). Studies indicate that biofilm formation by *Candida* species is associated with higher mortality rates in candidemia cases, underscoring the critical role biofilms play in the pathogenicity and persistence of these infections (Vitális et al., 2020; Atiencia-Carrera et al., 2022; Kovács et al., 2024).

Biofilm formation is a critical virulence factor for microorganisms, including *C. auris*, the *C. haemulonii* species complex, and closely related species (Fig. 3). This process offers significant advantages for fungal survival and adaptation, providing enhanced protection against environmental stressors and contributing to increased antifungal resistance (Taff et al., 2013; Wall et al., 2019). The antifungal resistance associated with biofilm formation is primarily attributed to the extracellular matrix, a complex structure composed of polysaccharides, (glyco)lipids, (glyco)proteins, extracellular DNA, and small bioactive molecules. This matrix serves as a physical barrier, reducing the penetration of antifungal agents and thereby diminishing their effectiveness (Mitchell et al., 2016; Dominguez et al., 2019).

Studies have reported differentiated resistance mechanisms between planktonic and biofilm-forming cells in *C. auris* and the *C. haemulonii* species complex. In *C. auris*, transcriptomic analyzes conducted by Kean et al. (2018) identified mechanisms associated with biofilm resistance, demonstrating that antifungal resistance is stage-dependent. Mature biofilms were found to exhibit resistance to all classes of antifungals. Furthermore, the expression of genes related to ABC (*CDR1* and *CDR2*) and the MFS (*MDR1*) transporter efflux pumps was upregulated, both of which are known to contribute to resistance to azoles, independent of antifungal exposure. Additionally, genes related to glucan modification (*KRE6* and *EXG*), which are involved in the formation of the biofilm extracellular matrix, were positively regulated (Kean et al., 2018). The extracellular matrix of biofilms is composed of polysaccharides, such as

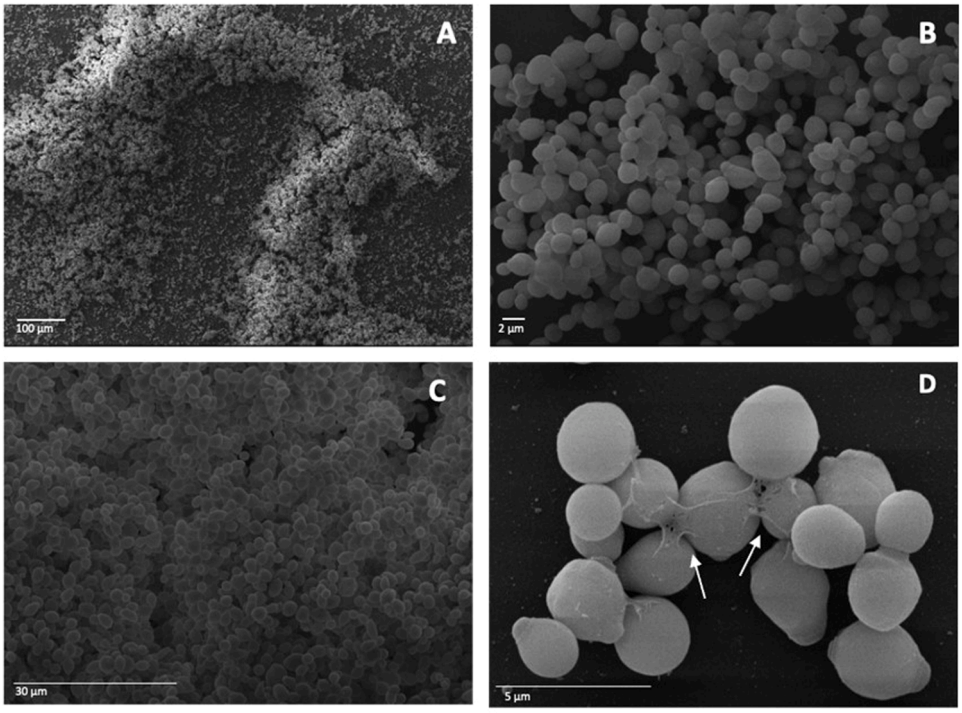

Fig. 3. Scanning electron microscopy (SEM) images of the biofilms formed by clinical isolates of the *C. haemulonii* species complex on polystyrene surface. Yeasts (200 µL containing 10^6 cells) were placed to interact with polystyrene coverslips at 37 °C for 48 h, and were then processed and visualized using SEM. The images reveal a dense network of yeast cells, forming three-dimensional structures by the three members of the *C. haemulonii* complex: *C. haemulonii* (A), *C. duobushaemulonii* (B) and *C. haemulonii* var. *vulnera* (C). The presence of an extracellular matrix (D) surrounding and holding the cells together can also be observed (white arrows).

glucan and mannan, which are primarily responsible for sequestering antifungal agents, especially azoles, within the biofilm (Dominguez et al., 2019) (Fig. 4). Regarding other classes of antifungals, the relationship between resistance mechanisms and their effectiveness remains underexplored. However, studies using MIC and minimum biofilm eradication concentration (MBEC) assays to compare the resistance profiles of planktonic cells versus biofilms have provided significant insights. These studies reported that biofilms exhibited MBEC values up to 512 times higher than MIC values, indicating considerably enhanced resistance to all antifungal classes. This stark difference underscores the challenges posed by biofilm-associated infections, where fungal cells, embedded in a protective matrix, are much less susceptible to antifungal treatments (Romera et al., 2019).

The resistance mechanisms in the *C. haemulonii* species complex remain incompletely understood. However, prior research conducted by our group has provided valuable insights into the antifungal resistance profiles of these isolates. Our observations indicate that, in their planktonic form, the isolates exhibit resistance to azoles and polyenes but remain generally susceptible to echinocandins (CSF and MFG), with geometric mean (GM)-MIC values of <0.5 mg/L. When susceptibility tests were performed on biofilms, we observed a susceptible profile for CSF and MFG, with a 20–60 % reduction in viability and biomass in nearly all isolates studied (Ramos et al., 2020). Interestingly, the MBEC for ANF and 5-FC was found to be twice as high in biofilms compared to planktonic cells for most isolates. Some isolates of *C. haemulonii* and *C. duobushaemulonii* exhibited biofilm resistance to ANF and 5-FC, whereas all isolates of *C. haemulonii* var. *vulnera* were susceptible to ANF, with half showing biofilm resistance to 5-FC (Ramos et al., 2022). These findings suggest that biofilm resistance mechanisms can vary depending on the species and specific isolates within the *C. haemulonii* complex. This variation underscores the need for further investigation into the unique mechanisms underlying resistance in biofilm-forming strains of this fungal group.

Conclusions

The emergence of MDR fungal pathogens, such as *C. auris* and the *C. haemulonii* species complex, poses a significant threat to public health, primarily due to the limited therapeutic options currently available. While considerable progress has been made in understanding the mechanisms underlying resistance in these species, many critical aspects remain poorly understood, particularly with respect to the *C. haemulonii* complex. Further investigation is urgently needed to fully elucidate the specific resistance mechanisms at play. Given the growing threat these resistant strains pose, it is crucial to accelerate the development of novel antifungal agents. Additionally, exploring the repurposing of existing drugs or utilizing drug combinations offers promising strategies to combat infections caused by these *Candida* species. Addressing this challenge is essential to mitigating the ongoing antifungal resistance crisis and improving treatment outcomes for patients infected with resistant fungal strains.

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CRediT authorship contribution statement

Lívia S. Ramos: Conceptualization, Writing – original draft, Writing – review & editing. **Pedro F. Barbosa:** Writing – original draft, Writing – review & editing. **Carolline M.A. Lorentino:** Writing – original draft, Writing – review & editing. **Joice C. Lima:** Writing – original draft, Writing – review & editing. **Antonio L. Braga:** Writing – original draft, Writing – review & editing. **Raquel V. Lima:** Writing – original draft,

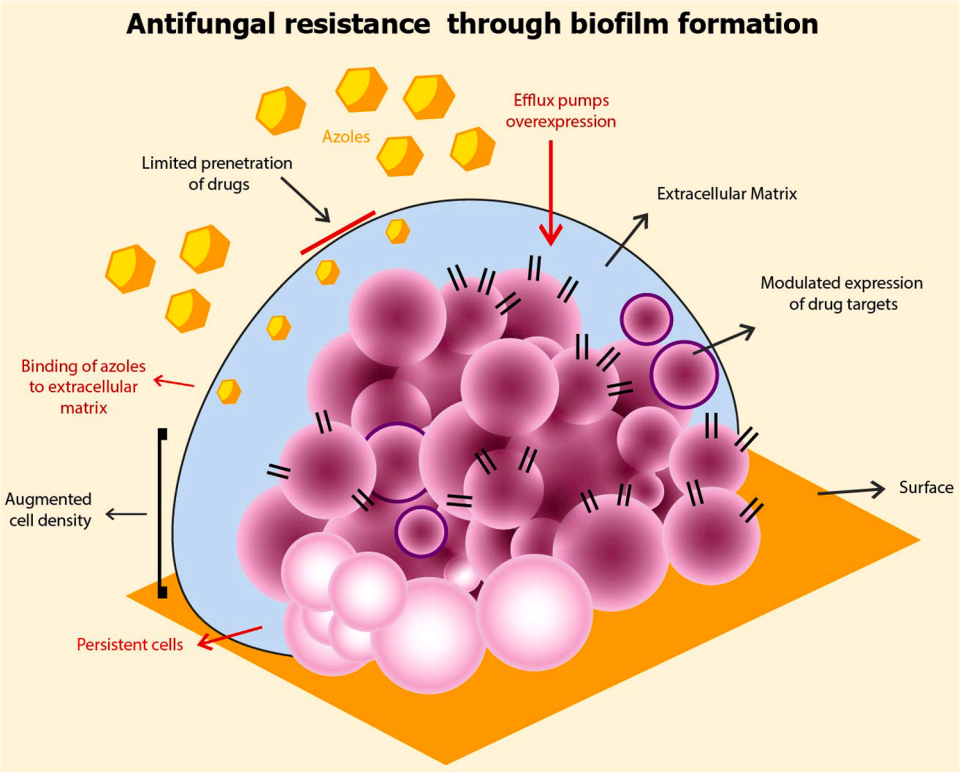

Fig. 4. Antifungal resistance mechanisms of fungal biofilms. The image includes the main antifungal resistance mechanisms described in *Candida* species biofilms (the red text refers to the resistance mechanisms associated with biofilms described in *C. auris* until now).

Writing – review & editing. **Lucas Giovanini:** Writing – original draft, Writing – review & editing. **Ana Lúcia Casemiro:** Writing – original draft, Writing – review & editing. **Nahyara L.M. Siqueira:** Writing – original draft, Writing – review & editing. **Stefanie C. Costa:** Writing – original draft, Writing – review & editing. **Célia F. Rodrigues:** Writing – review & editing. **Maryam Roudbary:** Writing – review & editing. **Marta H. Branquinha:** Conceptualization, Writing – review & editing. **André L.S. Santos:** Conceptualization, Writing – review & editing.

Declaration of competing interest

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Data availability

Data will be made available on request.

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