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REVIEW

Candida haemulonii Complex and *Candida auris*: Biology, Virulence Factors, Immune Response, and Multidrug Resistance

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Abstract: There is worldwide concern about the constant increase in infections caused by *Candida* species that are multiresistant to antifungal drugs. The most common candidiasis is caused by *Candida albicans*, however, the species of the *Candida haemulonii* complex and *Candida auris* are emerging opportunistic pathogens, which isolation from clinical samples has significantly increased in the past years. The special interest in the study of these species lies in their ability to evade the action of antifungal drugs, such as amphotericin B, azoles, and echinocandins. In addition, the phenotypic changes of these species have given them the ability to easily adapt to environmental changes, including the host milieu and immunity. In this paper, a detailed review of the current literature on the *C. haemulonii* complex and *C. auris* is shown, analyzing aspects such as biology, immune response, putative virulence factors, infection, treatment, and the current strategies for diagnosis.

Keywords: antifungal resistance, candidiasis, cryptic *Candida* species, emerging pathogens, virulence factors, *Candida haemulonii* complex, *Candida auris*

Introduction

Members of the genus *Candida* are common cause of invasive fungal infections in immunocompromised individuals,[1] and are associated with high morbidity and mortality rates.[2] A significant number of candidiasis cases have *Candida albicans* as the etiological agent, however, other *Candida* species, such as *Candida krusei, Candida glabrata, Candida parapsilosis*, and *Candida tropicalis* are frequently isolated from clinical samples.[3]

The *Candida haemulonii* complex comprises the opportunistic human pathogens *Candida haemulonii sensu stricto, Candida duobushaemulonii*, and *C. haemulonii var. vulnera*; but *Candida auris, Candida pseudoheamulonii*, and *Candida vulturna* are phylogenetically related species that often are included as part of the complex.[4,5] Candidiasis has increased in frequency in the last years,[6] and there is a concern because of the intrinsic antifungal resistance to amphotericin B, azoles, and echinocandins.[7,8] The ability of *C. haemulonii* to undergo dimorphism has been recently demonstrated;[9] along with phenotypic switching, a trait that other *Candida* species have to quickly adapt to changes in the environment and respond against antifungal compounds.[9] Currently, two phenotypic switching systems have been described in this species. The first one is white-pink switching, and the second is pink-filament switching; thus defining three phenotypes: white yeasts, pink yeasts, and filament cells., When cells are grown in phloxine B-containing media, white and pink yeast differ in colony color, gene expression profile, secreted aspartyl protease activity, and virulence.[9] Another complex member that can cause superficial and invasive infections in humans is *C. duobushaemulonii*.[8,10,11] It was originally classified as *C. haemulonii*, which led to an underestimation of actual clinical cases associated with this species. The new molecular techniques allowed the correct

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identification of this complex member, placing the isolates as a new species since conventional biochemical tests led to misleading identification. Some isolates of *C. duobushaemulonii* are resistant to azoles and polyenes.[12]

C. auris, currently distributed worldwide, was identified for the first time in Japan, in 2009.[4] To date, this specie has been isolated mainly in nosocomial outbreaks and the concern related to this pathogen is that the organism easily passes from one patient to another, especially in those who are immunocompromised.[13] This fungal species is a haploid yeast, phylogenetically related to *C. haemulonii* and *Candida lusitaniae*, and relatively distant to the diploid species *C. albicans* and *C. tropicalis*, whose clinical occurrence is more common.[14] *C. auris* can form biofilms more robust than those generated by other complex members, and undergoes dimorphism, generating true hyphae.[13] A feature of clinical concern found in *C. auris* is the multidrug resistance, especially to the azoles, polyenes, and echinocandins.[15–19]

C. pseudohaemulonii has been isolated from bloodstream infections and molecular studies showed a close phylogenetic relationship with the *C. haemulonii* complex. *C. pseudohaemulonii* can be distinguished from this species by the assimilation pattern of esculine, melezitose, L-rhamnose, trehalose, and glycerol.[20] Although the infections caused by this species are low, it is of clinical importance due to its capacity to form biofilms and its resistance to azoles and amphotericin B.[15,20] *C. vulturna*, another related species to the *C. haemulonii* complex has a natural habitat in plants. However, it has also been found in human bloodstream infections.[21–23] The occurrence of invasive candidiasis by this fungus makes it an emerging and opportunistic pathogen of clinical importance. Furthermore, it has been shown that some *C. vulturna* isolates are susceptible to echinocandins and azoles but resistant to amphotericin B.[22,23]

The emergence of *C. auris* and the *C. haemulonii* complex as causative agents of candidiasis has attracted attention in recent years and exposed the need to increase our knowledge on aspected related to their biology, pathogenesis, interaction with the host, and the correct identification of these organisms.

Epidemiology

Despite *C. auris* was isolated for the first time in 2009, retrospective studies found that the first isolates of this species date to 1996.[14,24] Analysis of cultures collected between the years 2009, 2013, 2014, and 2015 identified four types of *C. auris*, which were grouped in clades (clade I of South Asia, clade II of East Asia, clade III of South Africa, and clade IV of South America).[25] These findings indicate that *C. auris* may be a recently emerged pathogen.[25,26] In 2016, the Center for Disease Control and Prevention, the European Center for Disease Prevention and Control, and Public Health England issued an alert, informing medical centers about *C. auris* as a new infectious agent.[14] Thanks to genomic and epidemiological analyses, in 2017 different genetic populations of *C. auris* were found. These strains are known to have emerged almost simultaneously on three different continents.[25] A decade after its discovery as a bloodstream pathogen, *C. auris* was recovered from 4000 blood isolates from patients from more than 40 countries.[27–29]

As of 2021, 47 countries have reported a single case or outbreak of *C. auris* infection. By the year 2022, according to the Center for Disease Control and Prevention of the United States of America, a large part of the territory was affected by this pathogen. The total number of clinical cases was 2377 and 5754 cases were screened (https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html#counted accessed February 17, 2023). The epidemiology of the infection caused by *C. auris* has changed over time, in the early years this pathogen was known to cause sporadic invasive infections. However, currently, the infection has been replaced by nosocomial outbreaks, which have been reported more frequently.[27,28,30] This increase in the isolation frequency of this pathogen has meant that *C. auris* can affect susceptible patients in medical centers.[31,32] In addition to the data already known for the United States of America, other countries such as Canada, Mexico, the United Kingdom, Spain, India, Pakistan, Russia, Saudi Arabia, Oman, Kuwait, Kenya, South Africa, and Colombia have also reported *C. auris* outbreaks.[31,33–44]

In the case of American countries, such as Mexico and the United States, in the years from 2019 to 2020, 12 patients with candidiasis caused by *C. auris* were reported. In Mexico, the mortality rate was 67% and in the United States, 40%[44,45] Asian countries such as Kuwait, Oman, Russia, and Saudi Arabia, reported an increase in cases of candidiasis from 2018 to 2019. In Kuwait, there were a total of 71 patients infected by *C. auris*, of which the mortality rate was 51%, in Oman 32 cases were reported, and the mortality rate was 53.1%, in Russia the total number of cases in these years was 38 and the mortality rate was 55.3%. Finally, in Saudi Arabia, the reported cases were 35, with a mortality rate of

20%.[39,40,42,46,47] The European continent has also been affected by *C. auris*, in Spain from 2017 to 2020 47 cases were reported, with a mortality rate of 23.4%.[48]

The concern around *C. auris* lies in the characteristics that possess, which include the ability to persist and remain viable for several months. This could be associated with the formation of biofilms on plastic surfaces, in the hospital environment, and in medical devices.[49,50] Also, as mentioned below, rates of resistance to fluconazole and other drugs, such as amphotericin B make infection control challenging.[51,52]

Unlike *C. auris*, epidemiological data for the *C. haemulonii* complex are few. However, it is known that most cases caused by *C. haemulonii* and *C. pseudohaemulonii* are related to bloodstream infections and people with central venous catheters.[53,54] In 2009, 8 cases of fungemia caused by *C. haemulonii* and *C. pseudohaemulonii* were reported in Korea. In 2011, the same country saw an increase in the number of cases in both species.[15,53,55] In Belgium, of 142 isolates from patients, 27 of these (19%) were identified as *C. haemulonii*.[56] In countries such as Brazil, Mexico, Kuwait, and Argentina, the presence of species belonging to the *C. haemulonii* complex has also been reported.[7,54,57,58] In 2016, in Mexico, candidiasis by *C. haemulonii* was reported in a pediatric patient with congenital heart disease. To identify the isolate to a species level, it was necessary to carry out 28S and ITS sequencing analysis.[59] This case drew attention because the epidemiological and etiological reports of candidiasis in Mexico had not reported yet the presence of *C. haemulonii*.[59] Recently, *C. duobushaemulonii* was also identified in the country, which is responsible for superficial candidiasis in adults.[12]

In Brazil, from 2010 to 2015, 14,642 patient samples were cultured in 5 hospitals affiliated with the University of São Paulo. Of all the samples, 40 isolates from 31 patients belonged to the *C. haemulonii* complex.[60] Through molecular identification, it was possible to determine that of these 40 isolates, 14 corresponded to *C. haemulonii*, 8 to *C. haemulonii* var. vulnera, and 9 to *C. duobushaemulonii*.[60] Among the morbidities found in the 31 patients, the most frequent were diabetes mellitus and vascular diseases.[60] Studies carried out by the Laboratório Especial de Micologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, determined that from an 11 years collection of Brazilian yeasts, with a total of 3799 clinical isolates, there was a prevalence of 1.3% of the *C. haemulonii* complex members.[6] Surprisingly, in the last five years there has been a substantial increase in these species. In this study, it was found that *C. haemulonii* var. vulnera and *C. duobushaemulonii* were found in 57% of all isolates in this analysis.[6] In addition to the increase in the appearance of the species of this complex, through these studies it was possible to determine that these species exhibit high minimal inhibitory concentrations (MIC) against amphotericin B and fluconazole, similar to *C. auris*. This observation led to think that these fungal pathogens may be multi-resistant. Even though species of the *C. haemulonii* complex are considered rare human pathogens, concerns about incidence rates and resistance to antifungal drugs appear to be increasing worldwide.[5,6,61]

Candidiasis Caused by *C. auris* and the *C. haemulonii* Complex

The infections caused by *Candida* spp. can be superficial or systemic diseases. Cutaneous, mucocutaneous, and onychomycosis are some examples of superficial infections, while meningitis, sepsis, and candidemia are examples of systemic diseases.[62] The *C. haemulonii* complex has been isolated from human infections; however, due to the isolates misidentification, the clinical information regarding the incidence and epidemiology of the complex members is limited.[60] The clinical manifestations of infections caused by the *C. haemulonii* complex members are similar to that observed in the cases caused by *C. albicans* and other non-*albicans Candida* species.[54,63–65] The members of this complex are frequently isolated from immunocompromised patients or individuals with some other aggravated illness, for instance, pulmonary or renal diseases. Another feature of the fungemia caused by this complex is that tends to infect neonates and elder individuals. Central venous catheter insertion and prolonged stays in intensive care units are risk factors to develop a systemic infection.[7,57,64] Onychomycosis, peritonitis, leukocytosis, and high fever are features of systemic candidiasis caused by *C. haemulonii sensu stricto* and the infection is associated with peripheral vascular disease, lower extremity ulcers, and diabetes mellitus.[57,64,66] *C. duobushaemulonii* causes onychomycosis, and vulvovaginal candidiasis, and a characteristic of this species is that infects diabetic patients.[12,53,60,63,67] *C. haemulonii var. vulnera* causes onychomycosis, lower extremity ulcers, and fungemia;[12,67] while candidemia caused by *C. auris* has been found in patients with severe lung and kidney diseases, and in those who suffer from diabetes mellitus.[4,17]

Identification of *C. auris* and the *C. haemulonii* Complex

Fungal isolate identification is of utmost importance from an epidemiological and clinical point of view. In addition to this, understanding the resistance to antifungal drugs is important when providing treatment. When *C. auris* is cultivated in a broth added with glucose, yeast extract, and peptone at 25°C, grows as ovoid, ellipsoidal cells of 2 to 3–2.5 to 5 µM. The culture on solid medium produced butyric to viscous colonies, in white and gray tones, smooth and shiny.[4] Conventional biochemical methods are unreliable when trying to identify *C. auris* because they can be misidentified and confused with other *Candida* species. As an examples the VITEK2 system (bioMérieux, Marcy I'Etoile, France) misidentified 10 isolates as *C. haemulonii sensu stricto* and two as *Candida famata*. Similarly, the API20C system (bioMérieux) also misidentified them as *Candida sake*.[17]

An effective way to differentiate *C. auris* isolates from other *Candida* species is by growing them at 40–42°C because only *C. auris* can grow at this temperature.[5,17] Another form of differentiation is taking advantage of its ability to tolerate high salt concentrations[17,68] A culture in broth containing yeast nitrogen base, 10% NaCl supplemented with dextrose, ducitol, or mannitol, can differentiate *C. auris* from *C. haemulonii sensu stricto, C. duobushaemulonii, C. albicans*, and *C. parapsilosis*, which cannot grow under these conditions.[69]

Another method that is commonly used is the commercial CHROMOagar medium. When *C. auris* isolates are inoculated, they grow as white, pink, or dark purple colonies; while *C. duobushaemulonii* generates soft light pink colonies, and in the case of *C. pseudohaemulonii*, the colonies are violet.[70] On the other hand, analysis of the new CHROMagar *Candida* Plus medium showed better performance in the *C. auris* identification, although *C. pseudohaemulonii* resembles *C. auris* in mixed culture colonies, it tends to be much smaller and produces a distinctive blue halo after 72 h. This makes the misidentification of *C. pseudohaemulonii* with *C. auris* less likely when found in clinical specimens.[71]

By using Matrix-Assisted Laser Desorption/Ionization and Time of Flight (MALDI-TOF MS) it is possible to accurately differentiate *C. auris, C. haemulonii sensu stricto*, and *C. duobushaemulonii* from other fungal species.[13,14] Also, by using the sequencing of genetic loci such as the 28S rDNA D1/D2 region or the rDNA ITS region, they can accurately detect *C. auris*.[10,14,55] *C. duobushaemulonii* can be identified by sequencing the rDNA ITS (ITS1-5.8S-ITS2) and the D1/D2 region of 26S rDNA.[8,72] *C. vulturna* shows a great coincidence with *C. duobushaemulonii*, however, its sequence differs by 4% when using the D1/D2 domains, 7% when using ITS, and 1% when comparing it with the SSU 18S rRNA genes.[73]

Treatment of Candidiasis Caused by *C. auris* and the *C. haemulonii* Complex

The main antifungal drugs available to treat *Candida* infections are classified into four groups. The first are azoles, such as fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole; whilst the second group are polyenes, such as amphotericin B. The echinocandins anidulafungin, caspofungin, and micafungin are in the third group; and finally, in group four is the pyrimidine analog flucytosine, which is not licensed for monotherapy in *Candida* infection because the pathogen easily develops resistance. For this reason, its use is recommended in combination with some other antifungal drugs, such as amphotericin B, due to the synergistic effect observed.[74,75] The group of azoles has been widely used against *Candida* infections; however, antifungal resistance to this type of compound has been increasing in recent decades, highlighting that one of the factors for this to occur is the prolonged use of antifungals, for example in patients with acquired immunodeficiency syndrome.[76,77]

C. auris has intrinsic resistance to fluconazole, voriconazole, amphotericin B, and echinocandins.[78,79] Although the mechanism by which *C. auris* is resistant is unclear, it is known this organism contains *ERG3* and *ERG11* genes, whose products are enzymes involved in the ergosterol synthesis pathway. It has been found that substitutions in the amino acids Y132F and K143R of the C. *albicans ERG11* gene product cause azoles have less interaction with these enzymes, leading to reduced susceptibility to the antifungal drugs.[80] The same amino acid substitutions were found in the *C. auris ERG11*, and for *C. pseudohaemulonii* the substitution in the amino acid Y132F was also reported, which implies that the resistant mechanisms may be lower azoles binding to targeted enzyme.[81–83] In addition, the *ERG11* gene was found duplicated in some *C. auris* isolates.[82] The *C. auris* genes *FKS1, FKS2*, and *FKS3* are involved in glucan synthesis and are related to

echinocandin resistance.[84] A mutation with amino acid substitution S639F in the *FKS1* gene has been reported in several caspofungin-resistant strains.[85] In addition, although the main role of transport systems is to allow the uptake of essential nutrients and excretion of metabolic residues; these systems are also used for cellular detoxification, such as the ATP-binding cassette (ABC) family and major facilitator superfamily transporters, which are known to be important factors for *C. albicans* virulence. These genes have been recently found within the *C. auris* genome and are thought that contribute to its antifungal resistance.[82,86–88]

C. auris, C. haemulonii, C. duobushaemulonii, and *C. pseudohaemulonii* contain the glycosylphosphatidylinositol-anchored proteins Plb3, Iff4, Pga52, Pga20, Csa1, Hyr3, and Pga7, involved in *C. albicans* biofilm development and overexpressed in *C. auris* during biofilm formation; thus, these proteins may be related to antifungal resistance.[82]

The treatment options for patients with infections due to *C. auris* are complicated, however, the use of echinocandins or amphotericin B is the clinical recommendation,[78,79] with the risk that the different isolates show a variable susceptibility. Recently, Ibrexafungerp has been used to treat infections by multidrug resistance *Candida* species. This drug is an enfumafungin-derived that inhibits β-1,3-D-glucan synthase and is structurally different from echinocandins; thus having different interactions with the targeted enzyme.[89]

C. haemulonii sensu stricto, C. haemulonii var. vulnera, and *C. duobushaemulonii* have intrinsic resistance to fluconazole and amphotericin B,[4] and some isolates exhibit resistance to itraconazole, voriconazole, posaconazole, terbinafine, and echinocandins.[8,10,11,65] Some patients with fungal infections due to *C. haemulonii* have received combined treatment with amphotericin B and fluconazole with evident improvements in the patient's health, and another successful combination is amphotericin B deoxycholate plus fluconazole.[90]

Biological Attributes of *C. auris* and the C. *haemulonii* Complex

Recently, *C. auris* has been recognized as the causative agent of invasive infections and outbreaks with high mortality rates in patients admitted to intensive care units or other special care centers.[69] This organism is an oval yeast without pseudohyphae or germ tube formation in most of the isolates,[17] and smaller than *C. albicans* cells.[88] However, recent studies have shown that *C. auris* sometimes fails to release daughter cells after budding, resulting in the formation of pseudohyphal-like cell aggregates.[69,91] *C. auris* colonies appear pink, white, and dark purple in CHROMagar *Candida* medium at 37°C and 42°C.[17,69] Like other *Candida* species, *C. auris* can form biofilms, and undergo phenotypical switching, and some isolates are capable to generate true hyphae.[14,92] It is hard to discriminate *C. auris* and *C. haemulonii sensu stricto* by conventional microbiological tests because have similar assimilation carbohydrate profiles and both are resistant to several antifungal drugs. They are closely related phylogenetically, are part of the Metschnikowiaceae family, and as mentioned, are resistant to some drugs.[82,93]

The optimal growth of *C. haemulonii sensu stricto* isolates is at 30°C and tends to decrease at 37°C and is absent at 42°C.[93] When cultivated in YPD agar with phloxine B red dye at 25°C, white to pink colonies can be observed. Both phenotypes produce round and budding yeast cells but pink colonies produce two or three times larger cells than the white ones.[9] When cultivated in a yeast-peptone-glycerol medium plate at 25°C, wrinkled colonies containing elongated filaments are observed.[9] It has been shown that *C. haemulonii sensu stricto* isolates have glucose- and mannose-containing glycoconjugates on the cell surface.[94] In general, these glycoconjugates participate in the interaction between the pathogen and host cell receptors and help in the evasion of host immune responses.[95]

In 2012, *C. haemulonii* was classified into three species: *C. haemulonii sensu stricto, C. duobushaemulonii*, and *C. haemulonii* var. *vulnera*, which conform the complex.[5] In 2016, 14,642 yeast cultures from 5 hospitals in Brazil were analyzed, 40% were identified as species of the *C. haemulonii* complex and within these, 9 samples were identified as *C. duobushaemulonii*.[60] The correlative analyses performed in this study concluded that patients with diabetes mellitus are more likely than healthy populations to have infections caused by *C. duobushaemulonii*.[60,96] Furthermore, It has been reported as a causative agent of vulvovaginal candidiasis and wound infection in the lower extremities that can disseminate to the rest of the body.[10,96]

Also, in 2016, a taxonomic study of yeasts isolated from flowers on the island of Mindanao, Philippines, was carried out, and a species related to *C. duobushaemulonii* was identified, which was named *Candida vulturna*. Later, it was described in patients with systemic candidiasis from the Philippines and Malaysia.[73] When cultured in yeast extract broth

for 24 h at 25°C, it grows like ovoid cells (4–7 by 3–5 µm), alone or in pairs, with apical or subapical budding, forms sediments, and biofilms that contain pseudohyphae.[73] On yeast extract agar, after 3 weeks at 25°C, their colonies are usually white and butyric, white in appearance with a complete margin.[73]

C. albicans, C. tropicalis, C. parapsilosis, and *C. auris* are part of the CTG clade; which means that these species translate the CTG codon into serine instead of leucine.[97] *C. albicans* and *C. tropicalis* are clinically common diploid organisms, but *C. auris* and *C. haemulonii sensu stricto* are haploid fungi.[14] The *C. auris* genome is approximately 12.3 to 12.5 Mbp in size with 8527 predicted genes.[88,98] When compared to the *C. albicans* genome, a set of orthologs encoding for drug transporters, oligopeptides, proteinases, and mannosyltransferases was identified, and fungal virulence and drug resistance could be related to them. However, as most of the genome is not characterized, it can be expected that the hypothetical proteins may also contribute to cell virulence during interaction with the host.[88] The *C. haemulonii sensu stricto* genome spans 13.3 Mbp with 6155 predicted genes;[99] while *C. duobushaemulonii* is 12.5 Mbp long with 5943 predicted genes.[99] When compared, 81 genes from *C. haemulonii sensu stricto* showed homology with 71 genes from *C. duobushaemulonii*, but with no other organism, being classified as unique genes of the *C. haemulonii* complex.[99] In 2019, it was sequenced the *C. vulturna* genome, which contains 12.9 Mbp and 5560 predicted genes.[21] Later, in 2020, *C. haemulonii* var. *vulnera* was sequenced and, using an average nucleotide identity analysis, it was found that contains 13.21 Mbp, with more than 5400 predicted genes, and showed high identity with *C. haemulonii sensu stricto* (99%), whilst when compared with *C. duobushaemulonii, C. pseudohaemulonii, C. auris*, and *C. lusitaniae*, the identity was 77%, 77%, 75%, and 72%, respectively.[100]

Virulence Factors in *C. auris* and the *C. haemulonii* Complex

Various virulence factors have been recognized in different *Candida* species, and among these are adhesins, hydrolytic enzymes, biofilm formation, dimorphism, immune evasion, and thermotolerance.[14,82,101,102] For the study of virulence factors in *C. auris*, the species *C. albicans* has been used as a reference. Even though most of the virulence factors in *C. auris* and the members of the *C. haemulonii* complex have not been described, these could be predicted from the comparative genomic analysis between *C. albicans* and these species. The putative virulence factors found in *C. auris, C. haemulonii sensu stricto, C. haemulonii var. vulnera, C. pseudohaemulonii*, and *C. duobushaemulonii* are shown in Table 1.

Cell adhesion is an important trait that pathogens have to colonize host cells. Adherence gives pathogens the ability to form microbial communities or biofilms, an important virulence factor of *Candida* species.[103] Biofilms are known to confer increased resistance to antifungal drugs to microorganisms.[102,103] Different *Candida* species have been shown to have their machinery for adhesion, recognition, invasion, and colonization of host cells. In the case of *C. auris*, several studies have suggested that this species uses different mechanisms for cell adhesion.[88] For example, one characteristic of *C. auris* is its ability to adhere to and persist on abiotic surfaces, such as steel devices in hospital environments, as well as human skin.[49,104] In *C. haemulonii sensu stricto*, it has been reported that it can show variation in the cell wall when there is a phenotypic change between white and pink cells. This variation could be an important strategy used by this pathogen to adhere to the host cell surface, adapt to the environment, and escape the immune response.[9]

The genome of *C. auris, C. haemulonii sensu stricto, C. haemulonii var. vulnera, C. pseudohaemulonii*, and *C. duobushaemulonii* encodes several functional orthologs of *C. albicans* adhesins (Table 1). In *C. auris*, it has been reported that agglutinin-like sequence (ALS) proteins play an important role in fungal adherence.[105] Previous work has shown that sera containing anti-Als3 antibodies can prevent biofilm formation in *C. auris* species, corroborating its important role in biofilm formation.[106] Als4 is a well-characterized adhesin in *C. albicans*, and its ortholog is also differentially expressed during filamentous growth in *C. auris*.[92] Although there are no reports for *C. haemulonii sensu stricto, C. haemulonii var. vulnera, C. pseudohaemulonii*, and *C. duobushaemulonii* adhesins, bioinformatic predictions indicate that these adhesins could be also found in these species (Table 1). Two orthologs of the ALS family, Als1 and Als5, are also expressed in *C. auris* biofilms.[103] The different adhesins of the ALS family seem to play an important role in adhesion, biofilm formation, and persistence of *C. auris* in hospital settings.[102]

The *IFF4* gene is highly conserved, and its transcription increases during biofilm production in isolates of *C. auris, C. haemulonii sensu stricto*, and *C. duobushaemulonii*.[101] As observed during our Blastp analysis, this protein appears to be a functional ortholog of *C. albicans* Iff4, which is known to be associated with biofilm production and antifungal

Table 1 Putative Virulence Factors in *Candida auris, C. haemulonii*, and *C. duobushaemulonii*

Virulence Factor	*C. albicans*	*C. auris*	*C. haemulonii*	*C. duobushaemulonii*	E- value*	Similarity (%)*
Adhesins	Als1	CJI96_0005138	CXQ85_004547	CXQ87_001667	$5e^{-45}$	52
	Als5	CJJ09_005316	CXQ85_004547	CXQ87_004268	$1e^{-34}$	49
	Eap1	No found	No found	No found	-	-
	Ecm33	CJI96_0003481	CXQ85_001305	CXQ87_002344	$8e^{-109}$	74
	Hwp1	No found	No found	No found	-	-
	Iff4	FDK38_004751	CA3LBN_002465	CXQ87_001664	$3e^{-35}$	54
	Int1	CJI97_004446	CXQ85_004340	CXQ87_001341	0	59
	Mp65	CJI97_003871	CA3LBN_003990	CXQ87_004408	$7e^{-128}$	82
	Mnt1	CJI97_002568	CA3LBN_000314	CXQ87_000344	0	79
Biofilm formation	Bcr1	CJI97_004038	CXQ85_004690	CXQ87_002954	$4e^{-38}$	89
	Brg1	FDK38_005190	FT662_01339	CXQ87_004952	$1e^{-46}$	86
	Efg1	QG37_02326	CXQ85_002192	CXQ87_000637	$8e^{-82}$	96
	Hsp90	CJI97_005002	CXQ85_001622	CXQ87_003642	0	95
	Ndt80	QG37_08107	CXQ85_000348	CXQ87_003781	$4e^{-104}$	64
	Rob1	CJI96_0002486	CXQ85_004697	CXQ87_001650	$4e^{-18}$	59
	Csr1	QG37_01438	FT662_04426	CXQ87_003974	$1e^{-137}$	54
Dimorphism	Cph1	QG37_02170	CA3LBN_000777	CXQ87_000890	$5e^{-113}$	64
	Hgc1	CJI96_0003736	CXQ85_001596	CXQ87_003669	$8e^{-98}$	65
	Nrg1	CJI96_0004799	CA3LBN_003361	CXQ87_004169	$6e^{-32}$	84
	Tup1	CJI96_0003109	CXQ85_002914	CXQ87_003349	0	88
Hydrolytic enzymes	Lip5,6	CJI97_004237	CXQ85_004470 CXQ85_005044	CXQ87_004175 CXQ87_004891	$1e^{-131}$	66
	Lip7	QG37_04164	CA3LBN_003355	CXQ87_004175	$6e^{-82}$	57
	Lip8	CJJ07_002584	CXQ85_005044	CXQ87_004175	$6e^{-120}$	64
	Sap1-5	CJI97_001086 QG37_06522 FDK38_003693	CA3LBN_003236	CXQ87_003599	$6e^{-65}$	50
	Plb1	CJI96_0001982	CA3LBN_002387	CXQ87_001754	$7e^{-44}$	64
	Plb2	FDK38_001316	CXQ85_003530	CXQ87_001754	0	67
	Plb3	B9J08_003621	CA3LBN_002270	CXQ87_001881	0	73
Immune evasion	Hgt1	CJI97_005618	CA3LBN_003269	CXQ87_004697	0	81
	Msb2	CJJ09_002134	CXQ85_000170	CXQ87_002736	$9e^{-61}$	59
	Pra1	CJI96_0000822	CXQ85_002340	CXQ87_000786	$4e^{-82}$	65
Thermotolerance	Hsp60	CA7LBN_000129	CXQ85_004696	CXQ87_001649	0	96
	Hsp104	CJJ07_002319	CA3LBN_001741	CXQ87_002478	0	94
	Ssa1/Hsp70	FDK38_001195	CXQ85_001344	CXQ87_001126	0	94

Notes: *A BlastP analysis was performed using the database of The National Center for Biotechnology (https://www.ncbi.nlm.nih.gov/) using the *C. albicans* proteins as a query.

resistance mechanisms in this species (Table 1).[103] Although there are few functional orthologs of the *C. albicans* adhesins that have been characterized in these three species, through bioinformatic analysis it is possible to hypothesize that they can be found within the genome of these species, so cell adhesion is likely taking place through the adhesins Als1,3-5, Eap1, Ecm33, Iff4, Int1, and Mp65 (Table 1). Interestingly, the Hwp1 adhesin present in *C. albicans* did not yield any match for any of the five species under analysis (Table 1). This could be because Hwp1 is only expressed in hyphae,[107] and it is known that the species of the *C. haemulonii* complex cannot form true hyphae, and their formation also depends on the strain under study.[19]

C. albicans forms biofilms with a heterogeneous architecture, which combines the presence of blastoconidia and hyphae that are embedded within the extracellular matrix.[108] However, *C. auris* produces thin biofilms composed of blastoconidia and in some cases pseudohyphae, which are embedded within a limited extracellular matrix.[108] Studies of biofilm formation on polystyrene surfaces determined that species of the *C. haemulonii* complex could form biofilms to different degrees, which exhibit a specific isolate pattern. Through tests with crystal violet and safranin, the presence of biofilms formed only by a network of yeasts was observed.[94,109] In the case of *C. auris*, the biofilms showed lower susceptibility to different antifungal drugs, such as polyenes, azoles, and echinocandins, compared to those of *C. albicans*. These findings would suggest that other mechanisms in the biofilms of this species are more important than having low biomass or limited extracellular matrix.[87,88,110] Although the structure of these biofilms differs from those formed by *C. albicans*, biofilms formed by species of the *C. haemulonii* complex also contribute to fungal virulence, antifungal resistance, and survival.[14] In *C. albicans*, biofilm formation is regulated by several genes, such as *BCR1, BRG1, EFG1, HSP90, NDT80, ROB1*, and *CSR1*. According to the bioinformatic analysis carried out, these genes could also be found in the species of the *C. haemulonii* complex and *C. auris* (Table 1). As has been reported, the three species can form biofilms, which could be an indicator that these genes could be part of this biological process, but could be regulated differently. Nevertheless, it is necessary to experimentally address this hypothesis.

The species of the *C. haemulonii* complex are found within the members of the *Candida* genus that are not capable of forming true hyphae, in some cases only pseudohyphae, as has been reported for other species, such as *C. lusitaniae*.[94,111] Dimorphism in *Candida* species is an important factor that has been related to tissue invasion, pathogenicity, and the virulence factors expression that are morphology specific.[112,113] In *C. albicans*, several transcriptional regulators of dimorphism have been studied, including Cph1, Hgc1, Nrg1, and Tup1.[114] According to our bioinformatic analysis, the genome of *C. auris, C. haemulonii sensu stricto, C. haemulonii var. vulnera, C. pseudohaemulonii*, and *C. duobushaemulonii* contain possible functional orthologs of these genes (Table 1). Although these five species cannot form true hyphae, the process that controls dimorphism could be regulated by these genes, but with some differences when compared with *C. albicans*. Yeast morphology also plays an important role in species that cannot make dimorphism, this morphology is the one that is directly involved in fungal spread.[112,115]

The production of secreted hydrolytic enzymes, such as SAPs, lipases, phospholipases, and hemolysins are important for *Candida* pathogenicity since they contribute to host adhesion and invasion.[101,116] Comparative analyzes of the genome of *C. auris* with *C. albicans* and *C. dubliniensis* found that there is a similar amount of lipases between these species.[82] In *C. auris*, it has been shown that the ability to produce lytic enzymes depends on the different strains and isolates.[109] In addition, in vitro studies using different *C. auris* isolates from different geographical regions showed that 37.5% of the strains had phospholipase-type activity and 64% of these were positive for proteinases.[109] Recent studies showed that the levels of SAPs secreted by a *C. auris* isolate at a temperature of 42 °C were higher than the levels of SAPs in *C. albicans* at the same temperature.[68] These results would indicate that *C. auris* isolates adapt to temperature stress and can maintain their pathogenicity at high temperatures.[101] Several studies have demonstrated that *C. auris* expresses lytic enzymes, such as SAPs, phospholipases, and hemolysin; however, there is not much information on how the expression profiles of these are compared with the orthologs of *C. albicans* in vitro and in vivo.[67,92,109] In *C. auris*, it has been reported that filamentous cells produce lower levels of SAPs than yeast cells. The filamentous form could be better adapted to colonize the host skin, and according to this, it is suggested that *C. auris* is a primary colonizer of the skin, unlike *C. albicans*, which may be a primary colonizer of the gastrointestinal tract.[14,25,92]

Comparative studies in a murine model of disseminated infection and a model of *Galleria mellonella* infection showed that *C. auris* is less virulent than *C. albicans*, however, *C. auris* is more virulent than *C. glabrata* and

C. haemulonii sensu stricto in the same models.[101,117] These differences in virulence, when compared to *C. albicans*, may probably be because *C. auris, C. glabrata*, and *C. haemulonii sensu stricto* are unable to develop hyphae in the mammalian hosts.[91,92] Through our bioinformatic analysis, it was possible to find the putative orthologs of *C. albicans* genes that code for phospholipases, and lipases, in the species of the C. *haemulonii* complex and *C. auris* (Table 1). The gene products could be used to carry out specific functions, such as invasion of host cells and evasion of the immune response, as has been reported in *C. albicans*.

Other virulence factors that play an important role in *Candida* species are thermotolerance and immune evasion.[14] Thermotolerance is a characteristic that contributes to the persistence and survival of *C. auris* on biotic and abiotic surfaces for a long time.[14,103,118] *C. auris* is thermotolerant because it grows optimally at 37 °C, but it can remain viable at 42 °C. However, *C. haemulonii* and *C. duobushaemulonii* cannot grow at this temperature.[4,91] The *C. auris* thermotolerance gives the option to cause invasive candidiasis, including tolerance to fever.[119] This thermotolerance is believed to be related to climate change and global temperature changes, and this pathogen could be the first example of a fungus emerging from human-induced global warming.[120] Bioinformatic analysis suggests that the genome of *C. auris, C. haemulonii sensu stricto, C. haemulonii var. vulnera, C. pseudohaemulonii*, and *C. duobushaemulonii* contains orthologs of genes involved in thermotolerance, such as *HSP60, HSP70, HSP90*, and *HSP104*, which code for heat shock proteins (Table 1). Hsp90 is a chaperone that controls temperature-dependent filamentation in *C. albicans*, and in *C. auris*, it was reported that treatment with an Hsp90 inhibitor resulted in the formation of pseudohyphae.[121] However, when the treatment was administered to *C. albicans*, it showed a filamentous growth, which could suggest that in both species certain filamentation mechanisms are conserved.[14]

In the case of immune evasion, *C. albicans* uses different strategies, which involve biofilm formation, protease production, morphological changes, and protein synthesis.[122] In *C. albicans*, there are three genes involved in the immune evasion process, named *HGT1, MSB2*, and *PRA1*. In the *C. haemulonii* complex and *C. auris* possible orthologs of these genes were found (Table 1). These results could indicate that both the mechanisms of thermotolerance and immune evasion in these non-*albicans* species could be similar to the mechanisms used by *C. albicans*. However, more studies are required to corroborate these hypotheses. For the species *C. vulturna* its genome is not yet available, therefore it was not possible to carry out comparative Blastp analyzes.

Immune Response Against *C. auris* and the *C. haemulonii* Complex

Taking into account the importance of new emerging pathogens such as *C. auris, C. haemulonii sensu stricto, C. haemulonii* var. vulnera, *C. vulturna, C. pseudohaemulonii*, and *C. duobushaemulonii*, it is fundamental to understand the host's defense mechanisms and the fungal strategies to evade immunity. The mechanisms related to the immune sensing of these species after infection are still not fully understood. However, recent works have shed some light on this subject. The immune response against fungi is based on two classical immune branches, the innate and adaptive responses. Innate immune cells, such as monocytes, neutrophils, and macrophages recognize *Candida* cells through pattern recognition receptors (PRRs), which interact with pathogen-associated molecular patterns (PAMPs). These PAMPs are, in most cases, cell wall components such as β-glucans, chitin, mannose-based glycans, named mannans, and phospholipomannan.[95,123] For adaptive immunity, which contributes to the long-term host protection against *Candida* infection, the release of immunoglobulins, and activation of T cells are essential events, along with antigen presentation from myeloid cells.[124]

Thus far, anti-*Candida* immunity has been thoroughly studied in *C. albicans*. However, recent progress has been reported in the study of *C. auris* immune sensing. It is known that most of the *C. auris* strains that are resistant to different antifungal drugs show susceptibility when interacting with the antimicrobial peptide histatin 5, which is known to have significant antifungal activity against *C. albicans*.[125] Immune response cells, such as neutrophils, play an important role in controlling *Candida* infections, via the release of neutrophil extracellular traps (NETs).[126] To determine whether these cells effectively kill *C. auris*, fungal viability was measured in a time-course experiment.[127] After 4 h of interaction, a 75% growth inhibition of the reference species *C. albicans* was observed; however, *C. auris* was not affected.[127] In addition, it was also documented that human neutrophils were not capable of recruiting *C. auris* cells.[127]

Previous studies have shown that *C. auris* has a higher tolerance to oxidative stress than *C. albicans*, which may be correlated with survival within neutrophils if engulfed.[125]

It has been reported that species such as *C. albicans, C. tropicalis, C. guilliermondii, C. krusei*, and *C. auris* can differentially stimulate cytokine production by human peripheral blood mononuclear cells (PBMCs).[21] Incubation of yeast cells with human PBMCs and quantification of secreted cytokines determined that *C. auris* and *C. albicans* are barely able to stimulate cytokine production, such as TNFα, IL-6, IL-1β, and IL-10.[21] For *C. albicans*, it had already been reported that heat-inactivated cells stimulated the production of higher levels of TNFα, IL-6, IL-1β, and IL-10 than live cells. In the case of *C. auris*, it was reported that similar to *C. albicans* exposure of inner wall layers by heat inactivation positively affected the ability to stimulate both pro- and anti-inflammatory cytokines.[21] When interacting with human monocyte-derived macrophages, both *C. auris* and *C. albicans* were poorly phagocytosed, when compared with the ability of the human cells to uptake *C. tropicalis, C. guilliermondii*, and *C. krusei* yeast cells.[21] However, its interaction with neutrophils is different from that shown by *C. albicans*, which could suggest that once *C. auris* evades the neutrophil response, the next defensive line, including PBMCs and macrophages, is activated and could control the entry of this pathogen. However, more experiments are needed to help reinforce this hypothesis.[128]

Recently, in vivo and in vitro studies were carried out with the *C. auris* isolate BJCA001, to elucidate more about the immune response against this pathogen.[129] To study the possibility that *C. auris* cells could be efficiently eliminated by the host's innate immune response, immunocompetent female C57BL/6 mice were used, which were intravenously infected with yeast cells of *C. auris* BJCA001. In this experiment, the fungal load was also determined in different mice organs, such as the kidney, spleen, and brain. The results suggested that after infection with the fungus, the yeast cells could remain in the host, avoiding being recognized and eliminated by the innate immune system.[129] In addition, when the fungal load in the different murine organs was determined, abundant tissue colonization by yeast cells was found; however, they did not undergo dimorphism.[129] Inflammation and tissue damage were less severe than that observed in mice infected with *C. albicans*. From these experiments, it was hypothesized that *C. auris* could be developing an uncharacterized immune evasion strategy to combat destruction by immune cells. To test it, in vitro studies were carried out, examining the expression patterns of different proinflammatory cytokines in murine bone marrow-derived macrophages, which were treated with live cells of either *C. auris* isolate BJCA001 or *C. albicans*.[129] It was observed that the expression levels of different proinflammatory cytokines, such as IL-1β, IL-6, TNF-α, CXCL1, and CXCL2 were significantly upregulated after stimulation by *C. albicans*; however, the expression of these was modest when immune cells interacted with *C. auris*. These results could suggest that *C. auris*, compared to *C. albicans*, is a less potent inducer of the MAPK signaling pathway, which plays an important role in controlling the expression of proinflammatory cytokines in macrophages.[129] The reduction of the proinflammatory processes by *C. auris* could also be related to the exposure of the cell wall's outer layer, which seems to be different. This mannan-rich outer layer has been reported to help mask the inner β-1,3-glucan layer, thus, it is not easily recognized by host immune cell receptors.[129] Such masking could play a key role in protecting *C. auris*. Other *Candida* species, such as *C. albicans* and *C. glabrata*, are known to use this mechanism to evade the host attack.[130–132]

In vitro adhesion assays, using different types of human epithelial cells, such as human skin keratinocyte cells, and umbilical vein endothelial cells showed that *C. auris* has a reduced cell adhesion activity, compared to *C. albicans*.[129] However, when the experiment was carried out in vivo using murine skin, it was observed that *C. auris* was able to colonize the skin surface. The reason for these differences in both experiments is not clear, but the authors propose that it could be related to the structural variations of the monocultures and skin, in addition to the fact that *C. auris* could have different growth rates in the different experimental conditions.[129]

For a long time, *C. auris*, unlike *C. albicans*, has been recognized as a pathogen that does not tend to undergo cell dimorphism.[4,29,91] However, the isolate BJCA001 can transit from yeast to filamentous cells.[92] When the adhesion capacity was analyzed in both types of cells, no significant differences were found in cell adhesion, nor changes in cytokine production, and in the same way as reported for yeasts, the filamentous cells also failed to induce MAPK pathway activation.[129] Therefore, the *C. auris* innate immune evasion is morphology-independent.

The immune response against *C. haemulonii sensu stricto* and *C. duobushaemulonii* has not been studied as that described for *C. auris*; however, recent works have elucidated some characteristics of the *C. haemulonii sensu stricto*

immune response.[93] To understand this process, gene expression analyzes were carried out to observe the host immune response against this pathogen, using the zebrafish as an experimental model. Changes in gene expression levels in animals infected with *C. haemulonii sensu stricto* and *C. auris* species were compared with *C. albicans*.[93] It was found that most pro- and anti-inflammatory cytokine expression genes were upregulated in infection caused by *C. haemulonii sensu stricto* and *C. auris*. However, changes in the expression levels of the different cytokines genes (TNF-α, IL-8, IL-10) were found in the early times of infection with *C. auris*, but in the case of *C. haemulonii sensu stricto* those genes showed the top expression at late times of infection.[93] The activation of IL-17α, which is related to the neutrophils recruitment, showed a slow response once the infection by *C. auris* was carried out, in the same way, a significant reduction of IL-8 and leukocyte myeloperoxidase was observed in the later phase of infection by this pathogen.[93] These results suggest that the function of neutrophils in a host infected with *C. auris* may be diminished, due to a lower ability to recognize this pathogen, as has been reported in previous works.[93,127,133] In animals infected with *C. haemulonii sensu stricto* or *C. albicans*, neutrophils readily recognize both species. These findings could explain part of the virulence of *C. auris* and *C. haemulonii sensu stricto*, and how they are recognized by host immune cells.[93] Experiments carried out in immunocompetent mice and *Galleria mellonella* larvae showed that *C. haemulonii sensu stricto* is a fungus of low virulence, compared to *C. albicans* and *C. auris*.[102,117,134]

When evaluating the expressions of matrix metalloproteinases as possible mediators of leukocyte recruitment, it was found that the genes of these metalloproteinases were significantly regulated in zebrafish infected with *C. haemulonii sensu stricto* or *C. auris*.[135] In the case of *MMP9*, the animal group that was infected with *C. auris* showed a high expression in the late infection phase, while animals infected with *C. haemulonii sensu stricto* increased the expression in the early phase.[93] Regarding *JAK2* expression, it was increased in the animal group infected with *C. auris* at the early time point and NF-κβ, a key transcription factor for proinflammatory cytokine production, showed higher expressions after *C. auris* and *C. haemulonii sensu stricto* infection, than with *C. albicans*.[93] Because of the importance of the development and function of regulatory T cells during the immune response, the expression of two genes that are involved in this process, *FOXP3a* and *FOXP3b*, was determined.[136] *C. haemulonii sensu stricto* infection revealed that the expression of these genes had similar levels to *C. albicans* infection; however, *C. auris* infection led to significantly higher expression of both genes.[93] A different time point of gene expression was found between the different species, for *C. auris* it increased at the early time point, but for *C. haemulonii sensu stricto*, it increased at the late time point.[93] Based on these results, it could be inferred that *C. auris*, unlike *C. haemulonii sensu stricto*, could reduce the number of regulatory T cells at the late time point and thus increase the yeast population to continue the infectious process.

Although *C. auris* and *C. haemulonii sensu stricto* have a close phylogenetic relationship, the immune response seems to be different. Regarding *C. duobushaemulonii, C. pseudohaemulonii*, and *C. vulturna*, there are currently no reports on how the pathogen-host interaction takes place. Even though these species are phylogenetically related to *C. auris*, it is not feasible to extrapolate the information about the immune response of this species to other ones, because it is clear that this crosstalk with the host immunity is species-specific.

Conclusions

In recent years, the epidemiology of infections caused by *Candida* has changed, and the emergency of non-*albicans* species has been increasing, as is the case of *C. auris, C. haemulonii sensu stricto, C. haemulonii var. vulnera, C. vulturna, C. pseudohaemulonii*, and *C. duobushaemulonii*. These have been recognized as pathogens of concern, presenting intrinsic resistance to commonly used antifungal drugs. The infections caused by these species, especially *C. auris*, which is the most studied, can be fatal in immunocompromised patients.

The use of bioinformatics tools has become a key strategy to understand the biology of neglected organisms, such as the *C. haemulonii* complex and *C. auris*. These tools allow the predictions of genes and gene products, which can be used to build up working models to establish differences and similarities in virulence factors in species mentioned in this work.

From the information revised, it was evident that more information and studies are needed on the *C. haemulonii* complex and *C. auris*, especially on species identification and immune response. These could be opportunity areas to develop new methodologies that allow us to easily distinguish between species and learn more about pathogen-

host interaction. Knowledge of resistance to one or more classes of antifungals can be of great help in selecting a therapy to eliminate the causative agent of mycosis, for which, the correct identification of the pathogen and the determination of antifungal susceptibility is paramount. It is also vital to avoid the administration of the drug in subtherapeutic doses and for prolonged periods, as these are factors that contribute to the development of drug resistance.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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