Hindawi
Cellular Microbiology
Volume 2022, Article ID 2599136, 25 pages
https://doi.org/10.1155/2022/2599136

Review Article

Similarities and Differences among Species Closely Related to *Candida albicans*: *C. tropicalis*, *C. dubliniensis*, and *C. auris*

Dorota Satala,[1] **Magdalena Juszczak**,[1] **Ewelina Wronowska**,[1] **Magdalena Surowiec**,[1] **Kamila Kulig**,[2] **Andrzej Kozik**,[2] **Maria Rapala-Kozik**,[1] **and Justyna Karkowska-Kuleta**[1]

[1]*Department of Comparative Biochemistry and Bioanalytics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University in Krakow, 30-387 Krakow, Poland*
[2]*Department of Analytical Biochemistry, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University in Krakow, 30-387 Krakow, Poland*

Correspondence should be addressed to Justyna Karkowska-Kuleta; justyna.karkowska@uj.edu.pl

Received 31 March 2022; Revised 18 September 2022; Accepted 6 October 2022; Published 9 November 2022

Academic Editor: Sanket Kaushik

Although *Candida* species are widespread commensals of the microflora of healthy individuals, they are also among the most important human fungal pathogens that under certain conditions can cause diseases (candidiases) of varying severity ranging from mild superficial infections of the mucous membranes to life-threatening systemic infections. So far, the vast majority of research aimed at understanding the molecular basis of pathogenesis has been focused on the most common species—*Candida albicans*. Meanwhile, other closely related species belonging to the CTG clade, namely, *Candida tropicalis* and *Candida dubliniensis*, are becoming more important in clinical practice, as well as a relatively newly identified species, *Candida auris*. Despite the close relationship of these microorganisms, it seems that in the course of evolution, they have developed distinct biochemical, metabolic, and physiological adaptations, which they use to fit to commensal niches and achieve full virulence. Therefore, in this review, we describe the current knowledge on *C. tropicalis*, *C. dubliniensis*, and *C. auris* virulence factors, the formation of a mixed species biofilm and mutual communication, the environmental stress response and related changes in fungal cell metabolism, and the effect of pathogens on host defense response and susceptibility to antifungal agents used, highlighting differences with respect to *C. albicans*. Special attention is paid to common diagnostic problems resulting from similarities between these species and the emergence of drug resistance mechanisms. Understanding the different strategies to achieve virulence, used by important opportunistic pathogens of the genus *Candida*, is essential for proper diagnosis and treatment.

1. Virulence of *Candida* Pathogenic Fungi

The fungal kingdom includes many different virulent species that are able to infect, colonize, and cause diseases in humans [1, 2]. Virulence is defined as the relative ability of a microorganism to cause damage to the host during colonization, whereas virulence factors are defined as microbial attributes that mediate the destruction capacity. However, the virulence determinants are not merely proprietary and inherent attributes of the pathogen, but must be carefully considered with regard to host-pathogen interactions and the state of the host's immunity and strength of its response to the pathogen. Therefore, host damage can result from both the activity of the microorganism itself and the action of the immune system [3, 4]. If there is no harm to the host or is not clinically relevant, such microorganisms may be considered commensals that do not provoke an excessive immune response. However, under certain conditions, the balance can shift to pathogenicity with increasing damage and activation of the host's defense. In infections caused by *Candida* fungi, such conditions include a

disturbance of the beneficial microflora of the host or immune disorders [5]. In susceptible hosts, *Candida* fungi can cause different types of infections, manifested by superficial infection of the skin and mucous membranes or deep tissue infections and candidemia [6–9].

Of several hundred known species of the genus *Candida*, only some are indicated to be capable of causing human infection, and they even differ significantly in their virulence and adaptation strategies, thus locating at divergent points in a continuous spectrum of the types of interactions between the host and the microorganism. Recent considerations indicate that the evolution of fungal virulence could have taken many individual directions and depended on a variety of factors, and only some of them have been recognized so far [2, 10–13]. The ability to colonize the human host by some *Candida* species arose from using the available properties related to their cell biology and required to adapt to specific niche conditions. The transition between the commensal and pathogenic states, closely correlated with modulation of host immunity, is based on the differential adjustment of fungal virulence to ensure the survival and multiplication of fungi, in addition to avoiding microbe removal and causing excessive host damage [2, 14]. Throughout coexistence with the human host, particular *Candida* species have developed different mechanisms for adaptation to colonization. Observable manifestations of these adaptations related to the biological functions of the cell, i.e., the ability to grow at higher temperature, changes in cell morphology, and the range and level of production of manifold molecules, may be similar to some extent, or they may differ significantly for individual *Candida* species. This could not only result in the distinct virulence potential and adaptation ability of individual *Candida* species but can also be of great importance in practice, affecting the correct diagnosis and effective treatment of candidiases.

So far, the most widespread and best-characterized species of the *Candida* genus is *C. albicans*, representing the so-called CTG clade, in which the CTG codon is translated as serine instead of leucine [9, 15]. The frequency and type of infections caused by selected *Candida* species from the CTG clade in different groups of predisposed patients, their geographic distribution, and the severity of the disease course can vary, depending on the specific susceptibility of individuals, concomitant risk factors, and environmental determinants [16, 17]. Candidiases comprise fungal manifestations on the skin and mucous membranes, such as oral or vaginal thrush, which are relatively mild disorders, although extremely bothersome, as well as severe infections of internal organs, systems, and the entire organism with widespread inflammation and sepsis. The highest distribution is still observed for *C. albicans*, and among the other species discussed in this review, the average incidence was significantly higher for *C. tropicalis* than for *C. dubliniensis*. *C. albicans* and *C. tropicalis* belong to a group of five *Candida* species that account for more than 90% of all candidial infections, both superficial and invasive [18]. The number of confirmed identified infections with *C. auris* has increased markedly in the last decade, since its first identification in 2009, making this species an emerging pathogen [19]. Interestingly, among the discussed species, *C. auris* is not considered a component of the commensal intestinal microflora, but rather as environmental contamination, and it rather inhabits the skin surface, thus facilitating transmission between individuals and the development of infections after gaining access to the interior of the human organism [20].

Since changes in the epidemiology of fungal infections have been observed in recent decades, manifested by an increase in candidiases caused by species other than *C. albicans*, it seems that despite their close relationship (Figure 1), these species maintain different ways of survival and reproduction in the host [21–25]. Therefore, the main objective of this review was to compare current knowledge on observable differences and similarities in virulence factors, cointeractions, and susceptibility to antifungal drugs by *Candida* species most closely related to *C. albicans*, namely, *C. dubliniensis* and *C. tropicalis*, but also by a relatively newly identified species of global concern, *C. auris* [26–30], to indicate the impact of differences between these individual *Candida* species on practical issues related to candidial infections, especially problems in proper diagnosis and treatment of candidiasis.

1.1. Variety of Virulence Factors in the Fungal CTG Clade. *Candida* species belonging to the CTG clade have evolved multiple virulence factors that are used at different stages of infection in interactions with host proteins and cells and in the evasion of the immune system. Although the set of virulence factors differs within the CTG clade and their expression depends on the type of strain and the stage of infection [31], they involve primarily the production of different classes of proteins, including adhesins and a wide spectrum of hydrolytic enzymes (Figure 2) [32–35]. Comparative genomic analyses indicated that for *C. albicans*, a significant enrichment compared to nonpathogenic yeasts was found for genes encoding secreted proteases and lipases, acid sphingomyelinases, cytochromes P450, and various transporters. Also, noticeable differences in genes related to oxidative metabolism and environmental sensing and response were indicated in comparison with nonpathogens. Understanding the differences in the genomes of individual fungal species closely related to each other, but differing in virulence, may allow the determination of the genetic basis of adaptation of yeasts to pathogenicity [36, 37].

The first landmark study comparing the evolutionary pathways of the main fungal pathogens belonging to the *Candida* clade, including *C. albicans* and *C. tropicalis*, identified 64 gene families with positive selection, which through their participation in filamentous growth (e.g., *SWI*, *PMT*, and *CPH*/*STE*), biofilm formation (e.g., *CPH*/*STE* and *PGA*/*YWP*), and drug sensitivity (e.g., *ERG*) play an essential role in the pathogenesis of these species [10]. The genomic comparative analysis of *C. albicans* and *C. dubliniensis* indicated that since both species lost a common ancestor some 20 million years ago, the former species was enriched with the virulence-related gene families, while the latter consistently lost pathogenicity-related genes, including hyphal-associated *HYR1*, genes for particular secreted enzymes, or *IFA* gene family encoding transmembrane proteins, which compromised its virulence [38]. Moreover, the difference in the number of members of the telomere-associated (*TLO*) gene family, represented by 14 genes in *C. albicans* and only two in *C. dubliniensis*, may be significant in understanding discrepancy in the pathogenicity of these species, as they may

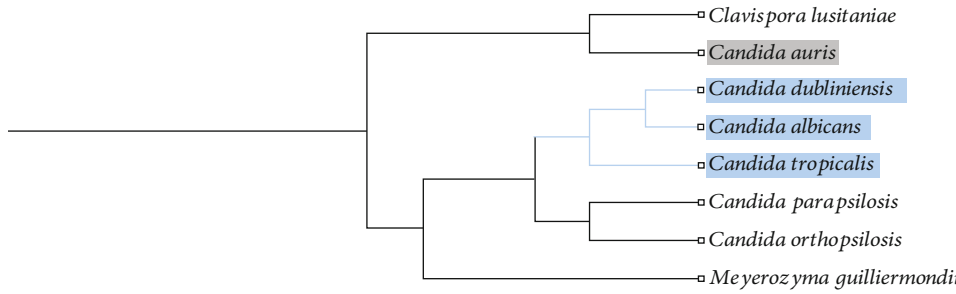

Figure 1: Phylogenetic tree of selected species of the CTG clade generated on the basis of the NCBI or GTD taxonomy available in the online version of the phyloT program.

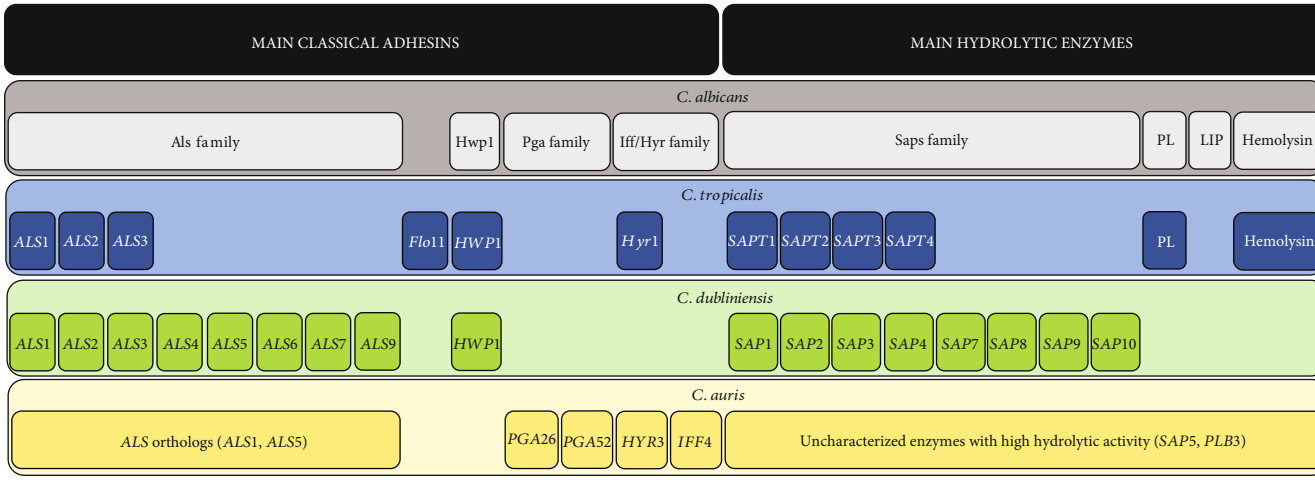

Figure 2: Main virulence factors of selected yeasts of the genus *Candida*.

possibly act as transcriptional regulators involved in different cellular processes [11, 38].

The key stage in the development of a fungal infection is the adhesion of the pathogen to a variety of biotic and abiotic surfaces [39]. The possibility of *C. albicans* binding to various ligands on the surface of host cells, as well as to artificial surfaces, is associated with exposition of glycosylphosphatidylinositol- (GPI-) anchored adhesins: agglutinin-like sequence protein family (Als1-7 and Als9), hyphal wall protein family (Hwp1), Eap1, Iff4, Ecm33, and also noncovalently cell wall-associated proteins, i.e., Mp65 and Phr1 [40, 41]. Phylogenomic studies have identified three main families of genes that encode cell wall components, including genes for Als adhesins, Hyr/Iff proteins, and Pga30-like proteins that are highly enriched in pathogenic species, including *C. albicans* and *C. tropicalis* [10]. Analysis of predicted cell wall proteins in *C. auris* did not reveal highly developed families, in contrast to the expansion of genes for transporters and lipases, which may also indicate different mechanisms of virulence in *C. albicans* and *C. auris* [42, 43].

In addition to classic adhesive proteins, this function is also performed by some cytosolic proteins, called moonlighting proteins, and located on the surface of yeast cells, where they perform completely different functions than at the primary location [44, 45]. For example, *C. albicans* cell wall-associated glyceraldehyde-3-phosphate dehydrogenase (Tdh3), an enzyme originally involved in the glycolysis pathway, has a high affinity for extracellular matrix (ECM) components such as fibronectin and laminin [46] or other glycolytic enzymes, phosphoglycerate mutase 1 (Gpm1) which allows adhesion to umbilical vein endothelial cells (HUVEC) and keratinocytes (HaCaT) [47] and to vitronectin and fibronectin [35] and triosephosphate isomerase (Tpi1), which interact with several ECM proteins [48]. *C. albicans* enolase (Eno1) was also indicated as an abundant moonlighting protein responsible for binding of human high-molecular-weight kininogen (HK), prekallikrein, coagulation factor XII, and plasminogen [34, 49, 50]. Furthermore, moonlighting proteins are also involved in binding to abiotic surfaces; for example, Eno1 plays a role in silicone and polyvinyl chloride adhesion and therefore is involved in biofilm formation on medical devices [51, 52].

Less is known about the profile of adhesins in *C. tropicalis*. Studies by Punithavathy and Menon evaluated the presence of *ALS* genes in the *C. tropicalis* genome in clinical isolates from HIV and non-HIV patients [53]. The results indicated that the genes *ALS2* (50% of isolates) and *ALS3* (48%) are more common than *ALS1* (28%). Recently, the use of DNA sequencing technology combining short-read (Illumina MiSeq) and long-read (Oxford Nanopore MinION) datasets allowed the identification of 13 distinct genomic loci in *C. tropicalis*, with predicted encoded proteins demonstrating Als structural features such as the N-terminal-binding domain, a central domain

of tandemly repeated sequences and the C-terminal domain rich in serine and threonine. Detailed comparisons indicated that the predicted percent sequence identity compared to *C. albicans* was highest (30-50%) in the N-terminal domain of the C. *tropicalis* protein. Moreover, the predicted *ALS* genes showed variability in relative expression depending on the culture conditions [54]. Furthermore, Himratul-Aznita et al. [55] showed that the *HWP1* adhesin-encoding gene is also present in the *C. tropicalis* genome and has a sequence identical to that of *C. albicans*. Bioinformatic studies conducted by Willaert et al. demonstrated the presence of the Flo adhesin family (Flo11 type), previously discovered in brewer yeasts [56]. Some reports indicated that the levels of proteins present on the surface of *C. tropicalis* vary with the growing conditions. For example, in plasma-containing medium, three times higher levels of Rbt1, Als-like, and also, Tdh3 were indicated [57]. Furthermore, Hyr1 adhesin was shown to have a significant affinity for ECM proteins and HK [58, 59]. In addition, *C. tropicalis* moonlighting proteins such as malate synthase Mls1, fructose-1,6-bisphosphatase Fbp1, Eno1, and Gpm1 may play a role in adhesion to components of ECM or plasminogen [48, 50, 58].

Several studies suggested that *C. dubliniensis* exhibits lower virulence than *C. albicans* [23, 60]. As adhesion is one of the key virulence factors, it was assumed that there may be differences in the adhesin profile of these two species. It seems that *C. dubliniensis*, despite its similar evolutionary origin, might have gradually lost several genes that are still present in *C. albicans* [38]. The percentage of homology of amino acids compared to *C. albicans* is less than 50 [61–63]. To date, several genes encoding proteins homologous to *C. albicans* adhesins have been identified in the genome of *C. dubliniensis*, including *ALS*-like sequences and *HWP1* [38]. However, a detailed phylogenetic analysis suggests that *C. dubliniensis* has evolved a new Als family. That is, *ALS3* located on the R chromosome in *C. albicans* was shown to be completely absent at its corresponding position in *C. dubliniensis*, similar to *ALS5* [38], while *ALS1* and *ALS2* do not show an ortholog sequence in relation to *C. albicans*, suggesting that these proteins are species-specific acquisitions [38]. Studies by Oh et al. demonstrated that the genes encoding Als proteins in *C. dubliniensis* strain CD36 differ in relative expression depending on culture conditions, with the greatest changes observed for *ALS2* and *ALS6* [54]. In the case of *HWP1*, there is a homologue in the *C. dubliniensis* genome, but this gene is very divergent due to the presence of major deletions [63].

Studies conducted in recent years show that *C. auris* is as virulent as *C. albicans* [64]; however, the range of virulence attributes used differs between species [65]. The genome of *C. auris* contains genes that encode several orthologs of adhesins found in *C. albicans*, which are well characterized as virulence factors [66]. Namely, *C. auris* biofilm-forming cells possess orthologs of the *ALS* protein, as well as proteins such as *IFF4*, *CSA1*, *PGA26*, *PGA52*, and *HYR3*, which are expressed during biofilm formation [67]. Genomic analyses showed that there are differences in the adhesin profile between *C. auris* strains. The less virulent Clade II strain of *C. auris* (East Asian type), responsible for ear infections, lacks significant fragments of subtelomeric regions encoding adhesins [43].

The virulence of the CTG clade is also associated with the production of a variety of hydrolytic enzymes that contribute to the invasion of host tissues by damaging cell surface structures and degrading a variety of host proteins. In the case of *C. albicans*, the following classes of enzymes can be distinguished: aspartic proteases (Saps), phospholipases (PL) and lipases (LIP), esterase, and hemolysin, where most are extracellularly secreted enzymes [68]. These enzymes are differentially regulated and produced during different stages of infection [68, 69]. In recent years, aspartyl proteases have been most extensively studied. These enzymes are involved in every stage of *C. albicans* infection, and their functions are not limited to substrate hydrolysis. Saps contribute to the adhesion and invasion of tissues and damage a variety of human proteins, including albumin, hemoglobin, keratin, collagen, laminin, fibronectin, mucin, and immunoglobulins [70]. The multigene Sap family in *C. albicans* consists of at least 10 members. Sap1-8 are secreted into the extracellular space, while Sap9 and Sap10 are GPI-anchored proteins. PLs are also a broad group of enzymes that catalyze the hydrolysis of ester bonds in glycerophospholipids. These enzymes were recognized as factors that allow penetration of host cells and interaction with host signaling pathways [68, 71]. PLs can be divided into several subclasses—PLA, PLB, PLC, and PLD—depending on the phospholipid substrate [68, 72]. PLs are particularly localized at the ends of penetrating hyphae and at initial budding sites. Lipases are a relatively poorly studied group of *C. albicans* enzymes, and their functions in infections are not precisely known. Genetic studies have shown the presence of ten (*LIP1-10*) genes in the genome of *C. albicans* [73].

Very high proteolytic activity was also found in *C. tropicalis*. A study by Zaugg et al. indicated the existence of the *SAPT* gene family (secreted aspartic proteinase tropicalis) in the genome of *C. tropicalis* (*SAPT1-4*) [74]. Although *SAPT2-4* genes are upregulated during the yeast-hyphal transition and are involved in oral mucosal invasion and damage [75, 76], earlier studies have shown that the high invasiveness of *C. tropicalis* may not be related to the specific expression of *SAPT1* [77, 78]. On the other hand, studies indicate a low activity of phospholipases in the majority of *C. tropicalis* isolates [79, 80]. However, 95.8% of the *C. tropicalis* strains isolated from the blood of patients admitted to the intensive care unit were characterized by high hemolysin and esterase activity [81]. Hemolysin secretion by *C. tropicalis* caused the release of hemoglobin from red blood cells for further use as an iron source; however, the production of hemolytic factor strictly depends on culture conditions [82].

C. dubliniensis is phylogenetically very closely related to *C. albicans*; however, it shows significantly reduced virulence in animal models of infection that may be related to the absence of certain proteolytic enzymes. The study by Loaiza-Loez et al. showed that *C. dubliniensis* expresses *SAP* orthologs (C*dSAP1*-4 and *CdSAP7*-9), but not *SAP5* and *SAP6* [83]. The absence of *SAP5* may partially explain the lower ability to invade host tissues because this enzyme is involved in the degradation of E-cadherin [83]. In addition, most of *C. dubliniensis* isolates also lack phospholipase activity [84].

Substantial proteinase activity was detected in 96% of *C. auris* strains [85]; however, hydrolytic enzymes have not been well characterized to date. Of the Sap family, *SAP5* has been shown to be present in the *C. auris* genome [67]. Research by Wang and coworkers indicated that *C. auris* exhibits a high Sap activity at 25°C, 37°C, 40°C, and even 42°C while *C. albicans* showed significantly reduced Sap activity above 37°C [86]. Studies on *C. auris* isolates from patients with invasive infections and colonization revealed also that more than half of the isolates had phospholipase activity (67.3%) [87]. Among this group of enzymes, phospholipase *PLB3* was identified in the *C. auris* genome [67]. In addition, more than 60% of the clinical isolates were also indicated to possess hemolytic activity [87].

In the microbial world, another important group of virulence factors includes toxins. Studies on prokaryotic microorganisms indicate that toxins are molecules that target host cells and manipulate cell signaling or induce cell death [88]. The first toxin discovered in the fungal pathogen was candidalysin, isolated from *C. albicans* [89]. Candidalysin is an amphipathic, α-helical peptide, derived from a polypeptide (Ece1) encoded by the *ECE1* gene [90]. Recent studies indicate that candidalysin is one of the key molecules involved in the destabilization of the epithelial plasma membrane and the induction of necrotic cell death [91, 92]. Orthologs of candidalysin from *C. albicans* have also been found in *C. dubliniensis* and *C. tropicalis* [92]. Interestingly, studies on oral epithelial cells and artificial lipid membranes presented by Richardson et al. [92] indicated that candidalysins produced by *C. dubliniensis* and *C. tropicalis* have stronger and faster cytolytic and immunostimulatory effects than candidalysin of *C. albicans*. Importantly, both species cause less damage to epithelial cells than *C. albicans*, which may be due to lower Ece1 production, processing, or secretion during contact with the host. Since candidalysin is a classic virulence factor that involves a strong host immune response, species that prefer a more commensal mode of existence are unlikely to exploit its potential to that extent [93]. In the case of *C. auris*, the *ECE1* gene has not been detected in the genome and, according to current knowledge, this species does not produce candidalysin [92].

1.2. Other Mechanisms Related to Virulence. Morphological change to filamentous form is considered strongly associated with the significant virulence of *C. albicans* and *C. tropicalis* [94]. In the case of *C. albicans* and *C. dubliniensis*, the different ability to produce hyphae under specific niche conditions indicates different adaptations to exist as a commensal or pathogen, as the transition to the filamentous form for which *C. albicans* is more predisposed is considered as increasing virulence potential, while the reduced filamentation is believed to be an adaptation of *C. dubliniensis* to a less virulent lifestyle [2, 23]. However, *C. auris* exists predominantly as blastospores [86, 95, 96], which indicates that in addition to the morphological transformation into hyphae, which is considered considerably important in virulence, there are other relevant factors that determine a species becoming the pathogen [97].

Phenotypic switching is another feature that allows yeasts to adapt to different niches [98, 99]. *C. albicans*, *C. dubliniensis*, and *C. tropicalis* are diploid yeasts that can exist in two different cell phenotypes. The first, called *white*, includes smooth and shiny cells, while the second, called *opaque*, includes flat and rough cells with a curved and elongated shape [100], although opaque cells, unlike white cells, did not release a strong chemoattractant for human polymorphonuclear leukocytes (PMN), thus gaining invisibility for host immune cells and protection against phagocytosis [101, 102]. On the contrary, in the case of *C. auris*, which is the haploid, three phenotypes were observed: *white*, *opaque*, and *sectored*, with all cells having shiny and smooth surfaces and the same size [95]. Interestingly, in the case of *white* cells, a higher rate of self-propagation was observed in liquid medium, suggesting increased stability of this phenotype [95].

An important factor contributing to the evolution of pathogenicity is reproduction, which includes three main models—sexual, parasexual, and asexual reproduction. While most fungi reproduce sexually, *C. albicans* has been shown to have parasexual cycles in which, after the fusion of diploid cells, rather than meiosis, coordinated loss of chromosomes occurs, resulting in viable progeny; this pathway of reproduction increases genetic diversity and contributes to adaptation to stressful environments, but also may mediate drug resistance [103]. The evolutionary role of reproduction, especially parasexual, in other medically important species of the genus *Candida* has become the subject of recent studies that discuss in detail the regulation of its mechanisms and importance in the evolution of pathogenicity [104–106]. Although *C. albicans*, *C. tropicalis*, and *C. dubliniensis*, due to their close relationship, share common features of the parasexual cycle, such as mating between diploid cells, the presence of a stable tetraploid form, coordinated loss of chromosomes, and the ability of diploid progeny to reenter the parasexual process, they also developed their unique attributes of those processes [104, 106]. For example, in the case of *C. tropicalis*, the possibility of generating hexaploid progeny has been reported by mating homothallic and heterothallic tetraploid products with diploid cells and the possibility of pheromone-assisted a-a homothallic mating without the need to white-to-opaque switch [104, 106]. In turn, *C. dubliniensis*, compared to *C. albicans*, shows a much higher *white*-to-*opaque* frequency and does not show clumping dependent on mating, which results in less efficient intraspecific mating than interspecies mating [104]. To date, parasexual reproduction has not been reported for *C. auris*; however, the presence of a complete mating-type locus suggests that this species may also be capable of parasexuality [105].

To maintain complete virulence, *Candida* species also need calcineurin activity, which is calcium/calmodulin-dependent serine/threonine-specific protein phosphatase composed of catalytic subunit A (Cna1) and a regulatory subunit B (Cnb1) [107, 108]. The main target of calcineurin-dependent dephosphorylation in fungal cells is the Crz1 transcription factor Crz1; however, there may be other substrates available, and signaling triggered by calcineurin activity influences many different aspects related to fungal biology, as well as their attainment of virulence [109]. For *C. tropicalis* and *C. dubliniensis*, calcineurin was shown to be crucial for hyphal growth, while for *C. albicans*, the role of this phosphatase in filamentation is discussed [110–112]. Furthermore, in the case of *C. tropicalis* and *C. dubliniensis*, it was also demonstrated that

calcineurin is important for cell wall integrity, resistance to echinocandins and azoles, and it is essential for virulence in a murine systemic infection model [110, 111]. When comparing the latter species with *C. albicans*, it is considered that calcineurin is more important in controlling acidic pH homeostasis, while for *C. albicans*, calcineurin is more essential in serum survival compared to *C. dubliniensis* [112]. Orthologous genes for calcineurin and Crz1 were indicated for *C. auris*; however, further detailed studies of their role are required for this species.

2. Formation of Mixed Species Biofilms within the CTG Clade: Competition or Assistance during Infection?

Although most available reports focus on studying biofilms produced by one *Candida* species, in vivo analysis shows that these are complex communities where multiple species can coexist in the same niches of the host organism [113–118]. The classical division of communication between them is divided into two paths. The first is synergism that promotes the formation of biofilms through coaggregation and jointly increases protection against the host's immune system. The second is antagonism based on competition for nutritional resources and mutual inhibition of growth [119]. Therefore, it is necessary to identify interactions involving several different species, as this can be of great importance in combating infections associated with the formation of a mixed fungal biofilm.

The studies presented by Pathirana et al. [118] focused on the analysis of biofilms produced under induced flow conditions that mimic the host oral environment in which *C. albicans* interacted with *C. dubliniensis* or *C. tropicalis* shown that after 4 hours of development of a dual-species biofilm, the percentage of adherent *C. dubliniensis* and *C. tropicalis* cells was higher compared to that of a single-species biofilm. Moreover, these species were quantitatively dominant over *C. albicans*, covering a larger biofilm area. However, as the biofilm reached maturity, *C. albicans* acquired quantitative dominance over both species. Interestingly, the coexistence of *C. albicans* and *C. dubliniensis* increased the area covered by mature biofilms compared to monospecies biofilms. In contrast, the presence of *C. albicans* inhibited hyphae production by *C. tropicalis*, and a mixed biofilm was formed more slowly than monospecies biofilms. Furthermore, it was found that the *C. tropicalis* cell clusters formed in sites not occupied by *C. albicans* cells showed high dispersibility. The authors of the study postulate that the observed interactions between *C. albicans* and *C. dubliniensis* are synergistic mainly due to the rapid growth rate of a typical mature biofilm [118], which may contribute to protection against the host immune system or to increased resistance to the antifungal drugs [120, 121]. These conclusions are consistent with the results obtained by Kirkpatrick et al. [122], who showed that *C. dubliniensis* could withstand competitive pressure from *C. albicans* and cocreate a biofilm in the urethral catheter model. Interestingly, *C. dubliniensis* cells were also shown to not adhere to *C. albicans* blastospores [118]. On the contrary, under the conditions of joint planktonic growth, *C. albicans* showed a significant competitive advantage over *C. dubliniensis* [122]. In vivo studies based on an oral-gastric infection model of murine infants showed that despite similar colony forming units (CFU), values were obtained for both species after 2 days of coinfection; the number of *C. dubliniensis* yeast cells was undetectable after 6 days [60].

Interestingly, in the mixed biofilm of *C. albicans* and *C. tropicalis* formed under induced flow conditions, the mature dual-species biofilm covered a much larger surface area compared to that produced by *C. tropicalis* itself, despite the inhibition of the morphological change of *C. tropicalis* cells by *C. albicans*. Thus, it appears that the in vivo coexistence of the two species may be beneficial to *C. tropicalis* [118], by the increased protection against antifungal agents noted in comparison to monospecies biofilms [123]. On the contrary, the results presented by de Barros et al. [124] suggested an antagonistic relationship between *C. tropicalis* and *C. albicans*, which was manifested by a decrease in the number of *C. albicans* cells and a decrease in metabolic activity in mixed biofilms. Moreover, in the presence of *C. tropicalis*, a significant reduction in the expression of genes involved in the morphogenesis and biofilm formation of *C. albicans* such as *ALS3*, *BCR1*, *CPH1*, *EFG1*, *HWP1*, and *UME6* was shown [124]. When comparing these reports, it seems that the experimental conditions are of critical importance in the analysis of interspecies interactions [118, 124]. *C. albicans* and *C. tropicalis* show apparent differences in the adhesion and growth of biofilms in different media, which can favor the growth of only one of them. Furthermore, the stationary growth of the biofilm differs compared to the biofilm formed in the induced flow [118, 124]. However, the effect of reduced pathogenicity of *C. albicans* in mixed biofilm formed with *C. tropicalis* was confirmed by analyses carried out on *Galleria mellonella* larvae, where contact with dual-species biofilm resulted in significantly higher larvae survival compared to the control group, in which infection was caused by *C. albicans* alone [124].

Although *C. auris* coexists in vitro with other species [125, 126], no studies on its interaction in mixed biofilms have been reported yet.

3. Communication of *Candida* Species with Host and Environment

To survive and reproduce, pathogenic yeasts have developed sophisticated mechanisms that allow them to adapt to changing niches in the host body where oxygen deficiency, nutrient deficiency, or oxidative stress can occur so as to pursue existence more as a commensal or pathogen. Despite the close relationship between *Candida* species, adaptation mechanisms, including intercellular communication through quorum sensing molecules, changes in fungal cell metabolism resulting from stress, and response to the emergence of host immune surveillance, show significant differences (Figure 3).

3.1. Quorum Sensing Molecules Produced by C. tropicalis, C. dubliniensis, and C. auris. Within the structures of biofilms, except for the physical cell-cell interactions, the key process in detecting and reacting to changing external conditions is

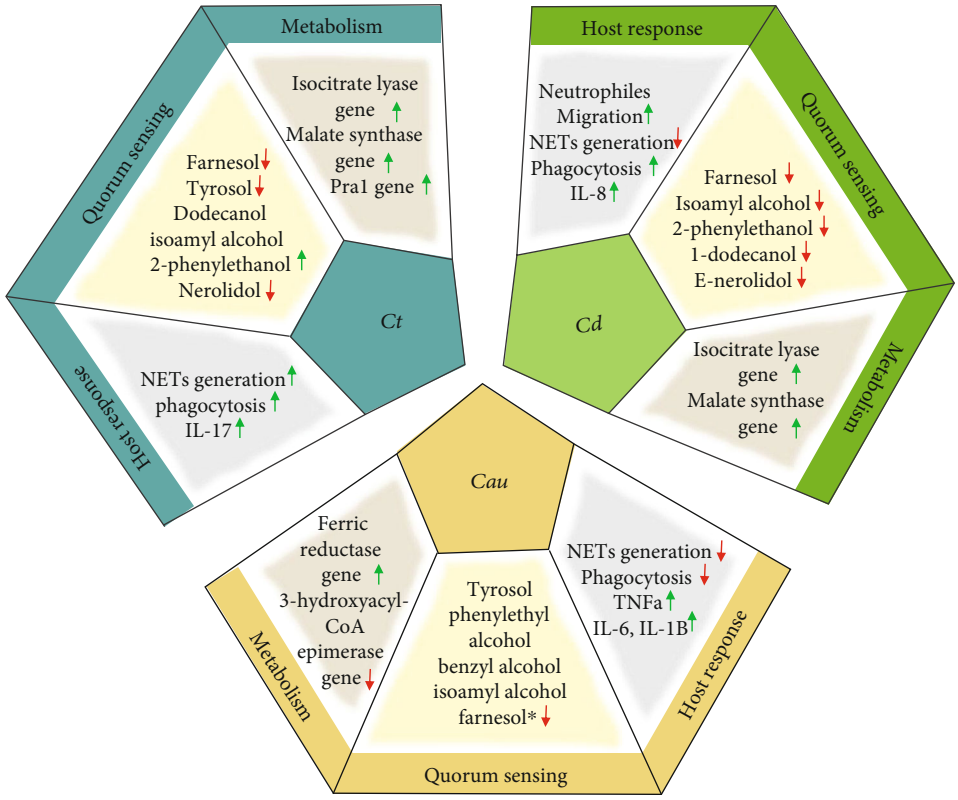

Figure 3: Selected factors of *C. tropicalis* (*Ct*), *C. dubliniensis* (*Cd*), and *C. auris* (*Cau*) related to their interaction with the environment and the host. The development of a fungal infection can enhance (green arrow) or inhibit (red arrow) some processes related to the host's immune response, and it differs depending on the species causing the candidiasis. In addition, the adaptation of the pathogen to the new environment influences the increase (green arrow) or decrease in the expression of genes (red arrow) involved in its metabolism. In turn, the variable repertoire of secreted quorum sensing molecules favors or inhibits fungal filamentation and biofilm formation (green and red arrows, respectively). *The use of external farnesol for testing.

performed by quorum-sensing molecules. By enhancing or inhibiting the activity of many genes, released signaling molecules regulate the change in morphological form, maintaining the structure of the cell wall or phagocytic and the response to heat shock [127, 128]. This strategy benefits biofilm communities by preventing overpopulation or competition for nutrients and contributing to the spread of pathogen cells to distal sites of infection [129–131]. In the case of *C. albicans*, the best-characterized quorum sensing molecule so far is the secondary product of sterol biosynthesis, farnesol, which, by inhibiting the hyphal formation process and the formation of biofilms, contributes to culture growth in the form of single cells [127, 132, 133]. Despite the growing importance of quorum sensing molecules in the regulation of communication within complex communities [128, 134, 135], limited information is available on other *Candida* species.

In the case of *C. dubliniensis*, the first studies showed that the use of spent medium inhibited morphological transformation to the hyphae, as did exogenous farnesol, suggesting that this species secreted farnesol or another compound with similar activity [136]. Similar results were obtained for the two reference strains of *C. dubliniensis*, which showed that the presence of exogenous farnesol did not affect growth and growth rate, but was effective in blocking both the morphological changes of yeast to pseudohyphae in RPMI 1640 medium and the formation of true hyphae in the presence of FBS, wherein the observed inhibition of the morphological transformation showed some dose dependency [137]. Interestingly, achieving 100% inhibition of *C. dubliniensis* morphological transformation required the use of doses of farnesol lower than was necessary for the reference strain of *C. albicans* [137]. Finally, the analysis of supernatants from both planktonic culture and *C. dubliniensis* biofilm, based on high performance liquid chromatography and gas chromatography coupled with mass spectrometry, showed that, in addition to farnesol, there are also four other compounds in the fungal external environment: isoamyl alcohol, 2-phenylethanol, 1-dodecanol, and E-nerolidol; however, these alcohols were secreted with different profiles depending on the stage of cell growth and the composition of the medium [138–141]. It was shown that synthetic alcohol mixtures, at physiological concentrations, produced a similar effect to the supernatants obtained from cultures of mature biofilms, resulting in inhibition of *C. dubliniensis* filamentation by approximately 50%. Interestingly, only two compounds—isoamyl alcohol and 1-dodecanol—showed an effect of inhibiting the growth of planktonic cells [138].

In the case of *C. tropicalis*, it was shown that this yeast, after exposure to exogenous farnesol, showed a significant reduction in the production of the biofilm on the polystyrene surface, and an additional enhancement of this effect was evident when cells

were grown in nutrient-poor solid medium, and the temperature was reduced to 30°C [141]. The analysis revealed the presence of quorum sensing molecules such as farnesol, tyrosol, dodecanol, isoamyl alcohol, or 2-phenylethanol [140, 142]. Analogously to *C. albicans*, farnesol was shown to inhibit pseudohyphae formation, mainly in the initial stage of adhesion, and reduce the number of viable cells in the mature biofilm of *C. tropicalis*. The opposite effect was demonstrated for 2-phenylethanol, whose presence promoted the production of pseudohyphae and stimulated an increase in the number of cells and the density of the biofilm [142]. In turn, the addition of high concentrations of exogenous tyrosol significantly reduced biofilm formation and reduced mature biofilms of *C. tropicalis*, manifested in a reduction in its metabolic activity [143, 144]. Moreover, the early stage of biofilm formation by *C. tropicalis* cells was inhibited by nerolidol, which was identified by a significant decrease in biofilm biomass and mitochondrial activity [140].

Metabolic profiling showed that the main compounds secreted by *C. auris* are aromatic alcohols such as tyrosol, phenylethyl alcohol, benzyl alcohol, and isoamyl alcohol, with only two compounds—phenylethyl alcohol and tyrosol revealed a significant gain [145]. According to the authors of the study, the lack of detection of farnesol may not only suggest its lower production compared to *C. albicans* species but also indicate that the metabolites inhibiting the development of the filamentous form of *C. auris* differ from those described for *C. albicans* [145]. Studies by Srivastava and Ahmad [146] demonstrated that the presence of exogenous farnesol in the initial stages of biofilm development significantly inhibits cell adhesion. However, along with the extension of the cell culture time of *C. auris* without the presence of farnesol, the created biofilms became more resistant to the action of this molecule, and to inhibit the development of the mature biofilm, it was necessary to use a higher concentration of the metabolite. By downregulating biofilm-related genes, such as *IIF4*, *PGA7*, *PGA26*, *PGA52*, and *HYR3*, farnesol reduces the thickness of the biofilm and reduces the viability of *C. auris* cells. Furthermore, farnesol has been shown to block the effect of drug resistance-promoting efflux pumps [146, 147]. A detailed report based on the analysis of genome-wide gene transcription using transcriptome sequencing (RNA-Seq) showed that the presence of farnesol causes significant changes in the expression of more than 700 genes, manifested by increased superoxide dismutase production, inhibition of manganese, zinc and iron transport by a simultaneous increase in copper content in fungal cells, as well as modulation of metabolism towards β-oxidation [147].

3.2. Environmental Stress Response and Related Changes in Fungal Cell Metabolism. Adapting to the novel environment related to the initiation or further dissemination of infection requires *Candida* fungi to respond immediately and effectively to the stress associated with the colonization of a new infectious niche, consisting of fluctuations in the availability of nutrients, limits in access to essential microelements, physicochemical changes in the surroundings, the influence of other microorganisms, and activity of host defense cells [148, 149]. One of the most important factors that influences *Candida* cell metabolism during infection is the availability and type of carbon source, where glucose is preferred. However, some environments, that is, blood or vaginal secretions, have limited glucose concentrations, or alternative carbon sources are available, including lactate, acetate, ethanol, glycerol, fatty acids, amino acids, and N-acetylglucosamine [150, 151]. When settling in a new niche, fungal cells must change their metabolism to adapt to the conditions in the existing environment and to face a combination of the different stresses encountered, i.e., thermal, osmotic, oxidative, and nitrosative stress, destructive impact of different substances on the cell wall, phagocytes, and antifungal drugs action [149, 152, 153]. In studies by Heaney et al., it was shown that different *Candida* species, including multidrug-resistant *C. auris*, displayed rather similar sensitivity to combinatory stress, including high salt concentration, alkaline, and thermal stress; however, for individual stresses, there were some important species and strain-dependent differences [154]. In *C. tropicalis*, high resistance to osmotic stress could also be correlated with the activity of ion efflux pumps, which could also explain the inherent drug resistance of environmental strains, especially those that inhabit marine environments [155].

Carbon assimilation by *Candida* cells takes place via glycolysis, the glyoxylate cycle, and gluconeogenesis, while the latter two appear to play an important role during the initiation of infection and phagocytosis of fungal cells by host immune cells, while further development of infection and tissue colonization causes metabolism to go through the glycolysis pathway [156–159]. Lactate-grown *C. albicans* cells were more virulent and resistant to osmotic stress, cell wall disruptors such as Calcofluor White or Congo Red, and antifungals caspofungin, tunicamycin, and amphotericin B than glucose-grown cells, while they were more sensitive to miconazole [160]. Additionally, *C. dubliniensis* cells grown in the presence of lactate instead of glucose were more resistant to osmotic stress and amphotericin B and *C. tropicalis* to amphotericin B [160]. Omic analysis showed that in *C. albicans*, the glycolytic pathway was enriched in proteins with higher abundance, while in *C. auris*, proteins involved in the tricarboxylic acid cycle were more abundant in yeast grown in Sabouraud broth [161].

Genes encoding key enzymes of the glyoxylate cycle in *C. albicans*, namely, isocitrate lyase (*ICL1*) and malate synthase (*MLS1*), were upregulated during phagocytosis and identified as necessary for complete fungal virulence [156]. Furthermore, many genes involved in β-oxidation of fatty acids were upregulated during the phagocytosis of *C. albicans*, which may prove that the acetyl coenzyme A that drives the glyoxylate cycle is the product of this process [157]. Orthologs of the *ICL1* and *MLS1* genes are specified for *C. dubliniensis* (Cd36_04240 for *ILC1* and Cd36_09130 for *MLS1*) and *C. auris* (B9J08_003374 for *ILC1* and B9J08_002919 for *MLS1*), and for *C. tropicalis*, both genes for Icl1 and Mls1 were reported to be regulated by the carbon source, and their expression is repressed in the presence of glucose and increased when cells grown with acetate [162, 163]. For *C. albicans*, disruption of the glyoxylate cycle could lead to disturbed drug efflux pumps belonging to the ABC superfamily, disorder of plasma membrane homeostasis, and decrease in chitin biosynthesis, which can increase

the susceptibility of fungi to azole drugs and echinocandins [164]. Contact with macrophages may represent a glucose-depleted location for *C. tropicalis*, and a similar mechanism of metabolic adaptation may be demonstrated as for *C. albicans* during phagocytosis [156, 165]. Using the complex model of ex vivo whole blood infection, the *C. tropicalis* genes *ICL1* and *MLS1* were shown to be strongly upregulated under these conditions [97]. In the case of *C. dubliniensis* cells phagocytized by macrophages, upregulation of genes encoding Icl1 and Mls1 was also demonstrated [166]. Interestingly, during such model infection caused by *C. auris*, unlike *C. albicans*, *C. dubliniensis*, and *C. tropicalis*, no upregulation of the *ICL1* and *MLS1* genes was observed, while downregulation of genes involved in β-oxidation including *CRC1* encoding mitochondrial carnitine carrier protein, *FOX2* for 3-hydroxyacyl-CoA epimerase, and the *POX1-3* gene for predicted acyl-CoA oxidase was detected. For *C. tropicalis*, the latter two were upregulated, suggesting differences in the use of various carbon sources between these species. In response to reactive oxygen species during engulfment by host phagocytes *C. albicans* upregulated the superoxide dismutase genes, i.e., *SOD5*, while *C. tropicalis* gene *AHP1* encoding alkyl hydroperoxide reductase and genes for putative after fungal infection reduces intestinal colonization by *C. tropicalis* [167].

For *C. albicans* virulence access to microelements during infection is crucial, as this species produces proteins responsible for binding zinc ions (Pra1p; pH-regulated antigen 1) and several proteins involved in iron acquisition, i.e., ferric reductase Frp1 [168], genes for these proteins were upregulated for both *C. albicans* and *C. tropicalis* in the whole blood infection model, but not for *C. auris* [97]. Although another protein gene was involved in iron acquisition, *FRE3* encoding ferric reductase was strongly upregulated in *C. auris*, but not in *C. tropicalis* in this model [97, 169]. For *C. auris*, significant upregulation of genes encoding ferrichrome siderophore transporters (i.e., *SIT1*) was observed, similarly to *C. albicans* and contrary to *C. tropicalis*; additionally, the *C. auris* gene *CSA1* encoding a protein belonging to the heme-binding protein family was also upregulated under these conditions [97, 170, 171]. As evidenced by the published data, there are also differences in this regard between the discussed species in obtaining micronutrients in various infection niches where access to them is often limited by the host.

3.3. The Effect of C. tropicalis, C. dubliniensis, and C. auris on the Host. The immune system response to fungal infections has been extensively studied for several years. The recognition of *Candida* spp. by host cells contributes to the development of a strong inflammatory state at the site of infection. The most important immune cells involved in the first line of the antifungal response are phagocytic cells such as neutrophils and macrophages. Due to differences in the level of virulence of individual species in the CTG clade, some variations in the host response are noticeable.

An important signaling pathway involved in the response to *Candida* spp. is Dectin-1/caspase-associated recruitment domain adapter 9 (CARD9)/IL-17 axis [172]. CARD9 is expressed in myeloid cells (neutrophils, macrophages, and dendritic cells), although the expression of CARD9 was observed in T and NK cells. Upon activation of the CARD9 receptor, it activates NF-kB and then induces the production of cytokines, including IL-6, IL-1β, IL-23, and TNF-α, which, in turn, are involved in inducing an IL-17/Th17 response. IL-17 is an important activator of the antifungal response, as it activates signaling through the IL-17 receptor that induces other proinflammatory cytokines, antimicrobial peptides, and neutrophil chemokines that are important for antifungal activity [173]. A study by Whibley et al. showed that *C. tropicalis*, unlike *C. albicans*, requires CARD9 and TNF-α, but not IL-17, signaling. CARD9-dependent TNF-α production plays an important role in the induction of the neutrophil response [174]. *C. tropicalis* induces robust formation of neutrophil extracellular traps (NET) even in the absence of filamentous structure [175]. Furthermore, *C. tropicalis* phagocytosis is more efficient compared to *C. albicans*, most likely due to differences in the structure of the cell wall [176].

Differential induction of the immune response was also observed for *C. albicans* and *C. dubliniensis*. *C. dubliniensis* induced increased neutrophil migration and phagocytosis compared to *C. albicans*, but in turn activated less NET release despite a high level of reactive oxygen species, myeloperoxidase, and lactoferrin excretion [177]. A possible explanation for this phenomenon is that *C. dubliniensis* is phagocytosed much more efficiently than *C. albicans*. Considering studies showing that *C. albicans* escape from the interior of neutrophils by changing the morphological form, capture and immobilization with NETs appear to be an essential neutrophil defence mechanism against this species, but not for *C. dubliniensis* [177]. Significant differences in response to these two related species determined by cytokine production were also shown. For example, *C. dubliniensis* increases the production of IL-8, a key cytokine responsible for enhancing neutrophil migration, but not IL-17A [177]. On the contrary, a comparison of macrophage responses to contact with *C. dubliniensis* and *C. albicans* showed reduced production of G-CSF, GM-CSF, IL-1α, IL-1β, IL-10, IL-16, serine protease inhibitor-1, and TNF-a, when exposed to *C. dubliniensis*. This research suggests that *C. dubliniensis* primarily activates the early immune response [177].

Research on *C. auris* began in 2009, and therefore, the immune system response to this species is poorly understood. One of the studies on the pathogenicity of *C. auris* indicates that this pathogen avoids the induction of antifungal neutrophil responses. The results obtained in the Zebrafish model indicated that *C. albicans* induces the recruitment of 50% more neutrophils than *C. auris* [178]. Furthermore, microscopic observations showed that only a small fraction of neutrophils (15-20%) attempted to phagocytose *C. auris*, while at least half of the neutrophils were able to neutralize *C. albicans* by engulfing [178, 179]. The results presented by Johnson et al. [178] indicated that neutrophils did not form NETs in contact with *C. auris*. It has been suggested that mannosylation pathways may be the reason for avoiding an immune response by *C. auris*. The *C. auris* cell wall efficiently masks strong immunogenic patterns such as β-glucan and chitin by forming a layer of mannoproteins. Mannosylation of *C. auris* may be crucial for protection against neutrophil phagocytosis and activation of other types of immune response. The mannosylation pattern

in *C. auris* differs from that of *C. albicans*, which may be important in its ability to be recognized by receptors such as Dectin-1 and correlate with the variation in neutrophil response in these two species [179]. Slightly different results were obtained in the work of Bruno et al. [180] where it was shown that the production of one of the neutrophil response markers—myeloperoxidase in *C. auris*-infected mice was comparable to *C. albicans*. PBMCs incubated with clinical isolates (in particular clades I and IV) of *C. auris* produced significantly higher amounts of proinflammatory cytokines TNF-α, IL-6, and IL-1β compared to *C. albicans* [180]. In these studies, it has been shown that the early (4 hours) PBMC cytokines were mainly induced by β-glucans, and it was similar to the response induced by *C. albicans*. On the contrary, the late host response (24 hours) was mainly activated by *C. auris* mannoproteins characterized by a specific structure that includes a unique M-α-1-phosphate side chain [180]. The results obtained so far indicated that the immune response induced by *C. auris* is complicated, and further work is required.

As mentioned above, candidal coinfection has been reported to be a serious problem that increases the risk of severe COVID-19 disease and increases the number of deaths [181, 182]. The high susceptibility of COVID-19 patients to fungal infections is associated with changes in the host immune system caused by the presence of the virus. It was shown that these patients had a higher level of proinflammatory cytokines such as IL-1, IL-2, IL-6, and TNFα. They also experienced dysregulation of monocytes, which showed a phenotypic shift from CD16+ to CD14+. In addition, BALF macrophages and neutrophil counts were increased, and the type I interferon (IFN-I) response was reduced or delayed, making it difficult to remove the virus. From the point of view of fungal infections, lymphopenia is also important, i.e., a decrease in the absolute number of T lymphocytes, which in patients with severe COVID-19 was manifested by a significant decrease in the number of CD4+ T cells, CD8+ T cells, NK, and B cells [183, 184].

4. Methods of Species Identification: Problems of Diagnostics

Despite advances in yeast identification techniques, diagnosing fungal infections remains a challenge. The specific nature of the fungi and the fact that yeast infections occur less frequently than bacterial infections make it difficult to quickly identify yeast pathogens [185]. Another problem is the correct differentiation of individual *Candida* species due to the fact that they are quite closely related and show similarities with each other. The selection of the appropriate diagnostic method is crucial for the efficient application of antifungal treatment. Previously, *C. dubliniensis* has often been misidentified as *C. albicans* [21, 186], and the first infections caused by *C. auris* were incorrectly assigned to *C. sake*, *C. haemulonii*, *S. cerevisiae*, and *Rhodotorula glutinis* [187, 188].

Various types of diagnostic methods can be used at present, and all have some advantages and disadvantages (Table 1). Currently, tests based on the comparison of fungal phenotypes could only play a complementary role when more specific methods are available.

Candida yeasts may exist in the form of single oval blastospores, which was reproduced by budding, and their size ranges between 2 and 8 μm and depends on the species. *C. tropicalis* cells are the largest (4-8 μm), slightly smaller are *C. dubliniensis* (3-7 μm) and *C. albicans* cells (4–6 μm), and the smallest are *C. auris* cells (2-3 μm) [86, 95, 96, 186, 189]. Moreover, they show the ability to change their morphological form in response to different external conditions. The yeasts can convert to the form of hyphae, which are tightly connected and form shared walls, and pseudohyphae, which are formed by budding without separation from the mother cell [22, 32, 60, 94, 186, 189–192]. These forms are similarly developed by *C. albicans* and *C. tropicalis* [94]. Additionally, large, spherical, thick-walled cells—chlamydospores—are produced only by *C. albicans* and *C. dubliniensis* [193]. In the case of *C. auris*, most reports indicated that it occurs in the form of blastospores [86, 95, 96], although there were reports indicating that some clinical isolates can form filaments and large aggregates of pseudohypha-like cells to which mother and daughter cells are attached [27, 96, 194, 195].

The methods based on chromogenic media are easy to perform and useful in preliminary tests, but due to the possible misidentification of closely related species, they require confirmations by more advanced methods. Several different commercially available biochemical systems based on fungal carbohydrate assimilation profiles are also often used to distinguish *Candida* species in addition with methods based on spectroscopy, including mass spectrometry characterized by significant precision [196–199]. The application of other spectroscopic methods in yeast identification, including rapid evaporative ionization MS (REIMS), vibrational spectroscopy, or surface-enhanced resonance Raman spectroscopy (SERRS) was described in detail in the review of Arastehfar et al. [200]. In addition to physicochemical techniques, methods based on the molecular identification of targeted DNA regions are implemented to identify *Candida* species. They meet the highest accuracy expectations, even for rare and uncommon species. Unfortunately, their disadvantage is still high costs and the fact that they are not widely available. Comprehensive descriptions of the different molecular diagnostic methods used in the identification of *Candida* species are included in several reviews [200–203] and will not be discussed in detail here.

5. Treatment of Infections and Drug Resistance

5.1. Methods for Treating Infections Caused by C. tropicalis, C. dubliniensis, and C. auris. Currently, several main classes of antifungal drugs are used to treat *Candida* infections, including echinocandins, azoles, allylamines, polyene antibiotics, and nucleoside analogues (mainly 5-fluorocytosine). One of the first classes of drugs introduced into widespread use in the treatment of mycoses is polyenes, complex macrolides with amphipathic characteristics, derived from the fermentation products of *Streptomyces* bacteria [164, 233]. Polyenes such as nystatin, amphotericin B, candicidin, and natamycin work by disrupting the fungal plasma membrane by binding to ergosterol and forming canals responsible for increased membrane permeability, adsorption to the membrane surface, and the formation of "sterol sponges" and

Table 1: Methods used to identify *Candida* species.

The type of method	The basis of detection	Problems in correct diagnosis	References
Phenotypic tests			
Comparison of fungal phenotypes	The ability to grow at 42°C and formation of germ tubes and chlamydospores	Incorrect identification of *C. albicans* and *C. dubliniensis*	[204, 205]
Chromogenic differential media			
Albicans ID (bioMérieux, Marcy l'Etoile, France)	Growth of colonies of different color; detection of hexosaminidase activity	Possible misidentification of *C. albicans* and *C. tropicalis; C. auris* cannot be identified	[206, 207]
Chromalbicans Agar (Biolife Italiana, Milan, Italy)	Growth of colonies of different color; detection of hexosaminidase activity	Possible misidentification of *C. albicans* and *C. dubliniensis*; *C. auris* cannot be identified	[208]
Brilliance Candida Agar (Oxoid, Hants, UK)	Growth of colonies of different color; detection of hexosaminidase activity with 5-bromo-4-chloro-3-indolyl N acetyl ß-D-glucosaminide as a substrate and alkaline phosphatase activity with 5-bromo-6-chloro-3-indolyl phosphate p-toluidine salt	Inability to distinguish *C. albicans* from *C. dubliniensis*; *C. auris* cannot be identified	[209]
CHROMagar *Candida* plates (CHROMagar, Paris, France)	Growth of colonies of different color; detection of species-dependent enzyme activity	Possible misidentification of *C. albicans* and *C. dubliniensis*; *C. auris* cannot be identified	[210–212]
CHROMagar™*Candida* Plus (CHROMagar, Paris, France)	Growth of colonies of different color; detection of species-dependent enzyme activity	Possible differences in color interpretation, although enabling *C. auris* identification from other *Candida*	[213]
Commercially available biochemical systems			
API 20C AUX, ID32C, and Vitek YBC System; Vitek 2 YST (bioMérieux, Marcy l'Etoile, France) Micronaut-*Candida* (Merlin Diagnostika GmbH, Bornheim, Germany) MicroScan (Beckman Coulter, Brea, CA, USA)	Determining the ability of fungi to assimilate, ferment, or decompose specific chemical compounds	Only known species might be identified; possible misidentification of *C. auris* as a different *Candida* species due to the similarity of assimilation patterns	[214–218]
Antibody-based tests			
PlateliaTM *Candida* antigen/PlateliaTM *Candida* antibody (Bio-Rad Laboratories, Marnes-la-Coquette, France)	Detection of the presence of *Candida* mannan antigen or anti-mannan antibodies	Does not distinguish between species	[219–222]
Germ tube antibody assay (CAGTA)	Detection of the immune response against the Hwp1 protein found in yeast hyphae	Low sensitivity; does not distinguish between species; does not identify *C. tropicalis*	[223–225]
Bichro-dubli Fumouze test (Fumouze Diagnostics, Asnières, France)	A latex agglutination test with monoclonal antibodies 12F7-F2	Detection only for *C. dubliniensis*	[226]
Physicochemical techniques			
Mass spectrometry	Differences in ribosomal proteins identified with the mass spectrometry-based proteomic technique with the MALDI-TOF detection system	Sophisticated equipment required; high costs	[188, 227–232]

by induction of oxidative stress leading to cell damage [164, 234, 235]. Another class of antifungals was azoles which can be divided into imidazoles and triazoles, depending on whether they have two or three nitrogen atoms in a five-membered ring. These two groups include clinically important drugs such as clotrimazole, tioconazole, and ketoconazole of the first category and fluconazole, itraconazole, and terconazole of the second [236]. The mechanism of action of azoles is the disruption of the fungal plasma membrane by altering the conversion of lanosterol to ergosterol by inhibiting the cytochrome P-450-dependent enzyme lanosterol demethylase, a product of the *ERG11* gene [237–239]. Also, allylamines, i.e., terbinafine, affect ergosterol synthesis by inhibiting squalene epoxidase, a product of the *ERG1* gene, although they are mainly used for the treatment of superficial candidiasis [237, 240, 241]. One of the newest group of antifungals is echinocandins, including anidulafungin, caspofungin, and micafungin—lipopeptides being derivatives of the fungal fermentation products that affect candidial cell wall integrity acting as inhibitors for beta-1,3-glucan synthase [238, 239, 242]. Azoles, echinocandins, and polyenes alter *Candida* morphogenesis (yeast to pseudohyphae and hyphae transformation); however, the vast majority of information about this phenomenon is related to *C. albicans* [243]. Nucleoside analogs, such as 5-fluorocytosine, are absorbed into the cytoplasm by cytosine permease, where after conversion to 5-fluorouridine by cytosine deaminase, they inhibit DNA or RNA synthesis [244, 245]; however, at higher doses, nucleoside analogs are toxic to humans, so they are not the first-choice drugs [246, 247]. The most recent drug introduced into use is triterpenoid ibrexafungerp, which is a glucan synthase inhibitor that weakens the fungal cell wall. It is an orally administered preparation used to treat vulvovaginal candidiasis that demonstrates antifungal activity against *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*, and *C. auris* [248, 249]. There are also other new drugs in clinical trials, including fosmanogepix, which is an inhibitor of the inositol acyltransferase Gwt1 involved in the early steps of GPI anchor biosynthesis, the novel triazole opelconazole and the novel echinocandin rezafungin, which are described in detail by Hoenigl et al. [250]. Both fosmanogepix and rezafungin have antifungal activity against *C. albicans*, *C. auris*, *C. dubliniensis*, and *C. tropicalis*, while for opelconazole, this activity has been demonstrated so far for the two first *Candida* species [250]. These are promising preparations that may significantly enrich the arsenal of currently available antifungal agents and overcome the resistance problem of some *Candida* strains to available antifungals.

In the therapies currently used against superficial and invasive candidiasis, different antifungals from the above-mentioned classes and their combinations are used; however, due to the emerging resistance among species other than *C. albicans*, problems with selecting the appropriate therapy often occur. As previously described, *C. albicans* and *C. dubliniensis* demonstrate common antifungal susceptibility patterns in vitro, and most of the *C. dubliniensis* isolates tested were susceptible to commonly used antifungal agents, although in several studies, some strains resistant to fluconazole were identified [251–255]. Interestingly, the in vitro test showed differences in the tolerance of fluconazole or echinocandins between *C. albicans* and *C. dubliniensis*. In the case of *C. dubliniensis*, incomplete growth inhibition in supraMIC, known as a trailing effect, was observed with echinocandins but not with fluconazole, while for *C. albicans*, the reverse has been observed [256]. *C. tropicalis* strains are largely susceptible to azole antifungals, polyenes, flucytosine, and echinocandins; however, worldwide recorded resistance to fluconazole or amphotericin B is increasing alarmingly [17, 189]. In 2015, Kawai et al. demonstrated that *C. tropicalis* biofilms are susceptible to liposomal amphotericin B in high concentrations (starting at 8 μg/ml). The same study with micafungin showed that this drug reduced biofilm formation when used at low concentrations (0.125-1 μg/ml), but surprisingly, biofilm metabolic activity increased in the presence of higher concentrations of micafungin (2-64 μg/ml) [257]. This could be the effect of slow resistance development against drugs present in the growth environment, possibly by reconstruction of the cell wall structure and modification of the expression of the *FKS* gene. However, Marcos-Zambrano et al. demonstrated that exposing mature *C. tropicalis* biofilm to micafungin resulted in changes in biofilm formation: the number of hyphae and pseudohyphae was significantly reduced, although the application of liposomal amphotericin B (16 μg/ml) caused only a few biofilm alterations [258].

In general, *C. auris* characterizes a significantly higher tolerance level for fluconazole than *C. albicans*, since approximately 90% of *C. auris* strains demonstrate intrinsic resistance to fluconazole; however, a considerable number of strains appear to be susceptible to echinocandins, some also to amphotericin B and voriconazole [259–261]. The use of echinocandin in the treatment of candidiases caused by *C. auris* is recommended, but there are also reports of strains resistant to these drugs [260–262]. Therefore, combinations of antifungal drugs can be used to treat infections with *C. auris*, some of which show a synergistic effect [263–265]. Antifungal susceptibility is higher for *C. auris* planktonic cells but extremely lower for biofilms. *C. auris* biofilm resistance may be related to high cell density and other resistance mechanisms, rather than to biofilm matrix formation and hyphal production as is the case of *C. albicans* [261, 266]. Interestingly, the use of farnesol to modulate *C. auris* biofilm formation and efflux pump activity, also in combination with classic antifungals such as echinocandins, might be a possible novel approach to combat biofilms [146, 267, 268]. Miltefosine, a medicament used in the therapy of leishmaniasis or infections caused by *Cryptococcus* spp. [269], has recently been revealed as a promising drug for the treatment of *C. auris* infections. Applied together with amphotericin B showed a synergistic effect for several isolates tested; however, more studies are required on its efficiency for *C. auris* candidiases [270–272].

5.2. Mechanisms of Drug Resistance. Resistance of *Candida* fungi to antifungal drugs is primarily related to quantitative or qualitative changes in target enzymes, reduced contact of the drug with its target, overexpression of genes encoding multidrug efflux pumps/transporters, and biofilm formation with a dense extracellular biofilm matrix [189, 273, 274].

In *C. tropicalis*, resistance to fluconazole was shown to be correlated with amino acid substitutions Y132F and S154F in lanosterol 14-alpha-demethylase (Erg11p) [275, 276]. Furthermore, the resistance of *C. tropicalis* to azoles could also depend on the expression level of *ERG11* and *UPC2*, the second of which encodes the zinc transcription factor involved in the regulation of ergosterol biosynthesis genes [277, 278]. Overexpression of the *ERG11* and *UPC2* genes was observed in drug-resistant isolates of *C. tropicalis* in the studies by Wang et al. [278] and Choi et al. [279]; however, not by Jin et al. [276], demonstrating the complexity and variety of resistance phenomena in *C. tropicalis*. In the case of the *C. tropicalis* biofilm, overexpression of *ERG11* and *MDR1* was associated with resistance to fluconazole [280]. Additionally, the presence of large amounts of dense biofilm extracellular matrix material was indicated as responsible for the *C. tropicalis* biofilm resistance for amphotericin B and fluconazole through impaired drug penetration [123]. The deletion of 132 nucleotides in *ERG11* and substitution S258F in ERG*11* play a role in the cross resistance of *C. tropicalis* to azoles and polyenes [281]. The lower susceptibility to antifungals might be also caused by overexpression of *MDR1* (multidrug resistance) and *CDR1* (*Candida* drug resistance) genes encoding plasma membrane MDR/MFS multidrug efflux pump and multidrug transporter of ABC superfamily, respectively. The higher expression of *MDR1* combined with mutations in *ERG11* was noticed for *C. tropicalis* fluconazole-resistant strains [276], as well as the overexpression of *CDR1* and *MDR1* genes [279]. Analogously to *C. albicans*, resistance to caspofungin in *C. tropicalis* might be determined by specific mutations in *FKS1* gene, encoding elements of beta-1,3-glucan synthase, i.e., change of amino acid L to W in position equivalent to position 644 in *C. albicans* Fks1p was reported for *C. tropicalis* drug-resistant strain [282]. Resistance to flucytosine could also be developed by *C. tropicalis* and may be determined by the mutation in the *FCY2* gene that encodes purine-cytosine permease [283].

Similarly to *C. albicans*, *C. dubliniensis* resistance to fluconazole was related to different molecular mechanisms, including upregulation of the genes *CdCDR1*, *CdMDR1*, and *CdERG11* and the presence of mutations in the CdErg11 protein [284]. In the case of itraconazole-resistant *C. dubliniensis* isolates, the expression level of the *CdERG11* gene was at least four times higher than for susceptible isolates, and also, the increased expression of the *CdCDR1* gene was shown, but not of the *CdMDR1* gene, as itraconazole is not a substrate for this protein [285–287]. Furthermore, the resistance of *C. dubliniensis* to itraconazole was correlated with mutations in the ERG3 gene, which encodes sterol C5,6-desaturase [287]. The resistance of *C. dubliniensis* also to 5-flucytosine was characterized, and a single-point mutation (substitution of serine at the 29 position by leucine) in the *CdFCA1* gene for cytosine deaminase has been identified as a potential factor in the appearance of flucytosine resistance [288, 289].

C. auris is a multidrug-resistant species, and the mechanisms of its drug insusceptibility are multifactorial and overlapped [290]. Some of them are similar to those previously indicated for *C. albicans*, while novel molecular mechanisms and their combinations are also identified, making the outbreak of multiresistance in *C. auris* an extremely important problem, which was described in great detail in several reviews previously; for a comprehensive overview, see [273, 274, 291, 292]. In the case of *C. auris* fluconazole-resistant strains, amino acid substitutions Y132F, K143R, or Y132F in *ERG11* gene have been identified as responsible for resistance to antifungal [260, 293] and additionally nonsense mutations E429* in *ERG11* and W182* in *ERG3* genes [294], overexpression of *ERG11* [260], mutation in gene encoding zinc-cluster transcription factor *TAC1b* resulting in *CDR1* overexpression [295], and aneuploidy including *ERG11* and *TAC1b* genes duplication and formation of an isochromosome [296, 297]. Additionally, the sequestration of fluconazole by biofilm extracellular matrix increasing fungal resistance was demonstrated for *C. auris* biofilms, similarly to *C. albicans* [298, 299].

The balance between expression ratios of *FKS1*/*FKS2* genes seems to be one of the main elements of echinocandin-resistance progression in *C. auris* [300]. Two mutations in hot spot 1 of the product of the *FKS1* gene were identified for *C. auris* in positions S639F and S639P and additionally deletion mutation ΔF635 [260, 293, 301, 302]. In the *C. auris* strain resistant to fluconazole and amphotericin B, two mutations were detected: Y132F in the *ERG11* gene and D709E in the *CDR1* gene in the studies carried out by Reslan et al. [303]. The resistance of *C. auris* to flucytosine is related to the mutation F211I in the *FUR1* gene that encodes uracil phosphoribosyltransferase [304].

5.3. Alternative Methods for Treating C. tropicalis, C. dubliniensis, and C. auris Infections. The increased prevalence of multidrug resistance in yeasts implicates an urgent need to develop new therapeutic strategies to combat infections caused by species other than *C. albicans*. In addition to the widely described chemical modification of the surface of medical devices by coating them, for example, with a chitosan hydrogel [305], other methods are still being sought that would allow combating biofilms produced within various niches of the host organism.

A promising alternative treatment for *Candida* infections is the combination of quorum sensing molecules manipulating fungal morphology with traditional antifungal drugs, which are the subject of clinical trials in *C. albicans* [143, 144, 306, 307]. Combining farnesol with traditional antifungal drugs such as amphotericin B, fluconazole, itraconazole, caspofungin, and natamycin has been shown to reduce minimum inhibitory concentrations (MIC) against resistant *C. tropicalis* cells [142, 308, 309]. In the case of fluconazole, it has been shown that the synergistic effect of farnesol is further enhanced when the quorum sensing molecule is previously incorporated into liposomes [310]. Similar effects were observed for exogenous tyrosol, which, when combined with traditional antifungal drugs such as amphotericin B, fluconazole, and itraconazole, significantly reduces biofilm formation and its metabolic activity; however, in the case of mature biofilms, similar effects were observed only for amphotericin B [144]. In the case of *C. dubliniensis*, which has the ability to develop resistance to fluconazole [285, 311, 312], the presence of farnesol increases the permeability of the cell membrane to exogenous compounds, which in turn significantly increases the sensitivity of yeast cells to fluconazole [136]. In addition,

in the treatment of infections caused by *C. auris*, farnesol is considered one of the supportive treatments. In vivo studies in a mouse immunocompromised candidiasis model showed that both preexposure to farnesol and daily farnesol treatment of infected mice significantly reduced the yeast load of the kidneys [268]. In addition, a significant synergy was observed between triazoles, echinocandins, and farnesol against *C. auris* biofilms [267, 268].

Another alternative method that has successfully passed preclinical and clinical trials in the case of *C. albicans* infection is the use of yeast-based probiotics [313–316]. It has been shown that *Saccharomyces boulardi* secreted into the medium active compounds, such as caproic acid, which reduce the virulence of *C. albicans* mainly by inhibiting the production of hyphae [314]. Also, in the case of other *Candida* species, it has been shown that two strains of probiotic yeast—*Saccharomyces cerevisiae* and *Issatchenkia occidentalis*—were shown to be able to inhibit adhesion to both abiotic surfaces and epithelial cells, inhibit morphological changes and biofilm formation, i.e., not only by *C. tropicalis* and *C. auris* species but also by mixed biofilms coproduced with *C. albicans* [315, 316]. Interestingly, the action of *S. cerevisiae* and *I. occidentalis* was more potent than that of *S. boulardi*, which best inhibited the biofilm of *C. albicans* [314–316]. Furthermore, in vivo studies using the *Caenorhabditis elegans* model showed that exposure of nematodes to probiotic yeast protected them from infection, while the use of probiotic yeast after fungal infection reduced intestinal colonization by *C. tropicalis* [316].

There are also reports in the literature showing that photodynamic therapy using a nontoxic dye photosensitizer, which when activated with visible light, produces reactive oxygen species having a cytotoxic effect on pathogen cells, is a promising method of treating superficial infections of the mucous membranes and skin [317–319]. In the case of *Candida* non-*albicans* species, it was demonstrated that the use of photodithazine formulated in hydrogel reduced the viability and biomass of biofilms produced by *C. tropicalis* [320], while curcumin-mediated photodynamic therapy in combination with LED light significantly reduced the metabolism of *C. dubliniensis* biofilms [321]. Furthermore, in the case of *C. auris*, blue and red lights in combination with photosensitizers were shown to inhibit biofilm formation and disrupt mature biofilms, with only blue light itself having antibiotic properties [322].

6. Conclusions

There are many different niches in the host organism that fungi can colonize, and various sophisticated and still insufficiently recognized factors may determine the outcome of the *Candida*–host relationship. Due to the wide variation within the genus *Candida* and the multitude of factors affecting virulence, there are still cases in clinical practice that, despite the available knowledge, show unpredictable disease evolution. Therefore, it is difficult to unequivocally answer the question of why some species may prefer a more commensal lifestyle, while others show increased pathogenicity [10, 323].

Currently, it is assumed that the four *Candida* species discussed, although so closely related, follow different pathways of adaptation during the colonization of the human host. Understanding the mechanisms leading to these divergences and based on the evolutionary history of individual species, resulting also in the differences in their genetic background, is undoubtedly very important to elucidate the emergence of pathogenicity among these fungi. However, the similarities observed, as well as differences in biology and virulence, between different species may have a direct impact on the practical aspect of our fight against fungal infections, which is a tough challenge during the diagnosis and treatment of candidiasis.

First, differences in virulence attributes and host invasion mechanisms may determine the design of distinct therapeutic strategies for infections caused by particular species. Moreover, as some niches may be shared by several *Candida* species that interact with each other, it is reasonable to consider the aspects of their virulence not only in isolation from each other but also in relation to other species to apply appropriately selected alternative therapy. Second, similarities in the biology of closely related species can make a correct diagnosis of candidiasis more difficult, especially when it is based on fast and inexpensive simple diagnostic tests. It seems, particularly when mixed infections are suspected, that it is necessary to use advanced diagnostic techniques based on physicochemical methods or molecular biology. Third, awareness of differences in antifungal drug resistance between species may outweigh the success of therapy and also lead to the search for new alternative treatments, especially in multiresistant species such as *C. auris*.

Therefore, in the case of such a multifactorial process as the development of infections caused by various pathogens of the genus *Candida*, the correct, multifaceted, and comprehensive approach to genetic and phenotypic differences is crucial not only to understand the entire infection process, but most of all to fight the invaders.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

This work was financially supported by the National Science Centre of Poland (grant no. 2019/33/B/NZ6/02284 awarded to MR-K).

References

[1] J. R. Köhler, B. Hube, R. Puccia, A. Casadevall, and J. R. Perfect, "Fungi that infect humans," *Microbiology Spectrum*, vol. 5, no. 3, 2017.

[2] S. Siscar-Lewin, B. Hube, and S. Brunke, "Emergence and evolution of virulence in human pathogenic fungi," *Trends in Microbiology*, vol. 30, no. 7, pp. 693–704, 2022.

[3] A. Casadevall and L. A. Pirofski, "Host-pathogen interactions: redefining the basic concepts of virulence and pathogenicity," *Infection and Immunity*, vol. 67, no. 8, pp. 3703–3713, 1999.

[4] A. Casadevall and L. A. Pirofski, "Host-pathogen interactions: the attributes of virulence," *Journal of Infectious Diseases*, vol. 184, no. 3, pp. 337–344, 2001.

[5] A. Casadevall and L. A. Pirofski, "Host-pathogen interactions: basic concepts of microbial commensalism, colonization, infection, and disease," *Infection and Immunity*, vol. 68, no. 12, pp. 6511–6518, 2000.

[6] J. M. Achkar and B. C. Fries, "Candida infections of the genitourinary tract," *Clinical Microbiology Reviews*, vol. 23, no. 2, pp. 253–273, 2010.

[7] J. Delaloye and T. Calandra, "Invasive candidiasis as a cause of sepsis in the critically ill patient," *Virulence*, vol. 5, no. 1, pp. 161–169, 2014.

[8] B. J. Kullberg and M. C. Arendrup, "Invasive candidiasis," *The New England Journal of Medicine*, vol. 373, no. 15, pp. 1445–1456, 2015.

[9] M. A. S. Santos, A. C. Gomes, M. C. Santos, L. C. Carreto, and G. R. Moura, "Code genetique du clade fongique CTG," *Comptes Rendus-Biologies*, vol. 334, no. 8-9, pp. 607–611, 2011.

[10] G. Butler, M. D. Rasmussen, M. F. Lin et al., "Evolution of pathogenicity and sexual reproduction in eight Candida genomes," *Nature*, vol. 459, no. 7247, pp. 657–662, 2009.

[11] G. P. Moran, D. C. Coleman, and D. J. Sullivan, "Comparative genomics and the evolution of pathogenicity in human pathogenic fungi," *Eukaryotic Cell*, vol. 10, no. 1, pp. 34–42, 2011.

[12] H. Hovhannisyan and T. Gabaldón, "Transcriptome sequencing approaches to elucidate host–microbe interactions in opportunistic human fungal pathogens," in *Current Topics in Microbiology and Immunology*, vol. 422, Springer, Cham, 2019.

[13] A. Rokas, "Evolution of the human pathogenic lifestyle in fungi," *Nature Microbiology*, vol. 7, no. 5, pp. 607–619, 2022.

[14] S. Siscar-Lewin, B. Hube, and S. Brunke, "Antivirulence and avirulence genes in human pathogenic fungi," *Virulence*, vol. 10, no. 1, pp. 935–947, 2019.

[15] D. A. Fitzpatrick, M. E. Logue, J. E. Stajich, and G. Butler, "A fungal phylogeny based on 42 complete genomes derived from supertree and combined gene analysis," *BMC Evolutionary Biology*, vol. 6, 2006.

[16] S. A. Turner and G. Butler, "The Candida pathogenic species complex," *Cold Spring Harbor Perspectives in Medicine*, vol. 4, no. 9, 2014.

[17] M. A. Pfaller and M. Castanheira, "Nosocomial candidiasis: antifungal stewardship and the importance of rapid diagnosis," *Medical Mycology*, vol. 54, no. 1, pp. 1–22, 2016.

[18] M. A. Pfaller, D. J. Diekema, J. D. Turnidge, M. Castanheira, and R. N. Jones, "Twenty years of the SENTRY antifungal surveillance program: results for Candida species from 1997-2016," *Open Forum Infectious Diseases*, vol. 6, Supplement_1, pp. S79–S94, 2019.

[19] N. A. Chow, L. Gade, S. V. Tsay et al., "Multiple introductions and subsequent transmission of multidrug-resistant Candida auris in the USA: a molecular epidemiological survey," *The Lancet Infectious Diseases*, vol. 18, no. 12, pp. 1377–1384, 2018.

[20] A. Sikora and F. Zahra, "Candida auris," in *Stat Pearls*, Stat Pearls Publishing, Treasure Island (FL), 2022.

[21] F. C. Odds, L. Van Nuffel, and G. Dams, "Prevalence of Candida dubliniensis isolates in a yeast stock collection," *Journal of Clinical Microbiology*, vol. 36, no. 10, pp. 2869–2873, 1998.

[22] D. Sullivan and D. Coleman, "Candida dubliniensis: characteristics and identification," *Journal of Clinical Microbiology*, vol. 36, no. 2, pp. 329–334, 1998.

[23] G. P. Moran, D. C. Coleman, and D. J. Sullivan, "Candida albicans versus Candida dubliniensis : Why Is C. albicans More Pathogenic?," *International Journal of Microbiology*, vol. 2012, Article ID 205921, 7 pages, 2012.

[24] A. M. Porman, K. Alby, M. P. Hirakawa, and R. J. Bennett, "Discovery of a phenotypic switch regulating sexual mating in the opportunistic fungal pathogen Candida tropicalis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 52, pp. 21158–21163, 2011.

[25] H. Du, J. Bing, T. Hu, C. L. Ennis, C. J. Nobile, and G. Huang, "Candida auris: epidemiology, biology, antifungal resistance, and virulence," *PLOS Pathogens*, vol. 16, no. 10, p. e1008921, 2020.

[26] S. Schelenz, F. Hagen, J. L. Rhodes et al., "First hospital outbreak of the globally emerging Candida auris in a European hospital," *Antimicrobial Resistance & Infection Control*, vol. 5, no. 1, p. 35, 2016.

[27] A. M. Borman, A. Szekely, and E. M. Johnson, "Comparative pathogenicity of United Kingdom isolates of the emerging pathogen Candida auris and other key pathogenic Candida species," *mSphere*, vol. 1, no. 4, 2016.

[28] M. Biswal, S. M. Rudramurthy, N. Jain et al., "Controlling a possible outbreak of Candida auris infection: lessons learnt from multiple interventions," *Journal of Hospital Infection*, vol. 97, no. 4, pp. 363–370, 2017.

[29] A. Ruiz-Gaitán, A. M. Moret, M. Tasias-Pitarch et al., "An outbreak due to Candida auris with prolonged colonisation and candidaemia in a tertiary care European hospital," *Mycoses*, vol. 61, no. 7, pp. 498–505, 2018.

[30] A. Ruiz-Gaitán, H. Martínez, A. M. Moret et al., "Detection and treatment of Candida auris in an outbreak situation: risk factors for developing colonization and candidemia by this new species in critically ill patients," *Expert Review of Anti-infective Therapy*, vol. 17, no. 4, pp. 295–305, 2019.

[31] M. Gharaghani, M. Shabanzadeh, H. Jafarian, and A. Zarei Mahmoudabadi, "ABC typing and extracellular enzyme production of Candida albicans isolated from Candida vulvovaginitis," *Journal of Clinical Laboratory Analysis*, vol. 36, no. 1, p. e24117, 2022.

[32] R. A. Calderone and W. A. Fonzi, "Virulence factors of Candida albicans," *Trends in Microbiology*, vol. 9, no. 7, pp. 327–335, 2001.

[33] M. Zawrotniak, O. Bochenska, J. Karkowska-Kuleta et al., "Aspartic proteases and major cell wall components in candida albicans trigger the release of neutrophil extracellular traps," *Frontiers in Cellular and Infection Microbiology*, vol. 7, 2017.

[34] J. Karkowska-Kuleta, E. Wronowska, D. Satala et al., "Als3-mediated attachment of enolase on the surface of Candida albicans cells regulates their interactions with host proteins," *Cellular Microbiology*, vol. 23, no. 4, p. e13297, 2021.

[35] D. Satala, A. Zelazna, G. Satala et al., "Towards understanding the novel adhesin function of Candida albicans phosphoglycerate mutase at the pathogen cell surface: some structural analysis of the interactions with human host extracellular matrix proteins," *Acta Biochimica Polonica*, vol. 68, no. 4, pp. 515–525, 2021.

[36] T. Jones, N. A. Federspiel, H. Chibana et al., "The diploid genome sequence of Candida albicans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 19, pp. 7329–7334, 2004.

[37] G. Janbon, J. Quintin, F. Lanternier, and C. d'Enfert, "Studying fungal pathogens of humans and fungal infections: fungal diversity and diversity of approaches," *Microbes and Infection*, vol. 21, no. 5-6, pp. 237–245, 2019.

[38] A. P. Jackson, J. A. Gamble, T. Yeomans et al., "Comparative genomics of the fungal pathogens Candida dubliniensis and Candida albicans," *Genome Research*, vol. 19, no. 12, pp. 2231–2244, 2009.

[39] Y. Liu and S. G. Filler, "Candida albicans Als3, a multifunctional adhesin and invasin," *Eukaryotic Cell*, vol. 10, no. 2, pp. 168–173, 2011.

[40] J. R. Naglik, D. L. Moyes, B. Wächtler, and B. Hube, "Candida albicans interactions with epithelial cells and mucosal immunity," *Microbes and Infection*, vol. 13, no. 12-13, pp. 963–976, 2011.

[41] F. L. Mayer, D. Wilson, and B. Hube, "Candida albicans pathogenicity mechanisms," *Virulence*, vol. 4, no. 2, pp. 119–128, 2013.

[42] J. F. Muñoz, L. Gade, N. A. Chow et al., "Genomic insights into multidrug-resistance, mating and virulence in Candida auris and related emerging species," *Nature Communications*, vol. 9, no. 1, p. 5346, 2018.

[43] J. F. Muñoz, R. M. Welsh, T. Shea et al., "Clade-specific chromosomal rearrangements and loss of subtelomeric adhesins in Candida auris," *Genetics*, vol. 218, no. 1, 2021.

[44] J. Karkowska-Kuleta and A. Kozik, "Cell wall proteome of pathogenic fungi," *Acta Biochimica Polonica*, vol. 62, no. 3, pp. 339–351, 2015.

[45] D. Satala, J. Karkowska-Kuleta, A. Zelazna, M. Rapala-Kozik, and A. Kozik, "Moonlighting proteins at the candidal cell surface," *Microorganisms*, vol. 8, no. 7, pp. 1–25, 2020.

[46] D. Gozalbo, I. Gil-Navarro, I. Azorín, J. Renau-Piqueras, J. P. Martínez, and M. L. Gil, "The cell wall-associated glyceraldehyde-3-phosphate dehydrogenase of Candida albicans is also a fibronectin and laminin binding protein," *Infection and Immunity*, vol. 66, no. 5, pp. 2052–2059, 1998.

[47] J. López-García, M. Lehocký, P. Humpolíček, and P. Sáha, "HaCaT keratinocytes response on antimicrobial atelocollagen substrates: extent of cytotoxicity, cell viability and proliferation," *Journal of Functional Biomaterials*, vol. 5, no. 2, pp. 43–57, 2014.

[48] D. Satala, G. Satala, M. Zawrotniak, and A. Kozik, "Candida albicans and Candida glabrata triosephosphate isomerase – a moonlighting protein that can be exposed on the candidal cell surface and bind to human extracellular matrix proteins," *BMC Microbiology*, vol. 21, no. 1, p. 199, 2021.

[49] K. Seweryn, J. Karkowska-Kuleta, N. Wolak et al., "Kinetic and thermodynamic characterization of the interactions between the components of human plasma kinin-forming system and isolated and purified cell wall proteins of Candida albicans," *Acta Biochimica Polonica*, vol. 62, no. 4, pp. 825–835, 2015.

[50] D. Satala, G. Satala, J. Karkowska-Kuleta et al., "Structural insights into the interactions of candidal enolase with human vitronectin, fibronectin and plasminogen," *International Journal of Molecular Sciences*, vol. 21, no. 21, p. 7843, 2020.

[51] R. C. Silva, A. C. B. Padovan, D. C. Pimenta, R. C. Ferreira, C. V. da Silva, and M. R. S. Briones, "Extracellular enolase of Candida albicans is involved in colonization of mammalian intestinal epithelium," *Frontiers in Cellular and Infection Microbiology*, vol. 4, 2014.

[52] A. Núñez-Beltrán, E. López-Romero, and M. Cuéllar-Cruz, "Identification of proteins involved in the adhesionof Candida species to different medical devices," *Microbial Pathogenesis*, vol. 107, pp. 293–303, 2017.

[53] P. Punithavathy and T. Menon, "Characterization of gene family that mediates the adhesion of biofilms formed by Candida tropicalis isolated from HIV and non-HIV patients," *BMC Infectious Diseases*, vol. 12, no. S1, 2012.

[54] S. H. Oh, A. Isenhower, R. Rodriguez-Bobadilla et al., "Pursuing advances in DNA sequencing technology to solve a complex genomic jigsaw puzzle: the agglutinin-like sequence (ALS) genes of Candida tropicalis," *Frontiers in Microbiology*, vol. 11, 2021.

[55] W. H. Himratul-Aznita, N. A. Jamil, N. H. Jamaludin, and M. A. F. Nordin, "Effect of Piper betle and Brucea javanica on the Differential Expression of Hyphal Wall Protein (HWP1) in Non-Candida albicans Candida (NCAC) Species," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 397268, 6 pages, 2013.

[56] R. G. Willaert, Y. Kayacan, and B. Devreese, "The flo adhesin family," *Pathogens*, vol. 10, no. 11, 2021.

[57] J. Karkowska-Kuleta, D. Zajac, O. Bochenska, and A. Kozik, "Surfaceome of pathogenic yeasts, Candida parapsilosis and Candida tropicalis, revealed with the use of cell surface shaving method and shotgun proteomic approach," *Acta Biochimica Polonica*, vol. 62, no. 4, pp. 807–819, 2015.

[58] A. Kozik, J. Karkowska-Kuleta, D. Zajac et al., "Fibronectin-, vitronectin- and laminin-binding proteins at the cell walls of Candida parapsilosis and Candida tropicalis pathogenic yeasts," *BMC Microbiology*, vol. 15, no. 1, p. 197, 2015.

[59] J. Karkowska-Kuleta, D. Zajac, G. Bras et al., "Characterization of the interactions between human highmolecular-mass kininogen and cell wall proteins of pathogenic yeasts Candida tropicalis," *Acta Biochimica Polonica*, vol. 63, no. 3, pp. 427–436, 2016.

[60] C. Stokes, G. P. Moran, M. J. Spiering, G. T. Cole, D. C. Coleman, and D. J. Sullivan, "Lower filamentation rates of Candida dubliniensis contribute to its lower virulence in comparison with Candida albicans," *Fungal Genetics and Biology*, vol. 44, no. 9, pp. 920–931, 2007.

[61] B. L. Decker and W. T. Wickner, "Enolase Activates Homotypic Vacuole Fusion and Protein Transport to the Vacuole in Yeast," *Journal of Biological Chemistry*, vol. 281, no. 20, pp. 14523–14528, 2006.

[62] L. L. Hoyer, R. Fundyga, J. E. Hecht, J. C. Kapteyn, F. M. Klis, and J. Arnold, "Characterization of agglutinin-like sequence genes from non-albicans Candida and phylogenetic analysis of the ALS family," *Genetics*, vol. 157, no. 4, pp. 1555–1567, 2001.

[63] D. J. Sullivan, G. P. Moran, and D. C. Coleman, "Candida dubliniensis: ten years on," *FEMS Microbiology Letters*, vol. 253, no. 1, pp. 9–17, 2005.

[64] H. Fakhim, A. Vaezi, E. Dannaoui et al., "Comparative virulence of Candida auris with Candida haemulonii, Candida glabrata and Candida albicans in a murine model," *Mycoses*, vol. 61, no. 6, pp. 377–382, 2018.

[65] A. M. Day, M. M. McNiff, A. da Silva Dantas, N. A. R. Gow, and J. Quinn, "Hog1 regulates stress tolerance and virulence in the emerging fungal pathogen Candida auris," *mSphere*, vol. 3, no. 5, 2018.

[66] L. Rossato and A. L. Colombo, "Candida auris: what have we learned about its mechanisms of pathogenicity?," *Frontiers in Microbiology*, vol. 9, 2018.

[67] R. Kean, C. Delaney, L. Sherry et al., "Transcriptome assembly and profiling ofCandida aurisReveals novel insights into biofilm-mediated resistance," *mSphere*, vol. 3, no. 4, 2018.

[68] M. Schaller, C. Borelli, H. C. Korting, and B. Hube, "Hydrolytic enzymes as virulence factors of Candida albicans," *Mycoses*, vol. 48, no. 6, pp. 365–377, 2005.

[69] M. Rapala-Kozik, O. Bochenska, D. Zajac et al., "Extracellular proteinases of Candida species pathogenic yeasts," *Molecular Oral Microbiology*, vol. 33, no. 2, pp. 113–124, 2018.

[70] J. Naglik, A. Albrecht, O. Bader, and B. Hube, "Candida albicans proteinases and host/pathogen interactions," *Cellular Microbiology*, vol. 6, no. 10, pp. 915–926, 2004.

[71] J. A. M. S. Jayatilake, Y. H. Samaranayake, and L. P. Samaranayake, "An ultrastructural and a cytochemical study of candidal invasion of reconstituted human oral epithelium," *Journal of Oral Pathology & Medicine*, vol. 34, no. 4, pp. 240–246, 2005.

[72] M. A. Ghannoum, "Potential role of phospholipases in virulence and fungal pathogenesis," *Clinical Microbiology Reviews*, vol. 13, no. 1, pp. 122–143, 2000.

[73] A. Gácser, F. Stehr, C. Kröger, L. Kredics, W. Schäfer, and J. D. Nosanchuk, "Lipase 8 affects the pathogenesis of Candida albicans," *Infection and Immunity*, vol. 75, no. 10, pp. 4710–4718, 2007.

[74] C. Zaugg, M. Borg-Von Zepelin, U. Reichard, D. Sanglard, and M. Monod, "Secreted aspartic proteinase family of Candida tropicalis," *Infection and Immunity*, vol. 69, no. 1, pp. 405–412, 2001.

[75] Y. Wu, Y. H. Li, S. B. Yu et al., "A genome-wide transcriptional analysis of yeast-hyphal transition in Candida tropicalis by RNA-Seq," *PLoS One*, vol. 11, no. 11, p. e0166645, 2016.

[76] S. Yu, W. Li, X. Liu, J. Che, Y. Wu, and J. Lu, "Distinct expression levels of ALS, LIP, and SAP genes in Candida tropicalis with diverse virulent activities," *Frontiers in Microbiology*, vol. 7, 2016.

[77] G. Togni, D. Sanglard, M. Quadroni, S. I. Foundling, and M. Monod, "Acid proteinase secreted by Candida tropicalis: functional analysis of preproregion cleavages in C. tropicalis and Saccharomyces cerevisiae," *Microbiology*, vol. 142, no. 3, pp. 493–503, 1996.

[78] S. Silva, S. J. Hooper, M. Henriques, R. Oliveira, J. Azeredo, and D. W. Williams, "The role of secreted aspartyl proteinases in Candida tropicalis invasion and damage of oral mucosa," *Clinical Microbiology and Infection*, vol. 17, no. 2, pp. 264–272, 2011.

[79] N. K. Tamura, M. F. N. Negri, L. A. Bonassoli, and T. I. E. Svidzinski, "Fatores de virulência de Candida spp isoladas de cateteres venosos e mãos de servidores hospitalares," *Revista da Sociedade Brasileira de Medicina Tropical*, vol. 40, no. 1, pp. 91–93, 2007.

[80] M. A. Galán-Ladero, M. T. Blanco, B. Sacristán, M. C. Fernández-Calderón, C. Pérez-Giraldo, and A. C. Gómez-García, "Enzymatic activities of Candida tropicalis isolated from hospitalized patients," *Medical Mycology*, vol. 48, no. 1, pp. 207–210, 2010.

[81] N. Pandey, M. K. Gupta, and R. Tilak, "Extracellular hydrolytic enzyme activities of the different Candida spp. isolated from the blood of the intensive care unit-admitted patients," *Journal of Laboratory Physicians*, vol. 10, no. 4, pp. 392–396, 2018.

[82] D. Favero, E. J. G. França, L. Furlaneto-Maia, R. M. B. Quesada, and M. C. Furlaneto, "Production of haemolytic factor by clinical isolates of Candida tropicalis," *Mycoses*, vol. 54, no. 6, pp. e816–e820, 2011.

[83] S. Loaiza-Loeza, B. Parra-Ortega, J. C. Cancino-Díaz, B. Illades-Aguiar, C. H. Hernández-Rodríguez, and L. Villa-Tanaca, "Differential expression of Candida dubliniensis-secreted aspartyl proteinase genes (CdSAP1-4) under different physiological conditions and during infection of a keratinocyte culture," *Fems Immunology and Medical Microbiology*, vol. 56, no. 3, pp. 212–222, 2009.

[84] R. Fotedar and S. S. A. Al-Hedaithy, "Comparison of phospholipase and proteinase activity in Candida albicans and C. dubliniensis," *Mycoses*, vol. 48, no. 1, pp. 62–67, 2005.

[85] S. Shaban, M. Patel, and A. Ahmad, "Improved efficacy of antifungal drugs in combination with monoterpene phenols against Candida auris," *Scientific Reports*, vol. 10, no. 1, p. 1162, 2020.

[86] X. Wang, J. Bing, Q. Zheng et al., "The first isolate ofCandida aurisin China: clinical and biological aspects," *Emerging Microbes & Infections*, vol. 7, no. 1, pp. 1–9, 2018.

[87] S. K. Carvajal, M. Alvarado, Y. M. Rodríguez et al., "Pathogenicity assessment of colombian strains of candida auris in the galleria mellonella invertebrate model," *Journal of fungi*, vol. 7, no. 6, p. 401, 2021.

[88] A. Do Vale, D. Cabanes, and S. Sousa, "Bacterial toxins as pathogen weapons against phagocytes," *Frontiers in Microbiology*, vol. 7, p. 42, 2016.

[89] D. L. Moyes, D. Wilson, J. P. Richardson et al., "Candidalysin is a fungal peptide toxin critical for mucosal infection," *Nature*, vol. 532, no. 7597, pp. 64–68, 2016.

[90] J. Liu, H. M. E. Willems, E. A. Sansevere et al., "A variant ECE1 allele contributes to reduced pathogenicity of Candida albicans during vulvovaginal candidiasis," *PLoS Pathogens*, vol. 17, no. 9, p. e1009884, 2021.

[91] M. Blagojevic, G. Camilli, M. Maxson et al., "Candidalysin triggers epithelial cellular stresses that induce necrotic death," *Cell. Microbiology*, vol. 23, no. 10, p. e13371, 2021.

[92] J. P. Richardson, R. Brown, N. Kichik et al., "Candidalysins are a new family of cytolytic fungal peptide toxins," *MBio*, vol. 13, no. 1, pp. 1–13, 2022.

[93] A. König, B. Hube, and L. Kasper, "The dual function of the fungal toxin candidalysin during Candida albicans-macrophage interaction and virulence," *Toxins*, vol. 12, no. 8, p. 469, 2020.

[94] E. Lackey, G. Vipulanandan, D. S. Childers, and D. Kadosh, "Comparative evolution of morphological regulatory functions in Candida species," *Eukaryotic Cell*, vol. 12, no. 10, pp. 1356–1368, 2013.

[95] M. L. Bentz, D. Joseph Sexton, R. M. Welsh, and A. P. Litvintseva, "Phenotypic switching in newly emerged multidrug-resistant pathogen Candida auris," *Medical Mycology*, vol. 57, no. 5, pp. 636–638, 2019.

[96] H. Yue, J. Bing, Q. Zheng et al., "Filamentation in Candida auris, an emerging fungal pathogen of humans: passage through the mammalian body induces a heritable phenotypic switch," *Emerging Microbes & Infections*, vol. 7, no. 1, pp. 1–13, 2018.

[97] S. Allert, D. Schulz, P. Kämmer et al., "From environmental adaptation to host survival: attributes that mediate pathogenicity ofCandida auris," *Virulence*, vol. 13, no. 1, pp. 191–214, 2022.

[98] S. S. Justice, D. A. Hunstad, L. Cegelski, and S. J. Hultgren, "Morphological plasticity as a bacterial survival strategy," *Nature Reviews Microbiology*, vol. 6, no. 2, pp. 162–168, 2008.

[99] N. Jain, F. Hasan, and B. C. Fries, "Phenotypic switching in fungi," *Current Fungal Infection Reports*, vol. 2, no. 3, pp. 180–188, 2008.

[100] J. M. Anderson and D. R. Soll, "Unique phenotype of opaque cells in the white-opaque transition of candida albicans," *Journal of Bacteriology*, vol. 169, no. 12, pp. 5579–5588, 1987.

[101] J. Geiger, D. Wessels, S. R. Lockhart, and D. R. Soll, "Release of a potent polymorphonuclear leukocyte chemoattractant is regulated by white-opaque switching in Candida albicans," *Infection and Immunity*, vol. 72, no. 2, pp. 667–677, 2004.

[102] D. R. Soll, "The role of phenotypic switching in the basic biology and pathogenesis of Candida albicans," *Journal of Oral Microbiology*, vol. 6, no. 1, 2014.

[103] R. J. Bennett, "The parasexual lifestyle of _Candida albicans_," *Current Opinion in Microbiology*, vol. 28, pp. 10–17, 2015.

[104] A. Mishra, A. Forche, and M. Z. Anderson, "Parasexuality of Candida species," *Frontiers in Cellular and Infection Microbiology*, vol. 11, 2021.

[105] Z. K. Ross and A. Lorenz, "Is Candida auris sexual," *PLoS Pathogens*, vol. 16, no. 12, p. e1009094, 2020.

[106] J. Xu, "Is natural population of Candida tropicalis sexual, parasexual, and/or asexual," *Frontiers in Cellular and Infection Microbiology*, vol. 11, 2021.

[107] H. S. Park, S. C. Lee, M. E. Cardenas, and J. Heitman, "Calcium-calmodulin-calcineurin signaling: a globally conserved virulence cascade in eukaryotic microbial pathogens," *Cell Host and Microbe*, vol. 26, no. 4, pp. 453–462, 2019.

[108] K. R. Iyer, N. Robbins, and L. E. Cowen, "The role of Candida albicans stress response pathways in antifungal tolerance and resistance," *iScience*, vol. 25, no. 3, p. 103953, 2022.

[109] S. J. Yu, Y. L. Chang, and Y. L. Chen, "Calcineurin signaling: lessons from Candida species," *FEMS Yeast Research*, vol. 15, no. 4, 2015.

[110] Y. L. Chen, A. Brand, E. L. Morrison et al., "Calcineurin controls drug tolerance, hyphal growth, and virulence in Candida dubliniensis," *Eukaryotic Cell*, vol. 10, no. 6, pp. 803–819, 2011.

[111] Y. L. Chen, S. J. Yu, H. Y. Huang et al., "Calcineurin controls hyphal growth, virulence, and drug tolerance of Candida tropicalis," *Eukaryotic Cell*, vol. 13, no. 7, pp. 844–854, 2014.

[112] J. Zhang, J. Heitman, and Y. L. Chen, "Comparative analysis of calcineurin signaling between Candida dubliniensis and Candida albicans," *Communicative & Integrative Biology*, vol. 5, no. 2, pp. 122–126, 2012.

[113] J. Jensen, P. Muñoz, J. Guinea, M. Rodríguez-Créixems, T. Peláez, and E. Bouza, "Mixed fungemia: incidence, risk factors, and mortality in a general hospital," *Clinical Infectious Diseases*, vol. 44, no. 12, pp. e109–e114, 2007.

[114] J. C. Junqueira, B. B. Fuchs, M. Muhammed et al., "Oral Candida albicans isolates from HIV-positive individuals have similar in vitro biofilm-forming ability and pathogenicity as invasive Candida isolates," *BMC Microbiology*, vol. 11, no. 1, p. 247, 2011.

[115] L. O. Sánchez-Vargas, D. Estrada-Barraza, A. J. Pozos-Guillen, and R. Rivas-Caceres, "Biofilm formation by oral clinical isolates of Candida species," *Archives of Oral Biology*, vol. 58, no. 10, pp. 1318–1326, 2013.

[116] I. Cavaleiro, L. Proença, S. Félix, and M. Salema-Oom, "Prevalence of yeast other than Candida albicans in denture wearers," *Journal of Prosthodontics*, vol. 22, no. 5, pp. 351–357, 2013.

[117] S. Tati, P. Davidow, A. McCall et al., "Candida glabrata binding to Candida albicans hyphae enables its development in oropharyngeal candidiasis," *PLoS Pathogens*, vol. 12, no. 3, p. e1005522, 2016.

[118] R. U. Pathirana, A. D. McCall, H. L. Norris, and M. Edgerton, "Filamentous non-albicans Candida species adhere to Candida albicans and benefit from dual biofilm growth," *Frontiers in Microbiology*, vol. 10, 2019.

[119] S. Elias and E. Banin, "Multi-species biofilms: living with friendly neighbors," *FEMS Microbiology Reviews*, vol. 36, no. 5, pp. 990–1004, 2012.

[120] H. T. Taff, K. F. Mitchell, J. A. Edward, and D. R. Andes, "Mechanisms of Candida biofilm drug resistance," *Future Microbiology*, vol. 8, no. 10, pp. 1325–1337, 2013.

[121] D. Sandai, Y. M. Tabana, A. El Ouweini, and I. O. Ayodeji, "Resistance of Candida albicans biofilms to drugs and the host immune system," *Jundishapur Journal of Microbiology*, vol. 9, no. 11, p. e37385, 2016.

[122] W. R. Kirkpatrick, J. L. Lopez-Ribot, R. K. Mcatee, and T. F. Patterson, "Growth competition between Candida dubliniensis and Candida albicans under broth and biofilm growing conditions," *Journal of Clinical Microbiology*, vol. 38, no. 2, pp. 902–904, 2000.

[123] M. A. Al-Fattani and L. J. Douglas, "Biofilm matrix of Candida albicans and Candida tropicalis: chemical composition and role in drug resistance," *Journal of Medical Microbiology*, vol. 55, no. 8, pp. 999–1008, 2006.

[124] P. P. de Barros, R. D. Rossoni, F. Freire et al., "Candida tropicalis affects the virulence profile of Candida albicans: an in vitro and in vivo study," *Pathogens and Disease*, vol. 76, no. 2, 2018.

[125] R. Mohd Tap, T. C. Lim, N. A. Kamarudin et al., "A fatal case of Candida auris and Candida tropicalis candidemia in neutropenic patient," *Mycopathologia*, vol. 183, no. 3, pp. 559–564, 2018.

[126] J. J. Ayala-Gaytán, A. M. Montoya, M. F. Martínez-Resendez et al., "First case of Candida auris isolated from the bloodstream of a Mexican patient with serious gastrointestinal complications from severe endometriosis," *Infection*, vol. 49, no. 3, pp. 523–525, 2021.

[127] M. Polke, I. Leonhardt, O. Kurzai, and I. D. Jacobsen, "Farnesol signalling in Candida albicans–more than just communication," *Critical Reviews in Microbiology*, vol. 44, no. 2, pp. 230–243, 2018.

[128] M. Cavalheiro and M. C. Teixeira, "Candida biofilms: threats, challenges, and promising strategies," *Frontiers in Medicine*, vol. 5, 2018.

[129] M. Kruppa, "Quorum sensing and Candida albicans," *Mycoses*, vol. 52, no. 1, pp. 1–10, 2009.

[130] P. Albuquerque and A. Casadevall, "Quorum sensing in fungi a review," *Medical Mycology*, vol. 50, no. 4, pp. 337–345, 2012.

[131] S. A. Padder, R. Prasad, and A. H. Shah, "Quorum sensing: a less known mode of communication among fungi," *Microbiological Research*, vol. 210, pp. 51–58, 2018.

[132] J. M. Hornby, E. C. Jensen, A. D. Lisec et al., "Quorum sensing in the dimorphic fungus Candida albicans is mediated by farnesol," *pplied and Environmental Microbiology*, vol. 67, no. 7, pp. 2982–2992, 2001.

[133] C. F. Rodrigues and L. Černáková, "Farnesol and tyrosol: secondary metabolites with a crucial quorum-sensing role in candida biofilm development," *Genes*, vol. 11, no. 4, p. 444, 2020.

[134] Molecular microbiology -2004- Hogan - a Pseudomonas aeruginosa quorum-sensing molecule influences Candida albicans. pdf.

[135] L. De Sordi and F. A. Mühlschlegel, "Quorum sensing and fungal-bacterial interactions in Candida albicans: a communicative network regulating microbial coexistence and virulence," *FEMS Yeast Research*, vol. 9, no. 7, pp. 990–999, 2009.

[136] M. A. Jabra-Rizk, M. Shirtliff, C. James, and T. Meiller, "Effect of farnesol on Candida dubliniensis biofilm formation and fluconazole resistance," vol. 6, no. 7, pp. 1063–1073, 2006.

[137] M. Henriques, M. Martins, J. Azeredo, and R. Oliveira, "Effect of farnesol on Candida dubliniensis morphogenesis," *Letters in Applied Microbiology*, vol. 44, no. 2, pp. 199–205, 2007.

[138] M. Martins, M. Henriques, J. Azeredo, S. M. Rocha, M. A. Coimbra, and R. Oliveira, "Morphogenesis control in Candida albicans and Candida dubliniensis through signaling molecules produced by planktonic and biofilm cells," *Eukaryotic Cell*, vol. 6, no. 12, pp. 2429–2436, 2007.

[139] K. Weber, R. Sohr, B. Schulz, M. Fleischhacker, and M. Ruhnke, "Secretion of E, E-farnesol and biofilm formation in eight different Candida species," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 5, pp. 1859–1861, 2008.

[140] M. Martins, M. Henriques, J. Azeredo, S. M. Rocha, M. A. Coimbra, and R. Oliveira, "Candida species extracellular alcohols: production and effect in sessile cells," *Journal of Basic Microbiology*, vol. 50, no. S1, pp. S89–S97, 2010.

[141] K. Weber, B. Schulz, and M. Ruhnke, "The quorum-sensing molecule E, E-farnesol - its variable secretion and its impact on the growth and metabolism of Candida species," *Yeast*, vol. 27, no. 9, pp. 727–739, 2010.

[142] M. D. R. Agustín, F. R. Viceconte, M. S. Vela Gurovic, A. Costantino, and L. I. Brugnoni, "Effect of quorum sensing molecules and natamycin on biofilms of Candida tropicalis and other yeasts isolated from industrial juice filtration membranes," *Journal of Applied Microbiology*, vol. 126, no. 6, pp. 1808–1820, 2019.

[143] S. Shanmughapriya, H. Sornakumari, A. Lency, S. Kavitha, and K. Natarajaseenivasan, "Synergistic effect of amphotericin B and tyrosol on biofilm formed by Candida krusei and Candida tropicalis from intrauterine device users," *Medical Mycology*, vol. 52, no. 8, pp. 853–861, 2014.

[144] R. D. A. Cordeiro, C. E. Teixeira, R. S. Brilhante et al., "Exogenous tyrosol inhibits planktonic cells and biofilms of Candida species and enhances their susceptibility to antifungals," *FEMS Yeast Research*, vol. 15, no. 4, 2015.

[145] M. H. Semreen, S. S. M. Soliman, B. Q. Saeed, A. Alqarihi, P. Uppuluri, and A. S. Ibrahim, "Metabolic profiling of candida auris, a newly-emerging multi-drug resistant candida species, by GC-MS," *Molecules*, vol. 24, no. 3, p. 399, 2019.

[146] V. Srivastava and A. Ahmad, "Abrogation of pathogenic attributes in drug resistant Candida auris strains by farnesol," *PLoS One*, vol. 15, no. 5, p. e0233102, 2020.

[147] Á. Jakab, N. Balla, Á. Ragyák et al., "Transcriptional profiling of the Candida auris response to exogenous farnesol exposure," *mSphere*, vol. 6, no. 5, p. e0071021, 2021.

[148] K. R. Eichelberger and J. E. Cassat, "Metabolic adaptations during Staphylococcus aureus and Candida albicans co-infection," *Frontiers in Immunology*, vol. 12, pp. 1–14, 2021.

[149] A. Pellon, N. Begum, S. D. S. Nasab, A. Harzandi, S. Shoaie, and D. L. Moyes, "Role of cellular metabolism during Candida-host interactions," *Pathogens*, vol. 11, no. 2, 2022.

[150] P. Miramón and M. C. Lorenz, "A feast for Candida: metabolic plasticity confers an edge for virulence," *PLoS Pathogens*, vol. 13, no. 2, p. e1006144, 2017.

[151] J. C. Oliver, L. Laghi, C. Parolin et al., "Metabolic profiling of Candida clinical isolates of different species and infection sources," *Scientific Reports*, vol. 10, no. 1, p. 16716, 2020.

[152] A. J. P. Brown, S. Budge, D. Kaloriti et al., "Stress adaptation in a pathogenic fungus," *Journal of Experimental Biology*, vol. 217, no. 1, pp. 144–155, 2014.

[153] R. B. Williams and M. C. Lorenz, "Multiple alternative carbon pathways combine to promote candida albicans stress resistance, immune interactions, and virulence," *MBio*, vol. 11, no. 1, 2020.

[154] H. Heaney, J. Laing, L. Paterson et al., "The environmental stress sensitivities of pathogenic candida species, including candida auris, and implications for their spread in the hospital setting," *Medical Mycology*, vol. 58, no. 6, pp. 744–755, 2020.

[155] D. L. Zuza-Alves, S. S. T. Q. de Medeiros, L. B. F. C. de Souza et al., "Evaluation of virulence factors in vitro, resistance to osmotic stress and antifungal susceptibility of Candida tropicalis isolated from the coastal environment of northeast Brazil," *Frontiers in Microbiology*, vol. 7, 2016.

[156] M. C. Lorenz and G. R. Fink, "The glyoxylate cycle is required for fungal virulence," *Nature*, vol. 412, no. 6842, pp. 83–86, 2001.

[157] M. C. Lorenz, J. A. Bender, and G. R. Fink, "Transcriptional response of Candida albicans upon internalization by macrophages," *Eukaryotic Cell*, vol. 3, no. 5, pp. 1076–1087, 2004.

[158] C. J. Barelle, C. L. Priest, D. M. Mac Callum, N. A. R. Gow, F. C. Odds, and A. J. P. Brown, "Niche-specific regulation of central metabolic pathways in a fungal pathogen," *Cellular Microbiology*, vol. 8, no. 6, pp. 961–971, 2006.

[159] S. Y. Chew, W. J. Y. Chee, and L. T. L. Than, "The glyoxylate cycle and alternative carbon metabolism as metabolic adaptation strategies of Candida glabrata: perspectives from Candida albicans and Saccharomyces cerevisiae," *Journal of Biomedical Science*, vol. 26, no. 1, p. 52, 2019.

[160] I. V. Ene, A. K. Adya, S. Wehmeier et al., "Host carbon sources modulate cell wall architecture, drug resistance and virulence in a fungal pathogen," *Cellular Microbiology*, vol. 14, no. 9, pp. 1319–1335, 2012.

[161] D. Zamith-Miranda, H. M. Heyman, L. G. Cleare et al., "Multi-omics signature ofCandida auris, an emerging and multidrug-resistant pathogen," *mSystems*, vol. 4, no. 4, 2019.

[162] K. Umemura, H. Atomi, T. Kanai et al., "Derepression of gene expression mediated by the 5' upstream region of the isocitrate lyase gene of Candida tropicalis is controlled by two distinct regulatory pathways in Saccharomyces cerevisiae," *European Journal of Biochemistry*, vol. 243, no. 3, pp. 748–752, 1997.

[163] K. Umemura, H. Atomi, M. Izuta et al., "Analysis of carbon source-regulated gene expression by the upstream region of the Candida tropicalis malate synthase gene in Saccharomyces cerevisiae," *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, vol. 1350, no. 1, pp. 80–88, 1997.

[164] H. Carolus, S. Pierson, K. Lagrou, and P. Van Dijck, "Amphotericin b and other polyenes—discovery, clinical use, mode of action and drug resistance," *Journal of Fungi*, vol. 6, no. 4, p. 321, 2020.

[165] M. Wellington, J. M. Bliss, and C. G. Haidaris, "Enhanced phagocytosis of Candida species mediated by opsonization with a recombinant human antibody single-chain variable fragment," *Infection and Immunity*, vol. 71, no. 12, pp. 7228–7231, 2003.

[166] A. W. Pountain, J. R. Collette, W. M. Farrell, and M. C. Lorenz, "Interactions of both pathogenic and nonpathogenic CUG clade Candida species with macrophages share a conserved transcriptional landscape," *MBio*, vol. 12, no. 6, pp. 1–22, 2021.

[167] P. Kämmer, S. McNamara, T. Wolf et al., "Survival strategies of PathogenicCandidaSpecies in human blood show independent and specific adaptations," *MBio*, vol. 11, no. 5, 2020.

[168] F. Citiulo, I. D. Jacobsen, P. Miramón et al., "Candida albicans scavenges host zinc via Pra 1 during endothelial invasion," *PLoS Pathogens*, vol. 8, no. 6, p. e1002777, 2012.

[169] S. A. B. Knight, G. Vilaire, E. Lesuisse, and A. Dancis, "Iron acquisition from transferrin by Candida albicans depends on the reductive pathway," *Infection and Immunity*, vol. 73, no. 9, pp. 5482–5492, 2005.

[170] C. Lamarre, N. Deslauriers, and Y. Bourbonnais, "Expression cloning of the Candida albicans CSA1 gene encoding a mycelial surface antigen by sorting of Saccharomyces cerevisiae transformants with monoclonal antibody-coated magnetic beads," *Molecular Microbiology*, vol. 35, no. 2, pp. 444–453, 2000.

[171] P. Heymann, M. Gerads, M. Schaller, F. Dromer, G. Winkelmann, and J. F. Ernst, "The siderophore iron transporter of Candida albicans (Sit1p/Arn1p) mediates uptake of ferrichrome-type siderophores and is required for epithelial invasion," *Infection and Immunity*, vol. 70, no. 9, pp. 5246–5255, 2002.

[172] A. Plato, J. A. Willment, and G. D. Brown, "C-type lectin-like receptors of the dectin-1 cluster: ligands and signaling pathways," *International Reviews of Immunology*, vol. 32, no. 2, pp. 134–156, 2013.

[173] B. G. Mengesha and H. R. Conti, "The role of IL-17 in protection against mucosal Candida infections," *Journal of Fungi*, vol. 3, no. 4, p. 52, 2017.

[174] N. Whibley, J. R. Jaycox, D. Reid et al., "Delinking CARD9 and IL-17: CARD9 protects against Candida tropicalis infection through a TNF-α–dependent, IL-17–independent mechanism," *The Journal of Immunology*, vol. 195, no. 8, pp. 3781–3792, 2015.

[175] L. Campos-Garcia, R. J. Jimenez-Valdes, R. Hernandez-Bello, J. Palma-Nicolas, G. M. Gonzalez, and A. Sanchez-Gonzalez, "Candida albicans and non-albicans isolates from bloodstream have different capacities to induce neutrophil extracellular traps," *Journal of Fungi*, vol. 5, no. 2, p. 28, 2019.

[176] M. J. Navarro-Arias, M. J. Hernández-Chávez, L. C. Garcia-Carnero et al., "Differential recognition of Candida tropicalis, Candida guilliermondii, Candida krusei, and Candida auris by human innate immune cells," *Infection and Drug Resistance*, vol. 12, pp. 783–794, 2019.

[177] E. Svobodová, P. Staib, J. Losse, F. Hennicke, D. Barz, and M. Józsi, "Differential interaction of the two related fungal species Candida albicans and Candida dubliniensis with human neutrophils," *Journal of Immunology*, vol. 189, no. 5, pp. 2502–2511, 2012.

[178] C. J. Johnson, J. M. Davis, A. Huttenlocher, J. F. Kernien, and J. E. Nett, "Emerging fungal pathogen Candida auris evades neutrophil attack," *MBio*, vol. 9, no. 4, 2018.

[179] M. V. Horton, C. J. Johnson, R. Zarnowski et al., "Candida auris cell wall mannosylation contributes to neutrophil evasion through pathways divergent from Candida albicans and Candida glabrata," *mSphere*, vol. 6, no. 3, p. e0040621, 2021.

[180] M. Bruno, S. Kersten, J. M. Bain et al., "Transcriptional and functional insights into the host immune response against the emerging fungal pathogen _Candida auris_," *Nature Microbiology*, vol. 5, no. 12, pp. 1516–1531, 2020.

[181] J. Katz, "Prevalence of candidiasis and oral candidiasis in COVID-19 patients: a cross-sectional pilot study from the patients' registry in a large health center," *Quintessence International*, vol. 52, no. 8, pp. 714–718, 2021.

[182] T. Bardi, V. Pintado, M. Gomez-Rojo et al., "Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome," *European Journal of Clinical Microbiology & Infectious Diseases*, vol. 40, no. 3, pp. 495–502, 2021.

[183] K. Bhatt, A. Agolli, M. H. Patel et al., "High mortality co-infections of COVID-19 patients: mucormycosis and other fungal infections," *Discoveries*, vol. 9, no. 1, p. e126, 2021.

[184] L. Yang, X. Xie, Z. Tu, J. Fu, D. Xu, and Y. Zhou, "The signal pathways and treatment of cytokine storm in COVID-19," *Signal Transduction and Targeted Therapy*, vol. 6, no. 1, pp. 1–20, 2021.

[185] B. L. Wickes and A. M. Romanelli, "Diagnostic mycology: Xtreme challenges," *Journal of Clinical Microbiology*, vol. 58, no. 4, 2020.

[186] D. J. Sullivan, T. J. Westerneng, K. A. Haynes, D. E. Bennett, and D. C. Coleman, "Candida dubliniensis sp. nov.: phenotypic and molecular characterization of a novel species associated with oral candidosis in HIV-infected individuals," *Microbiology*, vol. 141, no. 7, pp. 1507–1521, 1995.

[187] W. G. Lee, J. H. Shin, Y. Uh et al., "First three reported cases of nosocomial fungemia caused by Candida auris," *Journal of Clinical Microbiology*, vol. 49, no. 9, pp. 3139–3142, 2011.

[188] S. R. Lockhart, M. M. Lyman, and D. J. Sexton, "Tools for detecting a 'superbug': updates on Candida auris testing," *Journal of Clinical Microbiology*, vol. 60, no. 5, p. e00808-21, 2022.

[189] S. Silva, M. Negri, M. Henriques, R. Oliveira, D. W. Williams, and J. Azeredo, "Candida glabrata, Candida parapsilosis and Candida tropicalis: biology, epidemiology, pathogenicity and antifungal resistance," *FEMS Microbiology Reviews*, vol. 36, no. 2, pp. 288–305, 2012.

[190] M. Whiteway and C. Bachewich, "Morphogenesis in Candida albicans," *Annual Review of Microbiology*, vol. 61, no. 1, pp. 529–553, 2007.

[191] Y. Okawa and K. Goto, "Antigenicity ofCandida tropicalis-strain cells cultured at 27 and 37Â°C," *FEMS Immunology & Medical Microbiology*, vol. 46, no. 3, pp. 438–443, 2006.

[192] D. Larone, *Medically Important Fungi; A Guide to Identification*, ASM Press, Washington, 4th edn. edition, 2002.

[193] P. Staib and J. Morschhäuser, "Chlamydospore formation in Candida albicans and Candida dubliniensis - an enigmatic developmental programme," *Mycoses*, vol. 50, no. 1, pp. 1–12, 2007.

[194] R. Singh, M. Kaur, A. Chakrabarti, S. A. Shankarnarayan, and S. M. Rudramurthy, "Biofilm formation by Candida auris isolated from colonising sites and candidemia cases," *Mycoses*, vol. 62, no. 8, pp. 706–709, 2019.

[195] G. Bravo Ruiz, Z. K. Ross, N. A. R. Gow, and A. Lorenz, "Pseudohyphal growth of the emerging pathogen Candida auris is triggered by genotoxic stress through the S phase checkpoint," *mSphere*, vol. 5, no. 2, 2020.

[196] I. Mellman and G. Warren, "The road taken: past and future foundations of membrane traffic," *Cell*, vol. 100, pp. 99–112, 2000.

[197] R. Giebel, C. Worden, S. M. Rust, G. T. Kleinheinz, M. Robbins, and T. R. Sandrin, "Microbial fingerprinting using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS): applications and challenges," *Advances in Applied Microbiology*, vol. 71, pp. 149–184, 2010.

[198] E. De Carolis, A. Vella, L. Vaccaro et al., "Application of MALDI-TOF mass spectrometry in clinical diagnostic microbiology," *Journal of Infection in Developing Countries*, vol. 8, no. 9, pp. 1081–1088, 2014.

[199] A. Vlek, A. Kolecka, K. Khayhan et al., "Interlaboratory comparison of sample preparation methods, database expansions, and cutoff values for identification of yeasts by matrix-assisted laser desorption ionization-time of flight mass spectrometry using a yeast test panel," *Journal of clinical microbiology*, vol. 52, no. 8, pp. 3023–3029, 2014.

[200] Consortium OPATHY, A. Arastehfar, T. Boekhout et al., "Recent trends in molecular diagnostics of yeast infections: from PCR to NGS," *FEMS Microbiology Reviews*, vol. 43, no. 5, pp. 517–547, 2019.

[201] D. H. Pincus, S. Orenga, and S. Chatellier, "Yeast identification - past, present, and future methods," *Medical Mycology*, vol. 45, no. 2, pp. 97–121, 2007.

[202] S. E. Kidd, S. C. A. Chen, W. Meyer, and C. L. Halliday, "A new age in molecular diagnostics for invasive fungal disease: are we ready," *Frontiers in Microbiology*, vol. 10, 2020.

[203] P. L. White, J. S. Price, A. Cordey, and M. Backx, "Molecular diagnosis of yeast infections," *Current Fungal Infection Reports*, vol. 15, no. 3, pp. 67–80, 2021.

[204] É. S. Loreto, L. A. Scheid, C. W. Nogueira, G. Zeni, J. M. Santurio, and S. H. Alves, "Candida dubliniensis: epidemiology and phenotypic methods for identification," *Mycopathologia*, vol. 169, no. 6, pp. 431–443, 2010.

[205] A. Sampath, M. Weerasekera, A. Dilhari et al., "Comparison of duplex PCR and phenotypic analysis in differentiating Candida dubliniensis from Candida albicans from oral samples," *AMB Express*, vol. 7, no. 1, p. 141, 2017.

[206] V. Lipperheide, L. Andraka, J. Pontón, and G. Quindós, "Evaluation of the albicans IDR plate method for the rapid identification of Candida albicans," *Mycoses*, vol. 36, no. 11-12, pp. 417–420, 1993.

[207] V. M. Cooke, R. J. Miles, R. G. Price, G. Midgley, W. Khamri, and A. C. Richardson, "New chromogenic agar medium for the identification of Candida spp," *Applied and Environmental Microbiology*, vol. 68, no. 7, pp. 3622–3627, 2002.

[208] A. J. Carrillo-Muñoz, L. Abarca, and G. Quindós, "Colorimetric methods for in vitro antifungal susceptibility testing," *Revista Iberoamericana de Micologia*, vol. 18, no. 4, pp. 150–155, 2001.

[209] U. Scharmann, L. Kirchhoff, V. . S. Chapot et al., "Comparison of four commercially available chromogenic media to identify Candida albicans and other medically relevant Candida species," *Mycoses*, vol. 63, no. 8, pp. 823–831, 2020.

[210] G. Curtis and R. Baird, "Rambach agar propylene glycol deoxycholate neutral red agar," *International Journal of Food Microbiology*, vol. 17, no. 3, pp. 243-244, 1993.

[211] F. C. Odds and R. Bernaerts, "CHROMagar Candida, a new differential isolation medium for presumptive identification of clinically important Candida species," *Journal of Clinical Microbiology*, vol. 32, no. 8, pp. 1923–1929, 1994.

[212] W. R. Kirkpatrick, S. G. Revankar, R. K. Mcatee et al., "Detection of Candida dubliniensis in oropharyngeal samples from human immunodeficiency virus-infected patients in North America by primary CHROMagar Candida screening and susceptibility testing of isolates," *Journal of Clinical Microbiology*, vol. 36, no. 10, pp. 3007–3012, 1998.

[213] A. M. Borman, M. Fraser, and E. M. Johnson, "CHROMagarTM Candida plus: a novel chromogenic agar that permits the rapid identification ofCandida auris," *Medical Mycology*, vol. 59, no. 3, pp. 253–258, 2021.

[214] A. C. Gales, M. A. Pfaller, A. K. Houston et al., "Identification ofCandida dubliniensisBased on temperature and utilization of xylose and α-methyl-D-glucoside as determined with the API 20C AUX and Vitek YBC systems," *Journal of Clinical Microbiology*, vol. 37, no. 12, pp. 3804–3808, 1999.

[215] Z. Szabo, B. Toth, M. Kovacs et al., "Evaluation of the new micronaut-Candida system compared to the API ID32C method for yeast identification," *Journal of Clinical Microbiology*, vol. 46, no. 5, pp. 1824-1825, 2008.

[216] A. Jeffery-Smith, S. K. Taori, S. Schelenz et al., "Candida auris: a review of the literature," *Clinical Microbiology Reviews*, vol. 31, no. 1, 2018.

[217] S. Das, R. Tigga, G. Rai et al., "Candida auris colonization in an immunocompetent patient: A new threat in medical ICU," *Medical Mycology Case Reports*, vol. 21, pp. 54–56, 2018.

[218] G. Pulcrano, D. V. Iula, A. Vollaro et al., "Rapid and reliable MALDI-TOF mass spectrometry identification of Candida non- albicans isolates from bloodstream infections," *Journal of Microbiological Methods*, vol. 94, no. 3, pp. 262–266, 2013.

[219] J. E. Domer and R. E. Garner, "Immunomodulation in response to Candida," *Immunology Series*, vol. 47, pp. 293–317, 1989.

[220] N. A. R. Gow, J.-P. Latge, and C. A. Munro, "The fungal cell wall: structure, biosynthesis, and function," *Microbiology Spectrum*, vol. 5, no. 3, 2017.

[221] M. Mikulska, T. Calandra, M. Sanguinetti, D. Poulain, C. Viscoli, and the Third European Conference on Infections in Leukemia Group, "The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia," *Critical Care*, vol. 14, no. 6, p. R222, 2010.

[222] J. Held, I. Kohlberger, E. Rappold, A. B. Grawitz, and G. Häckera, "Comparison of (1→3)-β-d-glucan, mannan/anti-mannan antibodies, and cand-tec candida antigen as serum biomarkers for candidemia," *Journal of Industrial Microbiology and Biotechnology*, vol. 51, no. 4, pp. 1158–1164, 2013.

[223] M. C. Martínez-Jiménez, P. Muñoz, J. Guinea et al., "Potential role of Candida albicans germ tube antibody in the diagnosis of deep-seated candidemia," *Medical Mycology*, vol. 52, no. 3, pp. 270–275, 2014.

[224] M. D. Moragues, N. Ortiz, J. R. Iruretagoyena et al., "Evaluation of a new commercial test (Candida albicans IFA IgG) for the serodiagnosis of invasive candidiasis," *Enfermedades Infecciosas y Microbiologia Clinica*, vol. 22, no. 2, pp. 83–88, 2004.

[225] A. Laín, N. Elguezabal, S. Brena et al., "Diagnosis of invasive candidiasis by enzyme-linked immunosorbent assay using the N-terminal fragment of Candida albicans hyphal wall protein 1," *BMC Microbiology*, vol. 7, no. 1, 2007.

[226] A. Marot-Leblond, B. Beucher, S. David, S. Nail-Billaud, and R. Robert, "Development and evaluation of a rapid latex agglutination test using a monoclonal antibody to identify Candida dubliniensis colonies," *Journal of Clinical Microbiology*, vol. 44, no. 1, pp. 138–142, 2006.

[227] O. Bader, "MALDI-TOF-MS-based species identification and typing approaches in medical mycology," *Proteomics*, vol. 13, no. 5, pp. 788–799, 2013.

[228] S. Kathuria, P. K. Singh, C. Sharma et al., "Multidrug-resistant Candida auris misidentified as Candida haemulonii: characterization by matrix-assisted laser desorption ionization-time of flight mass spectrometry and DNA sequencing and its antifungal susceptibility profile variability by vitek 2, CLSI Broth Microdilution, and Etest Method," *Journal of Clinical Microbiology*, vol. 53, no. 6, pp. 1823–1830, 2015.

[229] A. Arastehfar, F. Daneshnia, M. Kord et al., "Corrigendum: Comparison of 21-plex PCR and API 20C AUX, MALDI-TOF MS, and rDNA sequencing for a wide range of clinically isolated yeast species: improved identification by combining 21-plex PCR and API 20C AUX as an alternative strategy for developing Countries," *Frontiers in Cellular and Infection Microbiology*, vol. 9, p. 21, 2019.

[230] S. Suarez, A. Ferroni, A. Lotz et al., "Ribosomal proteins as biomarkers for bacterial identification by mass spectrometry in the clinical microbiology laboratory," *Journal of Microbiological Methods*, vol. 94, no. 3, pp. 390–396, 2013.

[231] A. Pinto, C. Halliday, M. Zahra et al., "Matrix-assisted laser desorption ionization-time of flight mass spectrometry identification of yeasts is contingent on robust reference spectra," *PLoS One*, vol. 6, no. 10, p. e25712, 2011.

[232] F. Galán, L. García-Agudo, I. Guerrero et al., "Evaluation of mass spectrometry for the identification of clinically interesting yeasts," *Enfermedades Infecciosas y Microbiología Clínica*, vol. 33, no. 6, pp. 372–378, 2015.

[233] E. L. Hazen and R. Brown, "Fungicidin, an antibiotic produced by a soil actinomycete," *Proceedings of the Society for Experimental Biology and Medicine*, vol. 76, no. 1, pp. 93–97, 1951.

[234] M. L. Sokol-Anderson, J. Brajtburg, and G. Medoff, "Amphotericin B-induced oxidative damage and killing of Candida albicans," *Journal of Infectious Diseases*, vol. 154, no. 1, pp. 76–83, 1986.

[235] T. M. Anderson, M. C. Clay, A. G. Cioffi et al., "Amphotericin forms an extramembranous and fungicidal sterol sponge," *Nature Chemical Biology*, vol. 10, no. 5, pp. 400–406, 2014.

[236] D. J. Sheehan, C. A. Hitchcock, and C. M. Sibley, "Current and emerging azole antifungal agents," *Clinical Microbiology Reviews*, vol. 12, no. 1, pp. 40–79, 1999.

[237] N. H. Georgopapadakou and T. J. Walsh, "Antifungal agents: chemotherapeutic targets and immunologic strategies," *Antimicrobial Agents and Chemotherapy*, vol. 40, no. 2, pp. 279–291, 1996.

[238] C. Spampinato and D. Leonardi, "Candida Infections, Causes, Targets, and Resistance Mechanisms: Traditional and Alternative Antifungal Agents," *Bio Med Research International*, vol. 2013, article 204237, 13 pages, 2013.

[239] K. E. Pristov and M. A. Ghannoum, "Resistance of Candida to azoles and echinocandins worldwide," *Clinical Microbiology and Infection*, vol. 25, no. 7, pp. 792–798, 2019.

[240] N. S. Ryder, "Mechanism of action and biochemical selectivity of allylamine antimycotic agents," *Annals of the New York Academy of Sciences*, vol. 544, pp. 208–220, 1988.

[241] T. C. White, K. A. Marr, and R. A. Bowden, "Clinical, cellular, and molecular factors that contribute to antifungal drug resistance," *Clinical Microbiology Reviews*, vol. 11, no. 2, pp. 382–402, 1998.

[242] D. Cappelletty and K. Eiselstein-McKitrick, "The echinocandins," *Pharmacotherapy*, vol. 27, no. 3, pp. 369–388, 2007.

[243] J. Sharma, S. Rosiana, I. Razzaq, and R. S. Shapiro, "Linking cellular morphogenesis with antifungal treatment and susceptibility in candida pathogens," *Journal of Fungi*, vol. 5, no. 1, p. 17, 2019.

[244] A. Vermes, H. J. Guchelaar, and J. Dankert, "Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions," *ournal of Antimicrobial Chemotherapy*, vol. 46, no. 2, pp. 171–179, 2000.

[245] M. C. Arendrup and T. F. Patterson, "Multidrug-resistant candida: epidemiology, molecular mechanisms, and treatment," *Journal of Infectious Diseases*, vol. 216, supplement 3, pp. S445–S451, 2017.

[246] R. B. Diasio, D. E. Lakings, and J. E. Bennett, "Evidence for conversion of 5-fluorocytosine to 5-fluorouracil in humans: possible factor in 5-fluorocytosine clinical toxicity," *Antimicrobial Agents and Chemotherapy*, vol. 14, no. 6, pp. 903–908, 1978.

[247] J. F. Fisher, J. D. Sobel, C. A. Kauffman, and C. A. Newman, "Candida urinary tract infections—treatment," *Clinical Infectious Diseases*, vol. 52, Supplement 6, pp. S457–S466, 2011.

[248] N. Azie, D. Angulo, B. Dehn, and J. D. Sobel, "Oral Ibrexafungerp: an investigational agent for the treatment of vulvovaginal candidiasis," *Expert Opinion on Investigational Drugs*, vol. 29, no. 9, pp. 893–900, 2020.

[249] M. R. Davis, M. A. Donnelley, and G. R. Thompson, "Ibrexafungerp: a novel oral glucan synthase inhibitor," *Medical Mycology*, vol. 58, no. 5, pp. 579–592, 2020.

[250] M. Hoenigl, R. Sprute, M. Egger et al., "The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin," *Drugs*, vol. 81, no. 15, pp. 1703–1729, 2021.

[251] J. P. Lopes and M. S. Lionakis, "Pathogenesis and virulence of Candida albicans," *Virulence*, vol. 13, no. 1, pp. 89–121, 2022.

[252] M. A. Pfaller, S. A. Messer, S. Gee et al., "In vitro susceptibilities of Candida dubliniensis isolates tested against the new

triazole and echinocandin antifungal agents," *Journal of Clinical Microbiology*, vol. 37, no. 3, pp. 870–872, 1999.

[253] M. A. Pfaller, S. A. Messer, L. Boyken, H. Huynh, R. J. Hollis, and D. J. Diekema, "In vitro activities of 5-fluorocytosine against 8, 803 clinical isolates of Candida spp.: global assessment of primary resistance using National Committee for Clinical Laboratory Standards susceptibility testing methods," *Antimicrobial Agents and Chemotherapy*, vol. 46, no. 11, pp. 3518–3521, 2002.

[254] G. Quindós, A. J. Carrillo-Muñoz, M. P. Arévalo et al., "In vitro susceptibility of Candida dubliniensis to current and new antifungal agents," *Chemotherapy*, vol. 46, no. 6, pp. 395–401, 2000.

[255] F. Z. Delma, A. M. S. al-Hatmi, R. J. M. Brüggemann et al., "Molecular mechanisms of 5-fluorocytosine resistance in yeasts and filamentous fungi," *Journal of Fungi*, vol. 7, no. 11, p. 909, 2021.

[256] R. Ayadi, E. Sitterlé, C. d'Enfert, E. Dannaoui, and M. E. Bougnoux, "Candida albicans and Candida dubliniensis show different trailing effect patterns when exposed to echinocandins and azoles," *Frontiers in Microbiology*, vol. 11, no. 1286, 2020.

[257] A. Kawai, Y. Yamagishi, and H. Mikamo, "In vitro efficacy of liposomal amphotericin B, micafungin and fluconazole against non- albicans Candida species biofilms," *Journal of Infection and Chemotherapy*, vol. 21, no. 9, pp. 647–653, 2015.

[258] L. J. Marcos-Zambrano, P. Escribano, E. Bouza, and J. Guinea, "Comparison of the antifungal activity of micafungin and amphotericin B against Candida tropicalis biofilms," *Journal of Antimicrobial Chemotherapy*, vol. 71, no. 9, pp. 2498–2501, 2016.

[259] K. Satoh, K. Makimura, Y. Hasumi, Y. Nishiyama, K. Uchida, and H. Yamaguchi, "Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital," *Microbiology and Immunology*, vol. 53, no. 1, pp. 41–44, 2009.

[260] A. Chowdhary, A. Prakash, C. Sharma et al., "A multicentre study of antifungal susceptibility patterns among 350 Candida auris isolates (2009-17) in India: role of the ERG11 and FKS1 genes in azole and echinocandin resistance," *ournal of Antimicrobial Chemotherapy*, vol. 73, no. 4, pp. 891–899, 2018.

[261] D. Romera, J. J. Aguilera-Correa, I. Gadea, L. Viñuela-Sandoval, J. García-Rodríguez, and J. Esteban, "Candida auris: a comparison between planktonic and biofilm susceptibility to antifungal drugs," *Journal of Medical Microbiology*, vol. 68, no. 9, pp. 1353–1358, 2019.

[262] S. Kilburn, G. Innes, M. Quinn et al., "Antifungal resistance trends of Candida auris clinical isolates in New York and New Jersey from 2016 to 2020," *Antimicrobial Agents and Chemotherapy*, vol. 66, p. e02242-21, 2022.

[263] A. L. Bidaud, F. Botterel, A. Chowdhary, and E. Dannaouia, "In vitro antifungal combination of flucytosine with amphotericin B, voriconazole, or micafungin against Candida auris shows no antagonism," *Antimicrobial Agents and Chemotherapy*, vol. 65, no. 7, p. e02712-20, 2019.

[264] B. O'Brien, J. Liang, S. Chaturvedi, J. L. Jacobs, and V. Chaturvedi, "Pan-resistant Candida auris : New York subcluster susceptible to antifungal combinations," *The Lancet Microbe*, vol. 1, no. 5, pp. e193–e194, 2020.

[265] S. Jaggavarapu, E. M. Burd, and D. S. Weiss, "Micafungin and amphotericin B synergy against Candida auris," *The Lancet Microbe*, vol. 1, no. 8, pp. e314–e315, 2020.

[266] L. Sherry, G. Ramage, R. Kean et al., "Biofilm-forming capability of highly virulent, multidrug-resistant Candida auris," *Emerging Infectious Diseases*, vol. 23, no. 2, pp. 328–331, 2017.

[267] F. Nagy, Z. Tóth, L. Daróczi et al., "Farnesol increases the activity of echinocandins against Candida auris biofilms," *Medical Mycology*, vol. 58, no. 3, pp. 404–407, 2020.

[268] F. Nagy, E. Vitális, Á. Jakab et al., "In vitro and in vivo effect of exogenous farnesol exposure against Candida auris," *Frontiers in Microbiology*, vol. 11, 2020.

[269] N. P. Wiederhold, L. K. Najvar, R. Bocanegra, W. R. Kirkpatrick, T. C. Sorrell, and T. F. Pattersona, "Limited activity of miltefosine in murine models of cryptococcal meningoencephalitis and disseminated cryptococcosis," *Antimicrobial Agents and Chemotherapy*, vol. 57, no. 2, pp. 745–750, 2013.

[270] M. D. M. Castro, M. A. Gomez, A. E. Kip et al., "Pharmacokinetics of miltefosine in children and adults with Cutaneous leishmaniasis," *Antimicrobial Agents and Chemotherapy*, vol. 61, no. 3, 2017.

[271] Y. Wu, M. Totten, W. Memon, C. Ying, and S. X. Zhang, "In VitroAntifungal susceptibility of the emerging Multidrug-Resistant pathogen candida auris to miltefosine alone and in combination with amphotericin B," *Antimicrobial Agents and Chemotherapy*, vol. 64, no. 2, 2020.

[272] T. L. Barreto, L. Rossato, A. L. D. de Freitas et al., "Miltefosine as an alternative strategy in the treatment of the emerging fungus Candida auris," *International Journal of Antimicrobial Agents*, vol. 56, no. 2, p. 106049, 2020.

[273] F. Chaabane, A. Graf, L. Jequier, and A. T. Coste, "Review on antifungal resistance mechanisms in the emerging pathogen Candida auris," *Frontiers in Microbiology*, vol. 10, p. 2788, 2019.

[274] A. Chakrabarti and P. Sood, "On the emergence, spread and resistance of Candida auris: host, pathogen and environmental tipping points," *Journal of Medical Microbiology*, vol. 70, no. 3, 2021.

[275] C. Jiang, D. Dong, B. Yu et al., "Mechanisms of azole resistance in 52 clinical isolates of Candida tropicalis in China," *Journal of Antimicrobial Chemotherapy*, vol. 68, no. 4, pp. 778–785, 2013.

[276] L. Jin, Z. Cao, Q. Wang et al., "MDR1 overexpression combined with ERG11 mutations induce high-level fluconazole resistance in Candida tropicalis clinical isolates," *BMC Infectious Diseases*, vol. 18, no. 1, p. 162, 2018.

[277] D. L. Zuza-Alves, W. P. Silva-Rocha, and G. M. Chaves, "An update on Candida tropicalis based on basic and clinical approaches," *Frontiers in Microbiology*, vol. 8, 2017.

[278] D. Wang, N. An, Y. Yang, X. Yang, Y. Fan, and J. Feng, "Candida tropicalis distribution and drug resistance is correlated with ERG11 and UPC2 expression," *Antimicrobial Resistance & Infection Control*, vol. 10, no. 1, p. 54, 2021.

[279] M. J. Choi, E. J. Won, J. H. Shin et al., "Resistance mechanisms and clinical features of fluconazole-nonsusceptible Candida tropicalis isolates compared with fluconazole-less-susceptible isolates," *Antimicrobial Agents and Chemotherapy*, vol. 60, no. 6, pp. 3653–3661, 2016.

[280] F. C. Bizerra, C. V. Nakamura, C. de Poersch et al., "Characteristics of biofilm formation by Candida tropicalis and

antifungal resistance," *FEMS Yeast Research*, vol. 8, no. 3, pp. 442–450, 2008.

[281] J. Eddouzi, J. E. Parker, L. A. Vale-Silva et al., "Molecular mechanisms of drug resistance in clinical Candida species isolated from Tunisian hospitals," *Antimicrobial Agents and Chemotherapy*, vol. 57, no. 7, pp. 3182–3193, 2013.

[282] M. Desnos-Ollivier, S. Bretagne, D. Raoux, D. Hoinard, F. Dromer, and E. Dannaoui, "Mutations in the fks 1 gene in Candida albicans, C. tropicalis, and C. krusei correlate with elevated caspofungin MICs uncovered in AM3 medium using the method of the European Committee on Antibiotic Susceptibility testing," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 9, pp. 3092–3098, 2008.

[283] Y. N. Chen, H. J. Lo, C. C. Wu, H. C. Ko, T. P. Chang, and Y. L. Yang, "Loss of heterozygosity of FCY2 leading to the development of flucytosine resistance in Candida tropicalis," *Antimicrobial Agents and Chemotherapy*, vol. 55, no. 6, pp. 2506–2514, 2011.

[284] S. Perea, J. L. López-Ribot, B. L. Wickes et al., "Molecular mechanisms of fluconazole resistance in Candida dubliniensis isolates from human immunodeficiency virus-infected patients with oropharyngeal candidiasis," *Antimicrobial Agents and Chemotherapy*, vol. 46, no. 6, pp. 1695–1703, 2002.

[285] G. P. Moran, D. Sanglard, S. M. Donnelly, D. B. Shanley, D. J. Sullivan, and D. C. Coleman, "Identification and expression of multidrug transporters responsible for fluconazole resistance in Candida dubliniensis," *Antimicrobial Agents and Chemotherapy*, vol. 42, no. 7, pp. 1819–1830, 1998.

[286] G. Moran, D. Sullivan, J. Morschhäuser, and D. Coleman, "The Candida dubliniensis CdCDR1 gene is not essential for fluconazole resistance," *Antimicrob. Agents Chemother*, vol. 46, no. 9, pp. 2829–2841, 2002.

[287] E. Pinjon, G. P. Moran, C. J. Jackson et al., "Molecular mechanisms of itraconazole resistance in Candida dubliniensis," *Antimicrob. Agents Chemother*, vol. 47, no. 8, pp. 2424–2437, 2003.

[288] B. A. McManus, G. P. Moran, J. A. Higgins, D. J. Sullivan, and D. C. Coleman, "A Ser29Leu substitution in the cytosine deaminase Fca1p is responsible for clade-specific flucytosine resistance inCandida dubliniensis," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 11, pp. 4678–4685, 2009.

[289] M. Asadzadeh, S. Ahmad, N. Al-Sweih, and Z. Khan, "Population structure and molecular genetic characterization of 5-flucytosine-susceptible and -resistant clinical Candida dubliniensis isolates from Kuwait," *PLoS One*, vol. 12, no. 4, p. e0175269, 2017.

[290] D. Sears and B. S. Schwartz, "Candida auris : An emerging multidrug-resistant pathogen," *International Journal of Infectious Diseases*, vol. 63, pp. 95–98, 2017.

[291] R. Kean and G. Ramage, "Combined antifungal resistance and biofilm tolerance: the global threat of Candida auris," *mSphere*, vol. 4, no. 4, 2019.

[292] A. D. Chybowska, D. S. Childers, and R. A. Farrer, "Nine things genomics can tell us about Candida auris," *Frontiers in Genetics*, vol. 11, 2020.

[293] X. Hou, A. Lee, C. Jiménez-Ortigosa, M. Kordalewska, D. S. Perlin, and Y. Zhao, "Rapid detection of ERG11-associated azole resistance and FKS-associated echinocandin resistance in Candida auris," *Antimicrobial Agents and Chemotherapy*, vol. 60, no. 11, pp. 6532–6539, 2019.

[294] H. Carolus, S. Pierson, J. F. Muñoz et al., "Genome-wide analysis of experimentally evolved candida auris reveals multiple novel mechanisms of multidrug resistance," *MBio*, vol. 12, no. 2, 2021.

[295] J. M. Rybak, J. F. Muñoz, K. S. Barker et al., "Mutations inTAC1B: a novel genetic determinant of clinical fluconazole resistance in Candida auris," *MBio*, vol. 11, no. 3, 2020.

[296] S. Bhattacharya, T. Holowka, E. P. Orner, and B. C. Fries, "Gene Duplication Associated with Increased Fluconazole Tolerance in Candida auris cells of Advanced Generational Age," *Scientific Reports*, vol. 9, no. 1, p. 5052, 2019.

[297] J. Bing, T. Hu, Q. Zheng, J. F. Muñoz, C. A. Cuomo, and G. Huang, "Experimental evolution identifies adaptive aneuploidy as a mechanism of fluconazole resistance in candida auris," *Antimicrobial Agents and Chemotherapy*, vol. 65, no. 1, p. e01466-20, 2020.

[298] H. T. Taff, J. E. Nett, R. Zarnowski et al., "A Candida biofilm-induced pathway for matrix glucan delivery: implications for drug resistance," *PLoS Pathogens*, vol. 8, no. 8, p. e1002848, 2012.

[299] E. G. Dominguez, R. Zarnowski, H. L. Choy et al., "Conserved role for biofilm matrix polysaccharides inCandida aurisDrug resistance," *mSphere*, vol. 4, no. 1, 2019.

[300] V. Lara-Aguilar, C. Rueda, I. García-Barbazán et al., "Adaptation of the emerging pathogenic yeastCandida auristo high caspofungin concentrations correlates with cell wall changes," *Virulence*, vol. 12, no. 1, pp. 1400–1417, 2021.

[301] E. L. Berkow and S. R. Lockhart, "Activity of CD101, a long-acting echinocandin, against clinical isolates of Candida auris," *Diagnostic Microbiology and Infectious Disease*, vol. 90, no. 3, pp. 196-197, 2018.

[302] W. Alfouzan, S. Ahmad, R. Dhar et al., "Molecular epidemiology of candida auris outbreak in a major secondary-care hospital in Kuwait," *Journal of Fungi*, vol. 6, no. 4, p. 307, 2020.

[303] L. Reslan, G. F. Araj, M. Finianos et al., "Molecular characterization of Candida auris isolates at a major tertiary care center in Lebanon," *Frontiers in Microbiology*, vol. 12, pp. 1–8, 2022.

[304] J. Rhodes, A. Abdolrasouli, R. A. Farrer et al., "Genomic epidemiology of the UK outbreak of the emerging human fungal pathogen Candida auris article," *Emerging Microbes & Infections*, vol. 7, no. 1, pp. 1–12, 2018.

[305] M. Gosecka and M. Gosecki, "Antimicrobial polymer-based hydrogels for the intravaginal therapies—engineering considerations," *Pharmaceutics*, vol. 13, no. 9, p. 1393, 2021.

[306] A. Katragkou, M. McCarthy, E. L. Alexander et al., "In vitro interactions between farnesol and fluconazole, amphotericin b or micafungin against candida albicans biofilms," *Journal of Antimicrobial Chemotherapy*, vol. 70, no. 2, pp. 470–478, 2015.

[307] R. Kovács and L. Majoros, "Fungal quorum-sensing molecules: a review of their antifungal effect against Candida biofilms," *Journal of Fungi*, vol. 6, no. 3, p. 99, 2020.

[308] R. A. Cordeiro, C. E. C. Teixeira, R. S. N. Brilhante et al., "Minimum inhibitory concentrations of amphotericin B, azoles and caspofungin against Candida species are reduced by farnesol," *Medical Mycology*, vol. 51, no. 1, pp. 53–59, 2013.

[309] M. E. Fernández-Rivero, J. L. Del Pozo, A. Valentín, A. M. de Diego, J. Pemán, and E. Cantón, "Activity of amphotericin B and anidulafungin combined with rifampicin,

clarithromycin, ethylenediaminetetraacetic acid, N-acetylcysteine, and farnesol against Candida tropicalis biofilms," *Journal of Fungi*, vol. 3, no. 1, p. 16, 2017.

[310] C. F. Bezerra, J. G. de Alencar Júnior, R. de Lima Honorato et al., "Antifungal activity of farnesol incorporated in liposomes and associated with fluconazole," *Chemistry and Physics of Lipids*, vol. 233, p. 104987, 2020.

[311] D. J. Sullivan, G. P. Moran, E. Pinjon et al., "Comparison of the epidemiology, drug resistance mechanisms, and virulence of Candida dubliniensis and Candida albicans," *FEMS Yeast Research*, vol. 4, no. 4-5, pp. 369–376, 2004.

[312] S. Borecká, E. Pinjon, D. J. Sullivan et al., "Cdr2p contributes to fluconazole resistance inCandida dubliniensisclinical isolates," *Canadian Journal of Microbiology*, vol. 57, no. 5, pp. 416–426, 2011.

[313] S. Jawhara and D. Poulain, "Saccharomyces boulardii decreases inflammation and intestinal colonization by Candida albicans in a mouse model of chemically-induced colitis," *Medical Mycology*, vol. 45, no. 8, pp. 691–700, 2007.

[314] A. Murzyn, A. Krasowska, P. Stefanowicz, D. Dziadkowiec, and M. Łukaszewicz, "Capric acid secreted by S. boulardii inhibits C. albicans filamentous growth, adhesion and biofilm formation," *PLoS One*, vol. 5, no. 8, p. e12050, 2010.

[315] E. Pericolini, E. Gabrielli, N. Ballet et al., "Therapeutic activity of a Saccharomyces cerevisiae-based probiotic and inactivated whole yeast on vaginal candidiasis," *Virulence*, vol. 8, no. 1, pp. 74–90, 2017.

[316] L. Kunyeit, K. A. Anu-Appaiah, and R. P. Rao, "Application of probiotic yeasts on candida species associated infection," *Journal of Fungi*, vol. 6, no. 4, p. 189, 2020.

[317] F. Pereira Gonzales and T. Maisch, "Photodynamic inactivation for controlling Candida albicans infections," *Fungal Biology*, vol. 116, no. 1, pp. 1–10, 2012.

[318] C. F. Vecchi, R. Said dos Santos, J. Bassi da Silva et al., "Development and in vitro evaluation of buccal mucoadhesive films for photodynamic inactivation of Candida albicans," *Photodiagnosis and Photodynamic Therapy*, vol. 32, p. 101957, 2020.

[319] C. Rodríguez-Cerdeira, E. Martínez-Herrera, G. Fabbrocini et al., "New applications of photodynamic therapy in the management of candidiasis," *Journal of Fungi*, vol. 7, no. 12, pp. 1–28, 2021.

[320] J. C. Carmello, F. Alves, E. G. de Oliveira Mima, J. H. Jorge, V. S. Bagnato, and A. C. Pavarina, "Photoinactivation of single and mixed biofilms of Candida albicans and non- albicans Candida species using Photodithazine," *Photodiagnosis and Photodynamic Therapy*, vol. 17, pp. 194–199, 2017.

[321] P. V. Sanitá, A. C. Pavarina, L. N. Dovigo, A. P. D. Ribeiro, M. C. Andrade, and E. G. D. O. Mima, "Curcumin-mediated anti-microbial photodynamic therapy against Candida dubliniensis biofilms," *Lasers in Medical Science*, vol. 33, no. 4, pp. 709–717, 2018.

[322] P. S. Bapat and C. J. Nobile, "Photodynamic therapy is effective against Candida auris biofilms," *Frontiers in Cellular and Infection Microbiology*, vol. 11, 2021.

[323] N. A. Chow, J. F. Muñoz, L. Gade et al., "Tracing the evolutionary history and global expansion of candida auris using population genomic analyses," *MBio*, vol. 11, no. 2, 2020.