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Exploring the Biology, Virulence, and General Aspects of *Candida dubliniensis*

Manuela Gómez-Gaviria, Dario A Baruch-Martínez, Héctor M Mora-Montes

Departamento de Biología, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Guanajuato, Gto, Mexico

Correspondence: Héctor M Mora-Montes, Departamento de Biología, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Campus Guanajuato, Noria Alta s/n, col. Noria Alta, Guanajuato, Gto, C.P. 36050, Mexico, Tel +52 473-7320006 ext 8193, Fax +52 473-7320006 ext 8153, Email hmora@ugto.mx

Abstract: Fungal infections have become a growing public health concern, aggravated by the emergence of new pathogenic species and increasing resistance to antifungal drugs. The most common candidiasis is caused by *Candida albicans*; however, *Candida dubliniensis* has become an emerging opportunistic pathogen, and although less prevalent, it can cause superficial and systemic infections, especially in immunocompromised individuals. This yeast can colonize the oral cavity, skin, and other tissues, and has been associated with oral infections in patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), making it difficult to treat. The special interest in the study of this species lies in its ability to evade commonly used antifungal drugs, such as fluconazole, under different concentrations. In addition, it is difficult to identify because it can be confused with the species *C. albicans*, which could interfere with adequate treatment. Although the study of virulence factors in *C. dubliniensis* is limited, proteomic comparisons with *C. albicans* indicate that these virulence factors could be similar between the two species. However, differences could exist considering the evolutionary processes and lifestyle of each species. In this study, a detailed review of the current literature on *C. dubliniensis* was conducted, considering aspects such as biology, possible virulence factors, immune response, pathogen–host interaction, diagnosis, and treatment.

Keywords: candidiasis, emerging pathogens, host–fungus interaction, non-*albicans* species, virulence factors

Introduction

In recent years, infections caused by fungi have gained increasing attention, especially in susceptible hosts, owing to their increasing incidence.[1,2] Among these infections, those caused by *Candida* are among the most frequent, and are associated with high morbidity and mortality rates in immunocompromised patients.[2–4]

Candida is a fungal genus that groups approximately 200 species, of which only a few are opportunistic human pathogens that cause life-threatening infections.[5,6] About 80% of infections caused by *Candida* species are attributed to *Candida albicans*; however, infections by non-*albicans* species have increased in recent years. The most common species were *Candida glabrata*, *Candida tropicalis*, *Candida metapsilosis*, *Candida parapsilosis*, *Candida orthopsilosis*, *Candida lusitaniae*, *Candida krusei*, and *Candida dubliniensis*.[7–14] The infections caused by these species, named candidiasis, range from superficial skin and mucosal conditions, such as oral and vaginal candidiasis, to life-threatening candidemia, which affects internal organs.[5,15,16] Systemic infections are of particular concern because the fungus can spread to different organs through the bloodstream, causing organ failure and death. Common risk factors for invasive candidiasis include surgery, burns, prolonged hospital stay, and prior administration of drugs such as antibiotics and immunosuppressive agents.[5,17,18]

Candida dubliniensis is a dimorphic yeast, first described in 1995 in the oral cavity of human immunodeficiency virus (HIV)-infected individuals.[19,20] Although less well known than *C. albicans, C. dubliniensis* has gained importance in the past decade because of its ability to cause similar infections, especially in immunocompromised individuals.[21] Although it is less prevalent and virulent than *C. albicans, C. dubliniensis* can cause superficial infections, such as oropharyngeal candidiasis, and severe systemic infections, such as candidemia.[22,23] Its diagnosis can be complicated by phenotypic

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similarities to *C. albicans*, which can delay appropriate treatment. In addition, although it generally presents less intrinsic resistance to antifungals, resistant strains have been identified, particularly to azoles, which creates challenges in its clinical management.[22,24] Its virulence factors include biofilm formation and the production of hydrolytic enzymes, which allow it to colonize tissues and evade the immune system. Therefore, the identification and study of the pathogen are essential to improve therapeutic strategies in opportunistic fungal infections.[23] Since many aspects of *C. dubliniensis* remain unclear, we offer a comprehensive literature review that will be helpful in the study of this pathogen.

Biological Aspects

General Aspects

Candida dubliniensis is found worldwide and is closely associated with *C. albicans*.[25–27] Determination of the epidemiology of this species is possible only using identification methods that are 100% accurate, easy to perform, and cost-effective.[28] It is likely that *C. dubliniensis* has been misidentified because of its similarity to *C. albicans*.[27,28]

This yeast has fermentation and sugar assimilation profiles similar to those of *C. albicans. Candida dubliniensis* can ferment glucose, maltose, and trehalose; however, it cannot ferment xylose or cellobiose, which could help to differentiate it from *C. albicans*.[19,28,29] When xylose discs were used, all *C. albicans* strains grew after 72 h of incubation; however, *C. dubliniensis* strains failed to grow even after prolonged incubation.[28]

Candida dubliniensis can assimilate glucose, galactose, maltose, trehalose, and sucrose. However, unlike *C. albicans*, it cannot assimilate inositol.[19] Another distinctive feature of *C. dubliniensis* is its inability to express β-glucosidase, an enzyme important for the metabolism of some sugars.[19] In addition, assays have shown that some *C. dubliniensis* isolates are more susceptible to high salt concentrations and temperatures than *C. albicans*, which are easily adapted to stressful events.[28]

Morphology

Candida dubliniensis is a dimorphic yeast, which makes its identification in the laboratory challenging. The yeast phase is characterized by the presence of oval cells reproducing by budding, with a size of 4–7 µm (Figure 1A), and can form pseudohyphae and true hyphae, contributing to its invasiveness.[19,28] *Candida dubliniensis*, much like *C. albicans*, can form chlamydoconidia, which are thick spherical structures that appear under stress conditions and are less common in other species of the same genus.[19] Chlamydoconidia can be observed on specific media such as rice agar and tobacco agar, and are useful for identification.[28] This species can grow on different rich media, such as HiCrome Candida agar and CHROMagar, where colonies varying from light to dark green shades are observed over the incubation period.[28,30] On Sabouraud dextrose agar, it grows as round convex cream colonies (Figure 1B), and as cream–white colonies on potato dextrose agar (PDA).[19,20] On RAT agar or cornmeal–Tween 80 agar, pseudohyphae and some true hyphae with

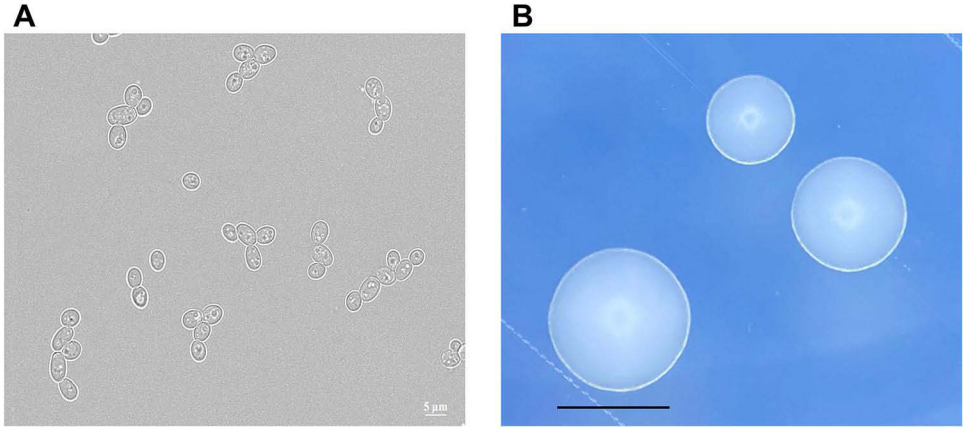

Figure 1 *Candida dubliniensis* yeast cells and colony morphology. (**A**) Yeast cells were grown at 28°C in Sabouraud medium, with the typical oval or round cells. Scale bar 5 µm. (**B**) *Candida dubliniensis* colony grown on a Sabouraud plate. Scale bar 4.0 mm.

unilateral, bilateral, or multilateral branching at the septa were formed. Chlamydoconidia formation occurs in triplets or pairs that are terminally attached by single suspension cells to extensively branched pseudohyphae. Importantly, this species grows well in the temperature range of 28–37°C, but not at 42°C.[19,20]

Cell Wall

The cell wall is known to play an essential role in the structure of yeast. Currently, a detailed model of the *C. albicans* cell wall is available, but information on this structure is scarce for other species, such as *C. dubliniensis*.

Cell wall components, such as mannans and mannoproteins, are responsible for immunological effects during host interaction and are potent inducers of humoral and cellular immunity.[31,32] Mannans, along with glucans, chitin, and proteins, are the wall components with major proportions in this structure. The first studies, based on the chemical composition, methylation analysis, and nuclear magnetic resonance (NMR) spectroscopy, showed that *C. dubliniensis* *N*-linked mannan has a highly branched structure with a backbone composed of α-1,6-linked mannose residues, 83% branched at O-2 by single mannose residues, and oligosaccharide side chains, which are common characteristics of *Candida* spp. *N*-linked mannans. However, differences in the length of the side chains, their frequency, and β-linked mannose content have been reported.[31,32] In addition, NMR spectra of the oligosaccharides showed that they consisted mostly of α-1,2- and α-1,3-mannose residues.[31] In addition, differences in cell surface hydrophobicity (CSH)-related proteins between *C. albicans* and *C. dubliniensis* have been reported, which may account for their differences in virulence.[22,33] Some surface mannoproteins, such as the hydrophobic surface glycoprotein CAgp38, are involved in the CSH status of *C. albicans*.[22,33] A comparison between *C. albicans* and *C. dubliniensis* cell wall proteins showed that the acid-labile phospho-oligomannoside of *N*-linked mannans was expressed at lower levels in *C. dubliniensis*.[22,33] In addition, most oligomannosides were less than five mannose residues in length. Three *C. dubliniensis* strains were used in this comparative study, all of which varied in their acid-labile phospho-oligomannoside profiles, leading to the conclusion that *C. dubliniensis* *N*-linked mannans differed from those of *C. albicans* (Figure 2).[22,33]

To date, information related to the composition and structure of the cell wall of *C. dubliniensis* is limited, and further studies are required to expand our understanding of the biology of this organism.

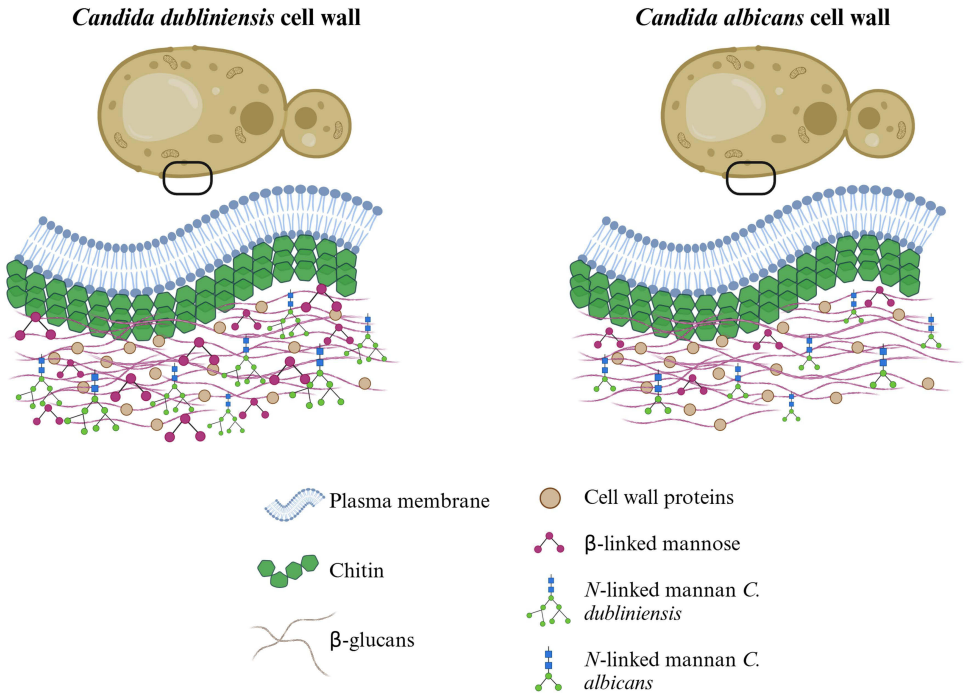

Figure 2 Comparison between the *Candida dubliniensis* and *Candida albicans* cell walls. The *C. dubliniensis* cell wall contains a higher percentage of β-linked mannose and a highly branched *N*-linked mannan structure compared to *C. albicans*. Created with BioRender. Gómez, M (2024) https://BioRender.com/u43s285.

Genome

Candida dubliniensis is the closest species to *C. albicans*, and although the two share many characteristics, *C. dubliniensis* is a less virulent and versatile pathogen.[34] In 2004, *C. albicans* and *C. dubliniensis* were analyzed by comparative genomic hybridization, and 168 genes were found to be species specific.[34,35] A comparative analysis obtained from rapid sequencing showed that the *C. dubliniensis* genome is 14.6 megabases (Mb) in size. However, it has a complex karyotype, comprising 10 haploid and three diploid chromosomes.[34,36] Chromosomal translocations have occurred since the separation of these two species, indicating that homologous chromosomes may occupy two genomic positions.[34] For example, one of the changes found is that chromosome 5 in *C. albicans* corresponds to part of chromosome VIII in *C. dubliniensis*, along with a part of chromosome R. Another difference is that the sequences corresponding to chromosome 5 in *C. albicans* are found on chromosomes I and IV in *C. dubliniensis*.[34] In addition, the *C. dubliniensis* genome is less polymorphic than that of other *Candida* species, with a single-nucleotide polymorphism frequency ranging from 635 bp (chromosome 6) to 12,555 bp (chromosome 1). The latter rate is similar to that observed in *C. parapsilosis* (15,553 bp).[34] The *C. dubliniensis* genome contains 6093 genes, of which 5859 encode proteins, and 6% of these identified genes contain at least one intron.[34] Furthermore, this genome has a GC content of 33%. Despite the karyotypic differences between *C. albicans* and *C. dubliniensis*, the order and composition of their genes are very similar. Conservation of the genome structure has been observed, which is understood to be a complex repeat region, such as subtelomeres and major repeat sequences (MRSs).[34,37] MRSs are a unique feature of *C. albicans* and *C. dubliniensis* genes, and could contribute to karyotypic variation between the two by acting as hotspots for chromosomal translocations. In *C. dubliniensis*, every chromosome has at least one MRS element, except for chromosome R and conserved HOK and RB2 regions.[34,38]

There are several inversions (fragment lengths between 8.5 and 185 kbp), insertion–deletions, and transposition events between the *C. dubliniensis* and *C. albicans* genomes that alter the gene order. These differences are thought to affect the genes known to play important roles in the pathogenesis of *Candida*.[34] Among these, the *SAP* family is responsible for the proteolysis of host components under different conditions and is among the most important virulence factors of *C. albicans*.[39] *Candida dubliniensis* lacks *SAP4* and *SAP5* loci, and one of the two SAP genes in *C. dubliniensis* is an ortholog of *SAP1* in *C. albicans*, while the other is similar for *SAP4* and *SAP6*, so there is no homolog of *C. albicans SAP5*.[34] It is likely that the two segmental inversions modified a pair of genes in tandem.[34] Similar to these changes in the *SAP* gene family, the *IFF* gene family, specifically the hypha-associated *HYR1* gene, does not appear to be present in *C. dubliniensis*.[34] Gene deletion is another trait of the *C. dubliniensis* genome. Genome analysis showed that this species has 115 pseudogenes, of which 78 have positional orthologs in *C. albicans*.[34] Another major difference in the genomic repertoire of *C. dubliniensis* is the expansion of the *TLO* family, which is associated with transcription factors, and the *IFA* family, which has transmembrane functions, representing new candidate virulence-associated factors.[34]

Analysis of the *C. dubliniensis* genome suggests that its evolutionary history differs from that of *C. albicans*. Both species are thought to have lost a common ancestor 20 million years ago, and although genes important in pathogenesis have been maintained in *C. albicans, C. dubliniensis* has lost its key pathogenic functions. This may explain why *C. albicans* is a more potent human pathogen than *C. dubliniensis*.[40]

Candida dubliniensis belongs to the CTG clade, and members of this group encode the CUG codon, which normally contains leucine as a serine residue.[41] This species is thought to have parasexual mating; most diploid species undergo this type of cycle, mating between diploid cells of the opposite type, followed by chromosome loss and reversion to the diploid state.[42] Currently, *C. dubliniensis MTL*a/α, *MTL*a/a, and *MTL*α/α strains have been identified, with higher proportions of a/a and α/α isolates.[43,44] It has also been demonstrated that opaque *C. albicans* and *C. dubliniensis* mate in vitro. However, there is no evidence of interspecific mating occurring naturally.[43]

Virulence Factors

Although *C. albicans* and *C. dubliniensis* share similar phenotypic characteristics, several studies have suggested that *C. dubliniensis* is less virulent than *C. albicans*.[21,40,45] The best-described virulence factors are adhesins, genes involved in biofilm formation, dimorphism, immune evasion, thermotolerance, and phospholipases and proteinases.

Adhesins

Adhesion is a key virulence factor that is involved in many biological processes. *Candida* has cell wall glycoproteins known as adhesins, which allow the organism to invade host tissues and abiotic surfaces.[46] One of the families involved in this process is the agglutinin-like sequence (*ALS*) family, which has been described as a virulence factor in *C. albicans*.[47] Southern blot analysis with *ALS*-specific probes identified this gene family in *C. dubliniensis*. However, northern blotting analysis showed that the mechanisms controlling *ALS* gene expression in *C. dubliniensis* and C. *albicans* are different.[47] Western blotting with anti-Als antibodies revealed that the cross-reacting proteins are bound by β-1,6-glucan in the *C. dubliniensis* cell wall. This may indicate that the cell wall organization is similar and that there is highly conserved processing of Als proteins in *C. albicans* and *C. dubliniensis*.[47] Phylogenetic analysis of the *ALS* genes of *C. albicans*, *C. tropicalis*, and *C. dubliniensis* revealed that, within each species, there is sequence diversification, which has allowed this family to have unique sequences.[47] Further analysis showed that *ALS3* was completely absent at its corresponding locus on the R chromosome in *C. dubliniensis*. Furthermore, *ALS1*, *ALS2*, *ALS4*, *ALS5*, *ALS6*, *ALS7*, and *ALS9* possess orthologous sequences in the *C. dubliniensis* genome.[34]

As adhesion is one of the key factors for virulence, several authors have suggested that there may be differences in the adhesin profiles of *C. albicans* and *C. dubliniensis*. It appears that *C. dubliniensis*, through an evolutionary process, may have gradually lost genes that are still present in *C. albicans*, such as *ALS3*.[34,40] This protein plays an important role in host cell attachment and hyphal formation, and has been shown to exhibit invasive effects and iron-sequestering activity.[21,48,49] Bioinformatics analysis revealed that all Als reported in *C. albicans* had putative orthologs in *C. dubliniensis* (Table 1). However, the taq loci of *ALS1* and *ALS3* were the same (Table 1); therefore, it is likely that

Table 1 Prediction of Some Important Virulence Factors in *Candida dubliniensis*

Virulence Factor	*Candida albicans* Protein	*Candida dubliniensis* Protein*	E-Value**	Similarity (%)**	References
Adhesins	Als1, Als3	CD36_64210	0	84	[34, 40, 46, 47]
	Als2, Als4	CD36_65010	6e-153	78	[34, 50]
	Als7	CD36_86150	4e-25	71	[34, 50]
	Als5	CD36_86290	0	94	[34, 50]
	Eap1	CD36_23630	1e-62	84	[51, 52]
	Ecm33	CD36_02990	0	90	[46]
	Iff4	CD36_25710	0	68	[50]
	Int1	CD36_52250	0	90	[46]
	Mp65	CD36_24090	0	94	[46]
	Phr1	CD36_44230	0	96	[46]
Biofilms	Bcr1	CD36_31890	0	76	[53]
	Brg1	CD36_04890	0	89	[51, 52]
	Efg1	CD36_33560	0	80	[52]
	Hsp90	CD36_71850	0	99	[51]
	Ndt80	CD36_25160	0	89	[51]
	Rob1	CD36_12600	0	72	[51, 52]
	Csr1	CD36_63460	0	96	[51]

(*Continued*)

Table 1 (Continued).

Virulence Factor	*Candida albicans* Protein	*Candida dubliniensis* Protein*	E-Value**	Similarity (%)**	References
Dimorphism	Cph1	CD36_06880	0	91	[21, 45, 54]
	Hgc1	CD36_00690	0	89	[21, 45, 54]
	Nrg1	CD36_73890	2e-151	84	[21, 45, 54]
	Tup1	CD36_00070	0	92	[21, 45, 54]
Immune evasion	Hgt1	CD36_01840	0	99	[12]
	Msb2	CD36_16640	0	83	[12]
	Pra1	CD36_46450	0	93	[12]
Phospholipases and proteinases	Lip5, Lip8	CD36_72520	0	94	[55]
	Lip6	CD36_09040	0	98	[56]
	Lip7	CD36_34600	0	93	[56]
	Sap2	CD36_33460	0	95	[55]
	Sap5, Sap6	Not found	–	–	[57]
	Plb1	CD36_62110	3e-142	96	[56]
	Plb2	CD36_62120	0	94	[56]
	Plb3	CD36_34860	0	97	[56]
	Plb5	CD36_07760	0	96	[56]
Thermotolerance	Hsp60	CD36_31990	0	99	[58–60]
	Hsp104	CD36_33850	0	99	[58–60]
	Ssa1	CD36_04050	0	99	[58–60]

Notes: *Protein nomenclature corresponds to accession codes of the National Center for Biotechnology Information database (https://www.ncbi.nlm.nih.gov/). The putative protein sequence encoded by the *C. albicans* gene was subjected to a standard protein BLAST analysis at https://www.ncbi.nlm.nih.gov/. **Comparing the encoded protein of *C. dubliniensis* with the putative ortholog in *C. albicans*. The best hit is reported in the *C. dubliniensis* protein column, and this was scored with the lowest E value. The similarity column refers to the comparison of amino acid sequences from the *C. albicans* encoded protein and the best hit.

C. dubliniensis ALS has homology with the two sequences reported for *C. albicans*. It has also been shown that some *C. dubliniensis ALS* are expressed at high levels, whereas others are barely transcribed.[50]

Bioinformatic analysis revealed that other *C. albicans* adhesin-encoding genes, such as *EAP1*, *ECM33*, *IFF4*, *INT1*, *MP65*, and *PHR1*, could have putative orthologs in *C. dubliniensis* (Table 1). This indicates that cell adhesion may also be mediated by these adhesins.

Biofilm Formation

Candida dubliniensis is the causative agent of oropharyngeal candidiasis in patients with HIV or AIDS. To colonize the oral epithelium, yeast cells must adhere to the host cells or prosthetic materials within the oral cavity.[33,51] This initial attachment is followed by proliferation and biofilm formation. Biofilm development has also been described as a virulence factor of great importance, considering that biofilm formation has certain clinical implications, including resistance to antifungal agents.[51,52,61] Although *C. dubliniensis* can grow at 37°C and produce biofilms under certain conditions, its growth rate has been reported to be lower than that of *C. albicans*.[51,62] In mixed cultures, *C. albicans* outcompeted *C. dubliniensis*, suggesting that *C. albicans* has competitive growth advantages under the tested conditions.[62] Using a semi-quantitative colorimetric method based on XTT (sodium 3′-[1-(phenylaminocarbonyl)-3,

4-tetrazolium]-bis (4-methoxy 6-nitro) benzene sulfonic acid hydrate) reduction, different stages of biofilm formation were observed. The presence of serum or salivary films, typical of the oral environment, provides binding sites that enhance the initial adherence of *C. dubliniensis* to biomaterials and facilitates biofilm formation.[51] On the other hand, scanning electron microscopy showed that mature *C. dubliniensis* biofilms consist of a mixture of yeast and filamentous forms embedded within the exopolymeric material. Furthermore, *C. dubliniensis* biofilms have been described to exhibit structural heterogeneity, showing a microcolony/water channel architecture similar to that described for bacteria.[63] This structure facilitated nutrient influx, waste product removal, and microniche establishment throughout the biofilm.[51,64] *Candida dubliniensis* biofilms are resistant to fluconazole, a drug commonly used to treat fungal infections.[51] In a study on *C. albicans* and *C. dubliniensis*, the influence of chemical signaling molecules on the morphogenesis of both species during planktonic and biofilm growth was investigated.[53] Supernatants from both species were analyzed by solid-phase microextraction and gas chromatography–mass spectrometry, and were found to contain isoamyl alcohol, 2-phenylethanol, 1-dodecanol, E-nerolidol, and E,E-farnesol.[53] These alcohols, the secretion of which varies according to species, culture mode, and growth time, inhibit the morphological transition from yeast to filamentous form by up to 50%. Indeed, these molecules act as active extracellular signals in *C. albicans* and *C. dubliniensis* morphogenesis, albeit with some specific differences between the species and culture conditions.[53] Biofilm production provides *C. dubliniensis* with a significant ecological advantage, allowing it to maintain its niche as a commensal human pathogen. This ability facilitates evasion of host immune mechanisms, resistance to antifungal treatments, and improved resistance to competition from other oral microorganisms. In addition, fungal biofilms can act as safe reservoirs for cell release into the oral environment. Thus, biofilm formation by *C. dubliniensis* is a key factor for its survival and adaptation to colonization of the oral cavity, with important clinical implications.[51,52] Based on bioinformatic analysis, it is possible to predict that *C. dubliniensis* has seven genes involved in biofilm formation (Table 1). However, further research is required to understand the functions of these genes in *C. dubliniensis*.

Dimorphism

Biofilm formation is closely related to dimorphism, which has been proposed to be an important virulence factor.[19] *Candida dubliniensis* produces germ tubes and hyphae. However, hyphal production differs from that in *C. albicans* and depends on the culture conditions used.[55,65] Histopathological analysis of infected kidneys in a mouse model of systemic infection showed that *C. dubliniensis* cells remained longer in the yeast phase, whereas *C. albicans* strains produced larger numbers of hyphae and pseudohyphae.[58,66] These results suggest a marked difference in the regulation and dynamics of hyphal induction between the two species.[66] It is known that, although *C. dubliniensis* is capable of producing germ tubes and true hyphae, it does so less efficiently than *C. albicans*, both in vivo and in vitro.[45,54] Hyphal induction assays using different media showed that none of the *C. dubliniensis* strains formed hyphae in the presence of GlcNAc, indicating that this organism may have a mutation in the pathway that controls hyphal induction in response to this monosaccharide.[65,67] *Candida dubliniensis* penetrates host tissues such as *C. albicans*, and may be primarily associated with superficial infections of the oral mucosa. This hypothesis was validated when oral isolates of *C. dubliniensis* showed increased adherence to buccal epithelial cells compared with *C. albicans*.[65,67] Subsequent work used the reconstituted human epithelial model of surface infection to assess the invasive potential of *C. dubliniensis*. This species grows exclusively in yeast morphology; therefore, invasion and tissue damage are relatively limited.[45,68] Concerning genes involved in fungal dimorphism, *C. albicans* showed higher expression of *CPH1*, *HGC1*, *NRG1*, and *TUP1*, whereas *C. dubliniensis* had a less robust transcriptional response.[21] Based on bioinformatic analysis, *C. dubliniensis* may have all the genes involved in dimorphism (Table 1); however, the process controlling dimorphism is likely to be regulated differently in this species than in *C. albicans*.

Phospholipases and Proteinases

The production of a variety of extracellular hydrolases, such as secreted aspartyl proteinases (Saps) and phospholipases (Lip and Plb), is implicated in *Candida* cell attachment and tissue invasion during infection.[55] Furthermore, a correlation between proteolytic activity and the virulence of different *Candida* strains has been reported.[55,65] Southern hybridization analyses have shown that *C. dubliniensis* encodes a variety of genes similar to those of the *C. albicans SAP* family.[66,69]

When phospholipase production was analyzed in both species, *C. dubliniensis* was found to produce lower levels of phospholipase than those reported for *C. albicans*.[55] Previous work has shown that *C. dubliniensis* expresses *SAP* orthologs, but not *SAP5* and *SAP6*.[57] Bioinformatics analysis using the Blastp tool confirmed this observation, as no functional orthologs were found for either protein (Table 1). It is thought that the absence of *SAP5* could negatively affect the ability to invade host tissues because this enzyme is involved in the degradation of E-cadherin.[57] It has also been reported that most *C. dubliniensis* isolates lack phospholipase activity.[56] The bioinformatics search indicated that *C. dubliniensis* has putative orthologs for different phospholipases (PLBs and LIPs) found in *C. albicans* (Table 1). However, there is no information on the functions of these genes in *C. dubliniensis*.

Immune Evasion and Thermotolerance

Other virulence factors, such as immune evasion and thermotolerance, play important roles in pathogenic fungi.[70] Thermotolerance contributes to colonization within host tissues, fungal dimorphism, and growth, and is involved in adaptation to stressful environments.[12,13] The bioinformatic analysis indicated that the *C. dubliniensis* genome contains putative orthologs of genes involved in thermotolerance, including *HSP60*, *HSP104*, and *SSA1* (Table 1). However, several reports indicate that *C. dubliniensis* is less tolerant to environmental stress conditions, such as temperatures above 42°C, osmotic pressure, and oxidative stress.[58–60] In the case of immune evasion, this process involves the mechanisms already mentioned, such as biofilm formation, morphological changes, and protease secretion.[12] The *C. albicans HGT1*, *MSB2*, and *PRA1* genes involved in immune evasion were also found in *C. dubliniensis* (Table 1). However, information regarding their possible functions in this organism is lacking.

The identification of virulence factors in *Candida* species is challenging because most *Candida* species are opportunistic pathogens that, under normal conditions, coexist with the host as part of the commensal microbiota, and only cause infections when there are immune system deficiencies.[21] Comparative virulence between *C. albicans* and *C. dubliniensis* is a complex issue and, although differences in virulence factors between the two species have been identified, there is also conflicting information that needs to be clarified through experimentation.

Although *C. dubliniensis* has genomic similarities with *C. albicans* and appears to have the virulence factors described for this species (Table 1), the differences in virulence may be related to the evolutionary processes of the two species. *Candida albicans* has evolved a more virulent phenotype, possibly because of its ability to exploit a wider range of niches in the human host and its ability to cause infections in different tissues.[71,72] This species has a greater ability to form biofilms, produce hydrolytic enzymes, and adapt to different physiological environments, giving it a competitive advantage in colonization and tissue invasion.[72] On the other hand, *C. dubliniensis*, although similar to *C. albicans* in many respects, appears to have evolved with lower virulence, which could be an adaptation to maintain a more commensal relationship with the host. This lower virulence may reduce the aggressive immune response of the host, allowing *C. dubliniensis* to persist in the oral environment and other niches with less selective pressure to develop highly virulent mechanisms.[20]

Candida dubliniensis–Host Interaction

To understand the clinical importance of different *Candida* species, it is essential to understand how they interact with the host immune cells.[10] Among the different species of the *Candida* genus, the interaction with host immunity that has been best described and studied is that with *C. albicans*. Although it has been reported that there are variations within each species, the recognition processes are similar, being mediated by pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs).[73,74] In addition, innate and adaptive immune responses play important roles in the control of these pathogens.[73,75,76]

A previous study compared the colonization and dissemination of *C. dubliniensis* and *C. albicans* in infant mice inoculated with both species in the gastrointestinal tract.[45] After 10 days, no *C. dubliniensis* was observed compared to *C. albicans*. The latter was isolated from the stomach, liver, and kidneys, thereby demonstrating the ability of this species to disseminate.[45] These results could be associated with the reduced ability of *C. dubliniensis* to form hyphae and retain a yeast-like morphology on the epithelial surfaces.[45]

When *C. dubliniensis* and *C. albicans* were incubated with the murine macrophage cell line RAW264.7, both species began to be phagocytosed after 1 h of interaction but, after 3 h, *C. albicans* began to form hyphae protruding from the macrophage. In contrast, *C. dubliniensis* was unable to form hyphae or exit phagolysosomes.[54] After 16 h, *C. dubliniensis* proliferation was significantly reduced compared with that in the growth controls.[54]

Both *C. albicans* and *C. dubliniensis* release chemotactic factors for neutrophils; however, the latter induces the migration of a higher number of neutrophils than *C. albicans*.[77] In terms of phagocytosis, after 40 min of incubation with human neutrophils, 70% of *C. dubliniensis* cells were phagocytosed, contrasting with the 20% of *C. albicans* cells. These differences are thought to be related to the cell wall components, especially β-glucans, and their expression in both species.[77] Moreover, a poor ability of *C. dubliniensis* to induce neutrophil extracellular traps (NETs) has been reported.[77] However, when myeloperoxidase (MPO) and reactive oxygen species (ROS) production was analyzed, they were found to be higher in *C. dubliniensis* than in *C. albicans*. Although these events (MPO and ROS) are related to NET formation, they are more frequently observed in neutrophils interacting with *C. albicans*.[77,78] This suggests that MPO and ROS production are not the determining factors for NET formation. However, it is thought that this may be related to the poor ability of *C. dubliniensis* to escape from phagocytes, which does not imply an NETosis event, compared with *C. albicans*, which forms hyphae and escapes from phagocytes.[77,79] Furthermore, cytokine stimulation was evaluated in both species. Interleukin-8 (IL-8) production was significantly higher after co-incubation with *C. dubliniensis* than with *C. albicans*.[77] Other inflammatory and regulatory cytokines and chemokines, such as granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-1α, IL-1β, IL-1ra, IL-10, IL-16, serine protease inhibitor-1, and tumor necrosis factor-α (TNF-α), were poorly induced by *C. dubliniensis*.[77] The hypothesis put forward to explain these differences places PRRs as the factors that cause differential induction of cytokines and chemokines by *C. albicans* and *C. dubliniensis*.[77]

Candidiasis Caused by *Candida dubliniensis*

Candida dubliniensis is a globally distributed species that is found in healthy individuals. However, it is most commonly recovered from the oral cavity of individuals infected with HIV and AIDS.[19,80] This organism has been isolated from patients in widespread geographical locations, and several studies are available on the incidence and clinical manifestations of infections caused by this fungus.[24,81–86]

In a 1997 study in Ireland, *C. dubliniensis* was recovered from the oral cavity of 27% of HIV-infected individuals and 32% of AIDS patients who had symptoms of oral candidiasis. It was also found in asymptomatic patients with HIV and AIDS, in 19% and 25%, respectively.[80,87] This fungus has also been isolated from healthy Irish individuals and recovered from five out of 150 samples.[87]

The occurrence rate of this pathogen was 14.6% in denture wearers.[20,67] In diseases such as diabetes, cystic fibrosis, and cancer, there is a high prevalence of *C. dubliniensis*, with percentages of 3.6–18.23%, 11.1%, and 2–4.64%, respectively. Furthermore, in patients with vulvovaginal candidiasis and candidemia, the percentage of occurrence was 0.17–2.43% and 0.5–7.95%, respectively.[80] In another study, *C. dubliniensis* was the sole species recovered from two patients with AIDS.[87,88] These findings indicate that *C. dubliniensis* can cause infections independent of other *Candida* species, at least in HIV-infected individuals and AIDS patients.[20] Erythematous candidiasis is another common clinical manifestation in these patients.[20,89]

Over the years, this pathogen has been related to recurrent oral infections in immunocompromised individuals; however, some studies have suggested that this condition does not necessarily have a positive result for *C. dubliniensis*.[80,90] Another study, conducted in 2003 in a South African population, showed that out of 253 HIV-positive black individuals, 66 healthy black individuals, 22 HIV-positive white individuals, and 55 healthy white individuals, the prevalence of *C. dubliniensis* was highest in healthy white individuals (at 16%), followed by HIV-positive white individuals (at 9%).[90] In addition, in black individuals, the prevalence in HIV-positive individuals was 1.5%, and 0% in healthy individuals.[90] In China, 3181 clinical samples from patients with vulvovaginal candidiasis were analyzed to evaluate the presence of *C. dubliniensis*, *C. albicans*, and *C. africana*. These results did not demonstrate the presence of *C. dubliniensis*, indicating a low incidence at this anatomical site.[91]

At the Kuwait University dental clinic, 370 patients seeking dental treatment were tested for the presence of different *Candida* species. The samples were obtained through oral rinses and, after analysis using different methods, it was shown that, out of the 370 samples, 160 showed *Candida* in culture. The prevalence was higher in patients with diabetes, in those with asthma, and in smokers than in healthy individuals. The presence of *C. dubliniensis* in these samples was 14.3%, with *C. albicans* being higher, at 63.7%.[92] The prevalence of *Candida dubliniensis* was higher in male patients who were smokers and were under some form of medical treatment.[92] In Baltimore, USA, at the University of Maryland Medical System, isolates were recovered from 88 patients with blood cultures positive for yeast and six hospitalized patients with fungemia at the same time.[93] *Candida albicans* was isolated from 35 samples, whereas *C. dubliniensis* was recovered from six samples, including two from patients with fatal outcomes.[93] This study demonstrated that *C. dubliniensis* causes lethal bloodstream infections.

Moreover, rare cases of *C. dubliniensis* infection have been reported. In 2016, a 75-year-old man with laryngeal cancer undergoing chemotherapy and receiving broad-spectrum antibiotics was diagnosed with pneumonia following an invasive *C. dubliniensis* infection of the lungs.[85] Cases of meningitis caused by *C. dubliniensis* have been reported. A 49-year-old patient with a history of hepatitis C virus-related cirrhosis, exposure to broad-spectrum antibiotic therapy, and a substance use disorder was diagnosed with invasive candidiasis caused by *C. dubliniensis*.[86] This patient was treated with liposomal amphotericin B and flucytosine but died shortly afterward. In line with this case, a 27-year-old woman with chronic fungal meningitis, a history of intravenous heroin use, and hepatitis C was diagnosed with *C. dubliniensis* infection.[24] Unlike the patient mentioned above, this patient was successfully treated with a combination of liposomal amphotericin B and fluconazole for 6 weeks.[24]

Candida dubliniensis fungemia has been reported in organ transplant recipients, in addition to several case reports of exogenous endophthalmitis. Common factors in the occurrence of endophthalmitis include the use of recreational intravenous drugs and infection with the hepatitis C virus.[81–84]

Candida dubliniensis Identification and Diagnosis

The identification of different *Candida* species is important in the clinical setting, considering that candidiasis and candidemia have increased in recent years, especially in immunocompromised patients.[94,95] The accurate identification of *C. dubliniensis* is complicated by the fact that it is impossible to distinguish between the colonies and morphology of *C. albicans* and *C. dubliniensis* on conventional media.[20,67] However, some strategies have been used to identify and diagnose *C. dubliniensis* using molecular, microbiological, and biochemical methods (Table 2).

Table 2 Methods Available in the Diagnosis and Identification of *Candida dubliniensis*

Conventional Media	Observations
HiCrome *Candida* agar	After 72 h, the colony color varies from light green to dark green
Tobacco agar	Rough, yellowish-brown colonies, hyphal fringes and chlamydospores after 48 h
Sunflower seed agar	Fringed and rough colonies and chlamydospore production
Rice–Tween agar	Contiguous pairs and triplets of chlamydospores
Plant and seed extracts media	Mycelial and chlamydospore formation
Sabouraud agar	Creamy white colonies
Potato dextrose agar (PDA)	Creamy white colonies
CHROMagar *Candida*	Dark green colonies
Candida ID2 agar	Turquoise blue colonies
Candi Select 4 agar	Dark green colonies

(*Continued*)

Table 2 (Continued).

Biochemical methods	**Observations**
API 20C AUX, ID32C, and Vitek YBC	It has been shown that *C. dubliniensis* and *C. albicans* can be differentiated by these methods. *C. dubliniensis* cannot express β-glucosidase activity
Xylose assimilation (XYL) and methyl-αD-glucoside (MDG) assimilation tests	
Immunological and physicochemical tests	**Observations**
Immunochromatographic test	Monoclonal antibodies specific for *C. albicans* and *C. dubliniensis*, 93–100% specificity
Latex agglutination	12F7-F2 monoclonal antibodies, sensitivity of 97% and specificity and 100%
Mass and infrared spectroscopy	These techniques have contributed to different profiles in polar lipid composition, acid esters, and ergosterol concentration
Gas or liquid chromatography	
Nuclear magnetic resonance (NMR)	
Molecular strategies	**Observations**
Pulsed-field gel electrophoresis (PFGE)	These molecular techniques have been reported to confirm that the genomic organization of *C. dubliniensis* is different from that of *C. albicans*, and therefore identification by these techniques is more accurate
Restriction fragment length polymorphism (RFLP)	
Randomly amplified polymorphic DNA (RAPD)	
Amplified fragment length polymorphism (AFLP)	
Microsatellite sequencing	
V3 variable region	Comparative analyses of the large and small ribosomal RNA (rRNA) genes are also a way to distinguish *C. dubliniensis* from other species. *C. dubliniensis* consists of three main clades of isolates, groups I, II, and III, and four separate genotypes
Cd25 fingerprinting	
ITS regions of the rRNA	
Multilocus sequence typing	
PCR fingerprinting	

Microbiological Methods

When *C. dubliniensis* strains are grown at 37°C on HiCrome *Candida* agar, light green colonies can be observed after 24–48 h. However, the colonies are similar to *C. albicans*; the only way to see a noticeable difference is to leave them for 72 h, as the colony color varies from light green to dark green for *C. dubliniensis* and light blue for *C. albicans*.[22,28,87] In tobacco agar, *C. dubliniensis* forms rough yellowish-brown colonies and produces hyphal fringes and chlamydoconidia after 48 h, whereas *C. albicans* does not do so during any incubation period. Despite this difference, only 60% of the *C. dubliniensis* strains tested showed these characteristics.[28,96,97] On sunflower seed agar, fringed and rough colonies and chlamydoconidia were observed.[96] *Candida dubliniensis* strains grown on rice–Tween agar at 30°C for 48 h formed contiguous pairs and triplets of chlamydoconidia, in contrast to *C. albicans*, which showed single chlamydoconidia.[19,98] Although this criterion could help to differentiate between species, other authors have indicated that it is not sufficiently sensitive to be used as an identification test.[99,100] *Candida dubliniensis* on media containing plant and seed extracts, such as niger (Staib agar and caffeic acid–ferric citrate agar), sesame seeds, rosemary and oregano extracts, and tomato juice, showed that mycelial and chlamydoconidia formation could be species-specific markers that can be used to identify *C. dubliniensis*.[80,96,101–107]

Candida dubliniensis isolates grow well at temperatures between 30 and 37°C on commonly used culture media. For example, when grown on Sabouraud agar or potato dextrose agar, colonies are characterized by a creamy white color, similar to those formed by *C. albicans*.[19] However, *C. dubliniensis* isolates often show phenotypic changes, which can be

observed as small colonies that appear after a prolonged incubation period.[19,20] One trait by which *C. dubliniensis* differs from *C. albicans* is its limited growth at temperatures between 42 and 45°C. Therefore, thermotolerance has been proposed as a simple and reproducible method for identifying *C. dubliniensis*.[19,108]

In CHROMagar *Candida* medium, dark green colonies can be observed for *C. dubliniensis*, which can be distinguished from *C. albicans* because they are light blue–green.[30,109] Other media, such as *Candida* ID2 agar and Candi Select 4, also allow *C. dubliniensis* identification; however, their accuracy is not 100%.[110–112] To distinguish between species, *C. albicans* colonies on *Candida* ID2 agar were stained cobalt blue, whereas *C. dubliniensis* isolates were stained turquoise blue.[110,111] On Candi Select 4 agar, *C. dubliniensis* colonies were characteristically dark green, whereas *C. albicans* colonies were pink.[112]

Biochemical Methods

Analysis of the profiles obtained using the API 20C AUX, ID32C, and Vitek YBC systems showed that *C. dubliniensis* and *C. albicans* could be differentiated using these methods. In addition, xylose and methyl-αD-glucoside assimilation tests were efficient in separating these species.[113–115] A notable difference between *C. albicans* and *C. dubliniensis* is that the latter cannot express β-glucosidase. This distinctive feature, initially identified by multi-locus enzyme electrophoresis, is the basis for a reliable assay to differentiate between the two species.[116] The Micronaut-*Candida* system correctly identified *C. dubliniensis* isolates.[117]

As microbiological and biochemical tests can yield false positives, immunological and physicochemical tests have also been used to differentiate *C. dubliniensis*.[118] The immunochromatographic test uses strips with two monoclonal antibodies specific for *C. albicans* and *C. dubliniensis*, is a rapid method, and provides 93–100% specificity. Latex agglutination using 12F7-F2 monoclonal antibodies helps to detect *C. dubliniensis* antigens with sensitivity and specificity of 97% and 100%, respectively.[119] Physicochemical identification methods such as mass and infrared spectroscopy, gas or liquid chromatography, and NMR imaging have been characterized by high resolution, accuracy, and sensitivity. Using these methods, it was possible to identify differences in the molecular compositions of *C. dubliniensis* and *C. albicans*. This contributed to the different profiles of the polar lipid composition, acid esters, and ergosterol concentrations between the two species.[120–123]

Molecular Methods

Molecular strategies have also been used to identify *C. dubliniensis*, including DNA fingerprinting methods, such as pulsed-field gel electrophoresis, restriction fragment length polymorphism, randomly amplified polymorphic DNA, amplified fragment length polymorphism, and microsatellite sequencing.[19] These molecular techniques have been reported to confirm that the genomic organization of *C. dubliniensis* is different from that of *C. albicans*; therefore, identification using these techniques is more accurate.[19,124] Comparative analyses of the large and small ribosomal RNA (rRNA) genes can also be used to distinguish *C. dubliniensis* from other species. Analysis of the 500 bp sequence of the V3 variable region of the *C. dubliniensis* large rRNA gene showed clear differences from *C. albicans*.[20] Cd25 fingerprinting, nucleotide sequence analysis of the internal transcribed spacer (ITS) regions of rRNA genes, multilocus sequence typing, and PCR fingerprinting have been used to determine that *C. dubliniensis* has less genotypic diversity and more clonality than *C. albicans*. These tools facilitate fungal identification.[80,125–128]

Sequence analysis of the introns and exons of *ACT1* and *PHR1* demonstrated that it was possible to identify *C. dubliniensis* and discriminate it from *C. albicans* isolates.[129,130] In addition, EcoRI digestion of *C. dubliniensis* isolates probed with the *C. albicans*-specific DNA fingerprint probe 27A showed fewer and fainter banding patterns than those of *C. albicans*.[20] Similarly, the digestion of *C. dubliniensis* genomic DNA with the restriction enzyme HinfI resulted in distinct restriction fragment length polymorphism patterns.[20]

Although several tools are available for the identification of *C. dubliniensis*, molecular tools appear to be the best option because of the specific markers that help to distinguish between species.

Treatment

The main antifungal drugs used to treat candidiasis are divided into four groups: azoles, including fluconazole, itraconazole, posaconazole, and voriconazole; polyenes, such as amphotericin B; echinocandins, such as caspofungin and micafungin; and the pyrimidine analog flucytosine.[131] These drugs are effective against various *Candida* spp. However, studies have shown that non-*albicans Candida* species can develop resistance to various classes of antifungal agents.[132]

Most clinical isolates of *C. dubliniensis* are susceptible to commonly used antifungal drugs, including fluconazole (Table 3), at an MIC range of 0.125–1.0 µg/mL.[133] However, oral isolates of *C. dubliniensis* obtained from AIDS patients previously treated with fluconazole have been reported to be resistant to fluconazole at an MIC range of 8–32 µg/mL.[133] In a study involving oropharyngeal isolates from HIV-infected patients, *C. dubliniensis* was shown to be resistant to fluconazole at different concentrations. Six isolates had an MIC ranging from 0.25 to 2.0 µg/mL and the other isolates ranged from 32 to 64 µg/mL. A common factor in this resistance is patients being immunocompromised owing to an underlying disease or having previously received fluconazole treatment.[134] In addition, the ability of *C. dubliniensis* to rapidly develop in vitro resistance to fluconazole has been reported.[20,133] This phenomenon is not easily observed in *C. albicans*, indicating that *C. dubliniensis* may be more responsible for the development of azole resistance than *C. albicans*.[134] In different fluconazole-resistant *C. dubliniensis* isolates, increased expression of multidrug resistance transporters such as *MDR1* has been observed in different fluconazole-resistant *C. dubliniensis* isolates.[22] These findings are in contrast to those reported in *C. albicans*, where overexpression of the ABC protein Cdr1 is associated with fluconazole resistance.[101,135]

The effects of itraconazole and ketoconazole, commonly used antifungals for mycoses caused by this species, have also been studied. MIC values for itraconazole and ketoconazole in clinical isolates of *C. dubliniensis* were higher than those of *C. albicans*. Clinical isolates of *C. dubliniensis* have been reported to be resistant to itraconazole and ketoconazole but susceptible to 5-flucytosine, amphotericin B, posaconazole, and voriconazole (Table 3).[22,109,136] It is thought that the ability of *C. dubliniensis* to develop resistance to fluconazole derivatives may be related to ecological adaptation mechanisms, which confer a selective advantage in patients undergoing prolonged fluconazole treatment. This could have significant therapeutic consequences, particularly in HIV-infected patients.[135]

Despite concerns regarding antifungal resistance in *C. dubliniensis*, reports of its treatment remain limited. The majority of the available literature is outdated, which creates a gap in the current knowledge about the most effective treatment options. The lack of recent studies makes it difficult to understand the evolution of resistance in this species and to optimize treatment strategies, especially in immunocompromised patients.

Table 3 Antifungals: Mechanism and Effectiveness Against *Candida dubliniensis*

Drug	Mechanism	Have Shown Effectiveness Against *C. dubliniensis*	Observations
Fluconazole	Inhibition of lanosterol 14 α-demethylase, essential in ergosterol biosynthesis	Yes	Resistant in AIDS and HIV patients previously treated with fluconazole
Itraconazole		No	Clinical isolates of *C. dubliniensis* have been reported to be resistant
Ketoconazole		No	
Voriconazole		Yes	Clinical isolates of *C. dubliniensis* have been reported to be susceptible
Posaconazole		Yes	
Amphotericin B	Binds to sterols in cell membranes, forming pores	Yes	
5-Flucytosine	Blocks DNA synthesis of the fungus	Yes	

Concluding Remarks

Research on candidiasis has increased in recent decades. However, most work has focused on understanding the biological, clinical, and epidemiological aspects of *C. albicans* and to a lesser extent on other species, such as *C. dubliniensis*, which also represent a health threat. *Candida dubliniensis* is a neglected pathogen because of its low frequency of isolation in hospitals. However, infections caused by this species can be life-threatening, especially in patients with HIV or AIDS. This species has proven resistant to first-line drugs, such as fluconazole, making it difficult to treat once an infection is established.

Although considerable progress has been made in understanding the biology and pathogenicity of *C. dubliniensis*, there are remaining gaps in our knowledge that require further and updated research. Moreover, it is crucial to investigate the comparative evolution between *C. dubliniensis* and *C. albicans* to better understand differences in virulence and adaptation to host environments.

The information collected in this work highlights the lack of data on this species, which is an area of opportunity for the scientific and medical community. In addition, it is necessary to update the available information, as most of the studies were published decades ago and the current state of the art in medical mycology requires revisiting of several aspects of this fungal species. These studies will contribute to a more comprehensive understanding of the biology of *C. dubliniensis*, and may reveal new therapeutic and preventive alternatives to treat fungal infections, as well as new identification strategies that could have an impact on early diagnosis.

Author Contributions

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

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Disclosure

The authors declare no conflicts of interest.

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