Chapter

Perspective Chapter: Candida and Candidiasis - Recent Taxonomic Developments, Invasion Biology, and Novel Active Compounds

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Abstract

Candida spp. infections are most predominantly caused by *Candida albicans*, followed by *C. glabrata*, *C. parapsilosis* and *C. tropicalis*. *Candida* spp. can cause a wide range of serious infections. Recent studies indicate that this genus has approximately 200 species. Candidiasis is a fungal infection caused by *Candida* spp. Sexual reproduction gives eukaryotic organisms some advantages, such as producing adaptable fertility to changing environments and eliminating harmful mutations. Relationships between epithelial cells and *Candida* spp. include responses to medically important fungal pathogens. Infection by *C. albicans*, which has significantly high virulence due to its biofilm formation feature, is rather difficult to manage. Invasive candidiasis is a serious infection that can affect the blood, brain, eyes, bones, heart or other parts of the body. Understanding *C. albicans* invasion kinetics is crucial to controlling the pathogen's intrusion into the cells. New and effective antifungal compounds are needed due to the limited number and competence of antifungal agents. The search for natural compounds with anti-candidiasis effects continues increasingly.

Keywords: *Candida*, candidiasis, invasion, diversity, antifungal resistance, sexual reproduction

1. Introduction

1.1 *Candida* and Candidiasis

Candida spp. (a kind of fungus) are ubiquitous. Candidiasis is a fungal infection caused by *Candida* species, such as oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis, candidal gingivostomatitis, intestinal candidiasis, invasive candidiasis, disseminated candidiasis and bloodstream infections. The rate of death in hospitalised patient with bloodstream infections are one in four. *Candida* can live naturally on the surface of the skin, in the oral cavity, vagina and intestine without causing any trouble. *C. albicans* lives commensally on mucous membranes in healthy people and causes widespread candidiasis in the digestive system in vulnerable people [1, 2].

Candidemia is a *Candida* bloodstream infection, a familiar form of invasive candidiasis which is a severe infection that can affect many parts of the body such as the eyes, bones, blood and brain [3]. *Candida* infections also occur in immunocompetent patients, primarily affecting their nails, scalp and skin (onychomycosis) [4, 5].

Most *Candida* infections (around 80%) in people are caused by *C. albicans*, though infections caused by other *Candida* spp. are becoming more and more frequent [6]. It has been shown that *C. subhashii* isolated from peritonitis is genetically closely related to *C. tropicalis*, *C. albicans* and *C. dubliniensis* [7]. Although *C. albicans* infections can be easily treated, their nosocomial nature translates to a high mortality rate [8]. Pappas et al. reported that higher than 250,000 people are affected by invasive candidiasis each year [9, 10]. According to the studies conducted by Ferrer [11] and Farr et al., [12], vulvovaginal candidiasis caused by *C. albicans* is seen in 75% of women of reproductive age, 5% of which experience recurrent infections.

In a study conducted on different genotypic distributions of *C. albicans* strains in oral cancers, it was shown that *C. albicans* genotype-A had a significantly higher frequency of occurrence in patients with oral cancer. *C. albicans* was classified into four different genotypes in this study based on their PCR amplification products. *C. albicans* genotype-A contained 450 bp. Similarly, other types comprised genotype-B (840 bp), genotype-C (450 and 840 bp) and genotype-D (1080 bp). The results of this study showed that *Candida* spp. that settles in the mouth may play a role in the formation of oral cancer [13]. *Candida* infections still have high mortality rates [14]. The reports showed that multidrug-resistant *C. auris* causes healthcare-associated outbreaks with high mortality rate [15–17].

1.2 History and taxonomic hierarchy

The genus *Candida* was created by Dutch mycologist Christine Berkhout (according to her thesis published in 1923) with nine species, and then, the genus *Monilia* was added [18]. However, Berkhout's definition of the genus was not found to be sufficiently distinctive and decisive. Thus, it was later edited by Lodder and Kreger-van Rij. The generic name *Candida* is based on *Pseudomonilia albomarginata*, published by Arthur Geiger which is presently called *Candida mesenterica* [19]. Subcultures of the strain type were kept as CBS-602 as per the Dutch Centraalbureau Voor Schimmelcultures.

According to Barnet [18], presumably, Pseudomonilia (named in a publication in 1910) was the first genus used for budding, filamentous and asexual yeast. Then, Langeron and Talice [20] classified the yeast into eight genera. Subsequently, Kurtzman and Robnett divided the family Saccharomycetaceae into 11 well-structured clades [21]. Diezmann et al. [22] separated three major clades within Saccharomycetales in a well-structured manner. According to this, Clade 1 arises with node 29, clade 2 arises at node 16 and clade 3 arises at node 4. Clade 1 comprised six *Candida* spp. (*C. albicans*, *C. dubliniensis*, *C. maltosa*, *C. tropicalis*, *C. viswanathii* and *C. parapsilosis*) and Lodderomyces elongisporus. The current taxonomic hierarchy is as shown below:

Fungi, Dikarya, Ascomycota, Saccharomycotina, Saccharomycetes, Saccharomycetidae, Saccharomycetales, Debaryomycetaceae, *Candida*/Lodderomyces clade, *Candida*, *Candida albicans* [23].

1.3 Diversity

Approximately, a quarter of all yeast species belong to the genus *Candida* [24]. Recent studies indicate that this genus has approximately 200 species [25]. *Candida*

spp. is very common in different environments as its vegetative cells proliferate by budding or forming pseudo or septate hyphae [26]. Krohn et al. [27] detected large numbers of *C. albicans* and *C. glabrata* and lesser numbers of *C. guilliermondii*, *C. lusitaniae*, *C. tropicalis*, *C. kefyr*, *C. krusei* and *C. rugosa* in the duodenal fluid of patients with liver cirrhosis.

Barnett et al. [28] identified 12 new species of *Candida* (They were *C. aaseri*, *C. albicans*, *C. atlantica*, *C. haemulonii*, *C. intermedia*, *C. maris*, *C. zeylanoides*, *C. maritima*, *C. norvegica*, *C. sake*, *C. torresii* and *C. tropicalis*) from the marine environment. Li-J et al. [29] isolated and identified a new yeast species, *C. pseudorugosa* sp. nov., from the sputum of an acute pneumonia patient. According to the sequence analysis of the 26S rRNA gene D1/D2 domain and the internal transcribed spacer (ITS) region, the new species was closely like *C. rugosa*. Therefore, they proposed the name *C. pseudorugosa* sp. nov. for the new species. Wang et al. [26] added six more species (*C. intermedia*, *C. parapsilosis*, *C. quercitrusa*, *C. rugosa*, *C. zeylanoides* and *C. membranifaciens*) as marine yeast species.

C. auris was isolated and first identified from the external ear canal of an inpatient in a Japanese hospital by Satoh et al. [30]. Afterwards, Oh et al. [31] investigated 27 isolates including *C. haemulonii* group I and *C. pseudohaemulonii* by sequencing their ITS region and D1/D2 regions of the 26S ribosomal DNA from blood samples and ear canal swabs were taken from 23 patients. As a result of the study, they identified 15 of 27 isolates as *C. auris* obtained from ear specimens.

Infection of some *Candida* species such as *C. famata*, *C. kefyr*, *C. lusitaniae* and *C. zeylanoides* is sporadic in the bloodstream and other systemic infections. These species are considerable because they might have antifungal-resistant isolates that are occasionally discovered among them and it is possible that these isolates might be misidentified by commercial yeast identification systems. DNA sequencing or MALDI methods are reliable in identifying these potential antifungal-resistant isolates. Some of these species are frequently reported using teleomorph genus names such as *Wickerhamomyces canadensis* (*C. melinii*) and *Debaryomyces hansenii* (*C. famata*) (**Table 1**). Yeast or fungi may exist in both teleomorph (sexual stage) or anamorph (asexual stage) stages [32]**.** This confusing situation caused the species to be classified into different genera (**Table 1**). Good example is *Kluyveromyces lactis* (sexual state) and *Candida sphaerica* (asexual state) [33, 34].

1.4 Sexual reproduction

Sexual reproduction in eukaryotes can take many different forms. It has been reported that sexual reproduction may be essential for pathogenic fungi to create genetically diverse populations under extremely different environmental conditions [50]. Sexual reproduction gives eukaryotic organisms some advantages such as producing adaptable fertility to changing environments, eliminating harmful mutations, providing favourable genetic change and increasing genetic diversity [51, 52].

Tao et al. [53] reported that during mating, white cells (WHCs) and opaque cells (OPCs), separated from each other by their function and appearance, show organised function. Researchers reported that *C. albicans* may contain these cell types, WHCs and OPCs which are functionally and morphologically different. They studied three configurations of the mating-type locus in *C. albicans*. These are locus MTLa/α, locus a/and locus α/α. Most natural isolates have heterozygosis at the mating-type locus [54]. *C. albicans* may often change between two distinct cell types, WHC and OPC, [55]. Before mating, *C. albicans* must first be homozygous at the mating-type locus and then

Anamorph	Teleomorph	References
Candida vini	*Kregervanrija fluxuum*	[35]
Candida melinii	*Wickerhamomyces canadensis*	[24]
Debaryomyces hansenii var. hansenii	*Pichia kudriavzevii*	[36]
Candida famata var. famata	*Debaryomyces hansenii var. hansenii*	[37]
Candida famata var. flareri	*Debaryomyces hansenii var. flareri*	[38]
Candida globosa	*Citeromyces matritensis*	[39]
Candida guilliermondii	*Pichia guilliermondii*	[40]
Candida krusei	*Issatchenkia orientalis*	[41]
Candida lambica	*Pichia fermentans*	[42]
Candida lipolytica	*Yarrowia lipolytica*	[42]
Candida lusitaniae	*Clavispora lusitaniae*	[39]
Candida nitrativorans	*Pichia sydowiorum*	[42]
Candida opuntiae	*Clavispora opuntiae*	[42]
Candida pulcherrima	*Metschnikowia pulcherrima*	[22]
Candida sphaerica	*Kluyveromyces lactis* var. *lactis*	[42]
Candida valida	*Pichia membranifaciens*	[35]
Candida globosa	*Citeromyces matritensis*	[39]
Clavispora lusitaniae	*Clavispora lusitaniae*	[43]
Candida famata	*Debaryomyces hansenii*	[39, 44]
Candida. homilentoma	*Hyphopichia homilentoma*	[45]
Candida utilis	*Cyberlindnera jadinii*	[45]
Candida kunwiensis	*Metschnikowia kunwiensis*	[45]
Candida deformans	*Yarrowia yakushimensis*	[45, 46]
Candida lipophila	*Wickerhamiella lipophila*	[44]
Candida molischiana	*Kuraishia molischiana*	[44]
Candida pignaliae	*Ogataea pignaliae*	[47]
Candida Molischian	*Kuraishia Molischiana*	[48]
Candida bornbicola	*Starmerella bombicola*	[49]
Candida sphaerica	*Kluyveromyces lactis*	[43]

Table 1.
Some of Candida anamorph and teleomorph names according to the recent taxonomic developments.

switch from WHC to OPC type because only OPC can mate efficiently [56]. WHC represents the majority cell population in nature. However, minority OPCs are capable of matching. In sexual reproduction, WHC secretes sexual pheromones to stimulate both cell types (OPC and WHC). To initiate mating, the presence of opaque cells, WHCs release sexual pheromones and consequently creates favourable conditions for OPCs to mate with both sexes. These OPC and WHC connect through a pheromone signalling system. This coupling of WHC and OPC is thought to be the key to the fungus being an evolutionarily compatible and successful pathogen in the host [53].

1.5 Invasion biology

C. albicans normally exists as a commensal microorganism in human gastrointestinal and genital tracts. Fungi use the advantages of anisotropic growth, thus offering it advantages in terms of nutrient acquisition, movement capability and niche colonisation and mating [57, 58].

1.5.1 Candida albicans and epithelial cell interaction

Moyes et al. [59] reveal that the relation between the fungal pathogen (*Candida* spp.) and epithelial cells (EPCs) contains the key to host responses to fungi. According to previous general views, epithelial cells were thought of as a static barrier against invading fungi. There was a widespread belief that epithelial cells provided both an attachment for colonisation and a food source for invading fungi. However, in the light of recent studies, this view has changed significantly. It is now known that epithelial cells play a more active role in the differentiation of commensal and pathogen, immunity and damage mending. The interaction of *C. albicans* with epithelial cells proceeds as follows. (i) It attaches to epithelial cells of *C. albicans*, (ii) the fungus is recognised by EPCs, (iii) induction of endocytosis is initiated by the fungus, and (iv) *C. albicans* was taken into the cell and then initiates early apoptotic events. These events damage the epithelial cell. Thus, it is protected from phagocytosis. Endocytosis is induced by the interaction of *C. albicans* Als3 adhesive with E-cadherin in epithelial cells and with N-cadherin in endothelial cells [59].

In the light of recent research, the stages of *C. albicans* invasion are as follows: (1) A series of signalling circuits are initiated when *C. albicans* adheres to the EPCs, (2) certain morphological *Candida* species are recognised by the EPCs and endocytosis is initiated by the host cell, and 3) to escape from phagocytosis, early apoptotic events are initiated by *Candida* and this damages the EPCs. Early recognition events are important to reduce some of the damage at this early stage (**Figure 1**) [60, 61].

C. albicans is a dimorphic fungus that can be in yeast form or in the form of hyphae (germ tube, we mentioned as hyphae here). The first adhesion takes place through the yeast form. However, *C. albicans* can also be in the form of hyphae [62, 63]. It provides enhanced bonding, especially using surface portions expressed in the hyphal form. Thus, *C. albicans* hyphae adhere more strongly to ECs than to yeast cells [64, 65].

Early recognition events are important to alleviate some of the damage in this early step. The host-fungus interactions in EPCs have increased over time, and more research and information are needed in this regard. It is now known that EPCs are an important part of the host reaction mechanisms against fungal infections.

When *C. albicans* infected the host epithelial cells, the initial contact of the adherence including colonisation and invasion of fungal cells start. Many factors play a role in this process. In this step, cell-to-cell adherence occurs *via* epithelial receptors and *Candida* adhesins [66]. E-cadherin coexists with clathrin around hyphae endocytosed by epithelial cells [67]. Therefore, the fungus hyphae enter the epithelial cell.

The Als family, an adhesin family, has an important role in epithelial attachment. Als3 is a key hypha-specific protein. [61, 66]. Furthermore, Als3 is one of the *C. albicans* invasins, which can induce endocytosis. It attaches to host cell receptors such as E-cadherin and N-cadherin and stimulates the host cells to endocytose the organism [68]. In the first step, adhesins such as Als3p bind to their target cellular receptors

or covalently bind to the host cell surface. In the second step, *C. albicans* invasins interact with target host receptors and initiate the activation of these receptors. [59]. E-cadherin and actin microfilaments are proteins belonging to the septin family.

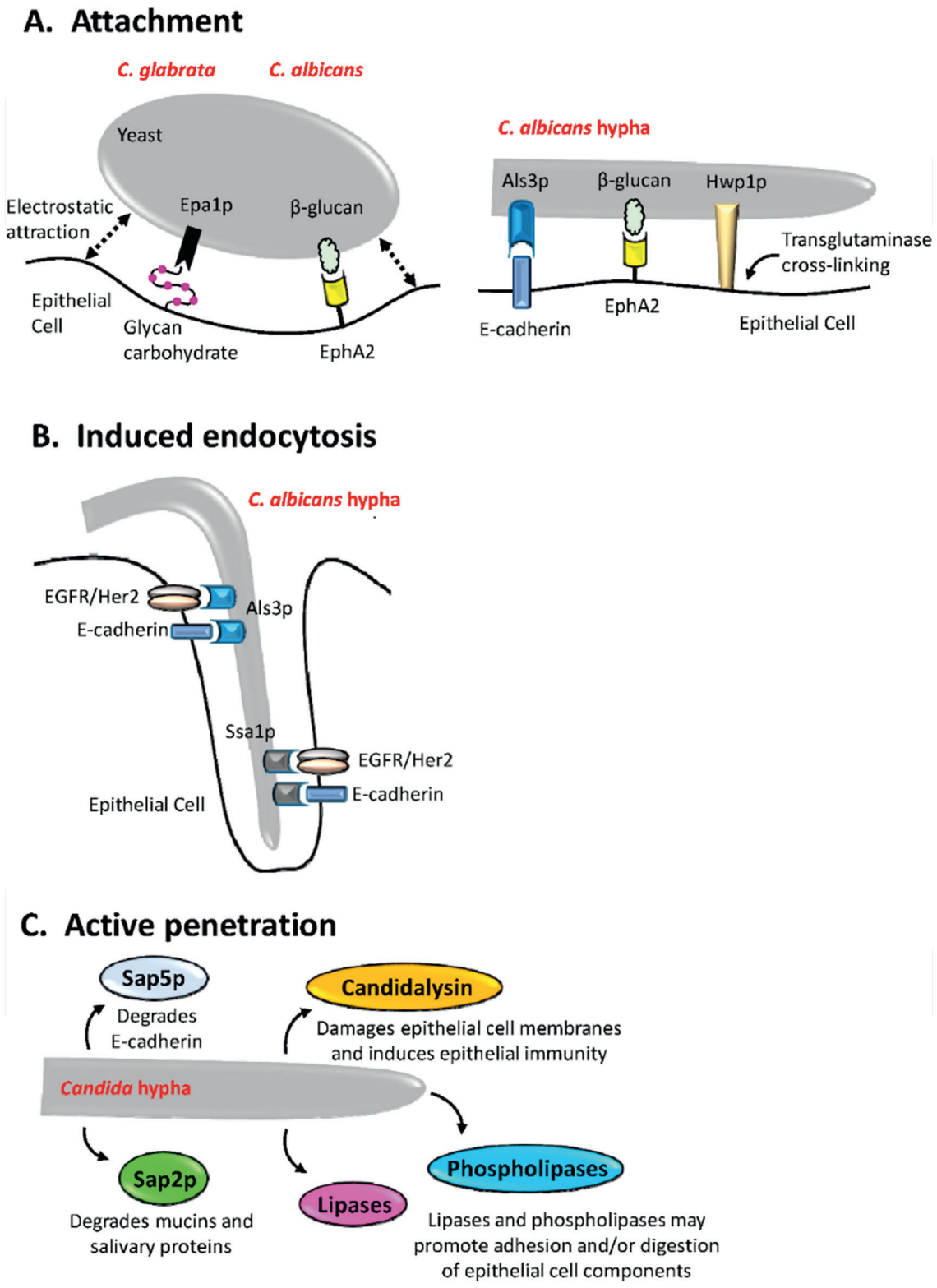

Figure 1.
Interactions of C. albicans *with host epithelial cells. (A)* C. albicans *binds to host epithelial cells in various ways via EphA2 and E-cadherin receptors or directly via transglutaminases. (B)* C. albicans *invasins interact with E-cadherin receptors to induce endocytosis. (C)* C. albicans *and some* Candida *species can reach mucosal tissues by secreting lipase, phospholipase, proteinases and secreted aspartic peptidases such as Sap2p and Sap5p. This figüre reproduced with permission of the authors [65].*

The septin family proteins are important as cytoskeletal elements for cell division in budding yeast. Septins play a key role in anchoring cell surface proteins of the specific regions of the cell membrane [69].

1.5.2 Candida albicans *and endothelial cell interaction*

C. albicans enter and invade endothelial cells by binding to N-(neural) cadherin (a transmembrane protein) and other cell surface receptors, acting as a mediator of cell–cell adhesion and affecting a range of biological activities (**Figure 2**) [71, 72]. Septin-7 is a filament-forming cytoskeletal GTPase and the septin family of proteins includes N-cadherin and actin microfilaments. Septins bind cell surface proteins to specific regions of the cell membrane in a particular way [71, 73].

Phan et al. [63, 70] investigated the accumulation of N-cadherin, SEPT7, and both N-cadherin and SEPT7 when yeast was added to endothelial cells. They showed that cells in the yeast phase germinated 30 minutes after adhering to the endothelium and were enveloped by SEPT7 after 60 minutes and they were surrounded by both SEPT7 and N-cadherin after 90 minutes. After this stage, endocytosis occurs in EPCs.

EPCs produce many cytokines such as GM-CSF, G-CSF, IL-1a, IL-1b and IL-6 in response to the presence of the fungus along with RANTES and IL-8. Today, the function of EPCs in terms of *C. albicans* is better understood. When *C. albicans* interact with EPCs, it turns into a dynamically reactive protector [59, 73]. It also produces antimicrobial peptides such as cathelicidin and b-defensins [74]. Adherence and recognition of *C. albicans* by EPCs result in cytoskeletal reorganisation. Neutrophils have great importance in epithelial anti-*Candida* defence. They release the secreting factors that stimulate EPCs preservation towards damage in a TLR4-dependent manner [75]. *Candida* can inactivate the antiapoptotic proteins in macrophages and neutrophils. Thus, it can cause apoptosis in EPCs. Furthermore, infection of EPCs by *C. albicans* causes premature initiation of apoptosis and then necrotic death [76, 77].

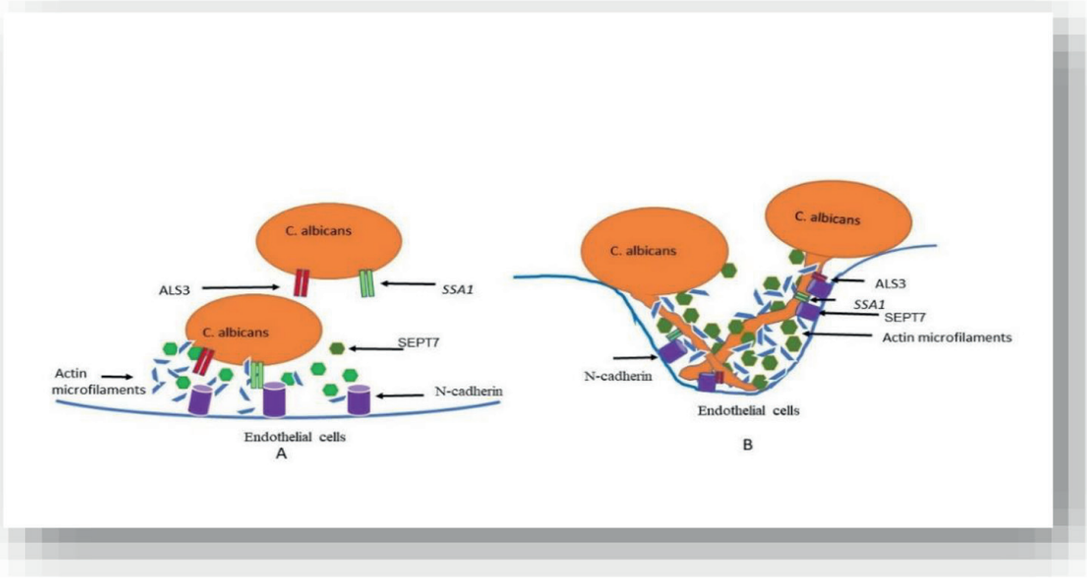

Figure 2.
Localization on the endothelial cell surface and endocytosis of C. albicans*. (A) Adhesion: At this stage, Als3 and Ssa1* C. albicans *proteins bind to endothelial cell-mediated N-cadherin. (B) Endothelial cell invasion: At this stage, SEPT7 and actin filaments gather around the hyphae.*

1.6 Antifungal resistance

C. albicans has very low levels of drug resistance; however, other types of *Candida*, such as *C. glabrata*, might be mostly resistant and more deadly. The most clinically important *Candida* spp. are *C. albicans*, *Candida parapsilosis* and *C. glabrata* [78].

There are various reports on fungal resistance mechanisms of several *Candida* spp. against fluconazole, itraconazole, voriconazole and several other azole drugs [79–81]. In a study, 27 mutations in the ERG11 gene were identified in azole-resistant *C. albicans* isolates. It is thought that these mutations may increase resistance to azole drugs and may be associated with the recurrence of vulvovaginal candidiasis [82].

Centers for Disease Control and Prevention reported that *Corynebacterium auris* is resistant to multiple antifungal drugs typically used to treat *Candida* infections, and identification of this species needs specific technology; therefore, standard laboratory methods are insufficient, and early identification and transmission prevention of *C. auris* for patients staying in the hospital is of great importance. Thus, it is possible to take precautions. Considering the above, it presents a dangerous global health threat. As a result of recent research, three classes of antifungals (azoles, echinocandins and amphotericin B) are found efficient against *Candida* spp. [17, 83].

Dagi et al. [84] tested 200 *Candida* strains isolated from bloodstream infections for drug resistance tests. The strains were *C. albicans*, *C. parapsilosis* complex and *C. glabrata* (47.5%, 14.0% and 18.0%, respectively). Except for *C. kefyr* strains, 11 *Candida* spp. were susceptible to amphotericin-B at an MIC value of 2 μg/mL. *C. glabrata* strains was resistant to fluconazole at MIC value ≥64 μg/mL. Others showed concentration-dependent susceptibility. The low MIC value of *C. pseudoaaseri* (0.016–1 μg/mL) against all types of antifungal drugs except flucytosine distinguished this species from *C. aaseri* with generally susceptible MICs between ≥0.008 and 0.5 μg/mL [7, 85]. *Candida auris* had a low MIC to echinocandin drugs (≤0.5 mg/L) and showed a close phylogenetic relationship to *C. haemulonii*; furthermore, resistance to azole, amphotericin B (AmB) and echinocandin had been reported in the species as well [7, 8].

In a recent study, Soliman et al. [86] investigated a green approach to control the proliferation of the 60-*Candida* species obtained from clinical samples. Tested *Candida* isolates were identified as *C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. krusei* and *C. glabrata*. *P. chrysogenum* was used as a biocatalyst for synthesising silver (Ag) nanoparticles. To do this, the metabolites of *P. chrysogenum* were used to reduce $AgNO_3$ to Ag-nanoparticles. The susceptibility test of *Candida* isolates to synthesise Ag-nanoparticles, fluconazole and amphotericin B was assessed. The 60 *Candida* isolates were found highly susceptible to Ag nanoparticles. Sensitivity to fluconazole and amphotericin B was 41.6% and 50.0%. This study shows very promise in eradicating *Candida* resistance.

Tan et al. [87] investigated how b-lactam antibiotics induce the spread of *C. albicans* in the gut. In their research, *C. albicans*, kept under pressure in the gastrointestinal tract of a healthy person, causes intensely released peptidoglycan production by autolysis of Gram (−) cells in the patients after treatment with b-lactam antibiotic and induces *C. albicans* hyphae production. They reported that the proliferation in hyphal cells causes penetration into mucosal barriers.

1.7 Identification and genetic structure of Candida

There are several methods using molecular technology for *Candida* spp. typing. These include the following methods: restriction fragment length polymorphism

analysis (RFLP), multilocus sequence typing (MLST), random amplified polymorphic DNA analysis (RAPD) and electrophoretic karyotyping [88, 89].

Studies for the correct identification of *Candida* spp., are ongoing. Arastehfar et al. [90] reported that they developed a precise, distinctive, saving cost and time, integrated and reliable test that can be incorporated into clinical laboratories without laborious DNA extraction steps. Using this method, they succeeded in distinguishing nine medically important complex species using a one-step multiplex PCR technique. The three cryptic *Candida* complex species found in samples were obtained from Iran (n = 135) and China (n = 145), which were *C. albicans* complex (*C. dubliniensis,* C. Africana*,* and *C. albicans*), *C. glabrata* complex (*C. bracarensis*, *C. nivariensis,* and *C. glabrata*) and C. parapsilosis complex (*C. metapsilosis*, *C. parapsilosis*, and *C. orthopsilosis*).

On the other hand, Al-Obaid et al. [91] examined 63 *C. tropicalis* strains identified by Vitek-2 and PCR isolated from different samples such as blood, respiratory tract, digestive tract and wound. They recorded 59 diploid-sequence-types (DST) with MLST. The study showed that most *C. tropicalis* isolates originated from diverse and unique strains. That is because they reported that 56 of the isolates from 48 patients were unique.

In MLST sequencing, various housekeeping genes (HKGs) of species responsible for infectious diseases are used to define DNA sequence polymorphisms between isolates. This technique has the advantage of providing information about the species' geographical origins and anatomical sources [92–93]. *Candida* spp. infections are most predominantly caused by *C. albicans*, followed by *C. glabrata*, *C. parapsilosis* and *C. tropicalis* [94].

Muñoz et al. [95] described the epidemiological profiles and the population structure of *C. albicans* by analysing the *C. albicans* MLST database. Therefore, they verified the general nature of *C. albicans* based on approximately 4300 database isolates with the inclusion of a group of DSTs from people. Some of them were exclusively healthy. The DST counts obtained from blood, oral and vaginal swabs were 32.4, 20.5 and 13.8, respectively. MLST was designed to allow the identification of unique DSTs based on nucleotide-polymorphisms in multiple HGKs. Selected HGK were those that encode ATP-dependent permease, aspartate aminotransferase, mannose phosphate isomerase, acetyl-CoA carboxylase and alanyl RNA synthetase [96]. They reported isolating the highest number of DSTs from blood (32.4%), oral swabs (20.5%) and vaginal swabs (13.8%). They described seven HGKs involved in the MSLT scheme with the highest genetic diversity.

1.8 Novel active compounds for candidiasis treatment

Its biofilm-forming ability makes it difficult to struggle and manage the highly virulent *C. albicans* infection. Therefore, studies for identifying effective novel compounds are ongoing. Some of the promising novel compounds reported during 2010–2020 are as follows. Nieminen et al. [97] reported the potent effects of D,L-2-hydroxyisocaproic acid on biofilm formation. They used XTT ((2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide) to measure biofilm metabolic activity and assessed the results using a biomass marker. Biofilms were monitored using scanning electron microscopy (SEM), and they recorded the formation of abnormal, collapsed hyphal structures on incubation with D,L-2-hydroxyisocaproic acid at acidic pH.

Wong et al. [98] reported a new antifungal molecule called SM21 with a very potent MIC (0.2–1.6 μg/mL) against *Candida* infections. This molecule was toxic to fungi and was effective against biofilms of *Candida* species. They also stated that SM21 was effective in reducing tongue lesions in rats in oral candidiasis and suggested that it may have potential as a new antifungal agent. Oh et al. [31] observed the isolates of *C. auris*, *C. haemulonii* and *C. pseudohaemulonii* in terms of creating plaques *in vitro* in glucose-containing Sabouraud dextrose broth and deduced that all *C. auris* isolates were biofilm-negative while all isolates of *C. haemulonii* and *C. pseudohaemulonii* formed biofilms. They also arrive at a judgement that *C. pseudohaemulonii* formed a biofilm to induce central venous catheter-related fungemia in patients. Alam et al. [99] developed a novel noisome-based diallyl disulphide, an effective nanocarrier system, to treat disseminated *Candida* infection in murine. They showed that diallyl disulphide-loaded niosomes complex decreased the fungal cells and increased the life of cell tissue in contrast to the free formulation. Pałkowski et al. [100] investigated the structure–activity relationship of gemini imidazolium compounds using the chemical structure and surface-active properties and antifungal activity against *C. albicans* ATCC 90028 strain. They remarked that antifungal activity depends not only on the surface-active properties of the compound but also on the substituent type and the position at the chloride moiety of substituents. Szafrański et al. [101] synthesised novel 4-substituted N- pyridine-3-sulfonamides and converted them to triazole derivatives; then, they tested them against *Candida* spp. isolated from patients and found *C. albicans* strains, to be highly sensitive to the tested compounds. According to the docking study, based on inhibition of the cytochrome P-450-dependent lanosterol 14α-demethylase, the most active three compounds binding to *C. albicans* were determined as N-phenylpiperazine, pyrazole, and an alkylthio moiety of the compounds. Another study on novel compounds was done by Lino et al. [102]. They synthesised a novel series of 15 hydrazine-thiazole derivatives and tested the efficacy on six *Candida* spp. They reported that while some of the derivatives exhibited activity at the minimum inhibitory concentration MIC of 0.45–31.2 mM, some of them showed comparable or higher activity than standard drugs.

1.9 Natural compounds

Natural compounds effective on fungi are generally phenolic and are obtained from edible plants. Kim et al. [103] asserted that natural products increased the *in vitro* activity of fluconazole against strains of resistant filamentous fungi. They showed that cinnamic acid, benzoic acid, salicylic acid, thymol and 2,5- and 2,3-dihydroxybenzaldehyde exerted mainly additive or synergistic effects against fungal growth [104]. Conversely, the search for natural products with antifungal activities against *Candida* spp. and the search for natural molecules that can treat candidiasis are ongoing. Zida et al. [105] classified the compounds according to MICs and MFCs as given by the other authors. They classified 40 of 142 phytochemicals as significant according to their MIC values <100 μg/mL, and 24 of 142 showed moderate activity with MIC values between 100 and 625 μg/mL. In this group, ascosterosides from *Ascotricha amphitricha* and papulacandin-A from *Papularia sphaerosperma* exhibited the strongest activity with a MIC value of 0.1 μg/mL. Minooeianhaghighi et al., [106] investigated the efficacy of some essential oils (*Lavandula binaludensis* and *Cuminum cyminum*) against pathogenic *Candida* spp., and treatments for recurrent vulvovaginal candidiasis. They identified the oil components by comparing their mass spectra against the GC–MS library as well as using the existing literature. They determined

13 components using GC–MS analyses. The main components of *C. cyminum* and *L. binaludensis* essential oils were g-terpinene and 1,8-cineole (21.07%, 71.56%, respectively). They reported that *C. cyminum* (MIC 8.00 mg/ML) and *L. binaludensis* oils MIC 7.91 mg/mL) showed inhibitory activity. *L. binaludensis* inhibited 80% of *C. albicans* vaginal strains at a concentration of 7.81 mg/mL ($P < 0.05$). They reported that essential oils could be used as natural therapeutic inhibitors to prevent or limit the growth of the most significant pathogenic *Candida* species and against recurrent vulvovaginal candidiasis. In another study, Marangoni et al. [107] studied a blue-green alga, *Spirulina platensis* against 22 strains of *Candida* spp. (*C. albicans*, *C. glabrata*, *C. lusitaniae, C. tropicalis*, *C. krusei*, *C. Parapsilosis*, *C. Guillermondii*, among others). Faria et al. [108] examined the fungicidal activity of 12 natural phenolics against nine reference strains of *Candida* (*C. albicans* (3 strains), *C. parapsilosis* (2 strains), *C. glabrata, C. tropicalis, C. krusei* and *C. lusitaniae*). They showed that cinnamic acid, benzoic acid, salicylic acid, thymol and 2,5- and 2,3- dihydroxybenzaldehyde had mainly additive or synergistic efficacy against *C. albicans*.

1.10 Interactions between *Candida* spp. and cancer development

Some findings suggest a relationship between candidiasis and cancer. Alnuaimi et al. [109] investigated the role of candidiasis in oral and oesophageal cancers. For this purpose, they studied oral *Candida* carriage by working with 52 oral cancer patients and 104 non-oral cancer subjects. The data obtained from the study showed that there is a significant relationship between the *Candida* species colonising the mouth in the formation of oral cancer. Li-D et al. [110] examined 207 invasive cancer patients. Patients with recurrent invasive candidiasis and patients with multiple infections were not included in this group. In their study, they detected 28% of deaths in 30 days. Invasive candidiasis was diagnosed based on the isolation of *Candida* species from the bloodstream. The rate of *Candida* species they obtained was as follows: *C. albicans* (48.3%), *C. glabrata* complex (24.2%) and *C. tropicalis* (10.1%), respectively. The results indicate that there may be a relationship between death cases and invasive *Candida* species. In another study performed by Choi et al. [111], they investigated the incidence of *Candida* infection in cancer patients (n = 17.797) and the risk of mortality in patients with *Candida*-infected cancer. Identified *Candida* species were 634, of which 75 had concerned bloodstream infection. The striking results were the high rate of *C. albicans* infections (85.8%) in the patients hospitalised in the intensive care unit.

2. Concluding remarks

Candida spp. contain the most common human fungal pathogens and *C. albicans* is a commensal inhabitant of the human mouth, gastrointestinal and genital region. *Candida* can weaken the mucosa and cause fatal conditions in situations such as the inadequacy of the host immunity or the presence of implanted medical devices. Immunocompromised patients can easily be exposed to *Candida*-related diseases. Therefore, the research and development of new anti-*Candida* drug active molecules are of great importance. There are various reports on fungal resistance mechanisms of several *Candida* spp. against fluconazole, itraconazole, voriconazole and several azole compounds. Natural compounds such as flavonoids contain a wide variety of biologically active compounds. Due to reasons such as low toxicity and rare side effects, they

have the advantage of potential usage. The synthesis of new compounds effective in *Candida* biofilm formation continues increasingly all over the world. On the other hand, the relationship between *Candida* and cancer is still somewhat blurred. More research is needed on whether *Candida* genus members cause cancer.

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