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## Review Article

# *Candida* Infections, Causes, Targets, and Resistance Mechanisms: Traditional and Alternative Antifungal Agents

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The genus *Candida* includes about 200 different species, but only a few species are human opportunistic pathogens and cause infections when the host becomes debilitated or immunocompromised. *Candida* infections can be superficial or invasive. Superficial infections often affect the skin or mucous membranes and can be treated successfully with topical antifungal drugs. However, invasive fungal infections are often life-threatening, probably due to inefficient diagnostic methods and inappropriate initial antifungal therapies. Here, we briefly review our current knowledge of pathogenic species of the genus *Candida* and yeast infection causes and then focus on current antifungal drugs and resistance mechanisms. An overview of new therapeutic alternatives for the treatment of *Candida* infections is also provided.

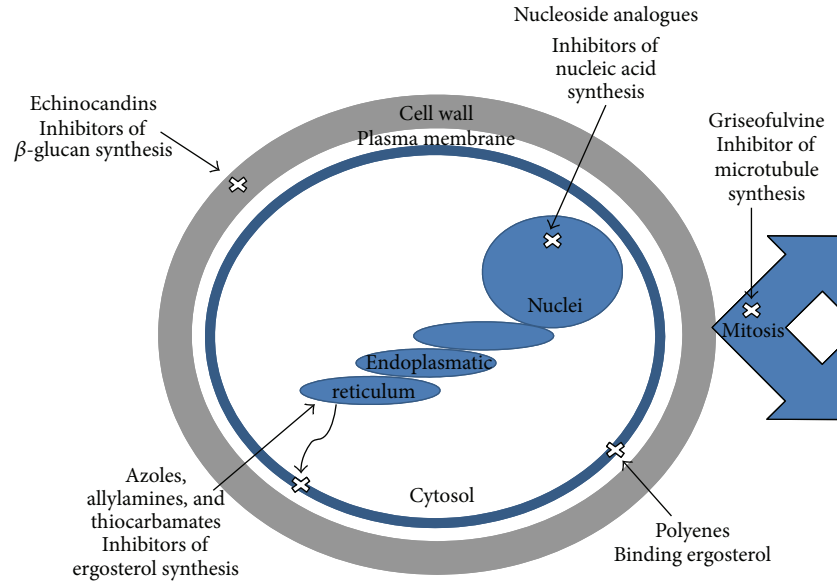
## 1. Introduction

*Candida albicans* is the most important fungal opportunistic pathogen. It usually resides as a commensal in the gastrointestinal and genitourinary tracts and in the oral and conjunctival flora [1–5]. However, it causes infection when the host becomes debilitated or immunocompromised. These infections can be superficial and affect the skin or mucous membrane [6] or can invade the bloodstream and disseminate to internal organs. Risk factors for invasive candidiasis include surgery (especially abdominal surgery), burns, long-term stay in an intensive care unit, and previous administration of broad-spectrum antibiotics and immunosuppressive agents [7–10]. Advances in medical management as anti-neoplastic chemotherapy, organ transplantation, hemodialysis, parenteral nutrition, and central venous catheters also contribute to fungal invasion and colonization [11]. Other *Candida* species found in healthy individuals include *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and

*Candida krusei* [12]. All five mentioned species cause more than 90% of invasive infections, although the relative prevalence of the species depends on the geographical location, patient population, and clinical settings [12–14]. Emergence of *Candida guilliermondii*, *Candida kefyr*, *Candida rugosa*, *Candida dubliniensis*, and *Candida famata* as pathogens has also been reported worldwide [6, 14]. In fact, the National Nosocomial Infections Surveillance System (NNISS) reports *Candida* species as the fourth most common nosocomial bloodstream pathogen [15]. Mortality rates are estimated to be as high as 45% [16], probably due to inefficient diagnostic methods and inappropriate initial antifungal therapies [17].

## 2. Antifungal Drugs in Clinical Treatments

Although the antifungal drugs used in clinical treatments appear to be diverse and numerous, only few classes of



| Antifungal class     | Mode of action                                     | Drugs  |
|----------------------|--|--|
| Azoles               | Inhibitors of lanosterol 14- $\alpha$ -demethylase | Miconazole<br>Econazole<br>Clotrimazole<br>Ketoconazole<br>Fluconazole<br>Itraconazole<br>Voriconazole<br>Posaconazole |
| Echinocandins        | Inhibitors of (1,3)- $\beta$ -D-glucan synthase    | Caspofungin<br>Micafungin<br>Anidulafungin   |
| Polyenes             | Binding ergosterol                                 | Nystatin<br>Amphotericin B   |
| Nucleoside analogues | Inhibitor of DNA/RNA synthesis                     | Flucytosine  |
| Allylamines          | Inhibitors of squalene-epoxidase                   | Terbinafine<br>Amorolfine<br>Naftifine   |
| Thiocarbamates       | Inhibitors of squalene-epoxidase                   | Tolnaftate<br>Tolciclate   |
| Antibiotic           | Interaction with $\beta$ -tubulin                  | Griseofulvin   |

FIGURE 1: Primary targets and mode of action of several antifungal agents.

antifungal agents are currently available to treat mucosal or systemic infections with *Candida* spp. (Figure 1) [18–20].

**2.1. Azoles: Inhibitors of the Lanosterol 14- $\alpha$ -Demethylase.** The largest family of antifungal drugs is the azole family. Azoles disrupt the cell membrane by inhibiting the activity of the lanosterol 14- $\alpha$ -demethylase [21], enzyme involved in the biosynthesis of ergosterol (Figure 1). Ergosterol, analogous to cholesterol in animal cells, is the largest sterol component of

the fungal cell membrane. Since ergosterol and cholesterol have sufficient structural differences, most antifungal agents targeted to ergosterol binding or biosynthesis does not cross-react with host cells. The azole family includes imidazoles (miconazole, econazole, clotrimazole, and ketoconazole) and triazoles (fluconazole, itraconazole, and the latest agent voriconazole (second-generation, synthetic triazole derivative of fluconazole) and posaconazole (hydroxylated analogue of itraconazole)) [21, 22]. Many azoles are effective

TABLE 1: Administration routes and pharmacokinetic parameters of representative antifungal agents belonging to the major families of compounds.

| Drug family          | Drug           | Adm. route <sup>a</sup> | Oral bioavailability (%) | Pharmacokinetic parameters    |   |                     |               | Elimination | References       |
|----------------------|----------------|-------------------------|--------------------------|-------------------------------|---|---------------------|---------------|-------------|------------------|
|                      |                |                         |                          | $C_{\max}^b$ $\mu\text{g/mL}$ | AUC <sup>c</sup> $\text{mg}\cdot\text{h/L}$ | Protein binding (%) | Half time (h) |             |                  |
| Azoles               | Fluconazole    | Oral                    | >90                      | 0.7                           | 400.0                                       | 10–12               | 27–31         | Urine       | [35, 37]         |
|                      | Itraconazole   | Oral                    | >55                      | 1.1                           | 29.2  | 99.8                | 21–64         | Hepatic     | [35, 37]         |
|                      | Voriconazole   | Oral                    | >90                      | 4.6                           | 20.3  | 60.0                | 6             | Renal       | [35, 37, 38]     |
|                      | Posaconazole   | Oral                    | >98                      | 7.8                           | 17.0  | 99.0                | 15–35         | Feces       | [35, 39]         |
| Echinocandins        | Caspofungin    | IV                      | <5                       | 9.5–12.1                      | 93.5–100.5                                  | 96.0                | 10.6          | Urine       | [20, 35, 40, 41] |
|                      | Micafungin     | IV                      | <5                       | 7.1–10.9                      | 59.9–111.3                                  | 99.8                | 11–17         | Feces       | [20, 35, 40, 41] |
|                      | Anidulafungin  | IV                      | <5                       | 3.4–7.5                       | 44.4–104.5                                  | 84.0                | 18.1–25.6     | Feces       | [20, 35, 40, 41] |
| Polyenes             | Amphotericin B | IV                      | <5                       | 1.5–2.1                       | 13–17                                       | >95                 | 6.8–50        | Feces       | [35, 42]         |
| Nucleoside analogues | Flucytosine    | Oral                    | 76–89                    | 80                            | 62  | 4                   | 3–6           | Renal       | [31, 35]         |

<sup>a</sup>Adm. route indicates administration route; fluconazole, itraconazole, and voriconazole can be administered by both intravenous and oral routes; IV: intravenous; <sup>b</sup> $C_{\max}$ : maximal concentration; <sup>c</sup>AUC: area under the curve.

both for topical use and for the treatment and prophylaxis of invasive fungal infections [22]. In this regard, these agents have the approval of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [23].

**2.2. Echinocandins: Inhibitors of the Glucan Synthesis.** Echinocandins (caspofungin, micafungin, and anidulafungin) are lipopeptidic antifungal agents that inhibit the synthesis of fungal wall by noncompetitive blockage of the (1,3)- $\beta$ -D-glucan synthase (Figure 1). This enzyme inhibition leads to the formation of fungal cell walls with impaired structural integrity, which finally results in cell vulnerability to osmotic lysis [24]. All three agents (caspofungin, micafungin, and anidulafungin) exhibit concentration-dependent fungicidal activity against most species of *Candida* [25, 26] and have been approved by the regulatory agency FDA for the treatment of esophageal and invasive candidiasis, including candidemia [27–29].

**2.3. Polyenes: Binding Ergosterol.** Polyenes such as nystatin and amphotericin B (both isolated from *Streptomyces* spp.) bind ergosterol and disrupt the major lipidic component of the fungal cell membrane resulting in the production of aqueous pores (Figure 1). Consequently, the cellular permeability is altered and leads to the leakage of cytosolic components and, therefore, fungal death [30].

**2.4. Nucleoside Analogues: Inhibitors of DNA/RNA Synthesis.** Flucytosine is a pyrimidine analogue. It is transported into fungal cells by cytosine permeases. Then, it is deaminated to 5-fluorouracil and phosphorylated to 5-fluorodeoxyuridine monophosphate. This fluorinated nucleotide inhibits thymidylate synthase and thus interferes with DNA synthesis (Figure 1, [31]). The 5-fluorodeoxyuridine monophosphate

can be further phosphorylated and incorporated to RNA, thus affecting RNA and protein synthesis (Figure 1, [32]).

**2.5. Other Antifungal Agents.** Allylamines and thiocarbamates also disrupt the cell membrane by inhibiting the squalene-epoxidase [33], enzyme involved in the biosynthesis of ergosterol (Figure 1).

Griseofulvin (a tricyclic spirodiketone, first isolated from *Penicillium griseofulvum*) acts by disrupting spindle and cytoplasmic microtubule production, thereby inhibiting fungal mitosis (Figure 1, [34]).

**2.6. Treatment of Systemic Infections.** The antifungal therapy is driven by whether the agents are being used to treat mucosal or systemic infections. Superficial infections can be treated successfully with topical antifungal drugs. Systemic infections can be treated with oral or intravenous (IV) preparations. Table 1 shows the pharmacokinetic parameters of the main antifungal agents used for the treatment of systemic candidiasis. Pharmacokinetic parameters are not always directly comparable because data derive from multiple sources and trials [20]. However, the routes of administration and excretion are often important considerations in selecting an appropriate antifungal agent. Some drugs are available only as IV preparations (e.g., caspofungin, micafungin, anidulafungin, and amphotericin B), only as oral preparations (e.g., posaconazole and flucytosine) or can be administered by both IV and oral routes (e.g., fluconazole, itraconazole, and voriconazole) depending on the drug solubility [35]. Since fluconazole and caspofungin are primarily excreted into the urine as active forms (Table 1), they are agents of choice for the treatment of urinary tract fungal infections. Unfortunately, some of these antifungal drugs have been extensively used and led to an increased selective pressure and the development of antifungal resistance [36].

TABLE 2: Resistance mechanisms of major systemic antifungal drugs. Antifungal resistance is based on different mechanisms, namely, (i) reduced drug intracellular accumulation, (ii) decreased target affinity/processivity for the drug, and (iii) counteraction of the drug effect.

| Antifungal class     | Genetic basis for resistance   | Functional basis for resistance  |
|----------------------|--|--|
| Azoles               | Upregulation of <i>CDR1/CDR2</i> and <i>MDR1</i> by point mutations in <i>TAC1</i> and <i>MRR1</i> transcription factors | (i) Upregulation of drug transporters  |
|                      | Point mutations in <i>ERG11</i>  | (ii) Decreased lanosterol 14- $\alpha$ -demethylase binding affinity for the drug                                    |
|                      | Upregulation of <i>ERG11</i> by gene duplication and transcription factor regulation                                     | (iii) Increased concentration of lanosterol 14- $\alpha$ -demethylase  |
| Echinocandins        | Point mutations in <i>ERG3</i>   | (iii) Inactivation of C5 sterol desaturase leading to alterations in the ergosterol synthetic pathway                |
|                      | Point mutations in <i>FKS1</i> and <i>FKS2</i>   | (ii) Decreased glucan synthase processivity for the drug   |
| Polyenes             | Point mutations in <i>ERG3</i> and <i>ERG6</i>   | (iii) Decreased ergosterol content in cells  |
|                      | Point mutations in <i>FCY2</i>   | (i) Inactivation of cytosine permease affecting drug uptake  |
| Nucleoside analogues | Point mutations in <i>FCY1</i>   | (iii) Inactivation of cytosine deaminase leading to alterations in the metabolism of 5-fluorocytosine                |
|                      | Point mutations in <i>FURI</i>   | (iii) Inactivation of uracil phosphoribosyl transferase leading to alterations in the metabolism of 5-fluorocytosine |

### 3. Mechanisms of Resistance against Antifungal Agents

Antifungal resistance is based on different mechanisms, namely, (i) reduced drug intracellular accumulation, (ii) decreased target affinity/processivity for the drug, and (iii) counteraction of the drug effect. Particularly, the mechanism of resistance will be different depending on the mode of action of antifungal compounds. Cellular and molecular mechanisms supporting resistance against antifungal classes mentioned above have been discussed in detail in previous reviews [43–46]. Below, we briefly summarize the main observations (Table 2).

**3.1. Azole Resistance.** Over the past 10 years, fluconazole and itraconazole have been used extensively for chemoprophylaxis and treatment of systemic fungal infections because of their favorable oral bioavailability and safety profiles [84–86]. Afterwards, fluconazole resistance has been described in a high percentage of patients [87]. In fact, azole-resistant *C. albicans* is frequent in HIV-infected patients with oropharyngeal candidiasis [88]. However, resistance is less important in patients with other diseases, such as vaginal candidiasis and candidemia [89]. An intrinsically reduced susceptibility to fluconazole has been also reported for non-*albicans* species of *Candida* like *C. glabrata*, *C. krusei*, and *C. lusitaniae* [90, 91]. It appears that variations in the structure of azoles are responsible for the cross-resistance patterns among *Candida* species [92–94]. Several major mechanisms leading to azole resistance have been elucidated (Table 2, [95]) and detailed below.

(i) *Reduced Drug Intracellular Accumulation.* A responsible mechanism for decreasing the intracellular concentration of azole relies on an upregulation of two principal families of

efflux pumps (reviewed in [96]). These transporters differ in the source of energy used to pump out the drug and in the specificity of the azole molecule. The Cdr pumps belong to the superfamily of ATP-binding cassette (ABC) transporters and are able to extrude all azole antifungals. These pumps are encoded by *Candida* drug resistance 1 and 2 (*CDR1* and *CDR2*) genes in *C. albicans* [96]. The other pump is a secondary transporter which utilizes proton gradient as a source of energy and is specific for fluconazole. This pump belongs to the major facilitator superfamily (MFS) transporters and is encoded by the *MDR1* gene in *C. albicans* [96]. Upregulation of *CDR1/CDR2* and *MDR1* arises from mutations in *TAC1* and *MRR1* transcription factors, respectively [97, 98]. Gain-of-function mutations generate hyperactive alleles in *C. albicans* and subsequent loss of heterozygosity (LOH) at the *TAC1* and *MRR1* loci [99]. Other transporter genes have been reported to be upregulated in azole-resistant *C. glabrata* (*CgCDR1*, *CgCDR2* (formerly named *PDH1*) and *CgSNQ2* (another ABC transporter)) [100–102], *C. dubliniensis* (*CdCDR1* and *CdCDR2*) [103], *C. krusei* (*ABC1* and 2) [104, 105], and *C. tropicalis* (*CDR1*-homologue) isolates [44]. In *C. glabrata*, *CgCDR1*, *CgCDR2*, and *CgSNQ2* genes are regulated by the *CgPDR1* transcription factor [106–108].

(ii) *Decreased Target Affinity for the Drug.* The target of azole antifungals is the lanosterol 14- $\alpha$ -demethylase encoded by the *ERG11* gene. Several point mutations have been characterized and associated to azole minimum inhibitory concentration (MIC) increases (reviewed in [95]).

(iii) *Counteraction of the Drug Effect.* Two mechanisms contribute to counterbalancing the drug effects. The first system involves an upregulation of the *ERG11* gene leading to an intracellular increase of the target protein. *ERG11* overexpression occurs by transcription factor regulation and

gene duplication (reviewed in [95]). The second mechanism, although very uncommon, has been identified in several clinical isolates of *C. albicans* [109]. Alteration of the late steps of the biosynthesis of ergosterol through *ERG3* inactivation leads to the total inactivation of the C5 sterol desaturase [110]. Thus, toxic 14 $\alpha$ -methylated sterols are no longer accumulated, and yeast strains produce cell membranes devoid of ergosterol but containing other sterols [110].

**3.2. Echinocandin Resistance.** Echinocandin drugs are recommended as the first line for invasive candidiasis. However, reports of echinocandin resistance in patients with infections due to *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. krusei* are rising [111–116]. In fact, resistance in *C. glabrata* increased from 4.9% to 12.3% between 2001 and 2010 [115]. Even more, emergence of coresistance to both echinocandins and azoles in clinical isolates of *C. glabrata* has been reported [115]. In addition, intrinsic echinocandin resistance of *C. parapsilosis*, *C. orthopsilosis*, *C. metapsilosis*, and *C. guilliermondii* has been described [117, 118].

Secondary resistance to echinocandins is associated with the following mechanism.

(ii) *Decreased Target Processivity for the Drug.* Resistance is attributed to point mutations in the *FKSI* and/or *FKS2* genes (Table 2, [119–121]) which encode the (1,3)- $\beta$ -D-glucan synthase complex [121]. Mutations in *FKSI* did not alter substrate binding but lowered  $V_{max}$  values [122].

**3.3. Polyene Resistance.** Despite more than 30 years of clinical use, minimal resistance to amphotericin B has been developed. However, the main problem associated with the prophylactic use of conventional amphotericin B has always been due to its well-known side effects and toxicity [123, 124]. Resistance tends to be species dependent. *C. glabrata* and *C. krusei* are usually considered to be susceptible to amphotericin B, although they show higher MICs to polyenes than *C. albicans*. In this regard, higher than usual doses of amphotericin B have been recommended by the Infectious Diseases Society of America for treating candidemia caused by *C. glabrata* and *C. krusei* [125]. In fact, a significant proportion of isolates of *C. glabrata* and *C. krusei* species resistant to amphotericin B has been reported [126]. Additionally, some *Candida* spp. including *C. lusitaniae* and *C. guilliermondii*, besides *C. glabrata*, are capable of expressing resistance to amphotericin B [127]. It is noteworthy that even the antifungal lipopeptide caspofungin led to drug resistance in transplanted patients [112]. When resistance to polyenes occurs, it may result from the following mechanism.

(iii) *Counteraction of the Drug Effect.* Acquired resistance is probably due to a decrease or lack of ergosterol content in cell membranes. In fact, membranes of polyene-resistant *Candida* isolates have relatively low ergosterol content, compared to those of polyene-susceptible isolates. These deficiencies are probably consequences of loss of function mutations in the *ERG3* or *ERG6* genes which encode some of the enzymes involved in ergosterol biosynthesis (Table 2, [128–130]).

**3.4. Flucytosine Resistance.** Primary resistance to flucytosine remains low (<2%). Secondary resistance relies on inactivation of different enzymes of the pyrimidine pathway (Table 2) as described below.

(i) *Reduced Drug Intracellular Accumulation.* Uptake of the drug is affected by point mutations in the *FCY2* gene which encodes the cytosine permease [46, 128].

(iii) *Counteraction of the Drug Effect.* Acquired resistance to flucytosine also results from point mutations in the *FCY1* gene which encodes for the cytosine deaminase or *FURI* gene which encodes for the uracil phosphoribosyl transferase. These enzymes catalyze the conversion of 5-fluorocytosine to 5-fluorouracil and 5-fluorouracil to 5-fluorouridine monophosphate, respectively. The most frequently acquired resistance to flucytosine is based on point mutations in the *FURI* gene. Several point mutations have been described in *C. albicans*, *C. glabrata*, and *C. lusitaniae* [46, 128, 131, 132].

The rapid development of antifungal resistance, the toxicity and the variability in available formulations of some agents, and the increase in the frequency of non-*albicans* *Candida* spp. infections support the need for more effective and less toxic treatment strategies.

## 4. Need of New Antifungal Agents

Potential pharmacological strategies include the use of (i) new formulations of antifungals, such as liposomal amphotericin B, amphotericin B lipid complex, amphotericin B colloidal dispersion, amphotericin B into a lipid nanosphere formulation, itraconazole, and  $\beta$ -cyclodextrin itraconazole or (ii) combination therapies of one or more antifungal compounds, for example, amphotericin B + flucytosine, fluconazole + flucytosine, amphotericin B + fluconazole, caspofungin + liposomal amphotericin B, and caspofungin + fluconazole.

Potential alternative therapies include the use of new active principles obtained from different general sources, as natural products, synthetic agents or polymeric materials that have been shown to be active *in vitro* (Table 3). Among the natural products, plants contain diverse components that are important sources of biologically active molecules [50, 133, 134]. In fact, the activity of plant crude extracts against different microorganisms has been reported, that is, strong antifungal activity of some major components of essential oils [135, 136]. In this regard, the antibiofilm activity of terpenes and the exceptional efficiency of carvacrol, geraniol, and thymol, in the treatment of candidiasis associated with medical devices, have been demonstrated [137]. In another work, terpenoids exhibited excellent activity against *C. albicans* yeast and hyphal form growth at concentrations that were nontoxic to HeLa cells [138]. Thus, terpenoids may be useful in the near future not only as an antifungal chemotherapeutic agent but also to synergize effects of conventional drugs like fluconazole [138]. Other compounds with antimycological activity obtained from plants are saponins, alkaloids, peptides, and proteins [47, 48]. Marine organisms, endophytic

TABLE 3: Some natural products, synthetic agents, and polymeric materials with reported antifungal activities.

| General source                            | Specific source  | Biological active molecules   | Examples   | References |
|---|--|---|--|------------|
| Natural products                          | Plants   | Essential oils; terpenoids; saponins; phenolic compounds; alkaloids; peptides; proteins | Steroidal saponins, sesquiterpenoids   | [47, 48]   |
|   | Marine organisms   | Anthracycline-related compounds; lipopeptides; pentacyclic compounds                    | Xestodecalactone B, seragikinone A   | [49]       |
|   | Endophytic fungi   | Secondary metabolites; peptides; pyrones  | cryptocandin, pestalopyrone  | [50]       |
|   | Microorganisms of terrestrial environment  | Lipopeptides; terpenoids  | Echinocandins, enfumafungin  | [50, 51]   |
| Synthetic agents                          | Organically synthesized or derived compounds (not polymeric materials)           | Compounds based on N,N-dimethylbiguanide complexes                                      | Me (N,N-dimethylbiguanide) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub> ·nH <sub>2</sub> O where Me: Mn, Ni, Cu, and Zn | [52, 53]   |
|   |  | Derived compounds from traditional antifungal structures                                | Imidazole derivatives, amine-derived bis-azoles  | [54, 55]   |
|   |  | Synthetic derived peptides  | Lactoferrin-derived peptides   | [56]       |
|   |  | Derived compounds from natural products   | Micafungin sodium, anidulafungin, caspofungin acetate, pneumocandin, and enfumafungin derivatives                          | [57, 58]   |
| Polymeric materials                       | Polymeric materials  |   | Polymers containing aromatic or heterocyclic structures  | [59]       |
|   |  |   | Cationic conjugated polyelectrolytes   | [58]       |
|   |  | Polymers with quaternary nitrogen atoms   | Polymers with quaternary nitrogen atoms within the main chain.   | [60]       |
|   |  |   | Block copolymers containing quaternary ammonium salt   | [61]       |
|   |  |   | Synthetic peptides, synthetic dendrimeric peptides   | [62, 63]   |
|   |  | Antifungal peptides mimics  | Arylamide and phenylene ethynylene backbone polymers   | [64]       |
|   |  |   | Polynorbornene derivatives   | [65]       |
|   |  |   | Polymethacrylate and polymethacrylamide platforms containing hydrophobic and cationic side chains                          | [66, 67]   |
|   |  | Polymers with superficial activity  | Fluorine-containing polymers   | [68]       |
|   |  | Polymers containing different contents of halogens                                      | Chlorine-containing phenyl methacrylate polymers   | [69, 70]   |
|   |  |   | Polymeric N-halamines  | [71]       |
|   |  | Chelates  | Polymer-copper(II)-bipyridyl complex   | [72]       |
|   |  |   | N-vinylimidazole copolymerized with phenacyl methacrylate  | [73]       |
| Imidazole derivative polymers             | 2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl methacrylate and ethyl methacrylate | [71]  |  |            |
| Polymers loaded with antifungal compounds | Organic compounds  | [74–76]   |  |            |
|   | Inorganic compounds  | [77–79]   |  |            |

fungi and microorganisms of terrestrial environment are also specific sources of antifungal compounds, although to a lesser extent [50, 139]. Among them, good antimicrobial activities of anthracycline-related compounds, peptides, pyrones, lipopeptides, and terpenoids isolated from these specific sources have been reported [49–51].

A second general source of antifungal agents comprises nonpolymeric synthetic agents, which can be classified into four groups (Table 3). The first group includes chemicals based on N,N-dimethylbiguanide complexes [52]. These compounds displayed low cytotoxicity and could be considered as potential broad-spectrum agents [53]. The second

group involves derived compounds of traditional antifungal structures [54, 55] where some of them present better antimicrobial action than the original structures [55, 140]. The third group is formed by synthetic derived peptides, that is, the “human lactoferrin derived peptide” which was well tolerated in preclinical tests and clinical trials [56]. Finally, the last group includes compounds which are derived from semisynthetic natural products, such as compounds derived from echinocandins: micafungin sodium, anidulafungin, caspofungin acetate, and pneumocandin. These agents showed improved properties over the parental compounds [50, 141]. Unfortunately, echinocandins derivatives are poorly absorbed when administered orally and, therefore, are used only for IV administration. A natural antifungal with comparable activity to that of caspofungin acetate against *Candida* pathogenic fungal strains was isolated [51]. The compound, named enfumafungin, is a new triterpene glycoside that inhibits the (1,3)- $\beta$ -D-glucan synthase. Several synthetic products derived from enfumafungin are currently under development in order to optimize *in vivo* antifungal activity and oral efficacy [57].

The third general source of antifungal compounds, namely, polymeric materials could be classified into seven groups (Table 3). (1) Polymers with quaternary nitrogen atoms [60] that can exist in different structures, that is, aromatic or heterocyclic structures [59], cationic conjugated polyelectrolytes [58], quaternary nitrogen atoms within the main chain [60], block copolymers [61], and synthetic and dendrimeric peptides [62, 63]. All of them were shown to be effective against a variety of microorganisms based on the exposure of its quaternary ammonium group. (2) Mimic antimicrobial peptides; among them are arylamide and phenylene ethynylene backbone polymers [64]; polynorbornene derivatives, which depending on their structure may exhibit substantial antimicrobial and low hemolytic activity [65], and polymethacrylate and polymethacrylamide with hydrophobic and cationic side chains [66, 67]. (3) Polymers with antimicrobial activity derived from their superficial activity (surfactants) based on fluorine-containing compounds [68]. (4) Polymers containing different contents of halogens, where the halogen group is the commander of the inhibition process, such as phenyl methacrylate polymers with different contents of chlorine [69, 70]. The halogen may form a covalent bond to nitrogen yielding polymeric N-halamines with a broad-spectrum antimicrobial activity without causing environmental concerns [71]. (5) Chelates; the antimicrobial activity of different chelates, such as N-vinylimidazole copolymerized with phenacyl methacrylate or poly(1,3-thiazol-2-yl-carbamoyl) methyl methacrylate with Cd(II), Cu(II), or Ni(II), has been analyzed in 2011 by Soykan et al. [73]. The Ni(II) complexes showed higher activity than those of Cu(II) and Co(II) ions. However, all of them exhibited lower activity than fluconazole. Another complex containing Cu(II) was found to have good antifungal activity due to electrostatic binding to fungal DNA [72]. (6) Imidazole derivatives, polymers and copolymers, with antimicrobial effectiveness depending on the polymeric structures [71, 142]. (7) Polymers loaded with antimicrobial organic or inorganic compounds. Antimicrobial organic agents are based on

organic drugs; that is, chlorhexidine has been incorporated into polymeric microparticles and into polymeric hydrogels to modulate the release of the drug [74, 75]. Another research group loaded triclosan into polymeric nanoparticles [76]. Antimicrobial inorganic agents frequently incorporate metals into polymers, such as silver. This metal exhibits much higher toxicity to microorganisms than to mammalian cells. Polymeric nanotubes [77] and nanofibers [78] with silver nanoparticles have been prepared by chemical oxidation polymerization of rhodanine. Other silver nanocomposites have been reported in the literature based on different silver-loaded nanoparticles such as silver-zirconium phosphate nanoparticles [79] or silver zeolites [142]. Another example of inorganic compound loaded into polymers is copper. Copper particles are also known for their antimicrobial activity, although they are relatively less studied than silver [143].

The mentioned agents have been tried *in vitro* against *Candida*; however, many of them are not used in clinical treatments; in this regard, there are three agents with actual promise: E1210, albaconazole, and isavuconazole (Figure 2).

E1210 is a broad-spectrum antifungal agent with a novel mechanism of action based on the inhibition of fungal glycosylphosphatidylinositol biosynthesis [144, 145]. The efficacy of oral E1210 was evaluated in murine models of oropharyngeal and disseminated candidiasis [80].

Results indicate that E1210 significantly reduced the number of viable *Candida* in the oral cavity in comparison to that of the control treatment and prolonged survival of mice infected with *Candida* spp. Therapeutic responses were dose dependent [80]. Table 4 shows the major pharmacokinetic parameters after administration of E1210 in mice. E1210 was also highly effective in the treatment of disseminated candidiasis caused by azole-resistant *C. albicans* or *C. tropicalis* [80]. Currently, E1210 is in Phase II.

Albaconazole is a new oral triazole with broad-spectrum antifungal activity, unique pharmacokinetics, and excellent tolerability [146]. It has been demonstrated that this compound was highly effective *in vitro* against pathogenic yeasts and also in animal models of systemic candidiasis [146]. Oral bioavailability was calculated to be 80% in rats and 100% in dogs [81]. Assays in healthy human volunteers showed that albaconazole was rapidly absorbed and presented good pharmacokinetic parameters (Table 4). In fact, the therapeutic efficacy of a single dose of albaconazole at  $\geq 40$  mg was more effective than 150 mg of fluconazole for the treatment of acute vulvovaginal candidiasis [81]. Currently, albaconazole is in Phase II. In addition, low toxicity was observed when albaconazole was administered to animals and human volunteers [82].

Finally, isavuconazole (the active metabolite of the water-soluble prodrug isavuconazonium) is a novel second-generation water-soluble triazole with broad-spectrum antifungal activity, also against azole-resistant strains. Studies carried out with neutropenic mice of disseminated *C. tropicalis* or *C. krusei* infections showed that the treatment significantly reduced kidney burden in mice infected with *C. tropicalis* and both kidney and brain burden in mice infected with *C. krusei* [147]. This azole is currently under Phase III trials in patients with systemic candidiasis. Both oral and

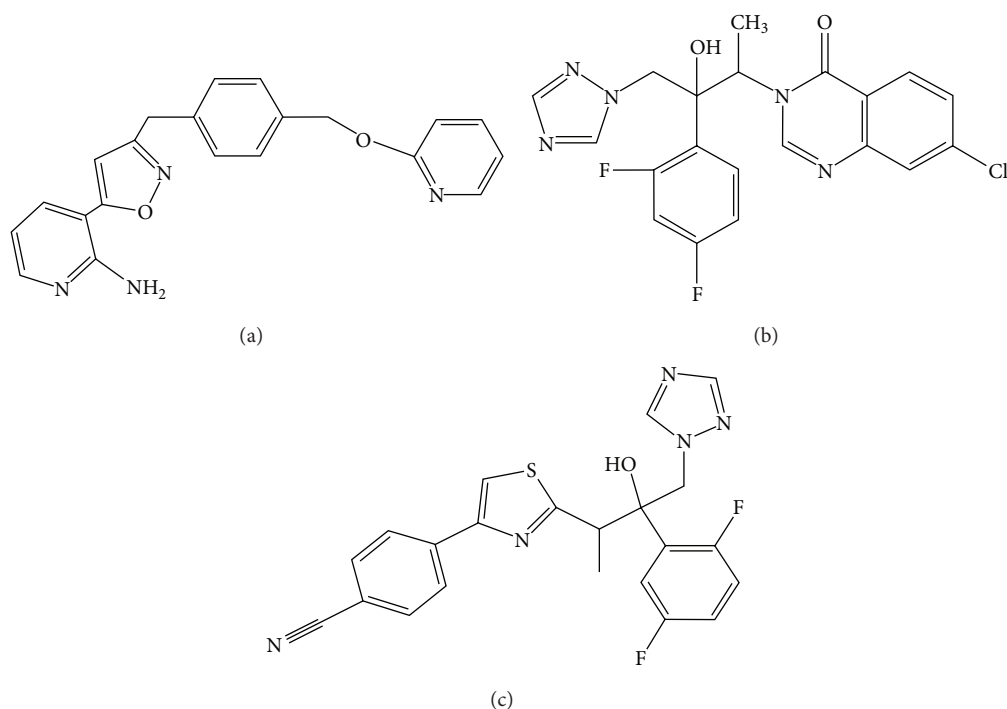


FIGURE 2: Chemical structures of three agents with actual promise: E1210 (a), albaconazole (b), and isavuconazole (c).

TABLE 4: Pharmacokinetic parameters of some lead drugs.

| Drug            | Available forms      | Experimental organisms   | Oral bioavailability (%) | Pharmacokinetic parameters        |                  |                     |               |                 | References |
|-----------------|----------------------|--------------------------|--------------------------|-----------------------------------|------------------|---------------------|---------------|-----------------|------------|
|                 |                      |                          |                          | $C_{\max}^b$ ( $\mu\text{g/mL}$ ) | $t_{\max}^c$ (h) | Protein binding (%) | Half time (h) | Elimination     |            |
| E1210           | Oral/IV <sup>a</sup> | Mice                     | 57.5                     | 0.11                              | 0.5              | High                | 2.2           | nr <sup>d</sup> | [80]       |
| Albaconazole    | Oral                 | Healthy human volunteers | nr <sup>d</sup>          | 5–80<br>(proportional to dose)    | 2–4              | 98                  | 30–56         | Feces           | [81, 82]   |
| Isavuconazonium | Oral                 | Healthy human volunteers | Very high                | 1.03<br>(100 mg dose)             | 0.75–1           | 98                  | 56–77         | Feces           | [81–83]    |
| Isavuconazole   | IV <sup>a</sup>      | Healthy human volunteers | nr <sup>d</sup>          | 1.45<br>(100 mg dose)             | 1.3–5            | 98                  | 76–104        | Feces           | [81–83]    |

<sup>a</sup>IV: intravenous; <sup>b</sup> $C_{\max}$ : maximal concentration; <sup>c</sup> $t_{\max}$ : time to reach maximal plasma concentrations after oral administration; <sup>d</sup>nr: not reported.

intravenous formulations showed favorable pharmacokinetic (Table 4) and pharmacodynamic profiles [82]. This drug has the potential to become an important agent for the treatment of invasive fungal infections, principally because of its relatively broad and potent *in vitro* antifungal activity, its favorable pharmacokinetic profile, and the absence of severe adverse effects [82, 148, 149].

## 5. Conclusions

Although the antifungal drugs used in clinical treatments appear to be diverse and numerous, only few classes of antifungal agents are currently available in oral and intravenous

forms. Additionally antifungal resistance based on different mechanisms continues to grow and evolve and exacerbate the need of new treatments against *Candida* infections. In this regard, new formulations of antifungals, combination therapies and development of new bioactive compounds might be useful for a better therapeutic outcome. Particularly, there are three compounds in Phase II or III studies with actual promise for the treatment of invasive candidiasis.

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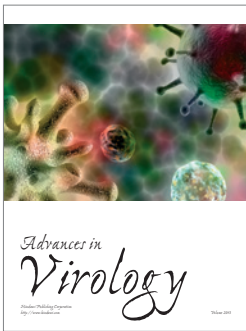
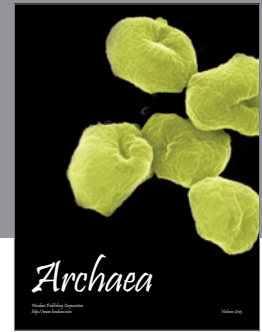
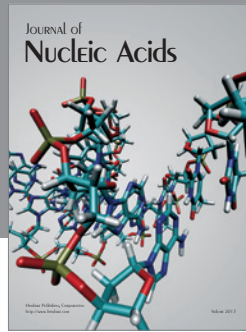
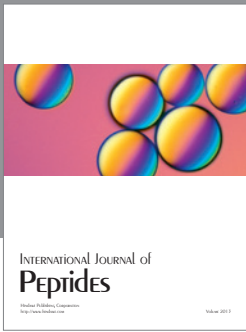
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