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RESEARCH ARTICLE

Candida Awareness: Overview of Characteristics, Resistance to Antifungal Agents, and Biocontrol by Natural Products

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ABSTRACT

Candida species have long been recognized as harmless commensals associated with humans. These organisms are typically located on the mucosal surfaces of the gastrointestinal and genitourinary tracts, as well as on human skin. Nonetheless, they can act as opportunistic pathogens in patients with weakened immune systems and those who are immunocompromised. The increase in morbidity and mortality associated with Candida is reported to be alarming on a global scale (Nosocomial infections), primarily because Candida is the primary cause of hospital-acquired infections. Over the past few years, there has been a tremendous gain in our understanding of the mechanisms and components that contribute to infections. Furthermore, new virulence mechanisms have been identified recently. In conclusion, this review provide an update on the understanding of the pathogenic mechanisms of this important human pathogen and explore the use of natural products as antifungal agents.

INTRODUCTION

A broad collection of eukaryotic organisms known as fungi perform important ecological tasks and are used in industry and medicine (Buckley, 2008). They appear in a variety of sizes, ranging from tiny unicellular bacteria to huge mushrooms, and they play a part in essential activities, such the breakdown of organic matter and their symbiotic relationships with plants (Lanfranco *et al.,* 2016). More than 300 different fungus species have the potential to harm people's health (Taylor *et al.,* 2001). Fungal pathogens pose a serious threat to global health, annually responsible for an approximated 1.5 million fatalities (Brown *et al.,* 2012). The second most common reasons for mortality globally are infectious diseases, followed by cardiovascular diseases (WHO, 2018). Opportunistic fungal infections have become more common during the last 20 years, increasing morbidity and mortality. Major opportunistic fungal infections are caused by fungus belonging to *Aspergillus, Penicillium, Rhizopus, Mucor, Candida, Fusarium, Dermatophytes, and Cryptococcus* families (Figure 1).

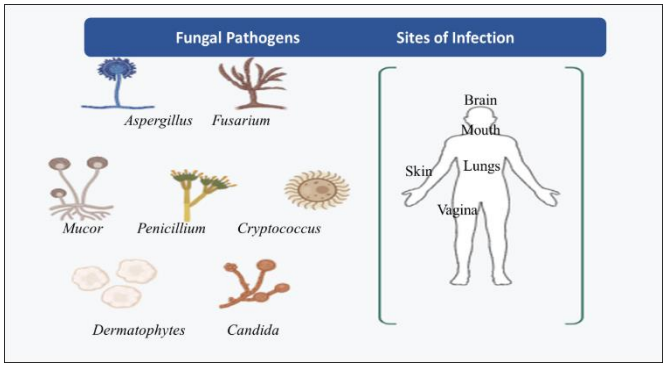

Figure1: Common Fungal Pathogens and Main Infections Sites (Created in BioRender.com).

According to Kainz *et al*. (2020), 1.7 million people died as a result of fungal diseases. Aspergillus and *Candida* spp. account for the massive of illnesses (Divyashree *et al.,* 2023). The medical strain of fungal infections, however, extends far beyond these serious death rates. Fungal infections impact over one billion people each year, with more than 150 million instances being severe and life-threatening. Importantly, the number of instances is always increasing (Houšť *et al.,* 2020).

It can result in a variety of infections that are typically referred to as fungal infections in humans. *Candida* are unicellular, usually dimorphic fungi and cause opportunistic fungal diseases (Nash *et al.,* 2017). *Candida* infections range from superficial cutaneous to mucosal infections to multiple organs widespread infections (Sardi *et al.,* 2013). These organisms can colonize human skin (Kuhbacher *et al.,* 2017), gastrointestinal (Neville *et al.,* 2015), and reproductive tracts (Barousse *et al.,* 2004). Since much research concentrates on its ability to cause infection, *Candida albicans* is the most widely researched member of the genus (Kojic & Darouiche, 2004; Spellberg *et al.,* 2005; Thompson III et al., 2010). The respiratory system, central nervous system, eye, bronchial region, cardiovascular area, and urine bladder can all get infected by invasive and multi-organ yeast infections (Sardi *et al.,* 2013; Vermitsky *et al.,* 2008). Immunocompromised individuals continue to be most susceptible to fungal infections, which have been identified as the most common cause of human disease since the end of the twentieth century (Pfaller & Diekema, 2007). Most of these infections occur in immunocompromised individuals and originate from the gastrointestinal tract (Miranda *et al.,*2009). According to Guessous-Idrissi *et al*., (2007), immunosuppression is still one of the most prevalent warning signs for infection. A significant rise in *Candida* infections has resulted from immunosuppressive disorders like AIDS and treatments that suppress the immune system like intense chemotherapy. These infections are currently one of the main reasons for hospital death and infection. Distributed forms of candidiasis can be fatal in immunocompromised cancer patients and those receiving multiple treatments, with mortality rates ranging from 35-60% (Seleem *et al.,* 2015*;* Eggimann *et al.,* 2015). While *Candida albicans* is the most isolated yeast in America, there are emerging non-*Albicans* species, and patient specimens from other countries show higher numbers of these species (Blot *et al.,* 2008). Nevertheless, it's crucial to note that the collection of species other than *Candida albicans* has increased recently (Taei *et al.,* 2019; Singh *et al.,*2020). These species include *C. parapsilosis, C. tropicalis, C. glabrata, C. dubliniensis, C. guilliermondii, C. kefyr, and C. krusei* (Aydemir *et al.,*2017). The pathogenicity of *Candida* is caused by several virulence factors, such as immunity of the host, adhesion and formation of biofilm, and the generation of hydrolysis enzymes, including as hemolysins, phospholipases, and proteases (Silva *et al.,* 2012).

1. Features of the *Candida* Species

Candida are opportunistic, eukaryotic, worldwide yeasts included in the group of Saccharomycetales family, the Ascomycota phylum, the Hemiascomycetes class, and the Candidaceae phylum. These are absence of pigmentation, non-encapsulated, aerobic or facultative anaerobic thallus organisms with single cells that reproduce asexually through budding spores (Lagane, 2007). *Candida auris* appeared oval under a light microscope after staining with crystal violet (Figure 2). They range in size from three to fifteen micrometers, and polysaccharide in the cell wall distinguishes yeast from other fungi and the capability to exhibit many forms. Depending on the environmental factors (temperature, pH, etc.), they can develop into pseudomycelia or mycelia, which are more elongated and cylindrical forms (Fitzpatrick *et al.,* 2006). The development of pseudomycelia is caused by the bud's ability to separate from the mother cell. On the opposite side, the true mycelium and germ tube were found only in *C. albicans* and *C. dubliniensis*. *C. albicans* differ from other members of the genus because it contains chlamydospores and pseudomycelia. Chlamydospores are huge structures at the extremities of hyphae, often spherical with a thick wall and a dimension from 7 to 13 m which formed under stressful conditions. Their presence is easy to determine because they are typically visible without staining. The vegetative form of filamentous fungi, which resemble threads, is called hyphae. The freshly divided cells of unicellular fungus are called pseudohyphae; the formation process is the primary distinction between hyphae and pseudohyphae.

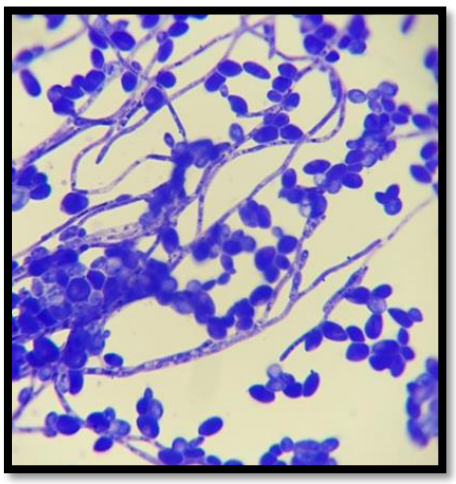

Figure 2: Candida auris cells mycelia that are involved in the infectious process under light microscope (Alzahrani et al., 2024).

2.*Candida* Infection and Diseases

The primary reason for nosocomial fungal diseases, particularly in medical centers, is diseases caused by the genus *Candida* (Dadar *et al.,* 2018). The prevalence of *Candida* species infections has been rising and treating them has become more challenging because the development of malnutrition, endocrine abnormalities, immunological diseases, an excessive utilization of immunosuppressive medications, the widespread utilization of internal medical devices, and broad-spectrum antibiotics (Li *et al.,* 2007; Garcia-Cuesta *et al.,* 2014). Only fifteen of the more than 150 species of *Candida* that are known to exist are infectious pathogens that have been identified from patients including *Candida albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, *C. guilliermondii*, *C. lusitaniae*, *C. dubliniensis*, *C. pelliculosa*, *C. kefyr*, *C. inconspicua*, *C. lipolytica*, *C. famata*, *C. rugosa*, and *C. norvegensis*. Human pathogenic *Candida* species can cause both superficial and deep-seated mycoses (Table 1), which are spread throughout the world (Douglas, 2003). However, *Candida* is growing in importance as a clinical issue and has the potential to cause infections known as candidiasis (Li *et al.,* 2007; Cuesta *et al.,* 2014; Douglas, 2003). As stated in reports by the USA, infections resulting from *Candida albicans* have a death rate of almost forty percentage, making it the deadliest type of infection compared to those brought on by bacteria or fungi (Talapko *et al.,* 2021). In Asian countries, non-albicans Candida spp. (NAC) is more prevalent than Candida albicans (Zhang *et al.,* 2020; El Zakhem *et al.,* 2021).

Globally, the most common fungal disease affecting humans is called candidiasis. Mucosal-cutaneous infections and visceral *Candida* are referred to as candidiasis (Segal & Frenkel, 2018). Oral candidiasis is one of the most common symptoms of HIV infection; more than 90% of HIV-positive individuals have this manifestation (Thompson III *et al.,* 2010). *Candida albicans* is the most common species, found in the oral membrane, and is thought to be more pathogenic in humans, accounting for about half of candidiasis (Cuesta *et al.,* 2014). Urogenital is common fungi affecting the female vaginal tract (Kamath *et al.,* 2013). Pregnant, diabetic, and patients receiving corticosteroid and antibiotic therapies are among the groups most likely to acquire this infection (Cateau *et al.,* 2012; Seleem *et al.,* 2017). Deep infections as osteomyelitis, peritonitis, and abdominal abscess are referred to as invasive candidiasis, which can significantly affect all organs (Dabas, 2017). In 2015, Hesstvedt and others define candidemia as the presence of a *Candida* infection in the blood of those who are overheated. Among non-*C. albicans*, *Candida parapsilosis* is the most typical reason for infections of the bloodstream (Miceli *et al.,*2011). Both pediatric and adult populations are affected by *Candida auris*, which has been primarily found in critical care patients (Chowdhary *et al.* ,2013 & Calvo *et al.,* 2016). Virulence factors of *Candida* relate to an organism's capacity to not only adhere and biofilm formation, but also to destroy host tissues, potentially with the help of hydrolysis enzymes released into the surroundings.

Table 1: List of *Candida* species and their Sites of Infection

Candida sp.	Sites of Infection	References
C. albicans	Mucosal and systemic fungal infection.	(Pfaller *et al.,* 2001).
C. glabrata	Vaginal, oral, Candidemia	(Pfaller *et al.,* 2001; Fidel *et al.,* 1999)
C. tropicalis	Blood cultures, Infection of neonates.	(Pammi *et al.,* 2013).
C.parapsilosis	Systemic candidiasis in neonates and intensive care unit patients (ICU).	(Silva *et al.,* 2012).
C. krusei	Bone marrow or stem cell transplant recipients' Haematological malignancy patients, UTI, endopthalmitis, osteomyelitis and endocarditis.	(Pfaller *et al.* ,2001; SC& Saini, 2015; Miceli *et al.,* 2011)
C. kefyr	Rare species, disease in immunocompromised host.	(Pfaller *et al.,* 2001).
C. dubliniensis	Oral cavities of HIV-positive patients and candidemia.	(Sullivan & Coleman, 1998)
C. arugosa	Catheters and parenteral nutrition.	(Minces *et al.,* 2009)
C. auris	ICU, candidemia.	(Jeffery-Smith *et al.,* 2018)

3. Identification of *Candida*

Sabouraud Dextrose Agar (SDA) is the most utilized for the isolation of *Candida*. Low pH of SDA allowing growth of *Candida* and inhibit bacterial growth. Additionally, chromogenic agars have been established, such as CHROM agar *Candida* (Figure 3) that enable the recognition of certain *Candida* species according to colony shape and color after primary culture (Williams & Lewis, 2000). The benefit of this medium is that allowing for the identification of numerous species of *Candida* present in a single infection, which can be crucial when choosing further treatment choices (Mars & Martin, 2009). Moreover, typical tests for recognizing *Candida albicans* is the "germ-tube test," using horse serum for inducing hyphal outgrowths (germ tubes) of *Candida albicans* and incubated at 37◦C for two to four hours. Also, the biochemical identification of *Candida* species is mostly depending on how they use carbohydrates. In a traditional technique, test isolates would have been cultured on basal agar without carbon sources. After that, solutions of carbohydrates were added to either the discs of filter paper on the agar surface or the wells of agar. The identical idea underlies commercial devices, but the test carbohydrate is kept in test plastic wells. Changes in color in some kit systems or variations in turbidity are used to determine the growth in each well. Using a database comparison, the test organism is identified using numerical codes derived from the test findings (Arjuna & Morrison Christine, 2005).

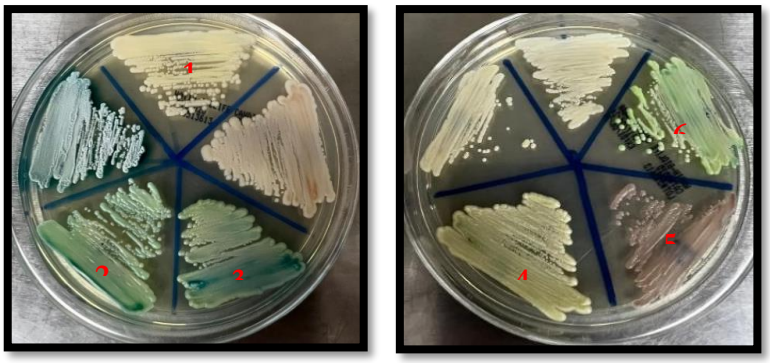

Figure 3: growth of different *Candida* spp. on Chromo agar (1) *Candida auris*; (2) C. *tropicalis*; (3) *Candida ciferrii* (4) *C. albicans*; (5) *C.glabrata* and (6) *C. parapsilosis* (Alzahrani *et al*., 2024).

The capacity of *C. albicans* and *C. dubliniensis* to develop morphological characteristics known as chlamydospores allows them to be distinguished from other species (Figure 3). Chlamydospores are cylindrical structures that form at the ends of the hyphae after samples are cultivated on a medium deficient nutrient, like cornmeal agar. Applying techniques that utilize phenotypic standards is not as stable as identifying through analysis of genetic variability. Genetic variation-based detection of *Candida* is accomplished through analysis of electrophoretic species variations and restriction

fragment length polymorphisms using gel electrophoresis (Williams & Lewis, 2000). PCR techniques specific to a species have also been applied to identify species of *Candida*.

4. Antifungal Agents Affecting *Candida* Cells and their Toxicities

According to Houšť *et al.* (2020), antifungal sensitivity testing is an essential prerequisite for defining the best course of treatment for a patient and identifying antifungal resistance. Antifungals that fall into several pharmacological classes and target distinct biological processes can be used to treat candidiasis may either inhibit (fungistatic) or kill (fungicidal) the growth of this pathogenic yeast. Five classes of antifungal agents (azoles, echinocandins, polyenes, Allylamines, and pyrimidine analogs) are used for the treatment of fungal infections. These agents and their mechanisms and toxicities are summarized in table 2 which work by either suppressing or inhibiting the growth of the harmful yeast. The pathway is summarized in Figure 4.

Table 2: List of Antifungal Agents and their Toxicities

Antifungal Agents	Mechanism of action	Toxicity	References
Polyenes (Nystatin & Amphotericin B)	Incorporates into the fungal lipid bilayer and binds to ergosterol, leading to pore formation.	Nephrotoxicity, In fusional toxicity, low blood potassium	(Diekema *et al.,* 2003; Vermes *et al.,* 2000)
Nucleoside analogs (5-flucytosine)	Inhibits fungal protein synthesis after being converted to 5-fluorouracil and incorporated into fungal RNA.	Colitis, bone-marrow suppression, and liver toxicity.	(Carmo et al., 2023).
Azole (Imidazoles)	Interfering with the enzyme lanosterol demethylase and leading to inhibition of fungal growth.	Elevation of transaminases and visual disturbances, rash and gastrointestinal symptoms.	(Maertens, 2004)
Echinocandin (Caspofungin)	Inhibition of β-D-glucan synthase: the important enzyme in cell wall synthesis.	Headache, fever, nausea, rash, phlebitis, vomiting, and diarrhea.	(Szymański *et al.,* 2022)
Allylamines (Terbinafine)	Inhibit ergosterol biosynthesis by binding to squalene epoxidase, leading to increased membrane permeability.	Bone marrow toxicity and Mild rash, nausea, loss of taste	(Carrillo-Muñoz *et al.,* 2008)

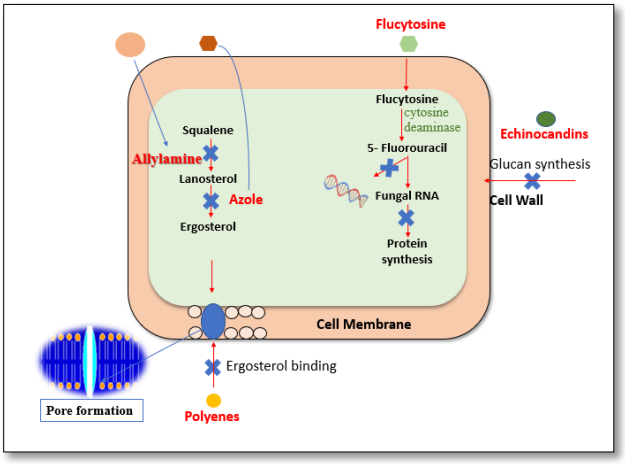

Figure 4: Antifungals classes and Mode of Action (Created on Power point Microsoft program).

4.1. Antifungals that Target Ergosterol and Its Biosynthesis

The primary sterol found in cell membranes of fungi, such as the membranes, is ergosterol. For fungi, sterol is essential to protect the structural integrity and function of plasma and mitochondrial. Lipid rafts are built up of sphingolipids and sterols together in the cell membrane. For treating and preventing *Candida* infections, since azoles affect the enzyme 14-demethylase (Erg11p), which is crucial for the manufacture of ergosterol, they are the most widely utilized class of antifungal drugs (Veen *et al.,* 2003). Azoles connect to Erg11p, which efficiently reduces the levels of ergosterol in the cell. Polyenes are fungicidal and target ergosterol in the plasma membrane through linking to ergosterol and producing pores (Efimova *et al.,* 2014). Pore formation causes rapid leakage of monovalent ions (K^+, Na^+, H^+, and Cl) and subsequent fungal cell death. Polyene medication such as nystatin and amphotericin B is used, but only amphotericin B is used for systemic infections.

4.2. Cell Wall Biosynthesis Inhibitors

Various antifungals target ergosterol, which is important in the biosynthesis of *Candida* cell walls (Figure 5). The fungal cell wall, which is its inflexible outside sheet, serves as the first layer of protection, protecting the cells from osmotic pressure. Due to the absence of cell walls in human cells, antifungal agents target the enzymes that contribute to the biosynthesis of cell walls (Popolo *et al.,* 2001). Antifungal medications echinocandins include micafungin, anidulafungin, and caspofungin, which affect the cell wall were documented. They specifically target the enzyme 1-3 glucan synthase, which is expressed by some genes called FKS1, FKS2, and FKS3 (Perlin, 2011). These medications are typically fungicidal and are frequently selected due to their low human toxicity (Munro, 2010).

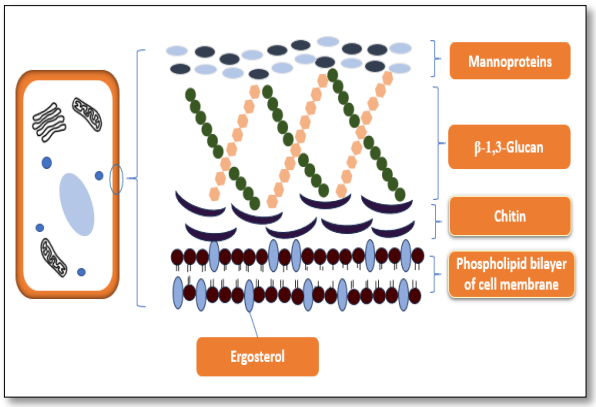

Figure 5: Fungal Cell Wall composition (Created on Power point Microsoft program).

4.3. Nucleic Acid Biosynthesis Inhibitors

Antifungals that interfere with nucleic acid production are also significant. One of the earliest groups of antifungal medications was created in the 1950s. Antifungal 5- flucytosine (5FC) interferes with the formation of nucleic acids. The cytosine permease enzyme allows sensitive cells to acquire 5FC (Vermes *et al.,* 2000). 5- Flucytosine (5FC) is transformed to 5-Fluorouracil (5FU), which is metabolized to other significant antifungals that inhibit nucleic acid production as summarized in Figure 4. Therefore, protein translation is affected due to fungal RNA containing fluorouridine triphosphate (5FUTP) rather than uridine triphosphate (UTP).

For invasive infections, the location of infection is crucial in the selection of antifungal agents. Echinocandins' high molecular weight prevents them from penetrating many sites, including cerebrospinal fluid, thus urine contains relatively little active medication. (Kofla & Ruhnke, 2011; Fisher *et al.,* 2011). Therefore, alternative treatments should be utilized for infections of the central nervous system (CNS) or urinary tract caused by *Candida*. For urinary tract infections, using formulations of amphotericin B with the potential adding of 5-flucytosine had been recommended (Fisher *et al.,* 2011). For CNS disorders, empirical amphotericin B and 5-flucytosine have shown some promise, with therapy optimization based on susceptibility testing (Pappas *et al.,* 2016).

Resistance to antifungal chemicals has been reported to be emerging more frequently as their use increases. The capacity to grow at concentrations of antifungal drugs that stop growth and/or kill

majority of the isolates of that species is known as antifungal resistance. Due to inefficient binding to drug targets and/or efflux activities seen in all members of a certain species, some species are naturally resistant to certain antifungals. For instance, *Candida krusei* and *Candida auris* are naturally resistant to fluconazole while acquired resistance is the term used to describe the development of resistance mechanisms that allow the fungus cells to proliferate at higher concentrations of the antifungal medication than those found in the wild-type population such as *C. glabrata* (Fisher *et al.,* 2022). Three mechanisms of resistance are found for the azoles in *Candida* species including 1) target gene mutation resulting in affinity loss for the azole, 2) target gene upregulation resulting in reduced drug efficacy simply due to competition between the drug and the target, 3) decreased intracellular drug concentration due to efflux pump stimulation (Arendrup, 2013), and finally 4) biofilm formation (Rodrigues & Henriques, 2017); the biofilm captures the antifungal in a matrix polymer rich in glucan, which decreases the drug's concentration (Nett *et al.,* 2010). Erg11 mutations linked to the emergence of fluconazole resistance in Candida albicans have also been identified in isolates of *Candida auris* (Lockhart et al., 2017). Only target gene mutations for the echinocandins have been characterized as the fundamental mechanisms in resistant isolates (Arendrup *et al.,* 2010; Arendrup *et al.,* 2011; Garcia-Effron *et al.,* 2008; Costa-de-Oliveira *et al.,* 2011). Two subunits make up the glucan synthase enzyme complex: Rho1p, a regulatory component, as well as the catalytic subunit, which three associated genes (FKS1, FKS2, and FKS3) encode. Mutations linked with resistance have been explained in FKS1 and FKS2, and naturally occurring alterations have been shown in those species with intrinsic reduced susceptibility (Arendrup *et al.,* 2010; Arendrup *et al.,* 2011; Garcia-Effron *et al., 200*8; Costa-de-Oliveira *et al., 2011*). Amino acid alterations in two specific hot spot areas of Fks1 for all *Candida* species and Fks2 in *C. glabrata* are linked to echinocandin resistance (Perlin, 2011). The main mechanisms of antifungal agents' resistance are summarized in Figure 6. Furthermore, resistance to multiple antifungal drugs has increased since 2017 principally in two species: *C. auris* and *C. glabrata* (Denning, 2022). The only two first-line monotherapeutic medications for invasive candidiasis, fluconazole and echinocandin class, are proven to be ineffective against these two species (Arendrup & Patterson, 2017). So, there is no effective antifungal treatment for *C. auris* isolates since 3–10% of these isolates are also resistant to the polyene amphotericin B (Denning, 2022). Because these C. auris isolates are resistant to at least one compound in each of the three drug classes, they fall into the category of XDR (extreme drug resistance) (Arendrup & Patterson, 2017).

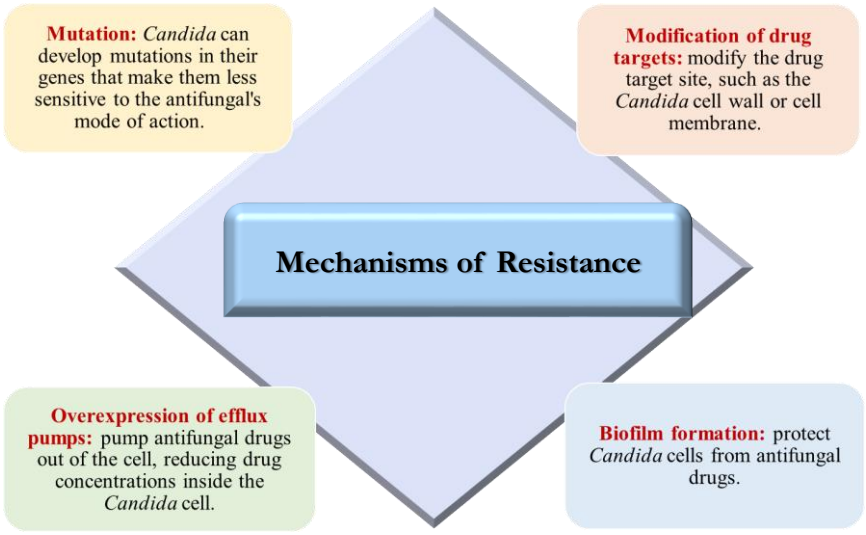

Figure 6: The main mechanisms of antifungal agents' resistance in *Candida* species.

5. Antifungal Agents from Natural Sources

5.1. Plant Secondary Metabolites as a Source of Active Antifungal Inhibitory Substances

Plants generate a diverse range of secondary metabolites that exhibit antifungal properties. Since the late 19th century, the antimicrobial and antitoxin properties of certain plants, herbs, and their components have been well-documented (Saadabi, 2006). Numerous studies have shown in lab experiments that various plant tissues, including roots, leaves, seeds, and flowers, contain

antibacterial, antifungal, and anti-insect qualities (Davicino *et al.,* 2007). *Piper betel* and *Piper nigrum* extracts demonstrated antifungal activity against *Candida albicans* at a concentration ratio of 1:1, v/v (Umadevi *et al.,* 2018). The chloroform extract of *Matricaria chamomilla* exhibited antifungal activity against *Candida albicans* and *Fusarium species* (Hameed et al., 2018). Another study reported that 4% *Lawsonia inermis* was more effective than clotrimazole against *C. albicans* infection in female rats (Yaralizadeh *et al.,* 2018). The *Camellia sinensis* crude extract combined with milk exhibited a slightly higher Minimum Fungicidal Concentration compared to the fluconazole drug (Sigei et al., 2018). Various plant extracts have been investigated for their antifungal properties, including Neem, Garlic, Ginger, Turmeric, and Clove (Mahmoud *et al.,* 2011; Li *et al.,* 2016; Sharma *et al.,* 2011; Murugesh *et al.,* 2019; Rifai *et al*., 2024).

5.2 Actinomycete Secondary Metabolites as a Source of Active Antifungal Inhibitory Substances

Actinomycetes, especially those from the genus *Streptomyces*, have been recognized as powerful antifungal agents against *Candida* species. These microorganisms produce a wide range of bioactive compounds that exhibit strong antifungal properties, making them valuable sources. The antimicrobial activity profile of *Streptomyces* sp. RAB12 demonstrated stronger antimicrobial effects against bacterial strains and *Candida albicans* than the typical actinomycin D (Rathod *et al.,* 2018). The isolate *Streptomyces mutabilis* which was isolated from a Saharan soil showed the highest anticandidal activities against *Candida albicans* and others pathogenic fungi (Belghit *et al.,* 2016). Sceliphrolactam is one of the new antifungal secondary metabolites which isolated from *Streptomyces* sp. in 2011 and showed strong antifungal efficacy against *C. albicans* that were resistant to amphotericin B, with a minimum inhibitory concentration (MIC) of 4 µg/ml (Oh *et al.,* 2011). Additionally, 15-glycidylfilipin III (polyene class) was isolated from the cultures of a soil actinomycete, *Streptomyces lavenduligriseus*, and showed a high inhibition of *C. albicans* with a MIC value of (6.25 µg/ml) when compared with MIC (3.13 µg/ml) for nystatin as control (Yang *et al.,* 2016). Furthermore, a novel polyketide glycoside (gilvocarcin HE) derived from the ethyl acetate extract of *Streptomyces* sp. QD01-2, demonstrated strong antimicrobial activity against *S. aureus, B. subtilis, E. coli, and C. albicans* with MICs ranging from 0.25 to 2.5 µg/ml (Hou *et al.,* 2012). Srivastava and Dubey in 2016 found that *Streptomyces chrestomyceticus* displayed strong anticandidal activity and had Strong inhibition of biofilms of several reference strains of *C. albicans*. In our previous study, we found that the isolate *Streptomyces plicatus* NM3 demonstrated excellent activity against resistant *Candida* isolates and produced secondary metabolites (Alzahrani *et al.,* 2024). More than 70% of the identified compounds were produced by different *Streptomyces* sp. strains and *Amycolatopsis, Kibdelosporangium, Pseudonocardia, Micromonospora*, and *Actinoalloteichus*, created the the remaining compounds (Jakubiec-Krzesniak *et al.,* 2018).

6. CONCLUSION

It is commonly acknowledged that the prevalence of infections caused by *Candida* is rising, and that treating these infections carefully will lower the percentage of infections and death in people with impaired immunological systems. Several time- and money-efficient tactics must be used to properly control *Candida* infections. The first step will be to stop the sickness from spreading by vaccinating or immunizing those who are susceptible and using the knowledge gathered from the transcriptomics, proteomics, and genomes of *Candia* and similar species. The next step is to immediately and seriously remedy *Candida* infections. Early detection of the *Candida* species is important for effective antifungal therapy. In a clinical setting, extremely sophisticated technologies such as real-time PCR, and DNA microarray should take the role of traditional approaches like phenotypic, morphological, biochemical, and immunological procedures. Facilities for identification and classification should be created in a way that makes the process quick, accurate, economical, and time-efficient. Following the identification of the strains, patients can get the correct antifungal medications, and the quantity of fungal strains in clinical specimens can be tracked. Any delay in starting antifungal therapy could result in systemic candidiasis and disseminated candidemia, which would cause a high level of *Candida* strain colonization across various internal organs. However, the percentage of resistance has been increased and the toxicity of antifungal agent, all these points to the need to discover antifungals from natural sources such as bacteria and plants extracts. Indeed, these natural products may provide novel and effective alternatives to synthetic antifungal agents,

potentially offering new treatments for resistant fungal infections and reducing the reliance on chemical drugs.

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