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Review Article

Recent Advance Study On Antifungal Drug Evaluation Method

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ABSTRACT

Thanks to the growing need to combat drug-resistant strains and new fungal infections, the field of antifungal medication research has made tremendous strides in recent years. Novel antifungal agents with enhanced efficacy and reduced side effects have been at the forefront of research efforts. From the development of new classes of drugs targeting specific fungal pathways to the repurposing of existing compounds, this review encapsulates the latest breakthroughs in antifungal therapeutics. Additionally, advancements in drug delivery systems have played a pivotal role in improving bioavailability and ensuring targeted action. The exploration of synergistic combinations and the integration of genomic insights further contribute to the promising landscape of antifungal pharmacotherapy.

INTRODUCTION

The appearance of fungus that can infect humans is a major public health concern that is only becoming worse. It is possible to classify important medicinal fungi as primary or opportunistic. While opportunistic infections affect people with compromised immune systems, primary infections occur in healthy populations that are not exposed to endemic fungus.[1] Modern medical technology and services make more people dependent on healthcare, which raises the number of vulnerable hosts. Fungal infections like pneumocystosis, aspergillosis, mucormycosis (zygomycosis), and candidiasis are frequently seen to arise and reappear. On the other hand, Aspergillus can infect over 45% of susceptible hosts, whereas candidemia is one of the most common blood-stream infection causes with a death rate of more than 30%. In diabetics, zygomycosis is frequent worldwide, especially in India. Invasive fungal infections have been linked to 67% of patient deaths in intensive care units.

Despite the availability of a greater variety of antifungal drugs, invasive fungal infections are

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still on the rise and continue to result in significant morbidity and mortality. Unfortunately, as medical progress continues, so does the burden of invasive fungal infections, since people are more susceptible to these illnesses as a result of external pressures brought on by antibiotic use. Mycobacterium tuberculosis infections in individuals have also been linked to the onset of mycotic infections, according to findings from India.[2]. The epidemiology and factors that contribute to the emergence of fungal infection are reviewed in this article. Each year, mycoses—diseases caused by fungi—affect over one billion people globally, however their impact on global disease rates is mostly ignored. An estimated 1.7 million deaths from fungal diseases were documented in 2020. This increase is closely related to the growth in immune compromised individuals brought about by modifications in medical practice, including the use of potent immunosuppressive drugs and intensive chemotherapy. Within the human microbiota, there exist microbes such as Candida spp. that can lead to both opportunistic infections in healthy individuals and potentially fatal infections (invasive candidiasis) in those with compromised immune systems, such as those living with HIV, undergoing chemotherapy for cancer, or taking immune-suppressive drugs. Fungal pathogens like Aspergillus, Fusarium, Candida, and Mucorales can cause healthcare-associated infections in people with underlying diseases, in addition to opportunistic and systemic infections.

Systemic fungal infections are often caused by the species Candida, Blastomyces, Coccidioides, Paracoccidioides, Histoplasma, and Cryptococcus. The fourth most frequent opportunistic infection in hospital settings is Candida albicans infection [3]. Even with antifungal medication, invasive candidiasis (IC) is deadly in about 42% of reported cases. Nowadays, azoles such as fluconazole, itraconazole, voriconazole (VOR), posaconazole, and isavuconazole (ISV), polyenes such as amphotericin B (AMB), and echinocandins such as caspofungin, micafungin, and anidulafungin are the most often used antifungal medications for IC. A main or secondary infection brought on by the Candida species is called candidiasis. The mouth, throat, skin, vagina, fingers, nails, trachea, lung, or gastrointestinal system can all become infected. Candida species can induce invasive candidiasis (IC), which includes deep-seated tissue infections and blood-derived infections (candidemia), when there is significant immune system impairment. Hospitalized patients with a variety of underlying illnesses may have invasive candidiasis (IC), which has been linked to deaths ranging from 27.5 to 55% in recent years. Even though C. albicans is still the most common cause of invasive candidiasis, non-albicans infections like C. krusei, C. glabrata, C. lusitaniae, C. tropicalis, and C. parapsilosis have become more common in recent years. These changes in species distribution are linked to various geographic locations, hospital-related factors, and antifungal medications that patients are prescribed. Any modification in the connection between Candida species and host can be a risk factor for the development of invasive candidiasis because Candida species are a natural component of mucosal flora. The risk of infection is greater in patients hospitalized to intensive care units (ICUs). This may be because of the patient's weakened immune system, prolonged hospital stay, and Candida colonization. Up to 80% of patients admitted to the intensive care unit have Candida colonization within the first week of their stay; only a small percentage of these mild colonizations progress to severe infections [4].

Need of Drug Evaluation

If the treatment results for invasive fungal infections were acceptable, the limited number of antifungal medications that are now on the market would not be an issue. Generally speaking, though, this is untrue. Distinguishing mortality attributable

to fungal infections from that resulting from comorbidities is a challenging task in research on fungal infection outcomes. For instance, the 90-day survival rate following a candidemia diagnosis ranges from 55% to 70%, contingent upon the underlying ailment of the patient and the particular species that is producing the illness. Even with the use of voriconazole, the results are even worse for aspergillosis. In resource-rich areas with access to amphotericin B and 5-flucytosine, the 1-year mortality rate from cryptococcosis is about 25%, while in resource-poor areas where fluconazole is the only treatment available, the mortality rate is significantly higher. According to a great essay on the state of the art in fungal disease detection and treatment, the need for more potent medication as well as relatively subpar diagnostic techniques are most likely to blame for the dismal outcomes for invasive fungal infections. It's crucial to remember, though, that the echinocandins, the newest class of antifungal medications, were only discovered in the 1970s and took 30 years to reach the clinic. Likewise, the most effective treatment for cryptococcosis is predicated on two medications that are almost half a century old. The number of individuals at risk for fungal infections is almost anticipated to rise due to ongoing medical advancements and the use of immunomodulatory medications. It is therefore improbable that the current rate of antifungal drug development will be able to meet therapeutic needs, especially given the increasing frequency of reports of resistance to current treatments.[5]

Mechanism of Action

Azoles

The azoles prevent lanosterol from being converted to ergosterol by inhibiting the enzyme lanosterol 14α demethylase, which is part of the ergosterol production pathway. Reduced ergosterol availability and intracellular 14α methyl sterol accumulation lead to modifications in membrane permeability, stiffer membranes, growth suppression, and eventually mortality.

A few azoles have other mechanisms of action that are helpful for the final result of treatment. For instance, sertaconazole binds directly to nonsterol lipids in the fungal cell wall, increasing permeability and causing mycelium lysis in addition to inhibiting the ergosterol synthesis pathway. Thus, sertaconazole shows fungicidal activity at higher concentrations. Sertaconazole's distinct ring of benzothiophene improves its lipophilic qualities, allowing for skin retention and the achievement of fungicidal concentration in the stratum corneum. Because liconazole's imidazole moiety is integrated into its ketone dithioacetate structure, it has a very low minimum inhibitory concentration (MIC) for Trichophytonrubrum and great effectiveness against dermatophytes. Additionally, it exhibits potent in vitro action against Aspergillus fumigatus and Candida albicans.

Allylamines

Allylamines prevent squalene from being converted into squalene 2, 3 epoxide, which is a precursor to ergosterol, by inhibiting squalene epoxidase of the ergosterol production pathway. The resulting build-up of squalene causes toxicity to the fungal cell membrane, which is why allylamines have fungicidal properties.

Ciclopirox

Because of its strong affinity for trivalent metal cations, ciclopirox inhibits the enzymes that break down peroxide inside fungal cells, including cytochrome oxidase and other metal-dependent enzymes. Ciclopirox targets cell growth and metabolism by targeting many proteins involved in cellular metabolism, such as DNA replication, DNA repair, and cellular transport.

Amorolfine

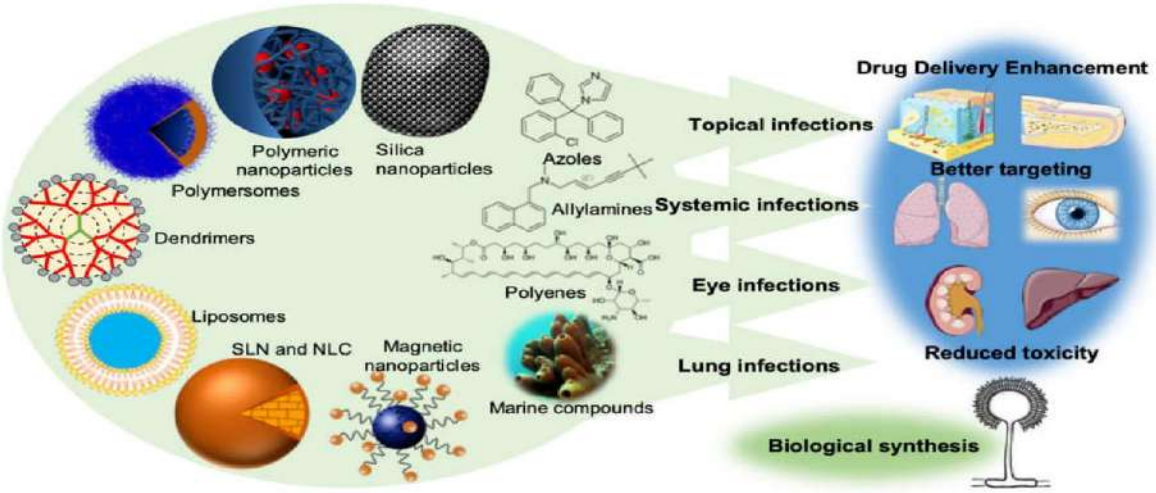
Two processes in the production of ergosterol—the delta 14 reduction and the delta 7–8 isomerization—are disrupted by amorolfine.

Ergosterol is reduced and delta 14 sterol ignosterol accumulates in the cell membrane as a result of this inhibition. It is fungicidal against most species and has a broad antifungal action against molds, yeasts, dermatophytes, and dimorphic fungi.

Additional Actions of Topical Antifungals

Anti inflammatory action

Additional anti-inflammatory properties of azoles, such as clotrimazole, econazole, miconazole, ketoconazole, and sertaconazole, can help to lessen symptoms. Interleukin 2 (IL 2), tumor necrosis factor alpha, interferon alpha, IL 4, and granulocyte macrophage colony stimulating factor are all inhibited by sertaconazole nitrate when released from activated human cells.[6] The emergence of resistance to antifungal medication is primarily responsible for the mycosis incidence, mortality rate, and difficulty of treatment, even with the availability of antifungal medicines. In individuals with weakened immune systems in particular, this illness is made worse. For example, as of November 2013, 19,262 organ transplants have occurred in the United States. This coincided with an increase in the immunocompromised patients' vulnerability to invasive fungal infections.



Recent Advances of Antifungal Drug

The ability of current antifungal medications to treat infections, particularly systemic infections, is restricted, and no significant advances in antifungal therapies have been established recently. Therefore, novel treatments are required to combat pathogenic fungus. Over the past few years, a number of strategies have been developed in an effort to identify fresh answers. Researchers try to find new antifungal medications by screening chemical compound libraries systematically, evaluating compounds from natural sources like plants, the sea, and microbes, or by testing already-approved medicinal compounds. The underlying biology of fungal microorganisms, both in vitro and in vivo, is another goal of research. All fungal diseases depend critically on their interactions with hosts. By focusing on this interaction, new treatments are offered that may be combined or used alone with already-approved antifungal medications. This combination might also influence the emergence of medication resistance to antifungals. The antifungal characteristics of so-called natural compounds (NP), also known as natural bioactive chemicals, which are extracted from plants, other microbes, or marine species, have been the subject of much analysis. Certain chemicals are studied due to their recognized fungus-related triggering mechanisms, whereas other compounds undergo blind testing to determine their antifungal efficacy. Though intriguing results were obtained, none of these research have yet to yield a drug acceptable for the clinical trial stage. Additional research

concentrated on in vitro screens of several medications that are already being used in clinical practice to see if they could enhance the antifungal action of the fungistatic agent fluconazole (FLC) against Candida albicans cells. This made it easier to find a number of drugs, including efflux pump inhibitors (compounds derived from milbemycin), inhibitors of the calcineurin or Tor pathways, and, more recently, antibodies against the heat-shock protein (HSP90). Specifically, it was demonstrated that calcineurin pathway inhibitors were completely efficacious in vivo in increasing the potency of fluconazole and also significantly reduced the pathogenicity of fungi. In an effort to find new antifungal chemicals, systematic screening of chemical compound libraries was also conducted, mostly by industrial laboratories. Recently, a novel glucan synthase inhibitor that is effective against both Candida albicans and Candida glabrata was discovered using high throughput screening of the historical Schering-Plough chemical collection [7]. Through the use of drugs, drug-treated Caenorhabditiselegans infected with Candida albicans were used to measure the survival of another type of high-throughput screening of chemical libraries. The ability to simultaneously screen compounds for both host toxicity and antifungal activity solves a major challenge in the current antimicrobial discovery process. Using this innovative C. elegans system, a pilot screen for antifungal compounds was conducted, and 15 compounds that extended the survival of worms infected with the medically significant human pathogen C. albicans were found. One of these substances, caffeic acid phenethyl ester (CAPE), demonstrated efficacious antifungal action against multiple additional fungus species in vitro and in a mouse model of systemic candidiasis. Furthermore, by using this whole-animal approach, it would be possible to identify substances that alter immune responses or fungal virulence factors that are only expressed during infection.

Genome-Wide Studies to Detect Potential New Antifungal Targets.

The development of currently available antifungal medications and the prevention of treatment resistance have contributed to our understanding of the fundamental biology of the fungal pathogen. Several organizations worked to create 16 systematic mutants, primarily for Candida albicans, for the International Journal of Microbiology collection in order to achieve this goal. Certain research groups have evaluated the essentiality of Aspergillus fumigatus and Candida albicans genes using the GRACE (gene replacement and conditional expression) or CPR (conditional promoter replacement) technologies. In C. albicans, 567 important genes were found in one investigation. 35 of the 54 A. fumigatus genes that were screened in a different investigation were determined to be essential in A. fumigatus based on ortholog functions and essentiality in C. albicans and S. cerevisiae [8]. Initially, by administering well-known antifungal medications to strains and examining factors like growth modification and subsequent transcriptional rewiring, some writers aim to gain a deeper comprehension of the mechanisms of action of the drugs and/or identify potential synergistic effects between them. It was discovered that the reaction to capsafungin involves the gene encoding the transcription factor Cas5. Additional research revealed that deletion of AGE3, which codes for the ADP-ribosylation factor GTPase activating effector protein, eliminates C. albicans' ability to withstand fluconazole. It's interesting to note that Brefeldin A, an inhibitor of ADP-ribosylation factor, had a synergistic effect with other medications for C. albicans, as well as for exposure to fluconazole and 5FC. Their analysis concludes that sensitivity to common antifungal medications was impacted in almost 25% of the

knockout strains. Aspergillus. Lastly, Homann et al. examined 143 transcription factor mutants in 55 different scenarios.[9]. In two further experiments, pools of previously tagged mutants were used to directly screen collections of C. albicans mutants in mice. Zn2-Cys6 transcription factor (TF) mutants were the only ones in one collection, whereas mutations affecting roughly 11% of the overall C. albicans genome without regard to gene class made up the other. More specifically, they discovered that the first small compounds that C. albicans particularly produces and that are necessary for virulence are glycolipid and glucosylceramide. Among the 77 tested, Vandeputte et al. found two Zn2-Cys6 TF mutants. In their pool test, these mutants showed reduced infectivity, which was further supported by independent single strain infections of mice harboring the ZCF13 and ZCF18 viruses [10].

Fungal Sphingolipids

Sphingolipids are widely distributed eukaryotic membrane constituents that are essential for pathogenic fungus pathogenicity, cell control, and signal transduction. The cell wall and membrane of fungi contain a range of sphingolipids that are unique to them, such as glucosylceramides (GlcCer), glycosphingolipids made of a glucose unit attached to a ceramide moiety by a glycosyl bond. Genetic studies have demonstrated that inhibiting sphingolipid production has potential to prevent fungal pathogenicity. GlcCer synthase 1 deficient strains of C. neoformans are avirulent in a mouse inhalation infection model. Similarly, C. albicans becomes avirulent when genes necessary for sphingolipid production are deleted [11].

Calcineurin

The Ca2+-calmodulin-activated proteinphosphatasecalcineurin is a key regulator of the cellular stress responses in all eukaryotes. Numerous physiological processes in pathogenic fungi, such as cell cycle progression, cation homeostasis, morphogenesis, virulence, and antifungal treatment responses, are regulated by calcineurin. In Candida albicans and Candida fumigatus, calcineurin is not necessary for growth, but it is necessary for survival at physiological temperatures in Candida neoformans [12].

Hsp90

The structure and function of several client proteins are regulated by the crucial molecular chaperone Hsp90. Hsp90 is responsible for maintaining important signal transducers, which in turn causes it to operate as a potentiator and capacitor for the storage and release of genetic variation, thereby modulating the link between genotype and phenotype. Hsp90 activity in pathogenic fungi is a promising target for antifungal strategies because it controls important cellular responses to stress caused by drugs.

Genetic depletion or pharmacological inhibition of Hsp90 in S. cerevisiae and C. albicans hinders the acquisition of azole resistance and nullifies resistance that has been acquired through several molecular processes. Azole properties change from fungistatic to fungicidal when Hsp90 function is compromised. In vitro azole activity is enhanced and growth is inhibited when C. neoformans and C. gattii exhibit pharmacological suppression of Hsp90[13]. Moreover, Hsp90 confers basal tolerance and resistance to the echinocandins in Candida albicans, Candida glabrata, and Candida fumigatus. As a result, Hsp90 significantly affects fungal pathogen resistance to various antifungal classes.

Acetyltransferases and Deacetylases

Lysine acetyltransferases (KATs) and lysine deacetylases (KDACs) catalyze the addition or removal of acetyl groups from lysine ε-amino groups. Gene expression and chromatin structure are altered as a result of these key histone alterations. KDACs and KATs therefore have pleiotropic effects on fungal stress responses and cellular signaling. Trichostatin A, a broadspectrum KDAC inhibitor, increases C. albicans azole

activity. Moreover, nicotinamide, an inhibitor of NAD+-dependent KDAC complexes, is effective against clinical isolates of Candida albicans and lowers the fungal kidney burden in a mouse model of disseminated candidiasis. Additionally, nicotinamide exhibits activity against A. fumigatus, Aspergillus nidulans, and other species of Candida, indicating its potential as a broad-spectrum antifungal agent. Additionally, MGCD290 (Mirati Therapeutics, San Diego, CA), a chemical believed to inhibit KDAC Hos2, exhibits synergistic efficacy with azoles and echinocandins against a variety of drug-resistant clinical isolates of Candida albicans. These investigations were limited to in vitro examination; however, in vivo investigations along with first clinical trials have bolstered the application of MGCD290 in conjunction with fluconazole for the management of C. albicans infections [14]. These results thus point to great potential for the combination of KDAC inhibitors with existing antifungals in the treatment of invasive fungal illness.

Antifungals Combination Therapy

When voriconazole cannot be used, current IDSA practice guidelines for invasive aspergillosis recommend using amphotericin B (AmB) and its lipid derivative for both initial and salvage treatment of invasive aspergillosis. The inclusion of echinocandins in salvage therapy, either alone or in combination, to treat invasive aspergillosis is a noteworthy aspect of these guidelines. IDSA acknowledged that certain preclinical studies indicate an additive or synergistic effect when polyenes or azoles are used with echinocandins, but they voiced confusion over how to interpret these results The IDSA has specified a few indications for combination antifungal (CAF) drugs for the treatment of candida infection, including ascending pyelonephritis, fluconazole-resistant candida endophthalmitis, azole-resistant Candida glabrata, and ascending pyelonephritis. For any of these ailments, AmB can be administered as the first line of treatment, either with or without flucytosine. Guidelines also suggest adding intravitreal injection of either voriconazol or AmB to the systemic antifungal medicine used in fluconazole-resistant Candida endophthalmitis when macular involvement is present if the illness is associated with vitritis. Surgical debridement and AmB or its lipid derivative are recommended as treatments for mucormycosis in the joint clinical guidelines for therapy of mucormycosis by the European Society of Clinical Microbiology and Infectious Disease and the European Confederation of Medical Mycology. It is highly advised to use posaconazole for the salvage therapy of mucormycosis. When used in conjunction with posaconazole or caspofungin, AmB is moderately supported for use in treating refractory disease or when previous antifungal medication has proven intolerable. As salvage therapy for fusarium infection, the same guidelines suggest voriconazole or lipid AmB monotherapy (associated with surgical debridement, reversal of the immunosuppressive state, and removal of venous catheters) or posaconazole [15].

New Regulatory pathways and Antifungals

Currently, virtually every medication on the QIDP list is an antibiotic. A new enfumafungin, SCY-078 (SCYNEXIS, Durham, North Carolina, in partnership with Merck), is currently in phase 1 trials for the treatment of Candida and Aspergillus infections. The other two antifungals that have been granted QIDP status are isavuconazole (Astellas, Northbrook, Illinois; and Basilea, Basel, Switzerland); and, most recently, Vical's VL-2397 (VicalInc, San Diego, California) for invasive aspergillosis. Recently, the US and Europe have approved isavuconazole for a number of applications (Table 3). A once-daily injectable or oral broad-spectrum medication, isavuconazole has been demonstrated to be effective against a

variety of fungi, including Candida, Aspergillus, Mucorales, and the real pathogenic fungi, such as Blastomycesdermatitidis and Histoplasma species. Three pivotal studies, SECURE (for IA), VITAL (open label for aspergillosis or dimorphic fungi), and ACTIVE (invasive Candida), made up the isavuconazole phase 3 program (Table 3). The FDA received the first two trials' New Drug Applications for IA and mucormycosis in July 2014. In March 2015, the FDA authorized isavuconazole, also known as Cresemba, for the treatment of invasive mucormycosis and IA. According to a recent report from the ACTIVE trial on invasive candidiasis, the primary aim of this study was not met. Review and debate are therefore necessary before submission to the FDA and European Medicines Agency [16].

Challenges Facing Current Antifungals

Antifungal medications work by taking advantage of differences in two key areas—the fungal cell wall and the cell membrane—between human and fungal cells. Antifungals belonging to three main types are commonly prescribed: azoles, echinocandins, and polyenes. The fungal cell membrane becomes perforated by amphotericin B and other polyenes, which results in cell death. Fluconazole and other azoles disrupt the structural integrity of the fungal cell membrane by inhibiting C14-α sterol demethylase. By preventing the synthesis of β-1,3-D-glucan, capsofungin and other echinocandins interfere with the formation of fungal cell walls [17]. The emergence of medication resistance is the main issue facing antifungals. C. auris drug resistance is a relevant illustration of this issue. 93% of the C. auris isolates examined in a 2017 study showed resistance to the azole fluconazole. Through point mutations and increased copy counts of the gene ERG11, which codes for 14α-lanosterol demethylase in the ergosterol biosynthesis pathway, C. auris gained resistance to fluconazole. It is known that point mutations in ERG11 at F126L, Y132F, and K143R lessen C. auris's susceptibility to azoles. Mutations here are thought to directly lower the binding affinity of azoles to ERG11 since residues F126 and Y132 are located inside the binding site of the protein. In addition, 35% of the C. auris isolates in this same investigation showed resistance to the polyene class of antifungals' amphotericin B. The resistance to amphotericin B is believed to be conferred by mutations in ERG3, another gene implicated in ergosterol production. These alterations encourage the build-up of substitute sterols in the fungal membrane, which thwarts amphotericin B's effects. Even though echinocandin resistance was uncommon—found in only 7% of clinical isolates of C. auris—it could signal the start of a concerning trend. A crucial enzyme in the formation of fungal cell walls, β-1,3-D-glucan synthase, is inhibited by capsofungin and other echinocandins. The glucan synthase gene FKS1 carries a mutation at S639F that causes C. auris to become resistant to echinocandin. The overexpression of gene orthologs from related Candida spp. that code for key facilitator superfamily transporters and ATP transporters, in addition to these specific resistances, is thought to decrease the effectiveness of all main classes of antifungals. Treating C. auris infections efficiently is hampered by the high rates of treatment resistance, delayed identification of the illness, and the immunocompromised groups it typically affects. The high patient mortality rate of 35–60% may be explained by these variables [18]. Increased rates of resistance by fungal diseases have been attributed to the widespread usage of antifungals. The azoles provide a prominent illustration of this phenomena. Since the 1960s, azoles have been employed extensively in agriculture due to their inexpensive cost and broad-spectrum activity. Agriculture exposes fungal diseases to the environment, which is one way that they can become resistant. Antifungal

resistance mechanisms can spread over the world, as demonstrated by the successful cultivation of isolates of triazole-resistant A. fumigatus from tulip bulbs shipped from the Netherlands by researchers. Another study from the Netherlands looked at A. fumigatus isolates from clinical and environmental settings. It discovered that both isolates had the same resistance mechanism and showed genetic similarities, which may support the idea that exposure to the environment fosters the development of resistance to antifungals.

CONCLUSION

resistance patterns, the continuous innovation in antifungal research becomes paramount. Moving In conclusion, the recent strides in antifungal drug discovery present a hopeful paradigm for the effective management of fungal infections. The diversified arsenal of antifungal agents offers clinicians and patients a broader spectrum of treatment options. As we navigate the complexities of evolving fungal forward, collaborative efforts between researchers, clinicians, and pharmaceutical industries will be crucial in translating these advancements from the laboratory to clinical practice, ultimately improving patient outcomes and addressing the challenges posed by fungal infections in the modern healthcare landscape.

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