"EXPLORING THE EFFICACY OF ANTIFUNGAL AGENTS: A SYSTEMATIC REVIEW"

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Abstract

The limited availability of drug classes to treat fungal diseases underscores the necessity, for new antifungal medications. Presently three options exist,. Their efficacy is compromised by various drawbacks such as host toxicity, drug resistance and unwanted side effects. Consequently these issues hinder their effectiveness in practice. The prevalence of infections has notably increased in recent decades accompanied by alarmingly high fatality rates. Moreover the emergence of resistance patterns including resistance to multiple antifungal classes poses a significant concern. Extensive research on the mechanisms of resistance and pathogenicity has revealed potential targets for future antifungal therapies. In the quest for chemicals researchers are employing diverse strategies like screening of the product based on chemical genomics and repurposing existing medications. However need newlly antifungal medicines the current drug research in pipeline. Some potential compounds are in the stages of clinical development each, with a distinct mechanism of action. Thus it is crucial to continue forging with the development of antifungal medications to address the shortcomings of existing treatments, combat resistance and reduce mortality rates associated with invasive fungal infections. The exploration of targets and the implementation of screening techniques bring a promising outlook, for the future. However significant progress is required to fulfill the growing need, for medications that're truly efficient.

Keywords: Fungal infection, treatment approach.

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Introduction

Human health is constantly threatened by fungal infections, which sadly lead to a number of deaths worldwide each year estimated to be, at least 1.5 million [1,2]. Specific types of these infections such as candidiasis, disseminated cryptococcosis and invasive aspergillosis have reported mortality rates ranging from 20-40% [3,4]. These infections are particularly prevalent in individuals with compromised systems due to treatments like anticancer chemotherapy, long term corticosteroid use organ transplantation or underlying conditions that suppress the immune system like HIV/AIDS. The main culprits responsible for 90% of these deaths are Candida, Aspergillus, Cryptococcus, Pneumocystis, Mucor and Rhizopus [5]. However there is a growing concern about the emergence of fungal pathogens such as Zygomycetes, Fusarium or Scedosporium that are now recognized as agents of invasive fungal infections [6].

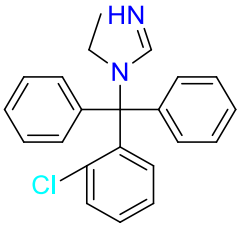
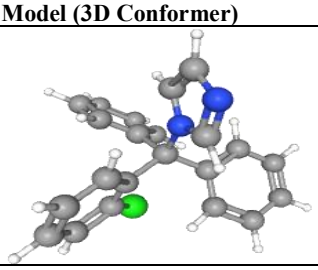
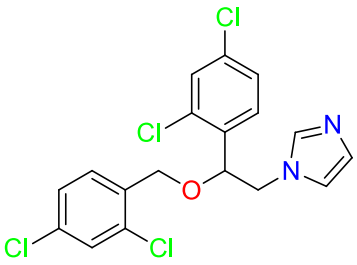
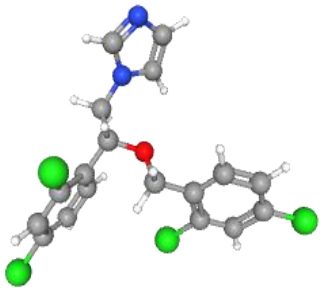
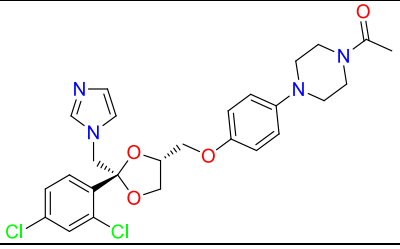
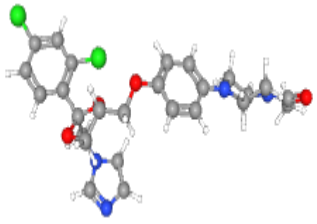
Apart, from infections fungi also cause severe superficial infections that primarily affect the mucosal layer of the skin. The superficial mycoses have more powerful in comparison of infections and significantly affect the quality of life. Examples include infections caused by Malassezia globosa and M. Furfur.Infections that affect the skin and underlying tissues keratinized structures are primarily caused by dermatophyte genera, like Trichophyton, Epidermophyton and Microsporum [7]. On the other hand mucosal infections are mostly attributed to the yeast with Candida being the most prevalent for causing such type of infections.

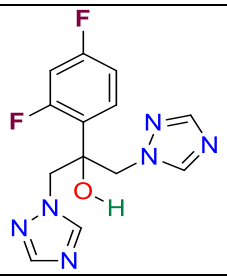
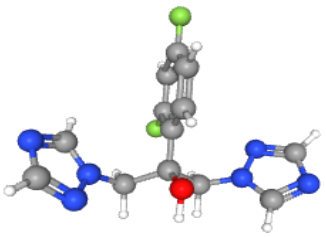
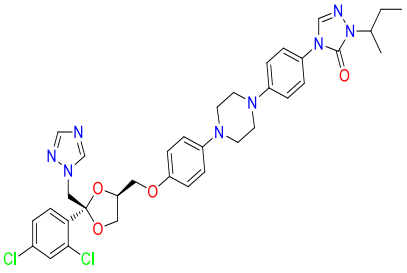
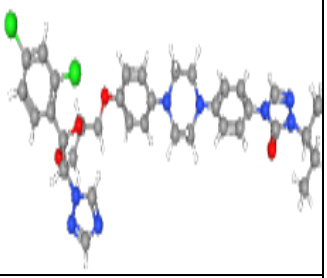
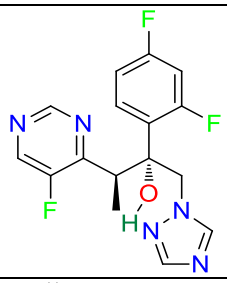
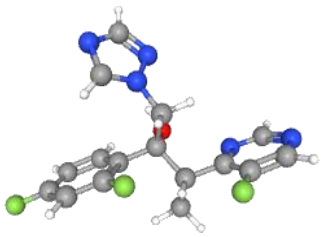
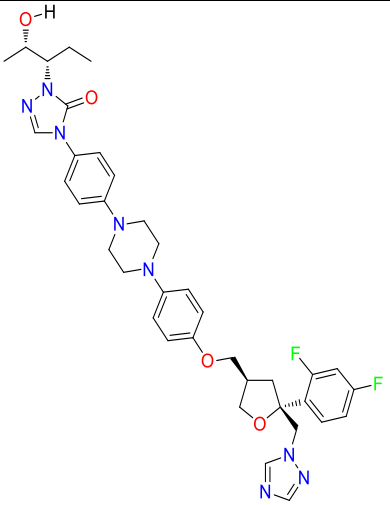
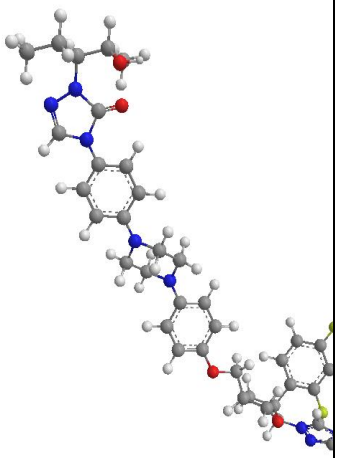
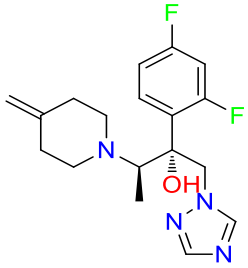
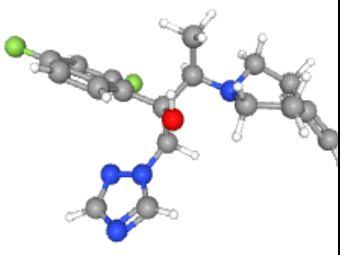
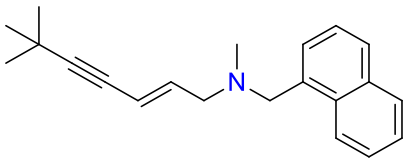
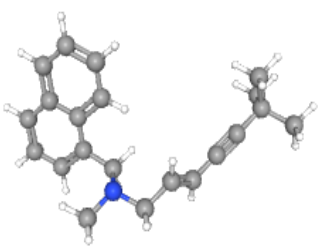
Developing drugs to treat infections is more challenging, than developing antibacterial drugs. Fungi are eukaryotes and sharing more potential targeted therapy with humans. This creates a risk of causing harm to the host [8,9]. Now four types of agents are available. such as: Azoles, echinocandins, polyenes and pyrimidine analogs. These drugs can be administered orally topically or intravenously to treat infections [6,9]. There is also another class called allylamines primarily used for treating infections. However, there are drawbacks to these antifungal drugs in terms of their toxicity, safety, and pharmacokinetic features [1,10]. The development of novel drug molecules with distinct modes of action that target the fungal protein, lipid, and cell wall synthesis [10].

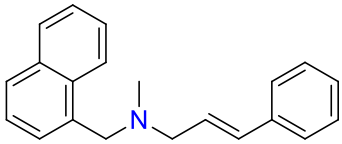
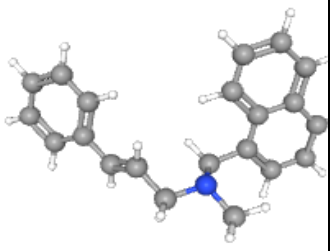
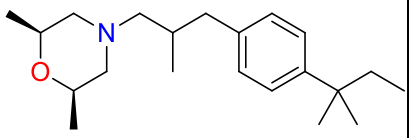
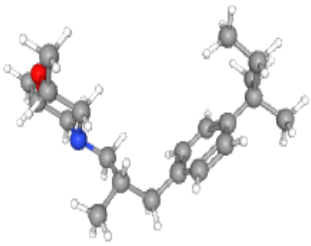
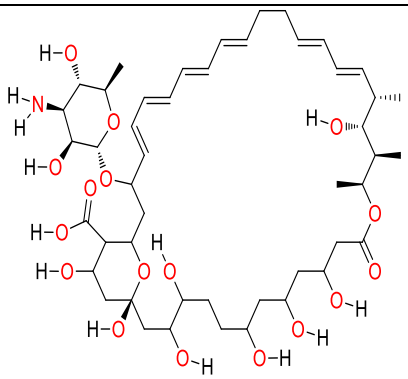
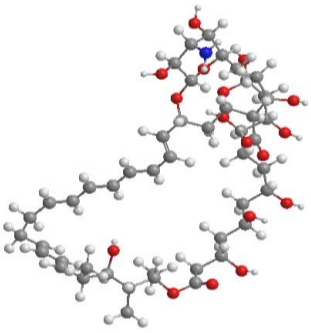
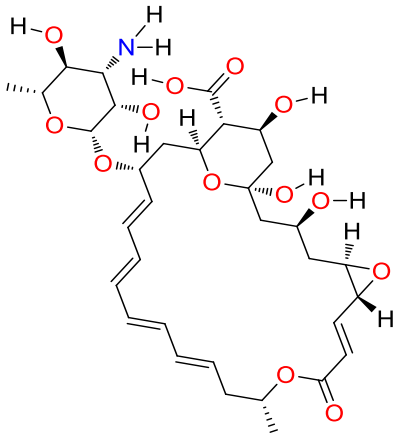
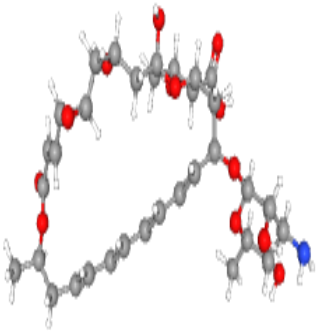
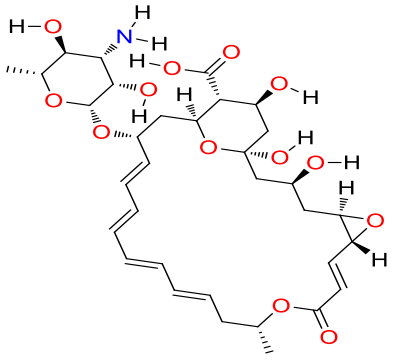
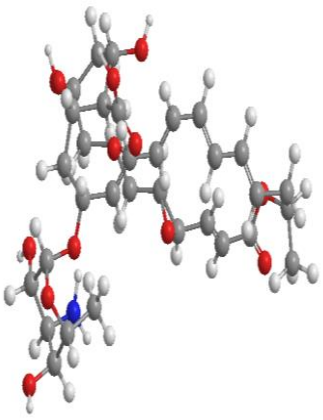
Classification of antifungal agents

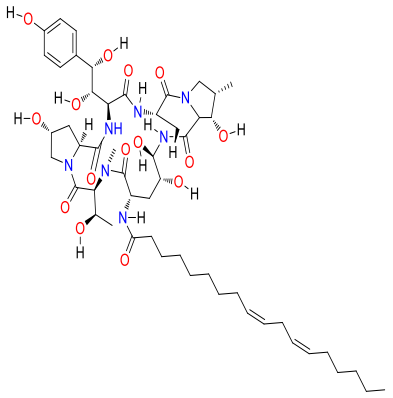
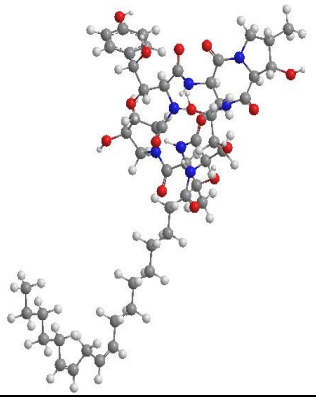
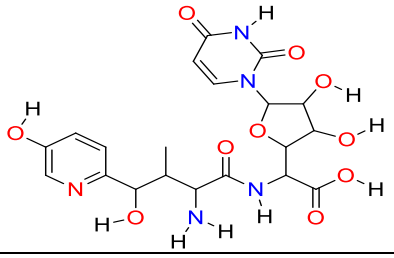
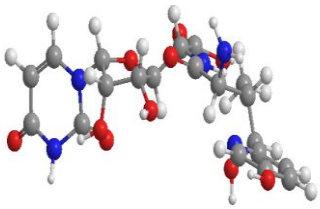
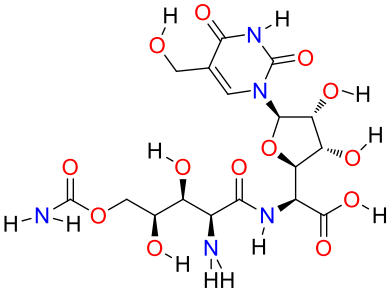
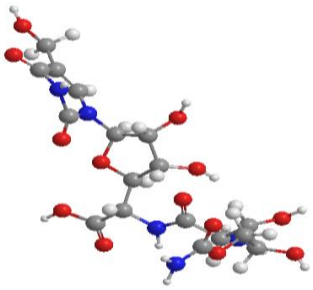
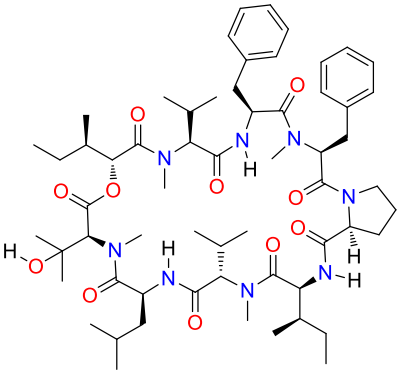
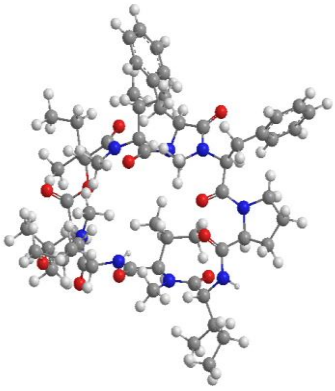
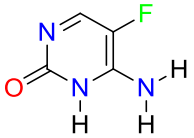
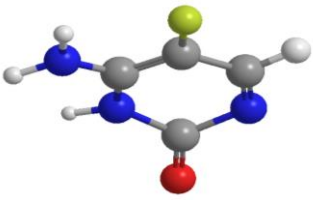
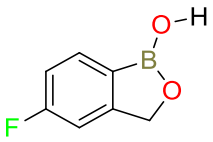
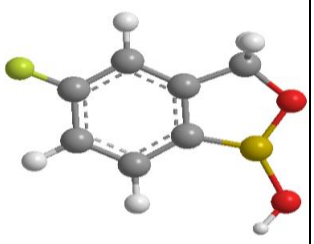
Classify the antifungal agents according to 2D and 3D structures with their chemical formula

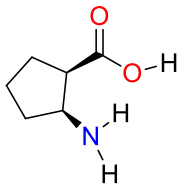
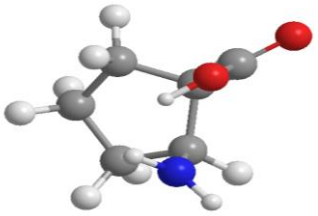
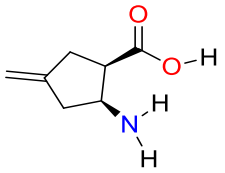
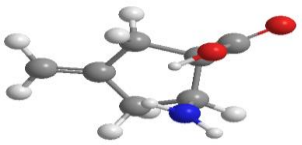
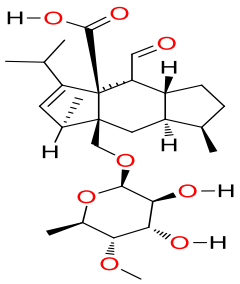
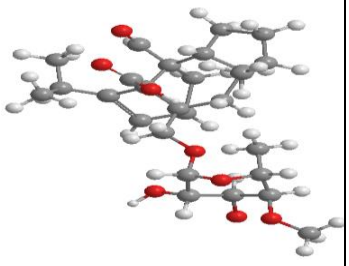
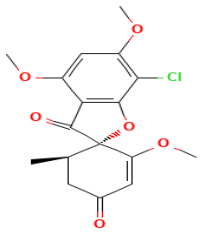
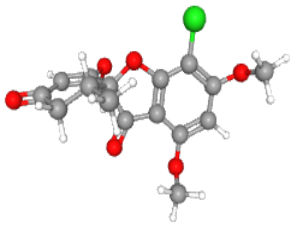
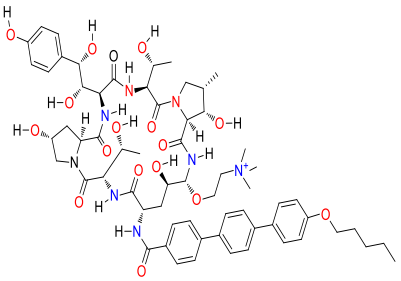
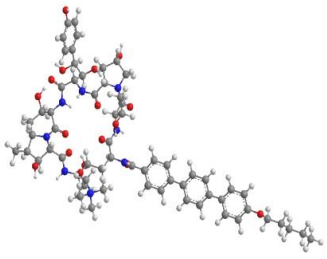
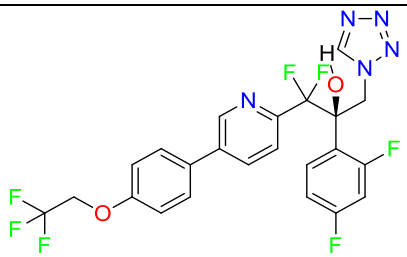
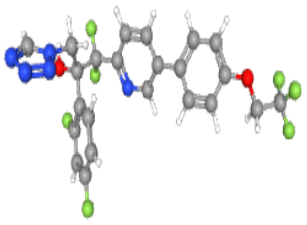
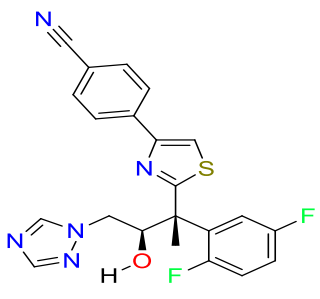
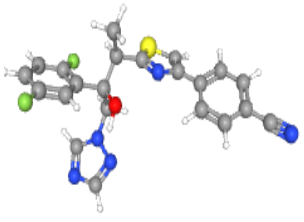
Table 1 Antifungal agents 2D and 3D structures with their chemical formula.

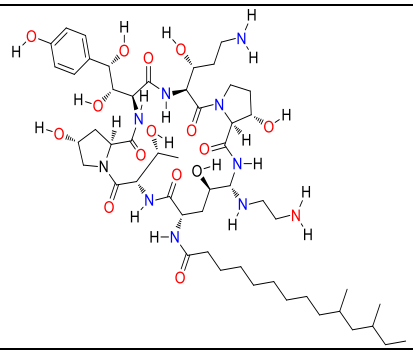
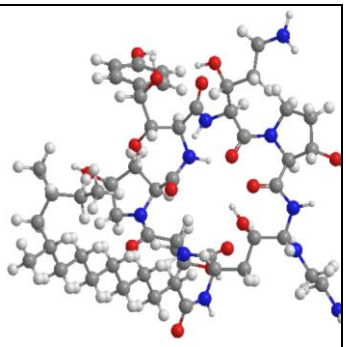
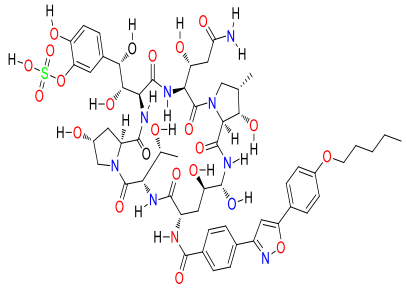
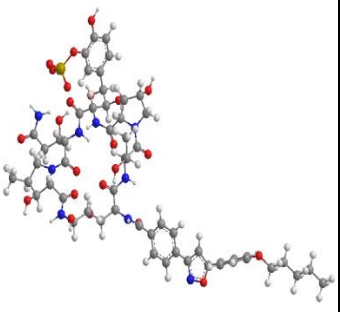
S. No	Name of Antifungal Agents	Molecular Formula	Chemical Structure Depiction (2D Structure)	Interactive Chemical Structure Model (3D Conformer)
1.	Clotrimazole	$C_{22}H_{17}ClN_2$		
2.	Miconazole	$C_{18}H_{14}C_{l4}N_2O$		
3.	Ketoconazole	$C_{26}H_{28}C_{l2}N_4O_4$		

4.	Fluconazole	$C_{13}H_{12}F_2N_6O$		
5.	Itraconazole	$C_{35}H_{38}C_{l2}N_8O_4$		
6.	Voriconazole	$C_{16}H_{14}F_3N_5O$		
7.	Posaconazole	$C_{37}H_{42}F_2N_8O_4$		
8.	Efinaconazole	$C_{18}H_{22}F_2N_4O$		
9.	Terbinafine	$C_{21}H_{25}N$		

10.	Naftifine	$C_{21}H_{21}N$		
11.	Amorolfine	$C_{21}H_{36}NO$		
12.	Nystatin	$C_{47}H_{75}NO_{17}$		
13.	Natamycin	$C_{33}H_{47}O_{13}N$		
14.	Amphotericin B	$C_{47}H_{73}NO_{17}$		

15.	Echinocandin B	$C_{52}H_{81}N_7O_{16}$		
16.	Nikkomycin	$C_{20}H_{25}N_5O_{10}$		
17.	Polyoxin B	$C_{17}H_{25}N_5O_{13}$		
18.	Aureobasidin A	$C_{60}H_{92}N_8O_{11}$		
19.	Flucytosine	$C_4H_4FN_3O$		
20.	Tavaborole	$C_7H_6BFO_2$		

21.	Cispentacin	$C_6H_{11}NO_2$		
22.	Icofungipen	$C_7H_{11}NO_2$		
23.	Sordarin	$C_{27}H_{40}O_8$		
24.	Griseofulvin	$C_{17}H_{17}ClO_6$		
25.	Rezafungin	$C_{63}H_{85}N_8O_{17}^+$		
26.	Oteseconazole (VT-1161)	$C_{23}H_{16}F_7N_5O_2$		
27.	Isavuconazole	$C_{22}H_{17}F_2N_5OS$		

28.	Caspofungin	$C_{52}H_{88}N_{10}O_{15}$		
29.	Micafungin	$C_{56}H_{71}N_9O_{23}S$		

Disruptor fungal membranes

Polyenes belong to a group of molecules known as macrolides. What sets them apart is their structure, which involves a ring made up of 20-40 carbon atoms connected to a d mycosamine group [11]. These molecules have the ability to interact with lipid bilayers by binding to ergosterol a component of fungal cell membranes. Through this interaction polyenes form complexes. Create pores in the membrane. These pores disrupt cell membrane leading to the escape of cell. Ultimately this results in the demise of cells [12-14].

Recent research studies have indicated that polyenes, namely amphotericin B bind with ergosterol and create a sterol sponge outside the membrane, which leads to the destabilization of its function [15]. Polyenes were the types of drugs used in medical practice and are known for having the widest range of activity against fungi among all antifungal molecules. Currently three polyenes are used in clinical settings [16-18].

Nystatin and natamycin possess activity against various bacterial species. This is commonly employed in vaginal and esophageal infections [19]. Amphotericin B exhibits activity against yeasts and filamentous fungi making it a spectrum antifungal agent [20,21].

Polyenes like nystatin, natamycin and amphotericin B also have an resemblance to cholesterol [22]. Nystatin and natamycin both are employed in treatments because they are poorly absorbed in the system and have considerable toxicity. On the contrary amphotericin B is widely used in infections and it is administered through intravenous due to minimum absorption through GIT [23].

In recent years there has been a focus on discovering the new drug molecules for reducing the toxicity associated with the three polyene [24]. As a result scientists have developed synthetic polyenes that have improved water solubility and lower levels of toxicity compared to amphotericin B [25,26].

Moreover researchers have made advancements in formulating amphotericin B to enhance its efficacy while reducing its harm to the patient. Lipid based formulations, such as liposomes have proven successful in achieving these objectives [27,28]. Further investigations are currently underway to explore formulations [29] with the goal of improving the properties of amphotericin B.

B-glucan synthesis Inhibitors

It is a carbohydrate made up of individual molecule of glucose joined by b-(1,3) or -(1,6) linkages [30]. The primary structural polysaccharide found in the cell wall's b-(1,3) D glucan, which constitutes, than half of the cell wall. It provides a base for additional cell wall. Currently, available antifungal drugs that target the cell wall synthesis [31,32]. Even though regulatory agencies, like the FDA and EMA approved the use of echinocandins in settings more than a decade ago they are considered the group of antifungal agents. Echinocandins work by acting as inhibitors for the b-(1,3) D glucan synthase enzyme complex by targeting the subunit FsK1. This disturbance in the structure of cell walls leads to instability. Ultimately causes the death of fungal cells. Echinocandins are derived from natural fungal products. Are modified through chemical processes to create lipopeptides [33,34]. Caspofungin, micafungin and anidulafungin are

examples of echinocandins each derived from fungal sources and possessing side chains that contribute to their antifungal properties [35,36]. These drugs have absorption rates in the tract due to their large molecular weights. However they have shown to be safe and have toxicity because they specifically target an enzyme absent in mammalian cells minimizing interactions, with other medications.

Nevertheless due, to their duration of action these medications must be administered intravenously on a basis, which restricts their application to hospital environments [37]. Caspofungin, micafungin and anidulafungin are effective, in killing types of Candida in the lab and in living organisms. They also have the ability to slow down the growth of Aspergillus species. Micafungin and anidulafungin have been approved for treating Candida infections, including those, in the esophagus. Caspofungin can also be used for treating aspergillosis [38-40].

It is important to put efforts into the development of echinocandins because these compounds have shown to be more effective against the wide range of fungal infections. By combining echinocandins, with azoles or amphotericin B we can potentially increase their efficacy in combating fungal pathogens [37].

Chitin synthesis inhibitors

Around 3% chitin constituent is used for the cell wall synthesis. It consists of a chain of N acetylglucosamine molecules linked together with glucan molecules [39,41]. The production of chitin relies on enzymes called chitin synthases. Chitin which is responsible for cell wall strength but if interrupted the cell wall synthesis in terms of osmotic balance. Since chitin is not found in cells it becomes a target, for antifungal drugs.

Nikkomycins and Polyoxins have been extensively studied as inhibitors of chitin synthase, which's an enzyme involved in cell wall formation. Nikkomycin is particularly effective, against types of pathogens with high chitin content but it doesn't have any impact on Candida albicans or C. Tropicalis [39]. On the hand Polyoxins are known to be active against fungi that cause damage, to plants [30].

These compounds are substances found naturally in nature. They function by attaching themselves to the location where chitin synthase operates. This attachment has a structure, to UDP N acetylglucosamine and competes with it [6]. However their use in treatments is currently limited because they break down easily and have effectiveness inside living organisms. Development of polyoxins ceased in 2012 while Nikkomycin Z is currently undergoing evaluation, in trials (Table 2) [9].

Nucleic acid synthesis inhibitors

Flucytosine (5-FC) also known as 5 fluorocytosine is a type of medicine that can stop the growth of fungi. It works by interfering with the way fungi make use of substances in their cells, such, as pyrimidine and proteins [42]. Flucytosine enters fungal cells through a channel called cytosine permease. Inside it gets converted into another compound called 5 fluorouracil (5-FU). This 5-FU then undergoes changes. Becomes 5-fluorouridine monophosphate (5-FUMP) which gets added to the RNA molecules of the fungi instead of their usual building block, UTP. This interruption in RNA production disrupts protein synthesis in the fungus [40,42,43]. Hampers its growth. Additionally 5-FU can also be transformed into another compound called 5-fluorodeoxyuridine monophosphate (5-FdUMP) which strongly inhibits an enzyme called thymidylate synthase. This inhibition affects the synthesis of DNA. Prevents proper division of their nuclei. It's worth mentioning that flucytosine specifically targets fungi because mammalian cells have very limited or no ability to convert it into its form [44].

While flucytosine shows effectiveness against strains of Candida and Cryptococcus, in laboratory tests and animal studies its range of action is mainly limited to yeasts that cause infections since filamentous fungi lack the specific enzyme thymidylate synthase [45]. Flucytosine resistance is quite common which is why it is usually utilized as a treatment, than the main course of action [45].

Protein biosynthesis inhibitors

Tavaborole was approved by the FDA in 2014 for the treatment of toenail onychomycosis caused by Trichophyton rubrum and T. Mentagrophytes. This substance has the ability to combat fungi, like yeasts, molds and dermatophytes. Tavaborole functions, by hindering the activity of leucyl synthetase, a fungal enzyme essential for protein synthesis. It attaches itself to the editing site of this enzyme alongside tRNA which prevents the transfer of acids to the ribosome effectively blocking protein synthesis [46].

Another group of agents that focus on protein biosynthesis are b amino acids, which inhibit isoleucyl synthetase. Cispentacin derived from Bacillus cereus culture broth and its derivative Icofungipen have displayed strong antifungal properties, against Candida albicans [47,48]. Discovered in 1969 Sordarin was initially isolated from Sordaria araneosa [49]. This compound specifically disrupts the functioning of translation

elongation factor 2 (EF2) while leaving its equivalent unaffected. The effectiveness and range of sordarin analogs are dictated by the group (R) positioned in 30 different position [50].
Scientists have discovered strains that produce variations of sordarin analogs. By replacing the glycoside portion with various components and successfully developed semi synthetic derivatives [51-54]. The unique targeting abilities of sordarin make it an exciting prospect, for the creation derivatives.

Microtubules biosynthesis inhibitors

Which is responsible for the structure of cells. They consist of alpha and beta tubulin units that join together to form organized structures. Some antifungal drugs, including griseofulvin and vinblastine fall into this category [55]. Griseofulvin is a earliest antifungal compound was isolated from Penicillium griseofulvin in 1939 [56]. However it has known liver toxicity. Its effectiveness is limited to dermatophyte fungi which're responsible, for conditions, like ringworm and athletes foot [57,58]. Griseofulvin works as an antifungal by binding to tubulin thereby disrupting the assembly of microtubules and preventing the mitosis.

Table 2 Mode of action of antifungal agents.

S. No.	Compound	Mode of Action	Indication	Development Stage	Ref
1.	Isavuconazole	Inhibits fungal cytochrome P450-dependent enzymes, particularly CYP51	Invasive aspergillosis, mucormycosis	Approved, widely used	[68]
2.	VT-1161	Targets fungal CYP51 and disrupts ergosterol biosynthesis	Vulvovaginal candidiasis	Phase 2 clinical trials	[69]
3.	VT1129	Biosynthesis of ergosterol	Cryptococcal meningitis	Phase 1 clinical trial, QIDP and Orphan drug status (US)	[69]
4.	Fluconazole	Inhibition of fungal cytochrome P450-dependent enzymes	Candidiasis, cryptococcal meningitis, prophylaxis in immunocompromised patients	Approved, widely used	[70]
5.	Amphotericin B	Binds to fungal cell membrane ergosterol, causing membrane disruption	Invasive fungal infections, systemic candidiasis, cryptococcal meningitis	Approved, widely used	[71]
6.	Caspofungin	Inhibits fungal cell wall synthesis by targeting β-(1,3)-D-glucan synthase	Invasive candidiasis, invasive aspergillosis	Approved, widely used	[72]
7.	Voriconazole	Inhibits fungal cytochrome P450-dependent enzymes, particularly CYP51	Invasive aspergillosis, candidiasis	Approved, widely used	[73]
8.	Posaconazole	Inhibits fungal cytochrome P450-dependent enzymes, particularly CYP51	Invasive aspergillosis, candidiasis	Approved, widely used	[74]
9.	Echinocandins	Inhibit fungal cell wall synthesis by targeting β-(1,3)-D-glucan synthase	Invasive candidiasis	Approved, widely used	[75]
10.	Nikkomycin Z	Inhibits chitin synthase, affecting fungal cell wall integrity	Experimental, preclinical studies	Early development stages	[76]
11.	Rezafungin	Inhibits fungal protein synthesis by targeting the 60S ribosomal subunit	Invasive candidiasis, invasive aspergillosis	Phase 3 clinical trials	[77]

Strategies to develop new antifungal compounds

The various variety of drugs options are available for treating fungal infections. This is because fungi are organisms that live off living organisms making it difficult to develop effective and safe antifungal medications that work against a broad range of fungal species. While there are an exceptions like amphotericin B, antifungal drugs currently on the market work, by inhibiting the growth of fungi rather than directly killing them [59].
There is research, in the field of drug development with a particular focus on finding new targets that are unique to fungi and crucial for their growth while having little similarity to human proteins. A potential target that scientists are exploring is production, which plays a role, in the virulence of various fungal species. Researchers have identified inhibitors that target the Tps2 enzyme, involved in

metabolism using the crystal structure of Candida albicans Tps2 as a basis [60].

Ras GTPases are signaling molecules that play a role, in the virulence of fungi. Researchers have been investigating them as targets for treatments. One approach involves developing inhibitors that can hinder the function of Ras such as farnesyltransferase inhibitors. These inhibitors have shown promise in targeting growth at high temperatures [61].

Another crucial regulator of stress responses in fungi is calcium/calmodulin signaling, which also affects resistance to treatment. While certain calcineurin inhibitors like tacrolimus are currently used as immunosuppressants they have demonstrated activity. Therefore exploring immunosuppressive calcineurin inhibitors could be a promising direction for developing antifungal drugs. Heat shock protein 90 (Hsp90) has also been studied as a target for drug development. In fungi Hsp90 is involved in resistance to azoles and echinocandins. Studies have shown that combining inhibitors like geldanamycin with existing drugs such as echinocandins or fluconazole can enhance their fungicidal effects [62].

Mechanisms of antifungal resistance

Observed the antifungal resistance when fungi evolve to survive and thrive in the presence of drugs. This natural selection process is widespread as microorganisms develop strategies to counteract the effects of these drugs.

Scientists have extensively studied the mechanisms of resistance for different types of antifungal agents and fungal pathogens [63-65]. Microorganisms employ three mechanisms to resist the killing or growth inhibiting effects of drugs. Microorganisms can reduce the concentration of the drug is, by increasing drug efflux. CDR1 and CDR2 both are transporter for azole derivative resistance for candida albicans. When these transporters are activated they enhance the removal of drugs. Reduce the accumulation of azoles within the fungal cells [66,67]. Apart from CDR1 and CDR2 there are ABC transporters identified as contributors to azole resistance in various species. For instance in Candida glabrata azole resistance involves CgCDR1, CgCDR2 and CgSNQ2 while in Cryptococcus neoformans AFR1 plays a role.

Conclusions

Over the years there has been a noticeable increase, in invasive fungal infections. In the current situation of these infection increase the number of patients due to the expansion of therapies. Although there are medications available they don't fully effective for the treatment of fungal infections and mortality rate is very high. We are seeing a frequent emergence of strains that are resistant, to azole and echinocandin drugs. Moreover current antifungal treatments often lead to chronic side effects. As a result researchers widely agree that we need drugs in the pipeline.

Although the FDA has made advancements in development through initiatives, like the GAIN Act and the Orphan Drug Acts there are still a few compounds, in the pipeline that have unique ways of functioning. These compounds are under the development phase or clinical trials. Henceforth proves a task to anticipate which of these compounds if any all will emerge as viable antifungal medications, for clinical use. While developing antifungals with a range of effectiveness poses challenges concentrating on medications with more specific targets could simplify the initial phases of drug development. Recent studies examining the interaction between genes and drugs have indicated that pinpointing pathogens in the process of drug development might yield more potent and efficient treatments for invasive fungal infections.

Progress in techniques. Our growing understanding of how fungi survive and exhibit virulence has facilitated the identification of fresh therapeutic targets. Consequently this has paved the way, for the exploration and creation of compounds that possess mechanisms of action.

List of Abbreviations

Declarations

Ethics approval and consent to participate- Not applicable

Consent for publication - Not applicable

Availability of data and materials – All data and material are available upon request.

Competing Interests- The author has declared that no conflicts of interest exist.

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