Discover Medicine

Review

Comprehensive review of fungal pathogenesis and antifungal therapeutics

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Abstract
Fungal infections, caused by a diverse kingdom of eukaryotic organisms, pose significant challenges to global health due to the increasing incidence of drug-resistant strains. These infections range from superficial to life-threatening systemic diseases, particularly in immunocompromised individuals. The emergence of drug-resistant pathogens like *Candida auris* has intensified the need for novel antifungal therapies. This comprehensive review explores the pathogenesis of various fungal diseases, the current landscape of antifungal agents, and the mechanisms underlying drug resistance. We discuss the latest advancements in antifungal drug development, including innovative agents in clinical trials, and emphasize the importance of enhancing diagnostic techniques to combat these resilient pathogens. The review aims to provide insights into future directions for effective antifungal strategies, addressing both therapeutic challenges and opportunities in this rapidly evolving field.

Keywords Novel antifungal agents · Spectrum of activity · Invasive fungal infections · Mucormycosis · Candidiasis · Aspergillosis

1 Introduction

Fungi, a kingdom of eukaryotic organisms, have coexisted with humans for a long period of time. Although many fungi are beneficial to industries and ecosystems, others can significantly infect humans. These pathogens can cause a wide range of diseases, ranging from minor skin infections to fatal systemic mycoses. Immerging new fungal infections by the emergence of new or resistant fungal pathogens leads to the growth of the newest antifungal drug. In this article, the distinctive characteristics of fungi as infective agents, the kind of fungal infections, and the current scenario of antifungal treatment are discussed. The increasing incidence of fungal diseases, along with the rise of antifungal resistance, has necessitated an imperative understanding of these pathogens and the development of efficient treatment strategies. An essential component of successful fungal management is the prompt diagnosis and use of suitable antifungal agents. This review will provide the information of existing diagnostic techniques and the classification of antifungal agents based on their targets and mode of action. This review aims to provide a better

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understanding of this emerging field and guide future clinical practices and investigations by offering an in-depth overview of fungal diseases and its treatment therapy.

1.1 Fungi: the pathogen

Fungi are eukaryotic and ubiquitous organisms of our environment and are generally benign. They are arbitrarily categorized into 4 categories based on Cellular and Structural features that is; yeasts, filamentous fungi, dermatophytes and dimorphic fungi. Here we will discuss about the pathogenic categories as those strains attracted the interest of modern medical sciences to develop new drugs. The extensive list of infectious fungi includes mostly *Candida* spp., pathogenic-filamentous-mold like *Aspergillus* spp., and dimorphic fungi- *Mucor* spp. Also, dimorphic fungi include other infectious fungi like *Blastomyces* spp., *Histoplasma* spp., *Fusarium* spp., *Coccidiodes* spp. respectively [1–4]. Other pathogenic dermatophytes which produce infections that may last months or years and cause huge discomfort include species such as *Trichophyton, Microsporum or Epidermophyton, Tinea infection/Jock itch,* ringworm etc. Fungal cells possess a cell wall with principal components are amino polysaccharide and chitin. The chitin layer consists of an overlying matrix of β-1,3-glucans and then β-1,6-glucans and overlying matrices of β-1,3-glucans and then α-1,3-glucans in yeast and filamentous fungi respectively. Galactos aminoglycans and proteins as the final variable layers in yeast and the same as galactos aminoglycans, galactomannas and proteins in filamentous cells. The basement layers of chitin defend against internal osmotic pressure that comes from the cytoplasm, resulting in a robust architecture. Also, the outer layer of the cell wall which is glucan-based gives chemical diversity which aids in swiftly and accurately recognizing fungal species. Fungal cells also contain cell membranes containing a sterol called as ergosterol [1].

1.2 Fungal infections

True pathogenic and opportunistic fungi have increased the risk of life-threatening infections over the past few years. And studies have found that the reason behind this increase is surely the increasing population. Transplant recipients, cancer patients, and others taking immunosuppressive medication are among the most vulnerable [5]. In immunocompromised patients, opportunistic invasive fungal infections are causing major mortality and morbidity. But here the diagnostic definition of the disease is categorized by taking three important terms Proven, Probable and Possible concerning clinical factors, host factor and mycological evidence. Certainly, in the diagnosis of Invasive Fungal Infections (IFI) differentiation between deep tissue infections and fungemia is included in the proven category. Fungemia is a blood stream infection. In the probable category IFI having each of the three elements has to be present and the cases which do not have clinical features or mycological evidence but at least 1 criterion from the host factor are placed under the possible category. The main objective of this kind of categorization is to identify the grouping of homogenous people for clinical research [6]. Recently there has been evidence of co-occurrences of fungal infectivity among COVID-19 patients which are considered as opportunistic. Patients in intensive care units who are getting broad-spectrum antibiotics, patients who are having invasive and non-invasive ventilation and those who are receiving immunosuppressive or corticosteroid therapy are more vulnerable to COVID-19. Thus, Invasive pulmonary Aspergillosis, oral Candidiasis or pneumocystis pneumonia [8] are the majority likely to be shown in SARS-COV2-infected patients. Tan et al. also suggested that lymphopenia or inadequate lymphocyte might be the key factor of secondary fungal infections such as *Oropharyngeal candidiasis* (OPC) and *Pneumocystis jiroveci* pneumonia (PJP) in covid-19 patients [7, 8]. Also, these systemic fungal infections can spread to many other organs and they usually originate from lungs or other endogenous flora. Thus, the systemic infection-causing organisms are divided as opportunistic for example *Aspergillus* and *Candida* spp. and the other ones which can invade and develop disease in normal tissues of the host are the true pathogen (or dimorphic fungi). Though opportunistic fungi are ubiquitous the estimates of their incidence are less as compared to their magnitude because many a time the cases go undiagnosed and unreported. On the other hand, true pathogen infections are sometimes asymptomatic or mild of short duration and have a restricted geographical distribution [9]. Antifungal prophylaxis and the use of medical devices can be the reasons for changing and emerging fungal infections [10]. Antifungal prophylaxis may include developing resistance to particular antifungal agents, breakthrough infections and others like changes in the host at risk.

1.2.1 Emerging fungal infection

Patients at risk of emerging fungal infection—the most witnessed factors include an increase in hematopoietic stem cell transplant (HSTC) [11] and solid organ transplant and also patients using some immune modifiers such as Tissue Necrosis Factor (TNF). The use of new biological therapies for treating other diseases increases the chances of many fungal infections such as *Pneumocystis jirovecii* pneumonia, histoplasmosis and Candidiasis [12]. For example, Histoplasma and Fusarium are two fungi that have been recognized for a long time by clinicians and thus are re-emerging. But *Candida auris* is truly an emerging pathogen causing major healthcare-associated outbreaks all over the world [14]. *C. auris* showed highly resistant to fluconazole, 7% resistance to echinocandins and 50% resistant to Amphotericin B. and two strains are multidrug/pan-fungal resistant [13]. *Purpureocillium lilacium* is another emerging fungal pathogen causing opportunistic fungal infection, bloodstream infection, invasive sinusitis, pneumonia, breakthrough infection etc. Infection occurring during exposure to any systemic antifungal agents is called a breakthrough infection. Thus to identify this increasing number of rare and emerging IFI-approved international web-based registry is there [14].

1.2.2 Invasive fungal infection

Invasive fungal infections are increasingly recognized in critically ill patients particularly because of lack of on-time or early diagnosis and as well as early antifungal treatment. *Aspergillus* spp. and *Candida* spp. are the reason behind 95% of IFI cases worldwide [15]. Intensive care unit (ICU) patients account for 17% of patients who develop IFI as studied by EPIC (European Prevalence of Infection in Intensive Care). Both *Candida albicans* and *non-albican candida* are detected frequently. Pittet et al. showed better evaluation of the dynamic of *Candida* colonization by studying critically ill surgical patients by using the colonization index. The severity of the disease and degree of colonization can predict the development of invasive Candidiasis in colonized patients [16–18]. The risk factor for breakthrough IFI can be host factors, fungal factors and iatrogenic factors. As the use of antifungal prophylaxis with fluconazole became more popular, the first breakthrough Candidiasis was identified decades ago when infections due to *Candida* spp. not responsive to fluconazole were noted. Although the rate of breakthrough candidemia (bIC) has decreased significantly by the use of broad-spectrum antifungal agents. Acute Leukemia, Neutropenia, Systemic Corticosteroids, Mucositis/Fungal translocation, and even genetics are the major host and iatrogenic risk factors of breakthrough invasive fungal infection (bIFI) in Haematological malignancies. Most of the time these IFI are under-diagnosed and under-reported and thus research and prevention efforts are less. So proper surveillance programs are necessary for individual medical centres and on a national basis [19].

2 Common fungal infections

See Table 1.

2.1 Candida species

Genus *Candida* contains probably 150 different species. Among them, few are pathogenic to humans. The first person to describe *Candida species* was a Botanist Christine Marie Berkhout *Candida albicans*is the most pathogenic one, others include *C. krusei, C. glabrata, C. tropicalis*, *C. parapsilosis, C. lusitanae, C. dublinienses, C. stellatoida* [20]. Infection caused by *C. albicans* is commonly referred to as Yeast infection/Candidiasis/ moniliasis/odiomycosis and the systemic infection is called as Candidemia [21]. Also in the recent coronavirus pandemic, Chowdhary (2020) discussed the scenario in India, where 60% of people die as a result of confirmed *C. auris* infection during coronavirus pandemic. In Mexico *C. auris* bloodstream infection in Covid-19 patients is approximately 83% which is very much enormous [21, 22]. Even *C. auris* is found to be transmitted from person to person because of its strong adherence to human skin [23]. The virulence of *C. albicans* might be acknowledged by yeast-to-hypha transition controlled by cyclic adenosine monophosphate (cAMP)/ protein kinase regulatory circuit pathway catalysed by a central component Cyrl (also known as Cdc35) [24].

Table 1 Most common fungal infections

Types	Species	Diseases
Yeasts	Candida species such as *Candida albican, C. krusei, C. glabrata, C.tropicalis, C. parapsilosis, C. lusitanae, C. dublinienses, C. stellatoida, C. auris, C. gattii*	*Oropharyngeal candidiasis , oral candidiasis , vulvovaginal candidiasis*, Candidemia **Yeast infection/Candidiasis/ moniliasis/ odiomycosis**
	Aspergillus species such as *A. fumigatus, A. flavus, A. niger, A. nidulans, A. tubingensis, A. felis, A. terreus, A. versicolor, A, flavipes, A. lentulus.*	*Allergic Bronchopulmonary Aspergillosis(ABPA), Invasive Pulmonary Aspergillosis (IPA)*
Dimorphic fungi	*Blastomyces spp., Histoplasma spp., Fusarium spp., Coccidiodes spp., mucor spp. Rhizopus, Absidia ,*	*rhino- cerebral-mucormycosis (ROCM), Blastomycosis, Histoplasmosis, Coccidioidomycosis, Fusariosis.*
Dermatophytes	*Trichophyton, Microsporum or Epidermophyton, Tinea versicolor, T. crusis, T. pedis, T. unguium, T. corporis etc.*	*Jock itch, dermatophytosis, Athlete's foot, scalp ringworm, Onychomycosis.*
Others	*Pneumocystis jirovecii or P. carinii*	*Pneumocystis jirovecii* pneumonia (PJP).

2.2 Aspergillus species

The genus *Aspergillus* contains 200 species of which more than 30 species cause infection in humans. The species are ubiquitous moulds, most abundant in soil and decaying vegetation. Mostly transmitted through conidia (spores) inhalation. The spore inhalation in blood vessels and leads to thrombosis, dissemination to other organs. The mortality rate is nearly 100% for untreated invasive *aspergillus* (IA) [25]. Malfunctioning of epithelial cell function and upregulation of extracellular matrix (ECM) protein increase conidial adhesion when the transcriptional factor ZNF77 is expressed abnormally in bronchial epithelia and it is found to be a strong genetic basis for *Aspergillus* colonization in Lung infections. *A. fumigatus* causes hypersensitive disease of the lung called as Allergic Bronchopulmonary Aspergillosis (ABPA). Fungal pneumonia caused by *Aspergillus* spp. leads to the death of 15–20% of patients with leukaemia. Also, IPA (Invasive Pulmonary Aspergillosis) surpassed IC (Invasive Candidiasis) as the most common fungal infection since the late 1990s [26]. Also, acute respiratory distress syndrome (ARDS) [27] has been linked to IPA in intensive care units, supporting the theory that alveolar injury favours fungal invasion. From this, it can be considered that COVID-19 is associated with pulmonary Aspergillosis. A study or evidence showed that out of 34 Covid-19 in ICU, 20 (59%) required invasive mechanical ventilation and 7 (35%) of them were suspected of IPA [27, 28].

2.3 Mucor species

Mucors are among other Mucorales fungi *Rhizopus* and *Absidia* are fungi found in soil or decomposing organic materials that are pervasive, saprophytic, and not fastidious. If fungi spores are inhaled into the bronchioles and alveoli leads to pulmonary mucormycosis thus Pneumonia or endobronchial pneumonia develops swiftly, with non-specific symptoms such as fever, dyspnea, coughing, and chest pain [29]. The overall mortality rate is 76 percent, but extra thoracic dispersion can raise that to 95% [29]. Mucormycosis was shown to have a greater mortality rate (71.4%) than *Aspergillus* (28.5%) because mucormycosis exhibited orbital invasion compared to *Aspergillus* [30]. Cases of rhino-orbital-cerebral mucormycosis with a distorted mental condition, proptosis are found in Covid-19 patients [2]. Taking of conidial spores through the paranasal sinuses of a susceptible host leads to rhino-cerebral-mucormycosis (ROCM). The last sign of tissue necrosis is a hallmark of Mucormycosis [31]. Though the biology and genetics of Mucorales are poorly understood, some studies provide us evidence of the Ricin-like protein toxin

that is Mucoricin which plays a vital role in Mucorales infection. Mucoricin leads to host cell apoptosis. There is homology in the toxicity domain of Mucoricin and Ricin, castor bean (*Ricinus communis*) protein [32, 33]. Mucoricin from *R. delemar* involved Type 2 ribosome-inactivating protein (RIP) resembling Ricin- chain A. Also, the protein is heat stable and only produced during hyphal growth. Mucorales or particularly Mucoricin protein has EEGRL and EAANQ motifs which are responsible for RIP activity and thus causes human disease. Mucoricin has been discovered to be quite active in pulmonary mucormycosis and maybe in rhino orbital illness [33].

3 Several neglected fungal diseases

Chromoblastomycosis (CBM) [34] is a common granulomatous mycosis of the skin and subcutaneous tissue and it can be very chronic, that is now widely recognized as a neglected fungal contagious disease caused by melanized or black fungi such as *Fonsecaea* spp., *Cladophialophora (C. carrion, C. yegresii), Phialophora* [35]. In 2017, the World Health Organization (WHO) added CBM to its portfolio of neglected tropical diseases (NTDs) under category B, alongside mycetoma and another deep mycosis. CBM is occasionally found to be co-infected with bacteria. People living in the world's poorest and most remote places are diagnosed with CBM. Cases were reported from remote areas of Africa, Asia, America, Europe and Oceania. A molecular reason for CBM infection is considered the inability of toll-like receptor 7 (TLR-7) to recognize CBM fungus [35]. The International Society of Human and Animal Mycology (ISHAM) adopted the word Chromoblastomycosis as the official designation for the mycosis from Terra et al. previous publication in 1922, which is exactly 70 years ago. Classification of the CBM clinical form recommended by Carrion in 1950 which is currently in use [35].

4 Antifungal agents

Itraconazole (200–400 mg per day) and Terbinafine (500–100 mg per day) are two antifungal medicines that are widely used in particular countries, such as Madagascar and China, where the number of cases is considerably high. Voriconazole, Posaconazole, and Isavuconazole are second-generation triazoles that are exclusively used in refractory disease [34]. Many fungal diseases cancircumvent antifungal medicines as well as immune system detection by forming biofilms as a barrier. As a result, they avoid detection by the immune system of the host and are successful in defending against antifungal drug treatment to the organism [1]. There are several steps of biofilm formation fungal cell attachment to surfaces and production of hyphal filaments for scavenging nutrients to enlarge their surface area. As the biofilm matures it produces an extracellular matrix, "glue" including Glucan and Manan polymers, as a result, the matrix prevents antifungal drugs from penetrating fungal cells, and it eventually opens, releasing fungal cells that scatter and build up new biofilm elsewhere. *Candida, Aspergillus, Cryptococcus, Fusarium, Coccidioides, Trichosporon, Malassezia, Blasto schizomyces, Mucor* and *Rhizopus* [36, 37] (Fig. 1).

4.1 History of antifungal agents

Beginning of the nineteenth century, do not provide any reports of any specific systematic antifungal agents. DeBeurmann and Gougerot in 1903 discussed potassium iodide to treat sporotrichiosis. Again, Whitfield compounded (1907) an ointment called Whitfield's ointmen**t** to treat superficial fungal infection. During the 1940s, the only pharmacologic treatments available for treating fungal infections were weak acids and phenolic dyes, sulfonamide and Undecylenic acid. Introduction of (antibiotic) Griseofulvin, mainly for dermatophytes, Tolnaftate and Polyene compounds primarily for *Candida* infection, the introduction of broad-spectrum antifungal that is iodinated trichlorophenol- Haloprogin all began in the 1960s [39]. In 1951 Hazen and Brown discovered Nystatin also known as fungicidin at that time as the first polyene antibiotic. Gold et al. reported the first significantly effective systemic antifungal polyene Amphotericin B, in 1956. In 1957 Flucytosin was developed as an antifungal drug. Chlormidazole is a pioneer of enormous research on azole antifungal [40]. Benzimidazole was the first azole discovered in 1944. Later others Thiabendazole and Mebendazole (1960); Imidazole, Clotrimazole, and Miconazole (1969); Econazole (1974); Ketoconazole (1977) were introduced; Itraconazole and Fluconazole (broad spectrum orally available Trizoles) were introduced in mid-1980. Thus, a considerable number of antifungal agents were discovered till now and are classified as shown below in the Table 2 [41].

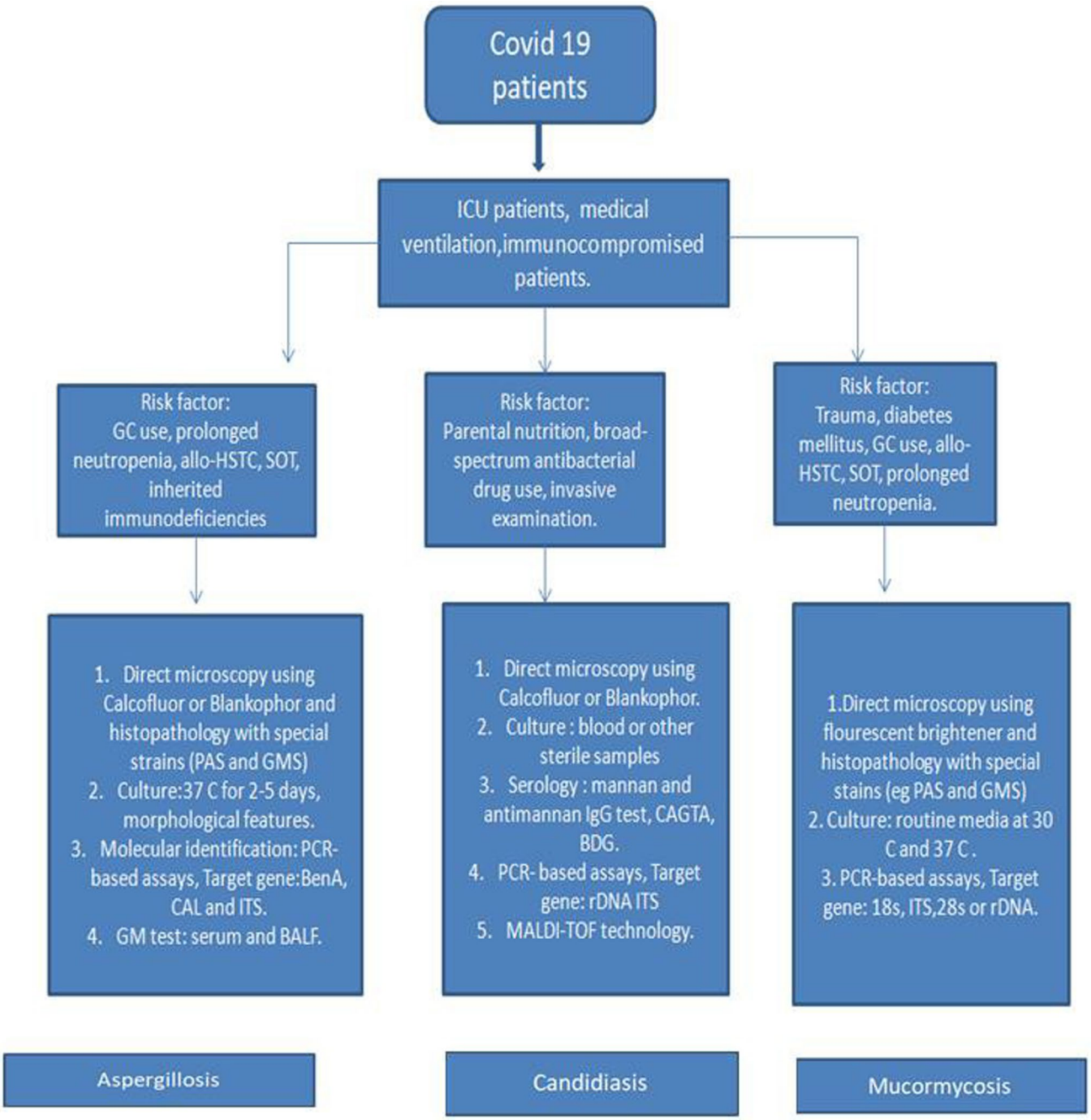


Fig. 1 Therapeutic pathway for the diagnosis of invasive fungal diseases that co-occur with Covid-19. *GC* gas chromatography, *allo-HSCT* allogeneic-hematopoietic stem cell transplants, *SOT* solid organ transplants, *GMS* galactomannas, *PAS* periodic acid-schiff stains, *GMS* Grocott-Gomeri's methenamine-silver stain, *BALF* Bronchoalveolar lavage fluid, *CAGTC C. albicans* germ tube antibody, *BDG* (1,3)-β-D-glucan [38]

4.2 Current armamentarium of antifungal agents

Four classes of antifungal drugs were already granted by the Food and Drug Association by now to combat fungal infections and are in major use for the treatment, these are Polyenes, Flucytosine, Azoles, and Echinocandins [42]. Allylamine is also included as a major agent based on its mechanism of action (Fig. 7) [43].

4.2.1 Polyenes

Amphotericin B (Fig. 2) is the first antifungal medication used for IFI treatment, with broad-spectrum type of fungicidal activities [44, 45]. AMP B deoxycholate—AMB deoxycholate is the conventional one and has long been used. Isolated from *Streptococcus nodosum*. The lipid formulation of AMB is a combinational complex of liposomal AMB and AMB lipid at specific ratios which provide a shielded protection and a much-needed modified formulation [43]. Nystatin (Fig. 2) is a tetrene antibiotic that hasa similar mechanism of action to AMB [41] Isolated from fermentation of *Streptomyces noursei*.

4.2.2 Azoles

Azoles family is a group under Trizoles and Imidazoles (Fig. 3). Triazoles contain 3-N atoms in a 5-membered azole ring, and Imidazole contains 2-N atoms [41]. Currently, 40 azole-containing drugs are classified into more than three generations.

4.2.2.1 First-generation Azoles Clotrimazole (1969), Miconazole (1969), Econazole (1974), and Ketoconazole.

4.2.2.2 First-generation Trizoles Fluconazole and Itraconazole; both having improved safety profile compared with Imidazole. Itraconazole has a larger field of activity than Fluconazole.

4.2.2.3 Next generation Triazoles Voriconazole and Posaconazole; Having improved pharmacokinetics and spectrum of activity and less drug-drug interaction. Voriconazole has similar chemical structure to is similar to fluconazole and Posoconazole to Itraconazole [44, 45].

4.2.3 Echinocandins

These cyclic lipopeptide molecules are the new subclass of antifungal drugs (Fig. 4); Caspofungin, Micafungin, and Anidulafungin [44, 45]. Discovered from *Aspergillus nidulans var echinalatus*and *A. rugulosus* in the 1970s. Belong to lipopeptides produced as a secondary metabolite, cyclic hexapeptide N-acylated having dissimilar aliphatic carboxylic acids [46].

Table 2 General classification of antifungal

Class	Subclass	Examples
Antibiotics	Polyenes	Amphotericin B, Nystatin
	Heterocyclic Benzofuran	Griseofulvin
	Echinocandins	Capsofungin, Micafungin, Anidulafungin
Azoles	Imidazole	Clotrimazole, Econazole, Miconazole, Oxiconazole(Topical) Ketokonazole (systemic)
	Triazoles	Fluconazole, Itraconazole, Voriconazole, Posaconazole
Allylamines	Not known	Terbinafine
Antimetabolite	Not known	Flucytosine
Miscellaneous	Not known	Tolnaftate, Undecylenic acid, Cyclopirox Olamine, Butenafine, (specific) Whitefield's ointment, Sodium thiosulfate, Gentian violet (nonspecific)

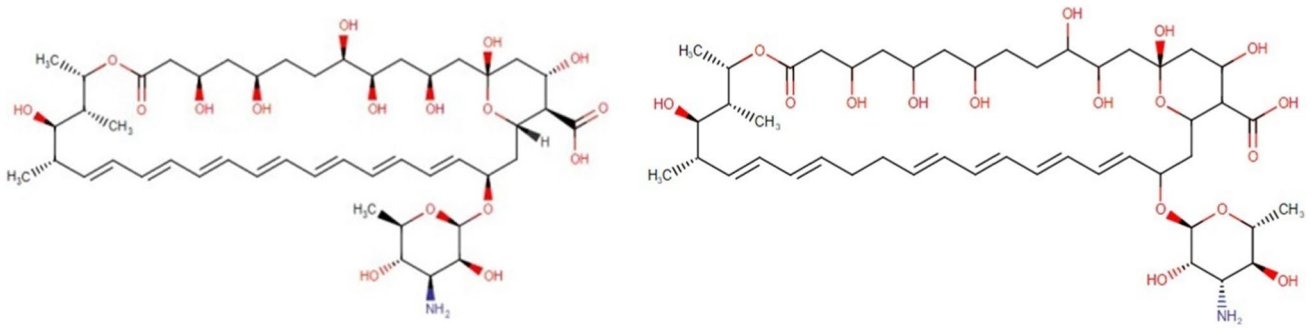


Fig. 2 Chemical Structures of Amphotericin B and Nystatin

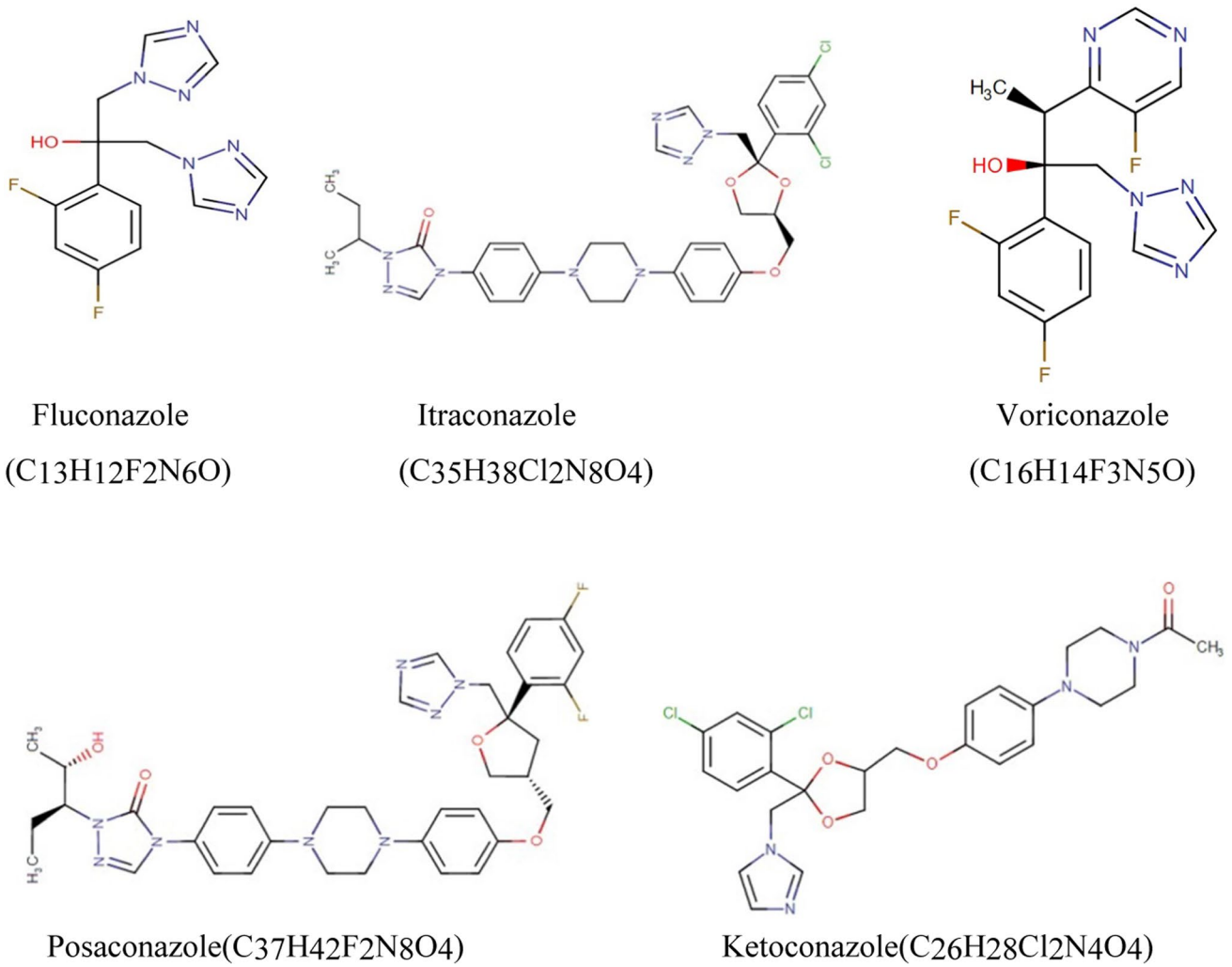
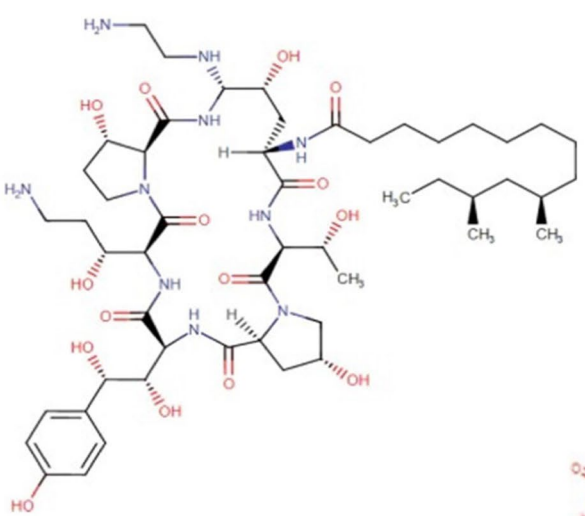
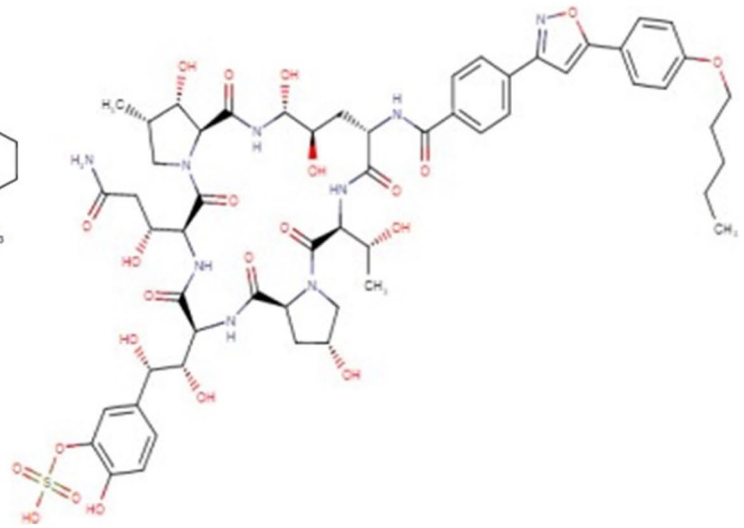


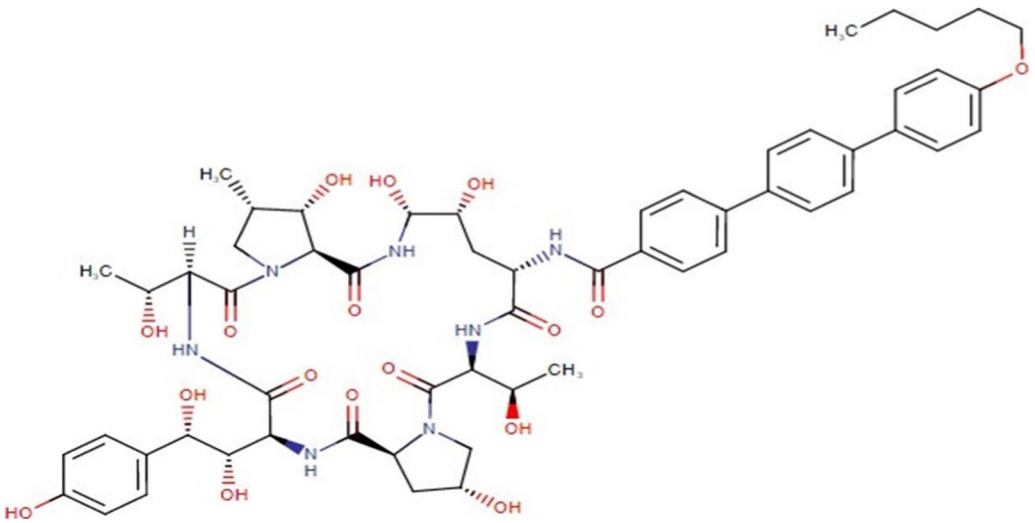
Fig. 3 Chemical Structures of some Triazoles



Caspofungin(C52H88N10O15)



Micafungin(C56H71N9O23S)



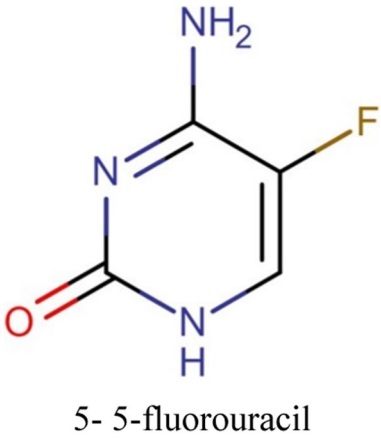
Anidulafungin (C58H73N7O17)

Fig. 4 Chemical Structures of Echinocandins

4.2.4 Flucytosine

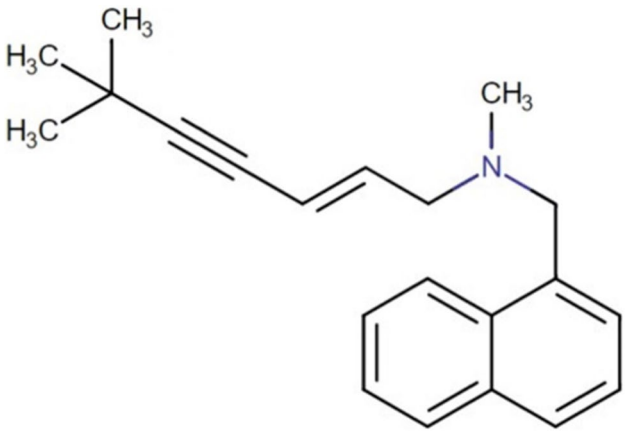
Flucytosin usually interferes with RNA and DNA, and it is a toxic 5- 5-fluorouracil (Fig. 5) compound, a Cytosine deaminase converted molecule. Used in combination with polyene [47]. Because of resistance, it is used as adjunctive with other antifungals [46].

Fig. 5 Chemical Structure of Flurouracil



5- 5-fluorouracil

Fig. 6 Chemical Structure of Terbinafine



Terbinafine ($C_{12}H_{25}N$)

4.2.5 Allylamine

Terbinafine (Fig. 6) is an allylamine available since May 1996. Fungicidal against dermatophytes, dimorphic fungi, is used as a topical medication for superficial mycoses and its target action is not known much (Table 3) [48].

The diagram (Fig. 7) illustrates key targets within fungal cells affected by various antifungal agents. Flucytosine inhibits DNA and protein synthesis by acting on the nucleus. Echinocandins block cell wall synthesis. Allylamines inhibit lanosterol synthesis by blocking squalene epoxidase. Azoles prevent ergosterol synthesis by inhibiting 14-α-demethylase. Polyenes bind directly to ergosterol in the cell membrane, disrupting membrane integrity. This multi-targeted strategy highlights different biochemical steps essential for fungal viability, exploited by antifungal therapies.

5 Antifungal resistance

Even though the presence of the above-mentioned very useful antifungal agent fungi somehow builds up nature with fewer susceptibilities to the antifungal agents. This resistance can be acquired/extrinsic-development of resistance in response to over exposure to antifungal agents and probably leads to altered gene expression and another one is inherent/intrinsic-when a fungus is inherently it may show less susceptibility to the antifungal agents [51]. For instance, 90% of *C. auris* isolates are highly unsusceptible to fluconazole, more than 30% are shown defensive to currently available drugs like Amphotericin B and few Echinocandins-resistant isolates have been found recently [52, 53].

Table 3 Antifungal agents currently in use

Agents	Bioavailability and route of administration	Dosages	Mode of action	Spectrum of activity	References
Ketoconazole	76% of bioavailability with oral or topical route	200–400 mg/day (oral)	Fungal ergosterol synthesis inhibitor	Broad spectrum; active against oral candidiasis, Coccidioidomycosis, endemic mycoses, dermatophyte infection	[48–50]
Itraconazole	Bioavailability is 55% (maximum with fullmeal) with oral route	200 mg 1–3×/day (oral)	Fungal ergosterol synthesis inhibitor	Anti-Aspergillus activity, active against chronic pulmonary- Aspergillosis, onychomycosis, histoplasmosis, sporotrichosis, blastomycosis	[48–50]
Fluconazole	Both Intravenous (IV) and oral route, bioavailability of oral administration is 90%	400-800 mg/day (oral and IV)	Fungal ergosterol synthesis inhibitor	Active against Vaginal candidiasis, oropharyngeal, oesophageal, non- neutropenic candidemia, disseminated candidiasis, cryptococcal meningitis, hepatosplenic candidiasis, funguria and focal urinary tract infection	[48–50]
Voriconazole	96% bioavailability in healthy adults with oral route	6 mg/kg for 2 days, then 4 mg/kg for 12 hourly (IV); 400 mg bid for 2 doses then 200mgfor12 hourly(oral)	Fungal ergosterol synthesis inhibitor	Active against invasive Aspergillus, Fusarium species, Candida species, Scedosporium	[48–50]
Posoconazole	Suspension	300 mg/day (IV); suspension:800 mg/day Tablet: 300 mg for 2 doses then 300 mg/day	Fungal ergosterol synthesis inhibitor	Active against Aspergillus, Candida, Cryptococcus, Histoplasma, better than Voriconazole against Zygomycetes	[48–50]
Ravuconazole	NA	NA	Fungal ergosterol synthesis inhibitor	Active against Candida species, opportunistic Candidiasis in HIV patients	[48–50]
Morpholine	NA	NA	Squalene epoxidase inhibitor	Treatment of nail infection, also in agricultural application	[48–50]
Amorpholine	NA	NA	Squalene epoxidase inhibitor (hyper fluidity of the membrane thus changes membrane permeability)	Fungistatic and fungicidal both, treatment of nail infection	[48–50]
Terbinafine	40% of bioavailability after first pass metabolism with oral route	NA	Squalene epoxidase inhibitor	Active against Aspergillus spp., fusarium spp., Fungicidal against dermatophytes, dimorphic fungi, topical treatment for mycoses	[48–50]
Amphotericin B	Bioavailability is 100% with intravenous infusion	0.71–1 mg/kg/day (IV)	Ergosterol disruption	Broad spectrum activity from yeasts to common dermatophytes	[48–50]
Nystatin	Oral or topical	NA	Ergosterol disruption	Effective topical agents for Oropharyngeal candidiasis	[48–50]
Caspofungin	Intravenous infusion does 92% of bioavailability after 36–48 h intake	70 mg for 1 dose then 50 mg/day (IV)	Glucan synthesis inhibitor	Active against *Aspergillus* spp., *H. capsulatum, C. immitis, B. dermatitidis, P. carinii*	[48–50]

Table 3 (continued)

Agents	Bioavailability and route of administration	Dosages	Mode of action	Spectrum of activity	References
Micafungin	IV administration	100–150 mg/day (IV)	Glucan synthesis inhibitor	Active against opportunistic Candidiasis then Fluconazole in relation to patients undergoing transplantation	[48–50]
Anidulafungin	NA	100–150 mg for 1 dose then, 50–200 mg/day	Glucan synthesis inhibitor	Active against opportunistic Candidiasis, Candidemia, peritonitis, Aspergillus species wide range of Candida species, and species showing less susceptibility to azoles, AMP B or other Echinocandins	[48–50]
Nikkomycin	NA	NA	Chitin synthesis inhibitor	Active against highly chitinous dimorphic C. *immitis, Blastomycese dermatitidis, H. capsulatum*fungicidal against *A.fumigatus* in combination with Caspofungin	[48–50]
Flucytosin	78–85% bioavailability with oral route	25 mg/kg 4x/d (oral)	Nucleic acid synthesis inhibitor	Adjunctive therapy toward Cryptococcus neoformans, Candida species	[48–50]
Griseofulvin	25–75% absorption by oral route and enhanced by administration with or after fatty meal	NA	Microtubule synthesis inhibitor; inhibits fungal mitosis	Active against dermatophyte fungi causing ringworm and athlete's foot	[48–50]

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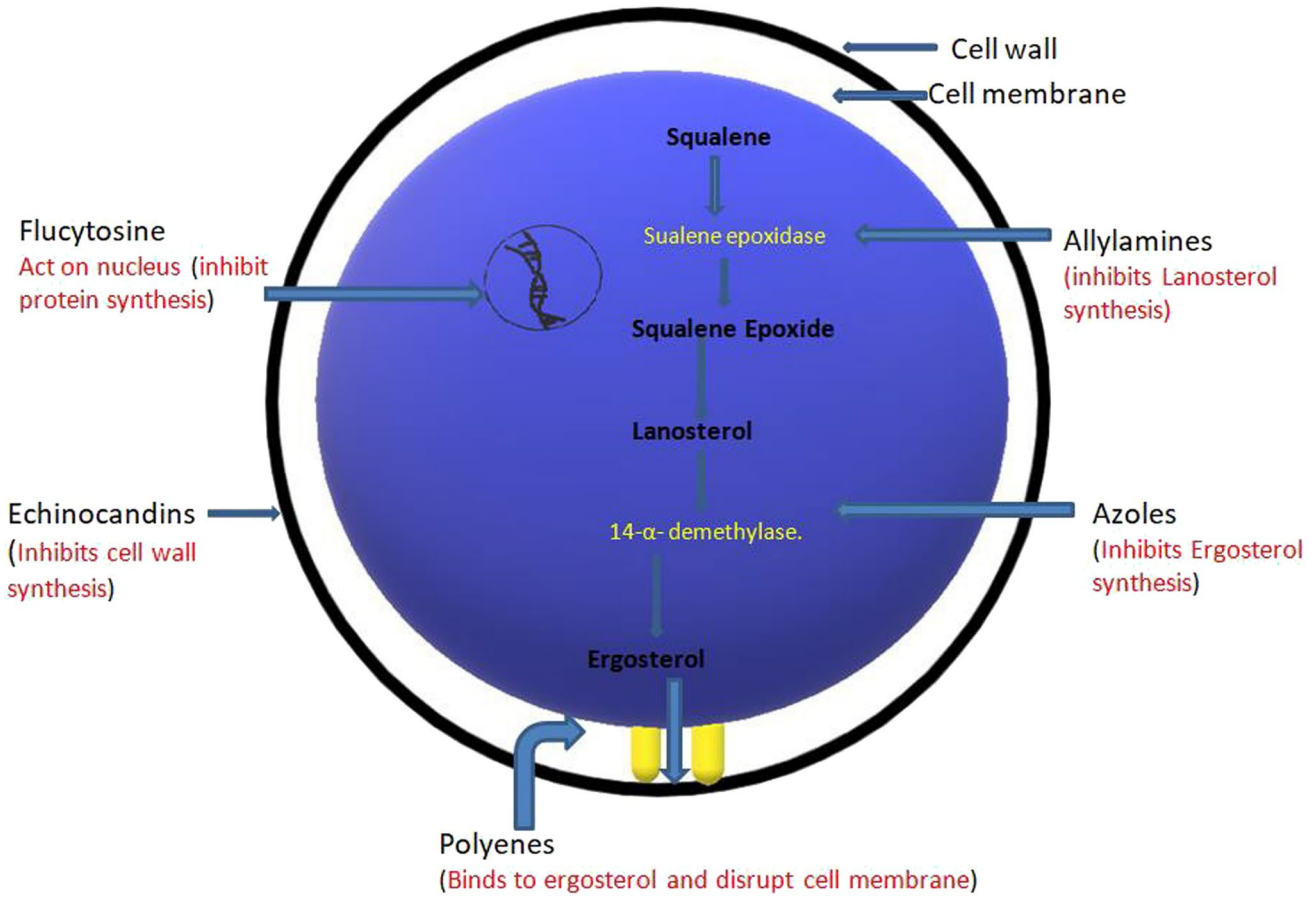


Fig. 7 Targets of antifungal agents

5.1 Mechanism of resistance

- Drug target alternation and over-expression: Antifungal drug binding and its efficacy is reduced due to mutation in the drug target gene [54].
- Reducing the accumulation of drug intracellularly by efflux pumps possibly because of the presence of MDR-associated proteins and Pleotropic drug resistance (PDR) families [54].
- Presence of effective molecular chaperones such as Hsp 90, as they respond to diverse cellular stresses including antifungal stress. TOR protein also controls cellular response to antifungal stresses [54].
- Genome plasticity and alternative also play a vital role in antifungal resistance (Table 4) [54].

Thus, multidisciplinary efforts need to be taken which may include the first and foremost control of antifungal resistance for instance particularly the spread of C. auris infection, frequent antifungal resistance testing, rapid and innovative diagnostic test of patient at high risk, standard infection control procedures, personal hygiene educations, patient isolation, environment cleaning [52]. And the most important is discovery and improvement of new antifungal agents and improving the efficiency of the existing ones. Additionally, another important reason for invention and improvement of novel antifungal agents is the toxicity or side effects associated with the existing ones which need to be delimited by innovative researches. Thus, the need of new or novel antifungal drug is at the peak.

Table 4 Mechanism of resistance of some fungi against antifungal agents

Agents	Mechanism of resistance	Resistant fungi	Reference
Azoles	Induction of efflux pumps of ABC pumps by expressing transcription factors like Tac1, Mrrl, Cgpdrl	*Candida albicans* *C. glabrata*	[54–56]
	Over expression of EGR11 due to mutation in factor UPC2	*C. albicans*	
	Substitution of amino acid of Cyp51A	*Aspergillus fumigatus*	
	Point mutation in Cyp51	*Aspergillus flavus* *A. terreus*	
Fluconazole	Chromosome 1 disomis (Genomic plasticity)	*Cryptococcus neoformans*	
Itraconazole, Miconazole	Heat shock protein 90	*C. albicans, Saccharomyces cerevisiea*	
Echinocandins	Mutation in drug target gene FKS1	*C. albicans*	[54–56]
	Amino acid substitution of FKS2 and FKS1at position Ser641, Ser645	*90% of Candida* spp. *(C. glabrata)*	
	Polymorphism at Pro649, Met638, Ala634	*C. parapsilosis* *C. guilliermondii*	
	Heat shock protein 90	*Trichophyton rubrum*	[55]
Polyenes (Amphotericin B)	Reduction in ergosterol content in cell membrane	*Saccharomyces* spp., *Candida* spp.	[54–56]
	Defective C8 isomer and diminished sterol content	*C. neoformans*	
	Drug detoxification by increased catalase activity	*Candida* spp.	
Terbinafine	Drug efflux	*Microsporum canis*	[55]
	Extra copies of squalene epoxidase	*Aspergillus fumigatus*	
	Extra copies of salicylate 1-monooxygenous	*A. nidulans* *Trichophyton rubrum*	

Table 5 Comparison of Properties of Anidulafungin and its Analogues

Properties	Compound	Values
MIC (μmg L^{-1}) for *Candida albicans C. krussei*	(1) Anidulafungin (2) New analogue	(1) 0.25, 0.25 (2) 1, 1
Hemolytic activity MLC (Minimum Lytic Concentration) in μg mL^{-1}	(1) Anidulafungin (2) New analogue	(1) 5 (2) >640
Water solubility in mg mL^{-1}	(1) Anidulafungin (2) New analogue	(1) <0.01 (2) 124.7
In vivo acute toxicity LD50 mg kg^{-1}	(1) Anidulafungin (2) New analogue	(1) 14.06 (2) 166.82

Table 6 Decreasing MIC value

Species	IONPS	CS	FLZ	IONPS-CS-FLZ
C. albicans	>140	>140	200	25
C. glabrata	>140	>140	100–200	50

6 Development of new drug

Currently, available drugs have been known to show less affectivity; along with it, some are known to develop insignificant drug-drug interaction, poor tolerability, drug distribution issues and most importantly toxicity. A drug like Echinocandins fails to penetrate to intrabdominal sites and it led finally to failure in treatment and development of antifungal resistance. Concerning delineating the action of current antifungals, novel antifungal drugs are of a much-needed state to improve the overall care of patients at risk of fungal infection [57]. For the problem to be minimized, we have options in our hands of drug repurposing-that allows new indication or improved form of an existing drug, or development of a completely new drug or also finding some new target to defeat/attack the pathogen [8]. It is considered that finding a new antifungal drug is of immense challenge because of the eukaryotic nature of the pathogen as it shares metabolic pathways with the host [58]. In simple words having an evolutionary relationship makes the task difficult [59]. Because we believe that we can circumvent the enlarging population of susceptible "Human Petri Dishes" by developing new antifungal agents [47].

6.1 Modification and synergistic combination of existing antifungal

6.1.1 Anidulafungin

Anidulafungin (the third-generation Echinocandins) shows certain deficiencies like poor oral absorption because of that it is injected intravenously once daily despite of its better properties. Thus, some amino acids with polar groups were used as drug modifiers into the side chain of Anidulafungin by choosing aromatic acid, fatty acid; Dab (2,4-aminobutyric acid) were utilized as a synergistic combination for developing a novel side chain. As a result, an N-acylated analogue was synthesized and its enhanced properties to that of the original Anidulafungin were evaluated as shown below (Table 5) [60].

MIC stands for Minimum Inhibitory Concentration is the least amount or concentration of the chemical or drug that will be able to kill the microorganism present in the given sample. This is important to measure the potency of any new agents as antifungal or any antimicrobial.

6.1.2 Fluconazole

The decrease in MIC value for *Candida albicans, C. glabrata* and *C. parapsilosis* [61] was observed when the use of solid–liquid nanoparticle was used with fluconazole (FLZ). The use of iron oxide nanoparticles or more specifically iron oxide magnetic nanoparticles (IONPS). The IONPS are functionalized by different compounds like Chitosan (CS), by covering their surface. CS are linear aminoglycan units, that are biodegradable [61]. MIC in μg mL^{-1} decreases as shown below (Table 6):

Table 7 Reduction of biofilm concentration

Species	Reduction in biofilm concentration (%)
C. albicans 324LA/94	42.8
C. glabrata ATCC90030	52.6
C. glabrata P1	75

Table 8 MIC values of Amphotericin B and Artemisinin (Art)

Isolates of *C. albicans*	MIC(μg/mL)		
	AMB	Art	AMB + Art
SC5314	1	>150	0.2 + 23
CCCC-1	1.5	>100	0.4 + 23
CCCC-2	3	>80	0.2 + 25
CCCC-3	2	>160	1 + 22

Table 9 Haemolytic effect of the griseofulvin

Sample combination	Blood group A	Blood group B	Blood group O
Griseofulvin 5×D[b]	15	18	10
Griseofulvin 1×a	100	100	97
Griseofulvin 1× + MO-CBP3-PEPI	15	12	9
RcAlb-PEPI 1 + Griseofulvin 1×	12	18	2
RcAlb-PEPIII 1× + Griseofulvin 1×	8	10	3
MO-CBP3-PEPI 10×D + Griseofulvin 5×D	0	0	0

Along with decrease in MIC, the nanosystem reduces total biomass of biofilm (Table 7).

6.1.3 Amphotericin B

The purpose of repurposing AMB is to reduce its drug dosage, lowering toxicity and thus enhancing the antifungal activity. Artemisinin (Art) extracted from *Artemisia annua* L. a sesquiterpene lactone used to potentiate Amphotericin B specially for *orophraryngeal Candidiasis caused by C. albicans* [62]. It is found that there was a twofold increase in the ergosterol synthesis in 100 mg/l of Art, the ergosterol content increased by 2.5-fold, which may trigger ergosterol biosynthesis genes that are ERG1, ERG2, ERG9 and ERG11. Along with it, there was an enhanced affinity between the C. albicans cells and polyene agent with Art treatment (Table 8) [62].

6.1.4 Griseofulvin

The viability of microconidia of very resistant dermatophytes was unable to be reduced by Griseofulvin alone. Griseofulvin usually disrupts fungal microtubules thus, inhibiting cell division, which needs to cross the cell membrane, and it requires an energy-dependent protein transporter. Thus, a synergistic combination of Griseofulvin with peptides like MO-CBP3-PEPI (and similar other compounds) or RcAlb-PEPII [63] etc. induces pores formation of size 6, 10, 20 kDa etc. Reduces approximately 100% viability of microconidial cell of *Trichophyton mentagrophytes* and *T. rubrum*. In addition, this synergistic combination reduces the haemolytic effect of the drug by preventing its interaction with the erythrocyte membrane as shown below (Table 9) [63].

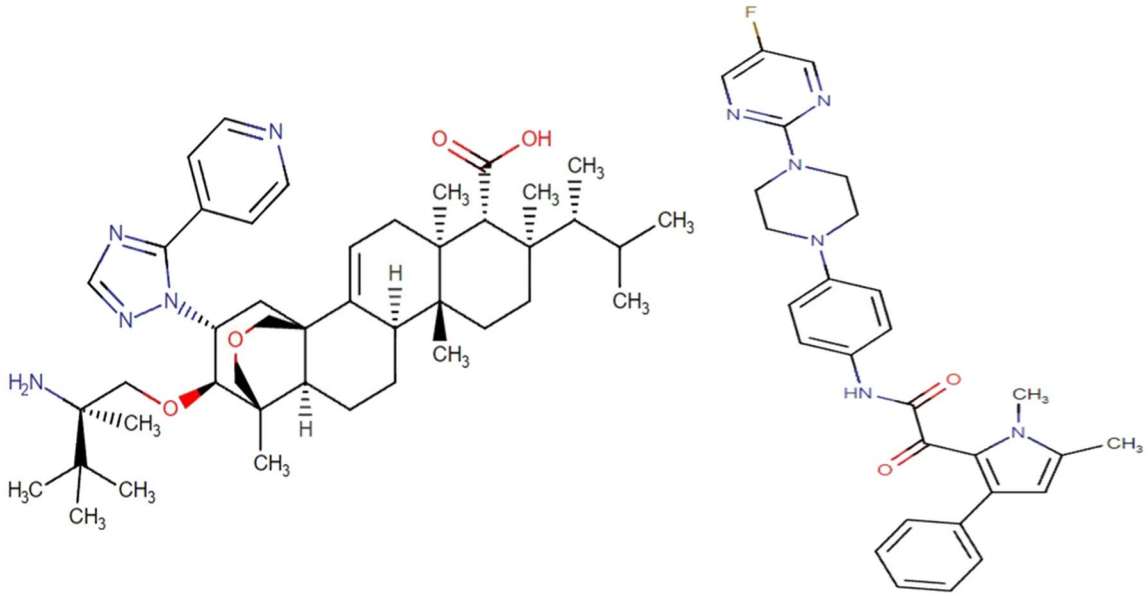
6.1.5 Some other notable examples

- Cochleates formation of Amphotericin B usually forms a crystalline phospholipid-cation structure which forms coiled lipid sheets [54] (Table 10).
- Replacement of 4-cynophenylthioazole of Ravuconazole with fluorophenylisoxazole resulted in a more active and wide-antifungal spectrum of Ravuconazole which is in current phase II clinical trial, the azole compound which generally binds to the active site of CYP51 and blocks ergosterol synthesis [78, 79]. Ravuconazole shows broad-spectrum activity against infectious yeasts as we already know their names and common dermatophytes. Fung-Tarae et al. found that Ravuconazole shows activeness against dermatophyte strains withMICs ≤ 0.13 µg/ml [78].
- β-amyrin, a terpenoid exhibits diverse biological activity including antifungal effects, antibacterial effects etc. β-amyrin has been found to do apoptosis in *Candida albicans* as a model organism. Characteristic marker from the apoptotic environment includes ROS accumulation, Cytochrome C release and externalization of Phosphatidylserine (PS), and DNA cleavage. In β-amyrin action, there is role of Ca^{2+} intake was investigated. Mitochondrial dysfunction occurs with a huge amount of Ca^{2+} intake [80]. The contribution of Ca^{2+} in fungal cellular apoptosis with β-amyrin treatment isconfirmed by Cyclosporin (CSA) pre-treated cells. CSA is a Calcineurin (Ca^{2+} homeostasis regulator) inhibitor. β-amyrin also showed cell apoptosis by DNA fragmentation and PS externalization [80].
- Glucose analogues like 2-deoxy-D-glucose (2DG) carefully impair the importation of zinc metal in the fungal cell as a decrease of zinc leads to the death of the fungal cell [81]. The evidence has been seen in macrophages infected by *Histoplasm capsulatum*, as 2DG manipulated the zinc availability it led to the killing of *H. capsulatum* in macrophages and 2DG leads to free zinc deprivation in fungal cells and the fungus cannot overcome zinc scarcity. This provides a new direction to target fungal cells [81].
- Dendrimers are branched polymers and are comprised of a core and Dendron. Dendrimers found to have strict antifungal properties or may have synergistic action by acting in different ways as follows [82]:
  - Interaction between the cationic terminal group of dendrimers and anionic group of cell membrane leading to membrane fluctuation and increased permeability.
  - Creating small pores and disrupting cell membranes and preventing them from rebuilding, the so-called "Carpet mechanism."
  - Inhibition of 1,3-β-D-glucan, leads to impairs cell wall synthesis and leakage of cell membrane.
  - Blocking microbial enzymes by using the Chelation mechanism as antifungal drug carriers' fungal activity and water solubility are found to increase in Clotrimazol (CTZ) and Ketoconazole (KET).
  - Amino acid-based dendrimers have much potential against *Candida species (albicans or non-albicans)* [82] with appreciably less MIC like 0.2 µg/ml, 1.5 µg/ml which is comparably very low [82]. Amino-based dendrimers are functional against *C. albicans, Kluyveromces fragilis, Rhodoterula rubra, Debaryomyces hansenii, Henseniaspora guilliermondii* [6].
- The new broad-spectrum antifungal activity of Triazole Albaconazole which has excellent bioavailability, good pharmacokinetics and is effective at a lesser dose (≥ 40 mg) than Fluconazole at 150 mg is a Phase II clinical trial. Aminocandin-1P960 or HMR3270, (semi-synthetic products from *Aspergillus sydowii*) having longer half-life creates a possible option for infrequent dosing shows promising activity against *Candida* and *Aspergillus* [54, 83].
- A combination of Terbinafine and Amorolfine (59% in treating onychomycosis) has shown higher success. Luliconazole for *Tinea pedis, T. corporis/T. crusis* and Efinaconazole and Tavaborole for onychomycosis were approved by the FDA recently [84, 85] (Fig. 8).

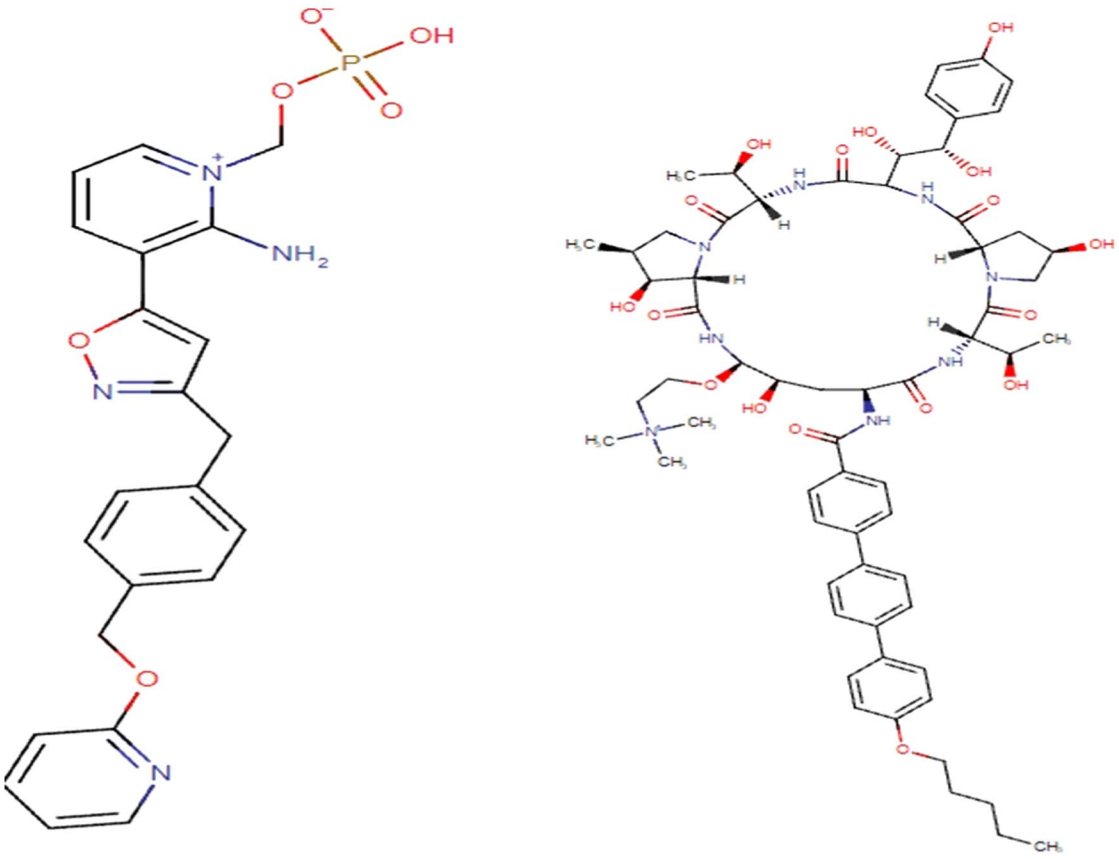
6.2 Fungal vaccines

Fungal vaccines are found to be effective in endemic areas to get rid of endemic fungal pathogens. At present time there are many examples of fungal vaccines (Fig. 9) but most of them are in pre-clinical studies or clinical studies [58, 86]. Along with the progress in fungal vaccine development. There lie some challenges in it like difficulties in determining of target population, and the complexity of eukaryotic fungal cells or specifically the similarities and marked differences with the host cell [86–90].

The strategies shown above may provide some promising treatment because they have a certain level of clinical trials (Fig. 10) [91]. However immune deficiencies caused by emerging IFI are one of the major limitations for such progress.



Ibrexafungrep/SYC-078(C44H67N5O4) **Olorofirm(C28H27FN6O2)**



Fosmanogepix/AX001(C22H21N4O6P) **Rezafungin(C63H85N8O17)**

Fig. 8 Targets of antifungal agents

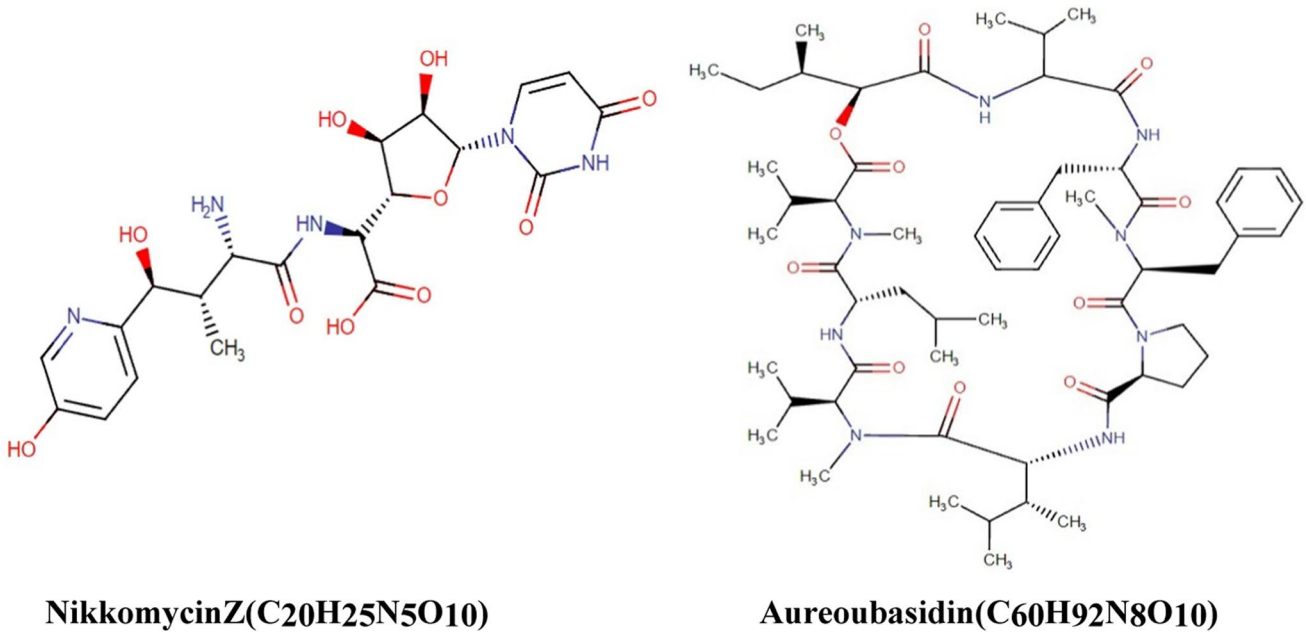


Fig. 8 (continued)

And so, the FDA has not approved any fungal vaccines at present (Table 11). This field requires more knowledge in the immunology of fungal infection and thus comes the effective designing of fungal vaccination [92]. Also, the very effective peptide and dendritic cell (DC) peptide vaccines need some more advanced studies for future use, and the advances in proteomics and genomics provided forwarding in vaccine proposals [86]. The use of adjuvants promotes adaptive immune responses by enhancing antigen immunogenicity for example-alums, β-1, 3-glucans, mannans etc. which usually stimulate Th or Th1 cell-mediated responses. But some adjuvants like complete Freunds can be toxic for routine use [93]. Even RNA interference (RNAi) technology and anti-*mucoricin* antibodies have neutralizing effects and decrease inflammation and host tissue damage. It was already found that the injection of anti-toxin IgG into mice model reduces the mucormycosis symptoms. It shows a new opportunity to use immunotherapy or anti-toxin-based treatments or strategies to prevent the morbidity of mucormycosis [32].

7 Discussion

Fungi are eukaryotic and ubiquitous organisms in our environment and are arbitrarily categorized into yeast, filamentous fungi, dermatophytes and dimorphic fungi. Fungal cells possess a cell wall with principal components are amino-polysaccharide and chitin. The chitin layer consists of an overlying matrix of β-1,3-glucans and β-1,6-glucan in yeast and β-1,3 glucan and α-1,3 glucan in filamentous fungi. Chitins as the basement layer resist internal osmotic pressure from the cytoplasm thus providing a strong shell-like framework. Fungal cells contain cell membranes containing a sterol called as ergosterol [1]. Besides being a useful organism for the ecosystem in many ways. They are highly detrimental in causing human diseases. True pathogenic and opportunistic fungi have increased the risk of life-threatening infections over the past few years. Transplant recipients, cancer patients, and others getting immunosuppressive medication are greater at risk, as they have less immunity overall. In immunocompromised patients, opportunistic invasive fungal infections are causing major mortality and morbidity. According to studies, the main cause of fungal diseases is an increase in population [5]. Invasive fungal infections (IFIs) are caused primarily by *Aspergillus* spp. and *Candida* spp. account for 95% of cases globally [15]. The possibility threatening factors for breakthrough IFI can be host factor, fungal factor and iatrogenic factor. The most pathogenic species in *Candida* genus are *C. albicans, C. krusei, C. glabrata, C. tropicalis, C. parapsilosis, C. lusitaniae, C. dubliensis, C. stellotoida* [20] and the recent most infectious one found in Covid-19 patients are C. auris. More than 30 species of the genus Aspergillus cause infection in humans. A. fumigatus causes a hypersensitive disease of the lung called as Allergic Bronchopulmonary Aspergillosis (ABPA). Since the 1990s IPA surpassed IC as the most common fungal infection [26]. Mucormycosis is caused by Mucorales *Rhizopus, and Absidia*, which are saprophytic fungi found in

Table 10 A completely new arsenal of antifungal agents with their stage of clinical phase, method of their antifungal action and other properties

Compound	Clinical Phase	Mode of action and other properties	Spectrum of activity	References
Ibrexafungrep/Syc-078/MK3118 (Triterpene)	Phase II	Glucan synthesis inhibitor, inhibit 1, 3- β-D-glucan synthase Developed for both oral and intravenous dosing Better biological distribution to kidney tissue at >12.5 mg/kg Same target as Echinocandins but are structurally different	MIC (µg/mL ranges from 0.06 to 2 for *Candida species (albicans or non- albicans).* And *active against Scediosporiumprofliicans, Aspergillus fumigatus, Paecilomyces-varioti.* Poorly active against *Mucorales, Fusarium*	[44, 45, 54, 58, 64–67]
VT-1129, VT- 1161, VT-1598 (Tetrazoles)	Phase I (VT- 1129), Phase III (VT-116), Preclinical (VT- 1598)	Inhibits lanosterol demythylase, interferes to fungal CYP51 enzyme, inhibit cell membrane formation, reduced p450 during interaction	VT-1129 is active against Candida spp., VT-1161 against *Coccidioides immitis, Trichophyton* spp. *Aspergillus flavus, A. terreus, vulvovaginal candidiasis* (MIC ranges from ≤0.03 to 4 mg/l VT-1598 has broader action against *Cryptococcus neoformans, C. gatti, Aspergillus* spp. *Rhizopus arrhizus*MIC ranges from 0.004 to >16 mg/l	[44, 45, 64–66, 68]
Olorofirm (F901318) (Orotomide)	Phase III	Inhibits pyrimidine biosynthesis by acting on enzymes such as dihydroorotate, dehydrogenase and oxidoreductase Lower toxicity and good tolerability, available in oral and intravenous form, no cross-resistnace, no drug- drug interaction	Active against *Aspergillus fumigatus, Lomentosporaprolificans, Candida* spp., *Mucorales, Cryptococcus*	[58, 64–66, 68]
Fosmanogepix (AX001)	Phase II	Broad spectrum activity. Inhibition of Gwt 1 (Glycosyl phosphatidylinostol, GPI) synthesis by inhibiting Inositol acetyltranferse Available in oral and intravenous form Synergistic combination with known antifungal	Active against *Candida, Aspergillus, Fusarium, Scedoposrium and Rhizopus arrhizus* Inactive to *C. krusei, Mucorales*	[64–66, 68]
VL-2397 (Antifungal peptide) (Siderophore class of antifungal)	Phase II	Intracellular sites are targeted and are transported intracellularly by Siderophore transporter Sit1	Active against Trizoles resistance *A. fumigatus, invasive Aspergillosis, Candidiasis*	[64, 65, 68]
Rezafungin (CD101) (Echinocandins class of antifungal)	Phase III	Target on β – 1,3-glucan synthesis Improve stability, long half life, and minimum interaction with CYP450 enzymes	Active against *Candida auris, PJP* and other *Candida* spp., MIC ranges from ≤ 0.008-2 mg/L)	[64–66, 68]
T-2307 (Aryl amine class of antifungal)	Phase I	Inhibits intracellular mitochondrial membrane potential. Shipped into cell by a specific polyamine transporter Equivalent efficacy to Amphotericin and Fluconazole Structurally similar to pentamide	Target *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp.	[65, 66, 68]

Table 10 (continued)

Compound	Clinical Phase	Mode of action and other properties	Spectrum of activity	References
ASP2397 (Siderophore class of antifungal)	Preclinical	Effect on intracellular target/disrupt fungal cell intracellularly after uptake via specific iron transporter siderophore Sit 1 Cyclic hexapeptide isolated from *Acremonium persicium*	Active against yeast, molds, azole resistant *Aspergillus* spp.	[54, 64–66, 68]
Nikkomycins (SP-920704)	Phase I	Inhibit chitin synthesis. Isolated from Streptomyces. Available in oral and intravenous form. Short half-life. Additive and synergistic activity with the enzyme1,3-β – glucan synthaseinhibitor	Poor antifungal activity in monotherapy. Active against *C. immitis, Blastomyces dermatitidis, C. albicans, C. neoformans, H. capsulatum*	[58, 65, 69]
Sordarins (Tetracyclic diterpene)	NA	Inhibit fungal protein synthesis Isolated from *Sordariaaraneoza*(Andriole, 1999)	Active against *C.* spp., *Aspergillus* spp., *Pneumocystis carinii* Synergic effect with Amp B and azole against *Aspergillus, Scedosporiumapiospermum*	[69, 70]
Aureobasidin A (Glycolipid inhibitor)	Preclinical	Inhibition of inositol phosphorylceramide synthase Produces by *Aureobasidium pullulans* Potent cyclic depsipeptide antifungal	Broad spectrum activity. Active against multi-drug-resistant fungal species	[65, 70]
Rustimicin (Glycolipid inhibitor)	NA	Inhibit sphingolipid biosynthesis Isolated from-*Micromonospora* spp.	Active against multi-drug-resistant fungal species	[60, 70]
Kafrefungin	NA	Inhibit sphingolipid biosynthesis Derivative of Aureobasidin A	Active against *C. albicans, Cryptococcus neoformans*	[60, 70]
Novexatin, Novamycin, VL- 2397, PAC-113, Histatins. (Antifungal peptides)	Phase II (NP213) Preclinical (NP3 39) Phase II (PAC113)	Cyclic cationic peptide. Poly –arginin basedcationic peptide	Effective for onychomycosis caused by dermatophytes and non- dermatophytes. For oral Candidiasis in HIV patients, fungal gingivitis, planktonic biofilm, *Aspergillus,Cryptococcus, Trichoderma*	[60]
AR-12	Phase I	Inhibition of fungal acetyl co-enzyme A synthethase I	Active against *Cryptococcus* spp., *Candida* spp. *like C. albicans, Mucorales* and considerably against *Fusarium* spp., *Scedosporium* spp.	[65]
MGCD290 (Histone deacetylase inhibitor, Hos2)	Phase II	Target on lysine's on core histone, Hsp90 or simply Histone deacetylase inhibitor, Hos2	Broad spectrum activity Synergize with fluconazole for better treatment to *vulvovaginal candidiasis*	[65]
Lactosmart	NA	Natural antimicrobial protein. Another derivative is Lactoferricin B	MIC for *C. species* ranges from *1- 5 mg/ml* Inhibits formation of biofilm of *Pseudomonas aeruginosa*	[71]

Table 10 (continued)

Compound	Clinical Phase	Mode of action and other properties	Spectrum of activity	References
Siramesine	Phase II	Potential inhibitor of sigma—1 receptor and Erg2 protein induces growth arrest and cell death Contain piperidne group. Other derivatives are Ozagrel, Talarozel, L- 778,123, MBX2982	MIC for *Candida species* is ≤12.5 µg/ml	[72]
PC945 (Triazoles)	Phase I completed	Inhibit ergosterol synthesis, targeting CYP51. Designed for inhalation Well tolerated and less toxicity	Active against 96 isolates *of A. fumigates, Candida* spp., *Cryptococcus* spp., *Rhizopus oryzae*	[66]
PUR1900	Phase II	Inhibit ergosterol synthesis. It is an inhaled Itraconazole formulation	Broad spectrum activity	[66]
Thymol	NA	Modifies fungal hyphal structure, reduction in hyphal diameter or lysis of fungal cell wall Phenolic monoterpenoid. Agricultural antifungal	Very effective against *Fusarium solani*MIC = 14 µg/ml	[73]
Benzimidazole -Triazoleshybrids	NA	Inhibits lanosterol 14α- demethylase inhibitors	MIC values range from 0.78 to 1.56 µg/ml for *Candida species*	[74]
Thiazoyle- Guanidine derivative	NA	Target lipophilic binding pocket through a Hydrogen – bond. Other derivatives inhibit ergosterol synthesis by SMT inhibition in *Aspergillus fumigatus* Combination of 6-membered ring Guanidine and 2, 4- substituted thiazole rings	MIC for *A. fumigatus* is 2 µg/ml	[75]
LY-303366 (Echinocandins)	Preclinical	Chitin synthesis inhibitor. Linear kinetic, long plasma half-life. Once daily dosing is anticipated	Excellent inhibitor for *Candida* and *Aspergillus* spp. reduces levels of *Aspergillus antigenaemia*	[69]
Arthrichitin and LLI5G256 (Echinocandins)	NA	Chitin synthesisinhibitors. Cyclicdepsipeptide Isolated from *Arthriniumphaseospermum*and *Hypoxylonoceanicum*	Broad spectrum against *Candida, Trychophyton, phytopathogen*	[70]
Fusacandin (Chaetiacandin)	NA	Cell wall biosynthesis inhibitor. Substitution of Carbon number6 fatty acyl on fusacandin contributes to protein binding and thus protein inhibition It is a trisaccharide. Isolated from *Fusarium sambucinum*	Broad spectrum activity	[70]
Monoclonal antibody (18B7,2 GB,efungamep)	18B7 (Phase I)	Direct target on fungal cell/ immunomodulation and enhancing immune response against fungi/ neutralizing fungal toxic compound to host	18B7 target Cryptococcus glucuronoxylomannan (GXM) 2 GB act against different types of Candidiasis and Aspergillosis	[76]
Cytokine Treatment (GM-CSF, IFN-ϒ)	GM-CSF(Phase IV)	Mediate protective immune response to the host by inducing Th1 cellular immunity	Target those fungi causing Transplantation related mortality, cumulative mortality, reduces IFI. IFN-ϒ- Fungal killing in *Cryptococcus neoformans meningoencephalitis (CM)* and *Paracoccidioides brasiliensis infections*	[77]

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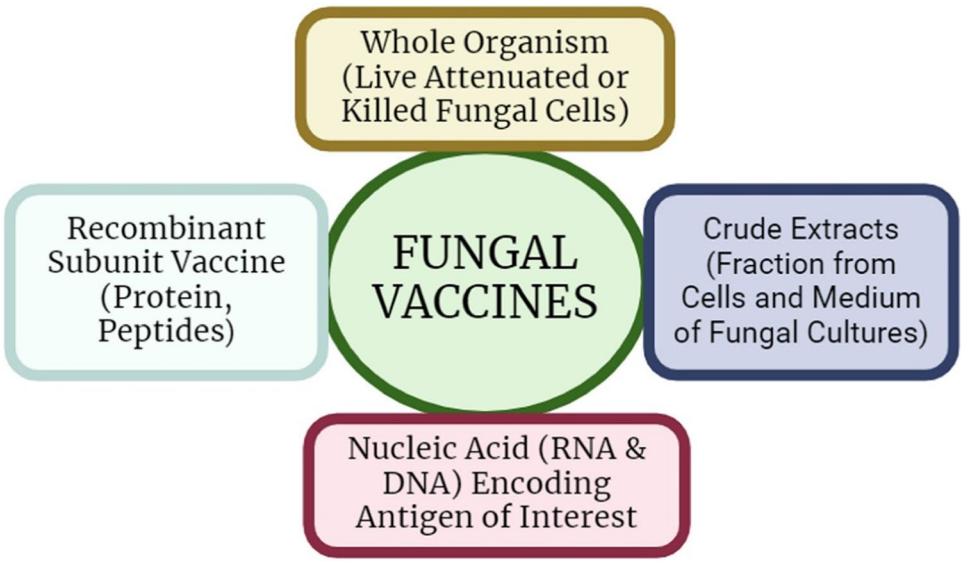

Fig. 9 Types of fungal vaccines

soil and decaying organic materials. Mucormycosis had a higher mortality rate 71.4% than Aspergillosis 28.5% as it has orbital invasions [30]. Cases of rhino-orbital-cerebral mucormycosis with altered mental status, proptosis is found in Covid-19 patients. Tissue necrosis is the last sign as a hallmark of mucormycosis. Ricin-like protein *Mucoricin* play a vital role in Mucorales infection leads to host cell apoptosis. *Mucoricin* has been discovered to be quite active in pulmonary mucormycosis and maybe in Rhino-orbital illness [34]. Other pathogenic dermatophytes which produce infections include *Trichophyton, Microsporum*or, *Epidermophyton, Tinea* infection/Jock itch/Ringworm etc. Chromoblastomycosis (CBM) [35] is a common chronic granulomatous mycosis of the skin and subcutaneous tissue caused by *Fonsecaea* spp.*, Cladophialophor* spp.*, Phialophora* spp., and *Rhinocladiella* spp. It is a neglected fungal illness caused by *Fonsecaea* spp. *and Cladophialophor* spp. [35]. Immerging new fungal infections by the emergence of new and resistant fungal pathogens leads to the development of new antifungal drugs. Some superficial treatment for fungal infection was reported in the early nineteenth century important by the use of Potassium iodide, and Whitfield ointment. The development of other important antifungal agents presently in use began approximately from 1950 for example first Polyene, Nystatin, Amphotericin B. From 1944 to 1980 the development of first generations azoles- Thiabendazole, Mebendazole, Imidazole, Clotrimazole, Miconazole, Econazole, Ketoconazole, Itraconazole, Fluconazole occurs. Other miscellaneous agents developed in the 1940s are Griseofulvin, Tolnafate, and Haloprogin etc. And accordingly, they are classified into their respective classes and sub classes. Consequently, the presence of five types of antifungals at present is helping the increasing population to combat fungal disease: Echinocandins, Polyenes, Flucytosine, Azoles, and Polyenes with the complete approval of the FDA thus are referred to as the current armamentarium of antifungal agents [42]. Polyenes include Amphotericin B ($C_{13}H_{73}NO_{17}$) and Nystatin ($C_{47}N_{75}NO_{17}$). Azoles include Fluconazole ($C_{13}H_{12}F_2N_6O$), Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$), Voriconazole ($C_{16}H_{14}F_3N_5O$), Posaconazole ($C_{37}H_{42}F_2N_8O_4$), Ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$). Echinocandins are cyclic lipopeptide molecules including Caspofungin, Micafungin and Anidulafungin. Flucytosin is a converted molecule by Cytosine deaminase to toxic compound 5-fluorouracil. Terbinafine is an allylamine used for the topical treatment of superficial mycoses. Azoles usually are fungal ergosterol synthesis inhibitors, Polyenes disrupt ergosterol, and Echinocandins are Glucan synthesis inhibitor, Flucytosine is a Nucleic acid synthesis inhibitor, Terbinafine is a squalene epoxidase inhibitor. Other agents for example Griseofulvin area microtubule synthesis inhibitor-inhibits fungal mitosis. Morpholine and Amorpholine are squalene epoxidase inhibitors. They have different dosage concentrations with oral/tropical/intravenous routes of administration and are of a broad and narrow spectrum of activity. Nowadays, fungi show high resistance to the antifungal stated above. This resistance can be acquired or extrinsic and inherent or intrinsic and the reasons can be resistance in response to our exposure to antifungal agents, which leads to altered gene expression and when a fungus is inherently ineffective to any kind of antifungal agents. *Candida albicans, C. auris, C. terreus, C. parapsilosis, C. guilliermond* [54], *Aspergillus fumigatus, A. flavus, A. nidulans* [44, 45], *Cryptococcus neoformans, Saccharomyces cerevisiea, Trichophyton rubrum, Microsporum canis* are among the most resistant fungal species to the antifungal agents currently at use. Thus, the need for new or novel antifungal drugs is at its peak. Concerning delineating the action of currently available drugs novel antifungal drugs are of much needed state to improve the overall care of the patient at risk of fungal infection. The

Table 11 Example of some fungal vaccines

Vaccine category/types	Target pathogen	Antigen strain	Route of injection	Underlying immune mechanism	Advantages
Live attenuated	*Aspergillus*	Heat killed cell of *Saccharomyces cerevisiae*	Subcutaneous injection	Th 1, Th2, Th17	Provide numerous antigen specific for the pathogen, strong and long-lasting immunogenicity
	Blastomycosis	Adhesion BAD1 gene	Subcutaneous injection	CD8 +T cells, MHC I, Th 1 Immunity (Silva and Taborda, 2020)	
	Histoplasmosis	live cells of *H*	Intravenously	Lymphoid cells *capsulatum* (Nami et al., 2019)	
Heat killed yeast cell	*Pan fungal*	β – Glucan of *Saccharomyces cerevisia*	subcutaneous	Th1, Th17, Antibodies to glucan and mannan (Nami et al., 2019)	Stable then live attenuated, cannot cause infection
Subunit vaccines (proteins, dendritic cells, peptides)	*Histoplasmosis*	HIS-62	Subcutaneously	Cellular immune response	Fewer antigens minimize the potential side- effects
	Histoplasmosis	Heat shock protein	Subcutaneously	Th 1	
	Candidiasis	SAP 2 (virulence factor)	Intravaginally	Protective antibodies	
	Aspergillosis	Asp16f	Intranasally	Th 1	
DNA vaccine	*Paracoccidiod mycosis*	Gp 43	NA	Immunological memories	Fast manufacturing process, strong immune response
	Paracoccidiod mycosis	*Mycobacterium leprae* derived—HSP 65	Intramuscular	Th 1	
Recombinant protein (NDV-3 and NDV-3A)	*Candidiasis*	NA	NA	B and T cells, Antibodies and $CD4^+$ Th1 cell	Protection against lethal *Candida auris*

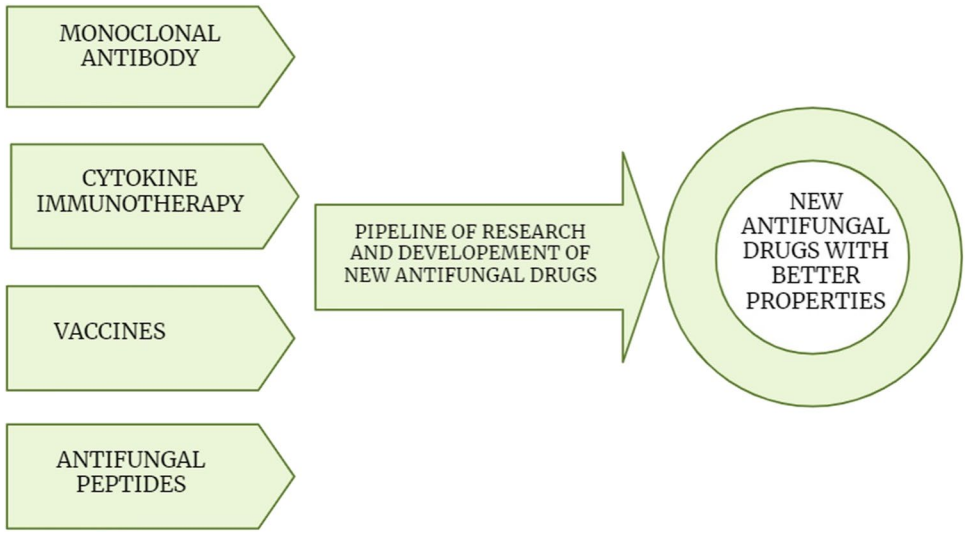

Fig. 10 New strategies to combat fungal diseases

eukaryotic nature of the pathogen makes it a difficult task for the development of new antifungals. Existing antifungals are modified or their activity is enhanced by synergistic combination. Anidulafungin is a 3rdgeneration Echinocandin with some better properties like lower toxicity, and longer half-life. Fluconazole activity is enhanced by iron oxide magnetic nanoparticles (IONPS). Chitosan (CS) at its surface, thus forming a complex IONPS-CS-FLZ. Repurposing of Amp B potentiating it with Artemisin (Art) against *C. albicans* and *Oropharyngeal Candidiasis.* Similarly, a synergistic combination of Griseofulvin with peptides induces cellular perforation in *T. mentagrophytes* and *T. rubrum* [63]. Different new antifungals with enhanced activity, altered mode of action, and wider or very specific spectrum of activity are at different clinical currently, for example, Triterpene (SYC- 078), Tetrazole, Olorofirm, Fosmanogepix (AX001), Antifungal peptides (VL-2397, ASP2397, NP213, NP339, PAC-113), Sordarins (inhibit fungal protein synthesis), MGCD290 (Histone deacetylase inhibitor Hos2), Lactosmart is a natural antimicrobial protein, Siramesin (induces growth arrest and cell death), Thymol (Modifies fungal hyphal structure) and many more. Monoclonal antibodies (18B7, 2 GB, efungamep) directly target fungal cells, enhance the immune response against fungi or neutralize fungal toxic compounds to host. Cytosine treatment (GM-CSF, IFN-α) may mediate a protective immune response to the host by inducing Th1 cellular immunity. Improved properties of Cochleates formation of Amphotericin B, β-amyrin (terpenoid) has properties of antifungal and has been found to do apoptosis in C. albicans as a model organism. 2-deoxy-D-glucose (2DG) impairs the impact of Zinc metal in the fungal cell as lessening of Zinc results in the death of fungal cells as seen in *Histoplasma capsulatum* [80]. Dendrimers, the branched polymers are foundto have strict antifungal properties. The combination of Terbinafine and Amorolfine treats 50% of Onychomycosis. Azoles such as Albaconazole, Luliconazole, Efinaconazole and Taraborole were recently approved by the FDA. Also, like other vaccine functions, fungal vaccines in many forms (live attenuated or killed fungal cells or it can be any fractions from cells and medium of fungal cultures or even recombinant subunit vaccines, and nucleic acid encoding antigen) have demonstrated to be quite effective [91, 92]. The use of adjuvants-Alums, β-1,3-glucans mannans etc. promotes adaptive immune responses by enhancing antigen immunogeneticity. Usually stimulates Th or Th I cell-mediated responses. RNAi technology and anti-Mucoricin antibodies show new opportunities for using immunotherapy or anti-toxin-based treatments or strategies to prevent the morbidity of mucormycosis.

8 Conclusion

As fungal resistance is on the rise and at risk, the development of novel antifungal agents at present is a very upcoming field for further research. Research in fields like monoclonal antibodies, antifungal peptides, and cytokine immunotherapy against fungal pathogens has shown very approaching results. Fungal vaccines though are not approved completely till now but are found to be very effective. But in the meantime, there are many limitations for the finding of novel antifungals such as poor diagnostic tests for fungal infections, as many fungal diseases remain undiagnosed and thus untreated. This may lead to the occurrence of pandemic formation. Existence of innovation gaps with antifungal discovery which is mainly due to discovery approval delays. There also exist innovation gaps in antifungal target discovery delays. Thus,

deep and intensive research on the above said field and approaches to remove and prevent the limitations by emerging researchers may speed up the progress in the field of development of novel antifungal agents because all these works are meant to mimic and manipulate what nature has already invented with better tools and techniques for the betterment of humankind.

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Declarations

Competing interests The authors declare no competing interests.

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