Fungal Cell Wall: Modifying Antifungals and Drug Resistance

Gudepu Renuka [1]
Assistant Professor, Department of Microbiology, Pingle Govt. College for Women, Waddepally, Warangal, Telangana, India, renumanduva@gmail.com

(Corresponding Author)

Smriti Aluri [2]
MBBS Final, Kaloji Narayana Rao University of Health Sciences, Warangal, Telangana, India.

Abstract

Antifungal therapy is a critical component of patient management for invasive fungal diseases. Yet, therapeutic choices are limited as only a few drug classes are available to treat systemic disease, and some infecting strains are resistant to one or more drug classes. The ideal antifungal inhibits a fungal-specific essential target not present in human cells to avoid off-target toxicities. The fungal cell wall is an ideal drug target because its integrity is critical to cell survival and a majority of biosynthetic enzymes and wall components is unique to fungi. Fungal infections are a worldwide problem associated with high morbidity and mortality. There are relatively few antifungal agents, and resistance has emerged within these pathogens for the newest antifungal drugs. As the fungal cell wall is critical for growth and development, it is one of the most important targets for drug development. The ideal antifungal inhibits a fungal-specific essential target not present in human cells to avoid off-target toxicities. The fungal cell wall is an ideal drug target because its integrity is critical to cell survival and a majority of biosynthetic enzymes and wall components is unique to fungi. Among currently approved antifungal agents and those in clinical development, drugs targeting biosynthetic enzymes of the cell wall show safe and efficacious antifungal properties, which validates the cell wall as a target.

Keyword : Cell wall , Antifungal , Drug, Antifungal Drugs, Fungal

DOI Number: 10.14704/nq.2022.20.9.NQ44450 **Neuro Quantology 2022; 20(9):3945-3952**

Introduction

Fungal homeostasis requires the cell wall to function properly. When it comes to developing antifungal treatments, human cells are ideal because they lack a protective outer layer. Cell wall modifications related to drug resistance can be caused by the host environment and antifungal stress. When combined with proteins and carbohydrates, the fungal cell wall forms an extremely strong but flexible structure that is approximately 40% of total fungal cell volume, making it one of the most important parts of the cell. Most cell walls are made up of two layers: an inner skeleton and an outer layer that is more diverse and unique to each individual species. When the cytoplasm and membrane exert a substantial hydrostatic pressure on the cell wall, the inner cell wall acts as a loadbearing, structural component of the cell wall. This layer consists of chitin and glucan, with 50% to 60% of the dry weight of the cell wall made up of β-(1-3)-glucan. Heavily mannosylated glycoproteins with modified N and O linked oligosaccharides form the outer layer of the outer layer. They have different structures depending on which fungal species you are searching at.[2]

A wide range of conditions are brought on by fungi. It is common for them to cause rashes or other conditions on the skin, but some can be more serious. Meningitis, blood infections, and lung infections can all be caused by fungi. Fungal infections can be treated with antifungal drugs. Antifungal medications can be taken orally, topically, or intravenously via an IV drip. [3]

Antifungal drugs target the fungal cell membrane and the fungal cell wall, which are both parts of the cell. These are two parts of the cell that can leak and kill the cell if they are damaged.

Types of antifungal drugs

Antifungal drugs can take a variety of forms, each influenced by a unique set of circumstances. There are a variety of ways to take specific medications. How a patient is treated will vary depending on the type of infection he or she has. Antifungal drugs fall into one of four categories. These include:

- polyenes

As the walls of the fungal cells become more porous, the fungi are more likely to burst.

- azoles

Two subcategories of imidazole antifungal medication are available: imidazolone and triazole antifungals.

- allylamines

By inhibiting an enzyme required for proper membrane function, allylamines work as a cell membrane inhibitor. In the absence of this membrane, the cell may not be able to carry out its basic functions. Terbinafine is an example of an allylamine, which is used to treat skin infections caused by fungal.

- echinocandins

These interfere with an enzyme that is critical to the formation of the fungal cell wall.

Systemic fungal infections can be treated with amphotericin B, lipid formulations of amphotericin B, 5-fluorocytosine, and the azoles miconazole, ketoconazole, fluconazole, and itraconazole, all of which are currently available antifungal agents. [4] New antifungal drug candidates should have properties such as inhibiting fungal cell wall biosynthesis, potency comparable to amphotericin B, safety comparable to fluconazole, and fungicidal activity in vitro and in vivo, all of which are currently sought after in the best possible way. [5]

Immunotherapeutic strategies against fungal infections

Both host and pathogen immunotherapy strategies for fungal disease prevention and treatment continue to be analysed. Aside from vaccines and fungal components, these mechanisms include: a) manipulating host immunity by fungus components; b) targeted activation fungal immune responses in the form of phagocyte, T cell, and antibody; and c) development of auxiliary components of immune response, such as cytokines/chemokine and antimicrobial peptides (AMPs). Among immuno-compromised patients, invasive fungal infections are a leading cause of death. [6] Many antifungal agents are available, but the overall mortality rate remains around 50%. Not restoring host immunity has the unfortunate side effect of making things even worse. As a result of these findings, new immunotherapeutic methods should be developed in order to improve the outcomes of patients with immune system disorders and invasive fungal infections. [7]

The fungal cell wall

Fungal cell walls can make up about 40% of the total cell volume and range in thickness from 0.1-1.0 μm, which can be boosted further in Cryptococcus neoformans and Histoplasma capsulatum, respectively, by the presence of an outer capsule layer. Many fungal cell walls are made up of galactomannoproteins surrounded by chitin and β (1-3)-glucans as the primary components of the cell wall. [8]

Chitin

Chitin, a polymer of β 1, 4-linked N-acetylglucosamine, is an essential component and defining feature of the fungal cell wall, accounting for only one to two percent of the total dry weight in Saccharomyces cerevisiae but ten to twenty percent in filamentous fungi. Chitin plays an important role in maintaining the cell wall's mechanical strength and structural integrity. Antifungal therapies that target chitin, which does not exist in human cells, are an appealing option because of its low human toxicity. [9] Since the fungus cannot function properly without chitin in its cell walls, inhibiting chitin biosynthesis can have several negative consequences, including delays in cell wall maturation, abnormal septum formation, or defects in cell division that lead to less than optimal fungus growth.

Glucans

The inner layer of the two-layered cell wall is particularly rich in β (1-3)-glucan, a long, linear glucose polymer important for maintaining the structural integrity of the cell wall. In the cell wall glucan (40–55 %), the most common type is β(1-3)-glucan, but glucans of other types, such as β(1-3)-linked, β (1-3)-linked mixed, and β (1-4)-linked, have also been found. These covalently bound polymers can interact with each other through hydrogen bonds to form an intricate three-dimensional network of microfibrils that includes β (1-3)-glucan, β(1-6)-glucan, and chitin. [10]

Mannans & mannoprotein

In the outer layer of the cell wall, glycoproteins are heavily mannosylated and modified with N- and O-linked oligosaccharides, where the structures of the oligosaccharide side chains differ between fungi. Model yeast S. cerevisiae and C. albicans cell walls contain proteins glycosylated with mannose-rich oligosaccharides (mannans), while the oligosaccharide side chains of N. crassa and A. fumigatus glycoproteins are composed of both mannose and galactose residues, referred to as galactomannan. [11]

Cell wall proteins

Als (agglutinin-like sequence) and Hwp (hyphal wall protein) proteins are found on the outer layer of the cell wall and play an important role in colonisation and biofilm formation [12]. Adhesion proteins produced by Candida species, which are closely related to Saccharomyces, are an important factor in determining the pathogenicity of Candida species, unlike Saccharomyces. [13]. The ALS family in C. albicans consists of eight genes that are involved in cell adhesion in the bacterium. Als1 and Als3 are considered to be the most important for biofilm formation. There are hydrophobic N and C termini, where the N terminus is involved in ligand binding; the C terminus is modified by the addition of a GPI anchor [14], which is necessary for linking the Als protein to fungal cell walls.

Review of Literature

Drugs that interfere with the integrity of the cell membrane have had the most success (Müller et al. 2013)[15]. Imidazole and triazole-targeting drugs have been the most effective in this regard to date. Although a number of new antifungal triazole molecules have been reported in recent years, they still have a long way to go before they can be considered successful antifungals (Ostrosky-Zeichner et al. 2010)[16]. Most human pathogenic fungi have developed resistance to fluconazole as a result of the overuse of azole drugs (Shor and Perlin 2015) [17].

Secondary transport proteins, ATPase family, and proteins involved in signal transduction, cell wall, and cytoskeleton synthesis are some of the major families of proteins found in the plasma membrane (Douglas and Konopka 2016) [18].

Fluconazole, voriconazole, and posaconazole are just a few of the azoles that have had their efficacy tinkered with. Fluconazole and amphotericin B (Amp B) were found to be ineffective against Ca. albicans and Cr. neoformans, but novel 1,2,3-triazole-linked β lactam–bile acid conjugates and dimers linked through 1,2,3-triazole and bis—lactam were found to be more effective (Vatmurge et al. 2008a,b) [19].

Studies on the antifungal activity of Ocimum sanctum essential oils against Candida strains were conducted by Khan et al. By damaging the membrane and decreasing the production of ergosterol, they found that methyl chavicol and linalool were effective antifungal agents in their study. Both cinnamon (Cinnamomum verum) and clove (Syzygium aromaticum) oils contain anticandidal compounds known as cinnamonaldehyde and eugenol that work by inhibiting ergosterol biosynthesis and, therefore, the synthesis of the cell wall (Mehmood et al. 1999[21]; Khan et al. 2013[22]).

Objectives

- To study the mechanism of action of antifungal families in fungal cells.
- To study the cell wall structure of fungal
- To study the cell wall of fungal and the development of antifungals
- Studying different antifungal drugs

Research Methodology

An exploratory research technique was used by the researchers, which was based on previous literature from various academic journals, annual reports, newspapers, and magazines. In line with the study's goals, the approach taken in conducting the investigation is purely descriptive. The study made extensive use of secondary data that was already out there.

Result and Discussion

Antifungals that specifically target the cell wall have been developed in recent years. It is anticipated that most of these drugs work by inhibiting the enzyme β-D-glucan synthase, but inhibitors of the chitin and GPI anchor pathways are also being developed (Fig 1). [23]

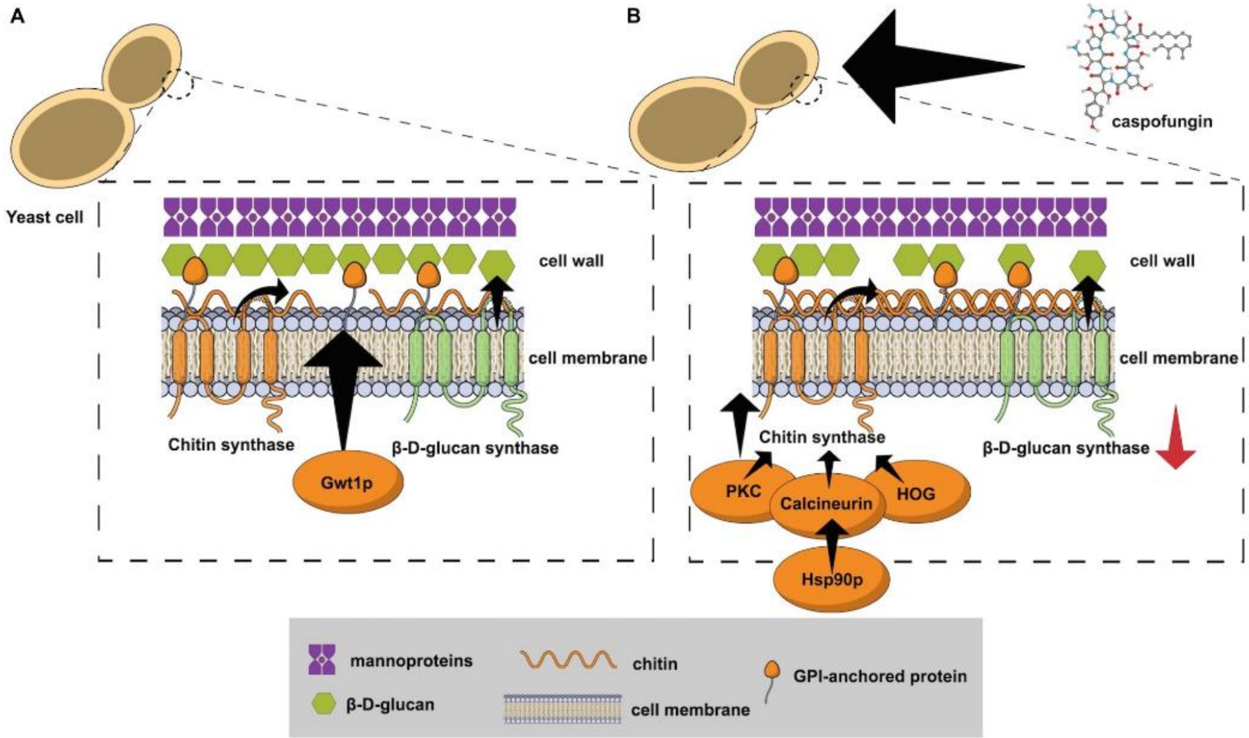

Fig. 1 A: The fungal cell wall and potential antifungal targets, including β-D-glucan synthase, chitin synthase, and the GPI anchor pathway enzyme Gwt1; (B) Cell wall stress is caused by exposure to echinocandin, which inhibits β-D-glucan synthase. When cells are damaged or over stimulated by chitin synthase or high levels of protein kinase C (PKC), the HOG and Ca+2-calcineurin pathways are activated. Deficiencies in the HSP90 chaperone reduce the tolerance mechanism for calcineurin, which is an important client protein for this chaperone to serve.

The fungal cell wall is a promising target for antifungal drugs due to its unique structure, which is not found in humans. Osmotic stress can lead to cell death in fungal cells, and the fungal cell wall serves as a passive barrier against the entry of potentially harmful macromolecules [24]. [20, 21]. For the most part, most fungi have cell walls that are composed of polysaccharides such as (chitin glucan) and glycoproteins (polypeptides) (Figure 2A). Xenobiotic toxic substances are protected from cells by proteins located on the cell wall, which play a role in adhesion to a surface, trafficking of macromolecules, cell-to-cell interactions. A potential target for antifungal agents is each of these cell wall components, which are essential for the normal development of the fungal cell. (Figure 2B).

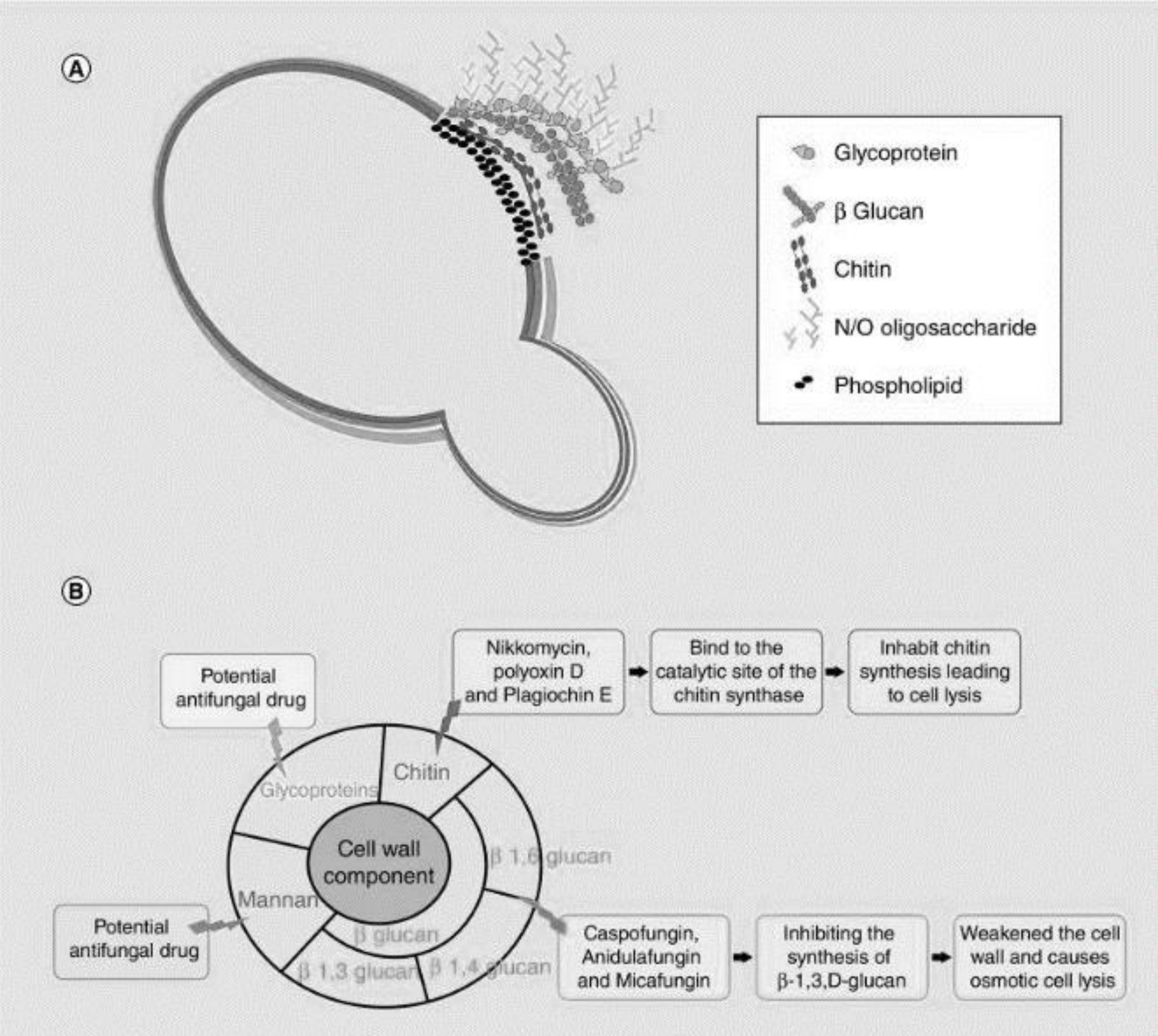

Fig. 2 Structure of the fungal cell wall and overview of compounds that target components.

There are two layers of fungal cell wall chitin/glucan with an outer layer of mannoprotein and other proteins linked by a glycosylphosphatidylinositol anchor to the cell wall of fungal cell wall (A). the antifungal agents that either target or impede the biosynthesis of the cell wall's constituent elements (B).

In terms of antifungal drugs, the most commonly used are azoles (fluconazole (FLZ), itraconazole (ITC), Voriconazole, Posaconazole, Isavuconazole), polyenes (AMB, Caspofungin, Micafungin, and Anidulafungin), and echinocandins (Cspofungin). Different parts of the fungal cell are targeted by these antifungal agents (Fig 3). An azole disrupts the fungal membrane's ergosterol biosynthesis, which is the primary component. Ergosterol and ergosterol interact to form pores in the cell membrane, while echinocandins prevent the synthesis of -d-glucan in the fungal cell wall. [25]

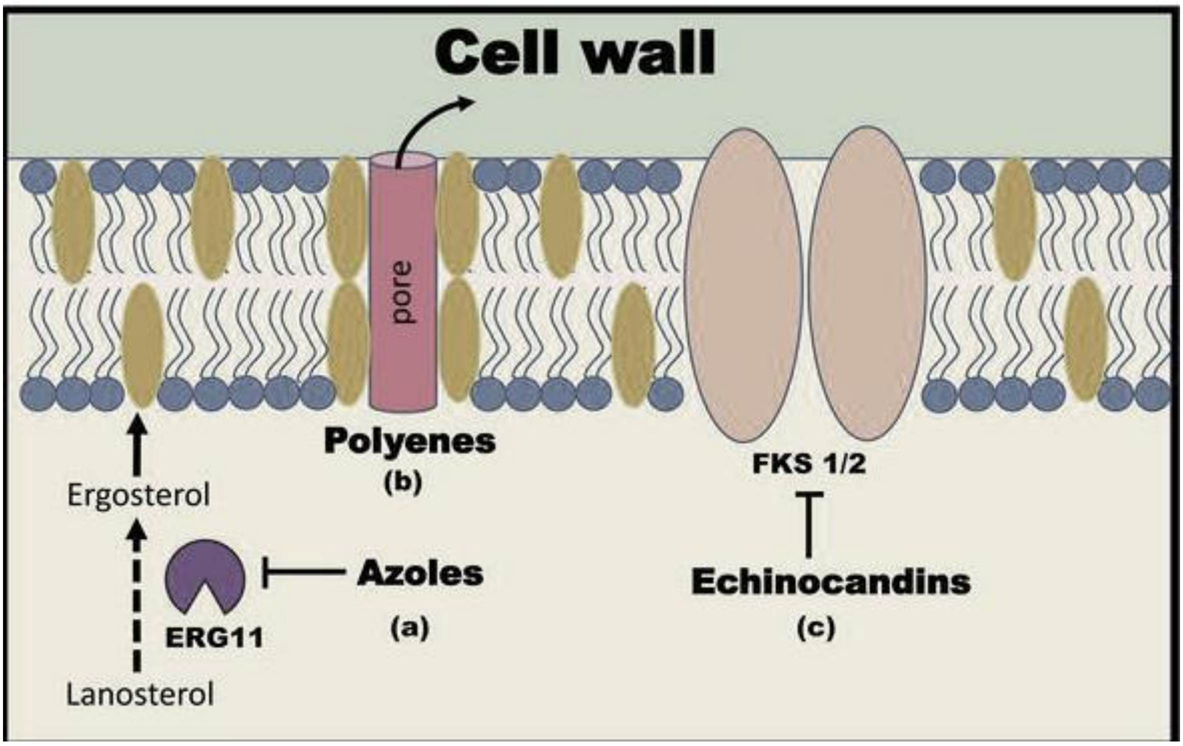

Figure of the antifungal drug families' mechanisms of action in the fungal cell (Fig. 3). (a) Azoles inhibit the enzyme 14--lanosterol demethylase (ERG11) in the endoplasmic reticulum, which is responsible for the transformation of lanosterol into ergosterol. The ergosterol binding of polyenes results in the formation of a pore in the cell membrane. (c) Echinocandins disrupt the cell wall by inhibiting 1,3-β-d-glucan synthase (FKS 1/2).

Conclusion

Infections caused by fungi can be treated with antifungal medications. As there are numerous fungi that can cause infections, there are a wide variety of medications. Antifungal resistance can be overcome and prevented by better understanding the mechanisms of azoles, polyenes, and echinocandins, as well as the discovery of new cellular and clinical factors promoting resistance. When a better understanding of the structure of the cell wall is gained through research, new therapeutic drugs may be developed for treatment purposes. Antifungal resistance can arise as a result of changes in the fungal cell wall caused by the infection site's microenvironment. Cell wall stress caused by echinocandin exposure results in the emergence of cells with high chitin content that are more tolerant.

References

1. Müller, C., Staudacher, V., Krauss, J., Giera, M. and Bracher, F. (2013) A convenient cellular assay for the identification of the molecular target of ergosterol biosynthesis inhibitors and quantification of their effects on total ergosterol biosynthesis. Steroids 78, 483–493.
2. Ostrosky-Zeichner, L., Casadevall, A., Galgiani, J.N., Odds, F.C. and Rex, J.H. (2010) An insight into the antifungal pipeline: selected new molecules and beyond. Nat Rev Drug Discov 9, 719– 727.
3. Shor, E. and Perlin, D.S. (2015) Coping with stress and the emergence of multidrug resistance in fungi. PLoS Pathog 11, e1004668.
4. Douglas, L.M. and Konopka, J.B. (2016) Plasma membrane organization promotes virulence of the human fungal pathogen Candida albicans. J Microbiol 54, 178– 191.
5. Vatmurge, N.S., Hazra, B.J., Pore, V.S., Shirazi, F., Chavan, P.S. and Deshpande, M.V. (2008a) Synthesis and antimicrobial activity of β-lactam–bile acid conjugates linked via

triazole. Bioorg Med Chem Lett 18, 2043–2047.

6. Vatmurge, N.S., Hazra, B.J., Pore, V.S., Shirazi, F., Deshpande, M.V., Kadreppa, S., Chattopadhyay, S. and Gonnade, R.G. (2008b) Synthesis and biological evaluation of bile acid dimers linked with 1,2,3-triazole and bis- β -lactam. Org Biomol Chem 6, 3823– 3830.
7. Mehmood, Z., Ahmad, I., Mohammad, F. and Ahmad, S. (1999) Indian medicinal plants: a potential source for anticandidal drugs. Pharm Biol 3, 237– 242.
8. Khan, M., Ahmad, I. and Cameotra, S.S. (2013) Phenyl aldehyde and propanoids exert multiple sites of action towards cell membrane and cell wall targeting ergosterol in Candida albicans. AMB Express 3, 54.
9. Meersseman, W., Lagrou, K., Maertens, J. & Van Wijngaerden, E. Invasive aspergillosis in the intensive care unit. Clin. Infect. Dis. 45, 205–216 (2007).
10. Richardson, M. & Lass-Florl, C. Changing epidemiology of systemic fungal infections. Clin. Microbiol. Infect. 14, Suppl. 4, 5–24 (2008).
11. Su, W., Wei, S. S., Hu, S. Q. & Tang, J. X. Preparation of TiO2/Ag colloids with ultraviolet resistance and antibacterial property using short chain polyethylene glycol. J. Hazard Mater. 172, 716–720 (2009).
12. Smith, J. G., Abruzzo, G. K., Gill, C. J., Flattery, A. M., Kong, L., Rosen, H. et al. (1996). Evaluation of pneumocandin L-743872 in neutropenic mouse models of disseminated candidosis and aspergillosis. In Program and Abstracts of the Thirty-Sixth Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, 1996. Abstract F41, p. 107. American Society for Microbiology, Washington, DC.
13. Najvar, L., Graybill, J., Montalbo, E., Barchiesi, F. & Luther, M. (1996). Evaluation of L-743872 (872) in the treatment of murine histoplasmosis. In Program and Abstracts of the Thirty-Sixth Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, 1996. Abstract F43, p. 107. American Society for Microbiology, Washington, DC.
14. M. Bassetti, E. Righi, F. Ansaldi, M. Merelli, C. Scarparo, M. Antonelli, et al. A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality Intensive Care Med., 41 (9) (2015), pp. 1601-1610
15. G. Lovero, O.De Giglio, S. Rutigliano, G. Diella, G. Caggiano, M.T. Montagna Invitro antifungal susceptibilities of Candida species to liposomal amphotericin B, determined using CLSI broth microdilution, and amphotericin B deoxycholate, measured using the Etest J. Med. Microbiol., 66 (2) (2017), pp. 213-216
16. M.C. Arendrup, T.F. Patterson Multidrug-resistant Candida: epidemiology, molecular mechanisms, and treatment J. Infect. Dis., 216 (suppl_3) (2017), pp. S445-SS51
17. A.M. Borman, A. Szekely, E.M. Johnson Comparative pathogenicity of United Kingdom isolates of the emerging pathogen Candida auris and other key pathogenic Candida species MSphere, 1 (4) (2016), pp. e00189-16
18. Bain JM, Louw J, Lewis LE, et al. Candida albicans hypha formation and mannan masking of β-glucan inhibit macrophage phagosome maturation. mBio. 2014;5(6):e01874.
19. Iqbal J, Anwar F, Afridi S. Targeted drug delivery systems and their therapeutic applications in cancer and immune pathological conditions. Infect. Disord. Drug Targets. 2017;17(3):149–159.
20. Chen M, Xu Y, Hong N, et al. Epidemiology of fungal infections in China. Front. Med. 2018;12(1):58–75.
21. Kerrigan AM, Brown GD. Syk-coupled C-type lectin receptors that mediate cellular activation via single tyrosine based activation motifs. Immunol. Rev. 2010;234(1):335–352.
22. Pfaller MA, Messer SA, Motyl MR, Jones RN, Castanheira M. In vitro activity of a new oral glucan synthase inhibitor (MK-3118) tested against Aspergillus spp. by CLSI and EUCAST broth microdilution methods. Antimicrob. Agents Chemother. 2013;57(2):1065–1068
23. Wu XZ, Chang WQ, Cheng AX, Sun LM, Lou HX. Plagiochin E, an antifungal active macrocyclic bis(bibenzyl), induced apoptosis in Candida albicans through a

metacaspase-dependent apoptotic pathway. Biochim. Biophys. Acta. 2010;1800(4):439–447.
24. Pianalto KM, Alspaugh JA. New horizons in antifungal therapy. J. Fungi. 2016;2(4):26
25. Kathiravan MK, Salake AB, Chothe AS, et al. The biology and chemistry of antifungal agents: a review. Bioorg. Med. Chem. 2012;20(19):5678–5698