WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 1, 155-168. Review Article ISSN 2277–7105

REVIEW: PHARMACOLOGICAL INTERVENTION OF FUNGAL INFECTION

Samiksha R. Onkar*, Aman Bondre, Vishnudas Lokhande, R. S. Bijwar, L. N. Barde

Jagadambha Institute of Pharmacy and Research, Kalamb.

Article Received on
13 November 2024,
Revised on 03 Dec. 2024,
Accepted on 23 Dec. 2024
DOI: 10.20959/wjpr20251-34998

***Corresponding Author**
Dr. Samiksha R. Onkar
Jagadambha Institute of Pharmacy and Research, Kalamb.

ABSTRACT

The high incidence of fungal infections has become a worrisome public health issue, having been aggravated by an increase in host predisposition factors. Despite all the drugs available on the market to treat these diseases, their efficiency is questionable, and their side effects cannot be neglected. Bearing that in mind, it is of upmost importance to synthetize new and innovative carriers for these medicines not only to fight emerging fungal infections but also to avert the increase in drug-resistant strains. Although it has revealed to be a difficult job, new nano-based drug delivery systems and even new cellular targets and compounds with antifungal potential are now being investigated. This article will provide a summary of the state-of-the-art strategies that have been studied in order to improve antifungal therapy and reduce adverse effects of conventional drugs. The bidirectional relationship between Mycology and Nanotechnology will be also explained. Furthermore, the article will focus on new compounds from the marine environment which have a proven antifungal potential and may act as platforms to discover drug-like characteristics, investigated the challenges of the translation of these natural compounds into the clinical pipeline.

KEYWORD: Mycology, Nanotechnology, fungal, investigated, investigated, conventional, Therapy.

1. INTRODUCTION

In humans, fungal infections can be classified into three broad groups: superficial, subcutaneous and systemic.[1] Superficial infections of keratinised tissues such as nails and hair are usually by dermatophytes, whereas mucous membranes are most frequently infected

by Candida spp. A variety of organisms cause sub- cutaneous infections, which are usually acquired by traumatic inoculation. The most serious life- threatening fungal infections are systemic. In some geographical locations systemic fungal infections are endemic, such as histoplasmosis in the Mississippi valley. However, immuno- compromised patients worldwide are at risk of systemic infection from commensal and ubiquitous species, primarily Candida spp. and Aspergillusspp. The recent increase in the number of patients at risk of systemic fungal infections (patients with HIV, cancer patients receiving intensive chemo- therapy)[2-3] has highlighted the need for effective therapy of fungal infections. Some superficial fungal infections can be treated or prevented with topical antifungal agents but others require systemic treatment with oral antifungals.

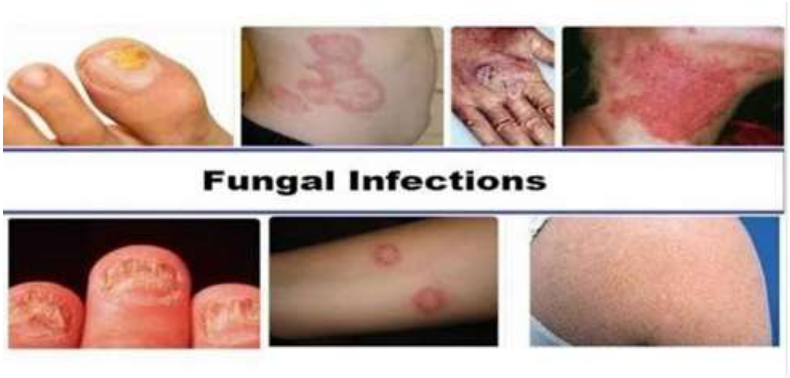


Fig. No. 1: Fungal infection.

2. Types of fungal infection

A. Superficial fungal infection
B. Cutaneous fungal infections
C. Subcutaneous fungal infections
D. Systemic fungal infections
E. Opportunistic fungal infections
F. Rare fungal infection
G. Fungal infections by organ system

3. Risk factors

A. Host-Related factors
B. Environmental factors
C. Medication-Related factors
D. Infection-Specific factors
E. Fungal-Specific factors

F. Lifestyle factors

G. Occupational factors

H. Other factors

4. Symptoms of fungal infection

General symptoms

Skin and Nail symptoms

Respiratory symptoms

Central nervous system symptoms

Gastrointestinal symptoms

5. Etiology of fungal infection

1.1. Endogenous sources

1. Normal flora: Fungi Naturally Present On Skin, Mucous Membranes, And Gut.[6]
2. Commensal fungi: Harmless Fungi Living On Or Within The Body.[7]

1.2. Exogenous sources

1. Environmental Exposure: Fungi In Soil, Water, Air, And Decaying Organic Matter.[8]
2. Human-To-Human Transmission: Direct Contact With Infected Individuals.[9]
3. Contaminated Objects: Fomites (E.G., Medical Devices, Clothing).[10]
4. Animal-To-Human Transmission: Zoonotic Infections (E.G., Ringworm).[11]

1.3. Fungal pathogens

1. Yeasts (E.G., Candida, Cryptococcus).[12]
2. Molds (E.G., Aspergillus, Fusarium).[13]
3. Dimorphic Fungi (E.G., Histoplasma, Blastomyces).[14]
4. Dermatophytes (E.G., Trichophyton, Microsporum).[15]

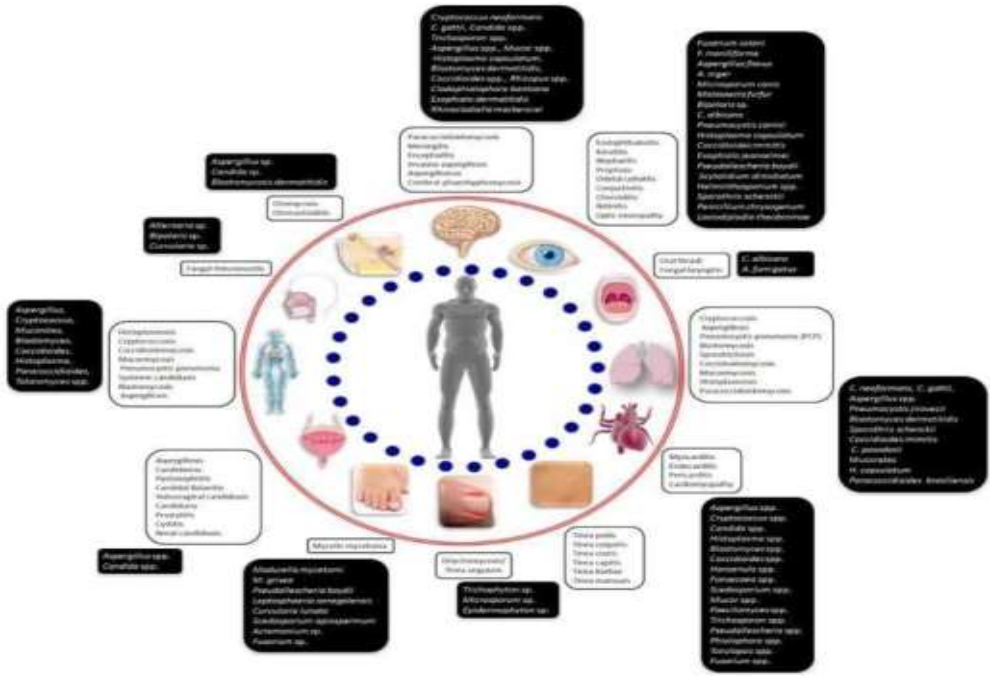


Fig. No. 2: Fungal Infection & Their etiological agent in human.

6. Pathophysiology of fungal infection

6.1 Fungal pathogenesis

1. Adhesion: Fungi attach to host cells via adhesins.[26]
2. Invasion: Fungi penetrate host cells through enzymatic degradation.[27]
3. Colonization: Fungi multiply and establish infection.[28]

6.2 Host-Fungal interactions

1. Recognition: Host pattern recognition receptors (PRRs) recognize fungal pathogens.[29]
2. Activation: Host immune cells (e.g., macrophages, neutrophils) respond.[30]
3. Phagocytosis: Host cells engulf fungi.[31]
4. Killing: Host cells kill fungi through oxidative burst, lysosomal degradation.[32]

6.3 Fungal virulence factors

1. Adhesins (e.g., Candida albicans Als).[33]
2. Enzymes (e.g., Aspergillus fumigatus proteases).[34]
3. Toxins (e.g., Candida albicans candidalysin).[35]
4. Biofilm formation[36]

7. Treatment

- Antifungal agents
- Polyenes

- Allylamines
- Imidazoles
- Triazoles
- Other agents

7.1 Immuno theraphy

- **Immunological aspects of fungal infections**

The host defense mechanisms against fungi range from the protective mechanisms provided by skin, mucosa and innate immunity to sophisticated adaptive mechanisms (adaptive immunity), which are specifically induced during the fungal infection/disease. The activation of the innate immunity is the first line of host antifungal defenses and is mediated by phagocytic cells (polymorphonuclear and mononuclear leukocytes and dendritic cells (DCs)), cellular receptors and several humoral factors that act by (i) direct destruction of the fungi through phagocytic process or secretion of microbicide compounds and/or (ii) initiation and subsequent direction of adaptive immune responses through the production of pro-inflammatory mediators (chemokines and cytokines), induction of co-stimulatory activity by phagocytic cells and uptake, processing and presentation of antigens.[54,55]

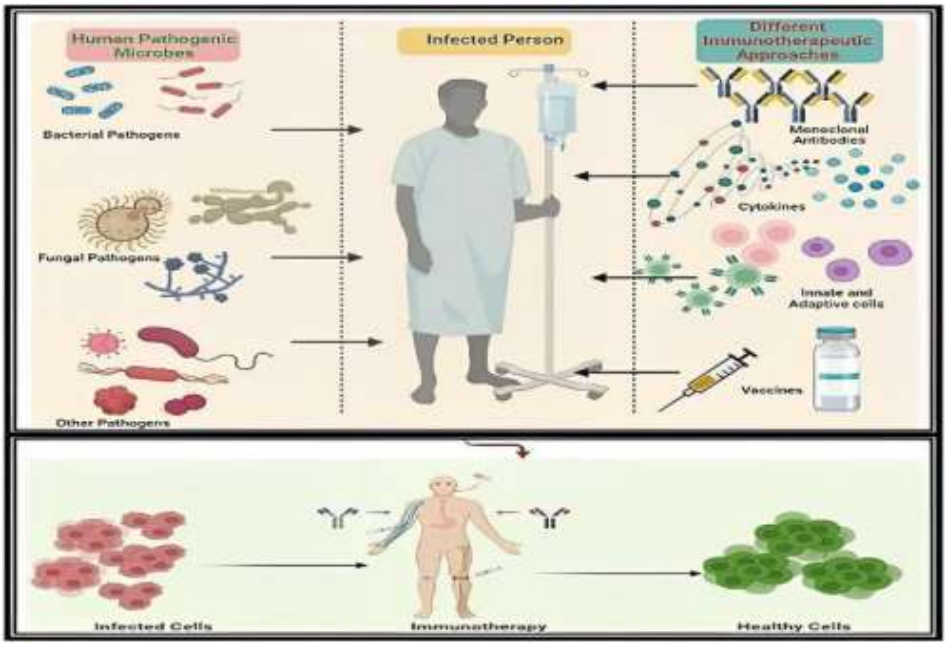
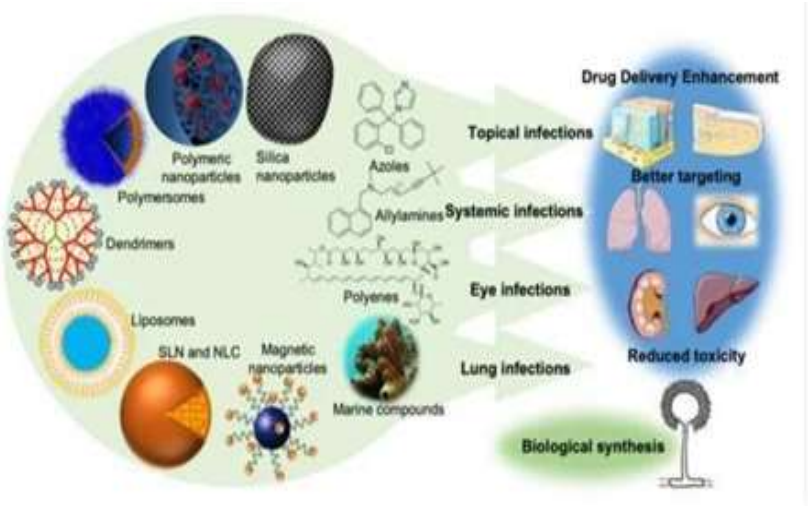


Fig. No. 3: Immuno theraphy.

- **Cytokine therapy**
- **Antifungal vaccines**

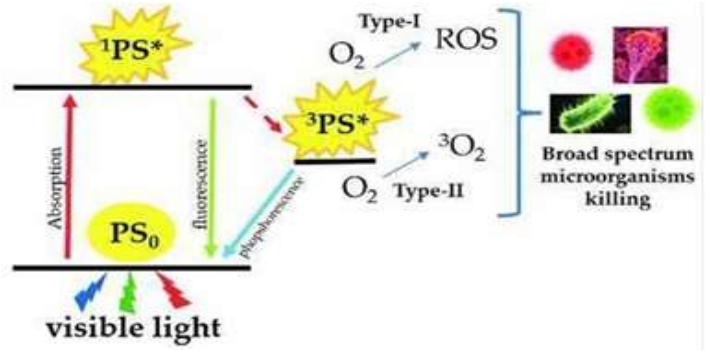
7.2 Nanotheraphy

A number of antibiotic drugs have been successfully used in the treatment of a wide range of dermatological diseases, such as acne, rosacea, folliculitis, inflammatory skin conditions anddeeper skin infections, such as cellulitis, carbuncles, and furuncles.[62] Resistance to the antifungal agents was very rare until the late 1990s. However, the occurrence of fungal yeast infections, including resistant infections, has increased during the last few years. The most common reasons include inadequate, irregular, uncontrolled, and overuse of drugs or increased incidence of immunodeficiency conditions.[62,63] Nanoparticles are nanomaterials measuring <100 nm in one dimension. They have small size and exhibit high surface-to-volume ratio. Due to this special attribute, nanomaterials such as biopolymeric nanoparticles, metal nanoparticles, and inorganic nanoparticles are known for promising antimicrobial activity against fungi causing skin infections.[64]



7.3 Antifungal photodynamic therapy

The great interest in alternative therapies for the treatment of fungal infections comes from the fact that the number of antifungal agents available for chemo- therapy is very restricted when compared with the number of antibacterial drugs. Furthermore, the cases of recurrent infections are a major issue for certain kinds of disease, such as candidiasis, dermatophytosis and chromoblastomycosis. Antifungal photodynamic therapy is a developing area of research,[65] and a majority of the literature in this area is concerned with in vitro experiments. Considering the potential of the technique in the treatment of fungal infections and the importance of developing new antifungal strategies, this is an area of great interest for future research studies.



7.4 Gene theraphy

- **RNA interferance theraphy**

First challenge is to define appropriate targets for RNA-based therapies that will specifically inhibit the fungal pathogen without detrimentally altering the host or commensal organisms Studies of model organisms such as Saccharomyces cerevisiae and Neurospora crassa have provided a wealth of knowledge into RNA regulation in fungi, yet our understanding of many of these same systems in fungal pathogens such as Candida albicans and A. fumigatus is still lagging. We do know that there can be differences between RNA regulatory pathways in pathogens and non-pathogens. For example, the model filamentous fungus Aspergillus nidulans has a functional RNAi system, as does its close relative, A. fumigatus; however, several RNAi proteins in A. nidulans are truncated compared with those of A. fumigatus.[67] The practical importance of these differences in RNAi functionality remain incompletely described in these systems. A. nidulans is not the only example of a modified RNAi system. In fact, the model yeast S. cerevisiae has actually lost the RNAi machinery in favor of maintaining a killer virus that provides a growth advantage.[68]

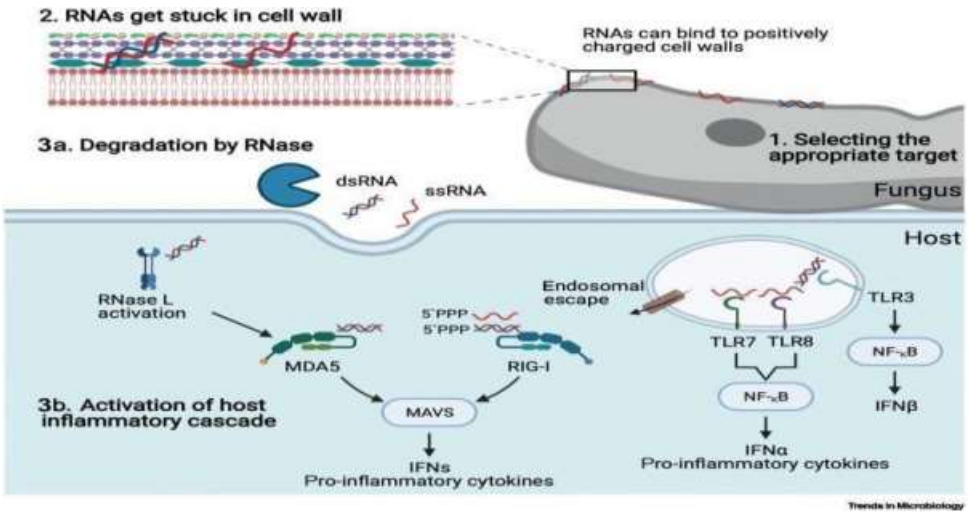


Fig. No. 6: Gene theraphy.

7.5 10 Combination theraphy

Antifungal combination therapy was recognized as an important area nearly a quarter of a century ago by Bennett et al.[74] who compared amphotericin B (AmB) alone and in combination with 5-fluorocytosine (5FC) in the treatment of cryptococcal meningitis. However, adoption of this approach for the treatment of invasive fungal infections has been slow, limited to AmB plus 5FC or 5FC plus fluconazole (FLU), and fraught with controversy regarding the use of a polyene combined with an azole. With the approval of the thirdgeneration azole voriconazole (VORI) and the candins (e.g., caspofungin [CAS]), there is rekindled interest in antifungal combination therapy, especially since these agents have different mechanisms of action. Unlike antibacterial and antiviral agents, studies of combinations of antifungal agents are in the early stages of investigation and, consequently, are highly dynamic.

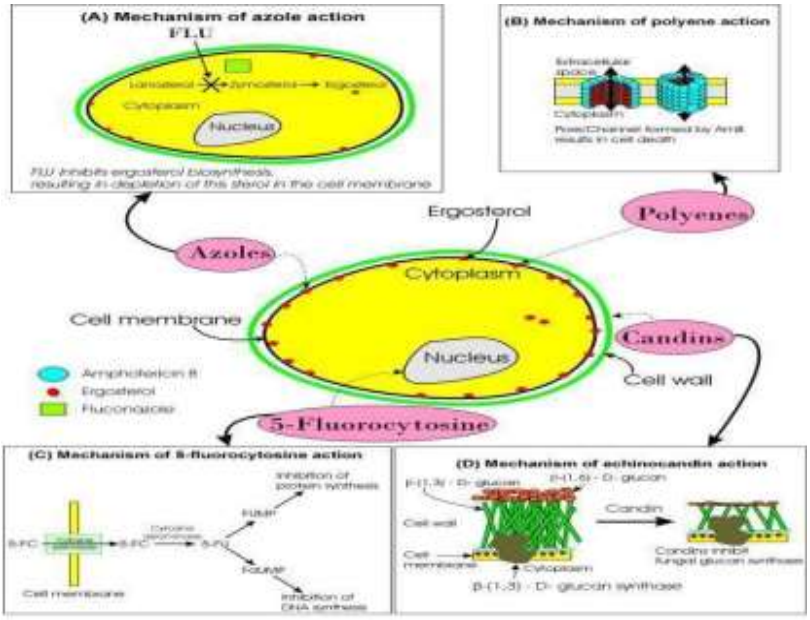


Fig. No. 7: Combination theraphy.

7.6 Molecular diagnostics

- **PCR (Polymerse Chain Reaction)**

The PCR method for DNA amplification was developed by Kary Mullis and colleagues in 1984 and was rapidly adapted to detect a variety of infectious agents, particularly viruses. Despite this success, PCR has not been widely adopted to detect fungal pathogens in human infections and has been eclipsed by other technologies such as fungal antigen detection assays. However, the diagnosis of human fungal infections continues to be a challenge. Conventional diagnostic techniques such as radiological imaging, culture and histology fall

short in terms of specificity, sensitivity and time to diagnosis. In addition, diagnostic tests based on galactomannan (GM) antigen and glucan do not detect all fungal pathogens and have problems with specificity.[80]

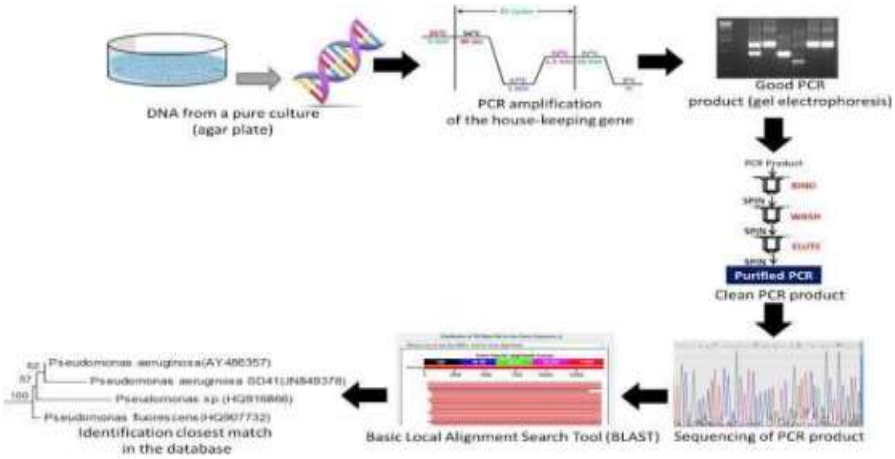


Fig. No. 8: Polymer chain reaction.

CONCLUSION

The increasing number of antifungal agents, reformulations of existing agents and novel treatment strategies have all improved the management of fungal infections in recent years. Although high cure rates can be achieved in the treatment of many superficial infections, systemic fungal infections are still associated with high mortality. For several years, amphotericin-B was the most effective agent for the treatment and prevention of systemic fungal infections. However, the introduction of the triazoles fluconazole and itraconazole – has challenged amphotericin-B as the gold standard. In particular, the triazoles have become the agents of choice in chemoprophylaxis; fluconazole has been widely used but the introduction of an itraconazole oral solution offers an agent with high bioavailability and a broader spectrum of activity than that of fluconazole. In the empirical treatment of systemic fungal infections, the lipid-associated formulations of amphotericin-B and the itraconazole IV formulation are at least as effective as conventional amphotericin-B and are less toxic. The high cost of lipidassociated formulations of amphotericin-B may make their use prohibitively expensive.

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