INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)

e-ISSN : 2583-1062

Impact Factor : 7.001

www.ijprems.com
editor@ijprems.com

Vol. 04, Issue 10, October 2024, pp : 239-245

A SCIENTIFICREVIEW ON: ANTIFUNGAL MECHANISMS STRATEGIES

Pathan Aman Y[1], Tandale Prashant S[2], Garje S. Y[3], Sayyed G. A[4], Mr. Tandale Prashant S[5]

[1,2,3,4]Shri Amolak Jain Vidya Prasarak Mandal's College of Pharmaceutical Science and Research Centre, Kada, Maharashtra, India, 414202.

[5]Department of Pharmaceutics), SAJVPM's College of Pharmaceutical Science and Research Center, Kada, Maharashtra, India, 414202.

Corresponding Author: Mr. Tandale Prashant S

ABSTRACT

Fungal infections, or mycoses, arise from pathogenic fungi affecting various body areas. These infections are categorized based on their location: superficial, subcutaneous, and systemic. Superficial fungal infections encompass common types of tinea, such as tinea corporis (ringworm), tinea pedis (athlete's foot), tinea cruris (jock itch), and yeast infections like pityriasis versicolor.

Fungal diseases, including conditions such as candidiasis (yeast infections), onychomycosis (nail fungus), and fungal dermatitis, require careful management to maintain skin health. Notably, these infections are prevalent among the population, highlighting the need for effective treatment options. Certain herbal plants possess antifungal properties, making them valuable in addressing these issues.

The objective of this study is to develop an antifungal herbal bath soap utilizing various herbal ingredients. The efficacy of the formulated soap was assessed using the agar diffusion method against the pathogen Candida albicans. The results indicated that the herbal soap formulations exhibited significant antifungal activity.

The formulation process for the antifungal herbal soap employed the melt-and-pour method. Various evaluation techniques were applied to assess the quality of the final product, ensuring its effectiveness and safety.

Keywords: Fungal infections, Mycoses, Superficial fungal infections, Tinea corporis, Tinea pedis, Tinea cruris, Candidiasis, Onychomycosis

1. INTRODUCTION

Candidiasis and ringworm are common fungal infections caused by various pathogenic fungi. Antifungal agents play a crucial role in identifying and eliminating these fungal pathogens. The fungal kingdom is vast, encompassing a diverse array of taxa that occupy different ecological niches, exhibit various life cycles, and display a wide range of morphologies. Remarkably, of the estimated 1.5 million species within this kingdom, only about 5% have been formally classified. Many fungi act as parasites, affecting plants, animals, and humans, while certain plant-infecting fungi can inflict significant damage on agriculture and forestry, such as the rice blast fungus, Dutch elm disease, and chestnut blight. Some fungi can cause severe diseases in humans, many of which may be life-threatening if untreated.

Currently, clinicians and veterinarians utilize four main classes of antifungal drugs for systemic treatment, each targeting different components of the fungal cell. The first class, polyenes, includes the heptaene amphotericin B (AMB), which binds to ergosterol, a vital component of the fungal cell membrane. AMB is particularly effective against the Candida genus and Aspergillus species, such as A. fumigatus and A. flavus.

The second class, triazoles (both first- and second-generation), inhibits ergosterol biosynthesis at the lanosterol demethylation step, demonstrating a fungistatic effect with fewer toxic side effects for the host. This property makes triazoles a preferred choice for treating various fungal infections.

Echinocandins represent another class of antifungal agents that inhibit the synthesis of β-D-glucans in the fungal cell wall. These agents exhibit both fungicidal and fungistatic properties against different fungal organisms, notably Candida and Aspergillus species. Finally, the pyrimidine analogue flucytosine (5-FC) targets the fungal nucleus, disrupting protein and DNA biosynthesis.

The overuse of antifungal agents has led to the emergence of drug resistance among opportunistic pathogens. The World Health Organization has identified antifungal resistance as a critical global health threat, particularly in the context of antimicrobial resistance.

Fungi can be classified into four primary groups:

Yeasts: Examples include Cryptococcus neoformans, which can cause various infections, including meningitis.

Yeast-like fungi: These organisms exhibit characteristics of both yeasts and filamentous fungi, such as Candida albicans, which can lead to oral thrush, vaginal thrush, and systemic candidiasis.

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Dimorphic fungi: This group can exist as either filaments or yeasts and is responsible for diseases such as histoplasmosis, coccidioidomycosis, and blastomycosis. Examples include Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatitidis.

Moulds: These filamentous fungi reproduce by forming spores and are typically associated with skin and nail infections, with examples including Trichophyton, Microsporum, and Epidermophyton species.

Objective: The objective of this review is to comprehensively assess the diversity of fungal organisms and their associated infections, explore the various classes of antifungal agents, and evaluate their mechanisms of action, pharmacokinetics, pharmacodynamics, and toxicity. Additionally, the review aims to address the emerging issue of antifungal resistance, highlighting its implications for treatment and public health.

Types of fungal infection:

1. Superficial **Fungal Infections:**

- Tinea (Ringworm)
- Tinea corporis (skin)
- Tinea capitis (scalp)
- Tinea pedis (athlete's foot)
- Tinea cruris (jock itch)
- Candidiasis
- Oral thrush
- Genital candidiasis

2. Cutaneous Fungal Infections:

- Dermatophyte infections
- Nail infections (Onychomycosis)

3. **Subcutaneous Fungal Infections:**

- Sporotrichosis
- Chromoblastomycosis

4. Systemic Fungal Infections:

- Histoplasmosis
- Coccidioidomycosis (Valley Fever)
- Blastomycosis

5. Opportunistic Fungal Infections:

- Candidiasis (systemic)
- Aspergillosis

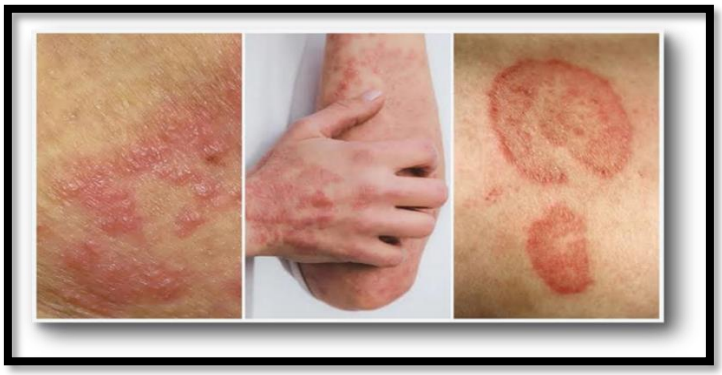

Fig1: Fungal Infection

Classification of Fungal Infection With Their Machanism of Action :

1 Polyenes:

Example: Amphotericin B (AMB), Nystatin

Mechanism of Action:

Binds to ergosterol, a key component of the fungal cell membrane, forming pores that disrupt membrane integrity, leading to cell death. Highly effective against a broad range of fungi, including Candida spp. and Aspergillus spp.

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2. Azoles:

First-Generation:

Example: Ketoconazole

Mechanism of Action:

Inhibits lanosterol demethylase, an enzyme involved in the biosynthesis of ergosterol. This disrupts the fungal cell membrane integrity.

Second-Generation:

Example: Fluconazole, Itraconazole

Mechanism of Action:

Similar to first-generation azoles, these drugs inhibit ergosterol synthesis but are more selective and have fewer side effects. Effective against Candida spp. and some molds.

3. Echinocandins:

Example: Caspofungin, Micafungin, Anidulafungin

Mechanism of Action:

Inhibit the synthesis of β-D-glucans, essential components of the fungal cell wall. This weakens the cell wall, leading to cell lysis. Effective against Candida spp. and some Aspergillus spp.

4. Pyrimidine Analogues:

Example: Flucytosine (5-FC)

Mechanism of Action:

Converts to 5-fluorouracil in the fungal cell, inhibiting DNA and RNA synthesis by interfering with thymidylate synthase and protein synthesis. Often used in combination with amphotericin B for enhanced efficacy.

5. Allylamines:

Example: Terbinafine, Naftifine

Mechanism of Action:

Inhibit squalene epoxidase, an enzyme involved in the early stages of ergosterol biosynthesis. This leads to the accumulation of squalene and a deficiency of ergosterol, compromising cell membrane integrity.

6. Morpholines:

Example: Amorolfine

Mechanism of Action:

Inhibits the synthesis of ergosterol by disrupting multiple enzymes involved in the pathway, thereby compromising the cell membrane structure. Used topically for nail infections.

7. Griseofulvin:

Mechanism of Action:

Disrupts fungal mitosis by binding to microtubules and inhibiting the formation of the mitotic spindle. Primarily used for dermatophyte infections affecting the skin, hair, and nails.

Some new and emerging antifungal drugs include:

1. Isavuconazole (Cresemba)
2. Lefamulin
3. Olorofim
4. Rezafungin
5. Fosmanogepix (APX001)
6. Tavaborole (Kerydin)
7. New Generation Echinocandins
8. Antifungal Combination Therapies

Antifungal herbal agent

1. Garlic (Allium sativum)
2. Tea Tree Oil (Melaleuca alternifolia)
3. Oregano Oil (Origanum vulgare)
4. Turmeric (Curcuma longa)

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5. Ginger (Zingiber officinale)
6. Cinnamon (Cinnamomum verum)
7. Neem (Azadirachta indica)
8. Echinacea (Echinacea purpurea)
9. Clove (Syzygium aromaticum)

2. ROUTES OF ADMINISTRATION

1. Oral

2. Form: Tablets, capsules, or liquid.

Examples: Fluconazole, Itraconazole, Terbinafine.

2. Intravenous (IV)

Form: Injectable solution.

Examples: Amphotericin B, Isavuconazole, Echinocandins (like Caspofungin).

3. Topical

Form: Creams, ointments, powders, or sprays.

Examples: Clotrimazole, Miconazole, Ketoconazole (for skin and mucosal infections).

4. Intravaginal

Form: Creams, suppositories, or tablets.

Examples: Clotrimazole, Miconazole (for vaginal candidiasis).

5. Inhalational

Form: Aerosol or nebulized solution.

Examples: Some formulations of Amphotericin B (for lung infections).

6. Intra-abdominal or Localized

Form: Direct application or injection into specific sites.

Examples: Certain treatments for localized infections.

7. Transdermal

Form: Patches or gels applied to the skin.

Pharmacological and Toxicological Study of Antifungal Drugs:

To minimize adverse effects on healthy cells surrounding the affected area, effective antifungal medications must be administered with care. Optimal antifungal dosages are determined by the patient population and take into account the patient's overall health and the specific type of treatment. Prescribing antifungal drugs for pregnant women can be challenging due to limited research on their potential embryotoxic or teratogenic effects.The Food and Drug Administration has designated amphotericin B (AMB) as the safest option for treating systemic fungal infections. However, AMB is associated with certain adverse effects. AMB is formulated with sodium deoxycholate due to its poor water solubility. After injection, AMB accumulates in the liver and spleen, where it binds to plasma lipoproteins and separates from deoxycholate. AMB has a long elimination half-life; it is not metabolized by CYP450 enzymes and is instead excreted largely unchanged, with approximately 33% in urine and 43% in feces. The toxicity associated with AMB deoxycholate administration is dose- and infusion-dependent. However, high doses can lead to nephrotoxicity due to non-selective damage to renal cells. To mitigate these adverse effects, AMB deoxycholate is available in lipid formulations that maintain its antifungal efficacy.

5-Flucytosine (5-FC), a small hydrophilic molecule, is rapidly absorbed and has a bioavailability exceeding 90%. Minimal liver metabolism occurs with 5-FC, which exerts potent antifungal effects in the bladder and is eliminated exclusively via glomerular filtration. Its clearance from plasma occurs rapidly, similar to that of creatinine. Frequent dosing of 5-FC is required due to its maximum four-hour half-life. When administered alongside cytarabine—used for treating acute myeloid leukemia—5-FC's antifungal efficacy may be competitively reduced because both drugs share the same transport pathway in sensitive cells. Notable adverse effects include gastrointestinal issues, myelotoxicity, and liver impairment.

Triazoles exhibit varying pharmacological properties based on their molecular weight, solubility, and protein-binding capacity. All triazoles can be administered intravenously or orally. Notably, isavuconazole is delivered as the water-soluble prodrug isavuconazonium. Itraconazole's sole metabolic pathway produces the active metabolite hydroxyitraconazole.

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In contrast, genetic polymorphisms in CYP2C19 and CYP3A4 influence the metabolism of voriconazole (VOR). Generally, triazoles are well tolerated, but the most common significant adverse effect associated with VOR is hepatotoxicity, observed in about 31% of cases. Other triazoles can counteract isavuconazole by shortening the QT interval—the duration between the onset of ventricular depolarization and the end of ventricular repolarization. The affinity of triazoles for CYP450 isoenzymes results in a concerning number of potential drug interactions.

Challenges

1. Resistance Development
2. Limited Drug Options
3. Side Effects and Toxicity
4. Patient-Specific Factors
5. Inadequate Research in Special Populations
6. Cost and Accessibility

Future Perspectives

1.Novel Antifungal Agents

2.Combination Therapies

3.Targeted Drug Delivery

4. Personalized Medicine

5. Vaccines and Preventative Strategies

6. Enhanced Diagnostics

7.Global Collaboration

Uses of Antifungal Medications

1 Systemic Fungal Infections

Treatment of severe infections like candidemia, aspergillosis, and cryptococcosis.

2 Superficial Infections

Management of skin infections (e.g., athlete's foot, ringworm) and fungal nail infections (onychomycosis).

3 Mucosal Infections

Treatment of oral thrush (oral candidiasis) and vaginal yeast infections.

4 Prophylaxis

Preventive treatment in immunocompromised patients (e.g., those undergoing chemotherapy or with HIV/AIDS) to reduce the risk of fungal infections.

5 Invasive Fungal Infections

Treatment of infections in patients with indwelling catheters or those undergoing surgery.

6 Dermatological Applications

Topical treatments for dermatophyte infections and other localized fungal skin infections.

7 Treatment of Specific Conditions

Use in conditions like histoplasmosis and blastomycosis, depending on the causative organism.

8 Adjunctive Therapy

Used in conjunction with other treatments (like cytarabine) for certain cancers to manage secondary fungal infections.

Toxicities of Antifungal Agents

The safety and tolerability of systemic antifungal therapy have greatly improved; however, there is a growing population of severely immunocompromised patients receiving prolonged treatment with these agents. Therefore, it is crucial for clinicians to be aware not only of the well-documented dose-limiting toxicities associated with these medications—such as infusion-related reactions and nephrotoxicity linked to amphotericin B, as well as hepatotoxicity from triazole antifungals—but also of the longer-term risks. These longer-term risks include recurring drug interactions, organ dysfunction, and the potential for cutaneous reactions and malignancies.

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Fig2: Ketovate 200mg tab.

Fig3: Nizoral Antidanruf 2% shampoo

3. CONCLUSION

The introduction of new systemic antifungal agents in the past decade has markedly altered the approach to treating invasive mycoses. However, the availability of these advanced therapies requires an increased understanding of their limitations, particularly concerning their spectrum of activity, pharmacokinetics, and the risk of pharmacokinetic drug interactions. It is important to note that newer broad-spectrum triazoles, including voriconazole and posaconazole, demonstrate significant variability in bloodstream concentrations among different patients, which may necessitate therapeutic drug monitoring (TDM) in specific situations to enhance drug efficacy and appropriate dosing. Furthermore, the long-term toxicities associated with these treatments have raised growing concerns, especially as outpatient individuals with chronic immunosuppression are undergoing antifungal therapy for prolonged periods. Nonetheless, for most patients, the benefits of employing safer and more effective antifungal treatments substantially outweigh the manageable risks linked to potential toxicity. Antifungal agents are essential in the treatment of fungal infections. Ongoing research is crucial to tackle the challenges posed by antifungal resistance and to create innovative therapeutic approaches.

4. REFERENCES

[1] Anaissie E, Hachem R, Tin-U C K-, Stephens L C, Bodey G P. Experimental hematogenous candidiasis caused by Candida krusei and Candida albicans: species differences in pathogenicity. Infect Immun. 1993;**61**:1268–1271. [PMC free article] [PubMed] [Google Scholar]

[2] Anaissie E J, Bodey G P. Nosocomial fungal infections—old problems and new challenges. Infect Dis Clin North Am. 1989;**3**:867–882. [PubMed] [Google Scholar]

[3] Arthur M, Reynolds P, Courvalin P. Glycopeptide resistance in enterococci. Trends Microbiol. 1996;**4**:401–407. [PubMed] [Google Scholar]

[4] Ather M A, Winner H I. Development of resistance by Candida species to polyene antibiotics in vitro. J Med Microbiol. 1971;**4**:505–517. [PubMed] [Google Scholar]

[5] Beck-Sagué C M, Jarvis W R National Nosocomial Infections Surveillance System. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. J Infect Dis. 1993;**167**:1247–1251. [PubMed] [Google Scholar]

[6] Beggs W H. Comparison of miconazole- and ketoconazole-induced release of K^+ from Candida species. J AntimicrobChemother. 1983;**11**:381–383. [PubMed] [Google Scholar]

[7] Beggs W H, Andrews F A, Sarosi G A. Combined action of amphotericin B and 5-fluorocytosine on pathogenic yeasts susceptible to either drug alone. Chemotherapy. 1981;**27**:247–251. [PubMed] [Google Scholar]

[8] Ben-Ami, R., Lewis, R. E., &Kontoyiannis, D. P. (2008). Immunocompromised Hosts: Immunopharmacology of Modern Antifungals. Clinical Infectious Diseases, 47(2), 226–235.

[9] Brauer, V. S., Rezende, C. P., Pessoni, A. M., De Paula, R. G., Rangappa, K. S., Nayaka, S. C., et al. (2019). Antifungal agents in agriculture: Friends and foes of public health. Biomolecules, 9(10), p.521.

[10] Bugeda, A., Garrigues, S., Gandía, M., Manzanares, P., Marcos, J. F., & Coca, M. (2020). The Antifungal Protein AfpB Induces Regulated Cell Death in Its Parental Fungus Penicilliumdigitatum. mSphere, 5(4).

[11] Cafarchia, C., Figueredo, L. A., & Otranto, D. (2013). Fungal diseases of horses. Veterinary Microbiology, 167(1–2), 215–234.

[12] Campitelli, M., Zeineddine, N., Samaha, G., &Maslak, S. (2017). Combination Antifungal Therapy: A Review of Current Data. Journal of Clinical Medicine Research, 9(6), 451–456.

[13] Campoy, S., &Adrio, J. L. (2017). Antifungals. Biochemical Pharmacology, 133, 86–96.

[14] Chakrabarti, A., & Singh, S. (2019). Challenges in invasive fungal disease. In Advancing Frontiers in Mycology and Mycotechnology: Basic and Applied Aspects of Fungi, pp.450 478.
[15] Chand, P., Kumari, S., Mondal, N., Singh, S. P., & Prasad, T. (2021). Synergism of Zinc Oxide Quantum Dots with Antifungal Drugs : Potential Approach for Combination Therapy against Drug Resistant Candida albicans, 3(May), 1–13.
[16] Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould Infections in haematopoietic stem cell transplant recipients. ClinInfectDis 2002; 34: 909-917.
[17] Lin S, Schranz J, Teutsch S. Aspergillosis case-fatality rate: systemic Review of the literature. Clin Infect Dis 2001; 32: 358-366.
[18] O, Gillespie S, Lee K, et al. Attributable mortality of Candidaemia, revisited. Clin Infect Dis 2003; 37: 1172-1177.
[19] Ullmann AJ, Cornerly OA. Antifungal prophylaxis for invasive mycoses inHigh risk patients. CurrOpin Infect Dis 2006; 19: 571-576.
[20] Bow EJ, Laverdière M, Lussier N, et al. Antifungal prophylaxis for severely Neutropenic chemotherapy recipients. A meta-analysis of randomized-Controlled clinical trials. Cancer 2002; 94: 3230-3246.
[21] Cornerly OA, Ullmann AJ, Karthaus M. Evidence-based assessment of Primary antifungal prophylaxis in patients with hematological malignan-Cies. Blood 2003; 101: 3365-3372.
[22] Georgopapadakou NH, Walsh TJ. Antifungal agents: chemotherapeutic Targets and immunologic strategies. Antimicrob Agents Chemother 1996; 40: 279-291.
[23] Boucher HW, Groll AH, Chiou C, Walsh TJ. Newer systemic antifungal Agents. Drugs 2004; 64: 1997-2020.
[24] Torres HA, Hachem RY, Chemaly RF, et al. Posaconazole: a broad-Spectrum triazole antifungal. Lancet Infect Dis 2005; 5: 775-785.
[25] Hajjeh RA, Sofair AN, Harrison LH, et al. Incidence of blood streamInfection due to Candida species and in vitro susceptibilities of isolatesCollected from 1998 to 2000 in a population-based active surveillance Program. J Clin Microbiol 2004; 42: 1519-1527.
[26] Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould Infections in haematopoietic stem cell transplant recipients. Clin InfectDis 2002; 34: 909-917.
[27] Lin S, Schranz J, Teutsch S. Aspergillosis case-fatality rate: systemic Review of the literature. Clin Infect Dis 2001; 32: 358-366.
[28] Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of Candidaemia, revisited. Clin Infect Dis 2003; 37: 1172-1177.
[29] Ullmann AJ, Cornerly OA. Antifungal prophylaxis for invasive mycoses inHigh risk patients. Curr Opin Infect Dis 2006; 19: 571-576.
[30] Bow EJ, Laverdière M, Lussier N, et al. Antifungal prophylaxis for severely Neutropenic chemotherapy recipients. A meta-analysis of randomized-Controlled clinical trials. Cancer 2002; 94: 3230-3246.
[31] Cornerly OA, Ullmann AJ, Karthaus M. Evidence-based assessment of Primary antifungal prophylaxis in patients with hematological malignan-Cies. Blood 2003; 101: 3365-3372.