Therapeutic Strategies with Antifungal Drugs against Black Fungus

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Abstract: ***There have been a lot of reports of "mucormycosis," sometimes known as the "black fungus," especially in Asian nations like India. The fungus Mucorales is the source of the uncommon angio-invasive disease known as mucormycosis. Black fungus treatment usually involves including Posaconazole, Isavuconazole, and Amphotericin-B. The creation of antifungal medications over 65 years. A major factor contributing to the high levels of morbidity and mortality of fungal infections is the limited number of antifungal drugs (Ostrosky-Zeichner L, 2010).***

Key words: Amphotericin, Antifungal drugs, Isavuconazole, Mucormycosis, Polyenes, Posaconazole.

I. INTRODUCTION

Over recent decades, the worldwide impact of fungal disease has expanded dramatically. It is estimated that fungal disease kills approximately 1.5 to 1.7 million people every year (Gupta AK, 2024) (GP, 2013). Dermatophytosis, superficial fungal infections, is also very common and difficult to treat. As the number of immunocompromised patients increases, especially during the COVID-19 pandemic, so does the occurrence of opportunistic fungal-like diseases and infections (Kathiravan MK, 2012) (Zhang H, 2020) (Bouz G, 2021).

Such as those with organ transplants and AIDS (acquired immune deficiency syndrome), in addition to those who are on prolonged immunosuppressive medications such as corticosteroids. The patients with antibiotics, cancer chemotherapies, and the ones in intensive care units (ICU) are also at greater risk to develop invasive fungal infections (IFI) (Shafiei M, 2020)..

II. HISTORY OF ANTIFUNGAL DRUGS

The image provides an overview of the growth of antifungal medications over 65 years. These medications are divided into different classes, each symbolized by a distinct color:
Polyenes (blue): Target fungal cell membrane sterols.

Pyrimidine analogues (purple): Interfere with fungal DNA/RNA synthesis.

Triazoles (green): Inhibit fungal ergo sterol biosynthesis.

Echinocandins (orange): Inhibit fungal cell wall synthesis.

Drugs under development or in clinical trials (black): Represent new antifungal innovations.

Timeline of Antifungal Drugs

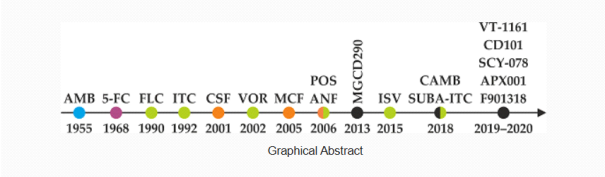


Figure1: Timeline of Drugs

1955: AMB (Amphotericin B) – A polyene antifungal.

1968: 5-FC (Flu cytosine) – A pyrimidine analogue.

1990: FLC (Fluconazole) – A triazole.

1992: ITC (Itraconazole) – A triazole.

2001: CSF (Caspofungin) – An echinocandin.

2002: VOR (Voriconazole) – A triazole.

2005: MCF (Micafungin) – An echinocandin**.**

2006: POS (Posaconazole) – A triazole.

2006: ANF (Anidulafungin) – An echinocandin.

2015: ISV (Isavuconazole) – A triazole.

2018: SUBA-ITC (Super bioavailable itraconazole) – A novel itraconazole formulation**.**

Drugs in Development or Clinical Trials (Black dots):

2013: MGC290.

2015–2020: VT-1161, CD101, SCY-078, APX001, CAMB, and F901318.

This progression highlights a steady discovery of antifungal agents, focusing on **i**mproving efficacy, reducing toxicity**,** and targeting resistance mechanisms.

III. MECHANISM OF ACTION OF ANTI-FUNGAL DRUGS

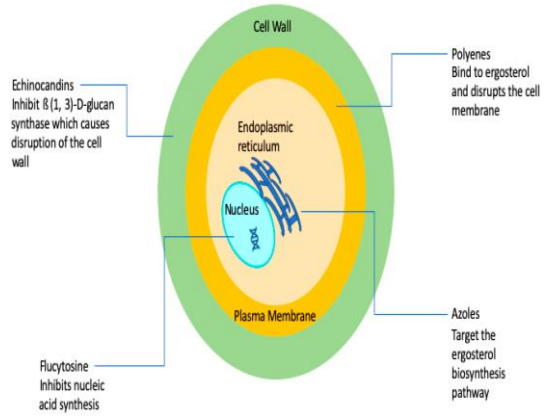


Figure: MOA of Anti-Fungal Drugs

IV. CURRENT ANTI-FUNGAL

A major factor contributing to the high levels of morbidity and mortality of fungal infections is the limited number of antifungal drugs (Ostrosky-Zeichner L, 2010)

In total, there are presently four classes of FDA-approved antifungal agents clinically utilised to treat invasive fungal infections, namely the polyenes, flu cytosine, the azoles, and the echinocandins (Odds FC, 2003)

Invasive Fungal Infections (IFI), Is concerning problem worldwide due to the resistance many pathogenic fungi have developed to every therapy option now available, unacceptable burdens on individuals and healthcare systems (Fisher MC, 2022) (Bongomin F, 2017) (DW, 2024).

Azole compounds are the most popular antifungal medications due to their affordability, wide range of activity and favorable safety profile (Andes D, 1999) (Hope WW, 2009).

V. BLACK FUNGUS

Recently, there have been numerous reports of "mucormycosis," sometimes known as the "black fungus," especially in Asian nations like India. The fungus Mucorales is the source of the uncommon angio-invasive disease known as mucormycosis, which frequently affects patients with weakened immune systems. There are pulmonary, gastric, disseminated, cutaneous, and rhino-orbit cerebral types of this uncommon fungal infection (FH, 2021).

A variety of fungi, including Saksenaea, Syncephalastrum species, Cunninghamella bertholletiae, Mucor species, Apophysomyces, Absidia, and Rhizomucor, are known as mucormycetes and can cause mucormycosis. Because mucormycosis is spread by inhaling mould spores from compost piles, decaying bread or vegetables, or soil, it is challenging to prevent. Although mucormycosis is widespread in the surroundings, it is typically not contagious (Roden MM, 2005).

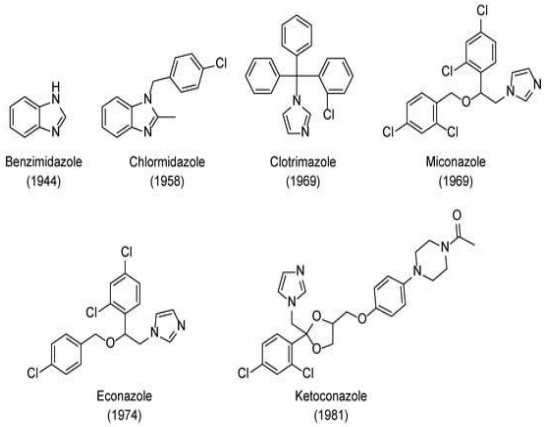
The frequent occurrence of opportunistic infections such as mucormycosis is resulting from the use of antibiotics, oxygen masks, and steroids during the handling of critically and very ill COVID-19 patients (Upadhayay P, 2023).

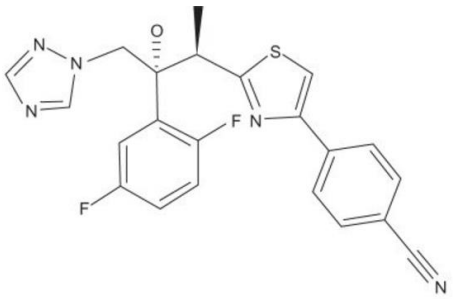
Although mucormycosis is extremely unlikely to occur, occurrences of the infection have sharply increased over the past 20 years, especially in Belgium, France, Switzerland, and India (Alom S, 2021).

Treatment

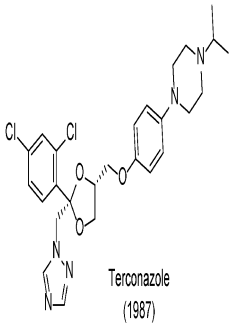
Black fungus treatment usually involves including Posaconazole, Isavuconazole, and Amphotericin B.

VI. AZOLES

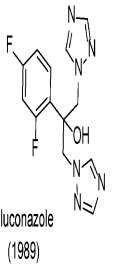




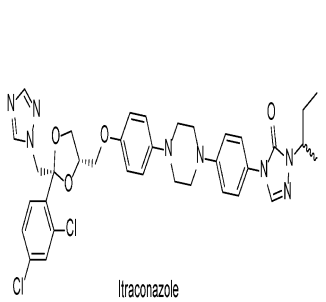
Isavuconazole (active drug BAL 4815)



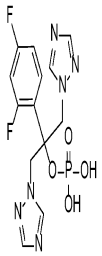
Terconazole
(1987)



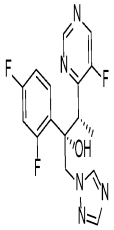
Fluconazole
(1989)



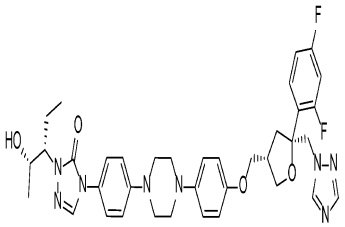
Itraconazole
(1992)



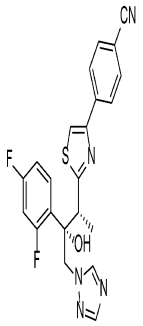
Fosfofluconazole
(2003)



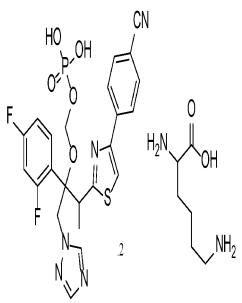
Voriconazole
(2002)



Posaconazole
(2006)



Ravuconazole
(replaced with fosravuconazole)



Fosravuconazole Bis(L-lysine)
(2018)

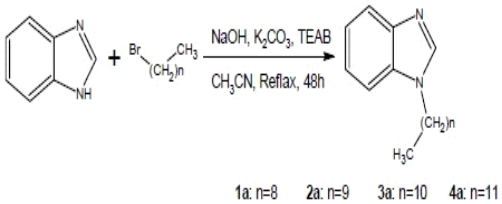
VII. GENERAL PROCEDURE FOR ANTI FUNGAL AZOLE SYNTHESIS

- Chemicals required:
- Begin with the starting materials: Benzimidazole or Benzotriazole, Bromoalkane, TEAB, Sodium hydroxide or Potassium carbonate, and Acetonitrile.
- Reaction Setup:
- Combine all starting materials in a reaction flask.
- Reflux:
- Reflux the mixture for 48 hours.
- Filtration:
- Filter the reaction mixture to remove insoluble materials.
- Concentration:
- Concentrate the filtrate in vacuo to remove acetonitrile and obtain the crude product.
- Extraction:
- Add water and Chloroform to the concentrated mixture.
- Separate the organic layer.
- Drying:

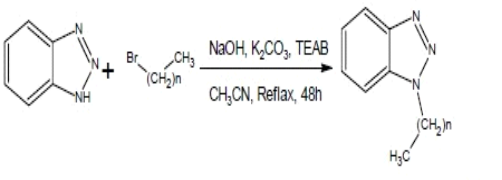
  Dry the layer of organic over Na_2so_4 to remove water.
- Final Concentration:

  Concentrate the layer of organic phase in a vacuum to obtain crude substance.
- Purification:

  Purify the unrefined substance with Silica Gel Column Chromatography with a solvent system of Petroleum Ether and Ethyl Acetate.
- Final Product:
- Collect the purified final product.



1a: n=8 2a: n=9 3a: n=10 4a: n=11



1b: n=8 2b: n=9 3b: n=11

VIII.STRUCTURAL ACTIVITY RELATIONSHIP

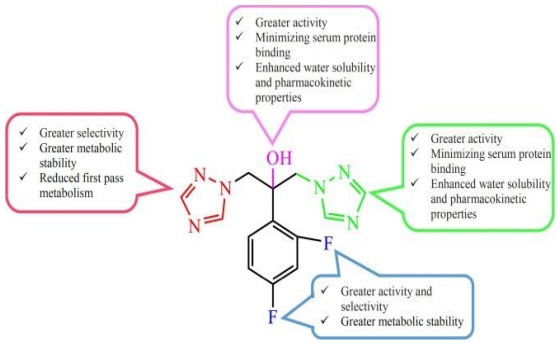


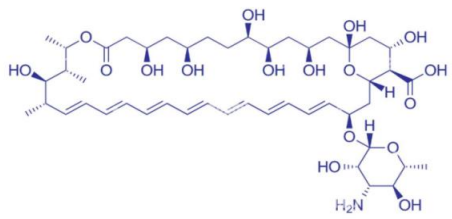
Figure: SAR of Anti-Fungal Azoles

The length of the alkyl chain substituent affects the antifungal activity. Electron- donating group (EDG) on phenyl rings improves anti-fungal activity. H is essential for anti fungal activity. Halogens{Cl, Br and F} increases potency and lipophilicity. AZOLE ring is essential for activity.NO_2,CF_3 at 7th position increases anti fungal activity than at positions 5, 6 and 8**.** Cl ,F show better antifungal activity than other EWD. Enhancing the number of F atoms leads to a decrease in activity. Para-chloro, Para-flouro, Para-cyano show more activity than ortho or meta compounds. Di chloro phenyl groups have more activity. Nitro group, phenyl group increases the antifungal activity. The halogen atom that yields the most potent compound is "F"

IX. DRUGS USED IN BLACK FUNGUS

Posaconazole, Isavuconazole, and

Amphotericin B



Isavuconazole

The cytochrome P450-dependent lanosterol 14α-demethylase, which is necessary for the production of ergosterol, a component of the fungal membrane, is inhibited by isavuconzaole. Cell death results from this disturbance, which also modifies the fungal membrane's structure and function (Livermore J, 2012).

Isavuconazole is superior to other antifungal drugs in a number of ways, such as its broad range efficacy, predictable pharmacokinetics, oral and IV formulations and fewer adverse effects compared to other triazoles. In patients with hematologic malignancies, isavuconazole is a great substitute for voriconazole when medication interactions and toxicities are a major issue (Ellsworth M, 2020).

Polyene

Antifungal drugs, the lipid formulations of amphotericin B, the novel triazoles posaconazole, and echinocandins in combination with amphotericin B (AMB) are all part of the treatment strategy for mucormycosis. Amphotericin B is the only antifungal medication authorised for the treatment of mucormycosis.

Drug	Recommended Dosage	Advantage & suppoting studies	Disadvantages
AMB	1.0-1.5 mg/kg/day	>5 decades clinical experience, only licensed agent for treatment of mucormycosis.	Highly toxic, poor CNS penetration
LAMB	5-10 mg/kg/day	Improved CNS penetration compared to AMB	Expensive
ABLC	5-7.5 mg/kg/day	Less nephrotoxic and retrospective clinical data suggest benefit of combination therapy with echinocandins	More nephrotoxic than LAMB

AMB- Amphotericin B

LAMB- liposomal Amphotericin B

ABLC- Amphotericin B lipid complex

X. COMBINATIONAL THERAPY

In spite of trustworthy clinical data, treating mucormycosis in a number of persons with weakened immune systems using a mix of antifungal is rising. Enhanced coverage and synergistic activity are benefits of this therapeutic approach, whereas antagonistic effects and medication drawbacks including toxicity, interactions, and cost. In both in vitro and in vivo animal model investigations, polyenes and echinocandins have been demonstrated to cooperate. But basically

echinocandins are thought to be ineffective against Mucorales when used in vitro.
The combination of echinocandin and AMB worked well in the prevalence of rhino-orbital or rhino-cerebral mucormycosis, was only 7 out of 22 diabetic patients (Chatur V. M., 2021)

XI. PREVENTION

Prevention of mucormycosis in the COVID-19 period necessitates the careful administration of steroids (both dosage and duration), the control of co-morbidities, especially diabetes, and the maintenance of cleanliness and hygienic conditions. The application of preventative drugs such as posaconazole.
Indian COVID-19 recommendations do not currently recommend it. According to worldwide standards, posaconazole prophylaxis is only suggested for people who have graft vs. host illness and neutropenia.In addition, it was moderately strong (Chatur V. M., 2021).

XII. CONCLUSION

This above article will give the brief information and treatment for black fungus by the action of anti-fungal and anti-biotic. To sum up, antifungal medications are crucial for treating fungal infections, which might vary from minor to fatal. Over the past few years, there has been considerable advancement in the creation of antifungal medications, leading to more targeted and effective therapy. Nonetheless, issues like medication resistance and the scarcity of available treatments for certain fungus species continue to exist. Enhancing results for people with fungal infections requires ongoing research and innovation in antifungal drugs, as well as the significance of appropriate diagnosis and treatment regimens. To successfully handle these issues, ongoing attention to detail and adjustment to new trends will be required.

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