

A REVIEW ON ANTIFUNGAL AGENTS RESISTANCE AND NATURAL ANTIFUNGAL**Pranut Maurya, Pranjul Shrivastava*, Khushboo Gupta, Sandip Prasad Tiwari****Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)***Corresponding Author's E mail: pranjul.shrivastava@kalingauniversity.ac.in

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ABSTRACT

Recent years have seen an increase in the occurrence of fungal infections, which calls for quick action. Rarely can fungal infections develop in the early stages, which would increase the infection's severity and make treatment more difficult. Several Strategies are used by fungal pathogens to avoid the enhance the host immune system and increase the intensity of infections. Antifungal medications from the available Repertoire are used to treat a variety of superficial and systemic infections. Antifungal therapy is complicated by the well-established evidence of fungal Resistance to the majority of antifungal medications, which makes disease control Difficult. Fungal resistance develops as a result of a number of physiological Adaptations, genetic alterations, and selection in the presence of antifungal drugs. The demand for antifungal therapy is driven by the scarcity of antifungal medications, resistance emergence, and biofilm-induced resistance.

Keywords: Mycology, Fungal pathogens, Antifungal resistance, natural antifungal.

INTRODUCTION

Another name for a fungal infection is mycosis. Fungi are the cause of this illness. Fungi are categorized into three groups based on the area of the body they affect: superficial, subcutaneous, and systemic. Hippocrates may have been referring to thrush when he reported oral Ulcers circa 500 BC. An invasive fungal infection (IFI) is defined as the presence of fungal components, such as mold or yeast, in deep tissues of Biopsy or needle aspirates that is verified on culture and Histopathological analysis .Fungi are abundant in nature, which is proof that they are incredibly adapted for survival. Less than 150–200 Of the Many hundred thousand species that are thought to exist, fungus were Thought to be human pathogens ¹.

Human microbiome organisms like Candida spp. Can lead to opportunistic infections in healthy people and potentially fatal infections (invasive candidiasis) in patients with impaired immune systems, such as those living with HIV. Individuals, Cancer patients undergoing chemotherapy, and individuals using

Immunosuppressive medications². Healthcare-associated infections (HAI). In patients with underlying disorders can be caused by fungal pathogens Such as *Candida*, *Aspergillus*, *Fusarium*, *Mucorales*, and molds in Addition to opportunistic and systemic infections. Fungal pathogens are known to be the cause of endemic mycoses that are frequently fatal, Including but not limited to Blastomycosis, Coccidioidomycosis, Histoplasmosis, Talaromycosis, Paracoccidioidomycosis, and Sporotrichosis .If a patient passes away in a teaching hospital, invasive Aspergillosis may be the cause³.

Eight to fifteen percent of nosocomial Bloodstream infections and the fourth most frequent isolate among ICU Patients are caused by *Candida* spp. certain patient populations experience extremely high fungus frequencies. 15% of Recipients of allogeneic hematopoietic stem cell transplants have a fungal Infection; approximately 20% of lung transplant recipients experience Colonization and infection. *Pneumocystis carinii* (jiroveci) pneumonia affects around 60% and 20% of AIDS patients, respectively. Candidiasis; In contrast, cryptococcal meningitis affects 30% of AIDS patients in Southeast Asia and Africa; and *Penicillium marneffei* infections affect around 30% of AIDS patients in Southeast Asia⁴. The incidence of Systemic fungal infections in India is not well-documented, despite the Country's diverse climate providing an ideal environment for a wide range of fungal infections. Nonetheless, a discernible upward tendency has been observed. At our facility, candidemia was found to have increased eleven times in the second half of the 1980s and eighteen Times more in the first half of the 1990s. Over a 23-month period, 379 Neonates and children (4.2% of all admissions) were found to have Fungemia caused by the uncommon yeast *Pichia anomala*, according to Reports from the same center⁵.

Prevalence and impact of fungal infections on human health.

Fungal infections represent a significant and growing concern in global health, affecting millions of individuals each year. These infections can range from superficial skin conditions to life-threatening systemic diseases. The prevalence of fungal infections is notably high in immunocompromised individuals, such as those with HIV/AIDS, cancer patients undergoing chemotherapy, organ transplant recipients, and individuals with chronic conditions like diabetes⁶.

Superficial fungal infections, such as dermatophytosis (athlete's foot, ringworm) and onychomycosis (nail infections), are widespread and affect a large proportion of the global population. *Candida* species are the most common cause of mucosal infections, including oropharyngeal and vulvovaginal candidiasis. Invasive fungal infections, although less common, pose a significant threat, particularly in hospital settings. *Candida* bloodstream infections (candidemia) and invasive aspergillosis are among the most prevalent invasive fungal diseases. According to the Centers for Disease Control and Prevention

(CDC), candidemia is one of the most common causes of bloodstream infections in hospitalized patients in the United States ⁷.

The impact of fungal infections on human health is profound, encompassing both direct and indirect effects. Superficial infections, while generally not life-threatening, can cause significant discomfort, disfigurement, and social stigma. Chronic fungal infections of the skin and nails can lead to secondary bacterial infections, complicating treatment and recovery ⁸.

Invasive fungal infections are associated with high morbidity and mortality rates. For instance, candidemia has a mortality rate of approximately 30-60%, depending on the patient population and healthcare setting. Invasive aspergillosis, predominantly affecting individuals with severe immunosuppression, has a mortality rate exceeding 50% despite antifungal treatment. These infections often require prolonged and intensive antifungal therapy, which can be expensive and associated with significant side effects ⁹.

The economic burden of fungal infections is substantial. Healthcare costs include prolonged hospital stays, expensive antifungal treatments, and the need for intensive care in severe cases. Moreover, fungal infections can lead to long-term health consequences, such as chronic lung conditions from pulmonary aspergillosis, which further strain healthcare systems and reduce patients' quality of life. Fungal infections also impact mental health, contributing to anxiety, depression, and decreased quality of life, especially in chronic and recurrent cases. The stigma associated with visible fungal infections can lead to social isolation and psychological distress ¹⁰.

Pathogenicity and Virulence

Depending on the virulence and pathogenicity there are generally two Types of fungus: truly pathogenic fungi and opportunistic fungi. Fungal Virulence can be linked to various factors. The fungi's capacity to Develop at 37°C and adjust to their surroundings is one of them. Inside The host tissues—particularly those of dimorphic fungi—assists in their Establishment and spread of infection. The fungus-specific factors that cause fungal pathogenicity are unique. The virulence and pathogenicity of different fungi are largely determined by their by-products, poisons, and enzymes. Proteases (elastin-serine Protease and elastin-metalloprotease) and aspartic acid proteinase are produced by *Aspergillus* species. Aflatoxin and restrictocin are the types of toxins that *Aspergillus* species make. *Cryptococcus* is an opportunistic Pathogen due to the formation of phenol oxidase and melanin and the Presence of a capsule. As a common fungus in human flora, *Candida* spp. Is an opportunistic fungal pathogen that can cause serious

infections ranging from superficial nail and skin infections to infections of the Urinary tract and candidemia ¹¹.

It has been observed that *Candida* species are capable of generating biofilms, which are defined as microbial Adhesion to biotic or abiotic surfaces creating a polymer matrix that serves as a substrate for the growth of microorganisms. Because of this Capacity, *Candida* spp. May be a source of nosocomial infections. A few Fungi, including *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans*, have been shown to produce sterol regulatory Element binding proteins (SREBPs), which aid in the fungus' ability to withstand hypoxic conditions in its hosts ¹². Tissues and exhibit resistance to antifungals. The process of fungal pathogenesis is intricate, and it has been documented that some proteins, such as polyketide synthases (PKS) And non-ribosomal peptide synthetase (NRPSs), are only slightly or Never present in saprophytes when it comes to pathogenic fungi that Affect plants. Neutropenia and organ transplant recipients (bone marrow, Stem cells, or solid organs) are risk factors for infection-free islands (IFIs). Premature new-borns, patients receiving long-term Immunosuppressive therapy, those receiving intensive care therapies, and HIV seropositive individuals with noticeable immunosuppression (AIDS). Long-term wide Individuals are also more susceptible to infection-causing Infections (FIIs) if they have chemotherapy for cancer, an indwelling Catheter or other medical device, are really old, or have other biological characteristics ¹³.

Fungal Pathogens

The lesser kingdom the phylum Ascomycota and Basidiomycota, which make up the dikarya of fungi, is primarily responsible for all human Diseases and fungal pathogens. It is well recognized that Ascomycota Organisms can cause oropharyngeal, otolaryngeal, dermatological Ophthalmology, infections in the heart, lungs, nervous system, genitourinary system, and system. Basidiomycota species like *Malassezia* and *Cryptococcus* are well-known for causing superficial skin infections and invasive meningitis, respectively ¹⁴. The primary modes of transmission for fungi are direct touch and/or inhalation. Fungal species that are Dermatophytic and fall under the following genera: *Microsporum*, *Epidermophyton*, *Trichophyton*, *Sporothrix*, and *Malasezia* spp. infect the skin injury through direct contact. In order to induce superficial Mycoses in keratinized tissues, they generate a variety of proteolytic Enzymes. The other main method of transmission is spore inhalation. Conidia responsible for lung infections. *Paracoccidioides brasiliensis* and *P. lutzii* (*Paracoccidioidomycosis*), *Blastomyces dermatitidis* (*Blastomycosis*), *Aspergillus fumigatus*, *Pneumocystis jirovecii* (*Pneumocystis pneumonia*), and *Histoplasma capsulatum* (*Histoplasmosis*) The primary mode of transmission for *A. flavus*

(aspergillosis), *Coccidioides immitis* and *C. posadasii* (coccidioidomycosis), *C. neoformans* and *C. gattii* (cryptococcosis), and *C. The* transmission routes of *talaromyces marneffei* (talaromycosis) Include inhalation and direct touch ¹⁵.

Antifungal Agents

Classes and targets of antifungal drugs include information on antifungal Families, modes of action, chemical names, and forms of therapy. Antifungals are used to treat and prevent fungal infections in humans, Animals, and crops. At the moment, four categories of antifungals are utilized to Polyenes, azoles, pyrimidine analogs, and echinocandins are Agents that are used to control and prevent fungal infections in crops and People. Notably, azoles are the main class of fungicides that are widely employed in both human medicine and agriculture ¹⁶. The medicinal Triazoles (i.e., isavuconazole, itraconazole, posaconazole, and Voriconazole) and the fungicidal azoles (i.e., difenoconazole, Epixiconazole, propiconazole, and tebuconazole) have structural Similarities take action. When these antifungals are used in tandem, the Environment becomes more resistant to pathogenic strains, which then Show up in clinics with reduced drug susceptibility profiles. As an Example, *Aspergillus fumigatus* has evolved resistance to azoles via a TR34/L98H mutation in the *cyp51A* gene upon environmental exposure. This mutation was found in *A. fumigatus* within infected individuals lacking prior exposure to azoles. The mutation is defined as the Substitution of leucine 98 with histidine in combination with a 34-bp Tandem sequence in the promoter gene. Furthermore, because fungi and their eukaryotic hosts have a tight evolutionary relationship, there are Issues related to target similarity that restrict efficacy and application, as Well as cytotoxic side effects that make long-term antifungal prescription Harmful for the host ¹⁷.

Antifungal medicinal plants

1. Holy basil ¹⁸

- This plant is herbaceous and spreads via seeds. In Hinduism, this plant Is considered sacred.
- Similar plants: Tulsi, Sacred Basil.
- Biochemical source: Made from both fresh and dried *Ocimum Sanctum* of leaves.
- Labiatae family Chemical constituents: The main chemical ingredient in it is volatile oil, Which ranges from 0.1% to 0.9%. Additionally, it contains 20% Eugenolmethyl ether, 3% carvacrol, and 70% eugenol.
- Caryophyllene, fixed oil, traces of alkaloids, saponin, and tannin are other ingredients tartaric acid, citric acid, maleic acid, and vitamin C. Organoleptic character: It has several branches and

stands around 30 cm Tall. The leaves are hairy on both sides and have an oblong, green shape with a serrated edge. It smells quite fragrant. It is reddish-black in tone, And the outfit includes purple flowers.

- Applications: At 200 µg/mL, *Ocimum Sanctum* leaves showed Antifungal efficacy against dermatologically isolated microorganisms. Moreover, it has antiviral, antibacterial, insecticidal, and antitussive Properties.

2. *Azadirachta indica*: ¹⁹

Known as Dogoyaro or Dogonyaro in Nigeria. It is indigenous to India and one of the two species in the genus *Azadirachta*. Subcontinent and The majority of African nations.

Synonyms: Indian lilac, neem, kadunimb, margosa, nimtree.

The plant's biological source is *Azadirachta Indica* leaves and other Aerial components, which belong to the Meliaceae family. The leaves Have a lanceolate serrate form and measure 20 to 37 cm lengthy. Its Bitter-tasting, green to yellow-colored leaves. The fragrant white flowers About 5 mm in length. The fruits are rectangular, 1.2–1.8 cm long, greenish yellow in color, and have a very harsh taste. Neem's bark is Tough, 10 mm thick, and has a grayish-brown color.

Chemical components: Nimbosterol, quercetin, azadirachtin, salannin, Meliantriol, and mellacin are the active ingredients in neem. The leaves Also contain these elements. There are nimbin, nimbinine, and nimbidine In the trunk bark. Margosine and nimbosterol both have bitter principles. Twenty percent acid and fifty percent is oleic acid.

Use: Nimbin, nimbidine, and neem oil have antifungal properties. Neem Leaves have potent antifungal qualities; they can eradicate fungus Infections such as *Aspergillus* and *Candida albicans*. Additionally, it has Insecticidal and antiseptic properties. It treats AIDS by having antiviral And antifertility qualities

3. *Aloe vera* ²⁰

It is a perennial evergreen. This kind of succulent plant belongs to the Aloe genus. Including over 500 species. Corpad is a synonym

Natural source: Made from the juice of *Aloe Barbadensis* Miller, *Aloe Detox* Miller, and *Aloe Africana* Miller leaves, belonging to the Liliaceae Family.

Organoleptic characteristics: It is dark brown in color, has a strong Bitter taste, a distinct smell, and occurs in masses of varying Sizes. Chemical components: barbaloin, aloe emodin, isobarbaloin, Aloinoside A, accompanying B, and p-caumaric acid are present.

Usage: It has potent qualities that can boost your immune system and Regulate your Candida. It has antiviral, antifungal, and anti-inflammatory

Properties. Anti-inflammatory and antifungal qualities.

CONCLUSION

Point mutations in transcription factors controlling resistance actors or Pharmacological targets. High throughput diagnostic technologies may Be utilized in the near future to identify resistance and modify treatment Plans during the process of treating fungal infections any clinical signs, Enabling a prompt modification of the antifungal therapy overview of the Several types of fungal infections, the organisms that cause them, the Pathophysiology, the various antifungal medications, and the resistance Mechanisms, such as the host immune system and evasion techniques. Here, we've highlighted significant advancements in the battle against fungal infections, including the discovery of innovative antifungal Medicines and other complementary strategies. Other natural plants are also employed in the treatment of fungus.

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