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EMERGING FUNGAL PATHOGENS: A GLOBAL HEALTH CONCERN

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Abstract: Although it seems that there are numerous medications available for the treatment of systemic and superficial mycoses, there are actually just a few effective antifungal medications for invasive fungal infections and dermatomycoses caused by fungal species with even modest virulence.

Fungi may be classified as yeasts or moulds according to their appearance and means of growth. Examples of yeasts are *Candida and Cryptococcus Spp.*, while moulds include *Aspergillus spp*., the dermatophytes and, and the Mucorales fungi are termed dimorphic they appear to be yeast like in the host, but grow as moulds *in-vitro*.

There are several classes of antifungals which are polyene, imidazole, triazole, thiazole, allylamines, echinocandins etc. As fungal cells are similar to human cells (both are eukaryotes) targeting is difficult and so it may lead to some side effects. . The identification of novel antifungal chemicals from medicinal plants has been made possible by the efforts of several researchers, especially those from nations with abundant biodiversity.

KEYWORDS: Fungal Infection, Topical, Candida**,** Clotrimazole, Resistance.

INTRODUCTION:

Over the last twenty years, fungus infections have become more common, particularly in people with weakened immune systems. Although it seems that there are numerous medications available for the treatment of systemic and superficial mycoses, there are actually just a few effective antifungal medications for invasive fungal infections and dermatomycoses caused by fungal species with even modest virulence. Many of the medications that are now on the market cause resistance, like flucytosine,

are fungistatic rather than fungicidal[1], have side effects, or are extremely toxic (like amphotericin B). Polak claims that the best medications to treat fungal infections have not yet been found. Meanwhile, resistance to antifungal medications that are currently on the market keeps increasing. "Even if combination therapy has emerged as a viable way to get around these drawbacks, a new generation of antifungal medications that are both safer and more effective is desperately needed. A chemical needs to be fungicidal rather than fungistatic, have a wide range of activity, a selective process of action, and a minimal emergence of resistant strains in order to be considered an effective antifungal agent. [2]

The agent should also be readily available and have minimal hazardous side effects. The development of resistance to current antifungal medicines and opportunistic infections in immunocompromised patients are driving the ongoing demand for novel antifungal drugs. Natural products provide an almost limitless supply of distinct compounds and act as a repository for fungal biology probes as well as novel, promising medications and therapeutic prototypes.

Isolating these substances from natural sources has been crucial to the development of novel antibiotics and antifungals. The likelihood of discovering novel prototype medications with radically different chemical structures and, consequently, distinct toxicities and cross-resistances with current therapeutic regimens is the main benefit of this strategy over chemical synthesis or

modification of existing agents. Despite the fact that microbes have historically been the main source of novel antibiotics, it has recently been demonstrated that higher plants can also provide a variety of antimicrobial compounds.

Finding novel structures from natural sources, ideally using an ethnobotanical approach, and screening plants that have been used in traditional medicine to treat a variety of infectious diseases is one trend in the hunt for novel antifungal chemicals. The identification of novel antifungal chemicals from medicinal plants has been made possible by the efforts of several researchers, especially those from nations with abundant biodiversity. The emergence of drug-resistant fungal infections and the shortcomings of current antifungal. Because of their varied biological activity and potential for fewer side effects, many natural compounds especially those derived from plants offer interesting leads for novel antifungal medicines. Fungi may be classified as yeasts or moulds according to their appearance and means of growth. Examples of yeasts are *Candida and Cryptococcus Spp.,* while moulds include *Aspergillus spp*., the dermatophytes and, and the Mucorales fungi are termed dimorphic they appear to be yeast like in the host, but grow as moulds *in-vitro*. Blastomycosis, chromoblastomycosis, coccidioidomycosis, histoplasmosis, para coccidioidomycosis and sporotrichosis are examples of diseases caused by dimorphic fungi. [3]

Classification of fungal Infection:

1. Superficial, 2. subcutaneous, 3.Deep or systemic mycoses.

Superficial infections are confined to the skin, hair, nails, or mucous membranes.

Subcutaneous infections are largely limited to the subcutaneous tissue but may spread to surrounding bone and skin.

Deep or systemic infections may involve organs such as the lung, spleen, or brain, or may affect the body as a whole, and tend to occur more frequently in immuno-compromised patients.[4,5]

Fungal infections are pretty common and can display up on the skin or transfer through the body. Fungal infections may also be described as local when they are restricted to one body area, as invasive when there is spread into the tissues, or as disseminated when the infections have spread from the primary site to other organs throughout the body. Fungal infections, also known as dermatomycoses, are common in everyday life and can happen anywhere in the world. Trichophyton, Microsporum, and Epidermophyton are examples of the fungi that cause superficial fungal infections. Fungal diseases that affect the skin, hair, and nails are particularly (very) strongly linked to these three generations. These infections are infectious illnesses brought on by dermatophyte (fungus) species that are either anthropophilic (affecting humans) or zoophilic (affecting animals). The common dermatophytosis is tinea pedis. Up to 70% of adults worldwide may be impacted. It affects the plantar surface and the space between the foot's fingers and can contain both inflammatory and non-inflammatory lesions. It is also referred to as athlete's foot or ringworm of the foot. [6]

The major types of Fungal disease:[7,8]

a) Athlete's foot (*Tinea pedis)*:

It is estimated that one in six people in the UK currently have athlete's foot. It is caused by a fungus that makes your skin itchy, flaky and red, and causes white cracks to appear, especially between your toes and on the side of your foot. Athlete's foot is often picked up from walking bare foot on damp, contaminated floors in communal shower facilities, swimming pools or saunas.

b) Nail infections (*Tinea unguium)*:

These can occur on any part of your nail and take a long time to develop. They cause your nail to discolours and become crumbly. The surrounding tissue may also thicken. Toenails are usually affected more than fingernails.

c) Ringworm of the groin (*Tinea cruris)*:

This is also called "jock itch" because it is more common in people that play sports and young males. It is contagious and can be passed from person to person by direct contact or contact with unwashed clothes. It can cause an itchy, red rash in your groin and the surrounding area.

d) Ringworm of the body (*Tinea corporis)*: This often affects exposed parts of your body, such as your arms, legs or face, and causes a red, ring shaped rash. Ringworm is contagious and can be caught by coming into contact with somebody who already has ringworm or touching contaminated items. Candida is thin walled small yeast that associates with humans as commensal and/or as pathogen. Candida is usually an opportunistic pathogen and can cause disease in humans, especially in immunocompromised patient. Nearly 150 species of Candida have been identified, out of them *C. albicans* is one of the most pathogenic species and it cause

candidiasis. *C. krusei, C. tropicalis, C.dubliniensis, C. parapsilosis* etc. are some other pathogenic species from genus Candida. Most Candida infections can be treated by topical administration of antifungal drugs such as clotrimazole, miconazole, nystatin, tioconazole or oral administration of drugs such as fluconazole and amphotericin B. Widespread and overuse of these drugs, leading microbes to develop a resistance mechanism against that particular drug especially in hospital environment. To solve this problem, scientists are trying to find new possible treatment substances from plants.

ANTIFUNGAL AGENTS:[9–11]

Antifungal medicines are used to cure fungal infections and prevent them from getting worse. They help treat conditions like athlete's foot, yeast infections, and more serious illnesses such as cryptococcal meningitis. There are several classes of antifungals which are polyene, imidazole, triazole, thiazole, allylamines, echinocandins etc. As fungal cells are similar to human cells (both are eukaryotes) targeting is difficult and so it may lead to some side effects. These drugs discovered over the years do not have very good effectiveness due to factors such as drug resistance, their inability to reach target sites, short residence time, poor bioavailability, lack of penetration etc. so to overcome these challenges one system is being investigated for effective delivery of these drugs which is novel drug delivery system. One such approach is vesicular delivery systems; these include liposomes, niosomes, ethosomes, transferosomes, pharmacosomes, sphingosomes, herbosomes, cubosomes, aquasomes, virosomes, enzymosomes, bilosomes etc.

Classification of antifungal drugs:

i) Antibiotics:

a) Polyene: Amphotericin B, nystatin, hamycin, natamycin

b) Heterocyclic benzofuran: Griseofulvin

ii) Antimetabolite: Flucytosine

iii) Azoles:

a) Imidazole: Clotrimazole, econazole, miconazole, oxiconazole, ketoconazole

b) Triazoles: Fluconazole, itraconazole, voriconazole

iv) Allylamines: Terbinafine

v) Other topical agents: Tolnaftate, undecylenic acid, benzoic acid, olamine, butenafine, Sodium thiosulfate

But these synthetic antifungal agents show different type of side effects like skin irritation, rashes, dryness, peeling, nausea, vomiting, headache and many more. Therefore, to reduce these side effect we can used herbal medicine which have less side effects as compared to synthetic drug. Almost the 30-50 plant shows the antifungal activity.

Resistance to antifungal drug:[12]

Antifungal drug resistance occurs when fungi evolve to the point where they are no longer effectively treated by antifungal medications. This resistance can be either intrinsic (meaning the fungus is naturally resistant) or acquired (meaning resistance develops over time). It's a growing concern, especially with the emergence of new resistant strains and limited treatment options.

Key Aspects of Antifungal Resistance:

Definition:

Antifungal resistance means the fungus is no longer inhibited or killed by a drug at concentrations typically achievable with standard dosing.

Types:

1. Intrinsic resistance: Some fungi are inherently resistant to certain antifungals due to their biological characteristics.

2. Acquired resistance: Fungi can develop resistance through genetic mutations, changes in drug targets or increased drug efflux (pumping the drug out of the cell). Resistance can occur through several mechanisms, including

a. Target site mutations: Changes in the fungal cell that prevent the drug from binding effectively.

b. Increased target expression: The fungus produces more of the molecule that the drug targets, reducing the drug's impact.

c. Drug efflux: The fungus pumps the antifungal drug out of the cell, preventing it from reaching the target.

Clinical Significance:

Antifungal resistance leads to treatment failures, prolonged illness, and increased mortality, particularly in vulnerable populations.

Emerging Threat: Resistant fungal infections, like those caused by *Candida Auris* and *Aspergillus fumigatus*, are recognized as urgent threats by organizations like the CDC.

Causes: Climate change and the limited development of new antifungals are contributing factors.

Strategies include in combating Resistance:

Antimicrobial stewardship programs: Optimizing the use of antifungal drugs to minimize resistance development.

Developing new antifungals: Researching and developing new drugs with different mechanisms of action.

Combination therapy: Using multiple antifungal drugs to target the fungus in different ways.

Preventing infection: Implementing infection control measures to reduce the spread of resistant fungi.

CONCLUSION: Fungal infections are a growing health problem around the world. Some are mild, like skin and nail infections, but others can be very serious, especially in people with weak immunity. Treating these infections is becoming harder because of drug resistance and limited treatment options. Although new tests and medicines are helping, there is still a need for faster diagnosis, better drugs, and more awareness.

Raising public knowledge about fungal diseases is important so people can seek help early. Doctors and researchers also need to work together to improve treatments and reduce the spread of resistant fungi. With continued research, early detection, and proper use of medicines, the overall impact of fungal infections can be controlled more effectively in the future.

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