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Fungal Infections: Pathophysiology, Allopathic Treatment and Herbal Alternatives – A Comprehensive Integrative Review

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ABSTRACT

Fungal infections have become a major global health issue, especially for people with weakened immune systems. These infections can range from mild, surface-level conditions to severe, life-threatening diseases caused by fungi like Candida, Aspergillus, and Cryptococcus. Several factors make someone more prone to these infections, including conditions such as diabetes, HIV/AIDS, obesity, the long-term use of antibiotics, and being in a hospital setting. While drugs like azoles, polyenes, and echinocandins are effective against fungal infections, using them for long periods can lead to problems like toxicity, resistance to the drugs, and high costs. To address these issues, there is growing interest in using herbal medicines as a safer and more sustainable alternative. Plants such as Calotropis gigantea, Aloe vera, and Curcuma longa contain active compounds like flavonoids, saponins, and alkaloids that can damage the structure of fungal cells, stop the production of ergosterol (which is important for fungi), and create oxidative stress within the fungal cells. These natural compounds not only show strong antifungal effects but also help support the immune system and lower inflammation. Combining herbal treatments with traditional antifungal medications could be a promising way to better manage and prevent fungal infections with fewer side effects and lower chances of drug resistance. However, more research and clinical testing are needed to create reliable, effective, and safe herbal-based treatments for fungal infections.

Keywords: Fungal Infections, Antifungal Agents, Herbal Medicine, Calotropis gigantea, Aloe vera, Curcuma longa, Phytochemicals, Antifungal Resistance, Medicinal Plants, Natural Therapy.

INTRODUCTION

Fungal infections are a major problem for public health worldwide.

They can be especially dangerous for people who already have other serious illnesses, such as COVID-19, leading to severe infections and even death. These infections can affect different parts of the body, ranging from the skin and mucous membranes to deeper tissues and organs. Some fungi, like Candida species, are normally present in the body without causing harm but can become harmful if someone's immune system is weakened, such as in people with HIV, cancer, or those taking immunosuppressive drugs. Other types of fungi, such as Aspergillus, Fusarium, Mucorales, and molds, can also lead to infections in people with existing health issues. In some areas, certain fungi cause diseases that are common in those regions, like blastomycosis, coccidioidomycosis, histoplasmosis, talaromycosis, paracoccidioidomycosis, and sporotrichosis [1].

Systemic fungal infections are becoming more common and are causing more deaths. The Centers for Disease Control and Prevention (CDC) recently set aside September 20–24, 2021, as Fungal Disease Awareness Week to emphasize the importance of early detection to avoid serious consequences (CDC website). This review covers the different types of human fungal infections, how they cause disease, how they avoid the immune system, the drugs used to treat them, how resistance develops, and new treatment options [1]. In recent years, the use of antibiotics has led to an increase in fungal infections, which are now among the top ten hospital-acquired infections.

About 7% of fever cases in people with low white blood cell counts are caused by fungal infections. Some Candida species are now the fourth most common cause of bloodstream infections in U.S. hospitals, even surpassing many traditional bacterial infections [2].

MYCOLOGY

Fungi are a separate kingdom in the biological world, different from plants and animals.

Their cell walls are made of chitin, which is not found in plants that use cellulose. Fungi can't make their own food through photosynthesis; instead, they get their nutrients from organic materials. They can be single-celled, like yeasts, or multicellular, forming long thread-like structures called hyphae. These hyphae come together to create a network known as mycelium. Scientists have identified more than 69,000 species of fungi, but it's believed the total number could be over 1.5 million [3].

Common types of fungi such as Aspergillus and Candida are found in various places like soil, on plants, and even on human skin.

These species can lead to serious infections, especially in people with weakened immune systems [3].

Fungi can reproduce in different ways. They can reproduce asexually by budding or releasing spores, and they can also reproduce sexually through a process called meiosis, which results in the production of sexual spores. Some fungal species do not have a known sexual stage and are referred to as Deuteromycetes or Fungi Imperfecti. Yeasts are single-celled organisms, while molds are made up of many hyphae. Some fungi, like

Histoplasma capsulatum and Blastomyces dermatitidis, are dimorphic, meaning they grow as molds in the environment but change into yeast form when they infect human tissues [3].

From a medical perspective, fungal infections are categorized as:

a) Dermatomycoses – infections that affect the skin

b) Disseminated mycoses – infections that spread to internal organs

c) Phaeohyphomycosis – infections caused by fungi that have dark pigmentation

d) Hyalohyphomycosis – infections caused by fungi that do not have pigmentation [3].

ETIOLOGY OF FUNGAL INFECTIONS

Fungal infections, known as mycoses, happen when fungi—typically harmless organisms found in the environment or living in harmony with the body—enter the body and bypass the immune system's natural defenses.

The likelihood of infection depends on various factors such as the specific type of fungus, the health status of the host, and the level of exposure to these organisms [4]

a) Source of organisms:

Pathogenic fungi can be found in soil, decomposing organic matter, the air, or as part of the normal flora in the human body, such as Candida species. Infections can occur when spores are inhaled (like Aspergillus and Histoplasma), when fungi are directly introduced into the skin (such as Sporothrix), or when commensal fungi begin to overgrow due to the weakening of natural protective barriers [4].

b) Host predisposition:

A weak immune system is a major contributor to fungal infections.

Conditions such as neutropenia, the use of corticosteroids, HIV/AIDS, chemotherapy, diabetes, and organ transplantation all make someone more vulnerable. Other factors like damaged skin or mucous membranes, the presence of medical devices, long stays in hospitals, and the use of broad-spectrum antibiotics also make it easier for fungi to invade the body [5].

c) Pathogen virulence and adaptation:

Some fungi are considered primary pathogens, such as Histoplasma capsulatum and Blastomyces dermatitidis, which can infect healthy people.

Opportunistic fungi like Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans generally cause illness in individuals with weakened defenses. These fungi have various traits that help them survive and cause disease, including the ability to grow at different temperatures, form dimorphic structures, produce enzymes, create biofilms, produce pigments, and avoid the immune system [6].

d) Environmental and healthcare-associated risk factors:

Being exposed to the air systems in hospitals, construction dust, or contaminated environments can increase the levels of airborne spores, such as Aspergillus, raising the risk of infection [7].

EPIDEMIOLOGY OF FUNGAL INFECTIONS

Fungi have been around for almost 1.6 million years and help the environment by breaking down dead material. In the past, they mostly affected plants and animals, but human actions like cutting down forests, industrial development, and changes in the climate have made people more exposed to harmful fungi [8].

Rising global temperatures have helped certain fungi that can survive at the temperature of the human body. This has led to more new fungal infections appearing. Right now, about 400 different types of fungi are known to cause infections in humans, and even more are becoming a problem because of changes in the environment and weather [8].

How common fungal infections are depends on the type of fungus, where you live, your immune system, and where the infection is in the body. Infections that are on the surface of the skin, like athlete's foot or ringworm, are more common in hot and humid areas and are connected to cleanliness and how well people can afford to take care of their health. On the other hand, serious infections such as those caused by Candida, Aspergillus, or Cryptococcus usually affect people whose immune systems are weakened, such as people living with HIV, those undergoing cancer treatments, and people who have had organ transplants [9].

In more developed countries, there have been fewer surface infections because of better hygiene practices. However, as people with weakened immunity are living longer due to medical advances, there has been an increase in serious fungal diseases. In places like Uganda, the spread of HIV has led to more cases of infections caused by Cryptococcus and Histoplasma. In China, fast industrial growth and changes in daily life have also contributed to a rise in serious fungal infections. Even though these infections are becoming more of a concern, there is not enough detailed information at the national level, so more monitoring and research are needed [9].

PATHOPHYSIOLOGY OF FUNGAL INFECTIONS

Only a small number of fungi are capable of infecting individuals who are otherwise healthy, while the majority cause illness in people with weakened immune systems. Typically, the skin, mucous membranes, and the body's natural immune defenses act as barriers that prevent fungi from entering the body. However, when these protective barriers are damaged, the risk of fungal infection increases. Additionally, genetic differences in immune-related genes, such as IL-10 and Toll-like receptors, can also make someone more vulnerable to infection [2]. Conditions that weaken the immune system, like chemotherapy, the use of corticosteroids, or certain cancers, increase the likelihood of fungal infections. High-dose chemotherapy, for instance, can damage mucous membranes and reduce the number of white blood cells and bodily secretions. Immunosuppressive drugs and central venous catheters further contribute to this risk, particularly in patients who have undergone organ transplants [2].

Fungal infections often start when a person comes into contact with fungi in the environment, through inhalation, ingestion, or touching contaminated surfaces. For example, Candida species, which are normally harmless, can multiply rapidly after the use of antibiotics or following damage to the mucosal lining, potentially leading to serious bloodstream infections. Aspergillus fumigatus causes lung infections when its spores are inhaled, especially in patients who have experienced prolonged neutropenia or those suffering from graft-versus-host disease [10].

In recent years, new types of opportunistic fungi, including Zygomycetes, Fusarium, and Scedosporium, have become more common in individuals with compromised immune systems. At the same time, non-albicans Candida species have increased in frequency due to the widespread use of prophylactic fluconazole. As a result, the outcome of a fungal infection is influenced by the complex interplay between the host's immune response, environmental exposure, and the virulence of the fungus itself [10].

FUNGAL IMMUNE EVASION AND THE HOST IMMUNE SYSTEM

The host immune system identifies fungi by using pattern recognition receptors (PRRs), such as dectins and toll-like receptors (TLRs), which spot pathogen-associated molecular patterns (PAMPs) like chitin and β-1,3-glucans. Once these receptors detect the fungi, they send signals that trigger processes such as phagocytosis, the production of reactive oxygen and nitrogen species, cytokines, and chemokines, all of which help eliminate the fungus [11].

The first line of defense against fungal infections comes from innate immune cells, including monocytes, macrophages, dendritic cells, and neutrophils. These cells can destroy fungal cells inside phagolysosomes or trap them in granulomas. They also release cytokines and present antigens to T cells, connecting the innate immune system with the adaptive immune system. However, fungal pathogens have developed various strategies to escape these defenses [12].

To avoid immune detection, fungi cover their surface PAMPs with layers of mannan, melanin, α-1,3-glucan, and hydrophobin, which prevent immune recognition. For example, Pneumocystis jirovecii hides its β-1,3-glucan, while Histoplasma capsulatum reduces pathogen recognition by modifying its surface glucans. The capsular polysaccharides of Cryptococcus neoformans can block T-cell activation and reduce the recruitment of neutrophils [12].

Fungal pathogens also alter their morphology to avoid immune detection. Candida can switch from a yeast form to a filamentous form to invade tissues and escape phagocytosis. Coccidioides forms spherules that resist reactive species, while Cryptococcus neoformans can survive inside macrophages and escape through a process called vomocytosis, allowing it to cross the blood-brain barrier and cause meningitis. Blastomyces dermatitidis produces a protein called BAD1, which stops complement activation, helping the fungus spread throughout the body [13,14].

Biofilm formation in fungi like Candida albicans, Cryptococcus neoformans, and Aspergillus fumigatus helps them survive in stressful environments and resist antifungal treatments [14].

SIGNS AND SYMPTOMS OF FUNGAL INFECTIONS

Fungal infections can show different symptoms depending on the type of fungus, where the infection is, and how strong the person's immune system is.

These infections can be mild, like on the skin, or severe, affecting the whole body.

a) Superficial and Cutaneous Infections:

These affect the skin, hair, and nails.

They are usually caused by Dermatophytes, Candida, or Malassezia.

Symptoms include itching, redness, burning, flaking, or cracking of the skin.

You might see a ring-shaped rash (Tinea), discolored or thickened nails (Onychomycosis), or white patches in the mouth or vagina (Candidiasis).

Examples include Tinea capitis (scalp), Tinea corporis (body), and Tinea pedis (athlete's foot) [15].

b) Subcutaneous Infections:

These affect the deeper layers of the skin and connective tissues.

They are often caused by Sporothrix schenckii, Cladosporium, or Madurella.

Symptoms may include swelling, nodules, or ulcers that develop slowly and spread along the lymphatic vessels.

Example is Sporotrichosis, also known as "rose gardener's disease" [16].

c) Systemic Infections:

These affect internal organs and the bloodstream, and are more common in people with weakened immune systems.

Symptoms can include a persistent fever that doesn't go away with antibiotics, fatigue, weight loss, cough, chest pain, or neurological issues if the brain is involved.

Examples include Cryptococcosis, Histoplasmosis, and Candidemia [17].

d) Athlete's Foot (Tinea Pedis):

This is a contagious infection that affects the feet and sometimes the nails or hands.

It is common among athletes.

Symptoms include itching, burning, peeling between the toes, blisters, dry and scaly soles, or a bad smell.

In long-term cases, the infection can spread to the nails (Onychomycosis) [18].

MECHANISM OF ANTIFUNGAL

a) Polyene Antifungal Agents

Amphotericin B is a wide-ranging antifungal drug given through a vein for serious infections.

It attaches to ergosterol, a component in fungal cell membranes, which breaks down the membrane structure and causes the contents of the fungal cell to leak out. It sticks more tightly to ergosterol than to cholesterol, which makes it more effective against fungi. Even though it works well, it can harm the kidneys. Newer forms like lipid-based versions (liposomal, ribbon, and disc) and advanced delivery methods like amphotericin B-cochleate help lower this side effect. Nystatin, another similar drug, is also being tested in liposomal form [19].

b) Azole Antifungal Agents

Azoles, such as imidazoles and triazoles, stop the 14α-demethylation of lanosterol, an important step in making ergosterol, by acting on the cytochrome P450 enzyme (Erg11p/Cyp51p).

This weakens the fungal cell membrane and interferes with enzyme function. The difference in structure between the fungal and human versions of this enzyme explains why azoles mainly affect fungi. Triazoles work better because they bind more strongly to the fungal enzyme. Resistance can happen due to changes in the enzyme or overactive pump systems that remove the drug, although this is rare except in cases of oral infections in people with AIDS [20].

c) Flucytosine

Flucytosine, also known as 5-fluorocytosine, turns into 5-fluorouracil inside fungal cells.

This stops the production of RNA and DNA. It needs certain enzymes like cytosine permease and cytosine deaminase, which are found in Candida and Cryptococcus neoformans. It is often used along with other antifungal drugs to avoid resistance. Recent studies show that resistance levels are low, making it a useful treatment option [21].

MAJOR RISK FACTORS OF FUNGAL INFECTION

Fungal infections can be influenced by a number of factors that make someone more likely to get them.

These include conditions like diabetes, obesity, HIV/AIDS, staying in the hospital for a long time, taking corticosteroids, undergoing chemotherapy, having an organ transplant, or being exposed to certain environments [22].

a) Diabetes

When blood sugar levels are high, it creates an environment where fungi can grow more easily.

It also affects how well the body's white blood cells work, which are important for fighting infections. People with diabetes are more prone to fungal infections like angular stomatitis, which is often linked to higher levels of glucose in saliva [22].

b) Obesity

Being overweight can lead to skin inflammation and changes in the immune system, making it easier for fungi to grow.

Fat cells produce substances like adiponectin, leptin, cytokines, and chemokines, which can cause a slow, ongoing inflammation in the body. This can make a person more likely to get infected [23].

c) AIDS/HIV

HIV attacks CD4+ cells, which are crucial for the immune system.

This weakens the body's ability to fight off infections, making individuals more vulnerable to opportunistic fungal infections. These can include oral candidiasis caused by fungi like Candida albicans, C. tropicalis, C. glabrata, and Talaromyces species. The use of long-term steroids and other co-infections, especially during the COVID-19 pandemic, have also led to an increased risk of fungal infections such as Aspergillus, Candida, and Mucor in intensive care unit patients [24].

d) Modifiable and Non-modifiable Risk Factors

Modifiable: It is possible to reduce the risk by avoiding unnecessary use of antibiotics or corticosteroids, keeping up with good hygiene, managing diabetes effectively, and making healthy lifestyle choices to maintain a healthy weight.

Non-modifiable: Some risk factors are not changeable, such as having cancer, HIV/AIDS, chronic lung disease, or having had an organ or stem cell transplant.

These conditions can cause long-term or permanent weakening of the immune system, which increases the chance of fungal infections taking hold [21].

DIAGNOSIS AND INVESTIGATION OF FUNGAL INFECTIONS

Diagnosing fungal infections involves looking at symptoms, using microscopes, growing fungi in the lab, examining tissue samples, and using advanced techniques.

Getting an accurate and early diagnosis is important for proper treatment and to avoid serious health problems [25].

a) Clinical Assessment

The diagnosis starts with checking for symptoms like a long-lasting fever, cough, skin sores that don’t heal, or white patches in the mouth.

Also, factors that increase the risk of infection, such as a weak immune system, diabetes, use of corticosteroids, or chemotherapy, are taken into account [25].

b) Direct Microscopic Examination

Samples from skin, sputum, or blood are looked at under a microscope after being treated with KOH mount, Gram stain, or Calcofluor white stain.

This helps spot fungal structures like hyphae, pseudohyphae, or yeast cells [26].

c) Culture Methods:

Fungi are grown on special media like Sabouraud Dextrose Agar (SDA), Potato Dextrose Agar (PDA), or chromogenic media at temperatures between 25 and 37 degrees Celsius. The way the colonies look helps identify fungi such as Candida, Aspergillus, Cryptococcus, and dermatophytes [27].

d) Histopathological Examination

Tissue samples are stained with Periodic Acid-Schiff (PAS) or Gomori Methenamine Silver (GMS) to confirm if fungi are invading tissue and to tell them apart from bacteria. This is very important for diagnosing serious infections like aspergillosis or mucormycosis [28].

e) Emerging Diagnostic Tools

New tools like MALDI-TOF mass spectrometry and metagenomic sequencing allow for faster and more accurate identification of fungi from patient samples [29].

HERBS USED IN TREATMENT OF FUNGAL INFECTIONS

a) Calotropis gigantea (Rakta Arka)

Fig :-Calotropis Gigantea

Calotropis gigantea, which belongs to the Apocynaceae family, is a medicinal shrub commonly used in Ayurveda in India and Southeast Asia.

Its leaves, roots, bark, and latex have active compounds like flavonoids (such as quercetin and kaempferol), cardiac glycosides (like calotropin and uscharin), alkaloids, triterpenoids, saponins, and phenolic compounds. These compounds have antifungal, anti-inflammatory, and wound-healing properties.

Antifungal Activity

Flavonoids, saponins, and alkaloids all affect fungal cell structure and function.

Saponins stick to ergosterol in the fungal cell membrane, causing it to leak. Flavonoids stop certain enzymes from working and make reactive oxygen species (ROS) that harm fungal DNA and proteins. The latex in Calotropis gigantea has enzymes like proteases and esterases that break down the fungal cell walls, leading to the death of the fungus. In traditional use, this plant is applied for treating skin infections and diseases related to Candida.[30]

b) Aloe vera

Fig : -Aloe Vera

Aloe vera, known as Ghritkumari, is rich in bioactive compounds such as anthraquinones (like aloe-emodin), chromones, flavonoids, saponins, tannins, vitamins (A, C, E, B12), enzymes, and polysaccharides such as acemannan.

Antifungal Activity

Anthraquinones change the lipids in the fungal cell membrane.

Saponins interfere with the production of ergosterol, and flavonoids create oxidative stress through the production of reactive oxygen species (ROS). These effects damage fungal mitochondria and DNA. Aloe vera gel has been found effective against Candida albicans, Aspergillus niger, and Trichophyton rubrum.[31]

c) Curcuma longa (Turmeric)

Fig :-Turmeric

Curcuma longa, which is part of the Zingiberaceae family, includes compounds like curcumin, demethoxycurcumin, and bisdemethoxycurcumin as its main active ingredients.

These, along with volatile oils such as turmerone and zingiberene, offer antifungal, antioxidant, and anti-inflammatory benefits.

Antifungal Activity

Curcumin damages the fungal cell membrane, stops the production of ergosterol, and causes oxidative stress through reactive oxygen species (ROS), which harms fungal DNA and proteins.

It has strong antifungal activity against Candida albicans, Aspergillus niger, Trichophyton rubrum, and Microsporum gypseum.[32]

DIFFERENCE BETWEEN ALLOPATHY AND HERBAL TREATMENT OF FUNGAL INFECTIONS

Aspect	Allopathic Treatment	Herbal Treatment
Common Treatment	Synthetic antifungal medicines are used to stop or kill harmful fungi, often to quickly control infections.[33]	Natural plant-based extracts and essential oils that have antifungal, anti-inflammatory, and immune-boosting qualities.[34]
Example Of Medicine / Herbs	Fluconazole, Itraconazole, Amphotericin B, Terbinafine.[33]	Curcuma longa (Turmeric), Aloe vera, Calotropis gigantea, Azadirachta indica (Neem).[34]
Mechanism Of Action	These medicines stop the production of ergosterol (Azoles), attach to ergosterol and break down fungal cell membranes (Polyenes), or stop the production of Î²-glucan (Echinocandins).[19,20,21]	Natural compounds like curcumin, aloin, and calotropin weaken fungal cell walls, stop spores from growing, and create oxidative stress on fungal cells. [33,35,38]
Potency	High and rapid; effective even in systemic infections.[34]	Moderate ; more effective for mild to moderate infections.[35]
Side Effects	These drugs can cause liver damage, kidney damage, stomach upset, allergic reactions, and drug resistance if used for a long time.[36]	These treatments usually have mild side effects, like local irritation or allergic reactions, and are safer for long-term use.[37]
Focus On Causes Vs. Symptoms	These treatments mainly deal with the symptoms and remove the fungus; they do not much support the immune system.[38]	These treatments aim to eliminate the infection and also address the root causes like weak immunity, oxidative stress, and inflammation.[39]
Preventive Aspect	Preventive use is mainly for people with weakened immune systems, with medicines used to prevent fungal infections; keeping the environment clean and dry is important.[40]	Regular use of herbal extracts with antifungal and immune-boosting properties can help stop infections from coming back and support the body's natural defenses.[41]

Table No. 11.1 :- Comparative Study Of Allopathy And Herbal Treatment Of Fungal Infection

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