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Herbal Antifungal Agents Used for the Treatment of Fungal Infections

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Abstract : Nowdays, fungal infection is one of the most common dermatological problems worldwide. The mycoses represent a diverse group of diseases caused by various fungi, impacting different body systems and ranging from superficial to life-threatening. These infections can be categorised into superficial, cutaneous, subcutaneous, and systemic types. Each requiring distinct diagnostic and therapeutic approaches. Common fungal pathogens include Candida species, Aspergillus species, dermatophytes, Histoplasma capsulatum, Coccidioides species, Cryptococcus neoformans . Symptoms can vary widely depending on the type and location of the infection involving topical, oral or intravenous .There are numerous *antifungal* agents used clinically to treat fungal infection, they are azoles, terbinafine and griseofulvin. But In recent years, use of plant-based products to fight fungal infections have attracted extensive attention. This is because of the use of medicinal herbs has many advantages such as decreased cost and fewer side effects and over 60% of all pharmaceuticals are plant based, have less toxicity while synthetic treatment have limited criteria So recent interest has also focused on complementary herbal treatments such as Garlic,Tulsi,Ginger,Turmeric,Neem,Aloevera,clove,Tea tree which offer adjunctive benefits in managing fungal infections. Early diagnosis and appropriate treatment are crucial for effective management and prevention of complications. The review focused on various fungal infections, symptoms, conventional treatments or the role of herbal medicine on fungal infection .

Key words **–** Antifungal Activity, Herbal remedies, Phytochemical constituents, Fungal infection.

INTRODUCTION :

Fungal infection, also known as mycosis, is caused by fungi. There are millions of species of fungi. Fungi can exist in the soil, water, air, plants and human body. Fungi that cause infections in people include yeasts and molds. Typically, yeasts are made up of a single, small, oval cell, while the colonies of mold are made up of filamentous strands known as hyphae. Some fungi are dimorphicv and exist either as yeasts or molds depending on the external environment, such as temperature. The types of fungi classified according to the part of the body affected, i.e., superficial (topical), subcutaneous, and systemic. A fungus that attacks the tissue can cause a disease that's confined to the skin, spreads into tissue, bones and organs of the body or affects the whole body. Its symptoms depend upon the area affected and also vary. Depending on type and location but may include itching, redness, rash, scaling, or discharge. [1][2][3]

Fungi are everywhere, but only cause disease; fungal infection occurs fungi either breathed in come into contact with skin or enter the body through the cuts, wounds or infection on skin. It is more likely to occur in people having weak immune systems; this includes people having illnesses like HIV/AIDS and people with cancer treatment.[4]

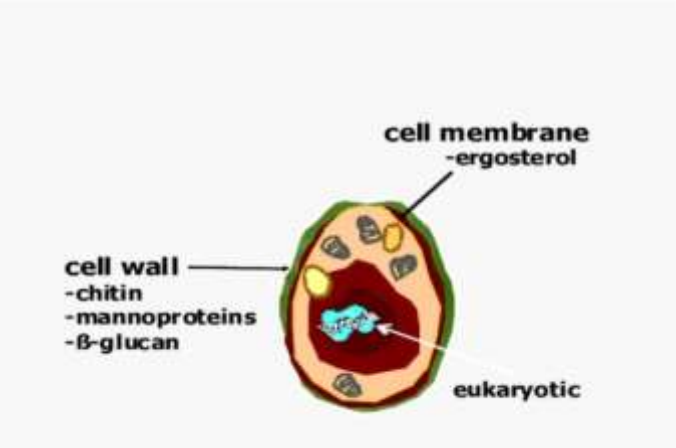

Figure 1: The fungi

TYPES OF FUNGAL INFECTIONS

A) Topical/Superficial infection

- Superficial fungal infections occur in the outermost layer of the skin, nails, hair, and mucous membranes. [5] These skin conditions, which impact millions of individuals globally are among the most common ones in the class.
- It is simple to detect and cure the majority of superficial fungal infections. One of the main cause of skin disease globally is fungal infection. In emerging and poor nations, the frequency of fungal infection is estimated to be around 40 million persons.
- During the first phase, fungi normally target the skin's surface, and then, through Desquamation, they infiltreate the deeper layer of skin, one of the fungi that cause the most superficial skin infection is candidia species.
- Fungal infection manifested as cutaneous mycoses in the dermal layer. A popular term for cutaneous fungal disease is "Dermatophytes." Tinea corporis,Tinea pedis and Tinea cruris are among the fungi that are frequently implicated in various dermatomycoses.
- Fungal infections, both superficial and deep, are treated with antifungal chemotherapy. Since topical distribution ensures direct access and better retention rate at the target, it may be the most effective method of delivering antifungal medication against major skin dermatophytes.
- Applying medication topically helps to prevent pre-systemic metabolism and lessen systemic toxicity.
- Many medications, such as clotrimoxazole, itraconazole and ketoconazole are applied. topically to the skin by rubbing or spreading.[6] [7]

Advantages of topical treatment for fungal infection [8][9]

- the site of infection is targeting
- Increases the efficacy of treatment and therapeutic effectiveness
- Reduction in the systemic side effects and toxicity
- Increase the patient compliance
- Improved bioavailability and site-specific drug delivery

Types of superficial fungal infection

1) Dermatophytosis

Dermatophyte fungi are organisms that digest keratin [10]. Dermatophytes infect the stratum. Corneum of the epidermis and keratinized tissues derived from it, such as hair or nail. Trichophyton spp., Microsporum spp., and Epidermophyton spp. are responsible for most of the superficial fungal infection, although the causative agents can be some Nondermatophytes molds. [11]

2) Superficial candidiasis

Superficial candidiasis infections are usually caused by Candida albicans,and this organism is a common commensal in the mouth, vagina, and gastrointestinal tract in healthy individuals. The prevalence of carriage is greater in hospitalized patients and those who are immuno-compromised .

3)Tinea corporis

Two major causative organisms causing tinea corporisare T.rubrum,T.mentagrophytes affecting neck ,trunk ,and the extremities. The classic tinea corporis lesion is a sharply defined circular lesion with erythema,scaling,and smallblisters or pustulesat the border.Its a circular lesion <5 cm in diameter,often transmitted form domestic animals,such as cats,dogs.hamsters and guinea pigs to humans.[12]

4) Tinea pedis

Tinea pedis is a dermatophyte infection of the foot,affecting particularly the toes and sole caused mainly by Trichophyton rubrum,Trichophyton mentagrophytes,and Epidermophyton floccosum pathogens.This infection affects 15-30% of the population.[12] And is the most common dermatophyte fungal infection that occurs in man[13].Individuals with tinea pedis may be susceptible to secondary bacterial infection with,for example Group A streptococcus[14].

5)Tinea capitis

Trichophyton tonsurans is the principal source of this infection, primarily causing sickness in children that manifests as scalp scaling and baldness.[15][16]

B) Subcutaneous infection

- subcutaneous mycosis is the term used to describe a fungal infection that penetrates deeper into the skin tissue. Fungal infection ,both superficial and subcutaneous are treated with antifungal chemotherapy.
- Although subcutaneous mycoses can disseminate,they are usually limited to the dermis and subcutaneous tissues.

Types of Subcutaneous fungal infection

1) Sporotrichosis

Sporotrichosis is caused by the dimorphic fungus Sporothrix schenckii and is the most current subcutaneous infection [17]. The fungus is set up in soil and foliage and generally causes complaints in farmers or gardeners, especially those who tend roses. It is a localized cutaneous or subcutaneous lesion, which may spread via the lymphatic system and form further lesions. Lymphocutaneous sporotrichosis is a non life-threatening disease [18]

2) Chronic mucocutaneous candidias

A rare illness known as chronic mucocutaneous candidiasis.It is caused by a persistent C. albicans infection of the mucous membranes, which can spread to the skin and nails. Although the underlying deficiency is yet unclear, the disorder is linked to compromised cell-mediated responses to Candida [19][20]. White fissured lesions; hyperkeratotic, granulomatous and vegetating lesions, as well as an autosomal recessive characteristic linked to endocrine disorders such as hypoparathyroidism, are only a few of the signs.

C) Systemic fungal infections

The two separate categories can be used to categorise systemic fungal infections: the dimorphic or endemic mycoses. Unlike yeast and mould infections, which are opportunistic and only enter hosts with impaired immune systems, these diseases are caused by real pathogenic fungi.These infections pose a serious risk to life and have a high fatality rate. Patients receiving solid organ transplants who are on immunosuppressive drugs to reduce the possibility of organ rejection are more vulnerable to systemic fungal infections. [21] [22].

Types of Systemic fungal infection

1) Invasive aspergillosis

Aspergillus species are common, mostly found in soil, water, and decomposing vegetation. The majority of Aspergillus infections are caused by respiratory tract inhalation and are linked to construction activities in hospitals or contaminated ventilation systems. It is also possible to contract an infection from plants or specific foods like pepper. Haemoptysis, pleural rub, pleural effusion, persistent fever, and pulmonary infiltrates following antibiotic therapy are some of the signs and symptoms. Radiography displays a single or many foci lesions, while computed tomography scans display the typical halo and air crescent signals [23].

2) Cryptococcus

Cryptococcal infection usually results from the inhalation of Cryptococcus neoformans, which is found primarily in soil contaminated by pigeon or chicken excreta. Cryptococcus has a particular affinity for the central nervous system, resulting in Cryptococcal meningitis, and is one of the most significant life-threatening fungal infections associated with HIV [24]. Cryptococcal infection may also be seen in non-immunocompromised individuals [25] and patients with impaired cell-mediated immunity, for example, that undergoing solid organ transplantation [26].

3) Histoplasmosis

Histoplasmosis caused by the dimorphic fungus Histoplasma capsulatum is set up worldwide, but particularly in North, Central, and South America. Depending on the vulnerable status of the host and the contagious cure, the clinical instantiations vary. In immunocompetent persons, the complaint is generally asymptomatic or manifests as an acute respiratory illness that is tone- limiting, whereas in immuno- compromised persons, it can affect in severe illness with progressive pulmonary complaint or circulated infection. Symptoms are generally mild, but due to heavy exposure of fungus in individualities may beget fever, chills, headache, myalgia, anorexia, cough, and chest pain [27-29].

4) Coccidioidomycosis

It's aboriginal in the southwestern corridor of the USA(California, Arizona, New Mexico, Utah, and Nevada) and corridor of Central and South America(Mexico, Brazil, and Argentina) and caused by the dimorphic fungi Coccidioides immitis and Coccidioides posadasii. The most common clinical instantiations are casket pain, cough, fever, weight loss, and fatigue, frequently associated with dermatological instantiations including erythema nodosum or erythema multiforme and rheumatological instantiations including myalgia and arthralgia. The complaint can also spread from the lungs hematogenously to bones, joints, skin, and the central nervous system [30- 36]

5) Blastomycosis

Blastomycosis is the dimorphic fungi caused by the pathogens Blastomyces dermatitidis and Blastomyces gilchristii, which are found in humid soil containing decaying vegetation or decomposed wood and are associated with freshwater drainage basins [60]. It is reported mainly in North America and in Africa but occasionally has also been reported in Central and South America, Mexico, India, and the Middle East [37].

Figure 2: Symptoms of Fungal infections

SYNTHETIC DRUG AND SIDE EFFECTS [38][39] :

The side effects are caused by uncontrolled drug release.Due to limited penetration, these adverse effects can result in prolonged treatment since the medicine may not reach the intended region, which could lead to incomplete infection clearance.

Figure 3: Side effect of Antifungal Drugs

Sr.No	Drug	Side effect
1.	Fluconazole	cause mild headaches, dizziness, and alopecia in high doses.[40]
2.	Amphotericin B	risk of hypotension, chills, headache, hypokalemia, hypomagnesemia, anemia, renal insufficiency, renal function abnormalities, injection site pain, nausea, vomiting, rigors, and fever.[41]
3.	Voriconazole	Non-melanoma skin cancer prolonged therapy.
4.	Ketoconazole, Clotrimazole.	Fever, chills.
5.	Flucytosine	Leukopenia,Thrombocytopenia.
6.	Caspofungin	Decreased renal function.

7.	Anidulafungin C, Micafungin.	Dark urine, clay colored stools.
8.	Flucytosine, Isavuconazole.	Abdominal pain .

HERBAL REMEDIES [42][43]

1) Garlic

- Biological source- Garlic is a species of bulbous flowering plants of allium sativum .
- Family – Alliaceae
- Chemical Constituents- Allin,Allicin or Ajoene .
- Parts used- Peel,Clove,Seeds,Bulb.
- Uses-

1) Garlic peel was most effective against several phytopathogenic fungi.
2) Garlic clove contain allicin which show antifungal activity.
3) Ajoene is an active compound found in garlic which plays important role in topical antifungal agent.[44]
4) Contain allicin,which has antifungal properties.consuming garlic raw or in supplement form may help combat candida.
5) The growth of candida albicans and Aspergillus species was inhibited by a gene at less thn 20 microgram/ml .[45][46]
6) It Exhibits antifungal activity against Aspergillus species,Histoplasma Capsulatum,Coccidioides Species,Cryptococcus Neoformans,Trichophyton, Microsporum, and Epidermophyton species by inhibiting the growth and sporulation.

2)Tulsi

- Biological source- Tulsi consists of the fresh and dried leaves of ocimum species like ocimum sanctum L.[47]
- Family- Lamiaceae
- Chemical Constituents- 70% Eugenol, Caryophylline,Volatile oil, essential oil .
- Parts- Leaves
- Uses-

1) Tulsi leaves possessed antifungal activity against clinically isolated dermatophyt at the concentration of 0.2mg/ ml.
2)Almost all ocimum species produced an essential oil that has antifungal property.Tulsi leaves have been proven to have strong antifungal effect against Aspergillus species [48]
3) In vitro antifungal activity against Candidia species.

3) Ginger

- Biological Source- It consist of dried rhizomes are Zingeber Officinale.
- Family- Zingiberaceae
- Chemical Constituents- Gingerol, Volatile oil, caprylic acid.
- Parts- Rhizome
- Uses-

1) It has good antigungal properties and antibiofilm formation by fungi against C.albicans and C.krusei.
2) Adding ginger in the tea helps to prevent and treat like candidia albicans.
3) Ginger contain compound caprylic acid,which has potent antifungal activity .
4) Ginger extract has good antifungal activity .

5) It Contains compound with antifungal properties and may help to support respiratory health and reducing inflammation, improving immune response.
6) It shows antifungal activity against Histoplasma Capsulatum,Coccidioides and Cryptococcus Neoformans Species.

4) Turmeric

- Biological Source- It consist of dried as well as fresh rhizomes of curcuma longa.
- Family- Zingeberaceae.
- Chemical Constituents- zingeberene,5%volatile oil,Curcumin.
- Parts- Rhizome
- Uses-

1) It perform powerful antifungal activity.
2) the antifungal effect included fungal cell membrane disruption and inhibition.
3) Curcumin in turmeric exhibits antifungal activity against Aspergillus species, reducing inflammation and oxidative stress.
4) It Contains curcumin, which has antifungal and anti-inflammatory properties.It Can be used topically or ingested.
5) Curcumin in turmeric exhibits antifungal activity against Histoplasma capsulatum,Coccidioides immitis,Cryptococcus Neoformans Species.

5) Neem

- Biological Source- It consist of leaves and other aerial part of Azadirachta indica.
- Family- Meliaceae.
- Chemical Constituents- Nimbin,Nimbidine,Nimbosterol,Quercetin, Azadirachtin.
- Parts-Leaves.
- Uses-

1)Neem oil ,nimbin,nimbidine are active against fungi.
2) It has strong antifungal activity and extremely good for the skin.The infected area is washed with neem water to treat fungal infection.
3) Neem leaves can kill fungal pathogens including aspergillus and candidia albicans.
4) Azadirachitim in neem exhibits antifungal activity against candida species,Aspergillus,Trichophytons,Microsporum and Epidermophytons,Histoplasma Capsulatum,Coccidioides Immities,Cryptococcus Neoformans Species.

6) Aloevera.

- Biological Source- It consist of juice of leaves of Aloe Barbadensis Miller .
- Family- Liliaceae
- Chemical Constituents- Barbaloin,Aloe emobin.
- Parts- Leaves.
- Uses-

1) It act as an antifungal and to cure any skin infection.
2) It harbors powerful properties to get your candidia under control and stimulate your immune system.

7) Clove

- Biological Source- It consist of dried flower buds of Eugenia Caryophyllus.
- Family- Myrtaceae
- Chemical Constituents- Eugenol.

- Parts-buds.
- Uses-
  1) Clove bud oil possess strong antifungal activity against opportunistic fugal pathogens such as candida albicans .Cryptococcus Neoforman and Aspergillus Famigatus.
  2) The ingredients responsible for its antifungal activity is eugenol .

8) Tea Tree Oil

- Biological source-It is derived form leaves of the tea tree Melaleuca alternifolia
- Family-myrtaceae
- Chemical Constituents- Monoterpenes-Terpinen-4-ol,terpenoline,alpha-pinene,1,8-cineole.
- Parts- Leaves.
- Uses-
  1) It Exhibits antifungal activity against Trichophyton, Microsporum, and Epidermophyton species. It effective for topical treatment of dermatophyte infections.
  2) Apply diluted oil directly to the affected area.
  3) It Has antifungal properties and can be used topically for skin infections.Dilute it before applying to avoid irritation.

ADVANTAGES OF HERBAL AGENT

1) Minimum development of resistance:

Some proponents of herbal medicines argue that the likelihood of developing resistance to herbal medicines may be lower compared to synthetic antifungals. This is because plant compounds often have a complex composition, which can make it difficult for fungi to develop resistance [49]

2) Possible combination with conventional treatment methods:

Some people may choose to use herbal remedies along with conventional treatments for yeast infections. However, it is important to communicate with health professionals to ensure that there are no interactions or contraindications [50]

3) Ease of joining a daily routine:

Many herbal products are easy to incorporate into your daily skin care routine. Ointments, oils and creams can be applied directly to affected areas, making them convenient for regular use .

4) Availability in different formats:

Antifungal herbs are available in various forms such as lotions, creams, essential oils, teas and supplements. This option allows people to choose the shape that best suits their preferences and skin type [51].

5) Cultural and traditional use:

Herbal medications have frequently been used in different societies and traditional drug to treat skin conditions. The accumulated knowledge and experience passed down through generations increases the popularity of herbal treatments for skin problems [52]

MARKETED PREPARATION

1) FUNGON ANTIFUNGAL CREAM

Fungon is used as an Ayurvedic antifungal cream for ringworm and skin infections. It is an natural antifungal cream that can treat various types of fungal infections that help to inhibit the growth of microorganisms. It has anti-oxidant properties that heal skin cells. It nourishes the skin and prevents it from getting dry, like moisturizer. Ingredients in it like Shuddha,Gandhak are antiallergic and promote natural skin health. Neem stop the mycelial growth of the fungi. Aloe vera prevents itching and redness.

2) FUNGICID GEL

Fungicid gel is an Ayurvedic product used to treat a variety of skin conditions including ringworm, jock itch, athlete's foot, and other fungal skin infections.Fungicidal gel is derived from a blend of natural herbs, including vitamin E, neem oil, kapoor oil, jaiphal oil, spearmint and pine oil. It is the best gel or cream for fungal infections and is used to treat a variety of fungal infections on the skin.

3) CASSIDY ANTIFUNGAL CREAM

CASSIDY is used as an Ayurvedic antifungal cream for various fungal skin infections. Cassidy cream contains ingredients like aloe vera and tea tree extract to combat the fungal infection effectively. It also contains clove oil which exposed a strong activity against topical skin infection.

4) HIMALAYA AACTARIL SOAP

Himalaya Aactaril Soap is treated as a sanctification cleaner for bacterial and fungal skin infections. It contains barbari (Ocimum basilicum), neem (Azadiachta indica), ushira (Vetiveria zizanioides), bomb (Citrus limon)and karanja (Pongamia glabra). These detergents play an important part in the treatment of skin infections. Aactaril is a treated cleaner designed for the effective operation of common superficial bacterial and fungal infections of the skin.

5) HERBAL TOOTH PASTE

The Neem toothpaste contains natural extrat of neem ,clove and babul which provide strong antibacterial and antifungal propertie .athis help to control of plaque and tarter build up, there by making the gum and teeth healthy and strong ,Thus reducing the incidence of cavity and tooth decay.It contains Neem,Babool,Clove Oil,Haldi,Pilu,Menthol Crystal.

6) SHAMPOO

Ketoconazole Shampoo is an antifungal medicine used to treat fungal infections of the skin. It works by killing the fungus that causes the infections. It kills fungi by destroying the fungal cell membrane. Ketoconazole , Aloe Vera and ZPTO which treat dandruff. Ketoconazole is an antifungal which stops the growth of dandruff-causing fungi by preventing them from forming their own protective covering Aloevera works as conditioner.

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