



COVID-19 ASSOCIATED MUCORMYCOSIS AND CANDIDIASIS IN INDIA AND HERBAL MEDICINE TREATMENT FOR FUNGAL INFECTIONS: A REVIEW

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ABSTRACT:

The coronavirus disease (COVID -19) has become one of the most threatening diseases of the world. COVID-19 is a respiratory tract infection caused by novel SARS-CoV-2 strain. The second wave of this pandemic emerged as challenges and concerns to India, because of Coronavirus disease associated fungal infections mucormycosis and candidiasis. Mucormycosis, otherwise called as black fungus is a emerging deadly infection caused by a group of fungi known as mucormycetes which is commonly present in the environment particularly in soils and in association with decaying organic matter. Candidiasis or white fungus disease is caused by *Candida albicans*. These fungi infects mainly immunocompromised people, since they are affected the diseases like diabetes mellitus and human immunodeficiency virus infection (HIV). Opportunistic fungal pathogens infects COVID patients, the reason is coronavirus disease managed by steroids. The current scenario in India mucormycosis cases are reported in 18 states and candidiasis reported in 2 states. Currently the treatment for black fungus and white fungus is by using drugs amphotericin and triazoles etc. In this study discuss about the scenario of black and white fungal infections in India and natural low-cost herbal plants as medicines for the management of associated fungal co-infections. Medicinal plants are a good source for antifungal properties, therapeutic value, and cost effective and broad-spectrum antifungal agents.

Keywords: SARS-CoV-2, *Candida albicans*, Mucormycosis, COVID-19 patients, Medicinal plants.

INTRODUCTION:

Coronavirus disease 2019 has become one of the most threatening diseases of the world. COVID-19 is a respiratory tract infection caused by SARS-CoV-2. Corona virus disease was first reported on 31st December, 2019 in the Hubei province at Wuhan Health commission of the Republic of China^[1]. This disease has spread over 72 countries in three months and it was declared as a pandemic disease by World Health Organization (WHO) on 11th March 2020^[2]. Coronavirus is an enveloped positive single standard RNA virus which causes infection in humans. The genome size of the coronavirus varies between 26 kb and 32 kb. SARS-CoV belongs to the beta-coronavirus which is closely related to SARS-CoV-2 and the four subfamilies such as alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus^[3].

The rapid increase in the second wave of COVID-19, several cases of rare fungal infections are being noted in many COVID-19 patients. These fungal infections include black fungus and white fungus which are being detected in Covid patients, and people who are diabetic, have kidney or heart problems, lung transplanted or people who are suffering from cancer or HIV, or are on high steroids^[4]. The main reason for the Covid patients being affected with these fungal infections are the use of steroids for treating their viral infection. In Covid patients, these steroids reduce inflammation in the lungs and help stop the damage in the immune system. But, the use of steroids leads to an increase in the blood sugar level and also reduces the immunity of the patients, thus leading to black fungus and white fungus infections^[5].

MUCORMYCOSIS:

Mucormycosis, otherwise known as black fungus is a deadly infection caused by a group of fungi known as mucormycetes which is commonly present in the environment particularly in soils and in association with decaying organic matter such as leaves, compost piles, and animal dung [6]. These fungi belong to the order Mucorales and the major infections are usually caused by the species of *Rhizopus*. The other types include *Mucor*, *Lichtheimia*, *Rhizomucor*, *Apophysomyces*, *Cunninghamella*, *Saksenaea*, and *Syncephalastrum* [7,8]. They have a wide range of tolerance of temperatures which are found in the psychrophyles and the thermophyles with a maximum growth temperature of 54°C -58°C [9]. Mucormycosis is an aggressive disease that can also affect immunocompromised patients, especially in people with immune or metabolic deficiency which includes people with diabetes mellitus, haematological malignancies and haematopietic stem cell transplant. Rhinocerebral and pulmonary infections of mucormycosis are caused by inhalation of spores whereas cutaneous infections are caused by the spores which enter through skin. Gastrointestinal mucormycosis can be caused by contaminated foods infecting the gastrointestinal tract [10].

CANDIDIASIS:

Candida albicans is one of the most common yeast pathogen. It is a dimorphic fungus grown at 30°C and its hyphae is formed at 37°C. It is commercial in humans and inhabits a broad range of warm-blooded animals [11]. It is a common member of human gut and it also survives in the outer surface of the body. The invasive rate of candidiasis has increased over the past. The patients at risk for candidemia are the ones who are immunocompromised because of the diseases like human immunodeficiency virus infection, malignancy, hematologic disorders, and bone marrow transplantation [12]. The three major forms of diseases are oropharyngeal candidiasis, vulvovaginal candidiasis, and invasive candidiasis, over 75% of women will suffer from *C. albicans* infection (vulvovaginal candidiasis) in their lifetimes and 40-50% of them will have additional occurrences. *C. albicans* are the 4th leading cause for nosocomial infection in the patients' bloodstream. This could result in an extremely life-threatening, systemic infection in the hospital patients with a mortality rate of 30% [13]. The HIV-positive patients will carry more variety of yeasts than the HIV-negative patients. The prolonged management of oral candidiasis in HIV patients might cause the development of drug resistance candidiasis. The introduction of antiretroviral therapy has had a major impact on the infectious complications of AIDS [14].

The number of mucormycosis cases discovered in Delhi, Maharashtra and Gujarat, these were mostly known to be detected among Covid-19 patients relatively affecting the skin, the lungs and the brain. Rhinocerebral mucormycosis which starts in the sinuses and can spread to the brain is the most common type of mucormycosis infection present among Covid-19 patients. According to the CDC, mortality rate of this particular infection is 46 percent whereas that which spreads through blood streams to other parts of the body has a mortality rate of 96 percent [15].

Candidiasis recently reports the increase of fungal coinfections during COVID-19 treatment, with the incomplete understanding of the pathogenesis and without any causative therapy; the secondary infections may be detrimental to the prognosis. The monitored COVID-19 patients with ARDS in their immune phenotype and plasma cytokines were observed and the clinical parameters noted on the day of ICU admission and on 4th and 7th day of their ICU shows very serious infection [16]. *Candida* isolates were identified by using Germ tube test, CHROM agar *Candida* and API *Candida* yeast identification system [17].

Medicinal plants act as a good source of drugs for different types of diseases and the knowledge about the medicinal plants were transferred to the next generation [1]. They are a valuable natural resource which acts as potential safe drugs and it can also cure all kinds of microbial infections [18]. In India there are many medicinal plants, but most of the population are still not aware of their medicinal values [19].

MODE OF TRANSMISSION:

MUCORMYCOSIS:

Mucor mycosis is an angioinvasive infection that is either caused by the inhalation of fungal sporangiospores released in the air or by the direct penetration of the organism into the skin or mucosa. The two main types of infections of mucormycosis depend on the route of exposure. Inhalation of fungal spores are usually seen in the pulmonary or sinus form which could lead to the development of infection in the lungs, sinuses, eyes, face and sometimes it may spread to the central nervous system. Spores can enter the body through respiratory tract, injured skin, ingestion of contaminated food or by percutaneous route i.e., through contaminated needles or catheters. Direct inoculations of fungus into the skin through cuts, puncture wounds or other forms of trauma to the skin are often noted in the cutaneous form [20]. The following angioinvasion by hyphae is the result of a specific interaction with the endothelial cells. This could lead to the systemic dissemination of the disease [21]. One of the clinical features of invasive mucormycosis is tissue necrosis which is caused by angioinvasion and thrombosis. There are high chances for the infection to get severe which may even lead to death. This could be partially prevented by correcting the risk factors and offering treatments with antifungal agents and surgical excision. Mucormycosis is not a contagious disease and thus does not spread from person to person [22-24].

CANDIDIASIS:

It is usually transmitted from mother to infant through childbirth, and remains as a part of normal human's microflora. The overgrowth of *Candida albicans* can lead to symptoms of disease and it occurs when there are imbalances – changes in the normal acidity of the vagina. The infections from *Candida albicans* very rarely spread through sexual intercourse. The typical reservoir of *Candida albicans* is in the normal human microflora, and is not found in animal vectors. People-to-people acquired infections mostly occur in hospital settings where immunocompromised patients acquire the yeast from healthcare workers [25].

There is no exact known infectious dose for *Candida albicans*, this is mostly due to the infection from the commensal population of *Candida albicans* in the human microflora. Candidiasis is caused by the abnormal growth of *Candida albicans*, which is usually due to an imbalance in the environment. Usually, this imbalance occurs in a woman's vagina – this infection is less likely to occur for men. The use of antibiotic can decrease the amount of Lactobacillus bacteria, which decreases the number of acidic products and pH of the vagina. Other conditions are complications in pregnancy, uncontrolled diabetes, impaired immune system, and irritation of the vagina. *Candida albicans* are able to take advantage of these conditions and outcompete the normal microflora, resulting in candidiasis or a yeast infection [26].

SYMPTOMS:**MUCORMYCOSIS:**

Symptoms such as fever, cough, chest pain and shortness of breath occurs during pulmonary (lung) mucormycosis. Headache, fever, swelling at one-side of the face and nasal or sinus congestion occurs during rhinocerebral (sinus and brain) mucormycosis. In gastrointestinal mucormycosis symptoms are abdominal pain, nausea, vomiting and gastrointestinal bleeding and visual problems occurs during vision mucormycosis [27].

CANDIDIASIS:

Symptoms such as redness in mouth, painful sensation, white spots and loss of taste occur when candidiasis infects mouth. Itching, irritation and pain in vagina causes vaginal candidiasis. Symptoms for urinary tract causes candidiasis infection such as increased need to urinate, pain, and burning sensation in [28].

DIAGNOSIS:**MUCORMYCOSIS:**

The diagnostic methods of mucormycosis are usually difficult to work on. Researchers prefer to find new methods for early diagnosis of mucormycosis as it could help to bring down the mortality rate. There are several steps and procedures to identify mucor mycosis or black fungus in living hosts. Mucorales mostly grow on bacterial and fungal culture medias, eg: chocolate agar, Sabouraud dextrose agar etc [29]. Laboratory and imaging tests are often performed to confirm the presence of mucormycosis. The studies on computerized tomography (CT) scan revealed the identification of reverse halo sign (RHS). It was identified that the presence of RHS on CT scan indicated the presence of pulmonary mucormycosis [30]. Another imaging technique for the diagnosis of mucormycosis is the positron emission tomography - computed tomography (PET/CT) with fluorodeoxyglucose (FDG) [31].

Samples are often collected from the respiratory system of suspected patients and are tested by histology, microbiology and advanced molecular method [32]. Histological diagnosis of mucormycosis normally occurs through observing the structure of hyphae that could invade the blood vessels. Non septate or minimally septated broad, ribbon like hyphae is observed which are further sent for microscopic examination in order to study their morphology. Another important method is biopsy which could be performed either directly or endoscopically. The most common anatomic location for performing biopsy is the paranasal sinuses [33,34]. Infarctions in the nearby tissues with angioinvasions are seen. Neutrophilic or granulomatous inflammation can also be observed which could be absent in some cases of immunocompromised patients [35,36].

Microscopical diagnosis includes direct microscopy which uses optical brighteners for the rapid presumptive diagnosis of the disease [37]. Some of the techniques included in direct microscopy are treatment with 20% of potassium hydroxide, Gomori's methenamine silver staining, haematoxylin and eosin staining, and periodic acid- Schiff staining. These staining techniques are used to clearly observe the detailed structure of hyphae and thus concluding its morphology [35,38,39]. The cultured specimens help in the identification and the susceptibility testing but the sensitivity of cultures may not be optimal, ie, not all positive cultures would be microscopically positive. These could be because of the fragile nonseptated growth of fungi that leads to its own damage during sample manipulation [39,40].

Molecular diagnostic methods commonly used for the detection of mucormycosis are conventional polymerase chain reaction (PCR), melt curve analysis of PCR products, restriction fragment length polymorphism analysis (RFLP), and DNA sequencing of the defined gene regions [41]. The internal transcribed spacer or the 18S rDNA genes are the loci that are commonly targeted by most of the molecular methods. Such studies are performed either on formalin fixed paraffin embedded tissue specimens or fresh tissue samples. This helped in the identification of mucorales at species level [42-44]. One of the non-invasive methods for the early diagnosis of mucormycosis is the real-time qPCR in blood samples [45]. On the other hand, patients with hematological malignancies and severely burned patients could undergo the serum/plasma mucorales q PCR [46-48]. Another method for detection is the probe-based mucorales-specific real-time qPCR which helps to identify DNA from a broad range of species [49]. Earlier the most frequently used serological methods for diagnosing mucormycosis were enzyme linked immunosorbent assays (ELISA),

immunoblots, and immunodiffusion tests. Recently, enzyme linked immunospot assay (ELISpot) is used to detect mucorales specific T cells in suspected patients. Further studies on serological diagnosis of the disease are still on process ^[50].

CANDIDIASIS:

The laboratory diagnosis of candidiasis involves direct identification, isolation of *Candida* species and culture identification ^[51]. The direct examination of clinical sample is done by preparing wet mount. The KOH facilitates the demonstration of fungal specimen; the percentage of KOH varies from 10 – 40% depending on the specimen. It digests the proteinaceous debris in the specimens and it makes the visibility of fungal elements clear. The direct microscopic examination is cost effective and is a rapid method for diagnosis of candida infection ^[52].

Candida species is a non-fastidious organism that can be diagnosed by culturing method in laboratory medium such as Sabouraud dextrose agar used for the isolation of fungus. It is the most frequently used media for primary isolation of *Candida* species ^[53]. *Candida* species produce creamy smooth paste like convex colonies on Sabouraud dextrose agar ^[54]. Culture media can be incubated at 28°C or 37°C for 24 to 72 hours. The chromogenic medias like CHROM agar, *Candida* medium, *Candida* ID medium and CandiSelect™ 4 medium are used for rapid identification of *Candida* ^[55].

Germ tube test formation was first reported by Reynolds and Braude which is also known as Reynolds and Braude Phenomenon. This test is a rapid method for identification of *Candida* species such as *Candida albicans* and *Candida dubliniensis* with its short, slender, tube like structures called germ tube when it is incubated in serum at 3°C for 2 hours. The time required to prepare human serum and inherent safety problems are concerned.

Many clinical microbiological laboratories are started using non-human serum media for the germ tube test; trypticase soy broth is found to be more stable, effective and safe than other media for the germ tube test. This test result is helpful to differentiate between germ tube and pseudohyphae ^[56].

OUTBREAK OF FUNGAL CO-INFECTION:

In India white fungus and black fungus co-infection infect the COVID-19 immunocompromised patients. Black fungus infects nearly 18 states in India, in Maharashtra 2007 cases were reported (Table 1).

Table 1: Outbreak of Coronavirus associated fungal Infections in India

SI.NO	STATES NAMES	NO. OF. CASES	REFERENCE NUMBER
MUCORMYCOSIS			
1.	Maharashtra	2007	57-59
2.	Rajasthan	1800	60
3.	Gujarat	1224	61
4.	Madhya Pradesh	1044	62
5.	Haryana	756	63
6.	Delhi	498	64
7.	Andhra Pradesh	200	65
8.	Tamil Nadu	181	66
9.	Uttar Pradesh	169	61
10.	Punjab	158	67
11.	Bihar	103	61
12.	Chhattisgarh	101	61
13.	Telangana	100	61
14.	Kerala	44	68
15.	Karnataka	40	69-73
16.	Jammu and Kashmir	10	74
17.	Puducherry	10	75
18.	Odisha	5	76
CANDIDIASIS			
19.	Uttar Pradesh	7	77
20.	Bihar	4	78

TREATMENT:

A herb is plant or part of a plant that has several properties. Some have the properties of pharmaceutical drugs. This has been under use from the past to cure illness. Medicinal plants widely used in traditional medicine practices. The medicinal plants are also used as food, flavonoid, medicine or perfume and also in certain spiritual activities. According to WHO, around 21,000 plants species are considered to be herbal. There is no side effect and it is safe to use medical plants for treatment. Plants which are being widely used are aloe, tulsi, neem, turmeric and ginger. Some are rich source of nutrition and most importantly have therapeutic values. [79].

SI.NO	HERBAL PLANTS NAME	DISEASES & PATHOGENS	REFERENCE NUMBER
1.	Allium sativum	Candidiasis (Oral infection)	80
2.	Tulbaghia voilacea		
3.	Polygala myrtifolia		
4.	Glycyrrhiza glabra		
5.	Combretum mole (root)	Candidiasis	81
6.	Piper Capense (bark)		
7.	Solanum aculeastrum (fruits)		
8.	Syzygium cordatum (bark)		
9.	Zanthoxylum davyi (bark)	Candidiasis	82
10.	Mentha pioerita		
11.	Rosmarinus officinalis		
12.	Arrabidaea chica		
13.	Tabebuia avellaneda		
14.	Punica granatum	Rhizopus oryzae	83
15.	Syzygium cumini		
16.	Thymus vulgari (leaf)	Mucormycosis	84
17.	Ferula assafoetida	Rhizopus	85
18.	Lycopus europaeus		
19.	Melissa Officinalis		
20.	Origanum vulgare	Rhizopus oryzae	86
21.	Cymbopogon citratus		
22.	Azadirachta indica		
23.	Ocimum gratissimum	Rhizopus oryzae	87
24.	Piper nigrum (seed)		
25.	Piper nigrum (leaf)		
26.	Aframomum meleguata (seed)		
27.	Ageratum conyzoides (leaf)	Mucor sp.	88
28.	Satureja khuzestanica (leaf)		
29.	Aloe ferox	Mucor hiemalis	89
30.	Salix Capensis		
31.	Schotia latifolia		
32.	Prunus persica		

Table 2: List of medicinal plants with antifungal activity

PREVENTION OF FUNGAL CO-INFECTIONS:**MUCORMYCOSIS:**

Prevention is the most effective treatment, much more than eradication of the fungal infection with antifungal agents. Mucormycosis is caused by the inhalation of the fungal spores which are present in the environment. The first preventive measure to be taken is to protect ourselves from the environment^[90,91].

- Avoid areas with lot of dust.
- Make a habit of using mask.
- Avoid direct contact with water damaged buildings.
- Wearing of shoes, long pants, long sleeved shirt and gloves helps to avoid direct contact with soil or dust.
- Skin injuries should be cleaned well with soap and water especially if they have been in direct contact with soil or dust^[92].

CANDIDIASIS:

Candida yeasts are commonly a part of the human body's oral and intestinal flora and are mostly present on the skin. A healthy balance of the oral and intestinal flora is maintained by a healthy diet^[93,94].

- Wearing cotton underwears would be preferable as it helps in avoiding skin and vaginal infections.
- Do not wear wet clothes for long period of time^[95].
- Personal and oral hygiene should be maintained^[96].
- People with dentures should disinfect their dentures regularly.
- Avoid hot tubs and extra hot baths^[97].

CONCLUSION:

Coronavirus disease COVID-19 is an aggressive disease which is caused by a newly discovered strain of coronavirus. Most people who fall sick with COVID-19 are recently being affected with some rare fungal infections which include white fungus and black fungus which are caused by *Candida albicans* and *Mucormycetes* respectively. In recent years, there are numerous new options for the treatment of these fungal infections. One such option is the use of herbal medicines which are considered to be a good source of medicine for all kind of infections. Accordingly, when comparing the herbal plants with the pharmaceutical drugs, herbal plants are considered to be more beneficial, easily available and have no side effects. Thus, different kinds of herbs could be used for the treatment such fungi.

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