Review Article

Black Fungus-Fungi in Chinese Cuisine and Deadly Triggered for India

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ABSTRACT

Data on therapeutically important black yeasts and their cousins, namely members of the Ascomycete order Chaetothyriales, are presented. The black fungus is a rare but deadly fungal infection known as mucormycosis. Mucormycosis is a fungal ailment caused by a group of moulds known as mucormycetes. Systemic glucocorticoids are being used to treat severe coronavirus illness (COVID-19). In such patients, opportunistic fungal infections are a worry. Depending on the patient's underlying condition and kind of mucormycosis, mortality rates can reach 100%. A satisfactory outcome requires early identification, treatment of the underlying medical issue, surgery, and the use of an amphotericin B product. Black fungus is a homologous fungus of medicinal and food at the same time. Its nutritional content defines its health value, and alternative materials can easily impact nutritional build-up. According to new research, black fungus provides a number of health benefits, including liver protection, cholesterol reduction, and improved gut health. It is also high in fibre and antioxidants. Despite the fact that this fungus has been used in traditional Chinese medicine, more research is needed to determine its efficacy. Furthermore, melanin, which can act as an antioxidant, has been discovered in black fungus.
INTRODUCTION:
Black yeasts have been recognized since the end of the nineteenth century, but they remain one of the most difficult fungal groups to detect, therefore knowledge on this group is still limited. The allocation of black yeast species to major groupings in the fungal kingdom has been made possible by molecular phylogeny. The constant relationship of human pathogenic taxa (black yeasts and their filamentous equivalents) to a tiny, well delineated group, the order Chaetothyriales, and the family Herpotrichiellaceae in particular, has been one of the most intriguing recent discoveries. This family is phylogenetically distinct from the other bitunicate ascomycetes. It has been proposed that the fungus went through a fast diversification process, most likely after entering a new substratum. It's tempting to think this substratum is the human body. [1]

Due to its dark, ear-like form, black fungus (Auricularia polytricha) is also known as tree ear fungus or cloud ear fungus. It flourishes in tropical conditions such as the Pacific Islands, Nigeria, Hawaii, and India, and is mostly found in China. It grows naturally on tree trunks and fallen logs, although it may also be grown. [2] The black fungus is an uncommon but devastating fungal infection known as mucormycosis, which is caused by a group of molds known as mucormycetes [Figure 1], [3] occur in the environment and have been discovered unusually often among COVID-19 patients in several Indian states. The condition frequently presents in the skin, but it may also damage the lungs and the brain. [4]

Mucormycosis, formerly known as zygomycosis, is a fungal infection caused by a variety of fungi from the fungus family "Mucorales." Fungi of this family are often found in the environment, such as soil, and are frequently connected with decaying organic matter such as fruit and vegetables [Figure 2]. Rhizopus oryzae is the member of this family most commonly responsible for human infections. However, another family member known as Apophysomyces, which is prevalent in tropical and subtropical climates, is also abundant in India. [5, 6] These Black fungi grow quickly in the lab and have a black-brown fuzzy look. Those that cause human disease to thrive at body temperature and in acidic settings, such as those seen in tissue that is dead, dying, or linked with uncontrolled diabetes. The verdict of this review paper is to provide an update on the epidemiology and diagnostic procedures for black fungus, a life-threatening malady.

HOWEVER WHAT CAUSES MUCORMYCOSIS?
Mucormycosis is the third most prevalent invasive fungal infection, after aspergillosis and candidiasis. [7] Mucorales fungi are opportunistic [Figure 3], which means they frequently infect humans who have a compromised immune system or damaged tissue. Immune function can be harmed by medicines that suppress the immune system, such as corticosteroids, as well as a variety of other immunocompromising illnesses, such as cancer or transplantation. Tissue damage can develop as a result of trauma or surgery. [8] Inhaling spores, eating spores in food or medications, or having spores infect wounds are the three ways humans might get mucormycosis. [9] The most prevalent method is inhalation. Every day, we inhale the spores of a variety of fungus. However, if our immune systems and lungs are in good shape, they are unlikely to cause an infection. According to scientists from the COVID-19 research team, it also affects people who are taking medicine for health concerns that impairs their capacity to resist environmental germs. After inhaling fungal spores from the air, these people's sinuses and lungs get infected. In several locations, Doctors have seen an increase in occurrences of mucormycosis among persons hospitalized or recuperating from COVID-19, with some requiring emergency surgery. Mucormycetes does not usually offer a significant hazard to those who have a good immune system. [10, 11] A study of over 900 recorded human cases of mucormycosis was conducted, Roden and colleagues discovered that fungus classified under the genera Rhizopus (47%), Mucor (18%), Cunninghamamella (7%), Apophysomyces (5%), Absidia species (5%), Saksenaea species (5%), Rhizomucorpusillus (4%), and other Mucorales genera produced the bulk of human mucormycosis cases, accounting for fewer than 3% of culture verified cases. [12]
Mucormycosis has a wide range of clinical manifestations, depending on the host's underlying immunosuppression. Although there is considerable overlap, the clinical presentation may be divided into six syndromes based on anatomic predilection: rhinocerebral infections, pulmonary, cutaneous, gastrointestinal, disseminated infections, and unusual mucormycosis presentations. A severe occurrence known as a "cytokine storm" can develop when the immune system goes into overdrive due to coronavirus and other diseases, causing organ damage. According to recent research, mucormycosis, or black fungus, is a notifiable illness that has been found in more than 8,848 cases in India. As a result, India is now dealing with a double burden, with one pandemic snuggled inside the other. Tragically, the black fungus outbreaks were sparked by the abuse of immunosuppressants and steroids. Black fungus has a 54% mortality rate and affects people with weakened immune systems. These could be diabetics, cancer patients, or people living with AIDS or HIV. Patients who have been on steroids for a long time, who have been hospitalized for a long time, who have been on oxygen support or ventilator, who have had poor hospital sanitation, or who have been on medicine for other disorders such as diabetes are all susceptible to the fungal condition. Steroids raise blood sugar levels in diabetics and non-diabetics alike. Long-term use of humidified oxygen can also cause the fungal infection. The black fungus infection might be lethal if not treated promptly.

**MODE OF TRANSMISSION AND DIAGNOSE**

In immunocompromised patients, these fungi can colonize a variety of tissues, but they most commonly infect the skin, sinuses, and lungs. Apart from the recognized reasons of steroid usage and diabetes, recent clinical investigations speculated that the use of excessive amounts of zinc and iron supplements might be one of the motives behind the black fungus infections in India. Mucormycosis is an uncommon illness, despite the fact that India has an infection incidence that is almost 80 times higher than the worldwide norm. The increased abundance of the fungal species mucormycetes, which are naturally abundant in the environment, is assumed to be the reason of the disease's prevalence. The species grows in the soil, mainly near rotting debris and animal manure. Although most people are exposed to the agents that cause mucormycosis on a regular basis, infections in healthy people are uncommon. Inhalation is the most common way to be exposed to spores from the environment, but they can also infect the skin through an injured area or the gastrointestinal tract if consumed. Respiratory mucormycosis primarily affects immunocompromised people, such as cancer patients or transplant recipients. Asexual spore formation causes mucormycosis infection. The microscopic spores become airborne and land on human oral and nasal mucosa. A phagocytic reaction will restrict these spores in the majority of immunologically competent hosts. If this reaction fails, germination and the formation of hyphae will occur. In immunocompromised patients, polymorphonuclear leukocytes are less successful in eliminating hyphae, and the infection gets entrenched. As the hyphae penetrate the arteries, they multiply inside the walls and lumens, causing thrombosis, ischemia, and infarction, as well as dry gangrene of the affected tissues. Hematogenous spread to other organs might cause sepsis (lung, brain, and so on). After the spores are ingested, the fungus proliferates by extending hyphae into the host's tissues. Upper and lower respiratory tract infections are possible. Mucormycosis is a fungal infection of the sinuses and brain that produces headaches, fever, facial edema, congestion, and tissue necrosis in the oral cavity, which results in black lesions. The symptoms of pulmonary mucormycosis, a lung infection, include fever, cough, chest discomfort, and shortness of breath. Infections can spread throughout the body and harm the central nervous system, leading to coma and death in extreme cases. Mucormycosis can be difficult to diagnose. There are currently no serological or PCR-based tests that can be used to detect these infections. The presence of fungal pathogens in tissue biopsy specimens must be checked. However, the causative agents are frequently confused with other filamentous fungi. Restriction fragment length polymorphism analyses (RFLP), traditional polymerase chain reaction (PCR), melt curve analysis of PCR products, and DNA
sequencing of specific gene areas are some of the molecular tests that may be used to determine the presence of Mucorales (pathogen responsible for black fungus disease). These tests are rarely routinely performed since a microscopic inspection is generally sufficient.

For direct microscopic identification of Mucorales, a variety of procedures (e.g., treatment with 20% potassium hydroxide, grocott-gomori’s methenamine silver staining (GMS), haematoxylin and eosin staining, periodic acid-Schiff staining) can be utilized. Mucorales have traditionally been described as having wide (10-50 µm), ribbon-like aseptate hyphae with right-angle branching on microscopy, however the hyphae are really pauciseptate, and the angle of hyphal branching can vary from 45 to 90°. Angioinvasion with surrounding tissue infarction is frequently seen histopathologically. Black fungus can also be detected using routine tests such as an outpatient endoscopic examination of the nose, which involves taking nasal scrapings, a biopsy to confirm the kind of fungus, and a contrast gadolinium-enhanced MRI (Magnetic resonance imaging).

Disseminated black fungus is difficult to diagnose since patients are generally sick with many illnesses and have almost invariably negative blood cultures. The diagnosis of mucormycosis should be explored if there is evidence of infarction in numerous organs. When disseminated mucormycosis is suspected, however, a thorough search for cutaneous lesions that may be biopsied for diagnostic purposes should be conducted.

**ZINC USE LINKED TO BLACK FUNGUS**

Zinc is hypothesized to concentrate iron in the body, allowing mucormycosis, a perilous but uncommon fungal illness caused by a group of molds known as mucormycetes, to thrive. In a human organism, mucor development depends on several host variables.

Mucor patients were less last year since there were less COVID’s. Whereas COVID is high in this year, COVID's virulence is increased, and steroids are employed indiscriminately, thus various elements play a part in black fungal propagation. Mucormycosis, on the other hand, has been present in India for decades. The most prevalent type of mucormycosis is rhino-orbito-cerebral mucormycosis, which has been around for decades. However, it used to only occur in immunocompromised people such as diabetics, cancer patients, transplant recipients, and so on. Due to COVID, it has reached the masses. The country has recorded 11,717 cases of black fungus to date with Gujarat, Maharashtra, Andhra Pradesh, Madhya Pradesh, Telangana and Delhi reporting the highest number of cases. As of now, there was no direct link between zinc and mucormycosis.

However, until approximately a year ago, mucormycosis was an extremely rare condition. There were other theories, such as increasing steam inhalation causing mucormycosis or persons taking high zinc supplements being one of the causes of the increasing prevalence. That is how there is a correlation currently that there may be a relation between excessive zinc consumption and mucormycosis, but further research is needed to corroborate it.

Fungi flourish in zinc-rich environments, whereas mammalian cells strive to keep zinc away from fungus to avoid infection, raising the potential of zinc being a role. Fungi feed on zinc, whereas mammalian cells strive to avoid fungal invasion by concealing zinc, thus starving the fungus. Nutritional immunity is the term for these antifungal defense mechanisms. During the pandemic, the unexpected development of significant cases of mucormycosis warrants a broad investigation for relevant variables. Zinc supplements and their impact in this fungal condition must be investigated further.

**ROLE OF IRON IN MUCORMYCOSIS (BLACK FUNGUS)**

Increased blood iron is a risk factor for mucormycosis, as iron is important in the infection's etiology. The Mucorales fungus do not have access to iron since it is generally bound to transferrin and ferritin. The ability of these proteins to bind iron is reduced in individuals with diabetic ketoacidosis or other kinds of acidosis. Patients with greater accessible serum iron are more susceptible to mucormycosis, according to a newly discovered clinical characteristic. For more than two decades, researchers have known that patients using the iron chelator deferoxamine have a significantly higher risk of invasive mucormycosis. Furthermore, it is now evident that deferoxamine does not promote mucormycosis infections by iron...
chelation. While deferoxamine acts as an iron chelator in the human host, mucormycosis uses deferoxamine as a siderophore to deliver previously inaccessible iron to the fungus as a xenosiderophore for acquiring iron from the host. On the other hand, deferasirox and deferiprone have no xenosiderophore activity. In liver transplant patients, iron excess has also been associated with an increased incidence of disseminated mucormycosis. Mucormycosis, on the other hand, is a dangerous infection that can develop in diabetic ketoacidosis patients.

**PREDISPOSING FACTOR**

According to the US Centers for Disease Control and Prevention, mucormycosis, also known as "black fungus," is caused by a mould found in soil and decaying organic matter such as rotting leaves (CDC). A major risk factor for mucormycosis is a haematological malignancy, with leukaemia or lymphoma being the underlying diagnosis in the majority of cases. Multiple myeloma, myelodysplastic syndrome, aplastic anaemia, and sideroblastic anaemia are some of the other haematological conditions linked to infection. Mucormycosis is uncommon in patients with solid tumors. Patients who have solid organ transplants are also at risk for mucormycosis, especially if they are given high-dose corticosteroids or anti-thymocyte globulin to treat acute rejection. Mucormycosis is more common in liver transplant recipients due to high intraoperative blood transfusion requirements, bacterial infections, and re-transplantation for graft failure. Mucormycosis is linked to desferrioxamine therapy for iron or aluminium overload, particularly in haemodialysis patients. Mucormycosis has also been reported in patients with other iron-overload conditions that require desferrioxamine therapy, such as myelodysplastic syndrome, β-thalassemia, and sideroblastic anaemia. Rhino-orbito-cerebral mucormycosis is more common in diabetics, especially those with ketoacidosis. Infection with the human immunodeficiency virus (HIV) does not appear to increase the risk of developing mucormycosis, possibly because neutrophils, rather than T-lymphocytes, play a key role in Mucorales defence. Certain infections, such as malaria, may make patients more susceptible to Mucorales infection. Mucormycosis has been linked to cirrhosis, congenital heart disease, malnutrition, carcinoma, anaemia, hepatitis, glomerulonephritis, uraemia, amoebiasis, typhoid fever, and gastroenteritis. 

*Figure 1: A magnified scan of black fungus*

*Figure 2: Mucor mold, often known as black fungus or bread mold fungi, is a kind of fungus that may be found in soil and digestive systems*
**Figure 3:** A mucor fungus mature sporangium under a light microscope. Mucormycosis, an uncommon but serious fungal illness, is becoming more common in India.

**Figure 4:** Mucormycosis pathophysiology

1. Caused by asexual spore formation
2. The nasal and oral mucosa are inundated with tiny spores
   - Immunologically competent host
   - Immunocompromised host
   - No disease process
   - Germination occurs
   - Hyphae invade blood vessels
   - Thrombosis, ischemia, and infarction are associated with dry gangrene and necrosis
Figure 5: Mucorales fungus sporangia on the skin. The inner canthus is surrounded by a red plaque. The ulceration in the plaque's core was seeping a faint yellow exudate. On the plaque, there were also several scales.

Figure 6: Mucormycosis (black fungus) in the oral cavity

Figure 7: Periorbital black fungal infection
CLINICAL EVIDENCE

Mucorales species all have comparable clinical manifestations. The type of mucormycosis that develops is determined by the underlying medical condition and risk factors. SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) is a new coronavirus that was originally discovered in Wuhan, Hubei Province, central China, and is the cause of the 2019-20 pandemic. COVID-19 instances have been linked to an increase in fungal infections, including black, white, and the more recently discovered yellow fungus. Many coronavirus patients have been compelled to return to hospitals due to the rising number of cases. While there is no clear relation between mucormycosis and coronavirus infections, and it is not a contagious infection like coronavirus, the increased incidence have led many to assume that India is facing a double catastrophe. Another reason for COVID-19 patients to be cautious throughout their recovery is the infection. There are a variety of variables that might enhance one's risk of developing the illness. In COVID-19 instances, it was discovered that patients who were admitted to the ICU for an extended period of time, were put on invasive oxygen treatment, were provided excessive steroids that depress immunity, or self-medicate were at serious danger. Patients with a history of uncontrolled diabetes (blood sugar levels above 500 mg/dL) are additionally at risk of serious complications.

While mucormycosis cases were seen during the first wave of the pandemic and even before that, though in small numbers, the severity caused by the mutant virus during the second wave, as well as the indiscriminate use of steroids, has contributed to the difficulties. This kind of fungal infection, which includes white and black fungus, can be fatal for persons with inadequate immunity or who have pre-existing comorbidities. The infection may be able to enter the body more easily and cause havoc if immunity is compromised. As a result, the only method to effectively combat the condition is to recognize the signs early on. Here are some signs and symptoms to be aware of black fungus:

i. Since the fungus attacks the nasal tube and the brain, pressing, persistent headaches might be one of the first indicators of inflammation and infection produced by the fungus.

ii. Infection with the black fungus can produce a variety of physical problems. Swelling on one side, localized discomfort, and heaviness in the lower portion of the face are seldom major indicators. Unusual lesions, as well as redness that might escalate to necrosis-like signs, should be on the alert.

iii. Facial deformation is one of the most noticeable symptoms of a black fungus infection. Black crusts around the nose, scabs, facial discoloration, and drooping eyes might all be symptoms that the illness is progressing. Seek assistance as soon as possible.

iv. The fungus spreads via the sinus passages and nasal cavities, eventually attacking the lungs in severe instances. Mild respiratory symptoms, such as nasal obstruction followed with pushing, should be avoided.

v. In some situations, the infection can spread quickly, resulting in facial disfigurement. Loosening of teeth has also been noted as a main symptom by some individuals. Some
people may develop jaw disorders that necessitate surgical intervention [Figure 6].

vi. Eyelid loss and distorted vision have been reported in rare cases of COVID, a black fungus infection [Figure 7].

vii. The infected patient's nose also has dark blotches surrounding it.

viii. Some patients' eyesight has also been entirely lost.

ix. A coma or impaired mental state can develop from a disseminated black fungus infection in the brain.

x. Nausea and vomiting, stomach discomfort, and gastrointestinal bleeding are all symptoms of a black fungus infection in the gastrointestinal system.

BLACK FUNGUS: SUPPLY OF KEY DRUG TO BE RAMPED UP FOR MUCORMYCOSIS TREATMENT

While India is in the grip of the second coronavirus wave, it is also dealing with mucormycosis, also known as black Fungus. Mucormycosis cases among COVID-19 positive people are increasing, and certain states and union territories have proclaimed it an epidemic. According to medical experts, if the infection is not treated quickly, it can become aggressive within two days of commencement, and patients are frequently forced to give up the organ that has been infected. Rapid identification, reversal of the underlying predisposing conditions (if feasible), adequate surgical debridement of diseased tissue, and adequate antifungal therapy are all important aspects in tackling mucormycosis. Small, isolated lesions may frequently be surgically removed before they spread to key tissues or disperse, therefore early detection is vital. [34,61]

Antifungal therapy with an amphotericin B preparation, surgery, and, if possible, correction of the underlying medical condition are the mainstays of treatment. [64,65] Antifungal medications Amphotericin B, including Liposomal Amphotericin B (LAmB) and Lipid Complex Amphotericin B, have been recommended for use in life-threatening fungal infections like mucormycosis. It is treated with a combination of surgical removal of affected tissues and antifungal therapy, usually Liposomal amphotericin B intravenously. LAmB has been recommended in the treatment of a variety of invasive fungal infections, including Mucormycosis, by several international clinical guidelines. Patients with Mucormycosis who were treated with LAmB had a successful clinical recovery, according to a few recently published reports. [66-71]
potency, daily two times 6 tablets each time for 5 days in the case of Cutaneous Mucormycosis, and Arsenic-Alb, Phosphorous, Nitric Acid; 200 potency, daily two times 6 tablets each time for 5 days in the event of Gastrointestinal Mucormycosis.\cite{75-78}

Black fungus has a high fatality rate and exists in India prior to the epidemic. Patients with weaker immune systems and underlying diseases, such as diabetes and excessive use of steroids, are more vulnerable to the fungal infection. Patients will require severe surgical therapy with antifungal drugs administered via the veins for many days if medicinal therapy alone is ineffective. Surgical excision of relevant tissues, such as the eyeball and eye socket, nasal cavity bones, and oral cavity, is frequently aggressive, resulting in disfiguring sequelae. However, if the condition is detected early on, there is a reasonable chance of survival.

**BLACK FUNGUS IN CUISINE**

The thought of eating something called "black fungus" is exceedingly unappealing. Black fungus is a natural mushroom that is also known as 'tree ear' or 'cloud ear' fungus due to its form [Figure 8]. Black fungus is a common culinary ingredient in Asian cuisine because of its jelly-like consistency and characteristic chewiness. Malaysian, Chinese, and Maori cuisines all use black fungus as an ingredient. Carbohydrates, amino acids, and trace elements abound. Polysaccharides, melanin, polyphenols, and flavonoids are among the many useful nutrients found in it.\cite{79} Since the 19th century, black fungus has been used as a traditional Chinese medicinal mushroom, mainly by Chinese ethnic groups to cure jaundice and sore throats. As a result, black fungus is one of the nutrient-rich and pharmacologically active edible fungi, according to traditional Chinese medicine. Immune-boosting, anti-inflammatory, antiviral, anticoagulant, and anticancer activities have all been documented in black fungus.\cite{80-82} Currently, sawdust from broad-leaved trees is often utilized in the forest to develop black fungus. Furthermore, the cost of sawdust has risen in recent years. As a result, finding a new agricultural resource to produce black fungus has become a pressing issue for the sector to address. The multinutrient content of black fungus is credited with several nutritional and health advantages.\cite{83-84}

Black fungus is high in antioxidants and prebiotics, which are beneficial to the intestines. More study is needed to see if it can help decrease cholesterol and preserve your liver and brain.\cite{85}

**CONCLUSION**

In India, there is a lot of skepticism about the black fungus. People are terrified, and a lack of knowledge just adds to their anxiety. While black fungus is not infectious, it does spread via the air and the surroundings due to fungal spores. However, it is important to note that both fungus and bacteria exist in our bodies, but they are kept under control by our immune systems. Mucormycosis (black fungus) is an invasive fungal infection that can be caused by a variety of conditions, including uncontrolled diabetes, renal failure, organ transplant, long-term corticosteroid and immunosuppressive medication, cirrhosis, burns, and AIDS malignancies such lymphomas and leukemia. It can be induced even by simple dental treatments, such as tooth extraction, in a diabetic patient. More efforts should be made to diagnose this condition early and treat the patient as soon as possible. As a result, indicators such as swelling in any part of the face, discomfort on one side of the face, a persistent headache, a clogged nose, or eyesight issues should not be underrated. The earlier a black fungal infection is diagnosed, the more efficient the treatment will be. According to new poll, black fungus is an edible mushroom that is commonly used in Chinese cuisine. It's usually marketed dry under the titles cloud ear fungus or tree ear fungus. Before eating, it should be fully soaked and fried. Based to new research, black fungus has a variety of health advantages, including liver protection, cholesterol reduction, and gut health improvement. It also contains a lot of fiber and antioxidants. Although this fungus has been utilized in traditional Chinese medicine, additional research is needed to determine its effectiveness. Furthermore, black fungus has been shown to contain melanin, which can serve as an antioxidant.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.
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