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# Evolving Epidemiology and Early Diagnostic Advances in Mucormycosis

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**Abstract- Mucormycosis is a fatal fungal infection caused by filamentous molds belongs to order Mucorales.. Mucormycosis is observed to be more prominent in immunocompromised patients. In certain developed economies, mucormycosis is seen to be an associated infection with a bad prognosis regulated diabetes mellitus (DM). Mucormycosis or commonly known as black fungus, has a strong tendency of invading blood, causing nacrosis, thrombosis, and tissue infraction. Mucormycosis is found to be predisposed in co-morbidity or in the non-diabetic patients of COVID-19 especially in those who were at high dosage of steroids for a longer period of time or on ventilator support. Additionally poor hygienic conditions or disturbed diabetic management provides favorable conditions for the pathogenic fungal infection. Other reasons which are responsible for mucormycosis can be excess of uncontrolled conventional precautions. One of them is regular steaming, which may cause affliction in the nasal tracts' beneficial microbiota and virome. Early diagnosis is crucial to initiate the therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery and improving outcome and survival. In this review, the black fungus causes and cures of Mucormycosis have been highlighted. It contains cases from Mucormycosis outbreak, the pathogenesis and diagnosis of the respective disease along with its available treatments. This review also suggests some natural treatments for black fungus disease.**

**Keywords: Mucorales, Mucormycosis, Black fungus disease, Nosocomial mucormycosis, COVID-19,**

## I. INTRODUCTION

Members of order Mucorales1 are ubiquitous and could be found anywhere including wet lands, bread, dust, dirt and rotten plant matter 2. The fungi from order Mucorales are responsible for various skin diseases. Members of this order are a permanent part of human environment as pioneer species on every kind of habitat. They are the main causative agents of spoilage mainly of refrigerated food. Mucrorlean fungi are very ordinary mold fond indoors and are behind several allergic symptoms. One of the most well-known, infection caused by members of Mucorales order is Mucormycosis. The Black fungus disease or Mucormycosis can be caught by absorption of infected meal, inoculation of damaged surfaces or injuries and inhalation of spores 3. Mucormycosis is observed to be more prominent in immune-compromised patients 4,5. In certain developed economies, mucormycosis is seen to be an associated infection with a bad prognosis regulated diabetes mellitus. Additionally, people who are predisposed to disease are prone to mucormycosis6. Mucormycosis or commonly known as black fungus, has a strong tendency of invading blood, causing nacrosis, thrombosis, and tissue infraction 7. The species belongs to order Mucorlaes are Rhizopus, Lichtheimia (formerly Absidia), Mucor, Cunninghamella, Rhizomucor,

Apophysomyces spp., and Saksenaea8,9. However, Cunninghamella, Rhizomucor, and Saksenaea are predicted to show similar classes of the genera10. Even though, some species unveil remarkable variation due to their origin and geographical features. For instance, Apophysomyces inhabit in subtropical and tropical environment11, and is principal cause of cutaneous infections12, widespread soft necrosis necrotizing fasciitis13.

Inhalation or absorption of sporangiospores or inoculation of conidia by puncture trauma or entry by wounds is the primary steps in pathogenesis14. Nosocomial mucormycosis outburst was ascribed to surgical instruments, infected bandages and also breathing systems, which are very rare15. Polymorphonuclear phagocytes (PMNs) and mononuclear destroy hyphae and fungal spores in healthy young people using oxidative and non-oxidative killing mechanism16. A deficiency in immune system of host encourages the organism's survival and development (neutropenia). Hyperglycaemia and acidosis, particularly hinder phagocytic killing and chemotaxsis. Rhizopus produces enzyme ketone reductase which allows it to grow in acidic and glucose rich medium, ketoacidosis17.

Mucorales are naturally susceptible which are killed by human phagocytes and are responsible for their virulency factors18. It is clinically proven that patients having iron overload are more prone to mucormycosis19. Whereas, deferoxamine stimulates fungal growth in-vitro by acting as siderophores20. Mucormycosis has affinity to penetrate blood vessels, causing thrombosis and tissue nacrosis 21. Angioinvasion may be aided by endothelial cell association with fungal association. Interaction with the receptors of endothelial cells in host can facilitates cell damage and fungal dissemination.

Mucormycosis is found to be predisposed in co-morbidity or in the non-diabetic patients of COVID-19 especially in those who were at high dosage of steroids for a longer period of time or on ventilator support. Additionally poor hygienic conditions or disturbed diabetic management provides favourable conditions for the pathogenic fungal infection. Previous studies states that poorly controlled diabetes (type -2) is more likably to get infected with Black fungus, whereas type-1 diabetes (15%) is also reported in few cases 1. Type-2 diabetes is insinuated as prime cause with 44-88% cases and half of the cases were diagnosed with ketoacidosis22,23. In a report, it is observed that among all the patients of COVID-19 associated mucormycosis (CAM) about 80.4-96.7% had diabetes mellitus 24,25,26. Aside from diabetes, various other elements counting the immune-suppressive therapy, organ transplant, immune-compromised health conditions and iron overload may also put at risk for mucormycosis 24,27.

Other reasons which are responsible for mucormycosis can be excess of uncontrolled conventional precautions. One of them is regular steaming, which may cause affliction in the nasal tracts' beneficial microbiota and virome. Dysbiosis or nasal microbial imbalance may harm local immunity and could be helpful to create favourable conditions for the growth of fungal infection. Throughout the time of COVID-19, for the prevention of viral infection, people in big counting have been using Zn disproportionately through vitamins or along other dilatory supplements. It is conspicuous that Zn deprivation inhibits the growth of fungus in body28. Hence, Zn-depletion-based could be used for the treatment of mucormycosis¬¬29. Additionally, various patients receiving medical treatment but oxygen therapy were infected and further diagnosed with Black fungus. It is stated that mucormycosis depends on climatic factors alike humidity, seasonal variations, and temperature; therefore, these factors must be investigated to find out potential conclusion and rational solutions¬ 30.

## II. EPIDEMIOLOGY AND INCIDENCE

Mucormycosis has been in highlights from last two decades around the world, especially in France, Belgium, Switzerland and India31,32,33. Mucormycosis is only observed in patients with immune-suppressed conditions34. Onwards, 2001 to 2010, National Hospital Discharge database

presented a data, which shows 35,876 invasive fungal infections (IFIs), in which mucormycosis was accounting for 1.5% 35.

Mucormycosis cases arose from 0.7 per million in 1997 to 1 per million in 2006 in France whereas 19 cases were diagnosed in a single center sample in spain during 2007 to 2015 accounting 3.2 per million cases compared to 1.2 per million cases from 1988 to 200636.

The frequent causative agents of mucormycosis are Rhizopus spp., Mucor spp., Licthemia spp., Rhizomucor, Saksenea, Cunninghamella and Apophysomyces37,38. In India, Rhizomucor being the prominent cause of mucormycosis, considering that Apophysomyces elegans, A. variabilis, and Rhizopus homothallicus are being emerging species39. Mucormycosis in immunocompromised patients' results from inhalation of spores present in air or from direct inoculation of organisms into disrupted skin or gastrointestinal tract mucosa. Seasonal variations also affect the incidence of mucormycosis with a peak in cases from August to November40. Necrotizing fasciitis, after being injected by intramuscular injections is also reported in India, caused by Apophysomyces variabilis or A.elegans and Saksenaea erythrospora41.

Mucormycosis is a consequential and is possibly able to cause lethal fungal infections caused by a group of opportunistic fungal pathogens known as mucoromycetes. Mucormycosis, currently well known as black fungus, caused grievous havoc in second wave of COVID-19 pandemic in India (April-June 2021) by its sudden rise and catastrophic gush resulting 50% mortality rate. The exact origin of its edged arise during devasting pandemic is still debatable, but it is notable that diabatic people are likely to get caught by mucormycosis. Since the dawn of mucormycosis in late 2019, COVID-19 has ravaged the human health worldwide with also great impact on the global economy. SARS-CoV-2 affected more than 220 countries with approximately 4176,185 deaths so far noted across the globe. During second wave of SARS-CoV-2 its fatal variant COVID-19 continues to affect people globally42,the great rise in multitude of infections specifically the deadly fungal manifestation-mucormycosis, has put the lives of COVID-19 patients at very high risk43,44. Mucormycosis along with COVID-19 as a co-morbid infection is worsening the effect of infection resulting in peak of mortality rate graph. Aggressive mucormycosis can infect eyes, sinus, nose and brain in some cases. In some severe cases eyes have to be removed to save the life of patients45.

Remarkably, the developing countries such as India, the second most COVID-19 affected country in the world, have been unexpected tide of mucormycosis with inconstant magnitude of severity and pathologies. More than 45,432 cases and 4252 deaths due to mucormycosis have been reported. Rhino-cerebral mucormycosis is the most common type of infection (77.6%) in either among COVID-19 infected patients or in patients who had recovered from COVID-1946.

Cytologically, mucormycosis is a serious life taking infection which is caused by a mold family known as mucormycetes. Mucormycetes are ubiquitous, mostly found in moist soils, decaying food and plant matter, feces, around construction site47. This group of fungi is opportunistic pathogens and are supposed to attack only immunocompromised people. Vasculotropism and invasion in blood vessels in immunosuppressed people leads to tissue infraction48,49. Recently it is noticed that patients with comorbid infections like neutropenia, diabetes, renal failure, deferoxamine therapy, cancer, protein-calorie malnutrition and other manipulations are at high risk of mucormycosis50,51,52. An empirical survey aimed on mucormycosis about two decades ago suggested that if black fungus infection left untreated could lead to death, with the probability of 54% mortality53. Earlier, the expected numbers of mucormycosis patients were about 14 cases per 100,000 populations, which is considered to be at peak in global. Considering that, lately, an explode in the numbers of patients of COVID-19 associated mucormycosis (CAM) in India is observed54. On account of this, mucormycosis has been announced as an epidemic in many states and territories by the Government of India. As there were no more cases

reported of COVID-19 associated mucormycosis (CAM) in all the time of first wave of SARS-CoV-2, questions rise about the reasons and factors responsible for mucormycosis particularly during the second wave of COVID-19. There are several opinions about outburst of mucormycosis in India. As per the data obtained by WHO, India has a total of 15.3% of world diabetic population55,56. It has been noticed that diabetic patients and suffered from COVID-19 are more prone of mucormycosis57. On another hand, it has been observed that about 85% of mucormycosis patients have diabetes or uncontrolled diabetes58.

## III. PATHOGENESIS

Pathogens use various strategies for virulence to establish home in hosts system. Microbial pathogenesis is the ability of pathogen to cause damage to host. Pathogenesis begins with adherence of pathogenic microbes to the host outer skin, followed by invasion in cells, colonizing and abundant growth inside the body. If the growth is left untreated, it can lead to severe damage to host59. The process of pathogenesis requires following steps:

Exposure to fungal spores via inhalation, direct contact, injection, implantation, inoculation by infected needle or any other surgical equipment.

- Adherence of pathogenic microorganisms and invasion in host's cell.
- Colonization followed by growth of fungal spores inside host body.
- Invasiveness (abundant growth of cells).
- Tissue damage or tissue narcosis.

Elevated serum iron available in immuno-suppressed patients enhances chances of mucormycosis. For virulence, the mucoralean fungi rummage on high serum iron available and evade from hosts phagocytic defence mechanism to disrupt and damage vasculature. Besides the ability of inhaled spores to germinate and from hyphae in host is critical for the establishment of infection. The skin acts as a barrier against cutaneous mucormycosis, disruption of this barrier may result in infections. The causative agents are incapable of penetrating skin. Although, traumatic disruption of skin wounds burns, cuts and persistent maceration of skin enable the fungi to invade deeper tissue60.

In a healthy individual sequestration of iron from serum by certain iron binding proteins encompasses primary defence. These various defence systems of host forbid the growth and development of fungus as well as endovascular invasion. Instead, the susceptible ones are not capable of avert invasion in blood vessels. Patients suffering from diabetic ketoacidosis, the dissociation of free iron from sequestering proteins results in acidic pH of serum which allows rapid fungal growth. Neutropenia i.e., deficiency in cell number, manifestations by corticosteroids, hyperglycaemia enhances fungal propagation59.

Into the bargain, proliferation of fungus to endothelial cells leads to angio-invasion, vessel thrombosis and subsequent tissue necrosis61. The angio-invasion contributes to capacity of causative agents to disperse to other organs. In a consequence, invasion in endothelial cells is critical step in pathogenic strategy of mucoralean fungi.

Table I. Different forms of clinical observations in mucormycosis and their possible symptoms62

| Mucormycosis variant | Indications |
|---|---|
| Pulmonary mucormycosis | Dyspnea, Chest pain, Hemoptysis |
| Rhinocerebral, rhino-orbitocerebral mucormycosis | Headache, Facial pain, loss of vision, Lethargy, Brownish, Black eschar on palate, Blood-stained nasal discharge, Chemosis, Ophthalmoplegia, Ptosis, Periorbital cellulitis, Dysfunction of cranial nerves Proptosis |

| | |
|---|---|
| Gastrointestinal mucormycosis | Non-specific, Diarrhea, Abdominal pain, Melena, Hematemesis, depend on site involved |
| Cutaneous mucormycosis | Resemble ecthyma gangrenosum, Painful lesions, Necrotizing fasciitis, Cotton-like growth |
| Focal mucormycosis | Mediastinitis, Endocarditis, Osteomyelitis, Peritonitis, Otitis external, Pyelonephritis, Corneal infection |
| Disseminated mucormycosis | Stroke, Pneumonia, Subarachnoid-hemorrhage, Cellulitis, Brain abscess, Gangrene |

**Risk factors for mucormycosis**

The predisposing factors of mucormycosis are poorly regulated diabetes mellitus1 (DM1), HemeM with neutropenia, chemotherapy, autoimmune disorders, immunosuppression, HIV, iron overloaded state, peritoneal, malnutrition, burns, wounds, trauma and recipients of VORI63,64. Mucormycosis appears to protect immunocompetent people65, even though infections are diagnosed after the damage of soft tissues, local cutaneous including rhino-orbital, cutaneous and also disseminated infection66,67. In a meta-statistic of 600 publicized from 2000 to 2007, including 851 cases from all over globe: burns (11%), natural disasters (11%), no underlying condition (18%), neutropenia (20%), HemeM (32%), trauma (33%), and DM (40%) 68. Diabetes mellitus (DM) is a major contribution to mucormycosis in Asia, whereas in Europe and North America organ transplant and HemeM are more responsible. While COVID-19-associated pulmonary aspergillosis (CAPA) has got a lot of attention69,70. The risk factors, consistent radiography and presence of Aspergillus in tissue culture or microscopy are all used to diagnose COVID-19-associated pulmonary aspergillosis (CAPA)71. All invasive mold infections have indistinguishable predisposing factors, clinical symptoms also radiological or serological findings. Proportionately COVID-19-associated mucormycosis (CAM) diagnose is considerably is more difficult. Mucormycosis may be not diagnosed for a long period of time due to lack of clinical symptoms and difficulty to isolate the pathogenic fungi. Additionally, biomarkers for invasive aspergillosis (beta-d-glucan, galactomannan) are not accessible for mucormycosis72. Diabetic patients who are in controlled condition may develop overt or covert renal impairment. Multiple risk factors or co-morbid conditions raise the net state of immune suppression in severe COVID-19 patients, predisposing them to mucormycosis.

## IV. DIAGNOSIS

**Clinical diagnosis**

A high index of suspicion, identification of host conditions and rapid evaluation of clinical symptoms are all needed for diagnosis of mucormycosis. Diplopia in a diabetic patient or pleuritic pain in a neutropenic patient may be signs of infection, prompting the use of imaging techniques and the eventual collection of specimens for histology, microbiology and advanced molecular research. Previously described, rhino cerebral, pulmonary, soft tissue and disseminated infection are the most frequently clinical infections of Mucorales6. Mucormycosis is superficially characterised by tissue necrosis. The appearance and syndrome-based methods of diagnosis lack sensitivity and are not accurate. Nevertheless, certain characters boost the fear of intrusive pulmonary mucormycosis73. Corzo-Leon74 and colleagues (2018) put forward an algorithm for consideration for detecting rhino-cerebral mucormycosis in diabetic patients. A cranial nerve palsy, sinus pain, diplopia, periorbital swelling, proptosis and palate ulcers orbital apex syndrome are the major sign and symptoms that can be visible “red flags”74.

Mucormycosis is said to be associated with numerous nodules and pleural effusion on radiography. The reverse halo symbol (RHS) is

another CT scan finding which can gives idea about the presence of mucormycosis. In a study done by Konttoyiannis75 (2012) the RHS was seen in 15 patients out of 16 within a week of disease. Other radiological observations appeared later. RHS technique is suggested to be a good indication of pulmonary mucormycosis in neutropenic patients than CT scan. The CT scan of 24 patients with lung mucormycosis were found to be similar to the CT scan of 94 patients' aspergillosis. Whereas, RHS was more prevalent in mucormycosis patients (54%) than in aspergillosis patient (6%)75. Despite the fact, these results are not conclusive, but can be only seen as starting point for further studies. The positron emission tomography-computed tomography (PET/CT) with (18F)-fuorodeoxyglucose (FDG) is yet transpiring imaging strategy which may be helpful in the diagnosis and management of mucormycosis76. Endobronchial ultrasound guided fne-needle aspiration is also a helpful tool in screening of mucormycosis77.

## V. CULTURE AND MICROSCOPIC EXAMINATION

Different microscopic techniques and other clinical culture specimens are diagnosing mucormycosis's cornerstone. The samples from infected individuals are examined under direct microscopy. Clinical samples which are white, are allowed for quick preliminary analysis of mucormycosis78. The hyphae of mucoralean fungi haver variable diameter generally 6-25 micron, are non-septate or pauci-shaped and are irregularly shaped. Branching angle varies with wide angle (90°) bifurcations being common. Fungal elements are easily visible on hematoxylin and eosin. Gomori's silver staining is frequently used to elucidate fungal hyphae with a detailed analysis of anatomy79. Inflammation usually dominates tissue histopathological results in a few cases. It is absent in immunocompromised patients. Prominent infarcts and angioinvasion are main characters of invasive disease. Perineural invasion can be seen if nerve structures are involved. Histopathological examination of tissue samples is not always capable to distinguish Mucorales hyphae with Aspergillus or other morphological characters related to fungi. Tissue identification is a strong diagnostic tool as it can easily discriminate between the presence of a pathogen in a tissue culture and culture contamination. Mucorales grow rapidly on most fungal culture media like Potato dextrose agar and sabouraud agar incubated at 25–30 °C(3 to7 days). A microaerophilic condition increases culture yield for certain varieties. Exceptionally, even though fungal hyphae are visible in the histopathological examination, only 50% of fungal cultures are positive. As fungal hyphae brittle, they could be harmed in tissue manipulation.

## VI. SEROLOGY

Certain rational tests i.e., enzyme-linked immunosorbent assay (ELISA), immunoblots and immune-diffusion were evaluated based on the degree of their effectiveness. Out of three hematological patients who developed invasive mucormycosis, enzyme-linked immunospot (ELISpot) assay has been used to identify Mucorales-specific T cells. In addition, Mucorales-specific T-cells were used in infected patients to recover over the disease80 albeit; further research is required towards the use of T-cells as surrogate diagnostic markers.

## VII. MOLECULAR ASSAYS

Conventional PCR, RFLP, and DNA sequencing of identified gene regions81,82,83 and melt curve analysis of PCR products are all examples of molecular-based assays84. Many of the assays mentioned above can be used to detect or identify Mucorales. The internal transcribed spacer or the 18S rRNA genes are the focus of the majority of molecular assays79. Several studies have been conducted using paraffin-embedded or fresh tissue samples, formalin-fixed, with varying results. The studies performed for sensitivity (70–100%) and specificity (not measured to 100%) shows varied results, but a lower number of patients examined being a critical shortcoming. Since the efficacy of these in-house assays has not been extensively tested and clinically evaluated, they cannot be put forward as a single, stand-alone in clinical routine

diagnostics, this approach is used. Molecular diagnosis from blood and serum has yielded positive clinical results in 39% of cases85,86. When opposed to culture, early diagnosis and overall confirmed culture-proven cases were achieved using molecular-based diagnosis from serum. At this time, molecular based diagnostic assays may put forth as useful supplements to traditional diagnostic procedures87.

## VIII. ADVANCEMENT IN DIAGNOSIS

Cultures and histopathology are used to diagnose mucormycosis88. Mucoralean fungi are vulnerable to vascular invasion and are capable of damaging the tissues. Tissue infraction occurs after blood vessel thrombosis, consequently leads to the formation of black eschar. Gram stain is ineffective for fungi. Fungi of order Mucorales have long non-septate ribbon like irregular hyphae with branches. Mucormycotic infections may comorbidly cause neutrophilic, granulomatous or non- specific inflammatory changes along with angioinvasion. Fine needle aspiration biopsy may be used to confirm the infection especially if pulmonary nodules or masses are present77,89. Even histopathology can revel false results. Grinding tissue specimens for culture are results in hyphae damage due to scarcity of septations which prevents growth in culture.

For certain causative agents of order Mucorales i.e., Rhizopus, Mucor, Rhizomucor, Lichthemia quantitative PCR in serum or tissues can be found90. Matrix- assisted laser desorption or ionization-time of fight tends to a great tool with high precision for separating mold from culture91,92. Next generation sequencing can detect IMIs in blood samples which could lead to earlier detection of mucormycosis93.

### THERAPY

Mucormycosis is an uncommon disease causing a deadliest opportunity in the immunocompromized patients. Various research groups from all across the globe are working on it. Many suggestions are provided by the researchers for its therapy and treatment. Several researchers advice that randomized controlled trials are not possible in millions of people due to rarity of mucormycosis. But, LFAB can be used as primary treatment to cure mucormycosis94,95. Triazole was approved by the FDA to treat adult mucormycosis in advance condition whereas, POSA with Mucorales activity was used earlier as salvage and induction therapy96,97. Laterally, surgical debridement serves an essential supporting part, especially when if it is related to soft tissue or rhino cerebral98,95. The significance of reversing the underpinning threat factors similar to glucocortico steroid discontinuation, neutropenia, deferoxamine discontinuation and diabetes regulation and immune-suppressant cannot be exaggerated99. Numerous antifungals are vulnerable to Mucorales. The most active agents are including LFAB100 along with some newer triazoles, POSA and ISAV. Furthermore, the echinocandins and VORI had inadequate exertion against mucoralean fungi. In-vitro, ISAV and POSA101 showed activity against various fungi and molds, including fungi from Mucorales order102,103. In spite of the fact that this amount of activity for both agents vary depending on the organisms and also on mucoralean fungi104. In refractory cases of black fungus, both POSA and ISAV are known to be a useful tool as therapy or salvage105. For the patients dealing with mucormycosis who have failed POSA, ISAV has shown to be a successful recovery therapy104. In the VITAL study, patients with disseminated mucormycosis were given ISAV, which was an open label, nonrandomized106.

### TREATMENT

Successful treatment of mucormycosis is based on multiple factors like reversal of underlying predisposing factors, early administration or introduction to antifungal agents, complete eradication of infected tissues from body along with getting therapies99. Early diagnosis is crucial to initiate the therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery and improving outcome and survival107. Mucoralean fungi are resistant to most of the antifungals in-vitro, for instance Fluconazole and Voriconazole. Amphotericin B is the most effective drug, except

for some species, Cunninghamella and Apophysomyces108. Posaconazole and Isavuconazole are effective to a certain limit, whereas itraconazole and terbinafine also showed anti-Mucorales activity against specific strains as reported by Borman et al. The mucormycosis response to antifungal agents is host dependent and particularly problematic in immunosuppressed individuals109. Causative agents of order Mucorales have ordinary characteristics with other molds and fugus including the mode of invasion in host body, innate host defence. Nevertheless, Rhizopus oryzae, Lichtheimia, Rhizomucor spp. are characterized by distinguishing virulence factors which able them to cause manifestation in patients with diabetic ketoacidosis or other manifestation, encouraging host invasion and progression in body despite the treatment37. Additionally, mucormycosis is specified by immense expansion of angio-invasion leading to vessel thrombosis and tissue necrosis111. Angioinvasion accelerates towards hematogenous dissemination of the organ although tissue necrosis prevents penetration in immune cells112. Some species like Rhizopus oryzae have diminished vulnerability to innate host defence as compared to Aspergillus and Candida, concluding these fungi difficult to treat113. Posaconazole and Isavucozole are used as salvage therapy. The surfacing of intravenous and oral drugs of Posaconazole has been enhancing the bioavailability and also increased drug exposure114.

Isavaconazole is also an emerging drug with a great spectrum of antifungal activity against various pathogens, Mucorales being included111. The oral formulations of antifungal agents such as Posaconazole and Isavuconazole are proffered over administration in medical health care unit112. Surgeries are only performed in severe cases, as in the healthy tissue around the damaged or necrotic tissues must be removed. The fungus spreads and proliferates aggressively.

## IX. NATURAL ANTIMICROBIALS FOR TREATMENT OF MUCORMYCOSIS

The Mucoralean fungi are mostly resistant to antifungal agents available commercially i.e., polyene such as Amphotericin B and triazoles such as Posaconazole. These drugs are only effective if introduced in early stages of infection113. The genetic information obtained from Rhizopus oryzae revealed that initial resistance of mucoralean fungi to the therapy is the result of duplication within the genome of ergosterol biosynthesis pathway genes and mitochondrial protein complexes associated with respiratory electron transport chains110. Accordingly, the need of newer antifungal agents with distinct methods of action for mucormycosis necessitates medicine.

### PLANTS WITH MEDICINAL PROPERTIES

Plant kingdom has been a tremendous pivot for natural compounds with novel properties, which leads scientist to lean towards plants till date. Recent researches showed that plants enhance bioactive secondary metabolites i.e., flavonoids, saponins, alkaloids, and terpenoids with antimicrobial properties. Hence, these bear potential for future source for antibacterial and antifungal drugs115. In current scenario obscurity lies with antifungal therapy for patients dealing with AIDS, diabetes, chemotherapy or organ transplant and also recent emergence of COVID-19, as the drugs become inactive due to co-morbidity of other infections116. The multidrug resistance obtained by various fungi and diminished number of available active antifungal agents attribute for the discovery of novel antifungal secondary metabolites. Medicinal plants have been in highlight for providing the treatment of both mankind and mycoses. These plants as well as endophytes residing inside them are thought to be invaluable source for the discovery of antimycotic drugs.

## X. CONCLUSION

Although the actual pervasiveness of mucormycosis is unknown, it is believed to be substantially greater in developing countries as compared to developed countries. The prevalence of Mucorales in the community and hospital environment, the immense number of susceptible hosts, peculiarly diabetics and also the Indian population's negligence for regular health check-ups are all major reasons contributing to high prevalence of mucormycosis. A number of people are still unaware of their diabetic

status until they develop mucormycosis. Pulmonary tuberculosis, chronic kidney disease and critically ill patients are all significant risk factors for mucormycosis. Due to late diagnosis of condition and also intricacy in sway over in the advanced stage of infection, the mortality rate linked with mucormycosis is comparatively high. Despite of crucial advances in mucormycosis treatment in recent years, the fatality rate is still at the peak. Although, interlude in medicaments remain due to delays in diagnosis, limited antifungals as resources and difficult management alternatives. The progress in the clinical trials advice to use the surgical procedures for the treatment of mucormycosis. The rapid rise in incidences of mucormycosis paves a greater appreciation and probabilities of the contriving the newer management techniques and medication protocols to reduce the mortality and fatality overall the globe117.

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