

Tangential Role of Therapeutics in COVID-19 Induced Mucormycosis: A Review

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ABSTRACT: Due to restricted treatment alternatives that were excessively expensive, people resorted to an integrated strategy with other relevant professions to reduce the burden on a single therapy. **Objective:** To estimate our ability to live with the limited disease load while reviewing the likely influence of holistic science on sustaining health dimensions. **Method:** PubMed, Google Scholar, and other embedded websites chose 205 Mucormycosis papers for examination, and 69 publications were chosen from diverse sources for the study. The study concentrated on clinical symptoms, risk factors for mortality, and future integrative therapeutic options, with a particular emphasis on Indian demographic data. Data were extracted from the study about India and Indian peoples based on descriptions and facts. **Conclusion:** Integrative preventive strategies and therapeutic approaches can reduce the burden on one drug and can prove cost-effective with better.

Keywords: Ayurved, Coronavirus associated Mucormycosis, Holistic Approach, Mucormycosis, Opportunistic Fungi.

Submitted: 07.05.2022; Revised: 12.05.2022; Accepted:23.05.2022

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DOI:

INTRODUCTION

The number of diabetics in India is the second-highest ([A. Patel et al., 2019](#)), ([Dr Sunil Kumar Mishra, 2020](#)). Diabetes is significantly more prevalent in metropolitan areas than in rural areas ([Choudhary, 2021](#)). The past exponential surge of Mucormycosis patients in India may be a result of this ([Petrikkos et al., 2012](#)). As it is difficult to endure a lot of a certain drug due to many reasons of like availability, cost, effect on the body, etc., several possibilities of antifungal therapy available in the traditional sciences must be considered. Different traditional therapeutics for Mucormycosis from a holistic standpoint, as well as potential Ayurveda profiling, has been discussed, because it offers a wide variety of anti-fungal drugs, is cost-effective, easily available with no or less negative effect.

METHODOLOGY

We conducted systematic reviews and meta-analyses for mucormycosis for the last 10 years and different word combinations were tried for searching, though Covid -19 been active from the year 2019 and mucormycosis was active before it. We searched with mucormycosis covid Ayurved (n=3), mucormycosis covid India (n=343), mucormycosis covid (n=477), covid associated mucormycosis (n=268), opportunistic infection covid-19 (n=382), Mucormycosis covid-19 (n=468), Mucormycosis covid19 India (n=334), systematic review mucormycosis covid19 (n=20) in Pubmed for which only (n=144) were selected, Mucormycosis covid-19 India (n=2130), systematic review mucormycosis in covid-19 (n=21) in google scholar out of which (n=162) were useful, and different comprehensive resources (n=19), 325 potential & additional titles were identified & 205 articles from all sources were scrutinized out of these (n=120) were removed for duplicates or not appropriate for inclusion, only full-text studies assessed for eligibility & quality (n=69), those studies concerning Indian sociology were enclosed within the study.

The study rejected methodologically poor articles, had limited applicability or presentation of findings, had uncomparable data, was fragmentary, or were only abstracts. For the meta-analysis, statistical data is gathered from a variety of research. Studies verifying the association of COVID-19 with comorbidities and immunocompromised patients, as well as studies demonstrating mucormycosis by biopsy, imaging, or histology, were also included for evaluation. The information is gathered based on demographics, mortality, risk factors, causes, kinds, and predisposing factors, as well as clinical symptoms.

Study Participants: Various research have included male and female subjects, and these are the only ones included in the current study. Children were also included as participants in certain studies, and such data is solely utilized to highlight the age-wise distribution of mucormycosis in India. For the sake of gender distribution, knowledge depicting children were eliminated.

Study Intervention: Liposomal amphotericin B and its derivatives, in addition to debridement, were interventions in several clinical and epidemiological

studies that were included for the current study, holistic treatment modalities that need to be investigated for their specific effectiveness in mucormycosis apart from being antifungal were included for review.

Study Comparison: Only probable risk variables other than underlying disorders affecting mucormycosis (n=14) and clinical presentation (n=6) were compared from various studies for common parameters.

Study Outcome: Males are more likely to be infected, and 41 to 60-year-old age group is more vulnerable to infection. Skin infections are the most prevalent manifestation, followed by rhino-orbito-cerebral mucormycosis. Diabetes has been identified as the most prevalent predisposing risk factor in all investigations.

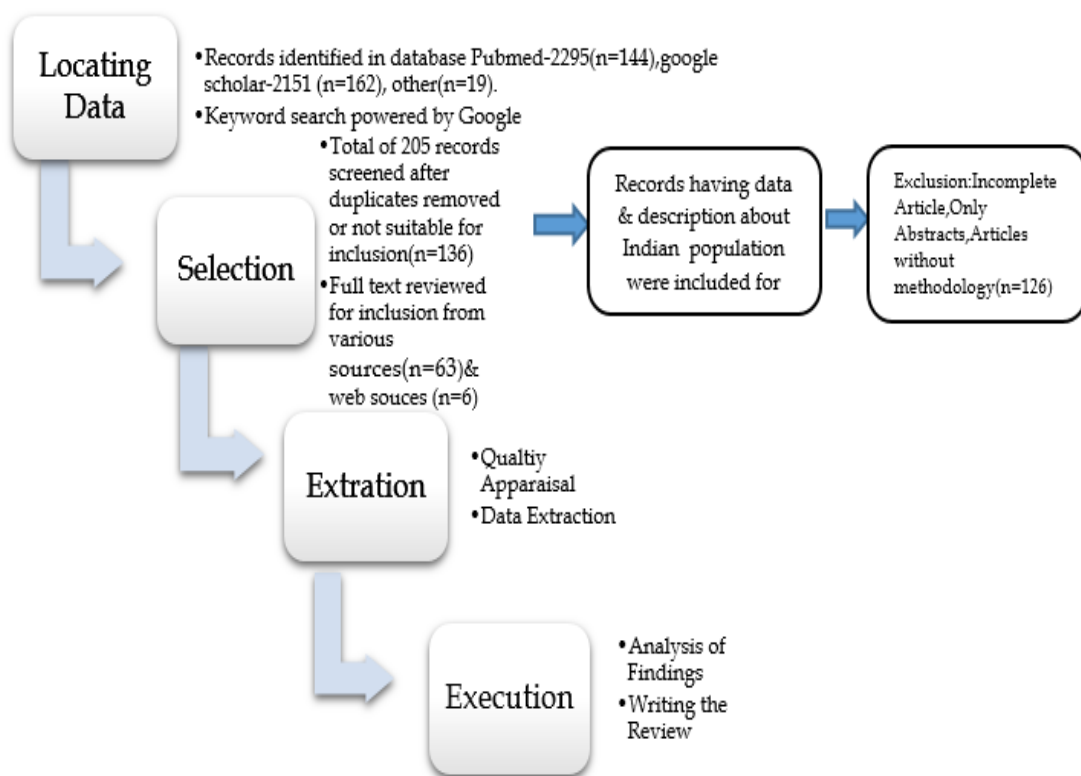


Figure 1: Showing method of collection of data

Probable incidence of mucormycosis:

Gujrat had the most cases of black fungus, with 2281 affected people. Similarly, Maharastra had more than 2000 black fungus instances. Andhra Pradesh showed more than 910 mucormycosis patients, accounting for (58.66%) of total cases in the country. Diverse risk factors influence the prevalence of mucormycosis. According to statistics from a global fungal infection registry, the most frequent underlying illness for mucormycosis (63 %) is a hematological malignancy. There were no obvious risk signs in (11.8%) of

mucormycosis patients. *R. arrhizus* was the most common pathogen ([A.Patel et al., 2019](#)). After including Indian data, the worldwide estimate of mucormycosis jumped to 910,000 cases ([Prakash & Chakrabarti, 2019](#)). Data from a single tertiary care hospital in India reveal that various risk groups have multiple series of mucormycosis disorders. The environment in India, such as tropical-subtropical areas, humidity, temperature variations, and people's lifestyle, all play a role in fungal survival and may have contributed to disease prevalence since these fungi can withstand heat. It should be emphasized that the number of confirmed cases is likely to be lower than the true prevalence of mucormycosis in the Indian community. Due to the frequently non-specific clinical signs and symptoms associated with this illness, the limited sensitivity of the currently available diagnostic techniques, as well as a general lack of knowledge among healthcare practitioners in the rapid detection of disease, all contribute to the fungi's prevalence ([Arunaloke Chakrabarti & Singh, 2014](#)).

According to the Tamilnadu-based retrospective study, the incidence of patients in South India is high ([Priya et al., 2020](#)). A rise in instances of invasive fungal sinusitis, especially mucormycosis, has been documented in several studies, as has a change in the incidence of mucormycosis infection of the sinuses ([S. Sharma et al., 2021](#)). Mucormycosis was shown to account for 24 % of all invasive mold infections in a multicentre investigation of Indian intensive care units ([Prakash & Chakrabarti, 2019](#)). The overall rate of mortality of mucormycosis is approx 40 %. Different study designs showed incidence and prevalence of mucormycosis genderwise and a high rate of infection is seen in men compared to females, the reason is unknown. In some studies, children were also put under surveillance for mucormycosis. Age-wise distribution of mucormycosis showed 46-60 years age group people have more infection of mucormycosis ([Chander et al., 2018](#))([Balasopoulou et al., 2017](#)), some showed 51-60 years are prone, might be due to high risk of predisposing factors with the mean age of 40 years ([Bala et al., 2015](#)). In another two studies mean age was 48 years ([A. Patel et al., 2019](#))([Priya et al., 2020](#)).

PATHOGENESIS:

The infection usually starts in the paranasal sinuses and spreads to the ocular orbit and palate, eventually reaching the brain. In diabetic acidosis, this infection is a fatal event, and death happens within a few days. Fungi are everywhere, and their role in human infection can be classified into three categories ([P. Chakraborty, 2005](#))

a) Colonization & Disease:

The majority of fungal infections are self-limited and minor. If the first line of protection, the skin, is broken, the fungus penetrates through the injured skin and begins the infection. The skin's fatty acid content, pH, epithelium turnover, and proper bacterial flora all contribute to fungus resistance. Protection against fungus relies heavily on cell-mediated immunity. Suppression of cell-mediated immunity

b) Hypersensitivity Diseases:

Humans are regularly subjected to airborne fungus spores and other fungal materials in the environment, which can serve as antigenic stimulants depending on an individual's immunological status, resulting in the synthesis of immunoglobulins or sensitized lymphocytes, causing hypersensitivity.

c) Disease caused by Fungal Toxins:

The ingestion of fungus toxins causes Mycotoxicosis. Aflatoxin is a fungus toxin generated by *Aspergillus flavus* that causes disease in humans by triggering a mutation in the p53 tumor suppressor, culminating in the loss of p53 protein and, as a result, a lack of growth regulation in hepatocytes, causing liver damage and producing cancer in humans. *Claviceps purpurea* is a mold that infects the brain and produces alkaloids such as ergotamine and lysergic acid diethylamide and these compounds cause serious vascular and neurological effects.

Causative Factors of Mucormycosis:

Rhizopus oryzae is the most common fungus isolated from clinical specimens of patients worldwide, including India, followed by *Apophysomyces variabilis*, *Mucor spp.*, *Lichtheimia corymbifera*, and two unidentified isolates. The failure to sporulate was the most significant impediment to isolating isolates. Deep tissue debridement was performed, and mycological techniques revealed *Apophysomyces elegans*. Unlike other fungi that are found all over the world and are mostly found in immunocompromised people, *A. elegans* has been found mostly in warm climates as cutaneous infections after injury. Although it does not normally produce spores in the environment, there have been reports of systemic infection with this fungus ([Priya et al., 2020](#)).

Rhizopus arrhizus was isolated from 75.3 % in ([Patel. et.al.,2019](#)) study participants followed by *Rhizopus microspores* and *Rhizopus homothallicus*. Other Mucorales isolated include *Apophysomyces variabilis* (7.9%), *Mucor spp.* (5.5%), *Lichtheimia corymbifera* (3.4%), and others ([A. Patel et al., 2019](#)). The most common agent causing mucormycosis massive global is *Rhizopus arrhizus*, followed by *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor*, and *Cunninghamella species*. In a hospital in the United States, healthcare-induced mucormycosis was collected from contaminated linens, and *Rhizopus* species were isolated from 42 % of clean linen samples A meta-analysis of mucormycosis cases found that *Rhizopus species* were frequently associated with the ROCM form of the disease, while *Cunninghamella species* were associated with pulmonary disease or disseminated disease. *Apophysomyces and Saksenaea* species, on the other hand, were frequently isolated from cutaneous mucormycosis.

Rhizopus species are predisposed to ketoacidosis, but not *Lichtheimia*, whereas corticosteroids are predisposed to *Lichtheimia*. Infection with *Cunninghamella species* resulted in significantly higher mortality than infection with any other *Mucorales species*. India accounts for roughly 60% of all documented *Apophysomyces species* mucormycosis cases. Infections caused by *R. microsporus*, in addition to *Apophysomyces variabilis* and *R. homothallicus* are on the rise in India. Infections caused by rare Mucorales such as *Cokeromyces*

recurvatus, *Syncephalastrum* species, and *Saksenaea* species are uncommon. In India, *Mucorirregularis* infection has been reported. Infections caused by uncommon Mucorales such as *Cokeromyces recurvatus*, *Syncephalastrum* species, and *Saksenaea* species are rare. *Mucor irregularis* infection has been reported in India ([Prakash & Chakrabarti, 2019](#)).

Apophysomyces elegans and *Rhizopus* *homothallicus* showed a high level of resistance, with all antifungals having high MICs (Minimum Inhibitory Concentration). *R. microsporus* members have been classified into several varieties based on their morphologic characteristics. *R. microsporus* var. *microsporus*, *R. microsporus* var. *rhizopodiformis*, *R. microsporus* var. *chinensis*, *R. microsporus* var. *azygosporus*, *R. microsporus* var. *oligosporus*, and *R. microsporus* var. *tuberosus* are all varieties of *R. microsporus*. *R. microsporus* has previously been linked to lung infections, cellulitis in a diabetic's leg, and nosocomial infection in preterm infants via wooden tongue depressors. *Apophysomyces* was the second most commonly isolated genus. Misra et al. isolated *A. elegans* from soil samples collected from a mango orchard in northern India in 1979, and it was the only species in the genus until recently.

Another significant finding in this study is *S. erythrospora*. *Saksenaea* is made up of three species: *S. vasiformis*, *S. erythrospora*, and *S. oblongispora*. These fungi, like *Apophysomyces*, are known to cause necrotizing cutaneous infections. *Saksenaea* has been linked to soft tissue infections in both healthy and immunocompetent people. We previously reported *S. vasiformis* from our institution; however, this time, we discovered 5 cases of *S. erythrospora* primary cutaneous infections in immunocompetent individuals following traumatic impingement. The main risk factor was an intramuscular injection into the gluteal region, with upper limb involvement following medicated adhesive tape application. This is the first time *S. erythrospora* has been found in India. *S. erythrospora* has been reported in the literature to cause infections in combat-injured patients. We isolated four *Syncephalastrum* strains. Members of this genus are typically isolated from cases of onychomycosis. In Southern India, *M. irregularis* (previously *Rhizomucor variabilis*) caused chronic infections. For the first time in North India, we isolated it in a farmer with lower-limb lesions ([Chander et al., 2018](#)).

Mucorales fungi diversity: Human infections are caused by a diverse range of mucoralean fungi. Globally, the most common causative agents of this disease are *Rhizopus*, *Mucor*, and *Lichtheimia* (Formerly *Absidia* or *Myocladus*) spp., which account for 70–80% of all cases. *Apophysomyces*, *Saksenaea*, *Rhizomucor*, *Cunninghamella*, *Cokeromyces*, *Actinomucor*, and *Syncephalastrum* spp. have also been reported rarely. In India, although Mucorales are considered opportunistic pathogens following penetrating trauma during accidents in tropical and subtropical areas, *Apophysomyces elegans* and *Saksenaea vasiformis* can cause disease in seemingly normal hosts. The majority of these patients have only cutaneous mucormycosis and no underlying disease; only a few patients have rhino-cerebral and pulmonary infections and risk factors for developing them. Intriguingly *Apophysomyces elegans* does not easily produce spores in the environment; its sporulation is carefully induced in the laboratory.

As a result, it is unclear how patients with pulmonary, renal, or disseminated mucormycosis acquire this agent from the environment. *Cunninghamella bertholletiae*, *Rhizomucor pusillus*, and *Rhizopus microsporus* can all cause infections in immunocompetent people. Many rare species have also been linked to infections in India. *Rhizopus homothallicus* has been identified in patients with cavitary pulmonary mucormycosis for the first time. 56 *Mucor irregularis*, previously thought to be involved in an emerging endemic cutaneous mucormycosis limited to China, has been found in a case of rhino-facial mucormycosis in India. 57 *Thamnostylum lucknowense*, a new mucoralean fungus, was recently isolated from a patient with rhino-orbital mucormycosis ([Arunaloke Chakrabarti & Singh, 2014](#))

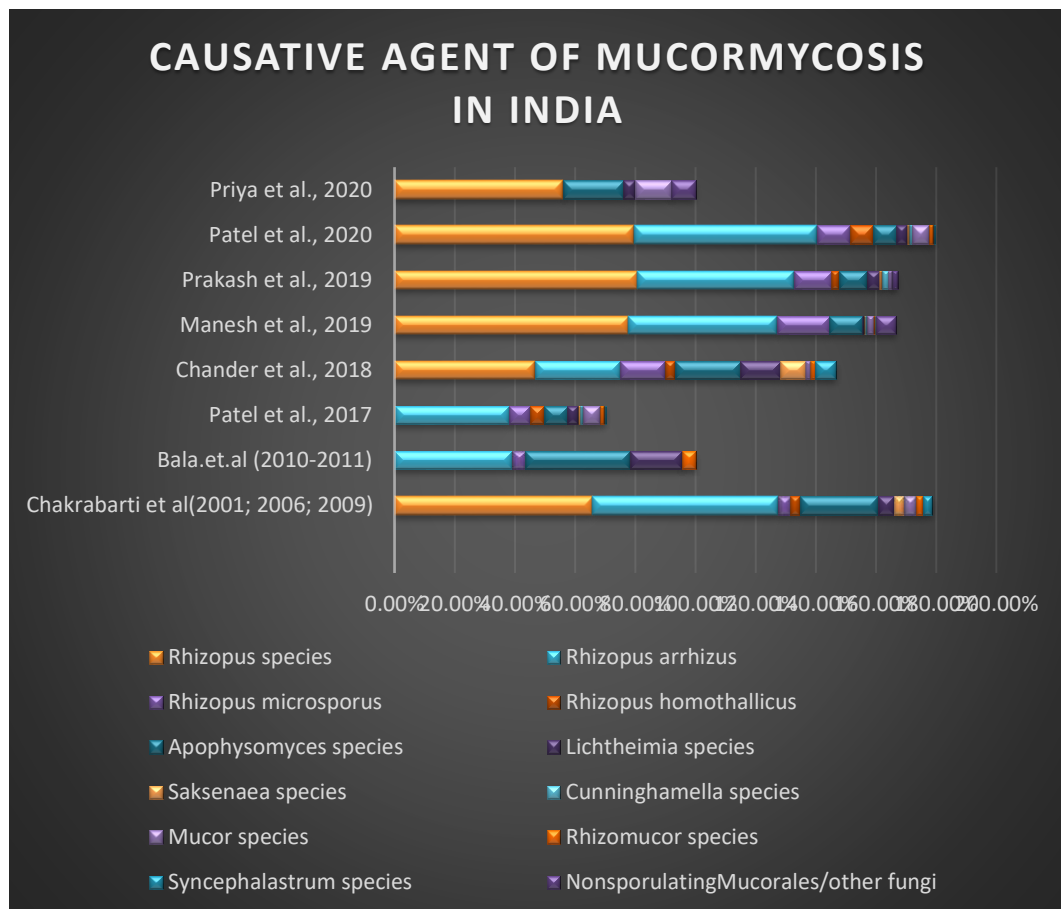


Figure 2: Showing causative agents found in some studies. The percentage of value given in the figure was calculated based on the data published in the scientific literature in different studies.

Predisposing factors:

As there are 6 types of mucormycosis named Rhino-orbital-cerebral mucormycosis (ROCM), Pulmonary, Cutaneous, Gastrointestinal, Renal, Disseminated, the kidney was implicated in 20% of instances of disseminated mucormycosis ([Priya et al., 2020](#)). In Patel et. al's (2020) study the majority of individuals (410/465, or 88.2 %) had underlying risk factors, the most prevalent

risk factor was uncontrolled diabetes mellitus (81.6 %). 14.6 % (50/342) had diabetic ketoacidosis. 50 % (7/14) of persons with isolated renal mucormycosis had no recognized risk factor ([A. Patel et al., 2019](#)). Patel et.al 2017 study also showed uncontrolled diabetes with or without ketoacidosis was a main predisposing factor in ROCM (55.6 %) & 87.5 % had Cutaneous Mucormycosis in common ([A. K. Patel et al., 2017](#)). Though there has been an increase in the number of cases with hematological malignancies and transplantation as risk factors in India in recent years ([Meis & Chakrabarti, 2009](#)).

Diabetes mellitus as a risk factor ranges from 17 to 88 % worldwide ([Prakash et al., 2018](#));([Skiada.A.et.al, 2011](#)). Three major case series from India reported diabetes as a risk factor over 50% of cases with mucormycosis, compared to 36 % - 40 % of worldwide data ([Arunaloke Chakrabarti et al., 2006](#));([A. Chakrabarti & Sakhuja, 2001](#));([A. Chakrabarti et al., 2009](#)). Diabetic ketoacidosis was much greater in north Indian sites in comparison to South India ([Prakash et al., 2019](#)). The majority of India's population does not receive regular health check-ups and mucormycosis was a diabetes-defining condition in 23 % to 43 % of individuals, according to various studies ([Arunaloke Chakrabarti et al., 2006](#)). The etiology of mucormycosis is heavily influenced by iron overload and deferoxamine treatment.

Deferoxamine was once widely used to treat iron/aluminum overload in patients with diabetic ketoacidosis (DKA), hemodialysis, renal failure, and transfusion-related diseases ([Boelaert JR, de Locht M, Van Cutsem J, Kerrels V, Cantinieaux B, Verdonck A, Van Landuyt HW, n.d.](#)); *Siderophores* on *Rhizopus species* collect the iron extracted by deferoxamine and the iron aids in the development of those fungi. Patients on deferoxamine treatment who developed mucormycosis had an extremely high death rate (80 %) ([Roden et al., 2005](#));([Boelaert et al., 1991](#)). However, novel iron chelators such as deferasirox and deferiprone successfully chelate iron while not exposing individuals to mucormycosis ([Spellberg et al., 2009](#)). HIV infection, intravenous drug use, low birth weight babies, malnutrition, persistent alcoholism, liver illnesses, chemotherapy, and the use of calcineurin inhibitors are all risk factors for mucormycosis([Vaughan et al., 2018](#));([Prakash et al., 2019](#)). A recent Indian study identified chronic renal disease (8.9 %) and post-pulmonary mucormycosis (6.9 %) as new risk factors for mucormycosis ([Prakash et al., 2019](#)).

In India, a healthy man developed a novel clinical entity of isolated renal mucormycosis ([Arunaloke Chakrabarti et al., 2006](#));([A. Chakrabarti et al., 2009](#));([Prakash & Chakrabarti, 2021](#)). *R. microsporus* employing wooden tongue depressors can cause lung infections, cellulitis in a diabetic's leg, and nosocomial infection in premature newborns. *Apophysomyces* is a kind of bacteria. This genus' species are mostly related to necrotizing fasciitis. *Saksenaea* has been linked to soft tissue infections in both healthy and immunocompetent people. Infections caused by *S. erythrospora* have been recorded in individuals with war injuries ([Chander et al., 2018](#)). In Bala. Et.al study 38 instances of mucormycosis were diagnosed and identified. Male patients (n = 27) outnumbered female patients (n = 11), and the average age of all patients was 40.43 years. Haryana state has the most residents (43.6 %), followed by Punjab

state (41.1 %). Various risk variables were linked to various clinical manifestations, only 12 of the 38 patients were immunocompetent, and the remaining 26 were immunocompromised as a result of underlying conditions ([Bala et al., 2015](#)). In Mohapatra et.al the most common presentation (45%) was rhino-cerebral zygomycosis, followed by disseminated zygomycosis (24 %).

The most common risk factor was hematological malignancy with associated neutropenia ([Mohapatra et al., 2010](#)). In Chakraborty. et.al in India, 24-64 % of mucormycosis cases occur in individuals with uncontrolled diabetes, with or without ketoacidosis. Patients with diabetic ketoacidosis have an acidic serum pH and high amounts of free iron, which is a key nutrient in determining vulnerability to Mucorales. Isolated renal mucormycosis in immunocompetent, young people is a new phenomenon in India ([Arunaloke Chakrabarti & Singh, 2014](#)).

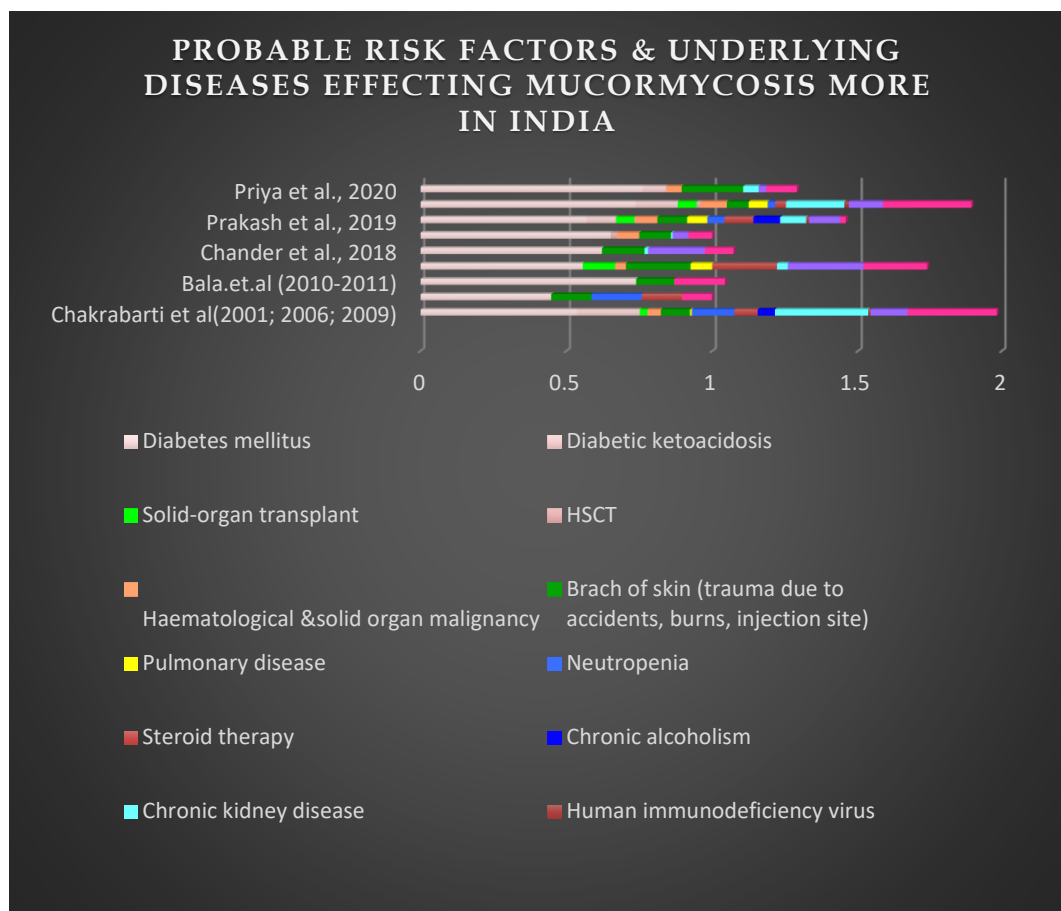


Figure 3: Clinical forms of mucormycosis reported from different studies across the globe. The percentage of values given in the figure was calculated based on the data provided in the literature. Multiple sites of infection were reported in a few studies.

Treatment Modalities Used:

Difficulties in Evaluating Mucormycosis: Because it is an uncommon illness with a variety of hosts and locations of infection, as well as a plethora of

offending Mucorales, there are fewer data available for therapy. As a result, no prospective, randomized clinical trials exist (Prakash & Chakrabarti, 2021), (Sipsas et al., 2018), (Alekseyev et al., 2021), (Espinel Ingroff & Dannaoui, 2021), (Sipsas et al., n.d.)

Regular Treatment of Mucormycosis:

- Risk stratification based on illness severity, with a focus on early clinical and laboratory diagnosis.
- Antifungal Therapy that is effective.
- Surgical removal of the necrotic lesion.
- Immunosuppression is reversed, and where possible, the underlying medical condition is controlled.

Antifungal Agent:

- Amphotericin-B (AMB) & its lipid formulations, Isavuconazole
- Salvage Therapy-Posaconazole
- New Triazoles-Depletes ergosterol from the fungal cell membrane.
- Combination Therapy

Surgery:

- The cornerstone of mucormycosis treatment is surgical excision of necrotic tissues.
- Surgical therapy for pulmonary mucormycosis+ Antifungal treatment has made great progress.
- Bouts of hemoptysis caused by cavitation of lesions suggest that the lesion has to be resected right away.
- Endoscopic surgery is favored over open surgery in cases with early circumscribed disease or major medical comorbidities. For severe diseases, open surgery is preferred.

Adjunctive Therapy:

- Immunosuppression reversal is a key part of mucormycosis treatment.
- Patients who have a poor recovery of bone marrow function or who require immunosuppressive medication for an extended period.
- Hematopoietic growth factors or transfusion of white blood cells
- Corticosteroid-induced immunosuppression should be reduced or shifted to alternate non-steroidal treatment in patients.
- To reestablish treatment, HIV/AIDS patients should be given antiretroviral medication.
- Aggressive glycemic control for individuals with uncontrolled diabetes/ketoacidosis
- Sodium bicarbonate inhibits *Rhizopus oryzae*'s capacity to infiltrate endothelial cells and restores host iron chelation and neutrophil activity, hence reversing acidemia.
- Hyperbaric Oxygen (HBO) therapy enhances neutrophil functioning, promoting AMB activity and reducing acidosis.

- Increased oxygen pressure limits fungal development and speeds up wound healing.
- Immune-stimulation, such as the administration of granulocyte colony-stimulating factor or interferon-, must be employed.

Treatment Duration:

- There is no standard treatment length for mucormycosis, decisions are chosen on an individual basis; and resolution of all clinical, biochemical, and imaging signs and symptoms of infection, as well as reversal of immunosuppression(Sipsas et al., n.d.)

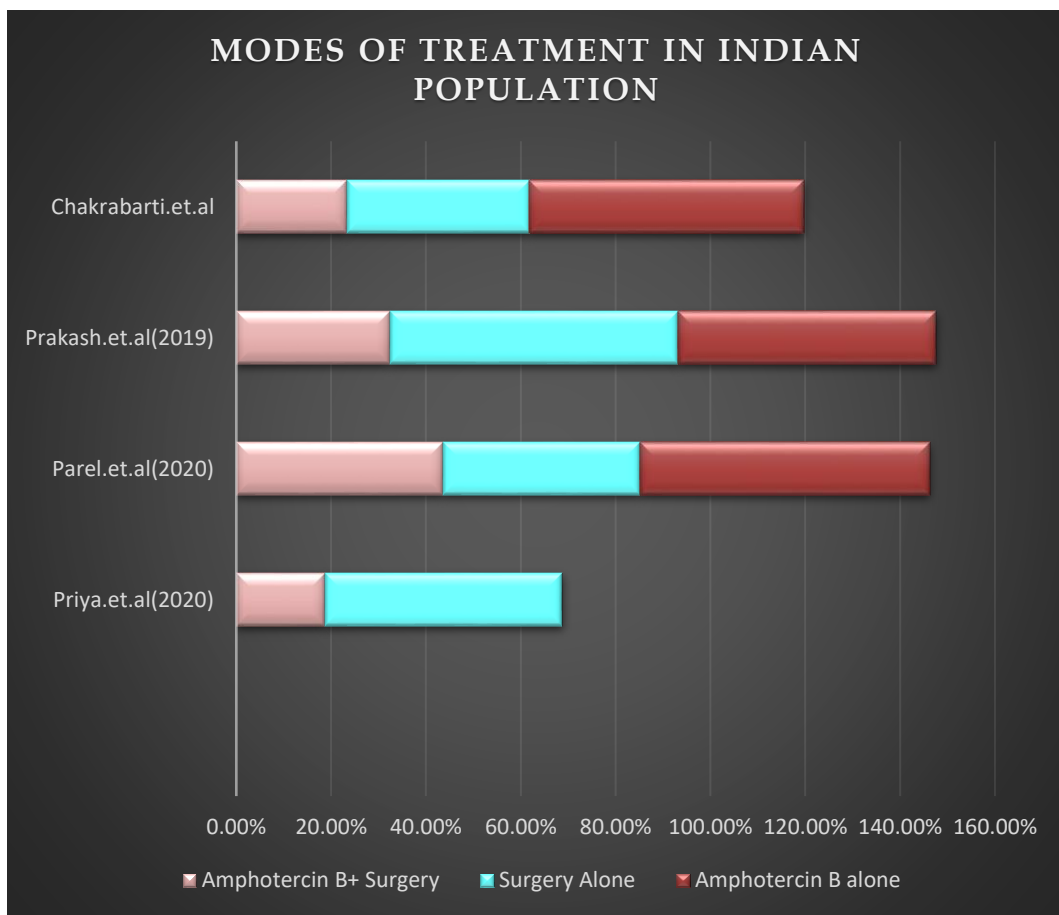


Figure 4: Data is pooled from the different study groups and treatment modalities given to the number of a patient in different study designs.

The holistic intrigue of mucormycosis :

Ayurvedic modus Operandi: Ayurveda is “*Swasthasya Swasthya rakshanam*”, “*Aturasya Vikara Prashamanam Cha*,” the context explains the importance of maintenance and promotion of health in healthy, along with treating a sickness (Godbole, 2016). We do not get the direct reference of mucormycosis in *Ayurveda* classical texts though we can correlate with many other pathological conditions. *Sushruta* included *Raktavahi Dhamini* (blood vessels). *Rakta* (blood) is a vital entity in the sense of maintaining a consistent internal environment. It is critical for the continuation of life. As *Dosha* is

responsible for the birth of the living body, a fourth entity known as *Rakta Dhatu* (blood) also plays a role in origin, sustenance, and death. *Sushruta* is referred to be the *Rakta Dhatu*'s fourth *Dosha* (blood). *Nidana Sevana* leads to *Dosha Dusti*, and when these *Doshas* reach *Rakta Dhatu*, they lead to *Rakta Pradoshaja Vikara*. The *Dosas, Dhatus, and Malas* have a pleasant connection in the human body when it is operating properly and harmoniously.

This is known as the *Asrayasrayee-Bhava* connection. However, there is a restriction to this positive association. So, as long as the *Dosas* are in a balanced state, they do not hurt the host, but when they get vitiated by the aforementioned etiological reasons, they fail to maintain the relationship. Initially, they become aggressive and attempt to injure the host by causing disruptions in their normal function, and after progressing to the next stage of *Samprapti*, they attempt to show several symptoms leading to a clinical entity at numerous places. *Dosha-Dusya Sammurchana* is the name given to this uncomfortable connection. When the *Dosha* vitiates *Rakta Dhatu*, it travels to various parts of the body, causing a range of symptoms. Though *Vagbhata* (A.S. & A.Hr) does not name the *Dhatu Pradosaja Vikaras* individually, the ailments described in *Siravyadha Vidhi Adhyaya* are quite similar to the ailments described by *Charaka* and *Susruta* as *Rakta Pradosaja Vikaras* ([Tadasad et al., 2018](#)), ([Kumar et al., 2020](#)).

Extensive research has previously been conducted to investigate the pathophysiology of immunological dysfunction in *Madhumeha* (Diabetes Mellitus) phagocytic mechanisms such as leukocyte chemotaxis and impairment during hyperglycemia and diabetic acidosis. According to certain research, increasing glycation/glucose in *Madhumeha* Patients (Diabetes Mellitus) is correlated with reduced production of Interleukin-1 and interleukin-6 by mononuclear cells and monocytes. Several studies have demonstrated that when HbA1c (glycated hemoglobin) is less than 8%, the proliferative activity of CD4T-lymphocytes and their antigen responsiveness is compromised. Overall, a damaged and unbalanced immune system exposes the hyperglycaemic individual's epidermis to microbial invasion by both infection and non-infection germs ([Gill Dimpal, 2020](#)).

Figure 5: Showing Probable Etiopathogenesis of Mucormycosis according to Ayurved

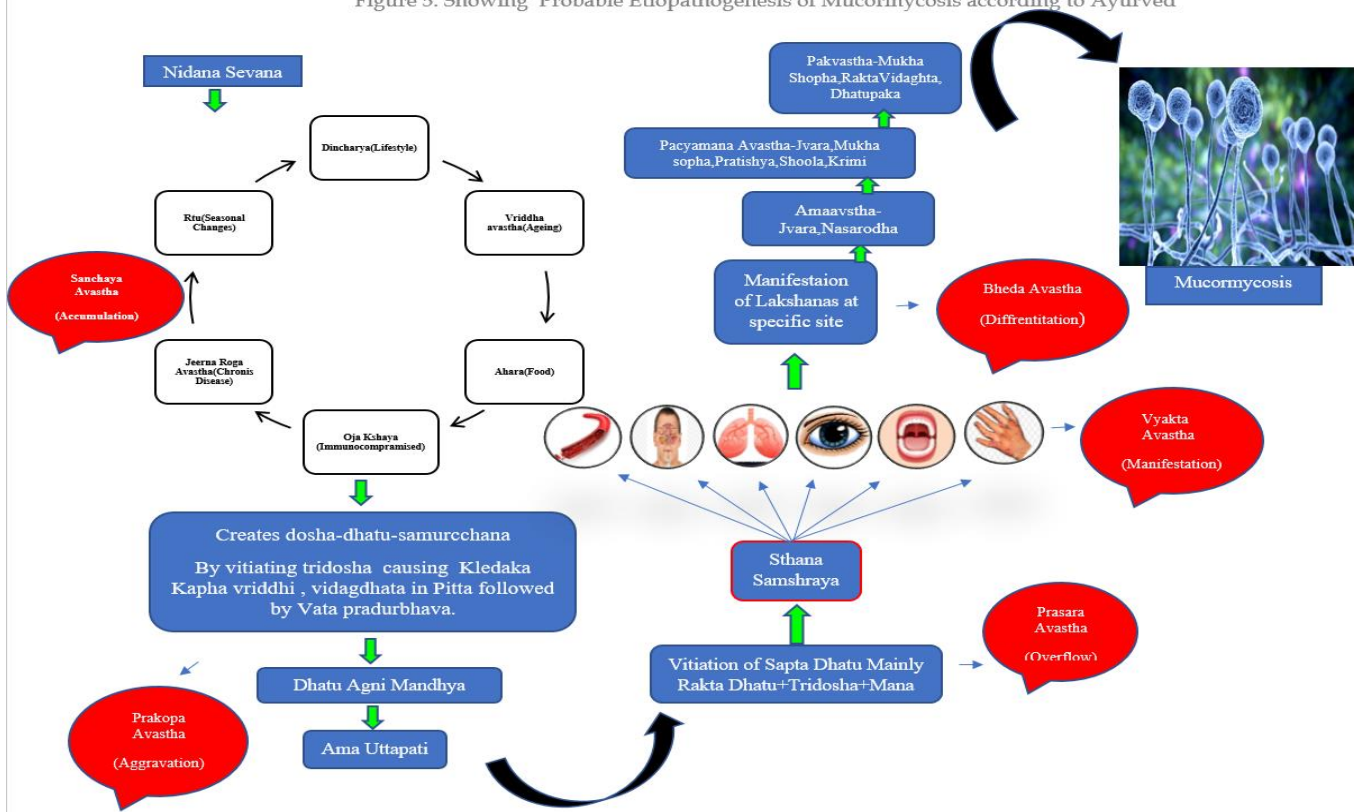


Figure 5: Showing Probable Etiopathogenesis of mucormycosis according to Ayurved.

Probable etiopathogenesis of mucormycosis according to Ayurved:

According to research, *Manobhitapakara Bhavas* (psychological stresses) have a significant influence on changing defensive systems and developing DM. As a result, psychotherapy, counseling, and *Manasa Doshahara Karma* (anti-stress techniques) should be favored above medications to halt the vicious pathogenesis of diabetes (R. Sharma et al., 2015). *Amashaya* is the seat of both the *Kapha* and *Pitta Doshas*. As a result, *Sthana Dushti* leads to *Pitta Dushti*. *Amashaya's* combination of *Vikruta Kledaka Kapha* aggravates the *Prakrit Pitta Dosh* *Rakta Dushti* is triggered by vitiated *Pitta* and *Kapha Doshas*, resulting in *Daha, Raga, Paka, and Shopha* (inflammation) in the body causing the development of different *raktapradosaja vikara* at various *sthana* affected (Kumar et al., 2020);(Thakur et al., 2021).

The significance of primary prevention lies in intervening at the pre-pathogenic phase, this can even be used to prevent chronic diseases. It can be understood by the following points :

- a) *Dinacharya* – Daily regimen to be followed by an individual.
- b) *Ritucharya* - Seasonal regimen to be followed by an individual.
- c) *Samshodhana* - Seasonal cleansing of the individual.
- d) *Adhaaraniya Vegas* - Non-retention of the natural urges.

- e) *Rasayanas* – Intake of Rasayanas.
- f) *Sattvavijaya* - Improving mental strength with the help of Yoga and Dhyana.
- g) *Ahara*-To builds a proper defense system & to the normal functioning of the bodily system which can prevent the spread of the disease ([Vasant Patil, Madhuri Rodd, Shruti Naik, 2020](#)).

Dincharya (Daily Regimen): Many notions are given in *Ayurvedic* literature to preserve dental and nasal health. *Mukhapaak* (Oral Hygiene) is a *Mukharoga* (Diseases of Mouth) that can be found throughout the oral cavity. *Acharya Kashyap* and *Charak* called it *Mukhapaka*, whereas *Acharya Sushruta* and *Vagbhata* called it *Sarvasara*. *Sarvasara* is a disorder that can develop over the buccal mucosa ([Ghadage & Landge, 2020](#)). Tongue scraping improves the elimination of anaerobic bacteria and reduces the development of microorganisms in the oral cavity. The use of *Neem* (*Azadirachta indica*) leaves is a powerful antibacterial, antifungal, antiviral, and antioxidant in the property, same as *Tulsi* (*Occimum sanctum*) leaves, *Haridra* (*Curcuma longa*), *Lavanga* (*Clove - Syzygium aromaticum*), and *Nagvelli* (*Piper betle* Linn) may be used to maintain oral cleanliness ([Vasant Patil, Madhuri Rodd, Shruti Naik, 2020](#)). *Shodhan Kaval* (Purificative Oil Pulling) uses astringent, sour, or salty medicinal decoctions for their cleaning function in *Kaphaj* illnesses of the mouth ([Shukla & Khuje, 2019](#)).

Mukharoga is dominated by *Kapha* and *Rakta Dusti* (Impure Blood), hence *Rakta Mokshana* (Bloodletting) is the primary treatment, followed by *Kosthashudhi* (Purification of Digestive System) by *Virechana* (Laxative), *Kavala Graha* (Oil Pulling), *Gandusha* (Mouth Irrigation), and *Nasya-Pratimarshya*. *Nasya* (oil or smoke forms is infused into the nostrils) with *Anu Taila* (Oil) is recommended to prevent the introduction of spores into the respiratory system and the destruction of germs. *Shirovirechana*, *Pratisarana*, *Dhooma* (Fumigation), *Agni karma* (Thermal Micro cauterly), and *Ksharakarma* (Caustic Therapy) are also beneficial in *Mukhrogas* (Diseases of Mouth). *Charak* has informed *Pradhamana Nasya*, *Virechana* (Laxative), *Vaman* (Vomiting), *Lekhana* (Scrapping), and *Shamanahara Dravyas* (Alleviating Drugs) in *Mukharogas* (Diseases of Mouth) ([Mukhapaka, 2019](#)).

Anjana (Application of Collyrium). Using a *Shalakha* (small metal stick) or a fingertip, apply medicinal collyrium to the inside area of the eyelid. *Ayurvedic* literature explains the daily usage of *Srotanjana* and the usage of *Rasanjana Shodhana* (Purification) by *Shirovirechana* (Medicated Errhine) with *Vidanga* (*Embeilia ribes*) *Taila* (Oil) / *Shigru* (*Moringa oleifera* Lam) *Taila* (Oil) and *Vairechanika Dhooma* is highly effective. *Dhupana Karma* (Fumigation Therapy). The *Samhitas* explain the common use of *Krimighna* (Anti-helminthic) and *Kusthahara* (Treats skin disease). *Guggulu* (*Commiphora mukul*), *Vacha* (*Acorus calamus* Linn), *Neem* (*Azadirachta indica*), *Haridra* (*Curcuma longa*), *Kustha* (*Saussurea lappa*), *Jatamansi* (*Nardostachys jatamansi*), *Sarjarasa* (*Vateria indica* Linn), and other antimicrobial and antifungal herbs ([Vasant Patil, Madhuri Rodd, Shruti Naik, 2020](#)). ([Debjit Bhowmik, Chiranjib, 2010](#)) are utilized in *Rakshoghna* (remove obstacles and miseries) and *Dhupana* (Fumigation)

medicines. The names of the majority of *Dhoopan Dravyas* are not revealed since the *Dravyas* are chosen depending on the predicted effects of the medicine. *Dhupana* (fumigation) with *Vidanga* (*Embeilia ribes*), *Khadira* (*Senegalia catechu*), *Sharshap* (*Brassica juncea*), *Vacha* (*Acorus calamus* Linn), *Devdar* (*Cedrus deodara*), *Nimba* (*Azadirachta indica*), etc is recommended for skin problems ([Shrestha et al., 2017](#)).

Rasayana (RejuvenationTherapy):Is an immunomodulator that can improve andincrease one's immune system if ingested appropriately and for a set length oftime, according to ancient writings. Immune system strengthening isaccomplished by the use of *Rasayana* (*Rejuvenation Therapy*) and *Vajikarana* (Sexual Health & Disease) treatments, as well as *Ojovardhaka* (*ImmunityBooster*) treatments *Aswagandha* (*Withaniasomnifera*), *Shilajit* (*Asphaltum*), *Amalaki* (*Phyllanthus emblica*), *Guduci* (*Tinospora cordifolia*), *Pippali* (*Piperlongum*), *Punarnava* (*Boerhaviadifussa*), and other natural immunomodulators ([Wankhede et al., 2021](#)).*Rasayana* (Rejuvenation Therapy) medicines aid in the healing of the lungparenchyma andincrease the qualitative and quantitative generation of T cells.

Preparations that arecommonly used asRespiratory immunomodulators are,

- A . *Mahalaxmi Vilasa Rasa*
- b. *Chyavanprasha Leha*
- c. *Pippali Vardhamana Rasayana*
- d. *Agastya Haritaki Rasayana*
- e. *Amalaki Rasayana* ([Vasant Patil, Madhuri Rodd, Shruti Naik, 2020](#)).

Methanolic fraction and an aqueous fraction of *Tulsi* (*Ocimum sanctum*) showed antifungal activityagainst dermatophytic fungus. Fixed oil and linolenic acid present in *Tulsi* (*Ocimum sanctum*) can block cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. Therefore they show anti-inflammatory activities against PGE₂, leukotrienes induce edema ([Kaushik Vilas Kulkarni, 2018](#))([Meena et al., 2010](#)). *Haridra* (*Curcuma longa* L.) *Curcumin* is a dynamic antiviral that reduces the replication of viruses. Several studies have shown that curcumin possesses some pharmacologicalproperties such as anti-inflammatory, anti-angiogenic, and anti-neoplastic, withouttoxicity. *Ginger* (*Zingiber officinale*) has antiemetic, antipyretic, analgesic, antiarthritic, and anti-inflammatory activities.*Cinnamon* (*Cinnamomum cassia*)several scientific studies have shownantimicrobial, antiviral, antifungal, antioxidant, antihypertensive, antidiabetic, antitumor, gastroprotective, and immunomodulatory effects.

Launga (*Clove -Syzygium aromaticum*) the main bioactive component of clove is eugenol Eugenol exhibits broad antimicrobial activities against both Gram-positive, Gram-negative, and acid-fact bacteria, as well asfungi. *Black pepper* (*Piper nigrum*) contains major pungentalkaloid piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological properties such asantihypertensive, anti-Alzheimer's, antidepressant, antiplatelets, anti-inflammatory, antioxidant, antipyretic, antitumor, antiasthmatic, analgesic, antimicrobial. *Garlic* (*Allium sativum* L) anthelmintics, anti-inflammatory, antioxidant, antifungal. *Giloy* (*Tinospora cordifolia*) has

antiviral action, immune booster ([N. A. Singh et al., 2021](#)). *Triphala* extracts *Amalaki* (*Phyllanthus emblica*), *Bibhitaki* (*Terminalia bellirica*), and *Haritaki* (*Terminalia chebula*), demonstrated antimicrobial property against *Lactobacilli* and *C. albicans* with a maximum zone of inhibition of 22 mm at 6% and 20 mm at 9% ([Chainani et al., 2015](#)).

Disc diffusion, micro broth dilution, and percent spore germination inhibition assays were used to assess antifungal efficacy against pathogenic *Aspergilli*. *Dhatuira* (*Datura metel*.Linn) and *Kantakari* (*Solanum xanthocarpum*) were shown to have high antifungal action ([Dabur et al., 2004](#)). *Gandhaka Rasayana* (Sulfur processed with herbal juice) the solution in higher concentration showed similar antifungal activity against *Aspergillus niger* ([Saokar et al., 2013](#)). *Shankhapushpi* (*Convolvulus pluricaulis choisy*) showed antimicrobial, insecticidal, antifungal, antibacterial, and anthelmintic activity. The alcoholic extract of CP possessed potent antifungal activity ([Amin et al., 2014](#)).

Secondary Prevention is fundamentally the realm of *Ayurveda* practice. It is mostly an important tool in controlling a disease process and prevents any further attack ([G.Vyas, 2020](#)).

Probable Principle of Treatment could be :

1. *Agnideepan* (Increase Appetite)
2. *Ojo Vriddhi* (Immunity)
3. *Krimighna Chikitsa* (Antihelminthic)
4. *NetraPrakshalan* (washing of eyes with decoction) -*Tankana* (Borax), *Sphatika*(Alum), *Yashada* (Zinc oxide prepared naturally), *Panchavalkala-Vata* (*Ficus benghalensis* L), *Peepal* (*Ficus religiosa* L), *Udumbar* (*Ficus infectoria* L), *Plaksha* (*Ficus infectoria* Roxb.) and *Shirisha* (*Albizia lebeck*) can be used effectively.
5. Management of *Tridosha* (three vital humours) -*Kapha-Pittahara Chikitsa* initially followed by *Vata*balancing. Different formulations like *Vati*, *Churna*, *Ghrita*, *Kashaya Kalpana* can be used. *Vati Kalpana*: *Panchanimba Gulika*, *Talakeshwara Rasa*, *Rasamanikya*, *Talasindhura*, *Mallasindhura*, *Cap Pentaphyte P-5* ([Vasant Patil, Madhuri Rodd, Shruti Naik, 2020](#)), *Kaisora Guggulu*, *Krimighnaghana Vati*, *Vishavilwadi Gullika*, *Arogyavardhini Vati*, *Mriganka Rasa* ([Dr.L.Mahadevan, Dr.G.Aishwarya, 2021](#)), *Nishamalki Vati* ([Dawane et al., 2016](#)) & *Madhu Snuhi Rasayan* ([Hebber, n.d.](#)) can be beneficial. In *Churna Kalpana*- *Panchanimba Churna*. *Sudarshan Churna* ([B. Singh et al., 2011](#)), *Triphala Churna* ([Gautam et al., 2012](#)), *Gandhaka Rasayan* ([Saokar et al., 2013](#)), *Suvarna Malini Vasant Rasa* ([J. Singh, 2014](#)), *Madhu Snuhi Rasayan* ([Dr.Jv.Habber, 2012](#)), *Navayas Loha*. Formulations like *Aragvadadi kashayam*, *Amrtottaram kashayam*, *Guducyadi kashayam*, *Nimbadi kashayam*, *Shonitamritam kashayam*, *Katakakadiradi kashayam* & *Katakakadiradi kashayam* can be used along with *ghrita* formulations like *Mahatikta Ghrita* ([Swagata Chakraborty, 2020](#)), *Gugglu Tikta Ghrita* ([Ayurvedline, 2018](#)) can be used.
6. Use of *Raktashodhan* (Blood Purifiers) & *Prasadhan* (Improving Blood Circulation), *YakrutShodha* (Liver Purifier) is needed.

7. *Pathya-Apathya Ahara*- Avoid excess of sour, salt, and spicy substances, fatty, heavy, curd, acidic foods (such as cabbage, cauliflower, beans, palak, mushroom, etc ([Vasant Patil, Madhuri Rodd, Shruti Naik, 2020](#)).
8. *Rakta Mokshana: Suptata* (Numbness) is a symptom of *Twakgata Vata* and can be considered a pathology of superficial nerve involvement. *Acharya Sushrut* recommends *Raktamokshana* (Bloodletting) to help relieve *Rakravrita. Vata* and remove. *Dushita Rakta* (Contaminated Blood) from *Twak* (Skin), thus providing relief in *Suptata* (Numbness), which is one of the early signs of mucormycosis. *Raktamokshana* (Bloodletting) aids in the relief of symptoms such as *Ruk* (Pain) by lowering *Amlata* (Sourness) in *Rakta* (Blood) ([Sethi & Rajan, 2018](#)), ([Kashyap et al., 2019](#)). *Jaluka* (Leech) can be proved beneficial in diabetes-related cutaneous mucormycosis and conditions like periorbital cellulitis as it has different bio active constituents which are the therapeutic saliva ([Anjali, Gunjan Sharma, 2016](#)). It can also be used in treating inflammatory conditions developed due to mucormycosis superficially ([Pundge & Kotangale, 2015](#)).
9. *Arka Tail* can be used externally for *Aspergillus niger* infection ([Dr. Ritika Shah, Dr. Ekta Tomar, 2017](#)), ([Vaghela et al., 2011](#)).
10. *Neti Kriya: Neti* cleanses the skull, improves vision, and relieves ailments that present above the base of the neck. *Neti* eliminates foreign things such as allergens and dust and improves nasal outflow by reducing mucus stasis. *Neti* can be used to treat *Kapha*-dominant disorders such as sinusitis, rhinitis, rhinosinusitis, and allergic rhinitis ([Meera et al., 2020](#)). These can be used depending upon the predominance of *Dosha Avastha* and *Rogi Bala*. *Kashya* (Astringent), *Tikta* (Bitter) *Rasa Prayoga, Rakta Prasadana* (Improving Circulation), *Ojo Vriddhi* (Immunity), *Krimighna* (Antihelminthic), the probable treatment protocol that can be followed is *Kapha Pittahara, Rukshan* (Dryness), *Dhatugata Jwara Chikitsa* (Fever), *Vishaghana Chikitsa* (Antitoxins).

CONCLUSION :

However, the range of chemicals that cause the illness is far broader than it looks. Early detection of the disease has become a big challenge in India due to a lack of public knowledge about disease diagnosis and delayed medical treatment, where individuals are less worried about their health and do not attend associated examinations. To undertake relevant research, it is also necessary to evaluate several viewpoints of antifungal therapy accessible in conventional systems of medicine and other associated disciplines, as relying solely on one drug might be difficult in such a densely populated nation as India. COVID-19 has been renovated several times, and "Black Fungus" will be remodeled as well. At this point, better laboratory technology is necessary. *Rhizopus arrhizus* is the most common causative agent in all studies through the brim of the causative agent is larger.

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