



The Unholy Consortium between COVID-19 and Mucormycosis and Identification of Some Potential Antifungal Herbs: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author TY conceptualized, searched the literature, wrote and edited the first and final draft of the manuscript. Author SS searched the literature, screened, and made a critical revision of the manuscript. Author AAK revised the first draft, made a critical revision and edited final draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: There has been a rise alarming in the number of Mucormycosis post COVID-19 infection. The enigmatic relationship between SARS CoV-2 and Mucormycosis is very complex. So far as the treatment is concerned, mankind is yet to discover a potent therapeutic drug that could effectively be used to treat this deadly fungal infection. For ages, mankind has always looked toward nature, and perhaps herbals are the best options in our quest to search for effective antifungal drugs against the ruthless and invasive Mucorales.

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Methods: A comprehensive literature search was conducted across the PubMed database, LILACS, the Cochrane Register of Controlled Trials, Google Scholar and others using key words COVID-19, SARS CoV-2, Mucormycosis, *Rhizopus*, vaccine, steroids, antifungal drugs and herbals. Full texts of the retrieved articles published in English were accessed.

Results: A handful of medicinal plants such as *Satureja khuzestanica Jamzad*, *Thymus danensis* and *Thymus carmanicus*, *Thymus vulgaris L*, *Lavandula angustifolia*, *Mentha piperita* and some species of pepper such as *Piper sp.*, *Piper tuberculatum* and *P. hispidum* have all shown to have a promising antifungal effect on Mucorales fungus.

Conclusions: Limited knowledge and resources on antifungal (anti-Mucorales) due to lack of adequate research and clinical studies limits our search to identify potent antifungal herbs. An intensified research and evaluation for antifungal herbs can boost the identification, design and development of newer drugs with lesser adverse drug reactions and better mortality rate.

Keywords: COVID-19; SARS CoV-2; Mucormycosis; *Rhizopus*; vaccine; steroids, antifungal drugs, herbals.

ABBREVIATIONS

AYUSH : Ayurveda Yoga and Naturopathy
Unani, Siddha and Homeopathy

ICU : Intensive Care Unit

FDA : Food and Drug Administration

1. INTRODUCTION

Mucormycosis is an Angio invasive disease caused by saprophytic fungi characterised by extensive angioinvasion that results in vessel thrombosis, subsequent tissue infarction and necrosis. It is caused by fungi of the Mucorales order of the class of Zygomycetes [1]. Furbinger first described the disease in Germany in 1876 [2]. Mucorales fungi are the next commonest pathogen after the genus *Aspergillus sp* in patients with haematological malignancy, solid organ transplantation and haematopoietic stem cell transplantation [3]. The major route of transmission occurs through inhalation of sporangiospores. However, other routes such as direct Implantation into injured skin, ingestion of spores, contact from contaminated soil and intravenous transmissions in drug users are some other routes. Usually, nasal inoculation is followed by rapid progression, extending to neighboring tissues, including the orbit, and sometimes to the brain [4]. Based on clinical presentations, Mucormycosis is classified accordingly as rhinocerebral, cutaneous, pulmonary, renal, gastrointestinal and disseminated. Other uncommon, rare forms, such as peritonitis, renal, endocarditis, osteomyelitis etc. [2]. Various studies have demonstrated that patients with Diabetes mellitus, haematological malignancy and chemotherapy, solid-organ transplant recipients on Immunosuppressive therapy, iron overload,

chronic kidney failures, extensive skin injury, human immunodeficiency syndrome and prolonged neutropenia are at increased risk of acquiring Mucormycosis [1-4].

There has been an alarming rise and considerable amount of Mucormycosis infection post COVID-19 treatment reported across various parts of the world. However, the exact cause and mechanism of the association between the two diseases largely remain idiopathic. The study aims to understand the correlation between the existence of these two diseases. It is also understood that most drugs used as antifungal treatments have various drawbacks regarding toxicity, efficacy, and cost. Their frequent use has also led to the development of resistant strains. Medicinal plants are a rich source of antimicrobial agents and can be used as antimicrobial remedies. Although extensive research has been done on medicinal plants and their antifungal properties against many fungal species, studies on the antifungal properties of medicinal plants for Mucorales remain scarce or limited to date. The study aims to identify some potential herbals with anti-Mucorales (antifungal) properties.

2. METHODS

A comprehensive literature search was conducted across the PubMed database, LILACS, the Cochrane Register of Controlled Trials, Google Scholar and others using key words COVID-19, SARS CoV-2, Mucormycosis, *Rhizopus*, vaccine, steroids, antifungal drugs and herbals. Full texts of the retrieved articles published in English were accessed.

2.1 Mucormycosis Post COVID-19 Treatment: Associated Risk Factors

The novel coronavirus disease COVID-19 is a highly contagious viral infection first reported in Wuhan, China, which subsequently spread worldwide [5]. Despite many people having recovered from the viral infection, very little is known about possible clinical sequelae that may persist after the viral infection. A study in Italy found that in patients who had recovered from COVID-19, 87.4% reported persistence of at least 1 symptom. At 60-day follow-up, (55%) reported three or more symptoms, fatigue (53%), dyspnoea (43%), joint pain (27%) and chest pain (22%). It is also noted that COVID-19 was associated with worsened quality of life among 44% of patients [6]. Among many other complications, there is a spurt of Mucormycosis in recovered and fresh COVID-19 cases reported worldwide. Many studies on Mucormycosis have been published in various journals, unearthing the incidences and clinical features of Mucormycosis among the post COVID-19 recovered population. The enigmatic relationship between COVID-19 and angioinvasive Mucormycosis also known as COVID-19 associated Mucormycosis (CAM) has not been fully understood to date as the study continues. Clinical studies and case reports suggest that post COVID-19 treatment; the fungal infection is largely attributed to low immunological functions, which could be associated with various predisposing factors and underlying causes like age, comorbidities, uncontrolled Diabetes mellitus, post-transplant, malignancy, rampant use of corticosteroids during the COVID-19 infection period etc. [7–9]. The pathophysiology in COVID-19 associated Mucormycosis (CAM) is very broad due to multiple predisposed factors involved and the complex immune interaction with the SARS-CoV 2.

Data suggest that the prevalence of Mucormycosis is around seventy times higher in India than that in global data. Among patients, the case fatality was observed to be highest with disseminated mucormycosis. Studies also indicate that in India, Diabetes mellitus is the most common risk factor associated with Mucormycosis whereas Rhino-Orbital-Cerebral Mucormycosis (ROCM) is the most common form of Mucormycosis. Globally, the most common fungal species or causative agent responsible for Mucormycosis infection is *Rhizopus arrhizus* [1–3].

2.2 Diabetes Mellitus and COVID-19 Associated Mucormycosis (CAMCR)

While reviewing the published COVID-19-associated Mucormycosis (CAMCR) cases (total of 41), it was found that CAMCR was typically seen in 94% of the patients with diabetes mellitus, of which 67% were patients with poorly or uncontrolled Diabetes mellitus. Diabetes mellitus, a "classic" risk factor for Mucormycosis, is associated with increased morbidity and mortality in COVID-19 [10]. A multicentred epidemiologic study of COVID-19 disease-associated Mucormycosis (CAM) across India also found that uncontrolled Diabetes mellitus was the most common underlying disease among CAM and non-CAM patients [11]. The "Diabetogenic state" in SARS CoV-2 infection and its severity could be suggested by the evidence that SARS CoV-2 induces damage to pancreatic islets, resulting in acute Diabetes and Diabetic ketoacidosis. These could be supported by the high expression of angiotensin-converting enzyme 2 (ACE2) receptors in pancreatic islets, along with increased insulin resistance due to cytokine storm [10,12]. Diabetes mellitus is the single most common risk factor being reported as prominent underlying predisposed risk factor for Mucormycosis in various studies. Although many other organs and tissues are also affected, studies have shown that the clinical manifestation is mostly attributed to rhino-orbital and rhino-orbital-cerebral presentation in Diabetic patients. There are various studies, reviews and case presentations reported on the linkage of uncontrolled Diabetes with COVID-19-associated Mucormycosis across various journals which indicates that Diabetes mellitus is a high-risk factor for the infection of Mucormycosis in immunocompromised individuals [6,10].

2.3 Immunosuppression by Steroids

In the backdrop of this COVID-19 expression, various studies have indicated that immunocompromised individuals with prolonged systemic corticosteroid use are more susceptible to Mucormycosis. Because of their anti-inflammatory effects, corticosteroids are commonly used as adjuvant therapy for acute respiratory distress syndrome. However, it is highly controversial for patients with severe viral pneumonia infections [13]. Over the past 20 years, case reports and various studies have indicated the growing number of Mucormycosis following Bone marrow transplants (BMT) and

Haematological malignancies (H.M.), which is due to prolonged treatment of the patients with steroids and immunosuppressive agents [14]. In a comparative study of influenza-associated Mucormycosis (IAM) versus COVID-19 associated Mucormycosis (CAM), patients with CAM and IAM received steroids as adjuvant treatment or for viral pneumonia or underlying medical conditions. The use of steroids was a prominent risk factor for developing Mucormycosis in 66.7% of patients with viral pneumonia [15]. The acute increase in Mucormycosis could be associated with the immunocompromising effects of corticosteroids and microangiopathy in Diabetes and possible peripheral microthrombi in COVID-19. The high incidence of Diabetes could further support this in our population and widespread use of corticosteroids such as Dexamethasone and methylprednisolone as a treatment intervention for COVID-19. Patients become more susceptible to secondary infections due to the immunosuppressive nature of glucocorticosteroids [16].

Prolonged Intensive care unit (ICU) stays:

Mucormycosis is a very severe infection that may be acquired in the Intensive care unit (ICU) or, when acquired elsewhere, require critical care. Infections caused by filamentous fungi, such as Mucormycosis infections, represent a major burden in the ICU. Over the years, many cases have been diagnosed in the ICU. This could be attributed to the challenges in diagnosis due to the non-specific signs and symptoms of the condition. Some characteristic clinical presentation includes progressing necrotising lesions in the rhino-sinus area, skin, lungs and soft tissues of immunocompetent hosts such as patients in the ICU. There is a lack of epidemiological data concerning ICU stay, but gradually Mucormycosis is frequently reported as individual case reports or as a small series in ICUs. A study from one centre found that 37% of Mucormycosis cases were diagnosed in patients treated in the ICU [17]. Despite the latest advances in ICU standard of care, the global ICU mortality for Mucormycosis remained very high, reaching 71.6%. A French multicentre cohort indicates that the prognosis of Mucormycosis in ICU remained poor, especially in those with haematological malignancies, older patients with malnutrition, and numerous predisposing factors [18]. These studies suggest immune-compromised patients with various predisposing factors, healthcare-acquired infections, and excessive or prolonged overuse of

corticosteroids associated with prolonged ICU stay, especially after COVID-19 infections, could be a major cause of Mucormycosis infections.

Comorbidities and malignancies: Prevalence of comorbidities and malignancies among the COVID-19 infected population has contributed to the severity and high mortality rate. Various studies have revealed that common comorbidities such as Diabetes mellitus, Hypertension, obesity, cardiac disorders, respiratory disorders, renal disorders etc., have been found to dampen the immunological functions, leaving the COVID-19 infected person in more critical condition [7]. A multicentre observational study involving 465 individuals diagnosed with Mucormycosis revealed that comorbid illnesses such as chronic kidney disease 93 (20%), Cardiovascular 67 (14.4%), Pulmonary 30 (6.5%), Liver disease 24 (5.2%), Neurological 18 (3.9%) were prevalent [19]. There is a rise in the reported case of Mucormycosis among patients with haematological malignancies (H.M.) such as acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) and in bone marrow transplant (BMT) recipients over last two decades. These could be due to neutropenia and immunodeficiency associated with chemotherapy and post-transplant steroid treatment leading to diminished or dampened immune functions in an individual [14]. The chances of survival increase in cases with better controlled comorbid conditions. These comorbidities and malignancies greatly affect the outcome of a patient's infection and mortality.

2.4 Post-transplant

Mucorales are angioinvasive and can infect any organ system; however, in solid organ transplant recipients, the lungs are the predominant site of infection. Post-transplant of any organs can virtually affect every organ, such as the skin, gastrointestinal, genitourinary, cardiovascular, and musculoskeletal systems, as well as infections of surgical wounds [20]. Studies have shown that infection is most commonly acquired during the nadir of immunosuppression between one- and six months post-transplantation. These could be associated with increased immunosuppression for the treatment of rejection or anti-rejection therapy and enhanced incidence of fungal infection [21]. Invasive fungal infections (IFIs) occur in up to almost 20% of recipients of renal transplantation. Among all the Mucorales,

Rhizopus species is the most common, accounting for 35%–73% of cases, followed by *Mucor* (13%–37%) and *Lichtheimia sp* (0%–13%) [20]. A recurrent pulmonary Mucormycosis after lobectomy in a non-smoking patient without any known predisposing risk factors has also been reported in a case study [22]. Donor-derived fungal infection has also been reported in two patients who developed renal Mucormycosis following transplantation of kidneys from the same infected donor [23]. A person with a post-transplant history, either with or without a history of Mucormycosis infection, when infected with SARS COV-2 is more prone to get a fungal infection due to the immunosuppressed conditions. These could result from prolonged and excessive immunosuppressive drugs, steroids, comorbidities, immunosuppressive therapies and other underlying risk factors [24].

Some of the underlying causes for the COVID-19 associated Mucormycosis (CAM) are enlisted in the Table 1.

Treatment/mitigation of mucormycosis: The therapeutic approach to Mucormycosis is multimodal, including antifungal agents, surgical debridement and correction of the underlying predisposing factor of the disease. The treatment outcome in Mucormycosis thus mostly depends on the influence or correction of underlying

metabolic conditions and immunosuppressive state such as neutrophil recovery in neutropenic patients, steroid tapering in patients receiving corticosteroids etc. [25]. Several other factors such as heterogeneity, pleiotropic clinical presentation, the multitude of the fungal species, factors related to surgery (e.g., timing, radicalness), can all contribute to the outcome of the treatment and management of Mucormycosis [26]. Given that cases of Mucormycosis infection in post COVID-19 patients are mostly due to the predisposing risk factors associated with prolonged use of corticosteroids for acute respiratory distress syndrome, the treatment is critical and challenging.

Primary antifungal therapy for Mucormycosis is mostly based on polyene, as Amphotericin B deoxycholate (AmB) remains the only licensed antifungal agent for the treatment of Mucormycosis. However, lipid formulations of AmB (LFABs) are significantly less nephrotoxic and can be safely administered at higher doses for a longer period as compared to AmB, which is recommended against due to substantial toxicity, but may be the only option in resource-limited settings [27,28]. The global guidelines for diagnosis and management of Mucormycosis recommends the first-line treatment with high-dose liposomal amphotericin B. At the same time, intravenous isavuconazole and intravenous

Table 1. Most common cause of COVID-19-associated Mucormycosis (CAM)

SI.No	Factors/underlying conditions	CAMCR
1	Uncontrolled Diabetes mellitus	Diabetogenic state" in SARS CoV-2 infection-SARS CoV-2 induces damage of pancreatic islets, resulting in acute Diabetes and Diabetic ketoacidosis [10–12,16]
2	Immunosuppression by steroids	Rampant use of corticosteroids/glucocorticoids leading to immunosuppression in the patient [13,15,16]
3	Prolonged ICU stays	Immunocompromised patients with predisposing factors and longer duration of ICU stay [17,18]
4	Comorbidities	Dampening of the immune system - Diabetes mellitus, Hypertension, obesity, cardiac disorders, respiratory disorders, renal disorders [7,14,19]
5	Malignancies	Neutropenia and immunodeficiency associated with chemotherapy and post-transplant steroid treatment-acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML), bone marrow transplant (BMT) [1–3]
6	Post-transplant	The nadir of immunosuppression - solid organ transplant recipients, e.g., lungs [20,21]

or delayed-release tablet Posaconazole are also recommended with moderate strength [28]. While some classes of drugs based on azoles such as fluconazole, itraconazole, isavuconazole, and voriconazole have been studied, studies suggest that fluconazole and voriconazole are not active against mucormycosis; however, itraconazole may yield some activity but may not be superior to Posaconazole [25,27,29]. Various studies have demonstrated that Posaconazole can be used as a salvage option for patients with Mucormycosis who are intolerant to polyene therapy. Despite dosing for months to years of administration, it also appears to be a safe alternate drug [27]. Adjunctive therapy with Isavuconazole and Posaconazole, hyperbaric oxygen, and recombinant cytokines, granulocyte transfusions can be considered for selected patients. Few studies also suggest that hyperbaric oxygen could be used as adjuvant therapy in treating Mucormycosis. This is based on the idea that increased oxygen concentration in tissues may increase neutrophil antifungal activity and the polyenes-induced putative oxidative killing mechanism [30]. Usually, hyperbaric oxygen therapy is well tolerated with a low risk of adverse events [31].

Prompt initiation of the treatment plan with amphotericin B and surgery is critical for successful management of Mucormycosis and has improved the mortality rate [29]. The surgical intervention is essential due to the angio-invasive nature of Mucormycosis agents, which results in extensive thrombosis in the blood vessels, leading to tissue infarction and necrosis that may impair or hinder the penetration of antifungal agents to the site of infection. Therefore, surgical debridement of necrotic tissues is essential for completely eradicating Mucormycosis from the body [27,28,32].

Search Result: A thorough literature search for antifungal properties against Mucorales was conducted across the various database. However, to date, few works are available on antifungals specifically against Mucormycosis. A handful of known or identified herbals with specific antifungal properties against Mucormycosis are discussed below.

2.5 Medicinal Plants with Antifungal Properties against Mucorales

It is also understood that most drugs used for antifungal treatments have various drawbacks

regarding toxicity, efficacy, and cost. Their frequent use has also led to the development of resistant strains [33,34]. We have identified some plant species with potential antifungal properties in our study, especially against Mucorales. Medicinal plants are a rich source of antimicrobial agents and can be used as antimicrobial remedies to prevent or treat various fungal infections. A study on effective medicinal plants on the important fungal strain and diseases suggests that certain plants exhibit antifungal activities against specific fungal species. The ethanolic extract of *Satureja khuzestanica Jamzad* leaves exhibited antifungal activity against saprophytic fungi *Rhizopus sp.* and *Mucor sp.* with minimal inhibitory concentration (625-5000 microg/ml). A study also found that *Thymus danensis* and *Thymus carmanicus* oils showed an inhibitory effect even at low concentration (300µl/L) against *Rhizopus stolonifer* at 600µl/L. Plate assays of the essential oil of *Lavandula angustifolia* and *Mentha piperita* also showed that the different concentrations of essential oils had antifungal activity against *Rhizopus stolonifera* [33]. The investigated antifungal activity of the essential oil of *Thymus vulgaris L.*, and its constituent thymol and p-cymene against *Rhizopus arrhizus* show that essential oil and thymol significantly inhibited mycelial development and germination of sporangiospores. Thus, relating to their interaction with ergosterol, the essential oils of *Thymus vulgaris* and thymol possess strong antifungal activity, which could be used in the treatment of Mucormycosis [34]. Another study also indicates the promising anti-*Rhizopus arrhizus* activity of *Piper sp.*, *Piper tuberculatum* and *P. hispidum* against planktonic cells, biofilm formation, and rhizopuspepsin. These essential oils possess a promising antifungal activity and could be useful in formulating adjuvants to limit the growth of *R. arrhizus* [35]. Evaluating the antifungal potential of *Syzygium aromaticum* (L.) essential oil against some common fungal pathogens of plants and animals, including *Mucor sp.*, and other fungal species, it was found that the fungus species were inhibited by the clove oil when tested through agar well diffusion method. The study concluded with findings that the antifungal action of clove oil is due to its high eugenol content present in *Syzygium aromaticum* (L.) [36]. A summary of some medicinal herbs with potential antifungal (anti Mucorales) properties is enlisted in the Table 2.

Table 2. Some medicinal herbs with potential antifungal (anti Mucorales) properties

Plant	Parts of plant	Action	Mucorales
<i>Satureja khuzestanica</i> Jamzad [33]	Leaves	Inhibitory	<i>Rhizopus</i> sp., <i>Mucor</i> sp.,
<i>Thymus danensis</i> , <i>Thymus carmanicus</i> [33]	Essential oil	Inhibitory	<i>Rhizopus stolonifer</i>
<i>Lavandula angustifolia</i> , <i>Mentha piperita</i> [33]	Essential oil	Fungistatic activity	<i>Rhizopus stolonifer</i>
<i>Thymus vulgaris</i> L [34]	Essential oil	Inhibit mycelial development and germination of sporangiospores	<i>Rhizopus arrhizus</i>
<i>Piper</i> sp., <i>Piper tuberculatum</i> and <i>P. hispidum</i> [35]	Essential oils	Against planktonic cells, biofilm formation and rhizopuspepsin	<i>Rhizopus arrhizus</i>
<i>Syzygium aromaticum</i> (L.) [36]	Essential oil	Inhibitory	<i>Mucor</i> sp.,

3. DISCUSSION

The main purpose of this article is to draw the attention of medical and pharmaceutical researchers to herbal medicine. Identifying new medicinal plants with strong antifungal properties against Mucorales fungal species could pave the way for the design and development of newer drugs with more efficacy and fewer side effects than the existing drugs.

There is an alarming rise in deadly fungal infections such as Mucormycosis among the population, especially after COVID-19. The authors aim to understand the enigmatic relationship between COVID-19 and Mucormycosis. Post COVID-19 treatment, the fungal infection could be largely attributed to the low immunological functions associated with various predisposing factors and underlying causes such as age, sedentary lifestyle, unhealthy eating habits, comorbidities, uncontrolled Diabetes mellitus, post-transplant, malignancy, rampant use of corticosteroids during the COVID-19 infection period etc.

Mucormycosis infection is caused by several fungi of the order Mucorales belonging to the class of Zygomycetes. These unusual associations between the two diseases could be due to multiple factors; however, Diabetes is the single largest known factor for Mucormycosis. An active ketone reductase system found in the Mucorales species such as *Rhizopus* enables them to thrive in hyperglycemic or high glucose and acidotic environment. Studies have also demonstrated that the serum in healthy

individuals could potentially inhibit *Rhizopus* unlike the serum in Diabetic ketoacidosis patients, which promotes its growth. These could also be associated with an impaired glutathione pathway which leads to decreased phagocytic activity in these patients [4].

The burden of viral infection and overuse of corticosteroids during the infection period could dampen the immune system, allowing opportunistic and invasive fungi such as Mucorales. During the initial phase of the pandemic, a higher methylprednisolone dose (approximately 70 to 140 mg) was recommended by Indian health authorities for the patients with severe and critical COVID-19. This was later reduced to a suggested dose of 32 mg/day by World Health Organization. Excessive use of Tocilizumab, an immunosuppressant in patients with COVID-19 can reduce patient's immunity and pose a significant risk for contracting CAM. The inappropriate use of such corticosteroids could have affected more immunocompromised patients, making them more vulnerable to Mucormycosis [37]. Rampant use of corticosteroids could also induce hyperglycemia in Diabetic patients which is also a risk factor for COVID-19 associated Mucormycosis infection. Various laboratory and biochemistry results has also provided the evidence for increased incidence of tissue damage and liver injury in rampant corticosteroid users. Age and immune mechanisms play a significant role during infection. Various studies have also observed that patients who survived the infections were mostly younger adults, free from any underlying predispositions such as Diabetes, Cardiovascular

disorders, Renal disorders and other immune deficiencies etc.

Currently, the options available for treating Mucormycosis are very limited to the rapidly growing number of infections. Several studies have also indicated that most available antifungal drugs have various drawbacks regarding toxicity, efficacy, increased drug resistance and cost. All these drawbacks contribute to the higher mortality rate of the patients with mucormycosis post COVID-19 treatment. The predisposing risk factors associated with low immune functions and increased resistance to the currently used antifungal drugs are intensifying the need for conducting pharmacological investigations to develop new antifungal drugs that could selectively act on new targets with the least side effects.

Medicinal plants' use to treat various diseases, including infectious diseases such as Mucormycosis, is not new to mankind. A significant number of drugs have been developed through plants and their derivatives. Although extensive research has been done on medicinal plants and their antifungal properties against many fungal species, studies on the antifungal properties of medicinal plants for Mucorales remain scarce or limited to date. The phytochemicals derived from various parts of the plants are of great importance in the production of antifungal drugs. Medicinal plants include *Satureja khuzestanica Jamzad*, *Thymus danensis* and *Thymus carmanicus*, *Thymus vulgaris L.*, *Lavandula angustifolia*, and *Mentha piperita* have been shown to exhibit interesting antifungal effects against the Mucorales. Studies have demonstrated that these medicinal herbs can inhibit the fungal activity of Mucorales such as *Rhizopus sp.*, *Mucor sp.*, *Rhizopus stolonifer* and *Rhizopus arrhizus* etc. Some herbals, such as *Lavandula angustifolia* and *Mentha piperita*, inhibit fungal growth through fungistatic activity. Medicinal herbs like *Thymus vulgaris L.* could potentially inhibit the mycelial development and germination of sporangiospores, whereas the essential oil extracts of *Piper sp.*, *Piper tuberculatum* and *P. hispidum* act against planktonic cells, biofilm formation, and rhizopuspepsin. Essential oil extracts of *Syzygium aromaticum (L.)* are also known to produce an inhibitory effect on the *Mucor sp.*

All these medicinal herbs have shown a promising antifungal effect on Mucorales fungus. Medicinal plants and their derivatives are the potential sources that can lift the lid on the

burden of mucormycosis infections. To this day, hundreds of thousands of plant species have been studied for their medicinal properties such as antimicrobial, antifungal, antiparasitic etc. However, many more plants yet remain to be studied and explored. The limited number of resources available on antifungal properties of plants against mucormycosis greatly limits our study. Therefore, understanding the exact mechanism of this herbal and fungal interaction is beyond the scope of our present work. More evidence on identified plants could allow us to understand their interaction with these powerful angioinvasive fungus.

4. FUTURE DIRECTIONS

Antifungal and anti-Mucorales drugs are still limited in the arsenal of the modern healthcare system. This has resulted in a higher mortality rate in the affected population, especially after the COVID-19 pandemic. Several studies have demonstrated that plants or herbal medicine can greatly influence and potentially discover newer drugs. However, very few researches or studies have been conducted on the anti-Mucorales herbs. Government agencies like the Ministry of AYUSH, various national and international healthcare institutions, pharmaceutical industries and FDA, etc., could play a more crucial role by funding various studies worldwide. Identifying more herbs or plants with potential antifungal properties through high-quality research can accelerate the process of newer drugs discovery. An adequate number of studies with high methodological qualities, using advanced and sophisticated techniques in pharmacognosy along with standard RCTs can boost the pursuit of newer and effective drugs against mucormycosis.

5. CONCLUSIONS

Multiple factors are responsible for the dampening of the immune system, which provides an opportunity for invasive Mucorales to attack the patients after a COVID-19 infection. Some herbals could be a potential asset in the discovery and development of newer antifungal drugs. However, extensive and intensified research should be carried out to identify further, design and develop new and safer antifungal drugs that can be powerful in treating mucormycosis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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