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Review Article

Eye Bird View on Natural Plants in the Management of Mucormycosis

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ABSTRACT

Mucormycosis, also referred to as Zygomycosis, is chiefly caused by filamentous molds belonging to the Mucorales group. It can be acquired through inhaling spores, consuming contaminated food, or through injury to the skin. Currently, the second most prevalent fungal infection disease is mucormycosis. It gained greatest attention following the COVID-19 pandemic. The review mainly focuses on several outlines like its history, epidemiology, pathophysiology, types, diagnosis and treatment of mucormycosis. In treatment of mucormycosis, conventional therapy against mucormycosis and some antifungal agents has been discussed. Several diverse contagious ailments were conventionally cured utilizing a widespread series of medicinal plants. Given that India is at the forefront of the Ayurvedic and Siddha medical systems, traditional herbal medicine from India is highly well-known. Antifungal chemicals derived from plants can be a viable option for developing novel and enhanced alternative formulations in the field of antifungal medicine. The main focus of the review is to explore the potential plants having the antifungal activity used for the treatment of mucormycosis. Some of the plants with antifungal activity have been explained, which includes garlic, tea tree oil, aloe vera, thyme, turmeric, neem, eucalyptus, clove, goldenseal, calendula, lavender, guduchi, and oregano. Animal models for mucormycosis study have been explained in the review.

Introduction

Mucormycosis, also called Zygomycosis, is a fungal infection primarily instigated through filamentous molds from the Mucorales and Entomophthorales order. While rare, it's becoming more recognized in immune-compromised patients. It can be divided into cutaneous, disseminated, gastrointestinal (GIT), pulmonary, and rhino-orbit-cerebral forms. The term "mucormycosis" is derived from two components: "mucor" and "mycosis." Mucor" refers to the genus of fungi known as Mucor and "Mycosis" is a term used to describe a fungal infection in the body. Mucorales thrive in various environments like dust, bread, decaying plant matter, and mud. Contagions can occur through inhaling spores, eating contaminated food, or through injury to the skin. In developing nations, mucormycosis is more common in hosts with severely impaired immune systems. Invasion of blood vessels by mucormycosis often leads to necrosis, thrombosis, and tissue death.[1] Some belonging genera of *Mucorales* are *Rhizopus*, *Lichtheimia* (formerly *Absidia*), *Mucor*, *Cunninghamella*, *Rhizomucor*, *Apophysomyces* spp., and *Saksenaea.*[2]

Currently, the second most prevalent fungal infection disease is mucormycosis. It gained greatest attention following the COVID-19 pandemic. Numerous researchers in academia, business, and hospitals are working to identify the most effective and precise methods, instruments, and procedures for diagnosing, comprehending the mechanism, and treating mucormycosis. This study focuses on several outlines to address mechanisms, treatments, and potential plant-based bioflavonoids as adjuncts to treat mucormycosis in any form.

Historical Perspectives

The initial case of mucormycosis was reported by German physician Paltauf in 1885, naming the condition Mycosis Mucorina. During the 1980s and 1990s, mucormycosis was predominantly observed in immunocompromised individuals. According to the prevalence rate, a French

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study found that the amplification rate increased by 7.4% annually. There have been reports of mucorales infection occurring worldwide and maybe varying seasonally.[3]

Epidemiology

Although mucormycosis is extremely rare, its instances have sharply increased over the past 20 years, especially in Belgium, France, Switzerland, and India. The Mucorales are widely distributed, thermotolerant, and exhibit high levels of activity in response to seasonal changes. A case study from Israel revealed that 16 out of 19 black fungus cases of rhino-orbito-cerebral mucormycosis (ROCM) occurred in the autumn, whereas six cases involving hematology patients in Japan were discovered to be infected between August and September. In humans, this type of infection was caused by direct pathogen inoculation through damaged skin or mucosa or by inhaling fungal sporangiospores. The prevalence of mucormycosis is directly correlated with industrialized and developing nations. In industrialized nations, it is generally recognized that patients with diabetes mellitus, stem cell transplants, and hematological complications are the only ones that become infected; nevertheless, in underdeveloped nations for example, India. It happens in people who have uncontrolled diabetes and strokes. Being an opportunistic pathogen, it can easily infect individuals with weakened immune systems, patients undergoing iron therapy or chemotherapy, patients with ketoacidosis, burn and trauma patients, and patients.[4]

During the global COVID-19 pandemic, there was an unexpected rise in mucormycosis, an uncommon and potentially fatal fungal infection. As of August 11, 2021, India had the most quantity of patients of mucormycosis among all countries impacted by SARS-CoV-2 (32,036,511 cases), particularly throughout the second upsurge of COVID-19. As per the data published by the Union Health Ministry of India in June 18, 2021, the cases of mucormycosis 40,845, so mucormycosis is declared as a notifiable disease. Drugs employed in the management of COVID-19 have caused a hyperglycemic condition, which has been linked to the unexpected rise in COVID-19-associated mucormycosis (CAM) patients. Only 19 cases from other regions of the world were documented in a recent comprehensive assessment of CAM cases during the pandemic, compared to 82 cases from India. Of these, hyperglycemia caused by impaired glucose metabolism or diabetes has been recognized as the primary threat issue, corroborated by the results of different recent research.[5]

Pathophysiology Of Mucormycosis

Mucormycosis has a different etiology than the fungus that causes it and the related diseases. Mucormycosis is primarily caused by fungal spores that enter the human body through the environment, hospitals, soil, and decaying matter. This causes the immune system to become activated, releasing phagocytes for example, mononuclear and polymorph nuclear cells that kill the spores by producing oxidative and non-oxidative radiation. However, iron overload in plasma presents an easy way for mucor substances to enter people with diabetes or diabetic ketoacidosis, which can lead to illness. Mucor spores in blood use iron and interfere with phagocytic cell activity. Therefore, a decrease in neutrophils permits an organism to grow quickly. Subsequently, mucor travels to other organs, where it adheres to endothelium and epithelial cells, causing angioinvasion and tissue necrosis.[6]

In nature, fungus is present everywhere. It can be found in soil, plants, decomposing organic materials, water, air, wet areas, animals, and even people. Together with bacteria, fungi are essential to the environment because they break down organic matter into simpler forms that plants can eat. Examples of fungi include household yeast, molds, mushrooms, and others. Basically, because plants are able to do photosynthesis, the black fungus is not a plant. There is no photosynthesis in these molds. The black fungus does not cook for itself. They must gather external fuels and transform them into nourishment. Plant and animal cells coexist in this fungus. Mucor is present in the environment naturally everywhere. Approximately fifty species are found all over the planet. Mucormycosis illness disorders arise as a result of the mucor species of mold and can impact the mucous membranes of the skin, eyes, lungs, and other areas. There are different types of fungus, which include black fungus, white fungus, and yellow fungus. The most widespread species worldwide is *Rhizopus arrhizus*, originally known as *R. oryzae*. *R. oryzae* causes cerebral mucormycosis, while the rhinocerebral form is most common among diabetics. Risk factors like iron overload, immunosuppression, and high-dose steroids can accelerate infection. *Rhizopus* is the predominant genus, causing typical symptoms such as headaches and facial pain. *Rhizopus* species are found on plants and parasitize animals, with eight known species including *R. schipperae* and *R. stolonifer.*[7-9]

Black Fungus

A dangerous but uncommon condition called mucormycosis is brought on by contact with mucor mold , which is found in the surroundings naturally. Usually found in plants, soil, decomposing fruits, vegetables, etc. It primarily disturbs those receiving medicine for medical conditions. For instance, hypertension (HT), diabetes, the body organs that are impacted at this time are the brain, lungs, sinuses, etc.

White Fungus

The fungal contagion brought on *via candida*. It is supplementary harmful to black fungus, which can infect the skin, lips, brain, nails, stomach, and intimate areas of the body. Both outside and indoors, white fungus grows. White fungal infections mimic the symptoms of

COVID-19 and are identified by CT scanning. People with compromised immune systems, those using medicine for diabetes mellitus, those using cancer steroids, and those receiving prolonged intensive care unit therapy are especially vulnerable to this fungal infection extremely crucial to preserving immunity. When severe, negative effects include liver and kidney damage

Yellow Fungus

Reptiles are the primary host of the yellow fungus infection, not humans. An infection with yellow fungus is more serious or hazardous than one with black and white fungus. This contagion begins inside, firstly resulting in a leak, as well as subsequently causing wounds in the direction of healing slowly. Serious cases result in cell damage and organ failure. The patient's sinuses, cavities, lungs, and chest cavity are all affected after inhaling fungal spores.[7]

COVID-19 Associated Mucormycosis[10]

Numerous reports of mucormycosis in COVID-19 patients have been made international, a condition known as CAM. Numerous factors, for example, glucocorticoids, deterioration of glucose in blood, and virally-induced lymphopenia, have been linked to the improvement of mucormycosis in COVID-19 cases, even if a causative relationship between the virus and the illness is still unknown. Pal R *et al.*,[10] studied the mucormycosis in COVID-19 and it was found that in case study, the usage of glucocorticoids for the controlling of COVID-19 was witnessed in 85% of the patients. The glucocorticoid that was furthermost frequently utilized was parenteral dexamethasone. Throughout the included articles, the glucocorticoid's dosage and duration were sporadically stated. The most prevalent type of mucormycosis was rhino-orbital (42%), which was monitored through rhino-orbito-cerebral (24%). Ten individuals (10%) had pulmonary mucormycosis. The most common fungus species found was *Rhizopus* sp. Four cases of mixed mold infection (a combination of aspergillosis and mucormycosis) were documented. Reports of the bulk of instances came from India. Most diabetic patients treated for COVID-19 with glucocorticoids were predominantly male. Throughout the subsequent six month period, the number of cases found was significantly greater than those that had presented in the previous three years.

In addition to unchecked hyperglycemia, free uncontrolled Fe in the blood is crucial for the development of mucormycosis. Because of acidosis and proton-mediated ferric iron supplanting from transferrin, diabetic ketoacidosis is linked to elevated serum levels of free iron, which is a significant threat issue for mucormycosis. Elevated serum ferritin causes an overabundance of iron to enter cells, which releases reactive oxygen species and kills hepatocytes. The situation is exacerbated by cytokines, particularly IL-6, which encourage the formation of ferritin and decrease the export of iron, resulting in excess of intracellular iron. Ferritin is discharged into the bloodstream following tissue damage, causing circulating ferritin to lose some of its internal iron content, thereby raising levels of free iron. Ketoacidosis development could be another connection between COVID-19 and mucormycosis. Even in the absence of diabetes mellitus, COVID-19 patients have been reported to have ketoacidosis and ketoemia.

Diagnosis of mucormycosis

As of right now, there are no particular biomarkers for mucormycosis diagnosis; instead, pathological examination methods for example biopsy and surgery are the sole options. Using direct microscopy, discover mucormycosis, in particular non-septate, wide hyphae. Stains for example periodic acid Schiff and Grocott methenamine silver, are utilized in histopathological examinations. In general, dyeing other fungi took less time, while mucormycosis took longer. Sometimes, biopsy results in defects in certain parts of the brain and lungs, so Mucorales samples are collected from the sinus, ear, nose, skin, GIT with an expert physician and a suitable procedure. Culture-independent technologies play a crucial role in identifying mucormycosis using blood and tissue samples as specimens. Examples include the use of a monoclonal antibody (2DA6) targeting alpha 1,6-linked mannose and PCR-based assays targeting the Cot-H receptor.[11,12] To date no specific test for the detection of mucormycosis but the following test helps:[13]

- Nasal endoscopic examination
- Blood tests like CBC to monitor the decreased count of neutrophils, monocytes, or increased erythrocyte sedimentation rate
- Radiological detection like an x-ray of nasal sinus, MRI of an optic neuron to check inflammation
- HRCT score

Prevention and treatment of mucormycosis

The management of mucormycosis through the continued use of sensible treatment and healthy environments.[14] Maintaining personal cleanliness and sanitation, avoiding the use of steroids, and closely monitoring comorbid conditions including diabetes, immunodeficiency, trauma, etc. The Government of India's Directorate General of Health Services, in accordance with the criteria of the National Centre for Disease Control, classified preventive measures into two categories: primary and secondary prevention.[15]

Conventional therapy against mucormycosis

The intensity and prevalence of this fatal fungal infection in the second upsurge of COVID-19 are unexpected, as well as this presents a challenge to the medical community. Because of arterial thrombosis and a significant ischemic necrosis barrier, which block the entrance of antifungal drugs at adequate concentrations, the antifungal treatment through itself is ineffective. Promptly perform radical tissue debridement and drainage of infected sinus cavities to minimize fungal tissue burden. Additionally, thorough debridement of the affected sinuses during functional endoscopic sinus surgery following amphotericin B sinus lavage may be linked to improved outcomes. The task force's medical professionals have been directed to control blood sugar levels, cut back on steroids, and stop using immunomodulatory medications, particularly for patients who have recovered from or are infected with COVID-19. Steroid treatment for COVID-19 individuals who also have other concomitant conditions for example, diabetes and hematological malignancies, provides the ideal conditions for this fungal development, which exponentially increases the risk of mucormycosis. To manage the patient's condition, adjust corticosteroids and immunosuppressive drugs carefully, considering substitution with stronger medications when possible. *In-vitro* studies show mucormycosis resistance to many antifungal drugs like voriconazole, fluconazole, and itraconazole. It is yet unknown what the ideal dosage of antifungal medications, particularly triazoles like posaconazole and isavuconazole, should be. This requires conclusive, prospective, and controlled clinical judgements.[16]

Surgical treatment of mucormycosis

Facts recommend the intensive surgical debridement method for the management of Rhinocerebral mucormycosis (RM). The exterior, or transantral, technique has historically been regarded as the conventional methodology. For radical resection, endoscopic sinus surgery (ESS) is a useful technique. According to a study, nine patients with RM were treated with ESS. Six of the patients received treatment solely through ESS, while the remaining three patients had treatment that included ESS with transantral surgery. According to a study, treating RM through ESS either by itself or in conjunction with conventional surgical techniques has the advantage of reduced operative morbidity as well as improved operating correctness.[17]

Antifungal Agents

Posaconazole (Traizoles)

Posaconazole functions by decreasing ergosterol levels within fungal cells. Triazoles are important in the treatment of mucormycosis, which is hard to cure. These medications' antifungal activity differs depending on the species. It is recommended to administer the oral suspension three to four times a day, with a dose range of 200 mg. Only in clinical situations where AMB is categorically contraindicated is this medication regarded as the first line; in these scenarios, isavuconazole has been advised by certain clinical investigations. Due to the medication therapy's variable PK and PD values, therapeutic drug monitoring is advised.[18,19]

Isovuconazole

Recently approved triazole isovuconazole has a broad range of antifungal action and is effective against mucorales. Based on the results of an open-label clinical trial, it is used as a first-line treatment for mucormycosis and is thought to be an alternative to AMB.[20] If necessary, this medication should be used for several months. Thankfully, the outcomes of the comparison between the effects of isovuconazole and the traditional AMB were promising and identical. Isovuconazole has not been associated with any known side effects, including hepatotoxicity, nephrotoxicity, QT prolongation, or eye toxicity. The main issue with this medication is that several recent clinical studies found that patients taking it for treatment or prophylaxis developed mucormycosis and other fungal infections. All of this information is included in the regulatory study for this medication. Extended prophylaxis with posaconazole may lead to cross-tolerance, resulting in breakthrough mucormycosis and resistance to isovuconazole in some patients. Therefore, in treating patients, especially those who are immunocompromised, these concerning reports should be taken into account.[18]

Hemofungin

This is a novel drug that also prevents the last stage of heme production and the *in-vitro* development of a number of funguses, including *Rhizopus.*[21]

VT1161-investigational Drug

It is an effective inhibitor of fungal CYP51 that acts on several mucorales. Preclinical *in-vivo* evidence validates VT1161's therapeutic efficaciousness. It is thought to be beneficial for the therapeutic management of mucormycosis since it raises the survival rate of neutropenic mice with the disease. More research is being done to confirm the effectiveness of this molecule.[22]

Possible Drugs Derived from Medicinal Plants to Combat Mucormycosis

Traditional medicine harnesses the wisdom and practices native to different cultures to address and manage both physical and mental health conditions, encompassing prevention, diagnosis, and treatment. Around 80% of individuals in developing nations rely on traditional medicine, while there's been a rise in complementary and alternative medicine (CAM), notably herbal remedies, in industrialized countries. Herbal medicines encompass herbs, plant materials, and preparations derived from plants, serving as active components in treatments. Plants usually comprise blends of various phytochemicals, which are sometimes referred to as secondary metabolites. These metabolites might operate singly, in combination, or individually to enhance health. In fact, medicinal plants frequently contain many compounds that interact catalytically, in contrast to pharmaceutical medications and cooperatively, to provide a cumulative effect that is superior to the entirety of the actions of the separate components. When these compounds work together, they tend to accelerate or decrease the body's assimilation of the major medicinal constituent, thereby increasing its action. Secondary metabolites derivative from plants may have an antagonistic, potentiating, or additive action in addition to reducing the rate of undesirable adverse events and increasing the stability of the active composite(s) or phytochemicals. There is a theory that these plants' incredibly diverse range of chemical structures aren't waste products but rather specialized secondary metabolites that play a role in how the organism interacts with its surroundings. Examples of these metabolites include signal products, attractants for pollinators, defensive compounds against parasites and predators, and resistance to diseases and pests.[23]

The majority of COVID-19 patients admitted to Indian hospitals have mucormycosis, which causes blindness and eventually results in death. In addition, mucormycosis is seen in COVID-19 patients who have recovered and have other medical conditions.[24] In COVID-19 patients, steroids lessen lung inflammation. Steroids will, therefore, assist the human body in halting some of the harm that may occur when the immune system overreacts in an attempt to combat the coronavirus. But steroids also increased blood sugar levels and decreased immunity in COVID-19 individuals, both with and without diabetes. Mucorales spread quickly, have a strong affinity for blood arteries and are highly contagious. Moreover, the characteristic feature of mucormycotic tissue lesions is hemorrhagic necrosis.[25]

In recent decades, there has been a significant increase in mortality and illness rates due to mucormycosis, a recognized and potentially deadly condition, especially among COVID-19 patients with compromised immune systems, particularly in developing countries.[26] At the most advanced stages of the infection, the primary symptoms of this illness include invasion of blood arteries, infarction, thrombosis, and tissue necrosis.

Inflammatory syndrome and pneumonia itself are the hallmarks of the infectious disease COVID-19, which causes decreased food intake and increased muscle catabolism. Because of this increased risk of malnutrition, nutritional treatment and prevention are crucial components of care for COVID-19 patients and mucormycosis patients.[27] Antifungal medications have a number of negative effects, and patients with COVID-19 have not developed resistance because of a variety of medical conditions, including high blood pressure, diabetes, cancer, and organ transplants. Many medical problems for example, high blood pressure, diabetes, cancer, and organ transplants, have prevented patients with COVID-19 from developing resistance to antifungal treatments, yet these drugs have a lot of undesirable side effects.[28,29]

Patients with mucormycosis and COVID-19 should be regarded as having a significant risk of malnutrition. Thus, acute malnutrition brought on by a COVID-19 infection would be linked to a greater loss of muscle mass and a weakened immune system as a result of the illness's severity. Hence, patients with mucormycosis and COVID-19 require intensive care unit as well as nutrition therapy as a part of supportive therapy.[27] The diet (foodstuffs) containing nutrients and bioactive compounds such as melatonin, vitamins, proteins, and carbs affect the immunological system and nutritional status of COVID-19 patients. Some nutritional deficiencies also addressed in these patients, like anorexia, nausea, vomiting diarrhea, hypermetabolism, and excessive nitrogen loss. Consequently, nutritional therapy seems to be the best course of action and ought to be incorporated into regular practice. The fundamental goal of a well-balanced diet system should be to consume the maximum amount of all nutrients, especially those that are essential to the immune system.[27,29]

The angiotensin-converting enzyme-2 (ACE2) receptor is the entry point for SARS and SARSCoV-2. A number of naturally occurring bioactive chemicals derived from plants interact with this receptor. Additionally, naturally occurring plant bioactive substances can lessen the inflammatory response brought on by SARSCoV-2. The most promising instruments for helping patients with mucormycosis with their dietary management are these plant-active substances. Key nutrients such as high-quality proteins, omega-3 fatty acids, vitamins A and C, dietary fiber, selenium, and copper possess anti-inflammatory properties. Polar lipids are effective in preventing blood clot formation. Additionally, vitamins C, A, and E, along with omega-3 fatty acids, act as antioxidants. Furthermore, vitamin E, iron, and zinc support immune function, while vitamins A, C, and D protect against respiratory infections.[28,30]

Various infectious diseases were historically managed using diverse medicinal plants. Given that India is at the forefront of the Ayurvedic and Siddha medical systems, traditional herbal medicine from India is highly well-known. Antifungal chemicals derived from plants can be a viable option for developing novel and enhanced alternative formulations in the field of antifungal medicine.[31-34]

Plants with antifungal activity

There is a pressing need for the effective cure of fungus related infections through the usage of herbal medicine, which will safeguard patients with COVID-19 and mucormycosis for a prompt recovery and a higher quality of life. Consequently, the usage of dietary as well as herbal therapy in combinationusing one another would be advantageous for managing black fungal infections during COVID-19 hospitalisation. There are several plants that have antifungal activity which are mentioned in Table 1.[35]

- *Garlic (Allium sativum)*

Garlic contains allicin, known for its antifungal properties, which can be consumed or applied topically for fungal infections. In a study by Sharma *et al.*, molecular docking showed promising antifungal activity of garlic constituents against mucormycosis, particularly Z-ajoene. Further research is required to fully understand garlic's effectiveness against this fungal infection.[36] Sadeghi Zali MH *et al.* investigated the antifungal effects of essential oils from garlic, thyme, aloe vera, and cinnamon against *Candida albicans*. Their findings indicated that garlic essential oil was the most effective, suggesting its potential as a supplement to conventional antifungal drugs.[37]

- *Tea Tree Oil (Melaleuca alternifolia)*

Terpene hydrocarbons, primarily monoterpenes, sesquiterpenes, and the alcohols that are linked to them, make up TTO. Terpenes are volatile, aromatic hydrocarbons that have the formula C5H8, and they can be thought of as polymers of isoprene. Research on the antifungal mechanisms has mainly concentrated on *C. albicans*. Moreover, tea tree oil (TTO) dose-dependently suppresses *C. albicans'* ability to breathe (49). Following therapy with 1.0% TTO, respiration was suppressed by around 95%, and following treatment with 0.25% TTO, it was suppressed by about 40%.[38]

Homeyer DC *et al.* examined the *in-vitro* effects of TTO on filamentous fungi and its toxicity to human cells. They found varying effectiveness of TTO against different fungal agents associated with invasive fungal infections (IFIs). Additionally, they observed decreased viability of crucial wound-healing cell lines with all TTO doses. Topical antibiotic therapy offers benefits such as direct application to the infection site, bedside use without surgical procedures or anesthesia, and avoidance of systemic side effects.[39]

Sevik *et al.* conducted a study on tea tree oil, examining its chemical composition and antifungal properties. They analyzed the essential oil derived from *Melaleuca alternifolia* leaves and evaluated its efficacy against food-borne molds isolated from meat products. The primary constituents of the essential oil were identified as α-pinene, γ-terpinene, terpinen-4-ol, limonene, and o-cymene. Among the tested molds, *Aspergillus niger* showed the highest susceptibility to the essential oil, followed by *A. fumigatus, A. flavus,* and *Penicillium notatum.*[40]

- *Aloe vera (Aloe barbadensis Miller)*

About 110 potentially active ingredients can be found in aloe vera, belonging to six main classes: flavonoids, phenylpropanoids and coumarins, phenylpyrone and phenol derivatives, phytosterols, anthraquinone and its glycoside derivatives, chromone and its glycoside derivatives, and others. Shilpa *et al.* explored the antifungal properties of aloe vera leaf and gel extracts against *C. albicans*. Their research revealed that the ethanolic extract of aloe vera gel demonstrated notable antifungal effects against *C. albicans.* Aloe vera has demonstrated greater consistency and efficacy than conventional antifungals in treating and preventing various oral fungal infections caused by *C. albicans.*[41]

- *Turmeric (Curcuma longa)*

Multiple studies have demonstrated the potent antifungal properties of *C. longa*. Its main chemical constituents include curcumenol, curdione, curcumin, isocurcumenol, curcumol, stigmasterol, zingiberene, and curcumene. The extract of *C. longa* inhibits over twenty harmful fungi, including *A. flavus, Fusarium oxysporum, F. moniliforme, A. niger, A. terreus, Fusarium verticillioides,* and *Curvularia pallescens.*[42]

Chen *et al.* investigated the antifungal properties of curdione, curcumenol, curzerene, curcumol, and isocurcumenol, individually and in combination with seven other chemicals. They employed two-dimensional gel electrophoresis (2-DE) to analyze the differential proteome expression *of F. graminearum*, focusing on proteins like GAPDH.[42]

Datta S *et al.*, carried out research on the antifungal activity of two different plants, including neem and turmeric. The target plants were deemed to be neem and turmeric, and an effort was undertaken to uncover several ways in which phytocompounds originating from these plants could be used to successfully manage the COVID-associated mucormycosis (CAM) threat. It was discovered that quercetin, which is generated from both neem and turmeric, is one of the primary phytocompounds against mudroema. In addition, myricetin, kaempferol, curcumin, caffeine acid, and tetrahydrocurcumin are essential in the fight against black fungus. A detailed examination of our findings indicated that we should target the fungal pathogens from three different angles: Necrosis inhibition, iron chelation, and immuno-boosting.[43]

- *Neem (Azadirachta indica)*

Neem is known for its variedseries of biological actions, comprising antimicrobial properties. The antifungal activity of neem is attributed to several chemical constituents present in its various parts. Some of the key antifungal constituents in neem, includes, azadirachtin, nimbin and nimbidin, gedunin, salannin, quercetin, and beta-sitosterol. It is noteworthy that the antifungal properties of neem are probably not attributable to a single component but rather to the combined action of several components. Combinations of these bioactive chemicals are found in neem oil and extracts, which are widely used in traditional medicine and have been studied for their potential antifungal effects.[44]

Table 1: Plants with antifungal activity

S. No.	*Family*	*Botanical name*
1	Myrtaceae	(Guava) *Psidium guajava*
2	Apiaceae	Indian pennywort (Gotukola) *Centella asiatica*
3	Meliaceae	(Neem) *Azidarachta indica*
4	Amaranthaceae	Mountain Knot Grass (Gorakhbuti or Chhaya) *Aerva lanata*
5	Verbenaceae	Indian privet or Wild. Jasmine) *Clerodendrum inerme*
6	Menispermaceae	Guduchi (Amruthballi) *Tinospora cordifolia*
7	Zingiberaceae	Ginger) (*Zingiber officinale*)
8	Lythreaceae	(Henna tree) *Lawsonia inermis*
9	Mimosaceae	*Mimosa tenuiflora*
10	Amaryllidaceae	(Garlic) *Allium sativum*
11	Euphorbiaceae	(Indian copperleaf) *Acalypha indica*
12	Apocynaceae	Trellis-vine) *Pergularia daemia*
13	Solanaceae	(Brinjal) *Solanum melongena*
14	Plumbaginaceae	(Wild white leadwort) *Plumbago zeylanica*
15	Myrtaceae	(Cherry) *Eugenia uniflora*

Parts of the neem (*A. indica*) plant have antibacterial properties due to their ability to suppress microbial development and perhaps break down cell walls. The effectiveness of different neem leaf extracts on the fungal species *Aspergillus* and *Rhizopus* that are carried by seeds, and the findings demonstrated that both the alcoholic and water extracts strongly inhibited and regulated the growth of both fungal species.

- *Thyme (Thymus vulgaris)*

Thyme's antifungal properties stem from its various chemical constituents, mainly found in its essential oils extracted from the leaves, which possess antimicrobial properties. Top of form some of the key antifungal constituents found in thyme essential oil include thymol, carvacol, p-cymene, linalool and camphor. These ingredients work in concert with other components of thyme essential oil to produce a broad-spectrum antibacterial action. The potential applications of thyme in food preservation and the synthesis of natural antifungal drugs have been investigated.[45]

Mota KS studied the antifungal effects of *T. vulgaris L*. essential oil and its phytochemical constituents against *R. oryzae*. Since they exhibit strong resistance to antifungal medications and the available therapeutic arsenal is small, it is imperative that therapeutic agent testing be prioritized in the fight against mucormycosis. The MIC of EO and thymol diverse 128 to 512 μg/mL, nevertheless, the MFC of EO and thymol diverse 512 to 1024 μg/mL and 128 to 1024 μg/mL, correspondingly. The findings also showed a considerable inhibition of sporangiospore mycelial development and germination by EO and thymol. Examining the antifungal activity mechanism revealed that ergosterol interacts with EO and thymol. These findings support the potential application of EO of *T. vulgaris* and thymol in the treatment of mucormycosis by showing that they have potent antifungal activity, which may be connected to their interaction with ergosterol.[46]

- *Eucalyptus (Eucalyptus globulus)*

The Australian native eucalyptus globulus, also referred to as blue gum eucalyptus, is highly prized for its fragrant leaves. It is well known that eucalyptus oil, which is made from the leaves, has a variety of biological qualities, including antibacterial ones. Although eucalyptus oil has been investigated for its antifungal properties, less is known about the precise components of eucalyptus oil and how well they work against mucormycosis. This is especially true of certain other herbs. The following are the main antifungal components of eucalyptus oil: 1,8-cineole (Eucalyptol), α-pinene and, β-pinene and limonene. One of the main constituents of *E. globulus* oil is 1,8-cineole or eucalyptol. Although there has been little research specifically examining its efficacy against mucormycosis, it has been examined for its antifungal action in contradiction of a variety of fungi. The terpenes α-pinene and β-pinene are present in eucalyptus oil. These substances add to the oil's overall biological activity and have shown antibacterial qualities. Another terpene found in eucalyptus oil is limonene. It is frequently present in a variety of essential oils and has demonstrated antibacterial properties.[47]

- *Clove (Syzygium aromaticum)*

The buds of the clove tree yield clove essential oil, which is especially rich in some chemical components with antibacterial and even antifungal effects. It's crucial to remember that although cloves and clove oil have shown antifungal action in lab tests, it's possible that their effectiveness against mucormycosis in particular, has not been thoroughly researched. Eugenol, β-caryophyllene, acetyl eugenol and α-humulene are the chemical constituents present in cove buds. Clove oil's main ingredient, eugenol, makes up a sizable portion of its composition. Strong antibacterial qualities of eugenol include antifungal action. Studies on its impact on different fungi have been conducted. Since clove oil and other herbal remedies are known to have antifungal qualities, it's crucial to use caution when using them, especially for serious illnesses like mucormycosis.[48]

- *Goldenseal (Hydrastis canadensis)*

Native Americans have long utilised the herb goldenseal (*H. canadensis*), which is native to North America, for its therapeutic benefits. The main active ingredients in goldenseal that give it its antibacterial qualities are hydrastine and canadine. It presented the antifungal action in contrast to *Alternaria* and *C. albicans*. It inhibits the RNA and protein synthesis.[49]

- *Calendula (Calendula officinalis)*

Calendula, frequently referred to as marigold, is a well-liked herb that has been utilized historically for a number of therapeutic uses. Although it is highly valued for its ability to reduce inflammation and heal wounds, compared to its other therapeutic qualities, there may not have been as much research on its precise antifungal activity or the identification of chemical elements with direct antifungal effects. Flavonoids, triterpenoids, and carotenoids are the main chemical constituents of this plant. Flavonoids, which have anti-inflammatory and antioxidant qualities, are found in calendula. Although flavonoids have varying direct antifungal effects, they may indirectly help the immune system.[50]

- *Oregano (Origanum vulgare)*

Oregano (*O. vulgare*) owes its antifungal properties to several key chemical constituents found in its essential oil, including carvacrol, thymol, terpinene-4-ol, γ-terpinene, and p-cymene. Carvacrol, a primary active ingredient, is renowned for its potent antibacterial and antifungal effects, extensively studied against various fungi. Due to its antifungal properties, oregano essential oil is widely researched and effective against a range of fungi such as *Aspergillus* sp., *Fusarium* sp., and *Penicillium* sp.[51]

- *Lavender (Lavandula angustifolia)*

The adaptable herb lavender (*L. angustifolia*) is well-known for its soothing scent and a number of medicinal uses, which may include antifungal effects. The chemical constituents in this plant are linalool, linalyl acetate and 1,8-cineole (Eucalyptol), camphor, and borneol. Lavender oil contains a bicyclic monoterpene called borneol. Its possible antibacterial activity—including against fungi—has been studied.[52]

- *Guduchi (Tinospora cordifolia)*

Due to its possible health benefits, the herb guduchi, formally known as *T. cordifolia*, has been employed in ancient medical systems, especially Ayurveda. Research on its particular antifungal effects and the identification of chemical elements with direct antifungal action may be restricted compared to its other therapeutic characteristics despite the fact that it is well respected for its immunomodulatory and antioxidant properties. Guduchi has a variety of alkaloids, steroids, glycosides, diterpenoid lactones, and polysaccharides among its chemical ingredients. A few of these substances might be involved in its entire biological activity, which might include antibacterial properties. Although detailed information about the antifungal components of guduchi is few, some research indicates that the plant may possess antibacterial qualities against a variety of pathogens, including fungi.[53]

- *Hirada (Termnalia chebula)*

It is anticipated that *T. chebula* will combat the fungal infection. The antifungal properties of *Terminalia* sp. were examined against various fungal strains, including *A. brassicicola*, *A. alternata, Helminthosporium tetramera, A. flavus*, and *A. niger* using aqueous, ethanolic, and alcoholic twig extracts. The outcomes demonstrated the limited effectiveness of aqueous extracts. Alcoholic extracts outperformed ethanol and aqueous extracts in terms of inhibition. It was also discovered that *T. chebula* suppressed *A. niger* more effectively.[54]

Ayurvedic treatment principles encompass kledahara (removing moisture), pramehahara (controlling diabetes), agnivardhaka (enhancing digestion), aampachaka (digesting toxins), krimihara (eliminating parasites), ojovardhaka (boosting immunity), rasayan (rejuvenation), and balya chikits (strengthening therapy). As a result, as a preventative measure, Ayurvedic immunomodulatory supplements along with a COVID-19 management plan may be initiated as soon as possible to address the mucormycosis infection. The preventative medications indicated in Table 2 can be taken either on their own or in conjunction with the additional medications indicated under the individual forms of mucormycosis.[55]

The Ministry of Ayush Drug Policy provides guidance to Ayurveda practitioners for preventing, managing symptoms, and treating suspected and diagnosed cases of mucormycosis, as outlined in Table 3.[55]

Animal Models for Mucormycosis Study

Animal models play a crucial role in comprehending infectious diseases and advancing therapeutic interventions. Since there is limited access to patient material for diseases like mucormycosis, they are perhaps even more crucial for a better understanding of these conditions. Because of the comparatively low

Table 2: Preventive medications in mucormycosis

Condition	*Medicine*
Post-COVID-19 regimen for preventing opportunistic infections/prophylactic	Dashmoolakwatha, Manjishthadi Kashaya, Aaragvadhadi Kashaya KaishorGuggulu, TriphalaGuggulu, Laxmi Vilas Rasa Amritarishta, Vidangarishta / Vidangasava, Kumari Aasava, AvipattikarChurna, Sudarshana churnaGuggulutiktaghrita, JeevantyadiGhrita

Table 3: Management of symptomatic, suspected and diagnosed cases of mucormycosis

S. No.	*Types of mucormycosis*	*Clinical features*	*Medicine*
1	Pulmonary mucormycosis	Fever, difficult breathing, cough, chest pain, pleural effusion.	GandhakaRasayana along with decoction of Neem Patra+ Triphala+ Giloy+ Madhuyastichurna, Kantkarighrita / Dadimadighrita
2	Disseminated mucormycosis	is often associated with patients who are already ill from other medical illnesses, making it challenging to identify which symptoms are specific to mucormycosis.	Rasamaikya, VyadhiharanRasayan, For local application, Jatyaditaila
3	Rhino-orbito-cerebral mucormycosis	Facial swelling, headache, visual loss, proptosis, and/or palatal ulcer, double vision, black lesions on nasal bridge	Amritadiguggulu, Saptamritalauh, Haridra Khanda T, riphalaGhrita
4	Gastrointestinal mucormycosis	Nonspecific abdominal pain and distention along with nausea	Sankha Vati, Bolbadha Ras, Kaharavapisti MauktikyuktaKamdudha Ras
5	Cutaneous mucormycosis	Necrotic scar surrounded by an erythematous	Nimbadi Kashaya, Khadirarishta, Kalyanaka Guda

incidence, wide range of causative agents, multiple entry points for contagions, and fluctuation in essential disorders as well as danger issues, designing clinical studies is challenging. Various model hosts, including mammals like mice, as well as other vertebrates and invertebrates, have been utilized. They help in evaluating the virulence of mucoralean species, studying pathogenesis, assessing potential risk factors, and testing antifungal efficacy.[56] Mammals are considered the primary choice for studying human diseases due to similarities in anatomy and physiology. The suitability of an animal model for infectious disease research depends on its susceptibility to the infectious agent and how closely the disease mirrors human pathology. Instances of mucormycosis in various mammalian species and birds have shown clinical symptoms akin to those seen in humans.[57,58] Nonetheless, the majority of research employed mice or rabbits, and Table 2 provides a summary of the published studies that concentrate on these two host species.[59] The use of rats and mice as animal models for the study of the following parameters in the case of mucormycosis pathogenicity, virulence traits, comparative virulence, diagnosis, therapy, and vaccines. The important parameter is the route of infection because of the type of fungi infected on which organ and interaction with the host.[60-62] Numerous animal studies provide insight into the various forms of mucormycosis. An essential factor in the majority of animal models is immunodeficiency. Taking into account that human immunology and mouse physiology are extremely similar. Therefore, immunodeficient mice, also known as neutropenic mice, are used as test animals to see whether new medications are helpful against mucormycosis. Mucormycosis develops in rabbits with acute alloxan diabetes when *R. oryzae* is injected intravenously and subcutaneously.[63] Table 4 describes pulmonary models of mucormycosis.

Sarfaty *et al.* investigated cutaneous and pulmonary mucormycosis in Rag1- and Il2rg-deficient Rats.[61] They found that a fungus from the Mucoraceae family was the main organism associated with these lesions in rats. Anand *et al.* developed an immunocompromised mouse model of rhinocerebral mucormycosis using alloxan.[62] Waldorf *et al.* studied pulmonary mucormycosis in cortisone-treated mice, finding evidence of infection and tissue damage.[63] The studies highlight the importance of animal models in understanding and managing mucormycosis.

Future Perspective

Now, many treatment approaches are available for mucormycosis, the use of antifungal agents of synthetic origin and surgical procedures, but it is costly. The existing data reveals there is a decrease in immunity in many individuals with comorbidities like diabetes and the use of steroids. So, plants with immune boosters and antifungal approaches are beneficial in the management of any type of mucormycosis.

Table 4: Pulmonary models of mucormycosis

Host species	*Route of infection*	*Fungi*
Rabbit	Intranasal	*Lichtheimia* spp.
		Rhizopus spp.
	Endotracheal	*Mucor* spp.
		Rhizopus spp.
		Cunninghamella spp.
Mouse	Instanasal	*Lichtheimia* spp.
		Mucor spp.
		Rhizopus spp.
	Intratracheal	*Cunninghamella* spp.
		Mucor spp.
		Rhizopus spp.

Conclusion

While the precise frequency of mucormycosis remains uncertain, it is thought to be significantly higher in developing nations relative to developed nations. The death rate from mucormycosis is still higher, even with significant advancements in the contemporary age in ailment therapy. However, there are still many therapy gaps because of challenging management options, a lack of antifungal medications, and delayed diagnosis. Antifungal chemicals derived from plants can be a viable option for developing novel and enhanced alternative formulations in the field of antifungal medicine. Exploring novel management techniques and treatment protocols is crucial to decreasing the morbidity and mortality rates linked with this illness.

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