

Relevance of Complementary and Alternative Medical Interventions in Prevention of Mucormycosis in Post-Covid-19 Patients

Dr. Sangeeth Somanadhapai^{1*}¹Professor & Dean, Faculty of Naturopathy & Yogic Science, SGT University, Gurugram, Haryana, IndiaDOI: [10.36347/sjams.2022.v10i03.007](https://doi.org/10.36347/sjams.2022.v10i03.007)

| Received: 11.02.2022 | Accepted: 15.03.2022 | Published: 17.03.2022

*Corresponding author: Dr. Sangeeth Somanadhapai

Professor & Dean, Faculty of Naturopathy & Yogic Science, SGT University, Gurugram, Haryana, India

Abstract

Review Article

Every day our bodies are exposed to several pathogens. In this invisible battle, a complex set of wheels comes into play, made up of millions of cells of different types and with different functions, responsible for ensuring the defence of the organism and maintaining the health of the body. It is the immune system that is responsible for this defence. The Covid-19 pandemic brought new problems, including pathogens that can take advantage of patients' weakness and worsen health conditions. Patients' after Covid-19 are facing a new threat, an infection caused by a fungus - mucormycosis. The main risk factors are taking corticosteroids and diabetes mellitus. The conventional medicine used in this type of treatment usually causes many adverse effects and there may be non-adherence. Alternatively, alternative medicine can be considered a useful approach and help improve wellness and even prevent complications of mucor infection. Complementary and alternative medicine treats emotional traits and mainly influences the patient's beliefs, thoughts, well-being, and mood and improves the immune system. Complementary and alternative medicine helps improve quality of life and can help patients reduce psychological distress. The present article discusses some key aspects of the role of alternative medicine and how complementary treatment can be considered in preventing complications of mucormycosis in post-Covid 19 patients.

Keywords: Mucormycosis, Covid-19, complementary alternative medicine, yoga, dietary therapy, essential oils, massage, aromatherapy, homeopathy, ayurvedic medicine.

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INTRODUCTION

While patients are struggling with Covid-19, they are affected by another disease caused by a fungus, mucormycosis. These fungi invade deep tissues via inhalation of spores, skin abrasions, or ingestion [1].

Mucormycosis can aggressively and rapidly invade blood vessels, and cause dissemination, thrombosis, and tissue necrosis [2]. Covid-associated mucormycosis is associated with high morbidity and mortality and exorbitant treatment costs and has led to a shortage of antifungal medications [3].

Complementary and alternative medicine (CAM) can be used to improve quality of life and even clinical outcomes. In this article, we present several aspects and evidence of the role of CAM in supporting patients with covid 19-associated mucormycosis

What is mucormycosis?

Mucormycosis is a rare fungal disease caused by species of fungi that belong to the Mucorales. These

fungi can live in the environment, especially in vegetables and organic material. Contact with the fungal spores through inhalation or through the skin is necessary for humans to become infected. With a highly aggressive tendency to infect and associated with a poor prognosis, it is considered a fungal disease [4].

The patient's eyes and nose are red. These are the first symptoms and may progress to black mucus, fever, difficulty breathing, sinus pain, nasal congestion, and headache. Nasal ulceration and thrombosis may occur [1, 2]. When the lungs are affected, pleuritic chest pain and dyspnea occur. Cutaneous manifestations are rare [4, 5].

The fungus can grow and invade the bones, after the eyes, orbits, muscles, nerves. Mucor can destroy any type of tissue that is in its path [5, 6].

Sporadically, the fungus can cross the bone and travel directly to the brain, which is almost always

fatal. Depending on how quickly the patient is treated, the mortality rate is 50% to 90% [7].

How to treat and prevent mucormycosis?

Since poorly controlled diabetes is the main problem, good glycemic control is required in the treatment of covid 19 patients. Oral steroids are contraindicated in patients and indicated only in patients with hypoxia, and in this case blood glucose should be monitored. The dose and duration of steroid therapy should be limited to 5-10 days and used at the lowest possible dose [3, 8].

Based on the global guideline for the treatment of mucormycosis, antifungal therapy consists of (i) liposomal amphotericin B, (ii) amphotericin B deoxycholate (iii) posaconazole or isavuconazole in patient's intolerant to amphotericin B [9, 10].

The Complementary and Alternative Medicine (CAM)

Non-pharmacological treatments consist of clinical interventions designed to treat the manifestations of the disease, considering the nutritional, emotional, social, and spiritual context. Alternative medicine is based on increasing the immune system [11].

The mind-body therapies

The practice of Yoga

Practicing yoga helps integrate the mind and body to improve health. Anxiety or stress usually triggers the sympathetic nervous system, which can manifest as increased blood pressure and blood sugar, and faster breathing [12].

There is growing evidence that yoga supports the pathophysiological mechanisms of diabetes [12] by activating the parasympathetic nervous system, improving metabolic and psychological profiles, increasing insulin sensitivity, glucose tolerance, and lipid metabolism [13].

A study conducted with patients showed a significant decrease in insulin levels, suggesting a positive effect of yoga on glucose utilization and fat redistribution [14].

A randomized controlled trial of yoga in patients with poorly controlled insulin-treated diabetes showed that the practice helped to keep insulin levels under control and also increased in control patients, proving that yoga can be an ally in controlling diabetes [15].

Another clinical study demonstrated the impact of yoga practice on clinical outcomes and glycemic control, showing significant improvement in glycemic control and reduction in doses of oral hypoglycemic agents [16].

Yoga practices induce the transport of stem cells from the bone marrow into the peripheral blood, resulting in tissue regeneration, reduction in fasting blood glucose, body weight, fat mass, skinfold thickness, triglycerides, and cholesterol [12, 17, 18].

The psycho-neuroendocrine and immune systems have effects on controlling diabetes and reducing the risk of infections, such as covid-19 and mucormycosis [12, 17, 19].

The Aromatherapy

Several researchers have investigated the antibacterial, antifungal, and antiviral properties of essential oils (EOs) [20, 21].

An in vitro study pre-treating EOs from *Illicium verum*, *Melaleuca alternifolia*, *Leptospermum scoparium*, and *Matricaria recutita* showed inhibition of infectivity of acyclovir-sensitive and -resistant human herpes virus (HSV), indicating a potential antiviral effect of EOs [22]. The in vitro and in vivo antifungal activity of tea tree oil (*Melaleuca alternifolia*) showed a potential effect in the therapy of fungal infections of the skin and mucous membranes [23].

Numerous studies in vitro and ex vivo have investigated the effects of eucalyptus oils and eucalyptol treatments on monocyte and macrophage recruitment in response to pulmonary inflammation and infection. These studies revealed an important immunomodulatory property. Treatment reduced the release of proinflammatory cytokines from monocytes and macrophages [24, 25].

A study was conducted to investigate the role of garlic oil compounds against SARS-CoV-2. The compounds studied showed interactions with both host protein (ACE2) and viral proteases, suggesting that garlic oil has potential for treating covid-19 patients [26].

Research has demonstrated the immunomodulatory properties of menthol. Menthol treatment significantly reduced the levels of pro-inflammatory cytokines, i.e., interleukin-1, interleukin-23, and tumour necrosis factor- α in treated rats, suggesting a potential strategy to improve the treatment of covid-19 [27, 28].

Interestingly, an in vivo study examined the effects of carvacrol, in an elastase-induced emphysema mouse model. The results showed that carvacrol reduced macrophage recruitment and concentrations of IL-1 β , IL-6, IL-8, and IL-17 in bronchoalveolar lavage fluid. Pulmonary inflammation was significantly lower in carvacrol-treated mice [29].

EOs of *Origanum vulgare* (oregano), *Thymus vulgaris* (thymus), *Salvia sclarea* (sage), and *Lavandula angustifolia* (lavender) were used for their medicinal properties [30]. Mint, basil, tea tree oil, savory, lavender, and oregano inhibit the growth and activity of *Candida albicans* more efficiently than the antifungal agent clotrimazole [31].

An in vitro study showed the antifungal activity of EO of *Thymus vulgaris* and its constituents against *Rhizopus oryzae*. The results showed the significantly inhibited mycelial development and germination of sporangiospores. This study supports the potential use of these products in the treatment of mucormycosis [32].

Oregano EO has been studied for its efficacy against bacteria and fungi. A study conducted by Santoyo *et al.*, showed the activity of oregano EO against *C. albicans* and *Aspergillus niger* [33]. The antifungal activity of peppermint EO (*Mentha piperita*) has been demonstrated against inhibition of *C. albicans* growth [34, 35].

Studies against *C. albicans* showed that lavender oil significantly inhibited growth and, depending on the concentration, could even inhibit it completely [36].

Lemongrass essential oil is used against inflammatory and infectious diseases. Recent studies showed that lemongrass oil is a potentially valuable antifungal and anti-inflammatory agent for the prevention of skin diseases. The vapor phase has effective antifungal potency and could perhaps be used as an air decontaminant in hospitals [37] and improve patients with mucormycosis.

A randomized trial investigated the effects of aromatherapy on immune system outcomes and found that lemon oil reliably increased positive feeling compared to water and lavender [38], being immunomodulatory and mood enhancing.

The efficacy of *Cinnamomum verum* (cinnamon bark) EO against fungi, such as *C. albicans*, has been scientifically demonstrated [39-41]. The EO of *C. verum* and *Santalum austrocaledonicum* (sandalwood) inhibits fungi, such as *Trichophyton mentagrophytes* with excellent activity against cutaneous fungi [39].

The Biologically based Practices

Dietary Supplements

Infections increase the need for various nutrients. Nutrition is a critical factor in modulating immune homeostasis [42, 43]. A study by Wu *et al.*, showed that nutritional counselling can reduce lung injury caused by coronavirus and other pulmonary infections [44].

Vitamin A has an important role in enhancing the function of cellular and humoral immune response [45]. It has already been observed that children with vitamin A supplementation have an increase in immune response to influenza virus vaccination [46].

Vitamin D deficiency is epidemiologically associated with increased susceptibility to acute viral respiratory infections [47]. A systematic review of the role of vitamin D in the prevention of respiratory infections shows an association between low vitamin D status and increased risk of respiratory infections [48].

A specific diet is promising for the prevention, management, and recovery of Covid-19 patients and reduces the risk of fungal infection. Some is known about the central role of vitamin D, and its deficiency has been associated with increased susceptibility to respiratory infections [49].

The active form of vitamin D is involved in the regulation of various metabolic processes, such as cell proliferation. A recent study suggests that vitamin D influences immune signaling pathways by boosting defences, controlling excessive inflammation, and plays a role in respiratory infections, as evidenced by reports linking low vitamin D levels to an increased risk of infection [50, 51]. Studies have shown that hypovitaminosis D is related to increased diabetes, and sunbathing may help increase vitamin D levels and prevent disease [52, 53].

Vitamin C is an antioxidant, and its action is particularly pronounced under conditions of increased oxidative stress observed during infections that release reactive oxygen species (ROS). The ROS is involved in killing viruses, bacteria, and fungi [54]. However, ROS is harmful to host cells and in some cases plays a role in the pathogenesis of infections [55, 56].

Vitamin C has been found to be beneficial against pathogens, including viruses and *Candida albicans*. In some studies, it has been observed that regular intake of vitamin C shortens the duration of colds, suggesting a biological effect [57].

Trace elements are also important in balancing the immune system. Zinc is involved in maintaining immune function [58, 59]. Zinc deficiency is associated with increased susceptibility to infection and plays a critical role and may affect immunity to viral infections [58].

A study of children with pneumonia showed a statically significant clinical improvement when zinc was added to the diet. In addition, the authors observed an increase in Th1 cytokines [60].

Another trace element important is selenium. Supplementation with selenium increases lymphocyte and phospholipid peroxidase activities, and the cellular immune response is enhanced by cytokines, T-cell proliferation, and increase in T-helper cells [61].

Magnesium also plays a critical role in the control of infections. The presence of magnesium affects immunoglobulin synthesis, immune cell adherence, immunoglobulin M (IgM), lymphocyte binding, and macrophage response [62]. Magnesium administration may promote bronchodilation and improve lung function in asthma [62], an interesting point to consider as an alternative therapy in covid 19 patients.

Fungal infections were positively associated with a high-carbohydrate diet. Dietary therapy may help control infection-associated hyperglycemia and improve survival in mucormycosis, as observed in an experimental model [63].

A study investigating the modulatory effect of carbohydrate supplementation on facilitating *C. albicans* invasion showed that dietary glucose intake is an important determinant of *C. albicans* growth in the gastrointestinal tract and should be considered as a strategy in immunocompromised patients [64].

In vitro studies have shown that coconut oil possess antifungal activity [65]. A study in mouse models showed that dietary coconut oil alters the metabolic program of colonizing *C. albicans*, suggesting that may be a dietary intervention to reduce *C. albicans* colonization GI [29].

Scientific evidence shows that xylitol has antimicrobial properties and may prevent fungal infections [66]. Conventional sugar and lactose products may promote yeast growth by lowering pH in the digestive tract. Dietary therapy excluding these foods may help patients with fungal infections [67].

Iron plays an essential role in the life of Mucorales and its utilization by the host is a critical pathogenetic mechanism of mucormycosis. Iron limitation is an important defense strategy known as nutritional immunity to this fungus. A specific diet contributes to nutritional immunity within immune cells and increases antifungal activity [68, 69]. Dietary therapy may help control the proinflammatory mechanism and reduce the risk of infection [63].

It has been reported that poor nutrition can affect patient outcome, and obesity, which predisposes to insulin resistance and compensatory hyperinsulinemia, could promote infectious diseases such as mucormycosis [70].

The Whole Medical System Ayurveda and homoeopathy medicines

Alternative medicine embraces Ayurvedic medicine as a system that considers the body, mind and mind equally and restores the innate harmony of the patient and can modulate immune response and inflammation [11].

Some medicinal plants have antifungal properties, as described below. *Allium sativum* has been studied in an in vitro system. The studies reported that a fraction of garlic inhibited the growth of *Aspergillus niger* and *C. albicans*. In addition, garlic is a very effective treatment for athlete's foot and other fungal infections [71].

Ginger (*Zingiber officinalis*) contains the compound caprylic acid, which has potent antifungal properties. One study showed that ginger extracts were active against 13 human pathogens and could be considered as antifungal agents for practical therapy [72]. A protein with antifungal property was identified and isolated from ginger and showed antifungal activity against various fungi including *Fusarium oxysporum* [73].

In Ayurveda, guduchi (*Tinospora cordifolia*) is a widely used plant because it is known for its immunomodulatory activity. In a study, the authors investigated the immunostimulatory properties and confirmed the immunomodulatory protein in Guduchi with lymphoproliferative and macrophage activating property [74].

Another Ayurvedic preparation, Ashwagandha (*Withania somnifera* L. Dunal) was studied against aspergillosis in BALB/c mouse model. The study showed that intravenous treatment prolonged survival by increasing phagocytosis and intracellular killing of macrophages [75].

Curcumin, the yellow pigment of turmeric, is widely used. Extraction of three fractions was tested for antifungal activity and showed activity against these pathogens, decreasing the growth of germ spores. Another study showed that turmeric oil could inhibit the growth of dermatophytes. And in an in vivo model, dermal application improved lesions and disappeared after 7 days of treatment [76].

A study conducted on animal models showed the role of homeopathy in controlling fungal infections. The authors observed that treatment with *Cantharis* extract increased proinflammatory cytokines and T-cell recruitment and decreased the number of fungi [77].

Neem tree (*Azadirachta indica*) is used in Ayurvedic medicine. Various concentrates of neem leaf on the dispatch of *Aspergillus* and *Rhizopus* showed that the development of both the pathogen species was

suppressed and controlled with both the alcoholic and aqueous extracts [78].

The plant *Aloe vera* is used in Ayurvedic and homeopathic medicine and shows anti-inflammatory activity and acts on immune response. It is already known that aloe vera reduces cell-damaging processes during stress and minimises biochemical and physiological changes in the body, leading to an improvement in well-being [79].

Studies have shown that aloe vera has an inhibitory effect on some fungi, such as *Fusarium*. Along with the antiseptic properties imparted by saponins, the cleansing power [79], and should be considered as an additional therapy. Therefore, in vitro studies have demonstrated the antifungal activity of *Aloe vera* extracts, which gives confidence in the therapy [80].

The Manipulative and Body Based Practices Massage and Hydrotherapy

Researchers have reported that the quality of sleep can be influenced by aromatherapy and this strategy can be used as a complementary treatment to improve clinical outcomes. In addition, aromatherapy with massage has good therapeutic effects and progressively improves sleep quality [81, 82].

A systematic review and meta-analysis showed the potential efficacy of lavender essential oil massage in reducing anxiety. After massage, its bioactive compounds (linalool and linalyl acetate) are detected in the bloodstream [83, 84].

Studies showed that hand massage is a simple, non-pharmacological care practise that can be used to reduce anxiety and stress and improve sleep quality [85]. The best results showed the association of massage and Reiki with improving mental and psychological aspects [86].

Hydrotherapy is an alternative medicine used in combination with various therapies that can relieve symptoms and improve sleep quality. Water immersion can induce physiological and cognitive behavioural changes and maintain brain function and homeostasis by reducing the concentration of cortisol, which helps improve sleep quality [87-89].

The importance of a balanced immune system has become increasingly apparent recently. Numerous studies indicate that the mental state of the patient influences health and infection.

Light Therapy (The UV lights)

Although ultraviolet (UV) light (especially UVC) is known to be highly germicidal, its application for the treatment of local infections is still at an early stage of development. A statistical analysis showed that

UVC treatment significantly reduced fungal burden in infected patients and was superior to a topical antifungal agent, nystatin cream [90].

A study on animal models showed that *C. albicans* was more sensitive to ultraviolet (blue light - aBL) than human keratinocytes. And a single exposure reduced the fungal load in infected mouse burns. The authors suggested that aBL could be a potential therapeutic agent for *C. albicans* infections [91].

Final Thoughts

The Covid-19 pandemic has contributed to increase mucormycosis infection due to comprise the immune system. Provided positive points discussed on the role of alternative medicine may be considered strategies to help patients post-covid19 in preventing complications of mucormycosis infection as an adjuvant treatment in the management of disease. Complementary and alternative medicine aims to balance the human being, treating and complementing conventional medical treatments and acting on the emotional, physical, mental, and spiritual aspects in a more holistic way. Mindfulness meditative practice also helps this patient to adapt better to stress, depression, and anxiety. Therapy, alternative therapies can play a vital role in controlling fungal infection in post Covid19 patients, preventing complications, and, especially, improving quality of life.

Ethics Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Conflict of Interest Statement

The author has no conflicts of interest to declare. Authors has seen and agree with the contents of the manuscript and there is no financial interest to report. The author certify that the submission is original work and is not under review at any other publication.

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