Review Article

Potential Application of Probiotics in Attenuating the Link Between COVID-19 and Mucormycosis

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Abstract

COVID-19 has caused a significant amount of mortality and morbidity worldwide. It has paved the way for a plethora of complications including increase in the incidence of some previously rare diseases. Mucormycosis is one such opportunistic infection that has gained prominence in certain developing countries, especially India, during the pandemic. It is a life-threatening condition that requires to be managed promptly. Rampant use of steroids, immunomodulators, and antibiotics for the treatment of COVID-19 has led to hyperglycemia such as state, immunosuppression, and gut dysbiosis. All these conditions in addition to the local tissue damage mediated by the severe cytokine storm in the later stages of the disease are the key culprits for this upsurge. There is evidence promoting the potential use of probiotics for the prevention as well as the treatment of COVID-19. They boost and regulate the native immunity of the individual, simultaneously reducing the dependence on steroids and other immunomodulators. This can help prevent the development of opportunistic infections such as mucormycosis in COVID-19 patients. This article correlates the beneficial effects of probiotics in improving the individual's immune status to halt the probable mechanism by which mucormycosis can develop in individuals with COVID-19.

Keywords: COVID-19, mucormycosis, probiotics

Mucormycosis

Mucormycosis, also called zygomycosis, is a rare opportunistic fungal infection which is caused by a group of ubiquitous moulds belonging to the family *Mucoraceae*. Immuno-compromised individuals are the most vulnerable to develop this infection. Therefore, conditions involving diabetes, organ transplants, neutropenia, long-term corticosteroid therapy, immunosuppressant therapy, and iron overload may make the person susceptible to this infection.[1]

The global incidence of mucormycosis ranges from 0.005 to 1.7/million population. In India, the prevalence of mucormycosis is estimated as 140/million population, about 80 times higher compared to that of developed countries. In a systemic review and meta-analysis of 851 cases reports published in 2018, death was reported in 389/851 (46%) patients. Case fatality was found to be highest among patients with disseminated mucormycosis (68%) and lowest among those with cutaneous disease (31%).[1]

This rapidly progressing life-threatening condition commonly colonizes sinuses and lungs after inhaling fungal spores and can also occur on the skin after skin injury. The condition requires early diagnosis and prompt treatment. Mucormycosis can be laborious to treat, sometimes requiring surgical excision in addition to intravenous antifungal therapy, demanding a multidisciplinary approach.[2]

COVID-19-Associated Mucormycosis

COVID-19 as a global pandemic has caused distressing rates of mortality and morbidity. It has caused various complications including the rise in the incidence of some previously rare diseases.[3] One such case is that of the rising incidence of invasive fungal infections, especially mucormycosis.[4] The government of India has declared mucormycosis as a notifiable disease in May 2021.[1] The prevalence of CAM has been

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high in India, as compared to the developed countries.[1,5] The most significant underlying cause is diabetes and the other risk factors include organ and stem cell transplantations, hematological malignancies, neutropenia, trauma and burns, use of steroids, voriconazole and broad-spectrum antibiotics, renal insufficiency, and an increase in iron in the body.[4] CAM has also been observed in patients even with no underlying conditions indicating that COVID-19 itself may also act as a trigger.[4] An array of pulmonary changes occurs in COVID-19,[6] which may act as a focal point of initiation for opportunistic fungal infections.[4] COVID-19 itself is also associated with lymphopenia and immune dysfunction.[7] The risk for developing mucormycosis is also increased due to hyperglycemic state induced by steroid administration and high ferritin levels which can lead to leakage of iron into circulation.[8,9,10] Prolonged hospital stays in the intensive care unit, supportive oxygen therapy, and mechanical ventilation act as a potential source of contamination.[11,12] Overall, it is safe to say that COVID-19 has a tangled relation with mucormycosis.[4,13] It is also difficult to reverse or attenuate the underlying triggers while the patient is being treated for COVID-19, taking into consideration the rampant usage of broad-spectrum antibiotics and steroids. Vigilant use of these drugs, better hyperglycemic control, and prevention of contamination may help prevent this to a certain extent.[11]

The general symptoms associated with mucormycosis coincide with that of COVID-19. These include fever, cough, and shortness of breath. The specific symptoms depend on the area impacted. They include blackish or bloody discharge, local pain or numbness on the face, vision problems or loss of vision, skin lesions, headache, nasal or sinus congestion, and worsening of respiratory symptoms. Mucormycosis may be rhino-orbit-cerebral, pulmonary, cutaneous, gastrointestinal (GI), and disseminated. In COVID-19, the eye, oral region, and brain have been reported to be affected the most. The mainstay diagnostic methods include biopsy and potassium hydroxide mount.[1] Imaging tests such as computed tomography scans may support the diagnosis.[1,8] The current treatment includes intravenous antifungal therapy, liposomal amphotericin-B being the drug of choice, and surgical excision. Because of high fatality, the diagnosis and treatment should be prompt without delta.[1,8]

Although the overall situation of COVID-19 disease has improved significantly over the past two years, the advent of new strains of SARS-COV2 such as the alpha, beta, gamma, delta, and omicron leaves the hosts vulnerable for superinfections such as mucormycosis.

Probiotics and Body Microbiota

According to the WHO Expert Consultation, a specific definition of probiotics is "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Fermented foods such as yoghurt, cheese, and pickles confer the benefits of probiotics as they contain lactic acid bacteria.[14] Probiotics include yeasts such as *Saccharomyces boulardii* and *Saccharomyces cerevisiae* and bacteria such as *Lactobacillus acidophilus, Sporolactobacillus inulinus, Lactobacillus amylovorus, Lactobacillus brevis, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus cellobiosus, Lactobacillus crispatus, Lactobacillus curvatus, Escherichia coli*, *Bacillus clausii, Lactobacillus delbrueckii* spp. *bulgaris, Bacillus subtilis, Limosilactobacillus fermentum, Lactobacillus gallinarum, Propionibacterium thoenii, Lactobacillus helveticus, Lactobacillus johnsonii, Lactococcus lactis, Lacticaseibacillus paracasei, Lactiplantibacillus plantarum, Limosilactobacillus reuteri, Lacticaseibacillus rhamnosus; Bacillus coagulans, Streptococcus thermophilus, Lactococcus lactis, Leuconostoc mesenteroides, Bacillus cereus, Pediococcus pentosaceus, Pediococcus. acidilactici, Bifidobacterium adolescentis, Bifidobacterium animalis, Bifidobacterium bifidum, Bifidobacterium breve, Enterococcus Faecium, Bifidus essensis, Bifidobacterium infantis, Brevibacillus laterosporum, Bifidobacterium thermophilum, Bifidobacterium longum, Propionibacterium acidipropionici, Propionibacterium freudenreichii, Propionibacterium jensenii, Enterococcus fecalis,* and *Bacillus alcolophilus.*

The native microbiota of the human GI tract, respiratory tract, and the oral cavity are in a commensal relationship with the host cells. Hence, considered prominent in human health and immunity.[15,16] These colonies start to flourish shortly after birth and attain stability after about an year.[17] They confer health benefits by competing with the pathogens concerning colonization in the host. Any imbalance in these colonies leads to dysbiosis, which aids the pathogens to cause diseases.[18,19] Probiotics reinforces the native microbiota, correcting or preventing this dysbiosis.

Probiotics in COVID-19

Dysbiosis of the gut microbiota has been observed correlating with the cytokine storm and the severity of COVID-19. Moreover, increased severity of the disease has been observed in patients presenting with GI symptoms such as diarrhea.[20,21] There is increasing evidence suggesting the role of bidirectional signalling between lung and gut, referred to as the gut-lung axis involved in immune homeostasis.[22,23,24] Balanced gut microbiota influences the immune functions in the lungs.[25] This has paramount importance as the clinical picture of COVID-19 infection involves GI presentations such as vomiting, diarrhoea, loss of appetite, nausea, GI bleed, haematemesis, melena, and abdominal pain.[26] The probable key mechanisms behind the involvement of the GI tract include dysbiosis because of acute lung injury mediated by the gut-lung axis, immune dysfunction, and the colonization of angiotensin-converting enzyme 2 (ACE2) receptors in the intestine by the COVID-19 virus.[22,27,28] Rampant use of antibiotics in COVID-19 patients may also contribute to this dysbiosis.[22] Besides causing GI symptoms, this may also pave the way to several opportunistic infections. Several studies have shown the potential use of probiotics for the prevention and treatment of viral respiratory tract infections including COVID-19.[27] Although exact mechanism through which probiotics exert antiviral action is still not clear, they seem to exert anti-viral action by various mechanisms including immunomodulation, direct probiotic-virus interaction, and production of inhibitory metabolites.[29]

Studies have been conducted to unveil the mechanism by which certain strains of probiotics aid in lung's defence mechanisms against respiratory viral infections. Pathogens entering the lung are recognized by the immune cells' Pattern Recognition Receptors (PRRs). These receptors' recognition of pathogen-associated molecular patterns (PAMPs) and disease-associated molecular patterns (DAMPs) leads to immune response against the offending pathogen. It is possible that LAB modulates these responses to activate the immune cells.[30] Lactobacillus plantarum DR7 strain reduces plasma peroxidation levels, suppresses pro-inflammatory tumor necrosis factor (TNF)-α, TNF-γ and enhances anti-inflammatory interleukins (IL-10), IL-4.[31] Studies in mice have shown the effect of lactobacillus acidophilus CMCC878 in reducing bacterial load and inflammation.[32] Bifidobacterium longum BB536 strain has improved innate immunity and thus prevented influenza viral infection.[33] Lactobacillus Plantarum DR7 strain has shown to have suppressing effect on the pro-inflammatory cytokines TNF-α, IFN-γ, enhances anti-inflammatory cytokines IL-10, IL-4 and also known to reduce plasma peroxidation levels.[31] It is reported that Lactobacillus acidophilus CMCC878 administration in mice infected with *Staphylococcus aureus*, and *Pseudomonas aeruginosa* decreased the lung damage by reducing the bacterial load and reducing the inflammation.[32] Bifidobacterium longum BB536 strain prevents infection from influenza and improves innate immunity.[33]

In general, probiotics impact the ACE enzymes as well. They produce bioactive peptides during fermentation that block the enzyme's active site. In addition, even the dead debris of these probiotics inhibits the ACE enzyme. Thus, they can block the gateway of the COVID-19 virus, i.e., the ACE receptors in both the gut and the lung.[22] The biota also releases various substances such as bio-surfactants and nitric oxide, which inhibit viral proliferation.[22] Thus, they cannot only hinder the viral entry but also the viral replication.

Probiotics are immunomodulators. They provide beneficial effects to both local and systemic immune responses.[27] There is potentiation of the local immunity by maintaining the gut wall integrity and strengthening the mucosal barrier.[27] They enhance the activity of phagocytes, leukocytes, help the dendritic cells (antigen-presenting cells) prime T-cells, and balance the Th1/Th2-mediated immunity.[22,27]

Interaction with Toll-like receptors on the epithelium, accentuating the production of cytokines, promoting epithelial cell productivity, and increasing epithelial survival by preventing apoptosis is also observed.[27] They activate immunoglobulin A secretion and enhance Peyer's plaques, mesenteric lymph nodes, and intraepithelial lymphocytes.[27] They modulate PRRs to accentuate the response of inflammatory cells to PAMPs and DAMPs in the lung as well. Thus, they boost the native immunity of the individual.

In severe disease, a hyper-inflammatory state also known as cytokine storm is observed in COVID-19.[34] It can lead to damage of multiple organs including the lungs, liver, kidneys, eyes, microcirculation, GI tracts, and cardiovascular system. By their immunomodulatory actions, probiotics can balance the pro-inflammatory, Th1 and anti-inflammatory, Th2 immune mechanisms, which can help abate the cytokine storm.[35,36] The core anti-inflammatory pathway is summarized in Figure 1. This is achieved by the interaction with various signaling pathways, gene expression, epithelial cells, and immune cells.[27,37]

Thus, they prevent the virus from entering the cells, impede the replication of virus, enhance the immunological response of host against the COVID-19 virus and also help mitigate the cytokine storm observed in the disease.

Specific counter measures such as vaccination are highly effective but has led to rapid mutations and rise of new variants of SARS-COV2. Hence, the usage of probiotics in these needed times not only help slowdown mutations but also provide the host a window period in which the body can strengthen the native immunity.

Probiotics to Elude Mucormycois in COVID-19

Probiotics are being proposed as an effective therapeutic option in the treatment modalities of COVID-19 as they improve immunity through a natural approach. A close inspection at the pathogenesis of mucormycosis and post-COVID-19 microenvironment has provided insights into the scope for probiotics to be used as supportive therapy for existing corticosteroid and immunomodulator therapy. Cytokine storm being a dreadful event, anti-viral drugs alone are not enough and hence are being combined with anti-inflammatory therapy, which is corticosteroids in most cases. However, the extent of corticosteroids and immune

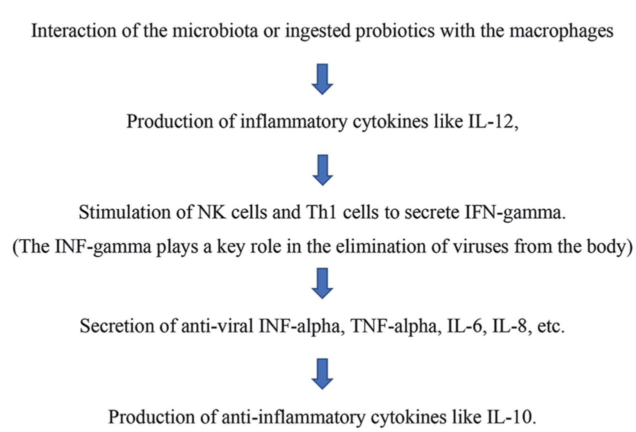

Figure 1: Immune modulation through probiotics

modulators being used in COVID-19 is ambiguous as there is evidence suggesting that these drugs, in turn may lead to CAM.[12] Cytokine storms also contribute toward immune deficiency due to significantly elevated levels of IL (mainly IL-2, IL-6, IL-7, interferon-gamma inducible factor, and granulocyte colony-stimulating factor), TNF-alpha, and also through cytokine-mediated atrophy of lymphoid tissue and production of lactic acidosis which inhibits lymphocyte proliferation.[38-41] Lymphocytopenia is, therefore, equivocally reported in patients with COVID-19.[42,43]

Lactic acidosis can also occur due to the direct damage to type II alveolar cells leading to reduced oxygen exchange capacity, causing hypoperfusion and anaerobic glycolysis raising the levels of lactic acid.[44]

The nonjudicial usage of systemic corticosteroids also results in immune suppression. Hence, this complex web of events causing immune suppression, in turn, promotes mucorales survival in the host.[44] Probiotics can be beneficial in such scenarios as they modulate host immune response, maintain gut homeostasis, and produce interferons, hence suppressing the virus-induced cytokine storm.[27] Moreover, there is evidence suggesting that strains such as lactobacilli and bifidobacteria show a promising beneficial effect against dysbiosis caused by COVID-19 by playing a role in improving and conserving the biological functions of the immune system.[35]

Probiotics impact the ACE enzymes as well as ACE receptors through colonization. Dysregulation of ACE2 expression is a prominent mechanism through which COVID-19 also sets a convenient microenvironment for mucorales in esophagus, ileum, pancreas, colon, cardiovascular, and renal tissues in addition to the lungs.[44] Acute diabetes such as state in COVID-19 is also explained based on this ACE 2 dysregulation in the pancreatic beta cells, which results in hyperglycemia.[45,46] Such ACE 2 dysregulation in vascular endothelium also leads to endothelial damage and vascular thrombosis, which further leads to elevated serum ferritin and serum iron levels due to hemolysis and acidosis, which provide a nourishing bed for mucorales.[47] Probiotics can keep this regulation in check as they impact the ACE enzymes as well as ACE receptors through colonization. All the above-described mechanisms are described in Figure 2.

Conclusion

This article intends to emphasize the use of probiotics in COVID-19 patients in not only treating COVID-19 but also to prevent the risk of developing secondary invasive fungal infections such as mucormycosis. As the safety of these probiotics is now well established, they are promoted as a potential therapeutic intervention in COVID-19. They cause immunomodulation and beneficial host colonization through a natural approach rather than a drug-based approach. This gives probiotics a unique advantage as they manifest minimal adverse effects while simultaneously decreasing the dependence on steroids. In addition, there is theoretical evidence suggesting the beneficial action of probiotics in hindering the potential vital pathways by which mucormycosis can manifest in COVID-19. Hence, it can be deduced that when used unerringly, probiotics can help break the link between mucormycosis and COVID-19 while promoting the patient's overall health. However, extensive research is necessary to elucidate various probiotic strains' beneficial effects for effective clinical use. The available literature is limited, and hence, more light needs to be thrown on this aspect, thereby opening the gates into the scientific era of applying probiotics in COVID-19.

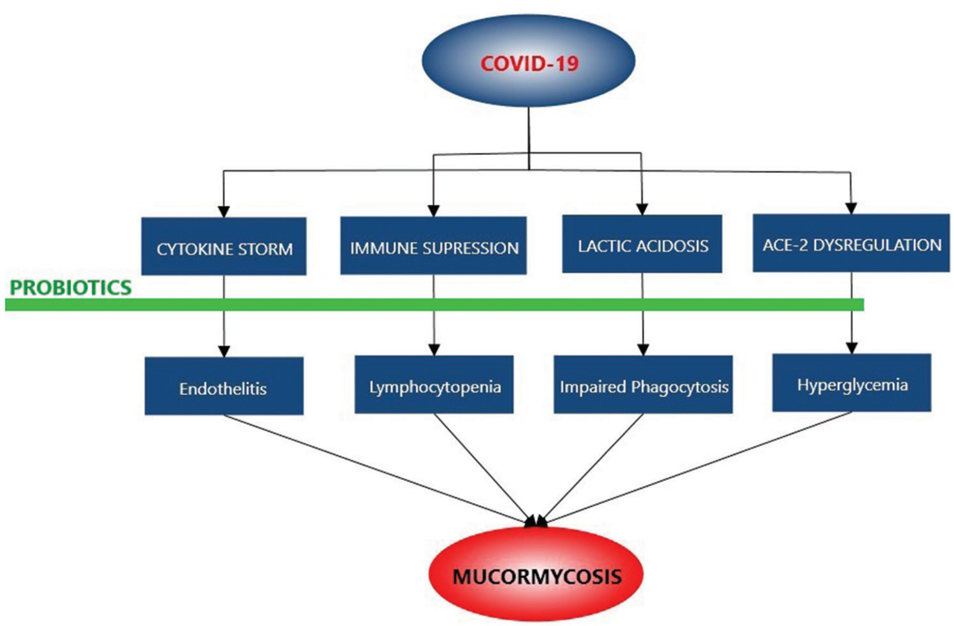

Figure 2: Role of Probiotics in attenuating the link between COVID-19 and Mucormycosis

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Conflicts of interest

There are no conflicts of interest.

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