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Review Article

Probiotic Therapy as a Complementary Treatment for Patients with COVID-19 and Other Upper Respiratory Tract Infections

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ABSTRACT

This literature review is aimed at assessing and summarizing relationships between the state of the microbiome and susceptibility to respiratory tract infections including COVID-19. It explores using probiotic therapy for patients infected with COVID-19, to improve outcomes, lessen the severity of symptoms, or prevent infection entirely. The coronavirus COVID-19 is known scientifically as severe acute respiratory syndrome coronavirus-2. The virus's binding sites for cell entry, the angiotensin-converting enzyme-2, are found in high concentrations in both respiratory and gut tissues. Probiotics may inhibit angiotensin-converting enzyme-2 receptor activity, thereby blocking viral entry into the cell. COVID-19 infection with alpha and delta variants has manifested clinically both in severe respiratory and gastrointestinal symptoms. The impact on the host's microbiome is significant and it has been shown that imbalanced intestinal microbiota can negatively affect respiratory function in an immune response known as the gut-lung axis.

The main nutritional outcomes for most people surviving a critical viral-induced respiratory illness include suboptimal protein and calorie intake, hypermetabolism, and rapid muscle wasting. A dysbiosis occurs in the microbiome, allowing opportunistic pathogens to thrive, while beneficial commensals are depleted. The current understanding of the potential mechanisms of probiotic therapy administration, strain specificity, and the effectiveness of these bacteria in preventing and treating COVID-19 infections is summarized. The known antiviral properties of probiotics and their metabolites suggest they may be used as adjunctive therapy in the fight against many respiratory infections.

Addressing dysbiosis with probiotics has shown it is possible to restore a stable intestinal microbiome. The potential role probiotics play in preventing or limiting the intensity and duration of upper respiratory tract infections needs further and wider exploration. Manipulating the gut-lung axis through probiotic therapy suggests great effectiveness in protection against the susceptibility to a wide range of respiratory tract infections.

Keywords: Probiotics; COVID-19; Respiratory tract; Microbiota

INTRODUCTION

Respiratory Tracts Infections (RTIs) caused by influenza and COVID-19 are currently one of the leading causes of death worldwide [1]. The gut microbiome and its health are essential for providing an adequate immune response [2]. Human gut microbiota provides protective responses against invading pathogens [3]. Dysbiosis is the persistent imbalance of the gut's microbial community, which increases the risk of developing infections and even autoimmune diseases [4]. Research has shown that people with inflammatory bowel disease are more susceptible to respiratory tract infections because of their dysbiosis. A disordered microbiome can affect how energy is produced, how vitamins and minerals are made, and how food is digested. Regulation of the immune system to protect the lung tissues during a viral illness is derived from microbiota signaling. Interaction between the gut and lung, plays a protective role against the development of serious respiratory infections [5,6]. Any alteration that occurs either in the microbiota or in their metabolites can influence the immune system. While the roles of the gut and lungs are vastly different, they developed from the same embryonic tissues and therefore share similar structural components. A specialized layer of mucosal cells lines both structures, protecting them against invading pathogens [7]. Being integrated as part of the mucosal immune system, the gut

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and lungs work in concert with the microbes sending signals in what is referred to as the Gut-Lung Axis (GLA) [8]. Although COVID-19 primarily compromises the lungs, it also affects other parts of the body, including the gut. Dr. Ajiz Ahmed and colleagues at Stanford University showed study results indicating that patients who had a COVID-19 infection with gastrointestinal symptoms were five times more likely to require hospital admission [9]. This connection is clear when considering the GLA.

With ninety percent of upper respiratory tract infections being viral in nature, several studies have explored the role probiotics may play in therapy. Meta-analyses and systematic reviews have explored the role of probiotic therapy and have concluded probiotic therapy is producing beneficial outcomes for people infected with RTIs [10-12].

Probiotics have been shown to modulate the human inflammatory response system in a way that can improve outcomes for a person experiencing an infectious disease process [13]. Studies have shown probiotic therapy is beneficial in other infectious states such as both upper and lower respiratory tract infections, ventilator-associated pneumonia, and sepsis. Recently, evidence has emerged suggesting that the health of the gut microbiome is linked to the risk of contracting the COVID-19 infection and the disease severity and symptom duration. Therefore, using probiotics to modulate the gut microbiome may be a promising strategy to use against COVID-19 transmission risk and to reduce the chance of negative outcomes for those who do become infected. As a result, this paper explores the role of probiotic therapy in treating COVID-19 and other RTIs.

LITERATURE REVIEW

A systematic search of PubMed and Cochrane Library identified recent meta-analyses and systematic reviews and five randomized, double-blind, placebo-controlled trials conducted in adults which examined the effects of probiotics on incidence, duration, and severity of COVID-19 symptoms, including improved immune response to the COVID-19 vaccine. The search was performed using keywords COVID-19, Probiotics, Gut-lung axis, Dysbiosis and Microbiome, limiting results from 2016 to 2022. Examination of ClinicalTrials.gov showed there remain four active clinical trials aiming to investigate the beneficial effects of probiotic therapy in reducing viral loads and leading to quicker recovery. One active clinical trial is aiming to show probiotic therapy with a specific strain will protect against contracting COVID-19. In these findings, an understanding of the actions and potential benefits of probiotic therapy in the management of COVID-19 have been summarized. A summation of probiotic therapy in preventing and treating COVID-19 infection has been performed. Future research needs have also been highlighted.

It is well established that various mucosal surfaces in the human body produce colonized resistance against pathogens through the direct action of the microbes themselves [7]. The gut microbiota regulates the integrity of the mucosal barrier that lines the intestines and the lungs. The mucosal barrier is the first line of defense against pathogens entering these systems. Angiotensin-Converting Enzyme 2 (ACE2) is a protein enzyme present in the mucosal lining of various tissue types within our bodies, including the heart, blood vessels, lungs, liver, kidneys, and the gastrointestinal tract. The ACE2 receptors perform many functions such as regulating blood pressure, accelerating wound healing, and decreasing inflammation. The mucosal lining is a protective barrier, intended to keep pathogens out [14]. It is at the ACE2 where COVID-19 enters the cell, by binding with ACE2 receptors. People with pre-existing deficits in their gut microbiota tend to have more ACE2 receptors lining their gut and lungs, making them increasingly vulnerable to a severe COVID-19 infection. When the COVID-19 virus gains entry, these receptors are then blocked. Probiotics have shown the ability to bind to an epithelial cell at the same site, and it is therefore believed probiotics may provide competitive inhibition against COVID-19 and other viral pathogens. Various studies have also suggested that inhibition of the ACE2 receptor is the responsible mechanism or suppression of immune response caused by the proinflammatory cytokine cascade.

Strong research has shown that the gut is our largest source of immunity. The gut is composed of mucosal lymphoid tissue, and within this tissue is a network of immune cells called Gut-associated Lymphoid Tissue (GALT) [15]. Within the gut, there are many bacteria commonly referred to as the microbiota which protect against harmful pathogens. The GALT and the gut microbiota interact closely and directly influence inflammatory responses to various pathogens [16]. In their single-center, quadruple-blinded, randomized trial in adults symptomatic with COVID-19, Gutierrez-Castrellon, et al. randomized three hundred subjects and allocated them 1:1 with a probiotic formula containing strains *Lactiplantibacillus plantarum* KABP022, KABP023 and KAPB033 plus strain Pediococcus acidilactici KABP021, or placebo, for thirty days [17]. Compared to placebo, those in the probiotic supplementation group showed a reduction in nasopharyngeal viral load, had fewer cases of lung infiltrates, and experienced a reduced duration of COVID-19 symptoms. They also had a significantly increased number of immunoglobulins IgM and IgG against the COVID-19 virus. Interestingly, there was no significant change in fecal microbiota composition in both the probiotic and the placebo group.

In their published double-blind, randomized, and placebo-controlled trial, Kazmierczak-Siedlecka et al. examined the benefits of the probiotic Lactobacillus plantarum 299v (Lp299v) on improving gastrointestinal symptoms and increasing tolerance to enteral nutrition in people with cancer receiving chemotherapy [18]. They hypothesized it was the probiotic itself that was protecting the mucosal surfaces. The researchers chose the particular probiotic strain as it was known to have good tolerance to the high acidic environment of the stomach, along with having immunomodulatory properties.18 Lp299v is known to increase transcription of the glycoproteins MUC2 and MUC3, which protect mucosal surfaces found in the intestine. The strain has demonstrated antibacterial properties against pathogens Escherichia coli, Listeria monocytogens, along with Clostridium difficile [19].

Recent studies have focused on exploring more specific actions and communication between the microbiota in the gut and the lungs. New evidence has indicated there is two-way communication, or "crosstalk" between body tissues and various microbes. This communication process is referred to as the Gut-Lung Axis (GLA).4,14 The immune status of both organs in communication can positively and negatively affect the other while the GLA is sending out immune responses. Respiratory status can be improved when microbes populating the gut send out messages to strengthen the immune response to the lung tissue, and vice versa. It is believed that communication occurs because of microorganisms sending out chemical messengers through the bloodstream, which are then received by the reciprocal body organ.

The composition of the microbes that populate our gut varies throughout different life stages, according to our diet, medications, or current state of health, and varies from person to person. The scientific literature strongly supports that gut microbiota populations

change when a person is hospitalized and treated for critical illness. Microbial imbalance or maladaptation is referred to as dysbiosis, which negatively influences the immune response and can contribute to increased severity of illness and worsened outcomes. Microbial populations in people who had a COVID-19 infection can remain in a state of dysbiosis even six months after recovery. Hawrylkowicz et al. hypothesized that treating COVID-19-related dysbiosis involved providing both prebiotic fiber and probiotics to those infected, but also hypothesized that the same treatment could be given prophylactically for immunomodulation. With the COVID-19 infection, dysbiosis is recurrent and recovery is associated with correction of dysbiosis, as this decreases proinflammatory cytokines [20]. Despite COVID-19 infection being significantly associated with respiratory distress, the virus also presents as a gastrointestinal infection [6]. Interestingly, research showed patients with greater gastrointestinal symptoms also experienced more severe respiratory infection, which was thought to be associated with gut dysbiosis [6]. When considering gut dysbiosis with patients being treated for COVID-19 infection, it is important to also consider the fact that most also receive antibiotic and antiviral therapy, which are also contributing to the dysbiosis [21]. Probiotic therapy is widely effective in improving gastrointestinal dysbiosis in many disease states [22].

DISCUSSION

The results of a recent meta-analysis indicated probiotic therapy may reduce both incidence and duration of Upper Respiratory Tract Infections (URTIs)10 Leal-Martinez et al. conducted a randomized, blinded, controlled clinical trial (n=80) in people infected with COVID-19 where the intervention group received various vitamins, minerals, fiber, omega-3 amino acids, B-complex, and probiotics. While this was a single-center, small study, outcomes for those in the intervention group was decreased mortality and shortened period of acute infection. In a similar study using probiotic therapy, Karl JP showed a reduction of incidence, duration, and decrease in the severity of RTIs in otherwise healthy, non-elderly adults when gut microbiota-targeted interventions were administered to military personnel. Baud et al. summarized data from multiple studies showing various probiotic strains proposed as able to lower the viral load of COVID-19 infection [23]. The specific strains included *Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnose, Lactobacillus gasseri, Bifidobacterium bifidum, Bifidobacterum longum, Bifidobacterum breve, Leuconostoc mestenteroids, and Pedicoccus pentosaces.* All authors of these studies agreed that further clinical trials were needed given only low-quality evidence supporting their findings. Recent large epidemiological studies have shown independent risk factors for RTIs, including those caused by COVID-19, as being overweight or obese, given these conditions are strongly associated with dysbiosis. In their placebo-controlled clinical trial of probiotic therapy in overweight and obese people with URTIs, Mullish et al. found study participants taking probiotics experienced a 27% reduction in their symptoms as compared to those taking the placebo p=.0194.22

The elderly have increased vulnerability to RTIs and COVID-19 infection, and often experience lower effectiveness from vaccination [24]. In their randomized, placebo-controlled, double-blind trial, Fernandez-Ferreiro et al. assessed the effect of probiotic Loigolactobacillus cornyiforis K8 CECT 5711 on the immune response generated by receiving the COVID-19 vaccine given to elderly nursing home residents who had never been infected with the virus. Of the two hundred subjects, all received the vaccine and then took a daily probiotic or placebo, starting ten days after receiving the first vaccine dose and continuing for three months. Subgroup analysis revealed significantly higher IgG levels than placebo (p=0.038), with the authors concluding probiotics may enhance specific immune responses, improving vaccine immunity among the elderly population.

In their ongoing double-blinded, randomized, placebo-controlled trial, Tang et al. randomized 1132 people who had a household member testing positive for COVID-19<7 days before starting the trial. Multivariate analysis of demographic, behavioral, temporal, and other variables were also conducted. Study subjects took either Lactobacillus rhamnosus GG (LGG) 20 billion species or a placebo for 28 days. Stool samples and nasal swabs were collected initially and at the end of day 28 to evaluate the microbiome by 16SrRNA sequencing. Subjects also kept a symptom journal. The researchers determined their primary endpoint goal was to evaluate the effectiveness of LGG in preventing transmission and/or symptom development among the exposed household contact by specifically studying the incidence of COVID-19 symptoms. They looked at the interactions of this specific bacterial strain and its effects on the microbiome, such as changes in intestinal bacterial diversity in those who did versus those who did not develop COVID-19 and LGG versus placebo. Secondarily, researchers believe their analytical approach will allow improved identification of favorable microbiome composition to help identify people at increased risk for COVID-19 infection and to predict which patients would respond best to probiotic therapy.

CONCLUSION

While many recent clinical trials, and a few meta-analyses, have suggested that using probiotics can lessen disease severity and improve outcomes in people with respiratory and gastrointestinal infections, significant limitations to these studies cannot be ignored. Most studies on probiotic therapy effectiveness have had small sample sizes. Most have over-relied on subjective outcome reporting. There has also been considerable variability between these trials. Most of the trials and meta-analyses reviewed focused solely on non-elderly, healthy individuals. In studies that did focus on the elderly population, there were limitations due to sample variability, as this population tends to be polymedicated and often has many comorbidities. There is currently low-quality evidence supporting the routine use of probiotic therapy to reduce or prevent URTIs in adult patients. Additional trials are needed to fully support this conclusion.

The human body has far more microbial cells than the number of human cells, making this a unique opportunity to utilize targeted interventions to modulate the microbiome and improve health while lessening the severity of disease processes. By modulating the gut microbiota, modulation of the lung microbiota also occurs. Probiotics are living bacteria that can be ingested easily in capsule form, or even as a powder added to foods. When administered using targeted strains and in adequate amounts, they can provide a positive health benefit without serious side effects. Probiotic therapy has already been proven effective in various disease states, including some viral illnesses because URTIs are both common and burdensome to our healthcare system, and the COVID-19 infections were so widespread, using relatively inexpensive, easy to administer, and widely available probiotic therapy is a potential preventive or adjuvant therapy to COVID-19. This could help avoid using antibiotics and contribute to the development of super-pathogens.

There have been advances in the fields of genomics and bioinformatics, which have helped support a paradigm shift towards a better understanding of the host and microbiome relationship. Within the field of clinical nutrition, incorporating a microbiome-oriented assessment in the traditional nutrition assessment could help identify those most at risk for developing dysbiosis, allowing early probiotic therapy. Prophylactic oral probiotics could be provided to many patients on admission to reduce the severity of GI and respiratory viral illnesses, alongside traditional antiviral therapies. In conclusion, antiviral therapy using targeted probiotics is safe for most people. It should be considered a cost-effective adjuvant therapy for those with URTIs or GI viral infections.

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