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Role Of Probiotics And Microbiota In Covid-19

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Abstract: *Identifying the mechanism of Covid-19 illness and its development can bring the discovery of new objectives for prevention or therapy. This might be accomplished by preventing viral entrance and replication, or just by suppressing the immune reaction elicited by the disease. Probiotics are described as "beneficial microorganisms that impose a health benefit on the host when given in suitable concentrations." There is strong scientific research to prove the capacity of probiotics in increasing human immune response, hence avoiding pathogen proliferation and lowering the occurrence and severity of diseases. We report clinical data on the usefulness of probiotic supplements to protect and cure respiratory system infections in this paper. The findings suggest that probiotics may be beneficial in lowering the likelihood of coronavirus infection. Furthermore, this domain needs to be explored to unleash the strength of probiotics and microbiota in fighting against COVID-19.*

Key Words: Covid-19, Microbiota, Probiotics, SARS-COV-2

Introduction

The end of 2019 marked the rise of coronavirus sickness 2019 (COVID-19), which is indeed caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Until now, it has been spreading all over the world, putting human life and health in grave danger (Li, G., et al., 2020; Chen, N., et al., 2020) Despite this, a continuous climb in COVID-19 cases around the world is being reported. COVID-19's severity has resulted in and seems to probably keep on resulting substantial medical and financial consequences for society. Thus, there is a dire need for cost-effective infection prevention strategies.

As the epidemic continues to spread and the number of individuals who have recovered grows, cases of patients with chronic symptoms such as dyspnea, tiredness, coughing, chest discomfort, myalgia, and arthralgia have been described even in individuals whose initial phase of the disease was mild (Chan, J.F.-W., et al., 2020). Headache, sore throat, rhinorrhea, and gastrointestinal problems are among the other symptoms [Sundararaman, A., et al., 2020; Lee, I.-C., T.-I. 2020). Several drugs were utilized to treat the sickness at the commencement of the pandemic which included remdesivir and favipiravir. Remdesivir proved to be one of the most successful among these, as it resulted in the

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successful treatment of the first COVID-19 patient in the United States (Holshue, M.L., et al., (2020).

A variety of effective vaccinations have been produced and are being available to the masses all around the world. The decline in abundance of gut microbiota and dysbacteriosis in COVID-19 patients made it difficult to achieve their normal levels even 6 months after recovery, and the protracted gut dysbacteriosis was related to severity of disease and inflammatory response (Chen, Y., et al., 2021).

Microbial diversity has been proven to be a key predictor of microbiological ecosystem functioning in previous studies (Gu, S., et al., 2020; Yeoh, Y.K., et al., 2021). The retrieval of gastrointestinal and pulmonary health in COVID-19 patients is hampered by hunger, but a proper gut environment increases colonization resistance against opportunistic infections (Lahti, L., et al., 2014; Dickson, R., et al., 2016). As a result, complete recovery from COVID-19 is likely to be facilitated by a focused supplemental micro-ecological treatment that aids in the restoration of healthy gut bacteria populations (Chen, Y., et al., 2021).

Probiotics have been successfully employed as an adjuvant medication in managing COVID-19 in a number of clinical investigations (Xu, X.-W., et al., 2020; Wu, C., et al., 2020), with more than six more in the works (Baindara, P., et al., 2021; Hu, J., et al., 2020). The current study summarized our existing understanding of probiotics' actions and possible mechanisms in the treatment of COVID-19, along with highlighting future requirements for probiotic researchers in the field.

Coronavirus Illness (2019)

SARS coronavirus-2 is the causative agent of coronavirus illness in humans, an illness of the respiratory system that initially emerged in December 2019 in a city in China. SARS-associated coronavirus belongs to the zoonotic family of coronaviruses (Rodriguez-Morales, A.J., et al., 2020; Xie, M. 2020). This virus has an envelope and a single RNA (+ve) sense strand [19]. Coronaviruses are called because of their crown-like structures and long surface spikes [20]. Humans and numerous other vertebrate carriers (including bats, civets, dogs, cats, and mice) host coronaviruses (Guan, W.-j., et al., 2020; Lu, C.-w., X.-f. Liu, & Z.-f.J.L. Jia. 2020).

According to one theory, coronavirus was first carried by bats and was eventually transmitted to humans via wildlife animals; however, the virus later advanced by human-to-human transmission (Zu, Z.Y., et al., 2020).

A high percentage of Covid-19 cases are self-limiting and totally resolved [18]. SARS-CoV-2, on the other hand, can induce serious infections, including septic shock, ARDS, acute heart damage, acute kidney damage, and multi-organ dysfunction, necessitating ICU admission. COVID-19 instances that are extremely severe might result in death (Xie, M. 2020; Guan, W.-j., et al., 2020). Adults and children are more likely to acquire moderate self-limiting illnesses. Meanwhile, aged adults with preexisting medical issues such as diabetes and cardiovascular disease might develop more severe COVID-19(Xie, M. (2020). Pregnant women typically experience illness symptoms comparable to non-pregnant patients. Although COVID-19 was once thought to be rare in children (Lee, P.-I., et al., (2020), a growing number of cases in children have been recorded globally, indicating that children are susceptible to COVID-19 in the very same way as adults are but display moderate or asymptomatic disease (Zimmermann, P. 2020).

COVID-19 infection is more likely if you've been in contact with sick people in the last two weeks (Zu, Z.Y., et al., (2020). The highly efficient technique for diagnosing COVID-19 is PCR. Another tool that can aid in the diagnosis of coronaviruses is a chest CT scan (Zu, Z.Y., et al., 2020).

COVID-19 is mostly transferred from one individual to another individual by cough or sneeze-induced secretions from the oral cavity or nasal cavity of diseased people. Disease spread via the eyes of an infected person has also been studied. Close contact with virus-infected places is also another method of COVID-19 transmission

(Rodriguez-Morales, A.J., et al., 2020; Lu, C.-w., X.-f. Liu, & Z.-f.J.L. Jia. 2020). Coronavirus was recently found in faeces, raising the likelihood of transmission through fecal-oral route (Guan, W.-j., et al., 2020). It was later confirmed in China and the United States, suggesting that coronaviruses can multiply in both the stomach and respiratory systems (Holshue, M.L., et al., 2020). COVID-19 infection appears to have a long-term negative impact on the gastrointestinal tract's architecture and function, as well as the gut microbiota (Xiao, F., et al., 2020; Kopel, J., et al., 2020). A substantial amount of published research now confirms that the gut population of microbes in coronavirus patients has altered. The increase of opportunistic pathogenic microbes and the loss of helpful bacteria in gut microbiota were clearly connected to the intensity of COVID-19 infections (Zuo, T., et al., 2020; Tang, L., et al., 2020).

Role of Microbiota

Microbiotas include all microbial populations that live in the host, including fungi, viruses, bacteria, and protozoans. Microbes outnumber human cells in the human body, populating mucosal surfaces and the body skin. The significance of the microbiota in creating an immune response and maintaining balance in the body has been intensively researched, especially in the GI tract, where microorganisms are prevalent (Dumas, A., et al., 2018). The number of commensal bacteria found in the gastrointestinal tract is similar to the number of cells present in humans (Sender, R., S. Fuchs., & R.J.P.b. Milo, 2016; Zhang, Y.-J., et al., 2015).

The GI microbiome can engage with cells, even with some cells of the immune system. Such interactions have a variety of health advantages in humans, including governing the motility of the gastrointestinal tract, destruction of toxic substances, genotoxins, and mutation inducing compounds, converting biliary acid as well as steroids, generating minerals and vitamins, carrying out biotransformation of substances, affecting intestinal absorption and protective functions, regulating immunity, and benefiting the skin and upper airways (Davison, G., 2016; Dickson, R.P., et al., 2017)

In order to support human health and wellbeing, these helpful microbes contend with pathogenic microbes for the settlement of human cells in various systems. This necessitates a large number of helpful bacteria, and any mismatch or disturbance in this system may result in dysbiosis, allowing pathogens to cause illnesses such as respiratory system infections (Barcik, W., et al., 2020; Bustamante, M., et al., 2020).

COVID-19 and Gut-lung Axis

The 'gut lung axis' (Pan, L., et al., 2020) has been discovered to directly affect lung health by linking interactions between the stomach and lungs. The gut-lung axis can be considered a two-way system, implying that microbial toxic compounds in the gut might have an effect on the lungs (Dhar, D. & Mohanty, A. J. V. R., 2020). The majority of the potential linkages between systems throughout the gut-lung axis are caused by immune cells or the intestinal microbiota along with its metabolites. Microbiomes and their byproducts pass through the intestinal epithelium, where they are rapidly absorbed by antigen-presenting cells and pass on to regional lymph nodes. These bacteria have the ability to stimulate B and T lymphocytes which may return to their original position, the gastrointestinal mucosa, after being stimulated, or these may get transferred to remaining parts of the body.

Researchers also noted the effect of the gut microbiome on the pulmonary system, such as mice having deficient intestinal microbiota had reduced clearance of pathogenic microorganisms from the lungs (Fagundes, C.T., et al., 2012). A study showed that the administration of intra-tracheal lipopolysaccharides (LPS) might affect the lung microbiome, resulting in instability of the GI microbiota and an upsurge in bacteria (Sze, M.A., et al., 2014).

ARDS and chest infections such as pneumonia are the most commonly found symptoms of coronavirus illness. The occurrence

of ARDS and infection has also been linked to gut microbiota (Dickson, 2016; Shen, Z., et al., 2020).

Many studies have confirmed the existence of GI signs and symptoms throughout the path of the illness and also the detection of RNA of the virus in faeces (Ng, S. C., & Tilg, H. J. G). Pilot research was also done, which gives evidence for long-term 'quiescent' GI illness even GI symptoms were absent. In the research, 7 (46.7%t) out of 15 coronavirus patients came out to be positive for COVID-19 in their faeces through viral RNA metagenomic sequencing. Three individuals remained infected with coronavirus for up to six days even after the virus was removed from their respiratory samples (Zuo, T., et al., 2021).

The residence of transmembrane protease serine-2 (TMPRSS-2) and Angiotensin Converting Enzyme (ACE-2) receptors in ileum and colon epithelium, which are required for coronavirus to enter and destroy cells, has been discovered (Hoffmann, M., et al., 2020; Zhang, H., et al., 2020). There's a probability that coronavirus infection in the enterocytes is causing these gastrointestinal symptoms (Nagpal, R., et al., 2018). It's also conceivable to speculate about the gut-lung axis, in which these GI abnormalities in coronavirus could be the outcome of significant respiratory changes; alternatively, the coronavirus could infiltrate enterocytes in the colon, causing gut dysbiosis and increased respiratory issues. The intestinal microbiota of older people is often less concentrated [51]. COVID-19 susceptibility in the elderly may potentially indicate a relationship between a less diversified microbiome and COVID-19 infection. This idea, however, requires more study and clinical trials.

Gut Microbiota, COVID-19 and Immunity

The host's interactions with the microbiota are multiple which are complicated, diverse, and bidirectional. Gut flora influences both the establishment and operation of innate and adaptive immunity (Negi, S., et al., 2019). Commensal bacteria in the intestine release antibacterial peptides, compete for habitat and resources and hence affect homeostasis (Moens, E. 2012). The gut flora and immunological homeostasis appear to interact, and this is a topic that has gathered massive concern and is the subject of active research in the infectious diseases domain (Negi, S., et al., 2019). Immunological gut homeostasis is induced by precisely balancing the regulations of the pro-inflammatory reactions like Th17 versus inflammatory T cells, which are ultimately regulated by commensal bacteria (Round, J. L., & Mazmanian, 2010). In order to avoid a reaction to morbid infections such as coronavirus, a healthy intestinal microbiota may be crucial in keeping an ideal immune response and preventing a variety of overactive immunological reactions that may be damaging to the lungs and other key organ systems.

In these instances, having a regulated immunological response is crucial because either a hyperactive or hypoactive immune response can exacerbate clinical outcomes such as ARDS and pneumonia in a viral infection like coronavirus. Both microorganism-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs) are found in microbes (PAMPs). MAMPs and PAMPs on host cells are identified by pattern recognition receptors (PRRs) including toll-like receptors (TLRs) and nucleotide-binding receptors (NODs) (Ivanov, I.I., 2012).

Gut flora-released metabolites and immune-regulatory signals like acetate and butyrate, as well as secondary bile acids produced naturally by commensals like lactobacillus and bifidobacteria, attach to particular receptors in innate cells, affecting metabolic activity and functions [Rooks, M.G., 2016; Jia, W., et al., 2018). Indeed, the administration of probiotics like Bifidobacterium lactis to healthy older subjects resulted in a substantial increment of mononuclear leukocytes as well as the antitumoral ability of NK cells (Gill, H.S., et al., 2001) (fig. 1).

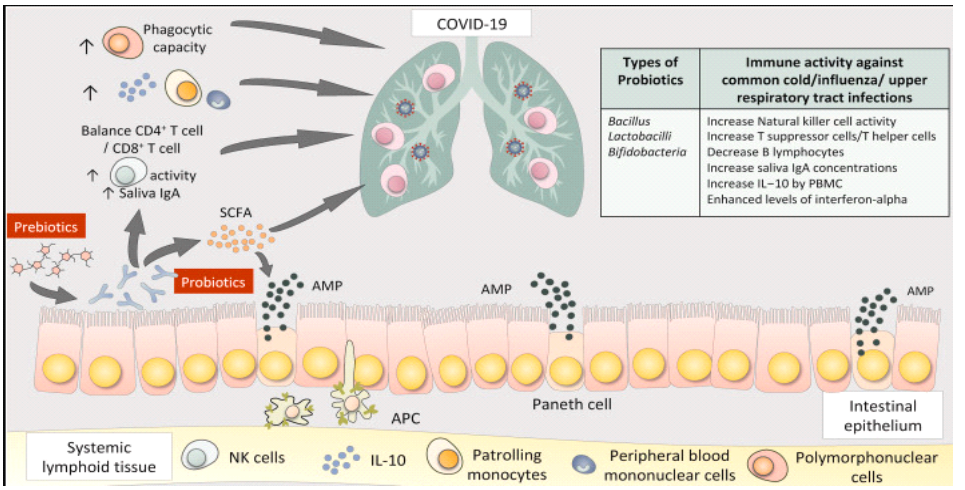

Figure 1. Associations between the lung and human gut, as well as the potential for probiotics and prebiotics to induce a beneficial immunological response

The organization of a healthy GI microbiota is recognized to have a significant impact on pulmonary immune efficiency. Germ-free mice (GF mice) were demonstrated to have decreased capabilities regarding clearance of pathogens from the lung due to a lack of intestinal flora (Fagundes, C.T., et al., 2012).

The disruption of GI microbiota due to extensive antibiotic usage could have a similar effect as seen in demographic studies that found that greater use of β - lactam antibiotics and quinolones were connected to a higher risk of lung cancer in people [60]. Excitingly, influenza virus infection enhances Enterobacteriaceae while decreasing Lactococci and Lactobacilli in the GI microbiota in rats (Looft, T., and Allen, H. K. J. G. M. 2012). Combined together, our findings imply that, because the GI microbiota serves such an essential part in immunity, coronavirus infections should be further investigated in terms of the involvement of intestine and lung commensal microbes.

COVID-19 and Dysbiosis

A balanced gut microbiome suggests enhanced lung immune efficiency (Bingula, R., et al., 2017), as observed in a germ-free animal with decreased pulmonary pathogenic clearance (Dhar, D. & Mohanty, A. J. V. R., 2020). Viral diseases may also disrupt the GI microbiota, which is observed in the case of H. influenza virus infection in mice, resulting in an upsurge in Enterobacteriaceae in the lungs and a decrease in Lactobacilli and Lactococci in the intestinal microbiota (Dhar, D. & Mohanty, A. J. V. R., 2020). Many heterogeneous disorders, including immunological, biochemical, inflammatory, neurological, and neoplastic diseases, have been associated with intestinal dysbiosis. Through processes such as the synthesis of antimicrobial peptides and IgA antibodies, adaptive and innate immune immunity regulate the colonization of the gastrointestinal microbiota. A dysbiotic microbiome can actively impact colonization by modifying innate and adaptive gut immune mechanisms. Dysbiosis is also associated with a variety of immune-related human diseases, but it is not always understandable whether dysbiosis is a causative factor or a response to the ailment (Xu, K. H. Cai; Kuba, K., et al., 2005). ACE2 regulates the amino acid transporter BoAT1, which regulates tryptophan absorption in the intestine (Zhao, Y., et al., 2018). The mTOR pathway is used by tryptophan to carry out the mRNA expression of bioactive peptides, and antimicrobial peptides might change the gut microbiota composition

(Liévin-Le Moal, V., & Servin, A. L. J. C. M. R. 2006). Gut absorption of tryptophan is reduced, as is the production of antimicrobial chemicals, as a result of ACE2 dysregulation, resulting in increased pathogen survival and gastrointestinal dysbiosis.

Gut Microbiota, Diet, and COVID-19

Because dysbiosis may affect the degree of sickness caused by the coronavirus, therefore the dire need to keep the gut healthy is important during this outbreak. Intestinal dysbiosis is frequently caused by high-carbohydrate, high-fat, low-fiber diets (Trompette, A., et al., 2014), and this alteration in homeostasis may be linked to decreased immune response. A fiber-rich diet reported to have substantial amounts of circulatory short-chain fatty acids in mice is thought to have an anti-allergic inflammatory effect on the lungs, according to research. As a result, a diet rich in fiber may change the gut microbiota of an individual along with the pulmonary microbiota which highlights the role of nutrition in pulmonary immunology (Valdes, A.M., et al., 2018).

Both acute and long-term dietary exposures cause the gut flora to react quickly. It has a lot of inter-individual variability in daily life and the ability to double in an hour (Thaiss, C.A., et al., 2016). Changes in gut flora have been connected to histone acetylation via epithelial histone deacetylase 3 (HDAC3). Regulation of nutrient intake is caused by HDAC3 which interacts with the body's circadian clock through metabolic gene expression. This relationship also modulates lipid intake, which contributes to diet-induced obesity (Kuang, Z., et al., 2019). Sleep habits of evening shift employees are interrupted, resulting in a changed and disturbed gut microbiota, which leads to an increase in food consumption. It has even been discovered that metabolic pressure is caused by an increase in an inflammatory reaction (Kaczmarek, J. L. 2017; Collado, M. C., et al. 2018).

Collado et al. published a randomised crossover research in 2018 on the effect of mealtime on gastrointestinal microbiota (Johnson, A. J., et al. 2019). According to the findings of this study, eating late alters the salivary microbial composition (at 17:30 in place of 14:30). Metabolism, body mass, glucose tolerance, temperature, and corticosteroid rhythm have all been shown to be affected by increased salivary species. (Johnson, A. J., et al. 2019), A cyclical seasonal change occurs in an individual s nutrition throughout the year, based on seasonal accessibility and diet preferences. Collectively, eating patterns, rather than day-to-day changes, greatly impacts changing gut microbial habitat and, ultimately, microbial composition (Williams, N. T., & Probiotics. 2010).

Prebiotics, including wheat fibre, polydextrose, and insulin has been found to improve gastrointestinal variety, motility, and immunity in the elderly. Prebiotics regulate a variety of pro-inflammatory and anti-inflammatory cytokines, such as whole-grain carbohydrates, which have been shown to lower IL-6 levels (Collado, M. C., et al., 2018), and butylated higher amylose content maize starch, which seems to enhance IL-10 (anti-inflammatory cytokine) levels (Johnson, A. J., et al., 2019). This suggests that prebiotics may have an immunological function in coronavirus infection. Prebiotics are thought to aid in the modulation of gut lymphoid and secondary lymphoid tissues by enhancing the synthesis of short-chain fatty acids (Agans, R., et al., 2011). The reasons for probiotics' antiviral properties are unknown at this time. Viral marketing is one of the ways that can be used.

Conflicting Evidence on Probiotics

Variations in metabolism and physiology exist across probiotic strains of different species, and as a result, their influence on the body varies. Even various strains of a single specie might have varying health consequences (Chen, N., et al., 2020). It's also vital to consider the dosage since a probiotic taken at an increased concentration might not be beneficial compared to the one taken at decreased concentration. Similarly, dissimilar dosages of the same probiotic strain show different results. Furthermore, different hosts may react

differently to the same probiotic strain. As a result, in order to establish efficacy, probiotic activities must be demonstrated at the strain level. As a result, probiotics should be carefully chosen in order to achieve the best results.

Probiotics have also been linked to various side effects. Using RNA sequencing (scRNA-Seq) , Feng Z et al. (Chan, J. F.-W., et al., 2020) showed that the SARS-Cov-2 receptor, ACE2, could be raised in the residence of invasive bacteria such as Salmonella and its counterpart, compartmentalised Filamentous Bacteria acting as probiotics in the small intestine of mice (Sundararaman, A., et al., 2020) and human enterocytes. In some other investigations, both Bacillus and Lactobacillus failed to reduce coronavirus receptor expression in the mouse gut following Salmonella infection (Lee, I.-C., 2020). Probiotic effectiveness and safety have become a source of debate. Even though the side effects of probiotics seem to be minor (mostly digestive flatulence or discomfort), serious outcomes have been observed in those with underlying health conditions. After probiotic therapy, there have been cases of fungemia (Holshue, M.L., et al., 2020) and bacteremia. Probiotic treatment in the absence of VDR expression results in severe illness in a Salmonella-colitis mouse model (Gu, S., et al., 2020). The fact that probiotic action is dependent on VDR expression could explain why certain IBD patients have different treatment outcomes. The utility of probiotics in treating COVID-19 is supported by secondary facts and shreds of evidence (Yeoh, Y.K., et al., 2021). Further research in this regard can help fully understand the fundamental mechanism of probiotics' antiviral activity against various coronaviruses like SARS-CoV-1, SARS-CoV-2, and MERS-CoV. Probiotic supplementation should be studied to see if it has any detrimental side effects.

Conclusion

Probiotics' significance in immune system control has been demonstrated in studies, revealing a specific function for probiotics in viral illnesses. Probiotics can work to circumvent cytokine storms by boosting innate immunity and preventing the amplification of adaptive immunity, which has a pressure to quickly respond to viral infections. Because probiotics reduce the inflammatory cytokine response, they may reduce the intensity and recurrence of ARDS, making them an intriguing adjuvant. The impact of the epidemic on individuals and the economy around the world will be reduced if viable therapies are developed. As a result, probiotic supplementation can decrease infection and straighten the COVID-19 curve in both high-risk and critically ill patients, as well as frontline healthcare workers. Several medication studies are being undertaken around the world to see how effective probiotics are in the treatment of various diseases.

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