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Probiotics as a Potential Immuno Modulator to Combat Coronavirus Disease (covid-19) Infection

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Abstract

The outburst of severe acute respiratory syndrome (SARS-COV-2) in December 2019 stumbled the mankind; the death of millions of people across the world stipulated the urge to combat COVID-19. Based on clinical data; COVID-19 along with causing upper respiratory infection managed to create gut dysbiosis and reduce immunity through gut-lung axis. Certain medication and vaccine are the current remedy; however, these are not full proof treatment to avoid COVID complications. Therefore, in this paper we highlighted the necessity to stabilize gut microbiota in order to strengthen immunity. Based on retrospective and pilot studies probiotic is proven effective as an antiviral agent or against diseases such as HIV, Influenza, Antibiotic Associated Diarrhoea and many more. In addition to this, two clinical studies and one patent filed so far provided the supportive evidence for probiotic as an alternative to combat COVID-19. Furthermore, after exploring, studying, and comparing existing statistical data we notified that the, consumption of probiotic amid COVID lessen the gut dysbiosis and re-establish beneficial gut microbiota. It also reduces the cytokine storm generated due COVID-19. Thus, it was found that probiotic enhance the immunity by increasing the count of immune cells and act as an immunomodulator and have profound effect against COVID-19. Albeit, there are supplement research data available in this field but there is still a gap in available research data and clinical studies. Henceforth, supportive clinical studies needed to be conducted to counter the limitations.

Keywords: Probiotics; Immune Modulation; Gut Microbiome; COVID-19; Immunity

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Introduction

In December 2019, the novel coronavirus outbreak occurred in Wuhan, China that took the lives of ≥ 4.3 million as of 17th August 2021. The virus is highly contagious and has spread across the world, where it caused loss of life worldwide, until WHO announced it as a pandemic [1]. International Committee on Taxonomy and Viruses scientifically classified the virus as a severe acute respiratory syndrome, SARS-CoV-2, and named as coronavirus due to its crown-like appearance [2]. This virus belongs to the order Nidovirales, Coronaviridae family, and from the beta subgroup [2]. The RT-PCR method is the gold standard as recommended by World Health Organization (W.H.O) used for its detection in infected patients along with Rapid Antigen Test [3]. Apart from the catastrophic effects on human health; psychological and social effects [3]. It has also brought economic uncertainty and the global economic growth annualized rate of -3.4% to -7.6% in 2020 and project to grow at 8% in 2021 by The World Bank.

Structure and Genome Analysis of Corona Virus

All these structural and genomic components of the coronavirus are responsible for virus infectivity and its transmission from an infected individual to a healthy individual through direct or indirect contact with infected people, droplets, and contaminated surfaces [4]. The virus shows 2-14 days of incubation period after binding to host receptor Angiotensin-converting enzyme 2 (ACE-2), which is present on the surface of endothelial cells, lungs cell and are also expressed by the intestine [4]. The genome analysis of the SARS-CoV -2 depicted that the virus is a single-stranded

positive-sense enveloped RNA virus. Its size ranges from 26-32 kb in length and undergoes post-modification [4]. Its structural composition indicates the presence of four major proteins ie, Spike protein(S), Membrane protein (M), an Envelope protein (E), and Nucleocapsid protein (N) [5]. Its genome comprises a set of the gene in order 5'¬replicase-S-E-M-N-¬3' with one to as many open reading frames which are named as accessory genes [5]. This virus can infect people of various ages, studies indicated that symptoms like fever, dry cough, shortness of breath, myalgia, and fatigue were the initial clinical manifestation of this virus whereas headache, rhinorrhoea, sneezing, sore throat, loss of odour, and pneumonia were also observed in patients thus, it displays sign of asymptomatic to severe illness [6]. Because of organ tropism ability, the virus affects host organs, starting from the nasopharyngeal cavity, lungs, kidney, eye, liver to the intestine where it creates an imbalance in the gut microbiota of the host and thus weakens the host immune defence [6, 7].

The Correlation between Gut Microbiome, Lung and COVID-19

The gut microbiota of humans is believed to confer many health benefits to the host by supplying nutrients, helping in digestion, vitamins production, reducing or destroying mutagens, toxins, metabolising various substances, and also communicating with intestinal cells, competing with pathogens, and providing immunity [8]. As per studies this beneficial microbiota also inhabits the upper and lower respiratory tracts of the lungs [2]. Crosstalk between gut and lungs microbiota called as 'Gut-Lung Axis' exist to generate immune responses [2]. The gut-lung axis shows bidirectional cross-talk for the transport of microbial metabolites, cytokines, hormones, and endotoxins via the bloodstream [9]. Extensive studies are going on to understand the underlying mechanism of bidirectional cross-talk of the gut-lung axis [9]. Some proposed mechanisms indicated that Toll-like receptors, regulatory T cells, mediators and inflammation cytokines, surfactant D, and various other factors might be involved [2, 9,10]. Likewise, studies conducted on humans and mice indicate that the gut-lung axis is synchronized through gut-associated lymphoid tissue (GALT) and inducible bronchus-associated lymphoid tissue (iBALT) [2]. This association imparts local immune responses by producing and secreting IgA at mucosal surfaces thereby indicate their involvement in the cell and cytotoxic retaliation [2].

Based on the data researchers conducted some studies to provide evidence that the coronavirus might create an immune imbalance in GIT [11]. They found that the patients from the US and China with COVID-19 show the presence of coronavirus in the stool sample [11]. This reveals that there is a higher probability that the coronavirus might also be transmitted through the fecal-oral route [12]. Hence infection with the coronavirus may create an imbalance in the GI tract microbiota along with the lung and exaggerate its pathogenicity [12]. Thus, as per the studies, there is a need to maintain host immune balance and defence to combat COVID disease [12]. Therefore, researchers draw their interest towards probiotics, that may be used as an alternative in the treatment and minimising the effect of COVID-19 [12].

Role of Probiotic in Immune Modulation against Inflammatory Agents

Probiotics are defined as the live, beneficial microorganisms such as Lactobacillus spp, bifidobacterium spp., Streptococcus spp. etc. which when used in appropriate quantity imparts health benefits to the host [13]. Probiotics are enormously explored in the treatment of diseases like type 2 diabetes, obesity, diarrhea, and respiratory infections [14, 15]. The research study indicated that probiotic is involved in maintaining the bacterial eco-system by enhancing the bioavailability of nutrients and it also modulates immune cells [12]. The probiotic L. reuteri and L. casei trigger the production of IFN-gamma and active proinflammatory Th-1 cells. The gut microbiota helps to drive dendritic cells to prime T-cells towards anti-inflammatory or pro-inflammatory phenotypes also the Lactobacillus strain probiotic led to the activation of NK cells which secrete IFN-gamma cytokine through the DC secreted IL-12 which reduces the infection caused by Staphylococcus aureus [12]. Other probiotics such as L. gasseri, L. delbrueckii ssp. bulgaricus, B. bifidum, L. acidophilus strain interact with the monocytes and trigger the secretion of IFN-alpha, whereas probiotic L. paracasei DG increases TNF-alpha, IL-6, IL-8 to eliminate viruses [16]. Probiotics can also interact with toll-like receptors present on epithelial cells and induce the production of different cytokines necessary for immune response [16]. It was observed that patients infected with coronavirus show imbalance in the gut microbiota and COVID disease produce certain cytokine storm that acts as inflammatory agents and affects different organs like lungs, eyes, GIT, kidney, etc [12]. Several studies provide theoretical data which states that probiotics interact and regulate with endothelial and mucosal immune cells by interacting with DC, B-cells, T-cells, NK cells, signaling pathways, and gene regulation [12]. Certain probiotics form biofilms that regulate the production of biological substances which show anti-inflammatory properties [17].

Probiotics an alternative for Viral Infections

Probiotic shows positive results as an antiviral agent. It was found that Lactobacillus spp. shows antiviral activity against human immunodeficiency virus 1(HIV-1) [18]. This activity is achieved by producing hydrogen peroxide and lactic acid that denatures the protein and inactivates HIV-1 likewise, Lactobacillus brevis is effective against HIV-2. Another probiotic E. faecium NCIMB 10415 inhibits the Influenza virus [18]. Thus, probiotics exhibit antiviral activity through direct interaction with the virus, triggering the host immune system or by producing antiviral substances [18]. For example, in a randomized study of Malaysian preschool children, probiotic Bifidobacterium longum BB536 has shown a decrease in upper respiratory diseases by modulating intestinal microflora [10]. A study conducted on 1783 school children shows that Lactobacillus brevis probiotic reduces the incidence rate of influenza virus. Where as in a randomized clinical trial of 55 infants, a combination of Bifidobacterium bifidum and streptococcus thermophilus was administered and the result indicated the reduction in the incidence of diarrhea and shedding of rotavirus [10]. An extensive clinical study on the efficacy of probiotics such as Lactobacillus reuteri, Lactobacillus rhamonas, Bifidobacterium infantis in the treatment of various respiratory

infections like cystic fibrosis, lung cancer [10]. The mice model suggested that these preclinical studies could be useful for the implication of probiotics in human treatment [19]. These studies will act as a boon in future disease treatment. Certain aspects such as pathogenicity, immune system modulation, viability, and stability in the GIT should be considered while designing or choosing a probiotic [19]. Studies indicated that microbes belonging to the genera Bifidobacterium, Lactobacillus, and Saccharomyces are most commonly used for the probiotics which include B. animalis subsp. Animalis, B. animalis subsp. Lactis, L. acidophilus, L. casei and S. boulardii [20]. Intake of antibiotics such as cephalosporins, aminopenicillins is one of the major reasons for diarrhoea. It is termed antibiotic-associated diarrhoea (AAD) [20]. As probiotic helps to maintain the gut microbiota, it was supposed that probiotic may help to rejuvenate the normal gut microflora and counter the effect of AAD patients [21]. A randomized control trial was conducted on 36 patients including 25 females and 11 males with antibiotic-associated diarrhoea due to amoxicillin-clavulanic acid treatment [21]. This study indicated that treatment with the probiotic combination of Lactobacillus and Bifidobacterium strains shows the decrease of AAD and reduced daily bowel [21].

Probiotics an alternative for COVID-19

A retrospective study and analysis were conducted at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China for understanding the role of probiotics may play a supportive role in the treatment of COVID-19 [22]. This study design includes 311 severely affected COVID patients, and they were given different medications which are divided into antiviral drugs, antimicrobial drugs, traditional Chinese medicine, immunopotentiators, and probiotics [22]. The patients were distributed based on probiotic group or non-probiotic group. Another medication was given to the non-probiotic group whereas to the probiotic group people combination of oral combined Bifidobacterium, Lactobacillus, Enterococcus and Bacillus tablets; Live combined Bifidobacterium and Lactobacillus tablets; Live combined Bacillus Subtilis and Enterococcus Faecium Enteric-coated Capsules was given and the results was analysed by observing whether probiotics reduce the inflammation and modulate the immune response in this patient or not [14]. As per the result and data analysis, it was observed that in presence of probiotics the count of immune cells i.e., NK cells, neutrophils B-cells, CD4 and CD8 T lymphocytes increased and, it was also observed that probiotic is effective in reducing the CRP inflammatory factor in COVID patients [14].

Similarly, a randomized clinical trial was conducted in China, Wuhan on healthy 200 frontline medical staff who remain in close contact with COVID patients. For this study oropharyngeal probiotic that is supposed to reduce upper respiratory tract infection was used [23]. It was successfully noted that the probiotic strain Streptococcus thermophiles ENT-K12 modulate the nasopharyngeal microbiota, it also colonizes the oral cavity It was believed that this probiotic maintains the balance of upper respiratory tract microbiota [23]. As per the findings this probiotic shows reduction of respiratory infection by 64.8% and symptoms of oral ulcers, time of respiratory infections by 78%. Another probiotic preparation Bactoblis shows protection and decrease in incidence rate from respiratory tract infection in medical staff who were taking probiotics orally. Infection with COVID-19 shown alteration in the fecal microbiome during hospitalization [23].

In Hong Kong, a pilot study on 15 patients infected with COVID-19 was conducted, they performed shotgun metagenomic sequencing on the fecal sample of these patients [24]. As a result, they found that the count of the beneficial microbiome is reduced and opportunistic pathogen increased. The baseline abundance of Coprobacillus, C. ramosum, and C. hathewayi correlated with COVID-19 severity [24]. Also, an inverse correlation between the abundance of F. prausnitzii and disease severity. Throughout hospitalization members of Bacteroides (B. dorei, B. thetaiotaomicron, B. massiliensis, and B. ovatus) downregulate the expression of angiotensin-converting enzyme 2 (ACE2) in the murine gut which inversely correlated with SARS-CoV-2 load in fecal samples [24].

A patent has been filled for using probiotics as a vaccine against COVID-19 using a live strain of modified probiotic Enterococcus faceium L3 [25]. A replacement of pspf region in the plasmid was done by a fragment of the SARS-CoV- 2 spike protein gene. The result indicated that this modification adds up the induction of specific antibodies, IgA and IgG against the viral infection along with induction of humoral and cellular immunity. In an invention, it was found that cows infected with SARS-CoV-2, have generated natural passive immunity against it [25]. The colostrum of the gestating immunized cows shows circulating anti -SARS-CoV-2 IgG antibodies. This natural probiotic containing IgG antibodies shows that COVID viral load is reduced and this can be used to prevent or cure the COVID infection [25].

Scope of Probiotic

The current outbreak of COVID-19 has spread over 220 countries and territories according to worldometers. Epidemiologists around the globe are constructing short- and long-term projections to find the spread; know the impact of COVID-19 and avoid loss of precious human life. Forecasting the long-term trend epidemic can help health authorities determine the transmission of the virus and take suitable prevention and control policies beforehand. Although their forecasts and timelines differ, COVID-19 is here to stay and a lot of factors are unknown, including whether people develop lasting immunity to the virus after the infection or vaccines, whether seasonality affects its spread rate; most importantly the choices made by individuals and governments.

Within few months of COVID-19 spread worldwide, pharmaceutical firms have produced a million doses of the COVID-19 vaccine. Generally, vaccines are near effective at protecting against hospitalizations & deaths due to COVID-19. Thus, vacations for the globe would take considerable time to reach low-income countries based on the current scenario where most of the vaccines are taken up by the high-income counties. This situation has resulted in temporarily waive intellectual property rights so that manufacturers in poorer countries can make the vaccines more quickly themselves.

Hydroxychloroquine, Dexamethasone, and other corticosteroids (prednisone, methylprednisolone), Tocilizumab (monoclonal antibody), Remdesivir, Baricitinib (in combination), Anticoagulation drugs, and Convalescent plasma are current few of the treatment regimens followed worldwide. These however are not effective at times but can reduce the severity of diseases. Also, a specific antiviral drug for COVID-19 is missing but if a new drug has to be made then it must be able to target the specific part of a virus's life cycle that is necessary for it to reproduce. In addition, an antiviral drug must be able to kill a virus without killing the human cell it occupies. And viruses are highly adaptive. Because they reproduce so rapidly, they have plenty of opportunities to mutate (change their genetic information) with each new generation, potentially developing resistance to whatever drugs or vaccines we develop.

As discussed above, probiotics modulate the innate and adaptive immune responses, facilitating the immune system's development and maturation. If we have a look at the market potential on probiotics indicated that after five years from now the demand for different probiotics will tremendously increase. The overall market of probiotics is to be assessed at USD 61.1 Billion in 2021 and is predicted to reach USD 91.1 Billion near 2026, at a CAGR of 8.3% in the upcoming period.

Conclusion

Thus, these studies indicated the vital role of probiotics in the treatment of bacterial as well as viral diseases. Some clinical studies provided the evidence that probiotic is fruitful in reducing the risk of COVID-19. Albeit, further clinical studies are needed to provide strong evidence on probiotic role against COVID-19, to give detailed insight on probiotics and their mechanism in the treatment of COVID-19. Hence, these studies will be beneficial for future references and will act as a bridging pathway in fulfilling the existing lacuna in this field. But we should also be considerate towards using probiotics against severely ill or immunocompromised patients.

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