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Probiotics - A supportive therapy and adjuvant for SARS Covid-19

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Abstract

Background: SARS-CoV-2 infection is linked to a variety of clinical symptoms, immunological dysfunction, and changes in the gut microbiota. Probiotics are live microbes that, when administered in adequate amounts, confer health benefits on their hosts. The intestinal microbiota, which may play a role in the defensive mechanisms against possible pathogens by fostering a wide variety of immune-host interactions, is influenced by the nutritional and biochemical quality of one's food. This study, aims to find out the therapeutic value of administering probiotics to COVID-19 patients with regards to reduction of symptoms.

Methods: An observation study was conducted among Covid-19 RT-PCR positive patients after getting informed consent. Total of 428 patients with or without symptomatic patients were included in this study. Probiotic dose of 120 millions CFU/day was given to the covid-19 patients for minimum of 10days and maximum of 20 days, irrespective of the severity of the disease. A semi-structured questionnaire was administered to obtain patients clinical history, comorbid conditions and sociodemographic details. Patients clinical conditions were compared after availing the treatment of probiotics.

Results: In this cohort, 428 cases were enrolled after getting informed consent from the patients. After consuming 10 days of probiotics, almost 99.9 % recovered from the symptoms and 75% of them did not required O2 supply or ventilator and hospital admission. Only few have (2%) post covid symptoms like joint pain and giddiness.

Conclusion: Probiotics significantly reduced the clinical symptoms of critically ill COVID-19 patients. Probiotics may have a good supporting role in the treatment of patients with COVID-19 and its early application is recommended to prevent complications.

Background

The new coronavirus pandemic of 2019 (COVID-19), an emerging infectious disease (EID) caused by several strains of SARS Coronavirus-2 (SARS-CoV-2) has spread to 216 nations and territories, wreaking havoc on world health and the economy [1]. The majority of COVID-19 infections are mild to moderate, resulting in self-limiting respiratory disease. Geriatrics, as well as people with hypertension, diabetes, heart disease, lung illness, or cancer, are particularly prone to COVID-19. During the ongoing pandemic spread of SARS-CoV-2, saving lives and flattening the curve are the top goals. Certain people's immune systems appear to be better at fighting COVID-19 than others [2]. Nutritional sufficiency enhances overall health and immunity, which helps to avoid and treat infections. However, COVID-19 necessitates a multifaceted therapeutic approach, spanning from early virus-targeted therapies to late immunomodulation. The lungs can be protected by suppressing the overactive immune response, but limiting the infection requires a working immune system. As a result, fine-tuning the host-microbiota balance in COVID-19 could be beneficial, especially with co-morbidities. We propose that a pleiotropic mechanism could be a preventive/curative alternative for COVID-19, based on the immunomodulatory, anti-inflammatory, antioxidant, and antiviral effects of probiotics [3,4]. The novel Coronavirus Infection (COVID-19), as well as COVID-19-related diarrhoea and liver damage, are difficult to cure. The best way to treat COVID-19 is still a work in progress. Alterations in the composition of the gut microbiota are thought to be linked to changes in the control of the immune response in the lungs in COVID-19 patients. These alterations in the gut microbiota, combined with the use of antibiotics during treatment, increase the risk of antibiotic-associated diarrhoea and C. difficile infection, as well as poor clinical outcomes in these individuals. Probiotics are live microbes that, when administered in adequate amounts, confer health benefits on their hosts. Probiotics aid in the restoration of the human gut microbiome as well as the enhancement of anti-inflammatory responses. Despite the numerous applications of probiotics, there is still a lack of evidence on the therapeutic usefulness of using probiotics in the treatment of COVID-19 patients. Probiotic pleiotropism involves the strengthening of biological barriers in the digestive tract and the modulation of the intestinal flora balance. Probiotics have antimicrobial properties, restore intestinal epithelial cell function, inhibit pathogen adhesion and growth via a space-occupying effect, enhance competitive antagonism, secrete antimicrobial substances such as bacteriocins, increase digestive enzyme activity, and synthesize organic acids, among other things. Probiotics improve epithelial integrity and mechanical barrier function, inhibiting the displacement of intestinal bacteria and endotoxins, by increasing the expression and release of mucous glycoproteins through increased tight junction protein synthesis between epithelial cells. Probiotics help the immune system develop and mature by modulating innate and adaptive immunological responses. Certain probiotics also have anti-viral effects, including against coronavirus [5]. Indirect evidence for a link between probiotics and COVID-19 has been cited in a few studies, most of which are based on past coronavirus and other viral illnesses. Differences in physiology and metabolism exist across probiotic strains of diverse species, and as a result, their effects on the human body differ. Even within the same species, different strains can have diverse health impacts [6]. The goal of this study was to provide new information and viewpoints on the use of probiotics to the prevention and treatment of microbiota in COVID-19 patients.

Methods

This study was conducted in a private clinic of Chengalpet District of Tamil nadu. After getting informed consent, patients were enrolled to this study. The study included patients with COVID-19 attended to the private clinic, in whom the disease

was confirmed using RTPCR on nasopharyngeal and oropharyngeal swabs to detect severe acute respiratory syndrome-related coronavirus 2 (SARS-COV-2). The cases were enrolled from June 2020 to July 2021 with the age range from 12 to 85 years. The exclusion criteria were refusal to participate and sign informed consent, pregnancy or breastfeeding, any chronic illness like cancer or mental illness, and severe renal or hepatic dysfunction at the time of enrollment. Patients who prematurely discontinued the consumption of probiotics for reasons not related to the development of side effects were excluded from the study. All the covid positive patients were treated with probiotics lactobacillus acidophilus with the dose of 120 million CFU /day for two times for minimum of 10 days and maximum of 20 days. Data collection was done using a semi-structured questionnaire. Questionnaire included basic demographic details, clinical symptoms, covid testing and vaccination status, and post covid symptoms. During this treatment, death from any cause was considered as the primary outcome. duration of hospitalisation, total duration of the disease, incidence of admission to intensive care unit, need for oxygen support or mechanical ventilation, were considered the main secondary outcomes.

Statistical analysis

All the collected data were entered in MS-excel. The SPSS 25 software was used for all statistical analyses. The t-test was applied for normally distributed quantitative data and the χ^2 test was applied to qualitative data, the significance level was set to $\alpha=0.05$.

Results

Patient’s characteristics

A total of 428 Covid-19 RT-PCR positive cases were enrolled in this research. Of which majority of them male (74%) and 97% living in rural area, 89% were married and only 0.7% were children

Table 1: Demographic characteristics

Variables	Frequency	Percent
	(n=428)	
Gender		
Male	318	74.3
Female	110	25.7
Area of living		
Rural	415	97
Urban	13	3
Marital status		
Children	2	0.5
Married	379	88.6
Unmarried	47	11
Occupational status		
Not working	99	23.1
Working	329	76.9

Around 97% were from rural area and 89% were married; only 0.7% was Children, Around 77% were employed in different nature. (Table-1) Among the total patients, the mean age of the participants were 43 years, (mode-45, SD-14.9) age group range from 12-85yrs and majority fall in the range of 25 to 55 years. (Table-2)

Table 2: Age Distribution

Age group	Frequency	Percent
Below18	11	2.6
19-25	44	10.3
25-35	92	21.5
36-45	92	21.5
46-55	97	22.7
56-65	65	15.2

66-75	19	4.4
above 75	8	1.9
total	428	100

Table 3: Clinical signs and symptoms (headache, fever, nausea, body pain, throat pain, Breathing difficult, wheezing)

Symptoms	Frequency	Percent
Asymptomatic	2	0.5
Symptomatic(headache,fever ,nausea,Body pain,throat pain, Breathing difficult, wheezing)	426	99.5
Total	428	100

Around 99% had symptoms related to Covid-19 and only 0.5% was asymptomatic. (Table-3) Majority of the symptomatic patients attended the hospital with the history of fever and body pain.

Table 4: Age wise probiotics consumption

Age group in years	Did you take probiotic?		Total	p-value
	Yes	No		
<18	9	2	11	0.147
19-25	42	2	44	
25-35	90	2	92	
36-45	86	6	92	
46-55	95	2	97	
56-65	61	4	65	
66-75	19	0	19	
> 75	7	1	8	
total	409	19	428	

The above table shows the consumption of probiotics by age group, but there was no significant association.

Table 5: Gender vs symptoms

Symptoms (headache,fever ,nausea,Body pain,throat pain, Breathing difficult, wheezing)		Gender		Total	p-value
		Female	Male		
	asymptomatic	1	1	2	0.448
	symptomatic	109	317	426	
Total		110	318	428	

While comparing symptoms with gender, there is no association (p-value 0.448)

In this study, those who consume probiotics (409 cases), 75% does not require O2 requirement and none of them admitted to ventilator. 424 patients (99.06%) relieved from major symptoms within ten days. Majority (83%) of the patients recovered from clinical symptoms within 10 days.

Table 6: Probiotics usage and reduction in symptoms

Have your disease condition / symptoms reduced after taking probiotic (lactobacillus acidophilus) tablets?		symptoms (headache,fever ,nausea,Body pain,throat pain, Breathing difficult, wheezing)		Total
		asymptomatic	symptomatic	
	No	0	4	4
	Yes	2	422	424
Total		2	426	428

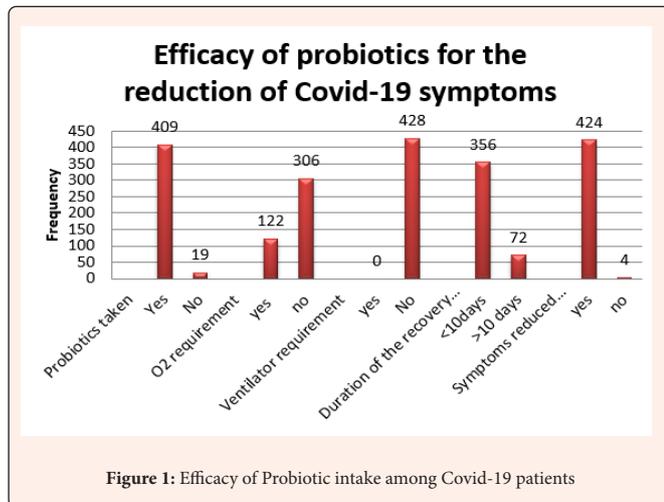


Figure 1: Efficacy of Probiotic intake among Covid-19 patients

Table 7: Comorbid conditions of covid-19 patients

co-morbid conditions	Frequency	Percent
Diabetes	120	28
Hypertension	53	12.4
Cardiac problem	36	8.4

Among the total patients, 28% were diabetes, 12.4% were Hypertension and 36% had cardiac problem

Table 8: Bacterial infection among covid-19 patients

		Bacterial infection		Total	p-value
		no	yes		
Did you take probiotic (lactobacillus acidophilus) added in your treatment?	no	19	0	19	0.872
	yes	406	3	409	
Total		425	3	428	

Only few (0.7%) of them had bacterial infection while taking probiotics.

Table 9: Comparison of probiotics consumption and improvement in health condition

		Are you feeling better while taking probiotic (lactobacillus acidophilus) tablets?		Total	p-value
		no	yes		
Did you take probiotic (lactobacillus acidophilus) added in your treatment?	no	1	18	19	0.044
	yes	0	409	409	
Total		1	427	428	

The above table shows that the consumption of probiotics significantly improves the health conditions of covid-19 patients. (P-value0.044)

Table 10: comparison of probiotic consumption and covid-19 recovery

		Duration of your recovery period?		Total	p-value
		10-15days	less than 10 days		
Did you take probiotic (lactobacillus acidophilus) added in your treatment?	no	6	13	19	0.005
	yes	66	343	409	
Total		72	356	428	

The above table-7 shows that the there was a significant association observed while comparing probiotics consumption and recovery period. (P-value 0.005).

Table 11: Covid-19 vaccination status

Covid vaccination	Frequency	Percent
Yes	423	99.5
No	2	.5

Among the total patients enrolled, majority of them taken atleast one dose of covid vaccination. Covid-19 vaccination may also helps to improve the health condition of the patients along with probiotics. Both vaccine and probiotics may have synergetic effect to prevent the covid-10 infection. Due to the fact, that covid vaccines are not 100 percent effective at preventing infection, some persons who have been fully vaccinated may nevertheless contract COVID-19. People who get vaccine breakthrough infections can be contagious.

Discussion

Probiotics have emerged as a biologically viable treatment or prevention option for a variety of viral, inflammatory, and autoimmune diseases. There is scarcity of evidence about the relationship between COVID-19 and gut microbiota. The role of probiotics in mitigation of the novel COVID-19 has not been established. So, whether or not these supplements can prevent or ameliorate COVID-19-associated symptoms is not fully understood. Improved gut barrier function, competitive suppression of harmful microorganisms, and modulation of the host inflammatory response are some of the proposed mechanisms of benefit for a wide range of disorders. It is generally known that probiotics, particularly lactic acid bacteria strains, can alter the human gut microbiota by inhibiting the growth of opportunistic bacteria [7]. Patients in this study came to our clinic after the commencement of symptoms, and probiotics were administered to them as soon as they arrived, regardless of the severity of their symptoms. As a result, the introduction of probiotic strains, as well as the stimulation of their growth and activity in the gut, can be considered as a viable strategy for controlling food-borne enteric infections. Furthermore, probiotics have been proven to improve immunity, lessen the severity of certain allergy disorders, and bestow some anticarcinogenic qualities in addition to their gut health effects. Among critically ill patients, randomized trials suggest that probiotics reduce infection rates by 20% [8] and may decrease the risk of Ventilator-Associated Pneumonia (VAP) by 25% to 30%. [9] It is generally known that probiotics, particularly lactic acid bacteria strains, can alter the human gut microbiota by inhibiting the growth of opportunistic bacteria. Consequently, the Patients with COVID-19 had microbial dysbiosis, with lower Lactobacillus and Bifidobacterium levels, according to a recent small study from China [10]. The same study suggested utilising prebiotics or probiotics as an additional therapy to balance the microbiota in the intestine and lower the risk of subsequent infection in those patients. Animal studies, on the other hand, showed that Lactobacillus acidophilus and Bacillus clausii did not diminish coronavirus receptor expression in the murine small intestine when compared to control and post-Salmonella infection models [11]. In this study, probiotics are very effective irrespective of comorbid conditions and covid positivity. Since this is a first study, there is no study available to correlate our findings among covid patients. The treatment of probiotics to COVID-19 patients shortened the duration of clinical symptoms and eliminated the requirement for a ventilator or oxygen assistance in this trial cohort. Additionally, probiotic therapy shortened a patient's hospital stay.

Probiotics' significance in immune system regulation is supported by evidence, implying that they play a crucial role in viral infections. COVID-19 morbidity and mortality could be reduced by taking probiotics. Probiotics' significance in immune system regulation is supported by evidence, implying that they play a crucial role in viral infections. COVID-19 morbidity and mortality could be reduced by taking probiotics. Developing viable treatments will have a huge impact on the pandemic's impact on people's lives and economies all across the world. As a result, probiotic supplementation in high-risk and critically ill patients, as well as frontline health workers, may help to reduce infection and flatten the COVID-19 curve. Studies have proved that probiotics have been found to be safe [12] and clinically efficacious [13] in lowering the severity and duration of upper respiratory tract infections in adults and children. These findings were supported by a review [14], which demonstrated the ability of different strains of lactic acid-producing bacteria to ameliorate or prevent various viral infections, such as decreasing Ebola and cytomegalovirus titres, as well as decreasing the severity and duration of upper respiratory tract infection or gastroenteritis. Based on



the findings of previous studies on anti-viral effect, modifying the gut microbiota with a decent selection of prebiotics and probiotics could provide a unique and cost-effective way for reducing the risk of viral infections. Because no published studies have yet assessed the use of probiotics as an add-on medication for COVID-19 management, their role is unknown. According to a recent IASPP science blog, several researchers across the world are exploring the association between the microbiome and COVID-19 susceptibility, as well as evaluating the capacity of diverse probiotic strains to lower viral load via multiple modes of action. [15] Two randomised controlled trials found that critically sick patients on mechanical ventilation who were given probiotics (*Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*) had considerably less ventilator-associated pneumonia than patients who were given a placebo [16-17]. As a result, it is possible that COVID-19-related pneumonia could be treated in the same way. However, there are currently no RCTs that can provide conclusive data. We are planning to do the Randomized Clinical Trial in future. Although it is too early to say, probiotics could potentially be one of the rational supplementary alternatives for the treatment and prophylaxis of viral infections, including COVID-19 infection, based on their antiviral and anti-inflammatory activities. To summarise, conventional probiotics for COVID-19 cannot be widely advised until additional information regarding the novel coronavirus pathogenesis and its impact on the gut microbiome becomes available. Although gut dysbiosis has been linked to the development of some respiratory diseases, more targeted and new methods are needed. As per Center for Disease Control, overall, there will be more vaccination breakthrough infections if there are more COVID-19 infections. Vaccinated persons, on the other hand, have a considerably reduced risk of illness, hospitalisation, and mortality than unvaccinated people but contradictory in this study most of the vaccinated get infected, this may be due variation in Covid strain. Many people are properly vaccinated however, they get COVID-19.

Conclusion

Probiotics dramatically decreased the clinical symptoms of COVID-19 patients who were seriously ill. Probiotics may be useful in the treatment of COVID-19 patients, and their use should begin as soon as possible to avoid problems. To better understand the effects of probiotic supplements on Covid patients or other flu-like disorders, more high-quality Randomized Controlled Trials are required.

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