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EXPLORING THE POTENTIAL OF PROBIOTICS: A SIGNIFICANT STRATEGY IN MANAGING THE COVID-19 PANDEMIC

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ABSTRACT:

The novel Corona virus SARS-CoV-2 virus causes the Coronavirus disease (COVID-19), first emerged at the end of 2019, quickly spread over the world and impacting millions of people by causing severe illness and enormous mortality. To yet, no specific drugs have been developed to reduce the severity of the disease. Hence we must focus on alternative approaches to prevent or mitigate the impacts of disease. Probiotics have been reported to play important role in several activities in the health benefits to the host. It also involve in the production of nitric oxide (NO), which acts as a vasodilator, which is absolutely essential in hypoxemia in Covid19 patients with acute respiratory distress syndrome (ARDS). Nitric oxide also acts as antiviral agents and suppresses the replication of several DNA and RNA viruses, including Corona viruses. Psychobiotics, a group of microorganisms with the potential to play significant role in psychiatric diseases and will undoubtedly be required to address potential mental stress problems during this pandemic in the current situation. Probiotics may also help patients recover faster from coronavirus by inhibiting or reducing the "cytokine storm," which damages the immune system's defenses and may contribute to COVID-19 patient mortality. Probiotics have been demonstrated to perform a wide range of important roles, suggesting that they could be one of the most effective and practical approaches for overcoming or decreasing the consequences of Covid19 disease. However, further research is required prior to the implementation of probiotics in the Covid19 treatment.

Keywords: Covid 19, Probiotics, Psychobiotics, Vasodilatation, Nitric Oxide, Gut-Lung axis

1. INTRODUCTION

A novel Corona virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus was identified as the source of a cluster of pneumonia cases in Wuhan, China's Hubei Province, at the end of 2019. It spread rapidly and causes epidemic throughout China, subsequently to global pandemic (McIntosh 2022). The World Health Organization (WHO) in February 2020 declared the Coronavirus disease (COVID-19) as a pandemic disease (WHO 2020). The COVID-19 caused by corona virus was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Approximately 300 million COVID-19 cases have been reported globally till date. According to the most recent data, there have been 328558243 confirmed cases of COVID-19 documented worldwide, with 5548696 deaths (ECDC 2022). Several variant of the SARS-CoV-2 evolved over the time which causes various level of disease severity. According to a recent report, the newly identified variant Omicron caused less severe disease than the other previously described variants (McIntosh 2022). COVID 19 disease is a major public health problem that affects human population worldwide through severs illness and death as well. Not yet any particular drugs have been developed to prevent the disease severity. However several countries are using several vaccines as a preventative measure against the COVID 19. In India, a total of 1622607516 vaccine doses have been administered till January 24, 2022 (GOI 2022). Despite this, most of the populations are getting infection with COVID-19 after vaccination; additional viral variant with greater transmissibility may evolve (Graham et al. 2021). Due to the lack of effective treatments and vaccines, we must rely on alternative approaches to prevent or reduce the effects of disease. Using the probiotics is one of the effective and realistic approaches to overcome or diminish the effect of disease Covid 19. Probiotics is live microorganism, when ingested in appropriate amounts; provide health benefits to the host (WHO/FAO 2014). Probiotic bacteria must be safe for human consumption, be able to reach the intestines alive in large quantities, and provide specific health benefits to the host. These bacteria have to maintain intestinal flora balance by modifying the gut environment in a way that promotes the growth of friendly beneficial bacteria while inhibiting the growth of detrimental disease-causing organisms. *Lactobacillus*, *Bifidobacteria*, and the yeast *Saccharomyces boulardii* are some of the most often used probiotic bacteria. In addition to being used as drugs, Probiotics are mostly used as probiotic dairy products and fortified meals (Tiwari et al. 2012). Recently it has been proved that probiotics provide numerous benefits to the host by alleviating lactose intolerance symptoms (Alvarez-Olmos et al. 2021). They have also been shown to help in the prevention of acute diarrhea, Rotaviral diarrhea, traveler's diarrhea, antibiotic-associated diarrhea (AAD), and cancer recurrence, particularly bladder and colorectal cancers (Bengmark 2003; Blum et al. 2000 & 2002; Bottazzi 1983; D'Souza et al. 2002; DuPont & Ericsson 1993; Elliott et al. 2005). The effect of the probiotics has also been evaluated in the blood pressure regulation, cholesterol reduction, and obesity reduction in adults (Tiwari et al. 2012).

Common health benefits of the probiotics:

Apart from the aforementioned roles, probiotics plays important role in a variety of many other activities, including:

- **Inflammation:** Probiotics help in the reduction of systemic inflammation, which plays a leading role for a variety of diseases (Lescheid 2014).
- **Weight loss:** Studies have found that certain strains of the *Lactobacillus* family *L. fermentum, L. amylovorus, L. rhamnosus* can help you lose weight and belly fat (Jaclyn et al. 2013; Sanchez et al. 2014).

- **Depression and anxiety:** The probiotic bacterial strains *Bifidobacterium longum* and *Lactobacillus helveticus* have been found to reduce the anxiety and depression symptoms in persons with clinical depression (Luna and Foster 2015).
- **Blood cholesterol:** Probiotics have been shown to reduce cholesterol levels through bile salt hydrolase (an enzyme of probiotics) and cholesterol assimilation (Jiang et al., 2019; Nagpal et al., 2012)
- **Blood pressure:** Probiotic bacteria may not only have metabolic pathways to lower blood pressure, but they may also alter receptor expression to re-sensitize the body to hypotensive signals. Several bacterial species of the *Faecalibacterium, Clostridium, Eubacterium*, and *Roseburia* can produce butyrate, which has recently been described to help lower blood pressure (Cookson 2021, Louis et al. 2017&2009).
- **Immune function:** Several probiotic strains have been shown to improve the body immunity, potentially lowering the risk of infections such as the common cold (Ozen et al. 2015; King et al. 2014).
- **Skin health:** Oral probiotics have been shown to be effective for treating topical skin problems such atopic dermatitis, acne, and rosacea, as well as other skin problems (Lolou et al 2019; Knackstedt et al. 2019).
- **Anti-aging:** There is evidence that probiotics have the potential to extend lifespan through increasing the ability of cells to replicate themselves, though research is extremely limited (Sivamaruthi et al. 2018).
- **Obesity and Insulin Control:** Researchers have found that infants with a high *Bifidobacterium* number and a low *Staphylococcus* number are less likely to gain weight in later stage of life (Kalliomäki et al. 2008).

In addition, probiotics may effective in the Lactose Intolerance, Diarrhoea, Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS), Constipation, Necrotizing Enterocolitis (NEC), Colorectal Cancer, Allergic Diseases (Atopic Disease, Eczema and Rhinitis and Asthma), Urinary Tract and Vaginal Infections, Cognitive Function and Mental Health, neurological disorders, Inflammation of the Joints etc.

Sl. No.	Probiotic bacterial genera	Species involved
1	Lactobacillus	L. plantarum, L. paracasei, L. acidophilus, L. casei, L. rhamnosus, L. crispatus, L. gasseri, L. reuteri, L. bulgaricus
2	Propionibacterium	P. jensenii, P. freudenreichii
3	Peptostreptococcus	P. productus
4	Bacillus	B. coagulans, B. subtilis, B. laterosporus
5	Lactococcus	L. lactis, L. reuteri, L. rhamnosus, L. casei, L. acidophilus, L. curvatus, L. plantarum
6	Enterococcus	E. faecium
7	Pediococcus	P. acidilactici, P. pentosaceus
8	Streptococcus	S. sanguis, S. oralis, S. mitis, S. thermophilus, S. salivarius
9	Bifidobacterium	B. longum, B. catenulatum, B. breve, B. animalis, B. bifidum

10	Bacteroides	B. uniformis
11	Akkermansia	A. muciniphila
12	Saccharomyces	S. boulardii

The microorganisms commonly used as probiotics

Probiotics, which are mainly bacteria, can be used as a complementary and alternative medicine (CAM) to prevent and treat several diseases as well as to improve overall health (Alvarez-Olmos et al. 2001). However, there is scarcity of evidence about the use of probiotics. For their use, detailed scientific knowledge is required including their safety and proper application. It has also been found that the impact of one probiotic species or strain does not always apply to others (Bengmark et al. 2003).

Significance of probiotics in the COVID-19 pandemic

Apart from its application and use in a variety of common diseases, probiotics have also been shown to have a significant role in the prevention and control of the covid 19 viral infection through various mechanisms.

1.1. Probiotic microbes and the production of nitric oxide (NO) for potential application in COVID-19

COVID-19 disease is a respiratory tract infection that causes hypoxemia in patients with acute respiratory distress syndrome (ARDS), a life-threatening situation of serious ill patients which is characterized by poor oxygenation, pulmonary infiltrates, and onset acuity (Diamond et al. 2021). The supplement oxygen supply is not always sufficient for the oxygen starvation hence an advance mechanism is require reversing the hypoxemia in COVID-19 that can provide the facility for easy transport of oxygen from alveoli to blood. Based on the recent Clinical and experimental study it has been evident that Inhaled Nitric Oxide (NO) plays significant role to restore oxygenation by helping in the normalization of shunts and ventilation/perfusion mismatches. Apart from the vasodilatation, Nitric Oxide plays important role in the suppression of the replication of a respiratory corona virus that is unique to other vasodilators. Another in vitro study found that nitric oxide may play a key role in the suppression of SARS-CoV-2; virus causes COVID-19 (Kingsland 2020).

Nitric oxide (NO), a free radical that has been reported earlier to suppress the replication of several DNA and RNA viruses, including coronaviruses, is a promising therapeutic compound that is now being studied in clinical trials for COVID-19 (Lisi et al. 2021). R-107 and COViNOX are two well-known NO-based prodrugs that are being tested in clinical trials against COVID-19 (Mir et al. 2021).

However, its involvement in the immunological host response to viral infections is complicated; depending on the type and concentration of the virus, it may be important for pathogen control or harmful to the host. These findings revealed that Nitric Oxide may have an important role in effective treatment of COVID-19, however urgent research is require into the best ways to use it to restore pulmonary physiology (Mel 2020; Kingsland 2020).

The metabolic pathway for the synthesis of nitric oxide (NO) in eukaryotic cells is well-known due to its role in a various important functions, including regional blood flow regulation through vasodilation, relaxation of smooth muscle, secretory and immunological modulation (Lisi et al. 2021; Levine et al. 2012; Luiking et al. 2010; Moncada et al. 1991). It has been shown in Fig 1 that the synthesis of NO is stimulated during inflammation.

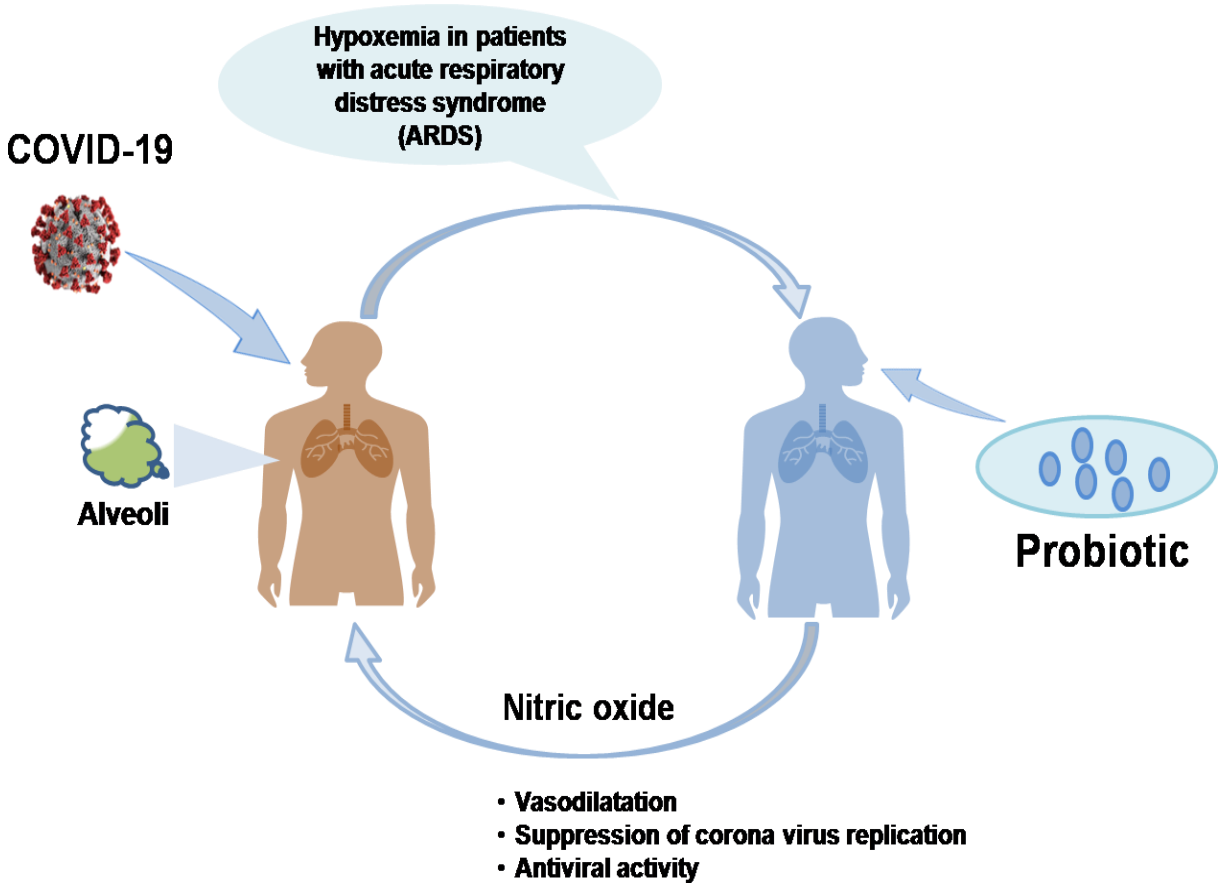


Fig 1: Synthesis of NO is stimulated during inflammation

In addition to eukaryotic cells, Gut bacteria can also produce NO, however the exact mechanism is unknown (Vermeiren et al. 2009). In the first approach, the bacterial nitric-oxide (NO) synthases (bNOSs), which resemble to eukaryotic nitric-oxide (NO) synthases (eukNOS) can synthesize microbial Nitric oxide synthesis from L-arginine.

The activities of bacterial Nitric oxide (bNO) have been reported in a group of gram-positive bacteria, and genome sequencing data revealed genes coding for proteins that are similar to eukNOS but are shorter (Gusarov et al. 2008; Johnson at al. 2008; Yarullina et al. 2006; Kuroda et al. 2001; Takami et al. 2000). *Bacillus anthracis*, *Bacillus subtilis*, *Deinococcus radiodurans*, and *Streptomyces* spp. were found to produce bacterial Nitric oxide (bNO) in vivo, which was dependent on arginine (Gusarov et al. 2008; Johnson at al. 2008; Adak et al. 2002a &2002b). In addition to L-arginine, Nitrate and nitrite can be used as an N-source for nitric oxide (NO) synthesis. *Lactobacilli* and *bifidobacteria* have also been found to produce a significant amount of nitric oxide (NO) from nitrite (Sobko et al. 2005).

Researchers have reported that the significant role for inhaled NO in the clinical management of COVID-19, however details information about the use of NO in treatment of acute respiratory distress syndrome (ARDS) of limited. Several important gastrointestinal bacteria have been reported to produce adequate amount of Nitric oxide (NO). These bacteria could be used as probiotics to combat Covid 19 viruses following the clinical trial procedure. Probiotics may act as defensive agents against COVID-19 infection by increasing nitric oxide production. The successfully use of probiotics in the fight against COVID-19 will be a revolution in the current Covid pandemic situation around the world.

1.2. Psychobiotics and their importance in mental health during the COVID-19

The gut-brain axis, a bidirectional communication between the gut microbes and the central nervous system, has recently been a significant topic for researchers (Clapp et al. 2017). This axis connects the central and an enteric nervous system of the body, the latter of which is responsible for digesting (Gunnars 2020). Certain gut microbes have been shown to influence your brain via this axis in both health and disease. These microorganisms belong to a new emerging field known as "psychobiotics" (Ochoa-Repáraz at al. 2016; Cheng et al. 2019; Sarkar et al. 2016). According to research, psychobiotics may be use to help in the treatment of several cognitive and neurological disorders such as Alzheimer's disease, autism, and Parkinson's disease etc. (Hills et al. 2019).

COVID-19 infections lead to social isolation, mortality in family, friends, and relatives, and a lack of effective drugs, all of which are stressful factors that causes feelings of loneliness, hopelessness and anger, as well as short-term post-traumatic stress disorder in people (Ahmed et al., 2020). Furthermore, epidemic spreads has overwhelmed health systems result in a lack of beds and personal protective equipment, leads to development of anxiety and emotional stress among medical professionals. Similarly, raising the death numbers, infection fears, a lack of medical equipment, unavailability of effective medicine, a long period of lockdown as well as frustration, depression, a longer quarantine period and financial loss, can all lead to psychiatric problems in the normal population (Brooks et al., 2020; Röhr et al., 2020; Roy et al., 2020). As a result, there is an immediate need to develop an effective strategy to reduce the mental stress of the community caused by the Covid19 Infection.

Thus, psychotropic drugs would almost definitely be needed to treat potential mental stress problems during this pandemic, although their use has several endocrine and metabolic side effects. They are responsible for changes in gut microbiota composition and gastrointestinal function, as well as causes hypertension, hyponatremia, hyperprolactinemia, hypothyroidism, diabetes, sexual dysfunction, hyperparathyroidism, weight gain, weight loss, metabolic syndrome, and dyslipidemia etc. (Bhuvaneswar, 2009, Cussotto et al., 2019). To overcome of the severe side effects associated with the use of psychiatric drugs, a safe, more effective and less side effect-prone therapy should be implemented. As shown in Fig 2.

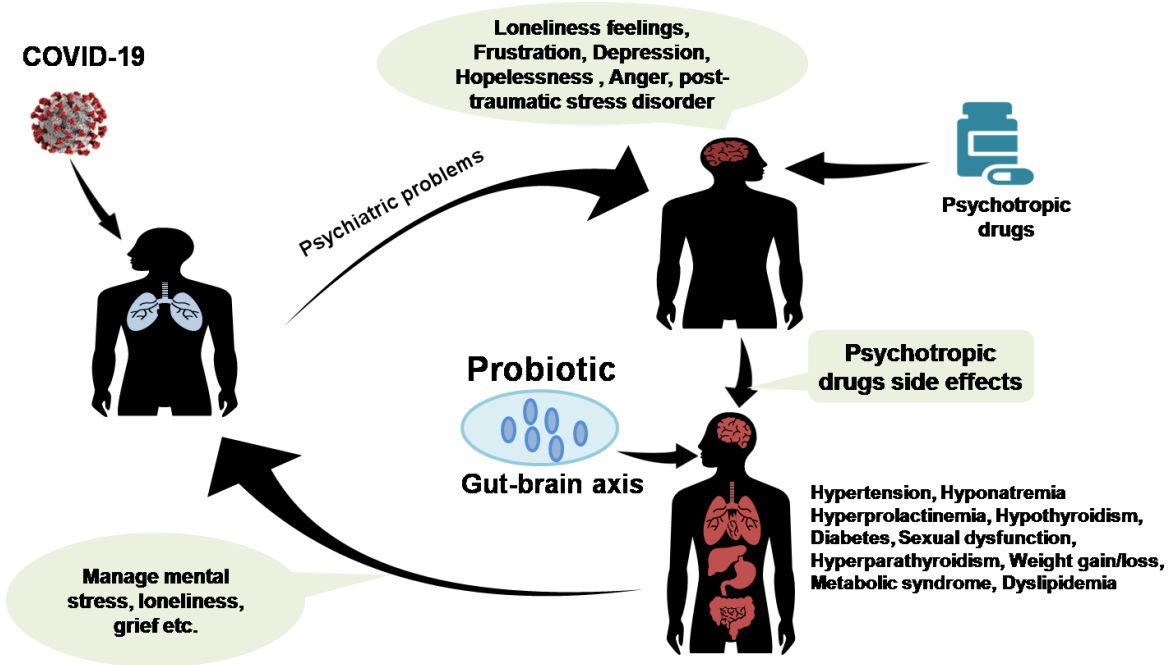


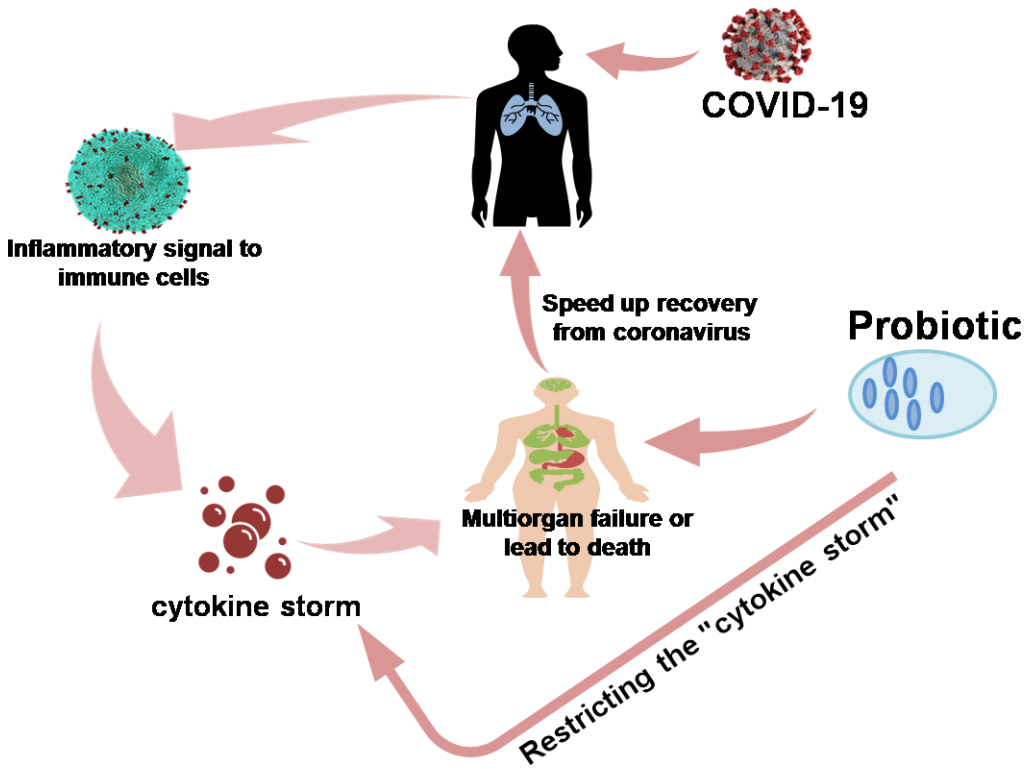
Fig 2: Side effects associated with the use of psychiatric drugs

It has been reported that several microorganisms have the ability to play important role in psychiatric diseases, which has gained great attention in the current scientific communities. The group of the bacteria which have potential therapeutic properties for the treatment of psychiatric diseases is known as Psychobiotics (Dinan et al., 2013). Several bacteria have been explored as potential psychotropic agents such as, *Streptococcus thermophiles*, *Bacillus coagulans*, *Bifidobacterium animalis*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus plantarum*, *Lactococcus lactis*, *Lactobacillus reuteri*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus*, *Lactobacillus helveticus*, *Clostridium butyricum*, and others (Cheng et al., 2019; Gualtieri et al., 2020; Vaghef-Mehrabany et al., 2020).
It has recently been suggested that supplementing with specific strains of probiotics rather than taking psychiatric medications may be a better approach for some people to manage with the mental stress, loneliness, and grief caused by the current COVID-19 pandemic (Araújo et al. 2020). Most current hot research topic is to determining which bacteria are involved and how they are interacting with the brain (Carabotti et al. 2015).

1.3. Probiotics and inhibiting effect on cytokine storm during COVID-19

Based on the several studies it has been confirmed that gut microbiota plays important role in the COVID-19 infection. Hence it is important to improve the gut microbiota which can be accomplished by probiotic supplements and diet which could be an effective approach for fighting and treating COVID-19 infection (He et al. 2020). In the severely ill patients of the COVID-19 excessive inflammatory cytokines “cytokine storm” have been observed which causes the damage defense of the body’s immune and maybe contributing to mortality (Tang et al. 2020). As shown in fig 3

Fig 3: cytokine storm



It has been proven that gut microbiota improves the immune system and reduces inflammation; therefore it is likely that probiotics could speed up recovery from coronavirus by inhibiting or restricting the "cytokine storm" (Akour, 2020). COVID-19 infected person may experience several other symptoms including diarrhea, abdominal pain, nausea, vomiting, loss of appetite etc. and it is well know that probiotics plays important role in the treatment all of these (Cholankeril et al. 2020).

Some researchers theorize that probiotics could help prevent the coronavirus by blocking the angiotensin-converting enzyme (ACE) receptor where the SARS-CoV-2 pathogen enters the body to invade gastrointestinal cells (Olaimat et al. 2020).

1.4. Probiotics and gut-lung axis responses

Another proposed link between COVID-19 and probiotics involves what is called the **"gut-lung axis".** This is a system of communication and interaction between the gut and lung tissues, which occurs via microorganisms of the human microbiome (Enaud et al. 2020). Imbalances of the intestinal flora are known to be related to lung diseases and respiratory tract infections. Researchers suggest that correcting those imbalances may promote optimum lung health, which might help guard against pathogens like SARS-CoV-2 (Shi et al. 2017, He et al. 2020). Other research suggests that probiotic supplementation may promote antiviral activity in general to improve immune, pulmonary, and anti-inflammatory response that might help clear the SARS-CoV-2 infection. As shown in fig 4. (Baud et al. 2020, Infusino et al. 2020).

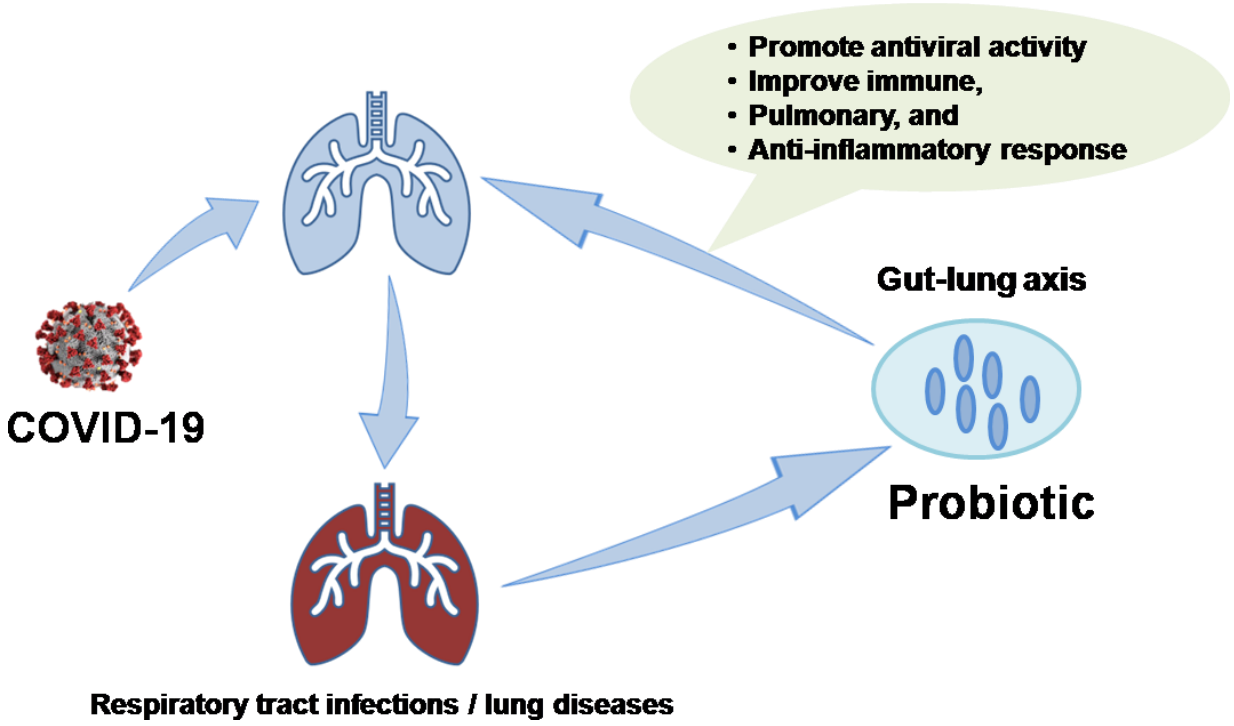


Fig 4: Probiotic supplementation may promote antiviral activity in general to improve immune system

One study advises caution, suggesting that not all probiotic strains will exert the same effects. It questions whether probiotic supplementation can alter the content of the gut microbiome enough to combat COVID-19. Research proposes that improving the gut microbiome through probiotic supplementation and diet may help treat the SARS-CoV-2 infection that causes COVID-19. Research is still in its early stages, and additional data and clinical trials are needed prior to implement to treat and control the Covid 19.

2. Conclusion

Due to the deadly covid situation in all over world, we need to think about the development of such a product that can help to save the humans life. During this pandemic, the majorities of people is isolated and have limited interaction with others, which can lead to develop the sentiments of loneliness, anger, as well as severe mental stress. However, it have been proved that the some probiotic stains including *Streptococcus thermophiles*, *Bifidobacterium animalis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, *Lactococcus lactis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus paracasei*, *Lactobacillus helveticus*, *Lactobacillus rhamnosus*, *Bacillus coagulans*, *Clostridium butyricum*, and others can suppress the mental stress at very below level. Using the bacterial strains we need to promote for the development such kind of product (psychobiotics) that can reduces the mental stress, which is important factor for the disturbance of blood pressure, hyper thinking, depression etc.

Many essential functions of nitric oxide have been reported, including improved oxygenation, blood clot inhibition, and antiviral properties. Nitric oxide forming activity have been reported by many gastrointestinal bacteria such as Lactobacilli, bifidobacteria Bacillus subtilis, Bacillus anthracis, Deinococcus radiodurans, and Streptomyces spp. Hypoxia is currently one of the most serious issues, with a high rate of mortality in covid patients. If there is any chance of developing probiotics using the reported bacteria, it could save a lot of lives.

Gut microbiome supplemented with probiotics and healthy diet might be an effective approach to combat and treat an infection with the new coronavirus SARS-CoV-2. Probiotic supplementation has been shown to boost immunological, pulmonary, and anti-inflammatory responses, which may help clear the SARS-CoV-2 infection. If the immune system is strong, the risks of infection are minimal, and probiotics can help to boost immunity. Therefore, it is necessary to promote and generate awareness among the normal person about the importance of consuming probiotics in daily life in order to reduce the effects of SARS-CoV-2 infection.

3. REFERENCE:

1. Adak S, Aulak KS, Stuehr DJ (2002) MDirect evidence for nitric oxide production by a nitric-oxide synthase-like protein from Bacillus subtilis, J Biol Chem 277(18), 16167–16171.
2. Adak S, Bilwes AM, Panda K, et al. (2002) Cloning, expression, and characterization of a nitric oxide synthase protein from Deinococcus radiodurans, PNAS USA 99(1), 107–112.
3. Ahmed MZ, Ahmed O, Aibao Z, Hanbin S, Siyu L, Ahmad A (2020) Epidemic of COVID-19 in China and associated psychological problems. Asian J Psychiatr 51, 102092. https://doi.org/10.1016/j.ajp.2020.102092.
4. Akour A (2020) Probiotics and COVID-19: is there any link? Lett Appl Microbiol 71, 229--234
5. Alvarez-Olmos MI, Oberhelman RA (2001) Probiotic agents and infectious diseases: a modern perspective on a traditional therapy. Clin Infect Dis 32:1567-76.
6. Baud D, Dimopoulou Agri V, Gibson GR, Reid G and Giannoni E (2020) Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic Front Public Health 8:186. doi: 10.3389/fpubh.2020.00186
7. Bengmark S (2003) Use of some pre-, pro- and synbiotics in critically ill patients. Best Prac Res Clin Gastroenterol 17:833-48.

8. Bhuvaneswar CG, Baldessarini RJ, Harsh VL, Alpert JE (2009) Adverse endocrine and metabolic effects of psychotropic drugs: Selective clinical review. CNS Drugs 23, 1003–1021. https://doi.org/10.2165/11530020-000000000-00000.
9. Blum S, Delneste Y, Donnet A (2000) The influence of probiotic organisms on the immune response. Nutr Immunol Prin Prac 1:451-5.
10. Blum S, Haller D, Pfeifer A, Schiffrin EJ (2002) Probiotics and immune response. Clin Rev Allergy Immunol 22(3):287-309. doi: 10.1007/s12016-002-0013-y
11. Bottazzi V (1983) Food and feed production with microorganisms. Biotechnol 5:315-63.
12. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, Rubin GJ (2020) The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. The Lancet 395(10227) 912–920. https://doi.org/10.1016/S0140-6736(20)30460-8.
13. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203-209.
14. Cheng LH, Liu YW, Wu CC, Wang S, Tsai YC, (2019) Psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders. J Food Drug Anal 27(3) 632-648. https://doi.org/10.1016/j.jfda.2019.01.002.
15. Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer SP, Kim D, Hsing A, Ahmed A (2020) High Prevalence of Concurrent Gastrointestinal Manifestations in Patients With Severe Acute Respiratory Syndrome Coronavirus 2: Early Experience From California. Gastroenterology;159:775–777
16. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield . (2017) Gut microbiota's effect on mental health: The gut-brain axis. Clin Pract 7(4):987. doi:10.4081/cp.2017.987
17. Cookson TA (2021) Bacterial-Induced Blood Pressure Reduction: Mechanisms for the Treatment of Hypertension via the Gut. Front Cardiovasc Med 8:721393. doi:10.3389/fcvm.2021.721393
18. Cussotto S, Strain CR, Fouhy F, Strain RG, Peterson VL, Clarke G et al. (2019) Differential effects of psychotropic drugs on microbiome composition and gastrointestinal function. Psychopharmacology 236(5), 1671–1685. https://doi.org/10.1007/s00213-018-5006-5.
19. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ (2002) Probiotics in prevention of antibiotic associated diarrhoea: Meta-analysis. BMJ 324:1361.
20. de Araújo FF, Farias DP (2020) Psychobiotics: An emerging alternative to ensure mental health amid the COVID-19 outbreak?. Trends Food Sci Technol. 2020;103:386-387. doi:10.1016/j.tifs.2020.07.006
21. Diamond M, Peniston HL, Sanghavi D, et al. (2022) Acute Respiratory Distress Syndrome. [Updated 2021 Nov 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing https://www.ncbi.nlm.nih.gov/books/NBK436002/
22. Dinan TG, Stanton C, Cryan JF (2013) Psychobiotics: A novel class of psychotropic. Biol. Psychiatry, 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001.
23. DuPont HL, Ericsson CD (1993) Prevention and treatment of traveler's diarrhea. N Engl J Med 328:1821-7.
24. ECDC (2022) COVID-19 situation update worldwide, updated 20 January 2022. European Centre for Disease Prevention and Control, 2022. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases. Accessed 24 January 2020.
25. Elliott DE, Summers RW, Weinstock JV (2005) Helminths and the modulation of mucosal inflammation. Curr Opin Gastroenterol 21:51-8.

26. Enaud R, Prevel R, Ciarlo E, Beaufils F, Wieërs G, Guery B and Delhaes L (2020) The Gut-Lung Axis in Health and Respiratory Diseases: A Place for Inter-Organ and Inter-Kingdom Crosstalks. Front. Cell. Infect. Microbiol. 10:9. doi: 10.3389/fcimb.2020.00009
27. Food and Agricultural Organization of the United Nations and World Health Organization (2001) Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. World Health Organization (2001). http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf
28. Government of India (GOI) (2022) Vaccination dose status, **24 Jan 2022.** https://www.mygov.in/covid-19/. Accessed 24 January 2020.
29. Graham MS, Sudre CH, May A, et al. (2021) Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. Lancet Public Health 6: e335–45.
30. Gualtieri P, Marchetti M, Cioccoloni G, De Lorenzo, A, Romano L, Cammarano A et al. (2020). Psychobiotics regulate the anxiety symptoms in carriers of allele A of IL-1β gene: A randomized, placebo-controlled clinical trial. Mediators Inflamm. 1–11. https://doi.org/10.1155/2020/2346126.
31. Gunnars K (2020) The rise of psychobiotics. Updated on December 9, 2020 (accessed on 28 Januay 2022) https://www.healthline.com/nutrition/probiotics-101#psychobiotics
32. Gusarov I, Starodubtseva M, Wang Z-Q, et al. (2008) Bacterial nitric-oxide synthases operate without a dedicated redox partner. J Biol Chem 283(19), 13140–13147.
33. He LH, Ren LF, Li JF, Wu YN, Li X, Zhang L (2020) Intestinal Flora as a Potential Strategy to Fight SARS-CoV-2 Infection. Front Microbiol 11:1388. doi:10.3389/fmicb.2020.01388
34. Hills RD Jr, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR (2019) Gut Microbiome: Profound Implications for Diet and Disease. Nutrients. 11(7):1613. Published 2019 Jul 16. doi:10.3390/nu11071613
35. Infusino F, Marazzato M, Mancone M, Fedele F, Mastroianni CM, Severino P, Ceccarelli G, Santinelli L, Cavarretta E, Marullo AGM, Miraldi F, Carnevale R, Nocella C, Biondi-Zoccai G, Pagnini C, Schiavon S, Pugliese F, Frati G, d'Ettorre G (2020) Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review. Nutrients 12(6):1718. https://doi.org/10.3390/nu12061718
36. Jaclyn M. Omar, Yen-Ming Chan, Mitchell L. Jones, Satya Prakash (2013) Peter J.H. Jones. Lactobacillus fermentum and Lactobacillus amylovorus as probiotics alter body adiposity and gut microflora in healthy persons. J. Funct Foods 5(1), 116-123. https://doi.org/10.1016/j.jff.2012.09.001
37. Jiang J, Feng N, Zhang C, Liu F, Zhao J, Zhang H, Zhai Q, Chen W (2019) Lactobacillus reuteri A9 and Lactobacillus mucosae A13 isolated from Chinese superlongevity people modulate lipid metabolism in a hypercholesterolemia rat model. FEMS Microbiol Lett 366 (24), 10.1093/femsle/fnz254
38. Johnson EG, Sparks JP, Dzikovski B, Crane BR, Gibson DM, Loria R (2008) Plant-pathogenic Streptomyces species produce nitric oxide synthase-derived nitric oxide in response to host signals, Chemistry & Biology 15(1), 43–50.
39. Kalliomäki M, Collado MC, Salminen S, Isolauri E (2008) Early differences in faecal microbiota composition in children may predict later weight-gain? Am J Clin Nutr 87: 534-8.
40. King S, Glanville J, Sanders ME, Fitzgerald A, Varley D (2014) Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. Br J Nutr 112(1):41-54. doi: 10.1017/S0007114514000075.

41. Kingsland J (2020) COVID-19: Nitric oxide shows promise as antiviral treatment. Medical News Today 2020. https://www.medicalnewstoday.com/articles/covid-19-nitric-oxide-shows-promise-as-antiviral-treatment
42. Knackstedt R, Knackstedt T, Gatherwright J (2020) The role of topical probiotics in skin conditions: A systematic review of animal and human studies and implications for future therapies. Experimental Dermatology 29:15–21. DOI: 10.1111/exd.14032
43. Kuroda M, Ohta T, Uchiyama I, et al. (2001) Whole genome sequencing of meticillin-resistant Staphylococcus aureus, The Lancet 357(9264), 1225–1240.
44. Lescheid DW (2014). Probiotics as regulators of inflammation: A review. Funct. Foods Health Dis 4(7):299-311
45. Levine AB, Punihaole D, Levine TB (2012) Characterization of the Role of Nitric Oxide and Its Clinical Applications. Cardiology 122:55-68. doi: 10.1159/000338150
46. Lisi F, Zelikin AN, Chandrawati R (2021) Nitric Oxide to Fight Viral Infections. Adv Sci 8, 2003895
47. Lolou V, Panayiotidis MI (2019) Functional Role of Probiotics and Prebiotics on Skin Health and Disease. Fermentatio 5(2):41. https://doi.org/10.3390/fermentation5020041
48. Louis P, Flint HJ (2009) Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiol Lett 294:1–8. doi: 10.1111/j.1574-6968.2009.01514.x
49. Louis P, Flint HJ (2017) Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol 19:29–41. doi: 10.1111/1462-2920.13589
50. Luiking YC, Engelen MP, Deutz NE (2010) Regulation of nitric oxide production in health and disease. Curr Opin Clin Nutr Metab Care 13(1):97-104. doi:10.1097/MCO.0b013e328332f99d
51. Luna RA, Foster JA (2015) Gut brain axis: diet microbiota interactions and implications for modulation of anxiety and depression. Current Opinion in Biotechnology 32(35-41). https://doi.org/10.1016/j.copbio.2014.10.007
52. McIntosh K (2022) COVID-19: Epidemiology, virology, and prevention. Wolters Kluwer. https://www.uptodate.com/contents/covid-19-epidemiology-virology-and-prevention
53. Mel AD (2020) Potential roles of nitric oxide in COVID-19: A perspective. Integr Mol Med 7: 1-4. doi: 10.15761/IMM.1000403
54. Mir JM, Maurya RC (2021) Nitric oxide as a therapeutic option for COVID-19 treatment: a concise perspective. New J. Chem 45, 1774-1784
55. Moncada S, Higgs EA (1991) Endogenous nitric oxide: physiology, pathology and clinical relevance. Eur J Clin Invest 21(4) 361–374.
56. Nagpal R, Kumar A, Kumar M, Behare PV, Jain S, Yadav H (2012) Probiotics, their health benefits and applications for developing healthier foods: A review. Fems Microbiology Letters 334 (1), 1-15, 10.1111/j.1574-6968.2012.02593.x
57. Ochoa-Repáraz J, Kasper LH (2016) The Second Brain: Is the Gut Microbiota a Link Between Obesity and Central Nervous System Disorders? Curr Obes Rep 5(1):51-64. doi: 10.1007/s13679-016-0191-1
58. Olaimat AN, Aolymat I, Shahbaz HM, Holley RA. Knowledge and Information Sources About COVID-19 Among University Students in Jordan: A Cross-Sectional Study. Front Public Health. 2020 May 29;8:254. doi: 10.3389/fpubh.2020.00254. PMID: 32574314; PMCID: PMC7274134.
59. Ozen M, Sandal GK, Dinleyici EC (2015) Probiotics for the prevention of pediatric upper respiratory tract infections: a systematic review. Expert Opin Biol Ther 15(1):9-20. doi: 10.1517/14712598.2015.980233.

60. Röhr S, Müller F, Jung F, Apfelbacher C, Seidler A, Riedel-Heller SG (2020) Psychosocial impact of quarantine measures during serious coronavirus outbreaks: A rapid review. Psychiatrische Praxis 47(4), 179–189. https://doi.org/10.1055/a-1159-5562.
61. Roy D, Tripathy S, Ka, SK, Sharma N, Verma SK, Kaushal V (2020) Study of knowledge, attitude, anxiety & perceived mental healthcare need in Indian population during COVID-19 pandemic. Asian J Psychiatr 51, 102083. https://doi.org/10.1016/j.ajp.2020.102083.
62. Sanchez M, Darimont C, Drapeau V, Emady-Azar S, Lepage M, Rezzonico E et al. (2014) Effect of Lactobacillus rhamnosus CGMCC1.3724 supplementation on weight loss and maintenance in obese men and women. Br J Nutr 111(8):1507-19. doi: 10.1017/S0007114513003875
63. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ (2016) Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals. Trends Neurosci 39(11):763-781. doi:10.1016/j.tins.2016.09.002
64. Shi, N., Li, N., Duan, X. et al. (2017) Interaction between the gut microbiome and mucosal immune system. Military Med Res 4, 14. https://doi.org/10.1186/s40779-017-0122-9
65. Sivamaruthi BS, Kesika P, Chaiyasut C (2018) A review on anti-aging properties of probiotics. Int J App Pharm 10(5), 23-27
66. Sobko T, Reinders CI, Jansson E, Norin E, Midtvedt T, Lundberg JM (2005) Gastrointestinal bacteria generate nitric oxide from nitrate and nitrite. Nitric Oxide. 13(4):272–8.
67. Takami H, Nakasone K, Takaki Y, et al. (2000) Complete genome sequence of the alkaliphilic bacterium Bacillus halodurans and genomic sequence comparison with Bacillus subtilis. Nucleic Acids Research 28(21) 4317–4331,.
68. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C (2020) Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. Front. Immunol. 11:1708. doi: 10.3389/fimmu.2020.01708
69. Tiwari G, Tiwari R, Pandey S, Pandey P (2012) Promising future of probiotics for human health: Current scenario. Chron. Young Sci 3(1), 17-28.
70. Vaghef-Mehrabany E, Maleki V, Behrooz M, Ranjbar F, Ebrahimi-Mameghani M (2020) Can psychobiotics "mood" ify gut? An update systematic review of randomized controlled trials in healthy and clinical subjects, on anti-depressant effects of probiotics, prebiotics, and synbiotics. Clin Nutr 39(5):1395-1410. https://doi.org/10.1016/j.clnu.2019.06.004.
71. Vermeiren J, Van de Wiele T, Verstraete W, Boeckx P, Boon N (2009) Nitric oxide production by the human intestinal microbiota by dissimilatory nitrate reduction to ammonium. J Biomed Biotechnol. 2009:284718. doi: 10.1155/2009/284718.
72. World Health Organization (WHO) (2020) Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media- briefing-on-2019-ncov-on-11-february-2020. Accessed 24 January 2022.
73. Yarullina DR, Il'inskaya ON, Aganov AV, Silkin NI, Zverev DG (2006) Alternative pathways of nitric oxide formation in lactobacilli: evidence for nitric oxide synthase activity by EPR. Microbiology759(6) 634–