The Possible Role of Probiotics in Combating COVID-19

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ABSTRACT

Since first reported in Wuhan in the end of 2019, COVID-19 infection has spread globally. However, our battle against COVID-19 is still limited with treatment modalities, yet giving a big challenge for researchers to explore promising treatment candidate. Probiotics, based on previous studies of its role in immune system and respiratory tract infection, seem to be potential candidate. Probiotics work in a distinct way through connectivity between gut and the lung, since both have expression of angiotensin converting enzyme2 (ACE2) of which highly bound by COVID-19. At present, no guidelines formally include probiotics as part of COVID-19 treatment. Hence, this study aimed to review the link of probiotics and immune system and its potential role as part of COVID-19 treatment.

Keywords: *probiotics, COVID-19, treatment.*

ABSTRAK

Sejak pertama kali dilaporkan di Wuhan di akhir tahun 2019, infeksi COVID-19 telah menyebar ke seluruh dunia. Namun, petempuran kita terhadap COVID-19 masih terbatas dalam modalitas terapi, sehingga memberikan peluang yang besar bagi peneliti untuk menemukan kandidat terapi optimal. Probiotik, berdasarkan penelitian sebelumnya berkaitan dengan peran pada sistem imun dan infeksi saluran nafas, terlihat dapat menjadi kandidat yang potensial. Probiotik bekerja melalui hubungan antara saluran cerna dan paru, dimana keduanya memiliki ekspresi angiotensin converting enzyme2 (ACE2), yang diikat kuat oleh COVID-19. Saat ini, tidak ada pedoman tatalaksana yang secara formal memasukkan probiotik sebagai bagian dari terapi COVID-19. Oleh karena itu, studi ini bertujuan untuk mengulas hubungan antara probiotik dan system imun dan potensi probiotik sebagai bagian dari terapi COVID-19.

Keywords: *probiotik, COVID-19, terapi*

INTRODUCTION

A wave of pneumonia with undetermined cause initially detected in December 2019 in Wuhan so called COVID-19.[1] SARS-Cov-2, the virus, is a member of the family Coronaviridae with Betacoronavirus as its genera. It can be spread from person-to-person by respiratory droplets produced when infected people sneeze or cough.[2] Over 30,000 confirmed cases reported worldwide in early February 2020,[1] and WHO declared COVID-19 as a pandemic on March 2020.[3] In less than five months COVID-19 had infected over 2 million people worldwide.[4]

The fast-paced infection pushes a great number of studies. Several trials consider corticosteroid, arbidol hydrochloride, chloroquine phosphate, and hydroxychloroquine to treat COVID-19. However, those treatments limited with small number of subjects and risk of adverse effects.[3] Another treatment taken into consideration is probiotics. Even though it is still early to suggest that probiotics might cure severe SARS-Cov-2 infections, it is undeniable that probiotics might have some beneficial effects in fighting COVID-19.[4–6] Probiotics are known for their anti-inflammatory effects in maintaining the balance of intestinal microecology and preventing secondary bacterial infections in COVID-19 patients.[5] The strains contained in probiotics change the balance between immunoregulatory and proinflammatory cytokines.[6] The action permits viral clearance while lowering the damage of immune response-mediated to the lungs.[6] Furthermore, several previous studies reported that probiotics may have a significant effect in reducing the incidence of ventilator-associated pneumonia, nosocomial infections and respiratory tract infections.[7–10] Therefore, their role in fighting COVID-19 is worthy of consideration.

This review aimed to elaborate the relationship between probiotics and the immune system and its role in COVID-19, including its safety aspects.

PROBIOTIC AND IMMUNE SYSTEM

Probiotics defined as microorganisms that may be beneficial to health when consumed in adequate amounts.[11] Human has various microorganisms residing in the intestine, mainly composed of Firmicutes, Bacteroides, and in lesser amount of Proteobacteria, Actinobacteria, Fusobacteria and Verucomicrobia.[11,12] The main role of gut microbiota in immune system is immunomodulatory and anti-inflammatory functions.[13] Probiotics regulate immune homeostasis by modulating the immune response and regulatory T cells.[13,14,15] Probiotics are able to decreasing intestinal inflammation by suppress TLRs expression, produce metabolites that inhibit TNF-α and inhibit NF-kB.[13,14,16] Probiotics might enhance immune system by stimulating production of secretory immunoglobulin A (sIgA), which has been known as the first defense line against pathogens.[13,15]

PROBIOTICS' ROLE IN RESPIRATORY TRACT INFECTION

There are various kind of probiotics, of which, *Lactobacillus* and *Bifidobacterium* are the most common and extensively studied.[14,17–23]

Genus Lactobacillus

Lactobacillus rhamnosus has a good effect in preventing viral respiratory tract infection, decreasing viral-related lung damage, maintaining gut barrier integrity, alleviating allergic disease, lowering risk of rhinovirus infection.[19,22] *L. plantarum* and *L. salivarius* might enhance host response to influenza vaccine, decreasing inflammatory reactions, increasing production of anti-inflammatory cytokines.[19,24,25] *L. acidophilus* is reported to be beneficial in reducing fever, rhinorrhea, cough incidence and antibiotic prescription in pediatrics patients.[26] Previous studies also demonstrated its usage for treatment of travelers' diarrhea and *Clostridium difficile* associated infection, decreasing the length of stay of children with acute diarrhea in hospital, and relieving irritable bowel syndrome.[19,22] *L. paracasei* (*L.casei* 431) has a good effect to relieve manifestation of upper respiratory tract infection and acts as immuno-modulator. Moreover, it enhances the innate viral defense system and decreases inflammation in the host. *L. paracasei* was showed to enhance the immune system in healthy people using a vaccination model.[20] A study showed that consumption of yogurt fermented with *L. delbrueckii* increasing activity of NK cell and diminishing common cold risk in elderly people. It also may play role in preventing respiratory tract infections caused by influenza virus.[19,20] *L. reuteri* has immunomodulatory effect and showed to decrease short-term sick leave caused by respiratory or gastrointestinal infections.[19,20]

Genus Bifidobacterium

B. animalis might increase IgA specific anti-poliovirus significantly. The combination of *B. animalis* and *L. acidophillus* showed to reduce fever, rhinorrhea, and cough incidence.[20,26–28] Study by Rerksuppaphol demonstrated B. bifidum, together with *L. acidophillus*, significantlyreduced the syomptoms of common cold in schoolchildren.[29]

PROBIOTICS IN COVID-19

The Gut-Lung Axis: Angiotensin-Converting Enzyme (ACE) 2 in Respiratory Tract and Gut

The Renin-Angiotensin-Aldosterone system (RAAS) is a system that has long been known and is important for regulating sodium and blood pressure.[30,31] The sequence of events in the RAAS system is that the angiotensinogen produced by the liver is converted to angiotensin I by the action of renin produced by granular cells in the kidney. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme 1 produced by the capillaries of the lungs, angiotensin II then stimulates the release of aldosterone for sodium homeostasis.[32] Angiotensin II will later be broken down by angiotensin converting enzyme 2 (ACE2) into angiotensin 1-7.[33,34,35]

ACE2 is now being a concern because of its association with the COVID-19. ACE2 is a membrane-bound peptidase with the majority of the protein comprising the extracellularly oriented NH2-terminal peptide domain including the catalytic location.[36] The highest levels of ACE2 expression is located in small intestine, testis, kidneys, liver, thyroid and adipose, and lowest level located in blood, spleen, bone marrow, brain, blood vessels, and muscle. Medium level of ACE2 expression are in lung, colon, liver, bladder, and adrenal gland expression levels. There is no different expression of ACE2 based on gender or age.[37] COVID-19 can be attached to ACE2 due to hydrophobic interactions and salt bridge formation with the spike protein of the virus.[38] Therefore, angiotensin II levels are increased compared to healthy people and directly proportioned to the viral load. There was evidence of ACE2 dysregulation and RAS imbalance, resulting in multiorgan damage from COVID-19 infection.[39] The attachment of COVID-19 causes excessive inflammation in the lungs, resulting fibrosis and pulmonary hypertension; meanwhile, it causes damage in gut blood barrier, gut dysbiosis and systemic inflammation.[40]

To date, there is scarce of evidence of relationship between probiotic and COVID-19. Researchers all over the world are racing to conduct trials evaluating the benefit of probiotic in combating COVID-19. Gastrointestinal symptoms might be the presenting symptoms in COVID-19 patient as reported by Azwar.[41] Moreover, a review of 15 studies from China, Singapore, and WHO European Region by Schmulson reported that the prevalence of gastrointestinal symptoms in COVID-19 varied from 3.0% to 39.6%, with diarrhea as the most common symptoms (7.5%).[42] Ji, et. al. reported probiotic, without specifying the strain, as the only treatment in a pediatric COVID-19 patient presenting with mild diarrhea.[43] Horowitz reported several different probiotics, including acidophilus, lactobacillus, bifidobacterium, and Saccharomyces boulardii, along with azithromycin, hydroxychloroquine, zinc, vitamin C, alpha lipoic acid, glutathione, N-acetylcysteine in a case of recovered adult COVID-19 patient in New York City, USA.[44] A greater number of COVID-19 patients receiving probiotics as complementary treatment reported by Xu et. al. in Wuhan, China. It was reported that most cases of 62 patients in this study received probiotics in addition to antiviral, steroids, gamma globulin.[1] A report from 55 COVID-19 patients in Wuxi, China by Jiang et. al. also noted the use of probiotics as part of treatment in 47.3% of COVID-19 patients. In addition, probiotics was given more common in severe than non-severe patients (87.5% vs 40.4%, p=0.037). Unfortunately, both studies did not specify the strain, dose, dan duration of probiotics treatment given to the patients. It is hypothesized that viral replication associated with gastrointestinal immunity; hence, gut microbiota dysbiosis plays role in COVID-19.[6,45] There is still a great task in exploring the efficacy of probiotics as part of COVID-19 treatment; many studies attempted to correlate pathophysiology of COVID-19 disease and previous knowledge of mechanism action of some probiotics.[6,18,45] Not all probiotics seem to have the same treatment efficacy. Up to now, researchers worldwide are still actively exploring the most beneficial strain of probiotics and its dose; therefore, there is a wide variety of strain, dose, and treatment duration in each published study. A *Lactobacilli* and *Bifidobacteria* are the most common used of probiotics in many studies. There is a cytokine storm involving various pro-inflammatory cytokines such as interleukin-17 (IL-17), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ). Blocking IL-17 decrease the inflammatory process; therefore, some Bifidobacterium strain having IL-17 inhibitory effect might be beneficial in treatment.[46] Also, Lactobacillus strain, such as *Lactobacillus reuteri*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, and *Lactobacillus acidophilus* exhibited anti-inflammatory effect through suppressing TNF-α, IFN-γ production, IL-8, and IL-12.[47–50] To deepen understanding and knowledge of probiotics' role in fighting COVID-19, there are ongoing trials in Belgium, USA using Lactobacillus strain in COVID-19 patients.[51] Whether probiotics might play role as adjuvant in vaccine against COVID-19 or prophylaxis of COVID-19 infection is an interested topic to be further evaluated. Moreover, probiotic is beneficial in restoring gut microbiome composition due to antibiotic treatment, which is commonly used as part of treatment in COVID-19 patients.[4,51,52]

At present, no specific therapeutic agents or vaccines for COVID-19 are available and most of the recommended drug are still under investigation. There are some published consensus and guidelines of COVID-19 treatment recommendation. However, probiotics have not been incorporated yet as part of treatment regimen since the rationale for using probiotics in treatment of COVID-19 is merely extrapolated from an indirect hypothetical evidence.[5,51,53–56]

SAFETY ASPECT OF PROBIOTICS

Neither mortality nor serious adverse effects reported in the studies described in above. The subjects were varied from children to elderly, involving both men and women. Moreover, a study by Reid and Kirjaivanen reported *Lactobacillus* strains was safe to be used during pregnancy.[57]

CONCLUSION

Probiotics supplementation might serve as a new hope in combating COVID-19. However, more studies involving greater number of subjects, similar strain and dose of probiotics are needed to establish the potency of probiotics as part of COVID-19 treatment.

REFERENCES

1. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ 2020;368.
2. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health 2020;13:667–73.
3. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic management of patients with COVID-19: a systematic review. Infect Prev Pract 2020;2:100061.
4. Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. Lancet Gastroenterol Hepatol 2020;5:644–5
5. Baud D, Dimopoulou Agri V, Gibson GR, Reid G, Giannoni E. Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic. Front Public Heal 2020;8:186.
6. Di Renzo L, Merra G, Esposito E, De Lorenzo A. Are probiotics effective adjuvant therapeutic choice in patients with COVID-19? Eur Rev Med Pharmacol Sci 2020;24:4062–3.
7. Kanauchi O, Andoh A, AbuBakar S, Yamamoto N. Probiotics and Paraprobiotics in Viral Infection: Clinical Application and Effects on the Innate and Acquired Immune Systems. Curr Pharm Des 2018;24:710–7.
8. Cook DJ, Johnstone J, Marshall JC, Lauzier F, Thabane L, Mehta S, et al. Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial-PROSPECT: A pilot trial. Trials 2016;17:377.
9. Nagai T, Makino S, Ikegami S, Itoh H, Yamada H. Effects of oral administration of yogurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1 and its exopolysaccharides against influenza virus infection in mice. Int Immunopharmacol 2011;11:2246–50.
10. Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, et al. Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials. Med (Baltimore) 2016;95(31).
11. Zhang CX, Wang HY, Chen TX. Interactions between intestinal microflora/probiotics and the immune system. Biomed Res Int 2019;2019:6764919
12. De Oliveira GLV, Leite AZ, Higuchi BS, Gonzaga MI, Mariano VS. Intestinal dysbiosis and probiotic applications in autoimmune diseases. Blackwell Publishing Ltd 2017;152:1–12.
13. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. Adv Nutr 2019;10:S49-S66.
14. Galdeano CM, Cazorla SI, Dumit JML, Vélez E, Perdigón G. Beneficial effects of probiotic consumption on the immune system. Ann Nutr Metab 2019;74:115–24.
15. Lazar V, Ditu LM, Pircalabioru GG, Gheorghe I, Curutiu C, Holban AM, et al. Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Front Immunol 2018;9:1830.
16. La Fata G, Weber P, Mohajeri MH. Probiotics and the gut immune system: indirect regulation. Probiotics Antimicrob Proteins 2018;10:11-21.
17. Amoruso A, Deidda F, Pane M, Mogna L. A Systematic evaluation of the immunomodulatory and functional properties of probiotic Bifidobacterium breve BR03 (DSM 16604) Lactobacillus plantarum LP01 (LMG P-21021). J Prob Health 2019;7:1–9.
18. Dhar D, Mohanty A. Gut microbiota and Covid-19- possible link and implications. Virus Res 2020;285:198018.
19. Fijan S. Microorganisms with claimed probiotic properties: An overview of recent literature. Int J Environ Res Public Health 2014:4745–67.
20. Prince CP. a Comprehensive review of probiotics and their uses for control of viral infections in the wake of pandemic COVID-19. Trop J Pharm Life Sci 2020;7:01–14.
21. Senapati S, Dash J, Sethi M, Chakraborty S. Bioengineered probiotics to control SARS-CoV-2 infection. Res Ideas Outcomes 2020;6:54802.
22. Sniffen JC, McFarland L V., Evans CT, Goldstein EJC. Choosing an appropriate probiotic product for your patient: An evidence-based practical guide. PLoS One 2018;13:1
23. Zhang H, Yeh C, Jin Z, Ding L, Liu BY, Zhang L, et al. Prospective study of probiotic supplementation results in

immune stimulation and improvement of upper respiratory infection rate. Synth Syst Biotechnol 2018;3:113–20.

24. Ren D, Wang D, Liu H, Shen M, Yu H. Two strains of probiotic Lactobacillus enhance immune response and promote naive T cell polarization to Th1 Two strains of probiotic Lactobacillus enhance immune response and promote naive T cell polarization to Th1. Foof Agric Immunol 2019;30:281–95.
25. Bosch M, Méndez M, Pérez M, Farran A, Fuentes MC, Cuñé J. Lactobacillus plantarum CECT7315 and CECT7316 stimulate immunoglobulin production after influenza vaccination in elderly. Nutr Hosp 2012;504–9.
26. Leyer GJ, Li S, Mubasher ME, Reifer C, Ouwehand AC. Probiotic effects on cold and influenza-like symptom incidence and duration in children. Pediatrics 2009;124:172-9.
27. Callaghan AO, Sinderen D Van. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. Front Microbiol 2016;7:925.
28. Pedret A, Valls RM, Calderón-pérez L, Llauradó E, Companys J, Pla-pagà L, et al. Effects of daily consumption of the probiotic Bifidobacterium animalis subsp. lactis CECT 8145 on anthropometric adiposity biomarkers in abdominally obese subjects : a randomized controlled trial. Int J Obes 2019;43:1863–8.
29. Rerksuppaphol S, Rerksuppaphol L. Randomized controlled trial of probiotics to reduce common cold in schoolchildren. Pediatr Int 2012;54:682–7.
30. Durante A, Peretto G, Laricchia A, Ancona F, Spartera M, Mangieri A, et al. Role of the renin-angiotensin-aldosterone system in the pathogenesis of atherosclerosis. Curr Pharm Des 2012;18:981–1004.
31. Nishiyama A, Kobori H. Independent regulation of renin–angiotensin–aldosterone system in the kidney. Clin Exp Nephrol 2018;22:1231–9.
32. Drawz P, Ghazi L. Advances in understanding the renin-angiotensin-aldosterone system (RAAS) in blood pressure control and recent pivotal trials of RAAS blockade in heart failure and diabetic nephropathy. F1000Res 2017;6:F1000 Faculty Rev-297.
33. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circ Research 2016;118:1313–26.
34. Singh KD, Karnik SS. Angiotensin receptors: structure, function, signaling and clinical applications. J cell Signal 2016;1:111.
35. Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. Int J Pept 2012:256294.
36. Lew RA, Warner FJ, Hanchapola I, Smith AI. Characterization of angiotensin converting enzyme-2 (ACE2) in human urine. Int J Pept Res Ther 2006;12:283-289.
37. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020;9:45.
38. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature 2020;581:221–4.
39. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364–74.
40. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020;126:1671–81.
41. Azwar MK, Kirana F, Kurniawan A, Handayani S, Setiati S. Gastrointestinal presentation in COVID-19 in Indonesia: a case report. Acta Med Indones 2020;52:63–7.
42. Schmulson M, Dávalos MF, Berumen J. Beware: Gastrointestinal symptoms can be a manifestation of COVID-19. Rev Gastroenterol México 2020;85:282-7.
43. Ji LN, Chao S, Wang YJ, Li XJ, Mu XD, Lin MG, et al. Clinical features of pediatric patients with COVID-19: a report of two family cluster cases. World J Pediatr 2020;16:267-270.
44. Horowitz RI, Freeman PR, Bruzzese J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respir Med Case Reports 2020;30:101063.
45. Xu K, Cai H, Shen Y, Ni Q, Chen Y, Hu S, et al. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. Zhejiang Da Xue Xue Bao Yi Xue Ban 2020;49:147-57.
46. Bozkurt HS. A hypothetic treatment model on coronavirus by Bifidobacterium strains 2020;2020:x.
47. Jones SE, Versalovic J. Probiotic *Lactobacillus reuteri* biofilms produce antimicrobial and anti-inflammatory factors. BMC Microbiol 2009;9:35.
48. Chong HX, Yusoff NAA, Hor YY, Lew LC, Jaafar MH, Choi SB, et al. Lactobacillus plantarum DR7 improved upper respiratory tract infections via enhancing immune and inflammatory parameters: A randomized, double-blind, placebo-controlled study. J Dairy Sci 2019;102:4783–97.
49. Oh NS, Joung JY, Lee JY, Kim Y. Probiotic and anti-inflammatory potential of Lactobacillus rhamnosus 4B15 and Lactobacillus gasseri 4M13 isolated from infant feces. PLoS One 2018;13:e019202.
50. Lopez M, Li N, Kataria J, Russell M, Neu J. Live and Ultraviolet-Inactivated Lactobacillus Rhamnosus GG Decrease Flagellin-Induced Interleukin-8 Production in Caco-2 Cells. J Nutr 2008;138:2264–8.
51. Akour A. Probiotics and COVID-19: is there any link? Lett Appl Microbiol 2020;71:229-34.
52. Vemuri RC, Gundamaraju R, Shinde T, Eri R. Therapeutic interventions for gut dysbiosis and related disorders in the elderly: Antibiotics, probiotics or faecal microbiota transplantation? Benef Microbes 2017;8:179–92.
53. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854–87.
54. Bhimraj A, Morgan RL, Hirsch Shumaker A, Lavergne V, Baden L, Chi-Chung Cheng V, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis 2020;x:ciaa478.
55. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. The Lancet. 2020;395:1015–8.
56. Chan KW, Wong VT, Tang SCW. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease. Am J Chin Med 2020;48:737–62.
57. Reid G, Kirjaivanen P. Taking probiotics during pregnancy: Are they useful therapy for mothers and newborns? Can Fam Physician 2005;51:1477.