Microbiology Research Journal International

Volume 34, Issue 9, Page 48-57, 2024; Article no.MRJI.121274
ISSN: 2456-7043, NLM ID: 101726596
(Past name: British Microbiology Research Journal, Past ISSN: 2231-0886, NLM ID: 101608140)

Probiotics as Potential Therapeutics for Managing COVID-19: Mechanisms and Implications

Aditya Chaudhary [a++], Baljeet Singh Saharan [b++*], Swati Tyagi [c], Chhaya Goyal [d], Neelam Kumari Mandal [e], Ramesh Kumar [f#], Joginder Singh Duhan [g*] and Prerana Badoni [h]

[a] Department of Health Sciences, University of the People, Pasadena, California 91101, USA.
[b] Department of Microbiology, Chaudhary Charan Singh Haryana Agricultural University, Hisar 125 004, India.
[c] Rice Breeding Platform, IRRI- South Asia Regional Centre, Varanasi 221106, India.
[d] Department of Dairy Science & Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India.
[e] Department of Botany, Government PG College, Panchkula, 134 112, India.
[f] Krishi Vigyan Kendra, Ambala 133104, 125 004, India.
[g] Department of Biotechnology, Chaudhary Devi Lal University, Sirsa 125055, Haryana, India.
[h] Forest Pathology Division, Forest research Institute, Dehradun, India.

Authors' contributions

This work was carried out in collaboration among all authors. Authors AC and BSS conceptualized the study and contributed to methodology. Author AC also drafted the manuscript. Authors ST and CG performed investigation and data analysis, respectively, and contributed to visualization and manuscript review. Author NKM provided resources. Author RK conducted formal analysis. Author JSD reviewed the manuscript. PB contributed to manuscript review. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/mrji/2024/v34i91480

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/121274

[++] These authors contributed equally to this work, and both are considered as the first author;
[#] SMS (Agrill. Extn.);
**Corresponding author: E-mail: Baljeetsaharan@hau.ac.in, duhanjs68@gmail.com;*

Cite as: *Chaudhary, Aditya, Baljeet Singh Saharan, Swati Tyagi, Chhaya Goyal, Neelam Kumari Mandal, Ramesh Kumar, Joginder Singh Duhan, and Prerana Badoni. 2024. "Probiotics As Potential Therapeutics for Managing COVID-19: Mechanisms and Implications". Microbiology Research Journal International 34 (9):48-57. https://doi.org/10.9734/mrji/2024/v34i91480.*

Review Article

Received: 26/06/2024
Accepted: 28/08/2024
Published: 04/09/2024

ABSTRACT

The transmission of viruses between different animal species and humans can lead to the emergence of new infectious diseases with unpredictable pathogenic potential. COVID-19, caused by SARS-CoV-2, has had a significant impact on human health and the global economy. The disease is characterized by symptoms such as dry cough, fatigue, muscle pain, fever, shortness of breath, gastrointestinal discomfort, nausea, vomiting, and runny nose. With limited vaccine accessibility for individuals between the ages of 18 and 45, exploring alternative therapies is essential. This paper aims to elucidate the preventive and supportive therapeutic role of probiotics in managing COVID-19. It discusses the specific mechanisms by which probiotics regulate the balance of gut microbes, promote gut homeostasis, and exert regulatory effects on the mucosal immune system, the gut-lung axis, and potential antiviral processes.

Keywords: Probiotics; COVID-19; gut-lung axis; pandemic; Psychobiotics; immunity.

1. INTRODUCTION

Over the past two decades, there has been an increase in the frequency of virus occurrences due to their rapid mutation. Various factors contribute to the resurgence of viruses, including a rise in immunocompromised individuals, changes in the environment, limited availability of antiviral agents, increased global mobility, and genetic alterations of viruses [1]. Respiratory diseases are among the leading causes of death worldwide in both developed and developing nations [2]. Acute respiratory infections result in millions of deaths each year.

The appearance of a new coronavirus identified as SARS-CoV-2 in December 2019 in Wuhan, China, led to the epidemic of COVID-19 [3]. Over the past two years, this respiratory virus has significantly impacted human health and the global economy, with approximately 3.27 million documented deaths and 165 million confirmed cases globally as of the time of this writing. India alone has reported 22.3 million cases and 235,000 deaths. SARS-CoV-2 belongs to the Coronaviridae family and the subfamily Coronavirinae, which includes viruses primarily infecting birds and mammals [4]. The characteristic crown-like appearance of coronaviruses is due to their large surface spikes. Humans serve as hosts for coronaviruses, along with other vertebrate reservoirs such as bats, camels, mice, dogs, and cats. It is believed that COVID-19 originated in bats and was transmitted to humans through intermediate animal hosts, potentially including pangolins [5].

Structurally, SARS-CoVs have three main proteins in their viral envelopes [6,7]. The spike glycoprotein (S) of SARS-CoV-2 interacts with ACE2 receptors on cells, facilitating the binding process [8]. The incubation period of COVID-19 ranges from one to fourteen days, according to the World Health Organization [9]. While the exact mode of transmission is not fully understood, current global epidemics suggest that the most common method is through surface contact with droplets containing the virus, followed by touching the nose, eyes, or mouth. It is important to note that individuals who do not exhibit any symptoms can still spread the disease [10,11]. Other reported symptoms include pneumonia, loss of smell, sore throat, headache, and sneezing [5]. Most cases of COVID-19 with mild symptoms resolve on their own and result in full recovery [11]. However, severe infections can result in multi-organ dysfunction, acute respiratory distress syndrome, cardiac and kidney damage, or septic shock, requiring intensive care unit (ICU) admission. The aim of the review paper is to study the potential benefits of probiotics in managing COVID-19.

2. PROBIOTICS AND THEIR USE IN IMMUNOMODULATION

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [12]. Examples include *Lactobacillus*, *Bifidobacterium*, *Leuconostoc*, *Pediococcus*, and *Enterococcus*. *Lactobacillus* and *Bifidobacterium* are commonly found in the gastrointestinal tracts of humans and are frequently used and considered safe in yogurt and other dairy products [13]. Immunomodulatory substances refer to chemicals that can alter the body's immunity (Table 1). They can modify or regulate the overall functioning of the immune system [14]. Immune modulators can be classified into two main categories: immune stimulants, which enhance the immune system, and immune suppressants, which dampen or inhibit immune responses [15].

The positive effects of probiotic bacteria on immunology and overall health are well-documented. They contribute to regulating the bacterial ecosystem, modulating immune cells, enhancing nutrient absorption, and maintaining general well-being [16]. In a healthy gut, dendritic cells (DCs) play a crucial role in maintaining immunological balance. Immature DCs can lead to T cell deletion or activation of regulatory T cells [17]. The gut microbiome influences the priming of these cells by dendritic cells. For instance, *L. reuteri* and *L. casei* activate pro-inflammatory Th1 cells and promote the production of IFN-gamma [18].

Monocytes encounter viruses, and native microbial flora impacts these monocytes, inducing the production of various cytokines as they differentiate into tissue macrophages. Macrophages release interleukins, which stimulate CD4+ Th1 cells and natural killer cells to produce IFN-gamma, crucial for virus elimination [19]. Additionally, specific probiotic strains like *L. gasseri*, *S. bulgaricus*, *B. bifidum*, and *L. acidophilus* stimulate monocytes to produce IFN-alpha [20]. *S. thermophilus* has also been found to induce the necessary biomolecule profiles for antiviral actions [21].

In the case of coronavirus, probiotic bacteria can adhere to mucosal epithelial surfaces, creating a steric hindrance that prevents viruses from binding to host cell receptors such as angiotensin-converting enzyme 2. The colonization of these bacteria is crucial for enhancing gut microbiota, reinforcing the mucosal barrier, and managing dysbiosis and diarrhea symptoms. Probiotic bacteria release various substances like bacteriocins, biosurfactants, lactic acid, hydrogen peroxide, nitric oxide, and organic acids, some of which may inhibit viral replication [22]. Additionally, the release of intestinal mucins and secretory antibodies like IgA from mucosal cells can help neutralize the coronavirus. When the virus attacks epithelial cells, probiotic bacteria play a key role in antiviral immunity by modulating the host's immune response, including the activation of NK cells, balancing Th1/Th2-mediated immunity, and triggering the production of

Table 1. Strains of probiotic bacteria and their mode of action in reducing the COVID infection

Probiotic bacteria	Mode of action	Reference(s)
L. reuteri; L. casei; Lactobacillus plantarum	Protection against upper respiratory tract infection; TLR-dependent inflammatory response; Diminish granulocyte and inflammatory-mediated tissue damage; reduce virus recovery; Enhance defensin expression and innate immunity	Jounai et al., [23]
Lactobacillus rhamnosus	Protection against cold-like/flu symptoms; Increase interferon-γ and interleukin-2	Al Kassaa et al., [24]
Lactobacillus delbrueckii	boost *Bifidobacterium* and *Lactobacillus* abundance.	Song et al., [25]
L. paracasei	Fight against cold viruses and boost immune system; Elevate Antigen-Specific IgA production and release	Kokubo et al., [26]
Enterococcus faecalis	Stabilize alveolar capillary cross	Ahren et al., [27]
Yeast (*S. boulardii*)	Reduce systemic and lung injury cytokines	Arai et al., [28]
Lactococcus sp.	Activating plasmacytoid dendritic cells enhances lung immune response and induces anti-viral response against respiratory viral infection.	Guillemard et al., [29]
Bifidobacterium infantis	IL-17 inhibitory effect	Karen et al., [30]
Bifidobacterium animalis	viral replication, anti-interleukin-17	Jounai et al., [23]
Bacillus subtilis	Competitively inhibits viral adherence	Al Kassaa et al., [24]

inflammatory cytokines and specific antibodies [22]. The activation of the immune system further leads to the differentiation of CD8+ T-lymphocytes into cytotoxic T-cells, which can eliminate virus-infected cells. Simultaneously, CD4+ T-cells differentiate into Th1 cells that activate phagocytosis through NK cells and macrophages, promoting pathogen destruction. They can also differentiate into Th2 cells, which stimulate B-cell proliferation, leading to antibody production that plays a key role in combating coronavirus replication. Therefore, probiotic bacteria may enhance immune responses and contribute to maintaining immune balance during coronavirus infections.

3. PROBIOTICS AND COVID-19

The beneficial impact of probiotics on ACE enzymes has been extensively documented. During the fermentation process, probiotics release bioactive peptides that can inhibit the active sites of ACE enzymes, leading to a reduction in their activity (Fig. 1). Even after the probiotic cells have died, their remnants continue to possess ACE inhibitor properties. These findings suggest that probiotics may have the ability to block the respective receptors, which serve as entry points for viruses targeting the gastrointestinal tract. While Esler and Esler [31] hold a different viewpoint, Fernández-Fernández [32] proposed the use of medications as a potential therapeutic strategy against COVID-19. According to Liu et al. [33], an ACE blocker may help alleviate respiratory distress syndrome.

Prebiotics, by promoting the growth and viability of probiotics, may also impact COVID-19. By blocking ACE activities, probiotics directly influence gastrointestinal symptoms associated with the virus. A comprehensive analysis of twelve research studies investigating the effects of prebiotic and probiotic supplementation on influenza transmission has been performed [34]. Researchers concluded that incorporating these into the diet could enhance hemagglutination inhibition antibody titers following influenza infection. Although there is currently no study on probiotics in COVID-19, employing probiotics in this context holds promising potential.

Several ongoing registered trials are currently evaluating the effectiveness of probiotics in treating COVID-19 patients. Some individuals with COVID-19 have exhibited an imbalance in their intestinal microbiota, specifically a deficiency in certain beneficial probiotic species like *Bifidobacterium* and *Lactobacillus*. To restore microbial equilibrium in the gut and mitigate the risk of infection, individuals may need quality food security along with probiotics. This imbalance could indicate a compromised immune system [35].

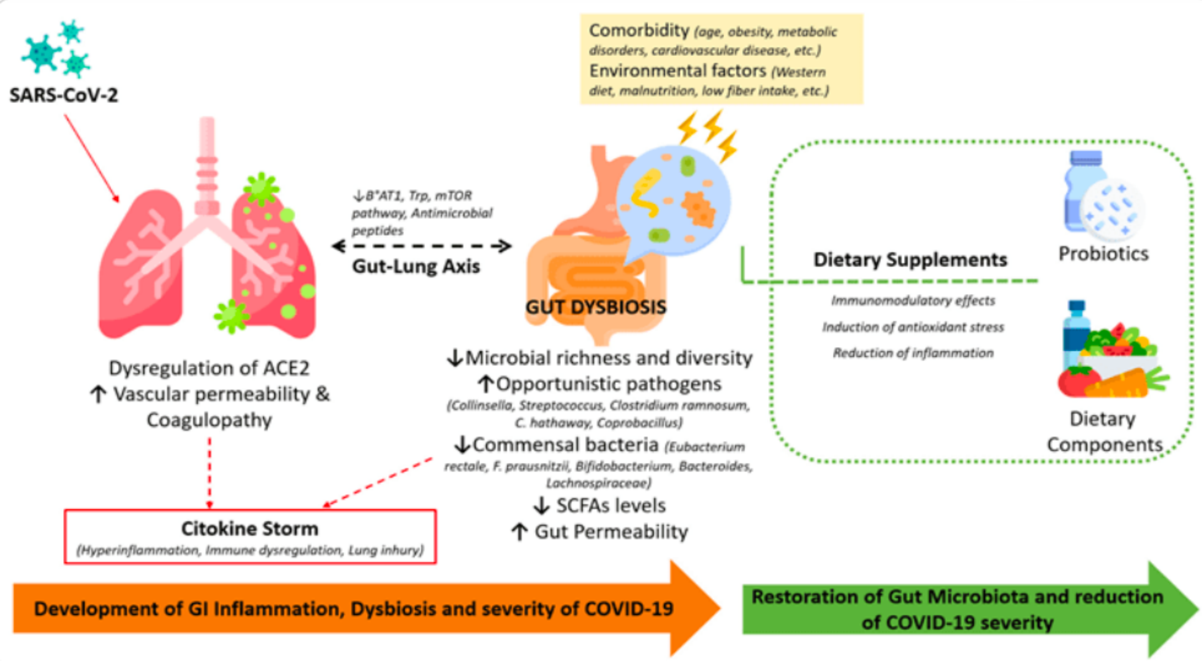

Fig. 1. Beneficial effects of probiotics in the alterations in the gut microbiota

Dietary habits significantly impact the levels, diversity, structure, and function of the gastrointestinal (GI) microbiota. A well-balanced diet that includes probiotic-rich foods and immune-provoking trace elements can alleviate the effects of COVID-19. Fermented foods, which are sources of probiotics, have shown potential in preventing COVID-19. Previous studies demonstrated a notable reduction in the incidence of upper respiratory tract infections in various populations consuming fermented milk with probiotic strains [36]. Considering the potential of these substances for treating and preventing COVID-19, they may be a reasonable choice. Therefore, it is reasonable to utilize probiotics to enhance defenses during this pandemic.

Earlier investigations have utilized probiotic strains, showing unique potential for immunity. Different strains of *Lactobacillus* offer distinct levels of protection against influenza virus infection [37]. When selecting the most effective probiotic strains, it is crucial to consider both human and animal research findings. To ensure the effectiveness of probiotic treatments, it is important to review specific studies assessing the impact of different strains, doses, and the potential for reducing the severity of COVID-19.

4. LIMITATIONS AND RISKS

While probiotics have shown potential benefits, there are limitations and risks to consider. The efficacy of probiotics in COVID-19 management remains uncertain due to limited clinical trials and potential variability in probiotic strains. Some studies have reported conflicting results, and there may be adverse effects or interactions with other treatments. Probiotic strains differ in their health effects and may not be universally effective against all pathogens or in all

Table 2. Probiotics, their dosage and outcomes in the treatment of COVID-19

Probiotics	Intervention	Dose (CFU)	Outcomes	Reference(s)
Lactobacillus plantarum	1 sachet/ once daily/ 12 weeks	1×10^9	Probiotic reduce the severity of the common cold	Ahrén et al., [39]
Lactobacillus plantarum	1 sachet/ 12 weeks	1×10^9	Probiotics alleviate the symptoms of upper respiratory tract infection by enhancing immunomodulatory properties	Chong et al., [40]
Lactobacillus rhamnosus	1 capsule/twice daily/ 4 weeks	1×10^{10}	Probiotic improve influenza vaccine immunogenicity	Davidson et al., [41]
Lactobacillus coryniformis	1 capsule/day/ 2 weeks	3×10^9	Probiotics boost influenza vaccine immunity and reduce respiratory illness symptoms.	Fonolláet al., [42]
Lactobacillus helveticus	1 capsule/ once daily/ 6 weeks	3×10^9	Probiotics improve cold/flu infection during acute stress	Langkamp-Henken et al., [43]
Bifidobacterium longum	1 sachet/ once daily/ 14 weeks	1×10^{11}	Probiotics boost innate immunity, reducing flu and fever symptoms.	Namba et al., [44]
Lactobacillus pentosus	1 tablet/ once daily/ 20 weeks	2×10^{10}	Probiotics minimise cold symptoms and boost mucosal immunity.	Shinkai et al., [45]
Lactobacillus lactis	o. 1 mL (JCM5805) yoghurt per o.d per 10 weeks	10×10^{10}	Probiotics reduce influenza-like illness via the enhancement of an IFN-α-mediated response to the influenza virus	Sugimura et al., [46]
Bifidobacterium animalis	1sachet/ o.d/ 4 70 days	2×10^9	Probiotics boost nose innate immunity to reduce rhinovirus symptoms.	Turner et al., [47];
Lactobacillus brevis	80 mL drinks/ 5 d per wk/ 8 weeks	6×10^9	Probiotics reduce the symptoms of influenza	Waki et al., [48];
Lactobacillus rhamnosus	2 capsules/ d/ 24 weeks	1×10^{10}	Probiotics fight respiratory viruses like influenza.	Wang et al., [49]

populations. Adverse effects such as gastrointestinal disturbances or infections, especially in immunocompromised individuals, have been documented [38]. It is crucial to balance the benefits with potential risks and to conduct further research to address these uncertainties.

5. CONCLUSION

Using probiotics as a complementary approach alongside vaccines to combat COVID-19 should be explored due to the potential antiviral effects of probiotics and their metabolites. The available evidence indicates that probiotics may primarily benefit COVID-19 patients by positively influencing their innate and adaptive immune responses. The potential advantages of probiotic administration include changes in the numbers and functioning of regulatory cells, enhancement of IgA production for improved mucosal immunity, promotion of phagocytosis and macrophage formation, and the stimulation of dendritic cell maturation. These probiotic effects are likely to have an impact on reducing systemic inflammation. As the relationship between the gut and lungs becomes increasingly apparent, further research should be conducted to explore the potential role of probiotics in mitigating the effects of COVID-19. The research should investigate whether probiotics directly interact with the lungs or exert immunomodulatory effects to reduce systemic inflammation. Given the variability among probiotics, it is essential to differentiate and identify the specific capabilities of different strains of probiotic bacteria when considering their potential use in managing COVID-19 and associated comorbidities. This level of specificity will enable the development of a more targeted and tailored approach. Furthermore, the molecular mechanisms of probiotics could offer new insights into how they help fight SARS-CoV-2 infection. With advancements in bioinformatics and computational studies, it is now possible to uncover the molecular actions of probiotics against SARS-CoV-2. Currently available data on probiotics, human microbiota, health profiles, and diet serve as valuable resources for research related to probiotics and viruses, including SARS-CoV-2. Researches can be further enhanced by employing computational approaches such as the microbiome-driven and ensemble-driven docking methods. Therefore, integrating probiotic data with existing computational tools could offer significant advantages to ongoing COVID-19 research.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zolnikova O, Komkova I, Potskherashvili N, Trukhmanov A, Ivashkin V. Application of probiotics for acute respiratory tract infections. Italian Journal of Medicine. 2018;12(1):32–38. Available:https://doi.org/10.4081/itjm.2018.931
2. Chaudhary A, Saharan BS. Probiotic properties of *Lactobacillus plantarum*. Journal of Pure and Applied Microbiology. 2019;13(2):933-949. Available:https://microbiologyjournal.org/probiotic-properties-of-lactobacillus-plantarum/
3. Heymann DL, Shindo N. WHO scientific and technical advisory group for infectious hazards. COVID-19: what is next for public health?. Lancet (London, England). 2020;395(10224):542–545. Available:https://doi.org/10.1016/S0140-6736(20)30374-3
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China novel coronavirus investigating and research team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020; 382(8):727-733. DOI: 10.1056/NEJMoa2001017 Epub. PMID: 31978945; PMCID: PMC7092803.
5. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus disease 2019 (COVID-19), A Perspective from China. Radiology. 2020;296(2):E15- E25. DOI: 10.1148/radiol.2020200490 Epub 2020 Feb 21. PMID: 32083985; PMCID: PMC7233368.
6. Malik YA. Properties of coronavirus and SARS-CoV-2. The Malaysian Journal of Pathology. 2020;42(1):3–11. Available:https://pubmed.ncbi.nlm.nih.gov/32342926/

7. Choudhury A, Mukherjee S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. Journal of Medical Virology. 2020;92(10): 2105–2113.
Available:https://doi.org/10.1002/jmv.25987
8. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8.
Available:https://doi.org/10.1016/j.cell.2020.02.052.
9. World Health Organization (WHO). Coronavirus disease (COVID-19) Pandemic; 2020.
Available:https://www.who.int/emergencies/diseases/novel-coronavirus-2019
10. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med. 2020;35(5):1545-1549.
DOI: 10.1007/s11606-020-05762-w
Epub 2020 Mar 4. PMID: 32133578; PMCID: PMC7088708.
11. Xie M, Chen Q. Insight into 2019 novel coronavirus - An updated interim review and lessons from SARS-CoV and MERS-CoV. International journal of infectious diseases: IJID: Official publication of the International Society for Infectious Diseases. 2020;94:119–124.
Available:https://doi.org/10.1016/j.ijid.2020.03.071
12. Hill C, Guarner F, Reid G, et al. The international scientific association for probiotics and *Prebiotics consensus* statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11: 506–514.
Available:https://doi.org/10.1038/nrgastro.2014.66
13. López-Moreno A, Aguilera M. Probiotics dietary supplementation for modulating endocrine and fertility microbiota dysbiosis. Nutrients. 2020;12:757.
Available:https://doi.org/10.3390/nu12030757
14. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics mechanism of action on immune cells and beneficial effects on human health. Cells. 2023;12(1):184.
Available:https://doi.org/10.3390/cells12010184
15. Nair A, Chattopadhyay D, Saha B. Plant-derived immunomodulators. In: New Look to Phytomedicine. Elsevier. 2019;435-499.
Available:https://www.sciencedirect.com/science/article/abs/pii/B978012814619400018 5
16. Dargahi N, Johnson J, Apostolopoulos V. *Streptococcus thermophilus* alters the expression of genes associated with innate and adaptive immunity in human peripheral blood mononuclear cells. PLoS ONE. 2020;15:e0228531,
Available:https://doi.org/10.1371/journal.pone.0228531.
17. Liu J, Zhang X, Cheng Y, et al. Dendritic cell migration in inflammation and immunity. Cell Mol Immunol. 2021;18: 2461–2471.
Available:https://doi.org/10.1038/s41423-021-00726-4
18. Fu L, Song J, Wang C, Fu S, Wang Y. Bifidobacterium infantis potentially alleviates shrimp tropomyosin-induced allergy by tolerogenic dendritic cell dependent induction of regulatory T cells and alterations in gut microbiota. Front. Immunol. 2017;8:1536,
Available:https://doi.org/10.3389/fimmu.2017.01536.
19. Li D, Wu M. Pattern recognition receptors in health and diseases. Sig Transduct Target Ther. 2021;6:291.
Available:https://doi.org/10.1038/s41392-021-00687-0
20. Balzaretti S, Taverniti V, Guglielmetti S, Fiore W, Minuzzo M, Ngo HN, et al. A novel rhamnose-rich hetero-exopolysaccharide isolated from *Lactobacillus paracasei* DG activates THP-1 Human Monocytic Cells. Applied and Environmental Microbiology. 2017;83(3): e02702-16.
Available:https://doi.org/10.1128/AEM.02702-16
21. Zendeboodi F, Khorshidian N, Mortazavian AM, G da Cruz A. Probiotic: Conceptualisation from a new approach. Current Opinion in Food Science. 2020; 32:103-123.
Available:https://www.sciencedirect.com/science/article/abs/pii/S221479932030028X
22. Singh K, Rao A. Probiotics: A potential immunomodulator in COVID-19 infection

management. Nutrition research (New York, N.Y.). 2021;87:1–12.
Available:https://doi.org/10.1016/j.nutres.2020.12.014

23. Jounai K, Sugimura T, Ohshio K. Oral administration of *Lactococcuslactis subsp.* lactis JCM5805 enhances lung immune response resulting in protection from murine parainfluenza virus infection. PLoS One. 2015;10(3): e0119055.
Available:https://doi.org/10.1371/journal.pone.0119055.

24. Al Kassaa I, Hober D, Hamze M, Chihib NE, Drider D. Antiviral potential of lactic acid bacteria and their bacteriocins. Probiot Antimicrob Protein. 2014;6:177-185.
Available:https://doi.org/10.1007/s12602-014-9162-6

25. Song JA, Kim HJ, Hong SK, Lee DH, Lee SW, Song CS, et al. Oral intake of Lactobacillus rhamnosus M21 enhances the survival rate of mice lethally infected with influenza virus. J Microbiol Immunol Infect. 2016;49:16-23.
Available:https://doi.org/10. 1016/j.jmii.2014.07.011

26. Kokubo T, Komano Y, Tsuji R, Fujiwara D, Fujii T, Kanauchi O. The effects of plasmacytoid dendritic cell-stimulative lactic acid bacteria, Lactococcus lactis strain plasma, on exercise-induced fatigue and recovery via immunomodulatory action. Int J Sport Nutr Exerc Metab. 2019; 1-5.
Available:https://doi.org/10.1123/ijsnem.2018-0377

27. Ahrén I,L Berggren A, Teixeira C. Evaluation of the efficacy of *Lactobacillus plantarum* HEAL9 and Lactobacillus paracasei 8700:2 on aspects of common cold infections in children attending day care: A randomised, double-blind, placebo-controlled clinical study. Eur. J. Nutr. 2020; 59(1):409-417.
Available:https://doi.org/10.1007/s00394-019-02137-8.

28. Arai S Iwabuchi N, Takahashi S. Orally administered heat-killed *Lactobacillus paracasei* MCC1849 enhances antigen-specific IgA secretion and induces follicular helper T cells in mice. PLoS One. 2018;13(6):e0199018.
Available:https://doi.org/10.1371/journal.pone.0199018

29. Gutierrez-Castrellon P, Lopez-Velazquez G, Diaz-Garcia L. Diarrhea in preschool children and *Lactobacillus reuteri*: A randomized controlled trial. Pediatrics. 2014;133(4):e904-909.
Available:https://doi.org/10.1542/peds.2013- 0652.

30. Karen M, Yuksel O, Akyürek N. Probiotic agent Saccharomycesboulardii reduces the incidence of lung injury in acute necrotizing pancreatitis induced rats. J. Surg. Res. 2010;160(1):139-144.
Available:https://doi. org/10.1016/j.jss.2009.02.008

31. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?. Journal of Hypertension. 2020;38(5):781–782.
Available:https://doi.org/10.1097/HJH.0000000000002450

32. Fernández-Fernández FJ. COVID-19, hypertension and angiotensin receptor-blocking drugs. Journal of Hypertension. 2020;38(6):1191.
Available:https://doi.org/10.1097/HJH.0000000000002468

33. Liu MY, Zheng B, Zhang Y, Li JP. Role and mechanism of angiotensin-converting enzyme 2 in acute lung injury in coronavirus disease 2019. Chronic Diseases and Translational Medicine. 2020;6(2):98–105.
Available:https://doi.org/10.1016/j.cdtm.2020.05.003

34. Antony MA, Patel S, Verma V, Kant R. The role of gut microbiome supplementation in COVID-19 Management. Cureus. 2023; 15(10):e46960. A vailable:https://doi.org/10.7759/cureus.46960

35. Brahma S, Naik A, Lordan R. Probiotics: A gut response to the COVID-19 pandemic but what does the evidence show?. Clinical nutrition ESPEN. 2022;51:17–27.
Available:https://doi.org/10.1016/j.clnesp.2022.08.023

36. Jabczyk M, Justyna N, Bartosz H, Zubelewicz-Szkodzińska B. Diet, probiotics and their impact on the gut microbiota during the COVID-19 Pandemic. Nutrients. 2021;13(9):3172.
Available:https://doi.org/10.3390/nu13093172

37. Wahab S, Almaghaslah D, Mahmood SE, Ahmad MF, Alsayegh AA, Abu Haddash

YM, et al. Pharmacological Efficacy of Probiotics in Respiratory Viral Infections: A Comprehensive Review. Journal of Personalized Medicine. 2022;12(8):1292.
Available:https://doi.org/10.3390/jpm12081292

38. Mitra AK, Asala AF, Malone S, Mridha MK. Effects of probiotics in adults with gastroenteritis: A Systematic Review and Meta-Analysis of Clinical Trials. Diseases (Basel, Switzerland). 20231;1(4):138.
Available:https://doi.org/10.3390/diseases11040138

39. Ahrén IL, Hillman M, Nordström EA, Larsson N, Niskanen TM. Fewer Community-Acquired Colds with Daily Consumption of *Lactiplantibacillus plantarum* HEAL9 and *Lacticaseibacillus paracasei* 8700:2. A Randomized, Placebo-Controlled Clinical Trial. The Journal of Nutrition. 2021;151(1):214–222.
Available:https://doi.org/10.1093/jn/nxaa353

40. 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. Journal of Dairy Science. 2019;102(6): 4783–4797.
Available:https://doi.org/10.3168/jds.2018-16103

41. Davidson LE, Fiorino AM, Snydman DR, Hibberd PL. Lactobacillus GG as an immune adjuvant for live-attenuated influenza vaccine in healthy adults: A randomized double-blind placebo-controlled trial. European Journal of Clinical Nutrition. 2011;65(4):501–507.
Available:https://doi.org/10.1038/ejcn.2010.289

42. Fonollá J, Gracián C, Maldonado-Lobón JA, Romero C, Bédmar A, Carrillo JC, et al. Effects of Lactobacillus coryniformis K8 CECT5711 on the immune response to influenza vaccination and the assessment of common respiratory symptoms in elderly subjects: A randomized controlled trial. European Journal of Nutrition. 2019;58(1): 83–90.
Available:https://doi.org/10.1007/s00394-017-1573-1

43. Langkamp-Henken B, Rowe CC, Ford AL, Christman MC, Nieves C, Jr, Khouri L, et al. Bifidobacterium bifidum R0071 results in a greater proportion of healthy days and a lower percentage of academically stressed students reporting a day of cold/flu: A randomised, double-blind, placebo-controlled study. The British Journal of Nutrition. 2015;113(3): 426– 434.
Available:https://doi.org/10.1017/S0007114514003997

44. Namba K, Hatano M, Yaeshima T, Takase M, Suzuki K. Effects of Bifidobacterium longum BB536 administration on influenza infection, influenza vaccine antibody titer, and cell-mediated immunity in the elderly. Bioscience, Biotechnology, and Biochemistry. 2010;74(5):939–945.
Available:https://doi.org/10.1271/bbb.90749

45. Fujiwara Y, Fukaya T, Matsumoto T, Tateda K, Yamaguchi K, Kohda N, Kohno S. Immunoprotective effects of oral intake of heat-killed *Lactobacillus pentosus* strain b240 in elderly adults: A randomised, double-blind, placebo-controlled trial. The British Journal of Nutrition. 2013;109(10): 1856–1865.
Available:https://doi.org/10.1017/S0007114512003753

46. Sugimura T, Takahashi H, Jounai K, Ohshio K, Kanayama M, Tazumi K, et al. Effects of oral intake of plasmacytoid dendritic cells-stimulative lactic acid bacterial strain on pathogenesis of influenza-like illness and immunological response to influenza virus. The British Journal of Nutrition. 2015;114(5): 727–733.
Available:https://doi.org/10.1017/S0007114515002408

47. Turner RB, Woodfolk JA, Borish L, Steinke JW, Patrie JT, Muehling LM, et al. Effect of probiotic on innate inflammatory response and viral shedding in experimental rhinovirus infection - a randomised controlled trial. Beneficial Microbes. 2017; 8(2):207–215.
Available:https://doi.org/10.3920/BM2016.0160

48. Waki N, Matsumoto M, Fukui Y, Suganuma H. Effects of probiotic *Lactobacillus brevis* KB290 on incidence of influenza infection among schoolchildren: An open-label pilot study. Letters in Applied Microbiology. 2014;59(6):565–571.
Available:https://doi.org/10.1111/lam.12340

49. Wang B, Hylwka T, Smieja M, Surrette M, Bowdish DME, Loeb M. Probiotics to prevent respiratory infections in Nursing Homes: A Pilot Randomized Controlled Trial. Journal of the American Geriatrics Society. 2018;66(7): 1346–1352.
Available:https://doi.org/10.1111/jgs.15396

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/121274