Immunol Genet J, Vol. 4, No. 2, June 2021, pp.67-75 **DOI: https://doi.org/10.18502/igj.v4i2.9982**

Review Article

The Immunomodulatory Effects of Probiotics on Respiratory Viral Infections: A Hint for COVID-19 Prophylaxis?

Hamid Ahanchian[1,2*], Rana Tafrishi[3]

[1] *Child Health Research Centre, University of Queensland, South Brisbane, Australia*
[2] *Allergy Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3] *Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

Received: 08 March 2021; Accepted: 10 April 2021

Abstract

The most common human illness is upper respiratory tract infection. It causes a high rate of absenteeism from school and work and decreases efficiency and productivity of individuals in daily life. People with chronic diseases such as asthma, preterm infants and the elderly are more susceptible to viral respiratory tract infections. Preliminary studies have shown that probiotics reduce allergic diseases and asthma and strengthen the immune system, reducing viral infections. This mini-review looks at how probiotics and prebiotics affect viral respiratory tract infection. Functional foods containing well-defined probiotic strains, such as probiotic milk or yogurt can reduce the risk of catching a cold. These probiotic strains represent an easy, healthy, reliable and accessible method for preventing respiratory infections, especially in developing countries. More research is needed to determine the role of probiotics and prebiotics in treating and preventing RTIs and determining whether any susceptible subgroups of respiratory diseases exist and how these subgroups benefit from probiotic supplementation.

Keywords: Probiotics; Prebiotics; Viral Respiratory Tract Infections; Covid-19

***Corresponding Author:** Hamid Ahanchian, MD
Child Health Research Centre, University of Queensland, South Brisbane, Australia; Allergy Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: ahanchianh@mums.ac.ir

How to cite this article
Ahanchian H, Tafrishi R. The Immunomodulatory Effects of Probiotics on Respiratory Viral Infections: A Hint for COVID-19 Prophylaxis?. Immunology and Genetics Journal, 2021; 4(2): 67-75.
DOI: https://doi.org/10.18502/igj.v4i2.9982

Introduction

The most common human illness is Upper Respiratory Tract Infection (URTI). It causes a high rate of absenteeism from school and work and decreases efficiency and productivity. According to data obtained from the United States, 12 percent of adults and 33 percent of children with URTI visit a doctor. In 1997, the direct medical costs of the common cold (such as doctor visits, secondary infections and medications) were estimated to be $17 billion. The annual indirect costs of loss of jobdue to illness or taking care of an ill child were estimated to be $25 billion. In addition to the financial losses, billions of dollars are spent on unproven treatments (1-3). For respiratory tract infections, probiotics in the US population could save costs and decrease antibiotic prescriptions (4).

Over 200 different types of viruses cause URTI. Human rhinoviruses (HRV) are the most common viruses which account for between 24 and 52 percent of clinical cases. Influenza viruses, respiratory syncytial virus (RSV) and adenoviruses are common causes of upper and lower respiratory tract infections. Other viruses, such as parainfluenza and coronaviruses, can cause respiratory illnesses ranging from mild upper respiratory infections to pneumonia. Several new viruses which are linked to respiratory diseases, have recently been identified, including human bocavirus, human metapneumovirus and new coronaviruses (1, 5).

HRVs have long been linked to URTIs, otitis mediaand sinusitis. In recent years, the widespread use of PCR assays for respiratory virus detection in clinical laboratories has aided the identification of HRV as a lower respiratory tract pathogen, especially in asthmatics, infants, the elderly and immunocompromised individuals (6, 7).

The role of the gastrointestinal tract microbiota in the generation of mucosal immune responses and the tolerance has been well established, but its association with respiratory pathology is a new field of investigation. Probiotics have been shown in some studies to be effective in preventing colds (8). Furthermore, these agents could decrease the sick-day of respiratory tract infections in the US population (4). According to a Cochrane Review of the 14 randomized controlled trials which represented no variations in the mean length of an episode or a rise in adverse effects of probiotics, probiotics are better than placebos in minimizing the number of episodes of acute URTIs and reducing antibiotic use. (9). Through the modulation of intestinal microbiota and enhancement of mucosal immunity, fortification with probioticsand functional foods can provide one feasible intervention to reduce the burden of common childhood morbidities and improve quality of life (10, 11).

On the other hand, antibiotics negatively impact the immune system, resulting in ineffective virus-specific CD4+ and CD8+ T cell responses in URTI patients (12). Individuals with chronic diseases such as asthma, preterm infants and the elderly are more susceptible to viral respiratory tract infections. This mini-review looks at how probiotics and prebiotics affect viral respiratory tract infection.

Viral infection

The most common cause of morbidity in infants is an infectious disease. It's worth mentioning that 12.9 million babies are born each year prematurely, accounting for 11% of all births. RTIs are one of the leading causes of death and morbidity in children, particularly in countries where the under-five childhood mortality rate is 50 per 1,000 (13). Modulating the gut microbiota with specific prebiotics, probiotics or both may be a cost-effective tool in the fight against RTIs, especially in developing countries (14, 15).

URTI is the leading cause of asthma exacerbations in children and adults in autumn and a significant risk factor for the hospital admission. Asthmatic patients are worried about acute asthma exacerbations caused by a common cold, and they want to know if they can reduce their risk during the winter viral season. The most common cause of asthma exacerbations in children (80-85 percent) is viral respiratory infections, a significant risk factor for hospitalization. Human rhinoviruses (HRVs) are the most common viral agents. According to epidemiological studies, Lower Respiratory Tract Infection (LRTI) caused by HRV (Odds ratio = 10) has been linked to an increased risk of asthma, even more so than RSV (Odds ratio = 2.6). (16) Current treatments for the prevention and treatment of virus-induced asthma exacerbations are ineffectiveand necessitate the

development of innovative alternative therapies. Probiotics, prebiotics and symbiotics are used in many clinical trials to prevent respiratory infections in asthmatic patients. Probiotics are thought to interact with pathogens, improve the barrier role of the respiratory epithelium, and have immunostimulatory effects by enhancing cellular immunity through the increased natural killer cell and macrophage activity in the airways (17, 18).

Arora et al. reviewed recent research about the effect of probiotic consumption in preventing viral respiratory infection. They found that probiotics could provide some elements to enhance the immune response. Moreover, they revealed that probiotics demonstrate direct and indirect mechanisms in exterminating enteric viruses. The efficiency of probiotics in the gut ecosystem is more applicable (19).

COVID-19 and probiotics

COVID-19 outbreak was started in Wuhan and spread rapidly around the world. Nevertheless, no antiviral drugs were approved for the treatment of COVID-19. Moreover, consumption of probiotics as safest, most affordable and easy to consume, which can enhance the immune system, and establish effective means to protect humans from viral infections are a bit challenging. Salman et al. reviewed some research on COVID-19and probiotics. They declared that using probiotics is inexpensive, safe and cost-effective in preventing viral infections (20). Another review showed the importance of probiotics in boosting the immune system against COVID-19. Probiotics decrease the severity of inflammation in the GI tract and respiratory system. It can also increase IgA expressing B cells in gut and lymph nodes associated with surging T follicular helper cells and IL-23–expressing dendritic cells (21). A recent research survey which was done among some COVID-19 patients reported an intestine microbiota imbalance, particularly a fall in probiotics such as Lactobacillus and Bifidobacterium, resulting from direct effects of COVID infection or antibiotic drugs, which may result in secondary infection. Modulators can make strides in the gastrointestinal symptoms of patients. It can decrease water within the feces, make strides in fecal character and defecation frequency, and diminish diarrhea by hindering intestinal mucosal atrophy. (22). Liu et al. revealed that modified Lactobacillus Plantarum could act as an effective antiviral agent against coronavirus infection in the intestinal epithelial cell (23, 24).

The immunomodulatory effects of probiotics are strain-dependent. Many trials confirmed that Lactobacillus Rhamnosus GG, Lactobacillus Plantarum, Lactobacillus Casei and Paracasei and some strains of Bifidobacterium could have preventive effects against respiratory infections. David Baud and colleagues provided a list of probiotic products with documentation in human studies that may have relevance to reducing the burden of the coronavirus pandemic (25). We previously showed that symbiotic Lactocare® could lessen the episodes of viral respiratory infections in asthmatic children (26). Interestingly, some strains of probiotics in Symbiotic Lactocare® are similar to Strains suggested by David Baud (25). We recently finished a clinical trial using symbiotic Lactocare® for the prevention of SARS-Cov-19 infection in high-risk hospital staff. This study showed that although 3 participants in the placebo group got SARS-COV2 infection,in comparison with the symbiotic group that no participants were infected, the difference was not statistically significant (27).

Mechanism of action

Certain probiotic lactic acid bacteria strains can exert their beneficial effect on the host through their immunomodulatory activity. Immunobiotics have been used to develop functional foods to stimulate mucosal immunity to protect other mucosal sites distant from the gut. The proposed mechanisms include the production of type I IFNs, the activity of NK cells, the generation of Th1 responses, the production of specific antibodies and the regulation of inflammatory lung injury (28, 29).

The preventive effects on the respiratory airway immunity induced by CRL 1505 suggested that if the target of probiotic administration is to prevent recurrent URTIs, an appropriate strain of L. rhamnosus should be selected (30). Zelaya et al. revealed that the protective treatment with the probiotic bacteria helpfully modifies the fine-tune equilibrium between dispelling respiratory viruses (RSV and influenza virus) and controlling

immune-coagulative reactions in the lung, permitting normal lung function to be sustained in the face of a viral outbreak. They also showed a crucial role for IL-10 in the immune protection induced by L. rhamnosus CRL 1505 during respiratory viral infections (29). Furthermore, studies determined that L. rhamnosus CRL 1505 is competent to enlarge the number of CD3+CD4+IFN-γ+ T cells in the gut. It prompted a mobilization of these cells into the respiratory mucosa and enhanced the production of IFN-γ and the activity of lung antigen-presenting cells (31).

RSV vulnerable infants present characteristics of Th2 responses, and on the whole, a Th2 immune reaction is preferred during RSV infection, especially in younger hosts (32). Chiba et al. demonstrated that L. rhamnosus CRL 1505 significantly diminishes viral lung loads and tissue injuries after the challenge with RSV through its competence to usefully moderate pro-inflammatory IL-10 and Th1/Th2 balances in the respiratory tract (33).

L. rhamnosus CRL 1505 administered CD3+CD4+IFN-+ T cells orally from the gut are mobilized into the respiratory mucosa by rhamnosus CRL 1505, which improves local IFN-γ development (31). Intranasally administered probiotics have also been shown to protect against respiratory virus infection by inducing innate immune responses in the respiratory epithelium (34). L. sublingual Rhamnosus enhanced mucosal secretory IgA development, T and NK cell function and lung IL-12 levels to protect against influenza virus infection (35). Lactobacilli and bifidobacteria strains defend against respiratory virus infections by stimulating the development of virus-specific immunoglobulins in respiratory secretions and serum (36).

Prebiotics are nondigestible yet fermentable foods that benefit the host by promoting the growth and activity of one or a small number of bacteria species in the colon. Symbiotics which are a combination of probiotics and prebiotics, are designed to improve proven probiotics' survival and activity in vivo while also stimulating native bifidobacteria and lactobacilli (37). Prebiotics modulate systemic immune function, but the exact mechanism is unclear. Modulating Th1/Th2 responses in the lungs can influence host innate and T-cell responses during a respiratory viral infection. Prebiotics can help to improve the gut's natural immune system. Numerous studies report a boost in intestinal mucosal surface IgA but not serum IgA, IgG and IgM concentrations. Changes in the microbiota caused by dietary oligosaccharides increased viral clearance and systemic Th1 responses in studies (38).

Clinical trial in pediatrics

Premature infants ignore initial maturation signals due to their immature immune system and disrupted production of their gut microbiota. LA et al., in a randomized trial, revealed that preterm infants who were treated orally with a liquid probiotic based on E. faecium L3 in a dose of 0.5 ml (5 × 103 CFU) 3 times a day for 14 days had a significant decline of the frequency of infectious complications compared with control group patients (20.7 percent against 53.9 percent) (39).

In a recent randomized, double-blind and placebo-controlled trial, 94 preterm infants were assigned to take oral prebiotics (galactooligosaccharides and polydextrose mixture, 1:1), a probiotic (L. rhamnosus GG, ATCC 53103), or placebo between days 3 and 60 of their life. A significantly lower occurrence of RTIs was perceived in infants receiving prebiotics or probiotics than in those receiving placebo. In addition, the frequency of rhinovirus-induced episodes, which constituted 80 percent of all RTI episodes, was substantially lower in the prebiotic and probiotic groups than in the placebo group (14).

Infants are predisposed to infections as their immune system is not fully developed (40). Infections are considered one of the principal causes of death in this age group (41). In a randomized trial, infants necessitating formula before two months age were enlisted, and formula supplemented with the probiotics L. rhamnosus GG and Bifidobacterium lactis Bb-12 or placebo was administered daily until the age of 12 months. Antibiotics are recommended for 10 out of 32 (31 %) infants receiving probiotics and 24 out of 40 (60 %) infants receiving placebo. During the first year of life, 9 out of 32 (28 %) infants receiving probiotics and 55% of infants receiving placebo confronted recurrent respiratory infections (15).

In a further RCT, 109 newborn infants were allocated randomly to receive Bifidobacterium

animalis ssp. lactis BB-12 or placebo up to 8 months. The infants receiving BB-12 were reported to have experienced fewer respiratory infections than the control infants (42). In healthy newborns, an amalgamation of L. rhamnosus GG and B. rhamnosus lactis Bb12 decreased the frequency of chronic RTIs but not acute otitis media (15).

In a randomized controlled trial, Hojsak et al. gave Lactobacillus GG or a placebo to 281 children who attended daycare centers. Children in the LGG group had a significantly lower risk of URTIs, a considerably lower risk of RTIs lasting more than three days, and fewer days with respiratory symptoms than the placebo group (43). Long-term ingestion of probiotic milk containing Lactobacillus GG resulted in a 17 percent reduction in the number of children suffering from respiratory infections with complications and a 19 percent reduction in antibiotic treatments for respiratory infection in the Lactobacillus community compared to the placebo group in a related study (44). In another analysis, L.rhamnosus GG and the control groups had no significant differences in respiratory symptom episodes (45).

A meta-analysis of RCTs was conducted to look into the function of L. rhamnosus GG in preventing respiratory infections in children, which was found that L. rhamnosus can decrease the incidence of upper respiratory infection and the use of antibiotics in children. L. rhamnosus GG can reduce the risk of URTIs, the occurrence of acute otitis media and the use of antibiotic. There were no notable variations between the L. rhamnosus GG and the control groups in lower RTIs (23).

Recurrent RTIs in children were reduced in an amalgamation of L. rhamnosus GG, L. rhamnosus LC 705, B. breve Bb99 and P. freudenreichii ssp. shermanii JS (46). In healthy children, a combination of L. Bifidobacterium acidophilus and B. bifidum shortened the period of acute RTI symptoms and absence from school (23).

According to some research, using a probiotic mixture may be more successful, though the effectiveness of probiotic mixtures may be hampered by inhibitory effects between probiotic strains (47). For example, in a study, Lina et al. discovered that a mix of 12 bacteria, including Lactobacillus, Bifidobacterium, Streptococcus and Enterococcus, could not reduce the amount of RTIs. Some interactions between probiotics may decrease their effect of them (48).

The authors concluded from a pilot study that laser acupuncture combined with probiotics (a suspension of E. faecalis) has a beneficial clinical impact on bronchial hyperreactivity in school-aged children with intermittent or mild chronic asthma, which may help prevent acute respiratory exacerbations (49). In a study, ninety-seven-month-old infants with atopic dermatitis were randomized to receive Breve M-16V and a galacto/fructo-oligosaccharide mixture for 12 weeks or the same formula was implemented without symbiotics. After a year, the symbiotic group had substantially less "frequent wheezing" and "wheezing or loud coughing apart from colds" than the placebo group. Children in the symbiotic community had begun taking asthma drugs at a lower rate than those in the placebo group (50).

Ahanchian et al., in a double-blind clinical trial on 72 children with mild persistent asthma, showed viral respiratory infections were significantly upper in the placebo group than in the symbiotic Lactocare® group during the first month of use, not during the second month. Salbutamol consumption was significantly lower in the symbiotic Lactocare® group. Infection duration also was meaningly lesser in the symbiotic group (26).

Clinical trial in adult and elderly

During two winter/spring periods, 479 healthy adults (ages 18-67) were supplemented daily with vitamins and minerals with or without probiotic bacteria (Lactobacillus gasseri, Bifidobacterium longum, Bifidum) for at least three months. The probiotic-treated group had a lower total symptom score, shorter common cold episodes and fewer days with fever during an episode than the control group (51). Another study found that taking Lactobacillus Plantarum and Lactobacillus paracasei reduced the risk of catching a cold from 67 percent in the control group to 55 percent in the probiotic group. Moreover, during the 12 weeks, the number of days with common cold symptoms was significantly ($p < 0.05$) reduced from 8.6 days in the control group to 6.2 days in the probiotic group (52). In another study, after

influenza virus vaccination, fermentum reduced the number of RTIs and increased antigen-specific IgA formation (53). Besides, a combination of L. rhamnosus GG and B. animalis decreased the duration and severity of upper respiratory infections (54).

In the case of Finnish conscripts who were given a daily chewable probiotic tablet containing L. acidophilus, the presence of picornaviruses reduced after three months. L. rhamnosus GG and B. animalis ssp. Lactis Probiotics, whether Lactis or a control tablet, did not affect the occurrence of nasopharyngeal viruses. However, after three months, probiotics reduced the presence of picornaviruses, suggesting that probiotics may play a role in preventing common cold viruses (55). In male runners, L. fermentum decreased the duration of RTI symptoms but not the number of RTIs or the severity of symptoms (56). Participants who received a probiotic intervention had fewer days of illness per person, shorter illness episodes for almost a day and fewer days absent from work than those who received a placebo, according to a recent systematic review by King et al. (57). In some studies, probiotics were ineffective in preventing the occurrence, duration, or severity of symptoms in adults (51, 58-60). Van Puyenbroeck et al. discovered that L. casei Shirota or a combination of L. rhamnosus GG, L. rhamnosus, B. breve and P. freudenreichii was unaffected by the number of RTIs or the length of RTI symptoms (61).

Makino et al. discovered that eating yogurt fermented with Lactobacillus rhamnosus (L. in older adults, bulgaricus OLL1073R-1) increased natural killer cell activity and decreased the chance of catching a cold (by around 2.6 times) (62). To investigate both URTIs and rhinopharyngitis, a multicentric, double-blind study involving 1072 volunteers randomized to consume dairy products containing the probiotic strain Lactobacillus casei or to consume dairy products without probiotics for three months found substantial reductions in both episode and cumulative durations (63).

In a multicenter study in Japan, 154 older adults were given fermented milk containing L. casei strain Shirota (LcS) and placebo drinks as control drinks. The researchers concluded that fermented milk containing LCS decreases the time of acute URTIs (64).

A meta-analysis survey of Fangyan Wang et al. systematically examined the effect of probiotics and prebiotics on respiratory tract infection. They showed that these agents significantly decreased the mortality of respiratory tract infection and viral load. These agents enhance innate and adaptive immune systems to prevent viral infection. They showed an increment in interferon (IFN)-α, IFN-γ, and interleukin (IL)-12, IL-1β; while the level of TNF-α and IL-6 were decreased (65).

Conclusion

Probiotics and symbiotics have been used successfully to treat various medical issues, and an increasing number of clinical trials have shown their efficacy in preventing and treating respiratory infections. Clinical trials in humans have revealed promising results showing that particular probiotic strains can minimize the duration or frequency of respiratory infections. However, the effects of probiotics on particular viruses have only been studied in a few clinical trials.

Functional foods containing well-defined probiotic strains, such as probiotic milk or yogurt, can reduce the risk of catching a cold and represent an easy, healthy, reliable and accessible method for preventing respiratory infections, especially in developing countries. More research is needed to determine the role of probiotics and prebiotics in treating and preventing RTIs and determining whether any susceptible subgroups of respiratory diseases exist and how these subgroups benefit from probiotic supplementation.

Ethical considerations

Not applicable.

Conflict of interest

The authors declare that they have no conflicts of interest.

Data availability statement

The data sets used or analyzed during the current study are available from the corresponding authors per request.

References

1. Allan G M,Arroll B. Prevention and treatment of the common cold: making sense of the evidence.

CMAJ. 2014;186(3):190-9.
2. Gern J E. The ABCs of rhinoviruses, wheezing, and asthma. J Virol. 2010;84(15):7418-26.
3. Rerksuppaphol S,Rerksuppaphol L. Randomized controlled trial of probiotics to reduce common cold in schoolchildren. Pediatr Int. 2012;54(5):682-7.
4. Lenoir-Wijnkoop I, Merenstein D, Korchagina D, Broholm C, Sanders M E,Tancredi D. Probiotics Reduce Health Care Cost and Societal Impact of Flu-Like Respiratory Tract Infections in the USA: An Economic Modeling Study. Front Pharmacol. 2019;10:980.
5. Lehtoranta L, Pitkäranta A,Korpela R. Probiotics in respiratory virus infections. Eur J Clin Microbiol Infect Dis. 2014;33(8):1289-302.
6. Goodall E C, Granados A C, Luinstra K, Pullenayegum E, Coleman B L, Loeb M, et al. Vitamin D3 and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial. BMC Infect Dis. 2014;14:273.
7. Jacobs S E, Lamson D M, St George K,Walsh T J. Human rhinoviruses. Clin Microbiol Rev. 2013;26(1):135-62.
8. Tabasi M, Ashrafian F, Khezerloo J K, Eshghjoo S, Behrouzi A, Javadinia S A, et al. Changes in Gut Microbiota and Hormones After Bariatric Surgery: a Bench-to-Bedside Review. Obes Surg. 2019;29(5):1663-74.
9. Hao Q, Dong B R,Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015(2):Cd006895.
10. Heydarian F, Kianifar H R, Ahanchian H, Khakshure A, Seyedi J,Moshirian D. A comparison between traditional yogurt and probiotic yogurt in non-inflammatory acute gastroenteritis. Saudi Med J. 2010;31(3):280-3.
11. Jafari S A, Mehdizadeh-Hakkak A, Kianifar H R, Hebrani P, Ahanchian H,Abbasnejad E. Effects of probiotics on quality of life in children with cystic fibrosis; a randomized controlled trial. Iran J Pediatr. 2013;23(6):669-74.
12. Ichinohe T, Pang I K, Kumamoto Y, Peaper D R, Ho J H, Murray T S, et al. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc Natl Acad Sci U S A. 2011;108(13):5354-9.
13. UNICEF. The state of the world's children: Oxford University Press for UNICEF; 1996.
14. Luoto R, Ruuskanen O, Waris M, Kalliomäki M, Salminen S,Isolauri E. Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants: a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2014;133(2):405-13.
15. Rautava S, Salminen S,Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy--a randomised, double-blind, placebo-controlled study. Br J Nutr. 2009;101(11):1722-6.
16. Jackson D J, Gangnon R E, Evans M D, Roberg K A, Anderson E L, Pappas T E, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008;178(7):667-72.
17. Hales B J, Chai L Y, Elliot C E, Pearce L J, Zhang G, Heinrich T K, et al. Antibacterial antibody responses associated with the development of asthma in house dust mite-sensitised and non-sensitised children. Thorax. 2012;67(4):321-7.
18. Holt P G,Sly P D. Interaction between adaptive and innate immune pathways in the pathogenesis of atopic asthma: operation of a lung/bone marrow axis. Chest. 2011;139(5):1165-71.
19. Sundararaman A, Ray M, Ravindra P V,Halami P M. Role of probiotics to combat viral infections with emphasis on COVID-19. Appl Microbiol Biotechnol. 2020;104(19):8089-104.
20. Salman J A-S, Mahmood N N, Abdulsattar B O,Abid H A. The Effectiveness of Probiotics against Viral Infections: A Rapid Review with Focus on SARS-CoV-2 Infection. Open Access Maced J Med Sci. 2020;8(T1):496-508.
21. Gohil K, Samson R, Dastager S,Dharne M. Probiotics in the prophylaxis of COVID-19: something is better than nothing. 3 Biotech. 2021;11(1):1-1.
22. 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(1):147-57.
23. Liu S, Hu P, Du X, Zhou T,Pei X. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. Indian Pediatr. 2013;50(4):377-81.
24. Liu Y S, Liu Q, Jiang Y L, Yang W T, Huang H B, Shi C W, et al. Surface-Displayed Porcine IFN-λ3 in Lactobacillus plantarum Inhibits Porcine Enteric Coronavirus Infection of Porcine Intestinal Epithelial Cells. J Microbiol Biotechnol. 2020;30(4):515-25.
25. Baud D, Dimopoulou Agri V, Gibson G R, Reid G,Giannoni E. Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic. Front in public health. 2020;8:186-86.
26. Ahanchian H, Jafari S A, Ansari E, Ganji T, Kiani M A, Khalesi M, et al. A multi-strain Synbiotic may reduce viral respiratory infections in asthmatic children: a randomized controlled trial. Electron

Physician. 2016;8(9):2833-39.
27. Ahanchian H, Ranjbar A, Reihani H, Yazdi A, Jafari S, Kiani M, et al. Synbiotic for Prevention of SARS-Cov2 Infection in High Risk Hospital Staffs: A Randomized Controlled Trial. Open J Nurs 2021(11):281-90.
28. Farid R, Ahanchian H, Jabbari F,Moghiman T. Effect of a new synbiotic mixture on atopic dermatitis in children: a randomized-controlled trial. Iran J Pediatr. 2011;21(2):225-30.
29. Zelaya H, Tsukida K, Chiba E, Marranzino G, Alvarez S, Kitazawa H, et al. Immunobiotic lactobacilli reduce viral-associated pulmonary damage through the modulation of inflammation-coagulation interactions. Int Immunopharmacol. 2014;19(1):161-73.
30. Esposito S, Rigante D,Principi N. Do children's upper respiratory tract infections benefit from probiotics? BMC Infect Dis. 2014;14:194.
31. Villena J, Chiba E, Tomosada Y, Salva S, Marranzino G, Kitazawa H, et al. Orally administered Lactobacillus rhamnosus modulates the respiratory immune response triggered by the viral pathogen-associated molecular pattern poly(I:C). BMC Immunol. 2012;13:53.
32. Becker Y. Respiratory syncytial virus (RSV) evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines and IgE, markers of allergy—a review. Virus genes. 2006;33(2):235-52.
33. Chiba E, Tomosada Y, Vizoso-Pinto M G, Salva S, Takahashi T, Tsukida K, et al. Immunobiotic Lactobacillus rhamnosus improves resistance of infant mice against respiratory syncytial virus infection. Int Immunopharmacol. 2013;17(2):373-82.
34. Park M K, Ngo V, Kwon Y M, Lee Y T, Yoo S, Cho Y H, et al. Lactobacillus plantarum DK119 as a probiotic confers protection against influenza virus by modulating innate immunity. PLoS One. 2013;8(10):e75368.
35. Lee Y N, Youn H N, Kwon J H, Lee D H, Park J K, Yuk S S, et al. Sublingual administration of Lactobacillus rhamnosus affects respiratory immune responses and facilitates protection against influenza virus infection in mice. Antiviral Res. 2013;98(2):284-90.
36. Kobayashi N, Saito T, Uematsu T, Kishi K, Toba M, Kohda N, et al. Oral administration of heat-killed Lactobacillus pentosus strain b240 augments protection against influenza virus infection in mice. Int Immunopharmacol. 2011;11(2):199-203.
37. Quigley E M. Prebiotics and probiotics; modifying and mining the microbiota. Pharmacol Res. 2010;61(3):213-8.
38. Schijf M A, Kruijsen D, Bastiaans J, Coenjaerts F E, Garssen J, van Bleek G M, et al. Specific dietary oligosaccharides increase Th1 responses in a mouse respiratory syncytial virus infection model. J Virol. 2012;86(21):11472-82.
39. Lo Skiavo L A, Gonchar N V, Suvorov A N, Shabalov N P,Grigor'ev S G. [Value of probiotic in reducing frequency of infectious complications in premature infants]. Antibiot Khimioter. 2014;59(1-2):30-5.
40. Holt P,Jones C. The development of the immune system during pregnancy and early life. Allergy. 2000;55(8):688-97.
41. Organization W H. Children: improving survival and well-being. fact sheets [Internet]. 2020:1-5.
42. Taipale T, Pienihäkkinen K, Isolauri E, Larsen C, Brockmann E, Alanen P, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in infancy. Br J Nutr. 2011;105(3):409-16.
43. Hojsak I, Snovak N, Abdović S, Szajewska H, Misak Z,Kolacek S. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. Clin Nutr. 2010;29(3):312-6.
44. Hatakka K, Savilahti E, Pönkä A, Meurman J H, Poussa T, Näse L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. Bmj. 2001;322(7298):1327.
45. Kumpu M, Lehtoranta L, Roivainen M, Rönkkö E, Ziegler T, Söderlund-Venermo M, et al. The use of the probiotic Lactobacillus rhamnosus GG and viral findings in the nasopharynx of children attending day care. J Med Virol. 2013;85(9):1632-8.
46. Hatakka K, Blomgren K, Pohjavuori S, Kaijalainen T, Poussa T, Leinonen M, et al. Treatment of acute otitis media with probiotics in otitis-prone children-a double-blind, placebo-controlled randomised study. Clin Nutr. 2007;26(3):314-21.
47. Kianifar H, Ahanchian H, Grover Z, Jafari S, Noorbakhsh Z, Khakshour A, et al. Synbiotic in the management of infantile colic: a randomised controlled trial. J Paediatr Child Health. 2014;50(10):801-5.
48. Lin J S, Chiu Y H, Lin N T, Chu C H, Huang K C, Liao K W, et al. Different effects of probiotic species/strains on infections in preschool children: A double-blind, randomized, controlled study.

Vaccine. 2009;27(7):1073-9.
49. Stockert K, Schneider B, Porenta G, Rath R, Nissel H,Eichler I. Laser acupuncture and probiotics in school age children with asthma: a randomized, placebo-controlled pilot study of therapy guided by principles of Traditional Chinese Medicine. Pediatr Allergy Immunol. 2007;18(2):160-6.
50. van der Aa L B, van Aalderen W M, Heymans H S, Henk Sillevis Smitt J, Nauta A J, Knippels L M, et al. Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. Allergy. 2011;66(2):170-7.
51. de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. Clin Nutr. 2005;24(4):481-91.
52. Berggren A, Lazou Ahrén I, Larsson N,Önning G. Randomised, double-blind and placebo-controlled study using new probiotic lactobacilli for strengthening the body immune defence against viral infections. Eur J Nutr. 2011;50(3):203-10.
53. Olivares M, Díaz-Ropero M P, Sierra S, Lara-Villoslada F, Fonollá J, Navas M, et al. Oral intake of Lactobacillus fermentum CECT5716 enhances the effects of influenza vaccination. Nutrition. 2007;23(3):254-60.
54. Smith T J, Rigassio-Radler D, Denmark R, Haley T,Touger-Decker R. Effect of Lactobacillus rhamnosus LGG® and Bifidobacterium animalis ssp. lactis BB-12® on health-related quality of life in college students affected by upper respiratory infections. Br J Nutr. 2013;109(11):1999-2007.
55. Lehtoranta L, Kalima K, He L, Lappalainen M, Roivainen M, Närkiö M, et al. Specific probiotics and virological findings in symptomatic conscripts attending military service in Finland. J Clin Virol. 2014;60(3):276-81.
56. Cox A J, Pyne D B, Saunders P U,Fricker P A. Oral administration of the probiotic Lactobacillus fermentum VRI-003 and mucosal immunity in endurance athletes. Br J Sports Med. 2010;44(4): 222-6.
57. King S, Glanville J, Sanders M E, Fitzgerald A,Varley D. 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. 2014;112(1):41-54.
58. Gleeson M, Bishop N C, Oliveira M, McCauley T, Tauler P,Lawrence C. Effects of a Lactobacillus salivarius probiotic intervention on infection, cold symptom duration and severity, and mucosal immunity in endurance athletes. Int J Sport Nutr Exerc Metab. 2012;22(4):235-42.
59. Tiollier E, Chennaoui M, Gomez-Merino D, Drogou C, Filaire E,Guezennec C Y. Effect of a probiotics supplementation on respiratory infections and immune and hormonal parameters during intense military training. Mil Med. 2007;172(9):1006-11.
60. Winkler P, de Vrese M, Laue C,Schrezenmeir J. Effect of a dietary supplement containing probiotic bacteria plus vitamins and minerals on common cold infections and cellular immune parameters. Int J Clin Pharmacol Ther. 2005;43(7):318-26.
61. Van Puyenbroeck K, Hens N, Coenen S, Michiels B, Beunckens C, Molenberghs G, et al. Efficacy of daily intake of Lactobacillus casei Shirota on respiratory symptoms and influenza vaccination immune response: a randomized, double-blind, placebo-controlled trial in healthy elderly nursing home residents. Am J Clin Nutr. 2012;95(5):1165-71.
62. Makino S, Ikegami S, Kume A, Horiuchi H, Sasaki H,Orii N. Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1. Br J Nutr. 2010;104(7):998-1006.
63. Guillemard E, Tondu F, Lacoin F,Schrezenmeir J. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. Br J Nutr. 2010;103(1):58-68.
64. Fujita R, Iimuro S, Shinozaki T, Sakamaki K, Uemura Y, Takeuchi A, et al. Decreased duration of acute upper respiratory tract infections with daily intake of fermented milk: a multicenter, double-blinded, randomized comparative study in users of day care facilities for the elderly population. Am J Infect Control. 2013;41(12):1231-5.
65. Wang F, Pan B, Xu S, Xu Z, Zhang T, Zhang Q, et al. A meta-analysis reveals the effectiveness of probiotics and prebiotics against respiratory viral infection. Biosci Rep. 2021;41(3).