Probiotics: An Alternative Therapeutic Strategy For COVID-19

Belapurkar Pranoti¹ and Goyal Pragya²*

¹Department of Biosciences, Acropolis Institute, Mangliya Square, Indore, Madhya Pradesh, India.  
²Department of Biotechnology, IPS Academy, Indore, Madhya Pradesh, India.

http://dx.doi.org/10.13005/bbra/2853

(Received: 12 August 2020; accepted: 23 September 2020)

The COVID-19 pandemic has made the scientists today all around the globe to look for its specific prevention and treatment modalities. The disease presents itself as asymptomatic to mild to severe respiratory symptoms along with lesser common gastrointestinal symptoms of diarrhoea, nausea and vomiting. The situation worsens due to lack of precise treatment strategy. Healthcare system is being overwhelmed, emphasizing on the need to look for alternate supportive therapy which can not only enhance the immune status of people worldwide but at the same time, ensure better prognosis. The relationship between the gut microbiota and upper and lower respiratory tract viral infections are well studied. Oral administration of probiotic microorganisms of genera Lactobacillus, Bifidobacterium and Bacillus in mice suffering from influenza infection have shown increased TNFα, IFN-γ and NK cell responses along with production of anti-Influenza IgG. At the same time they have shown immunomodulation by producing anti-inflammatory cytokines as well as cytotoxic T-cells and T-suppressor cells. Hence, probiotic strains of genera Lactobacillus, Bifidobacterium and Bacillus have shown a probability to be used as preventive and therapeutic agents for SARS- CoV-2.

Keywords: COVID-19, Dysbiosis, Gut microbiota, Probiotics, Respiratory tract infections.
patients. Probiotic bacteria are well documented for their role in correcting gut dysbiosis\(^8,9\), reducing pro-inflammatory reactions, increasing defense against various pathogens\(^10\) and upgrading mucosal immunity\(^11\). They are useful in treating gut dysbiosis\(^12\), antibiotic-associated diarrhea\(^13,14\), irritating bowel syndrome\(^15\) etc. Latest studies have shown their impact in treating disorders caused due to gut dysbiosis such as obesity and atopic dermatitis\(^16\). This review tries to assess the potentiality of the probiotic strains as an alternate or supplementary therapeutic option for treating the COVID-19 disease.

**Gut microbiota and Viral respiratory tract infections**

Numerous studies have focussed on the importance of gut microbiota in defending or providing better immune response against various diseases\(^17-21\) and respiratory viral infections are no exception. In a study, when mice were treated with antibiotics to deplete gut microbiota, a decrease in antibody production and reduction in influenza virus specific T-cells was observed\(^22\), along with increased morbidity and mortality\(^22,23\). This occurred due to decreased T-cell numbers and migration rate of dendritic cells. These mice were also unable to stimulate the response of CD4\(^+\) T-cell mediated to PR8 antigen. A decrease in number of influenza specific CD8\(^+\) T-cells was also observed.

Gut microbes also modulate the macrophage response during viral pulmonary infection. According to a study, the ability of macrophages to limit viral replication was impaired in mice treated with antibiotics along with reduced response to type I and type II IFNs\(^23\). The study highlighted the importance of gut microbiota in strengthening the immune system against viral infections.

Conversely, different studies have reported that viral respiratory infections, like influenza and Respiratory Syncytial Virus (RSV) causing common cold, have an impact on the gut microbiota\(^24-28\). These infections caused a disbalance of gut microbiota by increasing the phylum Bacteroidetes and leading to decrease in phylum Firmicutes\(^29\), especially *Lactobacillus*\(^24,29\). This change in gut microbiota composition after influenza infection is due to type-2 IFN which is produced by T-cells derived in the lung and recruited to the intestine\(^28\).

**COVID-19 and Gut**

Till 2019, there were six known species of coronavirus which caused human diseases. These include severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) causing severe respiratory tract infections and had high mortality rate. SARS-CoV-2, or COVID-19 as it is widely known, is the seventh to be added in this category\(^10\).

According to the document published by MoHFW\(^31\), Govt. of India in coherence with WHO guidelines, the disease presents itself in asymptomatic, mild to severe forms. The common symptoms range from flu like cough, cold, fever to non-specific flu like pneumonia to life threatening severe acute respiratory illness (SARI). It’s a droplet borne infection spreading through direct contact with the patient or through fomites. The lesser common symptoms includes production of sputum, headache, GI symptoms like diarrhoea, nausea, vomiting\(^1,5\), thus exhibiting gut-lung crosstalk. Some studies have reported diarrhoea in the range of 1-3.8% patients\(^1,32-34\) and other has observed a greater incidence of these symptoms i.e. nausea in 10.1% and vomiting in 3.6%\(^5\). These reports highlight the occurrence of gastrointestinal disorders in COVID-19 patients. This was proved by observing viral nucleic acid in anal swabs and fecal samples of COVID-19 patients\(^2,3,6\) as well as in fecal samples of patients who had recovered from COVID-19 infections, 11 days ago\(^35\).

Earlier studies have reported angiotensin-converting enzyme (ACE-2) as the receptor for binding of SARS-CoV in lung epithelia\(^36,37\). This receptor is also found on the cholangiocytes in liver and patients of COVID-19 have shown presence of SARS-CoV-2 in liver\(^38\) indicating that this virus is also using ACE-2 as receptor for binding host cell\(^39-41\). As this receptor is found in intestinal epithelia as well\(^2,3,4,42-46\), thus increasing the possibility of its infection by COVID-19. ACE-2 mutants have shown a decrease in expression of antimicrobial peptides in gut and have shown dysbiosis. Thus, it can be inferred that COVID-19 infection may be related to gut microbiota and its dysbiosis\(^47\).

Yet another study found that cellular serine protease known as transmembrane protease serine 2 (TMPRSS-2) is also necessary for entry of COVID-19 in cells along with ACE-2 receptor\(^48\).
This expression of TMPRSS-2 was found in lung alveolar type 2 cells, ileum, oesophageal upper epithelial cells and colon. Therefore, COVID-19 can easily gain entry into these enterocytes and cause infection.

**Probiotics and Viral Respiratory Tract Infections**

According to FAO/WHO, probiotics are defined as “live microorganisms, which when administered in adequate amounts confer a health benefit to the host”. Probiotic microorganisms suppress pathogens in host and stimulate the proliferation of epithelial cells and hence provide health benefits to the host. They also regulate the gut microbiota and play an important role in immunomodulation. Relation between gut microbiota dysbiosis and metabolic disorders and chronic low-grade inflammation has been established in different studies. Beneficial effect of probiotics in alleviating gastrointestinal diseases has been reported by different randomized clinical trials. These benefits may be due to alteration of diversity of gut microbiota by modulating the intestinal immunity, producing growth substrates and by competing for nutrients.

Viral respiratory tract infections are a major cause of severe morbidity and mortality in human adults worldwide. Both innate and adaptive immune response play an important role for defence against influenza virus infection. Under in vivo conditions, the innate system recognizes the influenza virus through pattern recognition receptors (PRRs), and lead to generation of adaptive immune response. Ichinohe et al. reported reduced influenza virus-specific antibody titre and CD4 T-cell response in antibiotic treated mice along with diminished cytokine secretion and influenza virus specific CTLs. Synthesis of pro IL-1β and pro IL-18 and NLRPs was also found to be diminished.

Oral administration of probiotic microorganisms have been shown to reduce duration and severity of viral infections. During influenza infection in mice *L. plantarum* has shown to stimulate type-I IFN responses and reduced viral titers in lung. In another study, *Lactobacillus* spp. stimulated production of TNF-α and IFN-γ in nasal lymphocytes during influenza infection has been reported. Ingestion of probiotic cocktail containing *Lactobacillus* has been shown to stimulate the signal pathways when infected with single-stranded RNA virus.

Similarly, *Bifidobacterium breve* YIT 4064 stimulates production of anti-influenza IgG in children. *Bifidobacterium* spp. has also lead to enhanced B-cell and T-cell immunity, IFN release and NK cells response. Even *L. rhamnosus* GG (ATCC 53103) consumption in children decreased incidence of respiratory tract infections during winter season. In a study by de Vrese et al. inclusion of *L. gasseri* PA 16/8, *B. longum* SP 07/3, *B. bifidum* MF 20/5 in daily diet reduced the duration of common cold infection. This may be due to immunomodulation by the test organism owing to release of anti-inflammatory cytokines and stimulation of cytotoxic T cells and T-suppressor cells.

Amongst the elderly, the fourth most common cause of death is influenza and pneumonia, while 77% deaths are due to infection in gastrointestinal tract whereas as reportedly ninety percent due to respiratory tract infections. This age-related diminution of innate and acquired immune system can be controlled by inclusion of functional foods like probiotics in daily diet. *L. casei* DN 114001 provided through a fermented dairy product reduced the duration of infection of gastrointestinal tract and respiratory tract, especially for upper respiratory tract infection like rhinopharyngitis. Others like *L. paracasei* and *L. johnsonii* reduced incidence of infection and improved systems of symptoms of respiratory tract infections.

Probiotics can also regulate the immune system of the intestine as they produce many factors and metabolites which aid in the immunomodulation of the intestine. Under in vitro conditions, *L. reuteri* 100-23 has been shown to reduce IL-2 production in bone marrow derived dendritic cells (BMDCs) and increase production of transforming growth factor beta (TGF-b) in mice. *L. reuteri* 100-23 colonization has shown to increase number of FoxP3 positive cells in spleen and mesenteric lymph nodes. This suggests that *L. reuteri* 100-23 regulates inflammation of the gastrointestinal tract by recruiting immune cells and it also regulates recruitment of T-cells to gut epithelium.
Bacteria of genus *Bacillus* are one of the largest known producers of antimicrobials, out of which more than 795 have been identified. These peptides have shown antibacterial, antifungal, and antiviral properties. Some species of this genus have also shown probiotic properties. In one such study, probiotic *B. subtilis* was able to inhibit influenza virus replication under *in vitro* conditions and saved 30% of mice from death due to the same virus. It also produced a peptide, P18 which showed homology to Influenza A neutralizing antibody. It had the ability to inhibit the virus completely *in vitro* from concentrations ranging from 12.5-100 µg/ml. In mice, it proved as a better treatment by preventing 80% of mice from death due to Influenza as compared to oseltamivir phosphate treatment i.e. Tamiflu, which provided protection to 70% of mice. Overall, it was found more effective than oseltamivir phosphate for elimination of virus after its infection in mice.

**Probiotics and COVID-19**

Many different studies have shown that ventilator-associated pneumonia and enteritis can be reduced by modulating the gut microbiota. As of now there is absence of data on whether gut microbiota modulation can help in alleviating symptoms of COVID-19. However, according to guideline of China’s National Health Commission and National Administration of Traditional Chinese Medicine, probiotics may prove useful in treating dysbiosis and preventing secondary bacterial infections and thus treating COVID-19 patients successfully.

*Lactobacillus rhamnosus* GG, a probiotic bacterium, has shown its role in improving gut/lung barrier and intestinal homeostasis. It has further shown to down-regulate pro-inflammatory cytokines, up-regulate regulatory T cells and also to better anti-viral defense in respiratory infections. These immunomodulatory actions of *Lactobacillus rhamnosus* GG can certainly help individuals with COVID-19, or persons at risk of contracting the disease.

**CONCLUSION**

The review of literature done suggests that probiotic bacterial genera *Lactobacillus, Bifidobacterium* and *Bacillus* have shown great impact on the reinforcement of the immune system and at the same time have balanced the intestinal dysbiosis to ensure improved gut-lung crosstalk. The use of these probiotics for prevention and treatment of COVID-19 requires in-depth scientific study using metaanalysis and randomized clinical trials. At the same time, they can be used as supportive or alternative therapeutic agents that can build good immune responses for better prognosis of COVID-19.

**ACKNOWLEDGEMENTS**

The authors wish to thank management of IPS Academy, Indore and Acropolis Institute, Indore for their encouragement and timely help in this review.

**REFERENCES**

1. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y., Xia J., Yu T., Zhang X., Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; **395**(10223): 507-513.

2. Jin X., Lian J.S., Hu J.H., Jin X., Lian J.S., Hu J.H., Gao J., Zheng L., Zhang Y.M., Hao S.R., Jia H.Y., Cai H., Zhang X.L., Yu G.D., Xu K.J., Wang X.Y., Gu J.Q., Zhang S.Y., Ye C.Y., Jin C.L., Lu Y.F., Xu X., Yu X.P., Huang J.R., Xu K.L., Ni Q., Yu C.B., Zhu B., Li Y.T., Liu J., Zhao H., Zhang X., Yu L., Guo Y.Z., Su J.W., Tao J.J., Lang J.G., Wu X.X., Wu W.R., Qv T.T., Xi X.D., Yi P., Shi D., Chen Y., Ren Y., Qiu Y.Q., Li L.J., Sheng J., Yang Y. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020; **69**(6): 1002–1009.

3. Lin L., Jiang X., Zhang Z., Huang S., Zhang Z., Fang Z., Gu Z., Gao L., Shi H., Mai L., Liu Y. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut*. 2020; **69**(6): 997-1001.

4. Pan Y., Zhang D., Yang P., Poon L.L.M., Wang Q. Viral load of SARS CoV-2 in clinical samples. *Lancet Infect. Dis.* 2020; **20**(4): 411–412.

5. Wang D., Hu B., Hu C., Zhu F., Liu X., Zhang, J., Wang W., Xiang H., Cheng Z., Xiong Y., Zhao, Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*. 2020; **323**(11): 1061-1069.
1.  Zhang W., Du R.H., Li B., Zheng X.S., Yang X.L., Hu B., Wang Y.Y., Xiao G.F., Yan B., Shi Z.L., Zhou P. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg. Microbes Infect. 2020; 9(1): 386-389.

2.  Caballero-Franco C., Keller K., De Simone C., Cabral A., McKay K. Antibiotic-associated diarrhoea: a randomized, double-blind, placebo-controlled clinical trial. J Median Pharmacol. Res. 2011; 42(10): 79–87.

3.  Fotedar S., Green S.L. Gut microbiota promote hematopoiesis to control bacterial infection. Cell Host Microbe. 2014; 15(3): 374-381.

4.  Patrick M., Gallo M., Goodridge H. S., Morelli L., Poli A., Pregliasco F., Zuccotti G. V. Probiotics and health: an evidence-based review. Pharmocol. Res. 2011; 63(5): 366-376.

5.  Strasburger S., Williams K.L., Erikson J. Commensal bacteria calibrate the activation threshold of innate immune responses. Front. Immunol. 2017; 8: 1-11.

6.  Horosheva T., Vodyanoy V., Sorokulova I. Efficacy of Bacillus probiotics in prevention of antibiotic-associated diarrhoea: a randomized, double-blind, placebo-controlled clinical trial. JMM Case Rep. 2014; 1(3): 1-6.

7.  Szajewska H., Kolodziej M. Systematic review with meta-analysis: Lactobacillus rhamnosus GG in the prevention of antibiotic-associated diarrhoea in children and adults. Aliment. Pharmacol. Ther. 2015; 42(10): 1149–1157.

8.  Sanders M.E., Guinan F., Guerrant R., Holt P.R., Quigley E.M.M., Sartor R.B., Sherman P.M., Mayer E.A. An update on the use and investigation of probiotics in health and disease. Gut. 2013; 62: 787–796.

9.  Reid G. The growth potential for dairy probiotics. Int. Dairy J. 2015; 49: 16 – 22.

10.  Smith P.M., Howitt M.R., Panikov N., Michaud M., Gallini C.A., Bohlooly-Y M., Glickman J.N., Garrett W.S. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Sci. 2013; 341(6145): 569-573.

11.  Khosravi A., Yañez A., Price J. G., Chow A., Merad M., Goodridge H. S., Mazmanian S.K. Gut microbiota promote hematopoiesis to control bacterial infection. Cell Host Microbe. 2014; 15(3): 374-381.

12.  Emry D., de Angelis A.L.H., Jaitin D., Wiegheör P., Staszewski O., David E., Keren-Shaul H., Mahlakov T., Jakobshagen K., Buch T., Schwierzec V., Utermöhlen O., Chau E., Garrett W.S., McCoy K.D., Diefenbach A., Staeheli P., Stecher B., Amit I., Prinz M. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 2015; 18(7): 965–977.

13.  Maríño E., Richards J.L., McLeod K.H., Stanley D., Yap Y.A., Knight J., McKenzie C., Kranich J., Oliveira A.C., Rossello F.J., Krishnamurthy B. Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. Nat. Immunol. 2017; 18(5): 552-562.

14.  Haase S., Haghkia A., Wilck N., Müller D.N., Linker R.A. Impacts of microbiome metabolites on immune regulation and autoimmunity. Immunology. 2018; 154(2): 230–238.

15.  Ichinohe T., Lee H.K., Ogura Y., Flavell R., Iwasaki A. Inflammasome recognition of influenza virus is essential for adaptive immune responses. J. Exp. Med. 2009; 206(1): 79–87.

16.  Abt M.C., Osborne L.C., Monticelli L.A., Doering T.A., Alenghat T., Sonnenberg G.F., Paley M.A., Antenus M., Williams K.L., Erikson J., Wherry E.J., Artis D. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity. 2012; 37(1): 158–170.

17.  Wang J., Li F., Wei H., Lian Z-X., Sun R., Tian Z. Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. J. Exp. Med. 2014; 211(12): 2397–2410.

18.  Deriu E., Boxx G.M., He X., Pan C., Benavidez S.D., Cen L. Influenza virus affects intestinal microbiota and secondary Salmonella infection in the gut through type I interferons. PLoSPathog. 2016; 12(5): 1-26.

19.  Bartley J.M., Zhou X., Kuchel G.A., Weinstock G.M., Haynes L. Impact of age, caloric restriction, and influenza infection on mouse gut microbiome: an exploratory study of the role of age-related microbiome changes on influenza responses. Front. Immunol. 2017; 8: 1-11.

20.  Yildiz S., Mazel-Sanchez B., Kandasamy M., Manicassamy B., Schmolke M., Influenza A virus infection impacts systemic microbiota dynamics and causes quantitative enteric dysbiosis. Microbiome. 2018; 6(1): 1-17.

21.  Groves H.T., Cuthbertson L., James P., Moffatt M., Goodridge H. S., Morelli L., Poli A., Pregliasco F., Zuccotti G. V. Probiotics and health: an evidence-based review. Pharmocol. Res. 2011; 63(5): 366-376.
M.F., Cox M.J., Treganong J.S. Respiratory disease following viral lung infection alters the murine gut microbiota. *Front. Immunol.* 2018; 9: 1-12.

29. Marin I.A., Goertz J.E., Ren T., Rich S.S., Onengut-Gumuscu S., Farber E., Wu M., Overall C.C., Kipnis J., Gaultier A. Microbiota alteration is associated with the development of stress-induced despair behaviour. *Sci. Rep.* 2017; 7: 1-10.

30. Gao Q.Y., Chen Y.X., Fang J.Y. 2019 novel coronavirus infection and gastrointestinal tract. *J. Dig. Dis.* 2020; 21(3): 125-126.

31. Ministry of Health & Family Welfare, Government of India, Directorate General of Health Services (EMR Division). Guidelines on Clinical Management of COVID – 19. 2020; 2-5.

32. Zhu N., Zhang D., Wang W., Li X., Yang B., Song J., Zhao X., Huang B., Shi W., Lu R., Niu P. A novel coronavirus from patients with pneumonia in China. 2019. *N. Engl. J. Med.* 2020; 382:727–733.

33. Guan W.J., Ni Z.Y., Hu Y., Liang W., Ou C., He J., Liu L., Shan H., Lei C., Hui D.S.C., Du B., Li L., Zeng G., Yuen K.Y., Chen R., Tang C., Wang T., Chen P., Xiang J., Li S., Wang J.L., Liang Z., Peng Y., Wei L., Liu Y., Hu Y.H., Peng P., Wang J.M., Liu J., Chen Z., Li G., Zheng Z., Qu S., Luo J., Ye C., Zhu S., Zhong N. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 2020; 382(18): 1708-1720.

34. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., Xie X., Yin W., Li H., Liu M., Xiao Y., Gao H., Guo L., Xie J., Wang G., Jiang R., Gao Z., Jin Q., Wang J., Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395(10223): 497–506.

35. Wu Y., Guo C., Tang L., Hong Z., Zhou J., Dong X., Yin H., Xiao Q., Tang Y., Qu X., Kuang L. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol. Hepatol.* 2020; 5(5): 434-435.

36. Anand K., Ziebuhr J., Wadhwani P., Mesters J.R., Hilgenfeld R. Coronavirus main proteinase (3Cpro) structure: basis for design of anti-SARS drugs. *Science.* 2003; 300(5626): 1763–1767.

37. Perlman S., Netland J. Coronavirus: update on replication and pathogenesis. *Nat. Rev. Microbiol.* 2009; 7(6): 439–450.

38. Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., Wang W., Song H., Huang B., Zhu N., Bi Y. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020; 395(10224): 565-574.

39. Wan Y., Shang J., Graham R., Baric R. S., Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J. Virol.* 2020; 94(7): 1-9.

40. Wan Y., Shang J., Sun S., Tai W., Chen J., Geng Q., He L., Chen Y., Wu J., Shi Z., Zhou Y. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J. Virol.* 2020; 94(5): 1-15.

41. Zhou P., Yang X.L., Wang X.G., Hu B., Zhang L., Zhang W., Si H.R., Zhu Y., Li B., Huang C.L., Chen H.D. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020; 579(7798): 270-273.

42. Liang W., Feng Z., Rao S., Xiao C., Xue X., Lin Z., Zhang Q., Qi W. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. *Gut.* 2020; 69(6): 1141-1143.

43. Mazza S., Sorce A., Peyvandi F., Vecchi M., Caprioli F. A fatal case of COVID-19 pneumonia occurring in a patient with severe acute ulcerative colitis. *Gut.* 2020; 69(6): 1148-1149.

44. Ong J., Young B.E., Ong S. COVID-19 in gastroenterology: a clinical perspective. *Gut.* 2020; 69(6): 1144-1145.

45. Song Y., Liu P., Shi X.L., Chu Y.L., Zhang J., Xia J., Gao X.Z., Qu T., Wang M.Y. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. *Gut.* 2020; 69(6): 1143-1144.

46. Zhang H., Kang Z., Gong H., Xu D., Wang J., Li Z., Li Z., Cui X., Xiao J., Zhan J., Meng T. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut.* 2020; 69(6): 1010-1018.

47. Hashimoto T., Perl T., Rehman A., Trichereau J., Ishiguro H., Paolino M., Sigl V., Hanada T., Hanada R., Lipinski S., Wild B., Camargo S.M.R., Singer D., Richter A., Kuba K., Fukamizu A., Schreiber S., Clevens H., Verrey F., Rosenstiel P., Penninger J.M. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature.* 2012; 487(7408): 477-481.

48. Bradley K.C., Finsterbusch K., Schnepf D., Crotta S., Llorian M., Davidson S., Fuchs S.Y., Staeheli P., Wack A. Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. *Cell Rep.* 2019; 28(1): 245-256.

49. FAO/WHO. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria, Cordoba, 2012.
50. Thomas C., Versalovic J. Probiotics-host microbiota interactions: modulation of signaling pathways in the intestine. Gut Microbes. 2010; 1(3): 148–163.

51. Cani P., Delzenne N. Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. Curr. Opin. Pharmacol. 2009; 9(6): 737–743.

52. Jumpertz R., Le D.S., Turnbaugh, P.J., Trinidad D.R., Ho J. H., Murray T.S., Iwasaki A. Microbiota regulates immune defense against influenza A virus via the regulation of caspase-1. Immunity. 2009; 30(4): 556–565.

53. O’Toole P., Cooney J. Probiotic bacteria influence the composition and function of the intestinal microbiota. Interdiscip. Perspect. Infect. Dis. 2008; 1–9.

54. Allen I.C., Scull M.A., Moore C.B., Holl E.K., McElvania-TeKippe E., Taxman D.J., Guthrie E.H., Pickles R.J., Ting J.P.Y. The NLRP3 innate immunity receptor mediates innate immunity to influenza A virus through recognition of viral RNA. Immunity. 2009; 30(4): 556–565.

55. Thomas P.G., Dash P., Aldridge Jr J.R., Ellebedy A.H., Reynolds C., Funk A.J., Martin W.J., Lamkanfi M., Webby R.J., Boyd K.L., Doherty P.C. The intracellular sensor NLRP3 mediates key innate and healing responses to influenza A virus through recognition of viral RNA. Immunity. 2009; 30(4): 556–565.

56. Ichinohe T., Pang I.K., Kumamoto Y., Peaper D.R., Ho J. H., Murray T.S., Iwasaki A. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc. Nat. Acad. Sci. USA. 2011; 108(13): 5354–5359.

57. De Vrese M., Winkler P., Rautenberg P., Harder T., Noah C., Laue C., Ott S., Hampee J., Schreiber S., Heller K., Schrezenmeir J. Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial. Vaccine. 2006; 24(44-46): 6670–6674.

58. Vouloumanou E.K., Makris G.C., Karageorgopoulos D.E., Falagas M.E. Probiotics for the prevention of respiratory tract infections: a systematic review. Int. J. Antimicrob. Agents. 2009; 34(3): 1–10.

59. Yoshikai Y. Oral administration of heat-killed Lactobacillus plantarum L-137 enhances protection against influenza virus infection by stimulation of type I interferon production in mice. Int. Immunopharmacol. 2009; 9(9): 1122–1125.

60. Hori T., Kiyoshima J., Shida K., Yasui H. Augmentation of cellular immunity and reduction of influenza virus titer in aged mice fed Lactobacillus casei strain Shirota. Clin. Diagn. Lab. Immunol. 2002; 9(1): 105–108.

61. De Vrese M., Winkler P., Rautenberg P., Harder T., Noah C., Laue C., Ott S., Hampee J., Schreiber S., Heller K., Schrezenmeir J. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium breve YIT4064, Lactobacillus casei Shirota and Bifidobacterium breve YIT4064 plus Lactobacillus casei Shirota in children attending day care centres: double blind, randomised trial. Br. Med. J. 2001; 322: 1–5.

62. De Vrese M., Winkler P., Rautenberg P., Harder T., Noah C., Laue C., Ott S., Hampee J., Schreiber S., Heller K., Schrezenmeir J. Effect of Bifidobacterium breve YIT4064 plus Lactobacillus casei Shirota on common cold episodes of children: a double blind, randomized, controlled trial. Clin. Nutr. 2005; 24(4): 481–491.

63. Hessle C., Hanson L. A., Wold A.E. Lactobacilli from human gastrointestinal mucosa are strong stimulators of IL-12 production. Clin. Exp. Immunol. 1999; 116(2): 276–282.

64. Christensen H.R., Frokier H., Pestka J.J. Lactobacilli differentially modulate expression of cytokines and maturation surface markers in murine dendritic cells. J. Immunol. 2002; 168(1): 171–178.
bacteria on cytokine secretion by human intestinal mucosa. Am. J. Gastroenterol. 2003; 98(4): 865-870.

70. LaCroix A.Z., Lipson S., Miles T.P., White L. Prospective study of pneumonia hospitalizations and mortality of US older people: the role of chronic conditions, health behaviors, and nutritional status. Public Health Rep. 1989; 104(4): 350-360.

71. Yoshikawa T.T. Epidemiology and unique aspects of aging and infectious diseases. Clin. Infect. Dis. 2003; 98(4): 865-870.

72. LaCroix A.Z., Lipson S., Miles T.P., White L. Prospective study of pneumonia hospitalizations and mortality of US older people: the role of chronic conditions, health behaviors, and nutritional status. Public Health Rep. 1989; 104(4): 350-360.

73. Yoshikawa T.T. Epidemiology and unique aspects of aging and infectious diseases. Clin. Infect. Dis. 2000; 30: 931–933.

74. Djuretic T., Ryan M.J., Fleming D.M., Wall P.G. Infectious intestinal disease in elderly people. Communicable disease report, CDR review. 1996; 6(8): R107-12.

75. Mouton C.P., Bazaldua O.V., Pierce B., Espino, D.V. Common infections in older adults. Am. Fam. Physician. 2001; 63(2): 257-262.

76. Bunout D., Barrera G., Hirsch S., V Gattas., de la Maza MP., Haschke F., Steenhout P., Klassen P., Hager C., Avendano M., Petermann M., Munoz C. Effects of a nutritional supplement on the immune response and cytokine production in free-living Chilean elderly. J. Parenter. Enteral. Nutr. 2004; 28(5): 348–354.

77. Fukushima Y., Miyaguchi S., Yamano T., Kaburagi T., Iino H., Ushida K., Sato K. Improvement of nutritional status and incidence of infection in hospitalised, enterally fed elderly by feeding of fermented milk containing probiotic Lactobacillus johnsonii La1 (NCC533). Br. J. Nutr. 2007; 98(5): 969-977.

78. 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):377–381.