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EXPLORING THE THERAPEUTIC POTENTIAL OF PROBIOTICS IN FIGHTING RESPIRATORY VIRAL INFECTIONS

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Abstract:
Viruses continue to be the primary microorganisms responsible for commencing respiratory tract infections in both community and health-care settings. They continue to be prevalent causes of morbidity in skilled hosts, and are particularly associated with significant transience in acknowledged entities. As a result of changes in the human ecology brought on by global warming and increased geographical movement of people and things, the risk of viral contagion has increased substantially. Virus-caused infections of the respiratory tract are the most prevalent disease in humans. Multiple etiologic surrogates impede the development of effective treatments. According to research, probiotics may reduce the risk or severity of respiratory infection symptoms. Probiotics can protect the host from a variety of health issues, such as infectious diseases. Until 1995, scholars speculated that probiotics had only one effect: they restored the intestinal flora, hence preventing harmful bacteria from provoking gastroenteritis. Recent changes suggest that the immunomodulatory effect of probiotics is the most important mechanism of action. Numerous studies have established that particular probiotics may possess antiviral action as a consequence of their immunomodulatory effect. This review aims to inform readers about the effect of probiotics on respiratory virus infections and shed light on the possible antiviral mechanisms of probiotics.

Keywords: Probiotics, Viral Infections, Respiratory Tract, Immunomodulatory

INTRODUCTION

Viruses continue to be the collective but largely unacknowledged source of respiratory tract illnesses (RTI). Along with recurrent upper respiratory tract infections (URTI), they are becoming increasingly anticipated as important pathogens in lower respiratory tract infections (LRTI), particularly community-acquired pneumonia (CAP). No specified pathogens are detected in 30%–60% of community-acquired LRTI cases1.

Around 200 distinct types of viruses are responsible for RTIs in humans. Human rhinoviruses (HRV) are the largest group of respiratory viruses, with approximately 150 serotypes2. In humans, the primary disease induced by HRV is acute upper respiratory tract infection, most commonly referred to as the common cold. The next most often infected viruses in humans are the human enteroviruses (HEV), which persist concurrently with clinical manifestations ranging from minor respiratory symptoms to life-threatening conditions. Influenza viruses, respiratory syncytial virus (RSV), and adenoviruses continue to be the most important causes of upper and lower respiratory tract infections (RTIs)3,4. Additionally, numerous additional viruses or viral groups are responsible for RTIs, including parainfluenza viruses and coronaviruses. They can cause a wide variety of respiratory diseases, ranging from simple upper respiratory tract infections to pneumonia4. With the rapid advancement of high-throughput molecular procedures in recent years. Human bocavirus, human metapneumovirus, and human coronaviruses such as 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), and SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome).

The common cold is the most frequent indication of viral infection of the respiratory tract (coryza). Additionally, rhinoviruses are the most usually responsible for this (of which around are more than 100 serotypes). Around 20% of colds are caused by coronavirus infection; similar symptoms can also be caused by influenza and parainfluenza viruses, adenoviruses, RSV, and an infinite number of enteroviruses5. Although both viruses originated from slide diseases of the respiratory system, their aetiology differs in their incidence. Adenoviruses are the primary cause of viral pharyngitis and tonsillitis, but croup (subglottic oedema secondary to laryngotracheitis) is most frequently associated with parainfluenza virus infection. These viruses can cause acute bronchitis in healthy individuals and viral exacerbations in patients with chronic obstructive lung disease when combined (COPD). Viral RTIs are also connected with asthma and cystic fibrosis exacerbations. While acute bronchiolitis is most usually the result of RSV infection in babies, this virus is also an under-recognized cause of decreased RTI in the elderly. Viral infection (most frequently via influenza, parainfluenza, and RSV) is a common cause of acute respiratory disorders that frequently result in hospitalisation in patients with chronic critical conditions. 6, primarily chronic obstructive pulmonary disease (COPD), asthma, cardiovascular illness, and diabetes.

FEASIBILITIES IN ANTI-VIRAL TREATMENT OF VIRAL RTI

Antiviral treatment for viral RTI is difficult. Leading, the total of existing agents contains inherent precincts. As a result, antiviral therapy is frequently not recommended for healthy immune-competent individuals since aids on the scientific sequence of the disease are frequently insufficient. For example, treating influenza with amantadine or neuraminidase inhibitors (NAI) assures that the sickness is only mildly contagious. Assistance is limited to one day if the antiviral is specified within 48 hours of disease onset. Clinical antiviral treatment aids are likely to be advanced in immune-compromised patients via subsequent severe infections. Third, it is critical to establish antivirals early on to prevent virus growth, collateral tissue damage, and induction of the pro-inflammatory response7.

The prevention of viral respiratory infections is a critical public health test. At the moment, the only effective antivirals and vaccines for the prevention and treatment of respiratory virus infections coexist with influenza viruses and adenoviruses. There are no effective treatments available for the viruses that cause the common cold (HRV, HEV). Numerous etiologic agents and cumulative

antibiotic and antiviral resistance present challenges for effective therapy. Subsequently, it is critical to develop alternative and safe strategies for reducing the threat of these infections8. Even moderately effective treatment in the management and prevention of viral RTIs such as the common cold may result in a decrease in morbidity and financial costs associated with this illness.

Inappropriately, while the majority of collective bacterial pathogens are susceptible to aetiological empathy and antibiotic liability testing within a few days, and appropriate pragmatic antibacterial exposure conceals the majority of pertinent pathogens, rapid viral identification is only possible for a few agents. While PCR and RT-PCR increased the number of diseases that can be detected, they are still not widely used in most ordinary laboratories and frequently do not provide same-day challenging results9. Antiviral susceptibility testing is virtually non-existent in these circumstances, while genotypic testing for mutations conducive to confrontation can be completed quickly in certain centres.

Increased immune-compromised patients play a vital role in the emergence and recurrence of infectious diseases (IDs); as a result, post-infection obstacles might pave the way for death. Public health is challenged with two significant impediments to eliminating IDs: (1) Antibiotics, which are required to continue preserving infected patients for an extended period of time. Inappropriately, the rapid spread of robust bacteria threatens the efficacy of antibiotics, which have transformed medicine and saved millions of lives10. (2) The absence of antiviral medications in addition to infectious viruses, which results in a high degree of handling among residents even when specific vaccines covering a restricted number of virus types are available11. Numerous ways have been proposed to circumvent this dilemma, including I the use of bacteriophages as antibacterial agents, (ii) the abstraction and refining of antimicrobial peptides12, and (iii) the avoidance of IDs through the use of vaccinations and recombinant vaccine strategies13.

Preventing contagious diseases appears to be the most foolproof method of bypassing ID obstacles. As a result, all of the previously unrevealed techniques have inherent drawbacks, such as side effects and persistence in the host. Immune system enhancement is a critical factor in preventing ID. Dietary stability in meals, management of additives such as fibre, and probiotics are three strategies for enhancing and arousing the immune system, thereby protecting the mucosa from pathogen access. Probiotics are defined as living microorganisms that confer health benefits on their hosts14. Probiotics have been shown to stimulate and suppress the immune system15. Finally, probiotic strains can reduce or eliminate virus infection through immunomodulatory action, prompting researchers to coin the term "immunobiotics." The most often utilised probiotic strains are lactobacilli and bifidobacteria, which are typically found in fermented foods such as yoghurts or nutritional supplements. Probiotic bacteria must meet the following criteria: (1) they must be capable of surviving in the gastrointestinal tract and proliferating in the gut; (2) they must provide assistance to the host during development and action in the human body; (3) they must be non-pathogenic and non-toxic; (4) they must protect against pathogenic microorganisms via multiple mechanisms; and (5) they must be devoid of convent. Diverse bacterial strains belonging to the same genus and species, as confirmed by genomic evidence, may exert radically different impacts on their hosts. Apart from their antibacterial activity, probiotic strains have been shown to exhibit beneficial antiviral activity, which may provide a solution to the dearth of antiviral medicines.

The most encouraging health outcomes of probiotics in human medication revisions include the alleviation of acute diarrhoea in children, the alleviation of children's milk allergy/atopic dermatitis, and the alleviation of irritable bowel syndrome17, 18. Probiotics are likely to exert an effect on the gut mucosa by regulating the local microbiota, preventing pathogenic microorganisms from spreading, and enhancing local and systemic immune responses20. They may also have an effect on the microbiota's structure and function in the intestinal components. Given the beneficial effects of probiotics in viral infections, certain probiotics have been recommended to be efficient in

alleviating the severity and duration of acute rotavirus gastroenteritis21. Additionally, aggregate evidence indicates that probiotics are beneficial in the treatment of RTIs22, the majority of which are viral in origin.

Probiotics work in tandem with the innate and acquired immune systems, providing the necessary strength to reduce the severity of respiratory tract infections. Recently, "ghost probiotics" or para-probiotics have been promoted as having immunomodulatory properties that outweigh their usefulness. Probiotics contain immunostimulatory components such as lipoteichoic acid, peptidoglycan, and nucleic acid, all of which are Toll-like receptor (TLR) ligands, as well as muramyl dipeptide, a Nod-like receptor ligand23.

TYPES OF PROBIOTICS

Probiotics are well-known for their explicit strain designations, which include the genus, the species, the subspecies, and an alphanumeric strain number24. Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia, and Bacillus are the seven major genera of microbial entities that are most frequently used in probiotic products. Lactobacillus and Bifidobacterium are two of the most frequently used probiotics for respiratory infections.

Lactobacillus casei Shirota (LcS): Antibodies against LcS compact plasma cytomegalovirus and Epstein–Barr virus in highly active individuals (university athletes) 25. Nonetheless, there was no significant difference in the prevalence of norovirus-associated gastroenteritis between the LcS and control groups in long-stay elderly patients in a health care facility26. Though the efficacy of LcS remnants is debatable, a plausible mechanism has been proposed in which LcS was introduced to inhibit the activity of natural killer (NK) cells, which are one of the primary mechanisms of resistance aside from viral infection27.

Lactobacillus rhamnosus (LGG): We estimated the preemptive effects of LGG on investigational rhinovirus infections in healthy volunteers. Following 6 months of LGG consumption, subjects were intranasally immunised with rhinovirus. The rate of contagion, the presence of cold signs, and their severity were evaluated. The incidence and severity of cold symptoms, as well as the number of subjects infected with rhinovirus, were lower in the LGG group than in the control group, though the difference between the groups was not significant28. When LGG was administered for four weeks to children with gastroenteritis who remained positive for either rotavirus or cryptosporidium species in stool, a significant increase in serum immunoglobulin (Ig)G intensities was observed post-intervention in children with rotavirus-induced diarrhoea who received standard LGG. Those acceptances LGG revealed a significant increase in intestinal permeability in children with cryptosporidial diarrhoea29. The mechanisms by which probiotics exert their immunomodulatory properties are not completely obvious. Nonetheless, LGG was shown to suppress innate and adaptive immune responses, particularly those directed against gastrointestinal pathogens, resulting in increased serum IgG and secretory IgA levels directed against enteric pathogens such as rotavirus.

Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1 (R-1): The revision discovered that ingestion of yoghurt stimulated with R-1 increased NK cell activity and decreased the risk of developing a common cold in elderly individuals30. Additional revisions demonstrated that R-1 and its concealed polysaccharides enhanced immune system functionality via the induction of NK cells. Thus, R-1 or its derivatives may help to prevent respiratory infections caused by respiratory or influenza viruses31.

Lactobacillus paracasei ssp. paracasei (L. casei 431): L. casei 431 was described to demonstrate its efficacy in reducing the severity of upper respiratory signs. Nonetheless, it had no effect on healthy adults' immune responses to influenza vaccination32. A different revision, L. casei 431, was discovered to suppress the immune system in healthy subjects during a vaccination model. Increases in vaccine-specific IgG, IgG1, and IgG3 titers in plasma, as well as secretory IgA titers in saliva, were suggestively greater in both probiotic groups than in the control group33. Though additional comprehensive revisions are necessary to elucidate the numerous mechanisms underlying L. casei

431's immunomodulatory and anti-infective effects, it is proposed that this probiotic stimulates the host's innate viral defence mechanisms and reduces inflammation.

Lactobacillus paracasei MCC1849 (MCC1849): MCC1849 was not viable, ensuring that it had no significant effect on the immune constraints associated with influenza vaccination in elderly people with immunosenescence34.

Lactobacillus casei strain DN-114 001 (DN-114): According to Pedone et al., the administration of DN-114 reduces the prevalence of acute diarrhoea in healthy children aged 6–24 months. The incidence and occurrence of diarrhoea were significantly reduced when DN-114 was added to the control group35. Merenstein et al. reported that DN-114 001 may help reduce the prevalence of common infectious diseases, such as diarrhoea, in children aged 3–6 years who attended daycare or school. Nonetheless, the exact mechanism is unknown36.

Lactobacillus plantarum L-137 (HK L-137): Previously, the immunomodulatory effects of heat-killed HK L-137 were evaluated, and the results indicated that HK L-137 enhanced innate and acquired immune responses in mice and human subjects, primarily via the production of type 1 interferons (IFNs) and interleukin (IL)-1237. Hirose et al. investigated the effects of 12 weeks of HK L-137 intake on URTI symptoms and immune utilities in human subjects undergoing high levels of psychological stress. URTIs were significantly less prevalent in the HK L-137-treated group than in the control group. In addition to the severity and duration of URTIs, the severity and duration of medication had significant negative correlations with the extent of HK L-137 ingestion. The percentage change from baseline in concanavalin A-induced peripheral blood mononuclear cell (PBMC) propagation was suggestively greater in the HK L- 137-treated group than in the control group. Despite this, serum IFN- production was not significantly different between these groups38.

Enterococcus faecalis FK-23: Oo et al. reported that the paraprobiotic FK-23 (Enterococcus faecalis strain FK-23) significantly decreased alanine aminotransferase (ALT) levels in adult HCV-positive subjects but did not result in a reduction in viral load. Though the precise mechanism remained unknown, they suggested that FK-23 potency altered the microbiota of HCV patients, which then contributed to the decline in ALT level39.

Saccharomyces boulardii: Oral Saccharomyces boulardii and rehydration significantly reduced the duration of diarrhoea in children with acute rotavirus gastroenteritis in Bolivia, when compared to control rehydration alone40.

Bifidobacterium animalis Bb12: The purpose of this study was to determine the effect on intestinal immunity and inflammation of an infant starter formulary containing the probiotic Bifidobacterium animalis subspecies lactis (Bb12). For six weeks, six-week-old healthy, full-term infants were enrolled in a potential revision (Control formula and Control + Bb12 (106CFU / g / head)). Antipoliovirus-specific IgA was evaluated, as well as anti-rotavirus-specific IgA. Bb12 amplified anti-poliovirus-specific IgA in a suggestive manner, but not anti-rotavirus-specific IgA, despite the trend toward increase41.

Bifidobacterium lactis B94: In Turkey, Erdoan et al. reported that combining Bifidobacterium lactis B94 with oral rehydration significantly reduced diarrheal duration in children with acute rotavirus gastroenteritis, when compared to control oral rehydration alone42.

Lactococcus lactis subsp. Lactis JCM 5805 (L. lactis JCM 5805): Plasmacytoid dendritic cells (pDCs) are critical for antiviral immunity due to their ability to synthesise large amounts of interferon (IFN). L. lactis JCM5805 was used to stimulate human pDCs in healthy volunteers' PBMCs, more specifically in a subgroup of volunteers with a low pDCs activity, and it also appeared to mitigate cumulative common cold symptoms43.

Table 1: Experimental ability of several chief probiotics strains for infectious diseases

S.No.	Strain	Target Viral Disease	Consequence	Reference
1.	*Lactobacillus casei* (Yakult)	Upper respiratory tract infection Epstein–Barr virus (EBV) Cytomegalovirus (CMV)	Reduced plasma CMV and EBV antibody titers	44
2.		Upper respiratory tract infection	No significant difference in the incidence of respiratory symptoms and influenza-vaccination immune response	25
3.		Norovirus gastroenteritis	No significant difference in the incidence of Norovirus infection in elderly people	26
4.	*Lactobacillus rhamnosus* GG	Experimentally induced Rhinovirus infection	The decrease in the occurrence and severity of cold symptoms and the number of subjects with Rhinovirus infection, but not significant	27
5.		Acute gastroenteritis (positive for Rotavirus or Cryptosporidium)	Significant decrease in repeated episodes of Rotavirus diarrhoea. Improvement in intestinal function in children with rotavirus and cryptosporidial gastroenteritis	28
6.	*Lactobacillus delbrueckii* ssp. bulgaricus OLL1073R-1	Common cold symptoms	Significant increase of natural killer cell activity and reduced risk of catching the common cold	29
7.	*Lactobacillus paracasei* ssp. paracasei, *L. casei* 431	Response to influenza vaccination	Significant reduction of the duration of upper respiratory symptoms No significant difference in immune responses to influenza vaccination and incidence or severity.	30
8.		Response to influenza vaccination	Significant increases of vaccine-specific IgG, IgG1, and IgG3 in plasma as well as vaccine-specific secretory IgA in saliva in both probiotic- treated groups	32
9.	*Lactobacillus paracasei* MCC1849 (Morinaga)	Antibody response against vaccination	No significant effect of non-viable *L. paracasei* MCC1849	33
10.	*Lactobacillus casei* (DN-114 001)	Incidence of acute diarrhoea	Significant reduction in the incidence and frequency of diarrhoea.	34
11.		Incidence of common infectious diseases	The significantly lower incidence rate of common infectious diseases in DN-114 group	35
12.	*Lactobacillus plantarum* L-137	Upper respiratory tract infection	Significant decrease in the incidence of upper respiratory tract infections	37
13.	*Enterococcus faecalis* FK-23	Hepatitis C virus	Significant decrease of ananie aminotransferase No substantial change in viral load	39
14.	*Saccharomyces*	Acute rotavirus diarrhoea	Significant decrease in the	40

	boulardii		duration period of diarrhoea and fever	
15.	*Bifidobacterium animalis* (Bb12)	Intestinal antibody responses to polio and rotavirus in infants	Bb12 significantly increased faecal anti-poliovirus specific IgA, and increased anti-rotavirus specific IgA.	41
16.	*Bifidobacterium lactis* B94	Acute rotavirus diarrhoea	Significantly decrease in the duration period of diarrhoea	42
17.	*Lactococcus lactis*JCM5805 (*L.lactis* plasma)	pDCs activity among PBMCs and symptoms of a common cold	*L. lactis* JCM 5805 activated pDCs among PBMCs and significantly reduced the risk of morbidity from the common cold	44
18.		Influenza-like illness and immunological response to influenza virus	Significant decrease in the cumulative incidence days of "cough" and "feverishness". Considerable increase in IFN-α-inducible antiviral factor, interferon-stimulated gene 15	45
19.		Influenza-like illness and immunological response to influenza virus	Significant decrease in the cumulative incidence days of "sore throat" and "cough". Considerable increase in IFN-α mRNA in PBMCs	46
20.		Antiviral immune response and physical condition	Significantly increased pDC activation and increased mRNA expression of ISG15 Significant decrease in the cumulative incidence days of cold-like symptoms	47
21.		Influenza Infection	Significant decreases in both the incidence rate and the cumulative incidence rate of influenza	48
22.		Antiviral immune response to influenza virus	Significant increase in secretary IgA in saliva Significant prevention of decrease in phagocytic activity of neutrophil during the common cold season	49

L. fermentum: It is a species that occurs naturally in both human and animal flora. This species is frequently used in humans as a probiotic. L. fermentum has been evaluated in RTIs in both human clinical trials, most notably in children and adults, and animal models to determine the mechanism of viral inhibition50.

L. acidophilus: It is a well-known probiotic strain that is frequently used in pharmaceutical supplements51. Only a few studies have examined the antiviral activity of L. acidophilus, which is typically used to treat gastrointestinal problems. All antiviral clinical trials conducted in humans used a combination formula containing additional probiotic strains. In comparison, one animal experiment demonstrated that L. acidophilus L-92 isolated from a healthy Japanese volunteer had anti-IFV A (H1N1) activity by increasing the number of active natural killer cells in the lungs. Additionally, L. acidophilus L-92 secreted more IFN-α 52.

L. pentosus: It significantly increased NK activity in spleen cells and induced the production of IFN-g by NK1.1-positive NK and NK T cells. The increase in IFN-g production was not caused by L. pentosus directly acting on NK cells, but rather by IL-12 produced by CD11c1 DC following a TLR2- and TLR4-dependent interaction between the DC and the bacteria53.

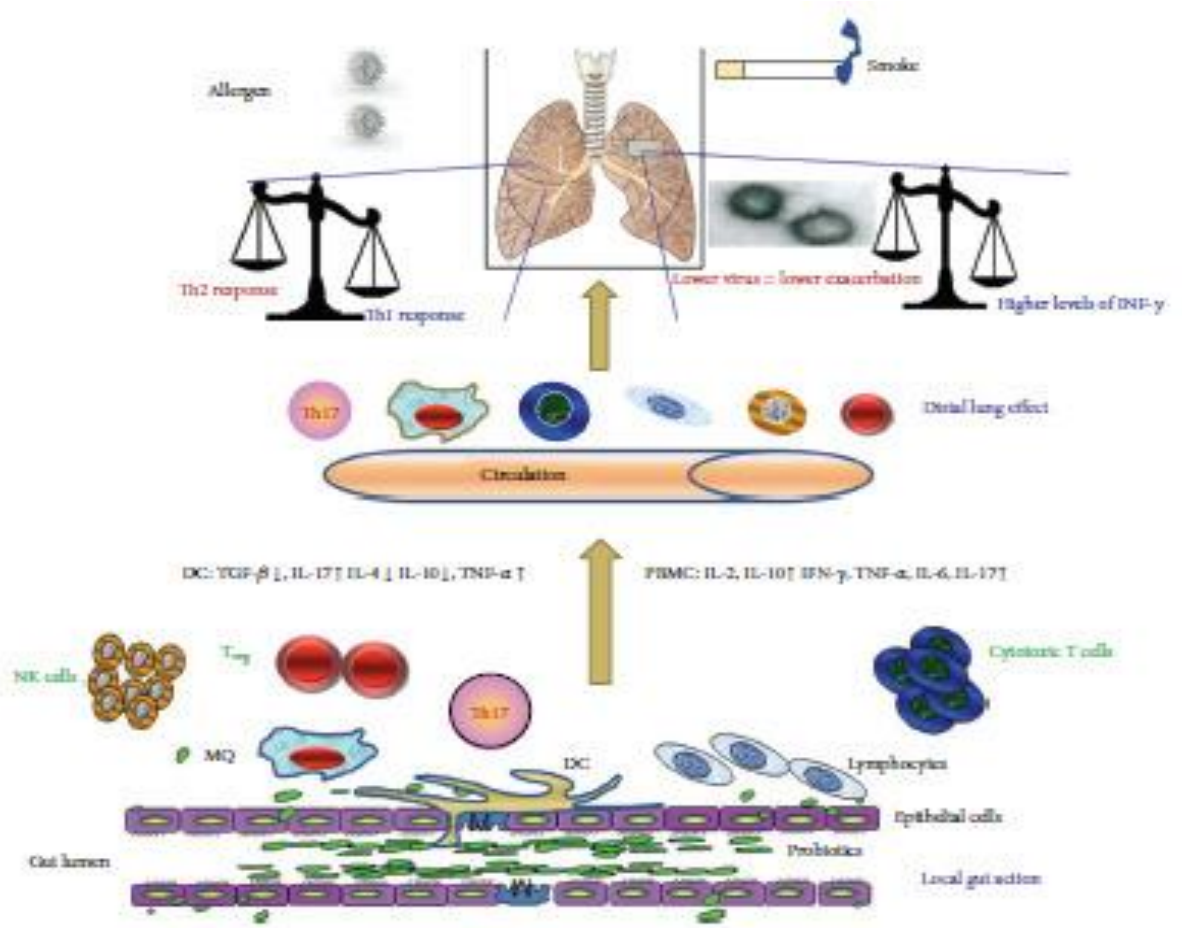

Figure 1: The putative immunomodulatory functions of probiotics on lung disease asthma and COPD. The immune and inflammatory drivers of allergic asthma (left side of figure) and of COPD (right side of figure) may be modified by strain-specific probiotics. The precise mechanisms by which gut-located probiotics can cause immunomodulation in the airway are unclear but may reflect changes in blood and local immune cells, including T-cell subsets.

Immunomodulatory Effects of Probiotics: The immune response to probiotics is generally believed to be strain-dependent, with variations attributed to their cell walls' diverse protein and glycan/carbohydrate profiles, their DNA's variable CpG content, and possibly the metabolites and other molecules they excrete54. Probiotics are thought to exert their beneficial effects in part due to their ability to differentially regulate the production of anti- and pro-inflammatory cytokines and the balance of various T cell responses such as Th1/Th2, Treg, and Th17 responses55, as illustrated in figure 1.

Probiotic treatment of infectious diarrhoea appears to be effective in both adults and children, although their efficacy in other diseases is frequently not confirmed in placebo-controlled randomised clinical trials56. In diarrhoea, the clinical benefit of probiotic therapy may be due to both antipathogenic mechanisms at the microbiota level and immunomodulation of host mechanisms. At the moment, the relative contribution of these various mechanisms is unknown. However, oral administration of Lactobacilli may modulate cytokine profiles not only in the gut but also systemically. Numerous LAB strains have been shown to enhance cell-mediated immune responses, including T lymphocyte proliferation, mononuclear cell phagocytosis, and natural killer cell tumoricidal activity56.

POSSIBLE MECHANISMS OF ACTIONS OF PROBIOTICS

Specific probiotics have been shown in clinical and animal studies to have antiviral properties, but the underlying mechanisms are unknown. Additionally, strain-to-strain variation in strain properties and efficacy may be quite significant. Probiotics may exert antiviral activity by (1) inhibiting virus

adsorption and (2) cell internalisation; (3) producing metabolites and substances with direct antiviral activity; and 4) crosstalk (immunomodulation) with the cells in order to establish antiviral protection. Probiotics' potential mechanisms of action against respiratory viruses are depicted in Figure 2.

Antagonism to respiratory viruses: The respiratory tract is lined with mucosal epithelial surfaces that are constantly exposed to a variety of microorganisms and act as primary entry points for respiratory viruses. Because virus attachment to a host cell is the first critical step in the disease process, disrupting this attachment may benefit the host. Probiotic bacteria may interact directly with viruses, preventing them from attaching to the host cell receptor. For example, specific strains of lactobacilli have been shown to bind and inactivate the vesicular stomatitis virus (flu-like virus) in vitro57.

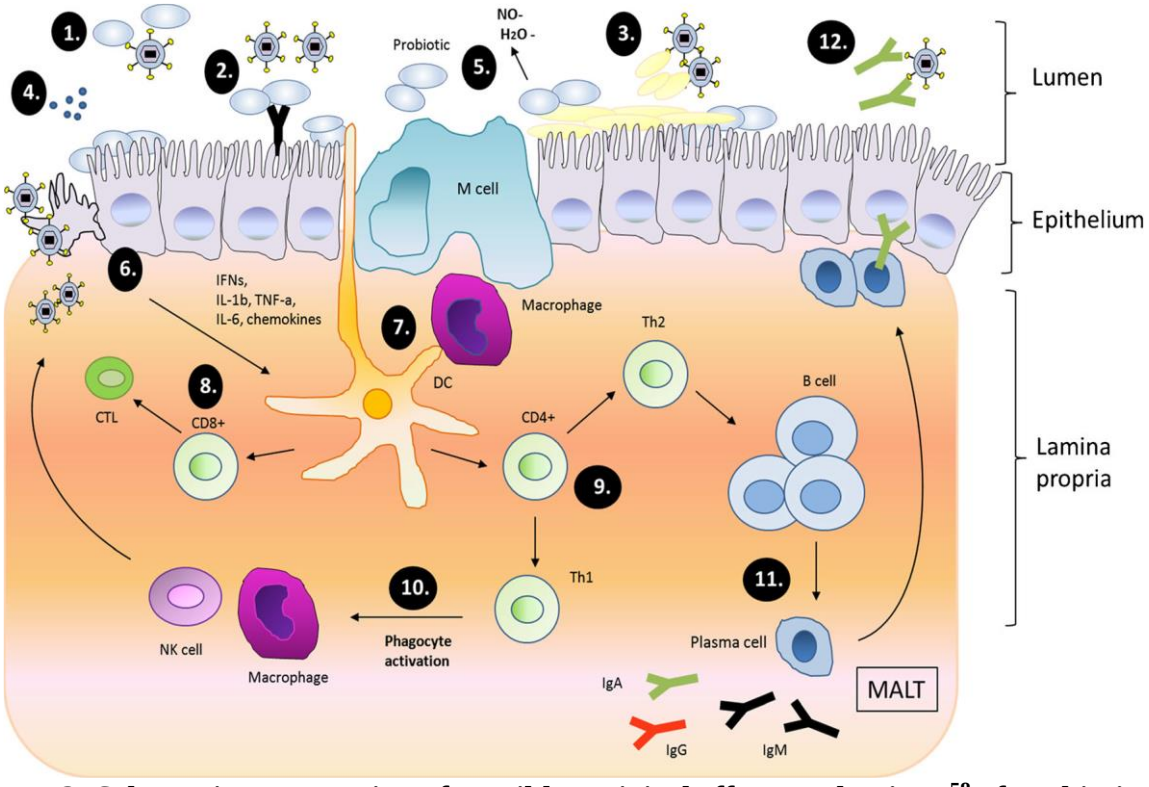

Figure 2: Schematic presentation of possible antiviral effect mechanisms[58] of probiotics in respiratory virus infections (adapted from Lehtoranta). 1 Probiotic bacteria may bind directly to the virus and inhibit virus attachment to the host cell receptor. 2 Adhesion of probiotics on the epithelial surface may block viral attachment by steric hindrance, cover receptor sites in a non-specific manner, or by competing for specific carbohydrate receptors. 3 Probiotics may induce mucosal regeneration: intestinal mucins may bind to viruses, and inhibit their adherence to epithelial cells and inhibit virus replication. 4 Probiotics also show direct antimicrobial activity against pathogens by producing antimicrobial substances. 5 Induction of low-grade nitric oxide (NO) production and dehydrogenase production may have antiviral activities. 6 Modulation of immune response through epithelial cells. 7 Modulation and activation of immune responses through macrophages and dendritic cells (DCs). 8 Upon activation, CD8+ T lymphocytes differentiate into cytotoxic T lymphocytes (CTLs), which destroy virus-infected cells. 9 CD4+ T lymphocytes differentiate into Th1 and Th2 cells. 10 T-helper cells type 1 (Th1) activates phagocytes, promoting virus killing. 11 Th2-cells induce proliferation of B-cells, which travel to secondary lymphatic organs in mucosa-associated lymphoid tissue (MALT) and differentiate into immunoglobulin (Ig)-producing plasma cells, which may migrate back to the infection site. 12 Secretory antibodies neutralize the virus

Additionally, probiotics may exhibit direct antimicrobial activity against pathogens through the production of antimicrobial substances such as organic acids, hydrogen peroxide, biosurfactants, and bacteriocins59. Experimental studies in epithelial cells and macrophages demonstrated that metabolic products from specific lactobacilli and bifidobacteria prevented strain-specific vesicular stomatitis virus infection. Additionally, bacteria metabolites found in yoghurts demonstrated antiviral activity, inhibiting influenza virus replication60. The induction of low-level nitric oxide synthesis may also be involved in probiotics' protective effects against viruses in respiratory cells, as demonstrated in alveolar macrophages in vitro61. However, it should be noted that respiratory viruses infect cells in a variety of ways and via a variety of receptors, and that probiotics' antiviral effects are strain-specific.

Cell-mediated immunity: The induction of antiviral cytokines such as interferons (IFNs), as well as proinflammatory cytokines and chemokines, in epithelial cells or underlying effector cells [macrophages, dendritic cells (DCs), and neutrophils] upon antigen recognition plays a critical role in virus infections by initiating cell-mediated viral elimination and adaptive immune responses. Probiotics may exert their antiviral effects against respiratory viruses by inducing systemic immune responses via the gut or by enhancing cellular immunity in the airways through increased natural killer cell and macrophage activity. Probiotics are recognised by toll-like receptors (TLRs) in gut epithelial cells and antigen-presenting cells 62, 63. As a result, probiotics may influence cytokine expression patterns via epithelial cells and underlying professional antigen-presenting cells such as macrophages and dendritic cells64.

Humoral immunity: Lactobacilli and bifidobacteria strains appear to protect against respiratory virus infections in part by inducing the synthesis of virus-specific immunoglobulins in respiratory secretions and serum65. Additionally, research indicates that certain probiotics may enhance the immunogenicity of viral vaccines.

FUTURE PERSPECTIVES ON THE EFFECTS OF PROBIOTICS IN RESPIRATORY VIRAL INFECTIONS

Ongoing research aimed at establishing a link between the presence of specific microbes and specific diseases will shed much-needed light on their interactions with the immune system. The effect of microbial influences on the immune system and on specific cell types has undergone a significant revision. Numerous unanswered questions remain regarding the gut commensal microbiota and its effect on the balance of pro- and anti-inflammatory forces in the immune system, including which immune cells are critical targets for probiotic action. It will be critical in the future to elucidate the mechanisms underlying the probiotic effect on the respiratory tract in diseased states. The ability of probiotics to enhance local and systemic innate immunity during virus infection in animal experiments is a likely, but unproven, mechanism of benefit and an exciting area of future research. Incorporating serological and immunological diagnostics into clinical research, such as the identification of virus-specific immunoglobulins and cytokines, would clearly benefit the field by providing valuable information on the effects of probiotics in respiratory virus infections.

CONCLUSION

Probiotic treatment of respiratory infections results in the activation of numerous innate immune signalling pathways and the production of IgA antibodies in respiratory tissue. Anti-inflammatory probiotics are not recommended for respiratory viral infections because they inhibit the virus's immune response. However, probiotics that promote the production of anti-inflammatory (IL-10, TGFβ) cytokines are critical in suppressing respiratory inflammation. Probiotics are capable of eradicating enteric viruses through both direct and indirect mechanisms. Probiotics' effectiveness in the gut ecosystem is more significant because they interact with viral infections via a variety of mechanisms, including immunomodulation, which is nearly the only mechanism available for probiotics in respiratory infections. Probiotic therapy may represent an exciting new option for

treating or preventing viral respiratory tract infections (RTIs), which are associated with significant health and economic costs for humans.

AAstV Avastrovirus	AAstV Avastrovirus
AdVs Enteric adenoviruses	AdVs Enteric adenoviruses
AEnP Anti-EnV probiotics	AEnP Anti-EnV probiotics
AMPs Antimicrobial peptides	AMPs Antimicrobial peptides
AMs Animal models	AMs Animal models
AVs Arboviruses	AVs Arboviruses
BALF Bronchoalveolar lavage fl uid	BALF Bronchoalveolar lavage fl uid
BCS Bacterial cell suspension	BCS Bacterial cell suspension
BLISs Bacteriocin-like inhibitory substances	BLISs Bacteriocin-like inhibitory substances
CA16 Coxsackievirus type A strain 16	CA16 Coxsackievirus type A strain 16
CFU Colony-forming unit	CFU Colony-forming unit
CRFK Crandell-Reese feline kidney	CRFK Crandell-Reese feline kidney
CTs Clinical trials	CTs Clinical trials
CXCL1 Neutrophil chemokine	CXCL1 Neutrophil chemokine
DLP Double-layered particle	DLP Double-layered particle
EnVs Enteric viruses	EnVs Enteric viruses
EU European Union	EU European Union
EV71 Enterovirus 71	EV71 Enterovirus 71
EVs Enteroviruses	EVs Enteroviruses
GIT Human gastrointestinal tract	GIT Human gastrointestinal tract
GRAS Generally recognized as safe	GRAS Generally recognized as safe
HBGAs Histo-blood group antigens	HBGAs Histo-blood group antigens
HFMD Hand, foot, and mouth disease	HFMD Hand, foot, and mouth disease
HRoV Human rotavirus vaccine	HRoV Human rotavirus vaccine
ID Infectious diseases	ID Infectious diseases
IFN-α Interferon-α	IFN-α Interferon-α
IgA Immunoglobulin A	IgA Immunoglobulin A
IL-10 Interleukin 10	IL-10 Interleukin 10
IL-12 Interleukin 12	IL-12 Interleukin 12
IL-17 Interleukin 17	IL-17 Interleukin 17
IL-2 Interleukin 2	IL-2 Interleukin 2
IL-6 Interleukin 6	IL-6 Interleukin 6
IL-8 Interleukin 8	IL-8 Interleukin 8
IVA-H1N1 Infl uenza virus type A	IVA-H1N1 Infl uenza virus type A
LAB Lactic acid bacteria	LAB Lactic acid bacteria
LPS Lipopolysaccharide	LPS Lipopolysaccharide
MAstV Mamastrovirus	MAstV Mamastrovirus
MMTV Mouse mammary tumor virus	MMTV Mouse mammary tumor virus
MuNoVs Murine noroviruses	MuNoVs Murine noroviruses
NK cells Natural killer cells	NK cells Natural killer cells
NRPS Non-ribosomal peptide synthetase	NRPS Non-ribosomal peptide synthetase
RTIs Respiratory tract infections	RTIs Respiratory tract infections
RVs Respiratory viruses	RVs Respiratory viruses
TGEV Transmissible gastroenteritis virus	TGEV Transmissible gastroenteritis virus
TGFβ Transforming growth factor beta	TGFβ Transforming growth factor beta
TLR Toll like receptors	TLR Toll like receptors
TNF-α Tumor necrosis factor alpha	TNF-α Tumor necrosis factor alpha
VLPs Viruslike particles	VLPs Viruslike particles
VP Viral protein	VP Viral protein
VP1 Viral protein 1	VP1 Viral protein 1

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