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Probiotics and the Upper Respiratory Tract - A Review

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Introduction

The interest in gut micro biota has emerged in recent decades. Gut micro biota has been associated with the promotion of health, the increased the risk of disease, and the maintenance of some diseases. Upper respiratory infections caused by viruses are among the most common health problems in humans [1]. In addition to the misery of sickness, these infections result in a significant burden on society in terms of healthcare visits, absences from work, and reduced school attendance. In addition, unnecessary medical costs are incurred. The careless use of antibiotics during respiratory tract infections has resulted in the constantly growing resistance of microbes to antibiotics [2]. The complications of upper respiratory infections, such as otitis and sinusitis, also result in high expenses and expose patients to potentially harmful operations. If viral upper respiratory infections could be prevented and treated, these outlays would be minimized.

According to a panel of international experts, "probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [3,4]. The strain should be precisely defined (i.e., identified and characterized), the dose should be defined, the health claim should be indicated, and the safety should be assessed. The properties of probiotics vary widely according to the strain. Even the manufacturing process influences the properties of certain strains [5].

Lactobacillus rhamnosus GG (L. GG, ATCC 53103) is one of the most-often studied probiotics. This bacterial strain of human origin has been isolated from the human gut. Its benefits in GI disorders have been demonstrated [6], and similar effects have been found in upper respiratory infections [7,8]. Although the colonization of the gut and the fecal recovery of specific probiotics, including L. GG, have been extensively studied, little information is available on the colonization of the upper respiratory epithelium where the lymphatic system is present. Even less is known about the effects of the possible colonization of the related mucosal tissues.

Probiotics are widely added to commercial dairy products and food products, and they are increasingly consumed as supplements [9]. The safety of L. GG has been monitored since 1989. A few case reports have described infections caused by probiotics, such as bacteremia, endocarditis, and internal organ abscesses. However, the incidence of *Lactobacillus bacteremia* has remained stable although the consumption of probiotic products has increased exponentially [10]. Infections seem to be very sparse and affect mostly immunocompromised or critically ill patients [11]. Probiotic consumption has been documented as safe in neonates and even in preterm infants [12]. A report from Finland suggested that L. GG is safe for premature infants based on 12 years of its administration to all premature and very low birth weight infants born in the area around one university hospital [13].

Probiotics and their health effects

Probiotics should fulfil the following criteria: they must survive in the gastrointestinal tract and be able to proliferate in the gut; they should benefit the host through growth and/or activity in humans; and they should be non-pathogenic and non-toxic [14]. Probiotic micro-organisms exist in multiple genus, species, and strains. Although recent evidence suggests that they have some common health effects, they have many strain-specific health effects [4]. The most common probiotic organisms are bacteria from the genus *Bifidobacterium* and the genus *Lactobacilli* [15]. The findings of broad meta-analyses of strain-specific probiotics support that common health benefits are derived from consuming an adequate dose of any safe strain of a species that is already known to be an effective probiotic. For example, a meta-analysis of different strains and 10,351 patients found that probiotics had a positive effect on eight gastrointestinal diseases across the all studied probiotic species [16]. However, the results showed differences in efficacy regarding specific diseases and specific differences in strains.

Professional medical organizations have made clinical recommendations of well-defined specific probiotics for specific clinical conditions. In particular, gastrointestinal conditions have shown health effects: probiotics are

recommended in the treatment and prevention of acute gastroenteritis, necrotizing enterocolitis, and antibiotic-associated diarrhea [17]. They can be supplemented with infant formula to enhance growth and improve clinical outcomes although evidence is still lacking [18]. Some evidence exists to support the use of probiotics in several conditions: constipation, irritable bowel syndrome, inflammatory bowel diseases, lactose intolerance, allergies, atopic eczema, certain cancers, hepatic diseases, hyperlipidaemia, *Helicobacter pylori* infection, genitourinary tract infections, and oral health [19,20]. In 2015, the World Allergy Organization (WAO) convened a guideline panel to develop evidence-based recommendations for the use of probiotics in the prevention of allergy [21]. The European Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) association has also established recommendations for the use of probiotics in the prevention and treatment of acute gastroenteritis in children [22]. ESPGHAN recommends the use of specific, well-studied probiotics to prevent and treat acute gastroenteritis in infants and children and to reduce the side-effects associated with antibiotics [22]. In addition, the meta-analysis of a specific probiotic strain concluded that L. GG was effective in preventing antibiotic-associated diarrhea in children and adults who were treated with antibiotics for any reason [23].

Mechanisms of action

The mechanisms of the action of probiotics in viral and bacterial infections are not completely understood. Specific probiotics show strain-specific potential for reinforcing the integrity of the intestinal epithelium and regulating immune components. In regulating complex immune responses, the gastrointestinal tract from the oral cavity to the rectum is considered the largest immune interface with the environment [24]. The potential mechanisms are studied mainly in the gastrointestinal epithelium. Some postulated mechanisms of probiotic action in intestinal epithelial defense are presented in Figure 1, Adapted from Wan et al. [25]. The potential mechanisms of action in the upper respiratory tract remain unknown, and similar mechanisms than in intestinal epithelium may exist, but the topic needs to be studied further.

It is possible that probiotic bacteria could bind to an invading virus, thus inhibiting virus attachment to the host-cell receptor [26]. Lactic acid bacteria may exert antiviral activity by the following: 1) direct interaction as an adsorptive or trapping mechanism; 2) stimulation of the immune system by interleukin, natural killer cells, Th1 immune response activity, and IgA production; 3) production of antiviral agents (e.g., hydrogen peroxide, lactic acid, and bacteriocins) [27].

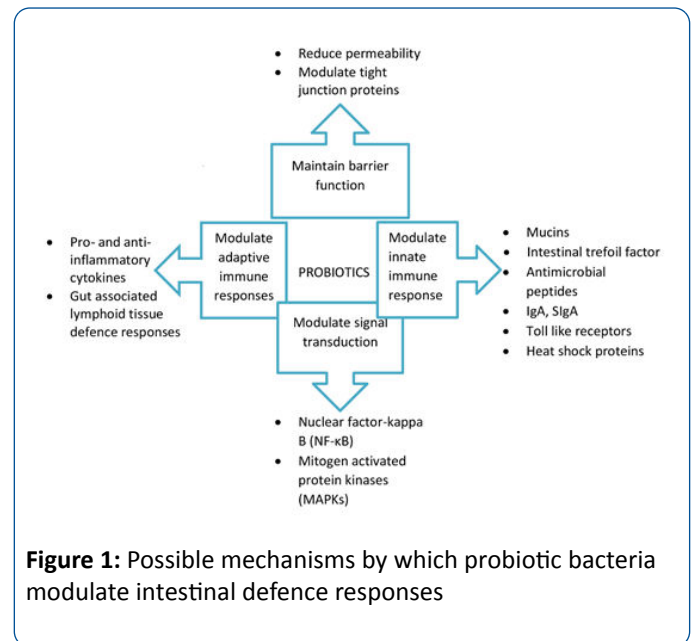


Figure 1: Possible mechanisms by which probiotic bacteria modulate intestinal defence responses

Acute viral respiratory infections

Acute viral upper respiratory infections (URI), which are also known as the common cold, are among the most common health problems in humans [28]. The economic burden on society of the otherwise usually benign disease is enormous because of absences from work, school, and daycare, as well as the utilization of health care providers and treatments. In the USA, 25 million health care visits a year are made because of URI [29]. On average, children 1-2 years of age experience 3-8 respiratory infections yearly, and children over 5 years of age experience about three respiratory infections yearly [30,31].

More than 200 viruses are known to cause respiratory infections in humans [32]. Major pathogens that induce URIs are human rhinoviruses (HRVs) from the family *Picornaviridae*, genus *Enterovirus* [33]. Other common causative agents are respiratory syncytial virus (RSV), parainfluenza virus, enterovirus (EV), coronavirus, influenza virus, and adenovirus [34]. Of these, influenza virus, RSV, and parainfluenza virus are more frequent causes of lower than upper respiratory infections [28,31,35]. The symptoms of URI arise after an incubation period that varies depending on the causative agent.

Colonization of upper respiratory tract with probiotics

Colonization of the gut epithelium by probiotics has been extensively studied [36-38]. Mucosal adhesion is incorrectly taught as essential for both non-immune and mucosal immune defense mechanisms. For example, noncolonizing probiotics, such as *Lactobacillus casei*, may exert their functions in a transient manner or by influencing the existing microbial community [39]. Thus far, few trials have investigated the colonization of upper respiratory tract with probiotics. In a pilot study, probiotic *Lactobacillus plantarum* DSM9843 was

cultured from the tonsillar surfaces of 6 subjects up to eight hours after the per oral consumption of fermented oatmeal gruel enriched with this probiotic [40]. Another small population trial investigated the recovery of *Streptococcus salivarius* K12 in the nasopharynx and oral cavity after oral intake [41]. In this study, one of 19 nasopharyngeal cultures was reported positive for the probiotic, and it was recovered from three adenoids of the seven examined. Tonsillar recovery of L. GG after per oral consumption was studied in 57 young adults in a placebo-controlled and randomized trial [42]. L. GG was recovered in 40% of the L. GG groups' tonsillar samples and in 30% of the placebo groups' samples. In a recent trial, 20 adults were treated with intranasal *Streptococcus salivarius* 24SMBc for three days [43]. The results showed that 95% of

the subjects were colonized in the nasopharynx with the probiotic at least four hours after spray administration; colonization persisted for at least six days in 55% of the subjects. L. GG was also recovered from adenoid tissue of children consuming probiotic per orally in a randomized double-blinded study [44]. Here, all subjects who consumed L. GG presented with the bacteria in the adenoid, as well as 76% of the placebo groups samples were positive. Twenty-five middle ear effusion samples of the same study population were studied in another trial [45]. In this study, 21% in the L. GG group presented with L. GG and 7% in the placebo group presented with L. GG in the middle ear. These studies are presented in Table 1.

Table 1: Characteristics of the previous studies investigating the colonization of upper respiratory tract with probiotics; RDBPC=randomized, placebo-controlled, prospective clinical trial

Subjects	Design and duration	Probiotic supplementation	Main findings	Reference
Healthy volunteers, mean age 38 (n=6)	Swab samples from tonsils after single per oral intake	<i>L. plantarum</i> (2×10^{11} cfu)	Colonization remained for 8 h	Stjernquist-Desatnik et al. [40]
Children scheduled for tympanostomy, aged 0.5-5 years (n=19)	Swab samples from tongue and nasopharynx, 10 days	<i>S. salivarius</i> K12 (1.7×10^{10} cfu)	33% colonized	Power et al. [41]
Young adults scheduled for tonsillectomy, mean age 24.5 years (n=57)	RDBPC Tonsil tissue samples, 3 weeks	L. GG (2×10^{10} cfu) or multispecies L. GG, Lc705, PJS, BB12	30-40% colonized NS in different intervention groups	Kumpu et al. [42]
Healthy adults aged 30-54 (n=20)	Nasal spray, rhinopharyngeal swabs, 3 days	<i>S. salivarius</i> 24SMBc (8×10^9 cfu)	95% colonized 55% remained for six days	Santagati et al. [43]
Children scheduled for adenotomy, median age 37,8 mo (n=31)	RDBPC Adenoid samples, 3 weeks	L. GG ($8-9 \times 10^9$ cfu) \times 2	100% colonized in L. GG group, 76% in placebo group	Swanlung et al. [44]
Children scheduled for tympanostomy, median age 31 mo (n=13)	RDBPC MEE samples, 3 weeks	L. GG ($8-9 \times 10^9$ cfu) \times 2	21% colonized in L.GG group, 7% in placebo group	Tapiovaara et al. [45]

Clinical effects of probiotics in the upper respiratory tract

The prevention of upper respiratory infections by the use of probiotics has been studied in several trials. For instance, L. GG alone or in combination with other probiotics was shown to reduce the incidence or risk of URI in children [46-48]. A recent systematic review found a favourable outcome of the use of probiotics in reducing the episodes of new respiratory infection in children [49]. However, further studies are required to confirm these results. A recent Cochrane database review of the use of probiotics in URI found 13 randomized controlled trials with participants in several age groups [50] (Table 2). Probiotics were found to be better than the placebo in reducing the number of subjects who experienced acute URI, the mean duration of acute URI, the number of antibiotic prescriptions, and cold-related school absences. However, the quality of evidence was considered low or very low.

A meta-analysis of randomized, placebo-controlled trials indicates that L. GG is able to reduce the incidence of acute otitis media (AOM) and antibiotic prescriptions and decrease the risk of URI in children [51]. However, in otitis-prone children with nasopharyngeal pathogen colonization, L. GG did not reduce the occurrence of AOM [52]. A novel treatment model of intranasal spray bacteriotherapy with *Streptococcus sanguinis* was found to be effective in decreasing MEE in children with prolonged otitis media with effusion (OME) [53]. Statistically significant recovery was achieved with *Streptococcus sanguinis*, and a more modest, yet positive effect was achieved with L. GG. In otitis-prone children, the consumption of L. GG, Lc705, BB99, and PJS significantly reduced the number of positive human bocavirus nasopharyngeal samples [54]. The colonization of the epithelium of the upper respiratory system with specific probiotics or lactic acid bacteria is not well known. *Lactobacillus plantarum* DSM 9843 was recovered from the tonsillar surface after oral administration, suggesting that the strain may possess the capacity to adhere to tonsillar cells [40].

Streptococcus salivarius K12 was cultured from the nasopharynx of infants after the consumption of an oral powder prepared with this probiotic bacterium [41]. Furthermore, L. GG was recovered from tonsil tissue after oral consumption, and prolonged adhesion (over 4 weeks) was suspected [42]. The consequences of colonization are

unknown. An *in vitro* experiment indicates that L. GG is able to inhibit the adherence of *Streptococcus pneumoniae* to human epithelial cells [55]. Two review studies suggested that specific probiotics interact with pathogens and have the potential to reduce pathogen colonization in the nasopharynx, thus potentially reducing AOM and URI [26,56].

Table 2: Characteristics of the included randomized controlled studies in Hao et al. 2015; RD=randomized, B=placebo-controlled, P=prospective, C=clinical trial

Subjects	Design and duration	Probiotic supplementation	Main findings: Probiotic vs. placebo	Reference
Healthy adults aged 18-65 (n=318)	RDBPC, 3 month	<i>L. plantarum</i> and <i>L. paracasei</i> (1 × 10 ⁹ cfu)	Incidence of common cold episodes ↓ Number of days with respiratory symptoms ↓	Berggren et al. [75]
Day-care children aged 1-5 (n=398)	RDBC, 3 month	<i>L. rhamnosus</i> HN001 (10 ¹⁰ cfu)	Number and duration of URI ↔ Level of secretory IgA ↑	Cáceres et al. [76]
Older volunteers in daycare facilities (n=154)	RDBPC, 5 month	<i>L. casei</i> strain <i>Shirota</i> (4 × 10 ¹⁰ cfu)	Number of acute URI and symptom score ↔	Fujita et al. [77]
Day-care children aged 13-86 month (n=281)	RDBPC, 3 month	<i>L. rhamnosus</i> GG (10 ⁹ cfu)	Risk of URI ↓ Days with respiratory symptoms ↓	Hojsak et al. [7]
Hospitalized in pediatric department, over 1-year-old (n=742)	RDBPC, duration of hospitalization	<i>L. rhamnosus</i> GG (10 ⁹ cfu)	Risk of URI ↓ Episodes of URI >3 days ↓	Hojsak et al. [8]
Healthy volunteers aged 69-80 (n=60)	RPC, 2 or 3 month	<i>L. bulgaricus</i> (1.8-3.2 × 10 ¹⁰ cfu) and <i>S. thermophilus</i> (5.7-7.9 × 10 ¹⁰ cfu)	Risk of URI ↓ Natural killer cell activity ↑	Makino et al. [78]
Healthy day-care or school children aged 3-6 (n=638)	RDBPC, 3 month	<i>L. casei</i> (2 × 10 ¹⁰ cfu), <i>S. thermophilus</i> and <i>L. bulgaricus</i> (10 ⁹ cfu)	Incidence for common infectious diseases ↓	Merenstein et al. [79]
Infants needing formula aged 0-2 month (n=81)	RDBPC, 12 month	<i>L. rhamnosus</i> and <i>B. lactis</i> BB-12 (1 × 10 ¹⁰ cfu)	Risk of URI ↓ Risk of AOM and antibiotics ↓	Rautava et al. [47]
Healthy children aged 8-13 (n=80)	RDBPC, 3 month	<i>L. acidophilus</i> and <i>B. bifidum</i> (1 × 10 ⁹ cfu)	Symptoms of URI ↓ Absences from school related to URI ↓	Rerksupphol et al. [80]
Children aged 6-25 mo (n=100)	RPC, 3 month	<i>L. acidophilus</i> and <i>L. casei</i> (10 ⁹ -10 ¹⁰ cfu)	Episodes of respiratory tract infections ↓	Rio et al. [81]
School children aged 3-12 years (n=251)	RDBPC, 5 month	<i>L. casei</i>	Duration of lower respiratory infections ↓	Cobo Sanz et al. [82]
College students aged 18-24 (n=198)	RDBPC, 3 month	<i>L. rhamnosus</i> GG and <i>B. animalis ssp. lactis</i> BB-12	Duration of URI ↓ Median severity score ↓ Missed school days ↓	Smith et al. [83]
Healthy adults, average age 38 ± 13 (n=479)	RDBPC, 8.5 month	<i>L. gasseri</i> , <i>B. longum</i> , and <i>B. bifidum</i> (5 × 10 ⁷ cfu)	Duration of URI ↓ Total symptom score ↓ Days with fever during URI ↓	de Vrese et al. [84]

Discussion

The nasopharyngeal and adenoid micro biota is a complex interactive system, and the consequences of changing the

proportions, such as by probiotic colonization, remain unknown. The nasopharynx harbors a wide variety of bacteria and viruses, both commensal and pathogenic [57,58]. The bacterial composition of nasopharyngeal micro biota differs

from other body parts, which was surveyed in healthy Chinese young adults [59]. The nasopharyngeal micro biota presented with potentially invasive bacteria, such as *Streptococcus pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, *M. catarrhalis*, and *Neisseria meningitidis* in an overall healthy population [60,61]. In children, the nasopharyngeal micro biota was noted to change according to the season [60]. Furthermore, certain commensal taxa were found to be negatively associated with AOM pathogens, and the proportions of taxa changed depending on the use of antibiotics [62]. Respiratory viruses have been shown to accomplish changes in bacterial adhesion [63], colonization [64] and immunological mechanisms [65] in the nasopharynx. Eventually, complex interactions between viruses and bacteria in the nasopharyngeal epithelium can evoke bacterial superinfections [66].

It has been suggested that nasopharyngeal micro biota could affect subjects' vulnerability to respiratory infections. In an experimental HRV challenge trial, significant differences in two nasopharyngeal genera (*Neisseria* and *Propionibacterium*) were identified between HRV-infected and non-infected subjects [67]. Furthermore, a previous study showed that young children presented with a small number of bacterial taxa in high total numbers in their nasopharynx, contrary to their parents who presented with much more diverse taxa with lower bacterial carriage [68]. This finding suggests that a greater variety of nasopharyngeal micro biota could protect the subject against URI. It is possible that the maturation of the host-associated microbial community happens similarly in the nasopharyngeal area and in the gut [69]. Interestingly, the development of nasopharyngeal micro biota was studied in 60 healthy infants, and certain micro biota patterns were found to be associated with decreases in URI episodes reported by the parents [70]. Furthermore, nasopharyngeal micro biota, especially *Streptococcus*, has been implicated to children's risk of developing asthma [71]. These aspects of microbial diversity in the nasopharynx are also considered when breastfeeding is recommended [70,72].

Microbes can adhere directly to each other, but effects can also occur through adhesion on the host's mucosal surfaces. Highly evolved relationships between the upper respiratory micro biota exist, and it is important to understand those interactions, especially when the micro biota is manipulated. In probiotic settings, knowledge of the colonization of the respiratory epithelium is valuable for further research to investigate the effects of probiotics on the natural micro biota.

Over the past decades, gut micro biota has been increasingly recognized as one of the main factors in the increasing prevalence of immunity-related disorders, such as inflammation, atopy, asthma, musculoskeletal disorders, liver fibrosis, diabetes mellitus type 2, metabolic syndrome, cardiovascular diseases, neurodegenerative diseases, atherosclerosis, and cancer, which is also known as the hygiene hypothesis [73]. The research on metagenomics has contributed information on how the micro biota interacts with the host's physiology and has started to provide new therapeutically targets. Finally, by better understanding the

role of gut micro biota, the individual's micro biota could be integrated into personalized healthcare, and the individual's diseases could be targeted and treated more efficiently. However, the complete understanding of the disease process is required to determine whether targeting gut micro biota would be effective or not [74].

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Competing Interests

All authors declare any competing interests.

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