Review Paper

Probiotic Effects Against Viral Respiratory Infections: A Novel Approach to an Old Problem

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ABSTRACT

Background: Upper respiratory tract infections (URTI) are the most common human illnesses, leading to high absenteeism from school and work.

Objectives Although the importance of viral respiratory infections is known, preventive strategies are not yet well understood, so this study aims to investigate the preventive strategies.

Methods: Several studies have confirmed that probiotics can reduce the frequency, duration and severity of upper respiratory tract infections.

Results: Probiotic consumption was also associated with a significant reduction in school absenteeism and antibiotic prescription, as well as a significant decrease in fever (OR=0.19), cough (OR=0.14) and rhinorrhea episodes (OR=0.18). However, few clinical trials have investigated the effects of probiotics or synbiotics on specific viruses.

Conclusions: Further research is needed to determine the role of probiotics and prebiotics, especially postbiotics, in the treatment and prevention of respiratory infections. This study aimed to review the effect of probiotics against various viruses.

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Introduction

The most common human illness is an upper respiratory tract infection (URTI), which leads to high absenteeism from school and work, as well as reduced productivity. More than 200 types of viruses cause URTIs, with human rhinoviruses (HPVs) being the most common, accounting for 24 to 52% of cases [1]. Each year, children experience 7 to 10 colds, while adults have 2 to 5. The estimated cost of treating colds and flu exceeds $40 billion and $87 billion per year, respectively [2]. Each year, there are approximately 1 billion cases of influenza worldwide, including 3 to 5 million severe cases and 29,000 to 650,000 deaths from influenza-related respiratory illness [3].

Although the importance of viral respiratory infections is well known, preventive strategies are not yet well understood. Several accepted recommendations include maintaining good personal hygiene, practicing hand washing, and avoiding cigarette smoke, all of which are likely to reduce respiratory viral infections. A healthy, balanced diet, active probiotic supplements, and bacteria-derived products, such as OM-85 can also help reduce recurrent infections [4].

The term "probiotic" is used for live microorganisms (usually *Lactobacilli* and *Bifidobacteria* species) that, when administered in sufficient quantities, have beneficial effects on the host. Prebiotics are nutrients, particularly oligosaccharides, which promote the growth of probiotics in the gut. The term "synbiotics" is used when a product contains both probiotics and prebiotics. The relatively new term "postbiotics" refers to a complex mixture of metabolic products secreted by probiotics in cell-free supernatants, such as enzymes, secreted proteins, short-chain fatty acids, and vitamins that mediate the beneficial effects of probiotics. These postbiotics are produced by the fermentation of probiotic gut bacteria or possibly structural fragments of these bacteria. Probiotics have been used in many different disorders mostly gastrointestinal diseases, allergic diseases, infectious diseases, etc. [5-11]. A variety of probiotics have been studied for their possible activity against viruses, including various lactobacilli, bifidobacteria, enterococci and streptococci; often, mixtures of different probiotic strains are used [12]. As a natural immune organism, *Lactobacillus casei* has excellent immunomodulatory functions related to respiratory immunity and plays an active role in respiratory diseases such as airway infections, asthma, lung cancer, cystic fibrosis and chronic obstructive pulmonary disease [13].

Mechanism of Action

Probiotic supplements may have several mechanisms of action that reduce viral respiratory infections. When viruses are exposed to the mucous membranes of the respiratory tract, they must overcome three major lines of defense: The mucus layer, the innate immune defense, and the adaptive immune defense. Commensal and probiotic bacteria affect each of these lines of defense, having important effects on viral infections: Strengthening mucosal barrier function (the shape and function of the mucus layer depend on the microbiome), secretion of antiviral antimicrobial peptides and bacteriocins, inhibition of virus attachment to host cells, and modulation of the antiviral innate and adaptive functions of leukocytes [14].

Probiotics and the gut microbiome influence the expression of IFN-α/β receptors on the surface of respiratory epithelial cells [15, 16]. Oral probiotics interact with intestinal epithelial cells and immune cells via Toll-like receptors and stimulate the synthesis of mediators, cytokines, and chemokines, including macrophage chemoattractant protein 1, which activates the mucosal immune system, assisted by an increase in immunoglobulin A secretion by cells of the mucosal tissue. Probiotics also activate T cells and stimulate T helper 1 cells with antiviral activity. In addition, probiotics stimulate regulatory T cells to produce IL-10, an important regulatory and anti-inflammatory cytokine [17].

Postbiotics

The use of postbiotics could be a valid and safer alternative to probiotics to avoid risks associated with bacteria. Postbiotics are defined as "nonviable bacterial products or metabolites of microorganisms that are biologically active in the host" [18]. Postbiotics can provide the health benefits of probiotics while eliminating the need to introduce live microorganisms, which are not always harmless. In addition, postbiotics can increase the effectiveness of active microorganisms or convert them into functional ingredients. This makes it easier to deliver the active ingredients to the desired location in the intestine, thereby increasing shelf life and simplifying packaging and transport [19]. In a recent systematic review, pooled results from two randomized controlled trials (RCTs) (n=537) showed that heat-inactivated *Lactobacillus paracasei* CBA L74 reduced the risk of pharyngitis (relative risk, RR 0.31) and laryngitis (RR 0.44) compared to the placebo [20]. Singh et al. in a RCT showed that a yeast enzyme-derived postbiotic resulted in a significant reduction in the severity of cold/flu symptoms

and reduced the use of cold/flu medications compared to the placebo. Additionally, it had a beneficial effect on immune system function in children aged 4 to 12 years attending school or daycare during flu season in Ontario, Canada [21].

Clinical Trials

Several studies have confirmed that probiotics can reduce the frequency, duration, and severity of URTIs [22-25]. In a recent Cochrane review, the authors concluded that probiotics can decrease the number of participants diagnosed with at least one episode of URTI (RR=0.76), reduce the incidence of at least three events (RR=0.59), and shorten the mean episode duration (MD=−1.22 days). In this study, based on the results of 23 CRTs, it was concluded that probiotics are more effective in preventing acute URTIs than the placebo [26].

A systematic review and meta-analysis assessed the potential impact of probiotic consumption on the symptoms and progression of the common cold, influenza, and influenza-like illnesses. The intake of probiotics significantly decreased the incidence of the common cold (odds ratio [OR]=0.50, 95% confidence interval [CI], 0.38%, 0.64%, P<0.001) and episodes of influenza-like illness (OR=0.24, 95% CI, 0.14%, 0.40%, P<0.001). However, probiotics did not demonstrate a significant effect on reducing influenza episodes (OR=0.91, 95% CI, 0.62%, 1.35%, P=0.831). In conclusion, probiotic supplementation appears to play a promising role in alleviating the frequency and symptoms associated with the common cold and influenza-like illnesses [2]. Probiotic intake was linked to a notable reduction in both school absenteeism and the number of antibiotic prescriptions. The analysis revealed that individuals who utilized probiotic supplements experienced significantly fewer instances of fever (OR=0.19), cough (OR=0.14) and rhinorrhea (OR=0.18) [2].

Probiotics may offer several potential benefits in reducing respiratory infections in specific populations, including children, the elderly and asthmatic patients.

Asthma

Some lactobacilli, such as *Lactobacillus rhamnosus* GG, *Lactobacillus paracasei* and *Lactobacillus fermentum*, have been orally administered in clinics and have beneficial effects on children's asthma. Because acute asthma is closely related to RTIs, especially rhinovirus infections, the administration of lactobacilli may help prevent RTIs and reduce asthma attacks [27]. In a randomized study in children with mild persistent asthma, we showed that the synbiotic multi-strain preparation LactoCare® significantly reduced the number of cold attacks. Salbutamol consumption was also significantly lower in the synbiotic group [28].

In an interesting study, the researchers showed that a mixture of *Ligilactobacillus salivarius* LS01 (DSM 22775) and *Bifidobacterium breve* B632 (DSM 24706) reduced the frequency of asthma attacks by more than one-third [29].

Probiotics not only prevent respiratory infections and asthma exacerbations but also improve asthma control and treatment. Huang et al. reported that two different probiotic strains (*L. paracasei* and *L. fermentum*) were associated with improved asthma severity and pediatric asthma control test scores after three months. Furthermore, *Lactobacillus gasseri* was associated with improved lung function tests and asthma symptoms after two months [30].

Elderly

Immune function declines with age, but it has been suggested that probiotic intake can reverse these age-related changes. A systematic review and meta-analysis of controlled trials showed that probiotic intake increased the phagocytic capacity of polymorphonuclear leukocytes and the tumor-killing activity of NK cells compared to controls [31]. Probiotic supplementation enhances cellular immune function in healthy elderly.

Various individual probiotic strains have been used in studies, including *Lactobacillus delbrueckii* subsp. *bulgaricus*, *L. paracasei* subsp. *paracasei* CNCM I-1518 and *L. paracasei* Shirota. Additionally, three more probiotic strains—*Leuconostoc mesenteroides*, *Bacillus subtilis* CU1 and *L. rhamnosus* GG—have been utilized as functional foods. Current evidence indicates that certain probiotic strains reduce the number of acute URTIs in older adults more than the placebo. It is important to remember that the effect of probiotics is strain-dependent, and not all probiotic strains are effective [32].

Oral or Topical

As mentioned previously, traditional oral administration is effective for pulmonary infections. For respiratory diseases, such as allergic rhinitis and asthma, direct administration to the nose and lungs has proven to be a more plausible and effective method of therapeutic delivery. Pulmonary delivery of probiotics has been widely

studied in animal studies but less so in human studies. The high heat and dryness stress caused by spray drying during the production of probiotic sprays significantly reduces probiotic viability. To improve viability, mild heat pretreatment has been shown to increase bacterial cell viability. Fortunately, the groundwork for the formulation of inhalable probiotic powders has been properly established, and their development is expected shortly [33].

Probiotics may also show promise as locally administered anti-inflammatory agents and for strengthening the immune system in the sinuses [34]. Several studies have investigated the use of topical probiotics for allergic rhinosinusitis, yielding some promising results [35-37]. The microbiome contents of the upper respiratory tract help improve the local immune system and act as a first line of defense against foreign pathogens. The microbiome strengthens mucosal immunity, including a physical barrier that prevents microbial invasion and contains antimicrobial agents and glycoproteins, such as IgA.

Exogenously applied probiotics to the skin may help maintain a positive bacterial balance and reduce or eliminate pathological conditions. Because the skin microbiome is important in controlling inflammation and immune responses, it is not surprising that various skin conditions are associated with negative bacterial balance, and topical probiotics may have the potential to treat skin problems, such as eczema [38]. In atopic dermatitis, topical probiotics have shown the ability to increase skin ceramides, reduce erythema and pruritus, and decrease concentrations of pathogenic *Staphylococcus aureus* [39].

Rhinosinusitis

The direct entry of probiotic microorganisms and contact with airway epithelial cells and mucosal immunity may be the reason why intranasal administration is more effective. It is worth noting that although intranasal administration of probiotics is most commonly used for acute airway infections, it may also be a promising approach for other chronic inflammatory diseases, such as allergic rhinitis and chronic sinusitis. In general, due to the limited number of studies conducted, it is difficult to determine the effect of intranasal administration of probiotics. In a study involving healthy volunteers, intranasal administration of lactic acid bacteria showed good tolerance to honeybees (*Lactobacillus* and *Bifidobacterium* genera). Since this exposure does not cause symptoms, does not affect symbiotic bacteria, and does not elicit an inflammatory response, it may be used to treat upper respiratory tract diseases, such as chronic rhinosinusitis [40]. Another study showed that adding the synbiotic agent Familact (Dysto-Takmil) to intranasal corticosteroids significantly improved quality of life and extranasal symptoms in patients with allergic rhinitis compared to intranasal corticosteroids alone. This finding contributes to the growing body of evidence demonstrating the benefits of intranasal probiotics in the treatment of allergic rhinitis in adults [36].

Recently, Mårtensson et al. confirmed that nasal microbiome transplants taken from healthy individuals and administered as a nasal irrigant to patients with chronic or recurrent rhinosinusitis without polyps (CRSsNP) significantly reduced the patient's symptoms and the sino-nasal outcome test (SNOT-22) scores. Microbiome analysis showed a significant increase in the frequency and diversity of local bacterial flora [41].

Antibiotic-induced Dysbiosis and Viral Immunity

Early exposure to antibiotics appears to impair antiviral immunity in humans. Manipulation of commensal bacteria impairs lymphoid tissue development, disrupts immune cell homeostasis, and alters susceptibility to infection. A reduction in the number of antigen-specific IFN-γ-producing cytotoxic $CD8^+$ T cells has been observed. Additionally, impaired innate and adaptive antiviral immune responses, along with significantly delayed viral clearance after mucosal exposure to the influenza virus, were also noted [14]. While the administration of antibiotics promotes the clearance of targeted infections, it simultaneously disrupts the commensal microbiota and reduces the host's resistance to antibiotic-resistant microorganisms. Antibiotic treatment can shift the balance and cause homeostatic imbalance through altered expression of tight junction proteins, mucins, antimicrobial peptides, and cytokines [42]. The antibiotic-induced impairment of immune homeostasis is not limited to the gut; depletion of the microbiota present there also impairs systemic immunity [43].

Functional Foods

Functional foods are described as "processed foods that not only provide nutritional benefits but also possess properties that help prevent diseases or promote health. Several functional foods from different food sources have been confirmed to have antiviral effects against several viruses. Polyphenols, flavonoids, propolis, curcumin, prebiotics, probiotics and supplements, such as zinc, vitamins C, D and E are examples of functional food ingredients that can be considered natural

immune boosters. Antiviral compounds found in various fruits and plants can act on viruses and host cells to prevent infection. Increased intracellular Zn^{2+} concentrations can affect the replication of various RNA viruses, including influenza viruses. Zinc deficiency reduces antibody synthesis. Probiotic foods, such as probiotic milk and yogurt containing well-defined probiotic strains offer a simple, safe, effective, accessible, and inexpensive way to reduce the risk of catching a cold and to prevent respiratory infections [4]. Pomegranate peel extract and its components can prevent influenza A virus replication in vitro. Crushed garlic, with or without honey, has immune-boosting and antiviral effects [13].

Conclusion

Human life is constantly threatened by various viral infections, including the common cold, seasonal influenza epidemics, and the COVID-19 pandemic. In addition to hygiene measures, effective vaccines are needed to provide comprehensive protection. However, several preventive therapies against viral respiratory infections are currently available. Human clinical trials and systematic reviews have provided promising results showing that certain strains of probiotics can reduce the frequency (by up to half in some studies) and duration of respiratory infections. These findings are particularly important for people with underlying conditions, such as asthma or heart disease, whose issues may be exacerbated by viral respiratory infections. However, only a few clinical studies have investigated the effect of probiotics or synbiotics against various viruses. Further studies are needed to clarify the role of probiotics, prebiotics and especially postbiotics, in the treatment and prevention of respiratory tract infections.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

Conceptualization and study design: All authors; Data collection and drafting the manuscript: Rana Tafrishi;Review and editing: Hamid Ahanchian and Javad Ghaffari.

Conflicts of interest

The authors declared no conflict of interest.

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