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Review

Review of *Streptococcus salivarius* BLIS K12 in the Prevention and Modulation of Viral Infections

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Abstract: The discovery and application of bacteriocin-producing probiotics, such as *Streptococcus salivarius* K12 (BLIS K12), represent significant advances in the prevention and management of bacterial infections, particularly in the oral cavity and upper respiratory tract. Originally developed for its bacteriocin-mediated inhibition of the important bacterial pathogen *Streptococcus pyogenes*, BLIS K12 has more recently also demonstrated potential in the modulation and prevention of viral infections, including COVID-19. Emerging evidence also suggests a broader role for BLIS K12 in immune regulation, with implications for controlling hyperinflammatory responses and enhancing mucosal immunity. Of particular interest is recent work indicating that BLIS K12 can modulate antibody responses against viral antigens, such as the SARS-CoV-2 spike protein, positioning it as a unique adjunct in managing viral infections. This review chronicles the pathway of BLIS K12's probiotic development, emphasizing its relevant bacteriocin mechanisms, oral health applications, emerging antiviral properties, and potential broader health benefits through immune modulation, all of which position it as a significant non-pharmacological adjunct in managing respiratory and immune health

Keywords: *Streptococcus salivarius*; BLIS K12; antiviral; probiotic; respiratory tract; immunity; COVID-19

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1. Introduction

The global health burden posed by viral respiratory infections such as influenza and rhinovirus and the recent SARS-CoV-2 pandemic highlights the urgent need for innovative and effective prevention strategies. Viral respiratory tract infections not only account for significant morbidity and mortality but also facilitate secondary bacterial infections which exacerbate clinical outcomes [1,2]. Mucosal immunity, including the composition of the resident microbes, in the oral and nasopharyngeal regions serves as a critical frontline defense against these pathogens, making it an ideal target for probiotic-based interventions [3].

The oral microbiota is a complex ecosystem in which commensal and pathogenic bacteria live and interact, influencing overall oral and systemic health [4]. Probiotics, especially bacteriocin-producing strains, offer a compelling strategy for managing oral infections and maintaining a healthy microbial balance [5–7]. The utility of probiotics has now broadened from their historically predominant gastrointestinal applications to complex roles in immune system modulation and infection prevention at growing numbers of anatomical sites [8]. Among the new-generation probiotics, *Streptococcus salivarius* K12 (BLIS K12) (also referred to as ENT-K12, ATCC BAA-1024, DSM 13084, and DSM 34540) stands out for its dual antibacterial and immune-modulatory capabilities [9,10]. The lantibiotics salivaricin A2 and salivaricin B produced by BLIS K12 inhibit a broad range of

bacterial pathogens, including *Streptococcus pyogenes* and *Streptococcus pneumoniae*, which are implicated in pharyngitis, otitis media, and other respiratory infections [10].

Clinical evidence now underscores BLIS K12's role in reducing the frequency and severity of bacterial upper respiratory tract infections, establishing its significance in the maintenance of oral and nasopharyngeal health [10–14]. Initially selected for development as a probiotic due to its efficacy in inhibiting *S. pyogenes*, BLIS K12 has increasingly become a cornerstone in the probiotic management of a variety of bacterial infections and dysbiosis in the oral cavity and upper respiratory tract [15]. However, the impact of BLIS K12 may ultimately be found to extend beyond bacterial infections, as emerging evidence now points to a role in controlling viral infections, including COVID-19 [16–18]. The combination of bacteriocin-mediated pathogen control, immune pathway and mucosal immunity modulation, and potential viral inhibition now positions BLIS K12 as a unique tool in the fight against respiratory infections, both bacterial and viral. This review charts the development of BLIS K12 based on its documented efficacy against bacterial pathogens and then speculates upon its potential for modulating inflammatory responses associated with viral infections, and more generally about its contribution to immune cross-regulation (Table 1).

Table 1. The key studies supportive of the beneficial immunomodulatory, antiviral, and antibacterial activities of BLIS K12.

Study Focus	Key Findings	References
BLIS K12 on bacterial infections	A total of 41 children on a 90-day course of BLIS K12 with a 90% reduction in strep pharyngitis and 40% reduction in AOM episodes.	[19]
	In total, 20 adults on a 90-day course of BLIS K12, showing an 80% reduction in strep pharyngitis.	[20]
	Significant reduction in strep infections in children over 90 days.	[21]
	A 70% reduction in AOM episodes in children receiving BLIS K12.	[22]
BLIS K12 on viral infections	Adjunct use of BLIS K12 to help control viral lung infections and improve immune function.	[16]
	Preliminary observation of reduced SARS-CoV-2 positivity in children taking BLIS K12.	[17]
	BLIS K12 improves the pathology of individuals hospitalized with COVID-19.	[18]
BLIS K12 on bacterial and viral infections	BLIS K12 reduces the prevalence of bacterial and viral pharyngotonsillitis in children.	[23]
	BLIS K12 reduced recurrent respiratory tract infections in children and reduced use of antibiotics and antivirals.	[11]
	Individuals with high adherence to the BLIS K12 treatment protocol had reduced incidence of upper respiratory tract infections.	[14]
BLIS K12 and immunomodulation	BLIS K12 induces rapid interferon-gamma release.	[24]
	Enhanced cytokine responses, such as IL-8, IL-10, and IL-12, due to BLIS K12.	[25]
	BLIS K12 induces interferon-gamma release in the mouth.	[26]
	BLIS K12 induces salivary IgA in individuals performing high-intensity exercise.	[27]
	BLIS K12 induces SARS-CoV-2 antibodies in vaccinated individuals through molecular mimicry.	[28]
	BLIS K12 reduces immune inflammatory cytokines induced by periodontal pathogens in vitro.	[29]
	BLIS K12 reduces febrile flares in pediatric patients with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.	[30]
The impacts of BLIS K12 on microbiota	BLIS K12 does not disrupt oral microbiome diversity in children.	[31]
	BLIS K12 supplementation maintains oral microbiome balance without disruption.	[32]

2. Bacterial Infection Control

BLIS K12 was originally isolated from the oral cavity of a child appearing to have low susceptibility to *S. pyogenes* pharyngitis, an infection sometimes leading to the development

of rheumatic fever [33,34]. Early studies demonstrated that BLIS K12 inhibited a variety of bacterial respiratory tract pathogens, especially *Streptococcus pyogenes*, a key cause of strep throat, and also *Streptococcus pneumoniae* and *Moraxella catarrhalis* [35].

The absence of a safe and effective vaccine to afford protection against *S. pyogenes* infections was the initial motivation for the identification and development of a probiotic alternative to vaccination. Since there is still no vaccine available for *S. pyogenes*, the probiotic approach remains an important preventative option [36]. The strong anti-bacterial activity of BLIS K12 appears to be primarily due to its production of a potent repertoire of bacteriocins that includes the lantibiotics salivaricin A2 and salivaricin B [9]. These lantibiotic-class bacteriocins disrupt bacterial cell membranes, leading to cell death. Bacteriocins help mediate competition between bacteria, and when produced by microbiota-associated commensal bacteria can help limit the adventitious growth of pathogenic bacteria attempting to become established within that microbiota. This concept of bacterial interference, supported by pioneering work on the bacteriocins of Gram-positive bacteria [37], provided the foundation for subsequent research into BLIS K12's efficacy in controlling bacterial infections and enhancing overall mucosal health [10,33]. Intriguingly, recent findings by Lawrence et al. [38] have also demonstrated the efficacy of salivaricin A and salivaricin B against *Fusobacterium nucleatum*, a key contributor to periodontal disease and also increasingly implicated in the etiology of colon cancer. This highlights the potential systemic applications of BLIS K12, extending its utility beyond the oral cavity to also benefit gastrointestinal cancer prevention.

As antimicrobial resistance poses a rising global threat, the inclusion of BLIS-producing probiotics like BLIS K12 in therapeutic protocols offers a promising alternative to antibiotics in preventing upper respiratory tract infections (URTIs). BLIS K12's role in preventing bacterial infections remains a feature of its efficacy, as demonstrated by Di Pierro et al. [19] and Gregori et al. [21], who reported significant reductions in streptococcal pharyngitis recurrences among children treated with BLIS K12. This ability to limit bacterial superinfections is particularly critical during viral infections, such as severe influenza and COVID-19, where secondary bacterial complications can exacerbate outcomes [39,40].

By reducing bacterial pathogen loads and preventing superinfections, BLIS K12 supports respiratory tract health and reduces some of the complications associated with viral illnesses. Additionally, growing evidence suggests that probiotics like BLIS K12 may help modulate viral infections by enhancing mucosal immunity and further mitigating the risk of secondary bacterial infections—common complications in viral diseases (see below).

3. Immune Modulation and Reduction of Inflammation

BLIS K12 exhibits immune-modulating effects by balancing pro-inflammatory and anti-inflammatory responses. Excessive inflammation, such as cytokine storms in viral infections like COVID-19, can cause severe tissue damage. Laws et al. [25] reported a reduction in the systemic anti-inflammatory cytokine IL-10. This cytokine is central to the inflammatory process, and its dysregulation can lead to harmful outcomes during viral infections. By modulating inflammatory responses without compromising the immune system's infection-fighting capabilities, BLIS K12 helps mitigate severe disease outcomes while promoting the clearance of viral pathogens. This fine-tuning of inflammation is particularly valuable in managing viral infections where balanced immune responses are critical.

Another key aspect of BLIS K12's action is its ability to enhance local mucosal immune responses, particularly in the upper respiratory tract. Di Pierro et al. [23] observed that children supplemented with BLIS K12 had a lower incidence of viral pharyngotonsillitis infections, which was attributed to increased production of gamma-interferon (IFN-γ).

This finding was validated by Laws et al. [26], who showed that individuals receiving a standard dose of BLIS K12 exhibited increased levels of IFN-γ in saliva. IFN-γ plays a pivotal role in antiviral immunity by activating macrophages and natural killer (NK) cells and promoting viral antigen presentation through the upregulation of MHC molecules. This enhanced immune response ensures effective recognition and clearance of viral threats, including SARS-CoV-2, the virus responsible for COVID-19.

BLIS K12 also plays a role in preventing hyperinflammatory responses, such as cytokine storms. Studies indicate that BLIS K12 supplementation does not increase levels of pro-inflammatory cytokines like TNF-α and IL-1β, which are associated with severe viral infections [25]. Furthermore, Macdonald et al. [29] reported that BLIS K12 can dampen inflammation caused by bacterial pathogens. By reducing hyperinflammatory responses, BLIS K12 minimizes collateral tissue damage, contributing to improved outcomes during infections.

The immunomodulatory properties of BLIS K12 extend beyond its role in viral infections. Li et al. [41] demonstrated that salivaricin A and salivaricin B, lantibiotics produced by BLIS K12, exhibit significant immunomodulatory effects in a murine model of rheumatoid arthritis (RA). The study found that RA patients had a deficiency of salivaricin-encoding genes in their tonsillar microbiome, correlating strongly with immune cell dysregulation. Mechanistically, salivaricins directly bound to and induced conformational changes in IL-6 and IL-21 receptors, thereby inhibiting the latter's downstream signalling pathways. This led to reduced T follicular helper (Tfh) cell differentiation and interleukin-21 (IL-21) production, key factors in autoimmune inflammation. Salivaricin administration provided both prophylactic and therapeutic benefits against experimental arthritis in mice. A follow up study showed that supplementation of BLIS K12 in mice could reduce RA symptoms [42]. These discoveries highlight the potential for BLIS K12 to modulate systemic immune responses via its lantibiotic production, offering new avenues for therapeutic applications in autoimmune and inflammatory diseases.

A particularly intriguing finding is BLIS K12's potential to influence antibody responses through mechanisms like molecular mimicry, which may lead to cross-reactivity between bacterial antigens and viral proteins. Bondareva et al. [28] demonstrated that children and adults with high levels of *S. salivarius* in their oral microbiota produced enhanced levels of salivary anti-spike IgG antibodies following SARS-CoV-2 vaccination. This phenomenon is hypothesized to result from homology between a bacterial protein (RSSL-01370) produced by *S. salivarius* and the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. In experimental models, immunization with RSSL-01370 led to the production of anti-spike IgG antibodies, suggesting that *S. salivarius* could elicit cross-protective immune responses. Following vaccination, BLIS K12 supplementation has been shown to further enhance the salivary IgG response to viral antigens like the SARS-CoV-2 spike protein [28].

The ability of BLIS K12 to modulate antibody responses at mucosal surfaces, such as the oral cavity, is particularly significant in enhancing vaccine efficacy. By fostering balanced immune responses, BLIS K12 not only reduces inflammation but also promotes the production of secretory IgA (sIgA) antibodies, which are critical for mucosal immunity and the first line of defense against respiratory viruses. Bertuccioli et al. [27] demonstrated that BLIS K12, when used in conjunction with high-intensity exercise, could induce a robust sIgA response in the oral cavity, suggesting specific benefits for athletes.

These findings underscore the broader potential of BLIS K12 beyond bacterial inhibition. Its capacity to elicit cross-reactive antibodies, modulate systemic immune responses, and enhance mucosal immunity positions it as a valuable tool for improving immune health and supporting vaccine strategies. With its multifaceted immune-modulating abilities, BLIS

K12 represents a promising approach to enhancing viral protection and overall respiratory health (Figure 1).

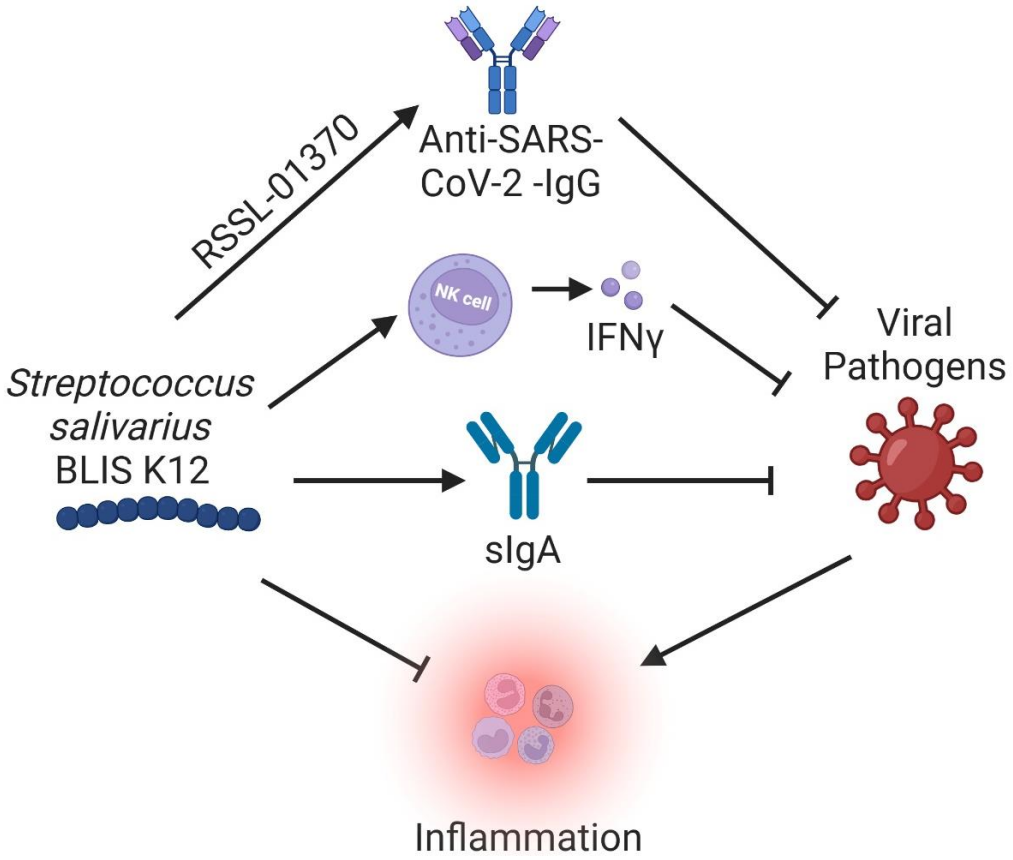

Figure 1. Summary of the mechanisms BLIS K12 utilizes to modulate the immune system to protect against viral pathogens. Created in BioRender. Hale, J. (2025); https://BioRender.com/k63a780 (Accessed 10 January 2025).

4. In Silico Insights on SARS-CoV-2 Modulation

Recent studies have suggested that certain bacteriocins may possess antiviral properties [43]. An in silico investigation by Erol et al. [44] explored the potential of salivaricin B, produced by BLIS K12, to bind the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. The spike protein plays a critical role in the viral entry into host cells by interacting with the ACE2 receptor. Erol's study demonstrated that salivaricin B exhibited strong binding affinity to the RBD, particularly for mutant forms such as the beta variant (B.1.351). The binding energy of −13.0 kcal/mol indicated significant potential for salivaricin B to block the interaction between the viral spike protein and the ACE2 receptor, thus preventing viral entry.

Interestingly, salivaricin B displayed greater binding affinity to double and triple mutations of the RBD compared to the wild-type virus, suggesting that it may be more effective against certain variants of concern. This discovery highlights the potential for bacteriocin-producing probiotics, like BLIS K12, to exert antiviral effects, particularly against respiratory viruses such as SARS-CoV-2.

Recently, Harold et al. [45] discovered that the production of the lantibiotics salivarcin A and B, which are produced by BLIS K12, could be enhanced by supplementation with the sugars raffinose or galactose. If the ability of salivaricin B to disrupt the delicate interaction of SARS-CoV-2 and ACE receptor is biochemically validated, the potential of these sugars to greatly improve BLIS K12s antiviral abilities cannot be ignored and will need to be clinically investigated.

This proposed receptor-binding inhibition antiviral mechanism complements the immune cross-regulation effects described by Bondareva et al. [28], suggesting a dual-action approach in which BLIS K12 both modulates antiviral immune defenses and inhibits viral entry (Figure 2). These combined effects reinforce the potential of BLIS K12, not only as a bacterial pathogen inhibitor but also as a modulator of viral infections, opening new avenues for its use in preventing and managing respiratory illnesses.

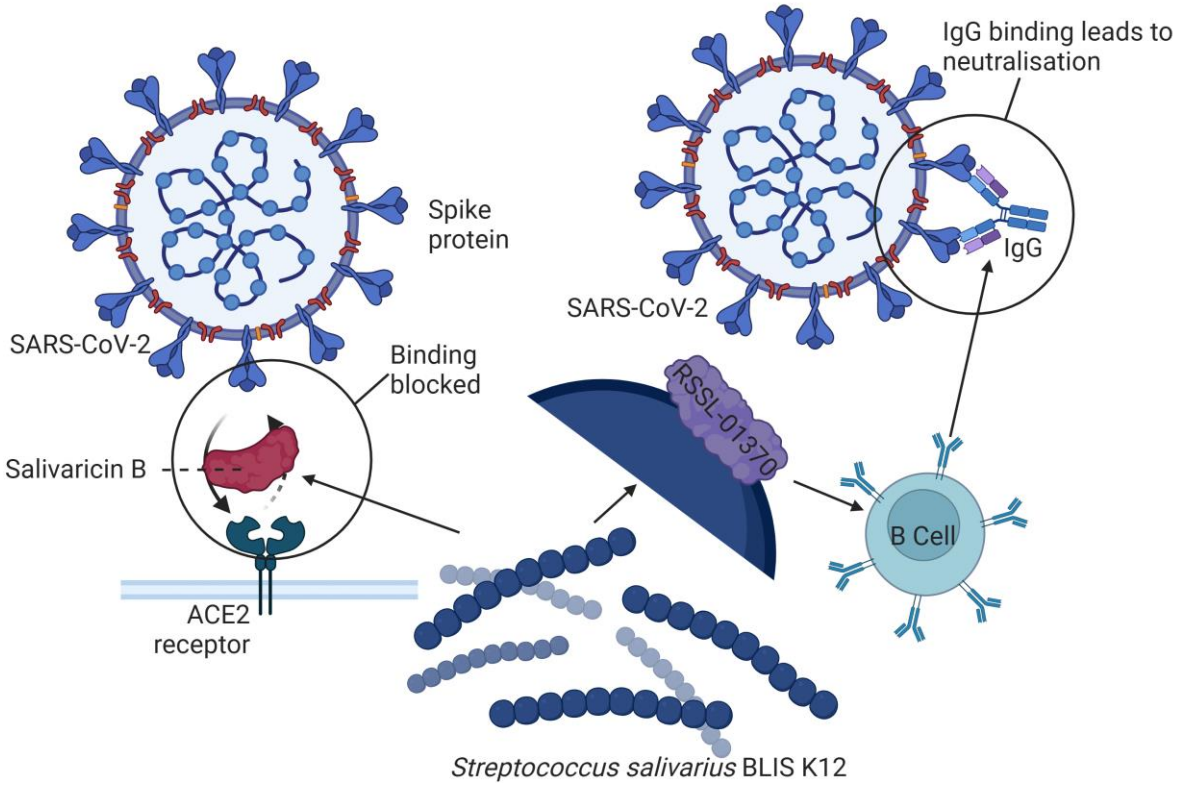

Figure 2. Two proposed mechanisms of BLIS K12 in disruption of SARS-CoV-2 infectivity. Created in BioRender. Hale, J. (2025); https://app.biorender.com/citation/67803a2d275900444cb54667 (Accessed 10 January 2025).

5. Modulation of Viral-Associated Bacterial Infections

Secondary bacterial infections frequently complicate viral respiratory illnesses, such as those caused by influenza and coronaviruses, significantly increasing morbidity and mortality [39]. Key bacterial pathogens implicated in these co-infections include *S. pneumoniae*, *Staphylococcus aureus*, and *S. pyogenes* [40]. Addressing these secondary infections is critical for improving patient outcomes, particularly during pandemics.

BLIS K12 offers a promising solution through its production of potent bacteriocins. These bacteriocins inhibit the growth of opportunistic pathogens, reducing bacterial loads in the oral cavity and nasopharynx. By maintaining microbial balance and limiting pathogen proliferation during viral illnesses, BLIS K12 plays a crucial role in the mitigation of bacterial superinfections.

Historical events, like the 1918 influenza pandemic, emphasize the catastrophic consequences of bacterial co-infections during viral outbreaks. Similarly, during the COVID-19 pandemic, bacterial co-infections were shown to exacerbate conditions such as pneumonia and acute respiratory distress syndrome [46]. Probiotics like BLIS K12 may potentially reduce such complications by preserving mucosal integrity and outcompeting pathogens and inhibiting their adhesion to mucosal surfaces.

BLIS K12's dual action—preventing bacterial colonization while enhancing mucosal immunity—creates an effective barrier against secondary bacterial infections. This reduces

reliance on antibiotics and addresses the growing issue of antimicrobial resistance. Its ability to disrupt bacterial membranes and restore mucosal balance highlights its role as a critical adjunct to antiviral therapies, offering a modern, integrative approach to managing viral respiratory illnesses and their bacterial complications.

6. Clinical Evidence of Efficacy for Viral Infections

Substantial clinical evidence supports the efficacy of BLIS K12 in preventing viral infections. A pivotal study by Di Pierro et al. [23] demonstrated that children receiving BLIS K12 experienced significantly fewer episodes of viral pharyngo-tonsillitis and acute otitis media compared to a placebo group. During the COVID-19 pandemic, another study by Di Pierro and Colombo [17] reported no SARS-CoV-2 infections in children who received BLIS K12, while infections occurred in the control group, suggesting a protective effect against viral pathogens. A study by Wang et al. [13] on medical staff fighting against COVID-19 showed a 64% reduction in the number of respiratory tract infections in the group taking BLIS K12. These findings are consistent with broader evidence showing BLIS K12's ability to reduce the incidence of respiratory viral infections, including those caused by influenza, rhinovirus, and even SARS-CoV-2. The probiotic achieves this by modulating mucosal immunity and competitively inhibiting viral adhesion, thereby enhancing immune responses against viral challenges.

Emerging research also indicates that BLIS K12 may lessen the severity of viral infections. Di Pierro et al. [18] found that hospitalized COVID-19 patients who received BLIS K12 showed improvements in key disease markers, including reduced supplemental oxygen demand and lower mortality rates. These results suggest that the immunomodulating and antibacterial properties of BLIS K12 extend beyond prevention, also playing a role in the mitigation of disease severity.

Ongoing research into bacteriocins and their potential interactions with viral proteins offers exciting possibilities for targeted probiotic therapies against specific viral pathogens. This innovative approach could position BLIS K12 as a key player in the future of viral infection management.

7. Microbiome Balance

The role of BLIS K12 in bacterial-infection prevention is well established, particularly in maintaining a balanced microbiome, which is crucial for respiratory health. Secondary bacterial infections, such as those caused by *S. pyogenes*, significantly worsen the outcomes of viral illnesses like influenza and SARS-CoV-2. BLIS K12 has been shown to reduce bacterial complications, with studies demonstrating a marked decrease in recurrent streptococcal pharyngitis among children treated with the probiotic [10].

By producing bacteriocins such as salivaricin A2 and salivaricin B, BLIS K12 inhibits the growth of opportunistic pathogens, helping to preserve oral and nasopharyngeal microbial balance. Studies by Cernioglo et al. [32] and Sarlin et al. [31] confirm BLIS K12's role in maintaining a healthy microbiome, which is critical in preventing secondary infections during viral illness. A balanced microbiome before viral infection can mitigate the risk of secondary bacterial complications, further enhancing respiratory health.

BLIS K12's capacity to regulate the microbiota, prevent bacterial superinfections, and reduce disease severity highlights its essential contribution to integrated respiratory health strategies. These findings reinforce its dual efficacy in both viral and bacterial infection control, offering a comprehensive, probiotic-based solution for improved health outcomes.

8. Broader Implications for Viral Infection Control

The dual capability of BLIS K12 to prevent viral infections and reduce bacterial superinfections holds significant promise for global health. As our understanding of the complex interplay between viral infections, bacterial pathogens, and immune modulation deepens, probiotics like BLIS K12 are emerging as vital tools for preventing and managing viral diseases.

Recent advances, including in silico models that predict bacteriocin interactions with viral proteins, present exciting opportunities for future applications [44]. These models may pave the way for the development of new BLIS-producing strains tailored to combat emerging viral pathogens, enabling rapid-response mechanisms during viral pandemics. By leveraging its dual functionality in bacterial and viral infection control and its ability to enhance immune adaptability, BLIS K12 offers a proactive strategy for addressing evolving viral threats, including variants of SARS-CoV-2.

Beyond respiratory health, the success of BLIS K12 suggests the potential for extending similar probiotic strategies to other mucosal sites, such as the gastrointestinal and dermatological systems, where viral–bacterial interactions significantly impact health outcomes. These broader applications highlight the versatility of BLIS-based approaches in managing diverse microbial and immune challenges.

9. Conclusions

S. salivarius BLIS K12 has established itself as a potent tool in managing bacterial infections and is emerging as a promising candidate in the prevention and modulation of viral infections. Its dual functionality—enhancing immune responses and directly interacting with pathogenic microbes—positions BLIS K12 as a unique and multifaceted approach to respiratory and viral infection management.

Recent studies, such as those by Bondareva et al. [28], indicate a potential role for BLIS K12 in cross-regulation of antibody responses, including enhanced immune responses to the SARS-CoV-2 spike protein. This finding underscores its broader antiviral applications, particularly as an adjunctive tool in enhancing vaccine efficacy or mitigating viral disease severity.

BLIS K12's ability to support mucosal immunity and maintain a balanced upper respiratory microbiome adds to its utility in preventing both primary viral infections and secondary bacterial superinfections. These attributes are especially critical for vulnerable populations, including the elderly, the immunocompromised, and individuals with chronic respiratory conditions. Prophylactic administration of BLIS K12 in these groups could significantly reduce the risk and severity of infections, supporting overall respiratory health.

Emerging evidence further suggests that bacteriocins produced by BLIS K12 may have applications beyond infection control, with preliminary research hinting at anticancer properties, including the ability to inhibit cancer cell proliferation through apoptosis induction and immune modulation. While this is an area requiring further investigation, it highlights the broader potential of BLIS K12 in health promotion.

Despite its promise, the current research has limitations, including small sample sizes, limited diversity in study populations, and short follow-up durations. To fully elucidate the relevant antiviral and broader health benefits, large-scale, controlled clinical trials are essential. These studies should explore optimized dosing regimens, potential synergistic effects with vaccines or antivirals, and the applicability of these findings across diverse populations and health conditions.

In summary, BLIS K12 represents a simple, versatile, and innovative probiotic-based approach to health management. Its demonstrated efficacy in bacterial and viral defense, coupled with its potential in mucosal immunity and emerging roles in broader health

applications, positions it as an invaluable asset in addressing a spectrum of health threats. With continued research, BLIS K12 could become a cornerstone of comprehensive strategies for safeguarding respiratory health, preventing infections, and potentially contributing to other areas of medicine, such as cancer prevention.

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