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Antiviral Potential of Lactic Acid Bacteria and Their Bacteriocins

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Abstract Emerging resistance to antiviral agents is a growing public health concern worldwide as it was reported for respiratory, sexually transmitted and enteric viruses. Therefore, there is a growing demand for new, unconventional antiviral agents which may serve as an alternative to the currently used drugs. Meanwhile, published literature continues shedding the light on the potency of lactic acid bacteria (LAB) and their bacteriocins as antiviral agents. Health-promoting LAB probiotics may exert their antiviral activity by (1) direct probiotic–virus interaction; (2) production of antiviral inhibitory metabolites; and/or (3) via stimulation of the immune system. The aim of this review was to highlight the antiviral activity of LAB and substances they produce with antiviral activity.

Keywords Probiotics · Lactic acid bacteria · Bacteriocins · Antiviral agents

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Introduction

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [1]. Probiotics are considered as nutraceutical, although they may serve as pharmaceuticals when administered under the medical professionals' supervision. The concept of probiotics was conceived by Hippocrates, who wrote: "Let food be the medicine, and let medicine be the food." Historically, deaths rising from infections were reduced upon improvements in nutrition. During the last decades, a large body of literature showed clear connection between nutrition, immune function and the rate of occurrence of infectious diseases [2]. LAB were first isolated from milk and then found in fermented products such as meat, vegetables, beverages, bakery and dairy products [3]. LAB are broadly used as starter cultures in food and feed fermentations, food protection, etc. In addition, last decades are marked by the increased interest in studying inhibitory substances produced by LAB, which include bacteriocins, lactic acid and hydrogen peroxide. Some LAB are a part of the normal microbiota on mucous membranes, such as the intestines, mouth, skin, urinary and genital organs of humans and animals, and may have a beneficial influence on these ecosystems [4].

Several LAB have gained the status of pharmaceutical preparations; each positive effect afferent was then supported by a number of clinical studies or human intervention trials and performed in a way that resembles the traditional pharmacological approach (placebo-controlled, double-blind, randomized trials) [5]. In addition, rapid development of tools and approaches for genetic manipulation of LAB created an avenue for the development of recombinant strains by expressing antigens leading to induction of protective immunity [2]. LAB used in

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Table 1 Basic criteria used for the design of LAB probiotics

General	Property
Safety in food and clinical use	Preferably human origin
	Absence of pathogenicity and virulence
Technological criteria	Stability of the LAB strain
	Viability during processing and storage
	Good sensory properties
	Phage resistance
	Ease scale-up production
Functional criteria	Tolerance to bile and acidity environment
	Adhesion to human intestinal cells
	Persistence in human intestines
	Clinically validated and documented health effects

probiotic foods were shown to stimulate the immune system and to increase resistance to infections [2]. In this case, LAB is also considered as "viable preparations in foods or dietary supplements to improve health of men and animals" [6]. The use of LAB probiotics as antiviral agents is relevant for aquaculture [7], poultry industry [8] and medical applications for treatment of various viral infections. The purpose of this mini-review is to highlight the antiviral potential of LAB probiotics or that of their inhibitory substances, with a focus on bacteriocins.

Key LAB Functions Considered for Probiotic Design

Industry-based consensus workshops agreed on criteria for the selection and assessment of probiotic lactic acid bacteria (LAB) without any defined mechanistic framework (Table 1) [9]. The recommended properties for LAB strains are listed in Fig. 1. Further, functions including probiotics' survival in different environments (e.g., digestive tract or vaginal mucosa) are of major importance. The capabilities of LAB probiotics antagonism to fight against adverse microorganisms are thought to be exerted by the production of nonspecific inhibitory metabolites, such as short-chain fatty acids, hydrogen peroxide (H_20_2), bacteriocins and bacteriocin-like inhibitory substances (BLIS), bacteriophages, lactic acid and polysaccharides.

How LAB Probiotics can Inhibit Viruses?

Prevention and alternative treatment are needed to face the emergence of new infectious viruses and increased resistance against the available antiviral drugs. Usually, treatment of viral infections is accompanied by using anti-inflammatory, analgesic and antipyretic drugs, making it often a treatment of broad-range secondary symptoms. When viral infections such as herpes are more complicated and life/health threatening, the use of antiviral drugs becomes essential. LAB probiotics may exert their antiviral effects by several mechanisms including direct interaction with viruses, production of antiviral inhibitory substances or/and by stimulation of immune system. Published literature analysis indicates that antiviral effect of probiotics is likely to be strain-dependent. Further, the main LAB probiotics and their antiviral activity are depicted in Table 3.

Direct Virus–Probiotic Interaction

This is likely to be the most frequently reported mode of virus inactivation by LAB probiotics. In most of the cases, it occurs as an adsorptive or trapping mechanism. For example, Botić et al. [10] showed that probiotics can trap vesicular stomatitis virus (VSV) by direct interaction between LAB cells including *L. paracasei* A14, *L. paracasei* F19, *L. paracasei/rhamnosus* Q8, *L. plantarum* M1.1 and *L. reuteri* DSM12246 and VSV envelope. Recently, Wang et al. [11] reported the ability of *E. faecium* NCIMB 10415 to inhibit influenza viruses upon direct physical interaction. On the other hand, *L. gasseri* CMUL57 isolated from vaginal microbiota [12] was able to inhibit enveloped

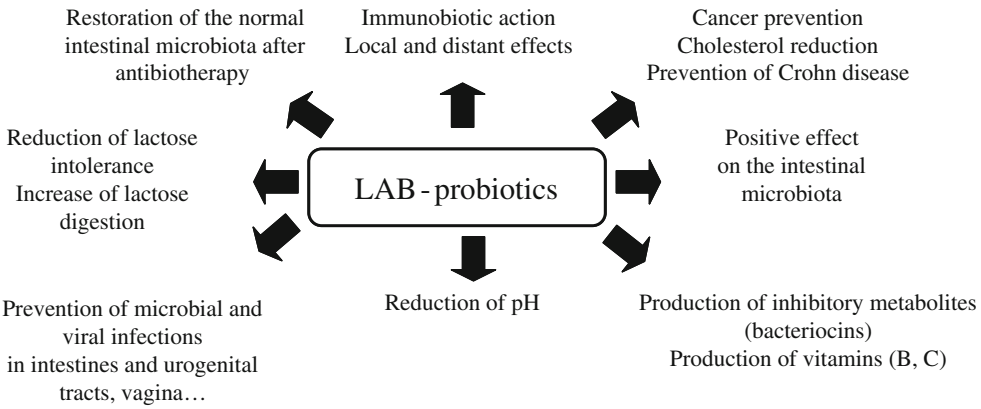

Fig. 1 Potential functions attributed to LAB probiotics

herpes simplex type 2 (HSV-2) but not naked coxsackievirus (CVB4E2) through a trapping mechanism [Al Kassaa, unpublished].

Stimulation of Immune System

LAB probiotics, especially the *Lactobacillus* species, can potentially play a significant role in the antiviral and antimicrobial activity as an important contributor to the host's immune system. *L. plantarum* strain YU, isolated from food products, showed high interleukin 12-inducing activity in mouse peritoneal macrophages [13]. Strain YU enhanced natural killer cell activity in spleen cells and production of IgA from Peyer's patch cells. Furthermore, activation of Th1 immune responses and IgA production induced anti-influenza virus H1N1 activity [13].

Production of Antiviral Agents of Nonproteinaceous Nature

Hydrogen peroxide (H_2O_2) produced by *Lactobacillus* sp. plays an important role as a natural microbicide within the vaginal ecosystem and is toxic to a number of organisms, including human immunodeficiency virus type 1 (HIV-1) and HSV-2 [14, 15].

Lactic acid, a final product of carbohydrate metabolism, is produced by all *Lactobacillus* species and is responsible for the homeostasis of the vaginal pH ($\leq$4.5). Acidic pH inactivates HIV [16] and HSV-2 [18]. Moreover, HSV-2 is irreversibly inactivated by concentrations of lactic acid at the pH value corresponding to that observed in the healthy human vagina [15].

It is appearing that lactobacilli could produce compounds that could help the host cells to defy viral replication [19]. Related to this, a nonprotein cell wall component extracted from a vaginal strain of *L. brevis* strongly reduced HSV-2 replication in cell culture [19], whereas acid *Lactobacillus* metabolic products decreased activation of T lymphocytes, which may result in decrease in lymphocyte susceptibility to HIV-1 infection [20].

LAB-Derived Antiviral Agents of Proteinaceous Nature

Bacteriocins are ribosomally synthesized small, mostly cationic, amphiphilic peptides, with antimicrobial properties directed against closely related bacterial species [21]. It should be noted that antagonism against distant organisms was also reported, but very rarely. Originally, four classes of bacteriocins were proposed based on their biochemical and genetic characteristics, structures and mechanisms of action [22]. Cotter et al. [23] reclassified bacteriocins and suggested only two simplified groups i.e., Class I, lantibiotics and Class II, non-lantibiotics. Most bacteriocins act by forming pores in the membranes of target cells [24, 25], causing a decrease in the intracellular pH and inhibiting enzymatic processes [26]. Class I bacteriocins (lantibiotics), such as nisin, have been shown to bind to lipid II, the main transporter of peptidoglycan subunits from the cytoplasm to the cell wall, and therefore prevent correct cell wall synthesis, leading to cell death [23]. Furthermore, they can use lipid II as a docking molecule to initiate a process of membrane insertion and pore formation that leads to rapid cell death [23]. Class II encompasses subclass IIa (pediocin-like bacteriocins), subclass IIb (two-peptide bacteriocins) and subclass IIc (circular bacteriocins). The mode of action of different class II bacteriocins is summarized by Drider and Rebuffat [27].

While the antibacterial activity of bacteriocins is somewhat deciphered, their antiviral activity remains to be understood. The repertoire of bacteriocins endowed with antiviral activities includes several reported or/and speculated as well as unknown models (Table 2). Bacteriocins including staphylococcin 188, enterocin AAR-71, enterocin AAR-74 and erwiniocin NA4 have been evaluated against coliphage HSA virus that was isolated from a raw waste water sample (collected from a local sewage treatment plant). Staphylococcin 188 and enterocin AAR-74 were shown to reduce viral progeny by tenfold, while enterocin AAR-71 and erwiniocin NA4 completely abolished viral progeny [28]. In addition, staphylococcin 188 was active against influenza virus and Newcastle disease virus when studied using in vitro and in vivo models [29]. HSV-2 was shown to be susceptible to peptide ST4V in a dose-dependent manner [32]. Indeed, the antiviral activity was obtained with 40 and 400 μg/ml, while the cytotoxicity (CC50) on Vero Cells was observed with concentration of STAV higher than 1,600 μg/ml [32]. These data are quite different from those reported for two other enterocins named ST5Ha and CRL35. The CC50 on confluent nongrowing Vero cells were 8,645 μg/ml for ST5Ha and 2,500 μg/ml for CRL35 [31, 32]. The antiviral activity, designed by the EC50 value (50 % effective concentration) of ST5Ha against HSV-1, was 50 μg/ml [30], while that of CRL35 against HSV-2 15 μg/ml [31] (Table 3).

Antiviral activity by enterocin CRL35 and ST4V has been observed against thymidine-kinase positive and deficient strains of HSV-1 and HSV-2 in Vero and BHK-21 cells, affecting intracellular viral multiplication, and inhibiting late stages of replication [31–33]. Remarkably, the amino-acid sequence of CRL35 is expected to play a role in anti-HSV-1 and anti-HSV-2 activities. Derivatives of CRL35 without at least two cysteine residues were assayed and shown to be devoid of antibacterial activity; and the authors hypothesized that these derivatives will be devoid of antiherpes activity as well [34].

Table 2 Bacteriocins endowed with antiviral activity reported in the text

Bacteriocin name	Producing strain	Antiviral activity tested	References
Staphylococcin 188	*Staphylococcus aureus* AB188	Newcastle disease virus Influenza virus Coliphage HSA	[29]
Enterocin AAR-71 Class IIa	*Enterococcus faecalis* AAR-71	Coliphage HSA	[67]
Enterocin AAR-74 Class IIa	*Enterococcus faecalis* AAR-74	Coliphage HSA	[67]
Erwiniocin NA4	*Erwinia carotovora* NA4	Coliphage HSA	[67]
Enterocin ST5Ha	*Enterococcus faecium* ST5Ha	HSV-1	[30]
Enterocin ST4V	*Enterococcus mundtii* ST4V	HSV-1 and HSV-2	[32]
Enterocin CRL35 Class IIa	*Enterococcus* mundtii CRL35	HSV-1 and HSV-2	[33]
Enterocin NKR-5-3C	*Enterococcus faecium* NKR-5-3	HSV-1	[Unpublished]
Labyrinthopeptin A1	*Actinomadura namibiensis*DSM 6313	HIV-1 and HSV-1	[68]
Subtilosine KATMIRA 1933	*Bacillus amyloliquefaciens* KATMIRA 1933	HSV-1	[69]
Bacteriocin	*Lactobacillus delbrueckii*	Influenza virus	[37]

HSV herpes simplex virus, *HIV* human immunodeficiency virus

Bacteriocin ST5Ha at 50 μg/ml reduced the viral production of HSV-1 in a cell culture by 50 % (EC_{50}), with a selectivity index (CC_{50}/EC_{50}) of 173 [30]. Pediocin-like enterocin NKR-5-3 C was shown to display strong anti-*Listeria* activity [35]. The anti-HSV-1 activity of NKR-5-3 was assessed, and its CC_{50} was lower than 1,200 μg/ml, while the EC_{50} value was 30 μg/ml [Al Kassaa et al. unpublished data].

Labyrinthopeptin A1 (LabyA1) is a prototype peptide of a novel class of carbacyclic lantibiotics [36]. LabyA1 exhibited a consistent and broad anti-HIV activity (EC_{50} 0.79–3.3 μM) in cell-line adapted HIV-1 strains [36]. Besides, LabyA1 showed a very consistent anti-HIV-1 activity with a median EC50 of 1.0 μM LabyA1 against nine different HIV-1 clinical isolates (eight from group M and one from group O) [36]. LabyA1 inhibited viral cell-to-cell transmission between persistently HIV-infected T cells and uninfected CD4+ T cells (EC_{50}: 2.5 μM), and inhibited the transmission of HIV captured by DC-SIGN+-cells to uninfected CD4+ T cells (EC_{50}: 4.1 μM) [36]. A synergistic effect in anti-HIV-1 and anti-HSV-2 activity was demonstrated using LabyA1 in dual combination with tenofovir, acyclovir, saquinavir, raltegravir and enfuvirtide [36].

In contrast to bacteria, the mode of action of bacteriocins against viruses remains to be determined. According to Wachsman et al. [33], bacteriocins could lead to aggregation of viral particles blocking the receptor sites on host cell, or they can inhibit key reaction in the viral multiplication cycle. Recently, a non-cytotoxic bacteriocin produced by *L. delbrueckii* subsp. *bulgaricus* 1043 was isolated and shown to be virucidal on influenza virus [37].

LAB Probiotics and Respiratory Viruses

Viral respiratory infections are the most common diseases in humans [38]. A large range of etiologic agents challenge the development of efficient therapies. Some studies suggest that probiotics can decrease the risk or duration of respiratory infection symptoms [38]. Probiotics with immunomodulatory and protective effects against viral respiratory infections in mice and humans have been reported [39, 40]. It was established that oral daily administration of *L. plantarum* L-137, a strain with proinflammatory activity, decreased influenza virus H1N1 titers in lungs of infected mice [40]. Other studies showed that *L. fermentum* CECT5716 and *L. casei* DN114-001 enhanced the effects of vaccination against influenza virus and improved antibody responses to influenza virus vaccination in humans, respectively [41, 42]. A mixture of *L. gasseri* PA 16/8, *B. longum* SP07/3 and *B. bifidum* MF 20/5 reduced the severity of symptoms related to common cold episodes in humans [43]. *L. rhamnosus* GG was tested in a clinical trial, either alone or in combination with *B. animalis* subsp. *lactis* BB-12, and reduced the incidence of respiratory virus infections (RVI) [44]. Moreover, a clinical trial using *L. acidophilus* strain NCFM alone or in association with *B. animalis* subsp. *lactis* BI-07 reduced influenza-like symptoms [45]. Boge et al. [41] demonstrated that the daily consumption of a probiotic-fermented dairy drink improved antibody responses to influenza virus vaccination in the elderly in two randomized, controlled trials. These successful preclinical and clinical trials highlight the potential of LAB probiotics as preventive and therapeutic agents in RVI. Chiba et al. [46] showed that

Table 3 Principle LAB probiotics and their antiviral activity reported in the text

Lactic acid bacteria strains	Origin	Antiviral activity tested	Mode of action	References
L. paracasei A14	Human and animal	VSV	Trapping mechanism	[10]
L. paracasei F19				
L. paracasei/rhamnosus Q8				
L. plantarum M1.1				
L. reuteri DSM12246				
E. faecium NCIMB10415	Human new born feces	Human influenza virus	Physical interaction	[11]
L. gasseri CMUL57	Human vagina	HSV -2	Trapping and inactivation	[12]
L. plantarum YU	Food product	Influenza virus (H1N1)	Activation of Th1 immune response	[13]
L. brevis	Vaginal flora	HSV -2	a nonprotein cell wall component extracted decreased viral replication	[19]
L. plantarum L-137	Fermented food	Influenza virus (H1N1)	Proinflammatory activity	[40]
L. fermentum CECT5716	Human breast milk	Influenza virus	Increase of the antibody response	[41]
L. casei DN114-001	Human breast milk	Influenza virus	Increase of the antibody response	[42]
L. gasseri PA 16/8,	Commercial probiotic strains	Decrease general infection	Immunomodulation	[43]
B. longum SP07/3				
B. bifidum MF 20/5	Human feces	Symptoms		
L. rhamnosus GG	Commercial probiotic strain	TGEV, RVI and RV infections	Immunomodulation	[44, 56]
	Human gut flora		Colonization	
B. animalis subsp. *Lactis* BB-12	Commercial probiotic strain	Reduce RVI infection	Immunomodulation	[44]
	Human gut flora			
L. acidophilus strain NCFM	New born feces	Reduce influenza like symptoms	Immunomodulation	[45]
B. animalis subsp. *lactis* BI-07 reduced	New born feces	Reduce influenza like symptoms	Immunomodulation	[45]
L. rhamnosus CRL1505	Commercial probiotic strains	RSV	Production of IFN-γ and ILs	[2, 47]
		Reduce mucosal infection		
	Human origin			
L. casei Shirota	Fermented food	Influenza viruses	Activated immature immune	[49, 54]
		RV, TGEV		
L. pentosus b240	Fermented tea leaves	Influenza virus (H1N1)	Immunomodulation	[50]
E. faecium NCIMB 10415	Pigs gut flora	Influenza virus	Increase IL10, decrease of TNF-α	[11]
L. paracasei ST11	Stool from breastfed healthy girl	Non-rotavirus diarrhea	Immunomodulation	[57]
E. faecium PCK38,	Fermented food	Enteric viruses	Increase production of NO-, ROS	[54]
L. fermentum ACA-DC179, *L. pentosus* PCA227			and H_2O_2	
L. plantarum PCA236 and PCS22				
B. adolescentis SPM1005-A	From healthy young stool	HPV infection	Suppression E6 and E7 oncogene expression	[63]
L. rhamnosus	Gut flora	HSV-1	Induce macrophage viability for elimination of HSV-1	[64]
L. curvatus VM25	Breast milk	HIV-1	Heat-killed bacteria: mucosal protection by immunity	[17]
L. fermentum VM21				
P. pentosaceous VM95				
P. pentosaceous VM21				

Table 3 continued

Lactic acid bacteria strains	Origin	Antiviral activity tested	Mode of action	References
L. salivarius VM5 *L. gasseri* VM22	Breast milk	HIV-1	Bacterial supernatants: mucosal protection by immunity	[17]

HSV herpes simplex virus, *HIV* human immunodeficiency virus, *TGEV* transmissible gastroenteritis, *RVI* respiratory virus infections, *RV* rotavirus, *RSV* respiratory syncytial virus, *VSV* vesicular somatic virus, *HPV* human papillomavirus

treatment of 3-week-old BALB/c mice with *L. rhamnosus* CRL1505 reduced lung viral loads and tissue injuries after the challenge with respiratory syncytial virus (RSV). Protective effect achieved by strain CRL1505 was related to its capacity to modulate respiratory antiviral immune response by secretion of IFN-γ and IL [47]. In direct line, Chiba et al. [46] showed that oral administration of *L. rhamnosus* CRL1505 to of BALB/c mice permitted a protective effect by modulating pulmonary innate immune microenvironment. Clearly, this protective effect was exerted through activation of $CD103^{+}$ and $CD11b^{high}$ dendritic cells and generation of CD3+CD4+IFN-γ+Th1 cells that attenuated strongly RSV challenge [46]. Thus, modulation of the common mucosal immune system by immunobiotics could favor protective immunity against respiratory viral pathogens with a high attack rate in early infancy, such as RSV [46]. Immunobiotics are useful microorganisms that exert beneficial immunomodulatory effects on the health of the host [48]. Further, Yasui et al. [49] reported that oral administration of *L. casei* Shirota activated immature immune system of neonatal and infant mice and protected against influenza virus infection. Therefore, oral administration of *L. casei* Shirota may accelerate innate immune response of respiratory tract and protect against various respiratory infections in neonates, infants and children, a high-risk group for viral and bacterial infections. Kiso et al. [50] found that oral administration of b240 on influenza A(H1N1) pdm virus infection enhanced protection against a lethal dose of CA04 virus. *E. faecium* NCIMB 10415 caused a modified cellular expression of selected defense mediators in 3D4 cells: while expression of TNF-α, TLR-3 and IL-6 were decreased in the swine influenza virus-infected and probiotic-treated cells, IL-10 expression was found to be increased [50].

LAB Probiotics and Enteric Viruses

Enteric viruses are present naturally in aquatic environments and usually acquired by humans from leaking sewage, septic systems, urban runoff, agricultural runoff, and, in the case of estuarine and marine waters, sewage outfall and vessel wastewater discharge [51]. They are transmitted via the fecal-oral route and primarily infect and replicate in the gastrointestinal tract of the host. Enteric viruses are shed in extremely high numbers in the feces of infected individuals, typically between 10^5 and 10^{11} virus particles per gram of stool [52]. Although enteric virus infections are associated primarily with diarrhea and self-limiting gastroenteritis in humans, they may also cause respiratory infections, conjunctivitis, hepatitis and diseases that have high mortality rates, such as aseptic meningitis, encephalitis and paralysis in immunocompromised individuals [53]. Beneficial effect of LAB probiotics against enteric viral infections was established in studies on rotavirus watery diarrhea [54]. *L. casei* DN 114001 and *L. rhamnosus* GG showed the most consistent effect in treatment of acute infectious diarrhea in infants and children [55, 56]. While *L. rhamnosus* GG was effective against rotavirus (RV) diarrhea [56], *L. paracasei* ST11 improved the recovery from non-rotavirus diarrhea [57]. Other strains were occasionally reported to stimulate host immunity or modulate inflammation. Probiotics such as *L. rhamnosus* GG and *L. casei* Shirota showed antiviral activity against RV and transmissible gastroenteritis virus (TGEV) [54]. Strong antiviral activities were attributed to *E. faecium* PCK38, *L. fermentum* ACA-DC179, *L. pentosus* PCA227 and *L. plantarum* PCA236 and PCS22. These strains showed increased release of NO^{-} and H_2O_2, up to 50 %, when co-incubated with intestinal epithelial cells and macrophages from human and animal sources. However, except for a small number of strains which were able to induce strong ROS release in more than one cell line, the results were found to be strain- and cell line-specific. The examined LAB strains ability to attach to the cell line monolayers was LAB strain-specific but not cell line-specific. Highest attachment ability was observed with *L. plantarum* ACA-DC 146, *L. paracasei* subsp. *tolerans*, *L. plantarum* ACA-DC 4037 and *E. faecium* PCD71. In addition, Cencic and Chingwaru [58] reported on antiviral effect of *L. casei* Shirota against TGEV and *L. plantarum* PCA236 against RV and TGEV.

LAB Probiotics and Sexually Transmitted Viruses (STV)

Viral infections, mainly HSV-2 and HIV-1, have proven particularly problematic to control from both scientific and public perspectives [59]. Epidemiological studies have established a link between the prevalence of HIV-1 and HSV-2 [59]. The burden of HIV-1 is important worldwide as 60 million individuals are infected and 30 million are living with the virus [60]. To date, treatment against HIV-1 and HSV-2 is based on vaginal application of 1 % tenefovir gel, which appeared to reduce transmission within participants of clinical study [61]. On the other hand, human papilloma viruses (HPV) infect squamous epithelial cells of cervix, low genitalia and oral cavity. The association of HPV with oropharyngeal carcinogenesis is well documented [62].

Using LAB and non-LAB probiotics for treatment of STV is a promising alternative, at least to reduce the virus burden. Related to this, Cha et al. [63] showed that *B. adolescentis* SPM1005-A had antiviral activity by suppressing expression of oncogene proteins E6 and E7. Another study showed a significant increase of macrophages viability in the presence of *L. rhamnosus* before and after HSV-1 infection [64], when compared against *Escherichia coli* as a non-probiotic bacterium [64].

Martin et al. [17] studied 38 LAB strains isolated from breast milk and showed that heat-killed bacteria and cell-free supernatants were active against HIV-1. Further, the highest anti-HIV-1 activity was observed with killed *L. curvatus* VM25, with 55.5 % of inhibition of HIV infectivity, followed by *L. fermentum* VM21 (52.5 %), *Pediococcus pentosaceous* VM95 (49.0 %) and *P. pentosaceous* VM21 (45.5 %). Inhibition of HIV was also reported with supernatants from eight LAB strains, and the most active ones were supernatants from *L. salivarius* VM5 (42 %) and *L. gasseri* VM22 (40 %) [17].

Recently, *L. gasseri* CMUL57 was isolated from human vagina [12] and showed to inhibit HSV-2 by direct interaction rather than by production of antiviral agents [Al Kassaa et al. submitted].

Conclusion and Future Prospects

The use of LAB probiotics and their constituents for screening of antiviral agents is a promising path in search for novel unconventional treatments and prevention strategies. This review highlighted the main mechanisms of virus inactivation by LAB probiotics reported in the literature. Further, combination of LAB probiotics and/or their products with traditional antiviral drugs may result in discovery of synergistically acting compositions and useful formulations for treatment of some viral infections.

In addition to already reported new emerging enteric viruses which include Norovirus and Sapovirus (belonging to the Caliciviridae family), Astrovirus and Adenovirus should be tested for possible inhibition by probiotics and their constituents. Last but not least, probiotics and their bacteriocins should be elucidated for activity against entroviruses responsible for various acute diseases and the role of which in chronic diseases especially type 1 diabetes is strongly suspected [65, 66].

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Conflict of interest The authors declare that they do not have any conflict of interest.

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