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MINIREVIEW

Lactobacilli, a Weapon to Counteract Pathogens through the Inhibition of Their Virulence Factors

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ABSTRACT To date, several studies have reported an alarming increase in pathogen resistance to current antibiotic therapies and treatments. Therefore, the search for effective alternatives to counter their spread and the onset of infections is becoming increasingly important. In this regard, microorganisms of the former *Lactobacillus* genus have demonstrated the ability to reduce the virulence of pathogens. In addition to the production of bioactive substances, self- and coaggregation, and substrate competition, lactobacilli influence gene expression by downregulating genes associated with the virulence of pathogens. As demonstrated in many *in vivo* and *in vitro* trials, lactobacilli counteract and inhibit various virulence factors that favor pathogens, including the production of toxins, biofilm formation, host cell adhesion and invasion, and downregulation of virulence genes linked to quorum sensing. The aim of this review is to summarize current studies on the inhibition of pathogen virulence by lactobacilli, an important microbial group well known in the industrial and medical fields for their technological and probiotic properties that benefit human hosts with the potential to provide an important aid in the fight against pathogens besides use of the current therapies. Further research could lead to the identification of new strains that, in addition to alleviating adverse effects, could improve the efficacy of antibiotic therapies or play an important preventive role by reducing the onset of pathogen infections if regularly taken.

KEYWORDS lactobacilli, virulence, probiotics, pathogen suppression

Lactobacilli, the term used in this work to refer to the former *Lactobacillus* genus (1), are lactic acid bacteria with fundamental roles in modern society and economies and are essential in the production and conservation of many food and feed products. Owing to their long history of safe use and their fermentative and bioprotective abilities, which ensure the quality and safety of products, they have received the designations of generally recognized as safe by the Food and Drug Administration and qualified presumption of safety by the European Food Safety Authority (EFSA) (2, 3). Due to their properties, several strains of this group have been identified as probiotics, defined by FAO and WHO as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (4, 5), and their inactivated cells or their cell-free supernatants (CFS) hosting numerous beneficial components are also considered postbiotics, defined as "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (6). They are also part of the human natural bacterial flora, in which they have a regulatory role in protecting hosts against colonization bypathogens and exert beneficial effects, such as increasing and improving nutrient assimilation during digestion or stimulating host tissues (7). Prolonged consumption of these bacteria leads to modification of the human gastrointestinal microbial flora, thus stimulating the immune system and decreasing pathogen adhesion (8). Owing to the interconnection between the gastrointestinal tract and the central nervous system, known as the gut-brain axis, these effects also arise from the production of signaling molecules with brain modulation abilities (9, 10).

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Lactobacilli are also effective in the prevention and treatment of gastrointestinal and urogenital tract diseases because of their antimicrobial properties (11, 12) and confer numerous beneficial effects, such as alleviating lactose intolerance, reducing blood cholesterol and incidence and progression of cancer, stimulating immunity, and preventing and treating diarrheal diseases, stomach ulcers, and infectious diseases (13, 14). Furthermore, lactobacilli inhibit pathogen growth through nutrient subtraction, competition for substrate, and the production of molecules such as bacteriocins, enzymes, organic acids, and hydrogen peroxide (15). Other important mechanisms include the ability to self-aggregate and coaggregate, which allow lactobacilli to adhere to each other or other microbial species. These adhesive properties provide lactobacilli with the ability to adhere to the mucosa, thereby limiting pathogen adhesion and creating a microenvironment in which their strict proximity allows the increase of inhibitory effects of the secreted substances (16).

In addition to these well-known properties, lactobacilli inhibit various virulence genes encoding transacting proteins associated with infective mechanisms, which are fundamental in bacterial virulence, as reviewed in Table 1. Among these mechanisms, one of the most important is the quorum sensing (QS) system, which leads to the production of different chemical molecules, named autoinducers, which alter gene expression. Through these signal-response systems, different bacteria coordinate their behaviors on a population scale, acting as multicellular organisms (17). QS systems regulate many microbial pathways, including biofilm formation, sporulation, antibiotic synthesis, induction of virulence factors, host infection, and bacteriocin synthesis. Autoinducer 2 (AI-2), produced by the LuxS enzyme (*luxS* gene), is of particular interest because it is associated with the expression of genes involved in pathogen motility, adhesion, and internalization. AI-2 also plays a fundamental role in biofilm formation, a common feature among pathogenic species that increases their adhesion to surfaces, provides them with nutrients, and confers resistance to external factors, thus making bacteria more virulent and resistant to antibiotic treatments (18–20). Moreover, antiviral activity, a property of particular interest in medical applications, has been observed in specific strains of lactobacilli and might be used to prevent viral adhesion and propagation (21).

Pathogenic bacteria are an important threat to human health, as they represent 4 of the top 10 causes of death worldwide (22). Currently, infections are treated mainly with antibiotics, whose discovery dates to the first half of the 20th century. However, the extensive and prolonged use of these substances has led to a natural evolutionary phenomenon of adaptation that has contributed to the spread of antibiotic resistance (23). Consequently, infections have become more difficult because antibiotics have become less effective in counteracting pathogens, thus enabling their survival and even replication in the presence of therapeutic levels of drugs. If no action is taken, multidrug-resistant pathogens have been expected to cause 10 million deaths by the year 2050. Therefore, identifying new effective methods will be critical to counteract the spread of pathogens and simultaneously decrease the use of antibiotics (24) in medical and zootechnical fields (25). The present review summarizes available data from original studies reporting the effectiveness of lactobacilli in counteracting the virulence of pathogenic species such as *Aggregatibacter actinomycetemcomitans*, *Bacillus cereus*, *Campylobacter jejuni* (*Cj*), *Candida albicans*, *Chlamydia trachomatis*, *Clostridium* spp., *Enterococcus faecalis*, *Escherichia coli* (*Ec*), *Gardnerella vaginalis*, *Helicobacter* spp., *Klebsiella* spp., *Listeria monocytogenes* (*Lm*), *Neisseria gonorrhoeae*, *Pseudomonas* spp., *Prevotella bivia*, *Salmonella* spp., *Serratia marcescens*, *Staphylococcus aureus* (*Sa*), *Streptococcus* spp., *Trichomonas vaginalis*, and *Yersinia enterocolitica*, as summarized in Fig. 1.

LISTERIA MONOCYTOGENES

Listeria monocytogenes (*Lm*) is the etiological agent of listeriosis, a severe foodborne disease with a low incidence rate but a high mortality rate that poses a serious public health concern (26). Internalization of this pathogen occurs via invasion of macrophages and nonphagocytic cells, a capability conferred by the internalin proteins InlA and InlB, while the production of hemolysin listeriolysin O (LLO) and PlcA and PlcB

TABLE 1 Summary of virulence genes affected by lactobacilli

Bacteria	Gene	Protein	Function	Reference
Listeria monocytogenes	*fbp*	Fibronectin-binding protein	Adhesion to epithelial cells	114
	flaA	Flagellin	Motility	28
	hly	Hemolysin listeriolysin O (LLO)	Survival inside macrophages	27
	iap	Invasion-associated protein	Invasion of epithelial cells	114
	plcA, *plcB*	PlcA and PlcB phospholipases	Survival inside macrophages	27
	prfA		Transcriptional activator of *hly* and *plc* genes	29
	sigB		Stress response regulon	31
		Autolysin amidase (Ami)	Bacterial adhesion on enterocytes	29
		Actin-polymerizing protein (ActA)	Required for actin polymerization allowing intracytoplasmic movement	30
		Internalin A (InlA) Internalin B (IlnB)	Adhesion and internalization inside enterocytes	27
		Listeria adhesion protein (LAP)	Bacterial adhesion on enterocytes	29
Salmonella spp.	*avrA*	AvrA	Inhibition of innate immunity	56
	hilA	HilA	Regulation of *Salmonella* pathogenicity island 1 gene expression	48
	hilC hilD	HilC, HilD	Transcriptional regulators of *hilA*	48
	invH	Outer membrane lipoprotein InvH	Facilitates the translocation of proteins, including SipC, from the cytoplasm to the membrane	53
	nmp	Outer membrane-associated protein	Bacterial porin formation	114
	prgK	PrgK periplasmatic protein	Type III secretion system	49
	sip	Sip effector protein	Induction of inflammation response	52
	sop	*Salmonella* outer Protein B	Lipid phosphatase critical in enteropathogenicity	50
	sptP	SptP effector protein	Recovery of the host cytoskeleton after the infection	55
	spv		Promoter of the virulence genes of nontyphoid *Salmonella* serovars	51
	ssrB	SsrB	Activation of genes needed for intracellular survival	57
Campylobacter jejuni	*cadF*	Outer membrane protein CadF	Adhesion to intestinal epithelial cells	76
	cdt	Cytolethal distending toxin	Toxin composed by three subunits, involved in cell adhesion and inhibition of cell division	76
	cia	*Campylobacter* invasion antigen B	Invasion potential	76
	fla	Flagellin	Motility and colonization	76
	flh	Flagellin	Motility and colonization	76
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	79
Escherichia coli	*eaeA*	Intimin	Attachment to cell surface	86
	fliC	Flagellin	Motility	96
	hly	Enterohemolysin and α-hemolysin	Toxins with hemolytic activity	87
	ler	LEE1-encoded regulator	Transcriptional activator of LEE genes	94
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	97, 98
	qseA	QseA effector protein	LEE1 gene activator	95
	stx	Shiga-like toxin Stx	Toxin causing diarrhea and other disorders	89
	tir	Translocated intimin protein	Adhesion to epithelial cells	93
		Adhesins	Adhesion on both abiotic and cell surfaces	91
		Intimin receptor EspE	Type III secretion system that allows attaching and effacing (A/E) lesions	92
Clostridium spp.	*luxS*	LuxS enzyme	Production of autoinducer 2 (AI-2)	125
	tcdA	Enterotoxin A	Toxin that causes diarrhea and intestinal damage	119, 120
	tcdB	Toxin B	Toxin with strong cytotoxic effect	119, 120
	txeR	σ factor	Induces RNA polymerase to recognize the promoters of *tdc* genes	121

(Continued on next page)

TABLE 1 (Continued)

Bacteria	Gene	Protein	Function	Reference
Staphylococcus aureus	*agr*		QS system that regulates virulence factors	130
	ica		Biofilm formation	137
	mecA		Methicillin resistance	136
	sae		Regulatory locus that activates the production of different exoproteins	131
	sbi	Ig-binding protein	Binding to IgG and blood coagulation	135
	sea	Enterotoxin A	Food poisoning	132
	spa	Protein A	Inhibition of phagocytosis	135
	ssl1	*Staphylococcus* superantigen-like protein (SSL-1)	Inhibition of metalloproteases	134
	tst	Toxic shock syndrome toxin 1 (TSST-1)	Superantigen that causes organ dysfunctions associated with high mortality rate	133
Helicobacter spp.	*cagA*	CagA cytotoxin	Alteration of intracellular signal transduction	148
	fla	Flagellin	Motility	149
	vacA	VacA cytotoxin	Fusion between endosomes and lysosomes in eukaryotic cells	148
Pseudomonas spp.	*exo*	Cytotoxins belonging to the type III effector proteins family	Toxins that cause different damage to the host	157
	fleSR	Flagellin	Flagella necessary for swimming/swarming motility	158
	lasI/R	LasI/R protein	QS system that regulates virulence factors	162
	ndvB		Biofilm formation	157
	pil	Pilin	Type IV pili necessary for twitching motility	158
	rhl/R	RhI/R protein	QS system that regulates virulence factors	162
Klebsiella pneumoniae	*sugE*		Biofilm formation	163
	treC			163
Streptococcus spp.	*ftf*	Fructosyltransferase	Adhesion	168
	gtf	Glucotransferase	Production of exopolysaccharides	167
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	171
	sag	Streptolysin S	Toxin that causes erythrocyte lysis	177
	tft	Glucosyltransferase (GTF)	Production of exopolysaccharides	167
Neisseria gonorrhoeae		Major outer protein porin PorB	Suppression of neutrophil oxidative burst and apoptosis	187
		N. gonorrhoeae lipooligosaccharide (LOS)	Adhesion and invasion of the host cells	187
		Opacity proteins (Opa)	Colonization of the mucosal epithelium	187
		Pilin	Type IV pili for twitching motility, immune evasion, and colonization	187
Trichomonas vaginalis		Lipophosphoglycan	Adherence factor	186
Gardnerella vaginalis	*sld*	Sialidase	Adhesion to cells and surfaces	188
	vly	Vaginolysin	Inhibition of immune response	
Candida albicans	*ALS3*	Adhesins	Adhesion properties	195
	BCR1		Biofilm formation	195
	CPH1		Biofilm formation	195
	ECE1		Yeast-to-hyphal morphogenesis	196
	EFG1		Biofilm formation	195
	HWP1	Adhesins	Adhesion properties	195
	MspI	Major peptidoglycan hydrolase	Chitin hydrolysis	204
	Saps		Hydrolytic enzymes	196
	TEC1		Biofilm formation	195
		CDR1, CDR2, and MDR1 proteins	Resistance to drugs and immune system	195
Aggregatibacter actinomycetemcomitans	*ltxA*	Leukotoxins	Induces the death of leukocytes	220
	cdtB	Cytolethal distending toxin	Diarrheal disease-causing toxin	

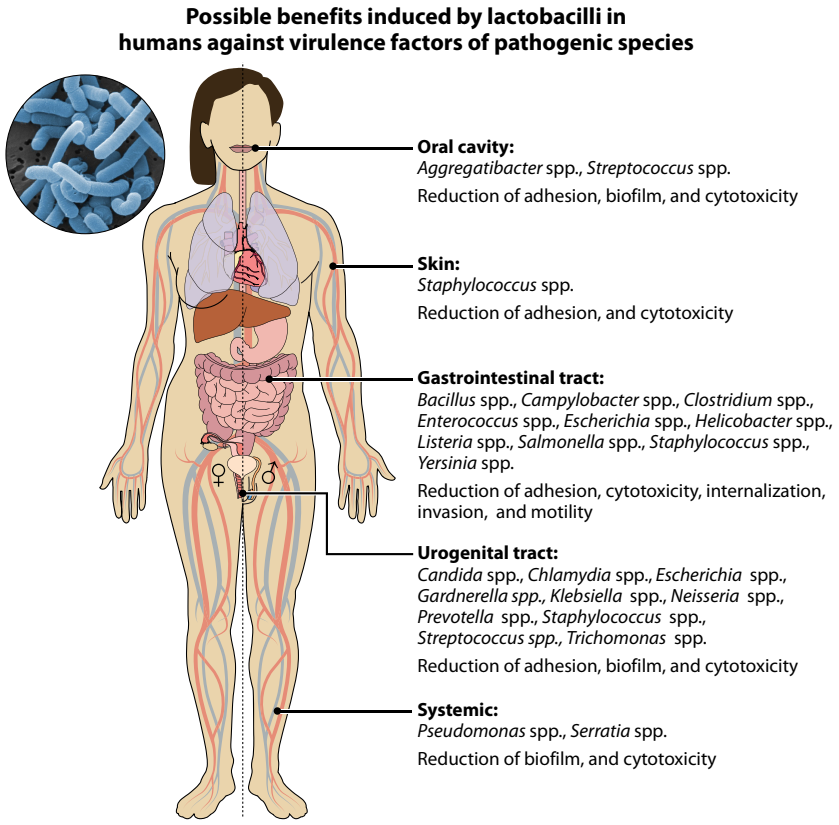

FIG 1 Possible benefits induced by lactobacilli in humans against virulence factors of pathogenic species.

phospholipases, encoded by the *hly* and *plc* genes, respectively, enables macrophage survival (27). The presence of *Listeria* adhesion protein (LAP) and autolysin amidase Ami, which enhance bacterial adhesion, *prfA* transcriptional activator, ActA actin polymerization protein, *sigB* stress response factor, and flagellin, encoded by *flaA* gene, all contribute to *Lm* virulence (28–31). Several studies have reported the reduction of all of these virulence factors (Table S1 in the supplemental material). *In vitro* trials have revealed that lactobacilli, through the production of organic acids and proteinaceous molecules and their interaction with mucosal epithelial cells, significantly decreased inflammation during the invasion of *Lm* (32). Coculture with *Lactiplantibacillus plantarum* significantly decreased *Lm* virulence toward HT-29 cells (33). On Caco-2 cells, *Lpb. plantarum* and *Lacticaseibacillus rhamnosus* coinoculation significantly reduced the *Lm* survival ratio under simulated digestion, thus inhibiting cell adhesion and invasion and downregulating the *sigB*, *hly*, *inlA*, *inlB*, and *prfA* genes (34, 35). This property was also observed for *Limosilactobacillus reuteri*, *Limosilactobacillus fermentum*, and *Lpb. plantarum* with lower LLO production, epithelial E-cadherin-binding ability, and expression of virulence genes, while in an *in vivo* trial, these strains increased survival of *Galleria mellonella* inoculated with lethal doses of *Lm* (36). In addition, preexposure to bioengineered *Lacticaseibacillus casei* and *Lacticaseibacillus paracasei* preserved tight barrier junction integrity and decreased *Lm*-mediated cytotoxicity and adhesion, whereas these effects were not observed on *Lm* already attached to Caco-2 cells (37, 38). Other *in vivo* studies confirmed the antilisterial activities of lactobacilli. In murine models, the administration of *Lcb. paracasei* and *Lcb. casei* systematically decreased the dissemination of *Lm* (39), whereas *Latilactobacillus sakei* 2a lowered lesions and edema of the intestinal villi (40). *Levilactobacillus brevis* reduced the propagation and dispersion of *Lm* in the intestines, spleen, and liver without affecting neutrophils and lymphocyte values

(41). In infected chickens, supplementation with *Lactobacillus acidophilus* and *Lpb. plantarum* attenuated *Lm* adhesion, pore formation, and invasion, downregulating the expression of LLO, InlA, InlB, Ami, and flagellin. Moreover, a decreased load of *Lm* in the cecum, skin, liver, and spleen, a decrease in serum cytokines, and an upregulation of anti-inflammatory-related genes were observed (42). In addition, *Lm* cocultured with bacteriocin-producing *Llb. sakei* 1 resulted in diminished hemolytic activity (43, 44), thus indicating the effectiveness of lactobacilli in preventing *Lm* adhesion to abiotic surfaces (45, 46).

SALMONELLA SPP.

Salmonella enterica (*Slm*) is a pathogen that affects both humans and animals. Septicemia and enteric fever are common clinical manifestations of serovars Typhi and Paratyphi, whereas bacteremia is typical of nontyphoidal *Salmonellae*, such as *S. enterica* serovar Typhimurium (*Slm*T), Enteritidis (*Slm*E), Heidelberg (*Slm*H), and Javiana (*SlmJ*) (47). *Salmonella* pathogenicity islands (SPI) group *hilA*, *hilC*, and *hilD* invasion genes (48) and *prgK*, which are associated with type III secretion system 1 (T3SS1) and T3SS2 systems (49), as well as *sop* genes, which are important in enteropathogenesis (50). The virulence traits of nontyphoid *Salmonella* serovars are also enhanced by the *spv* plasmidic gene (51). The *invH* gene promotes tissue invasion both *in vivo* and *in vitro* and is related to the expression of the *sip* gene, which is involved in host translocation (52, 53). During infection, *Slm* invades macrophages and dendritic and epithelial cells (54), thus promoting survival and replication thanks to *avrA*, *sptP*, and *ssrB* genes (48, 55–57). Several studies have demonstrated that lactobacilli and their metabolites downregulate genes associated with *Slm* virulence (Table S2 in the supplemental material). *Lactobacillus bulgaricus*, *Lcb. paracasei*, and *Lcb. rhanosus*, for example, downregulate the *sipA*, *sipB*, *sopB*, *spvB*, *hilA*, *hilD*, and *invH* genes in *Slm*E, *Slm*T, and *Slm*H (50), whereas *hilA* and *hilD* along with *hilC* and *sipC* are also downregulated by other probiotic lactobacilli (58). In *Slm*T-infected chickens administered lactobacilli, almost all SPI virulence genes (*hilA*, *hilC*, *hilD*, *sopB*, *sopD*, *sopE2*, *sipA*, *avrA*, and *sptP*, but not *sipC*) were downregulated, thus decreasing infection in the liver and spleen (59, 60). In addition, *Lbc. acidophilus* and *Lpb. plantarum* reduced the expression of the *invA*, *avrA*, *hilA*, *ssrB*, and *sopD* genes and the invasiveness of *Slm*T, thus altering the function of the type III secretion system (61, 62). A *Lbc. acidophilus* strain was also able to delay the internalization of *Slm*T, also altering its swimming motility (63). Other lactobacilli and their metabolites showed substantial antivirulence properties toward *Slm* in *in vivo* studies; for example, different *Lpb. plantarum* strains interfered with the growth and virulence of *Slm*T on Vero cells. These lactobacilli, which had higher ciprofloxacin resistance than the pathogen, significantly reduced its adherence, invasion, and cytotoxicity (64). Preexposure of HT29 cells to live *Lbc. acidophilus*, *Lcb. rhanosus*, and *Lcb. casei* decreased the induced cytotoxicity and the expression of virulence genes, particularly those related to the invasiveness of *SlmJ* (65). Also, on thermally stressed Caco-2 cells, *Lcb. rhanosus* reduced the severity of *Slm* infection (66). The adhesion of *Slm*T to the same cell line was inhibited by molecules secreted by lactobacilli, in particular lactic acid produced from *Lcb. casei* Shirota, *Lbc. acidophilus*, *Lcb. rhanosus*, and *Lbc. amylovorus*, whereas *Lactobacillus johnsonii* and *Lpb. plantarum* produced unknown inhibitory substances with anti-*Salmonella* activity (67). A bioengineered *Lcb. casei* strain overproducing conjugated linoleic acids (CLA) competitively excluded *Slm*T in a mixed culture and altered biofilm formation, adherence, and invasive activity toward INT-407 host cells, thus downregulating expression of the *invG*, *invH*, *prgK*, *hilA*, *hilC*, *hilD*, and *invF* genes (68, 69).

Live lactobacilli cells and their CFSs show antivirulence effects against *Slm*. *Lcb. paracasei* CFS lowered *Slm*E adhesion to Caco-2 cells (70), whereas the CFS produced by *Lbc. acidophilus* induced the release of lipopolysaccharide in *Slm*T, a decrease in intracellular ATP correlated with bacterial death, bacterial membrane permeabilization, and increased sensitivity to sodium dodecyl sulfate (71). In a trial evaluating the expression of the *Slm*E *hilA-lacZY* transcriptional fusion, 24 h of incubation with spent medium from a *Lactobacillus* species strain isolated from poultry resulted in an absence of

β-galactosidase activity. In comparison, *Slm*E, grown in *Slm*-spent medium, showed a 4-fold higher expression of *hilA* (72). Other properties of lactobacilli have been demonstrated *in vivo*. *Lcb. casei* inhibited the invasion and decreased the survival of *Slm*T in Caco-2 cells and mice, thus lowering the cecal colonization levels and the bacterial translocation rate to the spleen, liver, and mesenteric lymph nodes. In addition, administration of *Lcb. casei* to infected mice significantly delayed the occurrence of 100% animal mortality from 9 to 15 days (73). Pretreatment with washed cells and CFS of *Ligilactobacillus salivarius*, *Lactobacillus delbrueckii* subsp. *delbrueckii*, and *Lpb. plantarum* inhibited *Slm*T attachment to the cecal mucus of infected chickens (74). The immune system modulation ability of lactobacilli was observed in *Slm*-infected mice, in which *Lactobacillus zeae*, *Lpb. plantarum*, and *Lmb. reuteri* increased the proinflammatory cytokine response. This induced response was more effective with a combination of lactobacilli isolates than with a single strain (75).

CAMPYLOBACTER JEJUNI

Campylobacter jejuni (*Cj*) is a commensal microorganism that is found in both domestic and wild animals and is responsible for campylobacteriosis, a severe foodborne diarrheal disease. Its virulence and survival in humans are linked to a variety of factors, including flagellum motility conferred by *fla* and *flh* genes, adhesion capacity conferred by *cia* and *cadF* genes, and cytolethal distending toxin encoded by *cdtA*, *cdtB*, and *cdtC* genes, interfering with cell division (76). Lactobacilli, already recognized for their ability to relieve gastrointestinal symptoms caused by pathogenic infections, have been found to decrease *Cj* invasiveness (Table S3 in the supplemental material) (77). *In vitro* experiments revealed that the prolonged colonization of E12 cells with different lactobacilli attenuated *Cj* association, internalization, and translocation to the basolateral medium in transwells (78). On Caco-2 cells, various lactobacilli exhibited antagonistic effects against this pathogen, lowering the expression of genes involved in invasion (*ciaB*), motility (*flaA*, *flaB*, and *flhA*), and AI-2 production (*luxS*). These strains increased *Cj* macrophage phagocytosis and the expression of interferon-γ (IFN-γ), interleukin-1β (IL-1β), IL-12p40, IL-10, and chemokines in macrophages (79). Similarly, the CFS of a genetically engineered *Lcb. casei* overexpressing the *mcrA* gene decreased *Cj* adhesion to, and invasion of, HD-11 and HeLa cells and altered the expression of *cadF*, *cdtB*, *ciaB*, and *flaB* genes (80). The expression of *ciaB* and *flaA* virulence genes in *C. jejuni* was downregulated by *Lbc. acidophilus* CFS, according to real-time PCR (RT-PCR) analysis. The effect of the same strain has been tested on *luxS*-mutant *Cj* and downregulated only the *ciaB* gene, thereby suggesting an active role of *luxS* in the modulation of *Cj* virulence even when lactobacilli strains were added (81).

ESCHERICHIA COLI

Although *Escherichia coli* (*Ec*) is commonly part of the commensal intestinal microbiota in both human and animal intestines, some opportunistic strains transmitted via the fecal-oral route can cause disease in humans. Pathogenic *Ec* can be classified as extraintestinal or diarrhoeagenic and can be further subdivided into different pathovars: enteropathogenic (EPEC), enterohemorrhagic (EHEC), enterotoxigenic (ETEC), enteroinvasive (EIEC), enteroaggregative (EAEC), Shiga toxin-producing (STEC), adherent invasive (AIEC), and diffusively adherent (DAEC) (82, 83). Whereas EIEC is an intracellular pathogen that invades and replicates within epithelial cells and macrophages, other pathogenic *Ec* strains interact with the epithelium through the expression of specific genes such as the *eaeA* gene, which regulates attachment to intestinal cells (84–86). An important virulence factor is the production of toxins, such as cell-associated enterohemolysin and α-hemolysin, encoded by *hlyA*, *hlyB*, *hlyC*, and *hlyD* genes in STEC (87). ETEC and EHEC are the main causes of enteric diseases in humans each year (88) owing to the ability of EHEC to produce verotoxin and Shiga-like toxins (Stx1 and Stx2) (89) and the ability of ETEC to produce toxins and adhesins (90, 91). EHEC has a pathogenicity island called locus of enterocyte effacement (LEE), which encodes gene regulators, adhesin, the type III

secretion system, and proteins, including the translocated intimin receptor (*tir*) and Esp proteins that enhance adhesion to epithelial cells (92, 93). *LEE1*-encoded regulator (*ler*) activity is controlled by QS autoinducer 3 (AI-3) and by epinephrine and norepinephrine hormones (94), whereas the *qseA* gene encodes the QseA effector protein, which directly activates the *LEE1* gene (95). EHEC is further characterized by the presence of a flagellum encoded by the *fliC* gene (96). Different lactobacilli and their metabolites alter the gene expression and consequently the virulence of *Ec* (Table S4 in the supplemental material). For example, *Lmb. reuteri* downregulated the epinephrine-mediated induction of *ler* in EHEC (94). CFS from *Lbc. acidophilus* supplementation in yogurt reduced the severity of infection and the attachment and colonization of EHEC and downregulated tumor necrosis factor-α (TNF-α) in infected mice. These effects were supported by RT-PCR, which detected a decrease in the expression of the $stxB_2$, *qseA*, *luxS*, *tir*, *ler*, *eaeA*, and *hlyB* genes (97). Another study found that CFS of the same strain reduced extracellular AI-2 concentrations and downregulated other virulence-associated genes (*tir*, *espA*, *fliC*, *espD*, *luxS*, *eaeA*, *ler*, *hylB*, and *qseA*), but no modification in Shiga toxin production has been observed (98). CFS and lactic acid produced by *Lmb. reuteri* significantly inhibited uropathogenic *Ec* (UPEC), thus reducing the production of virulence factors involved in the adhesion process, such as adhesion outer membrane proteins A and X, urogenital tract adherence promoter factor type 1, and P fimbriae subunits (99). Furthermore, studies conducted on different cell lines have confirmed the anti-*Ec* activity of several *Lactobacillus* strains. The adhesion ability of two *Ec* strains on Hep-2 and T84 cells was reduced after pretreatment with *Lbc. acidophilus* and *Lcb. rhanosus* (100). Whereas *Lbc. jensenii* and *Lbc. gasseri* inhibited adhesion of DAEC to HeLa cells, *Lmb. reuteri* also reduced *Ec* internalization in the same cell line (101). Also, *Lpb. plantarum* and *Lcb. rhanosus* inhibited Ec adherence to HT-29 cells by increasing the expression of intestinal mucins MUC2 and MUC3 (102). Also, an interference of induced cell signaling against DAEC caused by *Lbc. acidophilus* abolished the structural and functional microvilli alteration in human enterocyte-like cells (103, 104). As also reported for *Slm*, CLA overproducer *Lcb. casei* strain altered biofilm formation and modified *Ec* adhesion and invasion in INT407 cells (68). The combination of *Lcb. rhanosus* with oligosaccharides resulted in an effective antidiarrheal formulation, owing to the increased autoaggregation and coaggregation properties of this strain. The inhibition of adherence to HT-29 cells was maximal with a *Lcb. rhanosus* and inulin combination and significantly decreased the production of cyclic AMP, cyclic GMP, and related toxins (105). In an *in vitro* EHEC infection model, *Lcb. rhanosus*, *Lbc. gasseri*, *Lcb. casei*, and *Lpb. plantarum* have been studied on C2BBe1 human colon epithelial cells. Among the tested strains, live *Lcb. rhanosus* cells significantly reduced pathogen internalization, whereas this effect has not been observed with dead *Lcb. rhanosus* cells or conditioned medium, thus implying that lactobacilli modulate the intracellular mechanism responsible for EHEC internalization (106). Multiple lactobacilli were also effective in inhibiting the *Ec* quorum sensing system, such as *Llb. sakei* and *Lbc. acidophilus* cell extract, which significantly inhibited AI-2-like activity without affecting EHEC growth. Moreover, *Lbc. acidophilus* cell extracts inhibited biofilm formation on abiotic surfaces and HT-29 cell adhesion and downregulated the expression of several virulence factors associated with AI-2-like activity, particularly proteins involved in sulfur metabolism and membrane-associated functions (107, 108). *In vivo* experiments have shown similar results, including a significant decrease in adhesion and improvements in the immune system of infected animals. In a murine model, *Lactobacillus kefiranofaciens* treatment prevented EHEC infection-induced symptoms, Shiga toxin penetration, bacterial translocation, renal and intestinal damage, and increased mucosal EHEC-specific IgA responses. Lactobacilli also had protective effects in Caco-2 cells, reducing cell death and epithelial integrity loss induced by the pathogen (109). The ability of *Ec* to adhere to pig intestine brush borders decreased in a dose-dependent manner after administration of recombinant engineered fimbriae-producing *Lbc. acidophilus* (110). In an *in vivo* trial, the ability of *Ec* to disrupt the intestinal barrier and

increase permeability was significantly reduced by administering *Lpb. plantarum* to rats, indicating a beneficial effect on the intestinal tract (111). *Lcb. casei* Shirota treatment of *Ec* in a murine urinary tract infection model inhibited growth and reduced inflammatory responses (112). In addition, exopolysaccharides produced during fermentation demonstrated *in vivo* anti-*Ec* activity, as reuterin and levan from *Lmb. reuteri* contained in weanling pig feed that reduced the number of *Ec* and the amount of heat-stable enterotoxin in colonic digesta (113). In addition, *Lcb. casei* strains decreased virulence gene expression in EHEC, *Slm*T, and *Lm*, particularly downregulating the *Ec eaeA*, *Slm*T *nmpC*, and *Lm fbp* and *iap* genes (114). Also, pretreatment of Caco-2 cells with live and heat-killed *Lbc. acidophilus* dose-dependently inhibited the adhesion and invasive properties of EPEC, *Lm*, *Slm*T, and *Yersinia pseudotuberculosis* (115, 116). Another study investigating the effect of pretreatment of Caco-2 and HT-29 cells with lactobacilli reported that one *Lvb. brevis*, two *Lpb. plantarum*, and two *Lcb. paracasei* strains inhibited EPEC and *Slm*E adhesion to both cell lines (117).

CLOSTRIDIUM SPP.

Hospital-acquired infections have severe consequences for already debilitated patients, and several studies have shown the effectiveness of lactobacilli in preventing the onset of such complications, as in the case of *Clostridium difficile* (*Cd*). This nosocomial bacterium infects the human gastrointestinal tract (118) and is characterized by two major virulence factors: enterotoxin A, expressed by the *tdcA* gene and causes diarrhea and intestinal mucosa damage, and toxin B, expressed by the *tcdB* gene and has strong cytotoxic effects (119, 120). Another important virulence factor is the *txeR* gene, which encodes a sigma factor that directs RNA polymerase to recognize the promoters of the *tcdA* and *tcdB* genes (121). Several lactobacilli have inhibitory effects on *Cd* virulence factors (Table S5 in the supplemental material), particularly on the production of toxins, as demonstrated by various *in vitro* studies. Coculture of lactobacilli with *Cd* on Vero cells significantly decreased TcdA and TcdB toxins in spent supernatants and increased their intracellular concentrations, thereby suggesting a possible antagonistic mechanism that could reduce the synthesis and/or secretion of toxins (122). S-layer proteins extracted from *Lentilactobacillus kefiri* strains inhibited the damage caused by *Cd*-spent culture supernatants in Vero cells, and this activity was higher in aggregating strains than in non-aggregating strains, thus indicating a direct interaction between S-layer proteins and clostridial toxins. The same results were not obtained with live *Lbc. kefiri* cells, thereby indicating a different interaction between the soluble S-layer proteins and those located on the surface of the bacterium (123). *Lbc. acidophilus* CFS significantly reduced the cytotoxic and cytopathic effects of a hypervirulent *Cd* strain culture filtrate on human epithelial cells by decreasing pathogen attachment on HT-29 and Caco-2 cells (124). Inhibition of *Cd* virulence factors has also been observed *in vivo*. The administration of *Lbc. acidophilus* in *Cd*-inoculated mice altered QS molecule production, lowering the transcriptional levels of *luxS*, *tcdA*, *tcdB*, and *txeR* genes and increasing mouse survival ratios by as much as 80% (125). Furthermore, the administration of *Lmb. reuteri* significantly decreased *Cd* colonization and concentrations of toxins in the cecum and decreased the numbers of rotavirus, a human virus that causes gastroenteritis in infants and children, after both pretreatment and coincubation of the pathogen and the probiotic with HT-29 cells (126). In a protection model, an engineered *Lactobacillus* strain expressing TcdB-neutralizing antibody fragments delayed the death of infected hamsters (127), whereas in mice, an engineered *Lcb. casei* expressing *Clostridium perfringens* alpha-toxin toxoid induced the production of antibodies capable of neutralizing *C. perfringens* alpha-toxin and increasing levels of cytokines and interferon-γ in the serum and spleen lymphocytes (128).

STAPHYLOCOCCUS AUREUS

Staphylococcus aureus (*Sa*) is an opportunistic pathogen accounting for 76% of all skin and soft tissue infections in humans (129) due to the expression of several virulence factors regulated by the *agr* QS system and the *sae* gene (130, 131). *Sa* produces

a variety of toxins, including *sea* enterotoxins, which cause food poisoning (132), toxic shock syndrome toxin 1 (TSST-1) expressed by the *tst* gene, a superantigen that causes multiple organ dysfunctions and is associated with a high mortality rate (133), and *Staphylococcus* superantigen-like protein 1 (SSL-1), which inhibits the activity of matrix metalloproteases (134). The ability to evade the host immune system is promoted by the production of protein A (*spa*), a surface protein that prevents phagocytosis, and immunoglobulin-binding protein (*sbi*), which binds IgG and is involved in blood coagulation (135). Furthermore, the *mecA* gene confers methicillin resistance to *Sa* (136), and the expression of the *ica* operon promotes biofilm formation (137). Several studies demonstrated that lactobacilli can effectively counteract the virulence factors of this pathogen (Table S6 in the supplemental material). Either cocultivation or CFS from different lactobacilli strains inhibited *Sa* biofilm formation, as in the case of the cocultivation with *Lcb. rhanosus* (138) and acid CFS from *Lbc. acidophilus* that also inhibited lipase from biofilm and planktonic cells with a significant effect on methicillin-resistant *Sa* (139). In a study conducted on CFS produced by *Lpb. plantarum*, inhibition of the growth of *Sa* was observed, whereas CFS produced by *Lmb. fermentum* inhibited the expression of the *icaA* and *icaR* operons, thus limiting biofilm formation (140). CFS obtained from *Lpb. plantarum*, *Lmb. fermentum*, and *Lmb. reuteri* strains dependently decreased the expression of the *sea*, *sae*, *agrA*, *tst*, *spa*, and *spi* genes (141), and, in particular, the production of SSL-1 was significantly reduced when *Sa* was grown in *Lmb. reuteri* supernatant (142). Furthermore, *Lbc. acidophilus* and *Lmb. fermentum* have demonstrated a significant reduction of *Sa* adherence even on abiotic surfaces, most notably catheters and surgical implants (143, 144), thus suggesting a potential for the application of lactobacilli in the medical field to prevent the spread of nosocomial infections. The inhibitory effect of lactobacilli on *Sa* has also been confirmed *in vitro*. For example, *Lbc. crispatus* and *Lactobacillus jensenii* coaggregated with *Sa*, preventing pathogen adhesion to vaginal cells (145), whereas live *Lcb. casei* cells affected *Sa* internalization, and both live and heat-killed *Lcb. casei* cells reduced *Sa* adhesion in bMEC cells (146). Depending on their growth phase, concentration, competition, and the presence of surface layer proteins, *Lgb. salivarius* and *Lpb. plantarum* significantly inhibited *Sa* adherence to Caco-2 cells (147).

HELICOBACTER SPP.

Helicobacter is an important genus involved in food-borne illness. The clinical manifestations are determined by the genetics and behaviors of the human hosts (i.e., diet or smoking status) as well as bacterial virulence. *cagA* and *vacA* cytotoxin-associated genes are important in this regard; *cagA* alters intracellular signal transduction, and *vacA* induces the fusion between endosomes and lysosomes (148). Another important virulence factor is the production of flagellin, which is induced by the expression of *flaA* and *flab* genes and provides the motility necessary for stomach colonization (149). Several studies have provided clear evidence that lactobacilli and their metabolites could decrease virulence factors of this species (Table S7 in the supplemental material). For example, the compounds produced by a *Lcb. casei* strain reduced the expression of genes codifying for flagellins in *Helicobacter pylori* (*flaA* and *flaB*) and *Slm*T (*flaC*), decreasing the motility and related internalization abilities (150). Similar results were obtained from a *Lmb. reuteri* strain, which significantly reduced the expression of *flaA* and *vacA* genes (151), whereas *Lactiplantibacillus paraplantarum* CFS reduced the adherence of *H. pylori* on AGS cells (152). Pretreatment with live and UV-killed *Lgb. salivarius* strains promoted the modification of the interleukin and chemokine response in the same cell line, in addition to downregulating 8 of 12 genes belonging to the *H. pylori Cag* pathogenicity island. This immunomodulatory effect was not dependent on adhesion or bacteriocin production, but after *Lgb. salivarius* exposure, CagA protein accumulated inside *H. pylori* cells, probably because of the loss of CagA secretion functionality (153). *In vivo* tests on *Helicobacter hepaticus*-stimulated macrophages from IL-10-deficient mice have been performed to investigate TNF-α-inhibitory *Lmb. reuteri* and *Lcb. paracasei*. These lactobacilli effectively decreased intestinal inflammation by lowering the levels of the

proinflammatory colonic cytokines TNF-α and IL-12 but had no effects on *H. hepaticus* vitality (154). *Lbc. acidophilus* eradicated *H. pylori* from colonized children in 6.5% of subjects, while no spontaneous clearance was observed in untreated children, demonstrating the efficacy of lactobacilli administration in humans (155).

PSEUDOMONAS SPP., *STREPTOCOCCUS* SPP., AND *KLEBSIELLA* SPP.

Biofilms are microorganism aggregations within an extracellular matrix composed of proteins, exopolysaccharides, water, nutrients (such as polysaccharides and amino acids), and ions. The ability to form biofilms is an important common property that increases pathogen virulence, conferring adhesiveness and resistance to the host immune system and antibiotics (156). Biofilm formation is a characteristic trait of *Pseudomonas* spp., *Streptococcus* spp., and *Klebsiella* spp., all of which can establish ecological niches in which they replicate and become infectious to humans. Also in this case, lactobacilli and their metabolites have proven to be effective in inhibiting specific virulence factors of these pathogens (Table S8 in the supplemental material).

Pseudomonas aeruginosa, one of the most common pathogens in the hospital setting, owes its pathogenicity to various virulence factors (besides biofilm formation), such as the secretion of toxins (157) and the presence of flagella and pili (158). *P. aeruginosa* biofilm formation and elastase production were effectively inhibited by *Lmb. fermentum*, *Lbc. zeae*, and *Lcb. paracasei* (159), whereas *Apilactobacillus kunkeei* exhibited *in vitro* antibiofilm properties and attenuated *P. aeruginosa* infection in a *G. mellonella* model (160). Other *in vivo* tests were performed to evaluate the effects of *Lpb. plantarum* on *P. aeruginosa* acyl-homoserine-lactones, elastases, and biofilm virulence factors. In a burned mouse model, lactobacilli inhibited *P. aeruginosa* colonization, thus improving tissue repair and enhancing pathogen phagocytosis (161). Crude extract from *Companilactobacillus crustorum* degraded *N*-homoserine lactone and significantly enhanced biofilm sensitivity to azithromycin, thereby inhibiting biofilm formation and reducing the thickness of already formed biofilms. Real-time quantitative PCR (RT-qPCR) analysis revealed downregulation of *lasI/R* and *rhlI/R* QS virulence genes as well as inhibition of chitinase, protease, rhamnolipid, alginate, pyocyanin, and exopolysaccharide synthesis (162).

Klebsiella pneumoniae, a pathogenic bacterium associated with urinary infections that occur primarily in hospitalized patients and are frequently connected with the use of medical devices, is another microorganism whose pathogenicity relies on the ability to form biofilms (163). In this regard, *Lmb. fermentum* cells and their acid supernatants exerted antibiofilm properties against *K. pneumoniae* on catheters (164). In addition, *Lbc. acidophilus* and *Lmb. fermentum* or their supernatants hindered pathogen spread within biofilms, since no *K. pneumoniae* live cells were found after treatment (165).

Streptococcus mutans is the main etiological agent of human dental caries, owing to its virulence factors such as the aforementioned ability to form biofilms (166) as well as glucosyltransferases encoded by *gtf* and *tft* genes, which enable the production of exopolysaccharides and thus the formation of plaque (167), and fructosyltransferase (*ftf*), which is essential in adhesion (168). Different lactobacilli produce biosurfactants that downregulate the expression of *S. mutans* biofilm-forming genes, for example, *Lmb. fermentum* and *Lbc. acidophilus*, which reduced *gtfB* and *gtfC* gene expression modifying the surface and adhesion properties of the pathogen (169, 170), *Lmb. reuteri*, which reduced *gftB*, *gtfC*, and *fft* gene expression (168), and *Lbc. acidophilus*, which downregulated *gtf* and *luxS* (171). Similar results were obtained with the coculture of *S. mutans* with *Lcb. casei*, which downregulated *luxS* and *gftB*, *spaP*, and *gbpB* adhesion genes (172). Likewise, *Lcb. casei*, *Lmb. reuteri*, *Lpb. plantarum*, *Lgb. salivarius*, *Lcb. rhanosus*, and *Lmb. reuteri* decreased biofilm formation and downregulated the *gtf* genes, significantly decreasing bacterial attachment to surfaces (173–175).

Lactobacilli were also effective against *Streptococcus pyogenes*, a pathogen that affects humans exclusively and causes a variety of disorders ranging from asymptomatic transport to mild and superficial infections of the skin and mucous membranes to systemic diseases (176). Its virulence depends on the production of toxins, in particular streptolysin

S encoded by the *sag* operon, which causes erythrocytes lysis (177). The combination of *Lcb. rhanosus* and *Lmb. reuteri* and their spent media were the most effective in reducing *S. pyogenes* adherence in FaDu and Detroit 562 host cells, inhibiting hemolytic activity through the downregulation of *sag* operon expression with a consequent decrease in streptolysin S production (178). In addition, a *Lpb. plantarum* strain decreased the levels of IL-17 and IL-23 in Hep-2 and A549 cells exposed to *S. pyogenes* by inducing the Toll-like receptor 2 (TLR2)/TLR4 surface receptors involved in the immune response (179).

UROGENITAL-CORRELATED PATHOGENS

Urogenital tract infections are major causes of disease in women. Several pathogenic species, including *Candida albicans*, *Chlamydia trachomatis*, *Ec*, *Gardnerella vaginalis*, *Neisseria gonorrhoeae*, *Prevotella bivia*, *Streptococcus agalactiae*, and *Trichomonas vaginalis*, are involved in the onset of disorders that, if untreated, can cause serious irreversible complications (180). In healthy individuals, the vaginal microbiota is dominated by lactobacilli (181), which protect against infections by inhibiting pathogen colonization via several mechanisms (Table S9 in the supplemental material), such as increasing microbiota adhesion through the production of biosurfactants, competition for host cell receptors, or direct killing through the production of hydrogen peroxide and bacteriocins (182). Inhibition of pathogen adhesion has been observed both in cell lines and on abiotic surfaces. *Lbc. acidophilus*, *Lbc. gasseri*, and *Lbc. jensenii* isolated from the human vagina were able to autoaggregate and strongly adhere to vaginal cell surfaces (183), whereas *Lpb. plantarum* coaggregated with pathogens such as *S. agalactiae*, *G. vaginalis*, and *Ec* (184). Moreover, a *Lbc. acidophilus* strain was able to inhibit *Staphylococcus epidermidis* and UPEC attachment on abiotic surfaces (185). Other urogenital tract pathogens include *Trichomonas vaginalis*, which causes trichomoniasis, *Neisseria gonorrhoeae*, which causes gonorrhea, and *Gardnerella vaginalis*, which is responsible for the initiation of bacterial vaginosis due to its ability to form biofilm. The most important virulence factor of *T. vaginalis* and *N. gonorrhoeae* is vaginal cell adhesion ability (186, 187), whereas *G. vaginalis* produces vaginolysin (*vly*), which inhibits the immune response, and sialidase (*sld*), an enzyme that releases salicylic acid, which improves adherence to cells and surfaces. Lactobacilli isolated from the human vagina showed significant inhibitory activities toward *T. vaginalis*, *N. gonorrhoeae*, and *G. vaginalis*. In particular, pretreatment with *Lbc. crispatus* competitively excluded *G. vaginalis* adhesion to HeLa cells, reducing the expression of *vly* and *sld* virulence genes (188), whereas *Lbc. gasseri* and *Lbc. jensenii* inhibited adhesion of *T. vaginalis* and *N. gonorrhoeae* to VEC and Hec-1-B cell lines, respectively (189, 190). Furthermore, a recombinant *Lbc. jensenii* secreting two domain CD4 proteins prevented the entrance of human immunodeficiency virus (HIV) into HeLa cells (191). Different trials observed the ability of *Lbc. gasseri*, *Lbc. crispatus*, and *Lbc. helveticus* to counteract vaginal-associated pathogens, specifically protecting cervix epithelial cells against the effects of *P. bivia*, toxin-producing *G. vaginalis*, and UPEC, inhibiting their adhesion to HeLa cells (192, 193). Similar results were obtained from *Lbc. helveticus*, which was able to inhibit the adhesion of *G. vaginalis* and UPEC to HeLa cells and internalization of UPEC and *Slm*T on HeLa and Caco2 cells, respectively (194).

Candida albicans is an opportunistic pathogenic yeast that resides in the oral cavity and gastrointestinal and urogenital tracts and is responsible for oral and vulvovaginal candidiasis. Its pathogenicity arises from multiple factors, including adherence promoted by various types of adhesins (*Als3* and *Hwp1*), biofilm formation (*Ece1*, *Als3*, *Bcr1*, *Efg1*, *Tec1*, and *Cph1*), resistance to drugs, and the immune system through overexpression of Cdr1, Cdr2, and Mrd1 proteins (195), yeast-to-hyphal morphogenesis (*Ece1*), and hydrolytic enzymes (*Saps*) (196). Probiotic lactobacilli are effectively used in medical treatments to limit the spread of *C. albicans* by maintaining the balance of microbiota and producing inhibitory substances active against the pathogen (197–199). Lactobacilli isolated from women produced biosurfactants that significantly reduced *C. albicans* adhesion and prevented the formation of biofilms, and maximal results were obtained with *Lbc. gasseri*, *Lmb. reuteri*, *Lbc. acidophilus*, and *Lcb. paracasei* (200).

Similar effects were obtained by coinoculating *Lpb. plantarum*, *Lmb. fermentum*, *Lbc. gasseri*, and *Lmb. reuteri* with *C. albicans*. Their autoaggregative properties, enhanced by low pH values and biofilm-forming ability, resulted in vaginal tract colonization, whereas coaggregation with *C. albicans* prevented yeast adhesion (201). *Lbc. gasseri* and *Lactobacillus crispatus* CFS coincubation with *C. albicans* significantly reduced the expression of *Hwp1* and *Ece1*, *Als3*, *Bcr1*, *Efg1*, *Tec1*, and *Cph1* genes, lowering biofilm formation, whereas CFS from *Lbc. crispatus* inhibited *C. albicans* adhesion to HeLa cells (202). Another important mechanism of virulence inhibition is the modification of the hyphal structure. Several studies found that *Lcb. rhanosus* reduced hyphal elongation (203), and *Lcb. rhanosus*, *Lcb. paracasei*, and *Lcb. casei* were effective against *C. albicans* hyphal morphogenesis because they expressed the MspI gene, encoding a major peptidoglycan hydrolase that hydrolyzes chitin (204). Proteinase and hemolysin activities were reduced in *C. albicans* grown with *Lcb. rhanosus*, with alterations to antifungal susceptibility (205). In addition, *Lcb. rhanosus* affected adhesion, invasion, and hyphal extension, preventing oral epithelial tissue damage. This effect was correlated with glucose depletion and repression of ergosterol synthesis (206). Several lactobacilli had different effects on *C. albicans*-induced interleukin in VK2/E6E7 cells; for example, *Lcb. rhanosus* alone or in combination with *Lmb. reuteri* inhibited the increase in IL-1α and IL-8, whereas their supernatants increased IL-8 and IP-10 levels (207). In addition, *Lbc. crispatus* lowered *C. albicans* adhesion to VK2/E6E7 cells, thus upregulating IL-2, IL-6, and IL-17 while downregulating IL-8 (208), and to HeLa cells, lowering IL-8 and increasing β-defensin 2 and 3 (209). In the same cell line, a reduction in adhesion was attributed to antifungal activity arising from the inhibition of histone deacetylase by *Lbc. crispatus*, *Limosilactobacillus vaginalis*, and *Lbc. gasseri* (210). Several studies have investigated the effects of lactobacilli on gene expression of this pathogen. An extract from a *Lactobacillus* species strain, owing to high levels of oleic and myristic acid, affected *C. albicans* virulence (hyphal formation, proteinase, and phospholipase secretion), thus decreasing also *Hwp1*, *Plb2*, and *Sap1* virulence gene expression (211). Moreover, CFSs of *Lbc. crispatus*, *Lbc. gasseri*, *Lbc. acidophilus*, and *Lbc. jensenii* effectively decreased the yeast-to-hyphal transition and the expression of hyphae-specific genes *Als3*, *Hwp1*, and *Ece1*, whereas *Nrg1*, a negative transcriptional regulator, was upregulated (212). *Lcb. rhanosus* and its supernatant reduced *C. albicans* filamentation and biofilm formation *in vitro*, altering the expression of *Bcr1*, *Hwp1*, and *Als3* adhesion genes and *Cph1* transcriptional regulatory genes. The same strain was tested on *G. mellonella* infected with *C. albicans*, and this treatment increased larval survival up to 80% (213). *Lcb. paracasei*, *Lmb. fermentum*, and *Lcb. rhanosus* also attenuated candidiasis in *G. mellonella* by increasing hemocyte quantity, upregulating galiomicin and gallerymicin antifungal peptide genes, slowing hyphal formation, and lowering biofilm development by downregulating the *Als3*, *Hwp1*, *Efg1*, and *Cph1* genes (214). In other studies, *Lbc. acidophilus* and its filtrate inhibited *C. albicans* filamentation and biofilm formation, increasing the *G. mellonella* survival rate (215).

OTHER PATHOGENS

Multiple studies have been conducted on other pathogens and have shown encouraging results (Table S10 in the supplemental material). The modulating effect of lactobacilli on the immune system had positive effects in both mice inoculated with *Yersinia enterocolitica* and children infected with *Enterococcus faecalis*. In the first case, *Lpb. plantarum* had an immunomodulatory effect on infected BALB/c mice, resulting in a decrease in the anti-inflammatory cytokine IL-10 and an increase in IgA production (216). The administration of *Lcb. rhanosus* to children colonized with vancomycin-resistant *En. faecalis* led to immune system modulation, preventing the onset of infection (217). *Lpb. plantarum* also increased the virulence of *Serratia marcescens*, which causes hospital-acquired infections and whose antibiotic resistance poses a severe risk to patients, and of *Bacillus cereus*, which causes food poisoning. In relation to inoculum concentration and temperature, *Lpb. plantarum* reduced the hemolytic activity and protease and lecithinase expression of *B. cereus* (218), whereas CFS from *Lbc. acidophilus*

and *Lpb. plantarum* affected the resistance of *Se. marcescens* to ceftriaxone and completely inhibited swarming motility (219). In addition, the CFS of *Lgb. salivarius* and *Lbc. gasseri* significantly reduced the virulence gene expression of *Aggregatibacter actinomycetemcomitans*, an oral pathogen that causes localized periodontitis by producing leukotoxins (LtzA) and cytolethal distending toxin (CdtB) (220).

CONCLUSIONS

Despite the development of various effective therapies, bacterial infections continue to pose a major threat to public health. In this regard, as described herein, lactobacilli capable of counteracting the virulence abilities of pathogenic microorganisms could be used to support existing treatments.

Some of these mechanisms include the reduction of the adhesive and invasive properties, the ability to self-aggregate and coaggregate with the pathogens, direct downregulation of virulence genes, and the production of metabolites with specific activities that can affect and modulate the host immune response. In addition, their presence has a bioprotective effect on both abiotic surfaces and cellular tissues. Lactobacilli, through competition for substrate and their steric hindrance, can inhibit pathogen activity and reduce their ability to adhere to epithelial cells, hence preventing the onset of diseases.

Although from review of the literature, many authors have demonstrated the ability to reduce virulence factors in pathogens by lactobacilli (our sincere apologies go to colleagues whose work was involuntarily not cited); however, there are still few studies conducted directly on humans validating all these capabilities observed in *in vitro* and *in vivo* tests on animals. Further research on this topic would thus help understand and advance the real applications of this microbial group to counteract pathogen virulence.

Lactobacilli, which have always been used by mankind and have a long history of safe use by humans in food preservation and processing, are currently also used as probiotics thanks to their proven beneficial properties. In addition to this, current whole-genome sequencing techniques provide additional assurance of safety, as evidenced by the recent EFSA statement, which recommends genetic characterization of all microbial strains before their use in food applications (221). Knowledge of the whole genome enables the identification of all potential risk factors present in lactobacilli (222), thus increasing the safety of use even in debilitated patients in hospital settings, where complete safety of the bacterial strains used must be ensured. In fact, beyond the current use as probiotics to alleviate the adverse effects of antibiotic therapies, lactobacilli could be used also as adjuvants for antibiotics, owing to their ability to counteract pathogens and their virulence properties. Infectious disease prevention is a fundamental achievement to limit the widespread use of drugs to strictly necessary cases, thus hindering the spread of antibiotic resistance. This issue has made treatment of infection more difficult in recent years; therefore, identifying alternative treatments is increasingly important to decrease the use of antibiotics while also improving host health. Given that the average age of the world population is rising, the consequences of demographic aging are expected to have severe repercussions on numerous social dynamics in the future, including an increase in the cost of public health. To reduce the number of hospitalizations and consequently the costs of health care, the condition of older and fragile people must be improved. The identification and study of strains with probiotic and antivirulence activity against pathogens may lead to the development of therapies that can be combined with current antibiotic treatments, thus reducing their adverse effects on patients while increasing their effectiveness. Furthermore, consistent intake of strains capable of reducing the likelihood of pathological manifestations in hosts, such as through the consumption of food formulations, could also be used to prevent infections, thereby reducing antibiotic use.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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