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Mechanisms and therapeutic effectiveness of lactobacilli

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ABSTRACT

The gut microbiome is not a silent ecosystem but exerts several physiological and immunological functions. For many decades, lactobacilli have been used as an effective therapy for treatment of several pathological conditions displaying an overall positive safety profile. This review summarises the mechanisms and clinical evidence supporting therapeutic efficacy of lactobacilli. We searched Pubmed/Medline using the keyword '*Lactobacillus*'. Selected papers from 1950 to 2015 were chosen on the basis of their content. Relevant clinical and experimental articles that used lactobacilli as therapeutic agents have been included. Applications of lactobacilli include kidney support for renal insufficiency, pancreas health, management of metabolic imbalance, and cancer treatment and prevention. In vitro and in vivo investigations have shown that prolonged lactobacilli administration induces qualitative and quantitative modifications in the human gastrointestinal microbial ecosystem with encouraging perspectives in counteracting pathology-associated physiological and immunological changes. Few studies have highlighted the risk of translocation with subsequent sepsis and bacteraemia following probiotic administration but there is still a lack of investigations on the dose effect of these compounds. Great care is thus required in the choice of the proper *Lactobacillus* species, their genetic stability and the translocation risk, mainly related to inflammatory disease-induced gut mucosa enhanced permeability. Finally, we need to determine the adequate amount of bacteria to be delivered in order to achieve the best clinical efficacy decreasing the risk of side effects.

INTRODUCTION

The impact of the gastrointestinal (GI) tract on brain functions and behaviour including anxiety, mood, cognition and pain regulation has been recognised since the 19th century as Hipocrates' dictum stated "Let the food be thy medicine and medicine be thy food".[1] Therefore, the gut-brain axis has been proposed as a homoeostatic route of communication using neuronal, hormonal and immunological pathways.[1–3] The GI tract, which is an active part of this axis, is harboured by approximately 100 trillion organisms, mainly anaerobes, which constitute the microbiome and exceed 10 times the overall number of cells present in the human body.[4 5] The microbiome plays a pivotal role in the development and functionality of the innate and adaptive immune responses.[1] Among microbiome-composing organisms, lactobacilli can inhibit the growth of pathogenic bacteria and have a favourable safety profile.[6] However, different species of the genus *Lactobacillus* (*L.*) can produce different particular responses in the host, and the effects exerted by some strains of the same species may not be beneficial.[7]

AIM AND SEARCHING CRITERIA

In this review, we summarise the experimental and clinical evidence on lactobacilli by providing a comprehensive overview of their efficacy for treatment of numerous pathologies and outlining new therapeutic trends. We searched Pubmed/Medline using the keyword '*Lactobacillus*'. Selected papers from 1950 to 2015 were chosen on the basis of their content. Relevant clinical and experimental articles that used lactobacilli as therapeutic agents and written in English language have been included. Clinical findings organised by pathology are summarised in tables 1–15.

EXPERIMENTAL EVIDENCE

Adhesion to the gastrointestinal mucosa

Dietary changes, antibiotic exposure and infections may cause dysbiosis, a perturbation of the microbiome-host symbiosis that favours the invasion and growth of pathogenic species to the detriment of health-promoting bacteria, including lactobacilli, within the GI tract.[8 9] Indeed, lactobacilli adhesion to the host's GI tract, by means of an interaction with toll-like receptors, is of crucial importance due to its ability to trigger the host's immune response.[10 11] Nevertheless, adhesion to the GI tract can also be driven by surface proteins and fatty acids, as observed for *L. rhamnosus* PEN,[12] and proteinaceous surface layer components, as observed for *L. plantarum* 91.[13] Therefore, the ability of lactobacilli to adhere and colonise the GI tract mucosa has been investigated in the clinical setting and is summarised in table 1.[14–17]

Antitumour activity

Intestinal bacteria produce mutagens such as deoxycholic acid from primary bile acids or by enzymatic conversion when foreign compounds, such as nitroaromatics, azo compounds and nitrates, are ingested.[18] Lactobacilli are capable of competitively inhibiting carcinogen and mutagen formation, altering overall metabolism, adsorbing and removing toxic and mutagenic metabolites and producing protective metabolites.[19] In the context of colorectal cancer, the prevention mechanism exerted by probiotics may be a combination of different actions such as intestinal microbiota modification,[20–26] inactivation of cancerogenic

Table 1 Lactobacilli displaying ability to adhere to the gastrointestinal tract mucosa

Bacteria	Dose	Ref. (Design)
L. gasseri SBT2055SR	10^{11} CFU in 200 mL of milk	[14](open study)
L. reuteri DSM 12246 *L. rhamnosus* 19070–2 *L. rhamnosus* LGG	10^{10} CFU (of each)	[17](double-blind cross-over study)
L. acidophilus 821–3	1×10^{10} CFU	[15](open study)
L. rhamnosus 19070–2 *L. reuteri DSM 12246*	1×10^{10} CFU (of each)	[16](open study)

compounds,[27–35] competition with putrefactive and pathogenic microbiota,[36–40] improvement of the host's immune response,[41–55] enhancement of natural killer cell cytotoxicity[56] and inhibition of interleukin (IL) 6 production in the colonic mucosa[57] counteracting cancer development by antiproliferative effects[58] via regulation of apoptosis and cell differentiation,[59–67] fermentation of undigested food[68–73] and inhibition of tyrosine kinase signalling pathways.[74] Experimental studies have also shown that lactobacilli contained in dietary supplements and fermented food, such as yogurt heat-killed *L. casei* strain *Shirota* (LC 9018)[54] reduce colon cancer risk.[75–77] These activities have been ascribed to the alteration of the gut microbiota and, subsequently, to the inhibition or the induction of colonic enzymes controlling the growth of harmful bacteria, improving immune function and stimulating the production of metabolites possessing antitumour activity. Clinical studies showing efficacy of lactobacilli for treatment of cancer have been summarised in table 2.

Antitoxic activity

Lactobacilli display detoxifying properties and their ability to neutralise toxins[81] or toxic compounds[82] is important to maintain the host's health. For instance, *L. reuteri* CRL 1098 and *L. acidophilus* CRL 1014 showed the ability to enhance tumour necrosis factor (TNF)-α response to ochratoxin A, a widespread mycotoxin from *Aspergillus* and *Penicillium* species. This mycotoxin can contaminate food products[83] and induce hepatotoxicity, nephrotoxicity and immunotoxicity,[84] thus increasing TNF-α production and diminishing toxin-induced apoptosis.[83] Individual treatment with *L. plantarum 2 017 405*, *L. fermentum* 353, *L. acidophilus* DSM 21007 and *L. rhamnosus* GG antagonised *C. difficile* isolated from faecal specimens from adult patients affected by diarrhoea, as observed by measurement of the inhibition zone.[85] Another *L.* strain, *L. reuteri* RC-14,[86] produced small signalling molecules able to interfere with a key regulator of virulence genes, *agr*. Additionally, *L. reuteri* RC-14 repressed the expression of toxic shock syndrome toxin-1 in menstrual toxic shock syndrome induced by *Staphylococcus (S.) aureus* strains. Quantitative real-time polymerase chain reaction (PCR) data revealed that transcription from the toxic shock *tst* promoter was strongly inhibited in culture supernatant in presence of *L. reuteri* RC-14. Moreover, a transcriptional level alteration of virulence-associated regulators was observed, providing a unique mechanism by which endogenous or exogenous lactobacilli can attenuate production of virulence factors. This study highlighted the existence of a crosstalk mechanism between two distinct bacterial signalling systems, that is, alteration in the transcriptional levels of virulence-associated regulators *sarA* and *saeRS* and transcription inhibition from *Ptst*, P2 and P3 promoters, providing a potential defensive mechanism against *S. aureus* infections. Therefore, administration of well-characterised lactobacilli can be helpful to overcome antibiotic-related complications, such as antibiotic resistance. Based on 16SrDNA sequences and non-coding fragments characterisation of different lactobacilli, Fei and coworkers reported a significantly high nitrite degradation capacity exerted by *L.* sp DMDL 9010 after a 24 h fermentation in the medium.[87] Compound degradation activity of lactobacilli has also been observed for cadmium after high dietary exposure.[88] In this regard, two *L. kefir* strains, CIDCA 8348 and JCM 5818, can remove cadmium cations when cocultured with a human hepatoma cell line, HepG2.[89] Particularly, *L. kefir* JCM 5818 is more efficient in protecting cells from cadmium toxicity. Therefore, since consumption of harmful metals is a growing medical issue, the regular administration of formulations containing the above mentioned strains might be useful to prevent toxin compound-induced lipid peroxidation and free radical production.

Vaginal colonisation

Vaginal microbiota is dominated by lactobacilli.[90] When the balance among bacterial species within this environment is altered, antibacterial defense mechanisms lose their efficacy leading to pathogenic bacteria proliferation.[90] For instance, reduction in the number of vaginal lactobacilli and their antimicrobial properties (such as lysostaphin expression in order to cleave the cell wall of *S. aureus* thus inhibiting its growth),[91] and H_2O_2 production,[92] cause bacterial vaginosis, the most common symptomatic microbial imbalance.[93] In patients affected by bacterial vaginosis, lactobacilli are replaced by *Gardnerella vaginalis*,[92 94] *Candida (C.) albicans*,[95] *S. aureus*,[91 96] *Neisseria gonorrhoeae*[40] or other anaerobic bacteria. Uncontrolled growth of anaerobic bacteria such as *C. albicans* and subsequent vaginal colonisation may lead to

Table 2 Clinical studies showing efficacy of lactobacilli for treatment of cancer

Bacteria	Dose	Pathology	Ref. (Design)
B. lactis Bb12 *L. rhamnosus GG* + *Oligofructose enriched inulin (SYN1)*	1×10^{10} CFU (total) 12 g	Colon cancer	[39](randomised, double-blind, placebo-controlled study)
L. rhamnosus LC705 *P. freudenreichii* subsp *Shermanii*	$2–5\times10^{10}$ CFU (of each)	Liver cancer	[78](randomised, double-blind, placebo-controlled study)
B. longum *L. acidophilus* *E. faecalis*	10^{8} CFU/g (0.21 g) (total)	Colorectal cancer	[79](open study)
B. natto *L. acidophilus*	10 mg 30 mg	Colorectal cancer	[80](open study)

Table 3 Clinical studies of lactobacilli showing efficacy for treatment of vaginal disorders

Bacteria	Dose	Pathology	Ref. (Design)
L. plantarum P17630	$>10^8$ CFU	Acute vulvovaginal candidiasis	[97](retrospective comparative study)
L. rhamnosus GR-1 *L. fermentum* RC-14	$>10^9$ CFU (of each)	Potential pathogenic bacteria and yeast vagina colonisation	[102](open study)
Kramegin® (*L. acidophilus*, lactic acid + *Krameria triandra* extract)	N/A	Abnormal cervical cytology	[103](open study)
Ellen AB® *L. gasseri* LN40 *L. fermentum* LN99*L. casei subsp rhamnosus* LN113 *P. acidilactici* LN23 + an inert carrying matrix of maltodextrin and magnesium stearate	 10^{8-10} CFU 10^{8-10} CFU 10^{8-10} CFU	Bacterial vaginosis and vulvovaginal candidiasis	[104](randomised double-blind placebo-controlled study)
L. fermentum LF10 *L. acidophilus* LA02 + Arabinogalactan + Fructooligosaccharides	0.4×10^9 CFU (of each) 340 mg 241 mg	Recurrent vulvovaginal candidiasis	[105](clinical study)
L. fermentum LF15 *L. plantarum* LP01 + Tara gum	0.4×10^9 CFU (of each) 50 mg	Bacterial vaginosis	[106](pilot study)
Florisia® (*L. brevis* (CD2), *L. salivarius* subsp *salicinius* (FV2), *L. plantarum* (FV9))	10^9 CFU (total)	Bacterial vaginosis	[107](randomised, double-blind, placebo-controlled study)
L. rhamnosus GR-1 *L. reuteri* RC-14	2.5×10^9 CFU (of each)	Vaginal flora overgrowth	[108](randomised, double-blind, placebo-controlled study)
EcoVag® (*L. gasseri* (Lba EB01-DSM 14869) *L. Rhamnosus* (Lbp PB01-DSM 14870))	10^{8-9} CFU (of each)	Bacterial vaginosis	[109](double-blind, randomised, placebo-controlled study)

vulvovaginal candidiasis,[97] which is estimated to occur at least once during the lifetime of 75% of the female population.[98] Vaginal microbial imbalance may also represent an important risk factor for increased risk of urinary tract infections and pregnancy complications, such as endometritis, chorioamnionitis, preterm birth and intrauterine death.[99] Intravaginal colonisation by bacterial strains with high haemolytic activity and pigment production [eg, group B streptococci (GBS)] is one of the most important risk factors for disease development in newborns.[100] Therefore, a murine model was proposed in order to determine if *L. reuteri* CRL1324 would exert a preventive effect on vaginal colonisation by *Streptococcus (St.) agalactiae* NH17.[100] Following *L. reuteri* CRL1324 administration, a reduced leucocyte influx induced by *St. agalactiae* NH17 and a preventive effect on its vaginal colonisation were observed prior to the GBS challenge. Although GBS colonization occurs in up to 50–70% of neonates born from colonized mothers,[101] the introduction of new antimicrobial agents, such as *L. reuteri* CRL1324, could be considered a valuable and safer alternative to antibiotics to reduce infections caused by GBS. Clinical studies of lactobacilli showing efficacy for treatment of vaginal disorders have been summarised in table 3.

Cholesterol-lowering activity

There is an increasing demand for non-pharmacological therapies to improve cholesterol profile due to the cost and side effects associated with available pharmacological treatments for cholesterol-related diseases. Hence great attention has been given to lactobacilli due to their effectiveness in modulating lipid metabolism reducing statin requirement (statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase that produces about 70% of the total body cholesterol)[110 111] and serum cholesterol level by means of bile salt hydrolase that has a direct impact on the host's bile salt metabolism accounting for the formation of deconjugated bile acids.[112] Furthermore, cholesterol-reducing properties were also observed for *L. oris* HMI118, HMI28, HMI43, HMI68 and HMI74 isolated from breast milk.[113] Although all the tested strains assimilated cholesterol even in the absence of bile salts, surviving in the acidic conditions of the intestine and tolerating high bile concentrations, *L. oris* HMI68 showed the highest cholesterol assimilation deconjugating sodium glycocholate (the most predominant bile salt in the human intestine) and sodium taurocholate. Cholesterol assimilation has also been evaluated as a possible

Table 4 Clinical studies of lactobacilli showing efficacy for treatment of hypercholesterolaemia

Bacteria	Dose	Ref. (Design)
L. plantarum CECT 7527 CECT 7528 CECT 7529	1.2×10^9 CFU (total)	[118](controlled, randomised, double-blind study)
L. acidophilus L1	N/A	[119](double-blind, placebo-controlled, cross-over study)
L. reuteri NCIMB 30242	5×10^9 CFU	[120](double-blind, placebo-controlled, randomised, parallel-arm, multicentre study)
L. acidophilus *B. lactis*	N/A	[121](single-blind and randomised cross-over study)

Table 5 Clinical trials of lactobacilli showing inhibitory activity against *H. pylori* infection

Bacteria	Dose	Pathology	Ref. (Design)
L. johnsonii La1	> 10^7 CFU/mL in 80 mL	Asymptomatic *H. pylori* infection	[173](double-blind, randomised, controlled clinical study)
L. gasseri OLL2716	1–1.4×10^7 CFU/g in 90 g	*H. pylori* infection	[174](open study)
Enterolactis® (*L. casei* subsp casei DG, Vitamin B1, B2 and B6)	1.6×10^9 CFU (total)	*H. pylori* infection	[182](open study)
Actimel®: (*L. casei* DN-114 001)	1×10^{10} CFU in 100 mL	*H. pylori* infection	[183](multicentre, prospective, randomised, double-blind controlled study)
AB yogurt (*L. acidophilus*, *B. lactis*, *L. bulgaricus*, *St. thermophilus*)	5×10^9 CFU/200 mL (total)	*H. pylori* infection	[184](open study)
L. reuteri ATCC 55730	1×10^8 CFU	*H. pylori* infection	[185](open study)
Will yogurt (*L. acidophilus* HY2177 *L. casei* HY2743 *B. longum* HY8001 *St. thermophilus* B-1)	 ≥1×10^5 CFU ≥1×10^5 CFU ≥1×10^6 CFU ≥1×10^8 CFU	*H. pylori* infection	[186](randomised triple-therapy study)
AB-yogurt (*L. acidophilus* La5, *B. lactis* Bb12)	10^7 CFU/mL in 230 mL (of each)	*H. pylori* infection	[175](open study)
Genefilus F19© (*L. paracasei sub. paracasei* F19)	12×10^9 CFU/2.5 g	*H. pylori* infection-related gastroesophageal reflux	[177](randomised, double-blind, placebo-controlled study)
L. reuteri Gastrus (*L. reuteri* DSM 17938 *L. reuteri* ATCC PTA 6475)	1×10^8 CFU (total)	*H. pylori* infection	[187](prospective, double-blind, randomised, placebo-controlled study)
L. gasseri OLL2716	≥10^9 CFU	*H. pylori* infection	[188](randomised, controlled clinical study)
L. brevis CD2	20×10^9 CFU	*H. pylori* infection	[189](open study)

therapeutic approach to reduce the risk for cardiovascular diseases.[114] In this regard, Tomaro-Duchesneau and coworkers investigated the ability of 11 *L.* strains (*L. reuteri* NCIMB 11951, 701359, 702655, 701089 and 702656, *L. fermentum* NCIMB 5221, 8829, 2797, *L. rhamnosus* ATCC 53103 GG, *L. acidophilus* ATCC 314 and *L. plantarum* ATCC 14917) to assimilate cholesterol. While *L. plantarum* ATCC 14917 was the best cholesterol assimilator in de Man, Rogosa and Sharpe broth, *L. reuteri* NCIMB 701089 assimilated over 67% of cholesterol under physiological intestinal conditions. The hypocholesterolaemic effect of all strains, particularly of *L. reuteri* NCIMB 701089, was linked to intrinsic bile salt hydrolase activity, assimilation and incorporation in cellular membranes and compound production, for example, ferulic acid,[115] able to inhibit the activity of enzymes, including 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[116] More recently, cholesterol-reducing *L.* spp. GI6, GI9, GI11 and GI15 were also isolated from traditionally fermented south Indian koozh and gherkin (a variety of cucumber).[117] *L.* GI9 was able to survive at pH 2.0 and 0.50% bile salt for 3 h without losing its viability also exhibiting the maximum cholesterol reduction. Nevertheless, all tested lactobacilli exhibited inhibitory activity against several pathogens including *Escherichia coli* MTCC 1089, *Pseudomonas (P.) aeruginosa* MTCC 2642, *S. aureus* MTCC 7443, *Klebsiella (K.) pneumoniae* MTCC 7028, *Bacillus subtilis* MTCC 8561 and *C. albicans* BS3 and were able to deconjugate bile salts. Clinical studies of lactobacilli showing efficacy for treatment of hypercholesterolaemia have been summarised in table 4.

Table 6 Clinical studies of lactobacilli showing efficacy for treatment of kidney-related diseases

Bacteria	Dose	Ref. (Design)
L. acidophilus, *L. plantarum*, *St. thermophilus*, *B. infantis* *L. brevis* (CD2)	8×10^{11} CFU (of each)	[197](open study)

Antioxidant activity

Lactobacilli can prevent lipid peroxidation[122] and free oxygen radical production[123] due to their ability to create the low oxidation-reduction potential required for their optimal growth.[124] Amaretti and coworkers combined the strains *Bifidobacterium* (*B.*) *animalis* subsp *lactis* DSMZ 23032, *L. acidophilus* DSMZ 23033 and *L. brevis* DSMZ 23034 and administered them for 18 days to rats previously treated with doxorubicin, an anthracycline antibiotic.[125] Analysis of plasma antioxidant activity, glutathione concentration, as well as levels of reactive oxygen species, revealed a reduction in doxorubicin-induced oxidative stress, thus supporting antioxidant activity of these probiotics.

Antibacterial and antiviral activity

Probiotic strains beneficially affect the host by replacing pathogenic bacteria in the GI tract and modulating immune responses.[126] Experimental studies have shown that lactobacilli, which can adhere to the enterocytes, are effective in preventing the enteropathogen-mediated infection by competing for nutrients[127] and binding sites (eg,inducing intestinal mucin gene expression),[128–132] by secreting antimicrobial substances[133] such as organic acids,[134–142] bacteriocins[143–145] and hydrogen peroxide[146–152] and eventually by counteracting the spread within the colonised body,[153–155] reducing gut pH[133 141 156] and producing

Table 7 Clinical studies of lactobacilli showing efficacy for treatment of mastitis

Bacteria	Dose	Pathology	Ref. (Design)
L. fermentum CECT5716 *L. salivarius* CECT5713	1×10^9 CFU/200 mg (of each)	Infectious mastitis induced by *S. epidermidis* or *S. aureus*	[202](open study)
L. salivarius CECT5713 *L. gasseri* CECT5714 + a matrix of methylcellulose	1×10^{10} CFU/200 mg (of each)	Mastitis induced by *S. epidermidis* or *S. aureus*	[203](open study)

biosurfactants.[157–159] As far as bacterial activity is concerned, *L. plantarum* GK81, *L. acidophilus* GK20 and *L. plantarum* JSA22 inhibit *Salmonella* spp infection in intestinal epithelial cells[160 161] and *L. acidophilus* strain inhibits various pathogenic bacteria including *P. aeruginosa*, *E. coli*, *Enterobacter* and *K.* spp.[150] With reference to antiviral activity, lactobacilli harbour surface layer proteins involved in the enhancement of viral entry.[162] Moreover, increasing data indicate that abnormal vaginal flora lacking lactobacilli can facilitate viral sexually transmitted disease diffusion such as in the case of HIV,[163] human papilloma virus[164] and herpes simplex virus 2.[165] In this context, lactobacilli can exert an important role protecting the vaginal environment and reducing the risk of virus transmission.

Helicobacter pylori infection

Helicobacter (*H.*) *pylori*, a gram-negative microaerophilic human gastric pathogen, is the main cause of chronic gastritis, gastric cancer and peptic ulcer disease.[166] Antibiotic treatment for *H. pylori* infection is associated with serious side effects and therefore there is an increasing demand for new treatments. Lactobacilli[167 168] have been extensively investigated for treatment of *H. pylori* infections. Numerous *L.* strains, that is, *L. gasseri Chen*, *L. plantarum* 18,[167] *L. gasseri* OLL2716,[168] *L. reuteri*,[169] *L. rhamnosus* GG, *L. rhamnosus* Lc705, *Propionibacterium* (*P.*) *freudenreichii* subsp *shermanii* Js,[170] *L. delbrueckii* subsp *bulgaricus* 48, 144 and GB,[171] *L. rhamnosus* LC705, *P. freudenreichii ssp shermanii* JS,[168] *L. acidophilus* LB,[172] *L. plantarum* MLBPL1, *L. rhamnosus* GG and *L. lactis*[137] possess a neutralising activity against *H. pylori*. The same activity was also observed for heat-killed *L. johnsonii* Lal and *L. helveticus*[173] as well as for *L. gasseri* OLL2716,[174] as measured by ^{13}C-urea breath test. The suppressive effect of lactobacilli on *H. pylori* infection in vivo and in vitro has been reviewed.[175–177] For instance, *L. johnsonii* 1088 suppressed gastric acid secretion in mice via decreasing the number of gastrin-positive cells in the stomach.[176] This result can be considered a valid add-on therapy during the gold standard treatment for *H. pylori* eradication by use of a proton pump inhibitor (PPI), amoxicillin and clarithromycin, and for prophylaxis of gastroesophageal reflux disease following *H. pylori* eradication. Nevertheless, the use of a PPI can also modify the gut microbiota causing dysbiosis.[178–180] In this regard, adding *L. paracasei* subsp *paracasei* F19 to triple therapy is a promising combination to counteract the effects of PPIs on intestinal dysbiosis.[181] Clinical studies of lactobacilli showing inhibitory activity against *H. pylori* infection have been summarised in table 5.

Kidney disease

The last stage of chronic kidney disease induces an increase in plasma concentration of uraemic wastes and requires kidney transplantation or chronic dialysis.[190] Many studies support the probiotic approach as an alternative therapy for management of end-stage renal disease[191] and to relieve the 'uraemic' condition.[189 192–194] In particular, a high urease activity was observed for *S.* spp, *L. casei*, *K. aerogenes* and *Enterococcus faecium* in the sheep rumen.[192] At the same time, the ability to degrade biogenic amines (BAs) was also assessed by Capozzi and coworkers.[193] They isolated two lactobacilli (*L. plantarum* NDT 09 and *L. plantarum* NDT 16) from wine and found that they were able to degrade tyramine (22.12%) and putrescine (31.09%), respectively. *L. casei* 4a and 5b, isolated from Zamorano cheese, also inhibited tyramine along with histamine, another BA.[194] However, BA degradation is not the only mechanism under investigation for treatment of end-stage renal disease and uraemic condition. The ability to degrade oxalate and to survive within the GI tract of a range of *B.* and *L.* species, isolated from the canine and feline GI tract, has also been evaluated. In vitro oxalate degradation was detected for 11

Table 8 Clinical studies of lactobacilli showing immunomodulatory activity in various pathologies

Bacteria	Dose	Pathology	Ref. (Design)
L. salivarius LS01 *B. breve* BR03 + maltodextrin	1×10^9 CFU (of each)	Moderate/severe atopic dermatitis	[223](randomised double-blinded active treatment vs placebo study)
proBiotik (*B. bifidum, L. acidophilus, L. casei and L. salivarius*)	2×10^9 CFU (total)	Atopic dermatitis	[207](double-blind, randomised, placebo-controlled study)
L. pentosus b240	2×10^{10} CFU	Common cold	[224](randomised, double-blind, placebo-controlled study)
Yakult® (*L. casei* Shirota)	6.5×10^9 CFU in 65 mL	Allergic rhinitis	[210](double-blind, placebo-controlled study)
L. paracasei -33	2×10^9 CFU in 200 mL milk	Allergic rhinitis	[216](randomised, double-blind, placebo-controlled study)
L. acidophilus L-92	N/A	Atopic dermatitis	[225](double-blind, randomised, clinical study)

Table 9 Clinical studies of lactobacilli showing efficacy for treatment of gastrointestinal pathologies

Bacteria	Dose	Pathology	Ref. (Design)
VSL#3® (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, *B. longum*, *B. breve*, *B. infantis* *St. thermophilus*)	5×10^{11} CFU/g in 3 g (total)	Chronic pouchitis	[230](open study)
Yakult® (*L. casei* Shirota)	6.5×10^{9} CFU in 65 mL	Constipation	[231](open study)
Lb. plantarum SN13T	2×10^{8} CFU	Constipation	[232](double-blind, randomised study)
VSL#3® (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, *B. longum*, *B. breve*, *B. infantis*, *St. thermophilus*)	5×10^{11} CFU/g in 3 g (total)	Ulcerative colitis	[233](open study)

out of 18 *L.* strains (8 *L. animalis* and 3 *L. murinus*), but not for any of the *B.* strains.[195] Rats were fed on four selected strains (*L. animalis* 223C, *L. murinus* 1222, *L. animalis* 5323 and *L. murinus* 3133) for 4 weeks; urinary oxalate levels were significantly reduced only in those rats fed on *L. animalis* 5323 and *L. animalis* 223C. Oxalate-degrading activity has also been assessed for other lactobacilli.[196] *L. paracasei* LPC09 displayed the highest oxalate-degrading activity converting 68.5% of ammonium oxalate followed by *L. gasseri* LGS01 (68.4%), *L. gasseri* LGS02 (66.2%), *L. acidophilus* LA07 (54.2%) and *L. acidophilus* LA02 (51.3%). The use of lactobacilli as agents able to integrate into the host's gut microbiota may thus be considered helpful in reducing oxaluria and preventing or decreasing the incidence and severity of kidney stone formation. Clinical studies of lactobacilli showing efficacy for treatment of urinary stones have been summarised in table 6.

Mastitis

Mastitis is an infectious inflammation of one or more breast lobules[198] with *S. aureus* and *S. epidermidis* being the most frequent aetiological agents[199] and with a prevalence of 3–33% among breastfeeding mothers.[200] Multidrug resistance and biofilm formation by pathogenic bacteria account for the lack of efficacy of antibiotics used for treatment of mastitis.[201] In this context, new strategies based on probiotics, as alternatives or complements to antibiotic therapy for the management of mastitis, are gaining a prominent role. Clinical studies of lactobacilli showing efficacy for treatment of mastitis have been summarised in table 7.

Immunomodulatory activity

Lactobacilli are potential adjuvants triggering mucosal and systemic immune responses.[204] The immunomodulatory effects of lactobacilli observed in various physiological systems include increased natural killer cell cytotoxicity[205 206] and induction of interferon-γ production[205–213] and cytokine expression.[205–210 212–216] In order to exert these immunomodulatory effects, lactobacilli must resist to digestive system processes[217] and adhere to the host's intestinal epithelium.[218] Lactobacilli (in particular *L. acidophilus*) can also be administered together with bifidobacteria in order to enhance the immune system.[219 220] This effect is accomplished by enhancing systemic/local immunity[221] and concurrently attenuating systemic stress response.[222] Clinical studies of lactobacilli showing immunomodulatory activity in various pathologies have been summarised in table 8.

Table 10 Clinical studies of lactobacilli showing ability to survive in the gastrointestinal tract

Bacteria	Dose	Site	Ref. (Design)
L. acidophilus 821–3	1×10^{10} CFU	Gastrointestinal tract	[15](open study)
L. acidophilus *B.* sp	1×10^{8} CFU/g 1×10^{7} CFU/g in 100 g fermented milk	Small intestine	[237](open study)
L. casei shirota	1×10^{8} CFU/mL in 100 mL	Gastrointestinal tract	[238](14-day baseline, ingestion and follow-up periods)
L. acidophilus LA02 (DSM 21717), *L. rhamnosus* LR04 (DSM 16605), *L. rhamnosus* GG, (ATCC 53103), *L. rhamnosus* LR06 (DSM 21981), *B. lactis* BS01 (LMG P-21384)	5×10^{9} CFU (of each)	Gastrointestinal tract	[239](double-blind, randomised, cross-over study)
L. plantarum LP01 (LMG P-21021) *B. breve* BR03 (DSM 16604)	1×10^{9} CFU (of each)	Gastrointestinal tract	[240](double-blind, randomised, cross-over study)
Lakcid® L (*L. rhamnosus* 573/1, 573 L/2 and 573L3)	1.2×10^{10} CFU in 2 mL 10% glucose	Gastrointestinal tract	[241](prospective, double-blinded, placebo-controlled randomised study)

Table 11 Clinical studies of lactobacilli showing efficacy for treatment of diarrhoea

Bacteria	Dose	Pathology	Ref. (Design)
Actimel® (*L. casei* DN 114001)	10^{10} CFU/100 mL	Antibiotic-associated diarrhoea	[249](observational study)
Balance (*L. casei*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, *B. strains* *B. breve*, *B. longum*, *St. thermophilus)*	1×10^{8} CFU (total)	*H. pylori* infection-associated diarrhoea	[250](randomised placebo-controlled triple-blind study)
L. acidophilus *L.rhamnosus* *B. bifidum*, *B. longum*, *E. faecium* + fructo-oligosaccharide	2.5×10^{9} CFU (total) 625 mg	Acute diarrhoea	[251](prospective randomised, multicentre single-blinded clinical study)
L. acidophilus CUL60 (NCIMB 30157), CUL21 (NCIMB 30156), *B. bifidum*; CUL20, NCIMB 30153), *B. lactis* (CUL34, NCIMB 30172)	6×10^{10} CFU (total)	Antibiotic-associated diarrhoea	[252](prospective, parallel group study)
Probiotical (*S. thermophilus*, *L. rhamnosus*, *L. acidophilus*, *B. lactis*, *B. infantis* + Fructooligosaccharides + Ascorbic ac	 6.5×10^{9} CFU (60 mg) 6.5×10^{9} CFU (28 mg) 6.5×10^{9} CFU (28 mg) 6.5×10^{9} CFU (20 mg) 6.5×10^{9} CFU (20 mg) 20 mg 1.2 mg	Acute gastroenteritis	[253](randomised, prospective placebo-controlled parallel clinical study)
NAN 1® (*L. acidophilus*, *L. rhamnosus*, *B. longum* *S. boulardii)*	 6.625×10^{7} CFU 3.625×10^{7} CFU 8.75×10^{6} CFU 1.375×10^{7} CFU	Acute rotavirus diarrhoea	[254](prospective, double-blind, randomised study)
L. rhamnosus 35	6×10^{8} CFU	Acute rotaviral gastroenteritis	[255](open-label randomised study)
L. rhamnosus (strains E/N, Oxy and Pen)	2×10^{10} CFU (of each)	Antibiotic-associated diarrhoea	[256](double-blind, randomised, placebo-controlled study)
L. acidophilus LB + spent culture medium	10^{9} CFU 160 mg	Non-rotavirus diarrhoea	[257](randomised, double-blind, placebo-controlled clinical study)
Lakcid® L (*L. rhamnosus* (573 L/1; 573 L/2; 573 L/3))	1.2×10^{10} CFU (total)	Infectious diarrhoea	[258](randomised, double-blind, placebo-controlled study)
L. paracasei ST11	10^{10} CFU	Non-rotavirus diarrhoea	[259](randomised, double-blind, placebo-controlled clinical study)
L. casei CERELA, *L. acidophilus* CERELA, *S. boulardii*	10^{11} CFU/g in 175 g (of each)	Persistent diarrhoea	[260](double-blind study)
L. rhamnosus 19070–2 *L. reuteri* DSM 12246	10^{10} CFU (of each)	Acute diarrhoea	[261](randomised placebo-controlled study)
L. casei CERELA, *L. acidophillus* CERELA	N/A	Bacterial overgrowth-related chronic diarrhoea	[262](randomised, double-blind study)
L. reuteri	10^{10-11} CFU/g in 1 g	Acute diarrhoea	[263](randomised, placebo-controlled study)

Table 12 Clinical studies of lactobacilli showing efficacy for treatment of periodontal disease

Bacteria	Dose	Pathology	Ref. (Design)
L. salivarius WB21 + Xylitol	6.7×10^{8} CFU 280 mg	Severe periodontitis treatment	[274](randomised clinical study)
L. reuteri ATCC 55730, *L. reuteri* ATCC PTA 5289	1×10^{8} CFU/gum (of each)	Gingival inflammation	[275](double-blind placebo-controlled study)

Table 13 Clinical studies of lactobacilli showing efficacy for treatment of diabetes

Bacteria	Dose	Pathology	Ref. (Design)
L. acidophilus, *L. casei,* *L. rhamnosus,* *L. bulgaricus,* *B. breve,* *B. longum,* *St. thermophilus* + fructo-oligosaccharide	2×10^9 CFU 7×10^9 CFU 1.5×10^9 CFU 2×10^8 CFU 2×10^{10} CFU 7×10^9 CFU 1.5×10^9 CFU 100 mg	Type-2 diabetes	[282](randomised double-blind placebo-controlled clinical study)

Gastrointestinal pathologies

Even if the pathogenesis of irritable bowel syndrome (IBD) remains unknown, the luminal microbiome plays a key role in triggering and maintaining a balanced environment within the GI tract.[226] Dysbiosis may also play a key role in IBD.[227] Evidence from animal models[228] and clinical observations[229] outlined the putative therapeutic role of probiotic strains for IBD treatment. Restoring microbiota-host symbiosis can represent a promising approach for treatment of the above mentioned conditions and can be applied to other GI pathologies, as summarised in table 9.

Gastrointestinal tract survival

Strains belonging to *L.* and *B.* genera are the most studied in clinical practice.[234] The number of bacterial strains that reach the gut mucosa and colon, depends on several factors such as strain used, gastric transit survival,[15 235] and acid and bile tolerance.[236] Clinical studies of lactobacilli showing ability to survive in the GI tract have been summarised in table 10.

Diarrhoea

Imbalance in the gut flora can cause diarrhoea, enteritis and colitis, among other diseases. VSL#3 (*St. thermophilus, B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. casei* and *L. bulgaricus*) and *L. casei* DN-114 001 administration decreased the incidence and frequency of radiation therapy-induced diarrhoea.[242] Diarrhoea is also frequent during antibiotic therapy causing gut flora imbalance.[243 244] *Clostridium (C.) difficile* infection, a gram positive, spore-forming anaerobe, can cause antibiotic-associated diarrhoea and colitis in humans.[245 246] Boonma and coworkers investigated the probiotic effect of *L. rhamnosus* L34 and *L. casei* L39, two vancomycin-resistant lactobacilli, on the suppression of IL-8 production in response to *C. difficile* infection.[247] While *L. casei* L39 suppressed the activation of phosphonuclear factor κ-light-chain-enhancer of activated B cells and phospho-c-Jun in HT-29 cells, *L. rhamnosus* L34 and *L. casei* L39 decreased the production of *C. difficile*-induced granulocyte-macrophage colony-stimulating factor. Moreover, *L. acidophilus* GP1B cell extract decreased transcriptional levels of luxS, tcdA, tcdB and txeR genes of *C. difficile*, thus reducing virulence in vitro.[248] In vivo, survival rates at 5 days for mice that received *C. difficile* and *L. acidophilus* GP1B cell extract or *L. acidophilus* GP1B were reduced up to 80%. Therefore, in vitro and in vivo investigations have showed that lactobacilli presented antibacterial effects. Clinical studies of lactobacilli showing efficacy for treatment of diarrhoea have been summarised in table 11.

Periodontal disease

Periodontal diseases can be divided into gingivitis and periodontitis.[264] While the first condition is characterised by

Table 14 Clinical studies of lactobacilli showing efficacy for treatment of various pathologies

Bacteria	Dose	Pathology	Ref. (Design)
L. casei Shirota	N/A	Ventilator-associated pneumonia	[291](prospective, randomised, open-label controlled study)
Synbiotic 2000: *P. pentosaceus 5–33:3* *L. mesenteroides 32–77:1* *L. paracasei 19* *L. plantarum 2362* + inulin, β-glucan, resistant starch and pectin	1×10^{10} CFU (of each) N/A	Severe acute pancreatitis	[292](prospective, randomised, double-blind study)
Ecologic 641®: *L. acidophilus* *L. casei* *L. salivarius* *Lact. Lactis* *B. bifidum B. lactis* + cornstarch and maltodextrins	10^{10} CFU (total) N/A	Severe acute pancreatitis	[293](multicentre randomised, double-blind, placebo-controlled study)
Genefilus F19©: *L. paracasei subsp paracasei* F19 + high-fibre diet	12×10^9 CFU/2.5g N/A	Symptomatic uncomplicated diverticular disease	[294](multicentre, randomised, controlled, open parallel-group study)
L. GG	$> 5\times10^{10}$ CFU	Cirrhosis	[295](open study)

Table 15 Clinical studies reporting side effects associated with therapy with lactobacilli

Bacteria	Effect/s	Patient(s) clinical history	Ref.
L. jensenii	Endocarditis	An immunocompetent 47-year-old man with mitral valve replacement treated with teicoplanin and meropenem	302
L. paracasei	Endocarditis	A patient (18 years) with trisomy 21 treated with chloramphenicol	303
L. rhamnosus GG	Bacteraemia	Eleven patients with immunosuppression, prior prolonged hospitalisation and prior surgical interventions treated with antimicrobials	317
L. acidophilus *L. bulgaricus*	Bloodstream infections	The maximum estimated incidence of bacteraemia during an 8-year period was 0.2%	322
L. rhamnosus	Bacteraemia	Sixteen nosocomial infections associated with immunosuppression (66%) and catheters (83%)	312
L. rhamnosus, L. curvatus *L. delbrueckii* subsp *Lactis* *L. paracasei*	Bacteraemia	Six cases of bacteraemia in hospitalised patients, five with a depressed immune status	306
L. rhamnosus	Hepatic abscess and bacteraemia	A 73 year-old woman with antecedent of diabetes mellitus treated with ampicillin plus gentamicin	316
L. rhamnosus	Catheter-related bacteraemia	A patient who underwent a single-lung transplant	308
L. rhamnosus	Bacteraemia	A 14-year-old girl with acute myeloid leukaemia, bacteraemia disappeared only after 13 months when the cytostatic therapy was terminated	314
L. plantarum	Bacteraemia	A patient (43 years) with a subacute endocarditis due to an immunovasculitis and a bloodstream infection	307
L. rhamnosus	Septicaemia	A 54-year-old woman with diabetes treated with amoxicillin	296
L. jensenii	Septicaemia	A 50-year-old woman with obstructive acute renal failure	297
L. paracasei	Purpura fulminans associated with liver abscess	N/A	323
L. acidophilus	Liver abscess	A 27-year-old man with a 6-month history of NOD2/CARD15-positive Crohn's disease	324
L. casei	Pneumonia and sepsis	A patient with AIDS because of CD4 lymphocyte depletion	325
L. rhamnosus	Septicaemia	A patient with a graft in the inferior vena cava	298
L. gasseri	Septic urinary infection	A patient (66 years) developed severe urinary stasis due to a concrement in his right ureter, treated with cefotaxime and amoxicillin	326
L. casei	Bacteraemia	A 75-year-old woman (a heavy dairy consumer)with severe thoracic pain due to dissection of the aortic arch and ascending aorta and treated with amoxicillin	327
L. rhamnosus Lcr35, ATCC53103	Meningitis Recurrent episodes of Bacteraemia	A child (10 years) undergoing allogeneic haematopoietic stem cell transplantation and treated unsuccessfully with clindamycin	320
L. casei	Bacteraemia	An immunocompetent 66-year-old man with a history of fever of unknown origin	319
L. jensenii	Bacteraemia and pyelonephritis	A 59-year-old woman with progressed follicular lymphoma, diabetes mellitus type-2 and arterial hypertension and kidney stone treated with antibiotics	309
L. jensenii	Bacteraemia and endocarditis	A 27-year-old woman with a 20-day history of fever and treated with penicillin and gentamicin	304
L. rhamnosus	Catheter-related bloodstream infections	A 38-year-old woman who underwent allogenic transplantation of haematopoietic stem cells from cord blood for a large granular lymphocyte leukaemia and initially treated with chemotherapy	328
L. delbrueckii	Pyelonephritis and Bacteraemia	A 68-year-old woman with fever, chills, nausea, and vomiting and ureteral calculus with mild left hydronephrosis treated with ampicillin	311
L. rhamnosus	Sepsis	A 24-year-old woman developed sepsis resulting from preoperative administration of probiotics following an aortic valve replacement	301
L. rhamnosus GG	Bacteraemia	A 69-year-old man with stage IIIA mantle cell lymphoma and treated with probiotic-enriched yogurt stopping	329
L. rhamnosus GG	Bacteraemia	An 11-month-old boy with fever and hypoxia and with a history of short bowel syndrome secondary to resection of approximately 80% of the small intestine	310
L. acidophilus	Sepsis	A 69-year-old man with stage IIIA mantle cell lymphoma	315
L. rhamnosus GG	Bacteraemia.	A 36-week-gestation male infant with short gut syndrome secondary to congenital intestinal atresia and volvulus	313
L. rhamnosus GG	Bacteraemia.	A 34-week-gestation male infant with gastroschisis	313
L. rhamnosus	Bacteraemia	A 43-year-old woman with ulcerative colitis	299
L. paracasei	Endocarditis	A 77-year-old man with a prostate cancer in remission, hiatal hernia, right hip prosthesis, mitral insufficiency, hypertension, bipolar disorder, and daily consumer of probiotics	330

inflammation of the gingiva,[265] the second is a progressive destructive disease which involves tooth supporting tissues such as the alveolar bone.[266] Periodontitis is mainly characterised by the presence of *Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans* which colonise the subgingival sites escaping the host defense system and eventually causing tissue damage.[267] Among antimicrobial and bacteriostatic agents, chlorhexidine is the gold standard for treatment of periodontitis because of its broad-spectrum antibacterial activity.[268–270] However, a number of side effects, such as brown teeth discolouration, salt taste perturbation, oral mucosal erosions and enhanced supragingival calculus formation, have been reported and they have limited chlorhexidine long-term use.[271] Evidence has shown the effectiveness of lactobacilli in reducing gingival inflammation and the number of cariogenic periodontopathogenic bacteria.[272] Further

studies have shown that lactobacilli reduced the prevalence of moderate-to-severe gingival inflammation and improved plaque index (clinically used to measure the state of oral hygiene)[273 274] as well as decreased the levels of the proinflammatory cytokines TNF-α, IL-8 and IL-1β.[275] Saha and coworkers investigated the role of selected lactobacilli in *St. mutans* inhibition.[276] *L. reuteri* strains NCIMB 701359, NCIMB 701089, NCIMB 702655 and NCIMB 702656 inhibited *St. mutans* to non-detectable levels (<10 CFU/mL) suggesting their use as therapeutic agents for caries and periodontal disease. Moreover, *L. fermentum* NCIMB 5221 inhibited *St. mutans* buffering the pH (4.18) of saliva containing this pathogenic microbe and coaggregating with it also showing high levels of sucrose consumption. Altogether, these studies suggest that lactobacilli may improve oral health and reduce periodontopathogenic bacteria. Clinical studies of lactobacilli showing efficacy for treatment of periodontal diseases have been summarised in table 12.

Diabetes

Diabetes, a chronic metabolic disease, is characterised by elevated blood glucose levels due to either insufficient insulin production by β-islet cells (type-1 diabetes) of the pancreas or impaired insulin sensitivity of insulin target organs, that is, adipose tissue, liver and muscle (type-2 diabetes or diabetes mellitus).[277] In this context, inflammatory immune responses play a crucial role in the progression of both types of disease.[278–280] As for type-2 diabetes, it is generally treated with intestinal α-glucosidase inhibitors.[281] In this regard, *Actinoplanes* spp have been shown to naturally produce potent α-glucosidase inhibitor compounds including acarbose. Panwar and coworkers first isolated and extracted lactobacilli from human infant faecal samples and evaluated their inhibitory activity against intestinal maltase, sucrose, lactase and amylase, all enzymes involved in hydrolysis of carbohydrates.[281] This study showed that several strains exert powerful inhibitory effects against the aforementioned enzymes and *L. rhamnosus* reduced glucose excursions in rats during a carbohydrate challenge by inhibiting β-glucosidase as well as α-glucosidase activities. Even if further studies are certainly needed, administration of lactobacilli may represent a promising novel therapeutic tool for treatment of diabetes. Clinical studies of lactobacilli showing efficacy for treatment of diabetes have been summarised in table 13.

Arthritis

Osteoarthritis, a chronic joint disease characterised by progressive cartilage degeneration, subchondral bone sclerosis, synovial inflammation and osteophyte formation,[283] mainly affects weight-bearing joints such as knees and hips. A chronic inflammatory response occurs in synovial membranes with increased expression of proinflammatory cytokines and mononuclear cell infiltration.[284] Oral intake of skimmed milk fermented with *L. delbrueckii* subsp *bulgaricus* OLL1073R-1 inhibits the development of collagen-induced arthritis in mice. Moreover, a reduced secretion of IFN-γ was also observed in these animals.[285] Moreover, *L. casei* suppresses experimental rheumatoid arthritis by downregulating Th1-type inflammatory responses[286] and its coadministration with type-II collagen and glucosamine decreased the expression of various proinflammatory cytokines and matrix metalloproteinases, upregulating anti-inflammatory cytokines.[287] The immunomodulating activity of lactobacilli in rheumatoid arthritis was also confirmed by a trial on 45 adult men and women affected by this pathology.[288] *Bacillus coagulans* GBI-30, 6086, administered for 60 days in addition to standard antiarthritic medications, resulted in an improvement in the Patient Pain Assessment score and statistically significant improvement in Pain Scale with respect to placebo.

Other pathologies

Lactobacilli have found application for treatment of several other pathologies. For instance, *L. plantarum* strain K21 that inhibits lipid accumulation in 3T3-L1 preadipocytes, alleviated body weight gain and epididymal fat mass accumulation, reduced plasma leptin levels, decreased cholesterol and triglyceride levels as well as mitigated liver damage in a mouse model of diet-induced obesity.[289] Antilipidemic effects of lactobacilli were also evaluated along with memory-enhancing activity in aged Fischer 344 rats.[290] A probiotic mixture of *L. plantarum* KY1032 and *L. curvatus* HY7601 was provided once a day for 8 weeks. A significant inhibition of age-dependent increase in blood triglycerides and a reduction in high-density lipoprotein cholesterol was observed. Moreover, the mixture restored age-reduced spontaneous alternation in the Y-maze task and age-suppressed doublecortin and brain derived neurotrophic factor expression. In addition, suppression of p16, p53 and cyclooxygenase-2 expression, phosphorylation of protein kinase B and mammalian target of rapamycin and activation of nuclear factor κ-light-chain-enhancer of activated B cells were observed, thus suggesting a therapeutic role of such mixture in ameliorating age-dependent memory deficit and lipidemia in aged subjects. Clinical studies of lactobacilli showing efficacy for treatment of various pathologies have been summarised in table 14.

SIDE EFFECTS OF LACTOBACILLI

The widespread clinical use of lactobacilli, even for pathologies that are challenging to treat, has highlighted potential translocations or mutations and untoward effects such as sepsis,[296–301] endocarditis,[302–305] bacteraemia[299 306–319] and even death.[320] Evidence regarding lactobacilli side effect profile has been summarised in table 15.

CONCLUSIONS

The mammalian gut microbiome interacts with several physiological systems within the host contributing to multiple biological processes. In vitro and in vivo investigations have shown that prolonged probiotic administration induces qualitative and quantitative modifications in complex, well-settled microbial ecosystems through bacteriocin substrate competition and possibly other mechanisms that still need to be acknowledged. Probiotics can modulate the GI tract microbial ecology exerting immunomodulatory effects that are therapeutic at least for treatment of specific pathologies.[331] Our review takes into account the available clinical and experimental evidence on the use of lactobacilli in order to give an overview of their suitability to be enclosed in well defined updated therapeutic protocols for specific pathologies. A limited number of studies have already tested the hypothesis that lactobacilli could be combined with bifidobacteria or other nutrients, such as fibres, in order to enhance the bioavailability, mucosal adhesion and therapeutic effectiveness of lactobacilli. Further studies are certainly warranted to determine the most effective combinations for treatment of individual pathologies. The claim that pools of lactobacilli could better survive within the gut lumen and even in the colon, and stably integrate within the pre-existing microbiome, has never been proved in terms of dose-effect and risk of sepsis and bacteraemia. We do not have enough information about the long-term genetic stability (with some exceptions such

as *L. paracasei* subsp *paracasei* F19[332 333]), the antibiotic susceptibility and translocation rate of *L.* strains.[334–336] Therefore, further investigations are required to fill in this gap. We would also like to point out the increasing interest in lactobacilli used for industrial food fermentation which has reached a high degree of sophistication that could be useful also for medical applications.[337] For example, various novel biological modifications have been introduced such as the lysostaphin-expressing gene to prevent growth of toxic shock syndrome toxin 1 producing strains of *S. aureus*.[338]

However, since data concerning the safety and genetic stability of lactobacilli is still limited, toxicological studies evaluating the effects of their genetic modification on the homeostasis of the host organism are still required. Ongoing research on the human microbiome composition will likely yield new species of the genus *L.* that might also have therapeutic applications for specific pathologies.

Take home messages

- Experimental and clinical evidence supports lactobacilli effectiveness for treatment of several pathological conditions.
- Long-term consumption of lactobacilli induces qualitative and quantitative modifications in the human gastrointestinal microbial ecosystem.
- Pharmacological profile of lactobacilli needs to be further characterised in order to avoid translocation-related risks.

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