Mechanisms and therapeutic effectiveness of lactobacilli

Alessandro Di Cerbo, 1 Beniamino Palmieri, 2 Maria Aponte, 3 Julio Cesar Morales-Medina, 4 Tommaso Iannitti 5

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 using 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 key 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 invasiveness and growth of pathogenic species to the detriment of health-promoting bacteria, including lactobacilli, within the GI tract. 8–9 Indeed, adhesion of lactobacilli 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, aza 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 carcinogenic
Table 1  Lactobacilli displaying ability to adhere to the gastrointestinal tract mucosa

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. gasseri SBT2055SR</td>
<td>10^11 CFU</td>
<td>14(open study)</td>
</tr>
<tr>
<td>L. reuteri DSM 12246</td>
<td>10^10 CFU</td>
<td>17(double-blind)</td>
</tr>
<tr>
<td>L. rhamnosus 19070–2</td>
<td>10^10 CFU (of each)</td>
<td>cross-over study</td>
</tr>
<tr>
<td>L. rhamnosus LGG</td>
<td>10^10 CFU</td>
<td></td>
</tr>
<tr>
<td>L. acidophilus 821–3</td>
<td>1×10^10 CFU</td>
<td>15(open study)</td>
</tr>
<tr>
<td>L. rhamnosus 19070–2</td>
<td>1×10^10 CFU (of each)</td>
<td>16(open study)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. lactis Bb12</td>
<td>1×10^10 CFU (total)</td>
<td>Colon cancer</td>
<td>39(randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>10^10 CFU</td>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td>+ Oligofructase enriched inulin (SYN1)</td>
<td>12 g</td>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus LC705</td>
<td>2–5×10^10 CFU (of each)</td>
<td>Liver cancer</td>
<td>78(randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>P. freudenreichii subsp Shermanii</td>
<td>10^10 CFU</td>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>10^9 CFU/lg (0.21 g) (total)</td>
<td>Colon cancer</td>
<td>79(open study)</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>10 mg</td>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td>B. natto</td>
<td>30 mg</td>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>10 mg</td>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td>Colon cancer</td>
<td></td>
</tr>
</tbody>
</table>
disorders have been summarised in Table 3.

Clinical studies of lactobacilli showing efficacy for treatment of vaginal disorders

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. plantarum P17630</td>
<td>&gt;10^9 CFU</td>
<td>Acute vulvovaginal candidiasis</td>
<td>97 (retrospective comparative study)</td>
</tr>
<tr>
<td>L. rhamnosus GR-1</td>
<td>&gt;10^9 CFU (each)</td>
<td>Potential pathogenic bacteria and yeast vagina colonisation</td>
<td>102 (open study)</td>
</tr>
<tr>
<td>L. fermentum RC-14</td>
<td>Not stated</td>
<td>Abnormal cervical cytology</td>
<td>103 (open study)</td>
</tr>
<tr>
<td>Kramergin® + lactic acid and Krameria triandra extract)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellen AB® (L. gasseri LN40, L. fermentum LN99, L. casei subsp rhamnosus LN113 and P. acidilactici LN23 + an inert carrying matrix of maltodextrin and magnesium stearate)</td>
<td>10^8–10^9 CFU (total)</td>
<td>Bacterial vaginosis and vulvovaginal candidiasis</td>
<td>104 (randomised double-blind placebo-controlled study)</td>
</tr>
<tr>
<td>L. fermentum LF10</td>
<td>0.4×10^9 CFU (of each)</td>
<td>Recurrent vulvovaginal candidiasis</td>
<td>105 (clinical study)</td>
</tr>
<tr>
<td>L. acidophilus LA02</td>
<td>Not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arabinogalactan</td>
<td>340 mg</td>
<td>Bacterial vaginosis</td>
<td>106 (pilot study)</td>
</tr>
<tr>
<td>Fructooligosaccharides</td>
<td>241 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. fermentum LF15</td>
<td>0.4×10^9 CFU (of each)</td>
<td>Bacterial vaginosis</td>
<td>107 (randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. plantarum LP01</td>
<td>Not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tara gum</td>
<td>50 mg</td>
<td>Bacterial vaginosis</td>
<td>108 (randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>Florisia® [L. brevis (CD2), L. salivarius subsp salicinus (FV2) and L. plantarum (FV9)]</td>
<td>10^9 CFU (total)</td>
<td></td>
<td>109 (randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. rhamnosus GR-1</td>
<td>2.5×10^9 CFU (of each)</td>
<td>Vaginal flora overgrowth</td>
<td>110 (randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. reuteri RC-14</td>
<td>10^8–9 CFU (of each)</td>
<td>Bacterial vaginosis</td>
<td>111 (double-blind, randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>EcoVag® [L. gasseri (Lba EB01-DSM 14869) and L. Rhamnosus (Lb P801-DSM 14870)]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 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. Therefore, a murine model was proposed to determine if L. reuteri CRL1324 would exert a preventive effect on vaginal colonisation by Streptococcus (St.) agalactiae NH17. 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 colonisation occurs in up to 50–70% of neonates born from colonized mothers, 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) 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. Furthermore, cholesterol-reducing properties were also observed for L. oris HMI118, HMI28, HMI43, HMI68 and HMI74 isolated from breast milk. 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.

Clinical studies of lactobacilli showing efficacy for treatment of hypercholesterolaemia

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. plantarum CECT 7527</td>
<td>1.2×10^9 CFU (total)</td>
<td>112 (controlled, randomised, double-blind study)</td>
</tr>
<tr>
<td>L. acidophilus L1</td>
<td>Not stated</td>
<td>113 (double-blind, placebo-controlled, cross-over study)</td>
</tr>
<tr>
<td>L. reuteri NCIMB 30242</td>
<td>5×10^8 CFU</td>
<td>114 (double-blind, placebo-controlled, randomised, parallel-arm, multicentre study)</td>
</tr>
<tr>
<td>L. acidophilus B. lactis</td>
<td>Not stated</td>
<td>115 (single-blind and randomised, cross-over study)</td>
</tr>
</tbody>
</table>
Cholesterol assimilation has also been evaluated as a possible therapeutic approach to reduce the risk for cardiovascular diseases. 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 hypocholesterolemic effect of all strains, particularly of L. acidophilus NCIMB 701089, was linked to intrinsic bile salt hydrolase activities. In this regard, Tomaro-Duchesneau and coworkers administered them for 18 days to rats previously treated with doxorubicin, an anthracycline antibiotic. 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. Experimental studies have shown that lactobacilli, which can adhere to enterocytes, are effective in preventing the enteropathogen-mediated infection by competing for nutrients and binding sites (eg,inducing intestinal mucus gene expression), by secreting antimicrobial substances such as organic acids, bacteriocins and hydrogen peroxide and eventually by counteracting the spread within the colonised body, reducing gut pH and producing biosurfactants. As far as bacterial activity is concerned, L. plantarum GK81, L. acidophilus GK20 and L. plantarum JSA22 inhibit Salmonella spp infection in intestinal epithelial

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. johnsonii La1</td>
<td>&gt; 10^7 CFU/mL (80 mL)</td>
<td>Asymptomatic <em>H. pylori</em> infection</td>
<td>173 (double-blind, randomised, controlled clinical study)</td>
</tr>
<tr>
<td>L. gasseri OLL2716</td>
<td>1.4×10^7 CFU/g (90 g)</td>
<td><em>H. pylori</em> infection</td>
<td>174 (open study)</td>
</tr>
<tr>
<td>Enterolactis® (L. casei subsp casei DG + Vitamin B1, B2 and B6)</td>
<td>5×10^8 CFU (total)</td>
<td><em>H. pylori</em> infection</td>
<td>176 (open study)</td>
</tr>
<tr>
<td>L. reuteri ATCC 55730</td>
<td>1×10^8 CFU</td>
<td><em>H. pylori</em> infection</td>
<td>178 (open study)</td>
</tr>
<tr>
<td>L. acidophilus HY2177, L. casei HY2743, B. longum HY8001 and St. thermophilus B-1</td>
<td>≥1×10^8 CFU (total)</td>
<td><em>H. pylori</em> infection</td>
<td>180 (randomised triple-therapy study)</td>
</tr>
<tr>
<td>Will yoghurt (L. acidophilus HY2743, B. longum HY8001 and St. thermophilus B-1)</td>
<td>1×10^8 CFU (total)</td>
<td><em>H. pylori</em> infection</td>
<td>182 (open study)</td>
</tr>
<tr>
<td>AB-yoghurt (L. acidophilus La5 and B. lactis Bb12)</td>
<td>1×10^8 CFU/mL (230 mL) (of each)</td>
<td><em>H. pylori</em> infection</td>
<td>184 (open study)</td>
</tr>
<tr>
<td>Genefilus F19® (L. paracasei sub. paracasei F19)</td>
<td>12×10^8 CFU</td>
<td><em>H. pylori</em> infection</td>
<td>185 (open study)</td>
</tr>
<tr>
<td>L. reuteri Gastrus (L. reuteri DSM 17938 and L. reuteri ATCC PTA 6475)</td>
<td>1×10^8 CFU</td>
<td><em>H. pylori</em> infection</td>
<td>187 (prospective, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. gasseri OLL2716</td>
<td>≥1×10^9 CFU</td>
<td><em>H. pylori</em> infection</td>
<td>188 (randomised, controlled clinical study)</td>
</tr>
<tr>
<td>L. brevis CD2</td>
<td>20×10^7 CFU</td>
<td><em>H. pylori</em> infection</td>
<td>189 (open study)</td>
</tr>
</tbody>
</table>

**Table 6** Clinical studies of lactobacilli showing efficacy for treatment of oxaluria

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. acidophilus</td>
<td>8×10^11 CFU (of each)</td>
<td>197 (open study)</td>
</tr>
<tr>
<td>L. plantarum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. thermophilus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. infantis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. brevis (CD2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
cells and L. acidophilus strain inhibits various pathogenic bacteria including P. aeruginosa, E. coli, Enterobacter and K. spp. With reference to antiviral activity, lactobacilli harbour surface layer proteins involved in the enhancement of viral entry. Moreover, increasing data indicate that abnormal vaginal flora lacking lactobacilli can facilitate viral sexually transmitted disease diffusion such as in the case of HIV human papilloma virus and herpes simplex virus. 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. Antibiotic treatment for H. pylori infection is associated with serious side effects and therefore there is an increasing demand for new treatments. Lactobacilli have been extensively investigated for treatment of H. pylori infections. Numerous L. strains, that is, L. gasseri Chen, L. plantarum and L. reuteri, possess a neutralising activity against H. pylori strains. The same activity was also observed for heat-killed L. acidophilus L. plantarum and L. rhamnosus GG, L. rhamnosus LC705, Propionibacterium (P) freudenreichii subsp shermanii JS, L. delbrueckii subsp bulgaricus 48, 144 and GB. L. rhamnosus LC705, P. freudenreichii sps shermanii, L. acidophilus LB, L. plantarum MLBPL1, L. rhamnosus GG and L. lactis possess a neutralising activity against H. pylori. The same activity was also observed for heat-killed L. johnsonii Lal and L. helveticus as well as for L. gasseri OLL2716, as measured by 13C-urea breath test. The suppressive effect of lactobacilli on H. pylori infection in vivo and in vitro has been reviewed. For instance, L. johnsonii 1088 suppressed gastric acid secretion in mice via decreasing the number of gastrin-positive cells in the stomach. Therefore L. johnsonii 1088 can be considered a valid add-on therapy to the gold standard treatment for H. pylori eradication consisting of a proton pump inhibitor (PPI), amoxicillin and clarithromycin, and can also be used for prophylaxis of gastroesophageal reflux disease that can develop following H. pylori eradication. Nevertheless, the use of a PPI can also modify the gut microbiota causing dysbiosis. 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. 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. Many studies support the probiotic approach as an alternative therapy for management of end-stage renal disease and to relieve the ‘uraemic’ condition. In particular, a high urease activity was observed for S. spp, L. casei, K. aerogenes and Enterococcus faecium in the sheep rumen. At the same time, the ability to degrade biogenic amines (BAs) was also assessed by Capozzi and coworkers. 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. 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 out of 18 L. strains (8 L. animalis and 3 L. murinus), but not for any of the B. strains. 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

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. fermentum CECT5716</td>
<td>1×10⁹ CFU (of each)</td>
<td>Infectious mastitis</td>
<td>200 (open study)</td>
</tr>
<tr>
<td>L. salivarius CECT5713</td>
<td>1×10⁹ CFU (of each)</td>
<td>Mastitis induced by S. epidermidis or S. aureus</td>
<td>201 (open study)</td>
</tr>
<tr>
<td>L. salivarius CECT5713 and L. gasseri CECT5714</td>
<td>1×10⁹ CFU (of each)</td>
<td>Mastitis induced by S. epidermidis or S. aureus</td>
<td>201 (open study)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. salivarius LS01 L. brevis BR03</td>
<td>1×10⁸ CFU (of each)</td>
<td>Moderate/severe atopic dermatitis</td>
<td>223 (randomised double-blinded active treatment vs placebo study)</td>
</tr>
<tr>
<td>maltodextrin proBiokt® (B. bifidum, L. acidophilus, L. casei and L. salivarius)</td>
<td>Not stated</td>
<td>Atopic dermatitis</td>
<td>207 (double-blind, randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. pentosus b240 Yakult® (L. casei Shirata)</td>
<td>2×10⁹ CFU 6.5×10⁵ CFU</td>
<td>Common cold Allergic rhinitis</td>
<td>228 (randomised, double-blind, placebo-controlled study) 229 (double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. paracasei-33 L. acidophilus L-92</td>
<td>2×10⁹ CFU</td>
<td>Atopic dermatitis</td>
<td>225 (double-blind, placebo-controlled study)</td>
</tr>
</tbody>
</table>

significantlly 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 oxaluria have been summarised in table 6.

### Mastitis

Mastitis is an infectious inflammation of one or more breast lobules199 with *S. aureus* and *S. epidermidis* being the most frequent aetiological agents199 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, interferon-γ production205 and induction of interferon-γ production205–213 and cytokine expression.203–210

Evidence from animal models228 and clinical observations229 outlined the putative therapeutic role of probiotic strains for treatment of mastitis,220 as the use of lactobacilli agents 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 oxaluria have been summarised in table 6.

### 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 production205–213 and cytokine expression.203–210

In order to exert these immunomodulatory effects, lactobacilli must resist to digestive system processes217 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 and concurrently attenuating systemic stress response.222 Clinical studies of lactobacilli showing immunomodulatory activity in various pathologies have been summarised in table 8.

### Gastrointestinal pathologies

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 models228 and clinical observations229 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,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.

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSL#3&lt;sup&gt;®&lt;/sup&gt; (L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp bulgaricus, B. longum, B. breve, B. infantis and St. thermophilus)</td>
<td>5×10&lt;sup&gt;11&lt;/sup&gt; CFU/g (3 g) (total)</td>
<td>Chronic pouchitis</td>
<td>230 (open study)</td>
</tr>
<tr>
<td>Yakult® (L. casei Shirota)</td>
<td>6.5×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Constipation</td>
<td>231 (open study)</td>
</tr>
<tr>
<td>L. plantarum SW13T</td>
<td>2×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Constipation</td>
<td>232 (double-blind, randomised study)</td>
</tr>
<tr>
<td>VSL#3&lt;sup&gt;®&lt;/sup&gt; (L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp bulgaricus, B. longum, B. breve, B. infantis and St. thermophilus)</td>
<td>5×10&lt;sup&gt;11&lt;/sup&gt; CFU/g (3 g) (total)</td>
<td>Ulcerative colitis</td>
<td>233 (open study)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Site</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. acidophilus</em> 821–3</td>
<td>1×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>236 (open study)</td>
</tr>
<tr>
<td><em>L. acidophilus</em></td>
<td>1×10&lt;sup&gt;8&lt;/sup&gt; CFU/g (100 g)</td>
<td>Small intestine</td>
<td>235 (open study)</td>
</tr>
<tr>
<td><em>B. sp</em></td>
<td>1×10&lt;sup&gt;7&lt;/sup&gt; CFU/g (100 g)</td>
<td>Gastrointestinal tract</td>
<td>230 (open study)</td>
</tr>
<tr>
<td><em>L. casei</em> Shirota</td>
<td>1×10&lt;sup&gt;9&lt;/sup&gt; CFU/mL (100 mL)</td>
<td>Gastrointestinal tract</td>
<td>230 (14-day baseline, ingestion and follow-up periods)</td>
</tr>
<tr>
<td><em>L. acidophilus</em> LA02 (DSM 21717)</td>
<td>5×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>237 (14-day baseline, ingestion and follow-up periods)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> LR04 (DSM 16605)</td>
<td>6.5×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>230 (open study)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> GG (ATCC 53103)</td>
<td>1×10&lt;sup&gt;8&lt;/sup&gt; CFU</td>
<td>Small intestine</td>
<td>238 (14-day baseline, ingestion and follow-up periods)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> LR06 (DSM 21981)</td>
<td>1×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>237 (14-day baseline, ingestion and follow-up periods)</td>
</tr>
<tr>
<td><em>B. lactis</em> BS01 (LMG P-21384)</td>
<td>1×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>238 (14-day baseline, ingestion and follow-up periods)</td>
</tr>
<tr>
<td><em>L. plantarum</em> LP01 (LMG P-21021)</td>
<td>1×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>238 (double-blind, randomised, cross-over study)</td>
</tr>
<tr>
<td><em>B. breve</em> BR03 (DSM 16604)</td>
<td>1×10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>238 (double-blind, randomised, cross-over study)</td>
</tr>
<tr>
<td>Lakcid&lt;sup&gt;®&lt;/sup&gt; L (L. rhamnosus 5731, 573 L2 and 573L3)</td>
<td>1.2×10&lt;sup&gt;10&lt;/sup&gt; CFU</td>
<td>Gastrointestinal tract</td>
<td>238 (double-blind, randomised, cross-over study)</td>
</tr>
<tr>
<td>B. infantis and St. thermophilus</td>
<td></td>
<td></td>
<td>230 (open study)</td>
</tr>
</tbody>
</table>


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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. Diarrhoea is also frequent during antibiotic therapy causing gut flora imbalance.

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. acidophilus</td>
<td>2.5×10⁹ CFU (total)</td>
<td>Acute diarrhoea</td>
<td>(prospective randomised, multicentre single-blinded clinical study)</td>
</tr>
<tr>
<td>Actimel® (L. casei DN 114001)</td>
<td>10¹⁵ CFU</td>
<td>Antibiotic-associated diarrhoea</td>
<td>(observational study)</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>625 mg</td>
<td>Antibiotic-associated diarrhoea</td>
<td>(prospective, parallel group study)</td>
</tr>
<tr>
<td>L. acidophilus (CUL60, NCIMB 30157 and CUL21, NCIMB 30156), B. bifidum (CUL20, NCIMB 30153) and B. lactis (CUL34, NCIMB 30172)</td>
<td>6.5×10⁹ CFU (of each)</td>
<td>Acute gastroenteritis</td>
<td>(randomised, prospective placebo-controlled parallel clinical study)</td>
</tr>
<tr>
<td>L. acidophilus (LB)</td>
<td>10⁹ CFU</td>
<td>Non-rotavirus diarrhoea</td>
<td>(randomised, double-blind, placebo-controlled clinical study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>Not stated</td>
<td>Bacterial overgrowth-related chronic diarrhoea</td>
<td>(randomised, double-blind study)</td>
</tr>
<tr>
<td>L. paracasei ST11</td>
<td>Not stated</td>
<td>Persistent diarrhoea</td>
<td>(double-blind study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>10¹⁰ CFU (of each)</td>
<td>Acute diarrhoea</td>
<td>(randomised placebo-controlled study)</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>10¹⁰ – 11 CFU/g (1 g)</td>
<td>Acute diarrhoea</td>
<td>(randomised, double-blind study)</td>
</tr>
<tr>
<td>L. acidophilus CERELA</td>
<td>10⁸ CFU</td>
<td>Non-rotavirus diarrhoea</td>
<td>(randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>S. boulardii</td>
<td>10¹⁵ CFU/g (175 g)</td>
<td>Persistent diarrhoea</td>
<td>(double-blind study)</td>
</tr>
<tr>
<td>L. rhamnosus 19070–2</td>
<td>10¹⁰ CFU</td>
<td>Acute diarrhoea</td>
<td>(randomised placebo-controlled study)</td>
</tr>
<tr>
<td>L. reuteri DS5 12246</td>
<td>Not stated</td>
<td>Bacterial overgrowth-related chronic diarrhoea</td>
<td>(randomised, double-blind study)</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>Not stated</td>
<td>Acute diarrhoea</td>
<td>(randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>Not stated</td>
<td>Persistent diarrhoea</td>
<td>(double-blind study)</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>6×10⁸ CFU</td>
<td>Acute rotaviral diarrhoea</td>
<td>(open-label randomised study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>10¹⁰ CFU</td>
<td>Non-rotavirus diarrhoea</td>
<td>(randomised, double-blind, placebo-controlled clinical study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>10¹⁰ CFU (of each)</td>
<td>Acute diarrhoea</td>
<td>(randomised placebo-controlled study)</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>2×10¹⁰ CFU (of each)</td>
<td>Antibiotic-associated diarrhoea</td>
<td>(double-blind, randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. casei</td>
<td>2×10¹⁰ CFU (of each)</td>
<td>Antibiotic-associated diarrhoea</td>
<td>(double-blind, randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. casei</td>
<td>2×10¹⁰ CFU</td>
<td>Antibiotic-associated diarrhoea</td>
<td>(double-blind, randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>10¹⁰ CFU</td>
<td>Non-rotavirus diarrhoea</td>
<td>(randomised, double-blind, placebo-controlled clinical study)</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>10⁸ CFU</td>
<td>Non-rotavirus diarrhoea</td>
<td>(randomised, double-blind, placebo-controlled study)</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>10¹⁰ CFU</td>
<td>Acute diarrhoea</td>
<td>(randomised placebo-controlled study)</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>10¹⁰ CFU</td>
<td>Acute diarrhoea</td>
<td>(randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>10¹⁰ CFU</td>
<td>Acute diarrhoea</td>
<td>(randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>Not stated</td>
<td>Bacterial overgrowth-related chronic diarrhoea</td>
<td>(randomised, double-blind study)</td>
</tr>
<tr>
<td>L. casei CERELA</td>
<td>Not stated</td>
<td>Acute diarrhoea</td>
<td>(randomised, placebo-controlled study)</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>Not stated</td>
<td>Acute diarrhoea</td>
<td>(randomised, placebo-controlled study)</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. salivarius WB21 + Xylitol</td>
<td>6.7×10⁸ CFU, 280 mg</td>
<td>Severe periodontitis treatment, Gingival inflammation</td>
<td>(randomised clinical study)</td>
</tr>
<tr>
<td>L. reuteri ATCC 55730, L. reuteri ATCC PTA 5289</td>
<td>1×10⁸ CFU (of each)</td>
<td>Gingival inflammation</td>
<td>(double-blind placebo-controlled study)</td>
</tr>
</tbody>
</table>

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 expression of phospho-nuclear factor-k-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 shown 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 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 anti-microbial 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 discoloration, 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 periodontopathic 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 insufficient insulin action (type-2 diabetes).

#### Table 13  Clinical studies of lactobacilli showing efficacy for treatment of type-2 diabetes

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. acidophilus</em></td>
<td>2×10^6 CFU</td>
<td>282(randomised double-blind study)</td>
</tr>
<tr>
<td><em>L. casei</em></td>
<td>7×10^6 CFU</td>
<td>placebo-controlled clinical study</td>
</tr>
<tr>
<td><em>L. rhamnosus</em></td>
<td>1.5×10^6 CFU</td>
<td></td>
</tr>
<tr>
<td><em>L. buccalis</em></td>
<td>2×10^6 CFU</td>
<td></td>
</tr>
<tr>
<td><em>B. breve</em></td>
<td>2×10^5 CFU</td>
<td></td>
</tr>
<tr>
<td><em>B. longum</em></td>
<td>7×10^5 CFU</td>
<td></td>
</tr>
<tr>
<td><em>St. thermophilus</em></td>
<td>1.5×10^5 CFU</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ fructo-oligosaccharide</td>
<td>100 mg</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Dose</th>
<th>Pathology</th>
<th>Ref. (Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. casei</em> Shirotas</td>
<td>Not stated</td>
<td>Ventilator-associated pneumonia</td>
<td>291(prospective, randomised, open-label controlled study)</td>
</tr>
<tr>
<td>Symbiotic 2000 (P. pentosaceus 5—33:3, L. mesenteroides 32—77:1, L. paracasei 19 and L. plantarum 2362 +)</td>
<td>1×10^10 CFU (of each)</td>
<td>Severe acute pancreatitis</td>
<td>292(prospective, randomised, double-blind study)</td>
</tr>
<tr>
<td>Ecologic 641B (L. acidophilus, L. casei, L. salivarius, Lactococcus lactis, B. bifidum and B. lactis + cornstarch and maltodextrins)</td>
<td>Not stated</td>
<td>10^10 CFU (total)</td>
<td>Severe acute pancreatitis</td>
</tr>
<tr>
<td>Genefilus F19 (L. paracasei subsp paracasei F19 + high-fibre diet)</td>
<td>Not stated</td>
<td>12×10^9 CFU</td>
<td>Symptomatic uncomplicated diverticular disease</td>
</tr>
<tr>
<td>L. GG</td>
<td>Not stated</td>
<td>Cirrhosis</td>
<td>295(open study)</td>
</tr>
</tbody>
</table>
First isolated and extracted lactobacilli from human infant faecal samples and evaluated their inhibitory activity against intestinal maltase, sucrase, lactase and amylase, all enzymes involved in hydrolysis of carbohydrates. 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 needed to confirm these findings, the potential of L. rhamnosus as a probiotic in the prevention and treatment of diseases associated with carbohydrate metabolism highlights the importance of targeting the intestinal microbiota for optimizing host health.

### Table 15: Clinical studies reporting side effects associated with Lactobacillus therapy

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Effect/s</th>
<th>Patient(s) clinical history</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. jensenii</td>
<td>Endocarditis</td>
<td>An immunocompetent 47-year-old man with mitral valve replacement treated with ticoplanin and meropenem</td>
<td>302</td>
</tr>
<tr>
<td>L. paracasei</td>
<td>Endocarditis</td>
<td>A patient (18 years) with trisomy 21 treated with chloramphenicol</td>
<td>303</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Bacteremia</td>
<td>Eleven patients with immunosuppression, prior prolonged hospitalisation and prior surgical interventions treated with antimicrobials</td>
<td>317</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>Bloodstream infections</td>
<td>The maximum estimated incidence of bacteraemia during an 8-year period was 0.2%</td>
<td>322</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Bacteremia</td>
<td>Sixteen nosocomial infections associated with immunosuppression (66%) and catheters (83%)</td>
<td>312</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Bacteremia</td>
<td>Six cases of bacteraemia in hospitalised patients, five with a depressed immune status</td>
<td>306</td>
</tr>
<tr>
<td>L. curvatus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. delbrueckii subsp lactis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. paracasei</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Hepatic abscess and bacteraemia</td>
<td>A 73-year-old woman with antecedent of diabetes mellitus treated with ampicillin plus gentamicin</td>
<td>316</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Catheter-related bacteraemia</td>
<td>A patient who underwent a single-lung transplant</td>
<td>308</td>
</tr>
<tr>
<td>L. plantarum</td>
<td>Bacteraemia</td>
<td>A 14-year-old girl with acute myeloid leukaemia, bacteraemia disappeared only after 13 months when the cytostatic therapy was terminated</td>
<td>314</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Septicaemia</td>
<td>A patient (43 years) with a subacute endocarditis due to an immunovasculitis and a bloodstream infection</td>
<td>307</td>
</tr>
<tr>
<td>L. jensenii</td>
<td>Septicaemia</td>
<td>A 54-year-old woman with diabetes treated with amoxicillin</td>
<td>296</td>
</tr>
<tr>
<td>L. paracasei</td>
<td>Purpura fulminans associated with liver abscess</td>
<td>A 50-year-old woman with obstructive acute renal failure</td>
<td>297</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>Liver abscess</td>
<td>A 27-year-old man with a 6-month history of NOD2/CARD15-positive Crohn’s disease</td>
<td>324</td>
</tr>
<tr>
<td>L. casei</td>
<td>Pneumonia and sepsis</td>
<td>A patient with AIDS because of CD4 lymphocyte depleton</td>
<td>325</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Septicaemia</td>
<td>A patient with a graft in the inferior vena cava</td>
<td>298</td>
</tr>
<tr>
<td>L. gasseri</td>
<td>Septic urinary infection</td>
<td>A patient (66 years) developed severe urinary stasis due to a concrement in his right ureter, treated with cefotaxime and amoxicillin</td>
<td>326</td>
</tr>
<tr>
<td>L. casei</td>
<td>Bacteraemia</td>
<td>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</td>
<td>327</td>
</tr>
<tr>
<td>L. rhamnosus Lcr35</td>
<td>Meningitis and recurrent episodes of bacteraemia</td>
<td>A child (10 years) undergoing allogenic haematopoietic stem cell transplantation and treated unsuccessfully with clindamycin</td>
<td>320</td>
</tr>
<tr>
<td>L. rhamnosus ATCC 53103</td>
<td></td>
<td>A 59-year-old woman with progressed follicular lymphoma, diabetes mellitus type-2 and arterial hypertension and kidney stone treated with antibiotics</td>
<td>309</td>
</tr>
<tr>
<td>L. jensenii</td>
<td>Bacteraemia and pyelonephritis</td>
<td>A 27-year-old woman with a 20-day history of fever and treated with penicillin and gentamicin</td>
<td>304</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Catheter-related bloodstream infections</td>
<td>A 38-year-old woman who underwent allogenic transplantation of haematopoietic stem cells from cord blood for a large granulocyte leukaemia and initially treated with chemotherapy</td>
<td>328</td>
</tr>
<tr>
<td>L. delbrueckii</td>
<td>Pyelonephritis and bacteraemia</td>
<td>A 68-year-old woman with fever, chills, nausea, and vomiting and ureteral calculus with mild left hydronephrosis treated with ampicillin</td>
<td>311</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Sepsis</td>
<td>A 24-year-old woman developed sepsis resulting from preoperative administration of probiotics following an aortic valve replacement</td>
<td>301</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Bacteraemia</td>
<td>A 69-year-old man with stage IIIA mantle cell lymphoma and treated with probiotic-enriched yogurt stopping</td>
<td>329</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Bacteraemia</td>
<td>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</td>
<td>310</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>Sepsis</td>
<td>A 69-year-old man with stage IIIA mantle cell lymphoma</td>
<td>315</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Bacteraemia</td>
<td>A 36-week-gestation male infant with short gut syndrome secondary to congenital intestinal atresia and volvulus</td>
<td>313</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Bacteraemia</td>
<td>A 34-week-gestation male infant with gastrochisis</td>
<td>331</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Bacteraemia</td>
<td>A 43-year-old woman with ulcerative colitis</td>
<td>299</td>
</tr>
<tr>
<td>L. paracasei</td>
<td>Endocarditis</td>
<td>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</td>
<td>330</td>
</tr>
</tbody>
</table>
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,315 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.325 Moreover, L. casei suppresses experimental rheumatoid arthritis by downregulating Th1-type inflammatory responses286 and its coadministration with type-II collagen and glucosamine decreased the expression of 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.286 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 Antihypertensive effects of lactobacilli were also evaluated along with memory-enhancing activity in aged Fischer 344 rats.290 A probiotic mixture of L. plantarum KY1052 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 lipedema in aged subjects. Clinical studies of lactobacilli showing efficacy for treatment of various pathologies have been summarised in table 14.

SIDE EFFECTS OF LACTOBA CILLI
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,306–308 endocarditis302–305 bacteraemia299 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.311 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 F19331 332), the antibiotic susceptibility and translocation rate of L. strains.314–316 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 lyostaphin-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.
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