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 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 vivo and in vitro investigations have shown that prolonged lactobacilli administration induces qualitative and quantitative modifications in the human gastrointestinal microbial ecosystem with encouraging perspectives in countering 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 homeostatic 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 1013, mainly anaerobes, which constitute the microbiome and exceed 1013 organisms, mainly anaerobes, which constitute the microbiome and exceed 1013 organisms, mainly anaerobes, which constitute the microbiome and exceed 1013 organisms, mainly anaerobes, which constitute the microbiome and exceed 1013 organisms, mainly anaerobes.3 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 invasion and growth of pathogenic species to the detriment of health-promoting bacteria, including lactobacilli, within the GI tract.8–10 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, 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 | 14 (open study) |
| L. reuteri DSM 12446            | 10^{10} CFU (of each) | 17 (double-blind cross-over study) |
| L. reuteri DSM 12446            | 10^{10} CFU (of each) | 15 (open study) |

Antitoxic activity

Lactobacilli display detoxifying properties and their ability to neutralise toxins. Toxins, such as heat-killed L. casei strain Shirota (LC 9018), have been shown to reduce colon cancer risk. These activities have been ascribed to the alteration of gut microbiota and, subsequently, to the inhibition of 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.

Vaginal colonisation

Vaginal microbiota is dominated by lactobacilli. The balance among bacterial species within this environment is altered, antibacterial defense mechanisms lose their efficacy leading to pathogenic bacteria proliferation. For instance, the 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) and H$_2$O$_2$ production, cause bacterial vaginosis, the most common symptomatic microbial imbalance. In patients affected by bacterial vaginosis, lactobacilli are replaced by Gardnerella vaginalis, Candida (C.) albicans, S. aureus, Neisseria gonorrohoea or other anaerobic bacteria. Uncontrolled growth of anaerobic bacteria such as C. albicans and subsequent vaginal colonisation may lead to 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, alteration in the transcriptional levels of virulence-associated regulators sarA and saeRS and transcription inhibition from Pst, 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 16S rDNA 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. Compound degradation activity of lactobacilli has also been observed for cadmium after high dietary exposure. In this regard, two L. kefiri strains, CIDCA 8348 and JCM 5818, can remove cadmium cations when cocultured with a human hepatoma cell line, HepG2. Particularly, L. kefiri 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.

| Bacteria       | Dose          | Pathology          | Ref. (Design)                |
|----------------|---------------|--------------------|------------------------------|
| B. lactis Bb12| 1×10^{10} CFU (total) | Colon cancer       | 39 (randomised, double-blind, placebo-controlled study) |
| L. rhamnosus   | + Oligofructose enriched inulin (SYN1) | 12 g | Liver cancer | 78 (randomised, double-blind, placebo-controlled study) |
| L. rhamnosus   | LC705         | 2–5×10^{10} CFU (of each) | Liver cancer | 79 (open study) |
| P. freudenreichii subsp Shermanii | | | | |
| L. longum     | 10^{7} CFU/g (0.21 g) (total) | Colorectal cancer | 50 (open study) |
| L. acidophilus | 10 mg         | Colorectal cancer  | 80 (open study) |

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

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disorders have been summarised in Table 3.

Although GBS colonization occurs in up to 50% of newborns,100 the GBS challenge. Although GBS colonization occurs in up to 50% of neonates born from colonized mothers,101 the introduction of new antimicrobial agents, such as L. oris HMI118, HMI28, HMI43, HM168 and HM174 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 HM168 showed the highest cholesterol assimilation deconjugating sodium glycocholate (the most predominant bile salt in the human intestine) and sodium taurocholate, 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, HM168 and HM174 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 HM168 showed the highest cholesterol assimilation deconjugating sodium glycocholate (the most predominant bile salt in the human intestine) and sodium taurocholate.

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

| Bacteria | Dose | Pathology | Ref. (Design) |
|----------|------|-----------|---------------|
| L. plantarum P17630 | >10^6 CFU | Acute vulvovaginal candidiasis | 97(retrospective comparative study) |
| L. rhamnosus GR-1 | >10^6 CFU (of each) | Potential pathogenic bacteria and yeast vagina colonisation | 102(open study) |
| L. fermentum RC-14 | Not stated | Abnormal cervical cytology | 103(open study) |
| Kramegis® (L. acidophilus + lactic acid and Krameria triandra extract) | Not stated | Bacterial vaginosis and vulvovaginal candidiasis | 104(randomised double-blind placebo-controlled study) |
| 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) | 10^5–10^6 CFU (total) | Bacterial vaginosis and vulvovaginal candidiasis | 104(randomised double-blind placebo-controlled study) |
| L. fermentum LF10 | 0.4×10^5 CFU (of each) | Recurrent vulvovaginal candidiasis | 105(clinical study) |
| L. acidophilus LA02 + Arabinogalactan | 340 mg | Recurrent vulvovaginal candidiasis | 105(clinical study) |
| Fructooligosaccharides | 241 mg | Recurrent vulvovaginal candidiasis | 105(clinical study) |
| L. fermentum LF15 | 0.4×10^5 CFU (of each) | Bacterial vaginosis | 106(pilot study) |
| L. plantarum LP01 + Tara gum | Not stated | Bacterial vaginosis | 107(randomised, double-blind, placebo-controlled study) |
| Florisia® (L. brevis (CD2), L. salivarius subsp salicinus (FV2) and L. plantarum (FV9)) | 10^5 CFU (total) | Bacterial vaginosis | 107(randomised, double-blind, placebo-controlled study) |
| L. rhamnosus GR-1 | 2.5×10^8 CFU (of each) | Vaginal flora overgrowth | 108(randomised, double-blind, placebo-controlled study) |
| L. reuteri RC-14 | 10^8–9 CFU (of each) | Bacterial vaginosis | 109(randomised, double-blind, placebo-controlled study) |
| EcoVag® (L. gasseri (Lba EB01-DSM 14869) and L. Rhamnosus (Lbp PB01-DSM 14870)) | Not stated | Bacterial vaginosis | 107(randomised, double-blind, placebo-controlled study) |

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

| Bacteria | Dose | Pathology | Ref. (Design) |
|----------|------|-----------|---------------|
| L. plantarum | 1.2×10^6 CFU (total) | Cholesterol-reducing properties | 119(controlled, randomised, double-blind study) |
| CECT 7527 | 1.2×10^6 CFU (total) | Cholesterol-reducing properties | 119(controlled, randomised, double-blind study) |
| CECT 7528 | 1.2×10^6 CFU (total) | Cholesterol-reducing properties | 119(controlled, randomised, double-blind study) |
| CECT 7529 | 1.2×10^6 CFU (total) | Cholesterol-reducing properties | 119(controlled, randomised, double-blind study) |
| L. acidophilus L1 | Not stated | Cholesterol-reducing properties | 119(double-blind, placebo-controlled, cross-over study) |
| L. reuteri NCMB 30242 | 5×10^7 CFU | Cholesterol-reducing properties | 120(double-blind, placebo-controlled, randomised, parallel-arm, multicentre study) |
| L. acidophilus B. lactis | Not stated | Cholesterol-reducing properties | 121(randomised, double-blind, placebo-controlled study) |

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
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, 702656, L. fermentum NCIMB 5221, 8829, 2797, L. rhamnosus NCIMB 701089, was linked to intrinsic bile salt hydrolase activity, assimilation and incorporation in cellular membranes, for example, ferulic acid, able to reduce the risk for cardiovascular disease.

Antioxidant activity
Lactobacilli can prevent lipid peroxidation and free oxygen radical production due to their ability to create the low oxidation-reduction potential required for their optimal growth. 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. Analysis of plasma 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 (e.g., 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. paracasei subsp. paracasei DSMZ 23033 and L. reuteri DSMZ 23034 were able to deconjugate bile salts. Clinical studies of lactobacilli showing efficacy for treatment of hypercholesterolaemia have been summarised in table 4.

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

| Bacteria               | Dose                  | Pathology                        | Ref. (Design)                        |
|------------------------|-----------------------|----------------------------------|--------------------------------------|
| L. johnsonii La1       | > 10^10 CFU/mL (80 mL) | Asymptomatic H. pylori infection | 173(double-blind, randomised, controlled clinical study) |
| L. gasseri OLL2716     | 1.4×10^6 CFU/g (90 g) | H. pylori infection              | 126                                  |
| Enterolactis® (L. casei subsp. casei DG + Vitamin B1, B2 and B6) | 1.6×10^9 CFU | H. pylori infection              | 182                                  |
| Actinomyces® (L. acidophilus HY2177, L. casei HY2743, L. longum HY8001 and St. thermophillus B-1) | 5×10^3 CFU (total) | H. pylori infection              | 184                                  |
| L. reuteri ATCC 55730  | 1×10^6 CFU | H. pylori infection              | 185                                  |
| Will yoghurt (L. acidophilus HY2177, L. casei HY2743, L. longum HY8001 and St. thermophillus B-1) | ≥1×10^5 CFU | H. pylori infection              | 186                                  |
| AB-yoghurt (L. acidophilus La5 and L. lactis Bb12) | 1×10^9 CFU/mL (230 mL) (of each) | H. pylori infection | 175                                  |
| Genefilus F19® (L. paracasei sub. paracasei F19) | 1×10^8 CFU | H. pylori infection-related gastroesophageal reflux | 177(randomised, double-blind, placebo-controlled study) |
| L. reuteri Gastrus (L. reuteri DSM 17938 and L. reuteri ATCC PTA 6475) | 1×10^9 CFU (total) | H. pylori infection              | 187                                  |
| L. gasseri OLL2716     | ≥1×10^6 CFU | H. pylori infection              | 188(randomised, controlled clinical study) |
| L. brevis CD2          | 1×10^10 CFU | H. pylori infection              | 189                                  |

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

| Bacteria               | Dose                  | Ref. (Design)                        |
|------------------------|-----------------------|--------------------------------------|
| L. acidophilus         | 8×10^11 CFU (of each) | 197(open study)                       |
| L. plantarum           |                       |                                     |
| St. thermophilus       |                       |                                     |
| B. infantis            |                       |                                     |
| L. brevis (CD2)        |                       |                                     |
cells and \textit{L. acidophilus} strain inhibits various pathogenic bacteria including \textit{P. aeruginosa}, \textit{E. coli}, \textit{Enterobacter} and \textit{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 HPV and herpes simplex virus. In this context, lactobacilli can exert an important role protecting the vaginal environment and reducing the risk of virus transmission.

\textbf{Helicobacter pylori infection}

\textit{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 \textit{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 \textit{H. pylori} infections. Numerous \textit{L.} strains, that is, \textit{L. gasseri} Chen, \textit{L. plantarum} 18, \textit{L. gasseri} OLL2716, \textit{L. reuteri}, \textit{L. rhamnosus} GG, \textit{L. rhamnosus} Lc705, Propionibacterium (P.) freudenreichii subsp shermanii JS, \textit{L. delbrueckii} subsp bulgaricus 48, 144 and GB, 171 \textit{L. rhamnosus} LC705, \textit{P. freudenreichii} ssp shermanii JS, 168 \textit{L. acidophilus} LB, 172 \textit{L. plantarum} MLBPL1, \textit{L. rhamnosus} GG and \textit{L. lactis} possess a neutralising activity against \textit{H. pylori}. The same activity was also observed for heat-killed \textit{L. johnsonii} Lal and \textit{L. helveticus} as well as for \textit{L. gasseri} OLL2716, 173 as measured by $^{13}$C-urea breath test. The suppressive effect of lactobacilli on \textit{H. pylori} infection in vivo and in vitro has been reviewed.\textsuperscript{174–177} For instance, \textit{L. johnsonii} 1088 suppressed gastric acid secretion in mice via decreasing the number of gastrin-positive cells in the stomach.\textsuperscript{176} Therefore \textit{L. johnsonii} 1088 can be considered a valid add-on therapy to the gold standard treatment for \textit{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 \textit{H. pylori} eradication. Nevertheless, the use of a PPI can also modify the gut microbiota causing dysbiosis.\textsuperscript{178–180} In this regard, adding \textit{L. paracasei} subsp \textit{paracasei} F19 to triple therapy is a promising combination to counteract the effects of PPIs on intestinal dysbiosis.\textsuperscript{181} Clinical studies of lactobacilli showing inhibitory activity against \textit{H. pylori} infection have been summarised in Table 5.

\textbf{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.\textsuperscript{190} Many studies support the probiotic approach as an alternative therapy for management of end-stage renal disease\textsuperscript{191} and to relieve the ‘uraemic’ condition.\textsuperscript{189–194} In particular, a high urease activity was observed for \textit{S. spp}, \textit{L. casei}, \textit{K. aerogenes} and \textit{Enterococcus faecium} in the sheep rumen.\textsuperscript{192} At the same time, the ability to degrade biogenic amines (BAs) was also assessed by Capozzi and coworkers.\textsuperscript{193} They isolated two lactobacilli (\textit{L. plantarum} NDT 09 and \textit{L. plantarum} NDT 16) from wine and found that they were able to degrade tyramine (22.12%) and putrescine (31.09%), respectively. \textit{L. casei} 4a and 5b, isolated from Zamorano cheese, also inhibited tyramine along with histamine, another BA.\textsuperscript{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 \textit{B.} and \textit{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 \textit{L.} strains (8 \textit{L. animalis} and 3 \textit{L. murinus}), but not for any of the \textit{B.} strains.\textsuperscript{195} Rats were fed on four selected strains (\textit{L. animalis} 223C, \textit{L. murinus} 1222, \textit{L. animalis} 5323 and \textit{L. murinus} 3133) for 4 weeks; urinary oxalate levels were

\begin{table}[h]
\centering
\caption{Clinical studies of lactobacilli showing efficacy for treatment of mastitis}
\begin{tabular}{llll}
\hline
Bacteria & Dose & Pathology & Ref. (Design) \\
\hline
\textit{L. fermentum} CECT5716 & 1x10\textsuperscript{9} CFU (of each) & Infectious mastitis induced by \textit{S. epidermidis} or \textit{S. aureus} & \textsuperscript{206} (open study) \\
\textit{L. salivarius} CECT5713 & & & \\
\textit{L. salivarius} CECT5713 and \textit{L. casei} CECT5714 & 1x10\textsuperscript{10} CFU (of each) & Mastitis induced by \textit{S. epidermidis} or \textit{S. aureus} & \textsuperscript{209} (open study) \\
& + a matrix of methylcellulose & & \\
& Not stated & & \\
\hline
\end{tabular}
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\begin{table}[h]
\centering
\caption{Clinical studies of lactobacilli showing immuno-modulatory activity in various pathologies}
\begin{tabular}{llll}
\hline
Bacteria & Dose & Pathology & Ref. (Design) \\
\hline
\textit{L. salivarius} LS01 & 1x10\textsuperscript{9} CFU (of each) & Moderate/severe atopc dermatitis & \textsuperscript{223} (randomised double-blinded active treatment vs placebo study) \\
\textit{B. breve} BR03 & & & \\
& maltodextrin & Not stated & \\
& probiotik (\textit{B. bifidum}, \textit{L. acidophilus}, \textit{L. casei} and \textit{L. salivarius}) & 2x10\textsuperscript{9} CFU (total) & Atopic dermatitis & \textsuperscript{207} (double-blind, randomised, placebo-controlled study) \\
\textit{L. pentosus} b240 & 2x10\textsuperscript{10} CFU & Common cold & \textsuperscript{228} (randomised, double-blind, placebo-controlled study) \\
& Yaku\textsuperscript{\textregistered} (\textit{L. casei} Shirota) & 6.5x10\textsuperscript{9} CFU & Allergic rhinitis & \textsuperscript{208} (double-blind, placebo-controlled study) \\
\textit{L. paracasei}-33 & 2x10\textsuperscript{9} CFU & & \textsuperscript{229} (randomised, double-blind, placebo-controlled study) \\
\textit{L. acidophilus} L-92 & & Atopic dermatitis & \textsuperscript{209} (randomised, clinical study) \\
\hline
\end{tabular}
\end{table}
Multidrug resistance and biofilm formation by pathogenic bacteria account for the lack of efficacy of antibiotics used for treatment of mastitis. In this context, 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 mastitis, are gaining a new strategies based on probiotics, as alternatives or complements to antibiotic therapy for the management of mastitis, are mentioned conditions and can be applied to other GI pathologies, as summarised in table 9.

### Mastitis

Mastitis is an infectious inflammation of one or more breast lobules with S. aureus and S. epidermidis being the most frequent aetiological agents and with a prevalence of 3–33% among breastfeeding mothers. Multidrug resistance and biofilm formation by pathogenic bacteria account for the lack of efficacy of antibiotics used for treatment of mastitis. 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 6.

### Immunomodulatory activity

Lactobacilli are potential adjuvants triggering mucosal and systemic immune responses. The immunomodulatory effects of lactobacilli observed in various physiological systems include increased natural killer cell cytotoxicity and induction of interferon-γ production and cytokine expression. In order to exert these immunomodulatory effects, lactobacilli must resist to digestive system processes and adhere to the host’s intestinal epithelium. Lactobacilli (in particular L. acidophilus) can also be administered together with bifidobacteria in order to enhance the immune system and concurrently attenuating systemic stress response. Clinical studies of lactobacilli showing immunomodulatory activity in various pathologies have been summarised in table 8.

### 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. Dysbiosis may also play a key role in IBD. Evidence from animal models and clinical observations 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. The number of bacterial strains that reach the gut mucosa and colon, depends on several factors such as strain used, gastric transit survival, and acid and bile tolerance. 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

| Bacteria | Dose | Pathology | Ref. (Design) |
|----------|------|-----------|---------------|
| VSL#3® | 5×10¹¹ CFU/g (3 g) (total) | Chronic pouchitis | 230(open study) |
| L. acidophilus LA02 (51.3%) | | | |
| Lactobacillus acidophilus Shirota | 6.5×10⁶ CFU | Constipation | 231(open study) |
| L. plantarum SW13T | 2×10⁸ CFU | Constipation | 232(double-blind, randomised study) |
| VSL#3® | 5×10¹¹ CFU/g (3 g) (total) | Ulcerative colitis | 233(open study) |
| L. acidophilus LA02 (51.3%) | | | |

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

| Bacteria | Dose | Site | Ref. (Design) |
|----------|------|------|---------------|
| L. acidophilus 821–3 | 1×10⁹ CFU | Gastrointestinal tract | 156(open study) |
| L. acidophilus | 1×10⁸ CFU/g (100 g) | Small intestine | 231(open study) |
| B. sp | 1×10⁷ CFU/g (100 g) | | |
| L. casei Shirota | 1×10⁸ CFU/mL (100 mL) | Gastrointestinal tract | 238(14-day baseline, ingestion and follow-up periods) |
| L. acidophilus LA02 (DSM 21717) | 5×10⁷ CFU (of each) | Gastrointestinal tract | 239(double-blind, randomised, cross-over study) |
| L. rhamnosus LR04 (DSM 16605) | 5×10⁹ CFU Constipation | | |
| L. rhamnosus GG (ATCC 53103) | 6.5×10⁹ CFU | Chronic pouchitis | 230(open study) |
| L. rhamnosus LR06 (DSM 21981) | | | |
| B. lactis BS01 (LMG P-21384) | | | |
| L. plantarum LP01 (LMG P-21021) | 1×10⁹ CFU (of each) | Gastrointestinal tract | 240(double-blind, randomised, cross-over study) |
| B. breve BR03 (DSM 16604) | | | |
| Lakcid® L (L. rhamnosus 573I, 573 I2 and 573L3) | 1.2×10⁷ CFU | Gastrointestinal tract | 241(prospective, double-blinded, placebo-controlled randomised study) |
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

| Table 11 | Clinical studies of lactobacilli showing efficacy for treatment of diarrhoea |
|----------|----------------------------------------------------------------------|
| **Bacteria** | **Dose** | **Pathology** | **Ref. (Design)** |
| Actimel<sup>®</sup> (L. casei DN 114001) | 10<sup>10</sup> CFU | Antibiotic-associated diarrhoea | 249 (observational study) |
| Balance™ (L. casei, L. rhamnosus, L. acidophilus, L. bulgaricus, B. strains, B. breve, B. longum and St. thermophilus) | 1 x 10<sup>8</sup> CFU (total) | H. pylori infection-associated diarrhoea | 250 (randomised placebo-controlled triple-blind study) |
| L. acidophilus | 2.5 x 10<sup>8</sup> CFU (total) | Acute diarrhoea | 251 (prospective randomised, multicentre single-blinded clinical study) |
| Balance™ (L. casei, L. rhamnosus, L. acidophilus, B. bifidum, B. longum and E. faecium) + fructo-oligosaccharide | 625 mg | Antibiotic-associated diarrhoea | 252 (prospective, parallel group study) |
| L. acidophilus (CUL60, NCIMB 30157 and CUL21, NCIMB 30156), B. bifidum (CUL20, NCIMB 30153) and B. lactis (CUL34, NCIMB 30172) | 6.5 x 10<sup>8</sup> CFU (of each) | Acute gastroenteritis | 253 (randomised, prospective placebo-controlled parallel clinical study) |
| Probiotical (S. thermophilus, L. rhamnosus, L. acidophilus, B. lactis and B. infantis) + Fructooligosaccharides + Ascorbic acid | 3.625 x 10<sup>7</sup> CFU | Acute rotavirus diarrhoea | 254 (prospective, double-blind, randomised study) |
| L. acidophilus, L. rhamnosus, B. longum and S. boulardii | 6.625 x 10<sup>7</sup> CFU | Acute rotavirus diarrhoea | 255 (open-label randomised study) |
| L. rhamnosus 35 | 6 x 10<sup>8</sup> CFU | Acute rotaviral gastroenteritis | 256 (double-blind, randomised, placebo-controlled study) |
| L. rhamnosus (strains E/N, Oxy and Pen) | 2 x 10<sup>10</sup> CFU (of each) | Antibiotic-associated diarrhoea | 257 (randomised, double-blind, placebo-controlled clinical study) |
| L. acidophilus LB | 10<sup>8</sup> CFU | Non-rotavirus diarrhoea | 258 (randomised, double-blind, placebo-controlled clinical study) |
| Lactid<sup>®</sup> L (L. rhamnosus (573 U1, 573 U2 and 573 U3)) | 1.2 x 10<sup>10</sup> CFU (total) | Infectious diarrhoea | 259 (randomised, double-blind, placebo-controlled study) |
| L. paracasei ST11 | 10<sup>10</sup> CFU | Non-rotavirus diarrhoea | 260 (randomised, double-blind, placebo-controlled clinical study) |
| L. casei CERELA | 10<sup>10</sup> CFU (of each) | Persistent diarrhoea | 261 (double-blind study) |
| L. acidophilus CERELA S. boulardii L. rhamnosus 19070–2 L. reuteri DSM 12246 | 10<sup>10</sup> CFU (of each) | Acute diarrhoea | 262 (randomised placebo-controlled study) |
| L. casei CERELA | Not stated | Bacterial overgrowth-related chronic diarrhoea | 263 (randomised, double-blind study) |
| L. acidophilus CERELA | Not stated | Bacterial overgrowth-related chronic diarrhoea | 264 (randomised, placebo-controlled study) |
| L. reuteri | 10<sup>10</sup>–<sup>11</sup> CFU/g (1 g) | Acute diarrhoea | 265 (randomised, double-blind study) |
| L. reuteri | Not stated | Acute diarrhoea | 266 (randomised, placebo-controlled study) |

**Di Cerbo A, et al. J Clin Pathol 2016;69:187–203. doi:10.1136/jclinpath-2015-202976**

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

| **Bacteria** | **Dose** | **Pathology** | **Ref. (Design)** |
|----------|----------------------------------------------------------------------|
| L. salivarius WB21 | 6.7 x 10<sup>8</sup> CFU | Severe periodontitis treatment | 267 (randomised clinical study) |
| L. reuteri ATCC 55730 | 1 x 10<sup>8</sup> CFU (of each) | Gingival inflammation | 268 (double-blind placebo-controlled study) |
Clostridium (C.) difficile infection, a gram positive, spore-forming anaerobe, can cause antibiotic-associated diarrhoea and colitis in humans. 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. While L. casei L39 suppressed the activation of phosphono-c-Jun in HT-29 cells, L. rhamnosus GP1B cell extract decreased transcriptional levels of luxS, tcdA, tcdB and txeR genes of C. difficile, thus reducing virulence in vitro. 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. While the first condition is characterised by inflammation of the gingiva, the second is a progressive destructive disease which involves tooth supporting tissues such as the alveolar bone. 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. Among antimicrobial and bacteriostatic agents, chlorhexidine is the gold standard for treatment of periodontitis because of its broad-spectrum antibacterial activity. 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. Evidence has shown the effectiveness of lactobacilli in reducing gingival inflammation and the number of cariogenic periodontopathogenic bacteria. 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) as well as decreased the levels of the proinflammatory cytokines TNF-α, IL-8 and IL-1β. Saha and coworkers investigated the role of selected lactobacilli in St. mutans inhibition. 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).\textsuperscript{277} In this context, inflammatory immune responses play a crucial role in the progression of both types of disease.\textsuperscript{278–280} As for type-2 diabetes, it is generally treated with intestinal \(\alpha\)-glucosidase inhibitors.\textsuperscript{281} In this regard, \textit{Actinoplanes} \textit{spp} have been shown to naturally produce potent \(\alpha\)-glucosidase inhibitor compounds including acarbose. Panwar and coworkers first isolated and extracted lacticobacilli from human infant faecal samples and evaluated their inhibitory activity against intestinal maltase, sucrase, lactase and amylase, all enzymes involved in hydrolysis of carbohydrates.\textsuperscript{282,283} This study showed that several strains exert powerful inhibitory effects against the aforementioned enzymes and \textit{L. rhamnosus} reduced glucose excursions in rats during a carbohydrate challenge by inhibiting \(\beta\)-glucosidase as well as \(\alpha\)-glucosidase activities. Even if further studies are

| Bacteria                  | Effect/s                          | Patient(s) clinical history                                                                 | Ref. |
|--------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------|------|
| \textit{L. jensenii}     | Endocarditis                       | An immunocompetent 47-year-old man with mitral valve replacement treated with teicoplanin and meropenem | 302  |
| \textit{L. paracasei}    | Endocarditis                       | A patient (18 years) with trisomy 21 treated with chloramphenicol                         | 303  |
| \textit{L. rhamnosus} GG | Bacteraemia                        | Eleven patients with immunosuppression, prior prolonged hospitalisation and prior surgical interventions treated with antimicrobials | 317  |
| \textit{L. acidophilus}  | Bloodstream infections             | The maximum estimated incidence of bacteraemia during an 8-year period was 0.2%                   | 322  |
| \textit{L. casei}        | Septicaemia                        | A 54-year-old woman with diabetes treated with amoxicillin                                    | 296  |
| \textit{L. jensenii}     | Septicaemia                        | A 50-year-old woman with obstructive acute renal failure                                       | 297  |
| \textit{L. paracasei}    | Purpura fulminans associated with liver abscess                                              | Not stated                                                                                  | 323  |
| \textit{L. acidophilus}  | Liver abscess                      | A 27-year-old man with a 6-month history of NOD2/CARD15-positive Crohn’s disease                | 324  |
| \textit{L. casei}        | Pneumonia and sepsis               | A patient with AIDS because of CD4 lymphocyte depletion                                         | 325  |
| \textit{L. rhamnosus}    | Septicaemia                        | A patient with a graft in the inferior vena cava                                              | 298  |
| \textit{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  |
| \textit{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  |
| \textit{L. rhamnosus} Lc35 | Meningitis and recurrent episodes of bacteraemia | A child (10 years) undergoing allogeneic haematopoietic stem cell transplantation and treated unsuccessfully with clindamycin | 320  |
| \textit{L. casei}        | Bacteraemia                        | An immunocompetent 66-year-old man with a history of fever of unknown origin                   | 319  |
| \textit{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  |
| \textit{L. jensenii}     | Bacteraemia and endocarditis       | A 27-year-old woman with a 20-day history of fever and treated with penicillin and gentamicin | 304  |
| \textit{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 granulocyte lymphoma leukaemia and initially treated with chemotherapy | 328  |
| \textit{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  |
| \textit{L. rhamnosus}    | Sepsis                             | A 24-year-old woman developed sepsis resulting from preoperative administration of probiotics following an aortic valve replacement | 301  |
| \textit{L. rhamnosus} GG | Bacteraemia                        | A 69-year-old man with stage IIIA mantle cell lymphoma and treated with probiotic-enriched yogurt stopping | 329  |
| \textit{L. rhamnosus} GG | Bacteraemia                        | An 11-month-old boy with fever and hypoxia and a history of short bowel syndrome secondary to resection of approximately 80% of the small intestine | 310  |
| \textit{L. acidophilus}  | Sepsis                             | A 69-year-old man with stage IIIA mantle cell lymphoma                                         | 315  |
| \textit{L. rhamnosus} GG | Bacteraemia                        | A 36-week-gestation male infant with short gut syndrome secondary to congenital intestinal atresia and volvulus | 313  |
| \textit{L. rhamnosus} GG | Bacteraemia                        | A 34-week-gestation male infant with gastrochisis                                               | 313  |
| \textit{L. rhamnosus}    | Bacteraemia                        | A 43-year-old woman with ulcerative colitis                                                      | 299  |
| \textit{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  |

\textsuperscript{1} Panwar and coworkers identified the role of \textit{L. rhamnosus} and \textit{L. casei} in the progression of both types of disease.\textsuperscript{278–280} As for type-2 diabetes, it is generally treated with intestinal \(\alpha\)-glucosidase inhibitors.\textsuperscript{281} In this regard, \textit{Actinoplanes} \textit{spp} have been shown to naturally produce potent \(\alpha\)-glucosidase inhibitor compounds including acarbose. Panwar and coworkers first isolated and extracted lacticobacilli from human infant faecal samples and evaluated their inhibitory activity against intestinal maltase, sucrase, lactase and amylase, all enzymes involved in hydrolysis of carbohydrates.\textsuperscript{282,283} This study showed that several strains exert powerful inhibitory effects against the aforementioned enzymes and \textit{L. rhamnosus} reduced glucose excursions in rats during a carbohydrate challenge by inhibiting \(\beta\)-glucosidase as well as \(\alpha\)-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 cartilaginous degeneration, subchondral bone sclerosis, synovial inflammation and osteophyte formation,243 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.244 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 responses286 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.249 Antihyperlipidaemic effects of lactobacilli were also evaluated along with memory-enhancing activity in aged Fischer 344 rats.250 A probiotic mixture of L. plantarum KY1032 and L. casei 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.

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.31 The 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 F1932 33), the antibiotic susceptibility and translocation rate of L. strains.334–336 Therefore, further investigations are required to fill 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 effectiveness of lactobacilli 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.

Correction notice Since this paper was published online the author has changed the formatting of tables 2–15, corrected the units in these tables and added italics to gene names throughout the paper.

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196

Di Cerbo A, et al. J Clin Pathol 2016;69:187–203. doi:10.1136/jclinpath-2015-202976

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Il microbioma intestinale non è un ecosistema silenzioso ma esercita diverse funzioni fisiologiche e immunologiche. Per molti decenni, i lattobacilli sono stati utilizzati come terapia efficace per il trattamento di varie condizioni patologiche mostrando un profilo di sicurezza generale positivo. Questa review riassume i meccanismi e le prove cliniche a sostegno dell'efficacia terapeutica dei lattobacilli.

Abbiamo effettuato una ricerca su Pubmed/Medline utilizzando la parola chiave “Lactobacillus”. I lavori selezionati dal 1950 al 2015 sono stati scelti sulla base del loro contenuto.

Sono stati inclusi articoli sperimentali e di rilevanza clinica che hanno utilizzato i lattobacilli come agenti terapeutici. Le applicazioni dei lattobacilli includono il supporto renale, la salute del pancreas, la gestione dello squilibrio metabolico e il trattamento e la prevenzione del cancro.

Ricerche in vitro e in vivo hanno dimostrato che la prolungata somministrazione di lattobacilli induce modifiche qualitative e quantitative nell’ecosistema microbico gastrointestinale umano con incoraggianti prospettive nel contrastare alterazioni immunologiche e fisiologiche associate a patologie. Sebbene pochi studi hanno evidenziato il rischio di traslocazione con conseguente sepsi e batteriemia dopo la somministrazione di probiotici, c’è ancora una penuria di indagini su dose/effetto di questi ultimi. Pertanto è richiesta grande attenzione nella scelta della corretta specie di lattobacillo, la sua stabilità genetica e il rischio di traslocazione che possono essere correlate ad un’aumentata permeabilità intestinale che si manifesta tipicamente in caso di patologia infiammatoria. Infine, abbiamo bisogno di determinare l’adeguata quantità di batteri da assumere durante ciascuna assunzione al fine di ottenere la miglior efficacia clinica diminuendo il rischio di effetti collaterali.