

ABSTRACTS - Lactoferrin – L.Plantarum - L.Reuteri - GI

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Isolates of *Lactobacillus plantarum* and *L. reuteri* display greater antiproliferative and antipathogenic activity than other *Lactobacillus* isolates.

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PURPOSE: Lactic acid bacteria (LAB) have been associated with many beneficial effects in human digestive physiology. The aim of this study was to evaluate such effect, including attachment, antiproliferation and anti-pathogenic/antibacterial/antimicrobial properties of LAB isolated from healthy humans.

METHODOLOGY: Thirteen isolates, obtained from fecal samples of healthy individuals, were identified by phenotypic and molecular methods. Human colon adenocarcinoma cell line HT-29 and the cell proliferation kit II (XTT) assay were used for examination of the *Lactobacillus* adherence and antiproliferative activity, respectively. In addition, the inhibitory effect of *Lactobacillus* isolates against pathogenic bacteria was examined.

RESULTS: Out of 13 *Lactobacillus* isolates, 5 (38%) isolates were non-adhesive, 4 (31%) were adhesive and 4 (31%) were strongly adhesive. Amongst the isolated lactobacilli, *L. reuteri* showed the highest degree of inhibitory effect against the attachment of the enteropathogens. The XTT assay showed that 3 different isolates had the strongest antiproliferative activity with the maximum effect observed by *L. plantarum* isolates.

CONCLUSION: Our results described that different *Lactobacillus* species isolated from normal fecal samples had different degrees of antiproliferative and anti-pathogenic/antibacterial/antimicrobial activities. However, no isolates showed all of the examined properties concurrently, suggestive that a combination of *Lactobacillus* species is needed for an active biological defense system.

KEYWORDS: HT-29 cells; *Lactobacillus* spp; XTT assay; healthy human; probiotic

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Exopolysaccharide from *Lactobacillus plantarum* LRCC5310 offers protection against rotavirus-induced diarrhea and regulates inflammatory response.

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We aimed to determine the effects of *Lactobacillus* strains against rotaviral infections. Rotaviruses are the major causative agent of acute gastroenteritis in infants and children worldwide. However, to date, no specific antiviral drugs for the treatment of rotavirus infection have been developed. We identified 263 *Lactobacillus* strains from 35 samples of the traditional Korean fermented vegetable food, kimchi. Among them, *Lactobacillus plantarum* LRCC5310, more specifically the exopolysaccharides produced by these cells, were shown to have an antiviral effect against human rotavirus Wa strain in vitro. In vivo, the oral administration of exopolysaccharides for 2 d before and 5 d after mouse infection with the murine rotavirus epidemic diarrhea of infant mice strain led to a decrease in the duration of diarrhea and viral shedding and prevented the destruction of enteric epithelium integrity in the infected mice. We demonstrated here that the exopolysaccharides extracted from *L. plantarum* LRCC5310 can be used for the effective control of rotavirus infection.

KEYWORDS: *Lactobacillus plantarum*; diarrhea; exopolysaccharide; rotavirus

Observational prospective study on *Lactobacillus plantarum* P 17630 in the prevention of vaginal infections, during and after systemic antibiotic therapy or in women with recurrent vaginal or genitourinary infections.

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We performed a prospective cohort parallel observational study on the use of *Lactobacillus plantarum* P 17630 in the prevention of vaginal infections. Eligible were women with a diagnosis of bacterial vaginosis (<15 days) and documented history of recurrent vaginal infections; and/or cystitis (<15 days); and/or treatment with antibiotics for bacterial respiratory tract infections during the week before the study entry. Study subjects were prescribed *Lactobacillus plantarum* P 17630 > 100.000.000 UFC one vaginal capsule per day for 6 days, then a capsule per week for 16 weeks. Eligible subjects were enrolled in two parallel cohorts: 85 women using (group A) and 39 not using (group B) *Lactobacillus plantarum* P 17630. The risk of recurrent infection within 4 months from the study entry, was higher among untreated women: multivariate OR 2.6 (95%CI 0.7-9.4). The modification of presence/intensity or symptoms was significant in both the study groups ($p < .001$). Impact statement What is already known on this subject? The *Lactobacillus plantarum* P 17630 has been shown to be active in the treatment of bacterial vaginosis and vaginal candidiasis. No data are available on its efficacy in the prevention of recurrent vaginal or urological infection or as a prevention strategy during systemic treatment with antibiotics. What do the results of this study add? This observational study suggests that *Lactobacillus plantarum* given for 4 months may lower the risk of recurrent infection in women with recurrent vaginal or genitourinary infection or after antibiotic systemic treatment for bacterial respiratory tract infection. The finding, however, is not statistically significant, possibly due to the lower than expected rate of infection observed in our population and consequently the limited power of the study. What are the implications of these findings for clinical practice and/or further research? New studies are needed in order to evaluate in different populations the role of *Lactobacillus plantarum* in lowering the risk of recurrent infection in a high-risk populations.

KEYWORDS: *Lactobacillus plantarum*; Prevention; bacterial vaginosis

Randomised double blind placebo controlled trial on *Lactobacillus reuteri* DSM 17938: improvement in symptoms and bowel habit in functional constipation.

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Dysbiosis may contribute to constipation and its symptoms, therefore probiotic administration could improve significantly gut health and functions. The aim of the study was to investigate the effects of a long-lasting administration of *Lactobacillus reuteri* DSM 17938 (LR DSM 17938) on symptoms and quality of life (QoL) score in patients with functional constipation (FC). 56 FC patients with normal colonic transit time and without anorectal disorders and pelvic floor dysfunctions completed the study. LR DSM 17938 was administered for 105

days in a randomised double-blind clinical trial (28 patients per arm). Individual and cumulative scores including the Constipaq, a modified Constipation Scoring System (CSS) that considers the patient assessment of constipation-QoL (PAC-QoL), were calculated during the preliminary visit (V0), at day 15 (end of the induction period with a LR DSM 17938 double dosage, 4×10^8 cfu), day 60 (intermediate evaluation) and day 105 (V4) after a standard dosage (2×10^8 cfu). At the end of treatment, the beneficial effect of LR DSM 17938 compared to placebo was significantly evident for symptoms related to gas content and dysbiosis (abdominal discomfort, pain and bloating), incomplete defecation and helps for defecation ($P < 0.05$). At the end of the whole LR DSM 17938 treatment, a marked and positive effect on both the CSS single and the cumulative items was evident with the exception of unfruitful attempt and Bristol score. Present findings indicate that LR DSM 17938 has an effect on symptoms different from stool consistency, and they suggest that this probiotic can effectively be used in association therapy rather than as single-drug therapy in the management of FC.

KEYWORDS: Constipaq; *Lactobacillus reuteri* DSM 17938; constipation; probiotics; symptoms

[Pediatrics](#). 2018 Jan;141(1). pii: e20171811. doi: 10.1542/peds.2017-1811.

Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis.

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CONTEXT: *Lactobacillus reuteri* DSM17938 has shown promise in managing colic, but conflicting study results have prevented a consensus on whether it is truly effective.

OBJECTIVE: Through an individual participant data meta-analysis, we sought to definitively determine if *L reuteri* DSM17938 effectively reduces crying and/or fussing time in infants with colic and whether effects vary by feeding type.

DATA SOURCES: We searched online databases (PubMed, Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, the Database of Abstracts of Reviews of Effects, and Cochrane), e-abstracts, and clinical trial registries.

STUDY SELECTION: These were double-blind randomized controlled trials (published by June 2017) of *L reuteri* DSM17398 versus a placebo, delivered orally to infants with colic, with outcomes of infant crying and/or fussing duration and treatment success at 21 days.

DATA EXTRACTION: We collected individual participant raw data from included studies modeled simultaneously in multilevel generalized linear mixed-effects regression models.

RESULTS: Four double-blind trials involving 345 infants with colic (174 probiotic and 171 placebo) were included. The probiotic group averaged less crying and/or fussing time than the placebo group at all time points (day 21 adjusted mean difference in change from baseline [minutes] -25.4 [95% confidence interval (CI): -47.3 to -3.5]). The probiotic group was almost twice as likely as the placebo group to experience treatment success at all time points (day 21 adjusted incidence ratio 1.7 [95% CI: 1.4 to 2.2]). Intervention effects were dramatic in breastfed infants (number needed to treat for day 21 success 2.6 [95% CI: 2.0 to 3.6]) but were insignificant in formula-fed infants.

LIMITATIONS: There were insufficient data to make conclusions for formula-fed infants with colic.

CONCLUSIONS: *L reuteri* DSM17938 is effective and can be recommended for breastfed infants with colic. Its role in formula-fed infants with colic needs further research.

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Micro Integral Membrane Protein (MIMP), a Newly Discovered Anti-Inflammatory Protein of *Lactobacillus Plantarum*, Enhances the Gut Barrier and Modulates Microbiota and Inflammatory Cytokines.

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BACKGROUND/AIMS: Recent studies have demonstrated that the manipulation of the gut microbiome represents a promising treatment for inflammatory bowel disease (IBD). We previously identified micro integral membrane protein (MIMP) as the smallest domain of surface layer protein from *Lactobacillus Plantarum*. However, the therapeutic relevance of MIMP in IBD remains unknown.

METHODS: We initially employed a dextran sodium sulphate (DSS)-induced colitis model and evaluated the effect of MIMP on the inflammation response, intestinal barrier and gut microbiota using histological examination, Fluorescein isothiocyanate-Dextran detection and pyrosequencing analysis respectively. We then established peripheral blood mononuclear cells (PBMCs) and an epithelial CaCO-2 co-culture model to investigate the regulatory role of MIMP in inflammatory cytokines. The level changes of inflammatory cytokines were detected using Enzyme-linked immunosorbent and real-time polymerase chain reaction assay. The involved regulatory mechanisms were investigated mainly using dual luciferase reporter and chromatin immunoprecipitation assay.

RESULTS: In the DSS-induced colitis model, we observed that MIMP intervention effectively improved the body weight loss, increased the colon length and decreased disease activity index. Consistently, the inflammation scores in the MIMP treatment group were significantly lower than those in the DSS treatment group. Furthermore, MIMP intervention was found to successfully neutralize DSS treatment by decreasing the expression of pro-inflammatory cytokines (IFN- γ , IL-17 and IL-23) and increasing the expression of anti-inflammatory cytokines (IL-4 and IL-10). Notably, the permeability assay demonstrated that the MIMP treatment group was remarkably lower than that in the DSS treatment group. We also showed that MIMP improved gut microbiota dysbiosis caused by DSS-induced inflammation. Additionally, in PBMCs and the CaCO-2 co-culture model, MIMP showed an obvious suppressive effect on lipopolysaccharide-induced inflammation in a time- and dose-dependent manner. Furthermore, we revealed that MIMP could modulate inflammatory cytokine expression through the toll-like receptor 4 pathway and histone acetylation.

CONCLUSIONS: Our results suggested that MIMP showed a significant anti-inflammatory effect through regulating the gut barrier, microbiota and inflammatory cytokines. MIMP may have translational relevance as clinically relevant therapy for IBD patients.

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KEYWORDS: Gut barrier; Inflammatory bowel disease; Inflammatory cytokines; MIMP; Microbiota

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CONCLUSIONS: Our results suggested that MIMP showed a significant anti-inflammatory effect through regulating the gut barrier, microbiota and inflammatory cytokines. MIMP may have translational relevance as clinically relevant therapy for IBD patients.

KEYWORDS: Gut barrier; Inflammatory bowel disease; Inflammatory cytokines; MIMP; Microbiota

Structural basis for the role of serine-rich repeat proteins from *Lactobacillus reuteri* in gut microbe-host interactions.

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Lactobacillus reuteri, a Gram-positive bacterial species inhabiting the gastrointestinal tract of vertebrates, displays remarkable host adaptation. Previous mutational analyses of rodent strain *L. reuteri* 100-23C identified a gene encoding a predicted surface-exposed serine-rich repeat protein (SRRP₁₀₀₋₂₃) that was vital for *L. reuteri* biofilm formation in mice. SRRPs have emerged as an important group of surface proteins on many pathogens, but no structural information is available in commensal bacteria. Here we report the 2.00-Å and 1.92-Å crystal structures of the binding regions (BRs) of SRRP₁₀₀₋₂₃ and SRRP₅₃₆₀₈ from *L. reuteri* ATCC 53608, revealing a unique β -solenoid fold in this important adhesin family. SRRP₅₃₆₀₈-BR bound to host epithelial cells and DNA at neutral pH and recognized polygalacturonic acid (PGA), rhamnogalacturonan I, or chondroitin sulfate A at acidic pH. Mutagenesis confirmed the role of the BR putative binding site in the interaction of SRRP₅₃₆₀₈-BR with PGA. Long molecular dynamics simulations showed that SRRP₅₃₆₀₈-BR undergoes a pH-dependent conformational change. Together, these findings provide mechanistic insights into the role of SRRPs in host-microbe interactions and open avenues of research into the use of biofilm-forming probiotics against clinically important pathogens.

KEYWORDS: *Lactobacillus reuteri*; SRRP; adhesin; biofilm; mucin

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Lactobacillus reuteri strains protect epithelial barrier integrity of IPEC-J2 monolayers from the detrimental effect of enterotoxigenic Escherichia coli.

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Lactobacillus reuteri is an inhabitant of the gastrointestinal (GI) tract of mammals and birds and several strains of this species are known to be effective probiotics. The mechanisms by which *L. reuteri* confers its health-promoting effects are far from being fully understood, but protection of the mucosal barrier is thought to be important. Leaky gut is a state of abnormal intestinal permeability with implications for the pathophysiology of various gastrointestinal disorders. Enterotoxigenic *Escherichia coli* (ETEC) can invade the intestinal mucosa and induce changes in barrier function by producing enterotoxin or by direct invasion of the intestinal epithelium. Our hypothesis was that *L. reuteri* can protect the mucosal barrier, and the goal of the study was to challenge this hypothesis by monitoring the protective effect of *L. reuteri* strains on epithelial dysfunction caused by ETEC. Using an infection model based on the porcine intestinal cell line IPEC-J2, it was demonstrated that pretreatment of the cells with human-derived *L. reuteri* strains (ATCC PTA 6475, DSM 17938 and 1563F) and a rat strain (R2LC) reduced the detrimental effect of ETEC in a dose-dependent manner, as monitored by permeability of FITC-dextran and transepithelial electrical resistance (TEER). Moreover, the results revealed that ETEC upregulated proinflammatory cytokines IL-6 and TNF α and decreased expression of the shorter isoform of ZO-1 (187 kDa) and E-cadherin. In contrast, pretreatment with *L. reuteri* DSM 17938 and 1563F downregulated expression of IL-6 and TNF α , and led to an increase in production of the longer isoform of ZO-1 (195 kDa) and maintained E-cadherin expression. Interestingly, expression of ZO-1 (187 kDa) was preserved only when the infected cells were pretreated with strain 1563F. These findings demonstrate that *L. reuteri* strains exert a protective effect against ETEC-induced mucosal integrity disruption.

KEYWORDS: *Lactobacillus reuteri* ; Enterotoxigenic *Escherichia coli* (ETEC); IPEC-J2; mucosal integrity

Crying Time and ROR γ /FOXP3 Expression in *Lactobacillus reuteri* DSM17938-Treated Infants with Colic: A Randomized Trial.

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OBJECTIVES: To evaluate crying time, retinoid-related orphan receptor- γ (ROR γ) and forkhead box P3 (FOXP3) messenger RNA levels (transcription factors that can modulate T cell responses to gut microbes), and to investigate gut microbiota and fecal calprotectin in infants treated with *Lactobacillus reuteri* for infantile colic.

STUDY DESIGN: A double-blind, placebo-controlled randomized trial was conducted in primary care in Torino from August 1, 2015 to September 30, 2016. Patients suffering from infantile colic were randomly assigned to receive daily oral *L reuteri* (1×10^8 colony forming unit) or placebo for 1 month. Daily crying times were recorded in a structured diary. FOXP3 and ROR γ messenger RNA in the peripheral blood was assessed with real-time TaqMan reverse transcription polymerase chain reaction. Gut microbiota and fecal calprotectin were evaluated.

RESULTS: After infants with colic were supplemented with *L reuteri* DSM 17938 for 30 days, crying times were significantly shorter among infants with colic in the probiotic group compared with infants in the placebo group (74.67 ± 25.04 [IQR = 79] minutes /day vs 147.85 [IQR = 135] minutes /day [$P = .001$]). The FOXP3 concentration increased significantly ($P = .009$), resulting in decreased ROR γ /FOXP3 ratios: 0.61 (IQR = 0.60) at day 0 and 0.48 (IQR = 0.28) at day 30 ($P = .028$). Furthermore, the probiotic increased the percentage of *Lactobacillus* ($P = .049$) and decreased fecal calprotectin ($P = .0001$).

CONCLUSIONS: Infants with colic treated with *L reuteri* for 30 days had a significantly decreased crying time and an increased FOXP3 concentration, resulting in a decreased ROR γ /FOXP3 ratio. The treatment reduced fecal calprotectin.

Efficacy of *Lactobacillus reuteri* DSM 17938 for infantile colic: Systematic review with network meta-analysis.

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BACKGROUND: 5% to 40% of infants cry excessively, usually accompanied by fussiness and excessive of gas. There are no uniform criteria for treatment of infantile colic. *Lactobacillus reuteri* DSM 17938 has been used with promising results. The objective of this network-meta-analysis (NMA) is to compare the efficacy of *L reuteri* DSM 17938 with other interventions for infantile colic.

METHODS: RCTs, published between 1960 and 2015 for the treatment of infantile colic were included. Primary outcome was duration of crying after 21 to 28 days of treatment. Different databases were searched. Information was analyzed using control group as central axis. A random effect model was used. Hedges standard mean difference (SMD) and odds ratio (OR) were calculated. A SUCRA analysis was performed to evaluate superiority for each intervention.

RESULTS: 32 RCTs were analyzed, including 2242 patients. Studies with *L reuteri* DSM 17938 versus Ctrl., Diet versus Ctrl. and Acupuncture versus Ctrl. were the most influential studies in the NMA. *L reuteri* DSM 17938 [WMD -51.3h (CI95% -72.2 to -30.5h), P .0001] and dietetic approaches [WMD -37.4h (CI95% -56.1 to -18.7h), P .0001] were superior compared to the other treatments.

CONCLUSIONS: *L reuteri* DSM 17938 and some dietetic approaches are better to other interventions for treatment of infantile colic.

[Pan Afr Med J](#). 2017 May 10;27:22. doi: 10.11604/pamj.2017.27.22.9707. eCollection 2017.

Antagonistic and Quantitative Assessment of Indigenous Lactic acid Bacteria in Different Varieties of Ogi against Gastrointestinal Pathogens.

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INTRODUCTION: *Ogi* is a popular fermented cereal gruel consumed mainly in the western part of Nigeria. Traditionally, uncooked *Ogi* is normally administered to diarrhoea patients to reduce the frequency of stooling. This study was therefore undertaken to identify, quantify and determine the antimicrobial properties of lactic acid bacteria (LAB) isolated from *Ogi*.

METHODS: The *Ogi* samples (Yellow, white, sorghum) were obtained from different market in Ibadan, Nigeria and *Ogi* control (cooked, uncooked and *Omidun*) were prepared with the viable counts of bacteria monitored over 5 days period. LAB were isolated from the varieties and identified by partial sequencing of 16S rRNA gene. The antimicrobial activities of the cell free supernatant (CFS) and the viable cells of the isolated LAB against *Escherichia coli* EC004, *Salmonella* sp. SS11, *Shigella* sp. SS10 were investigated by agar diffusion assay, agar overlay method, and coculture growth studies.

RESULTS: *Omidun* had the highest LAB count while cooked *Ogi* has the lowest LAB count. *Weissella paramesenteroides*, *L. brevis*, *L. rossiae*, *L. fermentum*, *L. plantarum*, *Acetobacter pasteurianus*, *Paenibacillus* sp. and *Bacillus* sp. were isolated from *Ogi* in this study. Large zone of inhibition ($11 \leq x \leq 20$) was observed with CFS against *Salmonella* sp. SS11 and *Shigella* sp. SS10 and also the overlay method. Coculture studies of *Weissella paramesenteroides*, *Lactobacillus fermentum*, and *L. plantarum* with *Salmonella* sp. SS11 showed a 5-8 log reduction of the pathogens' growth after 24 hours as compared with the control.

CONCLUSION: *Ogi* and its contents have antimicrobial properties against pathogenic organisms.

KEYWORDS: *Ogi*; acetobacter; coculture; fermentation; *omidun*; salmonella

[J Pediatr](#). 2017 Dec;191:170-178.e2. doi: 10.1016/j.jpeds.2017.07.036. Epub 2017 Sep 29.

Lactobacillus reuteri for Infants with Colic: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial.

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OBJECTIVE: To assess the safety of probiotic *Lactobacillus reuteri* strain Deutsche Sammlung von Mikroorganismen (DSM) 17938 with daily administration to healthy infants with colic and to determine the effect of *L reuteri* strain DSM 17938 on crying, fussing, inflammatory, immune, and microbiome variables.

STUDY DESIGN: We performed a controlled, double-blinded, phase 1 safety and tolerability trial in healthy breast-fed infants with colic, aged 3 weeks to 3 months, randomly assigned to *L reuteri* strain DSM 17938 (5×10^8 colony-forming units daily) or placebo for 42 days and followed for 134 days.

RESULTS: Of 117 screened infants, 20 were randomized to *L reuteri* strain DSM 17938 or placebo (sunflower oil) (in a 2:1 ratio) with 80% retention. Eleven of the 20 (55%) presented with low absolute neutrophil counts ($<1500/\text{mm}^3$), which resolved in all subjects by day 176. *L reuteri* strain DSM 17938 produced no severe adverse events and did not significantly change crying time, plasma bicarbonate, or inflammatory biomarkers. Fecal calprotectin decreased rapidly in both groups. In the infants with dominant fecal gram negatives (*Klebsiella*, *Proteus*, and *Veillonella*), resolution of colic was associated with marked decreases in these organisms.

CONCLUSIONS: Daily administration of *L reuteri* strain DSM 17938 appears to be safe in newborn infants with colic, including those with neutropenia, which frequently coexists. A placebo response of 66% suggests that many infants with colic will have resolution within 3 weeks.

[J Agric Food Chem](#). 2017 Dec 6;65(48):10464-10472. doi: 10.1021/acs.jafc.7b03390. Epub 2017 Nov 20.

Lactoferrin Exerts Antitumor Effects by Inhibiting Angiogenesis in a HT29 Human Colon Tumor Model.

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To investigate the effect and potential mechanisms of lactoferrin on colon cancer cells and tumors, HT29 and HCT8 cells were exposed to varying concentrations of lactoferrin, and the impacts on cell proliferation, migration, and invasion were observed. Cell proliferation test showed that high dosage of lactoferrin (5-100 mg/mL) inhibited cell viability in a dose-dependent manner, with the 50% concentration of inhibition at 81.3 ± 16.7 mg/mL and 101 ± 23.8 mg/mL for HT29 and HCT8 cells, respectively. Interestingly, migration and invasion of the cells were inhibited dramatically by 20 mg/mL lactoferrin, consistent with the significant down regulation of VEGFR2, VEGFA, pPI3K, pAkt, and pErk1/2 proteins. HT29 was chosen as the sensitive cell line to construct a tumor-bearing nude mice model. Notably, HT29 tumor weight was greatly reduced in both the lactoferrin group (26.5 ± 6.7 mg) and the lactoferrin/5-Fu group (14.5 ± 5.1 mg), compared with the control one (39.3 ± 6.5 mg), indicating that lactoferrin functioned as a tumor growth inhibitor. Considering lactoferrin also reduced the growth of blood vessels and the degree of malignancy, we concluded that HT29 tumors were effectively suppressed by lactoferrin, which might be achieved by regulation of phosphorylation from various kinases and activation of the VEGFR2-PI3K/Akt-Erk1/2 pathway.

KEYWORDS: HCT8 cell; HT29 cell; angiogenesis; lactoferrin; tumor-bearing model

[Am J Trop Med Hyg](#). 2017 Sep;97(3):774-776. doi: 10.4269/ajtmh.16-0804. Epub 2017 Jul 19.

Killing of *Cryptosporidium* sporozoites by Lactoferrin.

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Intestinal infection caused by *Cryptosporidium* is a major contributor to diarrhea morbidity and mortality in young children around the world. Current treatments for children suffering from cryptosporidiosis are suboptimal. Lactoferrin is a glycoprotein found in breast milk. It has showed bacteriostatic and antimicrobial activity in the intestine. However, the effects of lactoferrin on the intestinal parasite *Cryptosporidium* have not been reported. In this study, we investigated the anticryptosporidial activity of human lactoferrin on different stages of *Cryptosporidium*. Physiologic concentrations of lactoferrin killed *Cryptosporidium parvum* sporozoites, but had no significant effect on oocysts viability or parasite intracellular development. Since sporozoites are essential for the infection process, our data reinforce the importance of breastfeeding and point to the potential of lactoferrin as a novel therapeutic agent for cryptosporidiosis.

[Biochem Cell Biol.](#) 2017 Feb;95(1):133-141. doi: 10.1139/bcb-2016-0107. Epub 2016 Nov 30.

Bovine lactoferrin and Crohn's disease: a case study.

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A 22-year-old male suffering from abdominal pain, repeated diarrhea, and weight loss visited the Digestive Disease Department of Nagoya City University Hospital on 19 December 2011. He was hospitalized and diagnosed with Crohn's colitis. His Crohn's Disease Activity Index (CDAI) was 415. Treatment by granulocyte apheresis, mesalazine, and adalimumab was started. His CDAI was 314 on 30 December and 215 on 5 January. A colonoscopic examination on 19 January showed almost complete remission in the transverse colon and marked remission in the rectum. Mesalazine therapy was stopped on 28 February, and the patient was instructed to self-inject 40 mg of adalimumab every other week. His CDAI was 50 on 10 April, indicating clinical remission. His last self-injection of adalimumab was on 24 April 2012, and he started taking 1 g of bovine lactoferrin (bLF) daily. His CDAI was 35 on 8 January 2013. He continued taking 1 g of bLF daily without any other treatment for Crohn's disease. Laboratory blood tests on 7 September 2015 showed no sign of disease recurrence, and a colonoscopic examination on 23 October 2015 showed almost complete mucosal healing. This case indicates that ingestion of bLF to maintain Crohn's disease in a remissive state should be further explored.

KEYWORDS: Crohn's colitis; Crohn's disease; bovine lactoferrin; colite de Crohn; lactoferrine bovine; maladie de Crohn

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Bovine lactoferrin and lactoferricin exert antitumor activities on human colorectal cancer cells (HT-29) by activating various signaling pathways.

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Lactoferrin (Lf) is an iron-binding glycoprotein that is present at high concentrations in milk. Bovine lactoferricin (LfcinB) is a peptide fragment generated by pepsin proteolysis of bovine lactoferrin (bLf). LfcinB consists of amino acid residues 17-41 proximal to the N-terminus of bLf and a disulfide bond between residues 19 and 36, forming a loop. Both bLf and LfcinB have been demonstrated to have antitumor activities. Colorectal cancer is the second most common cause of cancer death in developed countries. We hypothesized that bLf and LfcinB exert antitumor activities on colon cancer cells (HT-29) by triggering various signaling pathways. bLf and LfcinB

significantly induced apoptosis in HT-29 cells but not in normal human intestinal epithelial cells, as revealed by the ApoTox-Glo Triplex Assay. The LIVE/DEAD cell viability assay showed that both bLf and LfcinB reduced the viability of HT-29 cells. Transcriptome analysis indicated that bLf, cyclic LfcinB, and linear LfcinB exerted antitumor activities by differentially activating diverse signaling pathways, including p53, apoptosis, and angiopoietin signaling. Immunoblotting results confirmed that both bLf and LfcinBs increased expression of caspase-8, p53, and p21, critical proteins in tumor suppression. These results provide valuable information regarding bLf and LfcinB for potential clinical applications in colon cancer therapy.

KEYWORDS: antitumor; bovine lactoferrin; bovine lactoferrin; cancer colorectal; colorectal cancer; lactoferrin bovine; lactoferrin bovine; signaling pathways; voies de signalisation anti-tumorales

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Parasiticidal effect of synthetic bovine lactoferrin peptides on the enteric parasite *Giardia intestinalis*.

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Giardia intestinalis is the most common infectious protozoan parasite in children. Despite the effectiveness of some drugs, the disease remains a major worldwide problem. Consequently, the search for new treatments is important for disease eradication. Biological molecules with antimicrobial properties represent a promising alternative to combat pathogens. Bovine lactoferrin (bLF) is a key component of the innate host defense system, and its peptides have exhibited strong antimicrobial activity. Based on these properties, we evaluated the parasiticidal activity of these peptides on *G. intestinalis*. Trophozoites were incubated with different peptide concentrations for different periods of time, and the growth or viability was determined by carboxyfluorescein-succinimidyl-diacetate-ester (CFDA) and propidium iodide (PI) staining. Endocytosis of peptides was investigated by confocal microscopy, damage was analyzed by transmission and scanning electron microscopy, and the type of programmed cell death was analyzed by flow cytometry. Our results showed that the LF peptides had giardicidal activity. The LF peptides interacted with *G. intestinalis* and exposure to LF peptides correlated with an increase in the granularity and vacuolization of the cytoplasm. Additionally, the formation of pores, extensive membrane disruption, and programmed cell death was observed in trophozoites treated with LF peptides. Our results demonstrate that LF peptides exhibit potent in vitro anti-giardial activity.

KEYWORDS: *Giardia*; LF chimera; chimère LF; giardiase; giardiasis; lactoferrin; lactoferrin; parasiticidal; parasiticide; peptides

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Impact of *Lactobacillus reuteri* colonization on gut microbiota, inflammation, and crying time in infant colic.

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Infant colic is a distressing condition of unknown etiology. An aberrant gastrointestinal microbiota has been associated, and *Lactobacillus reuteri* supplementation has been shown to reduce crying and/or fussing time ('crying time') in some infants with colic. The relationship between *L. reuteri* gut colonization and crying time has not been examined. We investigated the relationship between *L. reuteri* colonization and fecal microbiota

(microbial diversity and *Escherichia coli*), intestinal inflammation, and crying time in infants with colic, using a subset of 65 infants from the Baby Biotics trial, which randomized healthy term infants aged <13 weeks with infant colic to receive probiotic *L. reuteri* DSM 17938 (1×10^8 colony forming units) or placebo daily for 28 days. We observed an overall reduction in median crying time, regardless of *L. reuteri* colonization status ($n = 14$ colonized). There were no differences in *E. coli* colonization rates or densities, microbial diversity or intestinal inflammation by *L. reuteri* colonization status. We found that *L. reuteri* density positively correlated with crying time, and *E. coli* density negatively correlated with microbial diversity. As density of *L. reuteri* was associated with increased crying time, *L. reuteri* supplementation may not be an appropriate treatment for all infants with colic.

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The impact of lactoferrin with different levels of metal saturation on the intestinal epithelial barrier function and mucosal inflammation.

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Translocation of bacteria, primarily Gram-negative pathogenic flora, from the intestinal lumen into the circulatory system leads to sepsis. In newborns, and especially very low birth weight infants, sepsis is a major cause of morbidity and mortality. The results of recently conducted clinical trials suggest that lactoferrin, an iron-binding protein that is abundant in mammalian colostrum and milk, may be an effective agent in preventing sepsis in newborns. However, despite numerous basic studies on lactoferrin, very little is known about how metal saturation of this protein affects a host's health. Therefore, the main objective of this study was to elucidate how iron-depleted, iron-saturated, and manganese-saturated forms of lactoferrin regulate intestinal barrier function via interactions with epithelial cells and macrophages. For these studies, a human intestinal epithelial cell line, Caco-2, was used. In this model, none of the tested lactoferrin forms induced higher levels of apoptosis or necrosis. There was also no change in the production of tight junction proteins regardless of lactoferrin metal saturation status. None of the tested forms induced a pro-inflammatory response in Caco-2 cells or in macrophages either. However, the various lactoferrin forms did effectively inhibit the pro-inflammatory response in macrophages that were activated with lipopolysaccharide with the most potent effect observed for apolactoferrin. Lactoferrin that was not bound to its cognate receptor was able to bind and neutralize lipopolysaccharide. Lactoferrin was also able to neutralize microbial-derived antigens, thereby potentially reducing their pro-inflammatory effect. Therefore, we hypothesize that lactoferrin supplementation is a relevant strategy for preventing sepsis.

KEYWORDS: Bacterial translocation; Iron; Lactoferrin; Manganese; Sepsis

Micro Integral Membrane Protein (MIMP), a Newly Discovered Anti-Inflammatory Protein of *Lactobacillus Plantarum*, Enhances the Gut Barrier and Modulates Microbiota and Inflammatory Cytokines

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Immunomodulatory Effects of *Lactobacillus plantarum* Lp62 on Intestinal Epithelial and Mononuclear Cells.

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Probiotic lactic acid bacteria are known for their ability to modulate the immune system. They have been shown to inhibit inflammation in experiments with animal models, cell culture, and clinical trials. The objective of this study was to elucidate the anti-inflammatory potential of *Lactobacillus plantarum* Lp62, isolated from cocoa fermentation, in a cell culture model. Lp62 inhibited IL-8 production by *Salmonella* Typhi-stimulated HT-29 cells and prevented the adhesion of pathogens to these epithelial cells. The probiotic strain was able to modulate TNF- α , IL1- β , and IL-17 secretion by J774 macrophages. J774 activation was reduced by coincubation with Lp62. PBMC culture showed significantly higher levels of CD4(+)CD25(+) T lymphocytes following treatment with Lp62. Probiotics also induced increased IL-10 secretion by mononuclear cells. *L. plantarum* Lp62 was able to inhibit inflammatory stimulation in epithelial cells and macrophages and activated a tolerogenic profile in mononuclear cells of healthy donors. These results indicate this strain for a possible application in the treatment or prevention of inflammatory diseases.

Antiviral activity of *Lactobacillus reuteri* Protectis against Coxsackievirus A and Enterovirus 71 infection in human skeletal muscle and colon cell lines

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Antiviral activity of *Lactobacillus reuteri* Protectis against Coxsackievirus A and Enterovirus 71 infection in human skeletal muscle and colon cell lines.

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BACKGROUND: Recurrence of hand, foot and mouth disease (HFMD) pandemics continues to threaten public health. Despite increasing awareness and efforts, effective vaccine and drug treatment have yet to be available. Probiotics have gained recognition in the field of healthcare worldwide, and have been extensively prescribed to babies and young children to relieve gastrointestinal (GI) disturbances and diseases, associated or not with microbial infections. Since the faecal-oral axis represents the major route of HFMD transmission, transient persistence of probiotic bacteria in the GI tract may confer some protection against HFMD and limit transmission among children.

METHODS: In this work, the antiviral activity of two commercially available probiotics, namely *Lactobacillus reuteri* Protectis (*L. reuteri*Protectis) and *Lactobacillus casei* Shirota (*L. casei* Shirota), was assayed against Coxsackieviruses and Enterovirus 71 (EV71), the main agents responsible for HFMD. In vitro infection set-ups using human skeletal muscle and colon cell lines were designed to assess the antiviral effect of the probiotic bacteria during entry and post-entry steps of the infection cycle.

RESULTS: Our findings indicate that *L. reuteri* Protectis displays a significant dose-dependent antiviral activity against Coxsackievirus type A (CA) strain 6 (CA6), CA16 and EV71, but not against Coxsackievirus type B strain 2. Our data support that the antiviral effect is likely achieved through direct physical interaction between

bacteria and virus particles, which impairs virus entry into its mammalian host cell. In contrast, no significant antiviral effect was observed with *L. casei* Shirota.

CONCLUSIONS: Should the antiviral activity of *L. reuteri* Protectis observed in vitro be translated in vivo, such probiotics-based therapeutic approach may have the potential to address the urgent need for a safe and effective means to protect against HFMD and limit its transmission among children.

KEYWORDS: Coxsackievirus; Enterovirus 71; Foot and mouth disease; Hand; ***Lactobacillus reuteri***; Probiotics