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Lactobacillus reuteri DSM 17938: Review of Evidence in Functional Gastrointestinal Disorders

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Abstract

Lactobacillus reuteri DSM 17938 has been one of the most extensively studied probiotic in children and adults with functional gastrointestinal disorders. In order to gather evidence on the efficacy of *Lactobacillus reuteri* DSM 17938 for treating and preventing some of these disorders. MEDLINE and the Cochrane Library were searched till February 2018 for relevant randomized controlled trials, retrospective studies, and meta-analyses with no language restrictions. The recent probiotic literature strongly suggests that *Lactobacillus reuteri* may be effective in the prevention and treatment of certain clinical conditions, such as infantile colic, infantile regurgitation, functional constipation, functional abdominal pain, and necrotizing enterocolitis. No safety concerns with regard to the use of *Lactobacillus reuteri* in non-immunocompromised subjects were identified. A recent meta-analysis also supports the safety of using *Lactobacillus reuteri* even in preterm infants. This review presents the history of *Lactobacillus reuteri* DSM 17938 and the evidence base for its application in the health and disease.

Keywords: *Lactobacillus reuteri* DSM 17938; Probiotic; Infantile colic; Functional abdominal Pain; Functional constipation; Infantile regurgitation

Introduction

The human microbiota, a complex collection of commensal microbes, is superior to the whole human body in number as well as in genetic and metabolic diversity [1]. This human microbiota especially the gut microbiota (comprises more than 90% of all commensals) have profound effects in the development and maintenance of their body systems, including metabolism, immune regulation, and neuronal function [2]. Dysbiosis, disruption of the symbiosis between the gut microbiota and host, has been associated with inflammatory bowel disease, obesity, diabetes, metabolic syndrome, colon cancer, and other autoimmune diseases as well as even depression and neurodevelopment disorders [3]. Intriguingly, the probiotic administration has shown to reduce these health problems and their symptoms suggesting a significant role and great potential of probiotic applications in curing the disease, in part by rebalancing the gut microbial composition [4]. However, it is well known that every probiotic strain is distinct in its characteristics, properties, and effect. And, so each strain has to be evaluated separately for its mechanisms of action, efficacy, and safety.

Lactic acid-producing bacteria, including several Lactobacillus species, have perhaps been the most extensively studied probiotic agents in children and adults. Research on Lactobacilli has increased dramatically over the past two decades as can be seen from the fact that compared to 180 research articles published during 1980-2000, more than 8300 research articles were published during 2000-2018 on "probiotic Lactobacillus" ("Probiotic Lactobacillus" PubMed 2018) [5]. *Lactobacillus reuteri* (*L. reuteri*) is considered one of the true autochthonous species of the human gastrointestinal (GI) tract [6]. *L. reuteri* DSM 17938 has been shown to possess several characteristics like an excretion of the antimicrobial reuterin, lactic acid, and competitive exclusion by steric hindrance thereby contributing to its efficacy [6]. Their reported beneficial effects include amelioration of symptoms of lactose intolerance, improvement of intestinal health, and reduction of the risk of various other diseases including infantile colic, infantile regurgitation, functional constipation, necrotizing enterocolitis (NEC), and *Helicobacter pylori (H. pylori*) infection [7]. As a result, *L. reuteri* DSM 17938 is now available commercially, in 99 countries [8].

The goal of this review is to provide clinicians with an overview of the rationale and data which support or refute the role of probiotics *L. reuteri* DSM 17938 for treating and preventing commonly encountered functional GI diseases in humans. The information provided is based on a review of primary literature from Randomized Controlled Trials (RCTs), observational studies, meta-analyses, expert consensus panel recommendations, and academic society-based practice recommendations. References are provided for more in-depth reading and tables or figures summarize key information.

Search methodology

MEDLINE and the Cochrane Library search was conducted in February 2018 with no language restrictions, for relevant randomized controlled trials, observational studies, and meta-analyses to identify the scientific research that has been conducted up to that date with the *L. reuteri* DSM 17938 and to evaluate therapeutic efficacy.

L. reuteri DSM 17938: History of evolution

L. reuteri was named after the German microbiologist who discovered it, Gerhard Reuter [9]. Among a number of *L. reuteri* strains, *L. reuteri* DSM 17938, a strain of plasmid-cured ATCC 55730

from Peruvian mother's milk, is probably the best studied and most effective strain, normally present in corpus and antrum of the stomach, duodenum, and ileum of humans [9,10]. One study showed the similarity between these two strains in characteristics of temporary colonization [11]. Another in vitro study documented no differences between the strains with regard to the colony and cell morphology, chromosomal genes, mucin binding, fermentation pattern, and reuterin production [10].

Mechanisms of action

Adhesion of a probiotic strain to the host gastrointestinal tract (GIT) is important for colonization, interaction with host cells, inhibition of pathogen growth, and protection of epithelial cells or immune modulation [12]. Several studies have demonstrated *L. reuteri* capacity to colonize, and their ability to adhere to mucin and intestinal epithelial cells [13-16]. The possible mechanism involved in adhesion has been linked to surface protein [15], mucus-binding protein [17], exopolysaccharide [18], inulosucrase [19], D-alanyl-LTA [20], and glucosyltransferase A. Mechanism of action of *L. reuteri* DSM 17938 has been studied extensively as shown in Figure 1.

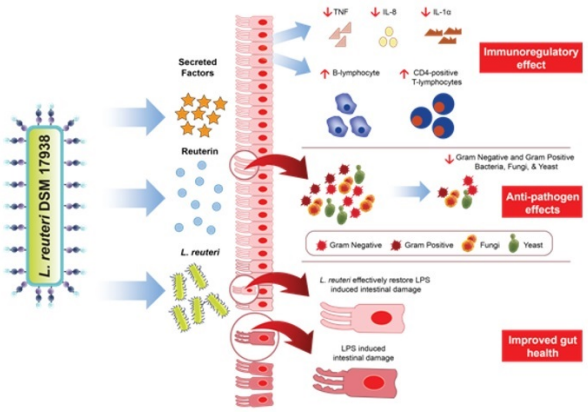

Figure 1: Mechanism of *L. reuteri* DSM 17938 (*L. reuteri*-*Lactobacillus reuteri*; TNF- Tumor necrosis factor; IL- Interleukin; LPS- Lipopolysaccharide).

Antimicrobial action

L. reuteri's antimicrobial activity is one of the best-documented probiotic pathogen- inhibiting mechanisms. *L. reuteri* produce a variety of antimicrobial substances such as hydrogen peroxide [21], lactic acid, reuterin [22-24], and reutericyclin [25]. These substances display inhibitory activity against both gram-positive and negative bacteria, yeast, fungi, as well as parasites [26].

Antioxidant effect

L. reuteri has also been reported to prevent oxidative damage caused by free radical [27].

Anti-inflammatory effect

L. reuteri strains may exert immunoregulatory effects in the human gut through controlling lipopolysaccharide (LPS)-induced TNF-α and intestinal damage [28,29]. An anti-inflammatory action of *L. reuteri* has been shown by in vivo animal studies demonstrating reduction of intestinal mucosal levels of pro-inflammatory cytokines (interleukin-8 (IL-8), IL-1α, interferon-α, TNF-α) in newborn rats with LPS-induced small intestinal and ileum inflammation [29]. *L. reuteri* DSM 17938 also inhibits a Toll-like receptor-4 signaling pathway thereby blocking cytokine expression, as has been shown in an experimental model of NEC [30].

Since 1994, about a dozen case-control studies have found differences in gut microflora among colicky and healthy infants. Studies have indicated infants with colic to be less frequently colonized by Lactobacillus species and more frequently by gram-negative organisms like Escherichia than those without colic [31-36]. In 2017, a study by Pratty et al suggested low-grade systemic inflammation among colicky infants, indicated by increased levels of cytokines [IL-8], chemokines monocyte chemotactic protein and macrophage inflammatory protein 1beta) [37]. The underlying mechanisms of altered gut microbiota in the colicky infant are not yet resolved but a possible pathway is through gut inflammation. *L. reuteri* may play a role in infant colic by altering gut microbiota, reducing gut inflammation and thereby reduce crying [38]. Few *In-vivo* human studies have demonstrated a significant reduction in crying time and fecal calprotectin level among colicky infants after treatment with *L. reuteri* DSM 17938 [39,40]. This treatment also increased FOXP3 concentration, resulting in a decreased RORg/FOXP3 ratio [40].

Down-regulation of pain

L. reuteri DSM 17938 strain has also been shown to act as a visceral anti-nociceptive agent through the antagonism of Transient Receptor Potential Vanilloid 1 (TRPV1) channel and also influences the activity of calcium channel intermediate conductance in enteric neurons [41].

Effect on gut motility

Microbiota has shown to control or influence gut motility complexes in mice models [42]. The bacterial flora influences intestinal motility by anaerobic fermentation of carbohydrates and proteins. In humans, the final products of this process are mainly Short-Chain Fatty Acids (SCFA), acetate, propionate, butyrate and, in a minor amount, H_2, CO_2, ammonia, and amines. The activity of these SCFA on the smooth muscle contributes to the normal gut function [43,44]. Wu et al. showed that *L. reuteri* increased both colonic myoelectric motility complex frequency and velocity. In addition, it also stimulates the production of SCFA that modifies gut motility [45].

Taken together, the above data shows that *L. reuteri* strains act through diverse mechanisms by inducing colonization, maintaining functional mucosal barrier and immunomodulation, exerting anti-inflammatory action, secreting antimicrobial substances and down-regulating pain as well as by stabilizing gut microbiota [7,46-48].

Health benefits of *L. reuteri* DSM 17938

There are evidence favoring beneficial effects attributed to *L. reuteri* DSM 17938, including improvement of intestinal health, enhancement of the immune response and possible role in the reduction of serum cholesterol, and cancer prevention [49]. While some of the health benefits are well-documented others require additional studies in order to be established. In fact, there is substantial evidence to support *L. reuteri* DSM 17938 used in the treatment of infantile colic, infantile regurgitations, functional abdominal pain and functional constipation,

and emerging evidence in the improvement of lactose metabolism, *H. pylori* infection and NEC.

Management of infantile colic

Colic is a highly distressing condition for infants along with their parents, which requires immediate medical consultation and therapy. Studies have suggested that the presence of gut dysbiosis among colicky infants may alter gut motor functions and production of gas, causing abdominal pain. Data from RCTs indicate that probiotics with *L. reuteri* are effective in the treatment of infantile colic [50,51] as shown in table 1 [50,52-55].

Author	Study detail	Treatment	Outcomes
Sung et al., (Individual patient data meta-analysis) [54]	Four trials involving 345 colicky infants	174 infants were treated with probiotic and 171 with placebo	*L. reuteri* DSM 17938 administration was associated with reduced crying time on day 21 (MD-25.4 min/day, 95% CI-47.3 to -3.5) as compared to placebo. Intervention effects were dramatic in exclusively or predominantly breastfed infants
Castrellón et al., (Meta-analysis) [52]	A total of 32 studies published between 1960 and 2015 involving 2242 colicky infants	Studies with *L. reuteri* DSM 17938 vs. Control, Diet vs. Control, drugs vs control, herbal vs control, manipulative vs control, massage vs control, reassurance/education vs control and Acupuncture vs. Control was included in the meta-analysis	L. reuteri DSM 17938 [WMD -51.3h (CI 95% -72.2 to -30.5h), p=0.0001] was superior to other treatments for infantile colic
Harb et al., (Meta-analysis) [50]	Six studies involving mothers and their colicky infants younger than 6 months	Studies with *L. reuteri* DSM 17938 vs. Control was the most important	*L. reuteri* DSM 17938 administration was associated with reduced crying time on day 21 (MD -55.8 min/day, 95% CI -64.4 to -47.3; p=0.001)
Szajewska et al., (RCT) [55]	80 exclusively or predominantly (>50%) breastfed colicky infants aged <5 months	Infants were randomly assigned to receive *L. reuteri* DSM 17938 or placebo for 21 days	Compared with the placebo group, in the *L. reuteri* DSM 17938 group, treatment success was significantly higher at day 7 (P=0.026), at day 14 (RR 4.3, 95% CI 2.3 to 8.7), at day 21 (RR 2.7, 95% CI 1.85 to 4.1), and at day 28 (RR 1.6, 95% CI 1.3 to 2.1)
Savino et al., (RCT) [53]	50 exclusively breastfed colicky infants	Infants were randomly assigned to receive *L. reuteri* DSM 17938 or placebo for 21 days	The daily crying time was significantly less in *L. reuteri* DSM 17938 group as compared to the placebo group at day 21 (90 vs. 35 min/day respectively; P=0.022). An earlier study in 2007 by Savino et al. have even found significant improvement within 1 week of treatment, compared with simethicone

L. reuteri- Lactobacillus reuteri; RCT- Randomized Controlled Trial; MD- Mean Difference; CI- Confidence Interval; RR- Relative Risk; WMD- Weighted Mean Difference

Table 1: Studies supporting the role of *L. reuteri* for the treatment of infantile colic.

In conclusion, *L. reuteri* DSM17938 is effective and can be recommended for infants with infantile colic, especially in exclusively or predominantly breastfed infants. Its role in formula-fed infants with colic needs further research.

Functional abdominal pain

In one RCT [56], a total of 55 children (age 4-18 years) were randomly assigned to receive *L. reuteri* DSM 17938, 108 Colony Forming Units (CFU) daily or placebo for 12 weeks and patients were also followed 4 weeks after intervention. Compared to placebo, the children administrating *L. reuteri* DSM 17938 had significantly more days without pain (median 89.5 vs. 51 days, P=0.029). Moreover, compared to placebo, abdominal pain was less severe in children administrating *L. reuteri* DSM 17938 during the second month (P<0.05) and fourth month (P<0.01).

Weizman conducted a randomized double-blind, placebo-controlled trial examining the effect of the *L. reuteri* DSM 17938 in Functional Abdominal Pain (FAP) of childhood. The results showed that *L. reuteri* DSM 17938 (n=47) was significantly superior to placebo (n=46) in relieving frequency (1.9 ± 0.8 vs. 3.6 ± 1.7 episodes/wk, P<0 . 02) and intensity (4.3 ± 2.2 vs. 7.2 ± 3.1 Hicks score/wk, P<0.01) of abdominal pain following 4 weeks of supplementation. While no difference was seen in school absenteeism rate or other GI symptoms, except for a lower incidence of bloating and perceived abdominal distension, favoring *L. reuteri* DSM 17938 [57].

In an RCT by Romano et al, Sixty patients were randomized to receive either oral supplementation with *L. reuteri* DSM 17938, 108 CFU (n=32) or matching placebo (n=28), twice daily for 4 weeks. The *L. reuteri*-supplemented children had significantly lower pain intensity at both 4 weeks and 8 weeks compared with placebo. Though there was no significant difference between the groups at any of the time points in the frequency of episodes of pain, in both groups of children, there was a significant reduction in the frequency with time [58].

In 2014, a systematic review and meta-analysis conducted on *L. reuteri* DSM 17938 reported a significant reduction in the intensity of abdominal pain and its long-lasting persistence even after the removal of the probiotic [59]. In conclusion, this high-quality evidence suggests *L. reuteri* DSM 17938 strain to be effective in FAP.

Regurgitation in infants with gastroesophageal reflux

Indrio et al. in double-blind RCT investigated the effects of a formula containing partially hydrolyzed, 100% whey protein, starch

and *L. reuteri* DSM 17938 on the gastric emptying rate and regurgitation frequency in 72 infants with functional regurgitation. The results showed greater percentage changes in gastric emptying rate (12.3% vs. 9.1%, p<0.01). Mean daily regurgitations decreased from 7.4 (0.8) to 2.6 (1.0) in the *L. reuteri* DSM 17938 group and from 7.5 (1.0) to 5.3 (1.0) in controls at week 0 and week 4 respectively (p<0.0001) [60].

Garofoli et al. conducted a double-blind RCT examining the effect of the *L. reuteri* DSM 17938 in infantile regurgitation. Forty breastfed full-term infants were randomly assigned to receive orally *L. reuteri* DSM 17938, 5 drops/daily (108 CFU), for 4 weeks. Treated infants demonstrated a significant reduction in regurgitation rates at the end of treatment (p=0.02), Therefore, early administration of *L. reuteri* DSM 17938 controls regurgitation episodes in infants during their first month of life [61].

Another double-blind RCT showed that compared to placebo (n=15), *L. reuteri* DSM 17938 (n=19), significantly reduced the median number of daily regurgitation episodes at day 30 in formula-fed infants [4.0 (3.0 to 5.0) vs. 1.0 (1.0 to 2.0), respectively; P<0.001]. Moreover, *L. reuteri* DSM 17938 also significantly reduced median fasting antral area and increased gastric emptying rate in infants with regurgitation as compared to the placebo group at the end of the intervention period [62].

Indrio et al. conducted a large multi-centric RCT to evaluate the effectiveness of *L. reuteri* DSM 17938 in functional gastrointestinal disorders (FGIDs). In this study, a total of 554 healthy breastfed or formula-fed term-born infants (aged <1 week) were randomly assigned to receive *L. reuteri* DSM 17938 or placebo for 90 days. *L. reuteri* DSM 17938 resulted in a significant reduction in crying time at 30 days (96 vs. 45 min/day, respectively; P<0.01) and at 90 days (71 vs. 38 min/day, respectively, P<0.01), in comparison to placebo. It also significantly reduced the episodes of daily regurgitation at day 90 (4.6 vs. 2.9, respectively; P<0.01), and increased the number of daily evacuations at day 30 (2.8 vs. 4.01, respectively; P<0.01) and at day 90 (3.6 vs. 4.2, respectively; P<0.01). Results from this study validate the prophylactic use of *L. reuteri* DSM 17938 in the prevention of infantile colic, regurgitation and functional constipation [63].

In conclusion, available evidence suggests that *L. reuteri* DSM 17938 improves gastric motility in infants with gastroesophageal reflux, thereby decreasing regurgitation episodes.

Functional constipation

Recently Riezzo et al conducted a randomized double-blind placebo controlled trial to investigate the effects of a long-lasting administration of *L. reuteri* DSM 17938 on symptoms and quality of life (QoL) score in patients with functional constipation. Herein, *L. reuteri* DSM 17938 was administered for 105 days in this trial (28 patients per arm). Compared to placebo, the beneficial effect of *L. reuteri* DSM 17938 was significantly evident for symptoms related to gas content and dysbiosis, incomplete defecation and helps for defecation (P<0.05) [64].

A retrospective study conducted by Ojetti et al in showed that four weeks of *L. reuteri* administration was associated with a significant decrease of mean methane production determined by Lactose Breath Test (LBT) (from 20.8 ± 15 to 8.9 ± 8.6; p<0.0001 [Confidence interval] CI 95%) and area under the curve (AUC) value (from 5101.5 ± 3571.13 to 2128.4 ± 2110.8; p<0.0001 CI 95%). This study highlights the beneficial effect of *L. reuteri* DSM 17938 on chronic constipation, via a significant decrease of methane production [65].

Another double-blind RCT published in 2014 involving 40 adult patients with symptoms of functional constipation (18M/22F, 35+/-15 years) suggested that *L. reuteri* significantly increased mean bowel movements/week as compared to placebo group at week 4 [2.6 (Standard deviation [SD] +/-1.14, 95% CI:1.6-3.6) vs. 1.0 (SD+/-1. 95% CI:0.12-1.88)]. At the end of treatment, the mean bowel movements/week was 5.28+/-1.93 and 3.89+/-1.79 in the *L. reuteri* and placebo group respectively [66].

Coccorullo et al., conducted an RCT involving 44 infants (aged ≥6 months) with functional constipation according to the Rome III criteria. Infants were allocated to receive *L. reuteri* DSM 17938 or placebo for 8 weeks. Infants in the *L. reuteri* group had a significantly higher frequency of bowel movements at week 2 (P=0.042), week 4 (P=0.008), and week 8 (P=0.027) in comparison to the placebo group, No statistically significant difference in stool consistency or inconsolable crying episodes was observed between the study groups throughout the study period. Considering the small sample size and unclear allocation concealment in this study, more confirmatory studies are needed to recommend the routine use of *L. reuteri* DSM 17938 in infants with constipation [67].

Reduction of feeding intolerance in preterm infants and necrotizing enterocolitis

Evidence from a large number of studies suggests that *L. reuteri* DSM 17938 supplementation may reduce the feeding intolerance in preterm infants. In one RCT study of 750 preterm infants with *L. reuteri* DSM 17938 intervention, a significant reduction in feeding intolerance (P=0.04) and duration of hospitalization (P=0.03) was found especially among a subgroup of premature infants ≤1,500 g [68]. Similarly, in 2014, a large placebo-controlled study involving 424 preterm infants also demonstrated significant reductions in the rate of feeding intolerance (P=0.015), the risk of proven sepsis (P=0.041) and duration of hospital stay (P=0.022) with *L. reuteri* DSM 17938 [69]. A meta-analysis was performed in 2015 to assess the effect of *L. reuteri* in preterm neonates showed a significant reduction in time to full feeds (MD, -1.34 days; 95% CI, -1.81 to -0.86; 2 RCTs), Late-Onset Sepsis (LOS) (RR, 0.66; 95% CI, 0.52 to 0.83; 4 RCTs), and duration of hospitalization (-10.77 days; 95% CI, -13.67 to -7.86; 3 RCTs) [70].

A recent study from Italy, evaluating the prophylactic use of *L. reuteri* DSM 17938 in preterm infants, has also shown improvement in feeding tolerance with clinical effects on growth, hospitalization, and antibiotic treatment [60].

The limited data show that *L. reuteri* supplementation has the potential to reduce the risk of NEC and late-onset sepsis while facilitating enteric nutrition in preterm infants. Larger definitive RCTs are needed to confirm these findings.

Guidelines and recommendations for use of *L. reuteri* DSM 17938 in GIT disorders

Increasing awareness towards the importance of these functional disorders has led to recent publications of consensus statements and international guidelines towards the appropriate management of these conditions. Both World Gastroenterology Organisation (WGO) and Latin-American Experts recommend *L. reuteri* DSM 17938 as level 1 evidence in the management of infantile colic. The recently published

Asia-Pacific region-specific recommendations for probiotics recommend *L. reuteri* DSM 17938 in the treatment of infantile colic. In addition, American Academy of Family Physicians has given grade B recommendation for the use of probiotic *L. reuteri* DSM 17938 in breastfeeding infants with colic.

WGO also recommends *L.reuteri* DSM 17938 as level 1 evidence for the management of abdominal pain-related functional gastrointestinal disorders.

Research and future treatment options

Currently, various placebo-controlled RCTs involving *L. reuteri* DSM 17938 are being conducted for a better understanding of their molecular mechanisms as well as for investigating their effect with (antibiotics, vitamin D and vitamin D plus sunflower oil) or without combination in the prevention and treatment of several functional GI disorders'. In addition, *L. reuteri* DSM 17938 is also being investigated in various formulation forms including lozenges, capsules and chewing gum to specific target populations such as infants, elderly, athletes and immunocompromised patients as some of these are shown in table 2 [71-76].

Clinical trial number	Title	Estimated enrollment	Arms	Primary outcome
NCT02871908 [81]	*L. reuteri* DSM 17938 in the Prevention of Antibiotic-associated Diarrhea in Children: Protocol of a Randomized Controlled Trial	250	*L. reuteri* DSM 17938 vs. Placebo	Frequencies of diarrhea and AAD [Time Frame: during antibiotic treatment, an average of 10 days and 7 days of follow up]
NCT02693028 [76]	*L. reuteri* feasibility study on probiotic treatment and perinatal microbiome	30	Drug: Probiotic lozenges Drug: Placebo lozenges Drug: Probiotic capsules Drug: Placebo capsules Drug: Probiotic chewing gum	Presence of *L. reuteri* in different compartments in the mother and the Child. [Time Frame: Mother: From weeks 28-36 of pregnancy until 6 weeks post-partum. Child: from birth till 4 years old.]
NCT02765217 [77]	Effect of *L. reuteri* DSM 17938 to Prevent Antibiotic-associated Diarrhea in Children (PEARL)	1440	*L. reuteri* DSM 17938 vs. Amoxicillin-Clavulanic Acid Placebo vs. Amoxicillin-Clavulanic Acid	The incidence of AAD [Time Frame: 8 week time period after the 1st day of antibiotic use]
NCT00893711 [78]	*L. reuteri* DSM 17938 Vs. Placebo in the treatment and prevention of Infantile Colic	155	*L. reuteri* 17938 vs. Placebo *L. reuteri* 17938+Vitamin D3 drops vs. Vitamin D3 drops	Reduction of the daily average crying time from baseline to the end of the treatment period, to less than 3 hours a day, the cut-off proposed by Wessel and number of responders versus non-responders in each group at the end of the treatment [Time Frame: time 0-7-21-30 days]
NCT02945683 [79]	Effects of *L. reuteri reuteri* plus vitamin D3 in children with atopic dermatitis	88	*L. reuteri*+vitamin D3 drops +sunflower oil,+medium chain triglycerides+silicon dioxide vs. sunflower oil+ medium chain triglycerides +silicon dioxide	Scoring atopic dermatitis (SCORAD) improvement [Time Frame: 3 months]
NCT03360253 [80]	Clinical Trial of *L. reuteri* in Infantile Colic 2017	244	*L. reuteri* DSM 17938 in drops vs. Placebo	Crying time [Time Frame: 21 days] Maternal depression
AAD- Antibiotic-Associated Diarrhoea; PEARL- Prevent Antibiotic-Associated Diarrhea in Children				

Table 2: The ongoing trials of *L. reuteri* DSM 17938.

Treatment of GI disorders with *L. reuteri* DSM 17938: Authors viewpoint

FGIDs are a group of GI disorders that include various combinations of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities [77]. Infantile colic and regurgitation are among the most widely recognized FGIDs in developing countries like India. Over the past two decades, the proposed cause of FGIDs has evolved from a view of psychosocial disorders to one that involves multiple body systems and interactions [78].

Thus the increased prevalence of functional GI disorders necessitates immediate attention towards finding the best and safe treatment method; i.e having efficacy, least implementation challenges as well as lower cost. Dysbiosis of the gut microbiota is associated with the pathogenesis of these disorders. According to the "hygiene", "microflora" and "old friends" hypotheses, the increasing incidence of

GIT diseases linked to immune dysregulation in India may be explained by changes in early microbial exposure. The parasitic helminths and commensal microbial organisms co-evolved with the human immune system have been found to be vital in promoting normal immune development. Lack of exposure to these infectious agents, because of hygiene or other reasons, maybe architecting the increase in the above disorders. Healthy gut microbiota has also shown protection against autoimmune diseases in clinical studies [79]. Thus, it's now possible to monitor, prevent, or even cure human disease through regulating the human microbiota, suggesting the usefulness of probiotics in GI disorders. *L. reuteri* has the most extensive safety assessment record among any probiotic strain. The studies also indicated that *L. reuteri* is safe for human consumption, even in large amounts.

Conclusion

The beneficial effects of *L. reuteri* in humans have been related to multiple modes of action and appear to be strain specific. Studies in both pediatric and adults populations have reported a beneficial effect of *L. reuteri* DSM 17938 on functional gastrointestinal disorders like infantile colic, infantile regurgitation, functional abdominal pain and functional constipation. Unfortunately, from India, there is very limited data on *L. reuteri* DSM 17938. Although studies in infantile colic and other GI disorders have not identified adverse events to date, clinical studies should be designed to assess both the short and long-term impact of *L. reuteri* DSM 17938 on improving dysbiosis and overall health status in India.

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