

## Role of *L. reuteri* in Maintenance and Genesis of GI Issues

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### Gut Microbiota and its association with FGIDs

The first two years of life are an important part of this period, which is characterized by accelerated growth rate and development of several organs and systems. Several gastrointestinal discomfort signs and symptoms can be observed in infants, which may be linked to several anatomical and functional changes observed at this stage of life [1]. Therefore, a Functional Gastrointestinal Disorder (FGID) is a physiological outcome of altered microbiota, physiological and functional immaturity and other environmental factors including diet [7].

The occurrence of FGIDs is common in infancy, such as regurgitation, colic, functional constipation, functional diarrhea etc. Many of these symptoms may be transient and are attributed to physiological and functional immaturity, dysbiosis and/or are considered as part of the development of the gastrointestinal tract [6]. The gut microbiota is a key player in determining gut health and function. Alterations in the gut microbiota composition have been well described in several functional gastrointestinal disorders and are reviewed exhaustively by the Rome Working Team in Rome III criteria [2].

### *L. reuteri* – gut friendly bacteria

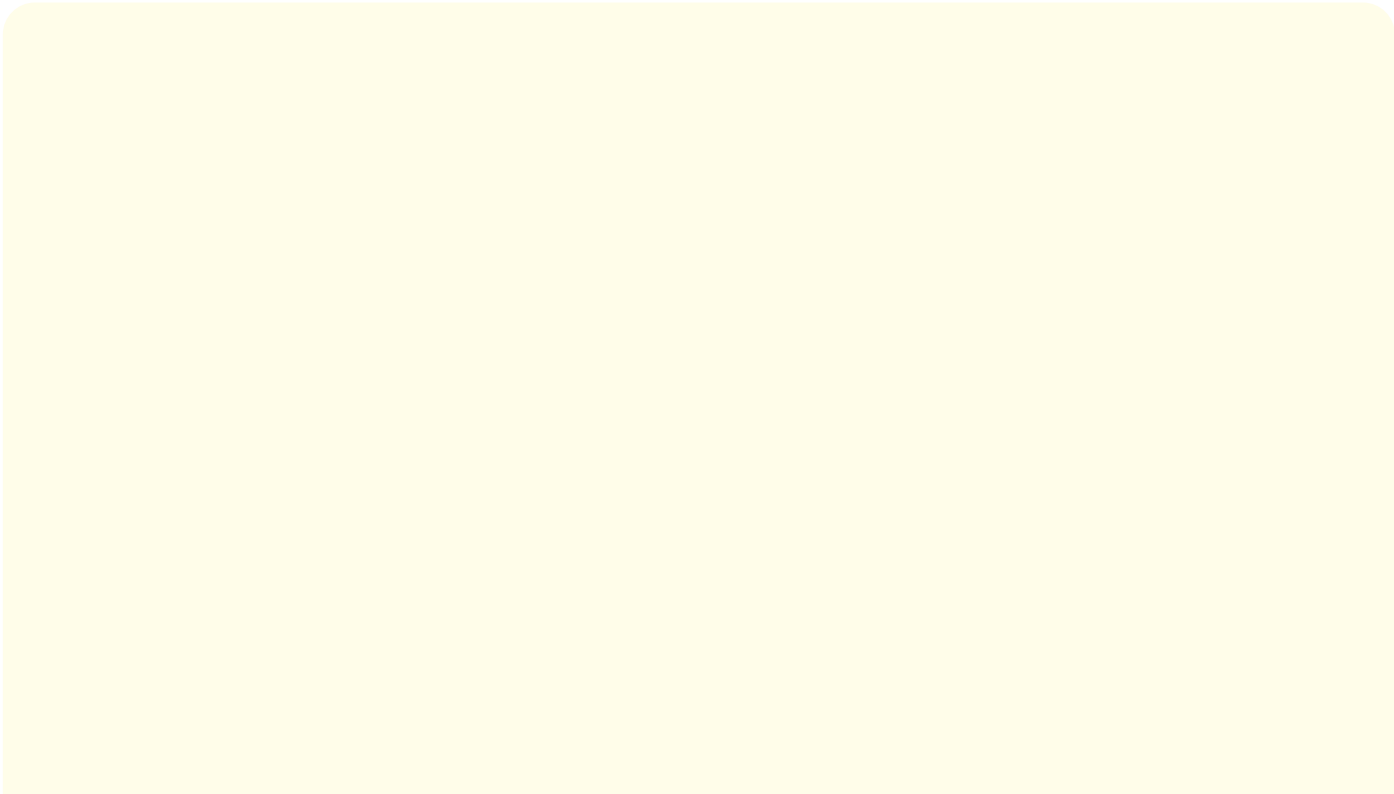
*L. reuteri* is found naturally in the breast milk, which is demonstrated to have probiotic properties [3].

Various studies have proved that *L. reuteri* improves the composition of the gut microbiota. As compared with placebo, *L. reuteri* promotes gut health through a reduction of *E. coli* colonization [5]. Therefore, breastfeeding becomes the way to ensure that an infant receives beneficial microbiota and optimal substrates for the growth of these bacteria [3].

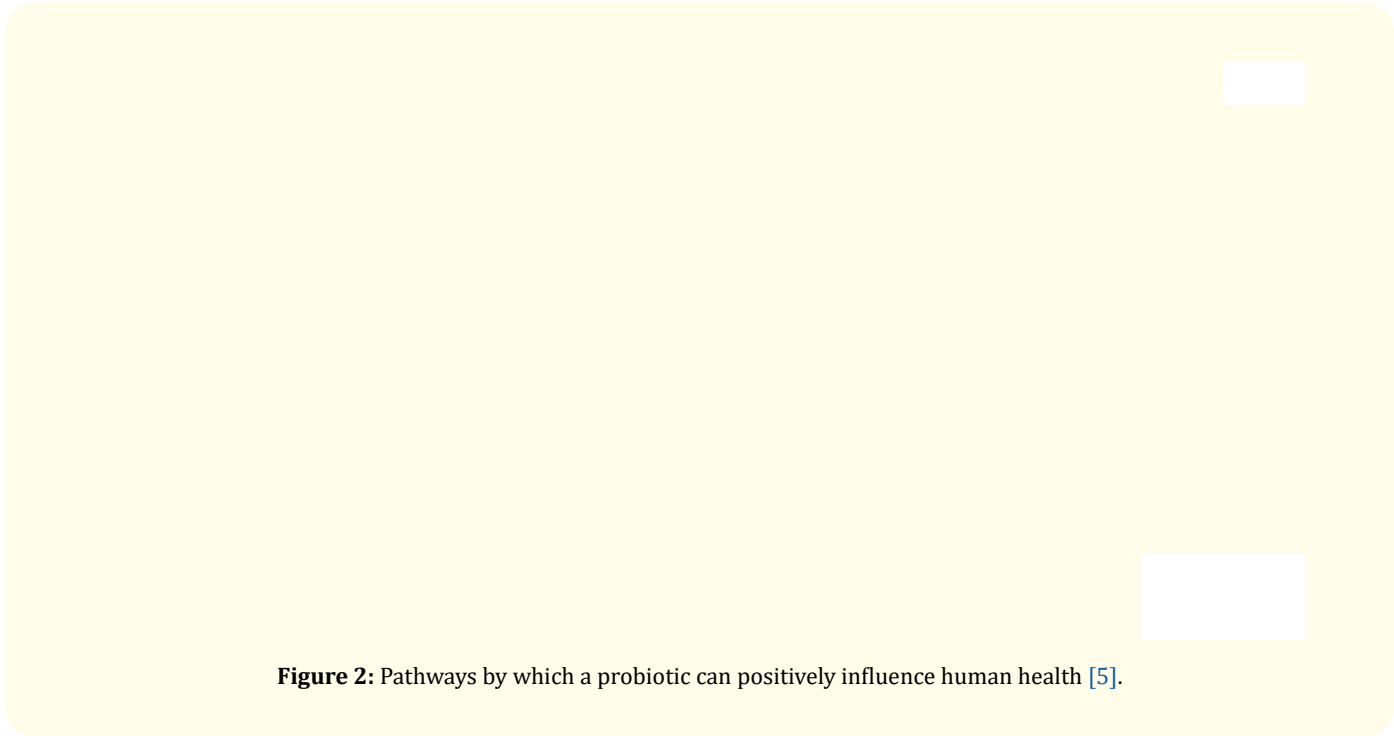
*L. reuteri* strains can positively influence human health as it produce reuttering, a broad-spectrum antibacterial substance, which is capable of inhibiting the growth of a wide spectrum of microorganisms such as Gram-positive or negative bacteria, yeast, fungi, or parasites [4]. It can also block pathogenic bacterial cells adhesion sites and allow the entry of entry of certain nutrients in gut lumen. It also facilitates the regulation of energy and modulation of the immune responses against antibodies [5] (Figure1).

Along with it, *L. reuteri* may be able to modulate the immune system in the gastrointestinal tract by stimulation of T-helper cells. This significant increase in T-helper cells may be a central mechanism of symbiosis for improving the health of the host gut and a key mechanism of action for this probiotic [6] (Figure2).

Clinical trials and a meta-analysis showed that *Lactobacillus reuteri* provides a reduction in daily crying time in patients with infantile colic. Also providing *Lactobacillus reuteri* in the diet can reduce the frequency of gastrointestinal symptoms like regurgitation, constipation and diarrhea in the first months of life [7-16].



**Figure 1:** Pathways by which a probiotic can positively influence human health [5].



**Figure 2:** Pathways by which a probiotic can positively influence human health [5].

Safety and Efficacy of *L. reuteri*

*Lactobacillus reuteri* is one of the few endogenous *Lactobacillus* species in the human gastrointestinal tract, which has been used safely for many years as a probiotic dietary supplement in adults, and recent data demonstrate the safety after long-term dietary supplementation for newborn infants [6].

*L. reuteri* DSM 17 938 at a dose of 108 colony-forming units per day in early breastfed infants improved symptoms of infantile colic and was well tolerated and safe [6] It is recognized safe by FDA's GRAS Notice Inventory Database pertaining to probiotic use in infant formula. "No adverse event reported for *Lactobacillus reuteri* DSM 17938 intended to use as an ingredient in term infant formula with an additional level of  $10^8$ -  $10^{10}$ CFU/d" [8].

Clinical evidences of *L. reuteri* helps in prevention and management FGIDs

Administration of *L. reuteri* has been proved to give various benefits in the management and prevention of gastrointestinal disorders like infantile colic, Functional Constipation, Diarrhea [10].

*L. reuteri* prevents FGIDs

A prospective, multicenter, double-masked, placebo-controlled randomized clinical trial suggest that oral supplementation with *Lactobacillus reuteri* DSM 17938 delivered at a dose of  $10^8$  CFU during the first 3 months of life can reduce the onset of colic, gastroesophageal reflux, and constipation in term newborns [10].

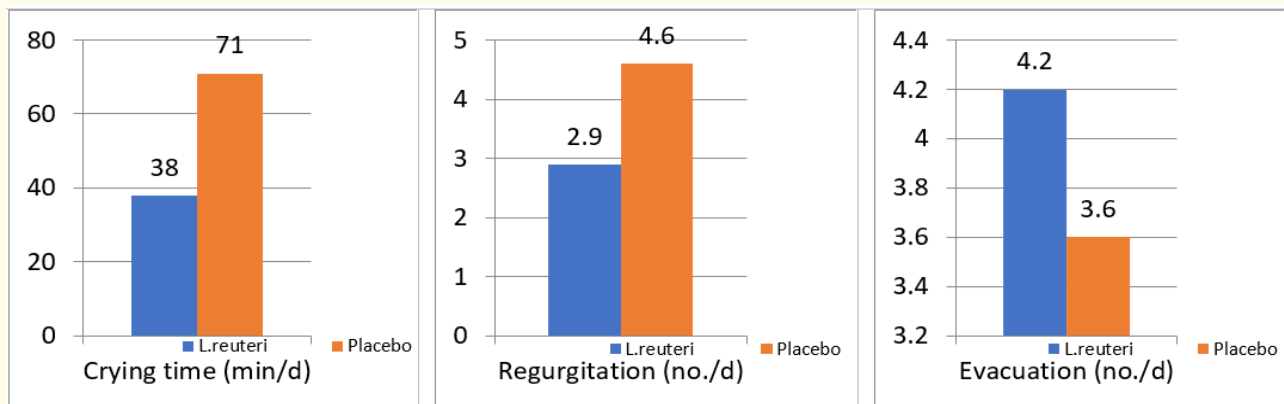


Figure 3: Impact of *L. reuteri* administration on regurgitation, colic and constipation.

*L. reuteri* for the management of colic

As many gastrointestinal disorders occur in infancy, which may be linked to several anatomical and functional changes observed in the first two years of life [9] Infantile colic is a common disturbance occurring in the first three months of life, which is a benign condition and one of the main causes of pediatric consultation because of its great impact on family life [10] Infantile colic occurs both in breastfed and formula fed infants equally.

Poor activity, swollen abdomen, excessive crying are the symptoms associated with colic. Gastroesophageal reflux, cow milk protein allergy can be some organic reasons for colic. Infected some suggest that swallowed air as a contributory factor but the colic pathophysiology is not well understood [7].

A randomized- double blind placebo control trial suggests that providing *L. reuteri* DSM 17938 to exclusively breastfed infants diagnosed with infantile colic proved superior to placebo in reducing daily crying and fussing times [11,12].

Figure 4: Proven to reduce 54% of crying time [11].

Figure 5

Multiple functional gastrointestinal disorders are more likely to be associated with affected quality of life leading to depression and irritation in mothers along with sleep issues, dietary issues and less comforting parent child relationship for both child and the mother than single functional gastrointestinal disorders [13]. Effective treatment of infantile colic with *L. reuteri* significantly improves quality of life for parents and families [13].

Figure 6: Impact of *L. reuteri* administration on family quality of life [13].

Figure 7: Response rate of *L. reuteri* vs Simethicone (most commonly prescribed medicine for infantile colic) [6].

Clinical evidences of *L. reuteri* helps in management of FGIDs other than colic

*L. reuteri* significantly reduces frequency of regurgitation

Functional gastroesophageal reflux (GER) is very common during infancy and most often manifests itself as episodes of regurgitation or vomiting. *Lactobacillus reuteri* administered to formula-fed preterm infants can results in a significantly increased gastric emptying rate and in a significant decrease in regurgitation [14].

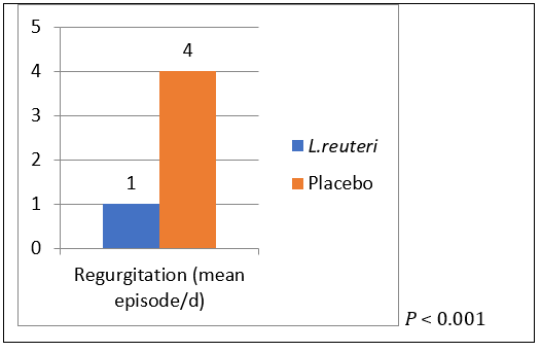


Figure 8: *L. reuteri* administration show a positive reduction in regurgitation [14].

Positive effect of *L. reuteri* in functional constipation

The administration of *L. reuteri* in infants with chronic constipation had a positive effect on bowel frequency. Evidence from a double-blind, randomized, placebo-controlled study conducted on 44 infants > 6 months old with chronic constipation (22 assigned randomly to treatment with *L. reuteri* (DSM 17938), and 22 assigned to receive a placebo) suggest that infants treated with *L. reuteri* had a significantly higher defecation frequency or bowl movements than infants in the placebo group at week 2 of treatment [15].

**Figure 9:** The frequency of bowel movements in the *L. reuteri* and placebo group [13].

### Therapeutic effect of *L. reuteri* on infant diarrhea

The therapeutic effect of *L. reuteri* on infant diarrhoea has also been supported by several studies. The frequency of watery diarrhoea per 24-h period was significantly reduced on the second day of intervention in *L. reuteri* group compared to placebo [16].

**Figure 10**

Administration of *L. reuteri* DSM 17938 significantly accelerates gastric emptying and ameliorated regurgitation in infants affected by non-complicated gastroesophageal reflux when used daily for 28 days with a dose of  $1 \times 10^8$  (CFU) [4].

Several studies have well documented the safety and tolerance of infant formulas containing probiotics. Moreover, the data from various studies suggest that infants receiving *L. reuteri* in a starter infant formula showed age appropriate growth up to 6 months of age. They also had more soft stools showing that infant formulas supplemented with probiotics *L. reuteri* are safe, well tolerated, and support normal infant growth in an Indian population.

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