

Review Article

# The Role of *Lactobacillus Reuteri* Probiotic for Preventing Functional Gastrointestinal Disorders in Toddlerhood

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## Abstract

Probiotic *Lactobacillus reuteri* has been shown to be useful for a number of gastrointestinal disorders. Its ability to secrete antimicrobial compounds, prevent pathogenic microorganisms from colonizing the host, and alter the composition of the commensal microbiota in the host are all major contributors to its therapeutic advantages. Not only that, but *L. reuteri* treatment strengthens the host's defenses against infection and pro-inflammatory cytokine production while enhancing the growth and functionality of regulatory T cells. Numerous pediatric illnesses, particularly those pertaining to the intestinal health of infants, have been found to be well managed by *L. reuteri*, according to systematic reviews and meta-analyses. According to current research on *L. reuteri*, it may be useful in the management and avoidance of a number of common clinical disorders, including functional constipation, infantile colic, regurgitation, and diarrhea. Probiotic treatment for pediatric illnesses has had favorable benefits on bowel regularity in individuals with chronic constipation and has been found to successfully reduce screaming and/or fussing time in newborns with colic. Additionally, it quickens the emptying of the stomach and lessens distension. Several research have even come to the conclusion that this probiotic strain reduces the frequency of regurgitation. The potential of this probiotic strain for application in the treatment of several gastrointestinal disorders is evident from all of these findings. Therefore, this study aims to encapsulate and condense the advantages of this probiotic strain in clinical settings, with a particular emphasis on how it supports babies' and toddlers' immune systems and gut health.

## Keywords

*Lactobacillus reuteri*, Probiotics, Gut Health, Immunomodulation, Infants, Functional Gastrointestinal Disorders, Functional Constipation, Infantile Colic

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## 1. Introduction

The human microbiota is a complex community of commensal bacteria that is larger than the human body overall in terms of both number and genetic and metabolic diversity. Human gut microbiota contains almost 90% of all commensals, which has a significant effect on the development and maintenance of the host's physiological systems, including metabolism, immune response, and brain function [1].

Since the gut microbiota coevolves with the host from birth along with its metabolic and neurological programs, the growth of this microbial community is crucial for maintaining health into old age. The symbiosis between the infant's gut microbiota and itself is formed over the first few years of life and is established from birth. The gut microbiota affects immune system development and prevents pathogen colonization in addition to metabolism and nutrition absorption [2]. Environmental variables including nutrition and lifestyle have a complicated interaction with the host that shapes the development of the gut microbiota [3]. Therefore, the dynamics of this community inside the host and any potential links it may have with disease risks can be illuminated by studying the gut microbiota from infancy to old age.

Remarkably, probiotic treatment has been demonstrated to reduce a wide range of health issues and their symptoms, suggesting a major role and increased potential for probiotic applications in the treatment of disease, in part through gut microbial composition balance [4]. Probiotics that produce lactic acid, such as various *Lactobacillus* species, have perhaps been the subject of the most research, both in infants and adults. Numerous gastrointestinal (GI) tract problems may be prevented and treated using lactobacilli, according to pre-clinical and animal research findings. It has been demonstrated that the *Lactobacillus reuteri* species has a number of advantageous impacts on host health [4, 5]. Since its first isolation in 1962, *L. reuteri* has been characterized as a heterofermentative species that grows in low-oxygen environments and colonizes animal and human gastrointestinal systems. Its tendency to colonize the GI tract may be the source of its potent probiotic properties. *L. reuteri* is present in the skin, gastrointestinal tract, urinary tract, and breast milk of humans, among other body parts [5]. It's interesting to note that a lot of clinical research has been done to look at *Lactobacillus reuteri*'s function in healthy people's intestines. These investigations have concentrated on the functions of the bacteria in controlling gut microbiota and mucosal homeostasis, in modulating the intestinal host immune system, and in lowering intestinal inflammation in pathological situations. This variety of actions demonstrates the dual functions *Lactobacillus reuteri* performs in improving gut health and human immunity [5].

## 2. Intestinal Microbial Colonization in Primitive Life

The gradual process of newborn gut colonization is influenced by dietary and environmental exposures, as well as maternal and genetic factors. These factors may have a greater impact than others. According to recent findings from clinical and experimental investigations, microorganisms found in the intrauterine environment may start colonizing the fetus's gut at any time [6, 7]. Despite being highly intriguing, these results require additional validation in sizable clinical trials with rigorous methodology to rule out.

The gut microbiota of infants and children progressively changes to match that of adults, and by the time they are two or three years old, it is believed to have stabilized and become more adult-like. One of the main factors influencing the maturation of the gut microbiota is the introduction of solid meals, and in particular, stopping nursing [8]. Nonetheless, it is important to highlight that the mature gut microbiota varies significantly depending on the region [9]. It is quite likely that eating behaviors have a greater role in explaining this occurrence than genetic variations do. Detrimental exposures, and the use of antibiotics in particular, can induce significant disruptions in gut microecology. Epidemiological studies indicating a link between early-life antibiotic exposure and chronic illnesses such as obesity, asthma, and inflammatory bowel disease highlight the possible therapeutic importance of these transient disruptions [10].

## 3. Role of *L. reuteri* in Functional Gastrointestinal Disorder (FGID)

Approximately one in two newborns have at least one Functional gastrointestinal disease (FGID) or associated signs and symptoms between the time of birth and six months of age. Although prevalence rates of functional gastrointestinal disorders in babies and toddlers vary greatly, they are frequent globally and include baby colic, regurgitation, functional diarrhea, and functional constipation [11]. For example, the prevalence rate of infant colic in the community has been reported to be between 5% and 25%, the prevalence rate of functional constipation in children 0-18 years old has been found to be between 0.5% and 32.3%, and the overall prevalence rate of any FGID in neonates and toddlers varies between 27.1% and 38.0% [12].

Because *L. reuteri* can withstand a wide range of pH environments, employ multiple mechanisms to effectively inhibit pathogenic microorganisms, and secrete antimicrobial intermediaries in addition to normally colonizing the GI tract, it has been shown to exhibit a number of beneficial effects, particularly on the host's gut health (Figure 1). The different probiotic effects of *Lactobacillus reuteri* on gut health are included in Figure 1 [5, 13].

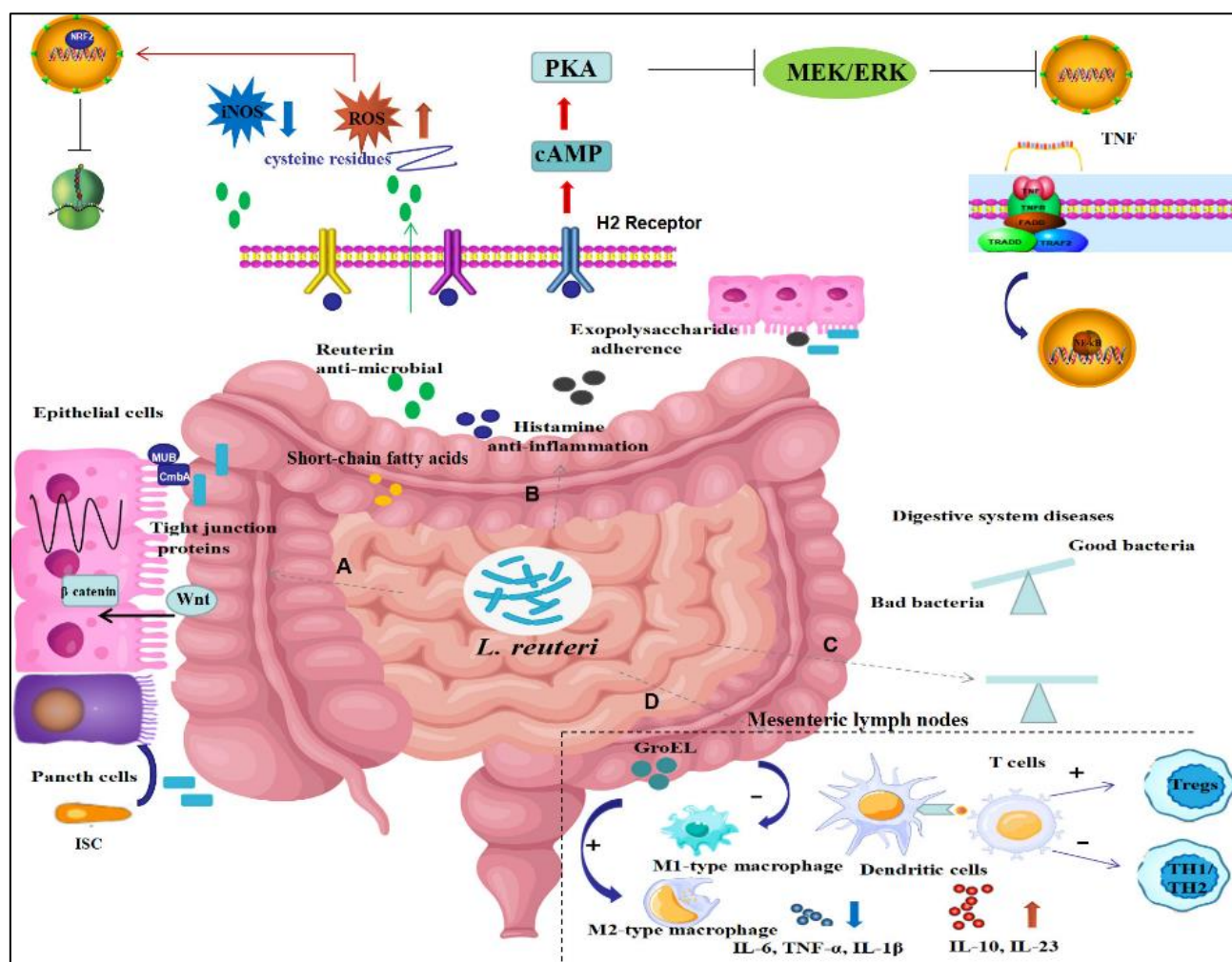


Figure 1. *L. reuteri* helps in the management of FGIDs [14].

## 4. Evidence Around the Function of *L. reuteri* in Managing of Pediatric Disorders

There are significant therapeutic and preventative opportunities due to the possible correlation between functional gastrointestinal disorders in children and disruptions in the gut microbiota. It is commonly known that *L. reuteri* inhibits calcium-dependent potassium channels in enteric neurons, which in turn affects gut motility, contractility, and pain perception [15, 16].

### 4.1. *L. reuteri* in Controlling Pediatric Functional Abdominal Pain Disorders

Numerous clinical observations suggest that dysbiosis is an IBS feature. First, in a considerable portion of IBS patients, symptoms are frequently preceded by gastroenteritis or an antibiotic course [17, 18]. Moreover, research has shown that the nonabsorbable antibiotic rifaximin is beneficial in the

treatment of adult patients with diarrhea-predominant IBS-D [19], although it was ineffective in the treatment of children who experienced chronic stomach pain [20]. Indeed, as was mentioned in [21] and above, alterations in the gut microbiota have been seen in both adults and children, supporting the therapeutic alteration of the gut microbiota in this patient group.

In the field, *Lactobacillus reuteri* DSM 17938 has been the most extensively researched probiotic. Five randomized clinical trials including children with FAP or IBS have examined its impact. In the initial investigation, 60 children were given either *Lactobacillus reuteri* or a placebo by Romana et al. [22]. While all groups had a comparable substantial reduction in pain frequency, only the probiotic group showed a significant reduction in pain severity. Nevertheless, the interpretation of the results was restricted because all of these data were only presented visually and not numerically [23].

In 80 children with FAP, Eftekhari et al. [23] could not find any significant differences in pain severity between the probiotic and placebo groups, despite a comparable large decrease among the groups as compared to the baseline. Four

weeks of follow-up were included in both of these studies, along with an intervention. Weizman et al. [44] evaluated the effects of *Lactobacillus reuteri* DSM 17938 in 101 children with FAP when compared to a placebo. At the end of the 4-week intervention, there was a significant reduction in the frequency and intensity of pain in the probiotic group as compared to the placebo arm. After the 4-week follow-up, only the latter group difference remained significant [24]. Over the course of sixteen weeks, Jadresin et al. examined *Lactobacillus reuteri* DSM 17938 in 55 children with FAP or IBS vs a placebo. During the trial period, children in the probiotic group experienced more days without discomfort than those in the placebo group. The former group also experienced less acute pain in the second and fourth months. Nonetheless, there was no difference in the groups' absences from activities or school [25]. In the most current trial, 54 children with FAP were compared to a placebo and *Lactobacillus reuteri* DSM 17938 by Maragkoudaki et al. [26]. There was no discernible difference in pain severity or frequency between the probiotic and placebo groups, yet both dramatically decreased from the baseline. Furthermore, tardiness to school and use of analgesics were comparable between the groups [26].

## 4.2. *L. reuteri* in the Management of Pediatric Functional Constipation

Coccorullo et al. [27] report that during an 8-week research, 44 neonates suffering from constipation were given either a placebo or an oil solution containing *Lactobacillus reuteri* DSM 17,938. Compared to the placebo group, a considerably greater proportion of patients in the probiotic group passed at least five stools per week at weeks two, four, and eight. The consistency of the stools among the groups did not differ [27]. Guerra et al. [28] examined the efficacy of goat yogurt with *Bifidobacterium longum* against yogurt alone in a 10-week crossover experiment including 59 children who had constipation. After analyzing all of the crossover data, significant differences were seen between the groups for frequency of defecation, discomfort during feces, and abdominal pain. However, the investigators did not say whether the probiotic goat yogurt or the goat yogurt on its own was the difference maker. Furthermore, the data were only presented graphically [28]. Tabbers et al. [29] compared the effects of a non-fermented milk-based dairy product with fermented milk containing *Bifidobacterium lactis* DN-173 010 in 159 children who were constipated. The response rates for both groups were similar. Furthermore, there were no differences between the groups in terms of the frequency of stools, discomfort during bowel movements, stomach pain, or bisacodyl consumption. However, throughout the three-week study, flatulence was much less common among those taking the probi-

otic supplement [29].

## 4.3. *L. reuteri* in the Management of Infantile Colic

Dysbiosis, or altered gut microbiota, has been related to the etiology of colic, which is why probiotic bacteria have been suggested as a possible therapy for colic tears. Most studies on interventions have focused on one specific probiotic, *Lactobacillus reuteri* DSM 17938. Meanwhile, a small number of studies have examined the role of other *Lactobacillus* species or combinations of other probiotics and synbiotics.

Seven randomized controlled trials including a total of 471 participants were included in a recent comprehensive research and meta-analysis with a low risk of bias [30]. In five included randomized controlled trials (RCTs) including 349 infants, the effects of *L. reuteri* DSM 17938 at a daily dosage of 108 colony-forming units (CFU) given for 21 or 28 days were evaluated [31–35]. *L. reuteri* was associated with treatment success (relative risk (RR) 1.67, 95% CI 1.10–2.81, number needed to treat (NNT) 5, 95% CI 4–8) and decreased crying times at the end of the intervention (mean difference (MD) -49 min, 95% CI 66–33), despite the fact that the effect was primarily seen in exclusively breastfed infants.

According to an individual participant data meta-analysis (IPDMA) that pooled raw data from four individual trials involving 345 infants [31–34] to create sufficient power for sub-group analysis, *L. reuteri* DSM 17,938 is helpful in treating breastfed infants with colic, but not formula-fed infants [36]. Compared to the placebo group, the probiotic group spent less time on average crying and/or fussing, and they had almost double the chance of experiencing therapeutic success. Furthermore, the intervention's advantages were minimal for babies fed formula but significant for those fed breastmilk (NNT 2.6, 95% CI 2.0–3.6). All of the infants included in the meta-analysis were entirely or mostly breastfed, with the exception of the participants in the largest Australian research, who were both breastfed and formula-fed. Probiotic treatments may be more effective in breastfed neonates due to the distinct gut microbiota makeup of breastfed infants compared to formula-fed infants. Nonetheless, the enhanced effectiveness of *Lactobacillus reuteri* in breastfed infants might be explained by the direct effects of bacteria or oligosaccharides in breast milk. Following the publication of these two meta-analyses, two further RCTs of *L. reuteri* DSM 17938 to treat infantile colic in breastfed kids were reported [37, 38]. A study with 60 colic infants revealed that *L. reuteri* significantly reduced daily crying time throughout a 30-day intervention period, despite a limited trial with just 20 colic children reporting no significant difference in daily crying time between the probiotic and placebo group [38].



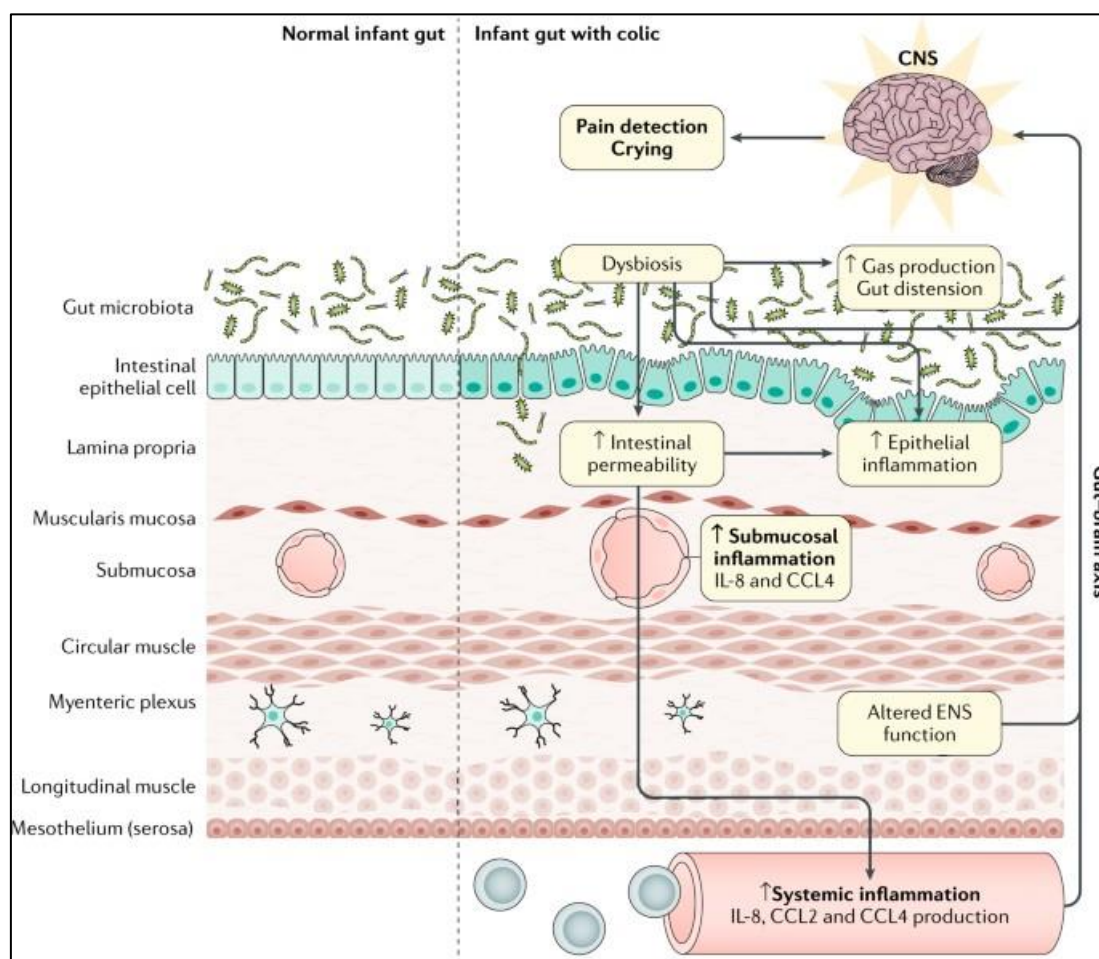


Figure 2. *L. reuteri* in the Management of Infantile Colic [14].

There has only been one small RCT that examined *Lactobacillus rhamnosus* GG (LGG)'s efficacy in treating infant colic over the course of a 28-day intervention [39]. The experiment comprised thirty colicky babies who were breastfed or given formula; there was no difference in the daily crying time between the babies who received placebo or probiotic treatment. It is noteworthy, however, that parental reports, rather than validated prospectively recorded Baby Day Diaries, were used to support the study's conclusions about the efficacy of LGG [40]. This finding emphasizes how important it is to evaluate newborn crying using reliable, dependable methods.

#### 4.4. Role of *L. reuteri* in Immunomodulation

It has been observed that *L. reuteri* modifies the immunological system. *L. reuteri* strains have the ability to increase the formation and activity of regulatory T cells while decreasing the production of pro-inflammatory cytokines [5]. Numerous investigations have demonstrated that *L. reuteri* may stimulate anti-inflammatory Treg cells, which adds to the plant's beneficial effects in a variety of disease- and non-disease-related situations. *L. reuteri*'s ability to induce Tregs is mostly strain-dependent. Nevertheless, the stimulation of Treg cells is not necessarily necessary for *L. reuteri* to

have an anti-inflammatory impact. Treg-deficient mice's Th1/Th2 response reduction mediated by *L. reuteri* is a nice example. Numerous pro-inflammatory cytokines can be inhibited by certain *L. reuteri* strains [5].

These studies have focused on the roles that bacteria play in regulating mucosal homeostasis and gut microbiota, in altering the host immune system in the intestine, and in reducing intestinal inflammation in pathological conditions. This range of behaviors illustrates the complementary roles that *Lactobacillus reuteri* plays in enhancing human immunity and gut health [5].

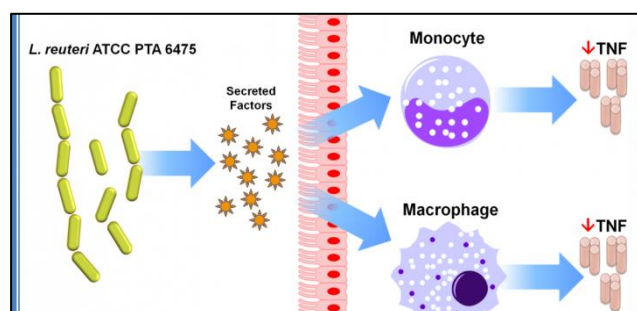


Figure 3. *L. reuteri* mediated immunomodulation.

Moreover, *L. reuteri* strains may control intestinal damage and TNF- $\alpha$  produced in humans by lipopolysaccharide (LPS), hence regulating the immune system in the intestines. *L. reuteri*'s anti-inflammatory effect has been shown to reduce intestinal mucosal levels of pro-inflammatory cytokines (interleukin-8 (IL-8), IL-1 $\alpha$ , interferon- $\alpha$ , and TNF- $\alpha$ ) in newborn rats with LPS-induced inflammation of the small intestine and ileum. In an experimental model of necrotizing enterocolitis (NEC), *L. reuteri* DSM 17938 has also been shown to block the toll-like receptor-4 signaling pathway, hence restricting the release of cytokines [4].

## 5. Reviews and Recommendations on the Use of *L. reuteri*

*Lactobacillus reuteri* The most extensively researched probiotics for the treatment of a wide range of pediatric gut health conditions are strains of *Lactobacillus reuteri* [30, 41, 42]. There were no unfavorable outcomes linked to the use of *L. reuteri* DSM 17938 in a research that examined its safety and effectiveness in treating acute diarrhea in children between the ages of 6 and 36 months [43]. Papagaroufalos et al. conducted a randomized, double-blind controlled safety experiment to assess the synthesis of d-lactic acid in healthy newborns given a formula containing *Lactobacillus reuteri*. The findings demonstrated that consuming a formula containing *L. reuteri* was safe and did not raise d-lactic acid levels after two weeks [44].

For the treatment of infantile colic, *L. reuteri* DSM 17938 is recommended as level 1 evidence by the World Gastroenterology Organization (WGO) and Latin-American Experts. Additionally, data suggests that *L. reuteri* DSM 17938 efficiently lowers newborn colic in babies who are breastfed. For newborns given formula, no recommendations have been provided, though. *L. reuteri* DSM 17938 was introduced to term baby formula in 2011 and given the Generally Regarded as Safe (GRAS) classification by the US Food and Drug Administration (FDA). For nursing babies with colic, the American Academy of Family Physicians has recommended *L. reuteri* DSM 17938 as a probiotic with a grade of B [4, 45]. There is some encouraging evidence to suggest the function of *Lactobacillus reuteri* DSM 17938 in the management of regurgitation, based on data from various research.

## 6. Conclusion

Numerous studies have demonstrated the positive impact of probiotic strain *L. reuteri* on human health. We draw the conclusion that *L. reuteri* is essential for preserving a healthy composition of the gut microbiota. Numerous clinical studies have demonstrated the probiotic's safety, effectiveness, and tolerance in treating and preventing a wide range of gastrointestinal illnesses and fostering immunological modulatory

effects. We believe that *L. reuteri* satisfies all the necessary conditions to have a positive impact on gut health. Additionally, the results of several experiments and published research show that administering *L. reuteri* does not carry any dangers or adverse effects associated with colic or other GI diseases. More clinical research is advised, therefore, in order to assess the immediate and long-term effects of *L. reuteri* strains on enhancing gut microbiota activities as well as how they interact with other organ systems. Since the probiotic properties of *Lactobacillus reuteri* vary depending on the strain, it might be advantageous to mix several strains to maximize their beneficial effects. Subsequent investigations in this field will not only augment our comprehension of this specific probiotic but additionally provide the catalyst for its broader use in the management of illnesses and health.

## Abbreviations

*L. reuteri*: *Lactobacillus reuteri*

*Lactobacillus reuteri* DSM: *L. reuteri* DSM is a probiotic that can colonize different human body sites, including primarily the gastrointestinal tract, but also the urinary tract, the skin, and breast milk

## Conflicts of Interest

The authors declare no conflicts of interest.

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