International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Role of Probiotic *Lactobacillus reuteri* in Improving Gut Health and Immunity in Infants and Toddlers: A Review

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ARTICLE INFO

Keywords:
Lactobacillus reuteri
Probiotics
Gut health
Immunomodulation
Infants

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Received: January 25, 2022
Revised: April 28, 2022
Accepted: May 5, 2022

ABSTRACT

The infant gut undergoes significant developmental phases that are fully dependent upon the colonization with microorganisms, beginning at birth. This colonization of gut microbiota has a powerful impact on host metabolic and immune homoeostasis. Probiotics strains exhibit a wide range of health benefits by modifying the intestinal microbiota and immunity. *Lactobacillus reuteri* is one of the most extensively studied probiotic strains. It promotes gut health by stimulation of mucosal gut barrier functions, production of antimicrobial substances (such as reuterin and lactic acid) and influencing acquired and innate immune responses. Reuterin produced by *L. reuteri* is a potent anti-microbial compound capable of inhibiting a wide spectrum of pathogenic microorganisms. Apart from antimicrobial metabolite production, *L. reuteri* creates biofilms that stimulate tumor necrosis factor production by lipopolysaccharide (LPS)-activated monocytoid cells. Interestingly, *L. reuteri* administration has emerged as a potential therapy for childhood functional gastrointestinal disturbances as these disturbances are associated with gut microbiota perturbations in early life. The current review summarizes the beneficial aspects of the probiotic *L. reuteri* strain in clinical practice with a special focus on its role in improving gut health and immunity in infants and toddlers.

Please cite this article as: Alam MDJ, Islam MMDZ, Tayab MDA, Alam HSK, Kamrul MDK, Mahmud S, Haque ATMA. Role of Probiotic *Lactobacillus reuteri* in Improving Gut Health and Immunity in Infants and Toddlers: A Review. Int J Nutr Sci. 2022;7(2):75-80. doi: 10.30476/IJNS.2022.94849.1182.

Introduction

The human microbiota is a complex collection of commensal microbes. The microbiota in the gut is larger in number than the whole human body and is genetically and metabolically diverse. The human microbiota, particularly the gut microbiota (which comprises more than 90% of all commensals) exhibits intense effects on the development and maintenance of the host's body, including metabolism, immune regulation, and neuronal function (1). From birth onward, the gut microbiota coevolves with the host and its metabolic and neurological programming. The infant–gut microbiota symbiosis is established from birth and is shaped during the first few years of life. Besides nutrient absorption and metabolism, the

gut microbiota also impacts the maturation of the immune system and averts pathogen colonization (2). The development of the gut microbiota is influenced by a complex interaction of the host with environmental factors such as diet and lifestyle (3). Hence, the dynamics of the gut microbiota from birth till old age can shed light on the variation of this community within the host and possible associations it has with disease risks.

The administration of probiotics alleviates several health problems, which is an indicative of the significant potential of probiotic applications in curing diseases, partly by rebalancing the gut microbial composition (4). Lactic acid-producing bacteria, including several *Lactobacillus* species, have perhaps been the most extensively studied probiotic agents in children and adults. Animal and preclinical studies have shown that lactobacilli may help in preventing and treating several gastrointestinal (GI) tract disorders. *Lactobacillus reuteri* exhibits multiple beneficial effects on the host (4, 5). *L. reuteri* was first isolated in 1962 and has been characterized as a heterofermentative species that grows in oxygen-limited atmospheres and colonizes the gastrointestinal tract of humans and animals. The fact that it normally colonizes the GI tract may be the reason why it possesses probiotic properties. In humans, *L. reuteri* is found in different body sites, including the gastrointestinal (GI) tract, urinary tract, skin, and breast milk (5). Several clinical studies have explored the function of *L. reuetri* in regulating intestinal gut microbiota and maintenance of mucosal homeostasis. The metabolites produced by *L. reuteri* influence the intestinal host immune system and ameliorate intestinal inflammation in pathological conditions. This gamut of functions reflects the dual role played by *L. reuteri* in improving gut health and immunity in human beings (5).

Adhesion of a probiotic strain to the host GI tract is important for colonization, interaction with host cells, inhibition of pathogenic growth, and protection of epithelial cells or immune modulation (6). Numerous studies have confirmed the capability of *L. reuteri* to colonize and adhere to mucin and intestinal epithelial cells. The probable mechanism involved in adhesion has been linked to surface proteins, exopolysaccharide, inulosucrase, mucus-binding protein, D-alanyl-LTA, and glucosyltransferase A (4). *L. reuteri* can successfully attach to mucin and the intestinal epithelia of its host (7). Colonization by *L. reuteri* decreases the microbial translocation from the gut lumen to the tissues, thereby strengthening the intestinal barrier function. Microbial translocation across the intestinal epithelium has been speculated as an originator of inflammation.

Role of L. reuteri in Gut Health

From birth to six months of age, approximately one out of two infants develops at least one functional gastrointestinal disorder (FGID) or related signs and symptoms. FGIDs such as infantile colic, regurgitation, functional diarrhea, and functional constipation are common worldwide, but their prevalence rates vary extensively (8). *L. reuteri* is beneficial to the host's health as it enables the colonization of the gut with beneficial bacteria. This occurs because *L. reuteri* strains are resistant to low pH and bile salts. These strains can attach to mucin and intestinal epithelia because they can produce exopolysaccharides (EPS), which are important for biofilm formation. The formation of biofilms helps *L. reuetri* to adhere to epithelial surfaces and enhances the probiotic effects of *L. reuteri* (5, 9).

Antimicrobial metabolites produced by *L.reuteri* such as reuterin inhibit a wide range of microorganisms, particularly gram-negative bacteria. Other metabolites such as lactic acid, acetic acid, ethanol, and reutericyclin are effective against numerous pathogenic bacteria. One of the key roles of the probiotic *L. reuetri* strain is to promote mucosal barrier functions by reducing bacterial translocation from the GI tract to the mesenteric lymph nodes. Apart from gut health, *L. reuteri* interacts with the gut–brain axis and modulates the afferent sensory nerves that influence gut motility (5, 9). The possible modes of action by which probiotic *L. reuteri* helps in the management of FGIDs are as follows (4, 5, 10): (i) *L. reuteri* improves gut motility, which reduces constipation and relieves functional abdominal pain. It also increases colonic contractility. (ii) *L. reuteri* modulates the gut's immune and inflammatory responses, which reduces the incidence of infections such as diarrhea. (iii) *L. reuteri* inhibits the visceral pain pathway and thus may have a role in relieving functional abdominal pain. (iv) *L. reuteri* reduces gastric distension and accelerates gastric emptying and thus helping reduce the frequency of regurgitation.

Evidence on Effectiveness of L. reuteri in Management of Pediatric Disorders

The potential connotation between gut microbiota perturbations and functional gastrointestinal disturbances in children reveals conspicuous therapeutic and preventive prospects. It is well-known that *L. reuteri* affects gut motility, contractility, and pain perception through the inhibition of calcium-dependent potassium channels in enteric nerves (11, 12).

Infantile Colic

Colic is a highly distressing condition and is linked with altered gut microbiota or dysbiosis. (11). It was proposed that the presence of gut dysbiosis among colicky infants may alter gut motor functions and cause the production of gas, leading to abdominal pain (4). Administration of *L. reuteri* DSM 17938 is likely to reduce crying times, especially in exclusively or predominantly exclusively breastfed infants (13).

Diarrhea

A total of 68% of diarrheal disease cases worldwide occur in young children and it is the fifth leading cause of death in children, accounting for approximately 2.5 million deaths (14). Several studies have demonstrated the methodological limitations related to the exact benefits of *L. reuteri* administration in children with diarrhea. However, compared with the placebo or no treatment group, the *L. reuteri*-administered group showed a reduction in diarrheal duration and duration of hospitalization (15). In a prospective, single-blind randomized controlled trial (RCT) involving 127 children aged 3 to 60 months (conducted by Dinleyici *et al.*), the effect of administration of *L. reuteri* on the duration of diarrhea and length of hospital stay in children with acute diarrhea was studied. No adverse effects related to the use of probiotics were noticed. Moreover, the duration of diarrhea was significantly reduced in the *L. reuteri* group when compared to the control. The number of stools per day was significantly lower in the *L. reuteri* group after 24, 48, and 72 hours. The mean length of hospital stay was significantly shorter in the *L. reuteri* group than in the control group (16). Another study, in which *L. reuteri* was used as an adjunct therapy, reported a significant reduction in the duration of watery diarrhea as compared with placebo and had a significantly lower relapse rate of diarrhea (17).

Constipation

Constipation is a widespread problem with a global prevalence rate of 9.5% in children. Approximately 90% of children have constipation with no underlying organic reported cause (18, 19). The presentation of functional constipation may vary in young children and may include hard, painful bowel movements and even fecal incontinence in some instances (19). Recently, it has been reported that excessive methane production by the methanogenic gut flora, which is found to be abundant in patients with constipation, slows colonic transit (4). In this regard, providing *L. reuteri* reduces methane production and improves gut transit time (20). Additionally, *L. reuteri* induces the production of short-chain fatty acids (SCFA), reduces the level of gut intraluminal pH, promotes colonic peristalsis, and influences the frequency and velocity of colonic myoelectric cells, resulting in beneficial effects on chronic constipation (9).

Current evidence states that although *L. reuteri* improved bowel movements in patients with chronic constipation, it did not affect stool consistency (10). Indrio *et al.* have highlighted the role of *L. reuteri* in reducing constipation during the first 3 months of life (21). Early life events could alter the balance of gut microbiota, increasing visceral sensitivity and mucosal permeability, which can be restored by the administration of lactobacilli (9). It is important to mention that several researchers have advocated the need for further clinical studies to elucidate the mechanisms through which *L. reuteri* modulates gut motility and reduces constipation in children.

Regurgitation

One of the most common conditions occurring during infancy is regurgitation. It is experienced by more than 50% of infants between 3 and 4 months of age (22). Many physiological factors have been listed for its occurrence including supine position, liquid meals, and loose gastroesophageal junction. Reflux is extremely common in infants and treatment is based on conservative measures, such as thickening the feeds and making the infant sit in an upright position after feeding (23). Administration of *L. reuteri* reduces the number of regurgitation episodes daily and improves gastric emptying in infants affected by functional regurgitation (15). In a double-blinded RCT, the effectiveness of partially hydrolyzed formula, 100% whey protein formula, a formula containing starch, and *L. reuteri* DSM 17938 on gastric emptying rate and regurgitation frequency was investigated. Mean daily regurgitations decreased significantly in the *L. reuteri*-administered group compared to the control group. The study also indicated higher percentage changes in gastric emptying rate in the *L. reuteri* DSM 17938 group compared to the placebo group (22). Large multicentric, double-blinded RCTs demonstrated that treatment with the probiotic *L. reuteri* improves gastric motility in infants with gastroesophageal reflux and eventually decreases regurgitation episodes (10, 22).

Role of L. reuteri in Immunomodulation

L. reuteri has been observed to modulate the immune system. *L. reuteri* strains can reduce the production of pro-inflammatory cytokines and stimulate regulatory T-cell development and function (5). Several studies have shown that *L.*

reuteri can induce anti-inflammatory Treg cells. The Treg-inducing property of *L. reuteri* is largely strain-dependent. However, the anti-inflammatory effect of *L. reuteri* does not always rely on the induction of Treg cells. A good example is the *L. reuteri*-mediated suppression of Th1/Th2 responses in Treg-deficient mice. Certain *L. reuteri* strains can reduce the production of several pro-inflammatory cytokines (5). Supplementation with live *L. reuteri* ATCC 55730 induces the colonization of *L. reuteri* in the stomach, duodenum, and ileum of humans. This is associated with a reduction in the number of gastric mucosal histiocytes, an increase in duodenal B-lymphocyte numbers, and a significant increase in CD4-positive ($CD4^+$) T cells (T helper cells) (24).

Furthermore, *L. reuteri* strains may exert immunoregulatory effects in the human gut by controlling lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α and intestinal damage. The anti-inflammatory action of *L. reuteri* reduces the intestinal mucosal levels of pro-inflammatory cytokines (interleukin-8 [IL-8], IL-1α, interferon-α, TNF-α) in newborn rats with LPS-induced inflammation of the small intestinal and ileum. *L. reuteri* DSM 17938 also inhibits a Toll-like receptor-4 signaling pathway, thereby blocking cytokine expression, as has been observed in an experimental model of necrotizing enterocolitis (4).

Reviews and Recommendations on Use of L. reuteri

L. reuteri strains have been the most widely studied probiotic strains in the management of pediatric gut health issues (11, 25, 26). A study was conducted to test the efficacy and safety of *L. reuteri* DSM 17938 in children aged 6–36 months with acute diarrhea. No adverse events associated with its usage were reported in the study (27). In a randomized, double-blind, controlled safety trial by Papagaroufalis *et al.,* D-lactic acid production in healthy infants who were fed an *L. reuteri*-containing formula was evaluated. The results demonstrated that the intake of *L. reuteri*-containing formula was safe and did not cause an increase in D-lactic acid beyond two weeks (28).

The World Gastroenterology Organization (WGO) and Latin-American Experts recommended *L. reuteri* DSM 17938 as level 1 evidence in the management of infantile colic. Furthermore, there is evidence that *L. reuteri* DSM 17938 effectively reduces infant colic in breastfed infants. However, no recommendation has been made for formula-fed infants (4). The American Academy of Family Physicians has given a grade B recommendation for the use of probiotic *L. reuteri* DSM 17938 in breastfeeding infants with colic (4). Based on data from several studies, there is promising evidence to support the role of *L. reuteri* DSM 17938 in the prevention and treatment of certain clinical conditions.

Conclusion

It is evident from various research studies that the probiotic strain *L. reuteri* exhibits beneficial effects on human health. Hence, it can be concluded that *L. reuteri* plays a key role in maintaining a balanced microbiota gut composition. Several clinical trials have proved the safety, efficacy, and tolerance of this probiotic in preventing and treating numerous gastrointestinal disorders and promoting immune modulation. Furthermore, the findings from some of the trials and published studies indicate that there are no adverse events or risks related to colic or other GI disorders upon administration of *L. reuteri*. However, additional clinical studies designed to evaluate the short- and long-term impact of *L. reuteri* administration are necessary, particularly in relation to improving gut microbiota functions and interactions with other organ systems. The probiotic functions of *L. reuteri* are strain-dependent and hence it may be advantageous to combine different strains of *L. reuteri* to enhance their effect. Future research in this area will make better our understanding of this probiotic microorganism and provide the impetus for its wider application in disease and health management.

Acknowledgment

No financial support was received for the review.

Conflict of Interest

None declared.

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