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Review Article

The Beneficial Effects of L. reuteri Probiotics in Development of the Toddlers' Immune Systems and Gut Health in Bangladesh

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Abstract: A well-researched probiotic bacteria called Lactobacillus reuteri (L. reuteri) has the ability to colonize several animals. L. reuteri can be found in the skin, breast milk, urinary tract, gastrointestinal tract, and other parts of the human body. Different people have varying amounts of L. reuteri. There are a number of advantages to L. reuteri. First, L. reuteri has the ability to create compounds that are antimicrobial, such as organic acids, ethanol, and reuteri. L. reuteri's antimicrobial activity enables it to prevent the colonization of pathogenic bacteria and alter the composition of the host's commensal microbiota. Second, L. reuteri can strengthen the immune system of the host. For instance, some L. reuteri strains can enhance the formation and activity of regulatory T cells while suppressing the production of pro-inflammatory cytokines. Third, because L. reuteri has the possibility to fortify the intestinal barrier, its colonization may lessen the number of bacteria that move from the gut lumen to tissues. It has been proposed that microbial translocation across the gut epithelium causes inflammation to start. Therefore, boosting the colonization of L. reuteri may help to alleviate inflammatory illnesses, including those that affect the gut as well as distant organs. Notably, during the past few decades, L. reuteri abundance in humans has declined, and at the same time, inflammatory illness occurrences in toddlers have increased. For the correct developmental growth of toddlers, obvious supplementation, or prebiotic modification of L. reuteri may be an alluring preventative and/or therapeutic pathway counter to inflammatory illnesses.

Keywords: Lactobacillus Reuteri, Microbiota, Probiotic, Immune System, Inflammatory Diseases, Toddler, Gut Health

1. Introduction

Probiotics are described as living microorganisms that, when used as dietary components in sufficient amounts, help the host's health. Three probiotics that are widely employed in both people and animals as probiotics are Lactobacillus, Bifidobacterium, and Saccharomyces [1]. Probiotics improve health when consumed in sufficient quantities. Probiotics are thought to improve human health through altering the gut flora and the host's response [2]. Through a variety of interactions, such as modifications in mucosal cytokine production, probiotics contribute significantly to preserving intestinal integrity. Probiotics increase the epithelium's resilience by vying with gut pathogens for mucosal receptors [3]. Reduced IgA production, which is a hallmark of an aberrant local immune response, allows bacterial antigens to be transported locally and adhere to enterocytes, which is what primarily triggers pathogenic outcomes. Colonic stasis can encourage the development of pathogenic bacteria, paving the way for the emergence of malignant porin bacterial strains. Human health is significantly influenced by the gut flora. The microbial community has a significant function in the host, contributing to the development of the immune system, the metabolic activity of probiotics to provide energy and nutrient absorption, and the prevention of pathogen colonization and illness.

For instance, probiotics are an illustration of the gut microbiota that significantly affects children's health. Only a few of the critical roles that probiotic populations play in the host include the development of the host immune system, the avoidance of pathogen colonization and infection, and the metabolic activity of probiotic communities to supply energy and nutrient absorption. Short-chain fatty acids (SCFAs) including acetate, propionic acid, and n-butyric acid are increased by probiotics, which affect the bacteria population of the large intestine's metabolism. SCFA, which is the main result of bacteria that break down carbs, is the main anion in the large intestine. The intestines are compressed by propionic acid and n-butyric acid to release fluid. Due to SCFA's role in colonization energy preparation and promotion of Na and water absorption from the large intestine, the host has less diarrhea [4]. As the composition of the gut microbiota changes, many illnesses develop. The manipulation of the gut microbiota with probiotics and other techniques is a therapy strategy to avoid or preserve its equilibrium [5].

The discovery that L. reuteri is one of the GI tract's really indigenous bacteria. Pigs, mice, and chickens are just a few of the many vertebrate species that it naturally colonizes. It has indeed undergone long-term evolution to diversify into host-adapted lineages [6].

Countless papers have also listed L. reuteri's advantages as a probiotic. These advantages include enhancing gut mucosal integrity, preventing bacterial translocation, improving feed tolerance, lowering infections, enhancing nutrient, mineral, and vitamin absorption, and modulating host immune responses [6]. In this review, we'll concentrate on a specific probiotic called L. reuteri and talk about how it helps toddlers stay healthy and protects them from many ailments and infections.

2. Properties of L. reuteri as a Probiotic

Potential probiotics must meet a few requirements in order to succeed, including the ability to endure low pH and surroundings rich in enzymes, adhering to the epithelium for host-probiotic interactions, competing with pathogenic microbes, and most crucially, safety. All of these conditions are satisfied by L. reuteri. Here, additional probiotic qualities of L. reuteri that support its range of beneficial effects on host health and illness prevention and/or amelioration are highlighted [7].

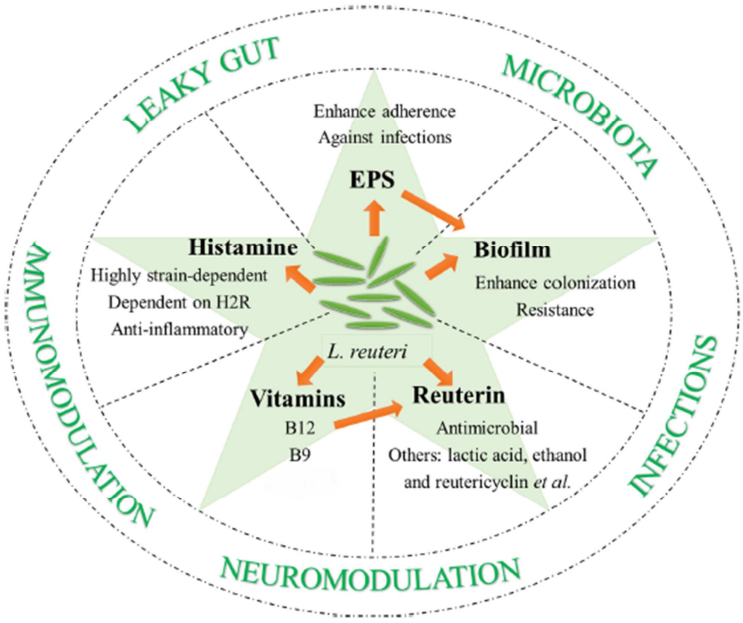

Figure 1. *Properties of Probiotic L. reuteri [6].*

The GI system has several regions that, although being intended for digestion and absorption, have proven challenging for bacteria colonization. Examples of this include the low pH conditions brought on by stomach acids and bile salts in the upper small intestine. Therefore, the first stage in colonizing the GI tract is to survive in such environments. Numerous L. reuteri stains are unaffected by low pH or bile salts [8]. This resistance is considered to be caused, at least in part, by its propensity to form biofilms. It has been demonstrated that a number of L. reuteri strains can stick to intestinal mucus and gut epithelial cells in a range of vertebrate hosts [9]. One putative mechanism for adhesion is the binding of chemicals from the bacterial surface to the mucus layer. Mucus-binding proteins (MUBs) and MUB-like proteins are generated by clusters of orthologous protein coding genes that are unique to the Lactobacillales and function as adhesion mediators, or so-called adhesins [10]. The variation in the quantity of cell-surface MUBs and the diversity of MUBs seen in different L. reuteri strains are closely connected to how well those strains bind mucus. The ability of MUBs to induce aggregation and/or play strain-specific functions in recognizing mucus components can both be used to explain how MUBs affect L. reuteri adherence. The attachment to the surfaces is made easier by a number of important surface proteins, including D-alanyl ester, MUB A, glucosyltransferase A (GtfA), and inulosucrase (Inu). Since L. reuteri that has colonized the host's GI tract may form biofilms, researchers have been studying the regulation of L. reuteri biofilm secretion and its connection to the attachment of bacteria to host GI epithelium. An in vitro biofilm experiment was conducted by Water, J. et al. to determine the involvement of GtfA and Inu in the biofilm development of L. reuteri TMW1.106 [10].

The L. reuteri strains' host origin appears to have an effect on how well the strains form in vivo biofilms. In one study, animals that had not been exposed to germs were given nine different L. reuteri strains from hosts including humans, mice, rats, chickens, and pigs. After two days, the biofilms were evaluated. Even while strains from different origins had similar luminal populations, it is intriguing that only rodent strains were able to form biofilms and adhere to the forestomach epithelium. The same researchers have demonstrated the SecA2-SecY2 system, which is exclusively found in strains from rodents and pigs [28]. They compared the secA2 mutant with the mouse strain L. reuteri 100-23 in terms of extracellular and cell wall-associated proteins. The sole surface protein absent from the secA2 mutant was L. reuteri 70902. Studies on in vivo colonization have shown that the absence of L. reuteri 70902 virtually completely prevents the formation of biofilm [11].

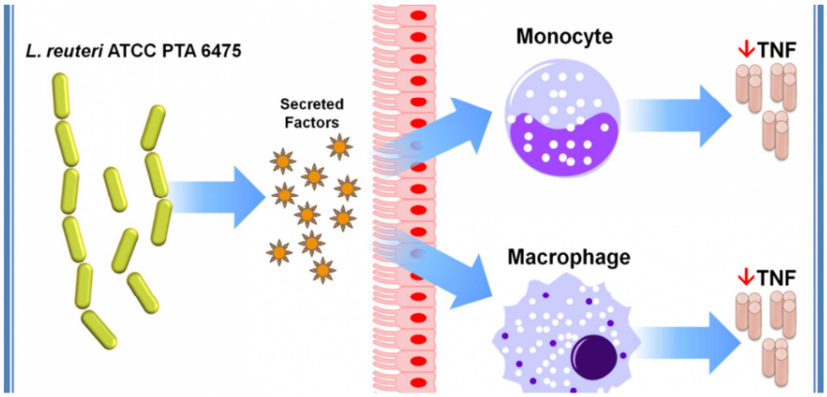

Figure 2. *Proposed mechanism of immunomodulation by secreted factors from L. reuteri ATCC PTA 6475, which results in decreased TNF production from monocytes and macrophages [22].*

3. Metabolites Production of Probiotics with Health-Promoting Effect

The antibacterial and immunomodulatory characteristics of several L. reuteri strains are correlated with their metabolite production patterns. Here, we discuss a few well studied metabolites in connection to the probiotic potential of L. reuteri. The majority of L. reuteri strains with human and poultry heritage may generate and excrete Reuterin, a well-known antibiotic compound [6]. Reuterin is a mixture of several forms of 3-hydroxypropionaldehyde (3-HPA) [29]. L. reuteri may metabolize glycerol to generate 3-HPA by a coenzyme B12-required, glycerol dehydratase-mediated mechanism. It has also been demonstrated that a few other bacterial species can make 3-HPA. The ability of L. reuteri to produce and secrete 3-HPA in a manner that goes above and beyond what is required for bioenergetics makes it unique [30]. Furthermore, reuterin's antimicrobial activity appears to be based on the spontaneous conversion of 3-HPA to acrolein, a cytotoxic electrophile [31].

Numerous microorganisms, mostly Gram-negative bacteria, can be inhibited by reuterin. Reuterin resistance is common among Lactobacillus species, with L. reuteri strains exerting the strongest resistance [12]. The ability of reuterin to conjugate heterocyclic amines, which is in addition to its antibacterial activity, also appears to be dependent on the production of acrolein. This shows that acrolein is a substance that is crucial to reuterin's function. Several additional

antimicrobial compounds, besides reuterin, have been identified as byproducts of various L. reuteri strains, including lactic acid, acetic acid, ethanol, and reutericyclin [13]. L. reuteri has been demonstrated to be effective against a number of GI bacterial illnesses by the manufacture of these compounds. Salmonella, E. coli, Clostridium difficile, Helicobacter pylori, and other infections are among them [6].

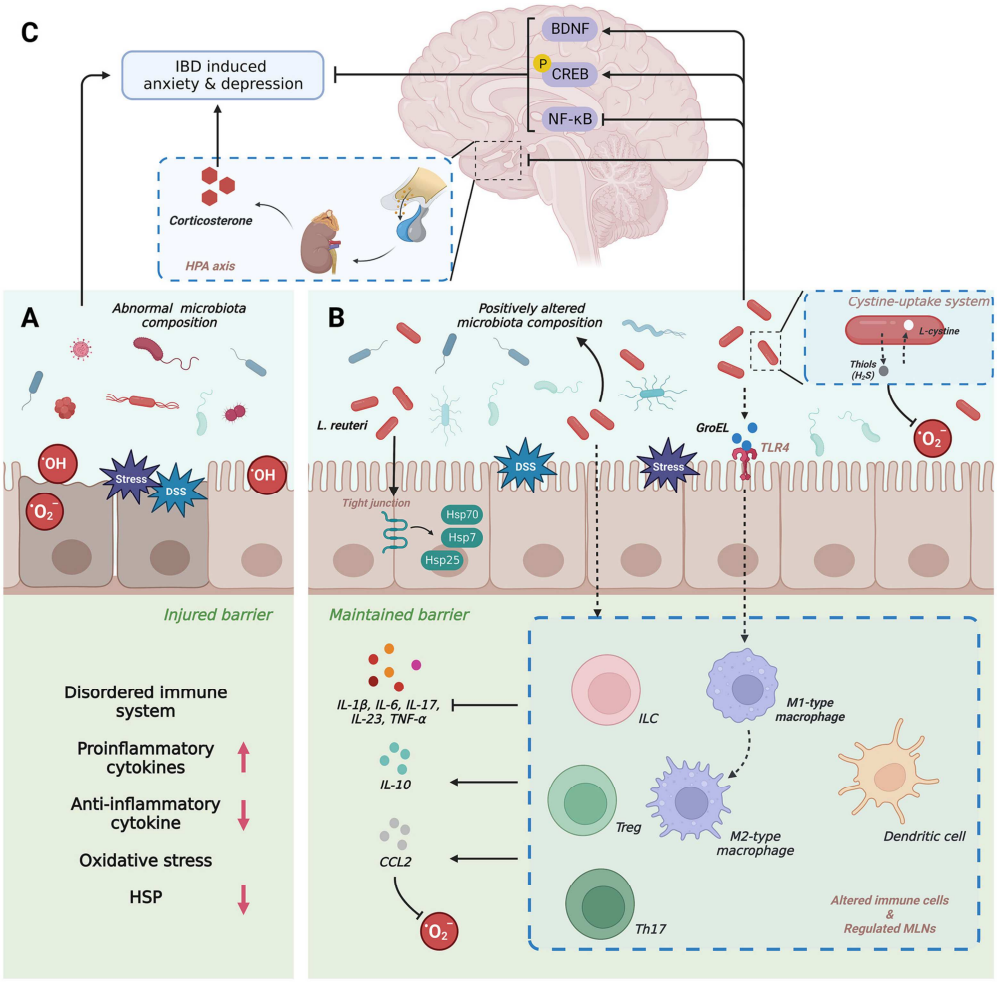

Figure 3. *(A–C) Schematic diagram depicting the pathogenic role and therapeutic potential of Lactobacillus reuteri in IBD. IBD, inflammatory bowel disease; BDNF, brain-derived neurotrophic factor; CREB, cAMP-response element binding protein; DSS, dextran sodium sulphate; HSPs, heat shock proteins; NF-kB, nuclearfactor-kB; IL, interlukin; TNF-a, tumor necrosis factor-k; CCL, C-C motif chemokine 2; Th, T helper cell; TLR, Toll-like receptors; ILC, innate, lymphoid cells; Treg, regulatory T cell; MLN, mesenteric lymph node [7].*

One of the best-known uses for L. reuteri as a probiotic against infections is the treatment of H. pylori. H. pylori infection is a substantial cause of chronic gastritis, peptic ulcers, and a risk factor for stomach cancer.

Numerous studies have examined how well L. reuteri fights H. pylori [Table 1] [6].

Table 1. *The use of L. reuteri against H.pylori has been explored in many studies.*

Strain	Treatment	Subjects	Result	Citation
DSM 17648	14 days	Adults	Decrease in pathogen load in the stomach	Holz et al., 2015
DSM 17938	14 days	Patients	93% successful eradication of the pathogen with inhibitor-tetracycline-metronidazole - L.reuteri therapy	Dore et al., 2016
ATCC 55730	20 days	Infected Children	Improvement of Gl symptoms	Lionetti et al., 2006
-	10 days	Patients	No improvement of the standard triple therapy	Scaccianoce et al., 2008
ATCC 55730	7 days	Patients	Significant decrease of pathogen load and improvement of dyspeptic symptoms	Francavilla et al., 2008
SD2112	4 weeks	Patients	Decrease of pathogen density and suppression of urease activity	Imase et al., 2007
DSMZ 17648	14 days	Patients	Decrease in pathogen Load	Mehling and Busjahn, 2013
DSM 17938, ATCC PTA 6475	During Therapy	Patients	Reduction of antibiotic-associated side effects in eradication therapy	Francavilla et al., 2014
DSM 17938	8 weeks	Patients	Decrease of urease activity in pantoprazole therapy	Dore et al., 2014

H. pylori and L. reuteri are said to compete with one another for access to glycolipid receptors, according to Mukai et al. The competition lowers the quantity of H. pylori bacteria and the symptoms they cause [32]. According to a number of studies, L. reuteri has the potential to entirely eliminate H. pylori from the colon. Since L. reuteri kills the virus without causing the typical side effects associated with antibiotic treatments, it is crucial to keep in mind that L. reuteri is successful in treating H. pylori.

3.1. Histamine

A few strains of L. reuteri are capable of converting the biogenic amine histamine from the amino acid L-histidine, which is found in food; [6]. L. reuteri 6475, a human commensal bacterium, served as the research strain for histamine in L. reuteri. According to team's findings, stimulated human monocytes producing tumor necrosis factor (TNF) were inhibited by L. reuteri 6475-derived histamine. Histamine H2 receptor activation, elevated intracellular cAMP and protein kinase A levels, and inhibition of MEK/ERK signaling were all necessary for this suppression. A full chromosomal histidine decarboxylase (hdc) gene cluster, which consists of hdcA, hdcB, and hdcP, controls the synthesis of histamine and the consequent in vitro TNF-suppressive action [33]. The same team of researchers discovered that oral treatment of hdcC L. reuteri may successfully reduce intestinal inflammation in a mouse colitis model generated by trinitrobenzene sulfonic acid (TNBS) [34].

Additionally, animals treated with TNBS also saw a comparable reduction of colitis after receiving intraperitoneal injections of L. reuteri 6475 culture supernatants. These findings clearly suggest that intestine immunomodulation is mediated by L. reuteri metabolites, including histamine. Further research revealed that the expression of the hdc gene cluster in L. reuteri 6475 required the gene rsiR. Reduced TNF inhibition in vitro and decreased anti-inflammatory efficacy in vivo were the results of the rsiR gene being inactivated. Additionally, a gene called folC2 appears to be responsible for controlling both the in vitro TNF suppression and the in vivo anti-colitis effects [35]. Particularly, L. reuteri strains play a major role in the generation of histamine, and human strains have been the subject of the majority of investigations.

3.2. Vitamins

Due to the incapacity of the human body to produce them, there are 13 necessary vitamins for humans [36]. Several L. reuteri strains may generate several vitamins, including vitamin B12 (cobalamin) and B9 (folate), like many other Lactobacillus spp. As was previously established, the formation of reuterin depends on the coenzyme B12 since glycerol must be reduced to 3-HPA. It has been discovered that at least 4 different L. reuteri strains may generate B12 [6].

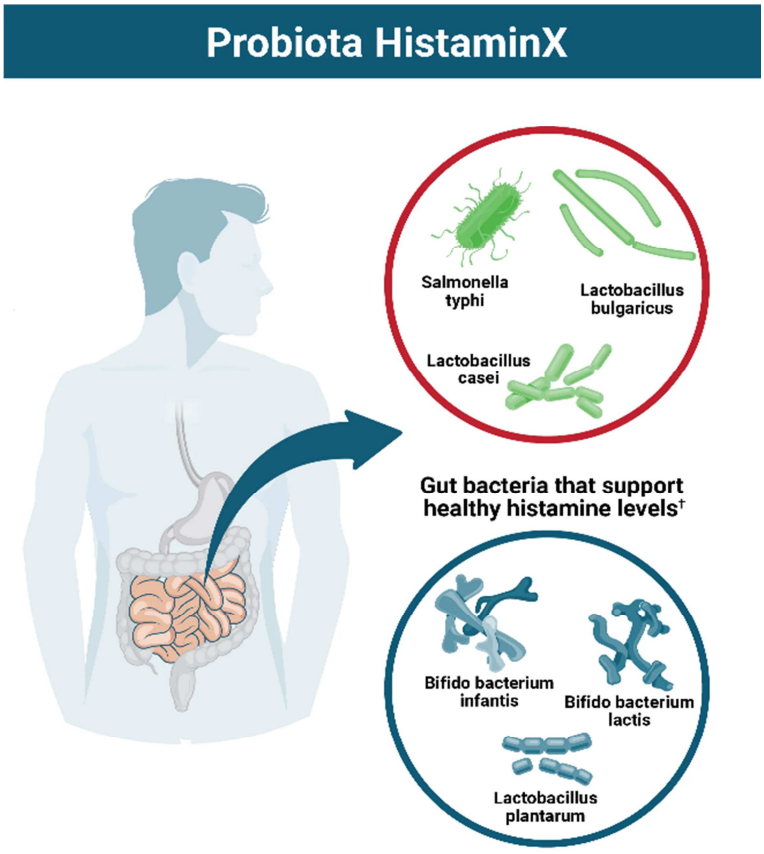

Figure 4. *L. reuteri are able to convert the amino acid L-histidine [23].*

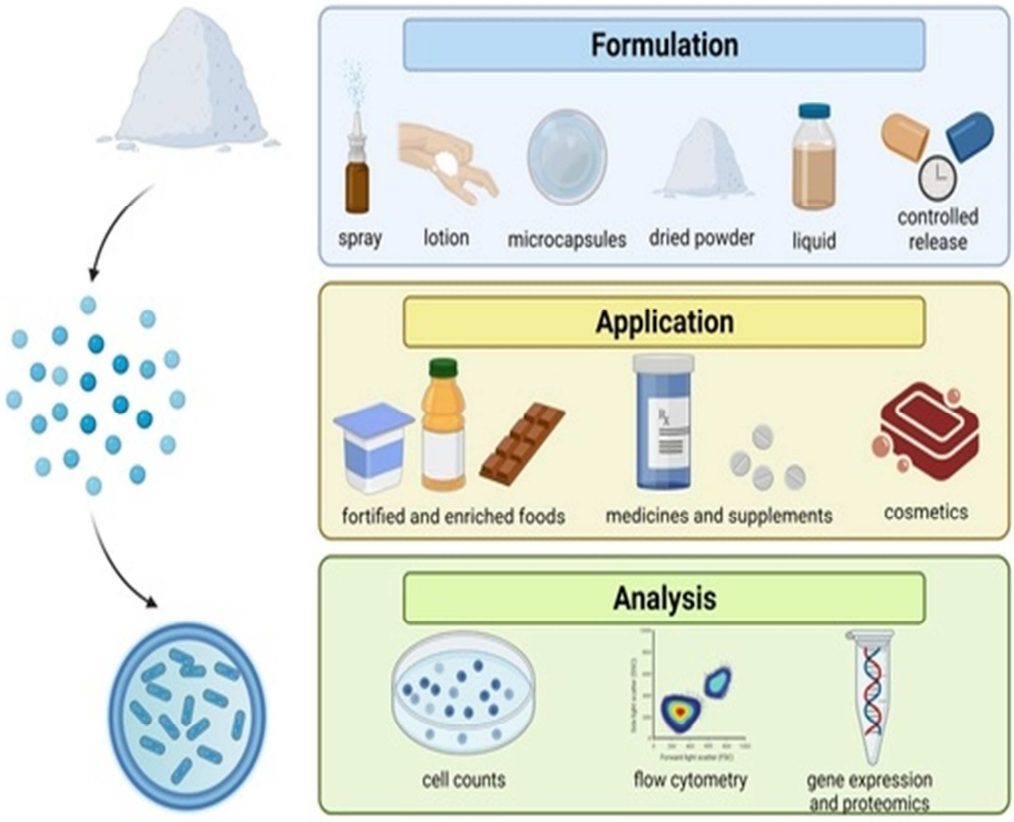

Figure 5. *L. reuteri strains are able to produce different types of vitamins [6].*

The two most researched strains of this group are L. reuteri CRL1098 and L. reuteri JCM1112. B12-deficient pregnant female mice and their progeny were reported to have diseases in one investigation when L. reuteri CRL1098 was given to them along with a diet low in the vitamin [37]. This amply supports L. reuteri's potential use in the treatment of B12 insufficiency. Some particular L. reuteri strains, such as L. reuteri 6475 and L. reuteri JCM1112, may also manufacture folate in addition to B12.

4. L. reuteri-Mediated Modulation of Host Microbiota

According to recent research, the immune system and host microbiota work together to preserve tissue homeostasis in healthy individuals. The disruption of the microbiota has been linked to several diseases (Mu et al., 2015), whilst the restoration of the microbiota has been shown to prevent or treat a number of diseases (Scott et al., 2015). The variety, makeup, and metabolic processes of the gut, mouth, and vaginal microbiotas can all be influenced by L. reuteri.

5. Role of L. reuteri in Gut Microbiota

Studies have shown that L. reuteri has a modulatory effect on the microbiotas of rats, piglets, and humans. In one experiment, an oral dosage of an L. reuteri strain with human origin was administered to scurfy mice (DSM17938), who had gut microbial dysbiosis due to the foxp3 gene mutation. The results showed that this strain of L. reuteri was capable of extending the lifespan of mice, decreasing multi-organ inflammation, and changing their gut microbiota. Changes in the gut microbiota included an increase in the phylum Firmicutes as well as the genera Lactobacillus and Oscilospira. Notably, even while the community composition was still different from that of wild-type littermates, L. reuteri's changed gut microbiota was the cause of the disease-ameliorating effect. Further studies showed that injection of L. reuteri boosted inosine production by the gut microbiota. Through activation of the adenosine A2A receptor, inosine can reduce Th1/Th2 cells and the cytokines they generate. These findings suggested a potential therapeutic strategy by focusing on the L. reuteri-gut microbiota-inosine-adenosine A2A receptor axis for diseases linked to Treg insufficiency. In addition, oral L. reuteri 6475 therapies increased the diversity of the microbiota in the ileum and jejunum of a mouse model of ovariectomy-induced bone loss. Particularly, there were less Bacteriodales and more Clostridiales. Further research is necessary to determine whether or not the altered gut flora was directly related to the prevention of bone loss. L. reuteri C10-2-1 has also been demonstrated to influence the variety of the gut microbiota in the ileum of rats.

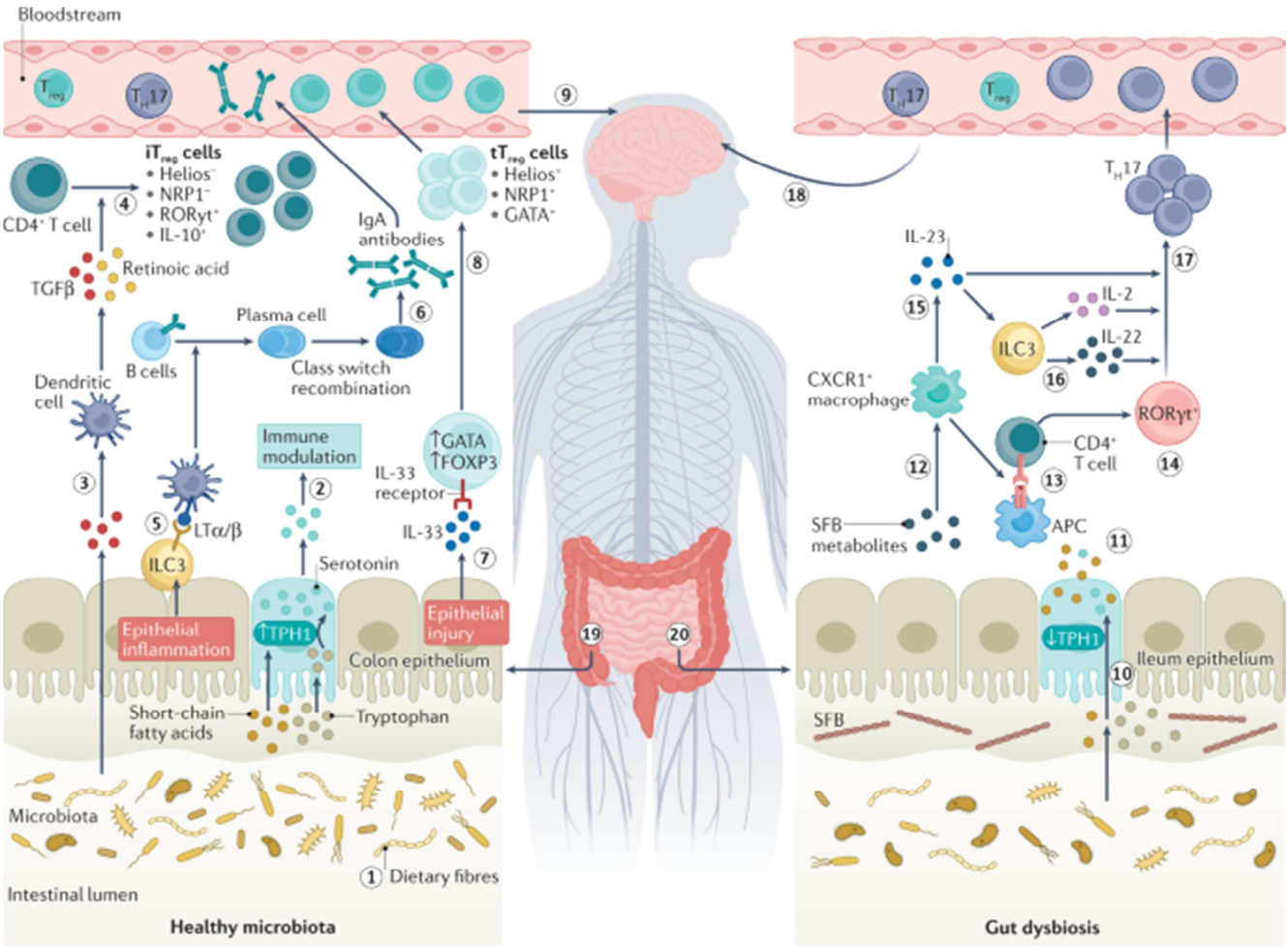

Figure 6. *The role of the gut microbiota in multiple sclerosis [24].*

Cesarean (C)-section delivered children exhibit a larger abundance of Enterobacter but less Bifidobacterium in their gut microbiota compared to vaginally delivered newborns (Garcia Rodenas et al., 2016; Nagpal et al., 2016). According to one study, treating C-section of age affected the development of the gut microbiota toward the community pattern seen in vaginally delivered infants. Following L. reuteri supplementation, the gut microbiota composition of vaginally delivered neonates remained unaffected.

Additionally, the treatment of L. reuteri DSM 17938 to cystic fibrosis (CF) patients improved the relative abundance of Firmicutes while decreasing Proteobacteria to treat gut microbiota dysbiosis.

There needs to be more research done to determine whether or if the altered gut microbiota in CF patients receiving probiotic treatment improved GI health. L. reuteri has a strain-specific impact on the microbial population in pigs' guts. For example, oral L. reuteri ZLR003 treatment had the power to alter the variety and makeup of the gut microbiota. The intestinal microbial structure of pigs receiving therapy with the I5007 strain was unaffected, nevertheless. In a separate investigation, weanling pigs' intake of L. reuteri-fermented feed affected the abundances of six distinct bacterial taxa, notably the family Enterobacteriaceae.

However, L. reuteri TMW1.656 rather than L. reuteri LTH5794 allowed for the detection of the key modifications, which included a rise in Mitsuokella and a decrease in a family belonging to the phylum Bacteroidetes. The fact that TMW1.656 produces reutericyclin whereas LTH5794 does not suggests that reutericyclin may have a role in modifying the gut microbiota of pigs.

6. Role of L. reuteri in Oral Microbiota

The human oral microbiome is dominated by the phyla Firmicutes, Bacteroidetes, Fusobacteria, Proteobacteria, and Actinobacteria. Although the bacterial species richness remained unaffected, 12 weeks of daily ingestion of two L. reuteri strains—DSM 17938 and PTA 5289—led to a change in the composition of the oral microbiota in a randomized controlled study [38]. The changes vanished 4 weeks after the treatments ended, indicating the oral microbiome's quick turnover. Although there was no clinical effect seen, oral L. reuteri therapy in a different human investigation decreased the number of periodontal pathogens in the subgingival microbiota.

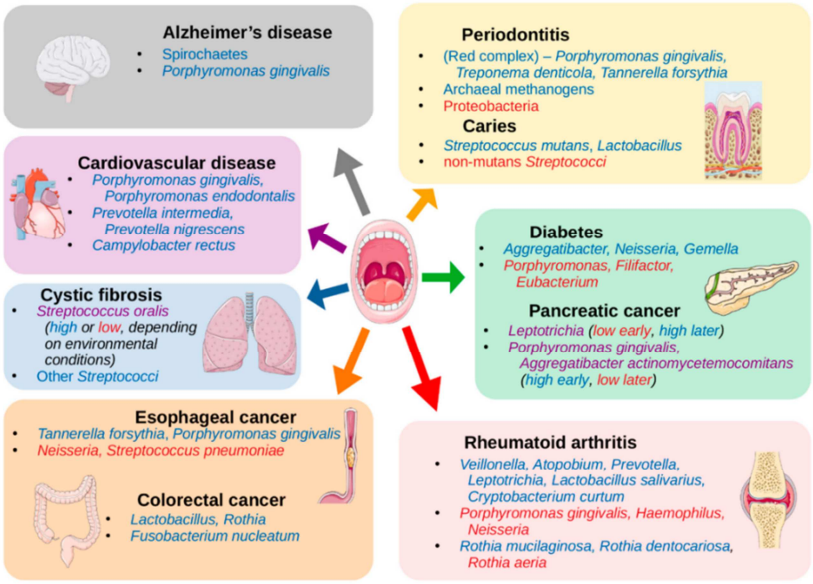

Figure 7. *Human Oral Microbiome in Health [25].*

7. Role of L. reuteri in Immunomodulation

Lactobacillus reuteri has been shown to increase the levels of free secretory IgA (sIgA) in rats. However, the rise of sIgA was totally eliminated in vitamin A-deficient mice, showing that L. reuteri functions in a vitamin A-dependent manner. When pregnant women ate L. reuteri, neither the levels of total IgA nor sIgA in breast milk changed. When it comes to L. reuteri's capacity to produce salivary IgA, the results are in dispute. Elevated salivary IgA levels have been associated with human chewing gum containing L. reuteri. However, other studies found that L. reuteri had no effect on the level of IgA in saliva. The many strains of L. reuteri used in the study may be responsible for the discrepancies in the results. IgA levels are higher in salivary L. reuteri-positive individuals, which is a striking similarity. To ascertain if L. reuteri directly regulates B cells to affect IgA levels, more investigation is required. Numerous studies have shown that L. reuteri may activate anti-inflammatory Treg cells, which likely contributes to L. reuteri's beneficial effects in a number of disease- and non-disease-related situations. The majority of strain variation affects L. reuteri's capacity to produce Tregs. However, the anti-inflammatory benefits of L. reuteri are not always reliant on the activation of Treg cells. The L. reuteri-induced suppression of Th1/Th2 responses in mice lacking Treg provides a good example. Certain L. reuteri strains can lower a variety of pro-inflammatory cytokines. L. reuteri GMNL-263, for example, can reduce blood levels of MCP-1, TNF, and IL-6 in mice fed a high-fat diet. Mice that had been heat-killed and then administered GMNL-263 had comparable outcomes.

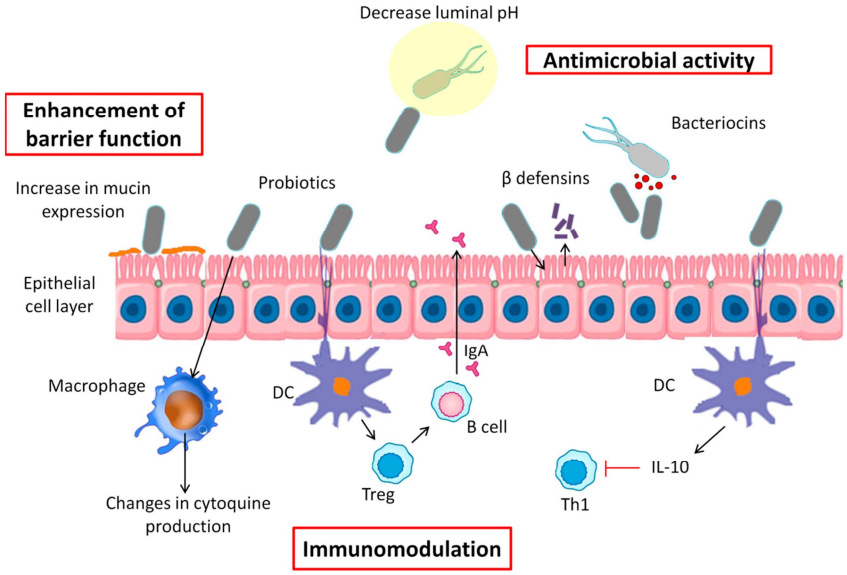

Figure 8. *Role of L. reuteri in Immunomodulation, antimicrobial activity, enhancement of barrier function [27].*

However, in other instances, L. reuteri's immunomodulatory actions seem to depend on its metabolites, as evidenced by the fact that L. reuteri BM36301's culture supernatant was able to lower TNF production from human myeloid THP-1 cells (Lee et al., 2016). It's interesting to note that L. reuteri's tryptophan catabolites have been identified as AhR ligands. L. reuteri can encourage local innate lymphoid cell (ILC) production of IL-22 by activating AhR. Additionally, L. reuteri-produced tryptophan derivatives can, in an AhR-dependent way, stimulate the growth of regulatory CD4CCD8aaC double-positive intraepithelial lymphocytes. L. reuteri and its metabolites may be able to affect many more types of immune cells besides ILCs and T cells because AhR is widely expressed.

8. Role of L. reuteri in Gut Barrier

Physical, biochemical, and immunological barriers make up the gut barrier function, which is required to stop the passage of external toxins and antigens. Any intestinal barrier flaws may lead to increased intestinal permeability and the development of a leaky gut. A well-known probiotic recognized for its ability to enhance mucosal barrier function is L. reuteri (Mu et al., 2017a). In colitis brought on by DSS, L. reuteri therapy may reduce bacterial translocation from the GI tract to the mesenteric lymph nodes (MLN). The expression of tight junction (TJ) proteins in intestinal epithelial cells in lupus-prone animals was also elevated after treatment with a number of Lactobacillus species, including L. reuteri. Following that, a less serious sickness was linked to a significant decrease in the translocation of pro-inflammatory molecules like LPS. In addition to studies using mice, many strains of L. reuteri have been shown to be able to change the expression of the TJ protein and maintain the integrity of the intestinal barrier in pigs.

Additionally, it has been demonstrated that L. reuteri lowers intestinal permeability in people. Children with atopic dermatitis who were treated with L. reuteri DSM12246 saw a substantial decrease in the frequency of GI symptoms. In this condition, the disruption of intestinal barrier function has been positively connected with disease etiology. This was accompanied by a decline in the lactulose to mannitol ratio, which shows that the leaky gut has reversed itself.

9. Anti-Microbial Effects of L. reuteri

One of the most common justifications for taking probiotics is protection against bacterial or viral illnesses. Various explanations for its anti-microbial action have been put forth. Studies conducted in vitro show that some probiotic strains create anti-microbial substances including organic acids, H2O2, and/or bacteriocins26, which have been shown to stop the development of Listeria monocytogenes, E. coli, and Salmonella spp. Although a large generation of H2O2 has been recorded, no lactobacillus that produces bacteriocin has been identified in human milk [14].

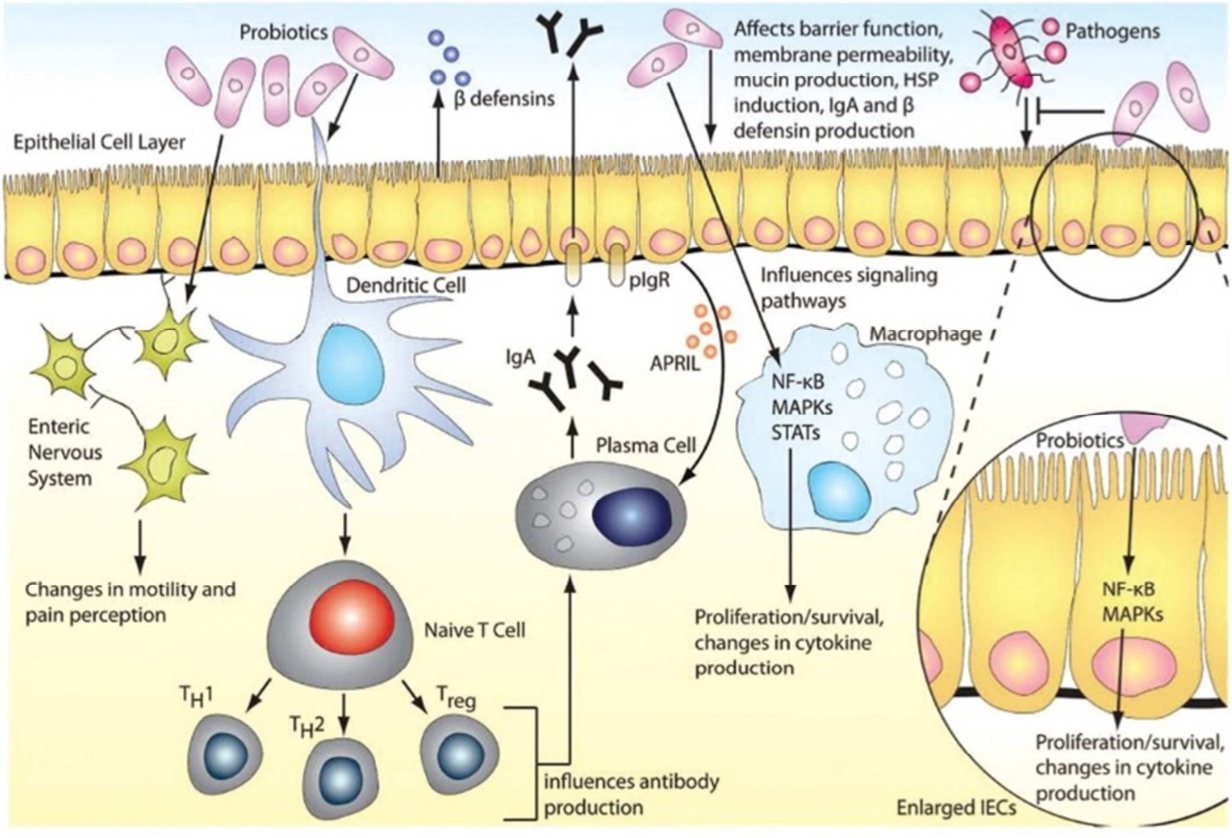

Figure 9. *Effects of Probiotics in Gut Microbiota [16].*

10. The Function of Probiotics in Promoting IgA Secretion and Production by B Cells in the Toddler Gut

B cells undergo plasma cell differentiation and release dimeric IgA antibodies in the intestinal lamina propria. Intestinal epithelial cells' basolateral IgA polymer receptors bind to IgA and carry it to the apical cell surface where it is released into the intestinal lumen [15]. T cells and the arrangement of lymphoid tissue components are not required for mucosal immune responses to commensal bacteria, including the generation of IgA. Epithelial cells and DCs release chemicals such ligand-inducing proliferation (APRIL), ligand DC40, and TGF that cause class switching IgA independent T cells. Bacillus subsites JH642, L. plantarum WCFS1, and TLR-activated bacterial products drive intestinal epithelial cells to generate APRIL, which causes IgA to transition to IgA2. Immunoglobulin IgA2, which is prevalent in the distal colon and more resistant to bacterial prostheses is found there [16].

It has been demonstrated that probiotics contribute to the host's increased IgA production. For instance, L. casei significantly contributes to the growth of IgA-producing cells in the lamina propria of the small intestine. The Lactobacillus helveticus peptides can boost the IgA response. Probiotics differ in how they affect sIgA production, though. Prebiotics (oligofructose enriched in inulin) and symbiotics (L. rhamnosus, Bifidobacterium, B. lactis, and inulin) stimulated sIgA production in mice, demonstrating a variety of triggers in the gut. Additionally, Saccharomyces boulardii can raise total sIgA levels in traditional and model mice, demonstrating that probiotics can trigger an immunological response against the host [17].

11. L. reuteri's Function in Boosting Host Immune Response

L. reuteri is one of the probiotic species found in the gastrointestinal tract (GIT) of vertebrates, such as people, pigs, and chickens. This probiotic has a long history of usage as a probiotic in humans, animals, and young children [40]. This bacteria is heterofermentative and is one of the several Lactobacillus species that may be found in both people and animals. Numerous investigations have determined the L. reuteri strain from human feces, breast milk, human vagina, human oral cavity, guinea pigs, pigs, and other sources. Numerous studies have shown that the L. reuteri strain has probiotic qualities that can improve the host's health [16].

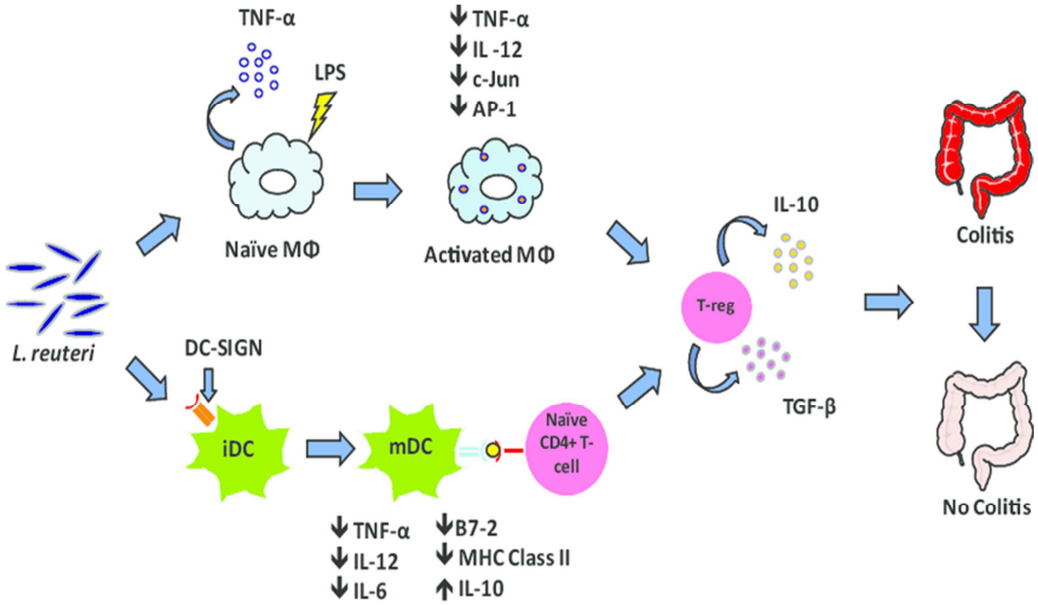

Figure 10. *Effects of L. reuteri on immune cells that contribute to tolerance [26].*

Within the first week of taking the probiotic L. reuteri ATCC 6475 (3.510 6 CFU) for 20–24 weeks, female mice's fur quality increased. This was connected to an increase in follicular sebocyte activity and proliferation or a thickening of the dermis by L. reuteri. The ATCC 6475 strain did not appear to lower IL-10 cytokines in mice in a way that would enable it to be used as an anti-inflammatory drug. L. reuteri ATCC 6475 oral therapy also alters the pro-inflammatory cytokine IL-17A in mice by boosting the production of the anti-inflammatory cytokine IL-10 via the histamine activity of the H2 receptor. IL-10 can stop Th17 cells from producing IL-17 after connecting to it [18].

L. reuteri DSM 17 938 increases CD4+ Treg cells+ CD8+ and CD4+ Treg cells+ in the gut and spleen compared to controls within the first few days (through food from their mothers) when administered to a puppy with necrotizing

enterocolitis (NEC) at a dose of 106 CFU/g of body weight per day [19]. This increase was related to puppy survival. A rise in the number of Treg cells has also been seen in other populations. For example, normal mice administered 109 CFU of L. reuteri (ATCC 23272) saw a 60% increase in the number of Treg cells in the spleen tissue within 9 days [20]. It's likely that L. reuteri's anti-inflammatory effects keep T-cell regulation in check by reducing pro-inflammatory cytokines (IL-6, TNF-alpha) and the increase of anti-inflammatory cytokines (IL-10).

Following a 2-month (5108 CFU) supplementation regimen with L. reuteri DSM 17938 in healthy individuals, calprotectin levels in the feces considerably increased. A sign of intestinal inflammation is calprotectin. Even while the increase in calprotectin levels was still within the normal range, it remained at modest levels for up to 6 months after L. reuteri supplementation was terminated. For people who have cystic fibrosis, which results in intestinal inflammation and a 40% reduction in calprotectin, the dosage remains the same. In hospitalized patients with antibiotic-associated diarrhea, supplementation with L. reuteri ATCC 55730 at 108 CFU for 1 month can reduce diarrhea frequency by 50% to 7.7% [21].

12. Conclusion

Even in young children, the probiotic L. reuteri can produce intestinal inflammation-mediated immunomodulation in humans through the production of pro-inflammatory cytokines that are both immunosuppressive and immunostimulatory. Pro-inflammatory cytokines and intestinal AMPs can be modified to regulate this occurrence. This AMP beta-defensin was released by local neutrophils, which produce large amounts of the AMP calprotectin, which helps destroy intestinal fungi and bacteria. The contemporary lifestyle (antibiotic usage, western food, greater cleanliness) is probably to blame for the recent decline in the prevalence of L. reuteri in humans. Over the same era, increasing occurrences of inflammatory disorders coexist with this decline. It may be beneficial to promote L. reuteri colonization and/or its probiotic capabilities as a novel and reasonably secure method against inflammatory disorders, even if there is insufficient data to prove the association. Additionally, L. reuteri exerts a remarkable influence on the prevention of infections and the attenuation of GI disorders as well as diseases in distant tissues by direct control or indirect modulation via the host microbiota in humans and Toddlers. Numerous clinical trials have validated L. reuteri's tolerance and safety. Numerous L. reuteri strains with various host ancestries exist, and many of the probiotic properties of L. reuteri are strain-specific. To enhance the positive benefits of several L. reuteri strains, it may be helpful to mix them.

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