Systematic Review

THE THERAPEUTIC EFFECTS OF LACTOBACILLUS REUTERI SUPPLEMENTATION IN VARIOUS CONDITIONS: A SYSTEMATIC REVIEW

ABSTRACT

Background: *Lactobacillus reuteri* (*L.reuteri*) is a probiotic which confers health benefits on the host when administered. The safety and efficacy of *L. reuteri* in human health and diseases were assessed through this study.
Objectives: To determine the efficacy of *L. reuteri* supplement in various diseases.
Method: PRISMA guideline was used and systematically searched the Cochrane Library and PubMed electronic databases for studies reporting effects of *L. reuteri* supplementation consumption in improving patient's health in different condition/diseases. Twenty-two eligible studies were selected and 1889 patients from general population have been included in our study.
Results and discussion: From included studies, the predictive performance of *L. reuteri* produces significant improvement in treatment of various conditions and diseases. It acts by improving the gut microbiota of several conditions and inflammatory diseases can be managed in a better manner. Supplementation with *L. reuteri* decreased the severity of various diseases and side effects such as antibiotic associated diarrhea.
Conclusion: The effect of *L. reuteri* varies depends on disease condition that was shown in our results. Hence, we conclude that administration of *L. reuteri* is considered safe and effective when taken as supplementation.

Keywords: *Lactobacillus reuteri*, *Probiotic, Inflammation, Colic disease*

1. INTRODUCTION

"Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" by the World Health Organization (WHO)" [1] Those probiotics having beneficial properties include Lactobacillus species pluralis (spp), bifid bacterium spp., Streptococcus spp., Bacillus spp., Enterococcus spp., and some strains of *Escherichia coli.* "A common mechanism in probiotics includes colonization, producing short chain fatty acid, regulating intestinal transit, normalizing perturbed microbiota and exclusion of pathogens. Some probiotic strains can improve host food digestion by metabolizing bile salt or supplementing the functions of missing digestive enzymes" [2]. "*L. reuteri* is a probiotic bacteria found in body sites, including the GI tract, urinary tract, skin, and breast milk. The *L. reuteri* inhibits the colonization of pathogenic microbes and remodel the microbiota composition in the host. The colonization of *L. reuteri* may decrease the microbial translocation from the gut lumen to the tissues" [3]. The benefits of *L. reuteri* are given below.

1.1 *H. pylori* infection

"It is commonly known that *H. pylori* infection causes peptic ulcer disease, gastric neoplasia and in non-ulcer dyspepsia. According to Maastricht III Consensus R export, the treatment of *H. pylori* infection involves probiotics. *L. reuteri* ATCC 55730 demonstrates to increase eradication of the *H. pylori* infection" [4]. Further *L. reuteri* prevents *H. pylori* from adhering to stomach epithelial cell thereby suppresses *H. pylori* urease activity [5]. The oral application of *L. reuteri* DSM 17938, when used in combination with pantoprazole twice a day for 8 weeks, resulted in reduction in the urease breath test [6] *L. reuteri* is

capable of reduce frequency of antibiotic-associated side-effects during eradication therapy for *H. pylori* [9].

1.2 Diarrhea

A study shows acute and chronic diarrhoea are frequently seen with aberrant stool pattern in geriatrics [10]. “The endogenous *L. reuteri* produces therapeutic effects in diarrhea. A new strain of probiotic *L. reuteri* DSM 17938 is produced by the removal of resistance traits for lincomycin and tetracyclines from *L. reuteri* ATCC 55730 strain” [11]. “In one meta-analysis in hospitalized children, it was disclosed that *L. reuteri* DSM 17938 and *L. reuteri* ATCC 55730 reduced the time span of diarrhea. *L. reuteri*n produces reuterin, a broad-spectrum antimicrobial agent, which may be responsible for the eradication of pathogens. Evidence suggests that *L. reuteri* ATCC 55730 seems to reduce antibiotics-associated diarrhea in adults and children, it also helps prevent diarrhea in paediatrics according to a study. Clinical study indicates that *L. reuteri* ATCC 55730 may reduce antibiotic-associated diarrhea in children and adults, it also helps avert diarrhea in paediatrics according to a study” [12].

1.3 Abdominal pain

Based on clinical studies, taking *L. reuteri*n DSM 17938 for a period of 4 weeks may reduce abdominal pain experience in children, it also reduced the prevalence and intensity of Familial Adenomatous Polyposis in children [13].

1.4 Colic disease

Infantile colic is defined clinically by Wessel’s criteria of crying ≥3 hours/day for ≥3 days/week for ≥3 weeks [14]. According to clinical research infantile colic can be improved by taking *L. reuteri* for one week. Evidences demonstrated that specific Lactobacillus strains inhibit the advancement of gas-producing coli forms isolated in infants with colic [15].

1.5 Constipation

The prevalence of chronic constipation in the general population ranges from 15% to 25% [16]. Authors, based upon the action of *L. reuteri* in adult mouse colon, speculated that *L. reuteri* is beneficial in constipated geriatrics [17]. Probiotics, particularly Lactobacillus *L. reuteri* DSM 17938, have been suggested as a treatment for children with chronic constipation. These probiotics increase defecation frequency and intestinal micro biota composition, reducing transit time and increasing bowel frequency [19].

1.6 Eczema

L. reuteri and *L. rhamnosus* supplementation may prevent or reduce eczema symptoms in children. Studies show that combining probiotics during pregnancy and early life reduces eczema at 2 years old [20]. Additionally, a 6-week supplement reduced eczema severity in 1- to 13-year-old children.

1.7 Metabolic Syndrome (METs)

L. reuteri, a commensal organism isolated from breast milk, has potential as a treatment for infantile colic and diarrheal disease. *L. reuteri* minimises swelling in young rat pups.and experimental enterocolitis involving necrosis by modulating TLR-4 and NF-kB signalling [21]. “Consumption of *L. reuteri* V3401 improves selected inflammatory parameters and modifies the GI microbiome in adults with METs. *L. reuteri* V3401 has been shown to reduce the absorption of fluoresterol by HT-29 human enterocytes, which is linked to insulin resistance and hypercholesterolemia. Research has revealed that *L. reuteri* V3401 can reduce cholesterol absorption by intestinal epithelial cells, potentially promoting standards for a balanced diet and frequent physical activity for obese persons with METs” [22].

1.8 Gastrointestinal tract (GIT)

“L. reuteri is a fermentative bacterium discovered in the human digestive system of humans and animals. Oraly giving of *L. reuteri* ATCC 55730 reduces diarrhea, infections, and inflammation in humans” [25]. It is also a probiotic, promoting health by colonizing the stomach, intestines and inhibiting *H. pylori* growth. Oral L. rhamnosus GR-1 and *L. reuteri* RC-14 reduce streptococcus colonization among expectant mothers and are antagonistic to intestinal and urogenital pathogens [27].

1.9 Immunomodulation

:"Clinical studies have determined that *L. reuteri* can stimulate anti-inflammatory Treg cells (Regulatory T cells). *L. reuteri*'s ability to stimulate Treg cells is mostly strain-dependent. The anti-inflammatory property of *L. reuteri* is not only because of its ability to stimulate Treg cells but also because of its ability to lower serum levels of tumour necrosis factor (TNF), interleukin-6 (IL-6), and MCP-1 Membrane Cofactor Protein, especially in strains such as GMNL-263 in mice on a high-fat diet was observed" [28]. Infant and toddler diseases such as necrotizing enterocolitis, diarrhoea, and infantile colic can be effectively treated and prevented with *L. reuteri* DSM17938 [11].

1.10 Modulation of host microbiota

Gut microbiota

A study assessed the relationship of *L. reuteri* (DSM17938) a human-origin strain, its capability to lower multi-organ inflammation and promote the lifespan of scurfy mice with dysbiosis of gut microbiota [30]. *L. reuteri* NCIMB 30242 was able to raise the Firmicutes to Bacteroidetes ratio in fit individuals. when given to adult humans as delayed-release capsules for 4 weeks. In randomized-controlled trials (RCT), it has been shown that the strain *L. reuteri* DSM 17938 improves growth and immunological function in preterm infants and decreases sepsis, intolerance of enteral nutrition and days on antibiotic treatment [31].

Vaginal Microbiota

"GeneralLy in women, lactobacilli predominate in the vaginal microbiome. People with bacterial vaginosis (BV) have a significantly lower Lactobacilli population. Probiotic lactobacilli can lessen BV, replace lactobacilli in non-pregnant women's vaginas, and decrease episodes of recurrent urinary tract infections (UTI). A prior study in non-pregnant women found that probiotic treatment with L. rhamnosus GR-1 and *L. reuteri* RC-14 (109 cfu) decreased BV occurrence and recurrence" [32].

1.11 Unusual applications

- In addition to mesalazine, local delivery of *L. reuteri* ATCC 55730 can reduce the symptoms of ulcerative colitis [33]. IL-8, a chemokine known to be a key mediator in the innate immune system response, is produced less when *L. reuteri* is present [34].
- A starting formula that has been starch thickened and partially hydrolyzed and is supplemented using *L. reuteri*, a probiotic has been demonstrated to improve gastric motility in animals and the frequency of regurgitation in infants who have been diagnosed with functional regurgitation [35].
- Probiotics have positive impacts on blood sugar regulation. One research indicated that *L. reuteri* strains ADR-1 and ADR-3 can be utilized as healthcare items for the therapy of T2DM because of lower insulin resistance [36].
- Probiotic and omega-3 polyunsaturated fatty acid supplementation during pregnancy may alter the bacteria in the intestines and thus affect the development of the immune system. It also operates synergistically through immune regulatory and anti-inflammatory pathways [37].
- Periodontitis is a multifactorial chronic inflammatory illness, and using the probiotic strains *L. reuteri* ATCC PTA 5289 and DSM 17938 has been shown to enhance periodontal health in patients with the condition. By blocking NF-Kb, *L. reuteri* significantly reduces overall body inflammation [38].
- According to the study, *L. reuteri* and *Porphyromonas gingivalis* might stimulate the balance between oral pathogenic bacteria and probiotics, causing human gingiva-derived mesenchymal stem cells (GMSCs) move around, develop into osteoblasts, and multiply in vitro. *L. reuteri* neutralize the LPS in *P. gingivalis* [39], preserving the equilibrium of probiotics and oral infectious bacteria. MSC therapies increase the repair of tissues and improve wound healing of skin and mucosa [50, 51]. The GMCs can be stimulated and wound healing enhanced by *L. reuteri* extracts.

Therefore, the present systematic review aims to evaluate the efficacy of *L. reuteri* supplementation in improving the therapeutic outcomes of various diseases.

2. METHODOLOGY

The current study followed the guidelines established by the Preferred Reporting items for Systematic Review and Meta-Analyses (PRISMA) guidelines [52].

2.1 Inclusion Criteria

The following inclusion criteria were applied to select the appropriate studies

1) Type of studies: RCT, randomized double blind cross over placebo controlled and single Centre trial (PROSIR), Randomized placebo-controlled pilot study, single blinded cross over design, prospective randomized double-blind placebo controlled multicenter allergy prevention trial (PROOM-3), Randomized masked trial, double blind placebo-controlled crossover study for studying the therapeutic effect of *L. reuteri* under various conditions.

2) Participants who are pregnant, children with antibiotic associated diarrhea, children with functional chronic constipation, infants with FR (Functional regurgitation), children with active distal UC, healthy adults, adults with METs, Pediatric outpatient setting, free living older adults, children in anti *H. pylori* treatment, humans who are *H. pylori* positive asymptomatic adults , patients with *H. pylori* infection without any treatment, Infant colic, extremely preterm infants, infants with acute diarrhea, adults with chronic *functional constipation (FC)*, obese adults with METs children with atopic dermatitis.

- Studies comparing the effects.
- Patients followed for atheist 4 weeks reporting the effect of *L. reuteri* supplement.
- Outcome: Therapeutic efficacy of *L. reuteri* under various conditions was evaluated.

2.2 Search Strategy

We systematically searched the PubMed and the Cochrane library electronic database for studies reporting effect of *L. reuteri* in pediatrics, pregnant and adults in different condition. The included studies were published from 2003 to 2021. Search items included *L. reuteri*, *H. pylori* infection, diarrhea, antibiotics associated diarrhea, abdominal pain, colic condition, constipation, eczema, gut immunomodulation, wound healing, inflammatory disease, allergic condition during pregnancy. We didn't find other studies in the normal research. In addition, we searched the reference list of included studies and of recent related review.

2.3 Outcome Analysis

Using *L. reuteri* supplementation the main outcome analyzed was the efficacy of *L. reuteri* under various conditions such as acute diarrhea in infant, acute infectious diarrhea in pediatric outpatient setting, *H. pylori* infection, and *Group B Streptococcus* (GBS) colonization. The secondary outcomes were to assess the median crying time in infant colic, severity by using *Gastrointestinal Symptom Rating Scale (GSRS)* scale and the mayo score & histological score in case of UC.

2.4 Selection of studies for inclusion and data extraction

Search results were combined and duplicates were removed. We first screened based on title and abstracts for relevance, after which full text was reviewed. The second-round selection involved the complete and careful review of articles to confirm whether those studies described the effects of *L. reuteri* supplement and various diseases such as diarrhea, IBS, eczema, vaginal infection, lactose intolerance, urinary infection, peptic ulcer disease (H. pylori). Studies that met the inclusion criteria were considered eligible for this systematic review. We independently assessed every article for inclusion and extracted data for articles. Data on age, gender, role of probiotic *L. reuteri*, estimated benefits of *L. reuteri* under various conditions and outcomes were recorded.

3. RESULTS

3.1 Description of included studies

A total of 393 studies were initially identified by the above-mentioned search strategies (58 in AAP News & Journals and, 35 in Elsevier, 12 in Cochrane library, 163 in biomed central and 125 in PubMed). 359 studies were excluded after reading the titles and abstracts. Other studies were excluded because

studies on cell (n=2); some studies on animal (n=6), studies on bacteria (n=1), studies on meta analysis (n = 1), studies on review article (n = 1) and insufficient data (n=1). Finally, 22 studies met our criteria which is shown in Figure 1.

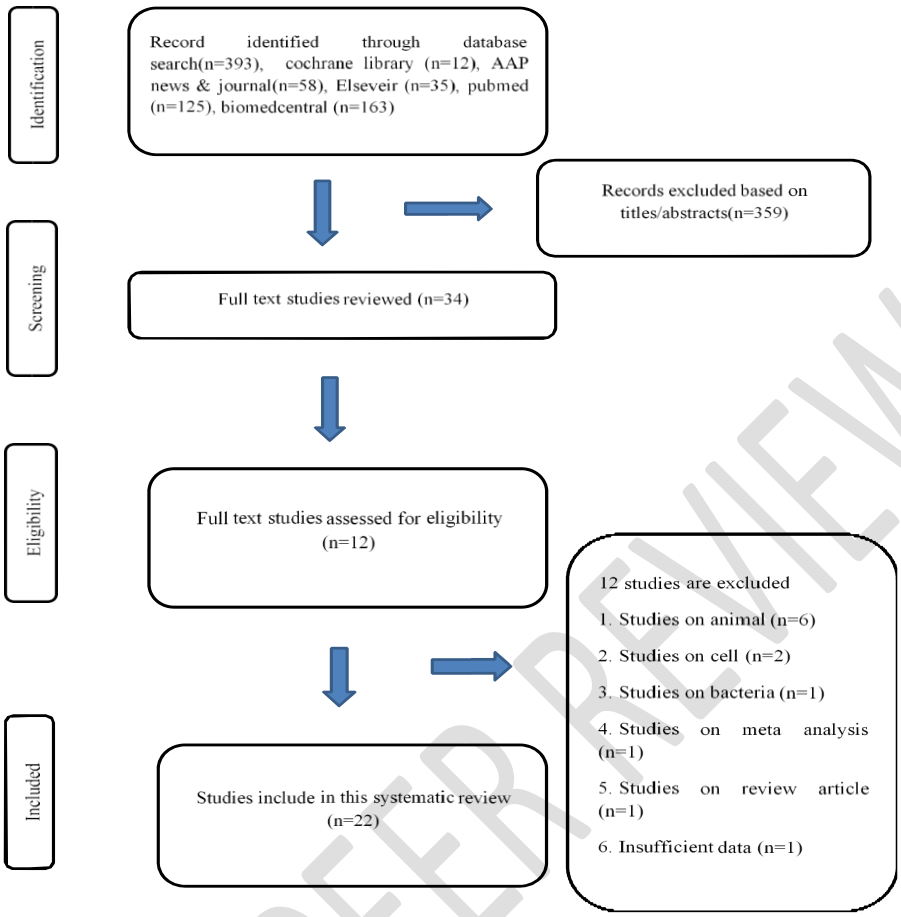

Figure 1: PRISMA flow chart

3.2. Summary of the included studies

Table 1 presents a summary of the studies assessed in this study. The title of the included studies, author, main objectives and the main results/conclusion are compiled in this table. The 22 eligible studies were conducted in Greece, Spain, Australia, Italy, Germany, Denmark, Canada, China, US, Poland, Japan, Sweden. A total of 1889 participants with mean age of infants (11 months), children (12 years), adults (45years), pregnant (during all trimester). Different strains used in this study are *L. reuteri* DSM17938, *L. reuteri* V3401, *L. reuteri* AICC 55730, *L. reuteri* DSMZ 17648, *L. reuteri* RC-14, *L. reuteri* DSM 122460, all studies were published in English only. Two studies were multi-centre trials. Duration of follow-up average is 8 months. Tables 2 represent a summary of the study characteristics for the accepted studies. Table 3 gives information regarding the severity of ADR in probiotic and placebo. Table 4 gives the information regarding efficacy of probiotics in various disease conditions. Table 5 gives the comparison of infant crying time supplemented with *L. reuteri* DSM 17938 with *L. reuteri* colonization and without *L. reuteri* colonization and also gives the information regarding the comparison of mayo score and histological score in patients with ulcerative colitis supplemented with *L. reuteri* ATCC 55730 with placebo.

Table 1: Summary of the studies assessed

S. No	Included Study Title	Objectives	Main Results/Conclusion	Author
1	Efficacy of an oral rehydration solution enriched with Lactobacillus reuteri DSM 17938 and zinc in the management of acute diarrhea in infants: a randomized, double-blind, placebo-controlled trial.	The aim of this double blind, randomized, placebo-controlled study, was to assess the efficacy of an ORS enriched with *L. reuteri* DSM 17938 and zinc (ORS+*L. reuteri* & Z) in well-nourished, non-hospitalized infants with acute diarrhea.	This randomized, double blind, placebo-controlled trial showed that ORS supplemented with *L. reuteri* DSM 17938 and zinc had comparable efficacy with ORS of similar composition and osmolality without added probiotic and zinc, in managing acute diarrhea, in well-nourished, non-hospitalized infants and toddlers with acute diarrhea. ORS enriched with *L. reuteri* DSM 17938 and zinc was well, tolerated without adverse effects.	Maragkoudaki M et al [55]
2	Lactobacillus reuteri DSM 17938 shortens acute infectious diarrhea in a pediatric outpatient setting.	Two randomized controlled clinical trials have shown that *L. reuteri* DSM 17938 reduces the duration of diarrhea in children hospitalized due to acute infectious diarrhea. This was the first trial evaluating the efficacy of *L. reuteri* DSM 17938 in outpatient children with acute infectious diarrhea.	The mean duration of diarrhea was significantly reduced in the *L. reuteri* group compared to the placebo the percentage of children with diarrhea was lower in the *L. reuteri* group after 48 h than the control group. No adverse effects related to *L. reuteri* were noted. *L. reuteri* DSM 17938 is effective, safe, and well- tolerated in outpatient children with acute infectious diarrhea.	Dinleyici EC et al [54]
3	Evaluation of the effect of Lactobacillus reuteri V3401 on biomarkers of inflammation, cardiovascular risk and liver steatosis in obese adults with metabolic syndrome: a randomized clinical trial (PROSIR).	The main objective isto evaluate the effectsof *L. reuteri* V3401 on the composition ofintestinal microbiota, Tenorio-Jimenez et al. BMC Complementary and Alternative Medicine of anthropometric parameters, and biomarkers of insulin resistance (inflammation, cardiovascular risk, and hepatic steatosis)in IRS patients.	The most commonly used strains of probiotics are Bifidbacterium and Lactobacillus spp. The consumption of L. acidophilus NCFM has been described to preserve insulin sensitivity without affecting systemic inflammation. Furthermore, *L. reuteri* LR6has been shown to decreasetotal cholesterol values and increase HDL-cholesterol levels in the plasma of rats fed a hypercholesterolemic diet. In humans, enrichmentof gut microbiota with *L. reuteri* SD5865 has been reported to increase insulin secretion, possibly due to augmented incretin release, although this strain does notseem to affect insulin sensitivity or body fat distribution.	Tenorio-Jimenez C et al [42]
4	Probiotics to improve outcomes of colic in the community: protocol forthe baby biotics randomized controlled trial.	This double-blind, placebo-controlled randomized trial aimsto determine whether the probiotic *L. reuteri* DSM 17938 benefits infants <3months old (<13.0 weeks) with colic by reducing daily duration of infant crying /fussing.	An effective, practical and acceptable intervention for infant colic would representa major clinical advance. Because our trial includes breast and formula-fed babies, our results should generalize to most babies with colic. If cost-effective,the intervention's simplicityis such that it could be widely taken up as a new standard of care in	Sung V et al [43]

		Secondary aims are whether there is reduced daily frequency of episodesof infant crying/fussing, and improved infant sleep, maternal mental health, and parent and family functioning.	the primary and secondary care sectors.	
5	Lactobacillus reuteri therapy to reduce side-effects during anti-Helicobacter pyloritreatment in children: a randomized placebo-controlled trial.	To determine whether adding the *L. reuteri* to an anti *H. pylori* regimen could help toprevent or minimize the gastrointestinal side-effects burden in children.	*L. reuteri* is capable of reducing frequency and intensity of antibiotic associated side-effects during eradication therapy for H. pylori.	Lionetti et al [9]
6	Non-Viable Lactobacillus reuteri DSMZ 17648 (Pylopass) as a new approach to Helicobacter pylori control in humans.	*L. reuteri* DSMZ17648 (Pylopass™/Lonza) specifically co-aggregates *H. pylori* in vitro and was shown to reduce C urea breath test in vivo. A single-blinded, placebo-controlled study was done in 22 *H. pylori* positive, asymptomatic adults.	There are many potential applications of *L. reuteri* DSMZ17648. It may reduce *H. pylori* load in high prevalence populations or beused as short-term prophylaxis during high stress periods. *L. reuteri* DSMZ17648 could also be utilized for chronic, long-term prophylaxis. *L. reuteri* DSMZ17648 may also be useful in populations with high *H. pylori* prevalence where antibiotic therapy has low compliance for cost reasons. Compared to living probiotic cells, dead cells areadvantageous in that storage and delivery is less demanding, shelf life is prolonged and production costs are reduced. Taken together, these characteristics could make the application of dead cells a realistic new approach to *H. pylori* control.	Mehling H et al [3]
7	Colonization and immunomodulation by Lactobacillus reuteri ATCC 55730 in the human gastrointestinal tract.	This study was designed to examine local colonization of the human gastrointestinal mucosa after Dietary supplementation with *L. reuteri* ATCC 55730 and to determine subsequentimmune responses at the colonized sites.	*L. reuteri* is known to be an indigenous species in the human ileum, and thus stimulation of T-helper cellsby this bacterium may be a central mechanism of symbiosis for improving thehealth of the host gut and a key mechanism of action for this probiotic. In conclusion,this study shows colonization of the human gastrointestinal tract by *L. reuteri* ATCC 55730 delivered in a tablet formulation and consequent modulation of local immunecell populations. It seems likely that this response to exogenous *L. reuteri*	Valeur N et al [26]

			may beinvolved in maintaining gastrointestinal well-being and defense against pathogens in an already- healthy recipient.	
8	Randomized clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis.	To assess in children with active distal UC the effectiveness of *L. reuteri* ATCC 55730enema on inflammation and cytokine expression of rectal mucosa.	In children with active distal UC, rectal infusion of *L. reuteri* is effective in improving mucosal inflammation and changing mucosal expression levels of some cytokines involved in the mechanisms of inflammatory bowel disease.	Oliva S et al [33]
9	The effect of Lactobacillus reuteri supplementation in adults with chronic functional constipation:a randomized, double- blind, placebo- controlled trial.	There is a growing interest for the use of probiotics for chronic constipation. A recent randomized controlled trial (RCT) showed a positive effect of *L. reuteri* on bowel movement frequency in infants with chronic constipation. The aim of the presentstudy was to evaluate the effects of *L. reuteri* in adult patients with FC.	*L. reuteri* is more effective than the placebo in improving bowel movement frequency in adult patients with FC as previously demonstrated in children, even if it seems to have no effect on stool consistency.	Ojetti V et al [46]
10	Effect of oral probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 on the vaginal microbiota, cytokines and chemokines in pregnant women.	The goal was to determine the effect of L. rhamnosus GR-1 and *L. reuteri* RC-14 administered orally, twice daily for12 weeks on the vaginal microbiota, cytokines and chemokines of low-risk pregnant women.	In conclusion, this study showed that oral probiotic treatment with probiotic GR-1 and RC-14 did not result in adverse outcomes, in agreement with other studies. The characteristics of L. rhamnosus GR-1 determined in vitro that predicted an ability to alter the vaginal environment of pregnant women via oral administration, did not translate to humans when the organism was administered orally with *L. reuteri* RC-14. That said, many women delivered normally which	Reid G et al [32]

			suggests that the probiotic was not essential for health in women consuming fermented foods, and the cohort was not devoid of lactobacilli or at risk of preterm labor. Future studies of probiotics should include women at risk of preterm delivery, administer a higher lactobacilli oral dose or use intravaginal instillation and more closely examine fermented food products and regularity of consumption.	
11	Effect of probiotic Lactobacillus strains in children with atopic dermatitis.	The purpose of this investigation was to evaluate the clinicaland anti- inflammatory effect of probiotic supplementation in children with AD.	A combination of L. rhamnosus 19070-2 and *L. reuteri* DSM 122460 was beneficial in the management of AD. The effect was more pronouncedin patients with a positive skin prick test response and increased Immunoglobin E(IgE) levels.	Rosenfeldt V [20]
12	Oral Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 to reduce Group B Streptococcus colonization in pregnant women: a randomized controlled trial.	This study is to examine the effect ofL. rhamnosus GR-1 and *L. reuteri* RC-14 taken orally before bedtime on GBS-positive pregnant women with respect to becoming GBS negative.	In conclusion, the study demonstrated that oral probiotics containing L. rhamnosus GR-1 and *L. reuteri* RC-14 could reduce the vaginal and rectal GBS colonization in pregnant women. authors propose thatoral probiotics should be administered early in pregnancy to reduce GBS colonization at 35 to 37 weeksof gestation. This could reduce early-onset GBS infection and the need for antibiotic treatment during labor. Moreover, it might help to overcome inadequate antibiotic treatment during labor in multiparous women and lead to a reduction of admission rate to the neonatal unit.	Ho M et al [45]
13	Impact of Lactobacillus reuteri colonization on gut microbiota, inflammation, and crying time in infant colic.	Authors investigated the relationship between *L. reuteri* colonization and fecal microbiota (microbial diversity and Escherichia coli), intestinal inflammation, and crying time in infants with colic, using a subset of 65 infants from the Baby Biotics trial, which randomized healthy term infants aged <13weeks with infant colic to receive probiotic *L.*	In this study, there were no differences in E. coli colonization rates or densities, microbial diversity or intestinal inflammation by *L. reuteri* colonization status.They found that *L. reuteri* density positively correlated with crying time, and E. coli density negatively correlatedwith microbial diversity. As density of *L. reuteri* was associated with increased crying time, *L. reuteri* supplementation may not be an appropriate treatment for all infants with colic.	Nation ML et al [40]

		reuteri DSM 17938 or placebo daily for 28 days		
14	Effect of a partially hydrolysed whey infant formula supplemented with starch and Lactobacillus reuteri DSM 17938 on regurgitation and gastric motility.	This double-blind, randomized controlled trial investigated the effects of a formula containing partially hydrolyzed, 100% whey protein, starchand *L. reuteri* DSM 17938 on gastric emptying rate (GE rate) and regurgitation frequency in infantswith Functional regurgitation (FR).	The use of a starch- thickened, partially hydrolyzed infant formula supplemented with the probiotic *L. reuteri* effectively decreases the daily frequency of regurgitation and significantly enhances gastric emptying in infants affected by FR. Targeted studies are needed to shed light on the exact mechanisms through which each component of this formula exerts its beneficial effects, and to evaluate long- term data on efficacy and safety.	Indrio F et al [15]
15	Safety and tolerability of Lactobacillus reuteri DSM 17938 and effects on biomarkers in healthy adults: results from a randomized masked trial.	The primary aim of this prospective, double-blind placebo-controlled trial was toinvestigate if daily treatment of adults with *L. reuteri* DSM 17938 for 2 months is safe and well- tolerated. Our secondary aim was to determine if *L. reuteri* treatment has immune effects as determined by regulatory T cell percentages, expression of toll-like receptors (TLR)-2 and 24 on circulating peripheral blood mononuclear cells (PMBCs), cytokine expression by stimulated PBMC, and intestinal inflammation as measured by fecal calprotectin.	*L. reuteri* is safe and well tolerated in adults, without significant changes in immunologic markers. Therewas a small but significant increase in fecal calprotectin,perhaps indicating some element of immune recognition at the intestinal level.	Mangalat N et al [21]
16	Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhea in children: a randomized clinical trial.	To assess the effectiveness of *L. reuteri* DSM 17938 for the prevention of diarrhea and antibiotic-associateddiarrhea (AAD) in Children.	*L. reuteri* was noteffective in the prevention ofdiarrhea or AAD in children.	Szajewska H [48]
17	Lactobacillus reuteri DSM 17938 and magnesium oxide in children with functional chronic constipation: a double-blind and randomized clinical trial.	Chronic FC is a frequent condition. The aim of the studywas to evaluate the efficacy of the probiotic *L. reuteri* DSM17938 and magnesium oxide	*L. reuteri* DSM 17938 and MgO were both effective in the management of FC in young children. MgO causedan imbalance in the gastrointestinal microbiome, which was not the case in theprobiotic group.	Kubota M et al [53]

		(MgO) for relieving chronic FC in children.		
18	Lactobacillus reuteri V3401 reduces inflammatory biomarkers and modifies the gastrointestinal microbiome in adults with metabolic syndrome: the PROSIR Study.	They aimed to evaluate the effects of *L. reuteri* V3401 together with healthylifestyle recommendations on adult patients with MetS.	Consumption of *L. reuteri* V3401 improved selected inflammatory parameters and modified the gastrointestinal microbiome. Further studies are needed to ascertain additional beneficial effects of other probiotic strains in MetS as well as the mechanisms by which such effects are exerted.	Tenorio-Jimenez C et al [42]
19	Helicobacter pylori eradication: sequential therapy and Lactobacillus reuteri supplementation.	To evaluate the role of sequential therapyand *L. reuteri* supplementation, in the eradication treatment of H. pylori.	The sequential treatment regimen achieved a significantly higher eradication rate of *H. pylori* compared with standard 7-d regimen. *L. reuteri* supplementation could reduce the frequency and the intensity of antibiotic-associated side-effects.	Efrati C et al [44]
20	Effects of Lactobacillus reuteri supplementation on the gut microbiota in extremely preterm infants in a randomizedplacebo-controlled trial.	They assessed the effect of *L. reuteri* supplementation, from birth to post- menstrual week (PMW)36, on infant gut microbiota.	In conclusion, daily supplementation of *L. reuteri* DSM 17938 in extremely low birth weight babies (ELBW) preterm infants modulated the gut bacterial composition, with increased bacterial diversity and a high abundance of the supplemented probiotic during the 1st month of life. Major effects on the other bacterial taxa were only observed during the1st weeks of life, with lower relative abundance of Staphylococcaceae and Enterobacteriaceae in the probiotic than the placebo group. No differences in the gut microbiota composition remained at the follow-up at 2 years of age.	Martı M et al [52]
21	Probiotic administration among free-living older adults: a double blinded, randomized, placebo-controlled clinical trial.	The aim of this double-blinded, randomized, placebo-controlled clinical trial was to evaluate the effect of the probiotic strain *L. reuteri* on digestive health and wellbeing in older adults.	The RCT failed to show any improvement in digestive health after daily intake of a probiotic supplement containing *L. reuteri*. Neitherwas any significant improvement in wellbeing, stress or anxiety observed. Even though the RCT had a negative outcome, the study highlights issues important to take into consideration when designing trials among older adults.	Ostlund-Lagerstrom L et al [10]
22	Changes in peripheral immune populations during pregnancy and modulation by probiotics and ω- 3 fatty acids.	The aims of the study were to investigate how maternal peripheral immunity is affected by pregnancy, and by probiotic and ω-3 fatty	In conclusion, some immunomodulatory effects were observed among circulating activated and resting Treg cells after around 20 weeks of treatment with *L. reuteri* during pregnancy, while ω-3PUFA	Forsberg A et al[47]

		acid supplementation.	supplementation had no effect in this substudy. Also, pregnancy was associated with several changes in systemic immune cell populations that indicate tolerance to the fetus while maintaining protection against infections.	

Table 2: Characteristics of included studies

Characteristics	No. of Studies	No. of Patient
Total	22	1889
Gender		
Male	8	207
Female	10	477
Not categorized	11	1205
Age (mean)	22	Infants :11 month Children:12 years Adults: 45 years
***L. reuteri* strains**		
L. reuteri DSM17938	12	1376
L. reuteri V3401	2	113
L. reuteri ATCC 55730	4	173
L. reuteri DSMZ 17648	1	22
L. reuteri RC-14	2	162
L. reuteri DSM 122460	1	43
Study Design		
Interventional		
Random (RTC)	19	165
Observational		
Prospective	3	232
Follow up (mean)	22	8 months
Publication year		
2002- 2011	4	133
2012- 2021	18	1766
Disease		
Colic disease	1	327
Acute diarrhea infection	2	111
H. pylori infection	3	145
Adult with metabolic syndrome	2	113
Chronic constipation disease	1	100
Antibiotics associated diarrhea	1	347
Group B streptococcus colonization in pregnant	1	96

women		
Atopic dermatitis	1	43
Ulcerative colitis	1	40
Study location		
Greece	1	58
Spain	2	113
Australia	1	287
Italy	5	275
Germany	1	20
Denmark	2	62
Canada	1	66
China	1	99
USA	1	40
Poland	1	247
Japan	1	60
Sweden	3	590

Table 3: Mean GSRS Scale

S. No	Study Title	Age	Probiotic	Placebo	Author
1	Lactobacillus reuteri therapy to reduce side-effects during anti-Helicobacter pylori treatment in children: a randomized placebo controlled trial.	<12.5 years	3.2±2	5.8±3.4	Lionetti E et al [9]
2	Probiotic administration among free-living older adults: a double blinded, randomized, placebo-controlled clinical trial	>65 years	3.76±2.0	4.93±1.7	Lionetti E et al [9]
3	Effect of Lactobacillus reuteri Supplementation in Adults with Chronic Functional Constipation: a Randomized, Double-Blind, Placebo-Controlled Trial	>35 years	3.89±1.79	5.28±1.93	Ojetti V et al [46]

Table 4: Efficacy of probiotics

***L. reuteri* strains**	**Disease/Condition**	**Composition**	**Efficacy of probiotics (%)**	**Efficacy of placebo (%)**	**Author**
L. reuteri DSM 17938	Acute diarrhea in infants	1) ORS with *L. reuteri* & zinc (probiotic). 2) ORS without *L. reuteri* (placebo).	64.3%	56.5%	Nation ML et al [40]
	Acute infectious diarrhea in paediatric outpatient setting	1) *L. reuteri* DSM17938. 2)Pacebo.	55.2%	13%	
L. reuteri ATCC 55730	H. pylori Infection	**7-days triple therapy:** 1) 7-days triple therapy (PPI + clarithromycin and amoxicillin or metronidazole) + *L. reuteri* during antibiotic treatment. 2) 7 days triple therapy + L.R after antibiotic treatment. **Sequential therapy:** 3) (5 days PPI+ amoxicillin therapy followed by a 5 days PPI +clarithromycin and imidazole) + *L. reuteri* during antibiotic treatment 4) Sequential regimen + *L. reuteri* supplementation antibiotic treatment.	88% 63%	- –	Oliva S et al [33]
L. reuteri RC-14	Group B streptococcus colonization in pregnant women	L. rhamnosus GR-1 and *L. reuteri* RC-14.	42.9%	18%	Reid G et al [32]
L. reuteri DSM122460	Children with atopic dermatitis	L. rhamnosus19070-2 and *L. reuteri* DSM122460.	56%	15%	Rosenfeldt V [20]

Table 5: Crying Time, Mayo Score, and Histological Score

***L. reuteri* strain**	**Study title**	**Disease/ Condition**	**Probiotics group**	**Median crying time day 0**	**Median crying time day 28**	**Author**
L. reuteri DSM17938	Impact of Lactobacillus reuteri colonization on gut microbiota, Inflammation and crying time in infant colic.	Infant colic	Infants colonized with *L. reuteri*	330 min/day	172.5 min/day	Nation ML et al [40]
			Infants not colonized with *L. reuteri*	328 min/day	180 min/day	

L.reuteri strain	Study title	Disease/ condition	Material	Mayo score	Histological score	Author
L. reuteri ATCC55730	Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis	Ulcerative colitis	Enema solution (*L. reuteri* ATCC55730 +Oral mesalazine	3.2±1.3 v/s 8.6±0.8 p < 0.01	0.6±0.5 v/s 4.5±0.6 p < 0.01	Oliva S et al [33]
			Placebo + oral mesalazine	7.1±1.1 v/s 8.7±0.7 NS	2.9±0.8 v/s 4.6±0.6 NS	

4. DISCUSSION

In this study, we compiled the characteristics (total population, gender, age, *L. reuteri* strains, follow-up, publication year, study location and study design), disease for disease conditions (Acute infectious diarrhea, *H. pylori* infection, GBS colonization in pregnant women, UC), infant colic condition assessment from the 22 included studies. The primary objective of this study is to assess the effectiveness of *L. reuteri* supplement in various conditions. In case of acute diarrhoea in infants the study showed that ORS with *L. reuteri* and Zinc and ORS alone with Zinc were both associated with reduction in the severity of diarrhea 2 days following the start of treatment in a group of well nourished, non-hospitalized infants and toddlers with acute gastroenteritis. In acute infectious diarrhoea in a pediatric outpatient setting ORS in combination with 5 days of *L. reuteri* DSM 17938 reduced the duration of acute infectious diarrhoea to approximately 15 hours in children aged between 3 and 60 months [40].

Administration of the dose of *L. reuteri* was well tolerated during days in treatment. The dose *L. reuteri* prevented diarrhoea in hospitalized adults. This safety study conducted in a vigorous randomized controlled manner, demonstrated that *L. reuteri* DSM 17938 is safe and well tolerated in healthy adults. In case of effects on biomarkers in this study there was not significant change in expression of cytokines including IL-10 and IL-12p70 by stimulated PBMC. However, there was a trend toward significance in decreased IL-1β expression in the probiotic treated group. This reduces the severity. In case of infant colic in the community, it impacts adversely on maternal mental health and is risk factors for shaken baby Syndrome. Since *L. reuteri* is cost effective, it could be widely taken up as a new standard of care in the primary and secondary care sectors. *L. reuteri* supplementation has been shown to reduce crying or fussing time in some infants with colic. Administration of *L. reuteri* ATCC 55730 at a dose of 4x108 cfu/day was well tolerated by both healthy individuals and subjects with an end ileostomy. It also induced a significantly higher amount of CD4-positive T-lymphocytes in the ileal epithelium [41]. Dietary supplementation with the probiotic *L. reuteri* ATCC 55730 induces significant colonization of the stomach, duodenum and ileum of healthy human and this is associated with the significant alteration of the immune response in the gastrointestinal mucosa [42]. This indicates a stronger immune system.

L. reuteri V3401 successfully reduces the absorption of cholesterol by intestinal in in-vitro and in -vivo assays [42]. Consumption of *L. reuteri* V3401 improved selected inflammatory parameters (decrease in IL-6 and sVCAM levels) and modified the gastro intestinal microbiome systemic low-grade inflammation has an important role in the development of METs. In this sense, IL-6 is the cytokine that has been associated with insulin resistance. Specifically, IL-6 is able to induced insulin resistance in both liver and adipocytes through reduction of phosphorylation of the insulin receptor substrate (IRS) or by transcription inhibition of the IRS. In addition, adhesion molecules, such as sVCAM-1 are necessary for normal development and function of the heart and blood vessels and they have been related to the development of CVD [42]. Supplementation of *L. reuteri* ATCC 55730 is capable of reducing frequency and intensity

of antibiotics associated side effects during eradication therapy receiving *L. reuteri* reported a significant reduction of the total symptoms score, which takes into account both the frequency and severity of the symptoms [9]. *L. reuteri* DSM17648 may reduce *H. pylori* load in high prevalence population or be used as short-term prophylaxis during high stress period it could also be for chronic, long-term prophylaxis. It showed significant decrease of *H. pylori* stomach colonization after *L. reuteri* supplementation in asymptomatic subjects with deterrable *H. pylori* infection [43]. *L. reuteri* colonizes the human gastric mucosa inhibits the binding of *H. pylori* to gastric epithelial cell lines and suppressors *H. pylori* urease activity in some studies monotherapy with *L. reuteri* showed a reduction in the *H. pylori* (bacterial load) [44]. In peripheral immune population during pregnancy changes and modulation by probiotics was reported that after around 20 weeks of supplementation during the 2nd half of pregnancy the number of activated and resting regulatory T cell is peripheral blood were lowest in the *L. reuteri* (it reduces cytotoxic immune population).

Approximately 15% to 40% pregnant women are colonized with GBS in the rectal and vagina. Reducing GBS colonization in pregnant women is the golden standard for the prevention early onset GSB disease in newborns. Taking probiotics showed that nearly 43% of GBS culture oral probiotics contain Rhamnus gr1 and *L. reuteri* RE-14 could reduce the vaginal and rectal colonization in pregnant women (administered to prevent GBS at 35-37 weeks of gestation early pregnancy) [44]. *L. reuteri* DSM 17938 supplementation led to relative abundance during the neonatal period and its abundance correlated with in bacterial composition at 2-4 weeks. In children with active distal UC, rectal infusion of *L. reuteri* ATCC 55730 is effective in improving mucosal inflammation and changing mucosal expression levels of some cytokines involved in the mechanisms of inflammatory bowel disease [45]. Supplementation with *L. reuteri* DSM 17938 significantly improved bowel movements, increasing the frequency of evacuations per week in adult patients affected by chronic FC [33]. In children with FC, supplemented with *L. reuteri* DSM 17938 and magnesium oxide supplementation defecation frequency of constipated children increased significantly in the probiotic and osmotic laxative groups compared with baseline. Furthermore, the consistency of the stool significantly decreased during treatment in the laxative group although not in the probiotic group. In case of regurgitation and gastric motility problems, when the patients were supplemented with partially hydrolyzed when infant formula supplemented with starch and *L. reuteri* DSM 17938 lead to a significant improvement in gastric motility and regurgitation frequency in infants diagnosed with FR [47]. It enhances gastric emptying time. Administration of probiotics lactobacillus strains (a mixture of L. rhamnous 190702 and *L. reuteri* TSM 12246) to children with atopic dermatitis was associated with the moderate important in clinical severity of eczema. Hospitalized children who received antibiotics were assigned to receive *L. reuteri* DSM 17938 or placebo it was effective in preventing diarrhea or AAD (antibiotic associated diarrhea) in children treated with antibiotic administered orally or intravenously [48]. When *L. reuteri* DSM 17938 was administered to infants with acute diarrhea in the form of ORS without *L. reuteri* and zinc and ORS with *L. reuteri* and zinc the proportion without disease in ORS without *L. reuteri* and zinc (56.5%) was lower than ORS with *L. reuteri* and zinc (64.3%). when *L. reuteri* ATCC 55730 was given in *H. pylori* infection in 7 days triple therapy and sequential therapy, the efficacy that is eradication rate was higher in 7 days triple therapy (88%) than the sequential therapy. When *L. reuteri* DSM 17938 was given for pediatric outpatient setting with acute the placebo (55.2%). In case of GBS infection colonization in pregnant women supplemented with *L. reuteri* RC-14 probiotic had decrease in GBS colonization (42.9%) higher than that of placebo (18%). In case of children with atopic dermatitis the improvement of eczema was higher in probiotic (*L. reuteri* DSM 122460) was 58% and the placebo was 15%. In children with FC supplemented with *L. reuteri* DSM 17938 increase in number of bowel movements and decrease in stool consistency was seen in all groups with *L. reuteri* DSM 17938. In case of *H. pylori* infection patients supplemented with *L. reuteri* DSM 17648 creatinine urea breath test had significance in both test product and placebo. Infant colic supplemented with *L. reuteri* DSM 17938 infants colonized with *L. reuteri* had decreased median crying time. In patients with UC supplemented with *L. reuteri* ATCC 55730 mayo score and histological score was significant. In adults with METs supplemented with *L. reuteri* V3401 the anthropometric and biochemical parameters were stabilized and the inflammatory biomarkers were decreased in some cases. *L. reuteri* hence,

produces improved significance in treatment of various conditions and diseases. Supplementation with *L. reuteri* decreased the severity of diseases and the prevalence of side effects. By improving the gut microbiota several conditions and inflammatory diseases can be managed in a better manner.

5. CONCLUSION

In this systematic review, when the efficacies of *L. reuteri* for various conditions were assessed, it was found to be more effective in *H. pylori* infection (88%). The crying time was reduced in infants colonized with *L. reuteri*. The mayo score and histological score were found to be reduced with *L. reuteri* supplementation in UC. A limitation of our review study is that no studies revealed about the cost for these supplementations. These studies consist of a small number of patients for certain conditions so we suggest that the results need to be validated through larger sample size in the future studies. Expert clinical skills are required to evaluate the safety & efficacy of *L. reuteri* supplementation.

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