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CURRENT EVIDENCE ON THE BENEFICIAL PROPERTIES OF LACTOBACILLUS SPECIES IN LACTOSE INTOLERANCE

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Abstract – ***Objectives:*** Lactose intolerance (LI) is a condition characterized by absent or strongly decreased levels of intestinal lactase. This is a key enzyme for the lactose hydrolysis to monosaccharides, glucose, and galactose. Colonic bacteria metabolize the unabsorbed lactose, producing short-chain fatty acids and gas and resulting in nausea, bloating and diarrhea. Probiotics are gaining interest as a potential compensation for lactase insufficiency, particularly the predominant ones in the gastrointestinal microbiota, such as Bifidobacterium and Lactobacillus. Among the latter species, medical attention is nowadays focusing on a gram-positive strain, *Lactobacillus Reuteri*, which is able to stabilize intestinal permeability and to reduce flatulence, diarrhea and nausea. The aim of this review is to collect and summarize the current evidence concerning the beneficial effects of *L. Reuteri* in the treatment of LI.
Materials and Methods: We conducted a thorough search on PubMed concerning evidence spanning from 2011 to 2021.
Results: *Lactobacillus Reuteri* has been demonstrated to stabilize intestinal permeability and to be effective in attenuating clinical signs and symptoms of LI. In particular, one study shows that Lactobacillus reuteri treatment significantly improves lactose digestion with respect to placebo; however, its effects were lower than those observed with tilactase supplementation.
Conclusions: Although literature is scant on this matter, *Lactobacillus Reuteri* seems to meet the requirements to be safely used in managing symptoms of lactose intolerance.

Keywords: Lactobacillus spp, Lactobacillus Reuteri (DSM 17938), Lactose intolerance, Probiotics, Microbiota, Lactase.

INTRODUCTION

Lactose intolerance (LI) is a lifelong disorder due to a reduced amount and/or a decreased activity of the enzyme lactase located in the brush border (microvilli) of the small intestine enterocytes, which causes a malabsorption of dietary lactose in the small intestine and results in a subsequent accumulation of undigested lactose in the colon. As a consequence, this causes an increase in fermentation by the resident flora and exerts locally osmotic effect that leads to gastrointestinal symptoms, such as bloating, excessive flatus, abdominal pain and diarrhea.

Three different forms of hypolactasia, or lactase deficiency, exist: primary, secondary, and congenital. Congenital lactase deficiency is an extremely rare autosomal recessive disorder associated with a decreased lactase activity[1]. It is a lifelong disorder characterized by growth retardation, where the very first exposure to lactose at birth leads to infantile diarrhea. The only way to treat this disease is to completely avoid lactose from birth. Primary lactase deficiency (lactase non-persistence) occurs in the majority of humans: the expression of lactase in the gut, maximum at birth, undergoes a gradual and progressive reduction after weaning in most mammals (up to 75-90% of the enzyme is lost), resulting in malabsorption of the lactose usually occurring not earlier than 6-7 years of age, and sometimes much later[2], showing an increase in prevalence even in the age groups over 65 years[3]. Acquired or secondary lactase deficiency represents the loss of lactase activity in a subject with prior normal levels of lactase. It is the consequence of diseases that damage the intestinal epithelium, e.g., untreated coeliac disease or intestinal inflammation[4,5] or can result from small intestine resections, and from gastrectomy[6].

Lactose intolerance can be usually diagnosed by conducting a thorough medical history supported by dietary changes. Patients usually have a history of flatulence and/or diarrhea after ingestion of milk and its derivatives. In case of diagnostic suspicion, it is necessary to carry out the hydrogen breath test, 50 grams of lactose are administered orally to the patient; this is followed by the measurement of the hydrogen produced by the bacterial metabolism of undigested lactose using a respirometer at a distance of 2, 3 and 4 hours from ingestion. The affected patients most of the times have an increase in exhaled H2> 20 parts per million from baseline. Sensitivity and specificity are > 95%[7].

Carbohydrate malabsorption, in the specific case of lactase deficiency, is easily controlled by following a lactose-free diet. The key treatment of lactose intolerance is to reduce the dietary quota of lactose until it is completely abolished. It is useful to use delactosed milk, containing a reduced percentage of lactose, obtained through enzymatic hydrolysis, to allow the intake of milk nutrients (calcium and glucose and galactose, that are the simple sugars constituents of lactose). Yogurt is usually well tolerated, since it contains a fair amount of intrinsic lactase produced by the strains of *Streptococcus thermophilus* contained therein[8]. As mentioned by Marteau et al[9], high levels of lactase are contained within yogurt bacteria, and this is quickly released when bile salts lyse bacteria in the gastrointestinal tract. Consequently, tolerance to yogurt shown by lactase deficient people seems to be due to the lactase content of the bacterial strains and to a lesser extent to the action of the bacteria themselves. In addition, other probiotics containing lactase, such as Lactobacillus acidophilus may also be effective, but their lesser efficiency compared to yogurt bacteria can be explained by a higher resistance to bile[10].

In this narrative review, we collected recent updates (Table I) on the beneficial properties of *Lactobacillus spp*, particularly *L. reuteri 17938*, and their potential niche in the management of lactose intolerant patients.

Role of Probiotics in the Management of Lactose Intolerance

Recently, the effectiveness of probiotics in the treatment of LI was examined using 15 randomized double-blind studies evaluating probiotic strains with the greatest number of proven benefits[11]. Various degrees of efficacy are reported in the results, but an overall positive relationship exists between probiotics and lactose intolerance. In particular, *Bifidobacteroium longum*, a Gram-positive, non-motile, non-sporulating lactic-acid bacteria, modifies the amount and metabolic activities of the colonic microbiota and alleviates symptoms in lactose-intolerant subjects. Supplementation acts by changing colonic microbiota, leading to attenuation of LI symptoms. Probiotic supplementation of *Bifidobacterium animalis*, a Gram-positive, anaerobic, rod-shaped bacteria found in the large intestine, can improve the symptoms of lactose intolerance in adults improving overall gastrointestinal transit time[12]. There is limited evidence to suggest that *Lactobacillus bulgaricus*, a Gram-positive, facultatively anaerobic, non-motile lactic acid bacteria, is effective in eliminating LI symptoms by improving lactose digestion. *Lactobacillus acidophilus*, a Gram-positive bacterium, analyzed in nine studies, did not show significant potential to

TABLE 1. SUMMARY OF THE MOST RELEVANT BIBLIOGRAPHY CONSIDERED FOR THIS REVIEW (KEYWORDS USED: "LACTOBACILLUS REUTERI (DSM 17938)", "LACTOSE INTOLERANCE", "PROBIOTICS", "MICROBIOTA", "LACTASE").

First Author	Type	–•Year of publication	No. of patients	Main Findings
Oak SJ[11]	Systematic	2018 review	/	The effectiveness of probiotics in the treatment of lactose intolerance was assessed using 15 randomized double-blind trials. Eight strains of probiotics with the highest number of proven benefits were evaluated. Different degrees of efficacy were shown but an overall positive relationship was found between lactose intolerance and probiotics.
Marteau P[12]	Double-blind,	2002 cross-over study	36	Bifidobacterium animalis DN-173 010 administration in healthy women reduces the colonic transit time and this fact is not explained by modifications of the secondary bile acids or faecal bacterial mass.
Yesovitch R[13]	Pilot study	2004	10	Direct consumption of the probiotic VSL3 may not improve parameters of lactose maldigestion without metabolic activation.
Ojetti V[14]	Randomized	2010 controlled trial	60	In lactose intolerants, tilactase strongly improves both gastrointestinal symptoms lactose and breath test results after lactose ingestion compared to placebo. *Lactobacillus reuteri* also is effective, but lesserthan tilactase. This probiotic may represent an interesting treatment option for lactose intolerants due to its simple use, and its effect may even last in the time after stopping its administration.
Duar RM16	Narrative Review	2017	/	An elucidation on the evolution and natural history of Lactobacillus genus: phylogenetic, genomic and metabolic metadata
Mu Q21	Narrative Review	2018	/	A detailed explanation of the different ways through which inflammatory diseases, including those located in the gut, may be ameliorated by increasing the colonization of *L. reuteri*
Abhisingha M[28]	Laboratory study	2018	/	Fifty-eight isolates consisting of *Lactobacillus reuteri*, *L. salivarius*, *L. mucosae*, *L. johnsonii*, and *L. crispatus* were selected and further analysed for probiotic properties, including production of antimicrobial substances and acid and bile tolerance.
Ang L. Y[29]	Laboratory study	2016	/	*L. reuteri* Protectis displays a significant dose-dependent antiviral activity against Coxsackievirus type A (CA) strain 6 (CA6), CA16 and EV71, but not against Coxsackievirus type B strain 2.

CONTINUED

TABLE 1 *(CONTINUED)*. SUMMARY OF THE MOST RELEVANT BIBLIOGRAPHY CONSIDERED FOR THIS REVIEW (KEYWORDS USED: "LACTOBACILLUS REUTERI (DSM 17938)", "LACTOSE INTOLERANCE", "PROBIOTICS", "MICROBIOTA", "LACTASE").

First Author	Type	–•Year of publication	No. of patients	Main Findings
Jorgensen M[33]	Laboratory study	2017	/	*L. reuteri* exhibited antifungal properties against five of the six most common oral Candida species. Further, the results reconfirms that the probiotic capacity of *L. reuteri* is strain specific.
Greifovà G[34]	Laboratory study	2017	/	All studied *L. reuteri* strains showed the ability to produce lactic acid, acetic acid, ethanol, reuterin and phenyllactic acid-a, a potent antifungal compound.
Thomas CM[36]	Laboratory study	2012	/	The identification of bacterial bioactive metabolites and their corresponding mechanisms of action with respect to immunomodulation may lead to improved anti-inflammatory strategies for chronic immune-mediated diseases.
Bene K[42]	Laboratory study	2017	/	Selected commensal bacterial strains are able to drive strong effector immune responses by moDCs, while in the presence of ATRA, they support the development of both tolerogenic and inflammatory moDC in a RARα-dependent manner.
Jones ML[46]	Randomized controlled trial	2012	127	The deconjugation of intraluminal bile acids results in reduced absorption of non-cholesterol sterols and indicate that *L. reuteri* NCIMB 30242 capsules may be useful as an adjunctive therapy for treating hypercholesterolemia.

LI treatment. The insufficient survival and viability of L. acidophilus in commercial food products has been associated to this lack of effect by researchers[13]. *Lactobacillus rhamnosus*, a Gram-positive lactic acid bacterium that is present in the gut microflora, seems to improve symptoms in LI subjects with a decrease in duration and frequency of diarrhea. There is limited evidence on the role of *Lactobacillus reuteri*, a Gram-positive probiotic strain that is naturally found in the gastrointestinal tracts. In a comparative study by Ojetti et al[14] (2010), *L. reuteri* and tilactase, i.e., a beta-D-galactosidase obtained from Aspergillus oryzae, were proven to ameliorate gastrointestinal symptoms after lactose intake with respect to placebo. This study involved 60 subjects with lactose intolerance. However, the effects of *L. reuteri*, checked by lactose breath test were lesser than that of tilactase. Finally, although *Saccharomyces boulardii* has been extensively used as a probiotic and dietary supplement, there has been a lack of research in proving the efficacy of this yeast in the context of lactose intolerance.

Lactobacillus spp and Limosilactobacillus Reuteri

Lactobacillus spp is one of the most used probiotic families in the clinical setting and numerous food products are a source of it. In fact, the genus Lactobacillus is composed of a vast and heterogeneous range of Gram-positive, non-spore-forming, and facultative anaerobic bacteria, including *L. bulgaricus, L. acidophilus, L. rhamnosus* and *L. reuteri*[15,16].

Among these, one should be remembered in particular, isolated for the first time in 1962: the *L. reuteri*. This probiotic grows in atmospheres with limited presence of oxygen and is able to colonize the GI tract of humans and animals, particularly by settling in the most proximal portions of the digestive tract[17,18].

This ability is linked to the fact that it is able to survive bile salts and environments with acidic pH, such as the gastric one. Furthermore, *L. reuteri* is regarded as a probiotic since it meets some fundamental prerequisites for GI colonization: through adhesins it can adhere to the epithelium, ensuring host-probiotic interaction; additionally, it competes with pathogenic microorganisms and is a safe product to administer[19-21].

The antimicrobial properties and immunomodulatory effects of *L. reuteri* strains are related to their metabolite production profile. In particular, many strains produce reuterin, a known antimicrobial compound which is a mixture of several forms of 3-hydroxypropionaldehyde (3-HPA). This molecule is spontaneously converted into acrolein, which is a cytotoxic electrophile with antimicrobial properties. Reuterin, in this way, can inhibit a series of microorganisms, in particular Gram-negative bacteria, but not only[22-24].

Yet, as far as *L. reuteri* is concerned, the beneficial effects of this strain are expressed, not only thanks to reuterin. In fact, it has been proven to be effective against a variety of gastrointestinal infections (such as *C. difficile*, *E. coli*, *Salmonella*, *H. pylori*) for the production of many other substances, including lactic acid, ethanol, acetic acid and reutericycline[25-28].

L. reuteri has also shown benefits when used in viral infections with circovirus, coxsackievirus, pneumovirus, rotavirus and papillomavirus, since it secretes metabolites with antiviral components. The same is true for the antifungal properties demonstrated in the context of candidiasis[29-33].

Some strains of *L. reuteri* are also capable of converting the amino acid L-histidine into histamine. An example derives from studies conducted on the production of histamine by *L. reuteri 6475*, which suppressed the production of tumor necrosis factor (TNF) by activated monocytes. This suppression is linked to the activation of histaminergic H2 receptors, an increase in intracellular cAMP and protein kinase A, and the simultaneous inhibition of the MEK/ERK signaling mechanism[34-37].

Another property of *L. reuteri* is the ability to produce different types of vitamins, including folic acid (vitamin B9) and cobalamin (B12)[38,39].

The production of exopolysaccharide is another important element for the biofilm formation and the adherence of *L. reuteri* to the intestinal epithelium. This substance, in studies on porcine models, prevented the adhesion of *E. coli* to the epithelial surface and, at the same time, suppressed gene expression that would have led to the production of proinflammatory cytokines such as IL-1beta and IL-6[40,41].

Another fundamental feature of *L. reuteri* is that of modulating the intestinal microbiota to restore tissue homeostasis in the event of a disturbed balance of the bacterial flora. To demonstrate this, a study on murine model with foxp3 mutation and consequent intestinal dysbiosis, revealed benefit in the administration of *L. reuteri* in terms of increased survival of mice and reduction of multi-organ inflammation[42-45].

L. reuteri NCIMB 30242, for example, is able to activate the hydrolase of bile salts and the consequent increase in circulating bile acids has been proposed as an explanation for the modulation of the intestinal microbiota[46].

Furthermore, the immunomodulation of *L. reuteri* was seen to be expressed through the induction of anti-inflammatory Treg cells, but also with the suppression of Th1 and Th2 responses in mice with Treg cell deficiency[21,45].

Thanks to this evidence, *L. reuteri* has been used therapeutically in a variety of gastrointestinal and non-gastrointestinal conditions. An example, there are the many studies conducted on the pediatric population, where *L. reuteri* has given promising results in the context of infant colic, diarrhea, functional abdominal pain, intolerance to food, allergies, regurgitation and atopic dermatitis[47].

The main aforementioned mechanisms of action of *L. reuteri* are summarized in Figure 1.

L. Reuteri and Lactose Intolerance: What We Know So Far

On the other hand, an aspect that has not been investigated in the literature is the use of this important strain in the context of food intolerances and, in particular, lactose intolerance.

In fact, therefore, many studies have expressed themselves on the immunomodulatory, anti-inflammatory, bactericidal and microbiota regulation properties by *L. reuteri*, but only one study, conducted by Ojetti et al[14], has investigated the role that this probiotic can exert in individuals with lactase deficiency.

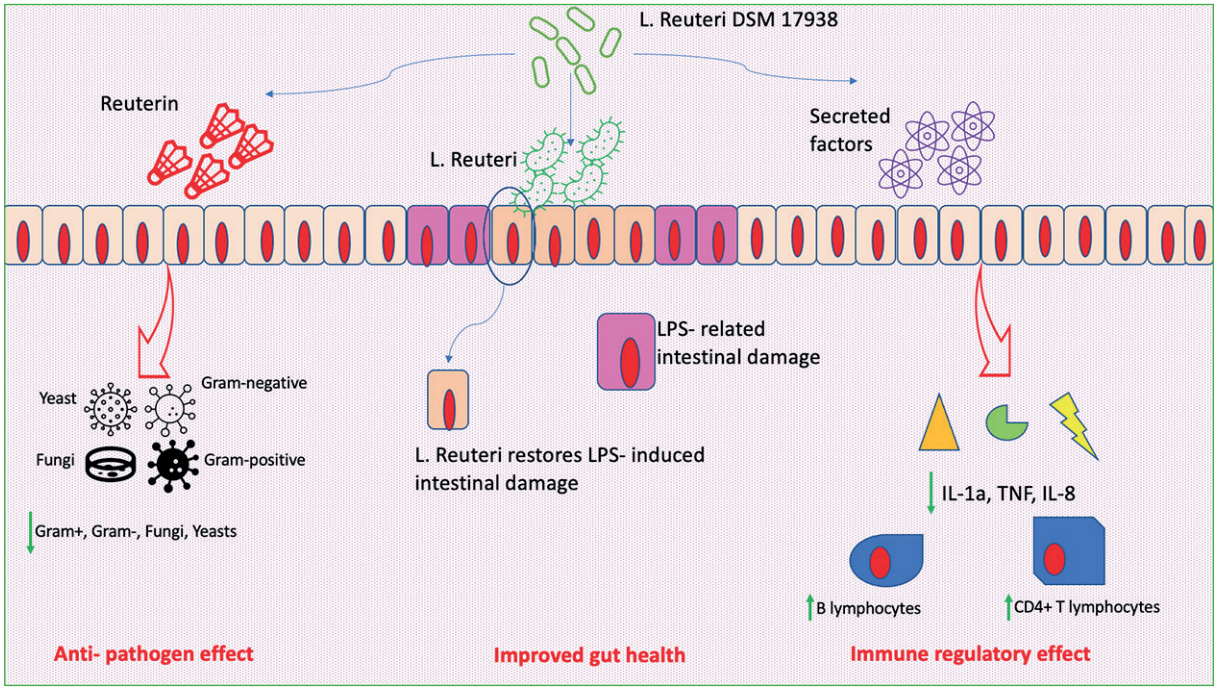

Figure 1. This figure summarizes the different mechanisms through which *L. reuteri* exerts its beneficial properties on the gut: it is able to restore lipopolysaccharide-induced (LPS-induced) intestinal damage; its secreted factors lead to reduced release of interleukin-1a (IL-1a), interleukin-8 (IL-8) and tumor necrosis factor (TNF); particularly, reuterin (one of the most important factors secreted by *L. reuteri*) has an anti-pathogen effect towards Gram + and Gram- bacteria, fungi and yeasts.

A few years ago, prospectively studied the effect of supplementation with tilactase compared to *L. reuteri* and placebo on hydrogen breath excretion and gastrointestinal symptoms in lactose intolerant patients during a H2-LBT standard.

They enrolled 60 patients with a randomization into three groups: Tilactase group, *L. reuteri* group and Placebo group. Primary outcomes were H2-LBT normalization rate and treatment effects on mean maximum H2 concentration and gastrointestinal symptoms.

80% of Tilactase patients, 35% of *L. reuteri* patients and 0% of Placebo patients were respectively LBT-control negative.

After treatment, a significant reduction in mean peak H2 excretion was observed in the Tilactase group and in the *L. reuteri* group, compared to baseline values, while no changes were found in the Placebo group.

Significant improvement in gastrointestinal symptoms was seen in both the tilactase and *L. reuteri* groups, while no changes occurred in the placebo group.

The authors suggested that the benefit given by the probiotic was linked to the adhesion to the biofilm in proximal portions of the small intestine, where it exerted the beta-galactosidase effect.

It is important to emphasize that the administration of tilactase was, however, more effective than *L. reuteri*, and the authors attributed this to the strong interindividual variability in the level of enzymatic lactase deficiency. This led to the hypothesis that those who had severe lactase insufficiency could only benefit from supplementation with tilactase at the time of the meal, while the probiotic found space and rationality where the deficiency was milder.

It is also interesting to observe the advantages that the use of *L. reuteri* has compared to tilactase: the dosage of the exogenous enzyme must always be calibrated based on the amount of lactose contained in the food that will be eaten and must always be taken in conjunction with the meal, while the probiotic does not require dosage changes, it must be taken regardless of the amount of lactose that will be ingested and the effect of beta-galactosidase lasts until the intestinal colonization by the probiotic takes place, therefore, even once its administration is stopped.

However, no studies have yet been conducted specifying the optimal dosage and recommended duration of treatment for patients with lactose intolerance, and for a probiotic that has already proven effective in numerous contexts, its potential is worth being investigated more also in this context with future studies.

CONCLUSIONS

Our review has highlighted the potential role of Lactobacillus species, particularly *L. reuteri*, in the therapeutical management of lactose intolerance patients.

Although literature is scant on this matter, *Lactobacillus Reuteri* seems to meet the requirements to be safely used in managing symptoms of lactose intolerance.

However, no studies have yet been conducted specifying the optimal dosage and recommended duration of treatment for patients with lactose intolerance, and for a probiotic that has already proven effective in numerous contexts, its potential is worth being investigated more also in this context with future studies.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

M. Brigida: manuscript writing, editing; A. Saviano: bibliographic selection; G. De Carlo: manuscript writing, editing; A. Piccioni: editing, final revision; V. Ojetti: ideation; final revision.

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