Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: www.tandfonline.com/journals/bfsn20

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To cite this article: Sophia J. Oak & Rajesh Jha (2019) The effects of probiotics in lactose intolerance: A systematic review, Critical Reviews in Food Science and Nutrition, 59:11, 1675-1683, DOI: 10.1080/10408398.2018.1425977

To link to this article: https://doi.org/10.1080/10408398.2018.1425977

Published online: 09 Feb 2018.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2019, VOL. 59, NO. 11, 1675–1683
https://doi.org/10.1080/10408398.2018.1425977

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The effects of probiotics in lactose intolerance: A systematic review

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ABSTRACT
Over 60 percent of the human population has a reduced ability to digest lactose due to low levels of lactase enzyme activity. Probiotics are live bacteria or yeast that supplements the gastrointestinal flora. Studies have shown that probiotics exhibit various health beneficial properties such as improvement of intestinal health, enhancement of the immune responses, and reduction of serum cholesterol. Accumulating evidence has shown that probiotic bacteria in fermented and unfermented milk products can be used to alleviate the clinical symptoms of lactose intolerance (LI). In this systematic review, the effectiveness of probiotics in the treatment of LI was evaluated using 15 randomized double-blind studies. Eight probiotic strains with the greatest number of proven benefits were studied. Results showed varying degrees of efficacy but an overall positive relationship between probiotics and lactose intolerance.

KEYWORDS
Probiotics; Lactose intolerance; Lactose; Lactose digestion; Lactose maldigestion; Lactase deficiency; Short chain fatty acids

Introduction

Lactose intolerance (LI) is a condition characterized by the inability to digest lactose due to low levels of lactase enzyme activity. Over 30 million people have some degree of LI by age 20 in USA. Lactase activity declines with age, resulting in unabsorbed lactose being metabolized by colonic bacteria to produce short chain fatty acids and gas (Mattar et al. 2012). Symptoms of LI include bloating, nausea, abdominal cramping, and diarrhea. Diagnosis is commonly done using one or more of the following tests: lactose tolerance test, hydrogen breath test and stool acidity test. Treatment of LI is currently limited to preventive supplements and symptom management medications. The most common products used are lactase containing pills, such as Lactaid, which are not FDA-approved for medical use.

Lactase enzyme activity is affected by several factors such as age, race, integrity of the small intestinal membrane and small intestinal transit time. Prevalence of LI in adult populations varies from 5% to 15% in European and North American countries, and 50% to 90% in African, Asian, and South American countries. Highest rates of LI are found in the Asian populations, while lowest rates are found in North American populations (Misselwitz et al. 2013). There are three types of LI (Deng et al. 2015). The most common type is primary LI, which is characterized by a progressive decline in lactase production. Secondary LI is caused by an illness, injury or surgery involving the small intestine. Celiac disease, bacterial overgrowth and Crohn's disease are common diseases associated with secondary LI (Heyman et al. 2006). Treatment of the underlying condition may restore normal lactase levels. The third type is congenital or developmental LI. Congenital LI is characterized by the absence of lactase activity. This rare disorder is also called congenital alactasia.

Probiotics have gained high interest in recent years as potential compensation for lactase insufficiency. Probiotics are live bacteria or yeast that supplements the gastrointestinal flora (Deng et al. 2015). In particular, strains belonging to *Bifidobacterium* and *Lactobacillus*, which are the predominant groups of the gastrointestinal microbiota, are the most widely used probiotic bacteria (Surendran et al. 2017). Probiotics promote lactose digestion in LI by increasing the overall hydrolytic capacity in the small intestine and increasing the colonic fermentation (Dhama et al. 2016). Probiotics can decrease lactose concentration in fermented products, and increase active lactase enzyme entering the small intestine with the fermented products (He et al. 2008). Common criteria for the selection of probiotic strains include (1) tolerance to gastrointestinal conditions, (2) ability to adhere to the gastrointestinal mucosa, and (3) competitive exclusion of pathogens.

The mechanisms underlying the beneficial effects of probiotics are multifactorial. Mechanisms related to the antagonistic effects of probiotics on various microorganisms include: (1) secretion of antimicrobial substances, (2) competitive adherence to the mucosa and epithelium, (3) modulation of intestinal permeability, and (4) strengthening of the immune system (Imani et al. 2013). The probiotic effect on the modulation of intestinal environments is considered the principal effect of probiotics and is considered the basis of other underlying benefits.

Recent evidence has demonstrated that probiotics communicate with the host by pattern recognition receptors, such as toll-like receptors, which modulate key signaling pathways, such as NF-κB and MAP kinase (Bermudez-brito et al., 2012). The resulting functions include increased epithelial barrier, increased adhesion to intestinal mucosa,

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and concomitant inhibition of pathogen adhesion (Zhong et al. 2003).

Strains such as *B. longum* and *L. bulgaricus* exhibit mechanisms characterized by blocked pathogen entry into the epithelial cell. Probiotics provide a physical barrier, which defends against external aggressions. Furthermore, these strains promote mucus secretion to improve barrier functions and exclusion of pathogens. In a recent study, *L. acidophilus* has been shown to increase mucin expression in vitro (Craveiro et al. 2012). Results showed increased mucin expression in the human intestinal cell lines Caco-2 (MUC2) and HT29 (MUC2 and 3), preventing pathogenic *E. coli* invasion and adherence. Another way probiotics can influence intestinal permeability is by increasing the intercellular integrity of apical tight junctions. Notably, *B. animalis* can upregulate the expression of zona-occludens 1 (a tight junction protein) and prevent the passage of pathogens into the lamina propria.

The aim of this study was to critically assess the role of eight probiotic strains in the treatment of LI. We sought to identify and address some of the shortcomings in current probiotic research in order to appropriately assess the efficacy of probiotics as an alternative treatment. This systematic review was a summary of evidence-based analyses from human studies. Based on the review of clinical trials from full text articles, the mechanism of eight probiotic strains, its advantages, limitations, and clinical potential against LI were assessed. The PRISMA-PICOS checklist was used as a guide in this review.

Method

Electronic searching (identification and screening)

For this study, a search strategy was developed for all steps of the review process. The search strategies used a combination of pertinent phrases and key words. Electronic searches were conducted using the following databases: ClinicalTrials.gov, PubMed, OLDMEDLINE (Ovid), Ovid MEDLINE, Cochrane Central Register of Controlled trials, Web of Science, Current Contents Connect, Food Science and Technology Abstracts and Google Scholar.

The key words we used were, *Lactose intolerance, Probiotics; Lactose digestion, Lactose maldigestion, Bifidobacterium longum, Bifidobacterium animalis, Lactobacillus bulgaricus, Lactobacillus reuteri, Lactobacillus acidophilus, Lactobacillus rhamnosus, Saccharomyces boulardii*, and *Streptococcus thermophilus*. The search results were combined and duplicates were removed. Following the 2009 PRISMA checklist, 97 reports were considered and 15 clinical studies were analyzed.

Data extraction (eligibility)

The objective of the review was to include as many reports, features and cases as the selection criteria would allow. Only full text articles were used. The selected articles spanned two decades. Information from each source was compiled while accounting for the weaknesses and limitations of each article. Each article was assigned a level (1–5) based on the strength of the evidence using the guidelines of the U.S. Preventive Services Task Force. Studies that were weak in subject number or contained evident biases were considered but not contributive in the summary.

The following criteria were considered in our study selection: (1) human randomized controlled trial, (2) included adults over 18 years-of-age with lactose intolerance (a minimum symptom score and positive lactose hydrogen breath test), (3) use of probiotic products as an intervention group, and (4) included the following information: doses and formulations of probiotic supplementation, criteria for assessing symptoms, and timing of administration and outcome measurement. Studies were excluded if (1) the total number of probiotic bacteria was not reported, (2) the formulation contained prebiotics as the intervention product, and (3) the subjects had irritable bowel syndrome or other probable causes of acute gastrointestinal symptoms. Studies that were weak in subject number or contained evident biases were considered but not contributive in the summary. All eligible studies were analyzed regardless of duration of follow-up.

Results

Study selection

Our electronic search of 10 databases produced a total of 370 citations, many of which were duplicates. The results for each of the search strategies are summarized in the flow chart (Figure 1). By eliminating duplicate articles and inapplicable citations using our eligibility criteria, the total number of full text articles was 94. After excluding review articles, 15 clinical trials were included in the systematic review (SR). The strength of evidence, number of subjects, limitations and main findings extracted from each of the case series are summarized in Table 1. The review was methodized by eight different strains of probiotics: *Bifidobacterium longum, Bifidobacterium animalis, Lactobacillus bulgaricus, Lactobacillus reuteri, Lactobacillus acidophilus, Lactobacillus rhamnosus, Saccharomyces boulardii, and Streptococcus thermophilus*.

Discussion

Bifidobacterium longum

Bifidobacterium longum is a Gram-positive, non-motile, non-sporulating lactic-acid bacteria. It is most prevalent in the human body during early infancy, being transmitted from mother to child through the process of natural birth and breast-feeding. A distinguishing characteristic of *B. Longum* is its ability to ferment carbohydrates, especially oligosaccharides (Zhong et al. 2003). *B. longum* produces several glycosyl hydrolases to metabolize complex oligosaccharides for carbon and energy. *B. longum* also positively influences amino acid fermentation, which can aid in muscle maintenance and overall cell structure (Iwabuchi et al. 2009).

B. longum has been reported to have various physiological effects, such as (1) anti-allergy effects, (2) reductions in harmful bacteria, and (3) improvements in the intestinal environment, defecation frequency and stool characteristics (He et al. 2008). The molecular mechanisms of these effects remain obscure due to the complex interactions within the gut microbial community.

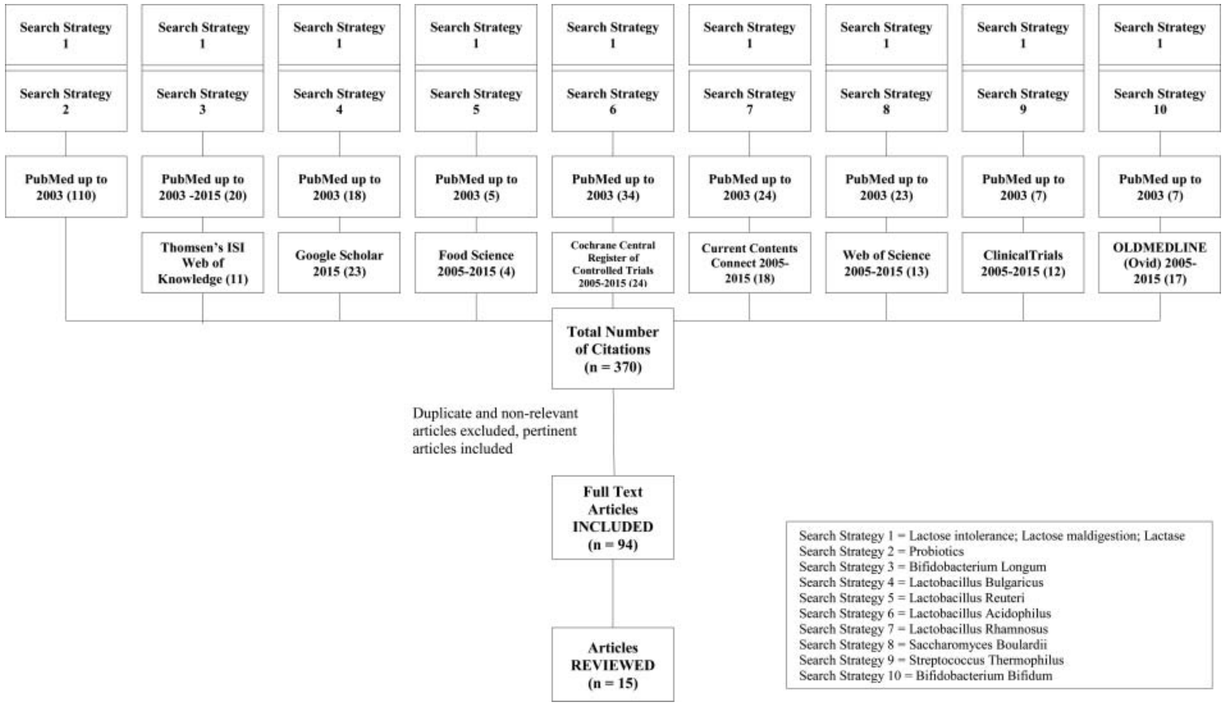

Figure 1. Flow chart of search strategies: Eight probiotic strains were searched in ten databases. The results are summarized in this figure. *Location in the text: Paragraph 1 of **RESULTS under Study Selection.***

He et al. (2008) assessed *B. longum* in a 2-week period study in 11 lactose intolerant participants. In the study, *B. longum* was shown to modify the composition and metabolic activities of the colonic microbiota when the total number of bacteria and *Eubacterium rectale / Clostridium coccoides* group in feces were measured. The results showed that β-galactosidase activity significantly increased during supplementation and the number of *Bifidobacterium* increased during and after supplementation. No change was shown in the degree of lactose digestion in the small intestine and the oro-cecal transit time before and after supplementation. Overall, the symptom scores after lactose consumption decreased after supplementation.

A study by Zhong (2003) corroborated that the addition that extraneous Bifidobacteria in Bifina capsule and yogurt could resists the effects of gastric acid and bile salt, and can survive in the colon. According to three additional clinical trials (Jiang et al. 1996; Zhong et al. 2003; He et al. 2008) that assessed the role of *B. longum* in LI, supplementation of *B. longum* influenced the colonic bacteria and diversity of colonic microflora and exhibited anti-inflammatory properties that protect the cells lining from toxins and help immune cells mature so they can function properly.

Collado et al. (2006) evaluated the adhesion of *B. longum* to human intestinal mucus and compared the results to those of control experiments that were run with the original acid-sensitive strains. They reported that in half of the four studied cases, the acid-resistant derivative shows a greater ability to adhere to human intestinal mucus than the original acid-sensitive strain. Therefore, the induction of acid resistance in Bifidobacteria may be a considerable strategy for selecting strains with enhanced stability and improved surface properties that favor their potential functionality as probiotics against specific pathogens.

In conclusion, six studies demonstrated that *B. longum* supplementation can improve intestinal conditions toward the amelioration of lactose intolerance. Of these studies, four measured the influences of different growth substrates, bile sensitivity, and lactose transport on lactose digestion by *B. longum*. The results suggested that *B. longum* modifies the amount and metabolic activities of the colonic microbiota and alleviates symptoms in lactose-intolerant subjects. The changes in the colonic microbiota might be among the factors modified by the supplementation, which can lead to the alleviation of lactose intolerance. Disadvantages may include potential health concerns for people with compromised immune systems, short bowel syndrome, central venous catheters, heart valve disease and premature infants.

Bifidobacterium animalis

Bifidobacterium animalis is a Gram-positive, anaerobic, rod-shaped bacteria found in the large intestines. *B. animalis* is one of the most common bacteria found in gut microbiota and one of the most documented probiotic Bifidobacterium. The suggested benefits of *B. animalis* include decreased serum cholesterol levels, protection against colorectal cancer, regulation of gut transit time, improvement of constipation, and reduction of gut inflammation through the maintenance of the gut microbiota (Bouvier et al. 2001). The strain characteristics and mechanisms have been studied through extensive in vitro testing. *B. animalis* exhibits gastric acid and bile tolerance and produced bile salt hydrolase. The strain has demonstrated strong mucus adherence properties, pathogen inhibition, barrier function enhancement, and immune interaction (Bottacini et al. 2011).

Table 1. Summary of the strength of evidence, number of subjects, limitations and main findings extracted from each case study.

Reference	Level (1–5)	Type	Data	Limitations	Main findings
Craveiro et al. (2012)	5	Case Study	1 participant with severe lactose intolerance	Larger sample needed	Probiotics can limit symptom severity depending on the different routes of administration, brand, strain and concentration
He et al. (2008)	4	Clinical Trial	11 lactose intolerant participants	Larger sample needed	Yogurt and bifidobacteria supplementation modifies the metabolic activities of the colonic microbiota and alleviates symptoms in lactose-intolerant subjects
Jiang et al. (1996)	5	Clinical Trial, Randomized Controlled Trial	15 lactose intolerant participants	Some inconsistencies in findings	*B. longum* and *B. animalis* reduces lactose intolerance by increasing production of the enzyme ß-galactosidas
Le Luyer et al. (2010)	5	Clinical Trial	15 infants with acute diarrhea and 13 in control group	Limited evidence	*S. boulardii* significantly shortens the duration of diarrhea and allows quicker weight regain than a standard formula.
Ojetti et al. (2010)	5	Randomized trial	60 lactose intolerant participants	Some inconsistencies in findings	In lactose intolerants, tilactase strongly improves both lactose breath test results and gastrointestinal symptoms after lactose ingestion with respect to placebo. *L. reuteri* is effective but lesser than *tilactase*.
Pakdaman et al. (2016)	5	Randomized Controlled Trial	30 lactose intolerant participants	Evidence is insufficient	DDS-1 strain of *L. acidophilus* improves abdominal symptom scores compared to placebo with respect to diarrhea, cramping, and vomiting during an acute lactose challenge.
Parra et al. (2007)	4	Clinical Trial	33 lactose intolerant participants	Some inconsistencies in findings	Fresh yogurt intake resulted in higher short-term leucine assimilation, while lactose intolerance appears to negatively affect the assimilation rate of leucine from dairy products.
Rampengan et al. (2010)	5	Clinical Trial	86 lactose intolerant participants	Findings were inconclusive	The administration of live or killed probiotic for 2 weeks can decrease the results of a breath hydrogen test in children with lactose malabsorption.
Rizkalla et al. (2000)	5	Randomized Controlled Trial	12 participants with or without Lactose intolerance	Larger sample needed	In men with LI, the chronic consumption of yogurt containing live bacterial cultures ameliorated the malabsorption, as evidenced by lower breath-hydrogen excretion, but increased propionate concentrations.
Ruchkina et al. (2013)	5	Clinical Trial	138 lactose intolerant participants	Short course of therapy	Probiotic bifiform benefits secondary lactase deficiency patients with impaired microbiota of the small bowel
Shcherbakov et al. (2014)	4	Randomized Controlled Trial	90 patients with gastrointestinal disorders	Some inconsistencies in findings	Multistrain probiotics produce a pronounced clinical effect in lactase deficiency
Wilt et al. (2010)	5	Clinical Trial	54 lactose intolerant participants	Evidence is insufficient	There are race and age differences in LI prevalence. Children with low lactose intake may have beneficial bone outcomes from dairy interventions.
Yan et al. (2003)	4	Clinical Trial	11 lactose intolerant participants	Larger sample needed	Supplementation of probiotics could influence the colonic bacteria, and increase the number of main groups of colonic microflora, especially for Bifidobacteria, which could play important role in alleviating LI symptoms.
Yesovitch et al. (2004)	5	Clinical Trial	10 lactose intolerant participants	Larger sample needed	Direct consumption of the probiotic VSL3 may not improve lactose maldigestion without metabolic activation.
Zhong et al. (2003)	4	Clinical Trial	11 lactose intolerant participants	Larger sample needed	Results suggest that supplementation modifies the amount and metabolic activities of the colonic microbiota and alleviates symptoms in lactose-intolerant subjects.

B. animalis has been reported to improve lactose digestion and eliminate the symptoms of LI. Studies have noted its protective effects against diarrhea and its role in modulating the colonic microbiota (Le Luyer et al. 2010; de Vrese et al. 2001). In the study by Le Luyer (2010), *B. animalis* and *B. longum* supplementation modified the composition and metabolic activities of the colonic microbiota. The mechanisms by which *B. animalis* exerts its effects are currently not fully understood, however, contributive factors may include (1) modifying gut pH, (2) expressing beta-galactosidase, and (3) positively influencing intestinal functions and colonic microbiota.

A study by Zhong (2006) demonstrated that LI symptoms were significantly decreased after *B. animalis* supplementation. In the study, eleven lactose intolerant subjects underwent a trial divided into 3 phases: 7-day basal period, 14-day supplementation period and 7-day post-supplementation period. Two lactose challenge tests were performed a day before and a day after the supplementation period and symptom scores and hydrogen tests were administered. Overall, the number of bacteria in the gut microbiota was significantly increased during the supplementation period. Extraneous *B. animalis* from capsule and yoghurt was detected in fecal samples during the supplementation period, conferring the strain's resistance to gastric acid and bile salt. The results showed that supplementation of *B. animalis* could (1) influence the colonic bacteria, and (2) increase the number of main groups of colonic microflora, which could play an important role in alleviating LI symptoms.

A study by Bouvier et al. (2001) performed with fermented milk containing *B. animalis* also demonstrated a reduced transit time in men and women with slow transit times. It was shown that daily consumption of fermented milk containing *B. animalis* can improve overall gastrointestinal transit time in subjects with lactose intolerance. The results showed that stool frequency was improved after supplementation.

In contrast, in a study by Levri et al. (2005), it was concluded that probiotic supplementation of *B. animalis* did not alleviate the symptoms of lactose intolerance in adults. There were no significant changes in the frequency of diarrhea, abdominal discomfort, and flatulence after consumption of milk or milk products with *B. animalis* supplementation.

In conclusion, the available clinical studies on *B. animalis* in LI show a potential role in treating LI symptoms. Of the six studies analyzed in this review, five studies yielded positive results and one study indicated negative results. However, the clinical trials were not consistent in concentrations and preparations. Further studies are required to elucidate the mechanisms of *B. animalis*.

Lactobacillus bulgaricus

Lactobacillus bulgaricus is a Gram-positive, facultatively-anaerobic, non-motile lactic acid bacteria. Like other lactic acid bacteria, *L. bulgaricus* are acid-tolerant and possess a strictly fermentative metabolism. It is one of the first strains of probiotics that have been studied. Bulgarian physician, Stamen Grigorov, discovered this probiotic in fermented sour milk. The *L. bulgaricus* plays several important roles in the digestive tract. Its mechanisms include reducing intestinal infections by excreting acids that alter the pH of the GI tract (Ruchkina et al. 2013). Lower pH ranges protect the GI tract from pathogens. The lactic acid produced by *L. bulgaricus* helps maintain the pH in the small intestine low. *L. bulgaricus* also produced natural antibiotics and blocks pathogen adhesion sites within the mucous layer of the intestine (Baricault et al. 1995).

Studies on *L. bulgaricus* have reported to improve lactose digestion and eliminate the symptoms of intolerance. In a study by Rizkalla et al. (2000), the effects of yogurt with (fresh) or without (heated) live *L. bulgaricus* and *Streptococcus thermophilus* were analyzed. The heated yogurt was produced with same procedure as the fresh yogurt, followed by pasteurization to destroy the lactic bacteria. In subjects with lactose malabsorption, 15 days of fresh yogurt consumption increased propionate production compared with values at baseline and in the same group, the production of breath hydrogen was lower after fresh yogurt consumption than after heated yogurt consumption. Four other studies (Parra, 2007; Le Luyer et al. 2010; Rampengan et al. 2010; Shcherbakov et al. 2014) corroborated that *L. bulgaricus* can lessen the symptoms of LI. This positive association may be related to the subtype, strain, or concentration of the probiotic supplementation.

In contrast, a 1991 study led by Lin, two probiotic strains, *S. thermophiles* and *L. bulgaricus* were compared at two concentrations with the control milk. The results showed that the probiotic treatments did not yield significant changes in mean breath hydrogen. Only 1 out of 8 probiotic treatments eliminated LI symptoms. A study by Ballesta et al. (2008) corroborated with this finding. Ballesta et al. (2008) found that there were no significant differences in the results obtained for microbiological or immunological parameters, gastrointestinal comfort, or lactose test in *L. bulgaricus* supplementation. The results showed that transit through the gastrointestinal tract affects the survival of *L. bulgaricus*.

In conclusion, it is important to understand the variations in probiotic concentration and preparation. In addition, the lack of standardized data presentation for breath hydrogen and symptoms is a limitation. Studies noted that with regard to β-galactosidase activity, intestinal adherence, cell wall thickness, and other factors that may affect the clinical efficacy of probiotic treatment. Overall, there is limited evidence to suggest that *L. bulgaricus* is effective in improving lactose digestion and eliminating the symptoms of lactose intolerance.

Lactobacillus reuteri

Lactobacillus reuteri is a Gram-positive probiotic strain that is naturally found in the gastrointestinal tracts. Although *L. reuteri* occurs naturally in humans, it is not found in all individuals. Oral intake of *L. reuteri* has been shown to effectively colonize the intestine of healthy people; Once present in the body, *L. reuteri* benefits its host in a variety of ways, particularly by fighting off harmful infections and mediating the body's immune system. Some of the noted advantages of *L. reuteri* include (1) guarding against harmful bacteria without impairing the balance of the microflora, (2) stabilizing intestinal permeability, and (3) reducing nausea, flatulence and diarrhea. *L. reuteri* has high beta-galactosidase activity and increases insulin secretion, possibly due to augmented incretin release.

One of the most well-documented effects of *L. reuteri* is in the treatment of diarrheal diseases in children, where it has been shown to significantly decrease the duration of symptoms. The positive effects of *L. reuteri* have been shown to be dose-dependent. With regard to prevention of gut infections, *L. reuteri* has been reported to be more potent than other probiotic organisms.

In a comparative study by Ojetti et al. (2010), tilactase and *L. reuteri* were shown to improve gastrointestinal symptoms after lactose ingestion with respect to placebo. This study involved 60 subjects with lactose intolerance. The effects of *L. reuteri* were lesser than that of tilactase as shown by the lactose breath test. Of two clinical trials analyzed, both studies showed that *L. reuteri* was shown to be a potential treatment option for lactose intolerance (Ojetti et al. 2010; Parra, 2010).

In conclusion, there is limited evidence on the role of *L. reuteri* in lactose intolerance. Two clinical trials were analyzed and both yielded positive results. However, more studies must be conducted in order to elucidate a potential therapeutic relationship. In the context of other intestinal disease, *L. reuteri* is one of the most scientifically well-documented probiotics, both in terms of efficacy and safety. It is now well-established as one of the most ubiquitous members of the naturally occurring gut bacteria.

Lactobacillus acidophilus

Lactobacillus acidophilus is a Gram-positive bacterium with a well-documented historical use in the dairy industry and more recently as a probiotic. It occurs naturally in the human and animal gastrointestinal tract and mouth. Many studies have shown that consumption of milk products containing *L. acidophilus* has the potential in (1) preventing or controlling intestinal infections, (2) improving lactose digestion in LI, (3) balancing serum cholesterol levels, and (4) exerting anticarcinogenic activity. As a probiotic, its role in lactose intolerance has been debated with multiple conflicting clinical trials.

In the study by Saltzman et al. (1999), 42 subjects with LI underwent breath-hydrogen tests after ingesting *L. acidophilus* over a week span. The result found that there was no significant change in the tests and the symptom scores. Mustapha et al. (1997) found similar results when 11 LI subjects exhibited no change in breath-hydrogen tests in four strains of *L. acidophilus*. The influence of bile sensitivity, lactose transport, and acid tolerance of *L. acidophilus* were studied in this report and the results indicated that bile and acid tolerance may be important factors to consider when *L. acidophilus* strains are selected for improving lactose digestion and tolerance.

Four other clinical trials (Yesovitch et al. 2004; Frese et al. 2010; Wilt et al. 2010; Craveiro et al. 2012) reported no notable changes among the test and control groups. Researchers have attributed this lack of effect to the insufficient viability and survival of *L. acidophilus* in commercial food products. Selecting better functional probiotic strains and adopting improved methods to enhance survival, including the use of appropriate prebiotics and the optimal combination of symbiotic may strengthen the effects of *L. acidophilus*. However, more studies must be conducted in order to reach a conclusion. Of the nine studies analyzed, *L. acidophilus* did not show significant potential to LI treatment.

In a study by Vesa et al. (1996), the digestibility and tolerance of lactose were evaluated in the context of *L. acidophilus*. Measurement of breath hydrogen tests of fifteen LI subjects showed that *L. acidophilus* supplementation increased the lactase content. Additionally, symptoms of LI lessened. However, the overall degree of maldigestion of lactose did not differ significantly. In conclusion, despite the differences in the lactase and bacterial content, lactose was not well-digested and tolerated from *L. acidophilus.*

In conclusion, there is limited evidence on the role of *L. acidophilus* in lactose intolerance. A study by Saltzman (1999) noted that lactose intolerance may be over-reported in subjects with gastrointestinal symptoms after lactose ingestion. Overall however, the treatment of lactose-maldigesting subjects showed a tenuous relationship with *L. acidophilus*.

Lactobacillus rhamnosus

Lactobacillus rhamnosus is a Gram-positive lactic acid bacteria that is present in the gut microflora. It is a well-researched probiotic strain, known to have strong adhesion to the intestinal wall. *L. rhamnosus* was first isolated in 1983 in the intestines of human subjects by researcher Barry Goldin and Sherwood Gorbach. Findings showed that *L. rhamnosus* has a remarkable tolerance for the harsh acids normally found in the stomach and digestive tract. It has been widely studied for its use in immune system stimulation. *L. rhamnosus* is commonly found in yogurt and dairy products such as fermented and unpasteurized milk and semi-hard cheese. While considered a health-promoting organism, *L. rhamnosus* may not be beneficial certain subsets of the population. In rare circumstances, especially those primarily involving weakened immune system or infants, *L. rhamnosus* may have a number of side effects.

L. rhamnosus has been reported to improve lactose digestion and eliminate the symptoms of LI. A study by Agustina et al. (2007) showed that the duration of diarrhea was significantly shorter in the study group than in the control group among 58 LI subjects. Other studies have examined the role of *L. rhamnosus* and supported that it can enhance systemic cellular immune responses and may be useful as a dietary supplement to boost natural immunity (Guandalini et al. 2000). Goldin (1999) reported that subject with LI did not have an inflammatory reaction after consuming dairy products with *L. rhamnosus*. The study noted that *L. rhamnosus* encourages the growth of organisms in the digestive tract that serve a similar function to lactase. In addition, it is able to survive the highly acidic conditions of the human stomach, as well as the intestinal tract.

A study by Conway (1987) showed that the probiotic strain's effectiveness relied on its ability to survive in gastric juice and to adhere to the intestinal cells. The adhesion mechanism is a nonspecific attachment. The result of the study showed that *L. rhamnosus* can have beneficial effects in LI subjects by preventing of diarrhea, regulating of bowel movements, and enhancing the immune system.

Of all of the studies found that tested *L. rhamnosus* in LI, majority yielded positive results and overall improvements in symptoms. Decreases in duration of diarrhea was noted, as well as decreased in the frequency of diarrhea.

Saccharomyces boulardii

Saccharomyces boulardii is a nonpathogenic tropical species of yeast. It is an acid-resistant, temperature tolerant microorganism that is not affected by anti-bacterial agents. *S. boulardii* is genetically and functionally distinct from common cooking yeast (*S. cerevisiae*) and different from pathogenic Candida yeast. *S. boulardii* increases the activities of intestinal enzymes such as disaccharidases, α-glucosidases, alkaline phosphatases, and aminopeptidases. It secretes a leucine aminopeptidase that guards against pathogens. *S. boulardii* increases the intestinal absorption of D-glucose that may enhance uptake of water and electrolytes during diarrhea. It has been reported to increase stool concentrations of short-chain fatty acids that nourish colon mucosal cells.

Although *S. 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. In recent years, a small number of research studies have examined the role of *S. boulardii* in infants with acute diarrhea. In a controlled study by Le Luyer et al. (2010), the efficacy of *S. boulardii* was tested in a 14-day course of therapy. Seventy infants participated in the study and the results showed significantly shortened duration of diarrhea and quicker weight regain than a standard formula.

Results of a study by Herbrecht (2005) showed that *S. boulardii* produces a protease that can digest toxins A and B of *C. difficile*. This finding may explain the protective effects of *S. boulardii* against *C. difficile*-associated diarrhea. Moreover, *S. boulardii* protease was shown to diminish the ability of toxins A and B to bind to human colonic brush border membrane receptors via competition inhibition. Overall, the results suggested that *S. boulardii* can be used as a preventive or curative treatment for LI.

Currently, *S. boulardii* has been studied as a therapeutic agent in several acute and chronic gastrointestinal diseases. Many clinical trials and experimental studies have suggested that *S. boulardii* has many protective effects of the normal healthy guy flora. With the exception of immunocompromised patients, no notable adverse effects have been noted in these studies. However, in current available studies, the mechanisms of action of the yeast must be further elucidated. Overall, the role of *S. boulardii* in LI needs more research in order for it to be deemed a potential treatment option.

Streptococcus thermophilus

Streptococcus thermophilus a lactic acid bacterium found in fermented milk products, and is generally used in the production of yogurt. *S. thermophilus* is physiologically and biochemically less versatile than other lactic acid bacteria. Live cultures of *S. thermophilus* have been known to make it easier for lactose intolerant patients to digest dairy products by breaking down the lactose.

The cell structure of *S. thermophilus* allows the bacteria to endure elevated temperatures and a low pH range. *S. thermophilus* lacks genes which contain surface proteins, which prevents harmful bacteria from using these surface proteins to attach to mucosal tissues and hide from the body's defensive actions. The efficacy of oral probiotics in adults with lactose intolerance was examined in 9 studies. Of these 9 randomized trials (Pelto et al. 1998; Armuzzi et al. 2000; Guandalini et al. 2000; Agustina et al. 2007; Manley et al. 2007; Schieszer, 2009; Ojetti et al. 2010; Imani et al. 2013) that measured hydrogen breath tests, three studies were positive, three were negative, and three had both positive and negative results. Seven studies measured symptoms scores and the results yielded one positive result, five negative results, and one with both positive and negative results.

Agustina (2007) studied the impact of *S. thermophilus* colonization on the colonic epithelium of LI patients was studied. Results of the study showed that *S. thermophilus* increased carbohydrate metabolism in the digestive tract in accord with the beneficial role of fermented milk consumption in improving LI. In contrast, in Schieszer's 2009 study, *S. thermophilus* did not decrease abdominal symptom scores compared to placebo with respect to diarrhea, cramping, and vomiting during an acute lactose challenge. This study was conducted over a limited time frame of four weeks, which may have been insufficient time for the probiotic bacteria to fully colonize. However, four other randomized, double-blind, placebo-controlled, clinical trials corroborated with the study's findings (Pelto et al. 1998; Armuzzi et al. 2000; Guandalini et al. 2000; Manley et al. 2007).

The observations drew that probiotic supplementation with *S. thermophilus* did not alleviate the symptoms and signs of lactose intolerance in adults. There was some evidence that suggested specific concentrations and preparations were effective, however, further clinical trials of specific strains and concentrations are necessary to delineate this potential therapeutic relationship.

Conclusion

There is some evidence suggesting the clinical potential of probiotics against LI. In order to elucidate the potential therapeutic relationship between probiotics and LI, new strategies concerning specific strains, concentrations, and preparations of probiotics must be developed. Of the 8 strains studied, *B. animalis* was among the most well-researched and effective strain. Further studies are needed to determine the varying efficacies of oral probiotic supplementation and their mechanisms of action.

Disclosure statement

No potential conflict of interest was reported by the authors.

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