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The Correlation Between Probiotics and Gastroesophageal Reflux Disease (GERD): A Comprehensive Review

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ABSTRACT

Background: It has been demonstrated that probiotics, or live microorganisms, can lessen GERD symptoms and enhance gut health. They can help with bowel movements and abdominal pain, which helps with managing GI tract disorders in general and irritable bowel syndrome in particular (IBS). **Methods:** We conducted a search without sample size restrictions in the PubMed and Web of Science databases to find prospective studies on dyspepsia, heartburn, regurgitation, and GERD. The analysis comprised a total of ten published prospective studies. **Result:** Studies have reported that probiotics can alleviate GERD symptoms, including reflux. These studies have shown that probiotics can reduce regurgitation, improve reflux or heartburn, alleviate dyspepsia, and improve other upper gastrointestinal symptoms like nausea, abdominal pain, and gas-related symptoms. **Conclusion:** In the general adult population, probiotics have been shown to lessen upper gastrointestinal symptoms of GERD, especially those derived from Lactobacillus and Bifidobacterium. By interacting with stomach mucosal receptors, they modify the immune response and antagonistic activity towards potential pathogens, accelerating gastric emptying.

Keyword: Probiotics, GERD, reflux, gastric, regurgitation.

INTRODUCTION

The esophagus and gastroduodenum are the primary targets of gastroesophageal reflux disease, a prevalent digestive condition. GERD not only impacts healthcare costs but also affects quality of life (QoL) significantly.[1] The chronic gastrointestinal illness known as gastroesophageal reflux disease (GERD) is typified by the regurgitation of stomach contents into the esophagus.[2] According to the Rome IV criteria, reflux hypersensitivity (RH) and functional heartburn (FH) can coexist with GERD.[1] Infant regurgitation (IR) is also defined by the Rome IV criteria as two or more episodes of regurgitation per day for three or more weeks, with spontaneous resolution and no association with adverse long-term consequences.[3,4] Distinguishing between GERD, FH, and RH can be challenging due to common symptoms such as heartburn and regurgitation. The Gastroesophageal Reflux Disease Working Group of the International Working Group for Gastrointestinal Motility and Function has developed a consensus document to specify criteria for the clinical diagnosis of GERD and identify current indications for esophageal testing to enhance the diagnosis of the condition.[5] Questionnaires like the Gastrointestinal Symptom Rating Scale (GSRS) and the Frequency Scale for Symptoms of GERD (FSSG) are commonly used in the diagnosis and research of GERD.[6] Although GERD and dyspepsia are distinct disorders, dyspepsia-related symptoms often coexist with GERD symptoms. Functional dyspepsia (FD) is characterized by epigastric pain or discomfort lasting for three months or longer in patients without organic causes for their regurgitation or predominant heartburn. Rome IV criteria categorize FD into two groups: epigastric pain syndrome (EPS), characterized by pain and burning, and postprandial distress syndrome (PDS), characterized by meal-related symptoms.[1]

GERD is estimated to impact a significant percentage of the global population, ranging from 8% to 33%. The prevalence of GERD varies widely across different regions, with higher rates in Western nations like the Americas, Europe, Australia-New Zealand, and the Middle East (10% to 30%). Data for Africa is not available, and the prevalence is lower in East Asia, at less than 10%. In the United States, between 10% and 20% of individuals report experiencing symptoms of heartburn and regurgitation on a weekly basis.[7] GERD poses a substantial healthcare burden, leading to significant costs in North America and Europe. In the United States alone, annual costs are estimated to exceed $10 billion.[7,8] Management of GERD typically begins with dietary and lifestyle modifications, followed by the use of medications such as proton pump inhibitors (PPIs) to reduce stomach acid secretion. Lifestyle and dietary changes, including consuming low-fat and low-protein foods, controlling portion sizes, and avoiding triggers like alcohol, caffeine, and nicotine, can play a crucial role in managing GERD. Additionally, dietary supplements such as probiotics, glutamine, magnesium, deglycerized licorice, and digestive enzymes have shown promise in reducing the frequency and severity of symptoms.[8]

Probiotics are described as "live microorganisms that confer a health benefit on the host when administered in adequate amounts".[9] There are many different ways to consume probiotics, including foods, powders, capsules, and baby formula.[10] Probiotics have been shown to improve bowel movements and symptoms related to the abdomen, thereby improving gut health.[11,12] Probiotics have been proposed to operate through a variety of mechanisms, such as direct interactions with the gut luminal microbiota, metabolic effects resulting from enzymatic activities, effects on barrier function, and cross-talk with the immune system and central nervous system.[9,11] Despite this, a full mechanistic understanding of the general function of probiotics is lacking; this also applies to GERD.[13] Numerous clinical trials have examined the clinical implications of probiotics in gut health in great detail.[11] Probiotic consumption during dysbiosis can promote gastrointestinal homeostasis and stimulate the growth of beneficial indigenous gut microbes, even though it does not appear to affect the gastrointestinal microbiota in healthy adults.[14] Additionally, taking probiotics before conditions that affect the composition of the intestinal microbiota, like using antibiotics, can lower the risk of dysbiosis.[15] A recent systematic review of 70 randomized clinical trials published between 2012 and 2017 found that probiotic supplementation generally has benefits in the management of various lower GI tract conditions. There has been strong evidence of improvements in the overall gastrointestinal symptoms and abdominal pain associated with irritable bowel syndrome (IBS), as well as a decrease in the risk of antibiotic-associated diarrhea and side effects related to H. pylori (H. pylori) eradication therapy. In IBS, there was moderate evidence of improved bowel movements along with bloating and distention.[11]

Since there has never been a systematic review of the topic, the goal of this one was to determine whether probiotics can effectively reduce the incidence, severity, and symptoms of GERD in the general adult population. We concentrated on studies with non-medicated subjects, even though probiotics might be helpful for patients receiving PPI treatment. This review will not distinguish between dyspepsia, regurgitation, and heartburn because of how difficult it is to diagnose GERD.

METHODS

Protocol

The author of the work meticulously adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This was done to ensure that the study met all the necessary criteria. The selected methodology was meticulously crafted to guarantee the precision and reliability of the research outcomes.

Criteria for Eligibility

The last ten years' worth of research on the connection between probiotics and acid reflux disease is thoroughly reviewed in this study. Through a careful analysis of the data, this study hopes to enhance and shed light on patient care practices. The main objective of this paper is to emphasize the importance of the

notable subjects that have been found in the literature.

In order to guarantee the caliber of the data incorporated in this investigation, stringent inclusion and exclusion standards are implemented. Papers published in English between 2012 and 2024 are required to be considered for inclusion. Certain submissions are excluded, including editorials, reviews that have already been published, submissions without a DOI, and duplicate journal entries.

Search Strategy

The terms "GERD OR dyspepsia OR heartburn OR regurgitation AND probiotic" were used to search for prospective controlled studies across all age groups in an advanced-mode electronic search of the PubMed and Web of Science databases. Additionally, we conducted targeted searches through Google Scholar, the Directory of Open Access Journals, the reference lists of the papers that were included, and relevant meta-analyses. Eligible articles published up until June 2019 were taken into consideration for inclusion during the final search.

Data retrieval

Before starting this systematic review, the authors carefully examined the abstract and title of every manuscript to determine how important each was. Only those articles that satisfied the inclusion requirements and complemented the goals of the article were chosen for additional review. Finally, a recurrent pattern discovered during multiple analyses produced a conclusive outcome. Submissions in the English language, only in full text, were accepted. After the most rigorous screening process, content that met all pre-established inclusion criteria and directly related to the topic of the study was included. Research that did not meet these standards were often disregarded and their findings not taken into account. Numerous pieces of information that were found during the research process were thoroughly analyzed, including titles, authors, publication dates, locations, study methodologies, and parameters.

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Quality Assessment and Data Synthesis

The research described in each article's title and abstract was evaluated independently by the writers to identify the papers that required more research. The next step involved going over each document that met the predetermined criteria to be included in the review. The outcomes of the evaluation process determined which articles would be included in the review. This criterion was able to facilitate a thorough analysis of prior research and the factors that qualified them for the review by expediting the selection of articles for additional evaluation.

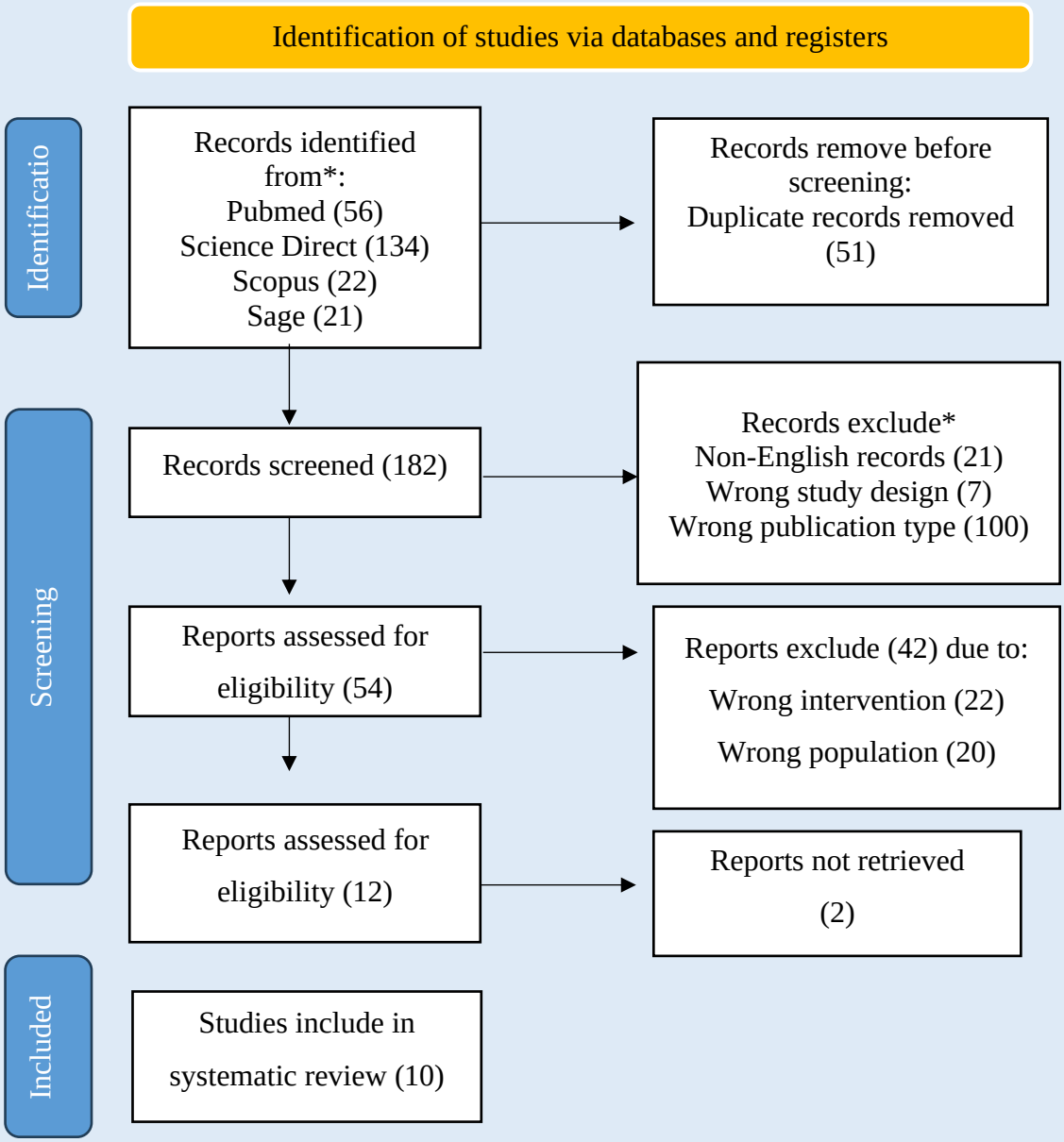


Figure 1. Article search flow chart

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RESULT

Initially, our research team collected more than 200 publications using reliable sources such as Science Direct, PubMed, and SagePub. After a comprehensive three-level screening process, only five papers were found to be directly relevant to our ongoing systematic review. After that, these articles were chosen for additional analysis and a comprehensive reading of the entire text. To make it easier to view, Table 1 gathers the literature that was analyzed for this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample Size	Result
Urita et al.[16] (2015)	Japan	Prospective Study	37 patients	After consuming fermented milk, symptoms of constipation, diarrhea, and abdominal pain significantly improved. Additionally, stress markers were reduced and subjective psychological symptoms were enhanced. Additionally, there was a slight rise in the "Vigor" subscale scores and a decline in anger-hostility during the consumption period. It is anticipated that regular consumption of fermented milk will alleviate digestive symptoms.
Igarashi et al.[17] (2014)	Japan	Prospective Study	24 patients	The study found that after receiving Lactobacillus gasseri OLL2716 (LG21) treatment, there was a reduction in GERD symptoms and an increase in Pepsinogen I (PGI) value. Strong correlations between PGI value and FSSG symptom scores were found in a multiple regression analysis with adjustments for gender and age, indicating potential roles

				for PGI level or regulating factors.
De Milliano et al.[18] (2012)	Italy	Prospective study	20 patients	Twenty women showed a significant reduction in the frequency of their feces along with a significant reduction in anorectal obstruction, incomplete evacuation, straining, episodes of abdominal pain, and reflux episodes. Other secondary outcomes, however, did not show a discernible decline, and no adverse effects were noted.
Ianiro et al.[19] (2013)	Italy	Prospective study	8 patients	Subjects following an oil diet enriched with probiotics or antioxidants saw a significant improvement in their dyspeptic symptoms; the latter effect was more pronounced. Now, larger research is required to validate these findings.
Nakae et al.[20] (2016)	Japan	Case Control	88 patients	Patients with functional dyspepsia (FD) experienced a reduction in postprandial distress-like symptoms and a restoration of the bacteriological change after receiving LG21 yogurt treatment. Prevotella abundance and the composition of the bacterial community in gastric fluid (GF) were substantially different from those in the healthy control (HC) group, and there was a noteworthy inverse relationship between the two.

Ohtsu et al.[21] (2017)	Japan	Randomized Controlled Trial	116 patients	The study involving 116 individuals found that the L. gasseri OLL2716 group had a more positive effect on gastric symptoms compared to the placebo group. The elimination rate for major functional dyspepsia (FD) symptoms was 17.3 and 35.3% in the placebo and L. gasseri OLL2716 groups, respectively.
Gomi et al.[22] (2015)	Japan	Randomized Controlled Trial	332 patients	The trial investigated the effects of fermented milk containing Bifidobacterium bifidum YIT 10347 on gastric and lower abdominal symptoms in adults without medication. Results showed a significant decrease in symptoms, with no side effects reported. The study suggests that fermented milk may provide health benefits in alleviating gastric symptoms.
Otslund-Lagerstrom et al.[23] (2016)	Sweden	Randomized Controlled Trial	290 patients	The primary and secondary outcome parameters of the study did not exhibit any enduring significant effects. Stress levels were found to have decreased at weeks eight and twelve in the probiotic arm, albeit somewhat. Likewise, we discovered that after 8 weeks of probiotic treatment, individuals with indigestion and abdominal pain, respectively, significantly reduced their anxiety

				levels; however, this effect did not hold true by week 12.
Nova et al.[24] (2012)	Spain	Randomized Controlled Trial	36 patients	The synbiotic group showed a statistically significant improvement in their self-reported gastrointestinal symptoms and bowel habits. L-selectin treatment had a marginal impact that resulted in a noteworthy decline in the synbiotic group. In healthy adults, consuming the synbiotic product enhanced self-perceived bowel habits and may help improve the adhesion molecule profile.
Gomi et al.[25] (2018)	Japan	Randomized Controlled Trial	89 patients	Comparing YIT10347 to the placebo group, there was a significant improvement in the rates of relief for epigastric pain, postprandial discomfort, and general gastrointestinal symptoms. There were no notable variations in the quality of life or mental symptoms, and there were no serious negative occurrences. This suggests that in healthy adults, gastrointestinal discomfort may be reduced by consuming YIT10347-fermented milk on a daily basis.

The study analyzed the effect of probiotics on the symptoms of GERD, specifically reflux and heartburn. Out of the 10 comparisons, two studies reported a significant reduction in acid regurgitation, while three did not show any improvement. Two studies reported a significant improvement in reflux or heartburn symptoms, while five did not. Dyspepsia-related symptoms improved or declined in five comparisons, while five reported no difference. Five comparisons recorded a significant reduction in pain, while two saw trends in reduced pain in the upper GI region. Three comparisons reported significantly less nausea, and four reported improvements in gas-related upper GI symptom severity. Overall, 10 comparisons reported probiotic benefits on the symptoms of GERD. Of the 10 former comparisons, five reported benefits for reflux symptoms, compared to five for dyspepsia symptoms and nine for other upper GI symptoms. Two high-quality RCTs showed efficacy (40%) in reflux symptoms and other upper GI symptoms, primarily gas-related symptoms. Three comparisons reported benefits for regurgitation, using frequency score as the endpoint. Four comparisons with Bifidobacterium YIT 10347 showed an effect on both regurgitation and dyspepsia, while none were associated with the probiotic intervention.

DISCUSSION

Ten prospective clinical studies were examined in this systematic review in order to assess the possibility of probiotics in reducing upper gastrointestinal symptoms of GERD in the general adult population. Probiotics' mode of action has mostly been studied in relation to the lower gastrointestinal tract; little is known about their effects in the upper GI tract.[13] However, through the synthesis of short-chain fatty acids like lactic acid, probiotics belonging to the genera Lactobacillus and Bifidobacterium are linked to adjustments in the immune response and antagonistic activity toward possible pathogens. Probiotics also hasten gastric emptying through their interaction with stomach mucosal receptors, which may be responsible for one of the pathophysiological mechanisms of GERD—the temporary relaxation of the lower esophageal sphincter. Probiotics may also help with small intestinal bacterial overgrowth, which can interfere with intestinal motility or immunity in a number of ways. These characteristics may be pertinent to how they affect GERD, as this article discusses.[1]

Probiotics were found to be beneficial in most (79%) of the comparisons that were included when it came to treating GERD symptoms like regurgitation, heartburn, dyspepsia, nausea, abdominal pain, and gas-related symptoms (belching, gurgling, burping). Nevertheless, a meta-analysis was not feasible due to the results' heterogeneity. When it comes to the frequency and presence of episodes associated with reflux, probiotics are beneficial.[17,18] In 20 pregnant women, the prevalence of reflux episodes decreased significantly by 40%.[18] To the best of our knowledge, the de Milliano et al. (2012) study is the first to report benefits for reflux, specifically in pregnant women who are constipated and is the first to use multi-strain probiotic supplements. The product

used in this study included six probiotic strains from six different species, including Lactobacillus and Bifibacterium, and was effective for treating a variety of upper- and lower-gastrointestinal symptoms, including constipation and abdominal pain.[18] After taking L. gasseri LG21 for 12 weeks, the frequency scores for reflux on the FSSG dramatically decreased, falling from 6.2 to 4.8. Remarkably, when the effects of age and gender were taken into account in the same study, the pepsinogen I (PGI) level was the only stomach-related biomarker that showed a significant negative correlation with the reflux symptom score. A higher PGI level denotes faster stomach protein digestion because PGI was thought to play a role in the onset of symptoms. This explains part of the inverse relationship observed between higher PGI levels and lower reflux symptoms, especially when dysmotility-like dyspepsia is present (FSSG: 3.5 to 4.0).[17]

Apart from its function in the digestion of proteins, two cohorts investigated the underlying mechanisms of Lactobacillus gasseri LG21 in reflux and dyspepsia.[20,21] No improvement in heartburn or regurgitation was observed in these two studies, but regardless of the experimental design (self-controlled or placebo-controlled), both reported decreased/lower dyspepsia, or decreased postprandial distress. In addition, Nakae et al. (2016) found that a higher pH value following treatment indicated increased gastric emptying as shown by the increased gastric fluid volume and suppressed gastric acid secretion.[20] Despite concentrating solely on symptomology, Ohtsu et al. (2017) used questionnaires other than the FSSG to more effectively distinguish PDS from EPS. The L. gasseri LG21 intervention was found to have a greater beneficial effect on PDS symptoms than EPS.[21] Notably, compared with the placebo, postprandial distress syndrome scores declined significantly with the L. gasseri LG21 intervention (37.5% vs. 17.8%). However, only a trend of improvement was observed for epigastric burning, with no improvement in epigastric pain. The aforementioned findings indicate a strong possibility that the mechanisms by which L. gasseri LG21 ameliorates FD-associated reflux are related to postprandial effects, specifically enhanced gastric emptying and improved protein indigestion.[20,21]

The role of the stomach microbiota in the pathophysiology of FD and GERD is poorly understood. According to Nakea et al. (2016), the bacterial communities of FD patients and healthy controls differed significantly in terms of overall community structure and bacterial taxonomic abundance. The majority of the taxa found in the stomach are Prevotella spp.[20] According to this study, there was a significant negative correlation between the severity of postprandial distress symptoms scores and the relative abundance of Prevotella spp. in FD patients compared to healthy controls. This suggests that Prevotella spp. may play a role in the development of FD symptoms. An H. pylori infection is linked to GERD symptoms. But getting rid of it doesn't always mean that symptoms get better.[26] Given this, it is regrettable that H. pylori has not been assessed in any of the studies. Probiotics have been shown to decrease the activity of H. pylori,

even though they do not completely eradicate it.[27] Thus, information about H. pylori carriage may have provided insight into some of the variations in efficacy.[1]

Due to the limited number of available trials, there is not enough data to compare the effectiveness of different probiotic strains. All three of the L. gasseri LG21 studies that were included, however, indicated improvements in a number of GERD symptoms. Additionally, four intervention trials showed improvements in FSSG and GSRS scores for B. bifidum YIT 10347. There weren't enough studies available for other strains to make generalizations. The chosen studies used a wide range of product formats, from fermented foods to different forms of dietary supplements. Three studies reported adverse events, but none of them showed a significant difference between the probiotic and placebo groups.[21-23] Furthermore, it was believed that the adverse events had nothing to do with the product.[1]

CONCLUSION

Studies have shown that probiotics can reduce upper gastrointestinal symptoms of GERD in the general adult population. Probiotics, particularly those from the genera Lactobacillus and Bifidobacterium, are linked to adjustments in the immune response and antagonistic activity towards potential pathogens. They also hasten gastric emptying through their interaction with stomach mucosal receptors, which may be responsible for the temporary relaxation of the lower esophageal sphincter. These effects may be relevant to how probiotics affect GERD. Probiotics have been found to be beneficial in treating GERD symptoms like regurgitation, heartburn, dyspepsia, nausea, abdominal pain, and gas-related symptoms. However, a meta-analysis was not feasible due to the heterogeneity of the results. The role of the stomach microbiota in the pathophysiology of FD and GERD is poorly understood, but probiotics have been shown to decrease the activity of H. pylori, although not completely eradicate it.

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