

## PROBIOTICS FOR INFANTILE COLIC : A SYSTEMATIC REVIEW

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### **Abstract**

*Colic in infants is a self-limiting ailment; nonetheless, it can be unpleasant for parents and tough for doctors to treat. Approximately 20% of infants suffer from infantile colic, which typically reaches its peak between 5 and 6 weeks of age. The challenge for the medical staff is in making an accurate diagnosis and coming up with a treatment plan for the ailment. In order to give doctors with a full grasp of the problem, current advancements, and future possibilities, the purpose of this review article is to outline the pathophysiology of infantile colic, as well as the treatment choices and prognosis for the condition. There are a few potential treatments for infantile colic, the most prominent of which is the use of probiotics, specifically lactobacillus. The most compelling evidence in support of probiotics comes from the prevention or treatment of these five conditions: necrotizing enterocolitis, acute infectious diarrhea, acute respiratory tract infections, antibiotic-associated diarrhea, and newborn colic. Inhibition of bacterial adhesion, improvement of mucosal barrier function, manipulation of both the innate and adaptive immune systems, release of bioactive metabolites, and control of the enteric and central nervous systems are some of the mechanisms of action that probiotics exhibit.*

**Katakunci:** *Colic; Gut; Infat; Lactobacillus; Probiotics.*

**INTRODUCTION**

Abdominal pain is a common condition found in children who enter the emergency room (ER).<sup>1,2</sup> Infantile colic is a self-limiting condition, but it can be stressful for parents and challenging for physicians. The difficulty for physicians resides in the correct diagnosis and management of the condition. This review article aims to summarize the pathophysiology, treatment options, and prognosis of infantile colic in order to provide clinicians with a comprehensive understanding of the condition, recent developments, and future prospects.<sup>3</sup>

The reported incidence of infantile colic varies between 10% and 40%. Many studies only employ data from specific populations. Variations may reflect differences in definitions, data collection methods, and study design.<sup>3,4</sup> Approximately 20% of infants suffer from infantile colic, which typically reaches its peak between 5 and 6 weeks of age.<sup>5</sup> Parents describe and interpret indicators to diagnose colic discomfort in children who cannot communicate. Thus, defining stomach pain in this age group is problematic. newborn regurgitation, newborn rumination syndrome, and cyclic vomiting syndrome are difficult to diagnose since patients cannot effectively report nausea or pain.<sup>6</sup>

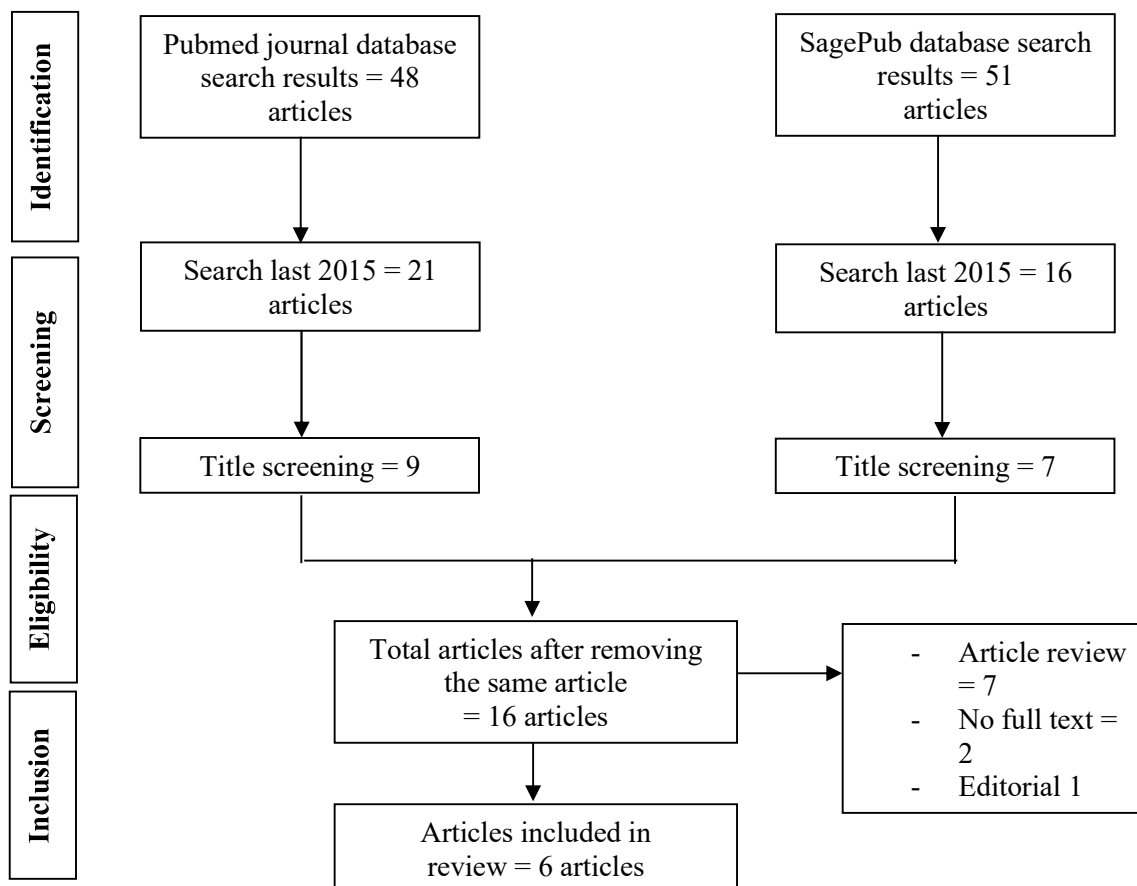
Triad three—crying for more than 3 hours a day, 3 days a week, and 3 weeks—defines abdominal colic. These criteria now focus on protracted, inconsolable, and inexplicable weeping, which parents find distressing. Clinical research may require additional diagnostic criteria.<sup>6</sup> Culture-independent analytical methods are helping us comprehend gut microbiota health and disease. Several organic and functional diseases alter gut microbiome. Functional colic in children has been studied for its efficacy in treating various diseases and ailments.<sup>2,7</sup>

Evidence suggests that certain strains of probiotics may be beneficial in children with functional colic, but are ambiguous for other colic disorders such as infant colic and functional constipation. Better understanding of the role of the gut microbiota in functional stomach pain is needed to develop new tailored therapeutic approaches that aim to modulate the gut microbiota that could benefit patients with functional stomach pain.<sup>2,7</sup> This article provided about benefit of probiotics for infantile colic.

**METHODS**

The methodology behind this systematic review was based on the criteria outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This comprehensive evaluation was carried out to investigate the potential benefits of probiotics for the treatment of infantile colic. The research that are now being taken into consideration center on the topic matter that is being examined. It is necessary that the previously conducted research fulfill specific requirements for it to be possible to conduct an accurate evaluation of the studies that have already been conducted.

These requirements are as follows: 1) Articles must be easily accessible online; 2) Articles written in English are preferred; and 3) The systematic review will only assess articles published between 2015 and the present.



**Figure 1. Article search flowchart**

The search for studies to be included in the systematic review was carried out from May 13<sup>th</sup>, 2023 using the PubMed and SagePub databases by inputting the words: “benefit”, “probiotics” and “infantile colic”. Where (“benefit”[All Fields] OR “benefited”[All Fields] OR “benefiting”[All Fields] OR “benefits”[All Fields] OR “benefitted”[All Fields] OR “benefitting”[All Fields]) AND (“probiotic s”[All Fields] OR “probiotal”[All Fields] OR “probiotics”[MeSH Terms] OR “probiotics”[All Fields] OR “probiotic”[All Fields]) AND (“colic”[MeSH Terms] OR “colic”[All Fields] OR (“infantile”[All Fields] AND “colic”[All Fields]) OR “infantile colic”[All Fields]) is used as search keywords.

After conducting a full literature review that included an analysis of the titles and abstracts of previously published research, the inclusion and exclusion criteria for the study were modified to reflect the findings of the investigation. Only research projects that were able to satisfy all of the conditions were considered for inclusion in the systematic review. When analyzing one research study in relation to another, it is critical to take into account the study's title, author, publication date, country of origin, research design, and the variables that were investigated.

In order to facilitate your assessment and analysis of this content, a certain format has been used to convey it. In order to decide whether or not the research studies might be included, the writers of the publications carried out impartial reviews of a number of the research projects that were stated in the titles and abstracts of the articles. After that, the full texts of the studies that meet the inclusion criteria for the systematic review will be assessed to determine which publications are eligible for categorical inclusion in the review. This will be done so as to ensure that the review is as accurate as possible.

**RESULT**

Korpela, et al (2020)<sup>8</sup> showed the newborns who later developed infantile colic (n = 19) had a decreased relative abundance of the genera Lactobacillus and Firmicutes in their first stool than the healthy newborns (n = 139). Using all microbiome data, the random forest algorithm distinguished between newborns with subsequent colic and those who remained healthy with an area under the curve of 0.66 ± 0.03, as compared to randomized samples (P <0.001).

Chau, et al (2015)<sup>9</sup> showed total average crying and fussing times throughout the study (from baseline to day 21) were significantly shorter among infants with colic in the probiotic group (1,719 ± 750 minutes vs 2,195 ± 764 minutes; P = 0.028). Infants given L reuteri DSM 17938 showed a significant reduction in daily crying and fussing times at the end of treatment period compared with those receiving (p = 0.045). On day 21, a significantly higher proportion of infants in the L reuteri DSM 17938 group responded to treatment with a ≥50% crying time reduction compared with infants given placebo.

**Table 1. The litelature include in this study**

Author	Origin	Method	Sample Size	Result
Korpela, 2020 <sup>8</sup>	Finland	Prospective cohort study	212 consecutive newborn infants	The microbiota of the meconium from the first bowel movement was found to have a correlation with subsequent infantile colic in this population-based, prospective investigation. According to the findings of our study, the pathophysiology of infantile colic appears to have intimate ties to the gut flora at the time of birth.
Chau, 2015 <sup>9</sup>	Canada	Randomized, double-blind, placebo-controlled trial	52 infants with colic	In breastfed Canadian newborns diagnosed with colic, the administration of L. reuteri DSM 17938 resulted in a considerable improvement in symptoms, including a reduction in the amount of time spent crying and fussing.
Mi, 2015 <sup>10</sup>	China	Prospective single blind randomized trial	42 infants with colic	During cases of infantile colic, L. reuteri (DSM 17938) helps minimize the amount of time spent weeping everyday as well as the severity of mother sadness. We have evidence to suggest that L. reuteri may be an alternative that is both safe and effective for minimizing baby colic.
Partty, 2015 <sup>11</sup>	Finland	Randomized clinical trial	30 infants with colic	Although parental reports of crying revealed that the probiotic intervention was successful, Lactobacillus rhamnosus GG (LGG) in babies treated in conjunction with behavioral support and a diet excluding cow's milk did not provide an extra treatment effect for diary-verified colic crying.
Fatheree, 2017 <sup>12</sup>	USA	Randomized clinical trial	117 screened infants	It indicates that giving newborn children with colic the L. reuteri strain DSM 17938 every day is safe, even for those newborn infants who also have neutropenia, which usually occurs along. A response to the placebo of 66% indicates that many infants who are experiencing colic will have remission within the next three weeks.
Turco, 2021 <sup>13</sup>	Italy	Randomized clinical trial	Two-hundred-forty-one infant	When compared to the intervention formula, the standard formula demonstrated a significantly shorter total amount of weeping time.

Mi, et al (2015)<sup>10</sup> showed all neonates in the probiotic group experienced successful treatment, whereas only 15.7% of infants in the placebo group did. In the probiotic group, the mean daily weeping time decreased to  $32.1 \pm 8.3$  minutes/day ( $P < 0.01$ ) from  $200.9 \pm 6.3$  minutes/day ( $P < 0.01$ ) in the placebo group ( $120.6 \pm 20.0$  minutes/day). In addition, parental satisfaction and improvement in maternal depression (Edinburgh postnatal depression scale) were substantially greater in the probiotic group throughout the study period. In our research population, weeping time decreased significantly ( $P < 0.01$ ) during the very first week of therapy.

Partty, et al (2015)<sup>11</sup> showed the daily amount of weeping time according to the parent diary was equivalent between the probiotic group (173 minutes;  $P = 0.99$ ) and the placebo group (174 minutes;  $P = 0.99$ ) at the conclusion of the intervention. However, parents of children in the probiotic group reported a drop in daily weeping of 68% (95% confidence interval [CI] = 58-78), whereas parents of children in the placebo group reported a decrease of 49% (95% CI = 32-66) ( $P = 0.05$ ). LGG in infants treated in tandem with behavioral support and a cow's milk elimination diet did not provide additional treatment effect for diary-verified colic crying although parental report of crying suggested the probiotic intervention effective.

Fatheree, et al<sup>12</sup> were randomized twenty infants in a 2:1 ratio to either L reuteri strain DSM 17938 or a placebo (sunflower oil) out of a total of 117 neonates screened, with 80% retention. Eleven of the twenty patients (55%) manifested with low absolute neutrophil counts ( $<1500/\text{mm}^3$ ), which all resolved by day 176. L. reuteri strain DSM 17938 did not result in any serious adverse effects and did not significantly alter weeping time, plasma bicarbonate, or inflammatory biomarkers. In both groups, fecal calprotectin decreased rapidly. The resolution of colic in neonates with prevalent fecal gram-negative organisms (Klebsiella, Proteus, and Veillonella) was associated with significant reductions in these organisms.

Turco, et al (2021)<sup>13</sup> conducted a study with 241 children infant were assigned at random to one of the therapy groups (Group A = 124, and Group B = 117). When compared to Group A, the mean daily weeping time in Group B was considerably reduced at the 28th day [104.7 (87-122.4) against 146.4 min (129.2-163.7), treatment effect -41.8 (95% CI= -66.5 to -17.1),  $p = 0.001$ ]. In neither of the two study groups was there a report of any severe adverse event.

## DISCUSSION

Family physicians, pediatricians, pediatric gastroenterologists, emergency department physicians, nurse practitioners, and obstetricians treat infantile colic. Infantile colic causes 10% to 20% of doctor visits in the first weeks of life and is upsetting for parents. 20% of newborns globally get colic. The illness normally begins in the second or third week, peaks at 6 weeks, and resolves between 12-16 weeks. Colic causes inconsolable sobbing, irritation, and yelling. Today, researchers utilize the Rome IV criteria to define infantile colic more consistently.<sup>14</sup>

Our comprehension of the function of the microbiota in the gut, both in terms of health and disease, is being improved by analytical methods that do not rely on culture. It has been shown that a number of organic diseases and functional abnormalities are associated with alterations in the microbiota of the gut. There have been a number of studies that have been conducted to investigate the efficacy of various treatments for a variety of diseases and conditions, including functional colic in children.<sup>2,7</sup>

The prevention or treatment of these five conditions provides the strongest evidence in favor of probiotics: necrotizing enterocolitis, acute infectious diarrhea, acute respiratory tract infections, antibiotic-associated diarrhea, and baby colic. Some of the mechanisms of action of probiotics include the inhibition of bacterial adhesion, the enhancement of mucosal barrier function, the modulation of the innate and adaptive immune systems, the secretion of bioactive metabolites, and the regulation of the enteric and central nervous systems. Probiotics are live microorganisms that have been shown to have a variety of health benefits.<sup>15,16</sup>

Microbial communities are increasingly important in immunologic development, infection prevention, and gut barrier maintenance. These functions suggest that probiotics, live organisms considered to benefit their host, might change the stomach microbiota. It's understandable why doctors believe probiotics "can't hurt, might help." Probiotics are supported by meta-analyses, review papers, and advertisements.<sup>17</sup>

There is some evidence that suggests that particular strains of probiotics may be beneficial for children with functional colic. However, the evidence is less conclusive on the effects of probiotics on other colic illnesses, such as baby colic and functional constipation. In order to create innovative personalized therapeutic methods that aim to alter the gut microbiota and that could be of use to patients who suffer from functional stomach pain, a better knowledge of the role that the gut microbiota plays in functional stomach pain is required.<sup>2,7</sup>

It has been determined that the function played by the gut flora in infantile colic is becoming increasingly important. An abnormal intestinal microbiome has been linked to infantile colic in a number of studies, both cross-sectional and prospective, involving infants. The microbiome of colicky infants was found to have a higher abundance of Proteobacteria and a lower abundance of the genera Bifidobacterium and Lactobacillus, as well as a lower bacterial diversity.<sup>18</sup> In addition, it has been demonstrated that lactobacilli-containing probiotics are useful in the treatment of infantile colic in breastfed infants.<sup>19</sup>

*Lactobacillus reuteri* has been shown to colonize human breast milk, as well as the gastrointestinal tract, urinary tract, and skin. *L. reuteri* has been shown in recent research to have the ability to have an anti-inflammatory function, including the inhibition of inflammatory mediators, eicosanoids, and pro-inflammatory cytokines.<sup>20</sup> *L. reuteri* was used as a single-stranded probiotic therapeutic intervention in three of the investigations that were included in this study because they fulfilled the criteria for inclusion.<sup>12</sup>

The bacterial species known as *Lactobacillus rhamnosus* GG may be found in their natural environment in the digestive system as well as in the flora of the vaginal canal. It has been demonstrated that this specific strain of bacteria is capable of preventing inflammation in epithelial cells. As a result, this bacterial strain is of special relevance to research in the context of disorders like colic, which may have an inflammatory root cause.<sup>21</sup>

The initial stages of intestinal colonization are critically significant for the establishment of gut barrier function, as well as the control of both local and systemic immune responses.<sup>22</sup> It has been demonstrated in a number of studies that even in healthy pregnancies, the first-pass meconium, which is the feces created before delivery, includes a complex microbiome. It has also been demonstrated that microbiome can be found in the placenta, which suggests that colonization of the newborn gut may begin even before birth.<sup>19,23</sup>

The idea of the fetal microbiome, which may be described as the transmission of microbial DNA or complete microorganisms from the mother to the fetus while the mother is pregnant, is contentious, and the implications of the meconium microbiome for a person's future health are not fully known.<sup>19,22</sup> Unknown is the cause of infantile colic. Few treatment options are available. There is evidence that probiotics may provide some benefit. The purpose of the study was to systematically evaluate the efficacy of probiotics in the treatment of infantile colic.<sup>24</sup>

Other survey results found that the majority of pediatricians relied only on their own clinical experiences to obtain a diagnosis of infantile colic (IC). Furthermore, these paediatricians favored probiotic supplements and simethicone as the only medical treatment available to treat IC, and they noticed clinical advantages from using these treatments. The insights gained from this study will be helpful in guiding future attempts by paediatricians to enhance the management of infantile colic.<sup>14</sup>

Infantile colic is a benign, self-limiting ailment that usually disappears between three and four months. However, newborns with colic may be more likely to have migraines without aura by 18. Early weeping is linked to preschool adaptation challenges, attention deficit hyperactivity disorder, and other behavioral issues, as well as parental worry and despair. Thus, educating parents about colic and helping them build coping mechanisms and colic treatment strategies appears reasonable.<sup>25</sup>

## CONCLUSION

There are a few potential treatments for infantile colic, the most prominent of which is the use of probiotics, specifically *Lactobacillus*.

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