Chettinad Health City Medical Journal
Volume 13, Issue 4 - 2024, Pg. No. 135-145
Peer Reviewed & Open Access Journal

Review Article

Lactobacillus rhamnosus GG in Paediatric Acute Diarrhoea: A Clinical Perspective and Systematic Review of Clinical Studies Published in the Last Decade

Dharmeshkumar B Kheni[1], Varun P Sureja[2], Shrikalp S Deshpande[3], Vishal P Dubey[4], Jignesh J Kansagra[5]

[1,2]Department of Pharmacology, Kadi Sarva Vishwavidyalaya, Gandhinagar, Gujarat, India.
[3]Department of Pharmacology, K B Institute of Pharmaceutical Education and Research, Gandhinagar, India.
[4,5]Department of Scientific and Medical Affairs, Sundyota Numandis Probioceuticals Pvt Ltd, Ahmedabad, Gujarat, India.
DOI: https://doi.org/10.24321/2278.2044.202470

I N F O

Corresponding Author:
Dharmeshkumar B Kheni, Department of Pharmacology, Kadi Sarva Vishwavidyalaya, Gandhinagar, Gujarat, India.
E-mail Id:
dharmeshbkheni341@gmail.com
Orcid Id:
https://orcid.org/0009-0003-1619-5922
How to cite this article:
Kheni D B, Sureja V P, Deshpande S S, Dubey V P, Kansagra J J. *Lactobacillus rhamnosus* GG in Paediatric Acute Diarrhoea: A Clinical Perspective and Systematic Review of Clinical Studies Published in the Last Decade. Chettinad Health City Med J. 2024;13(4):135-145.

Date of Submission: 2023-11-04
Date of Acceptance: 2024-05-03

A B S T R A C T

Gut dysbiosis is one of the risk factors to cause acute diarrhoea in children. *Lactobacillus rhamnosus GG* (*L. rhamnosus GG*) is one of the most studied probiotic strains and its efficacy in acute diarrhoea is validated in various clinical studies. The current systematic review aimed to evaluate the efficacy of *L. rhamnosus GG* in paediatric acute diarrhoea by using the clinical studies published in the last decade (till September 2023). Articles were retrieved from five online databases and screened as per the pre-designed protocol. The quality of the studies that qualified was assessed using the Physiotherapy Evidence Database (PEDro) scale. The studies were critically reviewed for the efficacy of *L. rhamnosus GG* in various parameters related to paediatric acute diarrhoea conditions. After screening 1758 articles for eligibility, six studies were considered in the current study. Every study that was included was of a moderate-to-good quality. *L. rhamnosus GG* supplementation in combination with standard therapy shows better improvement in diarrhoea duration, stool consistency, stool frequency, and duration of hospital stay as compared to standard therapy alone supplementation. The study's findings are consistent with the results of previous studies and suggest that the supplementation of Lactobacillus rhamnosus GG is an effective adjunct therapy in paediatric acute diarrhoea conditions.

Keywords: *Lactobacillus rhamnosus* GG, Diarrhoea, Children, Infant, Systematic Review

Introduction

Diarrhoea, a clinical condition characterised by frequent and abnormal passage of loose and watery stools, is one of the most common gastrointestinal disease conditions among the paediatric population.[1] Globally, diarrhoea is the second primary cause of death among children (especially among developing countries), affecting around 1.7 billion children and causing 525,000 children mortality each year.[2] Various studies have estimated the prevalence rates of acute diarrhoea among the Indian paediatric population, and it is estimated that acute diarrhoea is the third-most common cause of mortality among the Indian paediatric population of less than 5 years of age, causing approximately 13% (~ 300 000 children) mortality per year.[3] Diarrhoea is categorised into two types (based on the duration of symptoms): acute diarrhoea (symptoms lasting for 14 days or less) and persistent/ chronic diarrhoea (symptoms lasting for more than 14 days).[4]

As acute diarrhoea is highly prevalent among the paediatric population, various risk factors have been identified that might be responsible for the cause of acute diarrhoea including viral infections, bacterial infections, reduced water consumption, unhygienic sanitation practices, poor handwashing practices, unsafe faeces disposal method, less mother/ caregiver knowledge, travelling, improper eating habits, intestinal parasitic infections, and low immunity status.[5–10]

The human gastrointestinal tract is a hub for trillions of micro-organisms, collectively known as the gut microbiota, which is essential to several attributes of host physiology, such as digestion, nutrient absorption, immune regulation, and protection against pathogens.[11–14] Dysbiosis, defined as the imbalance in the composition and function of the residential microbiome, is a complex and multifaceted condition.[15] Various studies have concluded that gut microbiome plays an important role in mental health, respiratory health, metabolic parameters, dermatological health, and cardiovascular health and hence gut microbiome dysbiosis is linked with various disease conditions.[16] Gut dysbiosis can occur due to various factors, including diet, environmental exposures, and medications.[17] In paediatric individuals, the gut microbiota is still developing and evolving, making them particularly vulnerable to dysbiosis. One of the most prevalent and concerning outcomes of gut dysbiosis in children is the increased occurrence of acute diarrhoea.[18]

Probiotics, as defined by the World Health Organization (WHO), are live microbes that give the host health benefits when given in sufficient quantities.[19] Numerous studies have shown that probiotics have diverse mechanisms of action that provide many health benefits to the host.[20] While various micro-organisms are identified and the research of identifying newer microbes is still ongoing, currently microbes from the *Lactobacillus, Saccharomyces, Bifidobacterium, Enterococcus, Pediococcus, Streptococcus, Leuconostoc, Bacillus,* and *Escherichia* genus are identified as probiotics.[21]

Lactobacillus rhamnosus GG (*L. rhamnosus GG*), isolated from healthy human intestines, is one of the most widely studied probiotics.[22,23] Numerous clinical studies have demonstrated the benefits of *L. rhamnosus GG* in various disease conditions, including diarrhoea, gastroenteritis, allergy, necrotising enterocolitis, irritable bowel syndrome (IBS), neonatal hyperbilirubinemia, inflammatory bowel disease (IBD), infantile colic pain, oral and dental health, and hepatic health.[24–33] The present research aimed to investigate the effectiveness of *L. rhamnosus GG* in paediatric acute diarrhoea conditions by conducting a Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) compliant systematic review of randomised controlled studies published in the past decade (from 2012 to 2023).

Method

Study Conduction

The PRISMA reporting guideline was followed for conducting the current review study.[34] The review methods were previously established before the initiation of the review. The study was conducted as per a pre-developed study protocol.

Review Question

The review question was framed based on PICOS (population, interventions, comparators, outcomes, study design) criteria. The research question based on the PICOS criteria was as follows: Is *Lactobacillus rhamnosus GG* effective in the management of paediatric acute diarrhoea conditions?

Eligibility Criteria

All randomised clinical trials (RCTs) evaluating the efficacy of *L. rhamnosus GG* in paediatric participants with clinically diagnosed acute diarrhoea; articles available in the English language; and articles published after 2012 (till September 2023) were considered eligible. Non-randomised, single-arm studies or studies with design different than described in inclusion criteria; studies evaluating the efficacy of different probiotics; studies assessing the effectiveness of *L. rhamnosus GG* in different indication(s); studies involving adult or geriatric population; studies not available in English language; studies not retrievable; poster and/ or abstract presentation of clinical study with no availability of full-text article were excluded from the review.

Search Strategy

A systematic literature search was performed, and studies were identified through Google Scholar, PubMed/ MEDLINE, Scopus, Semantic Scholar, and ScienceDirect databases

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

from January 2012 to September 2023 (The last search was conducted on 19 September 2023). The terms used alone or in combination for the literature search were:

- "*Lactobacillus rhamnosus GG*" OR "*L. rhamnosus GG*" OR "Lacticaseibacillus rhamnosus GG" OR "LrGG" OR "Lgg" OR "*Lactobacillus rhamnosus* ATCC 53103" OR "*L. rhamnosus* ATCC 53103" OR "*Lacticaseibacillus rhamnosus* ATCC 53103"; AND
- "diarrhea" OR "diarrhoea" OR "acute diarrhea" OR "acute diarrhoea"; AND
- "infant" OR "children" OR "paediatric" OR "paediatric" OR "neonat*"; AND
- "randomised trial" OR "randomised study" OR "controlled trial" OR "controlled study" OR "clinical trial" OR "clinical study" OR "trial" OR "study".

Independent literature search was conducted by one review author and all articles were carefully evaluated, and their reference lists were examined additionally to identify grey literature that could be retrieved in the review.

Study Selection and Quality Assessment

Independently, two review authors assessed and selected the studies. The Rayyan software was used for conducting the article screening process. Initial screening involved the evaluation of the title and abstract of the studies. All studies deemed to be eligible for the study were further evaluated using the full text of the articles. Discrepancies were resolved by consensus, including a third review author using the full-text article of studies.

The internal and external validity and the statistical sufficiency of the included studies were independently assessed by two review authors using the Physiotherapy Evidence Database (PEDro) scale.[35,36] The PEDro scale categorises studies into the following three categories based on the 11-point scoring system: Low quality (≤ 3 points), moderate quality (4–7 points), and high quality (≥ 8 points).[35]

Data Collection

One review author independently extracted the following data from each eligible study: authors' names, year of publication, type of active intervention provided, type of control intervention provided, number of participants in each group, age of participants, and duration of study. All comparable outcome measures were collected in a separate pre-designed sheet. The complete study characteristics and outcome measure data were validated independently by other review authors.

Results

Study Selection Process

The literature search revealed in total of 2008 articles. After duplicate removal, 1758 articles were initially assessed using the title and abstract evaluation, while deemed eligible studies were assessed using full-text articles of the study. The complete evaluation process revealed six studies eligible and were included in the current study. The complete article selection process is presented in Figure 1.[37–42]

Quality Evaluation of Included Studies

The PEDro scale was used for evaluating the quality of included studies and it was observed all the included studies were of moderate-to-good quality. All included studies were randomised studies with pre-defined eligibility criteria. All the studies divided participants into groups similar at baseline (except the study conducted by Ali in 2019).[39] Allocation concealment was maintained by three studies,[38,39,42] while only one study was conducted as a double-blind, randomised, controlled study.[42] The rate of dropouts was less than 15% in all included studies, while the intention-to-treat analysis method was the final evaluation analysis in four included studies.[37–39,41] All the included studies conducted and provided the results of the between-group statistical comparison and provided point as well as variable data for the main outcome parameter. The outcomes of the quality evaluation are depicted in Table 1.

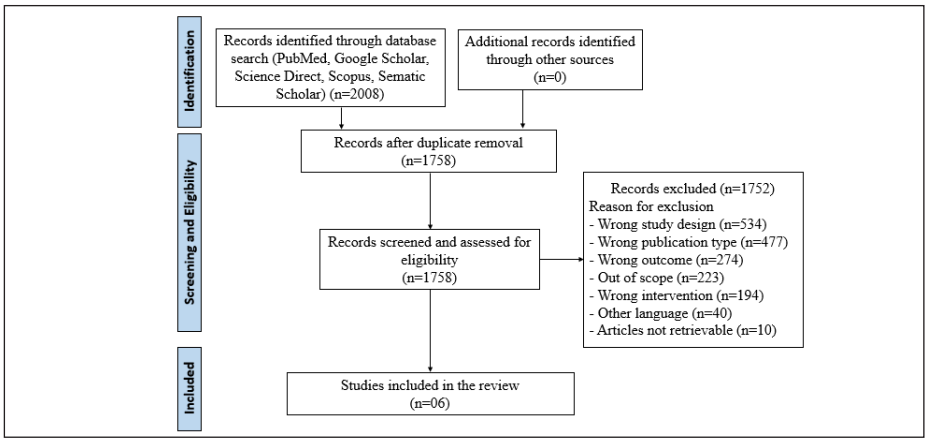

Figure 1.PRISMA Study Selection Flowchart

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

Table 1.Quality Assessment of Included Studies (PEDro Scale)

Evaluation Parameters	Study					
	Sharma et al.[37]	Aggarwal et al.[38]	Ali[39]	Dinleyici et al.[40]	Biswas and Bal[41]	Nixon et al.[42]
Eligibility criteria	1	1	1	1	1	1
Random allocation	1	1	1	1	1	1
Concealed allocation	0	1	1	0	0	1
Groups similar	1	1	0	1	1	1
Subject blinding	0	0	0	1	0	1
Therapist blinding	0	0	0	0	0	1
Assessor blinding	0	0	0	1	0	1
Less than 15% dropouts	1	1	1	1	1	1
Intention-to-treat	1	1	1	0	1	0
Between group statistical evaluation	1	1	1	1	1	1
Point measures	1	1	1	1	1	1
Overall score	**7**	**8**	**7**	**8**	**7**	**10**

Discussion

Efficacy of *L. rhamnosus* GG in Paediatric Acute Diarrhoea

Sharma et al. conducted a single-centre randomised controlled study in a hospital-based setting in Rajasthan, India.[37] After evaluating the participants as per pre-designed inclusion/ exclusion criteria, the study included paediatric participants (between 1 month to 18 years of age) with acute diarrhoea between 2020 and 2021. Most of the diarrhoea cases were observed between the ages of five and ten (49.17%), followed by participants in an age group of less than 5 years of age (35%), and lastly by participants with more than 10 years of age. The number of male participants was relatively greater (53.33%) as compared to female participants (46.67%). While the presence of dehydration was not found in 45% of participants initially enrolled in the study, 20.83% of participants presented with severe dehydration at baseline. Written informed consent was obtained and participants were allocated randomly to one of the three groups: Group A, Group B, or Group C. All the participants were treated with a standard therapeutic regimen (not disclosed in the study), while along with standard therapy participants in Group A were treated with *Saccharomyces boulardii (S. boulardii)* 2.5 billion units twice daily, participants in Group B were treated with *Bacillus clausii (B. clausii)* 2 billion units twice daily, and participants in Group C were treated with *L. rhamnosus GG* 6 billion units twice daily. All the probiotic regimen was continued for 5 days and participants were evaluated on day 1, day 2, day 3, day 4, and day 5 for the following parameters: change in stool consistency, change in stool frequency, number of participants showing improvement after therapy, and tolerability of probiotic therapy during the entire study duration. At baseline, all the participants had liquid stool consistency in all groups, and after the first day of probiotic therapy, all participants (except one) in Group C showed an increase in the consistency of the stool in comparison to 17 participants in Group A and 21 participants in Group B. On day 3, complete stool consistency improvement was observed in 72.5% of participants in Group C, as compared to 7.5% of participants in Group B and 2.5% of participants in Group A. The variations among the groups regarding stool consistency were statistically significant from day 2 ($p < 0.001$) showing better efficacy of *L. rhamnosus GG* as compared to other probiotics used. Similarly, the stool frequency at day 3 was significantly reduced in all three groups compared to baseline values, while the reduction was highest in Group C (61.19% reduction) as compared to Group A (49.94% reduction) and Group B (44.11% reduction). On day 4, the number of participants showing improvement in diarrhoea condition was significantly higher in Group C (87.5%) as compared to Group A (65%) and Group B (67.5%) ($p = 0.045$). All the given probiotics were well-tolerated and no side-effects to any included participants were observed. The study concluded that *B. clausii, S. boulardii*, and *L. rhamnosus GG* are safe probiotics and effective in paediatric acute diarrhoea conditions, and the efficacy of *L. rhamnosus GG* is significantly better in providing better and faster diarrhoea improvement.[37]

An open-label randomised controlled study evaluating the efficacy of *L. rhamnosus GG* in acute childhood diarrhoea was conducted by Aggarwal et al.[38] The study involved children (aged 6 months to 5 years) with acute diarrhoea in the study site (outpatient department of a medical college in Meerut, India) and was conducted between 2010 and 2012. A total of 200 participants were enrolled in the trial

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

and were randomised either to receive low osmolarity oral rehydration solution (ORS) and 20 mg zinc therapy (standard therapy group) or standard therapy group intervention and *L. rhamnosus GG* as a single capsule providing 10 billion colony forming unit (CFU) per day for 5 days. The primary evaluation parameters were duration of diarrhoea and time to improvement in stool consistency, while the secondary evaluation parameters included the mean number of stools per day (during illness), average duration of vomiting, and hospital stays. Additionally, the participants evaluated as rotavirus-positive and rotavirus-negative were evaluated separately to identify whether *L. rhamnosus GG* is effective in rotavirus-associated acute diarrhoea or not. The addition of *L. rhamnosus GG* to standard therapy significantly decreased the total duration of diarrhoea as compared to standard therapy alone ($p < 0.001$; Figure 2). *L. rhamnosus GG*-treated participants had 18 hours less diarrhoea duration compared to standard therapy-treated participants. In rotavirus-positive participants, the duration of diarrhoea was significantly reduced by 24 hours as compared to standard therapy alone treated participants ($p < 0.001$; Figure 2). Similarly, the time to improvement in stool consistency was significantly lower in *L. rhamnosus GG*-treated participants (6 hours less time duration) as compared to standard therapy-treated participants, while the rotavirus-positive participants showed similar improvement ($p < 0.001$; Figure 3). The participants treated with *L. rhamnosus GG* had significantly lesser number of stools per day during diarrhoea condition compared to the control group (9.17 vs 10.36; $p < 0.001$), while the difference in duration of vomiting (14.92 vs 19.32 hours) and hospital stay (80.00 vs 92.14 hours) did not reach significance. The trend of reduction in number of stools, duration of vomiting, and hospital stay were comparable in both rotavirus-positive and rotavirus-negative participants. The study showed that *L. rhamnosus GG* is an effective therapy in paediatric acute diarrhoea conditions, and its effect is independent of rotavirus status.[38]

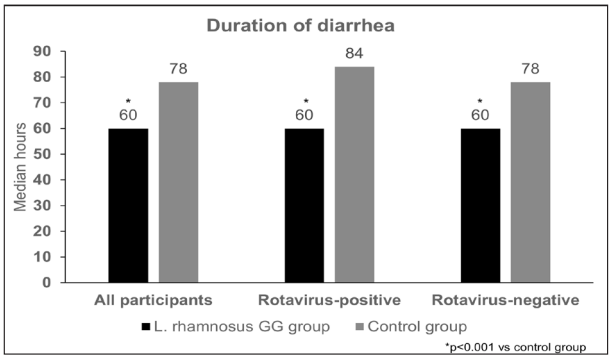

Figure 2.Effect of *L. rhamnosus GG* on Duration of Diarrhoea. Data is presented for all participants enrolled in the study, while the effect on rotavirus-positive and rotavirus-negative participants is also presented separately.[39]

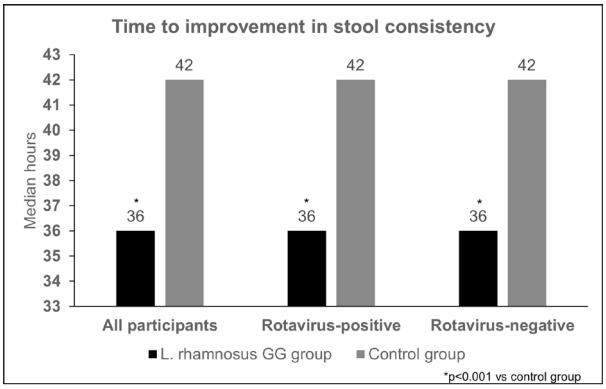

Figure 3.Effect of *L. rhamnosus GG* on Time Taken for Improvement in Stool Consistency. Data is presented for all participants enrolled in the study, while the effect on rotavirus-positive and rotavirus-negative participants is also presented separately.[39]

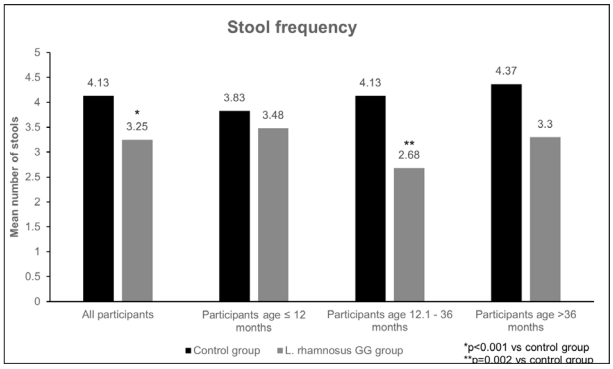

Figure 4.Effect of *L. rhamnosus GG* on Reducing Stool Frequency. Data for all participants enrolled in the study, along with data of sub-group evaluation based on the age of participants is presented.[40]

Ali conducted a similar randomised controlled study to evaluate whether the addition of *L. rhamnosus GG* to standard ORS therapy provides any additional benefits in comparison to ORS therapy alone in paediatric acute diarrhoea conditions.[39] The trial was conducted in 2017 as a single hospital-based study in Pakistan. 80 participants (aged 6 months to 5 years) presenting with acute diarrhoea were included and randomised into two groups: a control group treated with standard ORS therapy; and a probiotic group treated with ORS therapy and *L. rhamnosus GG* 5 billion CFU twice daily. The study duration was five days and the change in the number of stools was the primary evaluation parameter. After therapy, the mean number of stools was significantly lower in the probiotics group as compared to the control group ($p < 0.001$; Figure 4). On sub-group analysis based on the age of participants, it was observed that participants in the age group of 12.1–36 months had a significantly higher reduction in the number of stools compared to the control group, while other age groups did not reach significance (Figure 4).[39] In conclusion, *L. rhamnosus GG* is an effective therapy, while its efficacy is greatly dependent on the age of participants. The observations from this study were in-

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

line as compared with previous studies, while the result regarding the age-dependent efficacy of *L. rhamnosus GG* was different as compared to previous studies.

A multicentre, randomised, single-blinded, parallel-group, hospital-based study (the PROBAGE study) was conducted by Dinleyici et al. that assessed the effectiveness of *L. rhamnosus GG* and *Bifidobacterium lactis* BB12 combination in children with acute diarrhoea.[40] The study was conducted in Turkey and involved children (ages ranging from 6 months to 60 months) presenting with acute diarrhoea. The participants meeting the inclusion criteria were randomised to receive either hypo-osmolarity ORS therapy with probiotics combination (one billion CFU for both strains) or hypo-osmolarity ORS therapy alone. The study duration was five days, and the efficacy of interventions was evaluated using the duration of diarrhoea as the primary parameter and the change in duration of hospitalisation as the secondary parameter. After 5 days of therapy, the probiotics-treated participants showed a significant reduction in the duration of diarrhoea as compared to the control group ($p < 0.001$). The length of hospital stay was lower in probiotics-treated participants compared to the control group (5.03 vs 5.25 days), however, the comparison did not become significant. The percentage number of hospitalised participants with a prevalence of diarrhoea was significantly lower in the probiotics group as compared to the control group from the 48th hour of therapy. While the authors of the study identified certain limitations of their study including lack of double-blind placebo-controlled design, use of per-protocol analysis instead of intention-to-treat analysis, and failure to identify the cause of diarrhoea, the results of the study were still promising and in line with the results of previously conducted studies showing significant efficacy of *L. rhamnosus GG* in treating paediatric acute diarrhoea.[40]

The limitations of the PROBAGE study were previously fulfilled by a study conducted by Nixon et al.[42] The study was conducted as a double-blind, randomised, placebo-controlled study conducted in a paediatric emergency department and involved children (aged 6 months to 6 years) with acute infectious diarrhoea. The study was conducted in an urban public hospital conducted between 2008–2009. After obtaining consent, participants were either randomised to receive *L. rhamnosus GG* capsules or placebo capsules (containing inulin) for five days. The number of participants returning to normal stool, number of diarrhoeal stools, and time to normal stool, were the evaluation parameters used to compare the efficacy of interventions. After 5 days of therapy, the proportion of participants returning to normal stool, number of diarrhoeal stools, and time to normal stool were comparable between the groups. On sub-group analysis and evaluating the data of participants presenting with diarrhoea for more than 2 days, it was observed that a significantly higher number of participants in the *L. rhamnosus GG* group returned to normal stool by the end of the study (79% vs 58%; $p < 0.04$) as compared to the control group. Similarly, the time for normal stools was significantly lower in the *L. rhamnosus GG* ($p = 0.02$) as compared to the placebo group, and number of diarrhoeal stools was twice more in the placebo group as compared to the *L. rhamnosus GG* group (Figure 5). In conclusion, *L. rhamnosus GG* therapy is effective in reducing the duration and frequency of diarrhoea in paediatric participants.[42] The choice of using inulin as a placebo in the study prevented the extrapolation of the results of the study, as the inulin is considered a prebiotic product, which might have resulted in some of the anti-diarrhoeal effects observed in the placebo group.

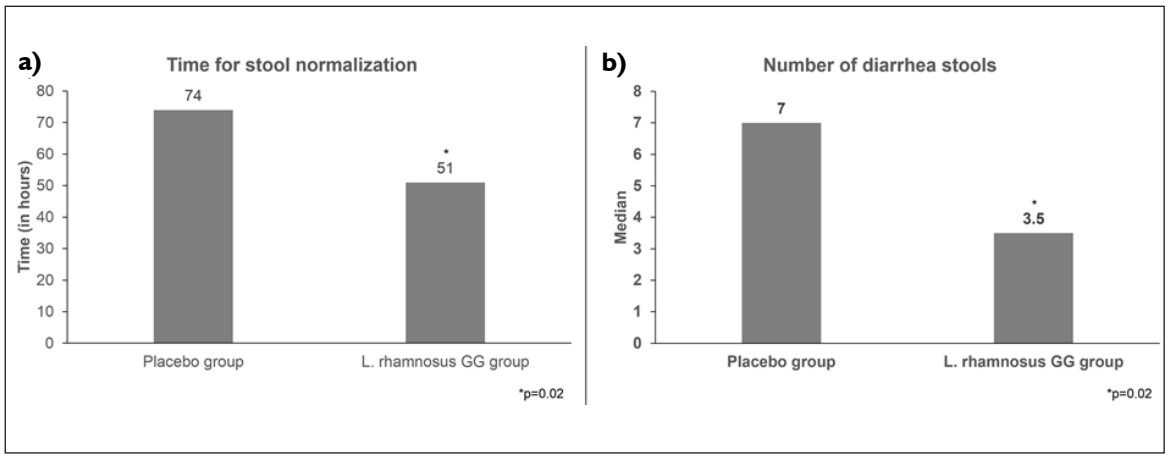

Figure 5.Effect of *Lactobacillus rhamnosus* GG on Reducing (a) Normal Stool Appearance Time and (b) Diarrhoeal Stool Number[43]

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

Recently, Biswas and Bal published the results of a single-centre, open-label, comparative, randomised controlled study (COMPARE-GG trial) conducted between 2019 and 2020 in Delhi, India.[41] The study enrolled 105 participants (aged 6–36 months; 80% participants positive for rotavirus) presenting with acute diarrhoea and randomised them into the following three groups: Group A treated with ORS + zinc therapy (standard therapy); Group B treated with standard therapy + *L. rhamnosus GG* 6 billion CFU sachet twice daily; and Group C treated with standard therapy + *S. boulardii* CNCM I-745 250 mg capsule twice daily. The study duration was five days, and the efficacy of therapy was evaluated on parameters of diarrhoea duration, duration of hospital stays, and stool frequency. On day 5, the participants in Group B had significantly lesser duration of diarrhoea as compared to Group A and Group C, while the duration of hospital stay was similarly less in Group B as compared to Group A and Group C. On day 1 of therapy, the stool frequency was significantly reduced in Group B as compared to Group A and Group C, and the difference was also observed on day 2, while on day 3, day 4, and day 5 the difference did not reach significance between the three groups. In conclusion, *L. rhamnosus GG* is a safe and effective therapy in paediatric participants presenting with acute diarrhoea. The use of *L. rhamnosus GG* along with standard therapies can result in better and faster improvement in acute diarrhoea compared to standard therapy alone.[41]

Recommendations for the Use of *L. rhamnosus* GG in Various Conditions

Based on the available scientific and clinical shreds of evidence, various global organisations have proposed certain recommendations for the use of *L. rhamnosus GG* in various disease conditions. The recommendations proposed by Latin-American experts suggest the use of *L. rhamnosus GG* for the management and treatment of acute infectious diarrhoea conditions, prevention of nosocomial diarrhoea and antibiotic-associated diarrhoea, and prevention of necrotising enterocolitis in neonates.[43] The experts from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Committee on Nutrition, and the ESPGHAN Working Group for Probiotics and Prebiotics provided a joint statement and recommended the use of *L. rhamnosus GG* for preventing and reducing the rates of necrotising enterocolitis.[44] The National Consultative Group of the Indian Academy of Pediatrics (IAP) has proposed using *L. rhamnosus GG* as an adjuvant therapy to treat acute diarrhoea and prevent diarrhoea brought on by antibiotics.[45] The ESPGHAN has recommended the use of *L. rhamnosus GG* for the management of acute gastroenteritis, prevention of nosocomial and antibiotic-associated diarrhoea, reduce the risk of necrotising enterocolitis in pre-term infants, and reduce the frequency and intensity of pain in paediatric patient with irritable bowel syndrome.[46] Additionally, the Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) working group (joint group involving experts from the ESPGHAN, Commonwealth Association of Paediatric Gastroenterology and Nutrition, the Asian Pan-Pacific Congress for Paediatric Gastroenterology, Hepatology, and Nutrition, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, and the Latin American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) have suggested that the routine use of antibiotics, anti-emetics, and anti-motility agents are not effective for the management of paediatric acute gastroenteritis, while the group have recommended the use of *L. rhamnosus GG* as adjunct to ORS therapy for the management of acute gastroenteritis in paediatric population.[47] The recent World Gastroenterology Organisation (WGO) global guidelines on probiotics and prebiotics have also recommended the use of *L. rhamnosus GG* in the most common paediatric complications including the treatment of acute gastroenteritis, functional abdominal pain, and IBS-associated abdominal pain, while for the prevention of antibiotic-associated diarrhoea, nosocomial diarrhoea, and necrotising enterocolitis.[48] A brief overview of all prominent recommendations is presented in Table 2.

Table 2.Current Recommendations for Use of *Lactobacillus rhamnosus GG* in Various Disease Conditions

Recommending Society/ Institution/ Organisation	Recommendations
Latin-American experts[43]	Prevention and treatment of acute infectious diarrhoea condition
	Prevention of nosocomial diarrhoea
	Prevention of antibiotic-associated diarrhoea
	Prevention of necrotising enterocolitis in neonates
European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics[44]	Preventing and reducing the rates of necrotising enterocolitis

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

Indian Academy of Pediatrics[45]	Adjuvant therapy for the treatment of acute diarrhoea
	Prevention of antibiotic-associated diarrhoea
European Society for Paediatric Gastroenterology, Hepatology, and Nutrition group[46]	Management of acute gastroenteritis
	Prevention of nosocomial diarrhoea
	Prevention of antibiotic-associated diarrhoea
	Reduce the risk of necrotising enterocolitis in pre-term infants
	Reduce the frequency and intensity of pain in paediatric patients with irritable bowel syndrome
Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition[47]	Adjunct to ORS therapy for the management of acute gastroenteritis in the paediatric population
World Gastroenterology Organisation[48]	Treatment of acute gastroenteritis, functional abdominal pain, and IBS-associated abdominal pain
	Prevention of antibiotic-associated diarrhoea, nosocomial diarrhoea, and necrotising enterocolitis

Strengths and Limitations of Current Study

The current study has several strengths. Firstly, the current study was aimed to evaluate the efficacy of *L. rhamnosus GG* therapy in paediatric acute diarrhoea condition using a systematic review methodology. As many literatures support the use of systematic review over conventional narrative review,[49] we consider the review methodology as one of the potential strengths of the current study. Secondly, we used the PICOS method for determining the research question and followed the PRISMA checklist guidelines to the fullest during the conduct of the current study, thereby maintaining the review article as per the recent guideline trends. Thirdly, the current study was conducted as per a protocol which was developed before the initiation of the study. Fourthly, all the included studies in the current review were of moderate-to-good quality studies, which were evaluated using the PEDro scale. Lastly, we included all the clinical studies that were in the last decade evaluating the efficacy of probiotic *L. rhamnosus GG* on acute diarrhoea parameters in the paediatric population. While many previous studies have evaluated the efficacy of *L. rhamnosus GG* in paediatric acute diarrhoea,[24] the results of the current study are completely in line with the results of previous studies, making the current study an extension to previous studies and also strong scientific support to the existing literature. The current study has a few limitations too. Firstly, we evaluated the efficacy of *L. rhamnosus GG* in a fixed target population (paediatric population) suffering from fixed disease indication (acute diarrhoea). As discussed above, *L. rhamnosus* GG is recommended in various paediatric disease indications, future systematic review studies can be conducted to evaluate the efficacy of *L. rhamnosus* GG in other target populations and on other disease indications as well. Secondly, the use of variable *L. rhamnosus* GG dose in the clinical studies justifies more clinical studies in the future to identify the optimal dose of *L. rhamnosus* GG that can be used effectively in paediatric acute diarrhoea. Lastly, the current study evaluated the efficacy of *L. rhamnosus* GG in paediatric acute diarrhoea, while currently various other probiotics are used in paediatric acute diarrhoea, and the inability of the current study to compare the effectiveness of individual probiotics with each other warrants future studies using statistical comparative methods to compare the efficacy of different probiotics therapy with each other on paediatric acute diarrhoea condition.

Conclusion

The current state-of-the-art systematic review study suggests that the supplementation of *Lactobacillus rhamnosus GG* is an effective therapy in reducing diarrhoea duration, stool frequency, and duration of hospital stay in paediatric acute diarrhoea. The findings of the current study are consistent with the results of previous studies conducted to estimate the effectiveness of *L. rhamnosus* GG in diarrhoea-associated conditions and the result of the current investigation further strengthens the observations of previous studies. The results of the current study can be accepted and applied in real-world clinical settings for the better management of acute diarrhoea in the paediatric population.

Acknowledgement

All the authors are thankful to the Department of Pharmacology, KB Institute of Pharmaceutical Education (Gandhinagar, Gujarat), Kadi Sarva Vishwavidyalaya (Gandhinagar, Gujarat) and Sundyota Numandis Probioceuticals Pvt Ltd (Ahmedabad, Gujarat) for providing us with the opportunity to work on the current project.

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

Conflict of Interest: None

References

1. Mahyar A, Ayazi P, Rad MS, Dalirani R, Javadi A, Esmaeily S. The correlation between vitamin D and bacterial diarrhea in children. Arch Pediatr Infect Dis. 2019;7(2):e84382. [Google Scholar]
2. Hartman RM, Cohen AL, Antoni S, Mwenda J, Weldegebriel G, Biey J, Shaba K, de Oilveira L, Rey G, Ortiz C, Tereza M, Fahmy K, Ghoniem A, Ashmony H, Videbaek D, Singh S, Tondo E, Sharifuzzaman M, Liyanage J, Batmunkh N, Grabovac V, Logronio J, Serhan F, Nakamura T. Risk factors for mortality among children younger than age 5 years with severe diarrhea in low- and middle-income countries: findings from the World Health Organization-coordinated Global Rotavirus and Pediatric Diarrhea Surveillance Networks. Clin Infect Dis. 2023;76(3):e1047-53. [PubMed] [Google Scholar]
3. Modgil V, Chaudhary P, Bharti B, Mahindroo J, Yousuf M, Koundal M, Mohan B, Taneja N. Prevalence, virulence gene profiling, and characterization of enteroaggregative *Escherichia coli* from children with acute diarrhea, asymptomatic nourished, and malnourished children younger than 5 years of age in India. J Pediatr. 2021;234:106-14.e5. [PubMed] [Google Scholar]
4. Nemeth V, Pfleghaar N. Diarrhea. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Sep 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448082/ [PubMed]
5. Najafi A, Najafi S, Vahdat K, Kargar M, Javdani N. Importance of viral pathogens in children with acute gastroenteritis in the south of Iran. Ann Saudi Med. 2013;33(2):124-9. [PubMed] [Google Scholar]
6. Ansari S, Sherchand JB, Parajuli K, Mishra SK, Dahal RK, Shrestha S, Tandulkar S, Pokhrel BM. Bacterial etiology of acute diarrhea in children under five years of age. J Nepal Health Res Counc. 2012;10(22):218-23. [PubMed] [Google Scholar]
7. Getahun W, Adane M. Prevalence of acute diarrhea and water, sanitation, and hygiene (WASH) associated factors among children under five in Woldia Town, Amhara Region, northeastern Ethiopia. BMC Pediatr. 2021;21(1):227. [PubMed] [Google Scholar]
8. Plourde PJ. Travellers' diarrhea in children. Paediatr Child Health. 2003;8(2):99-103. [PubMed] [Google Scholar]
9. Mohammed J, Shiferaw A, Zeleke A, Eshetu Y, Gebeyehu Z, Ayehu A, Adem Y. Prevalence and associated risk factors of intestinal parasites among diarrheic under-five children attending Bahir Dar and Han Health Centers, northwest Ethiopia: a cross-sectional study. J Parasitol Res. 2022;2022:7066529. [PubMed] [Google Scholar]
10. Chen MH, Deng SH, Wang MH, Yan XK. Clinical characteristics and influencing factors of infectious diarrhea in preschool children: an observational study. Medicine (Baltimore). 2023;102(17):e33645. [PubMed] [Google Scholar]
11. D'Argenio V, Salvatore F. The role of the gut microbiome in the healthy adult status. Clin Chim Acta. 2015;451(Pt A):97-102. [PubMed] [Google Scholar]
12. Krajmalnik-Brown R, Ilhan ZE, Kang DW, DiBaise JK. Effects of gut microbes on nutrient absorption and energy regulation. Nutr Clin Pract. 2012;27(2):201-14. [PubMed] [Google Scholar]
13. Sanidad KZ, Zeng MY. Neonatal gut microbiome and immunity. Curr Opin Microbiol. 2020;56:30-7. [PubMed] [Google Scholar]
14. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017;474(11):1823-36. [PubMed] [Google Scholar]
15. Bidell MR, Hobbs AL, Lodise TP. Gut microbiome health and dysbiosis: a clinical primer. Pharmacotherapy. 2022;42(11):849-57. [PubMed] [Google Scholar]
16. Gebrayel P, Nicco C, Al Khodor S, Bilinski J, Caselli E, Comelli EM, Egert M, Giaronni C, Karpinski TM, Loniewski I, Mulak A, Reygner J, Samczuk P, Serino M, Sikora M, Terranegra A, Ufnal M, Villeger R, Pichon C, Konturek P, Edeas M. Microbiota medicine: towards clinical revolution. J Transl Med. 2022;20(1):111. [PubMed] [Google Scholar]
17. Dixit K, Chaudhari D, Dhotre D, Shouche Y, Saroj S. Restoration of dysbiotic human gut microbiome for homeostasis. Life Sci. 2021;278:119622. [PubMed] [Google Scholar]
18. Xiao Q, Chen B, Zhu Z, Yang T, Tao E, Hu C, Zheng W, Tang W, Shu X, Jiang M. Alterations in the fecal microbiota composition in pediatric acute diarrhea: a cross-sectional and comparative study of viral and bacterial enteritis. Infect Drug Resist. 2023;16:5473-83. [PubMed] [Google Scholar]
19. Fijan S. Probiotics and their antimicrobial effect. Microorganisms. 2023;11(2):528. [PubMed] [Google Scholar]
20. Stavropoulou E, Bezirtzoglou E. Probiotics in medicine: a long debate. Front Immunol. 2020;11:2192. [PubMed] [Google Scholar]
21. Fijan S. Microorganisms with claimed probiotic properties: an overview of recent literature. Int J Environ Res Public Health. 2014;11(5):4745-67. [PubMed] [Google Scholar]
22. Gorbach S, Doron S, Magro F. *Lactobacillus rhamnosus GG*. In: Floch MH, Ringel Y, Walker AW, editors. The microbiota in gastrointestinal pathophysiology: implications for human health, prebiotics, probiotics,

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

and dysbiosis. Elsevier Inc.; 2017. p. 79-88. [Google Scholar]
23. Yan F, Polk DB. *Lactobacillus rhamnosus GG*: an updated strategy to use microbial products to promote health. Funct Food Rev. 2012;4(2):77-84. [PubMed] [Google Scholar]
24. Li YT, Xu H, Ye JZ, Wu WR, Shi D, Fang DQ, Liu Y, Li LJ. Efficacy of *Lactobacillus rhamnosus GG* in treatment of acute pediatric diarrhea: a systematic review with meta-analysis. World J Gastroenterol. 2019;25(33):4999-5016. [PubMed] [Google Scholar]
25. Szajewska H, Kołodziej M, Gieruszczak-Białek D, Skórka A, Ruszczyński M, Shamir R. Systematic review with meta-analysis: *Lactobacillus rhamnosus GG* for treating acute gastroenteritis in children - a 2019 update. Aliment Pharmacol Ther. 2019;49(11):1376-84. [PubMed] [Google Scholar]
26. Uberos J, Aguilera-Rodríguez E, Jerez-Calero A, Molina-Oya M, Molina-Carballo A, Narbona-López E. Probiotics to prevent necrotising enterocolitis and nosocomial infection in very low birth weight preterm infants. Br J Nutr. 2017;117(7):994-1000. [PubMed] [Google Scholar]
27. Jerzynska J, Stelmach W, Balcerak J, Woicka-Kolejwa K, Rychlik B, Blauz A, Wachulec M, Stelmach P, Majak P, Stelmach I. Effect of *Lactobacillus rhamnosus GG* and vitamin D supplementation on the immunologic effectiveness of grass-specific sublingual immunotherapy in children with allergy. Allergy Asthma Proc. 2016;37(4):324-34. [PubMed] [Google Scholar]
28. Pedersen N, Andersen NN, Végh Z, Jensen L, Ankersen DV, Felding M, Simonsen MH, Burisch J, Munkholm P. Ehealth: low FODMAP diet vs *Lactobacillus rhamnosus GG* in irritable bowel syndrome. World J Gastroenterol. 2014;20(43):16215-26. [PubMed] [Google Scholar]
29. Pagnini C, Paolo MC, Urgesi R, Pallotta L, Fanello G, Graziani MG, Fave GD. Safety and potential role of *Lactobacillus rhamnosus GG* administration as monotherapy in ulcerative colitis patients with mild–moderate clinical activity. Microorganisms. 2023;11(6):1381. [PubMed] [Google Scholar]
30. Mutlu M, Aslan Y, Kader Ş, Acar FA. Preventive effects of probiotic supplementation on neonatal hyperbilirubinemia caused by isoimmunization. Am J Perinatol. 2020;37(11):1173-6. [PubMed] [Google Scholar]
31. Savino F, Montanari P, Galliano I, Daprà V, Bergallo M. *Lactobacillus rhamnosus GG* (ATCC 53103) for the management of infantile colic: a randomized controlled trial. Nutrients. 2020;12(6):1693. [PubMed] [Google Scholar]
32. Näse L, Hatakka K, Savilahti E, Saxelin M, Pönkä A, Poussa T, Korpela R, Meurman JH. Effect of long-term consumption of a probiotic bacterium, *Lactobacillus rhamnosus GG*, in milk on dental caries and caries risk in children. Caries Res. 2001;35(6):412-20. [PubMed] [Google Scholar]
33. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, Puri P, Sterling RK, Luketic V, Stravitz RT, Siddiqui MS, Fuchs M, Thacker LR, Wade JB, Daita K, Sistrun S, White MB, Noble NA, Thorpe C, Kakiyama G, Pandak WM, Sikaroodi M, Gellivet PM. Randomised clinical trial: *Lactobacillus GG* modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. Aliment Pharmacol Ther. 2014;39(10):1113-25. [PubMed] [Google Scholar]
34. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hrobjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Setwart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. [PubMed] [Google Scholar]
35. Dixon A, Robertson K, Yung A, Que M, Randall H, Wellalagodage D, Cox T, Robertson D, Chi C, Sun J. Efficacy of probiotics in patients of cardiovascular disease risk: a systematic review and meta-analysis. Curr Hypertens Rep. 2020;22(9):74. [PubMed] [Google Scholar]
36. Aguiar AF, Casonatto J. Effects of citrulline malate supplementation on muscle strength in resistance-trained adults: a systematic review and meta-analysis of randomized controlled trials. J Diet Suppl. 2022;19(6):772-90. [PubMed] [Google Scholar]
37. Sharma AK, Puri N, Mathur M, Mathur A. A randomized controll trial to compare the efficacy of *Saccharomyces boulardii, Bacillus clausii*, and *Lactobacillus rhamnosus GG* preparation in the treatment of acute diarrhea in children. Asian J Pharm Clin Res. 2022;15(4):63-7. [Google Scholar]
38. Aggarwal S, Upadhyay A, Shah D, Teotia N, Agarwal A, Jaiswal V. *Lactobacillus GG* for treatment of acute childhood diarrhoea: an open labelled, randomized controlled trial. Indian J Med Res. 2014;139(3):379-85. [PubMed] [Google Scholar]
39. Ali R. The use of probiotic with ORS and ORS only in children with acute diarrhea. J Coll Physicians Surg Pak. 2019;29(12):1179-82. [PubMed] [Google Scholar]
40. Dinleyici EC, Ozen M, Dalgic N, Yasa O, Arica V, Metin O, Tanir G, Kurugol Z, Guven S, Yazar AS, Karbiz A, Nalbantoglu B, Sancar M, Eren M, Kra A, Vanderplas Y. Effect of *Lactobacillus rhamnosus* LGG and *Bifidobacterium animalis* subspecies lactis BB-12 combination on the duration of diarrhea and length of hospital stay in children with acute diarrhea in Turkey. Mucosa. 2020;3(2):34-41. [Google Scholar]
41. Biswas S, Bal B. Comparative, randomized-controlled

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470

trial on efficacy and safety of *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* in treatment of acute diarrhea in Indian children (COMPARE-GG trial). Int J Clin Trials. 2023;10(2):131-6. [Google Scholar]

42. Nixon AF, Cunningham SJ, Cohen HW, Crain EF. The effect of *Lactobacillus GG* on acute diarrheal illness in the pediatric emergency department. Pediatr Emerg Care. 2012;28(10):1048-51. [PubMed] [Google Scholar]
43. Cruchet S, Furnes R, Maruy A, Hebel E, Palacios J, Medina F, Ramirez N, Orsi M, Rondon L, Sdepanian V, Xochihua L, Ybarra M, Zablah RA. The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts. Pediatr Drugs. 2015;17(3):199-216. [PubMed] [Google Scholar]
44. Akker CH, Goudoever JB, Shamir R, Domellöf M, Embleton ND, Hojsak I, Lapillonne A, Mihatsch WA, Canani RB, Bronsky J, Campoy C, Fewtrell MS, Mis NF, Guarino A, Hulst JM, Indrio F, Kolacek S, Orel R, Vandenplas Y, Weizman Z, Szajewska H. Probiotics and preterm infants: a position paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2020;70(5):664-80. [PubMed] [Google Scholar]
45. Yachha SK, Sarma MS, Mohan N, Wadhwa N, Vr NK, Srinivasan R, Shah D, Soans S, Yewale V, Basavaraja GV, Parekh BJ. Indian Academy of Pediatrics consensus guidelines for probiotic use in childhood diarrhea. Indian Pediatr. 2022;59(7):543-51. [PubMed] [Google Scholar]
46. Szajewska H, Canani RB, Domellöf M, Guarino A, Hojsak I, Indrio F, Vecchio AL, Mihatsch WA, Mosca A, Orel R, Salvatore S, Shamir R, Akker CH, Goudoever JB, Vandenplas Y, Weizman Z; ESPGHAN Special Interest Group on Gut Microbiota and Modifications. Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications. J Pediatr Gastroenterol Nutr. 2023;76(2):232-47. [PubMed] [Google Scholar]
47. Guarino A, Vecchio AL, Dias JA, Berkley JA, Boey C, Bruzzese D, Cohen MB, Cruchet S, Liguoro I, Salazar-Lindo E, Sandhu B, Sherman PM, Shimizu T. Universal recommendations for the management of acute diarrhea in nonmalnourished children. J Pediatr Gastroenterol Nutr. 2018;67(5):586-93. [PubMed] [Google Scholar]
48. Guarner F, Sanders ME, Szajewska H, Cohen H, Eliakim R, Herrera-deGuise C, Karakan T, Merenstein D, Piscoya A, Ramakrishna B, Salminen S, Melberg J. World Gastroenterology Organisation global guidelines: probiotics and prebiotics. J Clin Gastroenterol. 2024 Jul 1;58(6):533-53. [PubMed] [Google Scholar]
49. Pae CU. Why systematic review rather than narrative review? Psychiatry Investig. 2015;12(3):417-9. [PubMed] [Google Scholar]

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202470