Article

Not peer-reviewed version

Effects of Probiotics in Adults with Gastroenteritis: A Systematic Review and Meta-Analysis of Clinical Trials

Amal Krishna Mitra *, Adetoun F. Asala , Shelia Malone , Malay Kanti Mridha

Posted Date: 6 September 2023

doi: 10.20944/preprints202309.0328.v1

Keywords: probiotics; clinical trials; adults; gastroenteritis, inflammatory bowel disease; PRISMA

Article

Effects of Probiotics in Adults with Gastroenteritis: A Systematic Review and Meta-Analysis of Clinical Trials

Amal K. Mitra [1,*], Adetoun F. Asala [1,2], Shelia Malone [1] and Malay Kanti Mridha [3]

[1] Department of Epidemiology and Biostatistics, College of Health Sciences, Jackson State University, Jackson, MS, USA; amal.k.mitra@jsums.edu (A.K.M.); shelia.malone@students.jsums.edu (S.M.)
[2] Epidemiologist Team Lead, Office of Preventive Heath, Mississippi State Department of Health, Ridgeland, MS 39157, USA; Adetoun.Asala1@msdh.ms.gov (A.F.A)
[3] Brac James P. Grant School of Public Health and Center for Non-Communicable Disease and Nutrition, Brac University, Dhaka, Bangladesh; malay.mridha@bracu.ac.bd (M.K.M.)
* Correspondence: amal.k.mitra@jsums.edu; Tel.: +1 601 979 8788

Abstract: Probiotics have been widely used in gastroenteritis due to acute and chronic illnesses. However, evidence supporting the effectiveness of probiotics in different health conditions are inconclusive and conflicting. The aim of the study was to review existing literature on the effects of probiotics in gastroenteritis among adults. Only original articles on clinical trials that demonstrated the effects of probiotics in adults with gastroenteritis were used for this analysis. Multiple databases such as PubMed, Google Scholar, MEDLINE and Scopus databases were searched for the data. The study followed standard procedures for data extraction using PRISMA flow chart. A quality appraisal of the selected studies was conducted using CADIMA. Finally, a meta-analysis was conducted. Thirty-five articles met the selection criteria; of them, probiotics were found effective in the treatment and/or prevention of chronic inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease in 17 (49%), and the treatment of *pouchitis* in 4 (11.4%), antibiotic-induced diarrhea in 3 (8.6%), *Helicobacter pylori* infection in 2 (5.7%) and diverticulitis in 1 (2.9%), while the remaining 7 (20%) were ineffective and 1 study results were inconclusive. Meta-analysis, on the contrary, didn't demonstrate any significant protective effects of probiotics. Having a τ^2 value of zero and I^2 of 6%, the studies were homogeneous and had minimum variances. Further studies are suggested to evaluate the beneficial effects of probiotics in IBDs and other chronic bowel diseases.

Keywords: probiotics; clinical trials; adults; gastroenteritis; inflammatory bowel disease; PRISMA

1. Introduction

Gastroenteritis poses serious public health concerns in both high- and low-income countries. It is one of the leading causes of morbidity and mortality worldwide [1]. Globally, the estimated annual cost of healthcare and loss of productivity due to gastroenteritis is about $60 billion of which developing countries bear the highest burden [1,2]. According to the Centers for Disease Control and Prevention (CDC), gastroenteritis is the most prevalent infectious disease syndrome in the United States, accounting for over 350 million illnesses annually and about 200,000 deaths, with the elderly having higher risks of mortality [3,4]. The symptoms of gastroenteritis could range from mild asymptomatic infections to life-threatening conditions and deaths [5].

Probiotics are supplements or foods that contain live non-pathogenic microorganisms, which can maintain and improve microbial balance in the gastrointestinal tract [6]. Some beneficial effects of probiotics relevant to the treatment and prevention of gastroenteritis include: reduction of invasion and colonization of the intestine by pathogenic organisms, modification of host immune response, and reduction of pH in the intestine [6,7]. Although, some studies confirmed that probiotics have anti-inflammatory and antimicrobial effects and help maintain good bacteria in the gut, results from some other studies are inconclusive and conflicting [8]. Use of specific probiotic preparations should be based on evidence from well-designed clinical trials. Therefore, the purpose of this study was to

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

present the results of a systematic review and meta-analysis carried out to examine the effects of probiotics in adults with acute and chronic gastroenteritis of multiple etiologies.

2. Materials and Methods

A systematic literature search was conducted from February – May, 2021 using PubMed database as the primary data source. Other research databases included were Google Scholar, MEDLINE, and Scopus. The search keywords in PubMed were "effects of probiotics in gastroenteritis", Medical Subject Headings (MeSH) Terms were: "effect*" OR "outcomes" OR "impact" OR "efficacy*" OR "efficaciousness*" AND "Probiotics" AND "Gastroenteritis" AND "Clinical Trial".

Articles which met the following criteria were included in the review: 1) Studies published between years 1990-2022; 2) Only clinical trial study designs; 3) Studies related to the effects of probiotics in gastroenteritis; 4) Studies with partcipants between 19 – 55 years of age; 5) Full text articles; and 6) Articles written in English language. **Figure 1** shows the detailed search strategies for this study using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [9].

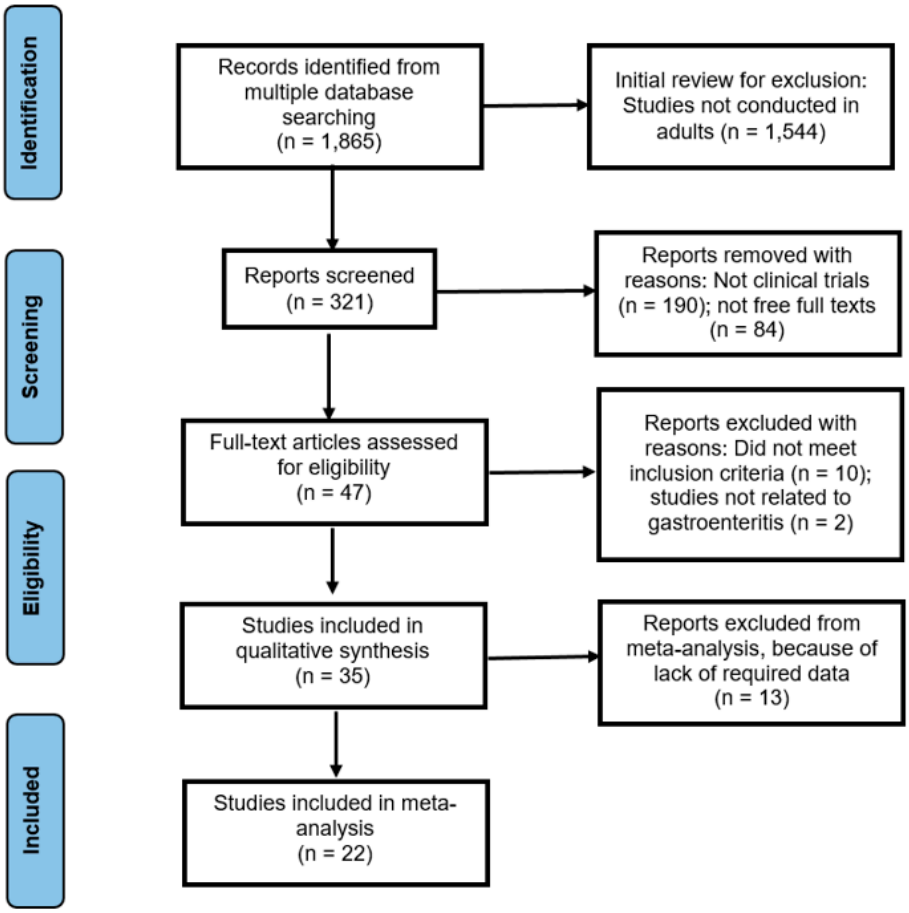

Figure 1. PRISMA flow chart showing inclusion and exclusion of studies

Quality appraisal methods

Studies were appraised for quality using CADIMA [10]. CADIMA is a free tool which is available online for managing articles for systematic review including automated duplicate removal, uploading PDF articles, and documentation fo the review process. Through CADIMA, standards for critical appraisal and the rating scale were defined. We followed the critical appraisal tools for systematic reviews developed by the University of Adelaide, South Australia [10]. A rating scale from 0 to 4 was based on the following criteria: (1) Sample size: greater than 30 = 1; smaller sample = 0; (2)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

Randomized controlled trials = 1; not randomized, no controls = 0; (3) Studied both safety and efficacy = 1; otherwise = 0; (4) Standard and objective evaluation criteria = 1, otherwise = 0. Based on the above-mentioned criteria, we rated each of the 35 studies independently from a range of 0 to 4.

3. Results

Of the 1,865 research articles identified through database search, 1,544 articles were excluded for not being done in adults. Of the remaining 321 studies, 190 were excluded because the studies did not involve clinical trials; 84 were excluded for not having full articles available; and 12 were excluded for studies not meeting the eligibility criteria, and/or not being related to gastroenteritis. The results presented below include analyses of 35 studies for the systematic review (**Figure 1**).

The total sample size for the 35 studies was 4,577, ranging from 15 to 777 samples in individual study, with a median of 44. Only 12 studies (34%) had a sample size of more than 100.

3.1. Type of Illnesses Associated with Diarrhea

We found that the majority of the studies (51%, 18 of 35) focused on effectiveness of probiotics in the treatment of IBDs (ulcerative colitis and Crohn's disease), 11% (4 of 35) of the study patients had pouchitis (inflammation that occurs in the lining of a pouch created during surgery to treat ulcerative colitis or certain other diseases), about 9% (3 of 35) had antibiotic-induced diarrhea, 6% (2 of 35) had diarrhea due to *Helicobacter pylori*, and one each (2.9%) had diverticulitis or acute watery diarrhea due to *Vibrio cholerae* and enterotoxigenic *Escherichia coli* infection, (**Figure 2**).

Detailed information about the 35 selected studies [11–45], the type of gastroenteritis studied, type of probiotics used and their effectiveness are presented in **Table 1**.

Table 1. Type of gastroenteritis, probiotics used, and their effectiveness.

Authors, year [ref.]	Disease condition and sample size	Type of probiotics used	Prevention / Treatment	Effective	Quality appraisal	Major findings / conclusions	Country
Alberda et al., 2018 [11]	Antibiotic-associated diarrhea (AAD) and *Clostridium difficile*-induced diarrhea; sample size = 32	*Lactobacillus casei*	Prevention	Yes	Score 3 out of 4 (Moderate)	Probiotic drink can prevent AAD and *Clostridium difficile* infections.	Canada
Altun, et al., 2019 [12]	Inflammatory bowel disease (IBD)[1]: ulcerative colitis (UC); sample size = 40	*Enterococcus faecium, Lactobacillus plantarum, Streptococcus thermophilus, Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium longum*)-and fructooligosaccharide	Treatment	No	Score 4 out of 4 (High)	The use of synbiotic therapy[2] had no statistically significant effect in the improvement of clinical and endoscopic parameters compared with controls.	Turkey
Bjarnason, et al., 2019 [13]	IBDs: ulcerative colitis (UC) (n = 81) and Crohn's disease (n = 61); total samples more than 500.	*Symprove contains multiple strains of probiotics such as Lactobacillus plantarum, Lactobacillus*	Treatment	Yes	Score 4 out of 4 (High)	Multi-strain probiotics decreased intestinal inflammation in patients with ulcerative colitis, but	United Kingdom

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

		rhamnosus, Lactobacillus plantarum, Lactobacillus acidophilus, and E. faecium			not in patients with Crohn's disease.	
Derwa, et al., 2017 [14]	IBDs; sample size = 777	*Probiotics vs.* 5-aminosalicylates (5-ASAs) (in one RCT); probiotics vs. placebo (in 7 RCTs).	Treatment	No	Score 4 out of 4 (High)	There was no benefit of probiotics over 5-ASAs[4] or placebo in inducing remission in active inflammatory bowel diseases. For ulcerative colitis, relative risk of failure to achieve remission = 0.86; 95% CI = 0.68-1.08.	Multiple countries
Fan, et al., 2019 [15]	IBDs[1]; sample size = 40	Bifico contains probiotic bacteria Bacillus Coagulans GBI-30, 6086. Bifico was given as an adjuvant treatment with Pentasa, which is an anti-inflammatory agent.	Treatment	Yes	Score 4 out of 4 (High)	Combination of probiotics and pentasa can improve microflora composition in patients with IBD and reduce the level of inflammatory cytokines.	China
Groeger, et al., 2013 [16]	IBDs[1]; chronic fatigue syndrome (CFS); Psoriasis. Sample sizes: UC = 22, CFS = 48, psoriasis = 26.	*Bifidobacterium infantis* 35624	Treatment	Yes	Score 4 out of 4 (High)	Microbiota in humans have immuno-modulatory effects on both mucosal immune system and systemic immune system.	Ireland
Hafer, et al., 2007 [17]	IBDs[1]; sample sizes: UC = 14, Crohn's disease = 17.	Standard treatment vs. standard treatment with oral lactulose.	Treatment	No	Score 3 out of 4 (Moderate)	Oral lactulose has no beneficial no clinical and immune-histological effects on IBD patients.	Germany
Kato, et al., 2004 [18]	IBD: ulcerative colitis (UC); sample size = 20	*Bifidobacteria-fermented milk (BFM)*	Treatment	Yes	Score 3 out of 4 (Moderate)	Supplementation with BFM has beneficial effects in managing active ulcerative colitis and is more effective than the conventional treatment alone.	Japan
Krag, et al., 2012 [19]	IBD: ulcerative colitis (UC); sample size = 39	Profermin, consisting of fermented oats, *Lactobacillus plantarum 299v, barley malt, lecithin, and water*	Treatment	Yes	Score 4 out of 4 (High)	Profermin is safe and may be effective in inducing remission of active ulcerative colitis.	Denmark
Kruis, et al., 1997 [20]	IBD: ulcerative colitis (UC); sample size = 120	*Escherichia coli* Nissle (Serotype 06: K5: H1), as an	Treatment	Yes	Score 4 out of 4 (High)	*E. coli* (Serotype 06: K5: H1) is effective in preventing remission	Germany, Czech Republi

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

		adjuvant treatment with mesalazine (also known as 5-aminosalicylic acid (5-ASA)[4]				of ulcerative colitis as a standard treatment with 5-ASA[4].	c, and Austria
Kruis, et al., 2004 [21]	IBD: ulcerative colitis (UC); sample size = 327	*Escherichia coli* Nissle 1917	Maintaining remission and prevention of relapses	Yes	Score 4 out of 4 (High)	Probiotic EcN has therapeutic effects and is safe for maintaining remission in ulcerative colitis. EcN can be used as an alternative of 5-ASA[4].	Germany
Kuehbacher, et al., 2006 [22]	Pouchitis[3]; sample size = 15	*VSL #3* consists of *Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifidobacterium longuum, B. breve, B. infantis, and Streptococcus salivarius* sub-spp. *Thermophillus*	Treatment	Yes	Score 3 out of 4 (Moderate)	Probiotic therapy with *VSL #3 increases the diversity, richness and total number of intestinal bacteria and bacterial microbiota.*	Germany
Kuisma, et al., 2003 [23]	Pouchitis[3]; sample size = 20	*Lactobacillus rhamnosus GG*	Treatment	No	Score 3 out of 4 (Moderate)	*Lactobacillus GG* can alter the microbial flora in ileo-anal pouches but was inefficient for clinically improving pouch inflammation.	Finland
Lahner, et al., 2012 [24]	Symptomatic uncomplicated diverticular disease; sample size = 45	*Lactobacillus paracasei* B21060 (symbiotic sachet Flortec©) plus high fiber diet (Treatment Group) vs high fiber diet only (Controls)	Treatment	Yes	Score 3 out of 4 (Moderate)	The treatment group having symbiotic sachet Flortec© plus a high fiber diet improved of clinical symptoms (abdominal pain, bloating) significantly more than the control group.	Italy
Lorea Baroja, et al., 2007 [25]	IBD: Crohn's disease (n = 15) and ulcerative colitis (n = 5), control, (n = 20); total sample size = 40	*Lactobacillus rhamnosus GR-1 and L. reuteri RC-14- supplemented yogurt vs. placebo*	Prevention	Yes	Score 4 out of 4 (High)	Short-term consumption of probiotic yogurt with *Lactobacillus rhamnosus GR-1 and RC-14* has beneficial immune modulatory effects.	Canada
Marteau, et al., 2006 [26]	IBD: Crohn's disease; sample size = 98	*Lactobacillus johnsonii LA1*	Prevention of relapses	No	Score 4 out of 4 (High)	*Lactobacillus johnsonii LA1 have no sufficient effect to prevent recurrence of Crohn's disease.*	*France*
Matsuoka, et al., 2018 [27]	IBD: ulcerative colitis (UC); sample size = 195	*Bifidobacterium breve* fermented milk (BFM)	Prevention	No	Score 4 out of 4 (High)	BFM had no effect on time to relapse in UC patients, compared with placebo.	Japan

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

Matthes, et al., 2010 [28]	IBD: ulcerative colitis (UC); sample size = 90 (70 with UC and 20 controls)	*Escherichia coli* Nissle 1917 (EcN)	Treatment	Yes	Score 3 out of 4 (Moderate)	*Escherichia coli* Nissle 1917 (EcN) may be an alternative treatment for moderate distal ulcerative colitis.	Germany
Mimura, et al., 2004 [29]	Recurrent or refractory pouchitis[3]; sample size = 36	VSL #3 contains *Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifidobacterium. longuum, B. breve, B. infantis Streptococcus salivarius* subsp. *Thermophillus*	Treatment of remission	Yes	Score 3 out of 4 (Moderate)	VSL#3 probiotic therapy is highly effective in maintaining treatment of recurrent pouchitis[3] and improving quality of life.	United Kingdom and Italy
Mitra & Rabbani, 1990 [30]	Acute watery diarrhea due to *Vibrio cholerae* and *E. coli* infection; sample size = 183	Bioflorin (*Streptococcus faecium* SF68), given orally along with intravenous rehydration, and followed by oral rehydration solution	Treatment	No	Score 4 out of 4 (High)	Bioflorin was not effective in treating acute diarrhea due to *V. cholerae* and enterotoxigenic *E. coli* infections.	Bangladesh
Montalto, et al., 2010 [31]	Non-steroidal anti-inflammatory drug-induced enteropathy; sample size = 20	VSL #3 contains *Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifidobacterium. longuum, B. breve, B. infantis Streptococcus salivarius* subsp. *Thermophillus*	Treatment	Yes	Score 2 out of 4 (Poor)	Probiotics mixture could be useful in decreasing indomethacin-induced intestinal inflammation.	Italy
Palumbo, et al., 2016 [32]	IBD: ulcerative colitis (UC); sample size = 60	A probiotic blend, which consists of *Lactobacillus salivarius, Lactobacillus acidophilus* and *Bifidobacterium bifidus* strain BGN4, given as an adjuvant therapy with Mesalazine	Treatment	Yes	Score 3 out of 4 (Moderate)	Long-term treatment modality of anti-inflammatory drugs and probiotics is viable and could be an alternative treatment for mild-to moderate ulcerative colitis.	Italy
Persborn, et al., 2013 [33]	Pouchitis[3]; sample size = 16 patients with pouchitis and 13 controls with a healthy ileoanal pouch	*Bifidobacterium bifidum (W23), B. lactis (W51), B. lactis (W52), Lactobacillus acidophilus (W22), L. casei (W56), L. paracasei (W20),*	Treatment	Yes	Score 3 out of 4 (Moderate)	Probiotics restored the mucosal barrier to *E. coli* in patients with pouchitis[3]. This can prevent recurrence during maintenance therapy.	Sweden

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

		L. plantarum (W62), L. salivarius (W24), L. lactis (W19)				
Shadnoush, et al., 2015 [34]	IBDs[1]; sample size = 305, of which 105 IBD patients received probiotic yogurt, 105 IBD patients received placebo, and 95 healthy controls received probiotic yogurt	Probiotic yogurt containing *Lactobacillus acidophilus La-5 and Bifidobacterium BB-12*	Treatment	Inconclusive	Score 3 out of 4 (Moderate)	Fiber and energy intake in the treatment group did not increase when compared with those of controls. However, consumption of probiotic yogurt by patients with IBD may help to increase the number of probiotic bacteria in the intestine, thus improving intestinal function.	Iran
Shen, et al., 2005 [35]	Antibiotic-dependent pouchitis[3]; sample size = 31	VSL #3 contains four strains of *Lactobacillus,* three *Bifidobacterium* species, *Streptococcus salivarius* subsp. *thermophillus*	Treatment	Yes	Score 3 out of 4 (Moderate)	The use of probiotics is useful, and the authors suggested it in routine clinical care.	United States
Steed, et al., 2010 [36]	IBD: Crohn's disease; sample size = 35	*Bifidobacterium longum* and Synergy 1 which contains Orafti, Tienen, Belgium	Treatment	Yes	Score 4 out of 4 (High)	Effective in improving clinical symptoms in patients with active Crohn's disease.	Scotland
Tomasz, et al., 2014 [37]	Pouchitis[3]; sample size = 43	*Lactobacillus acidophillus, L. delbrueckii subsp. bulgaricus,* and *Bifidobacterium bifidus*	Prevention	Yes	Score 4 out of 4 (High)	Long-term use of probiotics is safe and can be an effective method of preventing pouchitis[3].	Poland
Tongtawee, et al., 2015 [38]	*Helicobacter pylori*; sample size = 200	*Lactobacillus delbrueckii subsp. bulgaricus* and *Streptococcus thermophillus*	Treatment	Yes	Score 4 out of 4 (High)	Pretreatment with probiotic containing yogurt can potentiate the effects of triple therapy for *Helicobacter pylori*.	Italy
Tursi, et al., 2010 [39]	IBD: ulcerative colitis (UC); sample size = 144	*VSL #3* consists of *Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifidobacterium longuum, B. breve, B. infantis, and Streptococcus salivarius* sub-spp. *Thermophillus*	Treatment	Yes	Score 4 out of 4 (High)	High potency probiotic mixture supplementation is safe and improves rectal bleeding and reduce remission in relapsing ulcerative colitis patients after 8 weeks of treatment.	Thailand

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

Venturi, et al., 1999 [40]	IBD: ulcerative colitis (UC); sample size = 20	*VSL #3* consists of *Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifidobacterium longuum, B. breve, B. infantis, and Streptococcus salivarius* sub-spp. *Thermophillus*	Treatment	Yes	Score 3 out of 4 (Moderate)	Intake of VSL #3 preparation enhances the concentrations of some strains of protective bacteria in the intestinal microflora.	Italy
Yilmaz, et al., 2019 [41]	IBDs[1]; sample size = 45	Kefir, a cultured, fermented beverage, which contains *Lactobacillus* bacteria	Treatment	Yes	Score 3 out of 4 (Moderate)	Consumptions of kefir has short term effects on improving the quality of life of patients.	Turkey
Yoshimatsu, et al., 2015 [42]	IBD: ulcerative colitis (UC); sample size = 46	*Streptococcus faecalis (lactomin), Clostridium butyricum, and Bacillusmesentericus*	Prevention of relapse	Yes	Score 3 out of 4 (Moderate)	Probiotics may be effective for maintaining clinical remission in patients with quiescent ulcerative colitis.	Japan
Ziemniak, 2006 [43]	Chronic gastritis, or duodenal ulcer caused by *Helicobacter pylori*; sample size = 641	Lacidofil containing *Lactobacillus acidophilus and Lactobacillus rhamnosus*, as an adjuvant therapy with antibiotics and proton pump inhibitor (PPI)	Treatment	Yes	Score 4 out of 4 (High)	Lacidofil increases the efficacy of clarithromycin and amoxicillin and also reduces complications of antibiotic therapy.	Poland
Zocco, et al., 2006 [44]	IBD: ulcerative colitis (UC); sample size = 187	*Lactobacillus GG*	Treatment and prevention of remissions	Yes	Score 4 out of 4 (High)	*Lactobacillus GG* is effective and safe for maintaining ulcerative colitis remission and could be a good therapeutic alternative.	*Italy*
Zwolinsk, et al., 2009 [45]	IBD: ulcerative colitis (UC); sample size = 101, of which 56 had active phase of UC, 33 non-active phase of UC, and 12 IBS controls	*Lacidofil,* containing two well-characterized strains of Lactobacillus: *L. helveticus* R-52 and *L. rhamnosus* R-11.	Treatment	Yes	Score 4 out of 4 (High)	Probiotic therapy is beneficial in counteracting the effects of delayed healing of trinitrobenzene sulfonic acid induced colitis caused by *Candida*.	Poland

[1]Inflammatory bowel diseases include ulcerative colitis and Crohn's disease; [2]Synbiotic therapy: a combination of prebiotics and probiotics; [3]Pouchitis: inflammation of a J-shaped pouch, which is created by surgical procedures as a treatment of ulcerative colitis; [4]5-ASA: 5-aminosalicylates; mesalazine is a 5-ASA.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

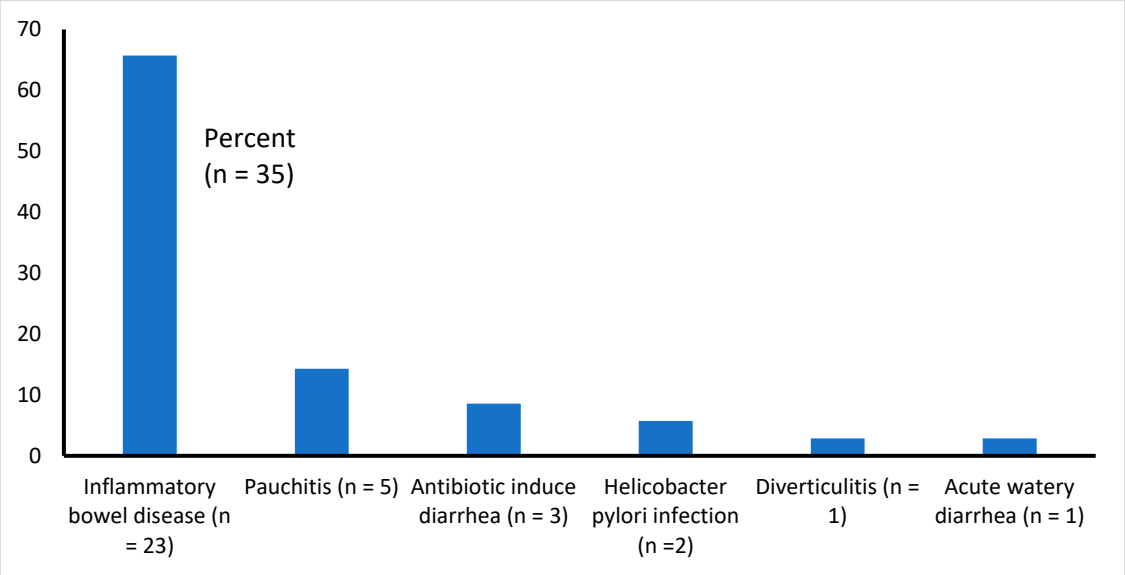

Figure 2. Types of infections causing diarrhea among the study samples (n = 35).

3.2. Probiotic Strains Used and Follow-up

Most of the studies (60%, *n* = 21) administered multiple strains of probiotics while the remaining 14 studies administered single strain of probiotics. The most commonly administered probiotic strains were *Lactobacilli, Bifidobacteria, Streptococcus,* and *Escherichia*. In a few studies, probiotics were administered as an adjuvant therapy with another conventional treatment, such as an anti-inflammatory drug for IBDs [15,20,32], rehydration therapy for acute watery diarrhea [30], or with a combination of treatments comprising antibiotics and proton pump inhibitor (PPI) (Esomeprazole) for chronic gastritis or duodenal ulcer due to *H. pylori* infection [43].

Patients' follow-up protocols varied widely, ranging from as low as 10 days to 2 years depending on the illness type. Ten studies followed patients for 12 months or more, 12 studies followed patients for 3-11 months while another 14 followed patients for 3 months or less.

3.3. Quality Appraisal Findings

Due to having no major inter-observer variations in the evaluation of the quality of the studies, an average of the 4 scores was presented in Table 3. Out of 35 studies reviewed, 19 (55%) scored high (4 out of 4), 15 (43%) scored moderate (3 out of 4), and only one was rated poor (2 out of 4). Among the 27 studies which were proven effective for the treatment of probiotics, the majority (63%, n = 14) were of high quality (score 4 out of 4), 44% (n = 12) scored moderate quality (score 3 out of 4), and only 1 (4%) scored poor rating (score 2 out of 4).

3.4. Efficacy and Safety of Probiotics

The outcome measures were considered favorable if studies reported resolution, remission, improvement or no relapse of gastroenteritis after treatment. Of the 35 studies reviewed, 27 (77%) showed a favorable response after using probiotics, 7 (20%) showed that probiotics were ineffective, and 1 study conducted in Iran [34] was inconclusive (Table 1). Probiotics were most effective in the treatment or prevention of gastroenteritis due to IBDs (Figure 2). Of the various forms of probiotics, a mixture of multiple probiotic strains, in the form of VSL #3, was found most effective in treating patients with IBDs [22,29,39,40] and drug-induced enteropathy [31,35]. However, probiotics were found ineffective in five studies in patients with ulcerative colitis or Crohn's diseases [12,14,17,26,27], and also in two other studies – one in 20 patients with pouchitis in Finland [23], and the other study in 183 patients with a severe form of acute watery diarrhea due to *V. cholerae* and *E. coli* infections in Bangladesh [30] (Table 1).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

All probiotics administered in these studies, including those which were proven ineffective, were well tolerated by patients and no adverse side effects were reported. However, several studies cautioned the use of probiotics among immunocompromised patients due to safety concerns in such patients [8,50].

3.5. Effectiveness of Probiotics, as Evaluated by Meta-Analysis of 22 Clinical Trials

Due to the unavailability of relevant data, meta-analysis was conducted using 22 out of 35 (63%) studies. Table 2 shows relative risk and 95% confidence intervals (CIs) of the effect of probiotics in each study. Risk ratios observed a protective effect in 50% of the studies (n = 11); however, 95% CI included 1 in each of them. The pooled relative risk was 0.99, with 95% CI being 0.90 and 1.09. Test for the overall effect showed a *p*-value of 0.37, meaning that there was not enough evidence to indicate that the intervention had a significantly more protective effect compared to controls. The value of τ^2 indicated low variation of true effects. The Higgins H test (I^2) was 6%, indicating a homogeneous nature of the weights of the studies evaluated in the meta-analysis.

Table 2. Effectiveness of probiotics, as evaluated by meta-analyses.

	Probiotics		Control Group			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Alberda 2018	11	16	10	16	3.7%	1.10 [0.67, 1.82]
Altun 2019	10	18	5	18	1.3%	2.00 [0.85, 4.69]
Bjarnason 2019	4	77	4	70	0.5%	0.91 [0.24, 3.50]
Fan 2019	7	21	9	19	1.6%	0.70 [0.33, 1.52]
Hafer 2007	6	15	6	16	1.2%	1.07 [0.44, 2.59]
Kato 2004	7	10	3	10	0.9%	2.33 [0.83, 6.54]
Kruis 1997	18	50	29	53	4.7%	0.66 [0.42, 1.03]
Kruis 2004	40	110	38	112	7.0%	1.07 [0.75, 1.53]
Kuisma 2003	9	10	9	10	10.0%	1.00 [0.75, 1.34]
Lahner 2012	27	30	20	22	21.8%	0.99 [0.83, 1.18]
Lorea Baroja 2007	4	20	4	20	0.6%	1.00 [0.29, 3.45]
Marteau 2006	30	47	21	49	6.0%	1.49 [1.01, 2.20]
Matsuoka 2018	22	97	19	95	3.2%	1.13 [0.66, 1.96]
Mimura 2004	7	20	11	16	2.1%	0.51 [0.26, 1.01]
Palumbo 2016	3	30	5	30	0.5%	0.60 [0.16, 2.29]
Shadnoush 2015	30	176	18	84	3.4%	0.80 [0.47, 1.34]
Steed 2010	5	13	6	11	1.3%	0.71 [0.29, 1.69]
Tomasz 2014	3	19	8	21	0.7%	0.41 [0.13, 1.34]
Tongtawew 2015	62	98	60	96	16.3%	1.01 [0.82, 1.26]
Tursi 2010	36	65	38	66	9.5%	0.96 [0.71, 1.30]
Yoshimatsu 2015	11	23	9	23	2.2%	1.22 [0.63, 2.38]
Yılmaz 2019	5	10	6	10	1.5%	0.83 [0.37, 1.85]
Total (95% CI)		**975**		**867**	**100.0%**	**0.99 [0.90, 1.09]**
Total events	357		338			
Heterogeneity: Tau² = 0.00; Chi² = 22.43, df = 21 (P = 0.37); I² = 6%						
Test for overall effect: Z = 0.18 (P = 0.85)						

In Figure 3, the Forest Plot, risk ratio and 95% CI included the line of no effect, and the *p*-value for overall effect was 0.85. Because of negligible heterogeneity among the studies, we can rely on the aggregated estimate more as the majority or all individual studies reached the same conclusion.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

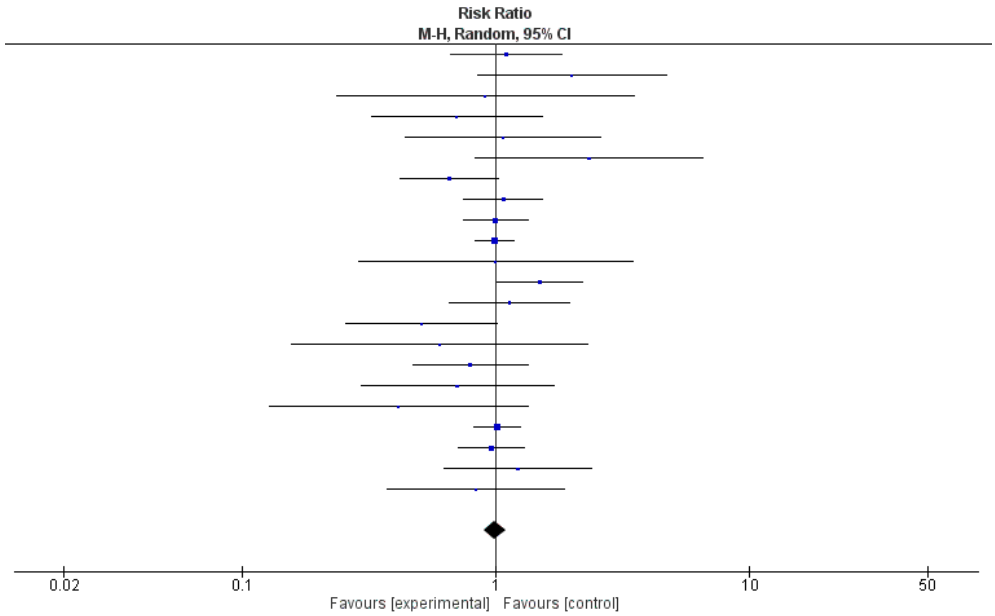

Figure 3. The Forest plot for the pooled analysis of 22 included studies.

3.6. Overall Risk of Bias by Categories of Bias

As shown in Figure 4 and Figure 5, the domains evaluated in this review were as follows: (a) Random Sequence Generation: It is a form of selection bias (biased allocation to interventions) resulting from insufficient generation of a randomized sequence; (b) Allocation Concealment: It is also a selection bias (biased allocation to interventions) owing to insufficient allocation concealment prior to assignment; c) Blinding of Participants and Personnel: This is a performance bias due to participants' and personnel's knowledge of the assigned interventions during the study; d) Blinding of Outcome Assessment: This is a detection bias due to outcome assessors' knowledge of the allocated interventions; e) Incomplete Outcome Data: This is an attrition bias due to the quantity, character, or treatment of incomplete outcome data; f) Selective Reporting: This is a bias in reporting owing to the selective reporting of outcomes; g) Other Bias: This category encompasses biases caused by issues not covered elsewhere in the table. In Figure 4 and Figure 5, the rating scales of bias were high (red), low (green), and unclear (yellow).

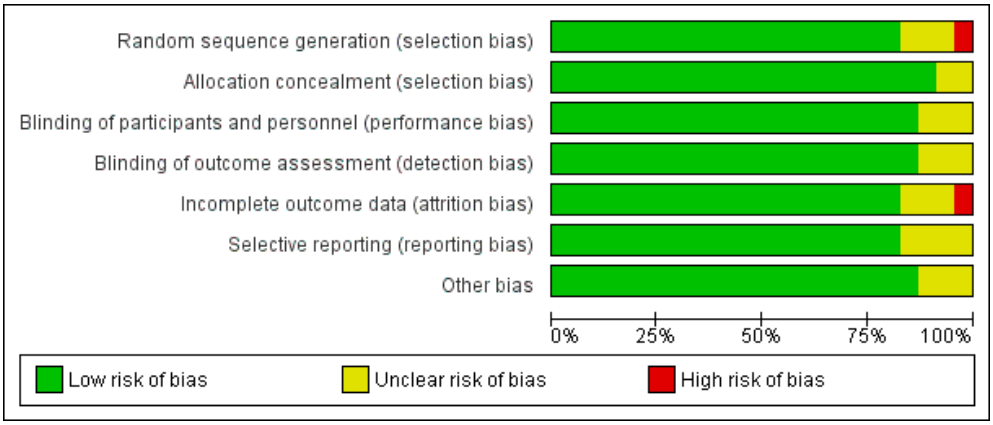

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2023 doi:10.20944/preprints202309.0328.v1

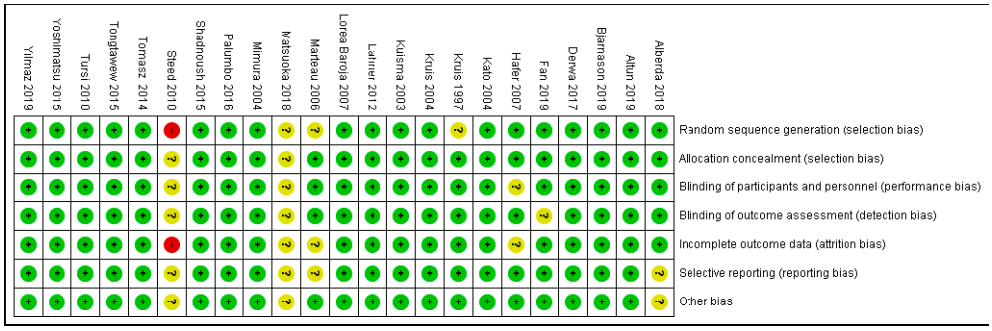

Figure 5. Risk of bias summary.

Based on Figure 5, only one study [36] (Steed et al. 2010) was judged having 'high risk' of bias for two domains: (1) Random Sequence Generation (selection bias). Reviewer's comments: There was no description of the randomization process, and the domain selection reporting (reporting bias); (2) Incomplete Outcome Data (attrition bias). Reviewer's comments: handling of incomplete outcome data was not described in detail.

3.7. Assessment of Publication Bias

Figure 6 shows that the larger studies cluster around the top of the plot, whilst smaller studies are spread across the bottom of the plot. This is an ideal funnel plot where the included studies have scattered either side of the overall effect line in a symmetrical manner. There is no severe asymmetry to either side, so we conclude that publication bias was not present.

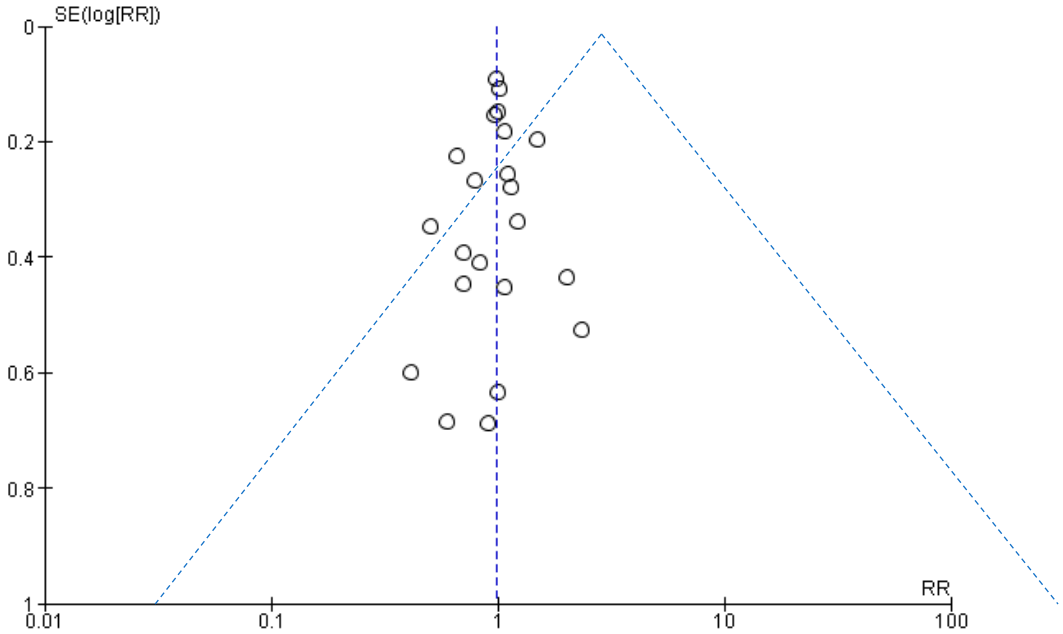

Figure 6. A funnel plot to assess publication bias.

4. Discussion

4.1. Effective Treatment with Probiotics

Out of 35 studies that were investigated for the systematic review, our meta-analysis included 22 (63%) studies. The overall results of systematic review and meta-analysis demonstrated a mixed effect of probiotics therapy in gastroenteritis in adults. However, studies found that either short-term or long-term administration of probiotics were safe.

 doi:10.20944/preprints202309.0328.v1

Our analysis suggests that based on the systematic review per se, probiotics were an effective therapeutic alternative or an adjuvant therapy for gastroenteritis in 27 out of 35 (77%) of studies, whereas meta-analysis of the aggregated data did not provide enough evidence to support statistically significant protective effects of probiotics in the study subjects with gastroenteritis. The systematic analysis also showed that probiotics were not effective in 7 (20%) patients with gastroenteritis.

Disease conditions that improved on probiotic treatment mostly included IBDs due to ulcerative colitis and Crohn's disease. Other disease entities were chronic gastritis, pauchitis, *H. pylori* infections, and drug-induced enteropathies. There were no particular disease entities that were found ineffective in the treatment with probiotics. In this review, a combined therapy of probiotics with either nonsteroidal anti-inflammatory drugs, proton pump inhibitors, or antibiotics showed effective results in the treatment of IBDs, chronic gastritis and infection due to *H. pylori*. Probiotics were also effective in the disease prevention or prevention of relapses in 8 studies [11,21,25–27,37,42,44]. Findings of this review also suggested that probiotics were useful in improving patients' quality of life in two studies (29, 41) in addition to reducing morbidity due to chronic gastroenteritis.

Our systematic review data are consistent with earlier reports which confirmed the effectiveness of probiotics in gastroenteritis. However, the effectiveness of probiotics is dependent on dose, strains used in probiotics, duration of therapy, and the type of illnesses [7,47]. One may compare the effects of probiotics in adults with the ones described in studies in children, primarily to evaluate the effectiveness of probiotics on gastroenteritis due to different etiologies [48].

4.2. Ineffectiveness of Probiotics

It is noteworthy that approximately 20% (n = 7) of the studies reported that probiotics were not effective in treating gastroenteritis, which creates an interesting discrepancy. The reasons for an ineffective outcome of these studies are mostly speculative at this point. The study of acute watery diarrhea due to *V. cholerae* and *E. coli* infections in Bangladesh [30] were more severe in nature compared to gastroenteritis due to other causes, and these patients with acute watery diarrhea needed intravenous rehydration. In such severe form of diarrheal diseases, the effectiveness of probiotics remains a question. However, in addition to the results of using a lyophilized form of *Streptococcus feacium* SF68, further studies may be evaluated by using other forms of probiotics or using a combination of probiotics and antibiotics in acute diarrhea. In the other cases of failure, all happened to be in patients with IBDs. Matsuoka et al (2018) [27] emphasized that the reason of lack of effectiveness may be due to inadequate dose of probiotics administered, the route of administration, or the inability to confirm improvement by using endoscopic and/or imaging procedures. Another report having no improvement after a synbiotic therapy in patients with mild-to-moderate degree of IBDs could be attributable to a small sample size and absence of more specific and objective biomarkers of inflammation such as fecal calprotectin and histologic scores to diagnose the disease [12].

4.3. Safety Issues

Our review did not find any safety concerns of probiotics in any of the studies. However, several studies described and warned about major safety issues in using probiotics, including but not limited to, systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gene transfer and gastrointestinal side effects [49,50]. Other studies cautioned that the administration of probiotics among vulnerable populations, especially immunocompromised individuals should be carefully considered [8,50]. However, a solution to this conundrum may lay in the idea of making the report of adverse events involving probiotics in a mandatory and standardized way, thereby improving safety of products and reliability of data [51].

4.4. Limitations of the Study

One limitation of this systematic review and meta-analysis is that it focused on limited sources of studies available for synthesis using PubMed, MEDLINE, Google Scholar, and Scopas. Our study cannot be generalized because only studies published in English language and those having free full texts were reviewed. However, the nature of a comprehensive systematic review, using 30 years of timeframe of the published reports, and inclusion of study findings of radomized controlled clinical trials only may limit possibilities of bias. In addition, risks of bias assessment were low in all studies except one in our meta-analysis. A very low value (6%) of Higgins test (I^2) of heterogeneity also indicates a homogeneous nature of the studies evaluated.

5. Conclusions

Our meta-analysis provided new information in contrast to the data obtained from the systematic review on the effectiveness of probiotics in gastroenteritis in adults. Even the data gathered from the systematic review had a mixed effect of probiotics – although probiotics were effective in the treatment and reducing relapses of chronic inflammatory gastrointestinal conditions in majority of the adults (78%), the review shows that probiotics are ineffective in about 20% of the patients. More importantly, the pooled data of the meta-analysis demonstrated no statistically significant protective effects of using probiotics. However, there were paucity of data from developing countries. Further studies are needed to confirm whether probiotics can restore the gut microflora and improve gastroenteritis as a single therapy or as an adjunct therapy with other conventional treatments of the infection.

Author Contributions: Conceptualization, A.K.M; Data Extraction, A.K.M., A.F.A. and S.M.; Validation, A.K.M. S.M., M.K.M.; Original Draft Preparation, A.F.A; Review & Editing, A.K.M., A.F.A. S.M. and M.K.M.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bartsch, S.M.; Lopman, B.A.; Ozawa, S.; Hall, A.J.; Lee, B.Y. Global economic burden of norovirus gastroenteritis. *PloS One* **2016**, *11*(4). e0151219. doi: 10.1371/journal.pone.0151219.
2. Nguyen, G.T.; Phan, K.; Teng, I.; Pu, J.; Watanabe, T. A systematic review and meta-analysis of the prevalence of norovirus in cases of gastroenteritis in developing countries. *Medicine* **2017**, *96*(40), e8139. doi: 10.1097/MD.0000000000008139.
3. Graves, N.S. Acute gastroenteritis. *Prim Care Clin Office Pract* **2013**, *40*(3), 727-741.
4. Jagai, J.S.; Smith, G.S.; Schmid, J.E.; Wade, T.J. (2014). Trends in gastroenteritis-associated mortality in the United States, 1985–2005: Variations by ICD-9 and ICD-10 codes. *BMC Gastroenterol* **2014**, *14*(1), 211. doi: 10.1186/s12876-014-0211-0.
5. Hall, A.J.; Patel, M.M.; Lopman, B.A.; Armah, G.E. Part 2: Viral Diseases - Norovirus. In *Hunter's Tropical Medicine and Emerging Infectious Disease*, 9th ed.; Magill, A.J.; Ryan, E.T.; Hill, D.R.; Solomon, T. Eds.; Saunders Elsevier Inc., China, **2013**; pp. 280-282.
6. Williams, N.T. Probiotics. *Am J Health Syst Pharm* **2010**, *67*(6), 449-458.
7. Tomasik, P.; Tomasik, P. Probiotics, non-dairy prebiotics and postbiotics in nutrition. *Appl Sci* **2020**, *10*(4), 1470; https://doi.org/10.3390/app10041470.
8. Wilkins, T.; Sequoia, J. Probiotics for gastrointestinal conditions: A summary of the evidence. *Am Fam Physician* **2017**, *96*(3), 170-178.
9. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.; et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* **2009**, 339:b2700. doi: 10.1136/bmj.b2700.
10. Joanna Briggs Institute .JBI Critical Appraisal Tools. Available at: https://jbi.global/critical-appraisal-tools, accessed 3 May, 2023.
11. Alberda, C.; Marcushamer, S.; Hewer, T.; Journault, N.; Kutsogiannis, D. Feasibility of a *Lactobacillus casei* drink in the intensive care unit for prevention of antibiotic associated diarrhea and *Clostridium difficile*. *Nutrients* **2018**, *10*(5), E539. doi: 10.3390/nu10050539.
12. Altun, H.K.; Yildiz, E.A.; Akin, M. (2019). Effects of synbiotic therapy in mild-to-moderately active ulcerative colitis: A randomized placebo-controlled study. *Turk J Gastroenterol* **2019**, *30*(4), 313-320.

13. Bjarnason, I.; Sission, G.; Hayee, B. A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease. *Inflammopharmacol* **2019**, *27*(3), 465-473. doi: 10.1007/s10787-019-00595-4
14. Derwa, Y.; Gracie, D.J.; Hamlin, P J.; Ford, A.C. Systematic review with meta-analysis: The efficacy of probiotics in inflammatory bowel disease. *Aliment Pharmacol Ther* **2017**, *46*(4), 389-400. DOI: 10.1111/apt.14203
15. Fan, H.; Du, J.; Liu, X.; Zheng, W.W.; Zhuang, Z.H.; Wang, C.D.; et al. Effects of pentasa-combined probiotics on the microflora structure and prognosis of patients with inflammatory bowel disease. *Turk J Gastroenterol* 2019, *30*(8), 680-685.
16. Groeger, D.; O'Mahony, L.; Murphy, E.F.; Bourke, J.F.; Dinan, T.G.; Kiely, B.; et al. *Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes* **2013** *4*(4), 325-339.
17. Hafer, A.; Krämer, S.; Duncker, S.; Krüger, M.; Manns, M P.; Bischoff, S.C. Effect of oral lactulose on clinical and immunohistochemical parameters in patients with inflammatory bowel disease: A pilot study. *BMC Gastroenterol* **2007**, *7*(1), 36. doi: 10.1186/1471-230X-7-36
18. Kato, K.; Mizuno, S.; Umesaki, Y.; Ishii, Y.; Sugitani, M.; Imaoka, A.; et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther* **2004**, *20*(10), 1133-1141.
19. Krag, A.; Israelsen, H.; von Ryberg, B.; Andersen, K.K.; Bendtsen, F. Safety and efficacy of Profermin® to induce remission in ulcerative colitis. *World J Gastroenterol* **2012** *18*(15), 1773-1780. doi: 10.3748/wjg.v18.i15.1773
20. Kruis, W.; Schütz, E.; Fric, P.; Fixa, B.; Judmaier, G.; Stolte, M. Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* **1997**, *11*(5), 853-858.
21. Kruis, W.; Frič, P.; Pokrotnieks, J.; Lukáš, M.; Fixa, B.; Kaščák, M.; et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut* **2004**, *53*(11), 1617-1623.
22. Kuehbacher, T.; Ott, S.J.; Helwig, U.; Mimura, T.; Rizzello, F.; Kleessen, B.; et al. Bacterial and fungal microbiota in relation to probiotic therapy (VSL# 3) in pouchitis. *Gut* **2006**, *55*(6), 833-841.
23. Kuisma, J.; Mentula, S.; Jarvinen, H.; Kahri, A.; Saxelin, M.; Farkkila, M. Effect of *Lactobacillus rhamnosus* GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther* **2003**, *17*(4), 509-515.
24. Lahner, E.; Esposito, G.; Zullo, A.; Hassan, C.; Cannaviello, C.; Di Paolo, M.C.; et al. (2012). High-fibre diet and *Lactobacillus paracasei* B21060 in symptomatic uncomplicated diverticular disease. *World J Gastroenterol* **2012**, *18*(41), 5918-5924. doi: 10.3748/wjg.v18.i41.5918.
25. Lorea Baroja, M.; Kirjavainen, P.V.; Hekmat, S.; Reid, G. Anti-inflammatory effects of probiotic yogurt in inflammatory bowel disease patients. *Clin Exp Immunol* **2007**, *149*(3), 470-479. doi: 10.1111/j.1365-2249.2007.03434.x
26. Marteau, P.; Lémann, M.; Seksik, P.; Laharie, D.; Colombel, J.F.; Bouhnik, Y. Ineffectiveness of *Lactobacillus johnsonii* LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut* **2006**, *55*(6), 842-847.
27. Matsuoka, K.; Uemura, Y.; Kanai, T.; Kunisaki, R.; Suzuki, Y.; Yokoyama, K.; et al. Efficacy of *Bifidobacterium* breve fermented milk in maintaining remission of ulcerative colitis. *Dig Dis Sci* **2018**, *63*(7), 1910-1919. doi:10.1007/s10620-018-4946-2.
28. Matthes, H.; Krummenerl, T.; Giensch, M.; Wolff, C.; Schulze, J. Clinical trial: probiotic treatment of acute distal ulcerative colitis with rectally administered *Escherichia coli* Nissle 1917 (EcN). *BMC Complement Altern Med* **2010**, *10*(1), 13. doi: 10.1186/1472-6882-10-13.
29. Mimura, T.; Rizzello, F.; Helwig, U.; Poggioli, G.; Schreiber, S.; Talbot, I.C.; et al. Once daily high dose probiotic therapy (VSL# 3) for maintaining remission in recurrent or refractory pouchitis. *Gut* **2004**, *53*(1), 108-114.
30. Mitra, A.K.; Rabbani, G.H. A double-blind controlled trial of Bioflorin (*Streptococcus faecium* SF68) in adults with diarrhoea due to *Vibrio cholerae* and enterotoxigenic *Escherichia coli*. *Gastroenterol* **1990**, *99*, 1149-1152.
31. Montalto, M., Gallo, A., Curigliano, V., D'Onofrio, F., Santoro, L., Covino, M., et al. Clinical trial: The effects of a probiotic mixture on non-steroidal anti-inflammatory drug enteropathy–a randomized, double-blind, cross-over, placebo-controlled study. *Aliment Pharmacol Ther* **2010**, *32*(2), 209-214.
32. Palumbo, V.D.; Romeo, M.; Gammazza, A.M.; Carini, F.; Damiani, P.; Damiano, G.; et al. The long-term effects of probiotics in the therapy of ulcerative colitis: A clinical study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*, **2016**, *160*(3), 372-377.
33. Persborn, M.; Gerritsen, J.; Wallon, C.; Carlsson, A.; Akkermans, L.M.A.; Söderholm, J.D. The effects of probiotics on barrier function and mucosal pouch microbiota during maintenance treatment for severe pouchitis in patients with ulcerative colitis. *Aliment Pharmacol Ther* **2013**, *38*(7), 772-783.

34. Shadnoush, M.; Hosseini, R.S.; Khalilnezhad, A.; Navai, L.; Goudarzi, H.; Vaezjalali, M. Effects of probiotics on gut microbiota in patients with inflammatory bowel disease: A double-blind, placebo-controlled clinical trial. *Korean J Gastroenterol* **2015**, *65*(4), 215-221.
35. Shen, B.; Brzezinski, A.; Fazio, V.W.; Remzi, F.H.; Achkar, J.P.; Bennett, A.E.; et al. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: Experience in clinical practice. *Aliment Pharmacol Ther* **2005**, *22*(8), 721-728.
36. Steed, H.; Macfarlane, G.T.; Blackett, K.L.; Bahrami, B.; Reynolds, N.; Walsh, S.V.; et al. Clinical trial: The microbiological and immunological effects of symbiotic consumption–a randomized double-blind placebo-controlled study in active Crohn's disease. *Aliment Pharmacol Ther* **2010**, *32*(7), 872-883.
37. Tomasz, B.; Zoran, S.; Jarosław, W.; Ryszard, M.; Marcin, G.; Robert, B.; et al. Long-term use of probiotics *Lactobacillus* and *Bifidobacterium* has a prophylactic effect on the occurrence and severity of pouchitis: A randomized prospective study. *Biomed Res Int* **2014**, *2014*, 208064. doi: 10.1155/2014/208064.
38. Tongtawee, T.; Dechsukhum, C.; Leeanansaksiri, W.; Kaewpitoon, S.; Kaewpitoon, N.; Loyd, R.A.; et al. Effect of pretreatment with *Lactobacillus delbrueckii* and *Streptococcus thermophillus* on tailored triple therapy for *Helicobacter pylori* eradication: A prospective randomized controlled clinical trial. *Asian Pac J Cancer Prev* **2015**, *16*(12), 4885-4890.
39. Tursi, A.; Brandimarte, G.; Papa, A.; Giglio, A.; Elisei, W.; Giorgetti, G.M.; et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL# 3 as adjunctive to a standard pharmaceutical treatment: A double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* **2010**, *105*(10), 2218-2227.
40. Venturi, A.; Gionchetti, P.; Rizzello, F.; Johansson, R.; Zucconi, E.; Brigidi, P. et al. Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. *Aliment Pharmacol Ther* **1999**, *13*(8), 1103-1108.
41. Yılmaz, İ.; Dolar, M.E.; Özpınar, H. Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory bowel disease: A randomized controlled trial. *Turk J Gastroenterol* **2019**, *30*(3), 242-253. doi: 10.5152/tjg.2018.18227.
42. Yoshimatsu, Y.; Yamada, A.; Furukawa, R.; Sono, K.; Osamura, A.; Nakamura, K.; et al. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. *World J Gastroenterol* **2015**, *21*(19), 5985-5994. doi: 10.3748/wjg.v21.i19.5985.
43. Ziemniak, W. Efficacy of *Helicobacter pylori* eradication taking into account its resistance to antibiotics. *J Physiol Pharmacol* **2006**, *57*, 123-141.
44. Zocco, M.A.; Dal Verme, L.Z.; Cremonini, F.; Piscaglia, A.C.; Nista, E.C.; Candelli, M. et al. Efficacy of *Lactobacillus* GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* **2006**, *23*(11), 1567-1574.
45. Zwolinska-Wcislo, M.; Brzozowski, T.; Budak, A.; Kwiecien, S.; Sliwowski, Z.; Drozdowicz, D.; et al. Effect of Candida colonization on human ulcerative colitis and the healing of inflammatory changes of the colon in the experimental model of colitis ulcerosa. *J Physiol Pharmacol* **2009**, *60*(1), 107-118.
46. Verna, E.C.; Lucak, S. Use of probiotics in gastrointestinal disorders: What to recommend? *Ther Adv Gastroenterol* **2010**, *3*(5), 307-319.
47. Jones EAK, Mitra AK, Bisht A, Edet PP, Iseguede F, Okoye E. Probiotics in gastroenteritis in children: A systematic review. *IMC J Med Sci*. **2023**; *17*(2):010. DOI: https://doi.org/10.55010/imcjms.17.020
48. Cameron, D.; Hock, Q.S.; Kadim, M.; Ryoo, E.; Sandhu, B.; Yamashiro, Y.; et al. Probiotics for gastrointestinal disorders: Proposed recommendations for children of the Asia-Pacific region. *World J Gastroenterol* **2017**, *23*(45),7952-7964. doi: 10.3748/wjg.v23.i45.7952.
49. Doron, S.; Snydman, D.R. Risk and safety of probiotics. *Clin Infect Dis* **2015**, *60* (Suppl 2): S129–S134. doi: 10.1093/cid/civ085.
50. Ciernikova, S.; Mego, M.; Semanova, M.; Wachsmannova, L.; Adamcikova, Z.; Stevurkova, V.; et al. Probiotic survey in cancer patients treated in the outpatient department in a comprehensive cancer center. *Integr Cancer Ther* **2017**, 16(2):188-195. doi: 10.1177/1534735416643828.
51. van den Nieuwboer, M.; Brummer, R.J.; Guarner, F.; Morelli, L.; Cabana, M.; Claassen, E. The administration of probiotics and synbiotics in immune compromised adults: is it safe? *Beneficial Microbes* **2015**, 6(1): 3-17. DOI 10.3920/BM2014.0079.