Review

Probiotic Formulations & Gastro-Intestinal Diseases: A State-of-Art Review

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Abstract: Probiotics are namely yeast and bacteria which are regarded as dietary supplements and food. Many probiotics are being commonly used now, the most frequently used, lactic acid bacteria are called Lactobacillus and Bifidobacterium. Many of the diseases associated with GIT are related to microbiota found in GIT, an imbalance of which causes gastrointestinal diseases. Probiotics, in light of scientific literature, are thought to play an important role in relieving symptoms of many diseases associated with GIT, i.e. beneficially regulating the microbiota composition. In the present review, we aimed to highlight the main considerations for main probiotic formulations to date. This study reviews the role of different probiotic formulations introduced so far in treating GI diseases in cohort ageing ≤18 years. We searched PubMed and Clinicaltrials.gov without any restrictions. This study comprises the descriptive and comparative analysis between Single-organism and Composite probiotics. These GI diseases include NEC, FAP, AGE, Acute Diarrhea, Ulcerative Colitis and etc. The results have been categorized according to title and outcomes. The positive outcomes emphasize the drug's effectiveness in improving health and the negative outcome elaborates on the adverse effects the drug may have shown. Conclusively, discussed practices will assist in reducing GI disorders and strengthening the gut. Further insight into the various gut microbes and microbiomes with specific demographic is recommended.

Keywords: Probiotics; gut flora; gastrointestinal diseases; Lactobacillus; Bifidobacteria; placebo; Diarrhea; microbiota; composite; single-organisms; Ulcerative Colitis

1. Introduction

Probiotics are namely yeast and bacteria which are regarded as dietary supplements and food. Many probiotics are commonly used now, the most frequently used, lactic acid bacteria are called Lactobacillus and Bifidobacterium(1). Probiotics have direct interaction with immune cells in the gastrointestinal tract (GIT), which makes them an important regulator of immunologic equilibrium(2). The interaction of probiotics with the GIT of its human host is at three various levels in the lower part of the GIT these levels are; the mucus layer, the epithelial layer, and the gut-associated lymphoid tissue(3).

Many of the diseases associated with GIT are related to microbiota found in GIT, an imbalance of which causes gastrointestinal diseases. Probiotics, in light of scientific literature, are thought to play an important role in relieving symptoms of many diseases associated with GIT(4). Probiotics beneficially regulate the microbiota composition, which makes their existence very vital in enteric infections. Probiotics regulate the microbiota composition by producing bacteriocins and creating a more acidic milieu, which is

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harmful to pro-inflammatory bacteria and inhibits the growth of potentially pathogenic bacteria while still promoting the multiplication of beneficial bacteria, namely Lactobacilli and Bifidobacteria (5).

According to data collected from the USA, the prevalence of digestive and GIT disorders has been marked up to 60 to 70 million people in 2010. Amongst these, there have been 21.7 million cases of hospitalization in 2010 and 245,921 deaths in 2009. Probiotics were seen to be beneficial in a variety of clinical conditions, including cancer, female urogenital infection, surgical infections, necrotizing enterocolitis, antibiotic-associated diarrhoea, relapsing Clostridium difficile colitis, Helicobacter pylori infections, and inflammatory bowel disease (6).

Probiotics are useful for acute infectious diarrhoea caused by bacteria, however, research on their efficacy for viral diarrhoea has shown mixed findings which cannot be taken as conclusive evidence for the efficacy of probiotics in infectious diarrhoea. Probiotics are effective for both the prevention and treatment of antibiotic-associated diarrhoea as well as for the prevention of Clostridium difficile-associated diarrhoea in both children and adults, yet the literature suggests that there are conflicting findings regarding the efficacy of probiotics in C. difficile infection(7). Patients with inflammatory bowel disease (IBD) frequently use probiotics, and their doctors routinely suggest them as an additional treatment. Although they are widely used and widely seen as safe, there isn't much data to back up their vast use(8).

There is an established criterion for the selection of probiotics, which includes a few points that need to be considered while selecting a probiotic for use. The first point discusses how to identify the genus, species, and strains that are being employed. The second point indicates that the probiotic being considered for usage must be safe for ingestion, not contagious, not carrying genes for antibiotic resistance, and not affect the intestinal mucosa or secretions of bile acids. The next requirement is that it should be able to survive in the intestinal environment, which means that it must be tolerant of bile and stomach acids while attaching to the gastric mucosa and colonising it to have the intended effect. Table 1 provides a concise pointwise criterion. These targeted outcomes include battling germs and displaying antimicrobial actions, which may have a demonstrable impact on health. Finally, it must maintain its stability during processing and storage(9). In the present review, we aimed to highlight the main considerations for main probiotic formulations to date. This study reviews the role of different probiotic formulations introduced so far in treating GI diseases in cohort ageing ≤18 years.

Table 1: Criteria for use as a probiotic, adapted from Borchers et al. [2009](9)

- The organism being utilized must be recognized, i.e. its genus, species and strain must be known.
- The organism must be deemed viable to consume:
  *Not infectious or harbouring genes for antibiotic resistance
  *Not converting to bile acids or degrading to the intestinal mucosa
- It needs to endure intestinal transit: tolerance of bile and acid
- It has to stick to the mucosa and colonize the gut (at least for a short period)
- It must have known and documented impacts on health:
  *Synthesise antimicrobials and combat harmful germs
  *A minimum of one phase 2 research demonstrating a benefit
- During storage and processing, it must remain stable.

2. Materials and Methods

a. Data Sources AND Search Strategy;

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We searched PubMed and Clinicaltrials.gov **from inception to 24th July 2022**, without any restrictions. In PubMed, two search strategies were combined i.e. S1 & S2 (see below) searches included Medical Subject Headings [MeSH] and limits to title and abstract [Title/Abstract]. S2 was added to exclude studies limited to animals while including studies involving both animal and human participants. Using an iterative process, we subsequently added papers through hand-searching citations contained within retrieved articles and relevant systematic reviews and meta-analyses.

Detailed Search Strategy: (S1: ((infant*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR newborn*[Title/Abstract] OR neonat*[Title/Abstract] OR neo nat*[Title/Abstract] OR child*[Title/Abstract] OR toddler*[Title/Abstract] OR adolescen*[Title/Abstract] OR teen*[Title/Abstract] OR teenager*[Title/Abstract] OR youth[Title/Abstract] OR juvenile*[Title/Abstract] OR "Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh])) AND (Probiotics[Title/Abstract] OR "Probiotics"[Mesh]) AND ("Gastrointestinal Diseases"[Mesh]))
NOT (S2: (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

b. Study Selection and Eligibility Criteria;

The Inclusion criteria for studies were as follows: 1) Freely accessible, full articles 2) randomized control trials, 3) Papers based on analysing the Efficacy of different Probiotics formulations in patients and beneficial outcomes in GI-related diseases, 4) No Animal-based studies were included 5) Published trials in peer-reviewed journals in English. However, all the unpublished trials, study designs i.e. pilot and observational studies, reviews, editorials, commentaries, case reports, case series and, 6) studies reporting incomplete data were excluded.

The studies with the following characteristics, i.e. **a**. Patient population: ≤ 18 years of age undergoing any gastrointestinal diseases. **b**. Intervention: Single-organism and composite Probiotic formulations irrespective of dosage and form were included.

3. Results

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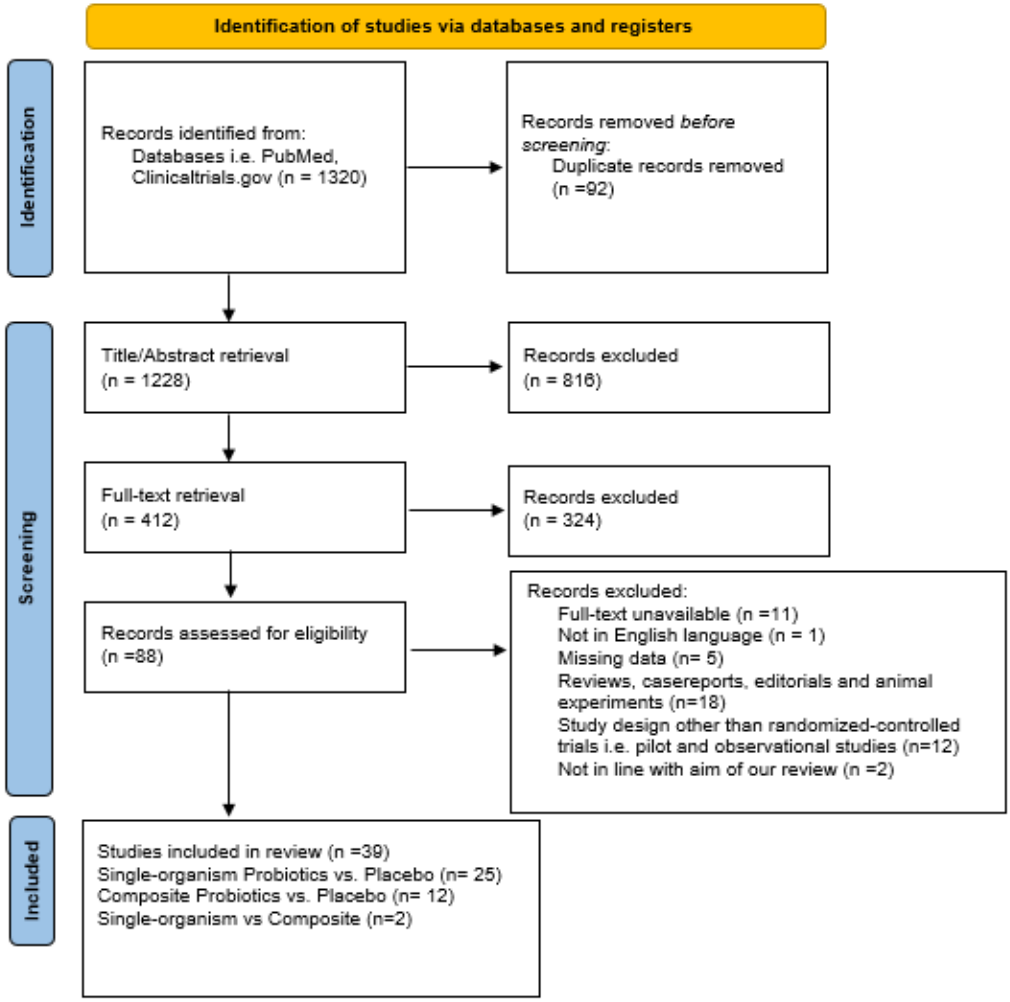

Data Selection;

Initial screening of 1,321 articles:

After removing duplicates, we screened 1228 articles for relevance. Additional articles were added through hand searches of reference lists or identification and agreement by the authors. A total of 39 articles were retained for the full review, summarised in table 3 of the article.

A list of selected examples of probiotic formulations is provided in Table 2. The studies are summarised in Table 3. A list of ongoing trials on analysing probiotic formulations in various gastrointestinal diseases is provided in table 4.

A. SINGLE-ORGANISMS PROBIOTICS VS PLACEBO

Positive outcomes

Of the 25 articles assessed, 22 reported at least one statistically significant positive outcome between single-organism probiotics vs placebo (10–31). The remaining 3 reported no statistically significant positive outcome attributed to single-organism probiotics(32–34). Outcomes are detailed below and summarized in Table 3.

A study reported that single-organism probiotics decreased the incidence of NEC in breastfed infants (10,20). Another study reported that intervention reduced the intensity of abdominal pain(11–13,31). Feeding intolerance and clinical sepsis were found to be significantly lower in the probiotic group according to another study(28,32). Pieścik-Lech M. et al reported that the combined use of LGG plus smectite and LGG alone are effective in treating young children with acute gastroenteritis(22). Single-organism probiotics were found to be beneficial in decreasing the frequency and duration of the disease (21,23–25). Additionally, it also improved mucosal inflammation and changed mucosal expression levels of some

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cytokines involved in the mechanism of inflammatory bowel disease(26). A higher frequency of bowel movements reduced gastric distension and accelerated gastric emptying was also reported with these probiotics (14,30). Hoisak et al. reported a decreased risk of respiratory tract infections and gastrointestinal infections with probiotics in children in daycare centres and pediatric facilities(15,16).

Negative outcomes

Of the 25 articles assessed, 15 reported no statistically significant negative outcomes between single-organism probiotics vs placebo (10–13,15,17,19,21,23–28,30,31). The remaining 10 reported at least one statistically significant negative outcome attributed to single-organism probiotics(14,15,18,20,22,29,32–34). Outcomes are detailed below and summarized in Table 3.

Few studies reported that single-organism probiotics did not decrease the incidence of NEC(20,22,29,32). Additionally, no improvement in stool consistency was seen, but accompanied episodes of inconsolable crying were reported(14). A study showed that intervention was ineffective in treating rectal bleeding in breastfed infants(34). Lactobacillus rhamnosus therapy in children with short bowel syndrome did not improve intestinal permeability and was associated with conversion to positive hydrogen breath test results(18).

B. COMPOSITE PROBIOTICS VS PLACEBO

Positive outcomes

Of the 12 articles assessed, all reported at least one statistically significant positive outcome between composite probiotics vs placebo (35–46). Outcomes are detailed below and summarized in Table 3.

One study reported that composite probiotics decreased clinical symptoms like bloating, vomiting, diarrhoea and abdominal pain (35,45). It also decreased disease severity, consequently improving the quality of life in the patient(35,36). Studies showed a lower incidence of NEC frequency with intervention in the HIV-exposed study group, pre-term infants and low-birth neonates (36–38,42,43,45,46). Taking composite probiotics within 24 hours significantly decreased the duration of diarrhoea compared to those who took it later(39). Xiaolin et al. reported that T lymphocytes, IFN-γ and IL-6 decreased, whereas IL-10 increased in patients treated with probiotics along with a decreased incidence of HAEC (3/30, 10%)(40). Another study reported a decreased risk of common infectious diseases in children with probiotics, leading to a lower risk of school day loss(44).

Negative Outcomes

Of the 12 articles assessed, 11 reported no statistically significant negative outcomes between composite probiotics vs placebo (35,37–46). The remaining 1 reported one statistically significant negative outcome attributed to composite probiotics(36). Outcomes are detailed below and summarized in Table 3.

A study reported that probiotics failed to decrease the incidence of NEC in HIV-exposed premature infants(36).

C. SINGLE-ORGANISM VS COMPOSITE PROBIOTICS

Positive outcomes

Of the 2 articles assessed, both reported statistically significant positive outcomes between single-organism probiotics vs composite probiotics(47,48). Outcomes are detailed below and summarized in Table 3.

One study reported that the median duration of diarrhoea (2-4 days) was shorter than the placebo group (4-5 days), associated with a decreased prescription of additional medications(47). Another study reported that remission was achieved in 13 patients and endoscopic and histological scores were significantly lower in the VSL #3 group ($P<0.05$)(48).

Negative outcomes

Of the 2 articles assessed, both reported no statistically significant negative outcomes between single-organism probiotics vs composite probiotics(47,48).

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Table 2: Selected Examples Of Probiotic Formulations.

Single-Organism Probiotic	Composite Probiotic
Saccharomyces Boulardii	Ecologic®Relief: Bifidobacteria (B.) Bifidum, B. Infantis, B. Longum, Lactobacilli (L.) Casei, L. Plantarum And L. Rhamnosus
	A Mixture Of Bifidobacterium Breve, Lactobacillus Casei And Galactooligosaccharides Probiotic Mixture (Bifidobacteria Infantis,
Lactobacillus Acidophilus	Streptococcus Thermophilus, And Bifidobacteria Bifidus
Bifidobacterium Longum CECT 7347	Infloran: Lactobacillus Acidophilus And Bifidobacterium Infantis
	Mixture Of Lactobacillus Plantarum 299 And Bifidobacterium Infantis Cure
Lactobacillus Fermentum CECT5716	21
Lactobacillus Sporogenes	Mixture Of Lactobacillus Rhamnosus GG And Bifidobacterium Infantis
	Mixture Of Oral Bifidobacterium, Lactobacillus Acidophilus, And
Lactobacillus Rhamnosus GG	Enterococcus Triple Viable Capsules
	Bifidobacterium Infantis, Streptococcus Thermophilus, And
Lactobacillus Reuteri (DSM 17938)	Bifidobacterium Lactis,
Lactobacillus Casei DN-114 001	Mixture Of Lactobacillus Acidophilus And Bifidobacteria Lactis
	VSL#3 is Composed Of Four Strains Of Lactobacillus, Three Strains Of Bifidobacterium, And One Strain Of Streptococcus Salivarius Subsp.
Lactobacillus GG (Dicoflor)	Thermophilus
	Mixture Of Lactobacillus Acidophilus, Lactobacillus Rhamnosus, Bifidobacterium Bifidum, Bifidobacterium Longum, Enterococcus Faecium
	Mixture Of Bifidobacterium Breve And Lactobacillus Casei
	Mixture Of Bifidobacterium Longum (BB536) And Lactobacillus Johnsonii (La1)
	Probiotic Mixture (Bifidobacteria Infantis, Bifidobacteria Bifidum, Bifidobacteria Longum And Lactobacillus Acidophilus
	Mixture Of Bifidobacterium Bifidum And Lactobacillus Acidophilus
	Mixture Of L. Acidophilus And B. Infantis

Figure 1. This is a figure. Schemes follow the same formatting.

4. Discussion

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Study	Study & Patient Characteristics			Intervention (Probiotic Formulation)	Positive Outcome	Negative Outcome
	Study location	*Sample size (n= number of individuals)*	*Study Population (Gastrointestinal disease)*			
Benor S. et al, 2014(10)	Israel	58	Necrotizing Enterocolitis (NEC)	L Reuteri DSM 17938 (1 108 Colony-Forming Units/D)	Intervention might decrease the incidence of NEC in breastfed infants.	N/A
Romano C. et al, 2014(11)	Sicily	60	Functional Abdominal Pain (FAP)	Lactobacillus Reuteri	The intervention reduced perceived abdominal pain intensity	N/A
Serce O. et al, 2013(32)	Turkey	208	Necrotizing Enterocolitis (NEC)	Saccharomyces Boulardii	N/A	The intervention did not decrease the incidence of NEC or sepsis.
Demirel G. et al, 2013(22)	Turkey	271	Necrotizing Enterocolitis (Bell's Stage ≥2)	S. Boulardii	Feeding intolerance and clinical sepsis were found to be significantly lower in the probiotic group.	The intervention was not effective at reducing the incidence of death or NEC in VLBW infants.
Pieścik-Lech M. et al, 2013(25)	Poland	88	Acute Gastroenteritis (AGE).	Lactobacillus GG (LGG) And Smectite Versus LGG Alone	LGG plus smectite and LGG alone are equally effective for treating young children with AGE. The combined use of the two interventions is not justified.	N/A
Francavilla R. et al, 2012(26)	Italy	74	Acute Diarrhea	Lactobacillus Reuteri DSM 17938 Derived From L. Reuteri ATCC 55730	The intervention was found beneficial in reducing the frequency, duration and recrudescence rate of the disease.	N/A
Oliva S. et al, 2012(27)	Italy	40	Mild To Moderate Ulcerative Colitis	L. Reuteri	The intervention was effective in improving mucosal inflammation and changing mucosal expression levels of some cytokines involved in the mechanisms of inflammatory bowel disease.	N/A

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Maldonado J. et al, 2012(28)	Spain	215	Incidence Of Infections	Lactobacillus Fermentum CECT5716 (L. Fermentum)	The intervention was found useful for the prevention of community-acquired gastrointestinal and upper respiratory infections.	N/A
Sari FN. et al, 2011(29)	Turkey	221	Necrotizing Enterocolitis (NEC)	Lactobacillus Sporogenes	Feeding intolerance was significantly lower in the probiotics group than in the control group	The intervention showed no significant difference in the incidence of death or NEC between the groups.
Dinleyici EC. et al, 2011(30)	Turkey	68	Blastocystis Hominis Infection	Saccharomyces Boulardii	Metronidazole or S. boulardii has potential beneficial effects on B. hominis infection	N/A
Indrio F. et al, 2011(31)	Italy	42	Regurgitation	Lactobacillus Reuteri	Intervention reduces gastric distension and accelerates gastric emptying. In addition, this probiotic strain seems to diminish the frequency of regurgitation.	N/A
Francavilla R. et al, 2010(12)	Italy	141	Irritable Bowel Syndrome (IBS) Or Functional Abdominal Pain	Lactobacillus Rhamnosus GG (LGG)	The intervention seemed to significantly reduce the frequency and severity of abdominal pain in children with IBS; this effect is sustained and may be secondary to the improvement of the gut barrier.	N/A
Martens U. et al, 2010(13)	Iran	52	Irritable Bowel Syndrome (IBS)	Lactobacillus GG (LGG)	The key IBS symptoms (abdominal pain, stool frequency), as well as the other symptoms (bloating, mucous and blood in stool, need for straining at stools, urge to defecate), improved significantly during treatment. Global assessment of therapy by	No adverse effects were shown.

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					parents and doctors was altogether positive.	
Coccorullo P. et al, 2010(14)	Naples	44	Functional Chronic Constipation	Lactobacillus Reuteri (DSM 17938)	The intervention caused a higher frequency of bowel movements.	The intervention showed no improvement in stool consistency and episodes of inconsolable crying episodes.
Hojsak I. et al, 2010(15)	Croatia	742	Nosocomial Gastrointestinal And Respiratory Tract Infections	Lactobacillus Rhamnosus Strain GG	The intervention caused the risk for gastrointestinal infections, respiratory tract infections vomiting episodes) and diarrheal episodes, episodes of gastrointestinal infections, episodes of respiratory tract infections that lasted 3 days to significantly decrease.	The intervention showed a lower risk for episodes of respiratory tract infection
Hojsak I. et al, 2010(16)	Daycare centres are located in 4 separate locations in the Zagreb area	281	Gastrointestinal And Respiratory Tract Infections	Lactobacillus GG (LGG)	Interventiontion reduced the number of days with respiratory symptoms, respiratory tract infections lasting longer than 3 days, and risk of gastrointestinal infections, vomiting episodes, and diarrheal episodes. However, intervention caused no reduction in the number of days with gastrointestinal symptoms.	The intervention caused no risk reduction concerning lower respiratory tract infections No side effects or adverse effects were noted during the study.
Baldassarre ME. et al, 2010(17)	Bari hospital	30	Hematochezia And Fecal Calprotectin	Lactobacillus Rhamnosus GG (LGG)	EHCF + LGG resulted in significant improvement of hematochezia and faecal calprotectin compared with the EHCF alone	N/A
Sentongo TA. et al, 2008(33)	Chicago, IL	21	Short Bowel	Lactobacillus Rhamnosus (Also Known As LGG)	N/A	Findings do not support empiric LGG therapy to

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			Syndrome (SBS)			enhance IP in children with SBS.
Szajewska H. et al, 2007(34)	Poland	29	Rectal Bleeding	Lactobacillus GG	N/A	The intervention was ineffective in treating rectal bleeding in breastfed infants. No adverse effects were reported.
Bauserman M. et al, 2005(18)	Children's medical centre pediatric gastroenterology	50	Irritable Bowel Syndrome (IBS)	Lactobacillus GG	The intervention showed improvement in abdominal distention.	Lactobacillus GG was not superior to placebo in the treatment of abdominal pain in children with IBS.
Sýkora J. et al, 2005(19)	Czech republic	86	Helicobacter Pylori	Lactobacillus Casei (L. Casei) DN-114 001	Eradication success was higher due to intervention	Side effects were infrequent.
Dani C. et al, 2002(20)	Italy	585	Urinary Tract Infection, Bacterial Sepsis And Necrotizing Enterocolitis	Lactobacillus Gg (Dicoflor),	It was found that infants who received Lactobacillus GG were less affected by NEC after 1 week of treatment.	The intervention was not effective in reducing the incidence of UTIs, NEC and sepsis in preterm infants.
Saran S. et al, 2002(21)	India	100	Diarrhoea	Lactobacillus Acidophillus	There were significantly fewer cases of diarrhoea and fever due to the intervention.	N/A
Rosenfeldt V. et al, 2002(23)	Denmark	43	Acute Diarrhea	L. Reuteri Dsm 17938	The intervention was effective in reducing the duration of diarrhoea	N/A
Guandalini S. et al, 2000(24)	11 centres in 10 countries	287	Acute Diarrhea	Lactobacillus GG	The intervention was deemed safe and results were obtained in a shorter duration of diarrhoea. There was less chance of a	No adverse effects (rash, drug-related fever or nausea, etc.) related to the

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					protracted course, and patients were discharged earlier from the hospital.	synbiotic use were noted
Study	**Study & Patient Characteristics**			**Intervention (Probiotic Formulation)**	**Positive Outcome**	**Negative Outcome**
	Study location	***Sample size (n= number of individuals)***	***Study Population (Gastrointestinal Disease)***			
Muhammed Majeed. et al. 2016(35)	Three clinical sites i) Mysore Medical College and K R Hospital, Mysore, India ii) Sapthagiri Institute of Medical Sciences and Research Center, Bangalore, India and iii) Kempegowda Institute of Medical Sciences, Bangalore, India	36	Diarrhea Predominant Irritable Bowel Syndrome	Bifidobacterium Breve, Lactobacillus Casei And Galactooligosaccharides	The intervention caused a significant change/decrease in clinical symptoms like bloating, vomiting, diarrhoea, and abdominal pain. Stool frequency disease severity also decreased and the quality of life increased in the patient due to the intervention.	No serious adverse effects were shown.
Evette Van Niekerk. et al. 2015(36)	Neonatal high care unit of	184	Necrotizing	Probiotic Mixture (Bifidobacteria Infantis, Streptococcus	reduced the incidence of NEC reduction in the severity of	The intervention failed to show that probiotics

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	Tygerberg Children's Hospital (TBCH), Cape Town, South Africa		Enterocolitis (NEC)	Thermophilus, And Bifidobacteria Bifidus; Solgar, Israel)	disease was found in the HIV-exposed study group	lowered the incidence of NEC in HIV-exposed premature infants.
Ali İşlek. et al, 2014(39)	Pediatric Emergency and Pediatric Gastroenterology Departments of the Akdeniz University Hospital	156	Acute Infectious Diarrhea	Infloran (Lactobacillus Acidophilus And Bifidobacterium Infantis)	The duration of diarrhoea was significantly shorter in the synbiotic group than in the placebo The duration of diarrhoea was shorter for patients who started the synbiotic therapy within the first 24 h than for those who started their treatment later	No adverse effects were shown.
Xiaolin Wang. et al, 2014(40)	Three medical centres—the Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; The First Hospital of Harbin Medical University;	60	Hirschsprung's Disease-Associated Enterocolitis	Lactobacillus Plantarum 299 And Bifidobacterium Infantis Cure 21	incidence of HAEC (three out of 30, 10.0 %) in the probiotic-treated group was significantly reduced the severity of HAEC in the probiotic-treated group was significantly reduced Probiotics-balanced T lymphocyte, IFN-γ, and IL-6 were significantly decreased inflammatory cytokine IL-10 was remarkably increased	N/A

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	and Anhui Provincial Hospital					
Marta Olivares. et al, 2014(41)	Hospital Universitari Sant Joan (Reus, Tarragona) and Hospital Universitario Sant Joan de Deu (Barcelona)	36	Colic Disease	37.3% Xylitol, 37.3% Sorbitol, 7.5% Microfibrous Cellulose, 3.0% Magnesium Stearate, And 1.9% Citrus Flavour (N=50.4%	The intervention caused a significant increase in the height percentile. There was no significant difference in the incidence of gastrointestinal symptoms (diarrhoea, constipation, abdominal pain and vomiting	No adverse events were reported during the intervention
Fernández-Carrocera LA. et al, 2013(42)	Mexico	150	Necrotizing Enterocolitis (NEC)	Bifidobacterium Infantis, Streptococcus Thermophilus, And Bifidobacterium Lactis Containing 1 × 10(9) Total Organisms)	The intervention caused a reduction of NEC frequency, significantly lowered risk for the combined risk of NEC or death	No adverse effects were shown during hospitalisation.
Braga TD. et al, 2011(43)	Northeast brazil	231	Necrotizing Enterocolitis (NEC)	VSL#3	The intervention reduced the occurrence of NEC (Bell's stage ≥ 2). It was considered that an improvement in intestinal motility might have contributed to this result.	N/A
Cazzola M. et al, 2010(44)	France	135	Prevention Of Common Winter Diseases In Children	Lactobacillus Acidophilus, Lactobacillus Rhamnosus, Bifidobacterium Bifidum, Bifidobacterium Longum, Enterococcus Faecium,	Intervention decreased the risk of occurrence of common infectious diseases in children and limited the risk of school day loss.	N/A
Guandalini S. et al, 2010(45)	Italy (4) and in India (1) Chicago, IL (1)	59	Irritable Bowel Syndrome (IBS)	Bifidobacterium Breve And Lactobacillus Casei	The intervention caused improvement in IBS symptoms.	No adverse event was recorded
Lin HC. et al, 2008(46)	Taiwan	217	Necrotizing	A Mixture Of Bifidobacterium Longum (BB536) And Lactobacillus johnsonii (La1)	The incidence of death or necrotizing enterocolitis	No adverse effect, such as sepsis, flatulence, or

			Enterocolitis (NEC)		(stage 2) was significantly lower	diarrhoea, was noted
Bin-Nun A. et al, 2005(37)	Shaare zedek medical center	145	Necrotizing Enterocolitis (NEC)	Probiotic Mixture (Bifidobacteria Infantis, Bifidobacteria Bifidum, Bifidobacteria Longum And Lactobacillus Acidophilus	reduced both the incidence and severity of NEC	No adverse effects were shown.
Kliegman RM. et al, 2005(38)	Houston, texas	155	Necrotizing Enterocolitis (NEC)	Bifidobacterium Bifidum And Lactobacillus Acidophilus	The incidence of death or NEC (stage 2) was significantly lower	N/A
Study	**Study & Patient Characteristics**			**Intervention (Probiotic Formulation)**	**Positive Outcome**	**Negative Outcome**
	Study location	***Sample size (n= number of individuals)***	***Study Population (Gastrointestinal Disease)***			
Vandenplas Y. et al, 2011(47)	Belgium	111	Acute Diarrhoea	Lactobacillus Acidophilus And Bifidobacteria Lactis	The median duration of diarrhoea was significantly 1 day shorter in the synbiotic than in the placebo group, associated with decreased prescription of additional medications.	N/A
Miele E. et al, 2009(48)	Italy	29	Ulcerative Colitis (UC)	Vsl#3	Endoscopic and histological scores were significantly lower in the VSL#3 group Remission was achieved in 13 patients.	No adverse effects were shown.

Table 4: List of ongoing trials analysing Single-organism and Composite Probiotic formulations against gastrointestinal diseases.

Trial ID	*Age*	*Intervention*
NCT04160767(49)	up to 14 Years	Drug: Probiotic Vivomixx Behavioural: Gluten-free diet Other: Placebo Other: Gluten-free diet
NCT03562221(50)	4 Months to 4 Months	Dietary Supplement: Probiotics Dietary Supplement: Placebo
NCT04103216(51)	12 Months to 36 Months	Nitazoxanide with Lactobacillus Reuteri DSM 17938 Nitazoxanide

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b. Composite Probiotics vs. Placebo

Trial ID	*Age*	*Intervention*
NCT04922476(52)	8 Years to 18 Years	Dietary Supplement: Alflorex®
NCT04021303(53)	4 to 12 months old	Dietary Supplement: Experimental cereal Dietary Supplement: Conventional cereal
NCT04541771(54)	28 Weeks to 34 Weeks	Drug: Lactobacillus Reuteri DSM 17938 Drug: Placebo
NCT04014660(55)	10 Years to 18 Years	Probiotic L.plantarum Heal 9 and L.paracasei 8700:2

This study comprises the descriptive and comparative analysis between Single-organism and Composite probiotics. Studies have shown the use of probiotics in their effectiveness for combating various GI disorders among children under 18 years of age, which have been compiled in the results section. These GI diseases include NEC, FAP, AGE, Acute Diarrhea, Ulcerative Colitis, Incidence of Infection, Blastocystitis Hominis Infection, Regurgitation, IBS, Functional Chronic Constipation, Nosocomial Gastrointestinal and Respiratory Diseases, Hematochezia, Fecal Calprotectin, SBS, Rectal bleeding, Helicobacter Pylori, Urinary tract infection, bacterial sepsis, Hirschsprung Disease, and Coeliac Disease. The results yielded a total of n= 39 studies which have been categorized according to title and outcomes. The positive outcomes emphasize the drug's effectiveness in improving health and the negative outcome elaborates on the adverse effects the drug may have shown. The probiotics are compared individually with a placebo. It can be seen in the studies that are titled "Single- organism vs Placebo", n=25 have been extracted. Out of these n=12 studies had statistically significant positive outcomes without any negative outcomes, n=3 studies had statistically significant negative outcomes without any positive outcomes and lastly, n=10 studies had statistically significant positive and negative outcomes combined. The GI diseases in the studies titled "Composite probiotic vs Placebo", n=12 have been extracted where n=11 showed only positive outcomes without any negative outcomes and n=1 showed statistically significant positive and negative outcomes.

A third category titled "Single-organism VS Composite" yielded n=2 studies, both of which showed that the interventions had statistically significant positive outcomes with no known negative outcomes for GI diseases. This category emphasizes the comparative performances of both probiotic drugs. The study conducted by Vandenplas Y. et al in 2011 claims using Lactobacillus Acidophilus and Bifidobacteria Lactis for the complaint of Acute Diarrhea among n=111 patients in Belgium (47). It was reported there are specific strains of probiotics whose performance affect the overall efficacy of the drug, as seen significantly in single and composite form. While the composition of L. Acidophilus and B. Lactis has shown tremendous results, L. acidophilus has been reported to have individually reduced diarrheal problems and improved GI mucosa more significantly (56). In terms of the duration of improvement in symptoms, composite probiotics have been seen to take the lead with the normalization of stool consistency as reported by Vandenplas (47). A second study by Miele. E et.al in 2009 has shown the efficacy of VSL#3 for UC among n=29 patients in Italy. While there were no adverse effects, 3 out of 14 patients (21.4%) on VSL#3 and IBS therapy had relapsed after 6 months and 1 year of follow-up (48). However, the complete eradication of UC symptoms was seen in 13 out of 14

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(92.8%) patients initially, which makes the use of VSL#3 statistically efficient (48). Both studies are familiar with the common conclusion of composite probiotics being more efficient with faster improvement and lesser adverse effects. However, to highlight differences, the latter study by Miele. E et.al does not provide more information on single-organism effects elaborately and does not have a significant sample size to formulate a conclusion.

According to our knowledge, this study evaluates the efficacy of probiotic drugs in a comparative fashion which has not been done before in prior pieces of literature. This study collectively provides the efficacy of probiotics on multiple GI diseases among children below 18 years of age. To further strengthen the comparison, all positive and negative outcomes have been highlighted for each probiotic. This provides data to compare and analyze how the specific strain in each probiotic is performed individually or in a group. While this study aims to be well-designed and strain-specific to cater for the response to GI disorders, further insight on this topic through research is required (57).

The limitations of this study would be to perhaps have a larger demographic or a specific one that involves more probiotics in a detailed fashion. As there have been multiple studies that highlight various unique gut microbiomes of residents in many areas of the globe who consume diets of different natures(56). It is also important to note that the reaction to any probiotic used for GI disorders is strongly individual based yet certain metabolites, genetics and environment may play a role(58). Further, there can be potential for biased results due to insufficient sample size and lack of randomization for it. Nevertheless, GI disorders among children have been one of the most common causes of pediatric mortality and probiotics prove to be a safe and effective intervention.

GI disorders among children and teenagers have been an alerting issue globally due to their life-threatening complications, delayed treatment, and lack of prevention. Fortunately, The National Institute of Health (NIH) has progressed with multiple ongoing clinical trials that aim to cater to various GI disorders. Table 4 comprises various interventions aimed at specific aged groups consisting of single-organism and composite probiotics alongside necessary dietary supplements and behavioural precautions needed. It is recommended that guardians of these age groups must be educated on the management of symptoms of GI disorders. Oral rehydration for diarrhoea, laxatives for constipation and anti-emetics for vomiting are baseline treatments, this information can be provided to guardians through their doctor visits, health-care helpline and even educational health campaigns. The guardians must also ensure to keenly observe their children's dietary and hygiene habits as that immensely affects gut health, routine checkup on bowel habits is recommended.

5. Conclusions

Conclusively, discussed practices will assist in reducing GI disorders and strengthening the gut. Further insight into the various gut microbes and microbiomes with specific demographic is recommended.

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