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Probiotics in infant healthcare: Promising benefits and underlying concerns

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ABSTRACT: Probiotics, viable microorganisms with demonstrated health benefits, are generally recognized as a safe and effective option to facilitate host wellbeing. At present, probiotics are attracting considerable interest and gaining acceptance in both the food industry and clinical practice for improving health outcomes, with current applications primarily target adult populations. However, systematic analyses integrating the varied therapeutic effects of probiotics as well as the underlying challenges and safety concerns in infant subjects remain scarce. This review highlights the existing evidence regarding the potential application of probiotics as an innovative approach for various infantile conditions. Moreover, we comprehensively summarize the safety issues and limitations associated with the usage of probiotic strategy and identify several corresponding solutions to promote their better use. Our study provides updated evidence for probiotic supplement in infant population, highlighting key considerations for developing safer and more effective probiotic products in the future.

Keywords: Infant; Gut microbiota; Probiotic; Therapy; Safety; Risk.

1. Introduction

Infancy, a vital biological window, constitutes the foundational milestone for a child's physical progression, maturation, and lifelong well-being^[1]. Therefore, investment in infants is argued to be a paramount strategy for fostering long-term health and reducing the risk of future illnesses. Currently, healthcare providers have widely adopted nutritional and medical interventions to optimize infant health, including probiotics, prebiotics, fortified cereals, fish oil, and infant formula^[2]. However, considering the rapidly evolving and physiologically immature state during infancy, a balanced awareness of both the advantages and possible adverse effects is essential for optimizing infant healthcare.

The gut microbiota constitutes a diverse and evolving ecosystem within the human gastrointestinal tract and exerts a central influence on host health maintenance^[3]. This complex microbial community, *via* specific

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host-microbe interactions, programs infant metabolism, immune defense, endocrine function and even neurological health^[4]. Unlike the resilient and stable gut microbiota in adults, the developing infant microbiota undergoes dynamic colonization and remains highly vulnerable to disruption^[5]. Early-life dysbiosis is closely linked to various health issues^[2,6], including obesity, type 1 diabetes (T1D), necrotizing enterocolitis (NEC), allergies, and autism spectrum disorder (ASD). Thus, the gut microbiota is considered to be a biological barometer for infant health status. This insight has driven the innovation of strategies to influence the infant microbiota by using nutraceutical supplements.

Probiotics, viable microbial organisms with demonstrated host-beneficial effects^[7], have garnered substantial research interest due to their capacity to reshape early gut microbiota, thereby enhancing infant fitness. Emerging evidence positions probiotics as multimodal therapeutics in infants, proving efficacy not only for gastrointestinal disorders, but increasingly for conditions affecting other bodily systems^[8]. Probiotics achieve these positive clinical outcomes primarily by strengthening intestinal barriers, modulating immune responses, competitively excluding pathogens, and mediating gut-organ interactions^[9,10]. However, their extensive benefits must be weighed against the specific drawbacks, especially in infant subjects. Such drawbacks, which are both intrinsic and extrinsic, include invasive infections, detrimental metabolic complications, horizontal transfer of antibiotic resistance genes, and discrepancies in probiotic authenticity^[11]. In light of infants' microbiological and immunological naivety, they are often perceived as a vulnerable population for probiotic intervention^[12]. Early or prolonged exposure to probiotics may increase susceptibility to adverse events, potentially leaving permanent impacts. As a result, probiotics still demand refined research to ensure their effective use in pediatric care.

This review comprehensively summarizes the implementation of probiotics in infant healthcare, and explores their underlying mechanisms of action. In parallel, we draw attention to the safety considerations and administration challenges associated with their use in early life. Our goal is to establish an evidence-informed framework and identify practical insights into the safety and efficacy of probiotics in the management of infantile conditions.

2. Infant gut microbiota: a critical window for lifelong health shaping

Infant physiological systems are characterized by rapid development and high plasticity, with the establishment of their gut microbiota representing a particularly unique process. The infant gut microbiome undergoes significant and dynamic shifts over time^[5]. Early colonization is characterized by aerotolerant and facultative anaerobic taxa including *Lactobacillus*, *Staphylococcus* spp. and Enterobacteriaceae, which rapidly diminish in relative abundance within days to weeks^[13]. In breastfed infants, this initial community is progressively supplanted by anaerobic Bifidobacteriaceae, which thrive on breast milk components^[13]. Concurrently, other anaerobic families such as Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae gradually expand throughout infancy and early childhood^[14]. Consequently, a stable, adult-like gut ecosystem is generally not established until approximately three years of age^[15].

However, before maturing into a stable stage, the composition of the infant gut microbiota is highly sensitive to a variety of extrinsic factors. This sensitivity not only shapes markedly divergent developmental trajectories of the microbiota among individuals but also establishes what can be described as a far-reaching “critical window” for long-term health^[16,17]. Thus, comprehending this delicate and intricate interplay during early years of life is of considerable importance. Premature infants, relative to full-term counterparts, show higher proportions of facultative anaerobes and lower levels of obligate anaerobes, including representative genera such as *Bifidobacterium*, *Bacteroides*, and *Atopobium*^[18]. Comparing the gut microbiome of infants and their mothers reveals that 72% of the microbial composition in vaginally delivered newborns matches that of their mothers in the early stages of life. In contrast, the corresponding proportion in infants born by caesarean section is only 41%^[19]. Additionally, maternal overweight is associated with infant gut enrichment of the *Lachnospiraceae* family, an early microbial signature that elevates the predisposition to obesity later in life^[20]. Human milk contains a median bacterial load of 10^6 cells/mL, establishing it as a key route for microbial transmission to the infant^[21]. Infants fed exclusively with formula do not acquire these bacteria, resulting in a distinct gut microbiota composition compared to those who are breastfed. A multinational meta-analysis encompassing 684 infants from five countries indicated that formula-fed infants display increased relative level of *Veillonella*, *Bacteroides*, *Firmicutes* and *Eubacterium*. While exclusively breastfed infants exhibited reduced alpha diversity, primarily driven by a higher prevalence of *Bifidobacterium*, which is linked to enhanced microbial metabolic pathways supporting lipid and vitamin metabolism^[22]. After weaning, the transition to solid foods coincides with a rise in butyrate-producing bacteria and a concurrent decline in *Enterobacteriaceae* and *Staphylococcus* populations^[23]. Moreover, antibiotic exposure substantially alters the developmental trajectory of the infant gut microbiota. With empirical antibiotic treatment in developing infants, a reduction in overall alpha diversity is commonly observed in infants’ guts, which is accompanied by a depletion of *Bifidobacterium* spp. and a concomitant expansion of *Klebsiella* and *Enterococcus* spp.^[24].

The gut microbiota of healthy infants plays a pivotal role in early development by modulating immune responses, promoting intestinal mucosal renewal, inhibiting opportunistic pathogens, and participating in key metabolic functions—including the breakdown of dietary components and biosynthesis of bioactive metabolites such as short-chain fatty acids (SCFAs), vitamins, and even neuroactive compound^[25,26]. However, accumulating evidence indicates that aberrant microbial colonization patterns caused by susceptible factors in infancy are potentially linked to adverse long-term health outcomes. An elevated prevalence of pathogenic microorganisms coupled with reduced commensal populations may provoke inflammatory cascades, impair intestinal barrier function, and drive hypersensitive immune maturation^[27]. Longitudinal studies reveal that infants predisposed to celiac disease develop characteristic gut microbial dysbiosis prior to clinical onset, marked by elevated levels of *Dialister invisus*, *Parabacteroides* spp., and *Lachnospiraceae* alongside tryptophan metabolite accumulation, while showing reduced abundance of anti-inflammatory species including *Faecalibacterium prausnitzii* or *Clostridium clostridioforme*^[28]. 16S rRNA gene sequencing

demonstrate the depletion of *Bacteroides* and enrichment of *Clostridium sensu stricto* 1 in the infant gut microbiota are strongly associated with the occurrence of eczema at one year of age^[29]. Evidence also suggests that infants at risk of T1D exhibit decreased microbial diversity and an elevated level of *Streptococcus infantarius* and *Ruminococcus gnavus*. Remarkably, *Coprococcus eutactus* and *Dialister invisus* were completely absent in T1D cases^[30].

Therefore, the establishment and maturation of the infant gut microbiota follow a dynamic trajectory that remains vulnerable to multiple disruptive influences. These early alterations can exert durable, even lifelong, effects on immune and metabolic programming. As a result, strategies that target the infant intestinal environment through microbial agents such as probiotics offer considerable promise for disease prevention and therapy.

3. Progress of the probiotic strategies for infant health management

Advances in gut microbiome research has facilitated the microbiota-targeted interventions to improve infant well-being. Probiotics are described as live microorganisms that, when administered in adequate amounts, confer health benefits to the host^[7]. By adhering to human guts, probiotics enhance and regulate intestinal functionality through various mechanisms including increase in beneficial gut microorganisms, reduces inflammatory responses, competitively suppresses pathogenic bacteria, and strengthens the intestinal barrier and mitigates associated diseases^[31]. Furthermore, probiotics may confer benefits extending well beyond the gut, contributing to the maturation and functional regulation of multiple organ systems^[8]. Thus, probiotics and their derivatives are now extensively utilized in fermented foods, infant formula, and pharmaceutical products, presenting a promising scheme for enhancing systemic health in infants (**Fig. 1**).

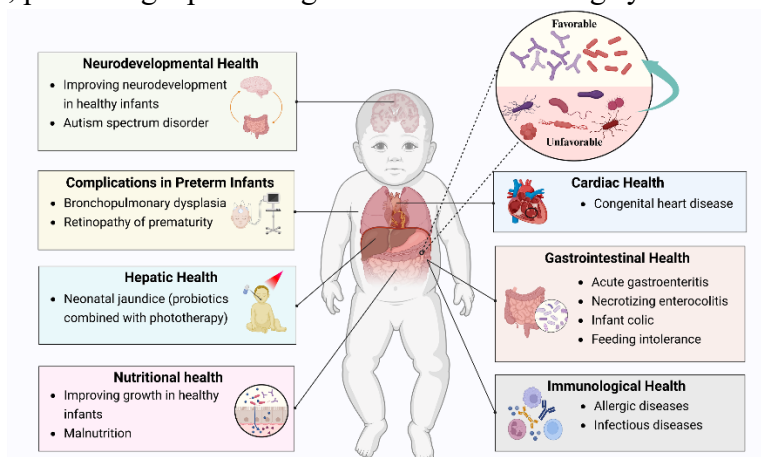


Fig. 1. Potential applications of probiotics in infant health and disease. Probiotics can ameliorate gut microbiota dysbiosis and are being applied across multiple fields, including gastrointestinal, neurodevelopmental, immunological, nutritional, hepatic, and cardiac health, as well as in the management of preterm infant complications.

In order to offer an integrated perspective on recent progress in infant probiotic applications, we have conducted a synthesis of relevant researches. **Table 1** summarizes all clinical trials of probiotic applications discussed herein in the infant population. These findings and advances stated the potential applications for various indications in infants, contributing to a deepen knowledge of this area and enabling more precise integration of probiotic agents into both medicinal products and functional food formulations.

Table 1. Summary of Clinical Trials on Probiotic Therapy in Infants.

Researching questions	Clinical trial identifier	Participants' Number	Strains (Formulation)	Dosage	Functions and outcomes	References
Gastrointestinal health						
Preterm infant gut microbiota development	NCT01670916	252	<i>L. rhamnosus</i> GG and <i>B. animalis</i> subsp. <i>lactis</i> BB-12	<i>L. rhamnosus</i> GG at 2×10^9 CFU daily and <i>B. animalis</i> subsp. <i>lactis</i> BB-12 at 2×10^8 CFU daily from day 3 to day 30 of life	Increased <i>L. rhamnosus</i> and <i>B. animalis</i> abundance; reduced <i>Weissella</i> , <i>Veillonella</i> spp., <i>Klebsiella</i> , <i>Citrobacter</i> , and <i>Chryseobacterium</i> colonization	[32]
Acute gastroenteritis	TCTR20201005005	48	<i>L. reuteri</i> DSM 17938	1×10^8 CFU daily for 5 days	Shortened the duration of diarrhea	[38]
Acute gastroenteritis	N/A	132	<i>L. reuteri</i> DSM 17938	2×10^8 CFU daily for 5 days	Reduced stool frequency and improved stool consistency	[39]
Acute gastroenteritis	NCT02096302	190	Infant formula containing <i>B. longum</i> subsp <i>infantis</i> CECT7210	1×10^7 CFU/g daily for 12 weeks	Decreased diarrhea frequency and lowered the rate of constipation	[42]
Acute gastroenteritis	NCT01773967	971	<i>L. rhamnosus</i> GG	1×10^{10} CFU twice daily for 5 days	No impact on improving patients' outcomes	[43]
Acute gastroenteritis	NCT01853124	886	<i>L. rhamnosus</i> R0011 and <i>L. helveticus</i> R0052	4×10^9 CFU twice daily for 5 days	No impact on improving patients' outcomes	[44]
Necrotizing enterocolitis	PACTR202011513390736	200	<i>L. acidophilus</i> , <i>B. bifidum</i> and <i>B. infantis</i>	2×10^9 CFU (total viable count) daily for 28 days	Reduced the incidence of necrotizing enterocolitis and feeding intolerances in preterm newborns	[49]
Necrotizing enterocolitis	CTRI/2012/08/002853	104	Multicomponent probiotic formulation of <i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>B. longum</i> and <i>S. boulardii</i>	1.25×10^9 CFU (total viable count) daily until discharge	Lowered the incidence of necrotizing enterocolitis and shortened the time to reach full enteral feeding	[52]
Necrotizing enterocolitis	ISRCTN:05511098; EudraCT: 2006-003445-17	1315	<i>B. breve</i> BBG-001	$8.3\text{--}8.8 \log_{10}$ CFU daily until 36 weeks postmenstrual age or discharge	No impact on reducing the occurrence of necrotizing enterocolitis and sepsis	[53]
Infant colic	<u>NCT04262648</u>	90	<i>L. reuteri</i> NCIMB 30351	2×10^8 CFU daily for 25 days	Reduced the incidence of functional gastrointestinal disorders including colic, reflux and other symptoms along with decreased frequency and duration of crying	[56]

Infant colic	N/A	108	<i>L. rhamnosus</i> GG ATCC 53103	5×10 ⁹ CFU daily for 28 days	Reduced levels of TNF-α, IL-6, and monocytes, along with decreased crying time	[58]
Infant colic	<u>NCT02988791</u>	80	<i>B. animalis</i> subsp. <i>lactis</i> BB-12	1×10 ⁹ CFU daily for 28 days	Alleviated infant colic symptoms, increased <i>Bifidobacterium</i> abundance, elevated butyrate, beta-defensin-2, cathelicidin, and sIgA levels, and reduced fecal calprotectin concentrations	[59]
Infant colic	NCT02813772	241	Reduced-lactose partially hydrolysed formula containing <i>L. reuteri</i> DSM 17938	Daily for 4 weeks	Significantly reduced total crying time	[60]
Gut microbiota and feeding tolerance	NCT03422562	102	<i>B. breve</i> HA-129, <i>B. bifidum</i> HA-132, <i>B. longum</i> subsp. <i>infantis</i> HA-116, <i>B. longum</i> subsp. <i>longum</i> HA-135, and <i>L. rhamnosus</i> HA-111	1×10 ⁹ CFU (total viable count) daily until the earlier of reaching 37 weeks corrected gestational age or hospital discharge	Accelerated enteral feeding establishment, increased the tolerance for cow's milk protein supplements, and modulated gut microbiota by increasing fecal <i>Bifidobacterium</i> and <i>Lactobacillus</i> and decreasing <i>Candida</i> abundance	[62]
Neurodevelopmental health						
Neurodevelopment	NTC02094547	170	New formula: LC-PUFA, MFGM and synbiotics (contains <i>B. infantis</i> IM1, <i>L. rhamnosus</i> LCS-74, FOS, inulin and sialic acid)	Experimental formula daily until 18 months of age	Enhanced intestinal probiotic growth and maturation, alongside improved neurodevelopmental outcomes	[76]
Autism spectrum disorder	ChiCTR2000035006	60	<i>B. fragilis</i> BF839	1×10 ⁶ CFU twice daily for 16 weeks	Improved core autism behavioral symptoms, enhanced gut <i>Bifidobacterium</i> colonization, and modulated metabolism of neuroactive compounds	[80]
Autism spectrum disorder	NCT00167700	75	<i>L. rhamnosus</i> GG ATCC 53103	1×10 ¹⁰ CFU daily prenatally to mothers for 4 weeks, and postnatally to infants or breastfeeding mothers for 6 months	Reduced incidence of attention deficit hyperactivity disorder and Asperger syndrome at 13-year follow-up	[81]
Immunological health						
Th 1 immune response and antibody response	N/A	300	Infant formula containing <i>B. longum</i>	1×10 ⁷ CFU/g daily until 6 months of age	Increased fecal <i>Bifidobacteria</i> abundance and the <i>bifidobacterial</i> <i>Enterobacteriaceae</i>	[88]

to vaccinations			BB536		ratio, enhanced IFN- γ secretion and IFN- γ /IL-4 balance, but had no impact on the antibody response after vaccination	
Cow's milk allergy	N/A	19	Hydrolyzed casein formula containing <i>L. rhamnosus</i> GG	$4.5\text{--}8.5 \times 10^7$ CFU/g daily for 6 months	Accelerated cow's milk allergy tolerance acquisition, enriched butyrate-producing genera <i>Blautia</i> , <i>Roseburia</i> and <i>Coproccoccus</i>	[89]
Atopic dermatitis	NCT03157284	58	Rice flour fermented with <i>L. paracasei</i> CBA L74 (heat-killed cells)	Rice-dried powder 8 g daily for 12 weeks	Reduced steroid use without altering SCORAD scores, and induced no significant changes in gut microbial structure or inflammatory biomarkers	[94]
Infectious diarrhea and lower respiratory tract infections	NCT02221687	460	Synbiotic: <i>L. fermentum</i> CECT5716 and GOS	$\geq 1 \times 10^6$ CFU/g daily until 12 months of age	Reduced incidence of lower respiratory tract infections, increased fecal sIgA levels, and lowered intestinal pH, but showed no effect on diarrhea incidence	[96]
Sepsis	CTRI/2015/04/005708	100	VSL#3®: <i>L. paracasei</i> , <i>L. plantarum</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> , <i>B. longum</i> , <i>B. infantis</i> , <i>B. breve</i> , <i>Streptococcus salivarius</i> , maltose and silicon dioxide	1 sachet twice daily for 7 days	Reduced proinflammatory cytokine levels, increased anti-inflammatory cytokine production, and lowered Sequential Organ Failure Assessment score, with no significant effect on infections, ICU study and mortality	[97]
Respiratory tract and gastrointestinal infections	NCT05734417	115	<i>B. longum</i> subsp. <i>infantis</i> B8762	5×10^9 CFU daily for 4 weeks	Shortened respiratory and gastrointestinal infection duration, reduced infection-related clinical visits, and modulated oral inflammatory cytokine TNF- α concentration	[98]
<i>Candida</i> infection	N/A	249	<i>L. reuteri</i> ATCC 55730 or <i>L. rhamnosus</i> ATCC 53103	<i>L. reuteri</i> at 1×10^8 CFU daily or <i>L. rhamnosus</i> at 6×10^9 CFU daily, until discharge from the NICU	Reduced gastrointestinal <i>Candida</i> colonization, decreased late-onset sepsis incidence, and improved neurological outcomes	[100]
Infectious diseases	NCT01625273	106	Synbiotic infant formula containing FOS, GOS and <i>L. paracasei</i> ssp. <i>paracasei</i> F19	1×10^9 CFU/L of formula daily until 6 months of age	Suppressed opportunistic <i>Klebsiella</i> colonization, enriched beneficial <i>B. breve</i> abundance, and increased antimicrobial metabolite D-3-phenyllactic acid production	[101]
Nutritional health						
Severe acute malnutrition	NCT0366657	67	<i>B. infantis</i> EVC001 alone or with the Lacto-N-neotetraose	8×10^9 CFU daily for 4 weeks	Increased rate of weight gain and elevated weight-for-age Z-score	[103]

Severe acute malnutrition	NCT03666572	62	<i>B. infantis</i> EVC001 alone or with the HMO lacto- <i>N</i> -neotetraose	8×10 ⁹ CFU daily for 4 weeks	Increased fecal <i>B. infantis</i> abundance, promoted weight gain, and reduced intestinal inflammation	[104]
Severe acute malnutrition	PACTR202108842939734	400	Ready-to-use therapeutic food with <i>L. rhamnosus</i> GG and <i>L. reuteri</i> DSM 17938	2×10 ⁹ CFU (total viable count, 1:1) daily for 1 month	Reduced diarrheal duration, decreased diarrheal incidence, and accelerated early nutritional recovery	[105]
Other conditions						
Jaundice	NCT03876678	83	<i>B. animalis</i> subsp. <i>lactis</i> CP-9	5×10 ⁹ CFU twice daily until stopping receiving phototherapy	Accelerated serum bilirubin decline, reduced phototherapy duration, and enhanced therapeutic efficacy of phototherapy	[116]
Jaundice	N/A	76	<i>S. boulardii</i>	125 mg twice daily until stopping receiving phototherapy	Shortened phototherapy duration, reduced hospitalization length	[117]
Cyanotic congenital heart disease	NCT01810978	100	Synbiotic: <i>B. lactis</i> and inulin	5×10 ⁹ CFU daily until discharge or death	Reduced incidence of sepsis, prevented necrotizing enterocolitis, and decreased mortality	[121]
Infants undergoing surgery for congenital heart disease	N/A	21	<i>B. breve</i> BBG-01	3×10 ⁹ CFU daily from 1 week before surgery to 1 week after surgery	Shortened ICU stay, accelerated enteral feeding attainment, and restored gut microbiota composition	[122]

Abbreviations: CFU, colony forming unit; N/A, not available; TNF, tumor necrosis factor; IL, interleukin; sIgA, secretory immunoglobulin A; LC-PUFA, long chain polyunsaturated fatty acids; MFGM, bovine milk fat globule membranes; FOS, fructo-oligosaccharides; IFN, interferon; SCORAD, SCORing Atopic Dermatitis; GOS, galacto-oligosaccharides; ICU, intensive care unit; NICU, neonatal intensive care unit; HMO, human milk oligosaccharides;

3.1. The potential applications of probiotics in infant gastrointestinal health

Probiotic supplementation is considered to shape the composition and functional maturation of the infant gut microbiota and gastrointestinal environment, potentially influencing the establishment and maturation of intestinal and gut-associated immune systems. Specific probiotic strains, including *Lactobacillus rhamnosus* GG (*L. rhamnosus* GG) and *Bifidobacterium animalis* subsp. *lactis* BB-12 (*B. animalis* subsp. *lactis* BB-12), have been shown to establish stable intestinal colonization, leading to remodeling of the gut microbiota, suppression of potentially harmful bacterial expansion, and reduced abundance of *Weissella*, *Veillonella*, and the opportunistic pathogen *Klebsiella* in preterm infants^[32]. Probiotics can also modulate the intestinal metabolic environment. Supplementation with *Bifidobacterium* and *Lactobacillus* has been shown to reduce fecal pH in preterm infants^[33]. Likewise, *Clostridia* species administration in newborn mice increased succinate production and decreased intestinal oxygen levels, thereby creating an environment unfavorable for pathogen growth^[34]. Furthermore, through microbe-associated molecular patterns (MAMPs), probiotics engage Toll-like receptors (TLRs) and downstream MyD88-dependent signaling pathways, contributing to intestinal barrier maturation and the development of innate immune responses during infancy^[35]. SCFAs represent another key mediator of probiotic effects. Acid-producing probiotics can elevate SCFA concentrations in the gut, thereby promoting immune homeostasis and defensive responses of intestinal immune cells^[35]. Additionally, SCFAs facilitate the expression of tight junction proteins in intestinal epithelial cells, strengthening the intestinal barrier function^[36]. Although the precise mechanisms underlying the effects of probiotics remain unclear, current understanding have provided valuable insights into their potential therapeutic roles and lay the foundation for understanding their application in various gastrointestinal diseases in infants.

3.1.1 Efficacy of probiotic therapy in acute gastroenteritis

Acute gastroenteritis (AGE), an exceedingly prevalent and burdensome pediatric disease that primarily and significantly impacts the infant population, contributes to nearly half a million global annual fatalities among children under five years of age. Patients with AGE frequently present with severe diarrhea and vomiting, which can lead to severe dehydration, accompanied by electrolyte homeostasis imbalances, alongside organ dysfunction and impairment^[37]. Emerging evidence supports that probiotics supplementation could confer therapeutic advantages for ameliorating clinical manifestations of AGE, providing novel insights for addressing this significant public health burden.

Certain strains like *L. reuteri* DSM 17938 have revealed desirable probiotic properties and showed consistent and durable clinical benefits in the treatment of AGE in infants. In outpatient settings, standardized oral consumption of the strain largely shortened the duration of diarrhea, with a greater proportion of patients achieving clinical resolution within 48 to 72 hours^[38]. Evidence from pediatric emergency departments further supports its efficacy with high-dose *L. reuteri* is associated with a reduction in stool frequency and a marked decline in the persistence of watery diarrhea beyond day five of treatment^[39]. Moreover, a yeast-based

probiotic, *Saccharomyces boulardii* (*S. boulardii*) CNCM I-745, has proven its efficacy in shortening the course of diarrhea and attenuating systemic inflammation in pediatric cohorts in China, highlighting its possible advantages in specific regional and demographic settings^[40]. Of particular interest, *B. infantis* IM1® is extensively characterized for its broad-spectrum anti-infective potential by an update review. Such bacteria can inhibit the infection of major AGE-inducing pathogens including *Salmonella enterica*, *Cronobacter sakazakii*, *Shigella sonnei* and a virus type, rotavirus, both *in vivo* and *in vitro*. A clinical trial further corroborated these findings, showing the strain significantly decreases the frequency of diarrhea episodes, enhances gastrointestinal tolerance, and lowers the incidence of constipation in infants under three months of age^[41,42]. However, conflicting evidence still exists; several high-quality, randomized controlled trials (RCTs) failed to confer significant clinical benefits over placebo in key clinical endpoints^[43,44]. Given the wide variation in the results of relevant studies, a more detailed and in-depth review of the available evidence is warranted to better delineate the value of probiotic interventions.

3.1.2 Efficacy of probiotic therapy in NEC

NEC, the most common inflammatory bowel necrosis in neonates, primarily affecting preterm infants. Despite significant considerable progress in neonatal medicine, NEC persists as a predominant contributor to disease burden and fatal outcomes in this vulnerable population^[45]. Currently, no specific therapeutic strategies have been proven to significantly improve prognosis, and the role of surgical intervention remains highly debated. In contrast to healthy controls, infants with NEC present a distinct gut microbiota composition, marked by a significant enrichment of potentially pathogenic bacteria, including *Klebsiella*, *Clostridium perfringens*, and *Enterococcus faecalis*, alongside a notable depletion of beneficial genera such as *Lactobacillus* and *Bifidobacterium*^[46,47]. Thus, probiotics for NEC management have emerged as a rapidly evolving and highly prioritized area of research.

In NEC mouse models, orally consumption of *L. gasseri* FWJL-4 and its derived acetate, suppressed necroptosis and remained the amount of the enterocytes and goblet cells. Mechanically, acetate inhibited the Mixed lineage kinase-like (MLKL) phosphorylation and upregulated the tight junction protein expression by activating receptors G protein-coupled receptor (GPR) 43 and GPR41^[46]. Next-generation probiotic *Bacteroides fragilis* (*B. fragilis*) secretes bile salt hydrolase to correct aberrant bile acid metabolism in NEC patients, thereby inhibiting pathological activation of the FXR-NLRP3 signaling pathway^[48]. For human studies, a landmark RCT by Sowden et al.^[49] demonstrated the remarkable efficacy of multi-strain probiotic supplementation (*L. acidophilus*, *B. infantis* and *B. bifidum*) in NEC prevention, with a striking 0% incidence of NEC in the probiotic group compared to 5 cases (stages 1A-3B) in the placebo-controlled arm. Multiple high-quality meta-analyses demonstrate that probiotic supplementation can reduce all-cause mortality in preterm infants by almost 50%^[50,51]. Another randomized double-blind trial in very low birth weight neonates observed a trend toward reduced necrotizing enterocolitis incidence, with 4% of infants receiving a bacterial formulation (*B. longum*, *L. acidophilus*, *L. rhamnosus*, and *S. boulardii*) affected, compared to 12% in the breast-milk-only control group^[52]. However, a phase 3 trial failed to prove any benefits in preventing NEC by

routine use of *B. breve* BBG-001 in very preterm infants^[53]. Thus, further identification of effective strains or combinations is crucial, as their efficacy appears highly dependent on specific colonization patterns and unique probiotic properties.

3.1.3 Efficacy of probiotic therapy in infant colic

Infant colic (IC) is a behavioral syndrome marked by recurrent and inconsolable crying episodes without a clearly defined cause. Emerging studies have explored microbiota-based therapeutic strategies as IC patients always show an altered microbiota profile^[54]. Multiple RCTs and meta-analyses reported that colonization with *L. reuteri* in IC infant reduced the overall crying time and crying episodes^[55–57]. While the efficacy appears to be reliable only in breastfed infants, whereas the evidence remains inconclusive for formula-fed counterparts. Moreover, Savino et al.^[58] have established a link between IC and the immunomodulatory effects of probiotics. Specifically, supplementation with *L. reuteri* significantly reduced concentrations of pro-inflammatory cytokines, including tumour necrosis factor α (TNF- α) and interleukin-6 (IL-6), in peripheral blood. Nocerino et al.^[59] reported that a 28-day intervention with *B. animalis* subsp. *lactis* reduced crying episodes in colic infants, potentially via *Bifidobacterium* restoration and immune maturation. Additionally, synbiotics represent another promising therapeutic approach. As demonstrated by Turco et al.^[60], a synbiotic infant formula incorporating *L. reuteri* and featuring lowered lactose content significantly alleviates pain in infants.

3.1.4 Efficacy of probiotic therapy in feeding intolerance

Feeding intolerance may result in interruptions of enteral nutrition delivery, prolonging the period of insufficient nutrient intake, thereby contributing to growth retardation and compromised physiological development^[61]. In this context, the use of effective medications as well as timely nutritional interventions are crucial for ensuring adequate nutrient intake. For example, administration of a five-strain probiotic blend—comprising *B. breve* HA-129, *B. bifidum* HA-132, *B. longum* subsp. *infantis* HA-116, *B. longum* subsp. *longum* HA-135, and *L. rhamnosus* HA-111—to 62 extremely low birth weight (ELBW) neonates significantly accelerated the attainment of full enteral nutrition relative to untreated infants^[62]. A meta-analysis of nine trials involving more than 1,200 preterm neonates indicated that probiotic administration markedly lowered rates of feeding intolerance and related sequelae^[63]. The latest systemic review suggests that probiotic intake may alleviate feeding intolerance; however, the overall evidence quality remains low, currently insufficient to guide clinical recommendations regarding optimal probiotic strains or dosages^[64].

3.2 The potential applications of probiotics in neurodevelopmental health

The gut microbiota profoundly influences infant neurodevelopment, including the establishment of the hypothalamic-pituitary-adrenal (HPA) axis, synaptogenesis, neurogenesis, and the establishment of neural circuits and the blood-brain barrier^[65]. Currently, the microbiota-gut-brain axis is considered a pivotal missing link in the progression of various mental disorders, prompting the emergence of the psychotropic probiotics

and growing interest in its potential for managing neuropsychiatric conditions^[66]. Overall, the efficacy of probiotics is mediated through the production and release of specific neurotransmitters, including gamma-aminobutyric acid (GABA)^[67], dopamine^[68], and serotonin^[69], a function that demonstrates clear strain-specificity^[70]. Research to date has also established that metabolic profiles linked to psychological and social disorders commonly demonstrate deficits in SCFAs, underscoring the essential contribution of these metabolites in maintaining neurological health^[71]. For instance, acetate can act on microglia to reverse the immaturity and defects and regulate the phagocytic capability, which is important in neurological disorders^[72]. Furthermore, SCFA administration can alleviate the neuroinflammation and enhance the secretion of neuroactive factors such as glucagon-like peptide 1 (GLP-1), serotonin and GABA^[73]. Probiotics may further modulate brain function through the regulation of tryptophan availability. Over 95% of tryptophan is considered to be metabolized through the kynurenine pathway, ultimately exerting neuroprotective effects. Certain probiotic strains like *L. plantarum*, *L. helveticus* and *B. longum* are thought to ameliorate cognitive deficits through modulation of serum tryptophan metabolism, subsequently altering kynurenine levels and reshaping gut microbial communities^[74].

A growing body of clinical studies emphasized the crucial role of psychobiotics in programming typical neurodevelopmental trajectories in healthy infants. A study involving 3,026 participants revealed that probiotic supplementation exceeding six months significantly enhanced neurocognitive outcomes in infants^[75]. The novel infant formula incorporating *B. infantis*, *L. rhamnosus*, and a blend of prebiotics modulates developmental paths of nervous system by facilitating gut microbiota maturation trajectories. Results demonstrated that a subset of infants receiving the intervention exhibited predominantly higher scores in both overall language and expressive language compared to those in the breastfed reference group at 12 months of age^[76]. A portion of tryptophan produced by probiotics is converted into melatonin, which plays a key role in regulating circadian rhythms and promoting sleep^[74]. Recent studies have linked biotics to infant sleep duration and settling patterns; however, no significant beneficial effects have been observed^[77].

3.2.1 Efficacy of probiotic therapy in ASD

ASD manifests primarily through deficits in social interaction, impaired communication capacities, and the exhibition of repetitive or restrictive behavioral patterns, with an estimated prevalence of 1 in 50 children^[78]. Though the cause of ASD remains incompletely understood, growing evidence suggests that its origins may be traced back to disruptions in the microbiota composition during early infancy. A latest investigation has unveiled that infants who later develop ASD often exhibit a marked depletion or absence of beneficial microbial taxa such as *Akkermansia*, *Bifidobacterium*, *Coprococcus*, and *Roseburia*, alongside an enrichment of opportunistic pathobionts, notably *Corynebacterium variabile*^[78]. In 2013, Hsiao et al.^[79] presented the first direct proof that probiotics can be used to treat ASD. In a maternal immune activation (MIA)-induced mouse model of ASD, treatment with *B. fragilis* significantly corrected intestinal permeability, microbial composition, and metabolic profiles. Notably, probiotic intervention also ameliorated behavioral abnormalities, including reduced stereotypic and anxiety-like behaviors, and improved sensory and

motor coordination. A pediatric cohort study involving 60 infants and young children with ASD further supported the above findings, showing that *B. fragilis* BF839 restored the abundance of *Bifidobacterium* and was associated with alterations in the neuroactive metabolic pathways, including increased activity in the pentose phosphate pathway and in the degradation metabolism of sucrose, valine, and ribose, alongside reduced activity in leucine degradation^[80]. Probiotic intervention is also considered a potential strategy for the early prevention of ASD. In a prospective cohort study, administration of *L. rhamnosus* GG during the neonatal period largely reduced the incidence of Asperger syndrome and attention-deficit hyperactivity disorder^[81]. Moreover, prenatal probiotic usage may enhance resistance to T helper 17 (Th 17) cells and pathogen-induced peripheral inflammation to prevent ASD occurrence. In particular, probiotic-derived metabolites such as tyrosol and xanthurenic acid have been implicated in suppressing neuroinflammation and mitigating aberrant myelination, thereby contributing to neurodevelopmental homeostasis^[82].

3.3 The potential applications of probiotics in immunological health

3.3.1 Efficacy of probiotic therapy in allergic diseases

The bidirectional interplay between the gut microbiota and the infant immune system plays a fundamental role in the maintenance of immune tolerance^[83]. The rising prevalence of allergic diseases among infants has emerged as a public health concern, with several risk factors now identified^[9]. Hoskinson et al.^[84] observed a higher incidence of allergies in infants with delayed maturation of the gut microbiome, characterized by a depletion of bacteria responsible for producing SCFAs. Recent investigations have explored dietary interventions designed to reshape the gut microbiota to alleviate allergic disorders, generating increased attention to probiotic applications^[85]. In infants, immune modulation by probiotics occurs within a context of immune immaturity characterized by Th2-biased responses, limited immunological memory, and the ongoing establishment of immune tolerance^[86], such that microbial signals during this developmental period may exert disproportionately strong and potentially long-lasting effects.

Previous studies indicate that certain probiotics contribute to host innate and adaptive immunity through the modulation of T-cell differentiation and regulation of cytokine and antibody production, thus preventing allergy occurrence^[87]. *B. longum* BB536 was shown to enhance *bifidobacterial* colonization in healthy full-term infants and to promote an immune shift from shift from IL-4-secreting cells (Th2) toward interferon- γ (IFN- γ) -producing cells (Th1)^[88]. Moreover, the introduction of *L. rhamnosus* GG has been proved to enrich butyrate-producing bacteria in infants with food allergies^[89]. Butyrate facilitates regulatory T cell (Treg) expansion, yet infants with food allergies display a defective MyD88–ROR γ t pathway, which is critical for Treg-mediated immune tolerance^[90]. Beyond SCFAs, bacterial cell surface polysaccharides derived from probiotics have also been identified as promoters of Treg expansion, functioning in part through a TLR2-mediated mechanism^[91]. Indeed, several recent meta-analyses have emphasized the effect of probiotic uptake in preventing allergic conditions, including asthma, atopic dermatitis (AD), and food allergy^[92,93]. It is noteworthy that heat-inactivated probiotics are also being explored for their protective effects in immune

disease. Although D'Auria et al.^[94] found no therapeutic benefit of heat-killed *L. paracasei* CBA L74 against AD, its administration was associated with reduced steroid use and fewer drug-related side effects.

3.3.2 Efficacy of probiotic therapy in infectious disease

Infantile well-being is always challenged by pathogenic infections due to their undeveloped immune defense and organ function. Accordingly, implementing targeted measures to address the health implications of this condition in infants requires prompt action. Previous studies have shown that the early-life microbiota defends against pathogens and promotes mucosal immune maturation through interactions with host cells and production of bioactive metabolites^[95]. In turn, advantageous factors on the maturing microbiota such as probiotic administration have been linked to decrease in acquired infections and improved resistance to pathogenic organisms.

Clinical evidence supports that the utilization of probiotics contributes to a reduction in both the incidence and persistence of infections in infant individuals. Certain studies propose that probiotics may enhance immunity in infants, thereby strengthening systemic protection against pathogenic agents. An RCT in 460 healthy infants found that the synbiotic formulation of *L. fermentum* CECT5716 resulted in a higher production of secretory immunoglobulin A (sIgA) production, which may be related to the prevention of respiratory tract infections (RTI)^[96]. Additionally, infections are frequently accompanied by cellular inflammation, while probiotic intervention can reverse this harmful process. In infants with sepsis, the probiotic compound formulation VSL#3[®] significantly reduced the expression of multiple pro-inflammatory cytokines and increased anti-inflammatory factor levels, thereby attenuating organ damage^[97]. Richmond et al.^[98] found that the frequency and duration of gut and respiratory infection remarkably decreased after treatment with *B. longum* subsp. *infantis* B8762. Notably, the probiotic group showed a lower level of pro-inflammatory cytokines such as TNF- α in infant fecal samples, indicating regulation of the immune response.

The antimicrobial activity of probiotics has been widely utilized in food industry and the pharmaceutical sector. Overall, they inhibit pathogen growth through the secretion of antimicrobial substances, including bacteriocins, hydrogen peroxide, and various enzymes, while also impeding harmful microorganisms colonization *via* competitive exclusion^[99]. In this context, a representative clinical study have demonstrated that the administration of *Lactobacillus*-based probiotics inhibits *Candida* species colonization in the gastrointestinal tract of infants, thus reducing the risk of fungal disease^[100]. The synbiotic product containing *L. paracasei* F19, FOS, and galacto-oligosaccharides (GOS) is intended to target RTIs in infants aged 1 to 6 months. Metagenomic sequencing and 16S rRNA gene amplicon analysis showed that the synbiotic diet greatly suppressed the abundance of *Klebsiella* and promoted an increase in the antimicrobial metabolite D-3-phenyllactic acid^[101].

In general, probiotics can enhance immune function, mitigate inflammatory responses, and inhibit pathogen growth, thereby protecting infants from infections and emerging as a promising alternative therapeutic strategy.

3.4 The potential applications of probiotics in nutritional health

The gut microbiota facilitates infant growth and nutritional status through multiple mechanistic pathways. The gut microbiota plays a key role in enhancing nutrient assimilation, modulating growth hormone signaling, regulating host metabolism, mediating satiety effects, and influencing systemic inflammation, ultimately governing standard weight and length outcomes^[6,102]. Harnessing this potential could aid in programming normal infant growth trajectories and mitigating the risks of malnutrition or stunting by live microbe strategy.

To date, studies involving severely acutely malnourished infants in Bangladeshi showed that a 28-day supplementation with *B. infantis* EVC001 restored gut bifidobacterial levels, reduced fecal inflammatory markers such as cytokines, myeloperoxidase (MPO), and calprotectin, and promoted weight recovery^[103,104]. In 2023, Kambale et al.^[105] performed a clinical study involved in 400 infants to assess the capability of the oral combination of *L. rhamnosus* GG and *L. reuteri* DSM 17938 against uncomplicated severe acute malnutrition. Based on their findings, probiotic combination remarkably reduced the risk of diarrhea and promoted earlier nutritional recovery by the sixth week. Further investigations were conducted to elucidate the underlying mechanisms, revealing that probiotics may promote organ and systemic growth by regulating the level of insulin-like growth factor-1 (IGF-1)^[105]. Schwarzer and his team^[106] stated that the viable bacterium *L. plantarum* stimulated intestinal crypt cell proliferation and nutrient absorption in malnourished mice with the elevated circulating level of IGF-1 and insulin. Notably, the beneficial outcomes are mediated by the cell wall-derived postbiotic muramyl dipeptide, which activates the nucleotide-binding oligomerization domain 2 (NOD2) receptor in intestinal epithelial cells to elicit its physiological responses^[106]. Similarly, human breastmilk-derived probiotic *B. longum* subsp. *infantis* CCFM1269 improves the overall structure of host microbiota and metabolites profile, while upregulating the grow hormone (GH)/IGF-1 axis to promote bone formation in infant mice^[107].

Although the available preclinical and clinical data are satisfying, meta-analyses and systematic reviews have highlighted significant limitations and considerable heterogeneity among these studies. Some systematic reviews and meta-analyses confirmed the role of some probiotic strains on infant growth and development. However, these effects were observed only in low- and middle-income countries and no significant improvements in weight or height were found in high-income settings^[108–110]. A meta-analysis of 11 RCTs papers on infant formula containing synbiotics failed to identify any significant improvement in growth or nutritional indicators among healthy infants, which need further large-scale researches to warrant the finding^[111]. Overall, the potential of probiotics in supporting infant development remains encouraging. Future research necessitates large-scale, high-quality trials to further clarify underlying mechanisms and validate efficacy. It will also be essential to stratify participants based on health status and conduct long-term follow-up to assess sustained outcomes in order to develop standardized guidelines in infant healthcare.

3.5 The potential applications of probiotics in other infantile conditions

Beyond the aforementioned benefits, probiotics may also function as complementary interventions for the management and amelioration of various other conditions, including neonatal jaundice, congenital heart disease (CHD), and common complications among preterm infants.

Jaundice, a common neonatal condition affecting approximately 80% of newborns, is characterized by elevated serum bilirubin levels resulting in visible yellowing of the skin and sclera^[112]. Currently, phototherapy remains the gold standard of care for neonatal jaundice, primarily due to its ability to irreversibly convert bilirubin into water-soluble lumirubin, which are more readily excreted *via* bile and urine^[113]. However, Fan et al.^[114] reported that phototherapy in neonates significantly altered metabolic profiles and disrupted gut microbiota, notably reducing *Bifidobacterium* and *Lactobacillus* abundance, which necessitate the need for probiotics to restore microbial balance. It was found that combining the novel beneficial bacterial strain *Clostridium butyricum* with phototherapy can enhance bilirubin clearance in jaundiced neonates, accelerate jaundice resolution, and reduce adverse events compared to phototherapy alone^[115]. In a clinical study conducted by Tsai et al.,^[116] consumption of *B. animalis* subsp. *lactis* CP-9 strengthened the efficacy of phototherapy in neonatal jaundice through the inhibition of β -glucuronidase activity produced by the intestinal pathogen *Escherichia coli* (*E. coli*). Additionally, Nasief et al.^[117] demonstrated that ingesting *S. boulardii* during standard therapy could shorten the required duration of phototherapy while lower the likelihood of nosocomial infections. These findings confirm the promises of probiotics as an adjunctive therapy for neonatal jaundice.

CHD, the most common birth defect worldwide, remains a significant contributor to infant mortality and morbidity^[118]. To date, some perspectives suggest that probiotics may confer cardioprotective effects through microbial-derived metabolites such as kynurenine and folate, direct mechanistic evidence and clinical validation remain scarce^[119]. It is worth noting that infants with CHD often exhibit a characteristic gut microbial dysbiosis, marked by depletion of *Bifidobacterium* and enrichment of *Enterococcus*. This dysbiosis promotes intestinal barrier impairment and systemic inflammation, thereby increasing postoperative risks^[120]. Consequently, researchers mainly propose incorporating probiotics into adjunctive therapies to restore intestinal homeostasis and improve prognostic outcomes by now. In 2013, Dilli et al.^[121] successfully incorporate synbiotic (*B. lactis* and inulin) into cyanotic congenital heart disease (CCHD) infants to prevent the occurrence of nosocomial sepsis and NEC. In a pilot study, *B. breve* supplementation restored *Bifidobacterium* abundance, inhibited the colonization of *Enterobacteriaceae*, and increased total organic acid concentrations in neonates who had undergone pediatric cardiac surgery^[122]. However, progress in this field has been largely halted due to reports of probiotic intake triggering sepsis in infants with cardiac defects^[123]. Therefore, comprehensive safety evaluations of probiotic interventions in this specific population are essential, and must be complemented by long-term follow-up to monitor the incidence of adverse effects.

We also noticed that probiotics may contribute to the regulation and resolution of severe complications in preterm infants, including bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). In a neonatal murine model of BPD, inhalation of a live *Lactobacillus* combination (*L. plantarum*, *L. acidophilus*,

and *L. rhamnosus*) preserved pulmonary architecture and attenuated neutrophilic inflammatory infiltration^[124]. Moreover, *L. plantarum* L168 can elevate serum levels of anti-inflammatory metabolites and alleviate BPD pathology via downregulation of the TLR4/NF- κ B/CCL4 signaling pathway^[125]. For ROP, Bai et al.^[126] revealed that live *Bifidobacterium* capsule was associated with a reduced incidence among very preterm infants and very low birth weight neonates. The authors propose that this protective role may be mediated through gut microbiota modulation, restoration of IGF-1 and vascular endothelial growth factor (VEGF) homeostasis, and enhanced antioxidant activity^[126].

Therefore, probiotics present novel opportunities for the development of alternative approaches to support infant health under a variety of conditions. Future research should broaden the exploration of its applications across more clinical contexts and refine both preclinical and clinical strategies to rigorously evaluate its efficacy and safety.

4. Underlying concerns regarding probiotic supplementation in infants

The extensive health benefits of probiotics, as well as their acceptable use, have been characterized in a wide scope of diseases and conditions covered above. However, a growing volume of evidence supported by case reports and clinical trials reveals the risks associated with probiotic intake the infant population. Infants are undergoing rapid growth and development, which can result in a series of significant physiological changes. Since their defensive systems are not yet fully formed and the gastrointestinal tracts struggle to build effective structural and functional barriers, infants may become more vulnerable to experiencing undesirable effects caused by probiotic products^[11,127]. Currently, long-term follow-up data on probiotic administration remain scarce, limiting our understanding of their sustained efficacy and safety profiles. Therefore, the application of probiotics among infants must be re-evaluated to maximize health gains (**Fig. 2**). Here we comprehensively summarize the potential concerns about safety considerations and regulatory issues of probiotics for infants.

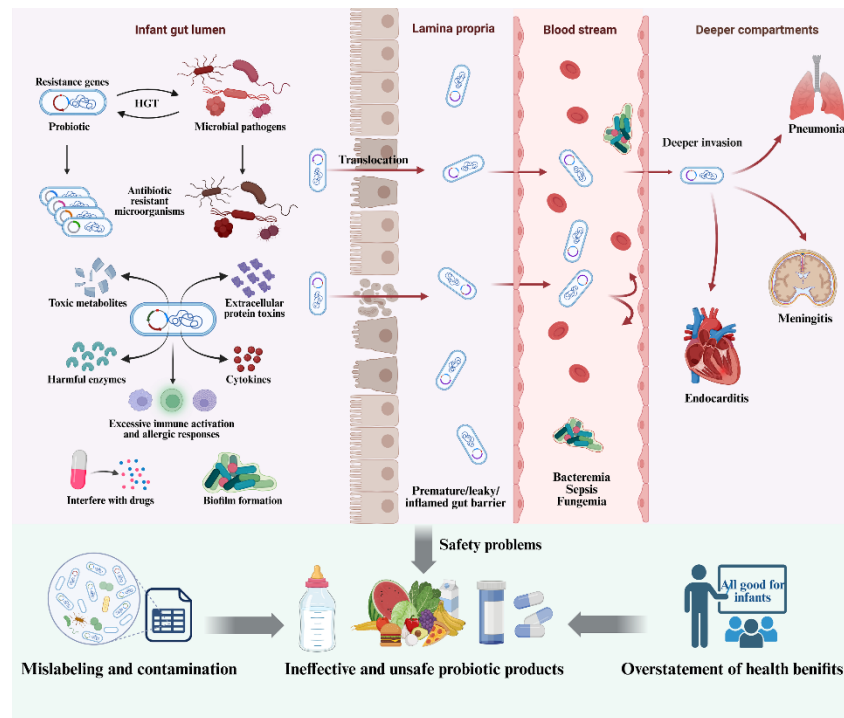


Fig. 2. Potential concerns regarding probiotic applications in infants. Key risks include invasive infection, antibiotic resistance dissemination, production of harmful substances, immune dysregulation and adverse drug interactions, compounded by regulatory deficiencies such as product contamination, mislabeling and unreliable health claims. HGT: Horizontal gene transfer.

4.1 Probiotic-associated invasive infections in high-risk infants

The most notable and well-documented risk associated with delivering probiotics to infants is invasive infection secondary to bacterial translocation. Bacterial translocation commonly describes the transfer of live commensal bacteria from the gastrointestinal tract into the bloodstream owing to various conditions such as weakened intestinal barrier, impaired immune system and dysbacteriosis^[128]. Intrinsic properties of certain probiotics, including mucosal adhesion capacity, mucolytic activity, and invasive enzyme production, have been identified to compromise intestinal barrier integrity and facilitate bacterial translocation^[11]. Probiotic translocation may precipitate a range of clinical infections, including bacteremia, sepsis, fungemia, endocarditis, meningitis and pneumonia, which can potentially result in debilitation or fatal outcomes in affected infants^[127,129].

In fact, the likelihood of probiotic-associated infection is highly dependent on host factors. Generally, healthy, full-term infants with no underlying medical conditions are unlikely to experience invasive events. However, when these occur, it often means the infant's health condition needs to improve (**Table 2**). Identification of these underlying risk determinants is crucial, especially in infants with compromised immune function or disrupted intestinal integrity.

Table 2. Documented Invasive Infections Following Probiotic Administration in High-Risk Infant Populations.

Article type	Case Number	Strain	Health state of infants	Infections	References
Meta-analysis	25	<i>Bifidobacterium</i> , <i>Lactobacillus</i> , and <i>Saccharomyces</i>	Preterm infants	Sepsis	[130]
Case reports	2	<i>B. longum</i> subsp. <i>infantis</i>	Preterm, low birth weight infants	Bacteremia	[131]
Case reports	3	<i>B. longum</i>	Preterm, low birth weight infants	Bacteremia	[132]
Case reports	1	<i>E. coli</i> Nissle 1917	Preterm, low birth weight infant	Sepsis	[133]
Case reports	1	<i>L. rhamnosus</i> GG	Preterm, low birth weight infant	Sepsis	[134]
Case reports	2	<i>L. rhamnosus</i> GG	Infants with short gut syndrome	Bacteremia	[135]
Case reports	1	<i>L. rhamnosus</i> GG	Infant with necrotizing enterocolitis and short gut syndrome	Bacteremia	[136]
Case reports	1	<i>L. rhamnosus</i>	Preterm low birth weight infant with a history of laparotomy	Late-onset sepsis	[137]
Case reports	1	<i>B. longum</i>	Preterm infant with perforated necrotizing enterocolitis	Bacteremia	[138]
Case reports	6	<i>B. breve</i>	Infants with gastrointestinal perforations, food protein-induced enterocolitis syndrome, adhesive ileus, or ileal volvulus	Bacteremia	[139]
Case reports	1	<i>L. paracasei</i>	Infant with a history of jejunostomy for hypoganglionosis	Bacteremia	[140]
Meta-analysis	49	<i>Lactobacillus</i> spp., <i>Saccharomyces</i> spp., <i>Bifidobacterium</i> spp., <i>Bacillus clausii</i> , and <i>E. coli</i>	Infants with prematurity or intravenous catheter use are the most frequent	Sepsis (most cases)	[141]
Case reports	1	<i>L. rhamnosus</i> GG	Infant with aortic coarctation	Sepsis	[123]
Case reports	1	<i>B. clausii</i>	Infant with congenital heart disease	Sepsis	[142]
Case reports	2 (including 1 infant)	<i>L. rhamnosus</i> GG	Infant with double-outlet right ventricle and pulmonic stenosis	Sepsis	[143]
Case reports	2	<i>L. rhamnosus</i> GG	An infant with trisomy 18 and triple-X syndrome, and an infant with pharmacologically closed patent ductus arteriosus and respiratory distress syndrome.	Sepsis	[144]
Case reports	1	<i>L. rhamnosus</i>	Infant with trisomy 21 and a history of esophageal atresia	Pneumonia	[145]
Case reports	1	<i>S. boulardii</i>	Infant with repeated antibiotic therapy	Fungemia	[147]

Preterm birth constitutes a significant risk factor, as intestinal immaturity and a weakened immune system collectively diminish resistance to bacterial invasion. A meta-analysis of 16 RCTs on probiotic sepsis by Kulkarni et al.^[130] reported 32 total cases, among which 25 were confirmed through full genomic analysis to be originate from the administered probiotic strain. In 2015, five cases of bacteremia linked to the introduction of *B. longum* for NEC prevention in preterm infants were documented^[131,132]. Another study reported sepsis linked to the *E. coli* Nissle 1917 probiotic strain in a preterm, low-birth-weight infant^[133]. Furthermore, Chiang et al.^[134] presented a *L. rhamnosus* infection in a female extremely preterm baby. They proposed that the organism's ability to form biofilms represents a key virulence factor contributing to probiotic-derived sepsis.

It is also necessary to assess whether the infant exhibits gastrointestinal structural abnormalities that could facilitate deeper microbial invasion. Several severe cases of sepsis occurred in infants with short gut syndrome after receiving *L. rhamnosus* supplementation have been proved^[135,136]. Brech et al.^[137] describe a rare case of premature infant with laparotomic intestinal surgery, who developed late-onset sepsis following taking *L. rhamnosus*. Pillai et al.^[138] reported that the use of *B. longum* in a neonate with NEC and intestinal perforation may have facilitated bacterial entry into the bloodstream, ultimately resulting in bacteremia. The results of Sakurai et al.^[139] revealed that nosocomial *B. breve* bacteremia is associated with the intestinal mucosal damage and ileus. A recent case report and review described an occurrence of *L. paracasei* bacteremia in an 8-month-old girl following jejunostomy performed for hypoganglionosis^[140].

Additional cases suggest the possibility of other risk scenarios. For example, D'Agostin et al.^[141] identified 49 pediatric cases of probiotic-associated infections occurring between 1995 and June 2021, 51% of which were linked to intravenous catheter use. Some species of bacterial probiotic such as *L. rhamnosus* and *Bacillus clausii* have been described to cause severe sepsis in infants with CHD^[123,142,143]. Moreover, such adverse events have been observed in infants with chromosomal structural variations. Dani et al.^[144] reported two cases of *L. rhamnosus*-associated infection, including one child with trisomy 18 and triple X syndrome accompanied by multiple severe congenital anomalies. Similarly, an 11-month-old female infant with trisomy 21 developed aspiration pneumonia following administration of *L. rhamnosus*^[145]. Meanwhile, several studies suggest that recurrent broad-spectrum antibiotic use may predispose individuals to probiotic translocation by disrupting intestinal barrier integrity and depleting commensal microbiota^[146]. A representative case published in 2019 involved a 3.5-month-old infant with a history of recurrent respiratory infections and antibiotic use, who developed fungemia following feeding with *S. boulardii*^[147].

Therefore, prior to probiotic supplementation, healthcare providers should conduct a comprehensive assessment of the recipient's health status to identify potential high-risk individuals. Subsequent extended monitoring is recommended to enable timely intervention should probiotic-related infection happen.

4.2 Probiotics may transfer antibiotic resistance genes in the infant gut

The wide application of antibiotics in infant healthcare has resulted in the antibiotic resistance gene (ARGs) expansion into the probiotic realm. Antibiotic resistance reservoirs in food-grade probiotic strains represent a concern parallel to that of pathogenic bacteria, as mobile genetic elements enable horizontal gene transfer (HGT) to both commensal and pathogens in the gut^[148]. A study analyzing 579 isolates from 12 commonly used probiotic species identified 169 strains carrying ARGs. Among these ARG-positive isolates, 66% contained at least one gene capable of facilitating plasmid conjugation or harboring integrative mobile genetic elements (iMGEs), which allows the potential transfer^[149]. A high level of multidrug resistance was present in lactic acid bacteria (LAB) isolated from Malaysian fermented foods, with 92% of strains showing resistance to β -lactam/cephalosporin antibiotics and other critically important antimicrobial agents^[150]. Even so, while the probability of transferring these traits to other microorganisms is generally low, documented cases of such events have been reported^[129]. The isolated *L. salivarius* and *L. reuteri* can transfer erythromycin and tetracycline resistance genes *erm* (B), *tet* (L), *tet* (M) and *tet* (W) to *E. faecalis* JH2-2 by bacterial conjugation. Notably, the process is replicated during food fermentation, as these resistance genes were disseminated to pathogens *Listeria monocytogenes* and *Yersinia enterocolitica*^[151]. In murine models, kanamycin-resistant plasmids and erythromycin/tetracycline-bearing transposons were transferred from *Enterococcus faecalis* to *E. coli* and *Listeria monocytogenes*^[152]. Additionally, many LAB strains can acquire ARGs from the pAM β plasmid present in specific *Lactobacillus* species like *L. fermentum*, *L. plantarum*, and *L. reuteri*^[153]. Due to the developing infant immune system and recurrent antibiotic exposure create a selective environment wherein probiotic misuse can accelerate the emergence of multidrug-resistant strains, raising the risk of refractory infections. An outbreak of vancomycin-resistant *Enterococcus* (VRE) in a Turkish neonatal intensive care unit (NICU) is highly associated with the probiotic preparation usage. The authors concluded that the acquisition of resistant trait of *Enterococcus* is mediated by probiotics, which necessitates a cautious assessment for safety profile^[154]. Hence, proactive and ongoing surveillance of transferable antibiotic resistance should be implemented in infant-targeted products for both food and pharmaceutical applications prior to their commercial release.

4.3 The toxic substances produced by probiotics

While probiotics synthesize a series of inactive microbial components and bioactive substances that modulate the intestinal physiology and distal organs^[74], their safety assessments must include an evaluation of potentially harmful probiotic-derived compounds, including metabolites, enzymes, extracellular toxins and biofilms (**Fig 3**).

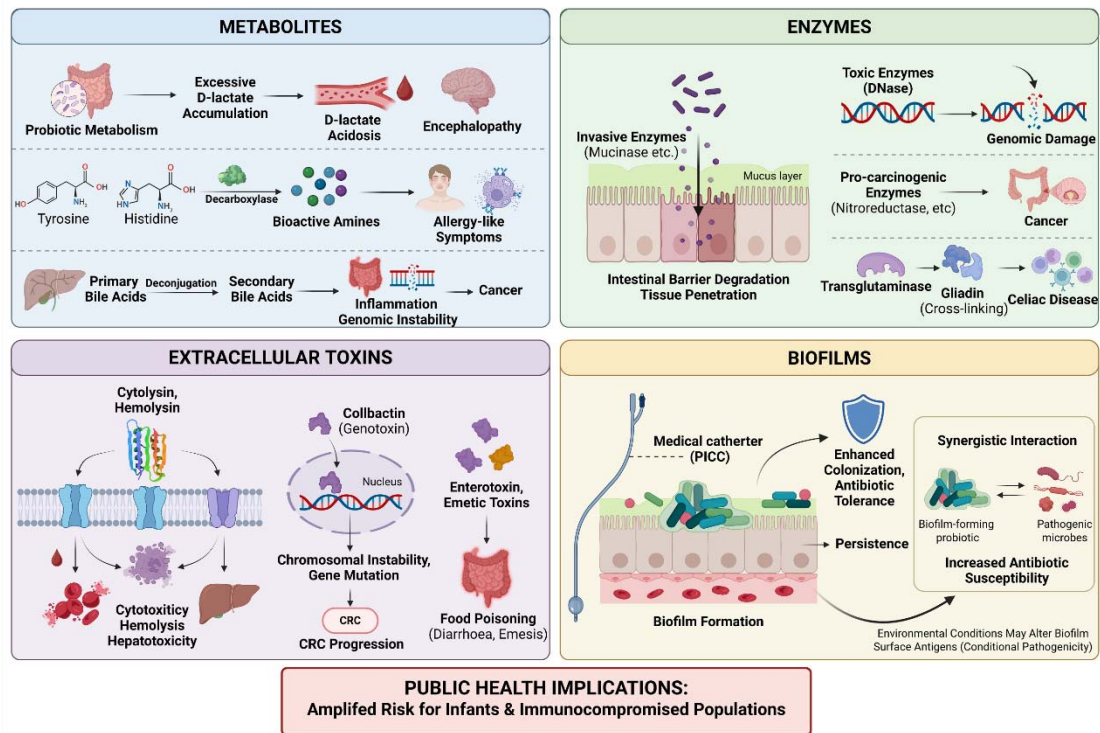


Fig 3. Overview of potentially harmful compounds and mechanisms derived from probiotics. The diagram categorizes and illustrates key safety concerns, including metabolites, enzymes, extracellular toxins, and biofilm formation, all of which require rigorous evaluation in probiotic safety assessment. CRC: Colorectal cancer; PICC: Peripherally inserted central catheter.

Probiotic strains can produce various metabolites with potential toxic effects. For example, several bacterial genera such as *Lactobacillus*, *Weisella*, *Oenococcus*, *Pediococcus*, and *Leuconostoc* can produce D-lactate, an isomer of lactic acid that has limited metabolic clearance in humans^[155]. Excessive accumulation of D-lactate is neurotoxic, which may cause severe D-lactate acidosis and associated encephalopathy. Reports of D-lactate acidosis in healthy individuals are uncommon. However, particular caution is warranted in neonates and in patients who have undergone intestinal surgery followed by short gut syndrome, due to impaired intestinal barrier function and reduced hepatic and renal excretion capacity^[156]. Moreover, some LAB exhibit amino acid decarboxylase activity to convert tyrosine and histidine into bioactive amines^[157]. Even though biogenic amines are vital for biological functions, they may induce allergy-like symptoms (flushing, respiratory distress, headaches, and vomiting et.al) in susceptible consumers when these amines are overproduced by ingested probiotics^[158]. In addition, some bacteria have intrinsic capability to catalyze the deconjugation of primary bile acids into secondary bile acids. It is generally regarded as a beneficial probiotic trait to some extent, as it confers bacterial adaptive advantages under bile acid stress in the gastrointestinal tract^[159]. Conversely, high concentration of secondary bile salt has been regarded as a risk factor implicated in inflammation, oxidative stress induction, and genomic instability, which may collectively contribute to various gastrointestinal malignancies^[160].

Harmful enzymes synthesized by probiotics contribute to their invasive potential and intestinal pathogenicity. Invasive enzymes such as mucinase, gelatinase, urease, and hyaluronidase facilitate bacterial invasion by degrading the intestinal barrier and outcompeting commensal microbiota, thereby enabling

penetration into deeper sterile tissues^[11]. Furthermore, specific probiotic strains are capable of secreting toxic enzymes. The DNase phenotype exhibited by certain probiotics poses potential harm to the host by cleaving phosphodiester bonds in the DNA backbone, leading to genomic damage^[158]. In the intestine, candidate probiotic strains have been shown to secrete various hydrolytic and reductase enzymes, namely nitroreductase, β -glucuronidase, β -glucosidase, and tryptophanase, which exhibit pro-carcinogenic properties^[158]. Probiotics may also secrete transglutaminase, an enzyme capable of crosslinking gliadin, which can induce the immunogenicity associated with celiac disease^[161].

Pathogenicity in probiotic organisms may stem from their ability to generate extracellular protein toxins. *Enterococcus*-derived cytolysin, a peptide bacteriocin, induces cytotoxicity through cytoplasmic membrane pore formation in gram-positive bacteria and β -hemolytic activity against human erythrocytes, while also demonstrating hepatotoxic effects *in vivo*^[162,163]. Additionally, the probiotic *E. coli* Nissle 1917 harbors the polyketide synthase (*pks*) genomic island, which encodes the polyketide-peptide genotoxin colibactin. This bacterial toxin triggers chromosomal instability and gene mutation, playing a pivotal role in colorectal cancer (CRC) progression^[164]. Laboratory analyses have confirmed hemolytic activity in certain LAB. Common members like *L. casei*, *L. paracasei*, and *L. rhamnosus* could secrete hemolysin and hemolysin-III, which lyse erythrocytes and induce hemoglobin release in the bloodstream^[165]. In *Bacillus* species, the production of various enterotoxins and surfactin-like emetic toxins has also been observed, which may lead to food poisoning characterized by diarrhea and emesis^[166].

Biofilms develop *via* the aggregation of microbes and their extracellular products, substantially contributing to microbial persistence through enhanced colonization, stress adaptation, and antibiotic tolerance. A variety of biofilm-capable probiotic strains, including *L. plantarum*, *B. subtilis*, *E. coli*, and *S. cerevisiae*, have been successfully identified and characterized^[167]. It must be weighed that the high stress tolerance of biofilm-state probiotics could result in excessive proliferation within application settings, rendering them challenging to eradicate should adverse events occur. Chiang et al.^[134] reported a case of persistent bloodstream infection in a preterm female infant with a peripherally inserted central catheter (PICC) who was receiving enteral *L. rhamnosus* GG. Cultures from both the catheter tip and the blood yielded the same pathogen, and isolates from both sources exhibited biofilm-forming capability. In contrast, fecal isolates lacked the trait, likely due to an impaired ability to adhere to the intestinal mucosa, leading to their expulsion^[134]. In addition, research is needed to examine whether probiotics may exhibit synergistic interactions with pathogenic bacteria, thereby potentially compromising human health. For instance, biofilm-forming Shiga toxin-producing *E. coli* strains have been observed to cooperate with LAB, resulting in increased antibiotic susceptibility^[168]. Another area requiring attention is the need to investigate whether alterations in environmental conditions can induce modifications in biofilm surface antigens, potentially leading to conditional pathogenicity.

Consequently, the potential for harmful substance production in specific probiotic strains raises substantive public health considerations. Such organisms may provoke or amplify pathological manifestations, with particular risk to infant and immunocompromised populations.

4.4 Probiotics may cause adverse immunological effects

The biofunction of ingested probiotics on immune pathway in infants remains controversial. Accumulating results indicated that probiotics can steer the differentiation of Th1 cells, modulate natural killer (NK) cell activity, and trigger cytokine secretion, thus fostering infantile immune maturation. Excessive immune deviation can lead to immune dysregulation, resulting in autoimmune phenomena or certain inflammatory conditions^[146]. Furthermore, certain metabolic enzymes produced by probiotics, for example, transglutaminase, can crosslink with gliadin, thereby inducing the onset of celiac disease^[161]. However, such risks remain speculative, with no documented evidence of their occurrence in infants to date.

In recent decades, the rising incidence of allergic disorders has emerged as a significant public health burden. Probiotics have gained considerable attention as a novel anti-allergic intervention; however, substantial evidence does not support their efficacy in either prevention or treatment of allergic diseases. Conversely, probiotic formulations may cause may promote immunological hyperreactivity, elevating the risk of multiple allergic conditions including wheezing bronchitis^[169], atopic sensitization^[170,171], allergic rhinitis, and severe asthma^[172]. It is noteworthy that this phenomenon has not been clearly elucidated and often occurs incidentally with contradictory results. Therefore, the reliability of the concern cannot be conclusively determined. As immune tolerance in infants is shaped by continuous challenges from external antigens, Sanders et al.^[127] proposed that high-dose use of limited probiotics during infancy fails to simulate natural gut colonization patterns and may thereby promote a heightened sensitization to antigens, especially in atopic population.

4.5 Probiotic-mediated alterations in drug metabolism and toxicity

The impact of gut microbiota on drug bioavailability, bioactivity, toxicity, and consequently on individual drug response, raises additional concerns regarding gut-derived probiotics^[173]. Multiple mechanisms have been identified, including the modification of gastrointestinal conditions through SCFAs production and alterations in transit time or mucus thickness; the regulation of intestinal drug transporter expression; the restructuring of gut microbial communities; the modulation of bacterial enzyme activity *via* induction or suppression; and the direct utilization of drugs as microbial growth substrates^[174]. *In vitro*, Shen et al.^[175] found that *L. paracasei* and *L. plantarum* can metabolize the lipid-lowering drug lovastatin into lovastatin hydroxy acid, thereby reducing its therapeutic efficacy. Matuskova et al.^[176] further investigated the impact of probiotics on the *in vivo* bioavailability of amiodarone. Administration of *E. coli* strain Nissle 1917 for 7 days enhanced the absorption and bioavailability of amiodarone in rats. Several mechanisms may explain this effect, including the production of SCFAs that facilitate drug ionization and enhance its diffusion across the intestinal mucosal layer. Additionally, the probiotic may have reduced levels of the inflammatory cytokine TNF- α , thereby upregulating the expression of drug transporters^[176]. Moreover, various anaerobic beneficial

bacteria produce β -glucuronidase, which can deconjugate the drug and promote the enterohepatic recirculation of parent drugs or toxic metabolites. The liberated agents (e.g., nonsteroidal anti-inflammatory drugs) may accumulate in the intestinal lumen and contribute to drug-induced enteropathy^[177,178].

4.6 Inadequate oversight of probiotic market may confuse consumers

Increased awareness of the possible benefits of probiotics has fueled exponential growth in existing commercial products across various formats. A diverse array of infant probiotic goods, such as infant formula, powders, drops, sprays, and functional foods, has entered the market with the aim of supporting health and well-being. Therefore, verifying the authenticity of probiotic products is critical. However, studies conducted worldwide have consistently revealed widespread issues in infant probiotic products, including contamination, inaccurate labeling, and exaggerated health claims.

As a result, purchasers are likely to blindly purchase ineffective or even unsafe probiotic commodities, thereby intensifying the existing crisis of confidence in the marketplace.

4.6.1 Contamination of probiotic products may cause undesirable events

Contamination by pathogenic or non-pathogenic microbes due to processing errors or improper storage represents a common and particularly concerning issue. Such contamination not only alters the sensory properties of the product but also undermine its safety. A seminal case from 2015 involved a preterm infant who developed severe gastrointestinal mucormycosis and subsequently died after ingesting a probiotic dietary supplement contaminated with fungi of *Rhizopus oryzae*^[179]. In another study, ribosomal RNA sequencing–based assessment of commercial probiotic products intended for infants identified contamination with non-viable fungi and inconsistencies between labeled and actual bacterial type^[180]. Given that probiotic supplements are commonly used to support immune development and health promotion in infants, microbial contamination in these products poses a particularly serious risk to the vulnerable infant population upon ingestion.

4.6.2 Inaccurate labeling compromises probiotic products authenticity and safety

A probiotic product is considered authentic when its content matches the claims on its label. However, approximately 60% of retail probiotic products are reported not comply with their label information, particularly concerning bacterial identity and the number of viable bacteria within the stated shelf life^[181].

Mislabeling may result from inaccurate or incomplete taxonomic description of probiotic strains. Considering that species-dependent and often strain-specific nature of probiotic functions, it is essential for suppliers and manufacturers to precisely verify the strains present in their commercial formulations^[182]. Functionally inadequate or misidentified probiotics pose potential risks to both product credibility and consumer health. *Bifidobacterium*-containing formulations are commonly used to support infant development and nutrition. Lewis et al.^[183] employed DNA-based and culture-dependent approaches to identify *bifidobacterial* species in 16 commercially available probiotic products. Their results indicated that the actual *bifidobacterial* strains in most products did not align with the listed ingredients, with only one product

matching its labeled *bifidobacterial* claims^[183]. A recent analysis of probiotic products in Ghana showed concerning labeling inaccuracies. Only 74% of probiotic supplements accurately reflected the labeled microbial composition, while compliance among probiotic food products was even lower, at just 44%^[184].

To ensure that commercial products deliver the claimed health benefits, prerequisite labeling should accurately specify the concentration of viable bacteria and, where applicable, indicate the quantity of non-viable bacterial cells. Inaccurate viability labeling may be fraudulent or result from improper storage that reduces probiotic cell activity along the production-consumption chain, thereby potentially compromising the functionality and efficacy of probiotic supplements^[185]. 16S rRNA sequencing by Morovic et al.^[186] revealed that 33% (17 of 52) of analyzed products contained colony forming unit (CFU) counts substantially lower than declared, even before the stated expiration date. Notably, non-viable probiotic cells or their fragments may retain partial metabolic activity and exert associated beneficial outcomes, which are often classified as postbiotics^[187]. On the other hand, it should also be recognized that the presence of undesirable dead bacteria and their components could potentially trigger immune responses—a particular concern in immunologically immature infants.

4.6.3 Unregulated health claims may raise consumers' concerns

As previously discussed, probiotics exhibit multifaceted effects on infants' physiology, encompassing health maintenance and disease alleviation. In order to legally assert structure-function claims regarding the nutritive properties of dietary supplements, manufacturers are not required to obtain pre-approval from the US Food and Drug Administration (FDA)^[129]. In this context, consumers often struggle to verify the validity of such health claims. This may lead to misguided purchases or excessive use of probiotic products, potentially exposing them to the unpredictable health hazards. While high-quality clinical trials have established the efficacy of certain probiotics for specific conditions, the market continues to see a range of cleverly marketed products, many of which lack robust evidence for their claimed health benefits. Furthermore, some studies rely on *in vitro* or animal models to claim the safety and functionality of probiotics. While such approaches can reveal certain aspects of metabolism and toxicity, they often fail to accurately predict effects in diverse infant populations due to the absence of key host and microbiome variables. Moreover, even in clinical settings, many current RCTs on probiotics suffer from methodological limitations, including flaws in experimental design, endpoint selection, analytical criteria, and susceptibility to placebo effects, which may introduce bias and compromise the validity of efficacy outcomes. To address this issue, the unrestricted use of the term “probiotic” or any implied health claims on food labels should no longer be permitted.

5. Future perspectives and strategies for infant probiotics

While incomplete safety data and insufficient regulatory oversight have justifiably raised concerns, the undeniable value of probiotics in infant nutraceutical and pharmaceutical fields continues to play an indispensable role in promoting early-life health. Here we propose several strategic approaches to address the current limitations of conventional probiotics and guide future research directions for novel probiotic development (Fig. 4).

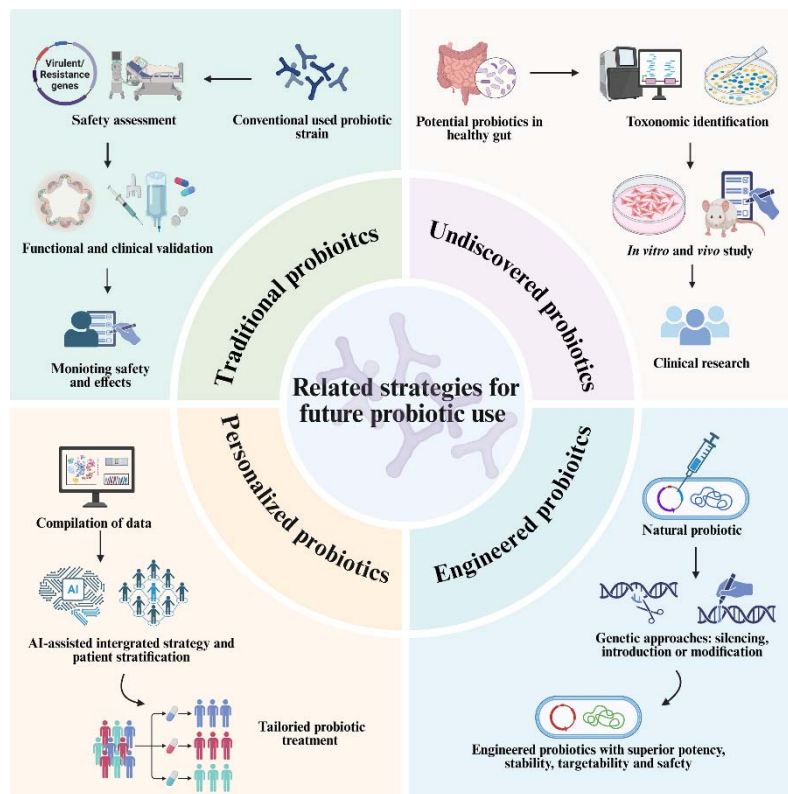


Fig. 4. Related strategies and future directions for probiotic researches. It is imperative to conduct comprehensive reassessments of conventional used probiotics and to systematically identify novel strains with enhanced therapeutic and safety profile. Moreover, employing gene editing technologies and advancing personalized probiotic formulations are also needed to enhance the probiotic performance.

Enhanced safety profiling of conventional infant-use probiotics like *Bifidobacterium* and *Lactobacillus* requires more systematic strain-level evaluation. Comprehensive risk assessment must include screening for antibiotic resistance genes, hemolytic activity, specific metabolic traits (e.g., D-lactate and biogenic amine production), virulence enzymes, and invasive factors. Prior to probiotic administration in infants, careful consideration of host risk factors including prematurity, compromised intestinal integrity, and immunodeficiencies is also essential, as these conditions may impair the ability to counteract pathogenicity of probiotics and increase the risk of bacterial translocation. Moreover, the limited understanding of how probiotics engage with the host's microbiome and immune system hinders their therapeutic effectiveness in clinics for infants. Some evidence supporting the use of certain probiotics for adult diseases has not been adequately extended or systematically investigated in infant populations. For example, species such as *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* can act as exogenous sources of intestinal lactase, thereby enhancing lactose hydrolysis and colonic fermentation efficiency^[188], which underlies their widespread use in the management of adult lactose intolerance^[189]. To overcome these barriers, multi-omics analyses should be leveraged to pinpoint strains linked to key infant disease phenotypes, thereby building a targeted probiotic repository for functional and clinical validation. Integrative multi-omics approaches combining metagenomics, transcriptomics, metabolomics, and host immune profiling may help clarify strain-specific functions and host–microbe interactions at high resolution^[190]. Importantly, future studies should incorporate causal inference frameworks to distinguish true therapeutic effects from confounding associations commonly observed in observational infant cohorts. In addition, advanced infant intestinal simulation and microbial

co-culture models provide mechanistic platforms to validate hypotheses derived from multi-omics profiling and causal inference, enabling controlled interrogation of complex strain–host–microbiome interactions. For clinical translation, evidence from adult studies must be cautiously extrapolated to infant populations, while concurrently establishing infant-specific, risk–benefit assessment frameworks to accelerate the application of live biotherapeutics in the treatment of infantile diseases.

Isolation and characterization of new probiotic strains constitute a persistent and critically important research priority. The intensive investigation into commensal bacteria for combating specific diseases, empowered by advanced functional profiling technologies, has unveiled a rich reservoir of novel probiotics within the human gut microbiome^[191]. Particular species such as *Ruminococcus bromii*, *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Anaerobutyricum hallii* have been identified as new probiotic candidates, presenting notable abundance as colonists within the healthy human gut ecosystem^[191]. Several candidates have recently garnered great interest due to their capacity to reshape gut ecology, regulate host metabolism, and mitigate inflammatory responses, with demonstrated efficacy in preclinical models in diabetes, obesity, and colitis^[192]. However, unlike generally recognized as safe (GRAS) conventional probiotics, most novel strains lack established safety history, precluding their entry into clinical trials. Even when investigated, such studies remain exploratory in nature, characterized by limited sample sizes and exclusion of vulnerable populations such as infants. Future research must emphasize systematic screening of candidate probiotics using integrated phenotypic and genotypic approaches to enable clear taxonomic identification. Before stepping into clinics and food market, thorough *in vitro* and *in vivo* studies are indispensable for elucidating their functional mechanisms and generating definitive safety evidence.

Despite the documented benefits of live natural probiotics in diverse infant diseases, there remains a lack of targeted, safe, and sustained therapeutic options for severe intestinal disorders or inborn metabolic diseases in this vulnerable population. Hopefully, the genetic adaptability inherent in probiotic systems opens new avenues for their engineered utilization in biotechnology. In contrast to conventional probiotic treatments, engineered probiotics can deliver therapeutic outcomes with greater reliability. Through the removal of adverse traits and the enhancement of beneficial functions, they exhibit stronger probiotic potential^[193]. More importantly, these microorganisms are genetically modified to synthesize targeted molecules or bioactive substances with disease-specific therapeutic effects, thereby enhancing their clinical value^[194,195]. For instance, yeast probiotics have been engineered to express a hypersensitive human P2Y2 receptor coupled with apyrase secretion, forming a self-regulated circuit that senses and degrades pro-inflammatory extracellular adenosine-5'-triphosphate (ATP). This self-tunable engineered yeast markedly attenuated intestinal inflammation in inflammatory bowel disease (IBD) models, offering a novel direction for early intervention^[196]. In a Phase 1/2a trial for phenylketonuria (PKU), the engineered *E. coli* Nissle 1917 strain SYNBI618 was engineered to express phenylalanine ammonia lyase, L-amino acid deaminase, and a high-affinity phenylalanine transporter in the bacterial chassis. The strain showed dose-dependent phenylalanine metabolism and a favorable safety profile in PKU patients, supporting its potential as an oral

therapy^[197]. In this way, such live biotherapeutic carriers enable the sustained release of targeted modulators within the intestinal lumen, thereby reducing the required dosage and minimizing systemic toxicity, a feature of particular importance for the safety of infants whose immune systems are still immature. By now, research on engineered bacterial strains in clinics remains in its infancy, with limited infant-specific safety data and minimal long-term follow-up evidence in other populations. Therefore, incorporating rigorous causal study designs and mechanistic validation is essential to ensure that engineered functions translate into predictable clinical benefits without disrupting developmental trajectories.

Probiotic efficacy is recognized as both host-specific and strain-dependent; thus, while their use as a therapeutic adjunct or nutritional supplement is justified, they cannot be regarded as a universal solution^[198]. This limitation highlights the emerging role of precision nutrition, which integrates host-specific biological and environmental data to guide targeted probiotic interventions and improve therapeutic predictability. Personalized probiotics differ conceptually from conventional probiotics by targeting individualized host benefits based on a person's unique microbiome profile and specific gut condition. The development of personalized probiotic regimens relies on a multi-omics platform (including genomics, metabolomics, and proteomics) combined with artificial intelligence (AI)-driven algorithms and data-integration strategies to enable precise strain selection. By applying computational approaches, researchers can predict candidate strains through analysis of strain-level genomic features, protein expression patterns under varying gut conditions, or metabolite production profiles. These molecular signatures, identified under specific physiological states, allow probiotic strains to be categorized according to desired functional traits prior to administration, thereby supporting targeted colonization within the host microbiota^[199]. Additionally, variations in the microbiome and host factors such as diet, age, and lifestyle, allow populations to be stratified into distinct subtypes. For instance, clinical information and microbial signatures of infants can be used to screen and classify them into high-risk and disease-affected groups^[200]. Despite promising conceptual advances, truly standardized personalized probiotic interventions have not yet been fully realized. However, by integrating individual-specific clinical data with AI-based analysis, tailored therapeutic strategies can be generated for different infants, supported by ongoing assessment of disease progression and health monitoring.

6. Conclusion

In conclusion, the infant gut microbiota undergoes dynamic succession and remains highly susceptible to external perturbations. Various extrinsic factors can induce dysbiosis, which is closely linked to health outcomes and disease susceptibility throughout infancy and into later life. In this context, the field of probiotic research has made substantial advances, offering promising avenues for therapeutic intervention across multiple domains of infant health. Accumulating evidence supports the efficacy of probiotics in managing certain gastrointestinal, neurodevelopmental, immunological, nutritional, and other health-related conditions. However, these perspectives have recently been challenged, revealing that probiotic use in infants is not uniformly beneficial. Potential safety threats and inadequate regulatory oversight may pose risks to this

vulnerable population, necessitating thorough evaluation before widespread adoption can be justified. Therefore, further investigation remains crucial to fully elucidate its therapeutic value and optimize its practical integration into healthcare protocols. With further refinement and validation, probiotic-based interventions could potentially provide a safe, efficacious, and holistic strategy for treating infantile disorders and enhancing their overall health outcomes.

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Declaration of competing interest

The authors declare no competing interest

Data availability

Data will be made available on request.

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