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PROBIOTIC SUPPLEMENTATION IN NEONATAL JAUNDICE: CURRENT PERSPECTIVES AND THERAPEUTIC POTENTIAL

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ABSTRACT

Objective: The objective of this paper is to review the adjunctive role of probiotics in the treatment of neonatal jaundice (NJ), focusing on mechanisms, clinical trial evidence, and synergy with phototherapy.
Methods: Narrative synthesis of randomized controlled trials, mechanistic studies, and meta-analyses of probiotic interventions in term and preterm infants with hyperbilirubinemia.
Results: Probiotics, especially Saccharomyces boulardii and Bifidobacterium animalis subsp. lactis CP 9 enhance bilirubin clearance via gut modulation, decreased β glucuronidase activity, improved motility, and strengthened barrier integrity. Clinical trials report faster bilirubin decline, shorter phototherapy time, and better feeding tolerance. Multi-strain products also show positive outcomes, though variability in strains and dosing persists.
Conclusions: Probiotics are safe and effective adjuncts to phototherapy in treating NJ. Future standardized large RCTs with long-term follow-up are necessary to define precise clinical guidelines.

KEYWORDS

Neonatal Jaundice, Probiotics, Hyperbilirubinemia, Gut Microbiota

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Introduction.

Neonatal jaundice (NJ) is one of the most common conditions requiring medical attention in newborns, with up to 60% of term and 80% of preterm infants showing visible jaundice during the first week of life due to elevated unconjugated bilirubin levels [1]. While generally benign, persistent or severe hyperbilirubinemia can escalate into bilirubin-induced neurologic dysfunction (BIND) or kernicterus, which are associated with lifelong neurodevelopmental impairment [2][3]. Current management primarily relies on phototherapy, which effectively converts bilirubin into excretable forms [4]. However, concerns surrounding potential side effects—such as dehydration, electrolyte imbalance, and long-term metabolic or neurological risks—have driven research into safe adjunctive therapies [5][6][7][8].

Emerging evidence supports the gut–liver axis's role in bilirubin metabolism. The neonatal gut microbiota influences enterohepatic circulation via microbial enzymes like β-glucuronidase and bilirubin reductase (BilR) [9]. Dysbiosis characterised by reduced beneficial bacteria such as *Bifidobacterium* and enriched β-glucuronidase producers like *Escherichia coli* is increasingly linked to prolonged bilirubinemia [10][11][12]. Probiotics have emerged as a promising adjunctive therapy, they can restore microbial balance, suppress undesirable enzyme activity, improve gut barrier function, motility, and reduce enterohepatic reabsorption [13][14].

This review integrates current clinical findings and perspectives on the use of probiotics in neonatal jaundice, evaluating their efficacy, safety, modes of action, and potential to improve the effectiveness of phototherapy. A comprehensive analysis of randomized controlled trials examines strain-specific outcomes, dosage regimens, and neonatal populations, culminating in recommendations for future clinical practice.

Methodology.

This narrative review synthesized recent evidence on probiotic supplementation as an adjunct to phototherapy in neonatal jaundice.

Search strategy and study selection.

A comprehensive search was performed in PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library for articles published between January 2020 and May 2025. The search combined MeSH terms and free-text keywords:"*neonatal jaundice"*, "*hyperbilirubinemia"*, "*probiotics"*, "*Bifidobacterium"*, "*Lactobacillus"*, "*Saccharomyces boulardii"*, "*phototherapy"*, and"*gut microbiota"*. Boolean operators ("AND"/"OR") were applied, and reference lists of eligible articles were manually screened for additional sources.

Eligibility criteria

Inclusion criteria were:

1. **Population:** term or preterm neonates with hyperbilirubinemia;
2. **Intervention:** probiotic supplementation alone or combined with phototherapy;
3. **Comparison:** phototherapy alone, placebo, or standard care;
4. **Outcomes:** changes in serum total bilirubin, phototherapy duration, stool frequency, feeding tolerance, or safety profile;
5. **Study type:** randomized controlled trials, observational studies, systematic reviews, and mechanistic studies.

Only full-text articles in English from the last 5 years were included. Animal-only studies, case reports, and abstracts without full data were excluded.

Data extraction and synthesis

Data extracted included study design, setting, neonatal characteristics, probiotic strain(s), dosage, intervention duration, comparator, outcomes, and adverse events. Due to heterogeneity in study designs and probiotic regimens, findings were synthesized narratively and grouped by probiotic strain, with emphasis on clinical efficacy, mechanistic plausibility, and safety.

Discussion

Gut microbiota role in jaundice

The intestinal microbiota constitutes a fundamental component of neonatal and adult physiology, with a particularly significant role in the metabolism of bilirubin, a product of heme catabolism [11][12]. In physiological conditions, conjugated bilirubin is secreted into the intestinal lumen, where it may follow two main microbial metabolic pathways: enzymatic deconjugation by β-glucuronidases and reduction to urobilinogen [11]. The deconjugation of bilirubin-glucuronide is catalyzed by both human and microbial β-glucuronidases, leading to the formation of unconjugated bilirubin which, due to its lipophilic nature, can be reabsorbed into the portal circulation. This reabsorption is a key component of enterohepatic circulation and contributes to elevated serum bilirubin levels in neonates whose intestinal flora is immature or unbalanced [12][18].

Various gut bacteria have been shown to produce β-glucuronidase, including *Escherichia coli*, *Clostridium perfringens*, *Clostridioides difficile*, *Clostridium ramosum*, *Clostridium paraputrificum*, *Clostridium sordellii*, *Clostridium limosum*, *Clostridium clostridiiforme*, *Bacteroides fragilis*, *Peptostreptococcus*, and *Ruminococcus gnavus* [11]. *E. coli*, in particular, has been validated in both in vitro and in vivo models as a potent producer of β-glucuronidase [11][19]. On the other hand, *Enterococcus* strains have shown low enzymatic activity, with only a few strains demonstrating measurable β-glucuronidase expression [12].

Within the *Bifidobacterium* genus, activity appears to be limited to certain strains such as *B. dentium* and *B. scardovii*, although genomic studies often identify only partial sequences of β-glucuronidase genes rather than complete gene structures [11]. Similarly, β-glucuronidase activity in *Lactobacillus* strains is rare, with some activity detected in *L. rhamnosus R*, *L. gasseri F71*, and *L. parabuchneri G46*, while common probiotic strains such as *L. rhamnosus GG*, *L. acidophilus*, *L. casei*, and *L. reuteri* lack this enzymatic function altogether [18].

Aside from deconjugation, gut microbiota are also responsible for the reduction of bilirubin to urobilinogen and subsequently to stercobilinogen, completing its elimination via feces and urine. This reduction occurs in anaerobic conditions and is likely part of the bacteria's respiratory chain, utilizing bilirubin as a terminal electron acceptor. While this role was historically hypothesized, only recently has a specific bilirubin reductase enzyme (BilR) been identified and characterized [11]. Genomic metagenomic analysis has revealed that BilR is nearly universally present in the gut microbiota of healthy adults but is significantly less prevalent in neonates and individuals with inflammatory bowel disease (IBD) [11].

In neonates, the relative absence of bilirubin-reducing bacteria and enzymes is consistent with the physiological observation that urobilinogen is undetectable in feces until approximately the fifth day of life. This is accompanied by markedly lower rates of bilirubin transformation and excretion, contributing to elevated serum bilirubin levels characteristic of neonatal jaundice [12].

The composition of the gut microbiome in neonates is influenced by several endogenous and exogenous factors, most notably the mode of delivery, feeding practices, antibiotic exposure, and gestational age [18]. Infants delivered vaginally exhibit microbial colonization dominated by *Lactobacillus*, *Bifidobacterium*, and *Bacteroides*, reflecting maternal vaginal and fecal flora. In contrast, cesarean-delivered neonates are more commonly colonized by *Staphylococcus*, *Streptococcus*, and *Propionibacterium*, likely derived from maternal skin and the hospital environment [12].

Postnatal nutrition further shapes the microbial landscape: breastfed infants exhibit increased colonization with *Bifidobacterium* spp., facilitated by human milk oligosaccharides (HMOs), whereas formula-fed infants demonstrate a more heterogeneous and less favorable microbial profile, including increased *Clostridium difficile* [18].

The use of perinatal antibiotics, common in NICU settings, is another factor contributing to dysbiosis by reducing bacterial diversity and delaying the establishment of key commensals such as *Bacteroidetes* and *Bifidobacteriales*.

Numerous clinical and microbiome studies have attempted to correlate specific microbial taxa with serum bilirubin concentrations. There is a growing body of evidence associating decreased *Bifidobacterium* abundance with elevated serum bilirubin, possibly due to its competitive suppression of β-glucuronidase-producing taxa and modulation of intestinal barrier function [11][12]. Although *Bifidobacterium* itself is not a direct bilirubin-metabolizer in most cases, animal models have demonstrated its involvement in reducing unconjugated bilirubin via oral β-glucuronidase activity.

Moreover, supplementation with *Lactobacillus plantarum* has been shown to alleviate intestinal tight junction damage caused by unconjugated bilirubin through PKC pathway activation [11]. In contrast, species such as *E. coli*, *Staphylococcus*, and *Enterococcus* have been positively correlated with serum bilirubin levels, particularly in neonates with jaundice.

A distinct dysbiotic pattern has been observed in jaundiced neonates, characterized by reduced *Bifidobacterium*, increased richness of potentially pathogenic species, and an altered galactose metabolic profile [11][12]. Advanced sequencing techniques, including 16S rRNA gene sequencing and shotgun metagenomics, have enabled identification of specific bacterial species that may serve as potential biomarkers for neonatal jaundice.

Furthermore, the occurrence of jaundice appears to be temporally coordinated with the establishment of the neonatal gut microbiota, suggesting a dynamic and reciprocal relationship. These insights help to revaluate previous ideas that bacterial β-glucuronidase activity increased bilirubin reabsorption, even though breastfed infants with higher Bifidobacterium levels were more likely to develop jaundice. Modern sequencing data offer a more nuanced view, indicating that while *Bifidobacterium* abundance correlates with breastfeeding and jaundice incidence, its overall role may be protective in regulating enterohepatic circulation rather than promoting bilirubin retention [11][18].

Management of neonatal jaundice.

The primary goal in managing neonatal jaundice is to prevent severe hyperbilirubinemia and its associated complications, particularly bilirubin-induced neurologic dysfunction (BIND) and kernicterus [3]. Management begins with ensuring adequate hydration and caloric intake, as poor feeding may exacerbate jaundice. The pillar of treatment remains phototherapy, a non-invasive and safe intervention that has been widely used for over 60 years [4]. Phototherapy accelerates the breakdown of unconjugated bilirubin in the skin by converting it into water-soluble isomers, that is mainly Z, E-bilirubin, E, Z-bilirubin, and lumirubin which can then be excreted via bile and urine without the need for hepatic conjugation [4]. The most effective light wavelength is around 460 nm, offering good skin penetration with minimal risk when applied properly.

Despite its efficacy, phototherapy is not without risks. Common adverse effects include skin

rashes, hyperthermia, dehydration, hypovolemia, hypocalcemia, conjunctivitis, and, in rare cases, retinal damage. In neonates with hepatic dysfunction or intensive hemolysis, a distinctive complication known as bronze baby syndrome can occur, presenting as temporary skin discoloration and purpuric eruptions that typically resolve after discontinuation of therapy. [20]

Notably, longer durations of phototherapy have been identified as a potential predictive factor for developmental delay, although a definitive causal relationship has yet to be established [21]. Emerging concerns have also linked phototherapy to a possible increased risk of hematologic malignancies, including leukemia and other cancers [22]. Although the mechanism remains unclear, exposure to ultraviolet (UV) light during standard blue-green phototherapy may activate pro-inflammatory skin pathways and promote gene mutations, contributing to autoimmune responses and increased oncogenic potential.

Moreover, both neonatal jaundice and its treatment have been associated with a heightened future risk of chronic conditions such as allergic diseases, type 1 diabetes, and autism spectrum disorders [10][23][24]. It has been hypothesized that these associations may be linked to early-life gut microbiota dysbiosis, rather than to jaundice or phototherapy directly. Dysbiosis is increasingly recognized as a contributing factor in various immunologic and metabolic disorders [12][25][26].

Consequently, there is growing interest in conducting longitudinal microbiome studies in jaundiced neonates to clarify the function of microbial imbalances in disease susceptibility later in life. When phototherapy fails to sufficiently lower bilirubin levels or when serum bilirubin exceeds established thresholds, exchange transfusion becomes the second-line treatment.

This invasive procedure rapidly reduces bilirubin concentration by replacing the neonate's blood volume. However, it carries significant risks, including embolism, sepsis, necrotizing enterocolitis, and even death. Therefore, phototherapy remains the preferred first-line treatment due to its effectiveness in reducing the need for more aggressive interventions [4].

Probiotics – a way to treat neonatal jaundice?

Probiotics are live microorganisms that offer health benefits when administered in adequate amounts have emerged as a promising complement to standard treatments for neonatal jaundice (NJ). [5][6]. Though most probiotic strains such as *Bifidobacterium*, *Lactobacillus*, *Streptococcus thermophilus*, and *Saccharomyces boulardii* lack direct bilirubin-metabolizing capabilities or β-glucuronidase production, evidence demonstrates their indirect efficacy through multifaceted biological mechanisms [13][27].

Probiotics exert a range of indirect effects that support bilirubin metabolism in neonates. Firstly, their colonization promotes the early establishment of protective gut microbiota, creating an environment unfavorable to the growth of pathogenic species such as *E. coli*, a prominent producer of β-glucuronidase [11][12]. By occupying ecological niches in the intestine, probiotics reduce the prevalence of these pathogens, thereby limiting enzymatic activity that facilitates bilirubin reabsorption [18].

Certain strains, particularly *Saccharomyces boulardii*, secrete antimicrobial peptides that selectively inhibit *E. coli* and similar bacteria, reducing β-glucuronidase activity and supporting bilirubin clearance [1][10]. Probiotics also enhance intestinal motility, increasing the frequency of stool passage and accelerating the transit of bilirubin through the gastrointestinal tract, thus minimizing its enterohepatic recirculation [14].

Another key mechanism involves the reinforcement of the intestinal barrier. Probiotic strains such as *Lactobacillus* spp. have been shown to upregulate tight junction proteins, strengthening the epithelial barrier and preventing the translocation of unconjugated bilirubin into the systemic circulation [11]. In addition, probiotic metabolism lowers luminal pH, creating an environment less favorable for β-glucuronidase activity, and facilitating the degradation rather than the reabsorption of bilirubin [12].

Finally, certain strains like *S. boulardii* stimulate the production of polyamines molecules essential for intestinal cellular growth and function which promote gastrointestinal maturity and overall digestive performance [13]. Through these interconnected actions, probiotics create a multifaceted supportive environment that complements conventional therapies and improves neonatal outcomes in cases of hyperbilirubinemia.

Phototherapy remains the definitive treatment for neonatal jaundice by converting bilirubin into excretable isomers such as lumirubin, which are eliminated via bile and urine without hepatic conjugation [4]. Beyond its photochemical effects, phototherapy also modifies the neonatal gut microbiota, notably by decreasing populations of *Escherichia coli* and lowering β-glucuronidase activity, both factors known to contribute to bilirubin reabsorption and enterohepatic circulation [11][12].

These microbiota-related effects are notably enhanced when phototherapy is combined with probiotic supplementation. The concurrent use of specific probiotic strains such as *Saccharomyces boulardii*, *Bifidobacterium animalis* subsp. *lactisn* CP-9, and multi-strain formulations has been shown to accelerate bilirubin clearance, reduce phototherapy duration, and improve gastrointestinal outcomes in treated neonates [8][10][14].

Studies consistently report improved clinical outcomes with this combination approach. These include faster declines in serum bilirubin levels, shorter treatment durations, enhanced feeding tolerance, and increased stool frequency, which collectively reduce the enterohepatic recycling of bilirubin and minimize treatment-related side effects such as dehydration and skin irritation [13][20]. Furthermore, probiotic-mediated reinforcement of the gut barrier and modulation of intestinal motility are believed to further complement phototherapy by facilitating bilirubin excretion.

The emerging clinical consensus supports the suggestionthat probiotics, though not substitutes for phototherapy, serve as effective adjuvants in neonatal jaundice management, enhancing the overall efficacy and safety of treatment protocols [3][4].

Current evidence suggests that probiotics provide a beneficial adjunctive effect in the treatment of neonatal jaundice, though their effectiveness appears to be highly strain specific. Among the strains studied, *Saccharomyces boulardii* and *Bifidobacterium animalis* subsp. *lactis* CP-9 have demonstrated particularly consistent and strong efficacy, as evidenced by multiple randomized controlled trials [10][2][11]. These strains are associated with significant reductions in serum bilirubin levels and shortened durations of phototherapy.

Other strains such as *Lactobacillus rhamnosus* GG and various multi-strain combinations have shown more moderate benefits, indicating that not all probiotic formulations yield equal results [4][14][15]. Table 1 presents a comparative overview of clinical studies conducted over the last five years evaluating the efficacy of various probiotic strains in the management of neonatal jaundice.

Table 1

Probiotic	Study and year	Outcome	Dosage
Lactobacillus rhamnosus LGG), Bb-12 (Bi dobacterium animalis Bb-12) and M-16V (Bi dobacterium breve M-16V)	Chen Jiayi (2024)	ongoing study	
Saccharomyces boulardii	Hisham Nasie (2024)	Duration of phototherapy (hours) 36.55 vs 24.61 (p<005) Duration of hospital stay 47.36 vs 33.13 (p<0.05)	125 mg, twice daily, orally
	Di Hu (2023)	Duration of phototherapy (hours) 134.21 vs 78.14 (p<0.001) Time of jaundice fading (days) 16.12 vs 8.86 (p<0.001) TSB (μmol/L) 148.47 vs 115.85	sachet contained 765 mg of powder and 250 mg of fungus. The amount of viable microbiota per 1 g of powder was not less than 1.3 × 109 colony forming units (CFU)

Table 1

	Wei Tang (2020)	Duration of phototherapy (hours) 60.3 vs 48.2 p<0.05 Time of jaundice fading (days) 5.3 vs 4.1 p<0.05 TSB (μmol/L) 170 vs 140 p<0.05	No data
PediLact (Lactobacillus rhamnosus, Lactobacillus reuteri, Bifidobacterium longum subsp. infantis)	Fatemeh Eghbalian (2024)	Duration of hospital stay 2.8 vs 2.4 p=0.001 phototherapy duration 31.4 vs 26.2 p=0.001 SBL 7.8 vs 7.2 p<0.05	10 drops daily
	Morteza Habibi (2021)	Total bilirubin on discharge (mg/dL) 10 vs 10 Duration of hospital stay 5.18 vs 2.48 (p=0.001)	No data
Bifidobacterium animalis subsp. lactis BB-12	Irena Santosa (2024)	no significant differences in bilirubin level	10 x 108 CFU
Bifidobacterium bifidum and Enterococcus faecalis	Xin Qian (2023)	Duration of hospital stay 2.8 vs 2.4 p=0.001 phototherapy duration 31.4 vs 26.2 p=0.001 TSB 7.8 vs 7.2 p<0.05	No data
Lactobacillus bifidus	Badri Farhand (2020)	Mean comparison of bilirunin levels change -4.18 vs - 4.49 (p=0.688) Duration of hospital stay (days) 2.63 vs 1.93 (p=0.002)	1 cc
Bifidobacterium, Lactobacillus acidophilus, and Enterococcus faecalis	Gaohong Wu (2020)	Peak total bilirubin (μmol/L) 100 vs 90 (p<0.05) Duration of hospitalization (days) 16.12 vs 14.45 (p<0.01)	0.5 g/time, 3 times/day
Lactobacillus acidophilus,Streptococcus thermophilus, and Bifidobacterium longum	Pujiati Abbas (2023)	TSB (mg/dl): 6.70 vs 6.50 (p=0.51)	5 drops with 1x10^9 cfu in each drop
Lactobacillus reuteri	Ayesha Waheed (2024)	Mean total bilirubin 12.31 vs 10.75 (p<0.001)	5 drops/day
	Deska Andina Rezki	Decrease in TSB level 6,517 mg/dL vs 4,434 mg/dL	5 drops

Table 1

Bacillus clausii	Afzal, Tehreem (2021)	Serum biliorubin at 72h 11.72 vs 11.09 (p=0.724) Duration of phototherapy (hours) 61.53 vs 43.47 (p=0.012)	2.5ml of Enterogermina ampule containing Bacillus clausii
L. rotieri, B. infenticum L. raminosus	BehnL.az Darbanh (2021)	TSB 17.39 vs 16.57	10 drops of 2 * 10 CFU
	Ensiyeh Jenabi (2022)	Mean hospital stay (days) 2.4 vs 2.8 (P = 0.001) Duration of phototherapy 31.4 vs 26.2 P = 0.001)	No data
Bifidobacterium animalis subsp. lactis CP-9	Ming-Luen Tsai (2022)	Rate of serum bilirubin decline -0.10 vs- 0.16 (p=0009) Duration of phototherapy 57.86 vs 44.82 p=.0011	5 × 109 CFU/capsule, 2 capsules/day

TSB - total serum bilirubin

The probiotics are grouped by strain for clarity, and each entry includes the study author and year, reported outcomes such as reduction in total serum bilirubin (TSB), phototherapy duration, or hospital stay, as well as dosage information when available. The table highlights the heterogeneity in probiotic formulations, strain-specific effects, and methodological variability across studies, offering a consolidated view of current clinical evidence supporting the use of probiotics as an adjunctive therapy in NJ.

The safety profile of probiotics in neonatal populations has been favorable. Across studies, no serious adverse effects were reported, even with complex multi-strain formulations [16][17]. This positions probiotics as a low-risk intervention suitable for integration into neonatal care, especially when tailored to specific clinical settings.

A compelling aspect of current findings is the demonstrated synergy between probiotic supplementation and conventional phototherapy. Probiotics have been shown to enhance the therapeutic effects of phototherapy by further reducing bilirubin levels, improving gastrointestinal function, and mitigating phototherapy-associated side effects such as dehydration and skin damage [2][4][9].

The combination strategy also appears to support immune development and gut maturation, contributing to a more holistic improvement in neonatal health.

Nonetheless, several limitations in the current body of evidence warrant careful consideration. There is substantial heterogeneity in probiotic strains used, dosage regimens, study designs, and outcome measures across trials. Moreover, long-term follow-up data remain sparse, limiting conclusions about the sustained benefits or potential risks of early probiotic intervention.

Further standardized, large-scale randomized controlled trials with long-term monitoring are needed to refine usage guidelines and establish strain-specific recommendations [13][12].

Though probiotics do not directly metabolize bilirubin, they positively influence host physiology by modifying gut microbiota, enhancing intestinal barrier function, and stimulating motility—all of which converge to improve bilirubin clearance. As the evidence base expands, probiotics may become an integral part of evidence-based protocols for managing neonatal jaundice, particularly as personalized neonatal microbiota-targeted strategies continue to evolve.

Across studies, probiotics do not directly degrade bilirubin but exert their beneficial effects through modulation of gut microbiota, stimulation of peristalsis, and reduction of β-glucuronidase activity [11][13][14]. The combination of probiotics with phototherapy yields superior outcomes compared to phototherapy alone [4][8][10]. However, probiotic efficacy is highly strain-specific, and more rigorously controlled randomized trials with larger sample sizes are required to standardize dosing, duration, and probiotic selection [12][13].

Conclusions and Future Directions

The promising results, particularly with strains such as *S. boulardii* and *B. animalis* CP-9, highlight the potential of microbiota-targeted interventions in the clinical management of neonatal jaundice. As further data accumulates, probiotics may become a routinely recommended adjunct in treatment protocols—especially in settings where early dysbiosis, prematurity, or impaired gut function are contributing factors to bilirubin accumulation.

Conflicts of Interest: No conflicts of interest to declare.

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