The Gut-Blood Axis: A Literature Review on the Role of Gut Microbes and Probiotics in the Management of Anaemia

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DOI: https://doi.org/10.51583/IJLTEMAS.2025.1411000039

Received: 18 November 2025; Accepted: 27 November 2025; Published: 05 December 2025

ABSTRACT

Anaemia, a condition characterized by a deficiency in red blood cells or haemoglobin, remains a global public health challenge affecting nearly a third of the world's population. Traditional management strategies primarily focus on nutrient supplementation (e.g., iron, vitamin B12, folate) and treating underlying causes. However, variable efficacy and side effects of these approaches have prompted the exploration of novel adjuvants. The human gut microbiome, a complex ecosystem of trillions of microorganisms, is increasingly recognized as a critical regulator of host physiology, including nutrient absorption and immune function. This literature review synthesizes current evidence on the mechanisms by which gut microbes and their therapeutic derivatives, probiotics, influence the pathogenesis and management of anaemia. We explore the triad relationship between the gut microbiota, iron homeostasis, and inflammation, detailing how specific bacterial taxa can enhance or inhibit iron absorption. Furthermore, we examine the direct role of microbes in the synthesis of folate and vitamin B12, essential cofactors for erythropoiesis. Evidence from preclinical and clinical studies demonstrating the efficacy of various probiotic strains, particularly Lactobacillus and Bifidobacterium, in improving haemoglobin status is critically appraised. The review also discusses the potential of synbiotics and postbiotics as next-generation therapeutic tools. Finally, we identify key research gaps and future directions, concluding that targeted modulation of the gut microbiome represents a promising, multifaceted strategy for the prevention and management of various forms of anaemia, moving beyond conventional nutrient-replacement paradigms.

Keywords: Anaemia, Microbiome, Probiotics, Iron, Inflammation, Folate, Vitamin B12, Gut-Blood Axis, Lactobacillus, Bifidobacterium

INTRODUCTION

Anaemia is a pervasive global health problem, with the World Health Organization (WHO) estimating that 1.8 billion people were affected in 2021, representing 27% of the world's population, with the highest burden among preschool children and pregnant women (WHO, 2024). It is a condition defined by a reduced oxygen-carrying capacity of the blood, resulting from a decrease in the number of circulating red blood cells or a reduction in the concentration of haemoglobin within them (Chaparro & Suchdev, 2019). The functional consequences are profound, including fatigue, impaired cognitive development in children, reduced work capacity in adults, and increased risk of maternal and child mortality (Peyrin-Biroulet et al., 2015).

The aetiologies of anaemia are multifactorial and often interconnected. Iron deficiency is the most common cause, accounting for approximately 50% of cases globally (Camaschella, 2019). Other significant causes include deficiencies in other micronutrients like vitamin B12 and folate, chronic inflammation (leading to anaemia of inflammation, AI), inherited haemoglobin disorders (e.g., thalassemia, sickle cell disease), and parasitic infections such as malaria and helminthiasis (Kassebaum et al., 2014). Conventional management has predominantly relied on oral or parenteral supplementation of the deficient nutrient, such as ferrous sulfate for iron deficiency anaemia (IDA). While effective, these approaches have limitations, including poor

ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue XI, November 2025

gastrointestinal tolerance of iron supplements (e.g., constipation, nausea), low adherence, and limited efficacy in anaemia of inflammation where iron sequestration is the primary issue (Paganini & Zimmermann, 2017).

In recent years, a paradigm shift has occurred with the recognition of the human gut microbiome as a virtual endocrine organ that profoundly influences host health. The gut microbiota, comprising bacteria, archaea, viruses, and eukaryotes, is integral to metabolic functions, immune modulation, and pathogen exclusion (Sender et al., 2016). The concept of the "gut-blood axis" has emerged, highlighting the bidirectional communication between gut microbial communities and systemic haematological parameters (Yan & Charles, 2018).

This literature review aims to critically synthesize and evaluate the current scientific evidence on the importance of gut microbes and probiotics in managing anaemia. It will delineate the mechanisms by which the microbiota influences iron homeostasis, inflammation, and the synthesis of erythropoietic vitamins. Furthermore, it will review interventional studies using probiotics, synbiotics, and postbiotics, appraising their efficacy and potential as novel therapeutic or adjuvant strategies. By integrating findings from molecular, animal, and human studies, this review seeks to provide a comprehensive overview of this rapidly evolving field and to identify future research priorities.

The Gut Microbiome: A Primer and Its Connection to Systemic Health

The human colon harbors the densest microbial community on Earth, with estimates of 10^13 to 10^14 microorganisms, the majority of which are bacteria from the phyla Firmicutes and Bacteroidetes (Lloyd-Price et al., 2016). The composition of this ecosystem is shaped by genetics, diet, age, geography, and medication use, and its stability is crucial for health. A state of dysbiosis, an imbalance in the microbial community, has been linked to a plethora of diseases, including inflammatory bowel disease (IBD), obesity, type 2 diabetes, and even neurological disorders (Lynch & Pedersen, 2016).

The microbiota contributes to host health through several key functions:

1. **Metabolism of Dietary Components:** Fermenting indigestible dietary fibers to produce short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which serve as energy sources for colonocytes and have systemic anti-inflammatory effects (Parada Venegas et al., 2019).
2. **Synthesis of Vitamins:** De novo synthesis of essential vitamins, including vitamin K and most B vitamins, such as folate (B9), riboflavin (B2), and cobalamin (B12) (Magnúsdóttir et al., 2015).
3. **Barrier Function and Immune Regulation:** The microbiota helps maintain the integrity of the gut epithelial barrier and educates the host immune system, promoting a balanced inflammatory response (Belkaid & Harrison, 2017).

The connection to anaemia becomes apparent when these functions are disrupted. For instance, gut inflammation can lead to dysbiosis, which in turn may impair iron absorption or increase systemic inflammation, creating a vicious cycle that perpetuates anaemia.

Mechanisms of Microbial Influence on Anaemia

The gut microbiota influences erythropoiesis and haemoglobin levels through three primary, interconnected mechanisms: modulation of iron absorption, regulation of systemic inflammation, and direct synthesis of haematopoietic vitamins.

Modulation of Iron Homeostasis

Iron absorption is a tightly regulated process occurring primarily in the duodenum and proximal jejunum. Dietary iron (Fe^{3+}) is reduced to the more soluble ferrous form (Fe^{2+}) by ferric reductases, then transported into enterocytes by the divalent metal transporter 1 (DMT1). It is either stored as ferritin or exported into the circulation via ferroportin, where it is oxidized and bound to transferrin (Ganz, 2013). The hormone hepcidin, produced by the liver, is the master regulator of iron homeostasis; it degrades ferroportin, thereby trapping iron in enterocytes and macrophages and reducing plasma iron availability (Ganz & Nemeth, 2012).

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The gut microbiota competes with the host for dietary iron. This is particularly evident in situations of dietary iron restriction, where the growth of certain pathogenic bacteria (e.g., Salmonella spp., Escherichia coli) is suppressed, while commensals like Lactobacillus spp. are more resilient (Dostal et al., 2014). However, the relationship is bidirectional and complex. Specific microbial metabolites can directly influence host iron absorption:

- **Short-Chain Fatty Acids (SCFAs):** Produced by bacterial fermentation of fiber, SCFAs (particularly butyrate) have been shown to downregulate the expression of hepcidin in vitro and in vivo (Shah et al., 2021). Lower hepcidin levels increase ferroportin activity, enhancing iron export from enterocytes and macrophages into the circulation. Butyrate also stimulates the proliferation of intestinal epithelial cells, potentially increasing the absorptive surface area (Parada Venegas et al., 2019).
- **Lactic Acid and Other Microbial Products:** Probiotic bacteria like Lactobacillus and Bifidobacterium produce lactic acid, which can lower the local pH in the gut lumen. This acidic environment helps maintain iron in its more bioavailable ferrous (Fe^{2+}) state and may stimulate DMT1 activity (Rusu et al., 2020).
- **Bacterial Iron Metabolism:** Bacteria have their own sophisticated systems for iron acquisition (siderophores) and storage. Some commensals possess high-affinity iron transporters that can sequester luminal iron, theoretically reducing host absorption. However, the overall impact of the community is likely a net positive, as SCFA-producing bacteria seem to promote host iron availability (Das et al., 2020).

Table 1: Microbial Mechanisms Influencing Iron Homeostasis

Mechanism	**Key Microbial Players / Metabolites**	**Effect on Host Iron Absorption**
SCFA Production	Faecalibacterium prausnitzii, Roseburia spp., Eubacterium spp. (Butyrate); Bacteroides spp. (Propionate, Acetate)	↓ Hepcidin expression → ↑ Ferroportin activity → Enhanced iron export into circulation.
Luminal Acidification	Lactobacillus spp., Bifidobacterium spp. (Lactic acid)	Maintains iron in soluble Fe^{2+} form; may upregulate DMT1.
Competition for Iron	Pathobionts (e.g., Salmonella, E. coli)	Can sequester luminal iron via siderophores, potentially limiting host access.
Modulation of Gut Barrier	SCFAs, Lactobacillus spp., Bifidobacterium spp.	Enhances intestinal integrity, reducing inflammation-driven iron malabsorption.

Regulation of Inflammation in Anaemia of Inflammation (AI)

Anaemia of Inflammation (AI), also known as anaemia of chronic disease, is the second most prevalent anaemia worldwide. It is characterized by a functional iron deficiency: despite adequate iron stores, iron is sequestered in macrophages and the liver, making it unavailable for erythropoiesis (Weiss & Goodnough, 2005). This is primarily mediated by hepcidin, whose expression is strongly induced by inflammatory cytokines, particularly interleukin-6 (IL-6) (Nemeth et al., 2004).

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The gut microbiome is a pivotal regulator of systemic immunity. A healthy, diverse microbiota promotes a state of immunological tolerance and maintains gut barrier integrity, preventing the translocation of bacterial lipopolysaccharides (LPS) into the portal circulation. LPS is a potent trigger of systemic inflammation, leading to the production of IL-6 and other cytokines that stimulate hepcidin production (Sebastian & Mostoslavsky, 2021).

In conditions of dysbiosis, such as in IBD, obesity, or chronic kidney disease, this barrier is compromised. Increased gut permeability ("leaky gut") allows for LPS translocation, fueling chronic, low-grade inflammation. This sustained inflammatory state leads to persistent hepcidin elevation, blocking iron absorption and recycling, there by driving AI (Deschemin & Vaulont, 2013). Probiotics and prebiotics can counter this process by:

1. **Restoring Microbial Balance:** Increasing the abundance of SCFA-producing bacteria, which have anti-inflammatory properties and strengthen the gut barrier.
2. **Reducing Pro-inflammatory Cytokines:** Certain probiotic strains can directly modulate immune cell responses, reducing the production of IL-6, TNF-α, and other hepcidin-inducing cytokines (Yan & Charles, 2018).
3. **Competitive Exclusion:** Preventing the overgrowth of pro-inflammatory pathobionts.

Microbial Synthesis of Haematopoietic Vitamins

Beyond iron, adequate levels of vitamin B12 and folate are non-negotiable for DNA synthesis and erythrocyte maturation. Deficiencies in either lead to megaloblastic anaemia. While humans must obtain most of their vitamin B12 from animal-derived foods, the gut microbiota is a significant source of folate (B9) and, to a lesser extent, B12 (Magnúsdóttir et al., 2015).

- **Folate Synthesis:** Numerous gut bacteria, including Lactobacillus spp., Bifidobacterium spp., and Streptococcus thermophilus, are prolific producers of folate (Rossi et al., 2011). This microbial folate can be absorbed across the colonic epithelium, contributing to the host's folate status. Studies have shown that probiotic supplementation can increase serum and erythrocyte folate concentrations in humans (Strozzi & Mogna, 2008).
- **Vitamin B12 Synthesis:** Although several gut bacteria synthesize B12, this occurs predominantly in the colon, a site where absorption of the vitamin is minimal, as the intrinsic factor-mediated absorption mechanism is active only in the ileum (Degnan et al., 2014). Therefore, the contribution of microbial B12 to host status is likely limited. However, a healthy microbiota may still play an indirect role by preventing the overgrowth of bacteria that compete with the host for dietary B12.

Table 2: Probiotic Strains with Documented Effects on Haematopoietic Nutrients

Probiotic Strain	Documented Effects	Proposed Mechanism
Lactobacillus plantarum 299v	Increased iron absorption; reduced hepcidin; improved Hb in IDA (Søndergaard et al., 2021).	Acidification, SCFA production, reduction of luminal iron-binding phytates.
Lactobacillus acidophilus	Improved iron status in animal models; increased folate production (Rusu et al., 2020).	Folate synthesis; luminal acidification; immune modulation.
Bifidobacterium longum	Reduced systemic inflammation; improved iron bioavailability in weaning	Anti-inflammatory cytokine profile; enhanced gut barrier function.

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Probiotic Strain	Documented Effects	Proposed Mechanism
	infants (Mitsuyoshi et al., 2021).	
Streptococcus thermophilus	High in situ production of folate in the gut (Rossi et al., 2011).	De novo folate synthesis.
Lactobacillus reuteri	Improved vitamin B12 status in deficient individuals (in combination with other interventions) (Degnan et al., 2014).	Potential reduction of competing microbes; local synthesis.

Evidence from Interventional Studies with Probiotics and Synbiotics

The mechanistic insights have been translated into numerous interventional studies investigating the efficacy of probiotics, often in combination with prebiotics (synbiotics), in managing anaemia.

Preclinical (Animal) Studies

Animal models have been instrumental in establishing proof-of-concept. For example, a study in iron-deficient piglets showed that supplementation with L. plantarum 299v significantly improved iron absorption and haemoglobin regeneration efficiency compared to controls (Kullen et al., 2019). Similarly, in a rat model of anaemia, a synbiotic containing L. acidophilus and fructo-oligosaccharides (FOS) led to a greater increase in haemoglobin and serum iron than iron supplementation alone (Hoppe et al., 2017). These studies consistently highlight the role of probiotics in modulating DMT1 and ferroportin expression and reducing systemic inflammation.

Human Clinical Trials

Human trials, though more variable in design and outcome, show promising results.

- **Iron Deficiency Anaemia (IDA):** A randomized controlled trial (RCT) in pregnant women with IDA found that co-administration of a probiotic mixture (L. acidophilus, B. bifidum, L. casei, L. fermentum) with iron supplements resulted in a significantly greater increase in haemoglobin and serum ferritin compared to iron supplements alone, with fewer gastrointestinal side effects (Rezaei et al., 2019). Another RCT in iron-deficient women showed that L. plantarum 299v, when combined with iron, was more effective at restoring iron status than iron with a placebo (Søndergaard et al., 2021).
- **Anaemia of Inflammation:** In patients with chronic kidney disease (CKD), who frequently suffer from AI, probiotic supplementation has been shown to reduce markers of inflammation (e.g., CRP, IL-6) and increase haemoglobin levels, allowing for a reduced dose of erythropoiesis-stimulating agents (ESAs) in some cases (Mirzaei et al., 2022). Similar anti-inflammatory and haemoglobin-boosting effects have been observed in studies on obese individuals and the elderly (Mitsuyoshi et al., 2021).
- **Other Forms of Anaemia:** Preliminary evidence suggests that probiotics may also benefit individuals with sickle cell disease or thalassemia by reducing inflammation and oxidative stress, though research in this area is still nascent (Yan & Charles, 2018).

Figure 1: Conceptual Framework of Probiotic Mechanisms in Managing Anaemia

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ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue XI, November 2025

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|  Probiotic / Symbiotic  |     |  Healthy Gut Microbiome  |
|  Supplementation        |----->|  (Eubiosis)
+------------------------+     +----------------------+
                          | (SCFAs, Barrier Integrity)
                          v
+--------------------------------------------------+
|            Multimodal Mechanisms                 |
+--------------------------------------------------+
| ↓ Systemic Inflammation | ↑ Iron Absorption | ↑ Vitamin Synthesis |
| ↓ Hepcidin              | ↑ DMT1/Ferroportin| (Folate, B2)        |
| ↓ Pro-inflammatory      | Acidic pH         |                     |
|  cytokines (IL-6)       | Phytate degradation|                    |
+--------------------------------------------------+
                          |
                          v
+--------------------------------------------------+
|            Improved Haematological Outcomes      |
+--------------------------------------------------+
| ↑ Haemoglobin (Hb)      | ↑ Serum Ferritin        |
| ↑ Erythrocyte Count     | ↓ Reticulocyte Production|
| Resolution of Anaemia   | Time                    |
+--------------------------------------------------+
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Table 3: Summary of Select Clinical Trials on Probiotics/Synbiotics in Anaemia Management

Study Population	**Intervention**	**Duration**	**Key Findings**	**Reference**
Pregnant women with IDA (n=80)	Ferrous Sulfate + Probiotic mix (L. acidophilus, B. bifidum, L. casei, L.	12 weeks	Significantly greater increase in Hb and ferritin in probiotic group. Fewer GI side effects.	(Rezaei et al., 2019)

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Study Population	Intervention	Duration	Key Findings	Reference
	fermentum) vs. Ferrous Sulfate + Placebo			
Iron-deficient women (n=60)	Ferrous Sulfate + L. plantarum 299v vs. Ferrous Sulfate + Placebo	12 weeks	Probiotic group had significantly higher iron absorption and Hb levels.	(Søndergaard et al., 2021)
Patients with CKD (n=60)	Synbiotic (various strains + FOS) vs. Placebo	8 weeks	Probiotic group had significant reduction in hs-CRP and IL-6, and increase in Hb.	(Mirzaei et al., 2022)
Weaning infants (n=120)	Iron-fortified cereal + B. lactis vs. Iron-fortified cereal alone	6 months	Probiotic group had better iron status and lower inflammation markers.	(Mitsuyoshi et al., 2021)

Beyond Probiotics: Synbiotics, Postbiotics, and Fecal Microbiota Transplantation

The therapeutic landscape is expanding beyond traditional probiotics.

- **Synbiotics:** These are combinations of probiotics and prebiotics designed to improve the survival and implantation of live microbial supplements. The prebiotic component (e.g., inulin, FOS) selectively stimulates the growth of endogenous beneficial bacteria as well as the administered probiotics, creating a synergistic effect. Studies using synbiotics often report superior outcomes in improving iron status and reducing inflammation compared to probiotics alone (Hoppe et al., 2017).
- **Postbiotics:** Defined as preparations of inanimate microorganisms and/or their components that confer a health benefit. This includes bacterial lysates, cell-free supernatants, and metabolites like SCFAs. Postbiotics offer advantages in terms of safety (no risk of bacterial translocation or antibiotic resistance gene transfer), stability, and shelf-life. Butyrate-producing postbiotic preparations are being explored for their potential to directly target hepcidin expression (Shah et al., 2021).
- **Fecal Microbiota Transplantation (FMT):** While primarily used for recurrent Clostridioides difficile infection, FMT represents the ultimate "microbial reset." Its application in anaemia management is purely speculative but intriguing. In theory, transferring a healthy, diverse microbiota from a donor with robust iron status could potentially correct dysbiosis-driven AI in a recipient, though significant safety and ethical hurdles exist.

Challenges, Limitations, and Future Directions

Despite the promising evidence, several challenges remain. The probiotic field suffers from a lack of strain-specificity; effects are not generalizable across different bacterial strains. The optimal dosage, duration, and formulation (single strain vs. consortium) for different types of anaemia are yet to be standardized. Many human studies have small sample sizes and are of short duration, limiting the strength of the conclusions.

ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue XI, November 2025

Future research should focus on:

1. **Large-scale, long-term, well-designed RCTs** in diverse populations and specific disease states (e.g., IBD, CKD).
2. **Mechanistic Elucidation:** Using gnotobiotic (germ-free) animal models and multi-omics approaches (metagenomics, metabolomics) to precisely delineate causal pathways.
3. **Personalized Nutrition:** Developing strategies based on an individual's baseline microbiome composition to predict and optimize response to probiotic intervention.
4. **Exploration of Postbiotics:** Rigorously testing defined postbiotic formulations as stable and safe alternatives to live bacteria.
5. **Investigating the Virome and Mycobiome:** Expanding research beyond bacteria to include the roles of gut viruses and fungi in haematological health.

CONCLUSION

The burgeoning field of microbiome research has unequivocally established that gut microbes are critical players in host nutrient homeostasis and immune function. This review has synthesized compelling evidence that the gut microbiota exerts a profound influence on the pathogenesis and management of anaemia through three core mechanisms: enhancing iron bioavailability via SCFA-mediated hepcidin suppression and luminal acidification, mitigating the chronic inflammation that underlies AI, and directly supplying essential haematopoietic vitamins like folate.

While oral nutrient supplementation remains the cornerstone of anaemia treatment, its limitations are clear. The adjunctive use of specific probiotic strains, synbiotics, and potentially postbiotics, offers a novel, safe, and multifaceted strategy to improve therapeutic outcomes. By targeting the gut-blood axis, these interventions can enhance the efficacy of iron therapy, reduce its side effects, and address the root inflammatory causes in AI. Future research must move from correlation to causation and towards personalized, microbiome-based therapeutics. Ultimately, harnessing the power of our microbial inhabitants promises to revolutionize our approach to combating this ancient and widespread malady.

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