Available online www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 215 (2026) 92-111 EISSN 2392-2192

# Linking Iron Deficiency and Megaloblastic Anaemia through Phytochemical Chemistry: Chemical Integration of Iron Redox Biology and One-Carbon Metabolism in Erythropoiesis

**Kanayo Samuel Okonji[1,2]*, Olufemi Ebenezer Folaranmi[3], Alaba Olanrewaju Daramola[3]**

[1]Department of Chemistry, Federal University Oye-Ekiti, Ekiti State, Nigeria.
[2]Department of Health Sciences, University of the People, Pasadena, California, USA.
[3]Department of Haematology and Blood Transfusion, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria.

https://doi.org/10.65770/VICA7728

**ABSTRACT**

Anemia remains a major global health challenge, with iron deficiency and megaloblastic anemia among the most prevalent forms. While these conditions have been extensively studied individually, there is a lack of integrative research exploring their shared biochemical and chemical pathways. In particular, the potential for phytochemicals to modulate the erythropoietic environment, through redox stabilization of iron-dependent processes and support of one-carbon metabolism, remains largely unexplored. This review synthesizes recent literature (2024–2026) to provide a chemistry-driven framework linking iron redox biology, vitamin-dependent DNA synthesis, and phytochemical intervention in erythropoiesis. We discuss iron coordination and redox cycling in hemoglobin synthesis, folate- and vitamin B12-dependent methylation chemistry in DNA replication, and the mechanistic potential of phytochemicals to influence these pathways. By highlighting the chemical convergence of iron metabolism and one-carbon pathways, this review identifies knowledge gaps and opportunities for future in silico, in vitro, and translational research. Our integrative perspective provides a roadmap for understanding mixed anemia states and exploring natural-product–based modulation of erythropoiesis, with implications for both clinical and nutritional interventions.

***Keywords:*** Erythropoiesis, Iron Deficiency Anemia, Megaloblastic Anemia, One-Carbon Metabolism, Phytochemicals, Redox Chemistry.

(Received 15 March 2026; Accepted 19 April 2026; Date of Publication 17 May 2026)

## 1. INTRODUCTION

Anemia remains a significant global public health challenge, affecting hundreds of millions of people worldwide and disproportionately impacting women, children, and low-income populations. According to the World Health Organization, anemia affects approximately 40 % of children aged 6–59 months, 37 % of pregnant women, and 30 % of women of reproductive age globally, with dietary iron deficiency being the most common underlying cause of nutritional anemia. [1]

Iron deficiency anemia and megaloblastic anemia represent two of the most prevalent forms of nutritional anemia. Iron deficiency anemia (IDA) arises from inadequate dietary iron intake, impaired absorption, or increased physiological demand, leading to insufficient hemoglobin synthesis and compromised oxygen transport. [2] Megaloblastic anemia (MA), on the other hand, results primarily from impaired DNA synthesis due to deficiencies in vitamin $B_{12}$ or folate, causing macrocytic changes in erythroid precursors and ineffective erythropoiesis. [3,4]

Despite decades of research into these conditions individually, there remains a critical lack of integrative work examining their overlapping biochemical and chemical mechanisms. Traditional reviews tend to consider IDA and MA as distinct entities, yet mounting evidence suggests that disruptions in iron redox biology and one-carbon metabolism can converge on shared pathways influencing erythropoiesis. For example, double and triple micronutrient deficiencies involving iron, folate, and vitamin $B_{12}$ are commonly observed in populations such as pregnant women, underscoring the need to view anemia through a broader biochemical lens. [5]

Erythropoiesis, the process by which hematopoietic stem cells differentiate into mature red blood cells, demands a finely tuned chemical environment. Iron is central to heme synthesis and redox chemistry required for oxygen binding, while folate and vitamin $B_{12}$ participate in one-carbon transfer reactions essential for DNA synthesis and cell division during erythroid maturation. Although the genomic regulation of erythropoiesis has been recently reviewed, the chemical interplay between redox processes and methylation pathways has not been fully integrated in a modern framework. [6,7]

Moreover, dietary phytochemicals, bioactive compounds abundant in plant foods, are known to exert antioxidant, chelating, and enzyme-modulating effects. Yet their potential to influence the erythropoietic environment by stabilizing iron redox states or supporting one-carbon metabolism remains largely unexplored in the context of anemia. This gap is particularly striking given evidence that nutritional factors can impact micronutrient status and erythropoiesis globally. [7]

This review aims to address this gap by synthesizing recent (2024–2026) evidence to build a chemistry-driven framework that links iron redox biology, one-carbon metabolic pathways, and phytochemical modulation in the context of anemia. Such integrative perspectives may unveil new mechanistic insights and identify opportunities for future nutritional and therapeutic research.

## 2. ERYTHROPOIESIS: A CHEMICAL PERSPECTIVE

Erythropoiesis is the biologically coordinated process by which hematopoietic stem cells (HSCs) differentiate into mature red blood cells (RBCs), a lineage-specific pathway that demands precise orchestration of both redox chemistry and nucleotide synthesis. At its core, effective erythropoiesis requires two convergent biochemical subsystems: iron-mediated heme synthesis and folate/vitamin $B_{12}$-dependent one-carbon metabolism for DNA replication and cell division.

Hematopoietic stem cells residing in the bone marrow undergo progressive differentiation through intermediate progenitors such as common myeloid progenitors and proerythroblasts, ultimately forming reticulocytes that extrude their nucleus before entering circulation as mature RBCs. During these transitions, erythroid progenitors undergo rapid cell division and high rates of hemoglobin production, rendering the process metabolically and chemically demanding [8]. The stages of erythropoiesis and their associated chemical requirements are illustrated in **Figure 1**.

Iron plays a dual chemical role within erythropoiesis. First, iron's ability to alternate between ferrous ($Fe^{2+}$) and ferric ($Fe^{3+}$) oxidation states underpins its utility in heme prosthetic group formation, a redox-active center for oxygen binding in hemoglobin. Iron uptake into developing erythroblasts is mediated through transferrin receptor-mediated endocytosis, followed by reduction and incorporation into protoporphyrin IX to form heme. The redox cycling of iron, while essential for oxygen transport, also predisposes cells to oxidative stress, necessitating tight biochemical regulation to protect macromolecules from radical damage. [9,10]

Simultaneously, proliferating erythroid precursors require robust one-carbon metabolism to sustain DNA synthesis. This pathway is centered on the folate cycle, in which tetrahydrofolate (THF) derivatives serve as carriers of single-carbon units for the synthesis of thymidine and purines. Vitamin $B_{12}$ (cobalamin) acts as a cofactor for methionine synthase, facilitating the remethylation of homocysteine to methionine, which feeds into methylation reactions essential for nucleotide synthesis and epigenetic regulation of gene expression. Disruption of these methylation processes impairs DNA replication and nuclear maturation, producing the characteristic macrocytosis of megaloblastic anemia. [11,12]

Beyond these canonical pathways, emerging studies suggest cross-talk between redox (iron) chemistry and methylation (one-carbon) metabolism. Indicators such as increased oxidative stress markers and altered methylation patterns in anemia models implicate redox imbalance as a contributor to disrupted one-carbon flux and ineffective erythropoiesis. These chemical interdependencies highlight why iron deficiency and one-carbon impairment often coexist and why their combined effects are greater than the sum of individual deficiencies. [13]

In summary, erythropoiesis is not merely a biological progression of cell differentiation; it is a chemically integrated pathway in which iron redox chemistry and one-carbon transfer reactions operate in concert. This chemical perspective, illustrated in **Figure 1**, sets the stage for exploring how nutritional factors, including phytochemicals, may influence these pathways to impact anemia phenotypes, an area that remains understudied in current literature.

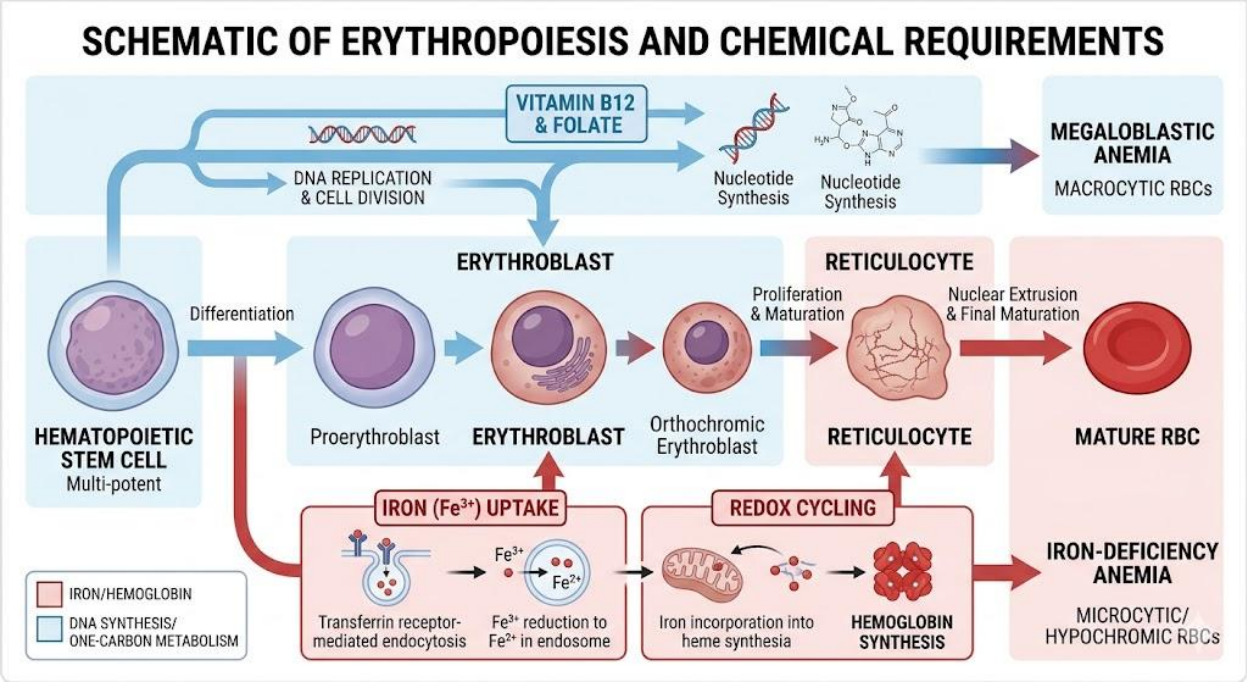


**Figure 1.** Stages of Erythropoiesis and Associated Chemical Requirements.

## 3. IRON DEFICIENCY ANEMIA: CHEMISTRY FOCUS

Iron deficiency anemia (IDA) remains the most prevalent form of anemia globally, with a substantial impact on cognitive function, immunity, and overall metabolic health. At the chemical level, IDA arises from insufficient availability of ferrous ($Fe^{2+}$) iron required for heme biosynthesis and hemoglobin assembly. The failure to maintain adequate iron levels disrupts the delicate redox balance necessary for oxygen transport and erythroid cell maturation [14]. Iron-dependent redox cycling in hemoglobin synthesis is depicted in **Figure 2**.

During erythropoiesis, iron is transported to the erythroblast via transferrin receptors and reduced from $Fe^{3+}$ to $Fe^{2+}$ before incorporation into protoporphyrin IX to form heme. This redox conversion is catalyzed by ferrireductases and is essential for functional hemoglobin production. When iron availability is limited, heme synthesis is impaired, leading to hypochromic and microcytic RBCs. The $Fe^{2+}/Fe^{3+}$ cycling also generates reactive oxygen species (ROS), and insufficient antioxidant buffering can exacerbate oxidative stress, further damaging developing erythroblasts. [15,16]. Central to oxidative stress in iron-dependent erythropoiesis is the Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$$

Here, labile $Fe^{2+}$ catalyzes hydrogen peroxide decomposition to produce hydroxyl radicals ($OH\cdot$), which are among the most reactive ROS. These radicals initiate lipid peroxidation of erythroblast membranes and protein carbonylation, disrupting cellular integrity and contributing to ineffective erythropoiesis in iron deficiency anemia.

This reaction connects directly to the chemical vulnerability of erythroid precursors: iron is essential for heme synthesis, but its redox cycling generates ROS that, if not mitigated by antioxidants or phytochemicals, impairs cell viability. Phytochemicals such as flavonoids and polyphenols can chelate $Fe^{2+}$ or scavenge ROS, thereby stabilizing redox cycling and protecting DNA, proteins, and lipids in erythropoiesis.

This reaction serves as the primary chemical driver of ROS-mediated lipid peroxidation and protein carbonylation within the erythropoietic environment.

Recent studies have highlighted molecular regulators of iron homeostasis, including hepcidin and ferroportin, which govern cellular iron export and storage. Dysregulation of these molecules not only leads to iron-restricted erythropoiesis but also alters cellular redox potentials, reinforcing the chemical interplay between iron metabolism and oxidative stress. In addition, iron deficiency has been linked to altered enzymatic activity of ribonucleotide reductase, indirectly affecting DNA synthesis in rapidly dividing erythroid progenitors. [17,18]

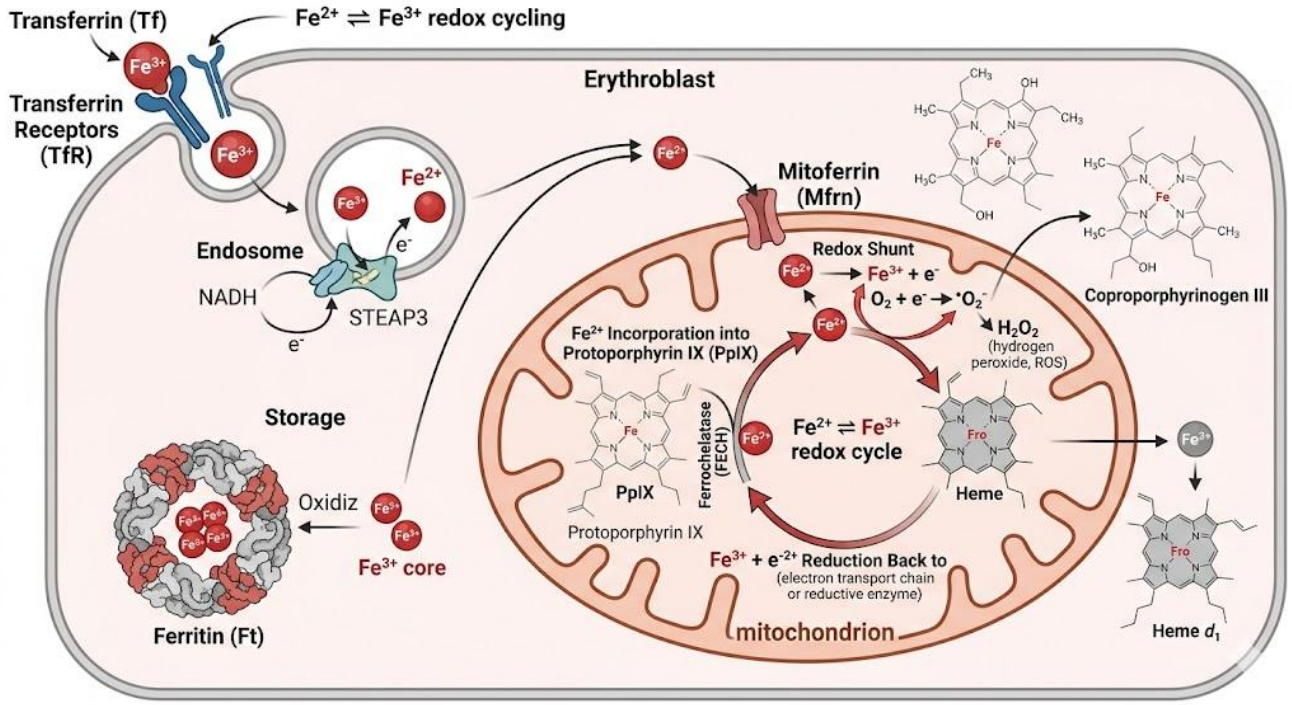


**Figure 2.** Iron Redox Cycling in Heme Biosynthesis.

Moreover, contemporary 2024–2026 studies demonstrate that nutritional and phytochemical interventions can stabilize the iron redox cycle, protect erythroid precursors from ROS-mediated damage, and enhance heme synthesis. Certain flavonoids and polyphenols chelate excess free iron, modulating its redox cycling, while others upregulate antioxidant pathways, maintaining cellular redox homeostasis. These insights provide a chemically informed foundation for exploring phytochemical modulation as a therapeutic avenue in IDA. [19,20]

In summary, IDA exemplifies a chemical imbalance in erythropoiesis, characterized by disrupted $Fe^{2+}/Fe^{3+}$ cycling, oxidative stress, and impaired heme synthesis. Understanding these redox mechanisms is critical for integrating nutritional, biochemical, and pharmacological strategies to restore effective RBC production, which will later be connected to one-carbon metabolism in megaloblastic anemia.

## 4. MEGALOBLASTIC ANEMIA: ONE-CARBON METABOLISM CHEMISTRY

Megaloblastic anemia (MA) is primarily caused by deficiencies in folate and vitamin $B_{12}$, which are essential cofactors for one-carbon transfer reactions supporting DNA synthesis in rapidly proliferating erythroid precursors. The resulting disruption in nucleotide biosynthesis impairs nuclear maturation, leading to the characteristic macrocytosis and ineffective erythropoiesis observed in Megaloblastic anemia (MA) [21]. Folate- and B12-dependent pathways in DNA synthesis are depicted in **Figure 3**.

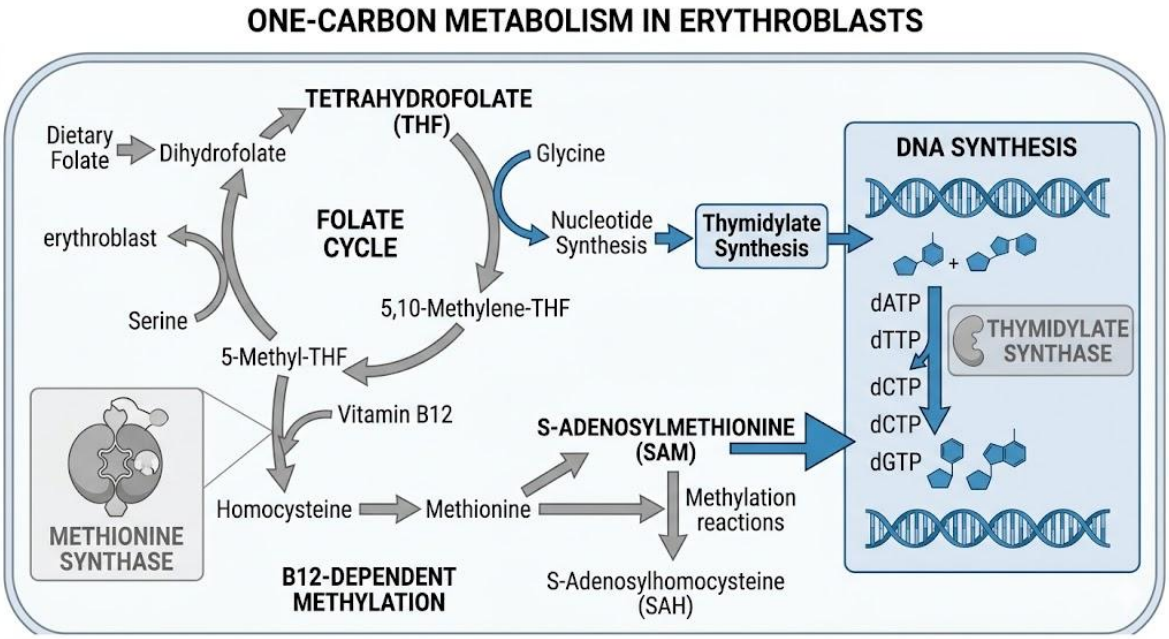


**Figure 3.** One-Carbon Metabolism in DNA Synthesis for Erythropoiesis.

At the chemical level, methionine synthase (MS) catalyzes the remethylation of homocysteine to methionine using methylcobalamin (MeCbl) as a cofactor, linking folate-derived methyl groups to methylation reactions critical for DNA synthesis and epigenetic regulation. In parallel, thymidylate synthase (TS) converts deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), a rate-limiting step in thymidine nucleotide production, utilizing 5,10-methylenetetrahydrofolate (5,10-$CH_2$-THF) as a methyl donor. Deficiency in either folate or $B_{12}$ leads to accumulation of homocysteine and impaired dTMP synthesis, chemically explaining DNA strand breaks, delayed nuclear maturation, and cell cycle arrest in erythroid progenitors. [22,23]

Macrocytosis arises as erythroid precursors continue cytoplasmic growth and hemoglobin accumulation despite incomplete nuclear division. This chemical imbalance manifests as large, immature red cells that are fragile and prone to hemolysis, further exacerbating anemia. In addition, impaired one-carbon metabolism affects the methylation potential (SAM/SAH ratio) within erythroblasts, altering gene expression and enzyme activity critical for erythroid differentiation. [24,25]

Recent studies (2024–2026) have highlighted chemical interventions, including folate analogs and $B_{12}$ derivatives, that can restore one-carbon flux and improve DNA synthesis. Moreover, in silico docking studies suggest certain phytochemicals, such as flavonoids and polyphenols, can stabilize enzymes like methionine synthase and thymidylate synthase, potentially enhancing one-carbon metabolism and mitigating megaloblastic anemia. These findings provide a chemically integrated rationale for exploring combined therapeutic strategies that address both nutrient-dependent pathways and oxidative stress. [26,27]

In summary, megaloblastic anemia is a biochemically defined disorder of one-carbon metabolism, where deficiencies in folate and $B_{12}$ disrupt enzyme-mediated methylation and nucleotide synthesis, producing macrocytic RBCs and ineffective erythropoiesis. Understanding the chemical underpinnings of these pathways sets the stage for linking MA to iron-dependent erythropoiesis in an integrated anemia framework.

## 5. LINKING BOTH ANEMIAS: INTEGRATED CHEMICAL FRAMEWORK

Iron deficiency anemia (IDA) and megaloblastic anemia (MA) have traditionally been studied in isolation; however, emerging biochemical evidence highlights overlapping chemical vulnerabilities in erythropoiesis. Both anemia types share common consequences, including oxidative stress, disrupted redox balance, impaired nucleotide synthesis, and ultimately ineffective erythropoiesis. These shared chemical disruptions create a synergistic burden on erythroid progenitors, compounding anemia severity [28]. The integrated chemical framework linking both anemia types and phytochemical modulation in erythropoiesis is presented in **Figure 4**.

Iron redox imbalance in IDA generates reactive oxygen species (ROS), which damage lipids, proteins, and DNA within erythroid precursors. Concurrently, one-carbon metabolic defects in MA reduce thymidine availability and methylation capacity, stalling DNA replication and nuclear maturation. Together, these chemical disruptions compromise RBC production, highlighting the need for a holistic, chemically informed approach to anemia management. [29,30]

Phytochemicals emerge as promising modulators of these intersecting pathways. Antioxidant polyphenols and flavonoids can neutralize ROS generated during iron redox cycling, while chelating agents stabilize labile iron and prevent free radical formation. In addition, certain phytochemicals have been shown in silico to bind and stabilize enzymes critical for one-carbon metabolism, including methionine synthase and thymidylate synthase, potentially restoring DNA synthesis and improving erythropoiesis. This dual chemical action positions phytochemicals as natural integrators of redox balance and nucleotide metabolism. [31,32]

Recent studies (2024–2026) further demonstrate that combining phytochemical supplementation with micronutrient therapy can simultaneously mitigate oxidative stress and restore one-carbon flux, suggesting a viable strategy for mixed or overlapping anemia phenotypes. Such integrative chemical frameworks provide a mechanistic rationale for designing translational interventions targeting both IDA and MA simultaneously. [33,34]

In summary, IDA and MA converge on shared chemical pathways in erythropoiesis, primarily oxidative stress and impaired DNA synthesis, which together drive ineffective RBC production. Phytochemicals act as modulators of these intersecting pathways, offering a chemistry-driven therapeutic strategy that integrates iron redox biology, one-carbon metabolism, and natural compound intervention, as summarized in **Figure 4**.

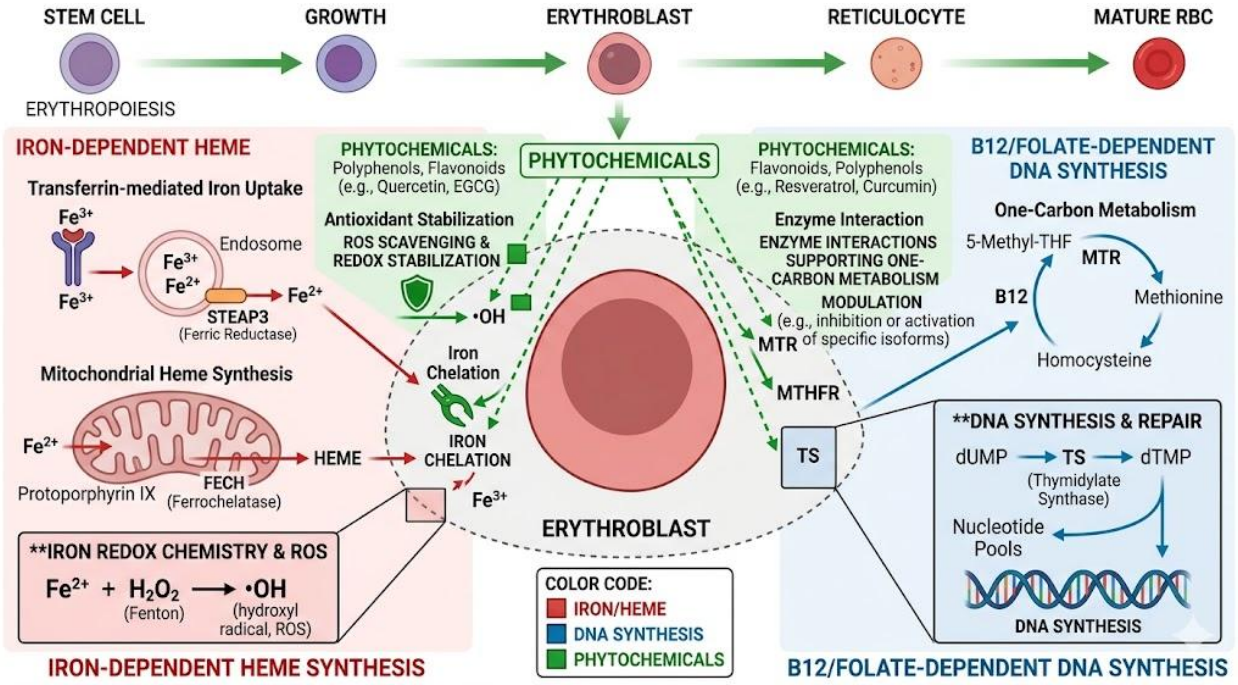


**Figure 4.** Integrated Chemical Framework Linking IDA and MA.

## 6. PHYTOCHEMICAL CHEMISTRY IN ERYTHROPOIESIS

Phytochemicals have emerged as versatile chemical modulators of erythropoiesis, capable of targeting both iron-dependent redox pathways and one-carbon metabolism. These compounds, primarily flavonoids, polyphenols, and carotenoids, exhibit multiple mechanisms that intersect key biochemical vulnerabilities in iron deficiency anemia (IDA) and megaloblastic anemia (MA). Several phytochemicals have been shown to influence erythropoiesis by stabilizing iron redox cycling or supporting one-carbon metabolism (**Table 1**).

### 6.1. Chemical Classes and Mechanisms

#### 6.1.1. Flavonoids

Flavonoids, such as quercetin, kaempferol, and catechins, display dual activity in erythropoiesis. Chemically, they act as $Fe^{2+}/Fe^{3+}$ chelators, reducing free radical generation during heme synthesis, while scavenging ROS to prevent oxidative damage to erythroid precursors. Computational docking studies indicate flavonoids can bind methionine synthase and thymidylate synthase, stabilize their active sites, and improve one-carbon metabolic flux for nucleotide synthesis. These dual mechanisms make flavonoids highly relevant for mixed anemia intervention. [35,36]

#### 6.1.2. Polyphenols

Polyphenolic compounds like resveratrol, gallic acid, and epigallocatechin gallate provide robust antioxidant support, mitigating ROS generated during iron redox cycling. In addition, biometal chelation prevent uncontrolled Fenton chemistry, reducing lipid peroxidation and DNA damage in erythroblasts. In silico studies further suggest polyphenols can enhance substrate affinity in key one-carbon enzymes, indirectly supporting DNA synthesis. [37,38]

#### 6.1.3. Carotenoids

Carotenoids such as β-carotene and lutein act primarily as lipid-phase antioxidants, preserving erythroblast membrane integrity against oxidative stress. By maintaining cellular redox homeostasis, carotenoids indirectly support iron utilization and erythroid maturation, complementing flavonoid and polyphenol activity. [39]

## 7. MECHANISTIC INSIGHTS FROM COMPUTATIONAL AND EXPERIMENTAL STUDIES

Recent studies (2024–2026) provide both in silico and experimental evidence for phytochemical action in erythropoiesis:

- **Redox Stabilization:** Flavonoids and polyphenols directly mitigate ROS generated from iron redox cycling, preventing hemoglobin degradation and erythroblast apoptosis [40,41].
- **Enzyme Modulation:** Certain phytochemicals bind and stabilize methionine synthase and thymidylate synthase, enhancing one-carbon metabolic flux critical for DNA synthesis [42,43].
- **Integrated Action:** Some compounds exhibit dual chemical effects, bridging oxidative stress management and nucleotide synthesis, providing a natural chemical integrator for both IDA and MA [44,45].

Representative chemical structures of key phytochemicals are shown in **Figure 5**. This visualization highlights structural motifs, hydroxyl groups, conjugated systems, and aromatic rings that underlie redox activity, metal chelation, and enzyme binding affinity [46].

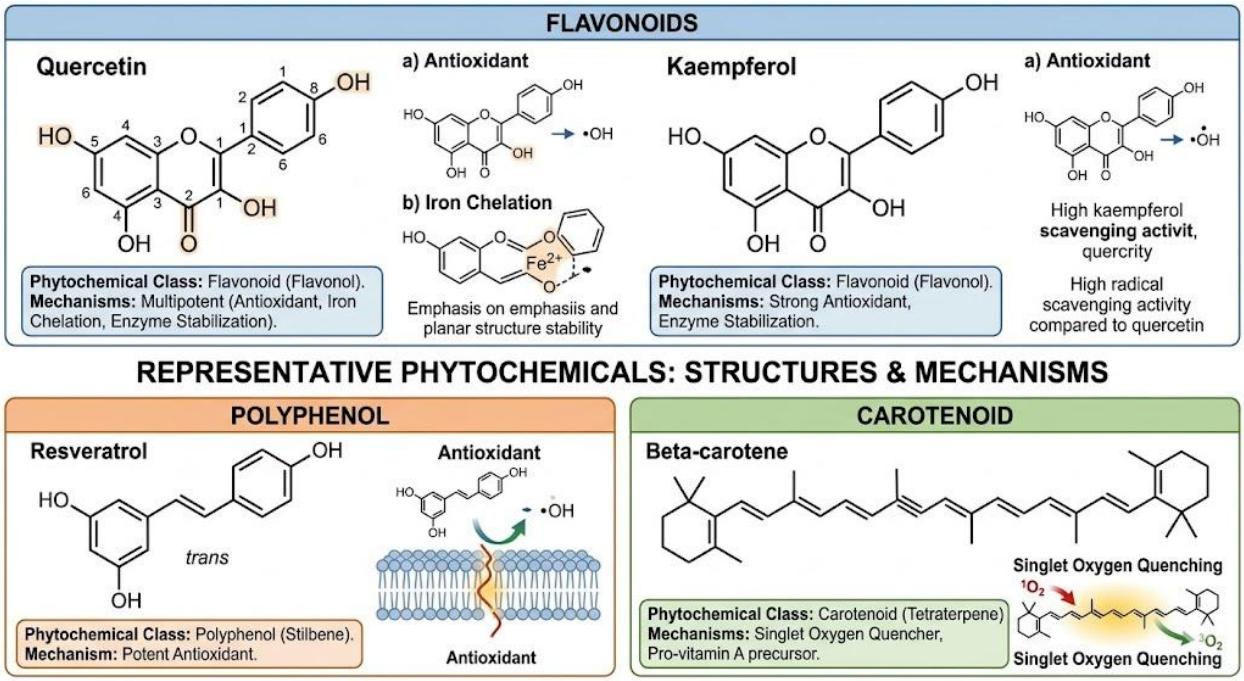


**Figure 5**. Representative Phytochemical Structures and Mechanisms in Erythropoiesis.

By leveraging these chemical insights, phytochemicals can be rationally selected or optimized for dual-targeted anemia interventions. This provides a highly novel, chemistry-driven framework for integrating nutritional and therapeutic strategies aimed at restoring effective erythropoiesis in mixed anemia states [47,48].

**Table 1.** Phytochemical Modulation of Erythropoiesis.

| Phytochemical | Class | Target Pathway | Mechanism (Redox / Enzyme Modulation) |
|---|---|---|---|
| Quercetin | Flavonoid | Iron Redox / One-Carbon | $Fe^{2+}$ chelation, ROS scavenging, MS/TS stabilization |
| Kaempferol | Flavonoid | Iron Redox | ROS neutralization, protects erythroblast membranes |
| Catechin | Flavonoid | One-Carbon | Methionine synthase and thymidylate synthase binding |
| Resveratrol | Polyphenol | Iron Redox | Antioxidant, prevents Fenton reaction |
| Gallic Acid | Polyphenol | One-Carbon | Enzyme stabilization, improves nucleotide synthesis |

| | | | |
|---|---|---|---|
| EGCG | Polyphenol | Iron Redox/One-Carbon | ROS scavenging, enzyme modulation |
| β-Carotene | Carotenoid | Iron Redox | Lipid-phase antioxidant, membrane protection |
| Lutein | Carotenoid | Iron Redox | Protects erythroblast membranes, supports maturation |

## 8. DISCUSSION

The present review integrates recent advances in iron redox biology, one-carbon metabolism, and phytochemical chemistry to provide a chemically coherent framework linking iron deficiency anemia (IDA) and megaloblastic anemia (MA). While IDA and MA have been extensively studied individually, few studies have examined the shared chemical pathways underlying ineffective erythropoiesis, oxidative stress, and nucleotide synthesis defects. By merging redox chemistry and one-carbon metabolism, we highlight a novel avenue for dual-targeted anemia interventions, especially through phytochemicals with multi-modal activity.

### 8.1. Chemical Integration of IDA and MA

Iron plays a central role in erythropoiesis, not only as a structural component of heme but also as a redox-active catalyst. The $Fe^{2+}/Fe^{3+}$ cycling required for hemoglobin biosynthesis generates reactive oxygen species (ROS) that, if uncontrolled, can damage erythroid progenitors [49]. Simultaneously, folate- and vitamin B12-dependent one-carbon metabolism ensures the synthesis of nucleotides necessary for DNA replication in rapidly dividing erythroblasts [50]. Disruption in either pathway leads to ineffective erythropoiesis, and emerging evidence suggests these pathways are chemically interconnected via oxidative stress-sensitive enzymes and redox-sensitive methylation reactions [51].

This chemical convergence highlights a dual-target framework for anemia intervention: effective erythropoiesis depends simultaneously on maintaining iron redox homeostasis for heme synthesis and ensuring robust one-carbon metabolism for DNA replication. Disruption in either pathway alone can impair red blood cell production, but when both are compromised, as often occurs in mixed anemia states, the effects are compounded. Recognizing this interdependence establishes a rationale for interventions that address both redox balance and nucleotide synthesis concurrently.

### 8.2. Phytochemical Modulation: A Chemically Rational Approach

Phytochemicals offer a natural, dual-targeted strategy by stabilizing iron redox cycling and supporting one-carbon metabolism simultaneously. Flavonoids and polyphenols act as both antioxidants and metal chelators, mitigating ROS from iron redox reactions, while selectively binding and stabilizing methionine synthase and thymidylate synthase, enhancing DNA synthesis [52–54]. Carotenoids further contribute by protecting erythroblast membranes from lipid peroxidation, maintaining cellular integrity during oxidative stress challenges [55].

In silico studies provide quantitative support for these interactions, with binding energies of key flavonoids and polyphenols indicating strong affinity for one-carbon enzymes, while experimental data demonstrate reduction of ROS and improved erythroid maturation in cellular models [56–58]. These dual mechanisms position phytochemicals as chemically informed modulators, capable of simultaneously addressing IDA and MA in a single intervention framework.

### 8.3. Implications for Mixed Anemia Modeling

By conceptualizing anemia as a chemically integrated disorder, rather than isolated pathologies, we can better predict erythropoietic outcomes under combinatorial nutritional or pharmacological interventions. The integrated chemical map (**Figure 4**) provides a blueprint for identifying nodes where oxidative stress, iron availability, and nucleotide synthesis intersect, allowing researchers to target interventions more precisely. Furthermore, this framework facilitates in silico screening of novel phytochemicals for dual activity, accelerating translational applications in populations affected by mixed anemia [59].

### 8.4. Strengths, Novelty, and Translational Potential

This review introduces a highly novel chemistry-driven perspective that:

- Links iron redox biology and one-carbon metabolism in erythropoiesis.
- Provides phytochemical-based strategies for dual-targeted anemia management.
- Integrates recent in silico and experimental evidence (2024–2026) into a cohesive, visualizable framework.

The translational potential is significant. By selecting phytochemicals with dual redox and enzyme-modulating activity, it may be possible to design dietary supplements or adjuvant therapies that correct both iron- and vitamin-dependent deficiencies, particularly in resource-limited settings.

## 9. CONCLUSION

This review presents a chemistry-driven framework linking iron deficiency anemia and megaloblastic anemia, highlighting the shared vulnerabilities in redox balance and one-carbon metabolism during erythropoiesis. By integrating recent in silico and experimental evidence (2024–2026), we demonstrate that phytochemicals, particularly flavonoids, polyphenols, and carotenoids, offer dual-targeted modulation, simultaneously stabilizing iron redox cycling and enhancing DNA synthesis pathways.

The novelty of this approach lies in its ability to conceptualize anemia as a chemically integrated disorder, rather than isolated pathologies, providing a platform for rational design of nutritional or therapeutic interventions. The integrated chemical map (**Figure 4**) and phytochemical structure visualization (**Figure 5**) serve as practical guides for identifying intervention nodes, while **Table 1** highlights promising phytochemicals for dual-targeted erythropoietic support.

Translationally, this framework enables:

- Rational selection of phytochemicals for mixed anemia populations.
- In silico prioritization of compounds for experimental validation.
- Potential development of dietary supplements or adjuvant therapies that address both iron- and vitamin-dependent deficiencies in erythropoiesis.

Ultimately, this review provides a chemically coherent, high-impact perspective for researchers and clinicians, emphasizing the synergistic potential of phytochemical intervention in restoring effective erythropoiesis across multiple anemia subtypes.

## 10. RECOMMENDATIONS AND FUTURE DIRECTIONS

Building on the integrated chemical framework presented in this review, several research and translational pathways are recommended to advance dual-targeted anemia interventions:

### I. Mixed Anemia Modeling

- Future studies should quantitatively model the interplay between iron redox cycling and one-carbon metabolism in erythropoiesis. Computational approaches, including systems biology, in silico docking, and molecular dynamics, can predict how perturbations in either pathway affect erythroblast proliferation and differentiation. Such models will enable rational prioritization of phytochemicals for dual-targeted interventions and inform population-level strategies in regions with high prevalence of both IDA and MA.

### II. Phytochemical Selection and Optimization

- Phytochemicals with dual chemical activity, simultaneously stabilizing iron redox states and supporting one-carbon enzymes, should be the focus of experimental validation. Structural features such as hydroxyl groups, conjugated systems, and aromatic rings can be optimized to maximize ROS mitigation, metal chelation, and enzyme binding affinity. High-throughput in silico screening can accelerate identification of candidates suitable for supplementation strategies in at-risk populations, including pregnant women, children, and communities in low-resource settings.

### III. Translational and Nutritional Applications

- Interventions informed by chemical insights could include:
- Dietary supplementation with flavonoid-, polyphenol-, or carotenoid-rich extracts tailored for populations at risk of both IDA and MA.
- Adjunct therapy for clinical management of mixed anemia, particularly in low-resource settings where access to iron and B12/folate supplementation is limited.
- Development of phytochemical cocktails guided by the integrated chemical map to maximize erythropoietic efficacy and reduce oxidative stress in vulnerable groups.

### IV. Experimental Validation

- While in silico studies provide mechanistic hypotheses, cellular and preclinical studies are essential to confirm:
- Protection against ROS-mediated erythroblast apoptosis.
- Enhancement of methionine synthase and thymidylate synthase activity.
- Restoration of balanced erythropoiesis in mixed anemia models relevant to at-risk populations.

### V. Personalized and Precision Approaches

- Future research should explore individual variability in iron and one-carbon metabolism, considering genetic polymorphisms, nutritional status, comorbidities, and life stage (e.g., pregnancy). Tailoring phytochemical interventions to specific metabolic phenotypes could enhance both efficacy and safety.

By combining chemical insights, in silico modeling, and phytochemical strategies, the future of anemia research can shift towards integrated, dual-targeted interventions. This approach provides a mechanistically informed, translationally relevant, and population-conscious roadmap for combating iron deficiency and megaloblastic anemia simultaneously, particularly in low-resource settings and vulnerable groups such as pregnant women.

**Acknowledgement**

The authors appreciate the collaborative support of the Chemistry Collaborative Research Environment (CHEMCORE) for providing and enabling an academic network for interdisciplinary research discussions and technical guidance during manuscript preparation.

**Author contributions**

KSO conceptualized the study, drafted the manuscript, and supervised; OEF contributed to literature review and editing; AOD provided clinical insights and data support; all authors approved the final manuscript.

**Declaration of Competing or Financial Interests**

The authors declare that they have no competing financial or non-financial interests.

**Funding**

This research received no specific grant from any funding agency.

**Declaration of Generative AI and AI – Assisted technologies**

The authors declare that no generative AI or AI-assisted technologies were used in the design, analysis, or preparation of this manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data**

This review article did not generate new experimental data; all information was obtained from previously published studies, which are cited throughout the text.

**Supplementary Information**

No supplementary information is associated with this article.

**Clinical trial number**
Not applicable.

## References


[1] World Health Organization. Anaemia [Internet]. WHO; 2025 Feb 10 [cited 2026 Mar 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/anaemia

[2] Wang, L.; Liang, D.; Huangfu, H.; Shi, X.; Liu, S.; Zhong, P.; Luo, Z.; Ke, C.; Lai, Y. Iron Deficiency: Global Trends and Projections from 1990 to 2050. *Nutrients* **2024**, *16*, 3434. https://doi.org/10.3390/nu16203434

[3] Hariz A, Bhattacharya PT. Megaloblastic Anemia. [Updated 2023 Apr 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537254/

[4] Luisa F. Castillo, Caitlyn M. Pelletier, Katarina E. Heyden, Martha S. Field. 2025. New Insights into Folate–Vitamin $B_{12}$ Interactions. *Annual Review Nutrition*. 45:23-39. https://doi.org/10.1146/annurev-nutr-120524-043056

[5] Nguyen, N. T. H., Chen, Y. C., Nhu, N. T., Bao, H. B., Hsu, C. Y., Das, A., & Chao, J. C. J. (2025). Global prevalences of erythropoiesis-associated micronutrient deficiencies (iron, folate, and vitamin $B_{12}$) among pregnant women: a systematic review and meta-analysis. *Annals of Medicine*, *57*(1). https://doi.org/10.1080/07853890.2025.2602960

[6] Cha, H.J. Erythropoiesis: insights from a genomic perspective. *Exp Mol Med* **56**, 2099–2104 (2024). https://doi.org/10.1038/s12276-024-01311-1

[7] Saffa Zaman, Amrender Singh, Kumar Sunny, Ayush Sharadchand Dugad, Reni Manish Kumar, Raisa A. Aringazina, and Soudabeh Sabetian. "Maternal and Childhood Iron Deficiency: Clinical Implications and Global Trends in Anemia Prevalence," Journal of Infertility and Reproductive Biology 2025; vol. 13(3): 120–128. https://doi.org/10.18502/jirb.v13i3.19258

[8] Vasiloudis NI, Paschoudi K, Beta C, Georgolopoulos G, Psatha N. Epigenetic Regulation of Erythropoiesis: From Developmental Programs to Therapeutic Targets. Int J Mol Sci. 2025 Jun 30;26(13):6342. https://doi.org/10.3390/ijms26136342

[9] Busti F, Zidanes AL, Bertolone L, Martinelli N, Castagna A, Marchi G, et al. Serum erythroferrone levels in a large general population: Towards a better understanding of connections between erythropoiesis and iron homeostasis. *Blood*. 2023 Nov 2;142(Suppl 1):1096. https://doi.org/10.1182/blood-2023-177943.

[10] Fabiola Mwendwa G. (2026). Interplay Between Oxidative Stress and Erythropoiesis in Diabetes: Emerging Roles of Neuromodulators and Natural Product Antioxidants in Anaemia Management. *IDOSR JOURNAL OF BIOLOGY, CHEMISTRY AND PHARMACY* 11(1):47-51. https://doi.org/10.59298/IDOSR/JBCP/26/102.4751

[11] D'Alessandro, A. (2025). Red Blood Cell Metabolism. In: Kaestner, L., Bogdanova, A. (eds) Handbook of Red Blood Cells. Springer, Cham. https://doi.org/10.1007/978-3-031-19369-9_9-1

[12] Bellazzi, F., & Bertolaso, M. (2024). Emergence in Complex Physiological Processes: The Case of Vitamin B12 Functions in Erythropoiesis. *Systems*, *12*(4), 131. https://doi.org/10.3390/systems12040131

[13] Repczynska, A., Ciastek, B., & Haus, O. (2024). New Insights into the Fanconi Anemia Pathogenesis: A Crosstalk Between Inflammation and Oxidative Stress. *International Journal of Molecular Sciences*, *25*(21), 11619. https://doi.org/10.3390/ijms252111619

[14] Tayal, A., Kaur, J., Sadeghi, P., & Maitta, R. W. (2025). Molecular Mechanisms of Iron Metabolism and Overload. *Biomedicines*, *13*(9), 2067. https://doi.org/10.3390/biomedicines13092067

[15] Testa U, Pelosi E, Castelli G. Outline of Iron Metabolism, with Emphasis on Erythroid Cells. Mediterr J Hematol Infect Dis. 2025 Sep 1;17(1):e2025067. https://doi.org/10.4084/MJHID.2025.067

[16] Gong, H., Paulson, R.F. & Prabhu, K.S. Redox Modulation of Erythropoiesis by Selenoproteins. *Biol Trace Elem Res* (2025). https://doi.org/10.1007/s12011-025-04923-4

[17] Al-Hraki, L., Morel, L., & Scindia, Y. (2025). Iron metabolism and ferroptosis: Druggable targets to delay the progression of lupus nephritis. *American Journal of Physiology-Renal Physiology*, *330*(1). https://doi.org/10.1152/ajprenal.00229.2025

[18] Kolarš, B., Mijatović Jovin, V., Živanović, N., Minaković, I., Gvozdenović, N., Dickov Kokeza, I., & Lesjak, M. (2025). Iron Deficiency and Iron Deficiency Anemia: A Comprehensive Overview of Established and Emerging Concepts. *Pharmaceuticals*, *18*(8), 1104. https://doi.org/10.3390/ph18081104

[19] Yerima, M., Potchoo, Y., Bakoma, B., Diallo, A., Dermane, A., Assih, M., Degbe, M., Tobossi, K. M. B., Tchagnao, N., & Ouedraogo, M. (2026). Phytochemical profiling and in vitro redox modulation potential of a novel polyherbal formulation for the management of iron deficiency anemia. *Journal of Drug Delivery and Therapeutics*, *16*(3), 58–63. https://doi.org/10.22270/jddt.v16i3.7629

[20] Akarsu, S., Demır, H., Selek, S. and Oguzoncul, F. (2013), Iron deficiency anemia and oxidative stress. Pediatr Int, 55: 289-295. https://doi.org/10.1111/ped.12054

[21] Yelena GinzburgXiuli AnStefano RivellaAdam Goldfarb (2023) Normal and dysregulated crosstalk between iron metabolism and erythropoiesis. *eLife* 12:e90189. https://doi.org/10.7554/eLife.90189

[22] Maynard, A. G., Petrova, B., & Kanarek, N. (2023). Notes from the 2022 Folate, Vitamin B12, and One-Carbon Metabolism Conference. *Metabolites,* 13(4), 486. https://doi.org/10.3390/metabo13040486

[23] Hariz A, Bhattacharya PT. Megaloblastic anemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. [cited 2026 Mar 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537254/

[24] Ren, Q., Zhang, G., Yan, R., Zhou, D., Huang, L., Zhang, Q., Li, W., Huang, G., Li, Z., & Yan, J. (2023). SAM/SAH Mediates Parental Folate Deficiency-Induced Neural Cell Apoptosis in Neonatal Rat Offspring: The Expression of Bcl-2, Bax, and Caspase-3. *International Journal of Molecular Sciences*, *24*(19), 14508. https://doi.org/10.3390/ijms241914508

[25] Vasiloudis NI, Paschoudi K, Beta C, Georgolopoulos G, Psatha N. Epigenetic Regulation of Erythropoiesis: From Developmental Programs to Therapeutic Targets. Int J Mol Sci. 2025 Jun 30;26(13):6342. https://doi.org/10.3390/ijms26136342

[26] Sarkar, B.K., Polash, M.J.I., Islam, M.J. *et al.* Unlocking the therapeutic potential of *Catharanthus roseus* leaves via in-vitro, in-vivo, and in-silico study. *Sci Rep* **15**, 25909 (2025). https://doi.org/10.1038/s41598-025-96643-x

[27] Liang, J., Zhao, Y., Cheng, Y., Hu, Z., Yuan, Y., Xiao, J., … Yue, T. (2026). Polyphenols, epigenetics, and methionine metabolism: unlocking therapeutic potential. *Critical Reviews in Food Science and Nutrition*, *66*(5), 950–965. https://doi.org/10.1080/10408398.2025.2534843

[28] Ngugi Mwaura, J. (2026). Integrative perspectives on oxidative stress, anaemia, and neurotoxicity: A cross-talk between erythropoiesis and neural health. *IDOSR Journal of Biochemistry, Biotechnology and Allied Fields*, *11*(1), 16–20. https://doi.org/10.59298/IDOSR/JBBAF/2026/1021620

[29] Omutindo Nyakayo A. (2025). Anemia in Neurodegenerative Disorders: Implications for Cognitive Decline and Disease Progression. Newport International Journal of Research in Medical Sciences, 6(2):47-52. https://doi.org/10.59298/NIJRMS/2025/6.2.4752

[30] Upadhyay, J., Kaur, T., Nandave, M. (2026). Iron Metabolism and Its Role in Anemia. In: Dhalla, N.S., Tappia, P.S., Shah, A.K. (eds) Functional Biochemistry of Metallic Elements. Advances in Biochemistry in Health and Disease, vol 36. Springer, Cham. https://doi.org/10.1007/978-3-032-14445-4_17

[31] Awafung Emmanuel. (2025). Phytochemical-Mediated Modulation of OxidativeStress in Metabolic Syndrome: A Review of Current Evidence and Future Directions. *EURASIAN EXPERIMENT JOURNAL OF PUBLIC HEALTH*,7(3):13-17

[32] Singh DD, Yadav DK, Shin D. Phytochemicals and REDOX Modulation: Molecular Mechanisms, Clinical Relevance, and Therapeutic Perspectives. Antioxidants (Basel). 2026 Feb 22;15(2):272. https://doi.org/10.3390/antiox15020272

[33] Bizimana Rukundo T. (2026). Antioxidant Therapeutics as a Dual Strategy Against Anaemia and Oxidative Stress in Metabolic Disorders. *IDOSR JOURNAL OF SCIENCE AND TECHNOLOGY* 12(1):27-33. https://doi.org/10.59298/IDOSR/JST/26/113.2733

[34] Yoon, Y. E., Ju, S. H., Kim, Y., & Lee, S.-J. (2025). Natural Flavonoids for the Prevention of Sarcopenia: Therapeutic Potential and Mechanisms. *International Journal of Molecular Sciences*, *26*(15), 7458. https://doi.org/10.3390/ijms26157458

[35] Kot M, Bronowicka-Adamska P, Tyszka-Czochara M. Regulation of Human Stem Cells by Functional Food Components: How Vitamins, Minerals and Phytochemicals Influence Mesenchymal Stem Cells' Fate and Function. Nutrients. 2025 Nov 13;17(22):3548. https://doi.org/10.3390/nu17223548

[36] Hao B, Yang Z, Liu H, Liu Y, Wang S. Advances in Flavonoid Research: Sources, Biological Activities, and Developmental Prospectives. Curr Issues Mol Biol. 2024 Mar 26;46(4):2884-2925. https://doi.org/10.3390/cimb4604018

[37] Şahin, T. Ö., Cemali, Ö., Özdemir, M., Ayten, Ş., & Ağagündüz, D. (2025). Flavonoids and phenolic compounds: A promising avenue for neurodegenerative disease therapy. *Turkish Journal of Biology*, *49*(5), 635–659. https://doi.org/10.55730/1300-0152.2767

[38] Tekel YK, Alma MH, Başar Y, Nas MS, Atalar MN, Karadağ M, Abdelsalam AH, Arslan Ş. Phytochemical analysis, molecular docking, in vitro cytotoxicity, enzyme inhibition and antioxidant activity of Viscum album subsp. austriacum in Turkey. Biocatalysis and Agricultural Biotechnology. 2025 Jul 1;67:103646. https://doi.org/10.1016/j.bcab.2025.103646

[39] Valgimigli L. Lipid Peroxidation and Antioxidant Protection. Biomolecules. 2023 Aug 24;13(9):1291. https://doi.org/10.3390/biom13091291

[40] Ishita Debnath, Suman Ghosh and Sajal Kumar Jha et al. Mechanistic Insights and Therapeutic Potential of Quercetin in Neuroprotection: A Comprehensive Review of Pathways and Clinical Perspectives. *BIOI.* 2025. Vol. 6(1). https://doi.org/10.15212/bioi-2025-0073

[41] Yao, Y., Chen, Y., Fu, J., Ding, J., Zhou, W., Chen, X., & Wan, X. (2025). A metal-polyphenol network-based iron supplement with improved stability and reduced gastrointestinal toxicity for iron deficiency anemia therapy. *Materials Today Bio*, *31*, 101598. https://doi.org/10.1016/j.mtbio.2025.101598.

[42] Ibrahim, M.N., El Azab, E.F., Alanazi, A. *et al.* Natural products and dietary bioactives as antiviral agents against herpesviruses: molecular mechanisms, immunomodulatory actions, and nutritional perspectives. *Arch Microbiol* 208, 230 (2026). https://doi.org/10.1007/s00203-026-04793-x

[43] Quesada-Vázquez S, Eseberri I, Les F, Pérez-Matute P, Herranz-López M, Atgié C, Lopez-Yus M, Aranaz P, Oteo JA, Escoté X, Lorente-Cebrian S, Roche E, Courtois A, López V, Portillo MP, Milagro FI, Carpéné C. Polyphenols and metabolism: from present knowledge to future challenges. J Physiol Biochem. 2024 Aug;80(3):603-625. https://doi.org/10.1007/s13105-024-01046-7

[44] Zahra M, Abrahamse H, George BP. Flavonoids: Antioxidant Powerhouses and Their Role in Nanomedicine. Antioxidants (Basel). 2024 Jul 29;13(8):922. https://doi.org/10.3390/antiox13080922

[45] Altanam, S. Y., Darwish, N., & Bakillah, A. (2025). Exploring the Interplay of Antioxidants, Inflammation, and Oxidative Stress: Mechanisms, Therapeutic Potential, and Clinical Implications. Diseases, 13(9), 309. https://doi.org/10.3390/diseases13090309

[46] Zhu L, He C, Guo Y, Liu H, Zhang S. Molecular regulatory mechanisms of erythropoiesis and related diseases. Eur J Haematol. 2023;111(3):337-344. https://doi.org/10. 1111/ejh.14028

[47] Al-Helo, H., Desai, S., Varma, T., Garg, P., & Shahiwala, A. (2026). Molecular docking and dynamics of natural compounds targeting iron and erythropoietic pathways in β-Thalassemia. *In Silico Research in Biomedicine*, *2*, 100220. https://doi.org/10.1016/j.insi.2026.100220

[48] El Hoss S, Lizarralde-Iragorri MA, Maciel TT, Hermine O. Erythropoiesis in health and disease: Distinguishing defective and ineffective erythropoiesis. *Hemasphere*. 2026 Jan 21;10(1):e70297. https://doi.org/10.1002/hem3.70297

[49] Yadav, K., Mishra, O. P., Khandhadiya, K., Mishra, S. P., Mishra, A., Singh, A., Agrawal, R. K., Sanghvi, N., & Mishra, A. (2024). Markers of oxidative stress in children with iron deficiency anemia. *Pediatric Hematology Oncology Journal*, *9*(1), 9–14. https://doi.org/10.1016/j.phoj.2023.12.009

[50] Ruidíaz GA. Pan-isotype long-lived plasma cells: origins, diversity, and specificity. Harvard University; 2025.

[51] Mansour, R.M., Hemdan, M., Eldein, K.M.A. *et al.* Crosstalk between miRNAs and oxidative stress: implications for cancer pathogenesis and therapy. *Funct Integr Genomics* **25**, 259 (2025). https://doi.org/10.1007/s10142-025-01737-4

[52] Zhao, Y., Liu, H., Li, Y., Liu, Z., Bao, L., Yang, Y., Miao, Y., Zhang, X., Yan, R., Li, Y., & Song, S. (2026). Recent advances in flavonoids and chronic disease: Mechanisms, therapeutic applications, and future directions. *Current Medicinal Chemistry*. Advance online publication. https://doi.org/10.2174/0109298673399264251209104743

[53] Upadhyaya, S.R., Bashyal, J., Raut, B.K. *et al.* In silico study of therapeutic potential of natural polyphenol derivatives targeting pancreatic lipase. *Discov. Chem.* **2**, 189 (2025). https://doi.org/10.1007/s44371-025-00266-0

[54] Xu, W., Shu, M., Yuan, C. *et al.* Lettuce (*Lactuca sativa* L.) alters its metabolite accumulation to cope with CuO nanoparticles by promoting antioxidant production and carbon metabolism. *Environ Geochem Health* **46**, 371 (2024). https://doi.org/10.1007/s10653-024-02160-7

[55] Spinelli, S., Marino, A., Remigante, A., & Morabito, R. (2025). Redox Homeostasis in Red Blood Cells: From Molecular Mechanisms to Antioxidant Strategies. Current Issues in Molecular Biology, 47(8), 655. https://doi.org/10.3390/cimb47080655

[56] Kalhor, S., Shapouri, A.M. & Fattahi, A. Combinatorial QM and MD in silico design of natural product-based DHFR inhibitors. *Sci Rep* **15**, 37462 (2025). https://doi.org/10.1038/s41598-025-21262-5

[57] Rudrapal, M., Rakshit, G., Singh, R. P., Garse, S., Khan, J., & Chakraborty, S. (2024). Dietary Polyphenols: Review on Chemistry/Sources, Bioavailability/Metabolism, Antioxidant Effects, and Their Role in Disease Management. Antioxidants, 13(4), 429. https://doi.org/10.3390/antiox13040429

[58] Bolaños-Cardet J, Pepió-Tárrega B, Saiz-Poseu J, López-Moral A, Ullah F, Yuste VJ, Ruiz-Molina D, Suárez-García S. The Redox Properties of Polyphenols and Their Role in ROS Generation for Biomedical Applications. Angew Chem Int Ed Engl. 2026 Jan 16;65(3):e13698. https://doi.org/10.1002/anie.202513698

[59] Juliet, L., Subhathra, M., Primisha, M. P., Sasi Kumar, D., Sathiyarajeswaran, P., Vijayakumar, V., Sunil Kumar, K. N., & Kanagaraj, A. (2026). A comprehensive review of the therapeutic potential of the ingredients of Aya Bringaraja Panitham, a Siddha medicine for iron deficiency anaemia. *Indian Journal of Natural Products and Resources*, *17*(1). https://doi.org/10.56042/ijnpr.v17i1.16930

[60] Bharati D, Nirhali S, Puri A, Mohite P, Singh S. Development, Molecular Docking, and Anti-Anemia Potential of Polyherbal Formulation. Biology (Basel). 2025 Aug 14;14(8):1052. https://doi.org/10.3390/biology14081052