INOSR APPLIED SCIENCES 13(2):77-81, 2025
©INOSR PUBLICATIONS
International Network Organization for Scientific Research
https://doi.org/10.59298/INOSRAS/2025/13.2.7781

ISSN: 2705-165X
INOSR13.2.000

Phytochemicals in Hematopoiesis: Unraveling the Role of Herbal Extracts in Nutritional and Inflammatory Anaemias

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ABSTRACT

Anaemia remains a global health burden with diverse etiologies, including nutritional deficiencies and chronic inflammation. Conventional treatments often face limitations due to poor adherence, toxicity, and cost, especially in low-resource settings. Phytochemicals derived from medicinal plants offer a promising alternative, modulating key pathways in erythropoiesis and iron metabolism. This review explores the role of herbal extracts in the treatment of nutritional and inflammatory anaemias. Key phytochemicals like flavonoids, alkaloids, saponins, and polyphenols-exert antioxidant, anti-inflammatory, and hematopoietic activities. Plants such as Moringa oleifera, Punica granatum, Zingiber officinale, and Vernonia amygdalina demonstrate potential in enhancing red blood cell production, improving iron absorption, and modulating cytokine-driven hepcidin expression. Mechanistic insights reveal interactions with erythropoietin signaling, iron transporter expression (DMT1, ferroportin), and inhibition of inflammatory cytokines (IL-6, TNF-α). The review also highlights preclinical and clinical evidence, limitations, and future directions for the integration of phytomedicine into anaemia management.

Keywords: Phytochemicals, Anaemia, Hematopoiesis, Iron metabolism, Herbal medicine

INTRODUCTION

Anaemia is a major global health concern that affects people of all ages, but disproportionately impacts women, children, and populations in low- and middle-income countries [1]. Defined by a decrease in red blood cell (RBC) count or hemoglobin concentration below reference levels, anaemia results in impaired oxygen delivery to tissues and a wide range of systemic symptoms including fatigue, pallor, dizziness, and impaired cognitive and physical performance [2]. According to World Health Organization (WHO) estimates, anaemia affects over 1.6 billion individuals worldwide, with iron-deficiency anaemia (IDA) being the most prevalent form [1]. The underlying causes of anaemia are multifactorial and include nutritional deficiencies (notably of iron, folate, and vitamin B12), chronic blood loss, hemolytic disorders, bone marrow suppression, and chronic inflammatory conditions [3]. Among these, nutritional anaemias and anaemia of chronic disease (ACD), also known as inflammatory anaemia, account for the majority of cases globally [4]. Inflammatory anaemia often coexists with infections such as tuberculosis and malaria, as well as autoimmune conditions and malignancies, further complicating diagnosis and management [4]. The pathophysiological mechanisms differ between these forms; however, both disrupt normal hematopoiesis and iron metabolism.

Standard treatments, including iron supplementation, erythropoiesis-stimulating agents, and blood transfusions, have improved patient outcomes but are associated with considerable limitations [5]. These include poor gastrointestinal tolerance, variable absorption rates, oxidative side effects, cost, and logistical challenges in resource-limited settings. Furthermore, in inflammatory contexts, iron supplementation may be ineffective due to functional iron blockade by elevated hepcidin levels, and ESA use is limited by risks of thromboembolism and hypertension [6]. Against this backdrop, there is a growing interest in phytomedicine as a complementary or alternative therapeutic strategy. Medicinal plants and their phytochemicals have been used for centuries in traditional systems of medicine for blood-building and vitality enhancement [7]. Modern scientific advances now provide evidence that certain bioactive compounds can support erythropoiesis, modulate iron regulatory pathways, and attenuate the

inflammatory milieu that suppresses hematopoiesis [8]. The holistic and multifaceted nature of these plant-derived compounds is particularly valuable in anaemia management, where oxidative stress, immune dysregulation, and nutritional deficiency often coexist. This review aims to explore the current understanding of phytochemicals in modulating hematopoiesis, particularly in the context of nutritional and inflammatory anaemias. It highlights the underlying pathophysiology, relevant phytochemical classes, their sources, molecular targets, and therapeutic implications based on preclinical and clinical evidence.

Pathophysiology of Nutritional and Inflammatory Anaemias

Anaemia results when red blood cell production fails to meet physiological demands or when RBCs are destroyed or lost at a rate exceeding their replacement [2]. Understanding the distinct yet overlapping mechanisms behind nutritional and inflammatory anaemias is critical to identifying therapeutic opportunities. Nutritional anaemias primarily result from deficiencies in iron, folate, or vitamin B12—micronutrients essential for erythropoiesis [9]. Iron is indispensable for hemoglobin synthesis, while folate and B12 are required for DNA replication and erythroblast proliferation [10]. In iron-deficiency anaemia, depleted iron stores impair hemoglobin synthesis, leading to microcytic, hypochromic red cells [11]. Causes include insufficient dietary intake, chronic gastrointestinal bleeding, malabsorption syndromes, and increased demands during pregnancy or growth [11]. Folate and B12 deficiency, on the other hand, causes megaloblastic anaemia due to impaired nuclear maturation and cell division [12].

Inflammatory anaemia, also called anaemia of chronic disease, is prevalent in patients with infections, cancer, autoimmune disorders, and chronic kidney disease [4]. In these states, inflammatory cytokines—particularly interleukin-6 (IL-6)—trigger hepatic production of hepcidin, the central regulator of iron homeostasis [13]. Hepcidin binds to and degrades ferroportin, the only known cellular iron exporter, thus blocking intestinal iron absorption and trapping iron within macrophages [14]. The net result is reduced serum iron availability despite adequate or elevated iron stores. Additionally, inflammation suppresses erythropoietin production, inhibits erythroid progenitor proliferation, and shortens RBC lifespan [15]. These pathologies are further aggravated by oxidative stress and impaired antioxidant defenses, which damage hematopoietic stem cells and erythrocytes [16]. Conventional interventions often address only one dimension of this complex pathology, underscoring the need for multi-targeted therapies. Phytochemicals, with their diverse bioactivities, offer a promising means of restoring hematological balance by targeting inflammation, oxidative damage, and nutrient bioavailability.

Phytochemicals and Their Hematopoietic Potential

Phytochemicals are naturally occurring compounds in plants that, while not essential nutrients, exert significant biological effects on human physiology. These include flavonoids, alkaloids, saponins, phenolic acids, tannins, lignans, and terpenoids [17]. Their therapeutic roles in hematopoiesis are gaining increasing attention due to their antioxidant, anti-inflammatory, immunomodulatory, and iron-enhancing properties. Flavonoids, found in plants such as Moringa oleifera, Camellia sinensis (green tea), and Punica granatum (pomegranate), exhibit strong antioxidant activity that protects hematopoietic tissues from oxidative injury [19]. They also modulate gene expression related to erythropoiesis and iron metabolism, such as those coding for erythropoietin, transferrin receptor, and divalent metal transporter-1 (DMT1) [18]. Polyphenols in green tea and red grape extract may suppress hepcidin synthesis and enhance ferroportin expression, improving iron mobilization and bioavailability [20].

Alkaloids from plants like Vernonia amygdalina and Carica papaya possess hematinic effects by stimulating erythroid precursor cells and enhancing hemoglobin synthesis [21]. Saponins from Gongronema latifolium and Panax ginseng improve nutrient absorption and modulate immune responses that affect iron status [22]. These compounds also support gastrointestinal health, which is essential for nutrient uptake and systemic iron homeostasis. Iron-rich botanicals such as Urtica dioica, Telfairia occidentalis, and Solanum nigrum are traditional blood tonics in African and Asian medicine [23]. These plants offer bioavailable iron in a food matrix rich in ascorbic acid and polyphenols that enhance absorption [24]. Unlike synthetic iron salts, which may generate free radicals and damage mucosal tissues, plant-based iron is associated with lower toxicity and improved tolerability [25].

Furthermore, some phytochemicals have been shown to enhance endogenous erythropoietin production or improve responsiveness to it, thus augmenting erythropoiesis. For example, quercetin and kaempferol may activate hypoxia-inducible factor (HIF-1α), a transcription factor involved in erythropoietin gene regulation [26]. In sum, phytochemicals act through diverse and complementary mechanisms to support hematopoiesis. Their role in the treatment of nutritional and inflammatory anaemias is not only rooted in tradition but increasingly supported by modern scientific inquiry. Continued investigation into their molecular actions and clinical effectiveness holds promise for integrative anaemia management.

Molecular Mechanisms of Action

Phytochemicals modulate hematopoiesis and iron metabolism through several key molecular pathways. One principal target is erythropoietin (EPO), the hormone responsible for red blood cell production [27]. Compounds

such as quercetin and kaempferol enhance hypoxia-inducible factor-1 alpha (HIF-1α), thereby promoting endogenous EPO synthesis and erythroid progenitor maturation in the bone marrow. Iron homeostasis is another critical axis [28]. Inflammatory states elevate interleukin-6 (IL-6), which induces hepatic hepcidin expression [29]. Hepcidin degrades ferroportin, impairing iron absorption and mobilization [6]. Phytochemicals including epigallocatechin gallate and curcumin inhibit IL-6 signaling, reducing hepcidin synthesis and restoring ferroportin function [30]. This facilitates the release of iron from macrophages and enterocytes, improving its availability for erythropoiesis.

Flavonoids also regulate iron transporters, such as divalent metal transporter-1 (DMT1) and transferrin receptors, enhancing dietary iron absorption and systemic utilization [31]. Their antioxidant action—through activation of nuclear factor erythroid 2–related factor 2 (Nrf2)—upregulates protective enzymes like superoxide dismutase and catalase, shielding hematopoietic tissues from oxidative injury [32]. Collectively, these mechanisms highlight the capacity of phytochemicals to support red blood cell production, counteract inflammation, and enhance iron bioavailability in both nutritional and inflammatory anaemias.

Preclinical and Clinical Evidence

Numerous animal studies have shown that extracts from Moringa oleifera, Telfairia occidentalis, and Gongronema latifolium improve hemoglobin concentration, red blood cell count, and iron parameters in anaemic models [33,34,35]. These effects correlate with increased ferroportin expression and decreased inflammatory cytokines. Clinical trials, although fewer, show encouraging results. In adolescent girls with iron-deficiency anaemia, Moringa oleifera leaf powder significantly improved hemoglobin and ferritin levels [36]. Punica granatum juice increased hemoglobin in pregnant women over an eight-week period [37]. Inflammatory anaemia improvements have also been observed with Nigella sativa and Allium sativum in chronic kidney disease patients [38]. Despite promising outcomes, these studies often suffer from small sample sizes, short durations, and inconsistent herbal formulations. Larger, well-designed trials are needed to validate therapeutic efficacy and guide standardized use.

Challenges and Future Directions

Key challenges include lack of standardization, poor bioavailability, and limited safety data. Variability in plant composition and extraction methods affects the reproducibility of results. Drug-herb interactions may alter the metabolism of conventional treatments, necessitating caution. To enhance clinical relevance, future research should focus on advanced delivery systems, mechanistic studies, and large-scale randomized trials. Regulatory frameworks must evolve to ensure quality, safety, and evidence-based integration of phytomedicines into anaemia management, particularly in underserved populations.

CONCLUSION

Phytochemicals offer a promising, multifaceted approach to managing nutritional and inflammatory anaemias through their effects on erythropoiesis, iron metabolism, and inflammation. Evidence from preclinical and emerging clinical studies supports their role in enhancing hematologic recovery and improving iron bioavailability with fewer side effects than conventional therapies. Standardization, rigorous clinical validation, and regulatory oversight remain essential for safe integration into clinical practice. Harnessing these plant-derived agents may significantly improve anaemia management, especially in resource-limited and high-burden settings.

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CITE AS: Taliikwa Nicholas Ceaser (2025). Phytochemicals in Hematopoiesis: Unraveling the Role of Herbal Extracts in Nutritional and Inflammatory Anaemias. INOSR APPLIED SCIENCES 13(2):77-81. https://doi.org/10.59298/INOSRAS/2025/13.2.7781