ISSN: 2579-0730

International Digital Organization for Scientific Research IDOSR JBCP/26/102.1700
IDOSR JOURNAL OF BIOLOGY, CHEMISTRY AND PHARMACY 11(1):47-51, 2026.
https://doi.org/10.59298/IDOSR/JBCP/26/102.4751

Interplay Between Oxidative Stress and Erythropoiesis in Diabetes: Emerging Roles of Neuromodulators and Natural Product Antioxidants in Anaemia Management

Fabiola Mwendwa G.

School of Applied Health Sciences Kampala International University Uganda

ABSTRACT

Anaemia is a common and underappreciated complication of diabetes that worsens quality of life, increases cardiovascular risk, and accelerates progression of diabetic complications. Multiple interacting mechanisms contribute to diabetes-associated anaemia, including reduced erythropoietin (EPO) production, iron dysregulation, shortened red blood cell (RBC) lifespan, bone marrow suppression, and chronic inflammation. Oxidative stress-driven by hyperglycaemia, dyslipidaemia, mitochondrial dysfunction, and advanced glycation end-products-is a central, unifying mediator that perturbs erythropoiesis at molecular and cellular levels. Beyond direct oxidative damage to erythroid precursors and mature RBCs, redox imbalance alters signaling pathways (HIF, JAK/STAT, NF-κB), disrupts iron handling (hepcidin–ferroportin axis), and modulates neuro-immune interactions that can influence hematopoiesis. Neuromodulators (endogenous and drug-like agents that alter neural input to hematopoietic and immune compartments) and natural product antioxidants (polyphenols, flavonoids, terpenoids, alkaloids, and omega-3 fatty acids) are emerging as promising adjuncts for correcting redox-driven defects in diabetic erythropoiesis. This review integrates mechanistic insights into oxidative stress–mediated suppression of erythropoiesis in diabetes, evaluates evidence that neuromodulatory pathways intersect with hematopoietic regulation, and examines preclinical and clinical data for natural antioxidants as supportive therapies in diabetic anaemia. We highlight therapeutic strategies, formulation and safety considerations, and research priorities needed to translate these biologically plausible interventions into clinical practice.

Keywords: Diabetic anaemia, oxidative stress, erythropoiesis, neuromodulation, natural antioxidants

INTRODUCTION

Anaemia complicates diabetes in both type 1 and type 2 patients and is more prevalent than commonly recognized, particularly among those with renal impairment, chronic inflammation, or poor glycaemic control [1]. Even modest reductions in haemoglobin correlate with fatigue, diminished exercise capacity, cognitive dysfunction, and worse cardiovascular outcomes [2]. Management currently focuses on correcting reversible causes (iron deficiency, vitamin deficits), optimizing glycaemic control, and, where appropriate, treating renal anaemia with erythropoiesis-stimulating agents (ESAs) [3]. However, ESAs have limitations and risks, and many patients have mixed pathophysiology-not purely iron deficiency or renal EPO insufficiency so adjunctive approaches that target upstream mechanisms are attractive. Oxidative stress is a pervasive feature of the diabetic milieu [4]. Hyperglycaemia accelerates mitochondrial ROS generation, non-enzymatic glycation produces reactive advanced glycation end-products (AGEs), and dyslipidaemia promotes lipotoxicity and mitochondrial dysfunction [5]. Oxidative and nitrosative stress damage erythroid progenitors, modify membrane proteins on circulating RBCs reducing their lifespan, and skew systemic and bone marrow cytokine profiles toward inflammation [6]. Importantly, oxidative stress also intersects with neurohumoral regulation and iron metabolism two key determinants of effective erythropoiesis [7]. These intersecting pathways suggest multi-target strategies could restore balanced hematopoiesis more effectively than single-target therapies.

2. Diabetes, oxidative stress, and erythropoiesis: mechanistic links

2.1 Sources and consequences of oxidative stress in diabetes

Oxidative stress represents a major biochemical disturbance in both type 1 and type 2 diabetes mellitus. Hyperglycaemia drives excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) through several converging biochemical routes [5]. Overloaded mitochondrial electron transport results in electron leakage and superoxide formation, while enzymatic systems such as NADPH oxidase, xanthine oxidase, and uncoupled nitric oxide synthase further amplify ROS production [8]. Glycation and subsequent formation of advanced glycation end-products (AGEs) also generate free radicals and activate their cellular receptors (RAGE), perpetuating redox imbalance [9].

The erythroid compartment is particularly vulnerable to oxidative stress because erythrocytes constantly handle oxygen and contain high levels of polyunsaturated fatty acids and iron that can catalyze radical reactions [10]. Excess ROS oxidizes hemoglobin and heme groups, producing methemoglobin and impairing oxygen-carrying capacity. Lipid peroxidation of erythrocyte membranes disrupts membrane fluidity, reduces deformability, and enhances mechanical fragility, promoting premature splenic clearance [11]. Oxidative modification of cytoskeletal proteins such as spectrin and band 3 further compromises structural integrity [12]. Collectively, these events shorten red cell lifespan and increase erythropoietic demand, setting the stage for anaemia in diabetic states.

2.2 Impact on erythroid progenitors and marrow microenvironment

Normal erythropoiesis depends on the coordinated regulation of hematopoietic progenitors, stromal cells, erythropoietin (EPO) signaling, and iron metabolism within the bone marrow niche. Oxidative stress interferes with several of these regulatory axes [13]. Persistent ROS accumulation destabilizes hypoxia-inducible factor-1α (HIF-1α), a key transcription factor that senses tissue oxygen tension and regulates EPO synthesis [14]. Under oxidative stress, prolyl hydroxylases remain active and promote HIF-1α degradation, thereby reducing endogenous EPO production and impairing adaptive responses to anaemia [15].

At the progenitor level, oxidative damage activates stress kinases such as p38 MAPK and JNK, leading to apoptosis or cell-cycle arrest in erythroid precursors. DNA and mitochondrial damage in erythroblasts further limit their proliferative potential [16]. The surrounding stromal and endothelial cells that provide paracrine support to erythropoiesis are similarly susceptible to oxidative damage, leading to reduced secretion of growth-promoting cytokines and disruption of adhesion molecule interactions critical for erythroid maturation [17]. The cumulative result is ineffective erythropoiesis characterized by a lower output of mature, functional erythrocytes.

2.3 Iron metabolism, hepcidin, and inflammation

Iron homeostasis is a central determinant of effective erythropoiesis. In diabetes, chronic low-grade inflammation drives overexpression of the hepatic peptide hormone hepcidin through IL-6/STAT3 and BMP/SMAD signaling pathways [18]. Elevated hepcidin levels decrease iron export from macrophages and intestinal enterocytes by degrading the iron transporter ferroportin, creating a functional iron deficiency even when total body iron stores are sufficient [19]. Oxidative stress can potentiate these effects by activating redox-sensitive transcription factors such as NF-κB, which further enhance hepcidin expression. Consequently, erythroid progenitors are deprived of available iron for hemoglobin synthesis, aggravating anaemia [20]. Furthermore, oxidative stress promotes ferritin oxidation and release of labile iron, which catalyzes Fenton-type reactions and produces hydroxyl radicals, amplifying tissue injury [21]. The interplay among oxidative stress, inflammation, and iron dysregulation therefore forms a self-reinforcing loop that progressively impairs erythropoiesis and erythrocyte survival in diabetic individuals.

2.4 Neuro-immune and neuromodulatory influences

Beyond metabolic and inflammatory factors, the nervous system exerts important regulatory influences on erythropoiesis. Sympathetic fibers innervating the bone marrow release norepinephrine, which modulates hematopoietic stem and progenitor cell proliferation and migration through β-adrenergic signaling [22]. Diabetes-related autonomic neuropathy reduces sympathetic tone, altering the circadian rhythm of hematopoietic cell release and compromising progenitor function [23]. In parallel, disruption of the parasympathetic (vagal) anti-inflammatory reflex removes an important brake on cytokine overproduction, indirectly heightening hepcidin synthesis and oxidative stress [24]. These neuroimmune disturbances contribute to the multifactorial suppression of erythropoiesis observed in diabetes.

3. Neuromodulators and hematopoiesis: conceptual and mechanistic rationale

The concept of neuromodulation in erythropoiesis refers to the ability of neuronal signals and neuromodulatory molecules to influence hematopoietic cell dynamics either directly within the bone marrow microenvironment or indirectly through systemic neuroendocrine and immune pathways [25]. Sympathetic, parasympathetic, and sensory nerves all form intricate networks within the bone marrow niche, where they interact with stromal, endothelial, and hematopoietic cells. Catecholamines released from sympathetic terminals act on β-adrenergic receptors expressed on stromal and progenitor cells, regulating their proliferation and differentiation [26].

Experimental studies have shown that stimulation of β-adrenergic pathways mobilizes hematopoietic stem cells into circulation and can influence lineage bias, favoring erythroid output under specific physiological contexts [27]. Conversely, vagal (cholinergic) neuromodulation exerts anti-inflammatory effects that may indirectly support erythropoiesis [28]. Activation of the cholinergic anti-inflammatory reflex suppresses proinflammatory cytokines such as IL-6 and TNF-α, leading to decreased hepcidin levels and improved iron bioavailability [29]. This pathway also mitigates oxidative stress by dampening macrophage activation and reactive oxygen species generation, creating a more favorable marrow microenvironment for erythroid maturation [29]. Other neuromodulators, including neuropeptide Y, substance P, serotonin, and dopamine, participate in hematopoietic regulation through receptor-mediated mechanisms [30]. Dopaminergic and serotonergic receptors have been identified on progenitor and stromal cells, suggesting that monoamines influence cell proliferation, apoptosis, and differentiation [31]. For instance, serotonin has been implicated in enhancing erythroid colony formation, while dopamine may exert both stimulatory and inhibitory effects depending on receptor subtype and concentration [32].

In diabetes, chronic hyperglycaemia and oxidative stress impair neuronal function, leading to autonomic imbalance and reduced neurotrophic signaling [33]. The resulting deficiency in neuromodulatory control contributes to dysregulated hematopoiesis. Emerging evidence indicates that pharmacological agents or lifestyle interventions capable of restoring healthy neurohumoral balance could indirectly improve erythropoiesis. For example, β-adrenergic agonists or vagus nerve stimulators might re-establish physiological regulation of the marrow niche, enhance perfusion, and normalize the inflammatory milieu [34]. Moreover, several natural product antioxidants exert neuromodulatory properties such as modulation of monoaminergic systems, protection of autonomic neurons, and attenuation of neuroinflammation, which could synergistically support erythropoietic recovery in diabetes-related anaemia [35]. While direct clinical data remain limited, the mechanistic intersections between oxidative stress, neuroimmune regulation, and erythropoiesis highlight an emerging paradigm in which neuromodulators either pharmacologic or phytochemical, may complement antioxidant therapy to restore redox balance, promote erythroid survival, and mitigate anaemia in diabetic populations.

5. Therapeutic strategies and practical considerations

An integrated approach to diabetic anaemia that targets oxidative drivers and supports erythropoiesis might include: optimized glycaemic control; identification and correction of iron, B12, and folate deficiencies; use of bioavailable natural antioxidants as adjuncts; neuromodulatory interventions (e.g., exercise, vagal stimulation, or selective pharmacologic agents) to restore neuroimmune balance; and cautious use of ESAs when indicated. Key considerations for natural products include bioavailability (use of phytosome, nanoparticle, or complexed formulations), dose-dependent effects (antioxidant vs pro-oxidant at high doses), potential iron-chelation by some polyphenols, and drug–nutrient interactions affecting concurrent medications (antiplatelets, anticoagulants, antihyperglycaemics). Safety and standardization are paramount.

CONCLUSION

Oxidative stress is a central, treatable contributor to impaired erythropoiesis in diabetes, acting through direct damage to RBCs and progenitors, dysregulated iron handling, and altered neuro-immune regulation. Neuromodulatory approaches and natural product antioxidants provide biologically plausible, multitarget strategies to complement conventional treatments for diabetic anaemia. Translating promise into practice requires rigorous clinical trials, optimized formulations, and integrated treatment pathways that address the multifactorial nature of diabetic anaemia. With these steps, antioxidant and neuromodulatory adjuncts could improve haemoglobin, functional capacity, and long-term outcomes in people living with diabetes.

REFERENCES

1. Aja O. A., Egba S. I., Omoboyowa D. A., Odo C. E., Vining-Ogu I. C., Oko F. O (2020) Anti-anaemic and immunomodulatory potentials of aqueous, chloroform and methanol leaf extracts of *whitfieldia lateritia* on 2, 4-dinitrophenylhydrazine induced anaemia in rats. World Journal of Pharmacy Research 2020; 9(10): 44-58
2. Alum, E. U., Ugwu, O. P. C., Aja, P. M., Obeagu, E. I., Inya, J. E., Onyeije, P. E., Agu, E. and Awuchi, C. G. Restorative effects of ethanolic leaf extract of *Datura stramonium* against methotrexate-induced hematological impairments, Cogent Food & Agriculture, 2023; 9:1, DOI: 10.1080/23311932.2023.2258774
3. Obeagu, E. I., Bot, Y. S., Obeagu, G. U. and Ugwu, O. P. C. Anaemia and risk factors in lactating mothers: a concern in Africa. *International Journal of Innovative and Applied Research*, 2023;**11**(2): 15-17. Article DOI: 10.58538/IJIAR/2012 DOI URL: http://dx.doi.org/10.58538/IJIAR/2012.
4. Orji, E. A., S. I. Egba, and B. O. Mgbenka. Influence of Sub-Chronic Administration of Fruit Extracts of Xylopia aethiopica on Haematopoietic System of Male Wistar Albino Rats. Asian Journal of Biology 2017; 4 (1):1-8. https://doi.org/10.9734/AJOB/2017/36422.
5. Uti DE, Atangwho IJ, Alum EU, Egba SI, Ugwu OPC, Ikechukwu GC. Natural Antidiabetic Agents: Current Evidence and Development Pathways from Medicinal Plants to Clinical use. Natural Product Communications. 2025;20(3). doi:10.1177/1934578x251323393

6. Obeagu EI, Igwe MC, Obeagu GU. Oxidative stress's impact on red blood cells: Unveiling implications for health and disease. Medicine. 2024;103(9):e37360. doi:10.1097/md.0000000000037360
7. Bresgen N, Eckl P. Oxidative stress and the homeodynamics of iron metabolism. Biomolecules. 2015;5(2):808–47. doi:10.3390/biom5020808
8. Ugwu, O. P.C., Okon, M. B., Aja, P. M., Obeagu, E. I. and Onyeneke, E. C. Ethanol root extract and fractions of *Sphenocentrum jollyanum* abrogate hyperglycemia and low body weight in Streptozotocin-induced diabetic Wistar albino Rats, *RPS Pharmacy and Pharmacology Reports.* 2023; 2,1-6. https://doi.org/10.1093/rpsppr/rqad010.
9. Krishnamoorthy, R., Gatasheh, M. K., Subbarayan, S., Vijayalakshmi, P., Uti, D. E. Protective Role of Jimson Weed in Mitigating Dyslipidemia, Cardiovascular, and Renal Dysfunction in Diabetic Rat Models: In Vivo and in Silico Evidence. Natural Product Communications. 2024;19(12). doi:10.1177/1934578X241299279
10. Spinelli S, Marino A, Remigante A, Morabito R. Redox homeostasis in red blood cells: From molecular mechanisms to antioxidant strategies. PubMed. 2025;47(8). Available from: https://pubmed.ncbi.nlm.nih.gov/40864809
11. Godfrey Ogochukwu Ezema, Ndukaku Yusuf Omeh, Egba Simeon Ikechukwu, Ejiofor C Agbo, Adachukwu Ada Ikeyiand Emmanuel Ifeanyi Obeagu. Evaluation of Biochemical Parameters of Patients with Type 2 Diabetes Mellitus Based on Age and Gender in Umuahia (2023) Asian Journal of Dental and Health Sciences 2023; 3(2):32-3.
12. Kriebardis AG, Antonelou MH, Stamoulis KE, Economou-Petersen E, Margaritis LH, Papassideri IS. Progressive oxidation of cytoskeletal proteins and accumulation of denatured hemoglobin in stored red cells. Journal of Cellular and Molecular Medicine. 2007;11(1):148–55. doi:10.1111/j.1582-4934.2007.00008.x
13. Ginzburg Y, An X, Rivella S, Goldfarb A. Normal and dysregulated crosstalk between iron metabolism and erythropoiesis. eLife. 2023;12. doi:10.7554/elife.90189
14. Iacobini C, Vitale M, Haxhi J, Pesce C, Pugliese G, Menini S. Mutual Regulation between Redox and Hypoxia-Inducible Factors in Cardiovascular and Renal Complications of Diabetes. Antioxidants. 2022;11(11):2183. doi:10.3390/antiox11112183
15. Haase VH. HIF-prolyl hydroxylases as therapeutic targets in erythropoiesis and iron metabolism. Hemodialysis International. 2017;21(S1). doi:10.1111/hdi.12567
16. Eom HJ, Choi J. p38 MAPK Activation, DNA Damage, Cell Cycle Arrest and Apoptosis As Mechanisms of Toxicity of Silver Nanoparticles in Jurkat T Cells. Environmental Science & Technology. 2010;44(21):8337–42. doi:10.1021/es1020668
17. Yang C, Suda T. Microenvironmental dynamics in steady-state and stress erythropoiesis. Blood Science. 2025;7(1):e00219. doi:10.1097/bs9.0000000000000219
18. Wunderer F, Traeger L, Sigurslid HH, Meybohm P, Bloch DB, Malhotra R. The role of hepcidin and iron homeostasis in atherosclerosis. Pharmacological Research. 2020;153:104664. doi:10.1016/j.phrs.2020.104664
19. Nemeth E, Ganz T. Hepcidin and iron in health and disease. Annual Review of Medicine. 2022;74(1):261–77. doi:10.1146/annurev-med-043021-032816
20. Alum, E.U., Uti, D.E. & Offor, C.E. Redox Signaling Disruption and Antioxidants in Toxicology: From Precision Therapy to Potential Hazards. *Cell Biochem Biophys* (2025). https://doi.org/10.1007/s12013-025-01846-8
21. Akwari, A.A., Okoroh, P.N., Aniokete, U.C., Abba, J.N., Uti, D.E. Phytochemicals as modulators of ferroptosis: a novel therapeutic avenue in cancer and neurodegeneration. *Mol Biol Rep* **52**, 636 (2025). https://doi.org/10.1007/s11033-025-10752-4
22. Cosentino M, Marino F, Maestroni GJM. Sympathoadrenergic modulation of hematopoiesis: a review of available evidence and of therapeutic perspectives. Frontiers in Cellular Neuroscience. 2015;9. doi:10.3389/fncel.2015.00302
23. Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. Methodist DeBakey Cardiovascular Journal. 2018;14(4):251. doi:10.14797/mdcj-14-4-251
24. Boeckxstaens G. The clinical importance of the anti-inflammatory vagovagal reflex. Handbook of Clinical Neurology. 2013:119–34. doi:10.1016/b978-0-444-53491-0.00011-0
25. Rey F, Balsari A, Giallongo T, Ottolenghi S, Di Giulio AM, Samaja M, et al. Erythropoietin as a Neuroprotective molecule: An Overview of its therapeutic potential in neurodegenerative diseases. ASN NEURO. 2019;11:175909141987142. doi:10.1177/1759091419871420
26. Khalil B, Rosani A, Warrington SJ. Physiology, catecholamines. StatPearls - NCBI Bookshelf. 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507716/

27. Nair R, Subramaniam V, Barwick BG, Gupta VA, Matulis SM, Lonial S, et al. β adrenergic signaling regulates hematopoietic stem and progenitor cell commitment and therapy sensitivity in multiple myeloma. Haematologica. 2022;107(9):2226–31. doi:10.3324/haematol.2022.280907
28. Bazoukis G, Stavrakis S, Armoundas AA. Vagus Nerve Stimulation and Inflammation in Cardiovascular Disease: A State-of-the-Art Review. Journal of the American Heart Association. 2023;12(19). doi:10.1161/jaha.123.030539
29. Ramos-Martínez IE, Rodríguez MC, Cerbón M, Ramos-Martínez JC, Ramos-Martínez EG. Role of the Cholinergic Anti-Inflammatory Reflex in central nervous system diseases. International Journal of Molecular Sciences. 2021;22(24):13427. doi:10.3390/ijms222413427
30. Liu Y, Chen Q, Jeong HW, Han D, Fabian J, Drexler HCA, et al. Dopamine signaling regulates hematopoietic stem and progenitor cell function. Blood. 2021;138(21):2051–65. doi:10.1182/blood.2020010419
31. Krishnamoorthy R, Gatasheh MK, Famurewa AC, Subbarayan S, Vijayalakshmi P, Uti DE. Neuroprotective Potential of Jimson Weed in Methotrexate-Induced Neurotoxicity: Insights into Anti-Oxidative, Anti-Inflammatory, and Anti-Apoptotic Mechanisms via Modulation of Caspase-3, Interleukin-6, and Tumor Necrosis Factor-Alpha: In Silico. Endocr Metab Immune Disord Drug Targets. 2025 Aug 15. doi: 10.2174/0118715303350736241220090850.
32. Alex KD, Pehek EA. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacology & Therapeutics. 2006;113(2):296–320. doi:10.1016/j.pharmthera.2006.08.004
33. Giri B, Dey S, Das T, Sarkar M, Banerjee J, Dash SK. Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity. Biomedicine & Pharmacotherapy. 2018;107:306–28. doi:10.1016/j.biopha.2018.07.157
34. Rey F, Balsari A, Giallongo T, Ottolenghi S, Di Giulio AM, Samaja M, et al. Erythropoietin as a Neuroprotective molecule: An Overview of its therapeutic potential in neurodegenerative diseases. ASN NEURO. 2019;11:175909141987142. doi:10.1177/1759091419871420
35. Nuzzo D. Role of natural antioxidants on neuroprotection and neuroinflammation. Antioxidants. 2021;10(4):608. doi:10.3390/antiox10040608

CITE AS: 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