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Natural Product-Based Neuromodulators in the Prevention of Diabetic Anaemia: Linking Antioxidant Defense to Erythroid and Neural Function

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ABSTRACT

Diabetic anemia is a common and often under-recognized complication of diabetes mellitus, characterized by impaired erythropoiesis, reduced erythropoietin production, and systemic oxidative stress. This condition not only compromises oxygen delivery to peripheral tissues but also exacerbates neurodegenerative changes, contributing to cognitive decline and heightened vulnerability to neural dysfunction. Natural product-based antioxidants, including polyphenols, flavonoids, carotenoids, and terpenoids, have emerged as promising therapeutic agents due to their dual capacity to mitigate oxidative damage and modulate key signaling pathways involved in erythroid and neuronal health. These compounds act by scavenging reactive oxygen and nitrogen species, enhancing endogenous antioxidant defenses, stabilizing mitochondrial function, and regulating hypoxia-inducible factors to promote erythropoietin synthesis. Additionally, they exert neuroprotective effects by activating the Nrf2 pathway, reducing neuroinflammation, and preserving synaptic integrity. This review provides a comprehensive overview of the molecular mechanisms through which natural antioxidants influence erythropoiesis and neural function in the context of diabetes-induced anemia. We also discuss translational and clinical perspectives, emphasizing the potential integration of these compounds into therapeutic strategies that combine dietary, pharmacological, and lifestyle interventions to prevent or mitigate the multifaceted impacts of diabetic anemia on systemic and neural health.

Keywords: Diabetic anemia, natural antioxidants, erythropoiesis, neuroprotection, oxidative stress, erythropoietin

INTRODUCTION

Diabetic anemia is a frequent complication in patients with both type 1 and type 2 diabetes mellitus, with prevalence estimates ranging from 14% to over 30% depending on disease duration and comorbidities [1]. It is primarily characterized by reduced red blood cell (RBC) mass, impaired erythropoietin (EPO) production, and shortened RBC lifespan. The pathophysiology of diabetic anemia is multifactorial, involving oxidative stress, chronic inflammation, iron dysregulation, and autonomic neuropathy [2]. Elevated reactive oxygen species (ROS) and reactive nitrogen species (RNS) in hyperglycemic states damage erythroid progenitors and mature RBCs, while chronic inflammation elevates hepcidin levels, restricting iron availability for erythropoiesis. Beyond hematologic complications, diabetic anemia contributes to systemic hypoxia, which negatively impacts multiple organs, particularly the central nervous system (CNS) [3]. Hypoxia-induced neuronal stress, combined with hyperglycemia-mediated oxidative damage, accelerates cognitive decline, neuropathy, and neurodegenerative processes [4]. Thus, addressing both oxidative stress and erythropoietic dysfunction is crucial for mitigating the multifaceted consequences of diabetic anemia [5]. Natural product-based antioxidants offer a promising therapeutic avenue. Compounds such as polyphenols, flavonoids, carotenoids, and terpenoids can modulate oxidative stress, enhance EPO production, stabilize mitochondrial function, and protect neural tissues. Additionally, some natural products act as neuromodulators, influencing autonomic and neuroimmune pathways that regulate erythropoiesis [6]. This review examines the mechanisms linking oxidative stress, erythropoiesis, and neural function in diabetic anemia and highlights the potential of natural antioxidants as dual erythroid and neuroprotective agents.

Pathophysiology of Diabetic Anemia

Oxidative Stress and Erythropoiesis

Chronic hyperglycemia in diabetes increases intracellular glucose flux through the polyol, hexosamine, and protein kinase C pathways, resulting in excess ROS generation [7]. Mitochondrial electron transport chain dysfunction further amplifies oxidative stress. ROS target erythroid progenitors in the bone marrow, impairing proliferation and differentiation, while also promoting apoptosis through activation of p38 MAPK and JNK signaling pathways [8]. Oxidative damage to mature RBCs, including lipid peroxidation and protein carbonylation of membrane proteins such as spectrin and band 3, reduces RBC deformability, increasing their clearance by the spleen. Additionally, oxidative modifications accelerate eryptosis, a form of programmed RBC death, further depleting circulating erythrocytes. Together, these effects contribute to anemia and increased cardiovascular and neural risk in diabetic patients [9].

Neurodegenerative Consequences

Reduced oxygen delivery due to anemia exacerbates neural hypoxia, triggering neuroinflammatory cascades and mitochondrial dysfunction. Oxidative stress promotes protein misfolding, synaptic dysfunction, and microglial activation, mechanisms associated with cognitive impairment and neurodegeneration [10]. Autonomic neuropathy in diabetes further disrupts neurohumoral regulation of erythropoiesis, illustrating the bidirectional interplay between hematologic and neural health.

Iron Metabolism and Inflammatory Modulation

Diabetes-associated chronic inflammation elevates hepcidin via IL-6/STAT3 signaling, restricting iron availability from macrophages and enterocytes [11]. Oxidative stress potentiates inflammatory pathways, reinforcing hepcidin-mediated functional iron deficiency. This cycle amplifies erythropoietic insufficiency and highlights the need for interventions that address both redox balance and iron metabolism [12].

Natural antioxidants play a pivotal role in preventing and mitigating diabetic anemia by simultaneously supporting erythropoiesis and protecting neural function. Their dual action arises from potent redox-modulating, anti-inflammatory, and neuromodulatory properties, which converge to stabilize both bone marrow and central nervous system environments under conditions of chronic hyperglycemia and oxidative stress [13].

Polyphenols, including resveratrol, quercetin, and curcumin, have been extensively studied for their multifaceted effects. Resveratrol, a stilbene found in grapes, berries, and peanuts, activates the SIRT1 and Nrf2 signaling pathways, enhancing mitochondrial efficiency, reducing ROS-mediated DNA and protein damage, and preserving erythroid progenitor viability [14]. These effects extend to neural tissues, where resveratrol improves synaptic plasticity and mitigates neuroinflammatory responses associated with diabetic neuropathy. Curcumin, derived from turmeric, inhibits NF-κB and MAPK pathways, limiting the production of pro-inflammatory cytokines, reducing apoptosis in erythroid progenitors, and enhancing erythropoietin expression [15]. In parallel, curcumin protects neurons by maintaining mitochondrial membrane potential and attenuating oxidative stress-induced degeneration. Quercetin, abundant in fruits and vegetables such as apples and onions, stabilizes redox homeostasis, promotes endogenous antioxidant enzyme expression, and supports EPO synthesis [16]. In neuronal tissues, quercetin reduces apoptosis, preserves synaptic function, and improves cognitive outcomes in diabetic models, exemplifying a compound with integrated erythroid and neuroprotective benefits.

Carotenoids, including β-carotene and lutein, contribute to both systemic and neural antioxidant defense [17]. β-Carotene acts as a membrane-stabilizing antioxidant, mitigating oxidative injury in erythrocytes and hepatocytes, improving hemoglobin synthesis, and prolonging RBC survival. Lutein accumulates in retinal and cortical tissues, where it scavenges free radicals, preserves mitochondrial integrity, and reduces synaptic damage, collectively supporting cognitive function in diabetes [18].

Terpenoids, such as ginsenosides from ginseng and withanolides from Withania somnifera, provide additional layers of protection. These compounds enhance mitochondrial bioenergetics, modulate neuroinflammatory signaling, and promote hypoxia-inducible factor-mediated erythropoietin synthesis [19]. By integrating neuromodulatory and erythropoietic effects, terpenoids serve as natural dual-function agents capable of addressing both systemic and CNS complications in diabetic anemia.

Mechanistically, these natural antioxidants converge on multiple protective nodes. They modulate oxidative stress, activate cytoprotective pathways such as Nrf2, stabilize mitochondria, attenuate inflammation, and enhance erythropoietin production [20]. In the CNS, they maintain synaptic integrity, prevent glial overactivation, and reduce neuroinflammation. Collectively, these actions support cognitive and neural resilience while sustaining erythropoiesis, establishing natural antioxidants as promising therapeutic agents for integrated management of diabetic anemia [21].

Neuromodulation and Erythropoiesis

Autonomic Influence

The sympathetic and parasympathetic systems play pivotal roles in regulating bone marrow niches through β-adrenergic and cholinergic signaling. Sympathetic stimulation promotes the mobilization of hematopoietic progenitors, supports erythroid precursor proliferation, and coordinates maturation processes, whereas parasympathetic (vagal) signaling influences erythropoiesis indirectly by modulating systemic inflammation [22]. In diabetic conditions, autonomic neuropathy diminishes both sympathetic and parasympathetic signals, impairing progenitor mobilization, reducing erythroid maturation, and limiting the responsiveness to erythropoietin [23]. Natural compounds with neuromodulatory properties, including polyphenols, terpenoids, and alkaloids, have demonstrated the ability to restore autonomic balance. These compounds enhance sympathetic-parasympathetic communication, improve marrow perfusion, reduce oxidative stress within progenitor niches, and support erythroid lineage progression, addressing both hematologic deficiencies and systemic complications associated with diabetic anemia [24].

Neuroimmune Crosstalk

Vagal anti-inflammatory signaling constitutes a crucial mechanism by which the nervous system influences erythropoiesis. Activation of this pathway reduces systemic pro-inflammatory cytokines, thereby downregulating hepatic hepcidin expression and improving iron availability for red blood cell synthesis [25]. Natural antioxidants, such as resveratrol, curcumin, and ginsenosides, enhance vagal tone, mitigate systemic inflammation, and indirectly facilitate erythropoiesis. By concurrently reducing oxidative stress and inflammation in neural and marrow environments, these compounds promote erythroid recovery while preserving neural integrity [26]. This dual functionality highlights the potential of neuromodulatory antioxidants to integrate erythropoietic and cognitive protection in diabetic patients.

Integrated Hematologic and Neural Benefits

Through combined actions on oxidative stress, neuroimmune signaling, and erythropoietin synthesis, natural antioxidants serve as dual-function agents [27]. They stabilize erythroid progenitor niches, prolong RBC lifespan, maintain synaptic integrity, reduce glial overactivation, and protect neuronal networks from diabetes-related oxidative and inflammatory damage [28]. Such integrative effects position natural antioxidants as ideal candidates for therapeutic strategies targeting both hematologic and neural complications of diabetic anemia.

Therapeutic Applications

Dietary and Supplement Strategies

Dietary intake of antioxidant-rich foods, including berries, green leafy vegetables, turmeric, and ginseng, enhances systemic redox balance, promotes hemoglobin synthesis, stabilizes erythrocyte membranes, and protects neural function [29]. Standardized nutraceuticals allow for controlled dosing, improved bioavailability, and synergistic effects of multiple bioactive compounds. Combining these dietary strategies with lifestyle interventions can reinforce erythropoiesis, maintain cognitive function, and strengthen the liver-brain-bone marrow axis [30].

Adjunctive Therapy

Natural antioxidants can complement conventional treatments such as erythropoiesis-stimulating agents, iron supplementation, and glycemic management [31]. Integrative use may reduce pharmacologic doses, minimize side effects, and improve patient outcomes. Exercise and cognitive training further support neuro-hematologic health by enhancing antioxidant defenses, promoting neurogenesis, and improving marrow perfusion [32].

Future Directions

Future research should focus on identifying reliable biomarkers that reflect liver-brain-bone marrow axis function, enabling early detection of diabetic anemia and personalized intervention. Long-term safety, dosing, and bioavailability of natural antioxidants require systematic evaluation. Multi-omics approaches, including genomics, proteomics, and metabolomics, can elucidate molecular mechanisms and uncover novel therapeutic targets [33]. Large-scale clinical trials are necessary to validate efficacy across diverse populations. Personalized medicine strategies that integrate metabolic profiling, genetic predisposition, and environmental exposure history may optimize outcomes, enabling targeted prevention and treatment of diabetic anemia while simultaneously protecting neural function.

CONCLUSION

Natural product-based antioxidants offer a promising strategy for preventing and mitigating diabetic anemia through dual erythropoietic and neuroprotective actions. By reducing oxidative stress, enhancing erythropoietin production, stabilizing mitochondrial function, and modulating neuroimmune and autonomic pathways, these compounds bridge erythroid and neural health. Integrating natural antioxidants with conventional therapy and lifestyle interventions holds potential for comprehensive management of diabetic anemia, improving systemic and neural outcomes. Continued research will be pivotal in translating preclinical findings into effective clinical strategies.

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