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Neuromodulatory Potential of Natural Antioxidants in Diabetic Neuropathy: Molecular Mechanisms and Therapeutic Insights

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ABSTRACT

Diabetic neuropathy is a common, debilitating complication of diabetes characterized by sensory loss, neuropathic pain, and autonomic dysfunction. Oxidative stress is a central pathogenic driver, promoting neuronal damage, mitochondrial dysfunction, and maladaptive neuroinflammation. Natural antioxidants-plant-derived polyphenols, flavonoids, terpenoids, and other phytochemicals-exert pleiotropic effects beyond simple free-radical scavenging, including modulation of ion channels, neurotransmitter systems, neurotrophic signaling, and inflammatory cascades. This review synthesizes current mechanistic evidence that natural antioxidants can act as neuromodulators in diabetic neuropathy, affecting neuronal excitability, synaptic function, neuroimmune interactions, and nerve repair. We discuss major compound classes (e.g., curcuminoids, resveratrol, quercetin, EGCG, ginsenosides), their molecular targets (mitochondria, NADPH oxidases, Nrf2, NF-κB, MAPKs, TRP channels, voltage-gated sodium channels, GABAergic and glutamatergic receptors), and preclinical/clinical evidence for symptomatic and disease-modifying effects. Therapeutic insights, formulation and bioavailability challenges, safety considerations, and rational combination strategies are outlined. We conclude by identifying promising translational paths and experimental priorities to move antioxidant neuromodulators from bench to bedside in diabetic neuropathy.

Keywords: Diabetic neuropathy, natural antioxidants, neuromodulation, oxidative stress, neuroinflammation

INTRODUCTION

Diabetic neuropathy (DN) represents one of the most prevalent and disabling complications of both type 1 and type 2 diabetes mellitus, affecting up to half of diabetic patients over time [1]. It encompasses a broad spectrum of clinical manifestations, including sensory loss, paresthesia, autonomic dysfunction, and chronic neuropathic pain, with distal symmetric polyneuropathy being the most common form [1]. The condition arises from complex metabolic and vascular insults resulting from prolonged hyperglycaemia, dyslipidaemia, and insulin resistance [2]. These metabolic disturbances initiate a series of interrelated biochemical pathways—such as excessive formation of reactive oxygen species (ROS), accumulation of advanced glycation end-products (AGEs), activation of the polyol and hexosamine pathways, and chronic microvascular ischemia that ultimately damage peripheral nerves [2]. Conventional management strategies for diabetic neuropathy largely focus on glycaemic control and symptomatic relief. Agents such as antidepressants, anticonvulsants, and opioids are commonly prescribed to mitigate pain perception by targeting ion channels or neurotransmitter systems [3]. However, these treatments fail to address the underlying molecular mechanisms of neuronal injury and often produce significant side effects, limiting long-term efficacy. Consequently, there is increasing interest in disease-modifying therapies capable of protecting or repairing neural tissue. Natural antioxidants-bioactive compounds found in plants, herbs, and dietary sources-have emerged as promising candidates due to their dual ability to neutralize oxidative stress and modulate neural signaling [4]. Beyond simple free-radical scavenging, many natural antioxidants exhibit neuromodulatory properties, influencing synaptic plasticity, neurotransmitter release, and neuronal excitability. Their multitargeted mechanisms suggest potential for both neuroprotection and functional recovery, offering a more holistic therapeutic approach to diabetic neuropathy [5].

2. Pathophysiological rationale: why neuromodulation via antioxidants?

Oxidative stress is a central pathophysiological factor in diabetic neuropathy, acting as both a trigger and amplifier of neuronal dysfunction. Chronic hyperglycaemia drives ROS and reactive nitrogen species (RNS) production through several biochemical routes, including mitochondrial electron transport chain overload, activation of NADPH oxidase, and formation of AGEs [6]. These reactive species damage cellular macromolecules-lipids, proteins, and DNA-while simultaneously impairing mitochondrial function and reducing ATP generation in neurons and Schwann cells [7]. As a result, axonal degeneration, demyelination, and altered neuronal firing patterns occur. ROS-mediated modifications of ion channels, such as voltage-gated sodium and calcium channels or transient receptor potential (TRP) channels, increase neuronal excitability and contribute to painful neuropathic sensations [8]. Concurrently, oxidative stress activates inflammatory transcription factors like NF-κB and AP-1, stimulating cytokine release from macrophages, microglia, and astrocytes [9]. This neuroinflammatory milieu disrupts synaptic homeostasis and propagates central sensitization, reinforcing pain transmission. Neuromodulation through natural antioxidants aims to interrupt this vicious cycle by restoring redox equilibrium, reducing inflammation, and stabilizing neuronal signaling. These compounds can scavenge ROS directly, activate endogenous antioxidant systems via the Nrf2/ARE pathway, and inhibit proinflammatory mediators [10]. Furthermore, some natural antioxidants regulate neurotransmitter systems, modulate receptor sensitivity, and improve mitochondrial bioenergetics, collectively enhancing neuronal resilience [11]. By targeting oxidative and excitotoxic mechanisms simultaneously, antioxidant-mediated neuromodulation provides both symptomatic relief and structural neuroprotection, representing a rational, multifaceted strategy for managing diabetic neuropathy [12].

3. Major classes of natural antioxidants with neuromodulatory evidence

Natural antioxidants comprise a broad and chemically diverse group of bioactive compounds that exhibit both antioxidant and neuromodulatory properties. Their therapeutic potential in diabetic neuropathy (DN) stems from their ability to modulate oxidative stress, inflammation, and neuronal excitability through multiple molecular pathways [13]. Among these, polyphenols, flavonoids, terpenoids, and certain alkaloids have received the most attention for their neuroprotective and neuromodulatory effects.

3.1 Polyphenols (resveratrol, curcumin, EGCG)

Polyphenols are among the most studied natural antioxidants with demonstrated neuromodulatory actions. Resveratrol, a stilbene found in grapes and red wine, activates the SIRT1 pathway, which enhances mitochondrial biogenesis, improves energy metabolism, and suppresses neuroinflammation [14]. Through SIRT1 and AMPK activation, resveratrol stabilizes mitochondrial membrane potential, prevents apoptosis of dorsal root ganglion neurons, and reduces hyperalgesia in diabetic models [15]. It also upregulates Nrf2 signaling, thereby strengthening endogenous antioxidant defense systems [16].

Curcumin, the active constituent of Curcuma longa, exhibits broad neuromodulatory effects by interacting with multiple cellular targets. It decreases oxidative damage, inhibits NF-κB and p38 MAPK pathways, and attenuates inflammatory cytokine production [17]. Curcumin also modulates neurotransmission by influencing monoamine levels and may enhance expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [18]. Experimental models show that curcumin alleviates mechanical allodynia and thermal hyperalgesia while preserving nerve conduction velocity and axonal structure [19].

Epigallocatechin gallate (EGCG), the major catechin in green tea, exerts strong antioxidant effects through both direct ROS scavenging and upregulation of antioxidant enzymes including superoxide dismutase (SOD) and heme oxygenase-1 (HO-1) [20]. EGCG also modulates excitatory glutamatergic neurotransmission, suppresses microglial activation, and maintains synaptic homeostasis [21]. This combined antioxidant and neuromodulatory actions contribute to improved neuronal survival and reduced pain behavior in DN models.

3.2 Flavonoids (quercetin, rutin, hesperidin)

Flavonoids, abundant in fruits and vegetables, modulate redox balance and neuroexcitability. Quercetin inhibits NADPH oxidase activity, reduces lipid peroxidation, and enhances mitochondrial antioxidant enzyme expression [22]. It also modulates calcium and sodium channels involved in nociceptive signaling, dampening neuronal hyperexcitability [23]. Rutin and hesperidin improve microvascular perfusion and strengthen antioxidant defense mechanisms, indirectly supporting neuronal energy metabolism [24]. In diabetic rodents, flavonoid supplementation improves thermal and tactile thresholds, promotes remyelination, and enhances sensory recovery, indicating their capacity for both neuroprotection and neuromodulation [25].

3.3 Terpenoids and saponins (ginsenosides, ginkgo biloba constituents)

Terpenoids and triterpenoid saponins, such as ginsenosides from Panax ginseng, display complex actions on neural systems. Ginsenosides modulate neurotransmitter receptors, including GABAergic and glutamatergic systems, and enhance the expression of BDNF and nerve growth factor (NGF) [26]. These effects support synaptic plasticity and nerve repair. Ginkgo biloba extract, rich in ginkgolides and bilobalide, acts as a potent free radical scavenger, inhibits

platelet-activating factors, and stabilizes mitochondrial function [27]. Together, these mechanisms improve endoneurial blood flow and promote neural resilience under diabetic stress.

3.4 Others (omega-3 PUFAs, alkaloids like berberine)

Omega-3 polyunsaturated fatty acids (PUFAs) derived from fish oils reduce systemic and neural inflammation and restore membrane fluidity, which influences ion channel function and synaptic transmission [30]. They also enhance neurotrophic signaling and myelin repair [30]. Berberine, an isoquinoline alkaloid found in Berberis species, exerts antioxidant and AMPK-activating effects, improving both glucose homeostasis and neuronal metabolism [29]. By suppressing oxidative stress and modulating neurotransmitter dynamics, berberine provides indirect neuromodulatory benefits that may alleviate diabetic neuropathic symptoms.

4. Molecular targets mediating neuromodulatory actions

The neuromodulatory efficacy of natural antioxidants in diabetic neuropathy arises from their capacity to influence key molecular pathways governing oxidative stress, inflammation, ion channel activity, and neurotrophic signaling.

4.1 Nrf2–ARE pathway

The Nrf2–antioxidant response element (ARE) axis is a master regulator of redox homeostasis. Activation of Nrf2 by polyphenols such as curcumin, resveratrol, and EGCG enhances transcription of detoxifying and antioxidant genes, including glutathione peroxidase, catalase, and HO-1 [30]. This adaptive response reduces oxidative injury, preserves mitochondrial function, and downregulates pain-related signaling, positioning Nrf2 activation as a central mechanism in antioxidant-mediated neuromodulation.

4.2 NADPH oxidases and mitochondrial ROS

Hyperglycaemia-driven activation of NADPH oxidases (NOX1, NOX4) is a major source of neuronal ROS [31]. Compounds such as quercetin and curcumin inhibit NOX expression, limiting superoxide generation at its origin [32]. Additionally, natural antioxidants improve mitochondrial electron transport chain efficiency, reducing electron leakage and ROS overproduction [33]. Stabilization of mitochondrial membranes also prevents calcium overload and apoptosis, supporting long-term neuronal survival [34].

4.3 Ion channels and sensory transducers

Ion channels are key determinants of neuronal excitability. In diabetic neuropathy, oxidative modification of TRPV1, TRPA1, and voltage-gated sodium channels (Nav1.7, Nav1.8) contributes to spontaneous firing and hyperalgesia [35]. Polyphenols and flavonoids can modulate these channels directly or through redox-sensitive cysteine residues, normalizing excitability and reducing nociceptive transmission. This ion-channel modulation represents a direct neuromodulatory mechanism beyond antioxidant effects.

4.4 Neuroinflammatory signaling (NF-κB, MAPKs)

Activation of NF-κB and MAPK cascades under hyperglycaemic stress drives cytokine release (TNF-α, IL-1β) and microglial activation [36]. Natural antioxidants inhibit these pathways, suppressing the neuroinflammatory feedback loop that maintains central sensitization. Reduction in spinal microglial activation correlates with improved sensory thresholds and reduced pain perception in experimental models [37].

4.5 Neurotrophic support and axonal repair

Natural antioxidants also exert trophic effects by upregulating BDNF, NGF, and other growth-associated proteins that enhance axonal repair and synaptic regeneration [38]. Restoration of neurotrophic signaling is critical for reversing structural degeneration in diabetic nerves. Thus, by integrating antioxidant, anti-inflammatory, and trophic mechanisms, natural compounds provide a holistic neuromodulatory approach to diabetic neuropathy therapy.

CONCLUSION

Natural antioxidants offer a promising, mechanistically grounded avenue for neuromodulation in diabetic neuropathy. Their multimodal actions-antioxidant, anti-inflammatory, mitochondrial protective, ion channel modulatory, and neurotrophic-align with the multifactorial pathogenesis of diabetic nerve injury. Translating these agents into clinically useful therapy requires rigorous standardization, improved delivery systems, and high-quality clinical trials that measure both symptomatic and structural outcomes. If these hurdles are addressed, natural antioxidant neuromodulators could complement existing treatments, offering both symptom relief and disease-modifying potential for patients with diabetic neuropathy.

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