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Neuromodulation and Metabolic Detoxification: Natural Compounds as Mediators Between Environmental Toxicity and Neurodegenerative Risks in Diabetic Conditions

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ABSTRACT

Diabetes mellitus alters systemic metabolism and increases vulnerability to both environmental toxicants and neurodegenerative processes. Environmental chemicals-heavy metals, persistent organic pollutants, pesticides, and air pollutants-can exacerbate oxidative stress, mitochondrial dysfunction, inflammation, and impaired proteostasis, mechanisms that overlap with metabolic derangements in diabetes and with pathways leading to neurodegeneration. Natural compounds derived from plants, marine organisms, and fungi possess dual activities: they can modulate neuronal signaling (neuromodulation) and support metabolic detoxification pathways (phase I/II enzymes, antioxidant defenses, metal chelation). This review synthesizes mechanistic evidence linking environmental toxicant exposure and heightened neurodegenerative risk in diabetic settings, and examines how selected natural compounds (polyphenols, flavonoids, terpenoids, alkaloids, marine carotenoids, and omega-3 polyunsaturated fatty acids) act as mediators that simultaneously attenuate toxicant burden and preserve neuronal function. We discuss modes of action-Nrf2 activation, mitochondrial stabilization, modulation of cytochrome P450 and conjugating enzymes, metal chelation, anti-inflammatory and anti-aggregate effects, and direct modulation of ion channels and neurotransmitter systems. Preclinical and emerging clinical data supporting neuroprotective and detoxification roles are summarized, along with formulation, pharmacokinetic, and safety considerations. We conclude by outlining research priorities to translate dual-action natural compounds into integrative strategies for reducing neurodegenerative risk in people with diabetes who face environmental chemical exposures.

Keywords: diabetes, environmental toxicants, neuromodulation, detoxification, natural compounds

INTRODUCTION

Diabetes mellitus imposes chronic metabolic stress characterized by hyperglycaemia, altered lipid profiles, insulin resistance, and chronic low-grade inflammation [1]. These systemic perturbations compromise cellular antioxidant capacity, mitochondrial resilience, and proteostatic mechanisms-creating a milieu in which additional external insults produce disproportionate harm [1]. Environmental toxicants are ubiquitous across air, water, soil, and food; chronic low-dose exposures to heavy metals (arsenic, lead, cadmium), persistent organic pollutants (PCBs, dioxins), pesticides (organophosphates), and airborne particulate matter have all been linked to increased risk of metabolic disorders and to direct neurotoxicity [2]. In diabetic individuals, the confluence of impaired metabolic detoxification and enhanced pro-oxidant pressure raises the possibility that toxicant exposures accelerate neurodegenerative processes such as cognitive decline, Alzheimer-type pathology, Parkinsonism, and small-fiber neuropathy [3]. Natural compounds-broadly defined as bioactive molecules produced by plants, algae, fungi, and some microbes-have long been studied for antioxidant, anti-inflammatory, and metabolic effects [4]. Critically, many natural compounds also influence neuronal signaling pathways (neuromodulation), including neurotransmitter systems, ion channel function, and synaptic plasticity. Simultaneously, some modulate xenobiotic metabolism by affecting cytochrome P450 enzymes, phase II conjugation systems, metal chelation, and induction of endogenous antioxidant programs such as Nrf2-ARE [5]. Viewed through an integrative lens, these dual activities position natural compounds as potential mediators that both reduce toxicant burden and preserve neural health in diabetic contexts. This review integrates current mechanistic understanding of how environmental toxicants interact with diabetic

biology to heighten neurodegenerative risk, and evaluates evidence that natural compounds offer combined neuromodulatory and detoxifying benefits relevant to prevention and therapy.

2. Why diabetics are more vulnerable: convergence of mechanisms

Several overlapping mechanisms explain the increased susceptibility of diabetic individuals to environmental neurotoxins. First, diabetes impairs antioxidant defenses: glutathione depletion, reduced superoxide dismutase and catalase activity, and dysfunctional Nrf2 signaling diminish the ability to neutralize reactive oxygen and nitrogen species generated by toxicants [6]. Second, mitochondrial dysfunction-common in diabetes due to substrate overload and impaired biogenesis-magnifies toxicant-induced electron leakage and ROS generation, precipitating energy failure and activating cell-death pathways in neurons [7]. Third, chronic systemic inflammation characteristic of diabetes primes microglia and peripheral macrophages to exaggerated responses, transforming otherwise subclinical exposures into sustained neuroinflammatory states that disrupt synaptic networks [8]. Fourth, diabetes alters phase I/II detoxification capacity and hepatic metabolism, sometimes increasing formation of reactive metabolites from environmental pro-toxins [9]. Finally, diabetic neuropathy and altered blood–brain barrier permeability can facilitate central nervous system entry of circulating toxicants or inflammatory mediators, directly exposing vulnerable neuronal populations [10]. Together, these factors create a feed-forward loop: toxicants increase oxidative and proteostatic stress; diabetes limits repair and clearance; neuronal networks succumb to dysfunction and degeneration. Addressing this interplay requires interventions that both lower toxicant burden and bolster neuronal resilience.

3. Dual-action natural compounds: classes and representative mechanisms

Natural compounds exhibit a remarkable capacity to influence both metabolic detoxification pathways and neuronal function, making them particularly relevant for diabetic individuals exposed to environmental toxicants. Polyphenols and flavonoids, including resveratrol, quercetin, and epigallocatechin-3-gallate (EGCG), are among the most extensively studied molecules. These compounds activate the Nrf2–ARE pathway, resulting in upregulation of endogenous antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and phase II detoxifying enzymes including glutathione S-transferases and NAD(P)H: quinone oxidoreductase 1 [11]. Through these mechanisms, polyphenols mitigate oxidative stress, facilitate conjugation and elimination of reactive xenobiotic metabolites, and restore cellular redox balance. Beyond detoxification, polyphenols modulate neurotransmission and synaptic plasticity by regulating glutamatergic and GABAergic systems, protecting against excitotoxicity, and preserving long-term potentiation, which is critical for cognitive function [12].

Curcuminoids and terpenoids, such as curcumin, oleanolic acid, and ginsenosides, also exert dual effects. These compounds stabilize mitochondrial membranes, enhance mitochondrial biogenesis, and prevent ROS accumulation [13]. Anti-inflammatory signaling is a key component of their activity; they inhibit NF-κB and MAPK pathways, thereby reducing cytokine-driven neuroinflammation and preventing activation of glial cells [14]. Terpenoids additionally influence ion channels, such as voltage-gated calcium and sodium channels, and support neurotrophic signaling through BDNF and NGF pathways, which promotes neuronal survival and axonal regeneration [14]. Some terpenoids modulate hepatic phase I and phase II enzymes, altering the metabolism of xenobiotics and reducing the formation of reactive intermediates [15].

Alkaloids and related small molecules, including berberine and l-theanine, offer complementary mechanisms. Berberine improves insulin sensitivity and mitochondrial function via AMPK and SIRT1 activation while also modulating cytochrome P450 enzymes to prevent bioactivation of environmental pro-toxins [16]. L-theanine exerts neuromodulatory effects by modulating monoaminergic systems, reducing excitotoxic neurotransmission, and enhancing parasympathetic tone, which indirectly regulates inflammatory pathways that could affect detoxification and neuronal health [17].

Marine-derived carotenoids such as astaxanthin and fucoxanthin, as well as omega-3 polyunsaturated fatty acids, provide robust membrane-stabilizing antioxidant activity and support mitochondrial integrity. These compounds reduce neuroinflammation through specialized pro-resolving lipid mediators, modulate neuronal excitability by altering membrane lipid composition, and maintain proteostasis in the context of oxidative and inflammatory stress [18]. Metal-chelating polyphenols, such as tannins and EGCG, limit the catalytic activity of transition metals like iron and copper, thereby suppressing Fenton-mediated hydroxyl radical formation, which is particularly relevant in environmental metal exposure scenarios [19]. Collectively, these compounds are pleiotropic: they simultaneously support redox homeostasis, enhance metabolic detoxification, reduce neuroinflammation, preserve neuronal excitability, and promote mitochondrial and synaptic health. This dual functionality positions natural compounds as unique therapeutic candidates to mitigate the compounded risks of environmental toxicants and diabetes-driven neurodegeneration.

4. Mechanistic intersections: how natural compounds reduce toxicant-driven neurodegeneration

The protective actions of natural compounds arise from multiple intersecting mechanisms that simultaneously modulate detoxification pathways and neuronal resilience. Activation of the Nrf2–ARE pathway is a central mechanism, driving the transcription of antioxidant and phase II detoxification genes [20]. By enhancing

glutathione synthesis, upregulating conjugating enzymes, and facilitating xenobiotic elimination, natural compounds reduce intracellular accumulation of reactive intermediates [21]. This pathway also attenuates neuroinflammation by suppressing NF-κB signaling, thereby protecting synaptic integrity and neuronal survival [20,21].

Mitochondrial protection is another critical intersection. Environmental toxicants and hyperglycaemic stress in diabetes converge on mitochondrial dysfunction, resulting in electron leakage, ROS overproduction, and ATP depletion [22]. Natural compounds stabilize the electron transport chain, promote mitophagy, and induce mitochondrial biogenesis through SIRT1/PGC-1α and AMPK pathways [23]. These effects preserve neuronal energy homeostasis, limit apoptotic signaling, and maintain synaptic function.

Modulation of xenobiotic metabolism represents a further mechanism. By selectively inhibiting or regulating cytochrome P450 isoforms, natural compounds reduce the formation of reactive metabolites while favoring safer detoxification pathways [24]. Upregulation of UDP-glucuronosyltransferases, sulfotransferases, and glutathione conjugation enzymes enhances hepatic clearance of environmental toxins [25]. Simultaneously, chelation of transition metals by polyphenols or carotenoids prevents radical generation through Fenton chemistry, mitigating oxidative damage in neurons and peripheral tissues [26].

Proteostasis and anti-aggregate effects also contribute to neuroprotection. Compounds such as curcumin, resveratrol, and ginsenosides inhibit misfolding and aggregation of neurotoxic proteins, including amyloid-β and α-synuclein, and promote autophagic clearance [27]. These processes are particularly relevant in diabetes, where oxidative stress and metabolic dysfunction exacerbate proteotoxicity.

Neuromodulatory actions complement detoxification. Polyphenols, terpenoids, and omega-3 fatty acids modulate ion channel function (TRP channels, voltage-gated sodium and calcium channels), regulate neurotransmitter receptors, and enhance synaptic plasticity [28]. Indirectly, they improve autonomic tone and reduce neuroimmune activation, restoring homeostatic control over inflammatory signaling that can otherwise exacerbate neuronal injury [29]. By converging on detoxification, redox homeostasis, mitochondrial function, and neuromodulation, natural compounds provide integrated protection against environmental and metabolic insults in diabetic individuals, offering a mechanistically plausible strategy to mitigate neurodegenerative risk.

5. Evidence: preclinical and clinical highlights

Preclinical models demonstrate that natural compounds can attenuate both toxicant burden and neurotoxicity in metabolic contexts. For example, polyphenol administration reduces heavy-metal accumulation, lowers oxidative markers, and preserves cognitive and motor function in toxin-exposed diabetic rodents [30]. Curcumin and resveratrol have been shown to improve mitochondrial markers and reduce protein aggregation in models combining metabolic stress and environmental insults [31]. Marine-derived astaxanthin and omega-3 PUFAs mitigate pollutant-induced neuroinflammation and synaptic loss [32].

Clinical evidence remains preliminary but promising. Epidemiological studies link diets rich in polyphenols and omega-3s to lower cognitive decline in populations with high pollutant exposure [33]. Small clinical trials report improvements in inflammatory biomarkers, oxidative stress indices, and cognitive scores with supplementation in at-risk populations, but large, rigorously controlled trials specifically addressing diabetic patients with environmental exposures are lacking.

CONCLUSION

Diabetes magnifies vulnerability to environmental toxicants through impaired antioxidant defenses, mitochondrial dysfunction, inflammation, and altered detoxification. Natural compounds with integrated detoxifying and neuromodulatory activities provide a biologically plausible strategy to blunt toxicant-driven acceleration of neurodegenerative processes in diabetic individuals. Translating this promise into clinical impact requires standardized, bioavailable formulations, rigorous safety assessments, biomarker-driven clinical trials, and integrative approaches that combine exposure reduction with metabolic and neurologic support. With these steps, dual-action natural compounds could become a practical component of strategies to reduce neurodegenerative risk in vulnerable diabetic populations.

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