

Carbofuran-Induced Neurotoxicity and Potential Neuroprotective Effects of Curcumin: Mechanisms, Evidence, and Translational Prospects

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Abstract Carbofuran, a widely used N-methyl carbamate pesticide, induces acute cholinergic toxicity and long-term neurotoxicity through acetylcholinesterase inhibition, oxidative stress, and mitochondrial dysfunction. These mechanisms contribute to neurobehavioral impairments and systemic toxicity, posing significant public health concerns. This review aims to elucidate the mechanistic insights of carbofuran neurotoxicity and evaluate the potential neuroprotective effects of curcumin, a natural antioxidant compound, highlighting translational prospects for mitigating pesticide-induced neuronal damage. A comprehensive literature survey was conducted focusing on carbofuran's toxic dynamic, oxidative and mitochondrial injury pathways, and preclinical and clinical evidence supporting curcumin's antioxidant, anti-inflammatory, and mitochondrial stabilizing actions in models of pesticide toxicity. Carbofuran toxicity involves reversible carbamylation of acetylcholinesterase, excessive reactive oxygen species generation, lipid peroxidation, TCA cycle disruption, and endocrine axis interference. Curcumin demonstrates neuroprotection by scavenging ROS, modulating NF- κ B signaling, restoring antioxidant enzyme activities, and improving mitochondrial function. Novel curcumin formulations improve bioavailability and efficacy against carbofuran-induced neurotoxicity in animal models. Curcumin presents a mechanistically promising neuro-nutraceutical candidate for attenuating carbofuran-induced neurotoxicity. However, challenges such as limited bioavailability and scarce clinical trials necessitate further research. Public health strategies should emphasize exposure prevention alongside exploring adjunct nutraceutical therapies.

Keywords: Carbofuran, Curcumin, Mitochondrial injury, Oxidative stress, Pesticides

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INTRODUCTION

Pesticides, classified based on their chemical structure into organochlorines, organophosphorus, carbamates, pyrethroids, amides, anilines, and azotic heterocyclic compounds, are widely employed in agriculture to control pests, thereby enhancing crop productivity.^[1] However, their environmental release leads to toxicity risks affecting non-target organisms including humans, with significant public health implications.^[2] Carbamate pesticides, including carbofuran (CBF), represent a major concern due to their high acute toxicity and broad-spectrum

applications as insecticides, nematocides, and acaricides in agricultural, household, and industrial settings.^[3,4] CBF's toxicity is primarily mediated through reversible carbamylation of the active site serine residue in acetylcholinesterase (AChE), leading to accumulation of acetylcholine (ACh) at synaptic junctions and consequent cholinergic crisis characterized by neuromuscular and central nervous system disturbances.^[5] Unlike organophosphate pesticides, carbofuran-inhibited AChE undergoes decarbamylation with potential recovery within hours; however, neurobehavioral impairments may persist longer.^[6]

Beyond cholinergic toxicity, carbofuran induces oxidative stress in mammalian brains by promoting lipid peroxidation and reactive oxygen species (ROS) generation, disrupting mitochondrial function and triggering neuro inflammation and apoptosis.^[7] These oxidative mechanisms contribute to lasting neurotoxicity, including cognitive and motor deficits observed in animal models.^[8] Additionally, carbamate pesticides disrupt endocrine signaling pathways, particularly the hypothalamic-pituitary-thyroid (HPT) axis, potentially causing developmental and reproductive toxicity (Campos and Freire, 2016; Gupta, 2011; Afzal *et al.*, 2018).^[9]

Exposure to carbamates also alters enzymatic antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, further compromising cellular redox homeostasis (Ibrahim and Harabawy, 2014; Pessoa *et al.*, 2011) ^[10] In aquatic models, such oxidative stress associates with impaired growth and development, supporting concerns about environmental and human health impacts.

Nutraceuticals, defined as bioactive compounds from foods or supplements, have shown promise in mitigating pesticide-induced neurotoxicity by virtue of their antioxidant, anti-inflammatory, mitochondrial protective, and anti-apoptotic properties.^[11] Curcumin, a polyphenolic compound derived from *Curcuma longa*, exemplifies such a neuro-nutraceutical with demonstrated efficacy in scavenging ROS, modulating nuclear factor-kappa B (NF- κ B) signaling, enhancing endogenous antioxidant defenses, stabilizing mitochondria, and reducing neuroinflammation relevant to carbofuran toxicity.^[12]

Despite curcumin's multifaceted neuroprotective potential, its clinical application is impaired by poor bioavailability due to low solubility, rapid metabolism, and elimination. Novel formulations including nanoparticles, adjuvant compounds such as piperine, and bioavailable complexes like curcumin-galactomannan have shown enhanced efficacy in preclinical models, significantly reducing carbofuran-induced behavioral deficits, oxidative stress, and mitochondrial dysfunction.^[13]

Animal studies demonstrate that antioxidant supplementation can restore acetylcholinesterase activity, decrease lipid peroxidation, and improve neurobehavioral outcomes following carbofuran exposure. However, translational evidence in humans remains limited, warranting well-designed preclinical and clinical trials to validate curcumin's therapeutic utility in pesticide neurotoxicity (Li *et al.*, 2020; Matthewman *et al.*, 2024).^[14]

Given carbofuran's extensive oxidative and cholinergic toxicity and its disruption of energy metabolism such as inhibition of the tricarboxylic acid (TCA) cycle, integration of exposure prevention strategies with adjunctive nutraceutical interventions represents a prudent public health approach.^[15] Nutraceuticals should complement but not replace established clinical antidotes or regulatory exposure controls.

CONCLUSION

In conclusion, carbofuran induces acute cholinergic toxicity and chronic neurodegenerative effects mediated by oxidative stress and mitochondrial impairment. Curcumin offers a promising neuroprotective strategy through its antioxidant and mitochondrial stabilizing mechanisms, though its clinical implementation is constrained by bioavailability challenges. Addressing these through innovative formulations and rigorous trials is essential to harness its full therapeutic potential while emphasizing exposure reduction as the cornerstone of public health safety.

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