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REVIEW ARTICLE

# ACRYLAMIDE-INDUCED NEUROTOXICITY: NARRATIVE REVIEW

**Zamzam Nasrallah Abdel-Moaty[1], Rana A. Ali[2], Ahmed Talaat Galal[3], Maha Abd-El Baki Ahmed[4]**

[1]Department of Human Anatomy & Embryology, Faculty of Medicine, South Valley University, Qena, Egypt.
[2]Department of Medical Biochemistry, Faculty of Medicine, South Valley University, Qena83523, Egypt.
[3]Department of Human Anatomy & Embryology, Faculty of Medicine, Assiut University, Assiut, Egypt.
[4]Department of Pharmacognosy, Faculty of Pharmacy, South Valley University, Qena 83523, Egypt.

**Corresponding author:** Corresponding Author: Zamzam Nasrallah Abdel-Moaty Department of Human Anatomy & Embryology, Faculty of Medicine, South Valley University, Qena, Egypt. **Email**: zamzamnasr @med.svu.edu.eg

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**ABSTRACT**

Acrylamide (ACR), a neurotoxic compound found in heat-processed foods, poses significant health risks, including neurotoxicity in both adult and offspring mammals. This review comprehensively evaluates the protective roles of hydroxyapatite (HA) and vitamin B12 (methylcobalamin) against ACR-induced neurotoxicity in male albino rats. By synthesizing findings from in vivo and in vitro studies, this article compares the mechanisms, efficacy, and potential synergistic effects of HA and vitamin B12 in mitigating oxidative stress, neuronal damage, and behavioural impairments caused by ACR exposure. The review highlights the biomaterial properties of HA and the neuromodulatory functions of vitamin B12, emphasizing their roles in neuroprotection. Gaps in current research, such as the need for transgenerational studies and optimal dosing regimens, are identified to guide future investigations. This article aims to provide a robust foundation for researchers and clinicians exploring therapeutic interventions for ACR-induced neurotoxicity.

**Keywords:** Acrylamide, Neurotoxicity, Hydroxyapatite, Vitamin B12, Male Albino Rats, Neuroprotection

## INTRODUCTION

Acrylamide (ACR) is a chemical compound formed during high-temperature cooking processes, such as frying and baking, through the Maillard reaction between reducing sugars and amino acids, particularly asparagine [1]. Recognized as a neurotoxin and probable human carcinogen by the International Agency for Research on Cancer [2], ACR exposure occurs primarily through dietary intake and occupational settings. In animal models, particularly male albino rats, ACR induces neurotoxicity characterized by oxidative stress, neuronal degeneration, and impaired nerve conduction, affecting both adult and offspring populations [3,4]. These effects are mediated through mechanisms such as reactive oxygen species (ROS) generation, mitochondrial dysfunction, and disruption of cytoskeletal integrity [5].

Hydroxyapatite (HA), a calcium phosphate biomaterial, has emerged as a promising neuroprotective agent due to its biocompatibility, antioxidant properties, and ability to modulate oxidative stress [6]. Conversely, vitamin B12 (methylcobalamin), a vital micronutrient, supports neuronal survival by regulating homocysteine levels, enhancing methylation cycles, and promoting nerve regeneration[7]. Both compounds have shown potential in ameliorating ACR-induced neurotoxicity, yet their comparative efficacy and mechanisms remain underexplored. This review aims to critically analyze and compare the protective effects of HA and vitamin B12 in adult and offspring male albino rats, addressing their mechanisms, efficacy, and potential for combined therapeutic applications.

**PRISMA Flow Diagram for Study Selection in the Review of Acrylamide-Induced Neurotoxicity**

| Stage | Description | Number of Studies |
|---|---|---|
| **Identification** | | |
| **Records identified through database searching** | PubMed, Scopus, Web of Science, and other sources | 60 |
| **Additional records identified through other sources** | Reference lists, manual searches | 10 |
| **Screening** | | |
| **Records after duplicates removed** | Unique records screened | 55 |
| **Records screened** | Titles and abstracts reviewed | 55 |
| **Records excluded** | Irrelevant topics, non-experimental studies | 20 |
| **Eligibility** | | |
| **Full-text articles assessed for eligibility** | Full-text review for relevance | 35 |
| **Full-text articles excluded, with reasons** | Non-rat models, unrelated interventions, non-English | 10 |
| **Included** | | |
| **Studies included in qualitative synthesis** | Studies on ACR, HA, or vitamin B12 in rats | 25 |
| **Studies included in quantitative synthesis** | Not applicable (narrative review) | 0 |

## 2. Acrylamide-Induced Neurotoxicity: Mechanisms and Effects

### 2.1 Mechanisms of Neurotoxicity

ACR exerts neurotoxic effects by forming adducts with sulfhydryl groups on proteins, disrupting neuronal cytoskeletal structures, and impairing axonal transport [8]. It also induces oxidative stress by depleting glutathione (GSH) levels and increasing ROS, leading to lipid peroxidation (LPO) and neuronal apoptosis [9]. Studies in male albino rats demonstrate that ACR exposure (e.g., 50 mg/kg/day) reduces nerve conduction velocity (NCV) and causes histopathological changes in the sciatic nerve and cerebral cortex [10]. In offspring, ACR exposure during gestation or lactation can impair neurodevelopment, leading to delayed myelination and cognitive deficits [11].

### 2.2 Effects in Adult vs. Offspring Rats

In adult male albino rats, ACR exposure results in motor dysfunction, reduced sensory nerve action potentials, and behavioral abnormalities such as ataxia and anxiety-like behavior[12]. Histologically, ACR induces degeneration in the dorsal root ganglion (DRG) and cerebellar neurons, accompanied by vasogenic edema [13]. In offspring, transplacental or lactational ACR exposure causes developmental neurotoxicity, including reduced dendritic arborization, impaired synaptic plasticity, and cognitive deficits [14]. These effects are exacerbated in offspring due to their immature blood-brain barrier and heightened susceptibility to oxidative stress [15].

## 3.Hydroxyapatite:Properties and Neuroprotective Mechanisms

### 3.1 Composition and Biocompatibility

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is a naturally occurring mineral in bone and teeth, widely used in biomedical applications due to its biocompatibility and bioactivity [16]. Nano-hydroxyapatite (nHA) enhances these properties by increasing surface area and cellular interactions, making it a candidate for neuroprotection [17].

### 3.2 Mechanisms of Neuroprotection

HA mitigates ACR-induced neurotoxicity through several mechanisms:

- **Antioxidant Activity**: nHA reduces ROS levels by scavenging free radicals and enhancing antioxidant enzyme activity (e.g., superoxide dismutase [SOD] and catalase) [18]. Studies in Wistar albino rats show that nHA administration (e.g., 100 mg/kg) restores GSH

levels and reduces LPO in ACR-treated groups [19].

- **Neuroregeneration**: HA promotes neuronal repair by supporting axonal growth and reducing inflammation in damaged neural tissues [20]. In rat models, nHA scaffolds enhance nerve regeneration in sciatic nerve injury models [21].

- **Metal Ion Chelation**: HA binds heavy metals and toxins, potentially reducing ACR's interaction with neuronal proteins [22].

### 3.3 Evidence in Adult and Offspring Rats

In adult male albino rats, nHA administration (50–100 mg/kg) ameliorates ACR-induced motor deficits and improves NCV by reducing oxidative damage in the sciatic nerve [23]. In offspring, nHA enhances bone and neural development, counteracting ACR's developmental toxicity [24]. However, limited studies explore nHA's transgenerational effects, warranting further investigation.

## 4. Vitamin B12: Properties and Neuroprotective Mechanisms

### 4.1 Biochemical Role

Vitamin B12 (methylcobalamin) is a coenzyme critical for one-carbon metabolism, DNA methylation, and homocysteine regulation [25]. Its deficiency is linked to neurological disorders, including demyelination and cognitive impairment [26].

### 4.2 Mechanisms of Neuroprotection

Vitamin B12 protects against ACR-induced neurotoxicity through:

- **Homocysteine Regulation**: Elevated homocysteine levels exacerbate oxidative stress and neuronal damage. Vitamin B12 supplementation (0.5–1 mg/kg/day) reduces homocysteine, mitigating ACR's neurotoxic effects [27].

- **Nerve Regeneration**: Methylcobalamin enhances axonal regeneration and synaptic plasticity by activating Erk1/2 and Akt pathways [28]. In ACR-treated rats, vitamin B12 (1 mg/kg/day) improves NCV and reduces neuropathic pain [29].

- **Antioxidant Effects**: Vitamin B12 upregulates GSH and SOD, counteracting ACR-induced oxidative stress [30].

### 4.3 Evidence in Adult and Offspring Rats

In adult male albino rats, vitamin B12 supplementation (0.5–1 mg/kg/day) improves motor function, reduces DRG neuronal loss, and enhances cognitive performance in ACR-treated models [31]. In offspring, vitamin B12 supports neurodevelopment by preventing delayed myelination and improving spatial memory [32]. Its efficacy in transplacental ACR exposure models is less studied, highlighting a research gap.

## 5. Comparative Analysis of Hydroxyapatite and Vitamin B12

### 5.1 Efficacy in Adult Rats

- **Hydroxyapatite**: Studies demonstrate that nHA (100 mg/kg) significantly reduces LPO and restores NCV in ACR-treated adult rats, with effects observed within 21 days [33]. Its biomaterial properties allow sustained release, enhancing long-term neuroprotection.

- **Vitamin B12**: Vitamin B12 (1 mg/kg/day) shows comparable efficacy in improving NCV and reducing neuronal apoptosis, with faster onset (14–21 days) due to its direct metabolic role [34]. However, its effects may diminish without continuous supplementation.

- **Comparison**:nHA offers sustained neuroprotection due to its structural stability, while vitamin B12 provides rapid metabolic support but requires consistent dosing.

### 5.2 Efficacy in Offspring Rats

- **Hydroxyapatite**: nHA supports neural and skeletal development in ACR-exposed offspring, reducing developmental delays [35]. Its efficacy is limited by sparse data on transgenerational effects.

- **Vitamin B12**: Vitamin B12 enhances neurodevelopment by preventing demyelination and improving cognitive outcomes in offspring [36]. Its role in maternal supplementation to mitigate ACR's effects is promising but underexplored.

- **Comparison**: Vitamin B12 appears more effective in offspring due to its direct influence on neurodevelopmental pathways, whereas nHA's benefits are broader but less specific to neural repair.

### 5.3 Mechanistic Synergies

HA and vitamin B12 target complementary pathways: HA reduces oxidative stress and supports structural repair, while vitamin B12 enhances metabolic and regenerative processes. Combined administration may yield synergistic effects, such as enhanced antioxidant capacity and accelerated nerve regeneration, though no studies have directly tested this hypothesis.

## 6. Experimental Evidence from Rat Models

### 6.1 Adult Male Albino Rats

Studies using Wistar albino rats exposed to ACR (50 mg/kg/day) demonstrate that nHA (100 mg/kg) reduces cerebellar degeneration and improves motor coordination [37]. Similarly, vitamin B12 (1 mg/kg/day) enhances DRG neuron survival and reduces anxiety-like behavior [38]. Both compounds show dose-dependent effects, with higher doses correlating with better outcomes.

### 6.2 Offspring Male Albino Rats

In offspring exposed to ACR via maternal diet, nHA (50 mg/kg) promotes bone formation and reduces neural damage, though cognitive outcomes are less studied [39]. Vitamin B12 (0.5 mg/kg/day) improves spatial memory and reduces homocysteine levels, supporting neurodevelopment [40]. Comparative studies are lacking, necessitating further research.

### 7. Challenges and Limitations

- **Dosage and Administration**: Optimal dosing for HA and vitamin B12 varies across studies, complicating comparisons. nHA's bioavailability depends on particle size, while vitamin B12's efficacy relies on absorption efficiency [41].
- **Transgenerational Effects**: Limited data on HA's effects in offspring highlight a gap in understanding its long-term impact. Vitamin B12's role in maternal supplementation requires further exploration [42].
- **Mechanistic Clarity**: The exact pathways by which HA mitigates ACR-induced neurotoxicity are not fully elucidated, unlike the well-characterized metabolic roles of vitamin B12 [43].
- **Synergistic Potential**: No studies have investigated combined HA and vitamin B12 administration, which could enhance therapeutic outcomes.

### 8. Future Directions

Future research should focus on:

1. **Comparative Trials**: Direct comparisons of HA and vitamin B12 in standardized ACR-induced neurotoxicity models, including dose-response studies.
2. **Transgenerational Studies**: Investigating HA and vitamin B12's effects on offspring exposed to ACR via maternal routes.
3. **Synergistic Therapies**: Exploring combined HA and vitamin B12 administration to leverage their complementary mechanisms.
4. **Biomarker Development**: Identifying biomarkers for ACR-induced neurotoxicity to monitor therapeutic efficacy.
5. **Clinical Translation**: Translating findings from rat models to human studies, considering differences in ACR metabolism between species [44].

## CONCLUSION

Hydroxyapatite and vitamin B12 offer promising neuroprotective effects against ACR-induced neurotoxicity in male albino rats, with distinct mechanisms and applications. HA's antioxidant and regenerative properties make it effective for structural repair, particularly in adults, while vitamin B12's metabolic support enhances neuronal survival and neurodevelopment, especially in offspring. Comparative studies highlight their complementary roles, suggesting potential for combined therapies. Addressing current research gaps, such as transgenerational effects and optimal dosing, will strengthen their therapeutic potential. This review underscores the need for further investigation to optimize neuroprotective strategies against ACR-induced neurotoxicity.

## DECLARATION

**Ethical Approval**

"Not applicable"

**Consent for publication**

"Not applicable"

**Ethical approval**

None

**Competing interest**

The authors declare that there are no competing interest.

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None

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