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REVIEW ARTICLE

The Persistent Threat of Cadmium: From Environmental Exposure to Multi-Organ Toxicity and Carcinogenesis

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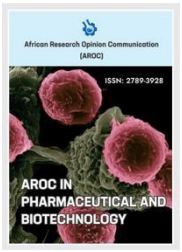

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ABSTRACT

Cadmium (Cd) is a persistent, non-essential heavy metal with widespread environmental and occupational exposure risks. It bioaccumulates in vital organs—particularly the kidneys, liver, lungs, and bones—due to its long biological half-life and limited excretion. Cadmium exerts toxicity through mechanisms including oxidative stress, mitochondrial dysfunction, calcium signaling disruption, and epigenetic alterations, contributing to apoptosis, autophagy dysregulation, and carcinogenesis. Organ-specific outcomes range from renal tubular damage and pulmonary fibrosis to bone demineralization and reproductive dysfunction. Recognized as a Group 1 carcinogen, cadmium also interacts synergistically with other toxicants, amplifying its health impact. This review highlights current biomarkers for cadmium exposure and evaluates therapeutic strategies such as chelation, antioxidants, zinc supplementation, and phytochemicals. Despite emerging interventions, prevention through environmental regulation and exposure mitigation remains the most effective approach to reducing cadmium-related disease burden.

Keywords: Cadmium toxicity; Oxidative stress; Epigenetic modulation; Bioaccumulation; Heavy metal detoxification
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1.0 Introduction

Cadmium (Cd) is a non-essential, highly toxic heavy metal that has become a major global environmental and occupational health concern due to its persistent nature and severe biological effects. It occurs naturally in the Earth's crust in association with ores of zinc, lead, and copper, but anthropogenic activities such as mining, metal refining, fossil fuel combustion, and the widespread use of phosphate fertilizers have significantly increased cadmium concentrations in air, water, and soil (Godt et al., 2006). Human exposure to cadmium arises primarily through the ingestion of contaminated food and water, inhalation of cadmium-laden dust and fumes in industrial settings, and tobacco smoking, which is a notable non-occupational source. It is estimated that tobacco smoke alone contributes up to 50% of total cadmium intake in smokers (Jarup & Akesson, 2009).

Once absorbed, cadmium is efficiently distributed to various organs—predominantly the kidneys, liver, bones, and lungs—where it accumulates due to its extremely long biological half-life, which ranges from 10 to 30 years in humans. Unlike essential metals, cadmium is poorly excreted, and its retention in tissues increases with age and cumulative exposure. It exerts toxicity at low concentrations through multiple mechanisms, including oxidative stress, mitochondrial dysfunction, impaired calcium signaling, and disruption of gene expression via epigenetic modifications. The combination of these pathways leads to cellular injury, organ dysfunction, and in some cases, malignant transformation (Cuypers et al., 2010).

Cadmium's toxicological profile is characterized by its insidious onset and systemic impact. In the kidneys, cadmium is known to cause irreversible damage to proximal tubular epithelial cells, leading to proteinuria and progressive renal failure. Pulmonary exposure results in inflammation, emphysema, and fibrosis, particularly in industrial workers. In the skeletal system, cadmium contributes to bone demineralization and fragility, notably described in the historical case of *itai-itai* disease in Japan. Furthermore, cadmium has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen due to its well-established association with cancers of the lung, prostate, kidney, and pancreas (Waalkes, 2003).

Breast cancer remains one of the most prevalent and deadly malignancies affecting women worldwide, posing a significant public health burden due to its rising incidence and complex etiology. Environmental toxicants, such as heavy metals like cadmium, have been implicated in breast carcinogenesis through their ability to induce oxidative stress, disrupt hormonal signaling, and trigger epigenetic alterations that silence tumor suppressor genes. Chronic exposure to such carcinogens may initiate or promote malignant transformation in

breast tissue, compounding genetic and lifestyle-related risk factors (Onah et al., 2024; Edema et al., 2023) . In recent years, natural products have gained considerable attention for their potential in breast cancer prevention and therapy (Ogunjobi et al., 2025). Compounds derived from plants, marine organisms, and microorganisms—such as curcumin, resveratrol, and epigallocatechin gallate—exhibit anti-inflammatory, antioxidant, and pro-apoptotic activities that can modulate multiple cancer-related pathways.

Importantly, cadmium's pathophysiological effects are not limited to direct cytotoxicity. Emerging research has shown that cadmium acts as a potent epigenetic modulator, altering DNA methylation patterns, histone modifications, and microRNA expression. These changes can persist long after exposure, contributing to chronic disease processes including carcinogenesis and developmental toxicity (Takiguchi et al., 2003; Zhou et al., 2012). In the reproductive system, cadmium disrupts hormone synthesis and gametogenesis, thereby impairing fertility in both males and females. Cadmium can also cross the placental barrier, exerting teratogenic effects on the developing fetus.

Given its multifactorial toxicity, cadmium intoxication represents a significant challenge in clinical toxicology and public health. Despite regulatory efforts to limit occupational and environmental exposure, cadmium continues to pose a threat due to its persistence and bioaccumulation. Understanding the complex mechanisms by which cadmium induces cellular and systemic toxicity is essential for developing effective diagnostic markers, therapeutic strategies, and policy interventions. This review explores in detail the molecular pathways and organ-specific consequences of cadmium intoxication, with an emphasis on its oxidative, apoptotic, and epigenetic effects, as well as its relevance to human disease.

1.1 Cadmium Transport, Distribution, and Bioaccumulation

Following entry into the human body—primarily through inhalation of particulate matter or ingestion of contaminated food and water—cadmium is absorbed into the bloodstream and begins a complex pattern of transport and tissue deposition (Figure 1). The extent and efficiency of cadmium absorption depend on the route of exposure and physiological conditions. Inhaled cadmium compounds, particularly cadmium oxide fumes from industrial sources, are rapidly absorbed through the alveolar epithelium, with up to 30–60% bioavailability. Ingested cadmium, often found in shellfish, rice, or leafy vegetables grown in contaminated soil, has lower but still significant absorption rates, typically 5–10%, which increase in states of iron, calcium, or zinc deficiency due to competition for transporters (Godt et al., 2006; Jarup & Akesson, 2009).

Once in circulation, cadmium exists initially in a loosely bound form to plasma proteins such as albumin. It is rapidly taken up by hepatocytes in the liver, where it induces the expression of metallothionein (MT), a low-molecular-weight, cysteine-rich protein with high affinity for divalent metal ions. Binding of cadmium to metallothionein serves both as a detoxification mechanism and a transport system. The cadmium–metallothionein (Cd-MT) complex formed in the liver is redistributed via the bloodstream, preferentially accumulating in tissues such as the kidneys, liver, and bone, where it can persist for decades (Nordberg et al., 2008).

Cadmium uptake into cells is mediated by several membrane transporters that do not specifically recognize cadmium but allow its passage due to its chemical similarity to essential divalent metals. Among these, ZIP (Zrt/Irt-like Protein) family transporters (particularly ZIP8 and ZIP14) and divalent metal transporter 1 (DMT1) are of primary importance. These transporters, normally responsible for zinc, iron, or manganese homeostasis, inadvertently allow cadmium entry into epithelial cells of the gastrointestinal tract, pulmonary epithelium, renal tubules, and placenta (Rizwan et al., 2009).

Within the kidney, the Cd-MT complex is freely filtered through the glomerulus and reabsorbed by proximal tubular epithelial cells through endocytosis. Inside lysosomes, metallothionein is degraded, releasing free cadmium ions into the cytosol, where they exert nephrotoxic effects. The kidney cortex becomes the principal site of long-term cadmium storage and toxicity. Similarly, in bone, cadmium displaces calcium in hydroxyapatite crystals and interferes with vitamin D metabolism, contributing to osteopenia, osteoporosis, and in severe cases, itai-itai disease (Kobayashi et al., 2009).

Cadmium is very poorly excreted, with renal clearance representing the primary elimination pathway. However, once cadmium accumulates in tissues—especially bound to metallothionein—it is retained for years to decades due to its resistance to metabolic breakdown and low rate of cellular export. This leads to a cumulative body burden, where toxicity intensifies with chronic exposure, even at low environmental levels.

The persistence of cadmium in the body, its non-specific use of essential metal transporters, and its preferential accumulation in metabolically active tissues underscore its potential for long-term systemic toxicity and organ damage. The pharmacokinetics of cadmium—marked by slow absorption, widespread distribution, intracellular binding, and inefficient excretion—make it particularly hazardous from both environmental and occupational perspectives.

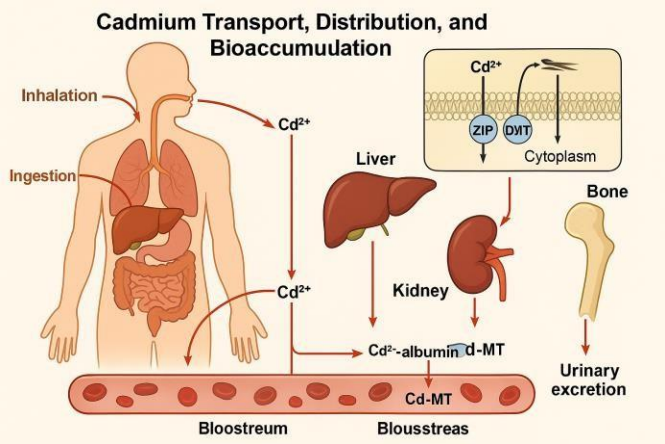

Figure 1. Cadmium Transport, Distribution, and Bioaccumulation. Cadmium (Cd^{2+}) enters the body mainly through inhalation and ingestion, then binds to albumin in the bloodstream and forms complexes with metallothionein (MT) in the liver. The Cd–MT complex circulates and accumulates in the kidneys, liver, and bone. In the kidneys, reabsorption by proximal tubule cells leads to toxicity, while bone serves as a long-term storage site. Cellular uptake occurs via ZIP transporters and DMT1. Cadmium is poorly excreted, resulting in bioaccumulation and a long biological half-life.

2.0 Cellular and Molecular Mechanisms of Cadmium Toxicity

2.1. Oxidative Stress and Mitochondrial Dysfunction

One of the most critical pathways in cadmium toxicity is the induction of oxidative stress. Although cadmium is not redox-active in the classical

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sense (unlike iron or copper), it promotes the generation of reactive oxygen species (ROS) through indirect mechanisms. A major contributor to ROS production is cadmium's interference with mitochondrial function. Specifically, cadmium disrupts the electron transport chain (particularly complexes I and III), leading to electron leakage and the formation of superoxide anions within the mitochondrial matrix. This initiates a cascade of oxidative reactions that impair cellular components (Figure 2).

In addition, cadmium competes with essential trace elements such as zinc, copper, and selenium, which serve as cofactors for antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase, and catalase. The inhibition or displacement of these enzymes reduces the cell's antioxidant capacity, thereby exacerbating oxidative damage. Lipid peroxidation of cell membranes, protein carbonylation, and oxidative DNA lesions, such as 8-hydroxydeoxyguanosine (8-OHdG), are common consequences of cadmium-induced oxidative stress (Cuypers et al., 2010; Waisberg et al., 2003).

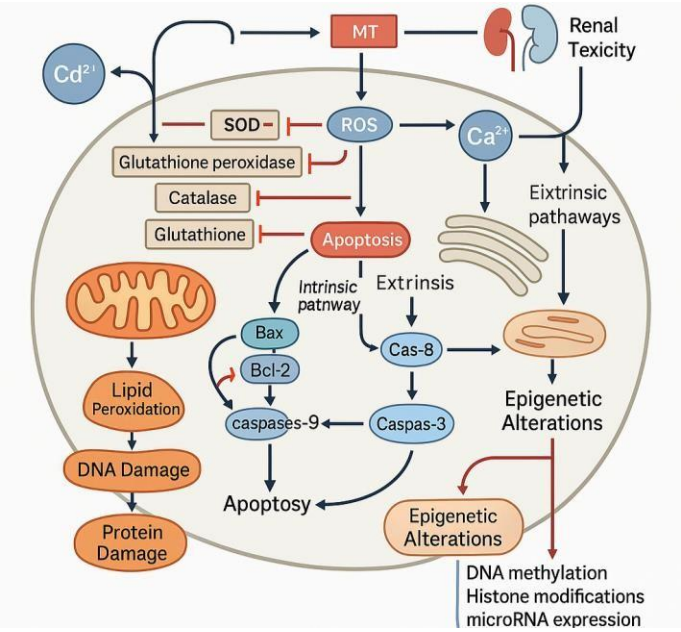

Figure 2. Mechanism of Cadmium Intoxication. This schematic depicts how cadmium (Cd^{2+}) induces cellular toxicity. Upon entering cells, cadmium binds to metallothionein (MT); dissociation of Cd–MT complexes releases free Cd^{2+}, particularly in the kidneys. Cadmium disrupts redox balance by depleting glutathione and inhibiting antioxidant enzymes, leading to reactive oxygen species (ROS) accumulation and oxidative damage. It triggers mitochondrial and death receptor–mediated apoptosis, involving caspase activation and cytochrome c release. Cadmium also mimics calcium, causing Ca^{2+} influx and signaling disruption, and induces ER stress. Additionally, it promotes epigenetic alterations that may silence tumor suppressor genes. Chronic exposure contributes to renal toxicity via Cd–MT accumulation in proximal tubule cells.

2.2 Depletion of Glutathione and Thiol-Containing Molecules

Cadmium exerts a high affinity for sulfhydryl (-SH) groups, particularly those found in glutathione (GSH) and cysteine residues of proteins. Binding to GSH results in the formation of cadmium-glutathione complexes, which may be sequestered in lysosomes or exported out of the cell. However, this process leads to a marked depletion of intracellular GSH levels, weakening the cell's ability to neutralize hydrogen peroxide and organic hydroperoxides. The reduction in thiol buffering also renders proteins more susceptible to structural alteration and functional loss (Waisberg et al., 2003). The net effect is an environment prone to oxidative injury, cellular senescence, and apoptosis.

2.3. Disruption of Calcium Homeostasis

Cadmium interferes with calcium signaling by mimicking Ca^{2+} ions due to similar ionic radii. It gains entry into cells via voltage-dependent calcium channels and accumulates in the cytosol, disrupting normal calcium-dependent processes. Once inside, cadmium activates calcium-dependent enzymes such as calpains and endonucleases, which degrade structural and nuclear proteins. These events culminate in DNA fragmentation and cytoskeletal breakdown, both hallmarks of apoptotic cell death.

Furthermore, cadmium perturbs calcium storage within the endoplasmic reticulum (ER), impairing protein folding and contributing to ER stress. This activates the unfolded protein response (UPR), and if the stress is unresolved, it triggers apoptosis through mediators such as CHOP and caspase-12 (Xu et al., 2011).

2.4. Activation of Apoptotic Pathways

Cadmium-induced apoptosis occurs via both the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways. The intrinsic pathway is initiated by mitochondrial membrane permeability changes, often facilitated by an imbalance in Bcl-2 family proteins— namely the upregulation of pro-apoptotic Bax and downregulation of anti-apoptotic Bcl-2. This promotes the release of cytochrome c into the cytosol, which binds Apaf-1 and pro-caspase-9 to form the apoptosome, leading to activation of caspase-9 and downstream caspase-3.

Simultaneously, cadmium can stimulate extrinsic apoptotic pathways by inducing the expression of death receptors such as Fas (CD95) and their ligands. This results in the activation of caspase-8, which directly activates caspase-3 or cleaves Bid to amplify mitochondrial-mediated apoptosis (López et al., 2006). Together, these pathways contribute to cellular demise, particularly in organs with high cadmium burden like the kidney and liver.

2.5. Induction and Dysregulation of Autophagy

Autophagy, a cellular process responsible for degrading damaged organelles and proteins, is initially upregulated in response to cadmium stress as a protective mechanism. However, with prolonged or high-dose cadmium exposure, autophagy becomes dysregulated. Studies show that cadmium impairs autophagic flux by blocking the fusion of autophagosomes with lysosomes, leading to an accumulation of autophagic vesicles and impaired cellular clearance. This dysfunctional autophagy ultimately contributes to cell death through autophagic or necrotic mechanisms (Zhang et al., 2017).

2.6. Epigenetic Modifications and Gene Expression Changes

Cadmium also induces long-term changes in gene expression through epigenetic alterations. Exposure to cadmium results in global DNA hypomethylation, a condition associated with genomic instability and increased mutation rates (Figure 3). More importantly, cadmium causes localized hypermethylation of specific tumor suppressor genes, including *p16^INK4a*, *RASSF1A*, and *E-cadherin*, leading to their transcriptional

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silencing and potential initiation of carcinogenesis (Takiguchi et al., 2003).

Moreover, cadmium modulates histone post-translational modifications such as acetylation and methylation, altering chromatin accessibility and gene expression. In parallel, cadmium affects the expression of several microRNAs. For instance, it has been shown to upregulate oncogenic miR-21 and suppress tumor-suppressive miR-34a, both of which contribute to disrupted cell cycle regulation and apoptosis resistance (Zhou et al., 2012). These epigenetic disturbances do not only affect cell viability but also predispose cells to transformation and malignant progression.

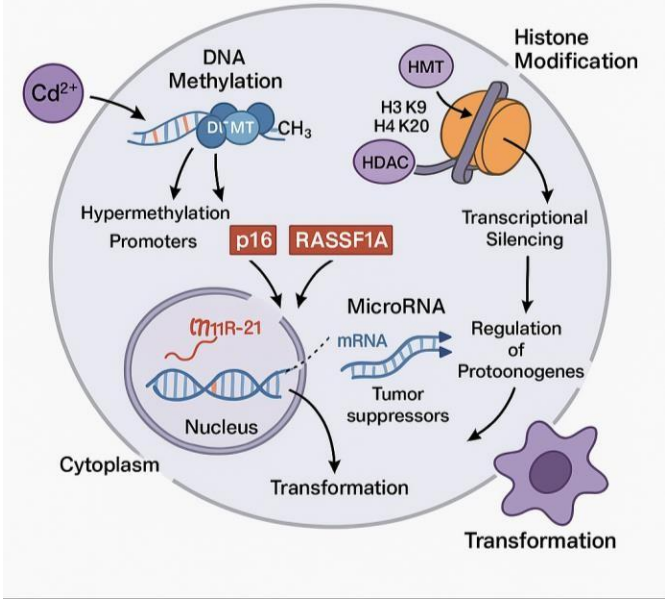

Figure 3. Epigenetic Modulation by Cadmium. This diagram illustrates how cadmium (Cd^{2+}) drives epigenetic changes linked to tumorigenesis. In the nucleus, cadmium activates DNA methyltransferases, causing hypermethylation and silencing of tumor suppressor genes (e.g., *p16^INK4a*, *RASSF1A*). It alters histone- modifying enzymes, leading to repressive marks on H3K9 and H4K20 that promote chromatin condensation. Cadmium also disrupts microRNA expression by upregulating oncogenic miRNAs and suppressing tumor-suppressive ones, contributing to aberrant cell proliferation and transformation.

2. Organ-Specific Effects of Cadmium Intoxication

A. Renal Toxicity

The kidneys are the principal target organs for cadmium accumulation and toxicity due to their role in filtering blood and reabsorbing essential solutes. Following systemic exposure, cadmium enters the bloodstream and binds avidly to metallothionein (MT), a cysteine-rich protein synthesized primarily in the liver. The cadmium-metallothionein complex is filtered by the glomeruli and reabsorbed into proximal tubular epithelial cells, where lysosomal degradation of the complex releases free cadmium ions (Figure 4). These ions accumulate within the cytoplasm, leading to direct tubular toxicity.

Initially, cadmium disrupts reabsorptive processes in the proximal tubules, resulting in a clinical syndrome that mimics Fanconi syndrome. This condition is characterized by polyuria (excessive urine production), proteinuria (loss of low-molecular-weight proteins in urine), glucosuria (glucose excretion despite normal blood glucose), and phosphaturia (loss of phosphate in urine). With prolonged exposure, cadmium induces chronic tubulointerstitial nephritis, marked by tubular atrophy, interstitial fibrosis, and eventual decline in glomerular filtration rate (GFR). If unrecognized and untreated, these changes may progress to irreversible renal failure. Epidemiological studies have shown a clear association between environmental cadmium exposure and increased incidence of chronic kidney disease in affected populations (Nordberg et al., 2008; Jarup & Akesson, 2009).

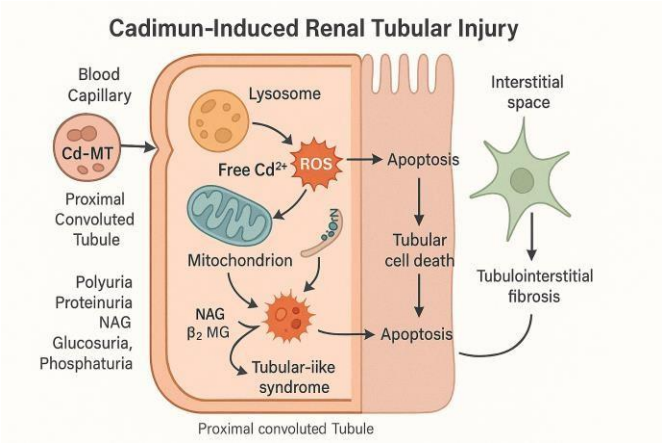

Figure 4. Cadmium-Induced Renal Tubular Injury**.** This diagram illustrates how cadmium (Cd^{2+}) causes nephrotoxicity in the proximal tubule. Filtered Cd–metallothionein complexes are reabsorbed and degraded in lysosomes, releasing free Cd^{2+} into the cytosol. Cadmium induces mitochondrial dysfunction and oxidative stress, damaging cellular components and triggering apoptosis. It also disrupts lysosomal and ER function, impairing tubular reabsorption. Clinically, this manifests as Fanconi-like syndrome with increased urinary excretion of proteins, glucose, phosphate, β_2-microglobulin, and NAG. Chronic exposure leads to tubular cell death, inflammation, fibrosis, and long-term kidney damage.

B. Pulmonary Effects

Inhalation of cadmium-containing fumes or particulates, especially in occupational settings such as metal smelting or battery manufacturing, leads to significant pulmonary injury. Acute exposure may cause chemical pneumonitis and pulmonary edema due to direct damage to bronchial and alveolar epithelial cells. Over time, cadmium induces a chronic inflammatory response within the lungs.

Cadmium stimulates the release of proinflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), from alveolar macrophages and epithelial cells. This inflammatory milieu contributes to the recruitment of neutrophils, destruction of lung parenchyma, and tissue remodeling, which manifests clinically as emphysema and interstitial pulmonary fibrosis. Additionally, cadmium impairs macrophage phagocytic function, reducing pulmonary defense mechanisms and increasing susceptibility to infections. Importantly, cadmium is strongly associated with the development of lung cancer. It acts as a genotoxic carcinogen that promotes DNA damage and inhibits DNA repair, especially in individuals with long-term occupational exposure. The International Agency for Research on Cancer (IARC) has classified cadmium as a human pulmonary carcinogen based on robust epidemiological and experimental evidence (Waalkes, 2003; Johri et al., 2010).

C. Hepatic Effects

Although the liver is not the primary site of cadmium accumulation, it plays a critical role in initial cadmium metabolism and detoxification. After absorption, cadmium enters hepatocytes and induces the synthesis of metallothionein, which binds and sequesters cadmium to limit its free ionic concentration. However, this protective mechanism is overwhelmed with prolonged or high-dose exposure.

Within the liver, cadmium induces activation of Kupffer cells, the resident hepatic macrophages. Activated Kupffer cells release inflammatory mediators and reactive oxygen species, which exacerbate hepatocellular injury. Histological changes include hepatocellular swelling, steatosis, and focal necrosis. Moreover, cadmium impairs the activity of hepatic cytochrome P450 enzymes, a superfamily involved in drug and xenobiotic metabolism. This inhibition can alter the pharmacokinetics of various medications, potentially leading to toxicity or therapeutic failure (Thijssen et al., 2007).

D. Bone Deformities and Itai-itai Disease

Cadmium has profound effects on bone metabolism, particularly under conditions of long-term environmental exposure. One of the most striking clinical manifestations is *itai-itai* disease, historically observed in Japanese populations exposed to cadmium-contaminated rice. The condition is characterized by severe bone pain, multiple fractures, and skeletal deformities.

Cadmium exerts its deleterious effects on bone through several mechanisms. It directly inhibits osteoblast activity, reducing bone formation, while simultaneously stimulating osteoclast-mediated bone resorption, thereby tipping the balance toward net bone loss. These changes culminate in osteomalacia, defined as defective mineralization of bone matrix, and osteoporosis, marked by decreased bone mass and increased fragility. Additionally, cadmium-induced renal dysfunction leads to impaired activation of 1,25-dihydroxyvitamin D_3, the hormonally active form of vitamin D, which is essential for calcium absorption in the intestines and normal bone mineralization. The combined effects of reduced calcium absorption, phosphate loss, and diminished vitamin D activity severely compromise skeletal integrity (Kobayashi et al., 2009).

E. Reproductive and Developmental Toxicity

Cadmium exerts toxicity on the reproductive organs of both males and females. In males, cadmium accumulates in the testes, where it disrupts the blood-testis barrier and damages the seminiferous epithelium. This leads to degeneration of Sertoli cells, loss of germ cells, and reduced sperm count and motility. Cadmium also impairs Leydig cell function, resulting in decreased testosterone synthesis, which further affects spermatogenesis and fertility (Monsefi et al., 2010).

In females, cadmium impairs folliculogenesis by inducing oxidative damage to ovarian granulosa cells and disrupting steroidogenic pathways. This results in hormonal imbalance, anovulation, and potential infertility. Moreover, cadmium interferes with placental development and function. Because it readily crosses the placenta, cadmium exposure during pregnancy has been associated with intrauterine growth restriction, spontaneous abortion, and long-term neurodevelopmental deficits in offspring (Thompson & Bannigan, 2008).

3. Carcinogenicity of Cadmium

Cadmium is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), indicating sufficient evidence for its carcinogenicity in humans. The oncogenic potential of cadmium is mediated through multiple mechanisms that disrupt genomic integrity and cellular regulatory networks.Cadmium induces DNA strand breaks, oxidative base modifications, and chromosomal aberrations by promoting the accumulation of reactive oxygen species and impairing antioxidant defenses. Additionally, cadmium inhibits the activity of DNA repair enzymes such as poly(ADP-ribose) polymerase (PARP), nucleotide excision repair proteins, and mismatch repair complexes. These impairments allow mutations to accumulate unchecked.

One of cadmium's most critical molecular targets is the tumor suppressor protein p53. Cadmium downregulates p53 expression and activity, thereby disabling the cell's ability to undergo growth arrest or apoptosis in response to DNA damage. This facilitates the survival and proliferation of cells with oncogenic mutations. Epidemiological studies have consistently shown associations between chronic cadmium exposure and increased risk of cancers of the prostate, kidney, pancreas, breast, and lung. Cadmium's ability to modulate epigenetic marks—such as DNA methylation and histone modifications—also contributes to silencing of tumor suppressor genes and activation of proto-oncogenes (Waalkes, 2003; Takiguchi et al., 2003).

4. Biomarkers and Detection of Cadmium Exposure

Monitoring cadmium exposure and its health effects requires reliable biomarkers that reflect both recent and cumulative burden. Blood cadmium levels are typically used to assess recent exposure, especially from inhalation sources. In contrast, urinary cadmium concentrations are better indicators of long-term, cumulative exposure and correlate with total body burden, particularly renal accumulation.

Urinary biomarkers of early tubular injury include β2-microglobulin and N-acetyl-β-D-glucosaminidase (NAG). These proteins are normally reabsorbed in the proximal tubules, and their presence in urine indicates tubular dysfunction. Elevated urinary NAG activity often precedes the onset of overt proteinuria, making it a sensitive early marker.

Emerging experimental biomarkers include the measurement of metallothionein mRNA in peripheral blood mononuclear cells and tissue samples, which reflects cellular response to metal stress. Additionally, oxidative stress markers such as malondialdehyde (MDA), a lipid peroxidation byproduct, and 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, provide insights into the extent of oxidative injury caused by cadmium exposure (Jarup & Akesson, 2009).

5 Interaction of Cadmium with Other Heavy Metals and Toxicants

Cadmium does not act in isolation in environmental or biological systems. In many real-world exposure scenarios—particularly those involving industrial pollution, contaminated water sources, or occupational hazards—cadmium coexists with other toxic heavy metals such as lead (Pb), mercury (Hg), and arsenic (As), as well as other chemical toxicants like ethanol or pesticides. The interaction between cadmium and these agents can result in synergistic, additive, or antagonistic effects, depending on the dose, route, timing, and specific target organ involved.

A synergistic interaction occurs when the combined effect of two toxicants is greater than the sum of their individual effects, whereas an

antagonistic interaction occurs when one toxicant reduces the effect of the other. For instance, combined exposure to lead and mercury has been shown to exert a greater-than-additive impact on neurotoxicity, as evidenced by increased oxidative stress and cognitive deficits in animal models and epidemiological studies (Singh et al., 2017). This implies that exposure to a mixture of heavy metals could pose greater health risks than those predicted by single-metal toxicity assessments alone.

Cadmium itself has demonstrated both synergistic and antagonistic interactions depending on the context. In a study by Desta (2018), the co-administration of cadmium and ethanol in rats significantly elevated norepinephrine levels in the hypothalamus and midbrain, more than cadmium or ethanol alone, suggesting a synergistic neurochemical effect on central catecholamine regulation. Ethanol is believed to potentiate cadmium's penetration across the blood-brain barrier and enhance its neurotoxic potential via alterations in blood flow, redox status, and neurotransmitter metabolism.

Moreover, cadmium may influence the bioavailability or toxicity of other metals by competing for transport systems. For example, cadmium shares transport pathways such as DMT1 (divalent metal transporter 1) and ZIP family proteins with iron and zinc, and this competition can exacerbate deficiencies in essential metals while increasing cadmium uptake. Such interactions may amplify the toxic burden in organs like the kidney or liver (Cuypers et al., 2010). These observations support the concept that co-exposure to multiple toxicants should be a critical consideration in environmental health risk assessments. Ignoring such interactions can lead to underestimation of true toxicity, particularly in vulnerable populations such as children, pregnant women, and individuals with preexisting diseases.

6. Management and Therapeutic Strategies for Cadmium Intoxication

The management of cadmium (Cd) intoxication presents a multifaceted challenge due to the metal's long biological half-life (10–30 years), high affinity for sulfhydryl groups, and capacity for bioaccumulation in tissues, particularly the kidneys and liver (Godt et al., 2006; Jarup & Akesson, 2009). Therapeutic interventions must therefore address both acute and chronic exposure scenarios, incorporating pharmacological, nutritional, and natural-product-based approaches to mitigate systemic damage.

6.1 Chelation Therapy

Chelation therapy has been applied primarily in cases of acute cadmium exposure, where circulating Cd levels are high and tissue deposition is still minimal. Chelating agents such as ethylenediaminetetraacetic acid (EDTA) and meso-2,3-dimercaptosuccinic acid (DMSA) can form soluble complexes with free Cd^{2+}, promoting urinary excretion (Flora, Mittal, & Mehta, 2012). However, their efficacy is limited in chronic exposure due to the metal's sequestration within intracellular compartments, particularly when bound to metallothioneins in hepatic and renal tissue (Nordberg et al., 2008). Additionally, non-selective chelation can deplete essential metals like zinc and calcium, leading to further metabolic imbalance.

6.2 Antioxidant-Based Therapy

Cadmium-induced toxicity is intricately linked to oxidative stress, which arises from the disruption of redox homeostasis, glutathione depletion, and mitochondrial impairment. One of the central pathogenic mechanisms involves the overproduction of reactive oxygen species (ROS), which damage cellular macromolecules, including lipids, proteins, and DNA (Cuypers et al., 2010). In response to this, antioxidant therapy has gained substantial attention as a protective modality in both experimental and clinical contexts.

Among the antioxidants investigated, N-acetylcysteine (NAC) has proven particularly effective due to its role as a precursor for glutathione biosynthesis. By restoring intracellular glutathione pools, NAC enhances the cellular capacity to detoxify ROS and maintain mitochondrial integrity (Flora et al., 2012). Selenium, another critical element in redox defense, functions as a cofactor for glutathione peroxidase, an enzyme that neutralizes peroxides and maintains redox stability across tissues, including hepatic and renal systems (Johri, Jacquillet, & Unwin, 2010). In parallel, vitamins C and E have demonstrated the ability to suppress lipid peroxidation and stabilize cellular membranes, thereby protecting against cadmium-mediated oxidative damage. These vitamins act as chain-breaking antioxidants and reduce oxidative lesions in cellular DNA and membranes (Waisberg et al., 2003).

In vivo and in vitro studies substantiate the efficacy of these antioxidants in attenuating cadmium-induced tissue injury. For instance, experimental models have shown that antioxidant administration mitigates morphological and functional degeneration in organs such as the kidney, liver, lung, and testes following cadmium exposure (Thijssen et al., 2007; López et al., 2006). These findings support the integration of antioxidant therapy as a valuable adjunct in managing cadmium toxicity, particularly in chronic exposure scenarios where tissue injury is progressive and cumulative.

6.3 Zinc Supplementation

Zinc supplementation has emerged as another effective strategy in mitigating cadmium toxicity due to its biochemical and physiological interplay with cadmium. Both metals share common transport mechanisms, including the divalent metal transporter 1 (DMT1) and ZIP8 transporter, which facilitate their cellular uptake (Jarup & Akesson, 2009). Zinc competes with cadmium for these transporters, thereby reducing cadmium influx into cells. Moreover, zinc induces the synthesis of metallothioneins, a class of low-molecular-weight, cysteine-rich proteins with a high affinity for heavy metals. These metallothioneins play a pivotal role in binding and sequestering cadmium ions, thus diminishing their bioavailability and cytotoxic potential (Cuypers et al., 2010).

Zinc deficiency has been associated with increased susceptibility to cadmium toxicity, as reduced metallothionein levels and compromised antioxidant defenses exacerbate cellular injury. Conversely, zinc supplementation has been shown to improve renal histopathology, restore antioxidant enzyme activities, and normalize serum biochemical parameters in experimental models of cadmium exposure. These findings underscore zinc's dual role as both a protective micronutrient and a functional competitor to cadmium at cellular and molecular levels, making it an essential component of therapeutic regimens, especially in populations with high environmental or occupational exposure to cadmium.

6.4 Natural Product-Based Therapeutics

6.4.1 Overview and Mechanisms of Action

Natural products, particularly phytochemicals derived from medicinal plants, offer a multifactorial defense against various diseases (Ogunlakin et al., 2025a, 2025b, 2025c). These agents exert protective effects through several mechanisms, including direct antioxidant activity, inhibition of pro-inflammatory cytokine release, regulation of

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apoptotic and survival pathways, and chelation of free cadmium ions. Additionally, some natural compounds have demonstrated the ability to restore mitochondrial membrane potential and stabilize cellular respiration under stress conditions (Monsefi et al., 2010; Xu et al., 2011; Zhang et al., 2017; Oluyemis et al., 2021; Adegbesan et al., 2021; Ogunlabi et al., 2020; Ogunlakin et al., 2024)

At the molecular level, these natural compounds modulate key regulatory transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2), which governs the expression of endogenous antioxidant enzymes, and nuclear factor kappa B (NF-κB), which regulates inflammatory signaling (Omiyale et al., 2024a, 2024b). Moreover, modulation of the mitogen-activated protein kinase (MAPK) pathways by phytochemicals further contributes to their protective effects in cells subjected to cadmium insult. These broad-spectrum molecular interactions position natural products as attractive therapeutic candidates for counteracting cadmium-induced cellular dysfunction (Tale 1).

Table 1 Representative Natural Compounds

Compound	Source	Effects	References
Curcumin	*Curcuma longa*	Antioxidant, anti-inflammatory, renal protection	Flora et al., 2012; Cuypers et al., 2010
Quercetin	Fruits, onions	Free radical scavenger, nephroprotective, fertility improvement	Thompson & Bannigan, 2008
Resveratrol	Grapes, red wine	Liver enzyme modulation, anti-apoptotic	Waalkes, 2003
Silymarin	*Silybum marianum* (milk thistle)	Hepatocyte regeneration, antioxidant	Jarup & Akesson, 2009
EGCG	*Camellia sinensis* (green tea)	Neuroprotective, mitochondrial stabilization	Xu et al., 2011
NAC	Synthetic	Glutathione precursor, ROS neutralization	Flora et al., 2012

6.4.2 Organ-Specific Protective Effects

The therapeutic efficacy of natural products against cadmium toxicity has been validated in multiple organ systems. In renal tissues, compounds such as quercetin and curcumin have been shown to ameliorate tubular damage, reduce proteinuria, and suppress the inflammatory response. These agents restore renal morphology and function by decreasing oxidative stress and inhibiting fibrotic signaling cascades (Flora et al., 2012).

Hepatic protection is conferred by natural products like resveratrol, silymarin, and thymoquinone, which modulate the activity of Kupffer cells, attenuate hepatic inflammation, and reduce lipid peroxidation. These effects collectively preserve hepatocyte viability and liver enzyme homeostasis (Waalkes, 2003). In the central nervous system, epigallocatechin gallate (EGCG), a green tea polyphenol, and NAC have demonstrated neuroprotective effects by reducing neuronal apoptosis and minimizing ROS accumulation in cerebral tissues (López et al., 2006; Xu et al., 2011).

Furthermore, reproductive toxicity induced by cadmium can be significantly mitigated by antioxidants such as vitamin E and plant-based extracts like *Nigella sativa*. These agents prevent testicular necrosis, improve spermatogenesis, and reduce oxidative lesions in gonadal tissues, thereby preserving fertility (Thompson & Bannigan, 2008; Monsefi et al., 2010).

6.4.4 Advantages of Natural Therapeutics

Natural agents provide a holistic, low-toxicity approach that targets multiple signaling pathways, unlike single-target chelators. These compounds can be sustainably integrated into dietary interventions or developed into adjuvant therapies. Their accessibility and favorable safety profiles make them particularly attractive for populations at risk of chronic cadmium exposure from industrial emissions or tobacco use (Godt et al., 2006; Flora et al., 2012).

6. Conclusion

Cadmium is a persistent environmental and occupational toxin that accumulates in the body due to poor excretion and a long biological half-life, leading to chronic multi-organ damage. The kidneys are the primary targets, often progressing from tubular dysfunction to irreversible failure, while the lungs, liver, bones, and reproductive system are also affected. Cadmium exerts its toxicity through oxidative stress, mitochondrial and calcium dysregulation, apoptosis, and notably, epigenetic modifications such as DNA methylation and microRNA alterations, which may contribute to carcinogenesis. Classified as a Group 1 carcinogen by IARC, cadmium poses a major global health risk via chronic low-dose exposure, especially through food, air, and tobacco. While therapeutic options remain limited, prevention through regulation, exposure monitoring, and public education is key to reducing cadmium-related disease.

Conflict of interests: The authors declare that they have no Conflict of interests.

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