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Mechanisms of Cadmium Toxicity: Metabolomics and Medical Approach

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Abstract

Heavy metals are harmful pollutants due to their toxicity at low concentrations, persistent nature and non-biodegradability that have attracted widespread attention. Heavy metals, such as arsenic, cadmium, chromium, lead and mercury are known to be toxic to plants and animals. Cadmium is a highly toxic heavy metal that adversely affects most organ systems. It is commonly found in humans, with primary sources of exposure being cigarette smoke, welding, and contaminated food and beverages. There is compelling evidence from recent studies linking exposure to cadmium to the development of cancer, liver damage, renal failure, skin and hair abnormalities and cardiovascular problems. Cadmium have been shown in epidemiological, basic, and clinical studies to increase the generation of reactive oxygen species. This, in turn, can aggravate the generation of reactive oxygen species and cause inflammation, which can lead to endothelial dysfunction, disruption of ion homeostasis and epigenetic modifications. According to recent research, metabolomics can be used to uncover possible biomarkers and biological pathways, as well as to get molecular snapshots of organisms following environmental exposure to stressors like cadmium. Thus, the purpose of this review is to give readers a thorough understanding of the biochemistry and mechanisms that give rise to cadmium toxicity. We

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also address antioxidants and other substances that have protective properties against cadmium toxicity, as well as the molecular underpinnings of cadmium-induced cellular damage.

Keywords: Cadmium; Neurotoxicity; Metabolomics; Oxidative Stress; Chelating Agents; Inflammation

Introduction

Understanding the complex relationships between environmental elements and human health has advanced significantly in recent decades (Dehghani et al., 2018; Gholizadeh et al., 2019; Nikoonahad et al., 2017; Omidi et al., 2019). Because of their widespread presence in the environment and propensity to affect human health, potentially toxic elements (PTEs), such as heavy metals (HMs), have become a major concern among the many agents that have a dramatic impact on health outcomes (Gholizadeh et al., 2019; Miri et al., 2016).

Metals having a specific gravity greater than 5.0 g/cm^3 are classified as heavy metals. Higher atomic metals and transition metals from groups III to IV of the periodic table are included (Salaudeen Abdulwasiu Olawale, 2020). These metals can remain in nature and cause bioaccumulation through food and/or drinking water, making them hazardous and nonbiodegradable even at low quantities (Olawale et al., 2022). For example, according to the World Health Organisation, humans need small amounts of copper and zinc, but at concentrations more than 1 mg/L, they become poisonous (C. Liu et al., 2019; Olawale et al., 2022).

The toxicity of these metals is widely recognised, and studies have been conducted on their impact on human health. Non-essential metals like Cd, Hg, Ni, and Pb can be dangerous primarily, but also because they disrupt metabolic functions by replacing necessary divalent cations (like Ca, Mg, Fe, and Zn) in proteins, enzymes, and hard structures like teeth or bones. When trace elements' concentrations surpass certain physiological thresholds, they can be harmful to humans. Their toxicity is specifically linked to their redox activity (with the exception of zinc), which can cause oxidative stress, the production of reactive oxygen species, and other negative effects in a Fenton (Fe) or Fenton-like (Cu, Cr, etc.) chain of reactions (Coradduzza et al., 2024).

The toxicity of heavy metals varies with dosage (Gorini et al., 2014). Heavy metals support specific physiological and biochemical processes in bodily systems at comparatively low concentrations, but they become harmful to human health at quantities above a threshold (Ohiagu et al., 2020). While there are many different ways that heavy metals may be hazardous, some of these pathways are not well understood. Every heavy metal exhibits toxicity via a unique process that is unique to it. The production of ROS, suppression of enzyme function, and attenuation of antioxidant defence systems are the main ways that the majority of heavy metals induce toxicity (Balali-Mood et al., 2021). It is widely recognised that heavy metal ions may disrupt nuclear proteins and DNA, leading to alterations that cause apoptosis, carcinogenesis, and cell cycle regulation, as well as structural and functional abnormalities (Okechukwu Ohiagu et al., 2022). Toxic levels of heavy metals change the function of the central nervous system, which leads to mental disorders. They also change the composition of blood, the functioning of the liver, kidneys, lungs, and other vital organs, which causes a number of human diseases to worsen (Azeh Engwa et al., 2019).

Similar mechanisms underlie the detrimental mechanism of heavy metals, which typically involves the generation of reactive oxygen species (ROS), the inhibition of enzymes and the suppression of the antioxidant defence. Nevertheless, a few of them have preferential binding to particular macromolecules and generate toxicities in a specific manner. We can control animal and human poisonings more effectively by understanding the many toxic processes of heavy metals and their detrimental effects on bodily organs (Balali-Mood et al., 2021).

The problem of comprehending metal toxicity is as wide-ranging and intricate as the ways in which metals affect cells. Although some recent research has started to clarify the mechanisms underlying the harmful effects that metals actually have on particular microorganisms and higher animals, a thorough comprehension of these occurrences is still a long way off. Thankfully, new technologies are making it possible to probe further and produce a more thorough understanding of the relationship between metals and cells. "Omics" technologies offer a system-wide perspective of how stress changes cell physiology. One such tool that has a lot of promise for researching metal toxicity and offering a distinct viewpoint on how metals alter the metabolic architecture of cells is metabolomics (Booth et al., 2011).

Because of its position at the base of the "omics" cascade and pertains to both the upstream input of the environment and the downstream output of the genome, metabolomics may provide answers to questions that other "omics" science fields might not be able to (Wishart, 2016; Zaitsu et al., 2016). According to David et al. (2014), the term "metabolome" refers to the biomolecules and metabolites that are produced endogenously, such as steroids, fatty acids, lipids, vitamins, carbohydrates, and amino acids; "exo-metabolome" refers to the metabolites that are produced outside of cells; and "xeno-metabolome" refers to the metabolites that are produced exogenously from xenobiotics or their metabolites from phase I or phase II metabolism (David et al., 2014). When it comes to variations in metabolite profiles under various settings, metabolomics aids in the detection of endogenous compounds in biospecimens such as tissues, hair, nails, blood, urine, cerebrospinal fluid, saliva, etc. These days, metabolomics is widely used in research on disease pathogenesis (Klein & Shearer, 2016; Ren et al., 2016; Würtz et al., 2016), drug discovery (Lu & Chen, 2017; Mercier et al., 2018), biomarker studies (Ambati et al., 2017; Klein & Shearer, 2016), toxicology, nutrition, pharmacology, and clinical trials (Cornelis et al., 2018; Wu et al., 2018).

Overview of Heavy Metal Toxicity

Human contact with heavy metals (HMs) can occur through many pathways, including ingestion, inhalation, and skin absorption, and is caused by industrial activity (Ali et al., 2019). HMs are classified as essential or non-essential according on how they work in biological systems. Excessive concentrations of essential or non-essential metals can cause genetic alterations or physiological or morphological abnormalities (Mitra et al., 2022; Verma et al., 2023).

As seen in Figure 1, heavy metals can also be categorised according to how hazardous they are.

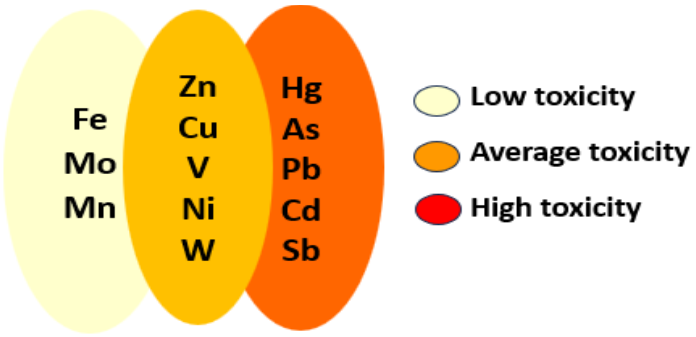


Figure 1: Basic classification of heavy metals

Cadmium

Cadmium is a soft and silvery-white metal that shares chemical similarities with mercury and zinc. It is extremely poisonous and damages the majority of organs (Salaudeen Abdulwasiu Olawale, 2020). Despite being uncommon, cadmium (Cd) can be found naturally in water, soil, and minerals such hydroxide, carbonate, chloride, and sulphide salts. Following industrial operations that may result in significant human exposure to Cd, high quantities of the metal can be found in soil, water, and air. Furthermore, taking contaminated food will expose you to high levels of cadmium. Smoking is another way that cadmium exposure can happen, and it can raise cadmium levels in the blood and urine. The presence of Cd in contaminated water may interfere with the body's vital functions, which might cause immediate or lasting problems. (Cao et al., 2018; Richter et al., 2017). According to Kim et al. (2020), the International Agency for Research on Cancer (IARC) has categorised cadmium as causing cancer (Group 1) (T.-H. Kim et al., 2020) and also listed as the seventh most dangerous substance by the Agency for Toxic Substances and Disease Registry (Arruebarrena et al., 2023). If ingested or inhaled, this strong gastrointestinal and lung irritant can be lethal. Itai-Itai, weight reduction and hypertension are among the health implications. Additionally, it is known to be toxic to the pancreas, lungs, liver, kidney, duodenum, reproductive organs, brain etc (Salaudeen Abdulwasiu Olawale, 2020) as shown in Figure 2.

Through a number of toxicological pathways, Cd can impair cellular processes and destroy tissue, resulting in a wide range of illnesses and placing a heavy financial cost on society. In order to thoroughly examine the harmful pathways and mechanisms of Cd, this research draws on this knowledge by gathering and reviewing a large number of publications from

the literature. The goal is to offer a comprehensive viewpoint on the health and environmental hazards related to Cd, influencing future studies and directing the creation of policies (Qu & Zheng, 2024).

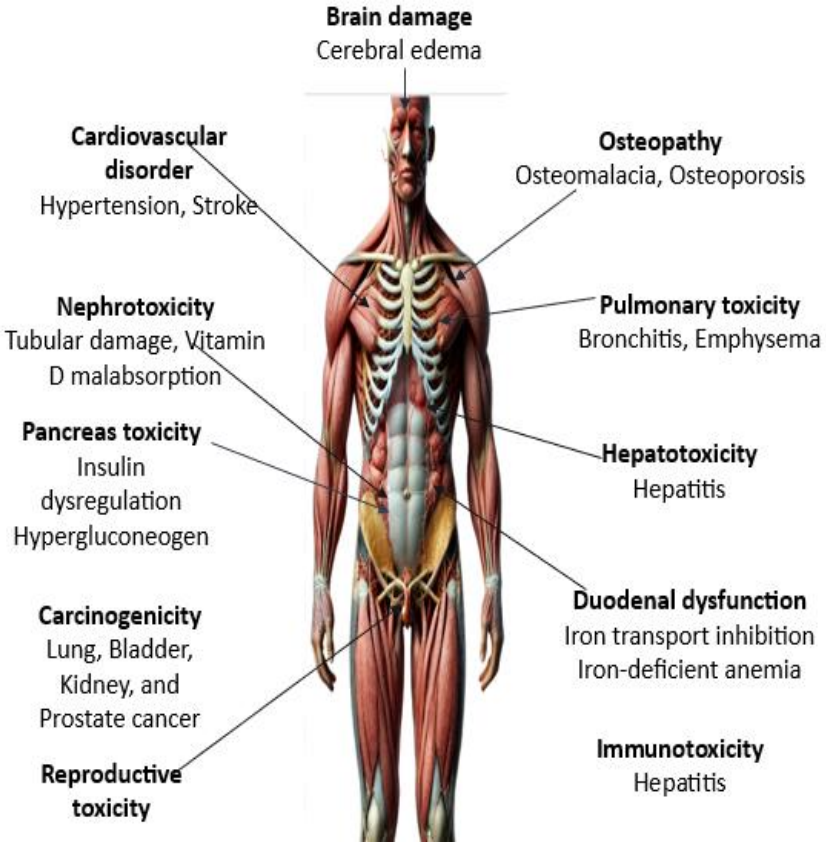


Figure 2: Consequences of exposure to cadmium

Sources of cadmium exposure

Both natural and man-made sources allow cadmium to enter the environment. However, anthropogenic activities (Maynaud et al., 2014), such as electroplating, mining, plastic stabilisation, alloy and cement production, pigment manufacturing, battery production, burning fossil fuels, high-phosphate fertilisers, and burning municipal and sewage sludge (Khan et al., 2022; Y. Liu et al., 2013) are principally the cause for the buildup of Cd in the soil–plant environment (Maynaud et al., 2014). Because of its great mobility in soils, Cd buildup in plants is a major health risk to both humans and animals (Chunhabundit, 2016; Sarwar et al., 2010). Environmental Cd contamination is also largely caused by natural processes such erosion, wind-blown dust, marine aerosols, volcanic eruptions, rock

weathering, and forest fires (Khan et al., 2022; Y. Liu et al., 2015). the potential food routes through which humans could be exposed to cadmium.

The Absorption, Distribution, Metabolism, and Excretion (ADME) Process of cadmium in the Body

The respiratory and digestive systems are the major ways that cadmium enters the human body. It is mostly breathed as fumes or particles, and the lungs have a comparatively increased rate of uptake, between 30% and 50% (C.-G. Elinder, 2019). Therefore, one of the primary ways that Cd is absorbed is by ingestion; however, the exact manner of absorption is still unclear (Lin et al., 2021). Between 3% and 7% of Cd is absorbed in the intestine in adults, but 20% to 40% is absorbed in young people after being released through the bile and reabsorbed through the enterohepatic circulation (Menke et al., 2009; Nucera et al., 2024)

95% of the 30–35 μg of cadmium that the average German consumes each day comes from food and beverages. This quantity can rise because of several causes, including inadequate consumption of calcium, vitamin D, and trace metals like copper and zinc (Godt et al., 2006).

It tends to build up in some essential organs, such the liver and kidneys, because it lacks a true disposal mechanism. These easily produce metallothionein (MT), a protein that firmly attaches to the Cd ion and facilitates its movement. Because of its lengthy half-life, which makes excretion challenging, Cd is more likely to accumulate in the kidney in particular (Alissa & Ferns, 2011; Nucera et al., 2024). Inhalation is the other exposure route. The typical amount of Cd in a cigarette is between 0.5 and 1 μg (Ganguly et al., 2018; Nucera et al., 2024)

A typical smoker consumes an extra 30 μg daily (Godt et al., 2006) as contrast to a nonsmoker. It enters the pulmonary system through the combustion and particle production processes, where it is easily absorbed (Cuello-Nuñez et al., 2018; Piadé et al., 2015). Data from the National Health and Nutrition Examination Survey (NHANES) research, which revealed that smokers had considerably higher mean amounts of cadmium in their urine and blood compared to those who do not smoke, support this (J. Kim et al., 2023). Although it is widely known that cadmium may cause lung cancer and kidney damage, its capacity to harm the body via a number of different routes has also led to its

inclusion as a significant cardiovascular disease indicator. According to studies, this metal causes oxidative stress, disrupting the balance between the body's antioxidant defense mechanisms and the generation of reactive oxygen species (ROS). This imbalance is caused by the activation of NADPH oxidase, which disrupts mitochondrial function (Valko et al., 2007). Elevated ROS concentrations have the potential to seriously harm lipids, proteins, DNA, and other biological constituents. This sets off a chain of events that exacerbate inflammation, lipid peroxidation, and endothelial dysfunction. Each of these elements is essential to the pathophysiology of atherosclerosis and other cardiovascular disorders (Incalza et al., 2018).

The human body absorbs Cd, which is then carried by the bloodstream (Qu & Zheng, 2024)mostly in the erythrocytes and is intracellularly attached to both protein fractions with low and high relative molecular masses (Nordberg, 1978) and progressively builds up mostly in the bones, liver, and kidneys (Qu & Zheng, 2024). The metallothionein-like fraction has a low relative molecular mass. Plasma metallothionein greatly facilitates cadmium transport. Cadmium linked to sulfhydryl groups can make up as much as 11% of its weight (C. G. Elinder et al., 1987). Cadmium accumulates selectively in the renal cortex as a result of free metallothionein's low relative molecular mass in plasma, which enables it to pass past the glomeruli and then be reabsorbed in the proximal tubules (Nordberg, 1978). While free cadmium is not as readily absorbed by the kidneys, cadmium bound to metallothionein is transported from the blood to renal tubular cells quickly and almost entirely (Johnson & Foulkes, 1980).

Multiorgan toxicity from chronic cadmium buildup mostly affects the kidney, bones, liver, and neurological system (Ma et al., 2022) with significant buildup taking place in the renal cortex, namely in the cells of the proximal tubules (Charkiewicz et al., 2023). The primary cause of this buildup is the high Cd-complex reabsorption capacity in the urinary tract, where the glomeruli filter Cd before it is reabsorbed and stored. renal damage and, in extreme situations, renal failure can result from prolonged exposure. Furthermore, it can disrupt the metabolism of calcium, build up in the bones, and competitively replace bone minerals, eventually resulting in osteoporosis and other skeletal problems (Qu & Zheng, 2024).

Cadmium exposure has been linked to lower cognitive function in older individuals, decreased focus, and poor learning outcomes in children (H. Li et al., 2018). Additionally,

neurodegenerative disease abnormalities seen in amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) have been linked to cadmium exposure (Forcella et al., 2020; Min & Min, 2016; Raj et al., 2021).

Oxidative Stress Caused by Cadmium

One important component of Cd's toxicity mechanisms is the oxidative stress it causes. It arises whenever there is an increase in oxidants and reduction in antioxidants causing build up of reactive nitrogen species (RNS) and reactive oxygen species (ROS) (Qu & Zheng, 2024) or a reduction in the oxidant defence systems' ability to eliminate ROS, which favours the former and causing cellular disruption (Das & Al-Naemi, 2019; Sies, 1997). However, typical cellular processes including signal transmission, cell division, gene expression, and immunological defence depend on physiological levels of ROS (Das & Al-Naemi, 2019).

While reactive nitrogen species (RNS) include nitric oxide radical (NO•), nitrogen dioxide radical (NO_2•), and peroxynitrite ($ONOO^-$), reactive oxygen species include hydrogen peroxide (H_2O_2), hydroxyl radical (HO•), superoxide anions (O_2^-), peroxyl (RO•), and alkoxyl radicals (ROO•) in varying amounts. Under typical physiological circumstances, redox balance maintains the production and removal of these radicals (Das & Al-Naemi, 2019).

Cell structure and function can be severely harmed by the rise in oxidants and fall in antioxidants, which can impair lipids, proteins, and nucleic acids, among other macromolecules (Lushchak, 2014). In addition to causing cellular signalling system abnormalities, this sequence of steady-state imbalances may also cause necrosis or cell death. Additionally, by interfering with the cellular antioxidant defence system, it might intensify its effects of oxidative stress (J. Liu et al., 2009; Qu & Zheng, 2024). In response to Cd, important antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) may exhibit reduced activities or inhibited expressions, impairing the ability to combat oxidative damage and escalating the negative consequences of oxidative stress in cells (Qu & Zheng, 2024).

The processes by which cadmium causes oxidative stress in people and the resulting health effects.

Mechanisms of Cadmium-Induced Oxidative Stress

Cadmium does not directly generate reactive oxygen species (ROS) due to its lack of redox activity. However, it indirectly promotes oxidative stress in a variety of ways:

Disruption of Mitochondrial Function: As Cd^{2+} enters the cell, it initially affects the mitochondria, which are the primary sites for cellular energy generation and the primary sources of ROS production. By attaching to thiol groups in Complex I and Complex III (coenzyme Q), Cd^{2+} interferes with the electron transport chain (ETC), reducing Complex I's (NADH dehydrogenase) capacity to move protons and shuttle electrons to produce and sustain ΔΨm (Arruebarrena et al., 2023). This interaction impairs these complexes' regular operation, decreasing effective electron transfer and raising the possibility of electron leakage (Qu & Zheng, 2024) and the subsequent production of ROS. Through its interaction with Complex III's Qo site, cadmium successfully circumvents the matrix antioxidant defences by rerouting ROS production towards the intermembrane gap (Appleby et al., 1999a; Arruebarrena et al., 2023). Because Complexes I and III are not functioning normally, the resulting drop in ΔΨm eventually results in a diminished capacity to synthesise ATP effectively and an increase in harmful cytosolic ROS (Arruebarrena et al., 2023). Studies show that because exposure to Cd increases the generation of ROS in the mitochondria, mitochondrial dysfunction is a crucial factor in cadmium-triggered oxidative stress (Matović et al., 2015).

Due to respiratory chain malfunction in the mitochondria brought on by Cd, the production of ROS can be accelerated by these leaked electrons reacting directly with oxygen to form superoxide anions (O_2^-), which are extremely reactive ROS that can further change into other reactive species like hydrogen peroxide (H_2O_2) and hydroxyl radicals (▪ OH) (Qu & Zheng, 2024; Schieber & Chandel, 2014).

Additionally, the permeability transition pore (PTP), a dynamic protein complex located at the boundary between the inner and outer mitochondrial compartments, is induced to open by cadmium (M. Li, 2003). Small molecules can diffuse across the inner mitochondrial membrane thanks to the PTP, which dissipates the DYm and stops the generation of ATP. By releasing cytochrome C reserves, PTP opening also serves as a signal for apoptosis. In a feedforward process, the PTP may open as a result of the inner mitochondrial gradient itself becoming weaker, ultimately leading to cell death. It is unclear if cadmium directly interacts with the PTP to enhance the chance of opening, how much it

opens the PTP by weakening the DYm in the ways mentioned above, or both (Arruebarrena et al., 2023).

Inhibition of Antioxidant Enzymes: Due to its strong affinity for thiol-containing groups, cadmium depletes essential antioxidants by binding with glutathione (GSH) and other cellular thiols. Furthermore, Cd hinders the body's capacity to neutralise ROS by interfering with enzymes such as catalase and superoxide dismutase (SOD) (Jomova & Valko, 2011).

Activation of Inflammatory Pathways: Nuclear factor-kappa B (NF-ϰB), a crucial transcription factor in inflammation, can be activated by cadmium exposure. By upregulating genes implicated in pro-oxidant pathways, NF-ϰB activation further encourages oxidative stress (Qu & Zheng, 2024).

Because it spreads the pro-inflammatory cascade, NF-ϰB activation is a powerful inducer of chemokine synthesis (Ptaschinski & Lukacs, 2018). In short, at the site of injury, cytokines trigger a signalling cascade that activates NF-ϰB. This activation promotes macrophage relocalization and activation at the damage site in an effort to heal the damage and stop the inflammatory response. A signalling cascade then increases macrophage activation and attraction to the site. Prolonged macrophage activation and chronic NF-ϰB activation have been linked to the pathophysiology of illness (Baker et al., 2011; Das & Al-Naemi, 2019). Therefore, NF-ϰB function disruption is essential to the pathophysiology of many diseases. The most prevalent way that NF-ϰB is activated is via cellular stimuli and stressors. Because of its redox sensitivity, NF-ϰB is also known to be triggered by metal-induced ROS., transactivating a number of genes related to the inflammatory response (Lingappan, 2018). Figure 3 shows a diagrammatic representation of the mechanism of oxidative stress caused by cadmium.

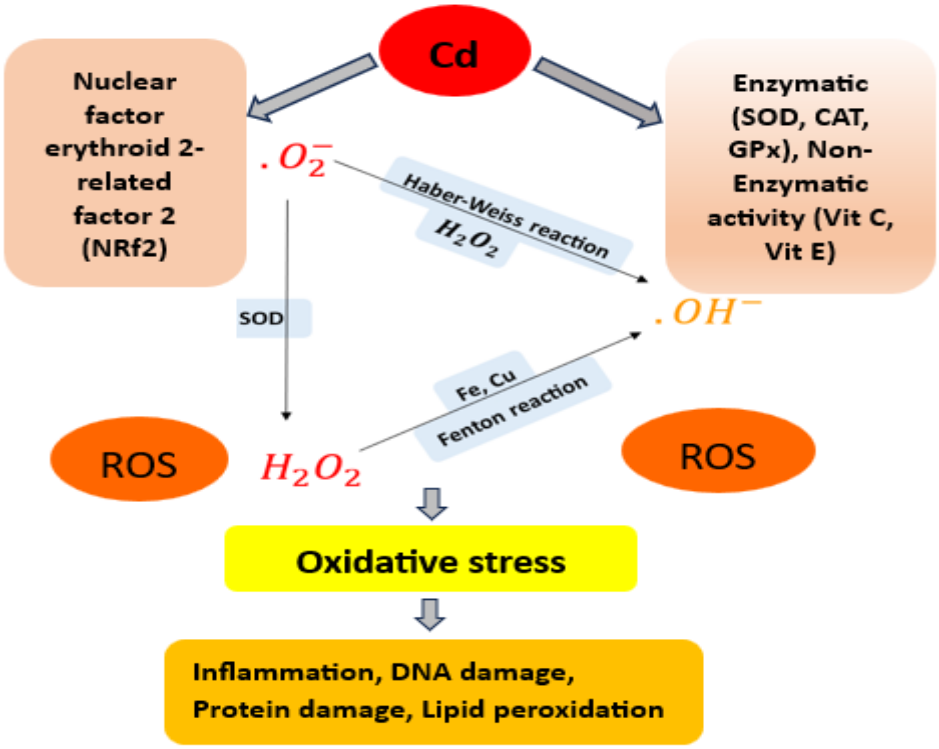


Figure 3: Mechanism of cadmium-induced oxidative stress

Cellular Damage from Cadmium-Induced Oxidative Stress

The following types of cellular damage are brought on by oxidative stress generated by cadmium:

Lipid Peroxidation: ROS generated by cadmium exposure initiate lipid peroxidation in cell membranes. This weakens the structure and integrity of membranes, which hinders cellular activity and may cause necrosis or apoptosis. Cadmium levels in exposed people's blood and urine samples have been found to positively correlate with lipid peroxidation, which is often recognised as a biomarker of oxidative stress (Qu & Zheng, 2024).

Protein and DNA Damage: DNA strand breakage and protein oxidation can result from oxidative stress caused by exposure to cadmium. 8-hydroxy-2'-deoxyguanosine (8-OHdG), a sign of oxidative DNA damage, is elevated in human tissues after cadmium exposure, according to studies (Ma et al., 2022). This DNA damage worsens the carcinogenic effects of long-term exposure to cadmium.

Health Impacts of Cadmium-Induced Oxidative Stress

Numerous health problems are linked to cadmium-induced oxidative stress, particularly in organs where cadmium builds up over time:

Kidney Damage: Although it may be present in other tissues including bone and the placenta, cadmium primarily builds up in the kidney and liver. Chronic exposure to cadmium can cause nephrotoxicity and renal failure, and the kidneys are especially vulnerable to its buildup. Because Cd-induced ROS harm the renal tubules, this is frequently characterised by tubular dysfunction and a reduced glomerular filtration rate (GFR) (Johri et al., 2010). It has long been known that the primary issue for individuals who are exposed to cadmium on a regular basis is kidney damage(Barbier et al., 2005). Cadmium-metallothionein (Cd-MT) is the form of cadmium that enters the kidney. Cd-MT is filtered by the glomerulus and reabsorbed in the proximal tubulus. Cadmium therefore stays in the tubulus cells to compensate for the bulk of the body burden. Cadmium levels in renal tubulus cells rise during the course of a person's lifetime (Godt et al., 2006). The reserve filtration capacity and glomerular filtration rate (GFR) will typically be reduced, and severe cadmium poisoning may result in nephrotoxicity with side effects as polyuria, aminoaciduria, glucosuria, hyperphosphaturia, hypercalciuria, and impaired buffering capacity (Gonick, 2008). Calcium, amino acids, enzymes, and proteins were lost in the urine as a result of cellular damage and compromised proximal tubule function. However, tubular proteinuria results from a reduced tubular reabsorption of a small number of molecular-weight proteins. Alpha 1-microglobulin, retinol-binding protein, β2-microglobulin (Bernard, 2004; Rafati Rahimzadeh et al., 2017) and N-acetyl-α-Dglucosaminidase (NAG) (Bernard, 2004) are the most prevalent proteins in urine (Rafati Rahimzadeh et al., 2017)

It's also known that a larger calcium excretion from an increased cadmium load in the kidney increases the incidence of kidney stones (Godt et al., 2006). Those with high blood cadmium concentrations had considerably greater urine β2-Microglobulin and RBP levels than those with normal values, according to the ChinaCad-Study (Jin et al., 2002). Both tubular and glomerular damage were noted in the first group. The reversibility of tubular injury has been debated (Hotz et al., 1999). However, most people now believe that it is irreversible (Godt et al., 2006).

Lung Damage: Lung inflammation and an elevated risk of lung cancer are linked to inhaling cadmium fumes, which are frequently present in work environments. Cadmium's carcinogenicity is mostly caused by oxidative DNA damage in lung tissues (Waalkes, 2003).

Cardiovascular disease: Additionally, exposure to cadmium has been linked to increased risk of cardiovascular disease. According to studies, endothelial dysfunction brought on by ROS may be the main way that cadmium-induced oxidative stress causes atherosclerosis and hypertension (Tellez-Plaza et al., 2013).

Cadmium-mediated endothelial cell death and endothelium integrity disruption are two effects of cadmium. Cadmium may permeate from the circulation into the media layer as a result of endothelial cell gaps (Prozialeck et al., 2006). After passing through endothelial cells, cadmium is mostly stored in smooth muscle cells. At low cadmium concentrations, it stimulates smooth muscle cell proliferation, interacts with ion homeostasis and calcium ion flux, and has cytotoxic effects on smooth muscle cells. These effects enable lipid accumulation in vessel walls and alter lipid profiles towards a more atherogenic state (Lin et al., 2021; Prozialeck et al., 2008).

Cadmium has been implicated in both carotid intima-media thickness (IMT) and endothelial dysfunction, according to in vitro research. Additionally, in vivo atherosclerotic plaque development was stimulated (Fagerberg et al., 2012). After cadmium poisoning, there may be thrombogenic events, endothelium malfunction when cardiovascular disease (CVD) first appears, and cell death as a result of lack of endothelial cell structural (Rafati Rahimzadeh et al., 2017). The basic mechanism by which cadmium causes atherosclerosis, compromising the stability and functionality of the vascular endothelium and consequently playing a role in vascular inflammation, is believed to be cadmium-induced endothelial cell death(Knoflach et al., 2011). Atherosclerosis is significantly influenced by cytokines and hyperactivated inflammatory responses (Fatkhullina et al., 2016). Atherosclerosis inflammation may be impacted by cadmium buildup, which raises a number of significant pro-inflammatory cytokines, including interleukin (IL)-6, IL-8, IL-1β, and tumour necrosis factor alpha (Bonaventura et al., 2018; Hossein-Khannazer et al., 2020). Furthermore, research using ApoE-/-mice revealed that long-term exposure to cadmium elevated levels of total cholesterol and inhibited cholinergic relaxation, which in turn lowered the bioavailability of nitric oxide (Oliveira et al., 2019). Potential reasons for how cadmium harm the cardiovascular system and increases the risk of atherosclerosis are provided by

this research**.** Figure 4 shows the pathway of atherosclerosis caused by cadmium (Lin et al., 2021).

Hypertension may occur from cadmium's suppression of acetylcholine-induced arterial relaxation and inhibition of endothelial nitric oxide synthase (EUM et al., 2008). It could cause endothelial damage and increase cytokine production. Peripheral artery disease may become more common as a result of these atherogenesis-causing pathways over time (Navas-Acien et al., 2004). Exposure to cadmium toxins may raise the risk of cardiovascular death (Menke et al., 2009).

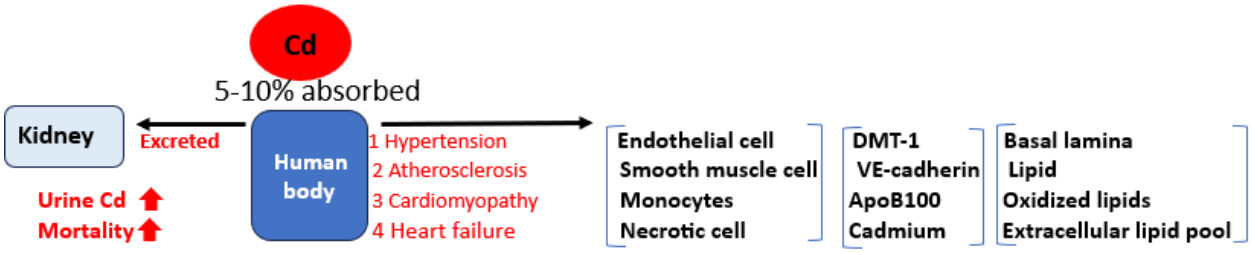


Figure 4: Relationship between cadmium and cardiovascular disease showing the link between absorption and excretion, as well as the possible methods of increasing atherosclerosis and significant adverse events (right).

Neurological Effects: Despite being poorly researched, new data indicates that cadmium may cause neurotoxicity through oxidative damage and interfere with the blood-brain barrier, which might lead to neurodegenerative illnesses (Wang & Du, 2013)**.** Oral intake is the main way that cadmium enters the nervous system. Once in the bloodstream, it can harm the blood–brain barrier (BBB) and build up in nervous system tissue (Arruebarrena et al., 2023).

Recent reports have highlighted cadmium's acute neurotoxicity affecting both the central and peripheral nervous systems. In the brain, cadmium may potentially cause lipid peroxidation and cellular damage. Monoamine neurotransmitters undergo oxidative deamination due to its impact on monoaminoxidase (MAO) (Xu et al., 2013). Cadmium weakens the body's defences against oxidation and raises the formation of free radicals in the central nervous system (Arruebarrena et al., 2023). This pathway often results in neurobehavioral attentional abnormalities, memory disorders, psychomotor activity disorders, and olfactory dysfunction (Appleby et al., 1999b; Arruebarrena et al., 2023). Parkinson's, Alzheimer's, and Huntington's disease are examples of neurodegenerative diseases that can result from poisoning and cause memory loss and behavioural

abnormalities (Rafati Rahimzadeh et al., 2017). Additionally, cadmium alters the regulation of glycogen metabolism and disrupts the blood-brain barrier. These processes together indicate multiple sites of metabolic disturbance that lead to progressive deterioration of the nervous system, raising the potential of neurological and neurodegenerative diseases (Arruebarrena et al., 2023) as shown in Figure 5.

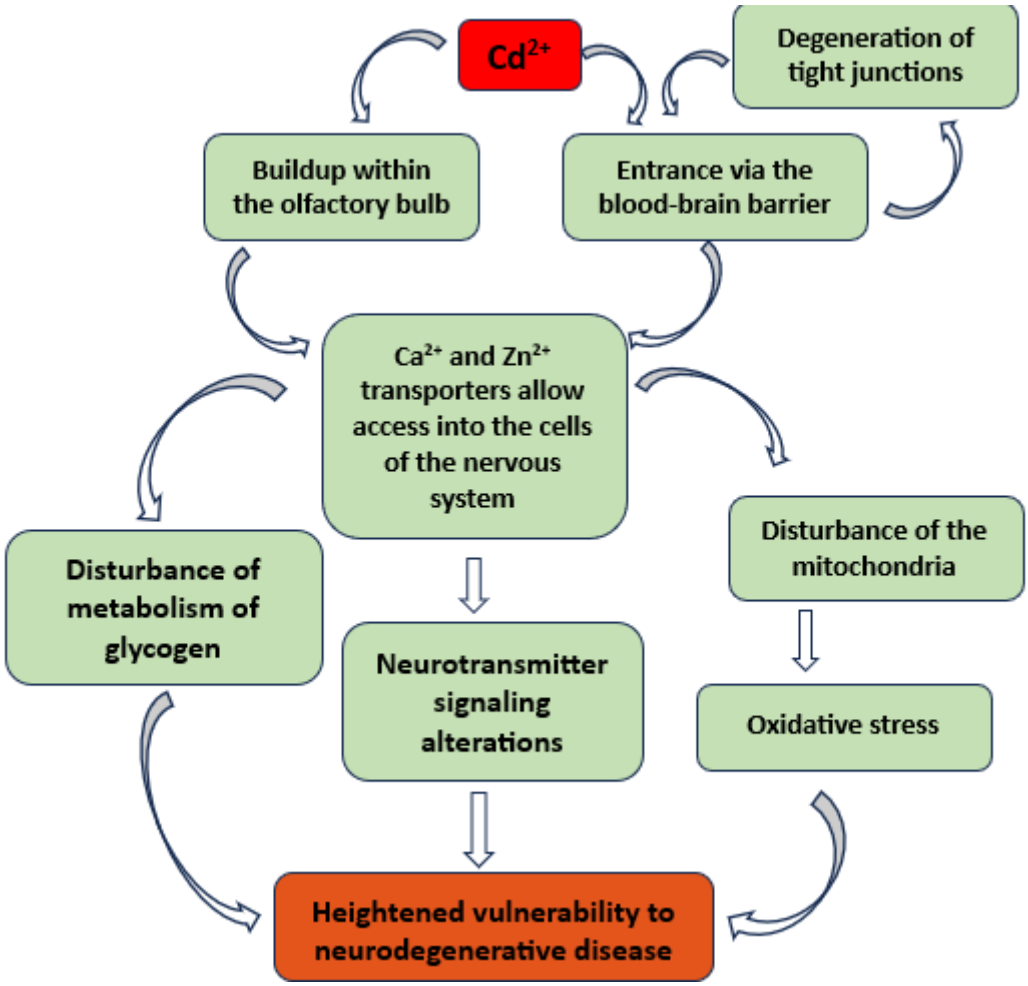


Figure 5: Pathways through which cadmium might raise the risk of neurodegenerative diseases

Carcinogenic effects: The International Agency for Research on Cancer (IARC) classified cadmium compounds as carcinogenic in humans (Kellen et al., 2007). In addition to causing kidney or prostate cancer, it may be regarded as a lung carcinogen. The key finding is that cadmium can lead to hyperplasia of testicular interstitial cells and abnormal testosterone production (Kellen et al., 2007). Several data suggest that cadmium may play a part in cancers of stomach, liver, hemotopoietic system, and bladder (Waalkes, 2003).

Moreover, cadmium can be a possible breast cancer risk factor. According to a different research, exposure to cadmium may raise the chance of developing pancreatic cancer via causing neoplasia (Rafati Rahimzadeh et al., 2017; Waalkes, 2003)

According to reports, oxidative stress is induced by Cd, which results in cell damage (Barsouk et al., 2021; L. Liu et al., 2015). Reactive oxygen species, nitric oxide, hydrogen peroxide, superoxide anions, and hydroxyl radicals can all be produced by Cd. All phases of carcinogenicity may be influenced by Cd-induced biochemical alterations, such as abnormal gene expression, E-cadherin malfunction, disruption of DNA repair, and cell death (Barsouk et al., 2021; Ledda, 2018). The effects of Cd can be attributed to (1) oxidative stress or reactive oxygen species (ROS)/free radicals, (2) alterations in apoptotic pathways, (3) epigenetic modifications, or (4) a combination of effects linked to many pathways (Tavakoli Pirzaman et al., 2023).

The activation of proto-oncogenes, inactivation of tumour suppressor genes, disruption of cell adhesion, and suppression of DNA repair are among the cellular and molecular processes linked to cadmium carcinogenicity (Ilyasova & Schwartz, 2005). In fact, a disease involving DNA-protein crosslinks or damage to DNA strands may totally prevent cell proliferation. In conclusion, it is hypothesised that exposure to cadmium may have an impact on apoptosis, cell signalling, differentiation, proliferation, and other biological processes. These actions may have a direct or indirect impact on carcinogenesis (Rafati Rahimzadeh et al., 2017; Waalkes, 2003)

The decrease of caspase activity, which results in apoptotic inhibition, is one of the detrimental mechanisms of Cd. It will cause defective cells to proliferate more. A similar process of cell damage that manifests as unchecked cellular proliferation has also been found to be caused by molecular alterations in apoptotic proteins like p53 (Buha et al., 2017; Tavakoli Pirzaman et al., 2023; Wallace et al., 2019).

Cadmium can attach to the thiol group in the p53 structure or replace zinc. The cell's capacity to react to DNA damages is diminished as a result of these alterations, which affect p53 activity (Anetor, 2012). Chronic low dosage exposure to Cd causes DNA hypermethylation through an increase in DNA methyltransferase activity, in addition to resistance to apoptosis (Cui et al., 2021; Wang et al., 2012). Because DNA-damaged cells may avoid apoptosis and multiply with innate DNA lesions, apoptotic resistance occurs in Cd-induced malignancy, ultimately leading to the malignant phenotype (Cui et al., 2021).

Mitigating Cadmium-Induced Oxidative Stress

Due to the harmful nature of cadmium, researchers have explored various strategies to mitigate its effects:

Antioxidants: It has been shown that antioxidants such as vitamin E, selenium, and N-acetylcysteine (NAC) can lessen the oxidative damage that Cd causes. These substances provide some protection against Cd-induced ROS by raising cellular GSH levels and preventing lipid peroxidation (Bagchi et al., 2000).

Dietary Interventions: The oxidative effects of cadmium may be mitigated by diets high in fruits, vegetables, and vital minerals (such as magnesium and zinc). Furthermore, a number of chelating substances and dietary fibres are recommended to decrease the absorption of cadmium in the stomach, hence minimising its bioavailability.

One of the main ways that cadmium causes its harmful effects is through oxidative stress. Despite not directly generating ROS, cadmium indirectly causes oxidative stress by lowering antioxidant levels, altering cellular redox conditions, and triggering inflammatory reactions. Renal failure, lung cancer, cardiovascular disease, and maybe neurodegeneration is among the serious health hazards linked to prolonged cadmium exposure. Possible approaches to lessen the harmful impacts of cadmium in exposed populations are being investigated in relation to antioxidant treatment and dietary changes.

Diagnostic Evaluation

Considered end-fate metabolic products, hair and nails are chronically laden with minerals and heavy metals. In comparison to urine or blood serum samples, human nails also show quantities of the end products of metals and minerals in the metabolism, which cause disease and toxicity risk, for at least three months to a year of exposure (Alshammari, 2022).

Metal levels have been estimated using urine, hair, nails, teeth, and blood as indicators. Because hair and nails provide a record of comparatively lengthy periods, but blood displays transitory levels that alter over time, the metal body load of trace/toxic elements is better reflected by the trace element contents in hair and nails than by those in blood. Additionally, compared to blood or teeth, hair and nails are inert, easy to sample, and may be preserved with little fuss. Additionally, carlier studies reveal elevated amounts of trace

metals in these tissues. In biological, medicinal, and environmental research, it is crucial to identify any trace or harmful substances in human hair and nails (Mehra & Juneja, 2004).

Paraclinic laboratory assays are frequently used to measure the amounts of cadmium in samples of blood, urine, hair, and nails. Recent exposure may have contributed to the short half-life of cadmium in blood (three to four months), but long-term cadmium accumulation in the body may have produced the long half-life (30 years). The detection limit for cadmium in blood is 0.3 μg/L (Silver et al., 2013). The biological sciences are interested in determining the amounts of trace elements in hair and nails (Rafati Rahimzadeh et al., 2017). Long-term accumulation of trace elements in the body can have an impact on metabolic and biological functions (I. Abdulrahman et al., 2012). Furthermore, it is simple and practicable to sample, transport, and store hair and nail samples, and it is inexpensive and quick to analyse the trace elements in the samples (I. Abdulrahman et al., 2012). An outstanding technique for the long-term identification of heavy metal exposure is saliva analysis. The human body's acceptable threshold limit for the mean amount of cadmium in saliva is less than 0.55 μg/l (Rafati Rahimzadeh et al., 2017).

Treatment of Cadmium Poisoning

Cadmium (Cd) is a toxic heavy metal often inhaled or ingested, posing significant risks to human health. Effective treatment of chronic cadmium poisoning is essential for human health since it can cause lung illness, bone abnormalities, and renal damage. Chelation therapy, supportive care, lowering Cd absorption, and methods to stop more exposure are the main treatment options for Cd toxicity. Chelation therapy is a popular method of treating heavy metal poisoning, including exposure to Cd. Chelating agents, such as ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA), and dimercaptopropane sulfonate (DMPS), bind to Cd and facilitate its excretion from the body. Although these agents have demonstrated efficacy in animal studies and in some human cases, their effectiveness for Cd in humans is limited and occasionally controversial due to possible side effects and the possibility of mobilising Cd to other organs. DMSA is particularly less toxic and safer, but its capacity to remove Cd in large quantities is still limited (Goyer, 1997).

Another strategy makes use of antioxidants, including vitamins C and E, which may lessen cellular damage and oxidative stress brought on by exposure to Cd (Flora et al., 2008). To control symptoms and reduce organ damage from Cd, supportive therapy is crucial. For example, treatments that preserve renal function, such hydration and electrolyte balance, may be helpful for those with Cd-induced nephrotoxicity. Dialysis and other renal replacement treatments may be required in extreme situations to control the harmful effects of cadmium on the kidneys (Bernhoft, 2013). Emphysema and other lung diseases brought on by cadmium inhalation necessitate supportive respiratory treatments and may entail corticosteroids to reduce inflammation (Järup et al., 1998).

In order to treat cadmium poisoning, it is essential to stop further exposure. This entails minimising exposure to sources of cadmium, whether in work-related, environmental, or lifestyle settings. For example, long-term health effects can be lessened by lowering Cd exposure in industrial settings (Godt et al., 2006). To reduce cumulative exposure, it is also crucial to regularly evaluate Cd levels in high-risk groups, especially industrial workers (Satarug & Moore, 2004).

In conclusion, chelation therapy, antioxidant support, symptomatic care, and exposure prevention are all part of the treatment for cadmium toxicity. Additional investigation into the efficacy of certain chelators and other therapy modalities may improve the management of Cd toxicity and lessen its long-term negative effects on health (Bernhoft, 2013; Flora et al., 2008).

Use of chelating agents

The foundation for treating metal toxicity is chelation therapy. Since the 1950s, a variety of chelating agents have been employed extensively.

The main treatment for heavy metal poisoning is chelation therapy. Chelation is the process by which ions or molecules of a ligand form a cyclic or ring-like structure by forming a coordination bond with the central metal atom or ions. An ion or molecule having two or more atoms that may give up a pair of electrons to create a covalent connection with a metal atom or ion is called a ligand. Three types of ligands may be distinguished by the type of bond that exists between the ligand and the covalent atom: [A] Unidentate (one donor atom, such as Cl^-, NH_3, H_2O), [B] Bidentate (two donor atoms,

such as $C_2O_4^{2-}$), and [C] Polydentate (more than two donor atoms, such as EDTA) (J.-J. Kim et al., 2019).

EDTA, DMPS, and DMSA are used to treat cadmium poisoning. EDTA is the preferred medication among these three chelating agents. DMSA outperformed DMPS in removing cadmium from an animal study. Research conducted both in vitro and in vivo indicates that EDTA is more effective than DMSA at releasing intracellular cadmium (Bernhoft, 2013; Blaurock-Busch, 2014; Rafati Rahimzadeh et al., 2017). Furthermore, the supplementary use of antioxidants such glutathione (Gil et al., 2011) enhances the efficiency of EDTA and guards against nephrotoxicity. The concurrent usage of antioxidants (Flora et al., 2008), such as methionine, mannitol (Tandon et al., 2003), thiamine (Tandon & Prasad, 2000), and zinc (Flora et al., 1998), as well as vitamins E and C may also increase the efficacy of EDTA (J.-J. Kim et al., 2019).

According to recent findings, chelating drugs are more effective in preventing or treating cadmium intoxication when vitamin E or methionine is administered during the cadmium chelation process. They may also be able to remove intracellularly bound cadmium from rats (Tandon et al., 1997; Tandon & Prasad, 2000). Previous research has demonstrated that the coadministration of calcium disodium ethylenediamine tetraacetate ($CaNa_2EDTA$) and thiamine (vitamin B13) enhances their respective effects on metal removal and intracellular metal mobilisation in animals. This could be useful in chelation therapy for other toxic metals that seek -SH groups (Tandon & Prasad, 2000).

Since cadmium has a strong affinity for sulfhydryl groups, chelation may require coordination between thiol chelators' sulphur and oxygen atoms. However, as cadmium binds strongly to metallothionein (MT) primarily in the liver and kidney shortly after exposure, such chelating agents must be lipophilic and able to enter the cell for efficient in vivo chelation and subsequent elimination of the resultant cadmium chelate (Tandon & Prasad, 2000).

The majority of chelating agents on the market now have detrimental side effects (Flora & Pachauri, 2010). Despite the hazards involved, $CaNa_2EDTA$ is a versatile chelating agent capable of forming complexes with a broad range of metal ions and is employed in therapeutic settings. The inability of $CaNa_2EDTA$ to penetrate cellular membranes restricts the removal of metal ions from their complexes in the extracellular fluid. DMSA, another

commonly used succimer, has the same extracellular dispersion restriction as DMSA, although being thought to be safer (Flora & Pachauri, 2010).

Table 1: Chelating agents, their chemical formula and generic name

S/N	Chelate	Formula	Commercial name	Common name
1	Trientine*	$C_6H_{18}N_4$	Syprine	
2	$CaNa_2EDTA$	$C_{10}H_{12}CaN_2Na_2O_8$	Calcium disodium versenate	Edetate calcium disodium; sodium calcium edetate
3	DMPS	$C_3H_8O_3S_3$	Dimaval and Unithiol	2,3-Dimercaptopropane-1-sulfonic acid
4	Deferoxamine	$C_{25}H_{48}N_6O_8$	Deferoxamine mesylate, Desferal	Desferrioxamine
5	DMSA	$C_4H_6O_4S_2$	Chemet	meso-2,3-Dimercaptosuccinic acid; succimer
6	BAL	$C_3H_8OS_2$	BAL in oil	Dimercaprol; British Anti-Lewisite (BAL); 2,3-Dimercaptopropanol
7	Penicillamine	$C_5H_{11}NO_2S$	Cuprimine, Cuprenyl, Depen	D-penicillamine

***** While trientine may theoretically bind to cadmium, it is not a first-line or widely accepted treatment for cadmium poisoning.

Metabolomics of Cadmium Toxicity

Metabolomics is an omics technology that focuses on the systematic identification and quantification of metabolites, the small molecules involved in cellular processes (Mashego et al., 2007). This approach is valuable for understanding the physiological responses of organisms to metal exposure by analyzing changes in their metabolic profiles. Overall, metabolomics offers a powerful tool for studying metal toxicity, revealing real-time physiological changes and providing insights into metabolic pathways affected by metal exposure (Booth et al., 2011). Despite technical and analytical challenges, its integration with other systems biology approaches holds great promise for future research.

According to Zong et al. (2018), exposure to Cd could alter the energy metabolism (glycolysis, TCA cycle, and fatty acid β-oxidation), cell signalling, cell membrane composition, anti-oxidation, and cellular detoxification system, resulting in notable metabolic alterations in lipids, amino acids, vitamins, organic acids, and acylcarnitines in PC-12 cells. These metabolites' variations were enough to set the treated groups apart from the control groups. Early detection and treatment of Cd neurotoxicity may benefit from focussing on these putative biomarkers as well as the vital metabolic pathways for heavy metal Cd exposure seen in endogenous small molecules (Zong et al., 2018).

Tian et al. (2021) examined the effects of low-level cadmium exposure on human bone cell Saos-2. The findings showed that intracellular cadmium endocytosed by Saos-2 cells was much less than the injected cadmium, and that cadmium exposure reduced cell viability in a dose-time-dependent way. The impact of the cadmium that did not reduce cell viability on Saos-2 was examined using the metabolomics approach. Significant variations in the metabolic levels of pyrimidine metabolism, amino acid metabolism, and energy metabolism were seen in the cells exposed to cadmium. Our pipeline assisted in determining the danger of low-level cadmium exposure, at which point conventional toxicity assessment methods produced unfavourable findings (Tian et al., 2021).

Hong et al, 2022 studies the metabolic toxicity of environment-relevant Cd exposure on pancreatic β-cells at the metabolome-wide level in MIN6 cells. It has been shown that modest levels of environment-relevant Cd exposure cause considerable cytotoxicity and inhibit the release of insulin. According to non-targeted metabolomics research, exposure to Cd clearly disrupts metabolic pathways, considerably increases lipotoxic metabolites, and greatly perturbs metabolites. Furthermore, the research showed that urine metabolites affected by Cd may be a useful biomarker for tracking metabolic damage at the population level (Zhang et al., 2025).

Non-targeted metabolomics investigation conducted by Zhang et al., 2025, essentially showed the metabolic alterations of ovarian granulosa cells exposed to low doses of Cd (subtoxic and not considerably influencing dosages for cell survival). In a concentration-dependent way, Cd altered cell metabolism and decreased cell viability. According to metabolomics research, exposure to Cd had a major impact on the metabolism of sphingolipids, glutathione, and nucleotides. Additionally, in KGN cells exposed to 3 and 10 μM Cd, respectively, alterations were seen in the metabolism of cysteine, methionine, and

tryptophan. These results serve to clarify the mechanism of Cd toxicity to the ovary by showing that granulosa cells' metabolism was changed by exposure to low doses of Cd (Zhang et al., 2025).

Finally, a study by Ellis et al, 2012 have shown that metabolic profiling may, in principle, be used to describe the metabolic effects of exposure to environmental toxicants, such cadmium and tobacco smoke, in a human population using an NMR-based method. Concluding that metabolic profiling can help enhance risk assessment models and eventually direct intervention to stop the course of illness by identifying new biomarkers and molecular signs of the effects of exposure to numerous environmental toxicants. Therefore, metabolic profiling is an essential component of any future efforts to identify the human exposome. Longer term, the techniques utilised in their study could be widely applied for baseline surveys in health impact assessments for development projects. They could also be crucial in monitoring populations residing close to industrial sites and other point sources of pollution (Ellis et al., 2012).

Conclusion

Through a variety of harmful processes, such as upsetting intracellular calcium homeostasis, generating oxidative stress, changing cell signalling, and resulting in epigenetic modifications, cadmium (Cd) poses a serious risk to human health. These interrelated pathways cause tissue damage and cellular malfunction, especially in the liver, kidneys, and bones. Concern over cadmium's effects on human health is developing because of its propensity to damage different organ systems depending on exposure route, dosage, and duration. Cd-induced oxidative stress interacts with the inflammatory response, frequently resulting in the production of cytokines and NF-$\varkappa$B activation. However, because biological systems, exposure techniques, and dosages vary, research indicates different degrees of inflammatory response. Notwithstanding these inconsistencies, oxidative stress, inflammation, and multi-organ damage are typically associated with Cd. By focussing on upstream signalling pathways, research on NF-$\varkappa$B, a crucial component of both inflammation and oxidative stress, may provide insights into avoiding damage caused by Cd.

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