

Metal-Induced Oxidative Stress and Antioxidant Defense: A Review of the Current State of Knowledge and Therapeutic Implications

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Abstract

Heavy metals such as lead, cadmium, mercury, and arsenic are persistent environmental and occupational toxicants that induce cellular damage primarily through oxidative stress. By generating reactive oxygen species (ROS) and disrupting the cellular redox balance, these metals impair mitochondrial function, DNA integrity, and protein structure. In response, organisms activate antioxidant defense systems involving enzymatic and non-enzymatic components to neutralize ROS and restore homeostasis. Chronic metal exposure overwhelms these defenses, contributing to neurodegenerative, cardiovascular, and renal diseases. This review examines the mechanisms of metal-induced oxidative stress, endogenous antioxidant responses, and emerging therapeutic strategies aimed at mitigating metal toxicity. Metal ions catalyze Fenton-like reactions and deplete glutathione, leading to elevated ROS levels and lipid peroxidation. Lead and cadmium primarily target the sulfhydryl groups of antioxidant enzymes, inhibiting superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Mercury binds directly to mitochondrial complexes, increasing superoxide production and triggering apoptosis. Arsenic induces oxidative stress via the activation of NADPH oxidase and disruption of cellular signaling pathways. Transcriptomic studies reveal upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) as a key adaptive response that enhances expression of antioxidant and detoxification genes. Exogenous antioxidants such as vitamin C, vitamin E, and N-acetylcysteine have shown protective effects in preclinical models by scavenging ROS and chelating metals. Phytochemicals including curcumin, quercetin, and resveratrol demonstrate dual roles as metal chelators and Nrf2 activators. Chelation therapy with EDTA and DMSA remains the clinical standard for acute metal poisoning but carries risks of renal toxicity and essential mineral depletion. Recent nanotechnology-based approaches using selenium nanoparticles and metal-organic frameworks show enhanced biocompatibility and targeted delivery for oxidative stress mitigation. Metal-induced oxidative stress is a central mechanism underlying metal toxicity and associated chronic diseases. While endogenous antioxidant systems provide initial protection, prolonged exposure necessitates therapeutic intervention. Current strategies combining chelation with antioxidant supplementation show promise but require optimization for safety and efficacy. Future research should focus on personalized antioxidant therapies, biomarker development for early oxidative damage, and environmentally sustainable chelating agents.

Keywords: Heavy metals, Oxidative stress, Antioxidant defense, Nrf2 pathway, Chelation therapy

INTRODUCTION

When heavy metals (such as lead, mercury, arsenic, cadmium, etc.) build up in organisms, the negative effects are referred to as metal poisoning. Cellular damage results from an imbalance between the generation of reactive oxygen species (ROS) and antioxidant defenses, which is known as oxidative stress (Jomova et al., 2023; Sies, 2020). ROS are crucial for cellular motility, apoptosis, necrosis, differentiation, and proliferation. Numerous critical physiological processes, redox equilibrium, and the control of essential transcription factors all depend on low to intermediate amounts of ROS and RNS. For instance, “all metals can lead to toxicity and oxidative stress when taken up in excessive amounts, imposing a serious threat to human health” (Jozefczak, Remans, Jaco, and Ann, 2012). This indicates that exposure to excess metals frequently causes oxidative stress. On the other hand, a disruption in redox homeostasis caused by an excess of ROS results in oxidative stress and damage to all significant biomolecules, such as proteins, membranes, and DNA (Liguori et al. 2018; Kudryavtseva et al., 2016; Dudzilah et al., 2026). Antioxidant defenses often neutralize ROS and repair damage. They can be enzymatic (such as glutathione peroxidase, catalase, and superoxide dismutase) or non-enzymatic (such as glutathione, vitamins C and E, and polyphenols) (Jomova et al., 2023). However, these defenses might be overpowered or exhausted in situations when metals are present.

Because it underpins numerous diseases and influences prevention and treatment methods, an understanding of metal-induced oxidative stress is vital. Many people experience low-level chronic exposures to heavy metals because they are present in the environment at all levels, from industrial pollution to contaminated water. According to Jomova et al. (2023), oxidative pathways connected to cancer, heart disease, dementia, and other conditions can be triggered by even low concentrations of hazardous metals. Arsenic and cadmium, for instance, are known carcinogens to humans and damage DNA through oxidative processes (Flora and Pachauri, 2013). It is well recognized that lead and mercury have neurotoxic effects that result in abnormalities in neurodevelopment and cognitive function. Exposure to cadmium is associated with cardiovascular disease and high blood pressure. Exposure to lead and cadmium also poses a serious risk of kidney damage. Public education, pollution management strategies, and strict laws are necessary to prevent exposure to harmful metals (Fatima, Raza, and Dhole, 2025; Sarah et al., 2026).

A sophisticated antioxidant defense system found in cells combats reactive oxygen species (ROS) and maintains redox equilibrium. According to Ngo and Duennwald (2022), these defenses can be broadly divided into enzymatic and non-enzymatic categories. The three main enzymatic antioxidants are glutathione peroxidase (GPx), which uses reduced glutathione (GSH) as a cofactor to reduce hydrogen peroxide and organic peroxides, catalase (CAT), which breaks down hydrogen peroxide into water and oxygen, and superoxide dismutase (SOD), which transforms superoxide anions into hydrogen peroxide. By preventing the buildup of ROS and the production of extremely reactive hydroxyl radicals, these enzymes work together to shield cellular macromolecules from oxidative damage (Ngo and Duennwald, 2022; Jomova et al., 2024). Small compounds known as non-enzymatic antioxidants directly scavenge radicals. A common tripeptide that protects cells from free radicals and preserves their redox state is glutathione. Ascorbate, a water-soluble antioxidant, regenerates damaged vitamin E and contributes electrons to quench ROS. Vitamin E (α -tocopherol) is a lipid-soluble antioxidant that stabilizes lipid peroxyl radicals to break lipid peroxidation chains in membranes; vitamin C recycling keeps it active.

Quercetin, curcumin, and resveratrol are examples of plant-derived polyphenols that also offer additional antioxidant potential through metal chelation and radical scavenging (Ngo and Duennwald, 2022). Antioxidant defense is coordinated at the transcriptional level via the Nrf2/ARE pathway. Under normal circumstances, Keap1 targets Nrf2 for degradation. In response to oxidative stress, Nrf2 translocates to the nucleus, stabilizes, and activates antioxidant response elements (AREs), which triggers the production of genes that encode phase II detoxification enzymes, SOD, CAT, and GPx (Bellezza et al., 2018). When together, these mechanisms create a cohesive defense system that is essential for reducing oxidative damage brought on by metals. Consequently, a comprehensive analysis of the state of the art regarding metal-induced ROS production, antioxidant defenses, and treatments is required.

The sources and processes by which heavy metals cause oxidative stress are reviewed in this study, along with the endogenous antioxidant defense systems

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(enzymes and small-molecule antioxidants, such as Nrf2/ARE signaling) and the health effects of metal-induced oxidative damage.

We also assess chelation techniques and antioxidant-based therapies (vitamins, polyphenols, thiol donors like

N-acetylcysteine, α -lipoic acid, etc.) that can reduce metal toxicity. Future directions and therapeutic implications, including chelation, nanotechnology, and antioxidant supplementation optimization, have also been considered. By highlighting knowledge gaps and future research needs in this quickly developing subject, this review attempts

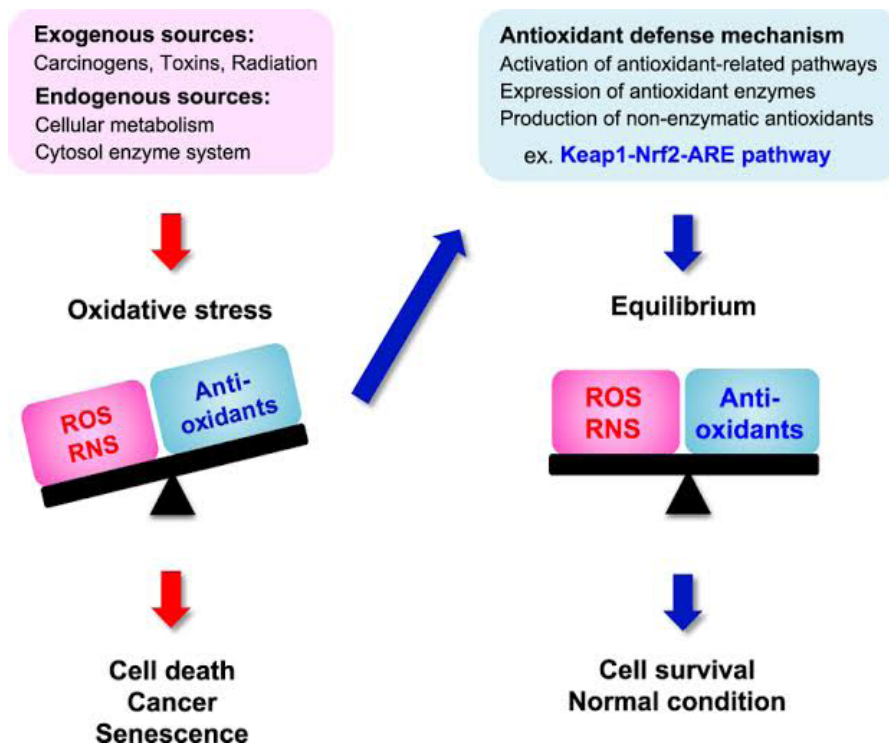


Figure1. Oxidative stress and antioxidant defense response

Source: Lee and Hu (2020)

to summarize existing knowledge of how heavy metals induce oxidative stress and how such damage might be prevented.

SOURCES AND MECHANISMS OF METAL-INDUCED OXIDATIVE STRESS

The environment is exposed to heavy metals through both man-made and natural processes. Mercury, arsenic, cadmium, and lead are all persistent in soils, water, and the atmosphere. People are exposed through consumer goods, mining, agriculture, and industrial pollutants (Fatima, Raza, and Dhole, 2025). Drinking water is the “most common source of arsenic in people,” for instance, because groundwater in portions of Asia and South America is frequently contaminated with arsenic. Arsenic can also get into food through tainted irrigation water. Through irrigation with tainted water, arsenic can potentially get into food (WHO, 2022). Peeling lead-based paint in older homes, leaded gasoline residues in soil close to roads, and lead pipes and solder in water systems are some examples of legacy sources of lead exposure.

Firing ranges and radiator repair shops are additional sources of dust (U.S. Environmental Protection Agency, 2020). Cigarette smoke is a significant source of cadmium since tobacco leaves absorb it readily and it is present in batteries, metal plating, and solder. Coal combustion and artisanal gold mining emit mercury, which concentrates in fish and biomethylates in aquatic environments. Since mercury in the food chain transforms into the deadly methylmercury, “the majority of human exposure occurs from eating contaminated fish and shellfish.”

All of these metals are at further danger from occupational exposures such as mining, smelting, welding, and battery manufacturing. There are multiple ways that heavy metals cause oxidative damage and ROS. Metals vary in how reactive they are: While non-redox metals like lead or cadmium cause ROS indirectly by destroying antioxidants and upsetting mitochondria, redox-active metals like iron or copper directly participate in Fenton chemistry to create hydroxyl radicals (Cuypers, Smeets, and Vangronsveld, 2009; Jozefczak et al., 2012). “Oxidative stress, a process

in which the cellular redox balance between pro- and antioxidants is disturbed in favor of the former,” is the effect of metals shifting the cellular redox balance in favor of pro-oxidants in all situations (Smeets et al., 2009). Then, the excess ROS (hydrogen peroxide, superoxide, hydroxyl radicals, etc.) target the biomolecules. “Excessive formation of ROS is responsible for disrupted redox homeostasis, oxidative stress and ROS-mediated damage to DNA, proteins, and membranes,” according to a recent study published by Jomova et al. (2023). Numerous studies have demonstrated that exposure to heavy metals increases tissue indicators of DNA damage and

lipid peroxidation, such as malondialdehyde (Koyama, Kamogashira, and Yamasoba, 2024).

Additionally, heavy metals weaken antioxidant defenses. These vital defenses can be diminished by their ability to attach to the sulfhydryl groups in glutathione (GSH) and antioxidant enzymes. According to Jozefczak et al. (2012), cadmium, for instance, has a strong affinity for the thiols in GSH and can block glutathione peroxidase, reducing the antioxidant capacity overall. In a similar manner, mercury damages mitochondrial activity and targets protein thiols, resulting in a vicious cycle of ROS production. In conclusion, heavy metals both produce ROS through

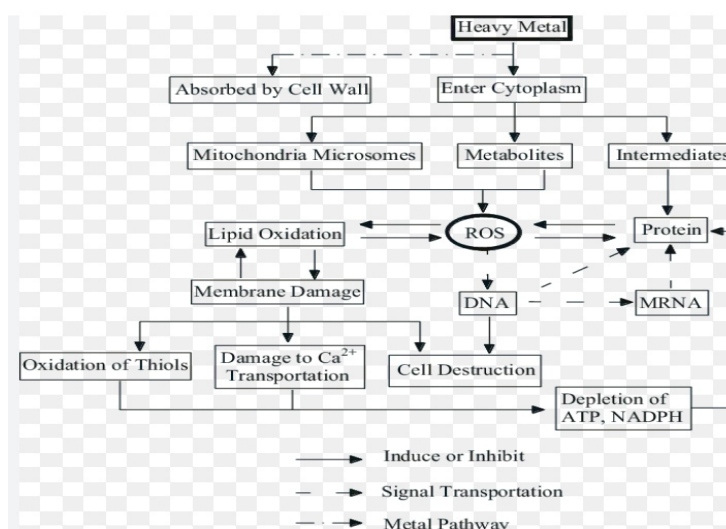


Figure2. Possible mechanisms involved in the metal-induced oxidative stress

Source: Zhang et al. (2014)

indirect redox cycling and catalytic processes, while also impairing the cell's capacity to detoxify ROS (Koyama et al., 2024).

SOME COMMON SPECIFIC METALS ARE DISCUSSED BELOW:

Lead (Pb): Lead readily crosses biological membranes (including the blood-brain barrier) and replaces calcium in bone. It induces ROS generation and oxidative stress as a key mechanism of toxicity (Lopes et al., 2016). In animal studies, lead exposure increases superoxide and hydroxyl radicals and causes DNA strand breaks (Lopes et al., 2016). Lead also inhibits δ -aminolevulinic acid dehydratase (ALA-D), causing accumulation of its pro-oxidant substrate. Clinically, lead accumulates in the brain and is a known neurotoxin, causing cognitive impairment and peripheral neuropathy (Fatima et al., 2025; Moses et al., 2025).

Mercury (Hg): Oxidative damage is significantly encouraged by exposure to mercury, particularly

methylmercury from fish or inorganic mercury from occupational sources. Because of mercury's strong affinity for thiol groups, glutathione and enzyme function are compromised, which permits ROS to build up. Exposure to mercury causes increased ROS in brain tissue and blood cells in both animal and cell tests (Koyama et al., 2024; Abah et al., 2026). Neuronal loss in the visual cortex and cerebellum that is associated with oxidative damage is a hallmark of chronic mercury poisoning, often known as Minamata illness (Koyama et al., 2024). Microtubules and neurodevelopment are also disturbed by mercury, partly due to ROS-mediated signaling.

Arsenic (As): Free radicals are produced by the biotransformation of the metalloid arsenic. For instance, superoxide and hydroxyl radicals can be produced when inorganic arsenic cycles between oxidation states (Flora and Pachauri, 2013). Additionally, arsenic depletes glutathione and inhibits pyruvate dehydrogenase, which indirectly increases ROS. Arsenic “is known to generate free radicals that play a fundamental role in inducing oxidative

stress-mediated toxicity,” according to a reputable review (Flora and Pachauri, 2013). According to epidemiology, chronic oxidative DNA damage is probably the mechanism by which arsenic exposure (via food and water) is linked to vascular disease as well as skin, lung, and bladder malignancies.

Cadmium (Cd): Although cadmium is not redox-active, it weakens antioxidant defenses, which leads to oxidative stress. Cadmium promotes lipid peroxidation and inhibits the catalase and glutathione enzymes. According to research on animals, exposure to cadmium significantly increases the amounts of malondialdehyde (MDA), a sign deplete glutathione and inactivate antioxidant enzymes, which upset cellular redox equilibrium.

of lipid peroxidation, in the kidney and liver. Additionally, exposed cells experience apoptosis and mitochondrial malfunction due to cadmium (Koyama *et al.*, 2024). According to Fatima *et al.* (2025), cadmium exposure from diet or smoking is clinically associated with hypertension and cardiovascular disease, which is believed to be caused by ROS-mediated vascular injury.

In summary, all heavy metals converge on oxidative stress pathways, even though their biochemistry differs. Exposure to cadmium, lead, mercury, and arsenic increases ROS and damages proteins, membranes, and DNA (Jomova *et al.*, 2023; Koyama *et al.*, 2024). Additionally, they

ANTIOXIDANT DEFENSES

Cells defend against ROS through multi-layered antioxidant systems, they include;

Table1. Environmental and occupational sources of heavy metal exposure

Metals	Major Sources	KeyTarget Organs	ROS Mechanism
Lead	Paint, pipes, batteries	Brain, kidney	↑Superoxide, inhibits antioxidant enzymes (Flora <i>et al.</i> , 2012)
Mercury	Fish, mining, coal	Brain	Binds thiols, depletes GSH, ↑ROS (Koyama <i>et al.</i> , 2024).
Arsenic	Contaminated water, food	Skin, lung, bladder	ROS generation, DNA damage (Rehman <i>et al.</i> , 2018)
Cadmium	Tobacco smoke, batteries	K i d n e y , cardiovascular	Inhibits CAT/GPx, lipid peroxidation (Cuypers <i>et al.</i> , 2010)

ENZYMATIC ANTIOXIDANTS

Enzymatic defense is the initial line of defense. The most dangerous ROS are neutralized by the combined action of three essential enzymes: glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) (Jomova *et al.*, 2024). Superoxide radicals ($O_2^{\cdot-}$) are quickly transformed into hydrogen peroxide (H_2O_2) by SOD. H_2O_2 is then broken down into water by catalase and GPx. This “first-line antioxidant defense” is essential because it lowers H_2O_2 levels and stops superoxide from building up, which could otherwise result in peroxynitrite. SOD/CAT/GPx, for instance, “plays an irreplaceable role in the dismutation of superoxide radicals and hydrogen peroxide,” according to one review (Jomova *et al.*, 2024). Since several of these enzymes (including Cu/Zn-SOD, Mn-SOD, and Se-dependent GPx) are metal-dependent, metal levels can have a direct impact on them. Because trace minerals like selenium are also cofactors for GPx, a shortage in selenium can affect GPx activity, which in turn increases oxidative stress. It is illustrated as follows;

i. SOD (superoxide dismutase) – Catalyzes

$2O_2^{\cdot-} + 2H^+ \rightarrow O_2 + H_2O_2$, preventing superoxide accumulation and peroxynitrite formation (Ngo and Duennwald, 2022).

ii. Catalase – Decomposes H_2O_2 to $H_2O + O_2$ (Ngo and Duennwald, 2022).

iii. GPx (glutathione peroxidase) – Reduces H_2O_2 (and organic peroxides) using $2GSH + 2H^+ \rightarrow GSSG + 2H_2O$ (Ngo and Duennwald, 2022).

These enzymes (with glutathione as cofactor) prevent formation of highly reactive hydroxyl radicals ($\cdot OH$)

NON-ENZYMATIC ANTIOXIDANTS

Low-molecular-weight (non-enzymatic) antioxidants are the second line of defense. These consist both dietary and endogenous substances that scavenge ROS. A key cellular antioxidant, glutathione (GSH) both directly neutralizes radicals and acts as a cofactor for GPx. Vitamin E (α -tocopherol) and vitamin C (ascorbate) are further small-molecule antioxidants that scavenge free radicals in the lipid and aqueous compartments, respectively. While vitamin E is a lipid-soluble antioxidant that breaks down membranes by donating a hydrogen atom to lipid peroxyl radicals, resulting in a relatively stable α -tocopheroxyl radical, vitamin C, a water-soluble reductant, donates electrons to quench ROS and can regenerate oxidized vitamin E (Jomova *et al.*, 2024).

Dietary flavonoids (such as quercetin, anthocyanins, and resveratrol) and carotenoids (lutein, lycopene, and β -carotene) also play a role (Jomova *et al.*, 2024). For example, polyphenols have the ability to alter signaling, bind metal ions, and neutralize ROS. As per Smirnova *et al.* (2023), research indicates that “other antioxidants such as vitamin C, vitamin E, β -carotene, etc, may also be useful in combating metal toxicity in animals.” Supplementing with vitamins C, E, and selenium is frequently investigated as an adjuvant in heavy metal exposure to strengthen these defenses.

ANTIOXIDANT RESPONSE ELEMENT-NRF2/ARE SIGNALING PATHWAY

The adaptive response and cellular repair systems are the third line of defense. Among these, the Nrf2/ARE pathway is crucial. Oxidative stress triggers the transcription factor Nrf2, which in turn triggers a series of genes related to detoxification and antioxidants. When Nrf2 is under stress, it separates from its inhibitor (Keap1), moves into the nucleus, and attaches to antioxidant response elements **Table2. Major antioxidants and their mechanisms of action**

Antioxidant	Type	Mechanism	Example in Metal Toxicity
SOD	Enzyme	Converts $O_2^{\bullet-} \rightarrow H_2O_2$	Protects neurons from Pb-induced ROS (Valko <i>et al.</i> , 2005)
Catalase	Enzyme	Decomposes H_2O_2	Limits Hg-induced oxidative damage (Fridovich, 1995)
Gpx	Enzyme	Reduces H_2O_2 using GSH	Defends against Cd toxicity (Brigelius-Flohé and Maiorino, 2013)
Glutathione	Small mol.	Direct ROS scavenger; GPx cofactor	Depleted by As, Cd (Lu, 2013)
Vitamin C	Non-Enzyme	Scavenges ROS; regenerates Vit. E	Protects against Pb/As toxicity (Padayatty <i>et al.</i> , 2003)
Vitamin E	Non-Enzyme	Stops lipid peroxidation in membranes	Counters Cd-induced lipid damage (Brigelius-Flohé and Traber, 1999)
Polyphenols	Phytochem.	ROS scavenging, metal chelation, Nrf2 activation	Curcumin reduces As-induced DNA damage (Scapagnini <i>et al.</i> , 2011)

(such as increasing GPx with selenium or activating Nrf2 with inducers) to lessen harm.

METAL-INDUCED OXIDATIVE STRESS AND DISEASE

Heavy metal-induced oxidative stress contributes to a spectrum of human diseases. The common thread is that chronic ROS/RNS damage from metals exacerbates pathological processes in brain, heart, and other organs. Some of these Diseases includes;

Neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's): Heavy metals have been linked to neurodegeneration, and the brain is extremely susceptible

(ARE) to increase the activity of several enzymes, including heme oxygenase-1, glutathione reductase, glutathione peroxidase, catalase, and others (Yang *et al.*, 2019; Baird and Yamamoto, 2020). According to Buha *et al.* (2021), Nrf2 essentially “positively regulates the expression of numerous detoxification and antioxidant genes that contain [ARE] in their promoter region.”

The cell's capacity to fend off further ROS is strengthened by this adaptive response. Numerous phytochemicals, such as curcumin and sulforaphane, activate Nrf2 to provide their antioxidant effects. Thus, oxidative damage can be exacerbated by genetic or functional impairment of Nrf2 signaling (for example, from long-term exposure to heavy metals). In summary, antioxidant defenses include stress-responsive gene programs (Nrf2/ARE), small molecules (GSH, vitamins, and polyphenols), and enzyme cascades (SOD, CAT, and GPx) (Buha *et al.*, 2021; Jomova *et al.*, 2024). Together, these layers preserve redox equilibrium. This equilibrium is upset by metal poisoning, but knowing these defenses points to potential therapeutic targets

to oxidative damage. Lead, mercury, and arsenic are among the metals that have been linked to Alzheimer's and Parkinson's disease by epidemiological and experimental studies. Lead and mercury, for instance, are well-known neurotoxins; exposure to lead during childhood results in behavioral abnormalities and cognitive impairments, while methylmercury damages the cerebellum and visual cortex (Minamata illness) (Fatima *et al.*, 2025). One important mechanism is oxidative stress, which causes lipid peroxidation, protein oxidation, and apoptotic cell death in neurons exposed to metal injury. All things considered, long-term metal exposure generates ROS, which can hasten the “common denominator” of neurodegenerative disease. The hallmarks of AD/PD, amyloid- β and α -synuclein,

aggregate in experimental models due to metals, most likely through oxidant-mediated protein misfolding. All things considered, oxidative stress caused by heavy metals is thought to worsen the evolution of neurodegenerative diseases and encourage neuronal damage. According to Fatima *et al.* (2025), lead and mercury are recognized to have neurotoxic effects that impair cognition and cause neurodevelopmental deficiencies.

Cardiovascular disease: Metals use oxidative processes to cause atherosclerosis and vascular damage. It has been demonstrated that arsenic and cadmium in particular increase the risk of cardiovascular disease. Even low-level exposures to arsenic and cadmium considerably raised subclinical atherosclerotic plaque in the carotid and femoral arteries, according to a large occupational investigation. Cadmium mimics calcium in smooth muscle and produces ROS in cardiac tissue, while arsenic can cause endothelial dysfunction and hypertension through inflammation and ROS. Chronic metal exposure has been connected to peripheral artery disease, coronary artery disease, and stroke, according to a recent Heart Association research that highlights “strong evidence that toxic metals, such as arsenic and cadmium, are cardiovascular risk factors” (ATVB Journal report, 2021; Fatima *et al.*, 2025). In fact, according to WHO projections, removing environmental contaminants, such as hazardous metals, might prevent more than 30% of the burden of cardiovascular disease worldwide (ATVB journal study, 2021). Mechanistically,

metal-derived ROS damage endothelium and oxidize LDL, which encourages the formation of plaque. Therefore, oxidative stress brought on by metals plays a significant role in CVD.

Cancer: Another significant effect of metal-induced oxidative stress is carcinogenesis. A number of heavy metals, including arsenic, cadmium, chromium, and nickel, are known to cause cancer, and the production of ROS is a major factor in DNA damage and mutation. For instance, arsenic biotransformation generates reactive oxygen species (ROS) and disrupts DNA repair, which is one of the reasons why exposure to arsenic is associated with skin, lung, and bladder cancer (Flora and Pachauri, 2013). Because it produces ROS and modifies gene expression, cadmium is linked to lung and prostate cancer. According to one review, “ROS production, antioxidant defense weakening, enzyme inactivation, and oxidative stress” are common toxicity pathways shared by heavy metals and can all contribute to the development of cancer (Parida and Patel, 2023). Experiments verify that cells exposed to metals develop oxidative DNA lesions (8-oxo-dG) and have higher rates of mutation. Therefore, long-term metal exposure fosters an inflammatory and genomically unstable milieu that is favorable to cancer.

In conclusion, there is experimental and epidemiological evidence linking metal-induced ROS to cancer, heart disease, and neurodegeneration. One “common denominator”

Table 3. Diseases Associated with Metal-Induced Oxidative Stress

Disease	Incriminated Metals	Mechanisms	Evidence
Alzheimer's	Pb, Hg, Cd	Amyloid aggregation, lipid peroxidation	Bakulski et al. (2020)
Parkinson's	Pb, Hg, As	Mitochondrial oxidative dysfunction	Cannon and Greenamyre (2011)
C V D	Cd, As	Endothelial dysfunction, LDL oxidation	Navas-Acien et al. (2005)
C a n c e r	As, Cd, Cr, Ni	ROS → DNA damage, impaired repair	Jomova and Valko (2011)

across these chronic illnesses is oxidative stress (Jomova *et al.*, 2024). This emphasizes the significance of public health since a significant portion of the illness burden may be avoided if metal exposure and oxidative damage could be avoided or reduced.

ANTIOXIDANT THERAPIES

Given the role of oxidative damage in metal toxicity, numerous antioxidant-based therapies have been explored. *These fall into several categories:*

Vitamins and minerals (dietary antioxidants): Many studies have been conducted on vitamins C and E as

preventive supplements. Ascorbate, or vitamin C, can chelate metal ions like iron and lead and lower free radicals in aqueous compartments. Lipid membranes are protected against peroxidation by vitamin E (tocopherol). In one study, vitamin C+E combination more successfully restored antioxidant enzymes and decreased lipid peroxidation in mice exposed to cadmium, demonstrating the often improved benefit of combined supplementation (Smirnova *et al.*, 2023). Another essential element is selenium, which is a cofactor for thioredoxin reductase and glutathione peroxidase. In situations where exposure to mercury and arsenic occurs, selenium supplementation

has been demonstrated to help restore GPx activity and avoid oxidative stress. Metal-induced ROS are generally neutralized by dietary antioxidants. Supplementing with “vitamin C, vitamin E... may be useful in combating metal toxicity,” according to one review (Smirnova *et al.*, 2023). The inconsistent outcomes of clinical trials, however, may be due to the fact that antioxidants by themselves are unable to eliminate the metal burden.

Polyphenols and phytochemicals: Plant chemicals called natural polyphenols have potent anti-inflammatory and antioxidant properties. One extensively researched example is curcumin, which is found in turmeric. It chelates metal ions, prevents lipid peroxidation, and directly scavenges ROS (Tanrikulu-Küçük *et al.*, 2019). Studies conducted on diabetic animal models show that the CUR supplement enhances microcirculation and lowers blood glucose and cholesterol levels. Apart from its pharmaceutical actions, CUR also protects the reproductive organs from oxidative damage brought on by metal toxicity (Jain, Rains, and Jones, 2006; Dia *et al.*, 2018). Curcumin significantly lowers tissue oxidative indicators and raises antioxidant enzyme levels in animal models of metal poisoning. Curcumin, for example, has been demonstrated to enhance arsenic excretion and reverse DNA damage caused by arsenic (Smirnova *et al.*, 2023). Quercetin, a flavonoid found in many fruits, and resveratrol, which is found in grapes, both increase Nrf2 and phase-II detox enzymes and inhibit the production of reactive oxygen species. These substances also lessen metal-induced inflammation by modifying cell signalling (NF- κ B, MAPK, etc.). Overall, animal studies consistently demonstrate that polyphenols “mitigate metal-induced lipid peroxidation and adverse effects on the antioxidant

system,” making them promising as supplements to traditional therapy (Smirnova *et al.*, 2023).

Thiols and other antioxidants: A number of substances improve the body’s natural glutathione system. Glutathione’s precursor, N-acetylcysteine (NAC), possesses chelating and antioxidant qualities. As an antidote for lead, mercury, and other metals, NAC has been employed in preclinical and clinical research. According to a systematic analysis, NAC therapy improved and chelated the excretion of lead, cadmium, arsenic, and mercury in animals. Some human case studies also demonstrated benefits without significant adverse effects (Rossignol, 2019). In addition to directly binding certain metals and restoring intracellular GSH, NAC aids in breaking the ROS cycle. Another powerful antioxidant is α -Lipoic acid (ALA), which chelates metals, regenerates other antioxidants, and is soluble in both water and lipids. According to a recent analysis (2024), ALA can lessen the toxicity of aluminum, arsenic, cadmium, and other elements while “significantly enhancing cellular defense mechanisms and antioxidant enzyme activity” (Vafaei *et al.*, 2025). ALA enhanced antioxidant status and reduced mortality in rats exposed with cadmium. Long-term use of ALA demonstrated some mercury-reducing effects, despite it not being as effective as EDTA as a chelator for lead. As a result, NAC and ALA work in tandem to increase GSH levels and directly counteract ROS. Antioxidant treatments are frequently combined in practice.

For instance, to reduce oxidative stress brought on by mobilized metals, chelation regimens may incorporate vitamin C, glutathione, or NAC (Rossignol, 2019). During heavy metal detox, polyphenols like curcumin are being developed as supplements (e.g., nanoparticles for

Table4. Antioxidant interventions against metal-induced oxidative stress

Therapy	Mechanism	Evidence
Vitamin C/E	ROS scavenging, regeneration	Padayatty <i>et al.</i> (2003)
Selenium	Cofactor for GPx	Smirnova <i>et al.</i> (2023)
Curcumin	ROS scavenger, Nrf2 activator	Scapagnini <i>et al.</i> (2011)
NAC	GSH precursor, chelator	Rossignol (2019)
ALA	Metal chelation, ROS neutralizer	Vafaei <i>et al.</i> (2025)

improved absorption). The majority of animal research supports the effectiveness of these medicines, despite the paucity of human trials. “Curcumin imparts promising metal toxicity-ameliorative effects that are related to its intrinsic antioxidant activity,” according to a recent review (Smirnova *et al.*, 2025).

THERAPEUTIC IMPLICATIONS AND FUTURE DIRECTIONS

Chelation therapy is still the major medical treatment

for severe heavy metal poisoning. Metal-binding agents that improve urine excretion include EDTA (for lead), dimercaprol (BAL), DMSA, and DMPS (for arsenic, mercury, and lead). Chelation can avoid acute toxicity by quickly lowering the body’s metal burden. Chelation has hazards and limitations, though. It may also eliminate necessary metals (such as copper and zinc), and its advantages for long-term low-level exposure are unclear. For instance, despite promising studies with NAC, a weaker chelator, one review identified little high-quality data on oral chelation

for mercury/lead (Rossignol, 2019). Chelation is most obviously advised in practice for acute or extremely high exposures.

To combat the spike in oxidative stress that can happen when metals are mobilized, co-administration of antioxidants is recommended even while chelators are being utilized. There is increasing interest in using vitamins, NAC, ALA, and other antioxidants as preventative or supplemental treatments. However, there is a discrepancy between clinical data and preclinical success. Numerous encouraging findings in animals and cells have not been replicated in extensive human trials. A “discrepancy between preclinical and clinical studies of low-molecular-weight antioxidant therapies” has been identified in the literature (Jomova *et al.*, 2024). This could be brought on by problems with dosage, bioavailability, or the intricacy of oxidative stress in human disease. Combinations (such as NAC+vitamin C) must be thoroughly tested in selected populations in future clinical study. Therapy needs to be tailored and balanced because several pathways have two functions (for example, Nrf2 activation can be both protective and perhaps protumorigenic in cancer cells; (Buha *et al.*, 2021; Micah *et al.*, 2026). Creating innovative delivery methods and tailoring interventions are exciting new areas. Individuals who are more vulnerable to metal toxicity may be identified through genetic and biomarker tests (e.g., polymorphisms in Nrf2 or metallothionein) and antioxidant therapy may be customized accordingly.

New opportunities are presented by nanotechnology: metal-based “nanozymes” (nanoparticles with enzyme-like properties) can directly scavenge ROS in tissues and imitate SOD or catalase (Jomova *et al.*, 2024). These nano-antioxidants might be made to specifically target the organs that are impacted by particular metals. Furthermore, the bioavailability of natural antioxidants like curcumin may be enhanced by sophisticated drug delivery methods (liposomes, polymeric carriers). A long-term objective is the integration of customized medicine, which combines genetic screening, exposure assessment, and targeted antioxidant/chelation therapy. Research in these fields must continue.

Crucially, public health initiatives continue to be crucial. The best “therapy” will always be lowering occupational and environmental metal exposures (cleaner industry, safer water, quitting smoking). Supplementing with antioxidants won’t stop ongoing exposure. Nonetheless, the data indicates that a combination of tactics, including reducing exposure, strengthening defenses, and utilizing chelators and antioxidants sparingly, may considerably lessen the risk of disease. According to the World Health Organization, for instance, removing environmental contaminants, such as metals, might avert more than 30% of instances of cardiovascular disease globally (ATVB Journal study, 2021). This demonstrates the usefulness of using our expanding understanding of metals, ROS, and antioxidants to enhance human health.

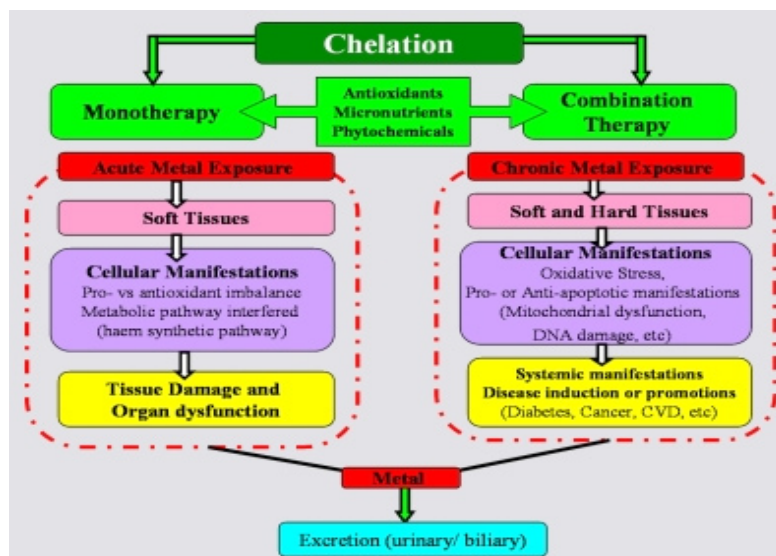


Fig3. Chelation in metal intoxication

Source: Flora and Pachauri (2010)

CONCLUSION

Excess heavy metals cause oxidative stress and weaken antioxidant defenses, according to recent research. The major metals (Pb, Hg, As, and Cd) all encourage the

production of ROS or the loss of glutathione, which leads to lipid peroxidation, damage to proteins and DNA, and death. In reaction, cells use tiny antioxidants (GSH, vitamins C/E, and polyphenols) and enzymes (SOD, CAT, and GPx)

Table5. Summary of key findings

Aspect	Key Findings
Metal toxicity & ROS	Heavy metals generate ROS and cause an imbalance of redox homeostasis. Redox-active metals directly produce radicals; others (As, Cd, Pb) induce ROS indirectly by depleting antioxidants. Common outcomes include lipid peroxidation and DNA damage (Jomova <i>et al.</i> , 2023; Koyama <i>et al.</i> , 2024; Adondua <i>et al.</i> , 2026).
Antioxidant defenses	Organisms employ multiple antioxidant systems. Enzymatic defenses (SOD, CAT, GPx) dismutate $O_2^{\cdot-}$ and H_2O_2 . Small molecules (GSH, vitamin C/E, flavonoids) scavenge radicals. The Nrf2/ARE pathway upregulates antioxidant genes (GSR, GPx, CAT) in response to stress (Buha <i>et al.</i> , 2021; Jomova <i>et al.</i> , 2024).
Disease associations	Chronic heavy metal exposure is linked to major diseases. Oxidative stress from metals contributes to Alzheimer's and Parkinson's pathology, promotes atherosclerosis and CVD (arsenic, cadmium are CVD risk factors), and fosters carcinogenesis (arsenic, cadmium are carcinogenic via ROS) (Fatima <i>et al.</i> , 2025).
Therapeutic implications	Strategies include chelation (EDTA, DMSA for acute toxicity), and antioxidant supplementation as adjuncts. Preventive measures (reducing exposure) are paramount. For future therapies, targeting Nrf2 activation, personalized antioxidant regimens, and novel nano-antioxidants are promising avenues (Rossignol, 2019).
Antioxidant therapies	Antioxidant compounds can mitigate metal toxicity. Vitamins C/E and selenium restore enzyme activity and neutralize ROS. Polyphenols (curcumin, resveratrol, quercetin) reduce lipid peroxidation and chelate metals. Thiol supplements (NAC, ALA) boost GSH and bind metals. Clinical evidence is emerging but still limited (Smirnova <i>et al.</i> , 2023; Vafaei <i>et al.</i> , 2025).

to counteract ROS. Chronic metal-induced oxidative damage has been linked to cancer, cardiovascular illness (hypertension, atherosclerosis), and neurological diseases (Parkinson's, Alzheimer's).

Key findings are summarized below:

These findings confirm that public health is significantly impacted by metal pollution and nutritional status. A sufficient intake of antioxidants from fruits, vegetables, and vitamins may protect against oxidative damage caused by inevitable low-level exposures. Disease risk can be considerably decreased by screening for and minimizing metal exposure sources (e.g., testing water for arsenic, removing lead paint). When used together, chelation and antioxidant therapy may help poisoned individuals recover in medical settings. When used together, chelation and antioxidant therapy may help poisoned individuals recover in medical settings.

Conflict of Interest

The authors declared that there are no conflicts of interest.

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To validate antioxidant therapies (dosage, timing, and combinations) in metal toxicity, further human trials are required. Oxidative damage biomarkers may direct treatment. Research should also elucidate the ways in which genetic variations (e.g. in Nrf2 or GST enzymes) impact therapeutic response and susceptibility to metal-induced oxidative stress. Lastly, the creation of specialized delivery systems (nanoparticles containing chelators or antioxidants) may improve the effectiveness of treatment. Filling up these gaps will aid in converting our expanding mechanistic knowledge into practical methods for treating and preventing oxidative damage caused by metals in humans.

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