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The Therapeutic Approaches to Cognitive Impairment Induced by Heavy Metals (Copper, Arsenic, And Lead): A review study

Narjes Soltani[1], Ayat Kaeidi[2], Ali Shamsizadeh[2], Jalal Hassanshahi[1*]

[1]Physiology-Pharmacology Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[2]Department of Physiology and Pharmacology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

*Corresponding Author: Jalal Hassanshahi, Emails: hasanshahij@gmail.com, hasanshahij@rums.ac.ir

Abstract

Background: Heavy metals such as copper, arsenic, and lead are primarily released into the environment through anthropogenic activities. Due to their high toxicity and persistence, these elements pose significant threats to both human health and ecological systems. The main health concern associated with heavy metal exposure is cognitive impairment.

Methods: This review examined studies on the neurotoxic effects of copper, arsenic, and lead, as well as therapeutic strategies aimed at mitigating cognitive decline. Research published between 2000 and 2024 was identified through databases including Google Scholar, PubMed, and Web of Science. Both qualitative and quantitative studies were included, and a dual-review process was employed to enhance the accuracy and reliability of data extraction.

Results: Sources of heavy metal pollution include the combustion of fossil fuels, industrial processes, wastewater discharge, and improper hazardous waste management, all of which contribute to elevated environmental levels of toxic metals. These metals inhibit natural biodegradation processes, leading to increased biological toxicity. While trace levels of certain metals, such as copper, are necessary for physiological functions, chronic or excessive exposure to copper, arsenic, and lead has been linked to cognitive impairments and neurological disorders. Lead exposure is especially associated with severe cognitive deficits in children.

Conclusion: Exposure to elevated levels of copper, arsenic, and lead is strongly associated with neurotoxicity and cognitive decline. Current therapeutic interventions focus primarily on chelating agents and antioxidant therapy to reduce the accumulation and toxic effects of these metals. Continued research is essential to develop more effective strategies for the prevention and treatment of heavy metal-induced cognitive impairment.

Keywords: Heavy metals, Copper, Arsenic, Lead, Cognitive impairment, Therapeutics

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Introduction

A set of metals with higher atomic numbers (above 20) and higher densities (5 g/cm^3), such as cadmium, lead, mercury, nickel, chromium, arsenic, copper, and zinc, are collectively referred to as heavy metals. Because of their potent inhibitory effects on biodegradation activities, these metals have a direct relationship with environmental pollution and biological toxicity issues (1). Some metals, such as copper, are typically cofactors in various enzymatic and metabolic pathways, required in small amounts as nutrients, and involved in these activities. All forms of life, including bacteria, plants, animals, and people, can become severely inhibited or killed by significant concentrations of these metals. Nevertheless, a select few metals, including cadmium (Cd), arsenic, and lead (Pb), are very toxic even at very low quantities (2). Lethal metal buildup in the human body causes serious health problems such as growth and developmental anomalies, carcinogenesis, neuromuscular defects, mental illnesses, and metabolic activity failure. As they accumulate in the ecological food chain and reach the body by ingestion or inhalation, heavy metals are persistent and bioaccumulative. They present a variety of risks to people, including carcinogens and poisoning through contaminated drinking water. Additionally, heavy metals enter the human body by breathing as a result of urbanization and traffic, industrial and agricultural operations, waste incineration, and mining (3). Exposure to heavy metals like copper (Cu), arsenic, and lead (Pb) can happen because of polluted food, water, or air, as well as risky jobs. Anthropogenic factors, such as the burning of gasoline with lead or uncontrolled industrial emissions, mining, and

recycling of electronic trash, are mostly to blame for this contamination (4). The ongoing use of hazardous metals in human activities, including electroplating, painting, tanning, textiles and dyes, papermaking, mining, and other industrial sectors, has increased dramatically and has become detrimental to the variety of life on Earth (5). Neurotoxicity caused by heavy metal exposure is a major problem, particularly for countries with industrialized economies. Even little amounts of heavy metal can change the neurodevelopmental trajectory, with lasting impacts on motor, emotional-social, and cognitive qualities even in later adulthood. Heavy metals such as arsenic, lead, and copper are well-documented neurotoxins that can have significant adverse effects on neurological health. Their mechanisms of action involve various biochemical pathways that disrupt normal neuronal function, leading to cognitive impairments and neurological disorders (6). However, a powerful medication capable of repairing brain-damaged tissue is required (7-10). Chelating drugs and antioxidants have shown some promise in the therapy of heavy metal-induced neurological deficits. However, it is not a permanent cure. As a result, a definitive therapy option for people suffering from cognitive impairment is required (11). This review article investigated cognitive impairment induced by heavy metals (copper, arsenic, and lead) and explored therapeutic approaches to mitigate the risk of neurotoxicity.

Methods

Search strategy

A comprehensive literature search was conducted to identify studies examining cognitive impairments linked to heavy metal exposure and therapeutic strategies aimed at mitigating neurotoxicity. The databases searched include PubMed, Google Scholar, and Web of Science, covering publications from January 2000 to March 2024. Keywords and Boolean operators were employed to refine the search, including terms such as heavy metals, copper, arsenic, lead, cognitive impairment, and therapeutic approaches. Filters were applied to include only peer-reviewed articles published in English.

Study selection

Studies were included if they met the following criteria: (1) addressed the neurotoxic effects of at least one heavy metal; (2) included qualitative, quantitative, or mixed-methods research; and (3) assessed therapeutic or interventional strategies to reduce cognitive impairment. The exclusion criteria included non-peer-reviewed papers, animal-only studies (unless directly relevant to therapeutic mechanisms), and articles lacking clear outcome measures related to cognition. Initial screening was based on titles and abstracts, followed by full-text reviews for eligibility.

Data extraction

Data were extracted independently by two reviewers using a standardized form. Extracted information included study design, sample size, type and duration of heavy metal exposure, intervention or therapeutic approach, outcome measures, and key findings. Any discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer to ensure consistency and objectivity.

Critical appraisal

The quality of the included studies was assessed using appropriate appraisal tools based on the study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool, while observational studies were assessed with the Newcastle-Ottawa Scale. Studies were rated as high, moderate, or low quality, and this assessment informed the strength of the conclusions drawn in the synthesis.

Results

Heavy metals and cognitive impairment

Heavy metals can lead to cognitive impairment, resulting in decreased activity and increased risk of disability (12). Globally, the cognitive function deficit is growing, and it is anticipated that the shortfall would grow proportionately greater in developing nations (13). As people age, their physical and mental abilities deteriorate, which is typically inversely correlated with an increase in oxidative stress and aberrant protein aggregation. Heavy metals have toxic effects in biological systems via bonding to sulfhydryl groups and reactive oxygen species generation. Additionally, the risk of cognitive processes deteriorating is considerably enhanced if they are exposed to numerous chemicals that lead to oxidative stress (14). Toxic metals that obstruct crucial developmental processes, such as cellular proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis in the central nervous system, can harm the growing brain (15). Neuronal functions are disrupted, and the risk of neurodegeneration is raised, due to the growing CNS's limited ability to make up for cell loss and neural network disturbances (16). Heavy metals, such as mercury, lead, manganese, copper, iron, aluminum, bismuth, thallium, and arsenic, have a significant influence on cognitive impairment, particularly in the etiology of Parkinson's disease, according to an epidemiological study (17, 18). The authors of a recent study have claimed that these metals can also activate the production of genes that may cause neurodegeneration. These molecular flaws result in neurodegeneration, which causes motor abnormalities, cognitive impairments, memory problems, and learning problems (19).

Researchers have discovered that lead, arsenic, and copper operate as poisons that can impair cognitive

function, cause neurological issues, and increase the likelihood of Alzheimer's and Parkinson's disease (20). Then, future studies will be more effective if researchers are aware of these correlations. In both people and animal models, metal poisoning disrupts brain development and hinders cognition, memory, and learning (21). Clinically, chronic ingestion of excess metals usually results in neurological symptoms such as headaches, dizziness, and motor, cognitive, and memory problems (22). Additionally, symptoms could be the first indicator of a neurodegenerative process. It is the result of the fusion of various elements, including genetic makeup, poor lifestyle, and external stressors (23).

Lead and cognitive impairments

The World Health Organization (WHO) has identified lead (Pb) as one of ten chemicals of major public health concern that require action by Member States to protect the health of workers, children, and women of reproductive age (24). Even though lead has been banned from petrol, paint, and water pipes, significant amounts of lead still exist, especially in underprivileged areas of modern cities, transition zones, and city centers. There are also high concentrations near lead mines and in developing nations, but even for the remaining areas, there is no safe threshold. The environmental element lead has always increased neurologic and psychiatric illness. In particular, in underprivileged communities, it also results in developmental abnormalities (25). According to a study by Wu et al high blood levels of lead are associated with impaired cognitive functions, as confirmed by correlation studies, and patients with severe cognitive impairment had the highest blood levels of lead (26). Lead is primarily absorbed through inhalation and ingestion, with inhalation being more efficient than ingestion. Absorption occurs through passive and facilitated diffusion, with passive diffusion playing a minor role in total absorption. Evidence suggests that cumulative environmental lead exposure in adulthood is neurotoxic, with impaired memory, judgment, attention span, and problem-solving skills being hallmarks of Alzheimer's disease. So, a 4-year prospective evaluation of cognitive function showed that learning and memory were associated with lead exposure long after exposure ceases (27). Some carrier proteins, such as divalent metal transporter 1 (DMT1) and calbindin, have been proposed for basolateral Ca^{2+}transfer in enterocytes. Lead exposure not only can mimic calcium ions (Ca^{2+}) due to its similar charge and size, allowing it to interfere with calcium-dependent processes, but also negatively affects synaptic plasticity mechanisms such as long-term potentiation (LTP). These disruptions affect memory and learning through synaptic transmission and impair neurotransmitter release, particularly affecting systems like acetylcholine and changes in the expression of brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDA) receptor (28). Furthermore, lead exposure triggers inflammatory responses in the brain, leading to the activation of microglia and the release of pro-inflammatory cytokines. This neuroinflammatory environment can disrupt neuronal function and contribute to cognitive decline. Lead exposure has been linked to mitochondrial impairment, resulting in decreased ATP production and increased oxidative stress. This dysfunction contributes to neuronal cell death, especially in Alzheimer's disease (29).

Lead is available for ingestion through the digestive tract, where it quickly distributes to soft body tissues such as the kidney, bone marrow, liver, and brain, but bio-accumulates in the bloodstream and bones. Numerous mechanisms, including the inhibition of enzymatic activity, the induction of oxidative stress, the disruption of the actions of necessary cations, particularly calcium, zinc, and iron, the disruption of the integration of cellular membranes and organelles, and the modification of cell signaling, are used to cause the toxic effects of lead (30).

Research indicates that lead exposure reduces glucose uptake, which leads to impaired energy metabolism in neurons by down-regulating GLUT4 transporters. Moreover, it can compromise the integrity of the BBB, leading to increased permeability and allowing toxins to enter the CNS, which these disruptions contributes to cognitive decline (31).

Biologically significant processes like metal transport, energy metabolism, apoptosis, ionic conduction, cell adhesion, inter- and intracellular signaling, various enzymatic processes, protein maturation, and genetic regulation can all be affected by lead poisoning because of its capacity to replace other polyvalent cations in the molecular machinery of living organisms. The long-term effects of lead poisoning may result in behavioral changes as well as cognitive and motor impairment (32). Furthermore, it has been reported that children who are exposed to lead may suffer from encephalopathy, which manifests as hyperirritability, ataxia, convulsions, stupor, coma, and even death. Lower lead exposure levels can cause non-fatal neurobehavioral consequences. Lead is thought to have permanent impacts on the brain and behavior (33). Lead is a neurotoxicant that has been connected to brain changes in kids, including IQ reduction, a worsening of attention deficit and hyperactivity disorder, memory loss, and problems with academic performance. Lead exposure during the developmental stage has neurotoxic effects on the brain's final stages of development, such as synaptogenesis and differentiation. Lead exposure during nursing and pregnancy permanently alters future cognitive and behavioral development (34).

Arsenic and cognitive impairments

Arsenic is a widespread environmental contaminant,

causing health issues globally. It is promoted through anthropological actions like smelting, burning fossil fuels, and pesticide production. Arsenic impacts brain morphology and physiological changes, leading to increased oxidative stress and neurotoxicity (35). Arsenic exposure causes neurological disorders through molecular mechanisms like cytotoxicity, increased reactive oxygen species, chromosomal aberrations, and DNA damage. Studies show a correlation between increased arsenic in drinking water and behavioral disorders like decreased locomotor activity, impaired cognitive functions, and prenatal complications. Arsenic can cross the blood-brain barrier, accumulating in brain areas like the striatum and hippocampus (31). Long-term exposure to arsenic can result in arsenicosis, a chronic condition that can cause cancer, diabetes mellitus, cardiovascular disease, and hypertension. Arsenic is a "silent pandemic" since it can impair cognitive function in low quantities (36). Arsenic can breach the blood-brain barrier and has detrimental effects that are only partially reversible on learning, IQ, brain weight, working memory, and spatial memory, especially in the developing brain (37). Also, it has been reported that arsenicosis alters neurobehavioral function by altering the ultra-structure of the hippocampus and spatial memory in animal models and causes oxidative stress, inflammation, and angiogenesis in neurons (32). This process is mediated by the upregulation of bone morphogenetic protein-2 (BMP2) signaling pathways, which subsequently inhibit BDNF /TrkB signaling, essential for neuronal survival (33). Additionally, elevated heavy metal release and the absorption of these chemical substances through the mouth, skin, and eyes have an impact on human health and cause cognitive diseases. Arsenic exposure raises the levels of beta-amyloid protein and causes hyperphosphorylation of tau protein, both of which lead to neurodegeneration, according to research conducted in ex vivo cell cultures (38). Additionally, all areas of the brain are enhanced in terms of cellular apoptosis pathways, including caspase-3 and caspase-9, which increase oxidative stress and neuronal cell death (39). Brinkel et. al, claimed that long-term exposure to arsenic might cause mental retardation as well as developmental disorders as physical, cognitive, psychological, sensory, and speech problems (40). According to some studies using the mini-mental state examination test, estimated regional groundwater arsenic concentrations were found to be negatively correlated with neuropsychological performance, adding more evidence to the possibility that exposure to arsenic at low concentrations may have an adverse effect on neurocognitive functioning (41).

Based on research, Kumar reviewed the neurotoxicity of the lead, cadmium, and arsenic mixture and discovered that long-term exposure to these environmental toxins puts the brain at extreme risk for damage. They discovered that even at low concentrations, as cause's cognitive deficit by modulating the N-methyl-D-aspartate (NMDA) receptor and significantly deactivates the protective enzymes (antioxidants) such as Glutathione peroxidase (GPx) and Glutathione (GSH), which leads to programmed cell death, with the brain hippocampus as its primary target region (42). High amounts of arsenic in drinking water and/or urine are linked to peripheral nerve abnormalities, decreased conduction velocity, neuropathy, and altered sensory function (42). Arsenic exposure has also been linked to altered adult cognition and mental health. In children aged 8 to 11 years, exposure to arsenic has been associated with a decline in working memory and full-scale IQ scores (43). Long-term arsenic exposure may induce epigenetic modifications that alter gene expression related to neurodevelopment and cognitive function. Such changes can have transgenerational effects, impacting not only the exposed individuals but also their offspring (44). The cumulative effects of these molecular mechanisms manifest as behavioral deficits, including impaired attention, working memory issues, and reduced verbal comprehension in affected populations (44).

Copper and cognitive impairments

Every tissue in the body contains copper, which is necessary for vital bodily processes and is the third-most abundant trace metal (after iron and zinc) (45). Diet is a person's main exogenous supply of copper. Legumes, potatoes and potato derivatives, meat, nuts and seeds, chocolate, and shellfish all contain copper. Depending on the regional area and the copper level of the diet, the daily consumption is approximately 1.5 mg. The relationship between intake and bioavailability is inverse, ranging from 60 to 70% (45). The maximum safe dose is 10 mg per day when there is no liver dysfunction. Chemical forms of copper, competitive rivalry with other metals (zinc, iron, selenium, and cadmium), and malabsorption syndromes all affect absorption. Ceruloplasmin, an enzyme found in serum, binds 96% of the serum's total copper content in healthy humans; the remaining 4% is found in copper-amino acid complexes, albumin, and transcurrent. The largest quantities of copper are found in the liver, brain, kidney, and heart, and they vary with age and gender (46). Cu transporter 1 (Ctr1) and divalent metal transporter 1 (DMT1) are two transporter proteins that mediate the import of copper into cells (47). The cerebellum, hippocampus, basal ganglia, many synaptic membranes, and cell bodies of cortical pyramidal and cerebellar granular neurons are the main locations of copper in the brain (48). For metabolic usage, the brain accumulates heavy metals like copper. Cu is a key player in numerous physiological pathways in the brain, either as a structural component or as a cofactor of several enzymes (49). Cu is abundant in the locus coeruleus and the substantia nigra, both of which are pigmented tissues and contain catecholaminergic cells (50). Due

to its ability to interact with oxygen species and bind to SH groups, copper can cause an unbalanced state of copper homeostasis in the brain, which has been linked to neurodegenerative diseases (51). The Blood Brain Barrier (BBB) and/or Blood CSF Barrier (BCB), which divide the brain interstitial space from the blood and cerebrospinal fluid (CSF), are sources of peripheral Cu that are transferred over to the brain. The BCB helps to maintain the Cu homeostasis in the extracellular fluids of the brain, whereas the BBB controls the input of Cu into the brain. Neurodegenerative illnesses have been linked to changes in Cu homeostasis (52). Wilson's illness, a hereditary impairment of copper metabolism, manifests as Parkinsonism. Anxiety and depression are caused by brain function being disrupted by excess and insufficient copper (53). Also, multiple sclerosis patients may have a greater Cu/Zn ratio than controls (54). Studies have demonstrated that the reduction-oxidation cycles of oxidative stress that result in the production of H_2O_2 are caused by the hypermethylation of a peptide. The precursor protein binds to copper and lowers it, which controls the toxicity and oxidative stress of copper. Excessive copper promotes the production of reactive oxygen species (ROS), which can damage cellular components such as lipids, proteins, and DNA. This oxidative damage exacerbates neuronal toxicity and contributes to cognitive deficits (44). In addition, elevated copper levels can disrupt glutamate signaling pathways, leading to excitotoxicity. This mechanism has been implicated in neuronal death within critical brain regions associated with memory and learning, such as the hippocampus (55). Copper has been shown to inhibit the phosphorylation of cAMP response element-binding protein (CREB), a key regulator of BDNF. Reduced BDNF levels are associated with impaired synaptic plasticity and cognitive decline (56). The biochemical underpinning of copper toxicity in Alzheimer's disease is provided by metal ionophores, which enhance neurodegenerative processes. So, copper, peroxides, and their activity were shown to be higher in Alzheimer's patients than in healthy controls (57). By examining ceruloplasmin level and activity, Arredondo et al evaluated the function of copper in multiple sclerosis etiology. They discovered that free copper levels dramatically rose in the serum of multiple sclerosis participants, along with an increase in ceruloplasmin levels and a decrease in its activity (58).

Medication therapy for heavy metal poisoning

Chelation therapy

Chelation therapy is a medical treatment designed to remove heavy metals from the body through the administration of chelating agents (59). This therapy is particularly effective for treating heavy metal poisoning, including exposure to lead and arsenic, thereby potentially decreasing neurotoxicity associated with these substances (60). The process involves the binding of chelators to toxic metal ions, forming stable complexes that facilitate their excretion from the body, typically via urine. Chelators are either water or lipid-soluble. They work by forming complex structures with heavy metals. These agents contain specific binding sites that interact with metal ions, effectively "trapping" those (61). Although aqueous solubility facilitates transport and elimination via the kidney, a lipophilic chelator may be able to penetrate cellular membranes (including those in the central nervous system) to chelate intracellular components. A lipophilic chelator may also be excreted in larger amounts through the bile (61). Not only animals, but also plants, create chelating chemicals, and the metallothionein content of meals may impact hazardous metal bioavailability and metabolism (62). Furthermore, glutathione is a powerful chelator implicated in cellular response, metal cation transport, and excretion, as well as a biomarker for toxic metal overload (63). Chelation therapy, while potentially lifesaving for individuals suffering from heavy metal toxicity, is associated with various risks and side effects. Commonly reported adverse effects include nausea, vomiting, diarrhea, and headaches. More serious complications can arise, such as kidney damage and electrolyte imbalances, particularly hypocalcemia (low calcium levels), as well as allergic reactions. Additionally, chelators may inadvertently bind to essential metals like calcium and zinc, which can lead to deficiencies if not carefully monitored throughout the treatment process (61).

Pharmaceutical chelators

Small organic compounds that form coordination complexes with sulfur, oxygen, and/or nitrogen atoms create pharmaceuticals that chelate metal ions in solution. They play a crucial role in treating heavy metal poisoning and managing conditions associated with metal overload.

Dimercaprol

Dimercaprol (British anti-lewisite, BAL) is a chemical that comprises two -SH (sulfhydryl) and one hydroxyl group and is often used for arsenic, mercury, lead, and gold, but has significant side effects. Chelation occurs when a metal atom/ion binds with a thiol group to form a stable metal-ligand complex, which is then eliminated by the kidneys. Arsenic and lead react with BAL to generate a stable 5-membered ring complex. Despite its effectiveness, dimercaprol has a narrow therapeutic window and can cause significant side effects, including hypertension, tachycardia, nausea and vomiting, pain at the injection site, and nephrotoxicity and increased renal concentration of certain metals like cadmium (64).

Dimercaptosuccinic acid (DMSA)

This chemical, commonly known as succimer, is a BAL

analog which have been developed due to the potential adverse effects of 2, 3-Dimercaprol. They are less toxic and can be administered orally (65). DMSA has two carboxylic groups and two thiol groups, the latter of which participates in the metal-ligand process. This substance is used to treat lead, mercury, and arsenic poisoning, especially in children (66). Although DMSA is generally well-tolerated, with fewer side effects compared to other chelators, it has some side effects, like gastrointestinal discomfort, rash, elevated liver enzymes, and neutropenia. Furthermore, because of its ability to bind with essential minerals, it is recommended that patients avoid taking trace mineral supplements on the same day as DMSA administration (67).

Penicillamine

This chemical is primarily used to detoxify the body of excess copper. Penicillamine is a derivative of penicillin but lacks antimicrobial properties. It is often used to treat Wilson's disease as a rare autosomal recessive copper metabolism disorder in which copper accumulates in the brain and other organs. Nevertheless, it causes neurological problems to deteriorate in 20-30% of Wilson's disease patients. Penicillamine works by binding to toxic metals, such as copper, lead, mercury, and arsenic, forming soluble complexes that are excreted in urine (67). This chelation process helps reduce the toxic effects of these metals on the body. In addition to its chelating properties, penicillamine can also form disulfide bonds with cysteine, aiding in the treatment of cystinuria by preventing the formation of cystine stones. Trientine hydrochloride and tetrathiomolybdate are utilized in such circumstances. Penicillamine has a significant risk of adverse effects such as neutropenia, thrombocytopenia, renal toxicity, rash, fever, nausea, vomiting, and anorexia, which necessitates close monitoring during treatment (68).

Ethylenediaminetetraacetic acid (EDTA)

EDTA is a synthetic chelating agent widely used in the treatment of severe and moderate lead poisoning. It can bind tightly to lead ions, forming stable complexes that are then excreted by the kidneys. This process reduces the toxic effects of lead on various body systems, particularly the nervous system (69). However, healthcare providers must carefully monitor patients for side effects, such as local pain at injection sites, malaise, fatigue, headaches, urinary frequency, and even nephrotoxicity. They should adjust treatment protocols as necessary to ensure safety and efficacy (70).

Natural chelators

Natural chelation is the process of utilizing naturally occurring substances to bind and eliminate toxic metals from the body (71). These natural chelators play a crucial role in reducing the harmful effects of heavy metal exposure, an issue that has become increasingly significant in today's world due to pollution and industrial activities.

Allium sativum

Allium sativum, commonly known as garlic, has been studied for its potential role in the chelation therapy of heavy metals. Its sulfur-containing compounds, particularly allicin, contribute to its ability to bind and facilitate the excretion of toxic metals from the body. Two mechanisms may aid in the detoxification of heavy metals; 1. Sulfur compounds that can form complexes with heavy metals, thereby enhancing their solubility and facilitating their excretion through urine and feces (72) and, 2. Antioxidant properties which help mitigate oxidative stress caused by heavy metal exposure, reducing cellular damage and promoting overall detoxification processes (73).

Cilantro

Cilantro (Coriandrum sativum) is a Mediterranean plant native to Europe. Cilantro contains biochemical constituents, such as citric acid and phytic acid that can bind to heavy metal ions. This binding enhances the solubility of these metals, allowing them to be excreted more easily through urine and feces. Studies suggest that cilantro can help remove significant amounts of lead (87%), mercury (91%), and aluminum (74%) from the body within approximately 45 days when used in conjunction with chlorella, a green alga known for its detoxifying properties (74). Moreover, cilantro is rich in antioxidants, which help mitigate oxidative stress caused by heavy metal exposure. This action reduces cellular damage and promotes overall detoxification processes. By protecting cells from free radicals generated during heavy metal toxicity, cilantro contributes to improved health outcomes. In mice, cilantro hindered localized lead insertion in the brain (75).

Ginkgo biloba

Ginkgo biloba is one of the herbal medicines that can be used as a supplement for lead-poisoned patients. Ginkgo biloba prevents lead poisoning and restores metabolic characteristics. A patented method outlines a process for removing lead from ginkgo biloba extract, which involves soaking the leaves in water and using iron sulfide (FeS) to replace toxic metal ions with iron ions, significantly reducing lead content to safe levels (76). Furthermore, Ginkgo biloba causes free radicals to be trapped, resulting in decreased oxidative stress and increased glutathione levels, and ameliorating neurotoxicity. Although ginkgo biloba is generally considered safe for most individuals when taken at the recommended dose, it can interact with blood-thinning medications and may increase bleeding risk. Individuals should consult healthcare providers before starting ginkgo biloba, especially those

with pre-existing health conditions or those taking other medications (77).

Curcumin

Curcumin, a bioactive compound derived from the rhizome of Curcuma longa (turmeric), has gained attention for its potential role in detoxifying heavy metals from the body. It has been shown that curcumin has a neuroprotective effect on cadmium-induced hippocampal neurodegeneration. The fundamental method involved decreasing prefrontal cortical neuroinflammation and oxidative stress while increasing the amount of viable prefrontal cortex neuronal cells. They discovered that curcumin can treat these behavioral and biochemical deficits caused by heavy metals (78). In addition, Flora et al investigated the effects of curcumin on cognitive impairment caused by a heavy metal mixture. Because of its high gastrointestinal absorption and capacity to penetrate the blood-brain barrier, curcumin's physicochemical properties and pharmacokinetics are consistent with its therapeutic effects in cognitive impairment (79). Curcumin can be consumed in various forms, including turmeric powder used as a spice in cooking, curcumin supplements in capsule or tablet form for higher doses, and golden milk (80). Curcumin is generally considered safe for most individuals when consumed in moderate amounts. However, high doses may cause gastrointestinal discomfort or interact with certain medications like anticoagulants. It is advisable to consult a healthcare provider before starting curcumin supplements, especially for individuals with underlying health conditions or those taking other medications.

Silymarin and silymarin-encapsulated liposome nanoparticles

Silymarin is well-known for its hepatoprotective, antioxidant, and anti-inflammatory properties. However, its efficacy is diminished due to limited oral bioavailability. They discovered that creating silymarin-encapsulated liposome nanoparticles was substantially more successful than typical zinc therapy in terms of decreasing immobility and lowering liver enzymes. Creating silymarin-encapsulated liposome nanoparticles improved oral silymarin delivery and alleviated symptoms of copper poisoning (81).

Vitamin C (ascorbate)

Gracia et al investigated the effectiveness of vitamin C (ascorbate), a neuroprotective and neuromodulatory antioxidant, in preventing lead-induced neuronal impairments. Their findings suggest that redox and bioenergetics changes are an underlying aspect of the synaptic dysfunction seen in embryonic lead neurotoxicity, perhaps contributing to abnormalities in the creatures' motor, behavioral, and psychological features. Furthermore, they establish ascorbate as a critical component of a treatment strategy against lead-induced neurotoxicity, particularly for early-life exposures (82). Research suggests that adequate levels of vitamin C can reduce the accumulation of heavy metals in vital organs such as the liver and kidneys. This effect is particularly important in preventing long-term damage associated with chronic exposure to toxic metals. Vitamin C is generally safe for most individuals when consumed at recommended doses (2,000 mg per day). However, excessive intake may lead to gastrointestinal discomfort or diarrhea. It is essential to consult a healthcare provider before starting high-dose vitamin C supplementation, especially for individuals with underlying health conditions or those taking other medications (74).

Epigallocatechin-3-gallate (EGCG)

The polyphenolic substance EGCG is the main component of green tea. Research has shown that EGCG can help mitigate the toxic effects of various heavy metals through several mechanisms. EGCG can bind to heavy metals, such as lead, cadmium, and mercury, forming stable complexes that facilitate their excretion from the body. This chelation process reduces the bioavailability of these toxic metals, thereby decreasing their harmful effects on cellular and organ function. Additionally, as a powerful antioxidant, EGCG scavenges ROS generated during heavy metal exposure (80). Neutralizing these free radicals helps protect cells from oxidative stress and damage associated with heavy metal toxicity. EGCG activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which plays a crucial role in cellular defense against oxidative stress and inflammation. This activation enhances the expression of various detoxifying enzymes and antioxidants, further aiding in the detoxification process (83). Despite its potential benefits, there are challenges associated with using EGCG for heavy metal detoxification, such as bioavailability and dosing. However, green tea polyphenols are relatively powerful metal chelators, binding to metal ions such as copper and iron, and have been shown to reduce neurotoxicity (84).

Carvacrol

Carvacrol, as a phenolic monoterpenoid compound, exists in the essential oils of thyme. It has been shown that carvacrol alleviated the inflammation and apoptosis-related proteins' heavy metal-induced neurotoxicity in the rat. Caracole scavenges free radicals and reduces oxidative stress in cells (85). This property is particularly important in the context of heavy metal toxicity, where oxidative stress is a significant contributor to cellular damage. By mitigating oxidative damage, carvacrol may enhance the body's ability to detoxify heavy metals. Carvacrol is commonly considered safe when consumed in typical dietary amounts. However, high doses or

concentrated forms may lead to gastrointestinal irritation or other adverse effects. As with any supplement or natural product aimed at detoxification, it is advisable to consult healthcare professionals before use, especially for individuals with pre-existing health conditions or those taking medications (80).

Herbal fibers

Herbal fibers have an essential function in heavy metal detoxification. According to research, eating fiber decreases toxicity exposure due to enhanced gastrointestinal motility. The most essential plant fiber is pectin. It is a type of soluble fiber found in a variety of fruits. Consumption of pectin-rich fruits in the diet improves digestion and, due to pectin's high propensity to bind heavy metals, can aid in the detoxification process. While herbal remedies offer a complementary approach to conventional treatments for heavy metal poisoning, caution is advised. Herbal treatments should not replace medical interventions but can be integrated into a broader detoxification strategy that includes dietary adjustments and lifestyle changes (86).

Other therapeutic methods

Plasma exchange/plasmapheresis

If there is high metal toxicity, plasma exchange treatment can be employed as an alternative therapy in an emergency. This procedure involves the removal of plasma from the blood and its replacement with a substitute solution, effectively reducing the concentration of harmful substances, including heavy metals, in the bloodstream. According to several studies, plasma exchange is most effective for inorganic mercury and may be therapeutic when combined with chelation therapy during the early stages of poisoning (87). However, plasmapheresis represents a valuable tool in the management of heavy metal toxicity, offering rapid detoxification and improved patient outcomes.

Enriched environment (Animal studies)

An independent investigation revealed that low-dose co-exposure to lead can produce cognitive and synaptic plasticity deficits, and that prompt intervention with an enriched environment can rectify these abnormalities. The enriched environment included pre- and post-weaning enrichment methods designed to give significant sensory and social stimulation. Various stimuli, including lemon water and peppermint oil, rough abrasive paper and a smooth marble plate, various flavors of candy, a hard paper tube, warm water, and a flash lamp, were used to assess rat pups' senses of smell, touch, taste, vestibule, heat, and vision (82).

Wet cupping therapy (WCT)

It has been shown that wet cupping therapy is a classic blood-letting method that can be used to treat a variety of ailments. The goal of their investigation was to evaluate heavy metal contents in wet cupping blood with venous blood samples. This study included 24 healthy volunteers. Wet cupping therapy was conducted after venous blood samples were drawn, and wet cupping blood samples were taken. All samples were analyzed using Inductively Coupled Plasma Mass Spectrometry to determine heavy metal levels. In the study, moist cupping blood had considerably greater levels of selected heavy metals than venous blood. Heavy metals may be removed from the body via wet cupping therapy (88).

Discussion

This review provides a comprehensive synthesis of the current knowledge regarding cognitive impairments caused by three prevalent heavy metals- copper, arsenic, and lead- and examines the spectrum of therapeutic interventions available. The evidence demonstrates that exposure to these metals poses a serious threat to neurological health, contributing not only to cognitive decline but also potentially aggravating neurodegenerative diseases.

The neurotoxic mechanisms underlying copper, arsenic, and lead toxicity are complex and often converge on shared pathways such as oxidative stress, neuroinflammation, and disruption of neurotransmitter systems, while also exhibiting distinct metal-specific effects. For example, lead's capacity to mimic calcium interferes with vital cellular signaling and synaptic plasticity; arsenic's ability to cross the blood-brain barrier and induce DNA damage results in widespread neuronal dysfunction; and copper's dual role as both an essential nutrient and a potent toxin highlights the delicate balance necessary for maintaining neurological homeostasis. The review underscores that even low-level, chronic exposure-especially during critical developmental periods-can cause lasting impairments in cognitive functions such as memory, attention, and learning, and may contribute to the pathogenesis of disorders like Alzheimer's and Parkinson's disease (Fig. 1) (89).

In addressing these challenges, therapeutic strategies have primarily focused on chelation therapy and antioxidant supplementation. Pharmaceutical chelators-including DMSA, BAL, penicillamine, and EDTA-are well-established in managing both acute and chronic poisoning by facilitating metal excretion (Fig. 1). Nevertheless, their use is often limited by significant side effects, a lack of specificity that can lead to depletion of essential minerals, and restricted effectiveness in reversing established neurological damage or crossing the blood-brain barrier. This highlights the review's assertion that while these agents can be life-saving, they do not represent a definitive cure for cognitive impairments induced by metal toxicity (90).

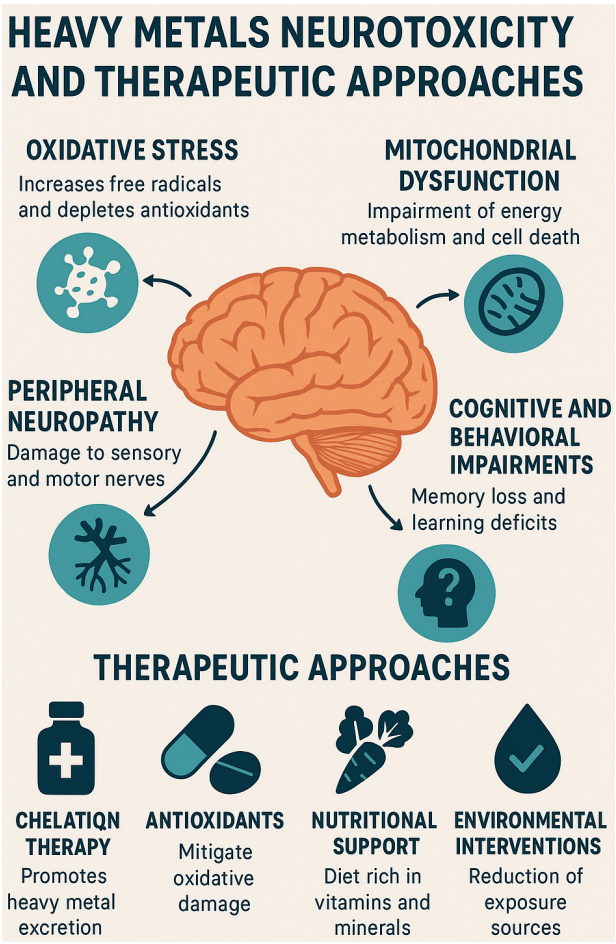

Fig. 1. Impact of heavy metal neurotoxicity and strategies for prevention and treatment. Heavy metals can negatively affect the nervous system. Therapeutic approaches, including chelation therapy, antioxidants, nutritional support, and reducing environmental exposure, can mitigate these effects.

Natural chelators and antioxidants, derived from sources such as garlic, cilantro, ginkgo biloba, curcumin, silymarin, vitamin C, and EGCG, offer a promising complementary or alternative approach. These compounds frequently exhibit multiple mechanisms of action, including direct metal binding, potent antioxidant capacity, anti-inflammatory effects, and neuroprotection. Notably, curcumin, Quercetin (91), and EGCG have demonstrated the ability to cross the blood-brain barrier and attenuate neuroinflammation and oxidative stress. Moreover, nanoparticle formulations of silymarin have improved bioavailability, addressing a common limitation of natural compounds (89). However, enthusiasm for these natural remedies must be tempered by the need for more rigorous, large-scale clinical trials to confirm their efficacy, optimal dosing, safety, and standardization. While preliminary and preclinical studies are encouraging, robust validation remains essential. Additionally, emerging and less conventional therapies- such as plasma exchange for severe acute toxicity, enriched environmental stimulation (which has shown promise in reversing some deficits in animal models), and wet cupping therapy (with preliminary evidence suggesting metal removal)- expand the therapeutic landscape. Nonetheless, these approaches require further investigation to establish their clinical effectiveness and underlying mechanisms (89).

The strength of this review lies in its comprehensive examination of copper, arsenic, and lead neurotoxicity alongside a broad spectrum of therapeutic strategies. However, a key limitation- reflective of the current state of the field- is the gap between understanding the mechanisms of toxicity and developing truly restorative treatments. Most existing therapies primarily focus on detoxification and limiting further damage, rather than repairing established neuronal injury or fully recovering lost cognitive functions. Additionally, the complexity of mixed metal exposures, which are common in real-world settings, remains insufficiently explored. This area requires deeper investigation to better understand potential synergistic or additive toxic effects and to guide more effective interventions.

Conclusion

Heavy metals like copper, arsenic, and lead pose serious risks to biodiversity and human health. Long-term exposure to these metals has been associated with neurodegenerative conditions and cognitive decline in adults. These metals not only can disrupt normal brain function by interfering with neurotransmitter systems and causing oxidative stress, but also damage neuronal cells, impairing memory, attention, and language skills. Therapeutic and preventive strategies-including removal of exposure, chelation, antioxidant support, and emerging novel therapies-hold promise in preventing neurotoxicity induced by heavy metals. Given the persistent cognitive and neurological risks posed by even low-level, chronic exposures, particularly during critical developmental periods, ongoing research is crucial to optimize interventions that not only reduce metal burden but also restore neurological function and prevent long-term neurodegenerative consequences.

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Authors' Contribution
Conceptualization: Jalal Hassanshahi.
Data curation: Narjes Soltani, Ayat Kaeidi, and Ali Shamsizadeh.
Formal analysis: Jalal Hassanshahi and Ali Shamsizadeh.
Investigation: Narjes Soltani and Jalal Hassanshahi.
Methodology: Narjes Soltani, Ayat Kaeidi, and Ali Shamsizadeh.
Project administration: Jalal Hassanshahi.
Resources: Jalal Hassanshahi.
Software: Narjes Soltani and Ayat Kaeidi.
Supervision: Jalal Hassanshahi.
Validation: Ayat Kaeidi and Ali Shamsizadeh.
Visualization: Jalal Hassanshahi, Ayat Kaeidi, and Narjes Soltani.
Writing – original draft: Jalal Hassanshahi and Narjes Soltani.
Writing – review & editing: Jalal Hassanshahi, Ayat Kaeidi, Ali Shamsizadeh, and Narjes Soltani.

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The authors declare that they have no conflict of interest.

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References

1. Mishra S, Bharagava RN, More N, Yadav A, Zainith S, Mani S, et al. Heavy metal contamination: an alarming threat to environment and human health. In: Sobti RC, Arora NK, Kothari R, eds. Environmental Biotechnology: For Sustainable Future. Singapore: Springer; 2019. p. 103-25. doi: 10.1007/978-981-10-7284-0_5.
2. Chandra R, Bharagava RN, Kapley A, Purohit HJ. Bacterial diversity, organic pollutants and their metabolites in two aeration lagoons of common effluent treatment plant (CETP) during the degradation and detoxification of tannery wastewater. Bioresour Technol. 2011;102(3):2333-41. doi: 10.1016/j.biortech.2010.10.087.
3. Neal AP, Guilarte TR. Mechanisms of lead and manganese neurotoxicity. Toxicol Res (Camb). 2013;2(2):99-114. doi: 10.1039/c2tx20064c.
4. Dhal B, Thatoi HN, Das NN, Pandey BD. Chemical and microbial remediation of hexavalent chromium from contaminated soil and mining/metallurgical solid waste: a review. J Hazard Mater. 2013;250-251:272-91. doi: 10.1016/j.jhazmat.2013.01.048.
5. Yadav A, Chowdhary P, Kaithwas G, Bharagava RN. Toxic metals in the environment: threats on ecosystem and bioremediation approaches. In: Handbook of Metal-Microbe Interactions and Bioremediation. CRC Press. 2017. p. 128-41.
6. Yu G, Wu L, Su Q, Ji X, Zhou J, Wu S, Tang Y, Li H. Neurotoxic effects of heavy metal pollutants in the environment: Focusing on epigenetic mechanisms. Environmental Pollution. 2024;345(5):123563. doi: 10.1016/j.envpol.2024.123563.
7. Ashraf Ganjooei N, Sheibani V, Jafari M, Hajializadeh Z, Shamsara A, Dehghani A, et al. Dual effects of aspirin on spatial learning and memory of male rats following induction of permanent cerebral ischemia. J Kerman Univ Med Sci. 2025;32(1):1-11. doi: 10.34172/jkmu.3837.
8. Hakimizadeh E, Kaeidi A, Hassanshahi J, Mehrbani M, Rahmani M. Ameliorating effect of pistachio hydroalcoholic extract on cisplatin-induced nephrotoxicity in mice. Res J Pharmacogn. 2021;8(1):73-9. doi: 10.22127/rjp.2020.119426.
9. Saffar S, Fatemi I, Rahmani M, Hassanshahi J, Sahamsizadeh A, Allahtavakoli M, et al. The effect of epigallocatechin-3-gallate on morphine-induced memory impairments in rat: EGCG effects on morphine neurotoxicity. Hum Exp Toxicol. 2020;39(7):994-1002. doi: 10.1177/0960327120909540.
10. Mozafari N, Hassanshahi J, Ostadebrahimi H, Shamsizadeh A, Ayoobi F, Hakimizadeh E, et al. Neuroprotective effect of *Achillea millefolium* aqueous extract against oxidative stress and apoptosis induced by chronic morphine in rat hippocampal CA1 neurons. Acta Neurobiol Exp (Wars). 2022;82(2):179-86. doi: 10.55782/ane-2022-016.
11. Hakimizadeh E, Kaeidi A, Taghipour Z, Mehrzadi S, Allahtavakoli M, Shamsizadeh A, et al. Ceftriaxone improves senile neurocognition damages induced by D-galactose in mice. Iran J Basic Med Sci. 2020;23(3):368-75. doi: 10.22038/ijbms.2019.40344.9556.
12. Halabicky OM, Giang CW, Miller AL, Peterson KE. Lead exposure, glucocorticoids, and physiological stress across the life course: a systematic review. Environ Pollut. 2024;345:123329. doi: 10.1016/j.envpol.2024.123329.
13. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med. 2008;148(6):427-34. doi: 10.7326/0003-4819-148-6-200803180-00005.
14. Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, et al. Age-associated cognitive decline. Br Med Bull. 2009;92:135-52. doi: 10.1093/bmb/ldp033.
15. Mathers C. The Global Burden of Disease: 2004 Update. World Health Organization; 2008.
16. Mattson MP, Magnus T. Ageing and neuronal vulnerability. Nat Rev Neurosci. 2006;7(4):278-94. doi: 10.1038/nrn1886.
17. Meramat A, Rajab NF, Shahar S, Sharif RA. DNA damage, copper and lead associates with cognitive function among older adults. J Nutr Health Aging. 2017;21(5):539-45. doi: 10.1007/s12603-016-0759-1.
18. Haghdoost-Yazdi H, Nigjeh S, Hadi Hosseini SA, Sharifi S, Kaveh F, Piri H. Assessment of serum levels of phosphate and corticosterone as possible biomarkers for early diagnosis of Parkinson's disease in rats with 6-OHDA-induced Parkinson. J Kerman Univ Med Sci. 2024;31(3):104-12. doi: 10.34172/jkmu.2024.18.
19. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet. 2006;368(9553):2167-78. doi: 10.1016/s0140-6736(06)69665-7.
20. Vellingiri B, Suriyanarayanan A, Selvaraj P, Abraham KS, Pasha MY, Winster H, et al. Role of heavy metals (copper (Cu), arsenic (As), cadmium (Cd), iron (Fe) and lithium (Li)) induced neurotoxicity. Chemosphere. 2022;301:134625. doi: 10.1016/j.chemosphere.2022.134625.
21. Ullah I, Zhao L, Hai Y, Fahim M, Alwayli D, Wang X, et al. "Metal elements and pesticides as risk factors for Parkinson's disease - a review". Toxicol Rep. 2021;8:607-16. doi: 10.1016/j.toxrep.2021.03.009.
22. Venkatesan D, Iyer M, Narayanasamy A, Siva K, Vellingiri B. Kynurenine pathway in Parkinson's disease-an update. eNeurologicalSci. 2020;21:100270. doi: 10.1016/j.ensci.2020.100270.
23. Karri V, Schuhmacher MP, Kumar V. A systems toxicology approach to compare the heavy metal mixtures (Pb, As, MeHg) impact in neurodegenerative diseases. Food Chem Toxicol. 2020;139:111257. doi: 10.1016/j.fct.2020.111257.
24. Squitti R. Copper subtype of Alzheimer's disease (AD): meta-analyses, genetic studies and predictive value of non-ceruloplasmim copper in mild cognitive impairment conversion to full AD. J Trace Elem Med Biol. 2014;28(4):482-5. doi: 10.1016/j.jtemb.2014.06.018.
25. Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HE, Abd El-Moneam N. Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food Chem Toxicol. 2018;111:432-44. doi: 10.1016/j.fct.2017.11.025.
26. Wu ML, Deng JF, Lin KP, Tsai WJ. Lead, mercury, and arsenic poisoning due to topical use of traditional Chinese medicines. Am J Med. 2013;126(5):451-4. doi: 10.1016/j.amjmed.2013.01.001.
27. Bauer E, Toepper M, Gebhardt H, Gallhofer B, Sammer G. The significance of caudate volume for age-related associative memory decline. Brain Res. 2015;1622:137-48. doi: 10.1016/j.brainres.2015.06.026.
28. Eid A, Mhatre I, Richardson JR. Gene-environment interactions in Alzheimer's disease: a potential path to precision medicine. Pharmacol Ther. 2019;199:173-87. doi: 10.1016/j.pharmthera.2019.03.005.

29. Vorvolakos T, Arseniou S, Samakouri M. There is no safe threshold for lead exposure: α literature review. Psychiatriki. 2016;27(3):204-14. doi: 10.22365/jpsych.2016.273.204.
30. Iqbal G, Zada W, Mannan A, Ahmed T. Elevated heavy metals levels in cognitively impaired patients from Pakistan. Environ Toxicol Pharmacol. 2018;60:100-9. doi: 10.1016/j.etap.2018.04.011.
31. Wright RO, Tsaih SW, Schwartz J, Spiro A 3rd, McDonald K, Weiss ST, et al. Lead exposure biomarkers and mini-mental status exam scores in older men. Epidemiology. 2003;14(6):713-8. doi: 10.1097/01.EDE.0000081988.85964.db.
32. Ramírez Ortega D, González Esquivel DF, Blanco Ayala T, Pineda B, Gómez Manzo S, Marcial Quino J, et al. Cognitive impairment induced by lead exposure during lifespan: mechanisms of lead neurotoxicity. Toxics. 2021;9(2):23. doi: 10.3390/toxics9020023.
33. Virgolini MB, Aschner M. Molecular mechanisms of lead neurotoxicity. Adv Neurotoxicol. 2021;5:159-213. doi: 10.1016/bs.ant.2020.11.002.
34. Santa Maria MP, Hill BD, Kline J. Lead (Pb) neurotoxicology and cognition. Appl Neuropsychol Child. 2019;8(3):272-93. doi: 10.1080/21622965.2018.1428803.
35. Mohammed RS, Ibrahim W, Sabry D, El-Jaafary SI. Occupational metals exposure and cognitive performance among foundry workers using tau protein as a biomarker. Neurotoxicology. 2020;76:10-6. doi: 10.1016/j.neuro.2019.09.017.
36. Weisskopf MG, Proctor SP, Wright RO, Schwartz J, Spiro A 3rd, Sparrow D, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology. 2007;18(1):59-66. doi: 10.1097/01.ede.0000248237.35363.29.
37. Keck ME, Welt T, Müller MB, Landgraf R, Holsboer F. The high-affinity non-peptide CRH1 receptor antagonist R121919 attenuates stress-induced alterations in plasma oxytocin, prolactin, and testosterone secretion in rats. Pharmacopsychiatry. 2003;36(1):27-31. doi: 10.1055/s-2003-38092.
38. Garza A, Vega R, Soto E. Cellular mechanisms of lead neurotoxicity. Med Sci Monit. 2006;12(3):RA57-65.
39. Lidsky TI, Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain. 2003;126(Pt 1):5-19. doi: 10.1093/brain/awg014.
40. Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med. 2003;348(16):1517-26. doi: 10.1056/NEJMoa022848.
41. Olympio KP, Gonçalves C, Günther WM, Bechara EJ. Neurotoxicity and aggressiveness triggered by low-level lead in children: a review. Rev Panam Salud Publica. 2009;26(3):266-75. doi: 10.1590/s1020-49892009000900011.
42. Chung JY, Yu SD, Hong YS. Environmental source of arsenic exposure. J Prev Med Public Health. 2014;47(5):253-7. doi: 10.3961/jpmph.14.036.
43. Tyler CR, Allan AM. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr Environ Health Rep. 2014;1(2):132-47. doi: 10.1007/s40572-014-0012-1.
44. Thakur M, Rachamalla M, Niyogi S, Datusalia AK, Flora SJ. Molecular mechanism of arsenic-induced neurotoxicity including neuronal dysfunctions. Int J Mol Sci. 2021;22(18):10077. doi: 10.3390/ijms221810077.
45. Pandey R, Rai V, Mishra J, Mandrah K, Kumar Roy S, Bandyopadhyay S. From the cover: arsenic induces hippocampal neuronal apoptosis and cognitive impairments via an up-regulated BMP2/Smad-dependent reduced BDNF/TrkB signaling in rats. Toxicol Sci. 2017;159(1):137-58. doi: 10.1093/toxsci/kfx124.
46. Andrade VM, Aschner M, Marreilha Dos Santos AP. Neurotoxicity of Metal Mixtures. Adv Neurobiol. 2017;18:227-65. doi: 10.1007/978-3-319-60189-2_12.
47. Giasson BI, Sampathu DM, Wilson CA, Vogelsberg-Ragaglia V, Mushynski WE, Lee VM. The environmental toxin arsenite induces tau hyperphosphorylation. Biochemistry. 2002;41(51):15376-87. doi: 10.1021/bi026813c.
48. Kadeyala PK, Sannadi S, Gottipolu RR. Alterations in apoptotic caspases and antioxidant enzymes in arsenic exposed rat brain regions: reversal effect of essential metals and a chelating agent. Environ Toxicol Pharmacol. 2013;36(3):1150-66. doi: 10.1016/j.etap.2013.09.021.
49. Brinkel J, Khan MH, Kraemer A. A systematic review of arsenic exposure and its social and mental health effects with special reference to Bangladesh. Int J Environ Res Public Health. 2009;6(5):1609-19. doi: 10.3390/ijerph6051609.
50. Edwards M, Johnson L, Mauer C, Barber R, Hall J, O'Bryant S. Regional specific groundwater arsenic levels and neuropsychological functioning: a cross-sectional study. Int J Environ Health Res. 2014;24(6):546-57. doi: 10.1080/09603123.2014.883591.
51. Wang X, Huang X, Zhou L, Chen J, Zhang X, Xu K, et al. Association of arsenic exposure and cognitive impairment: a population-based cross-sectional study in China. Neurotoxicology. 2021;82:100-7. doi: 10.1016/j.neuro.2020.11.009.
52. Mochizuki H, Phyu KP, Aung MN, Zin PW, Yano Y, Myint MZ, et al. Peripheral neuropathy induced by drinking water contaminated with low-dose arsenic in Myanmar. Environ Health Prev Med. 2019;24(1):23. doi: 10.1186/s12199-019-0781-0.
53. Calderón J, Navarro ME, Jimenez-Capdeville ME, Santos-Diaz MA, Golden A, Rodriguez-Leyva I, et al. Exposure to arsenic and lead and neuropsychological development in Mexican children. Environ Res. 2001;85(2):69-76. doi: 10.1006/enrs.2000.4106.
54. Wasserman GA, Liu X, Parvez F, Factor-Litvak P, Ahsan H, Levy D, et al. Arsenic and manganese exposure and children's intellectual function. Neurotoxicology. 2011;32(4):450-7. doi: 10.1016/j.neuro.2011.03.009.
55. Vaidya N, Holla B, Heron J, Sharma E, Zhang Y, Fernandes G, et al. Neurocognitive analysis of low-level arsenic exposure and executive function mediated by brain anomalies among children, adolescents, and young adults in India. JAMA Netw Open. 2023;6(5):e2312810. doi: 10.1001/jamanetworkopen.2023.12810.
56. Styczeń K, Sowa-Kućma M, Siwek M, Dudek D, Reczyński W, Misztak P, et al. Study of the serum copper levels in patients with major depressive disorder. Biol Trace Elem Res. 2016;174(2):287-93. doi: 10.1007/s12011-016-0720-5.
57. Ma J, Betts NM. Zinc and copper intakes and their major food sources for older adults in the 1994-96 continuing survey of food intakes by individuals (CSFII). J Nutr. 2000;130(11):2838-43. doi: 10.1093/jn/130.11.2838.
58. Arredondo M, Núñez MT. Iron and copper metabolism. Mol Aspects Med. 2005;26(4-5):313-27. doi: 10.1016/j.mam.2005.07.010.
59. Choi BS, Zheng W. Copper transport to the brain by the blood-brain barrier and blood-CSF barrier. Brain Res. 2009;1248:14-21. doi: 10.1016/j.brainres.2008.10.056.
60. Desai V, Kaler SG. Role of copper in human neurological disorders. Am J Clin Nutr. 2008;88(3):855s-8s. doi: 10.1093/ajcn/88.3.855S.
61. Scheiber IF, Mercer JF, Dringen R. Metabolism and functions

of copper in brain. Prog Neurobiol. 2014;116:33-57. doi: 10.1016/j.pneurobio.2014.01.002.
62. Dusek P, Roos PM, Litwin T, Schneider SA, Flaten TP, Aaseth J. The neurotoxicity of iron, copper and manganese in Parkinson's and Wilson's diseases. J Trace Elem Med Biol. 2015;31:193-203. doi: 10.1016/j.jtemb.2014.05.007.
63. Zheng W, Monnot AD. Regulation of brain iron and copper homeostasis by brain barrier systems: implication in neurodegenerative diseases. Pharmacol Ther. 2012;133(2):177-88. doi: 10.1016/j.pharmthera.2011.10.006.
64. Lorincz MT. Neurologic Wilson's disease. Ann N Y Acad Sci. 2010;1184:173-87. doi: 10.1111/j.1749-6632.2009.05109.x.
65. Dudzik CG, Walter ED, Abrams BS, Jurica MS, Millhauser GL. Coordination of copper to the membrane-bound form of α-synuclein. Biochemistry. 2013;52(1):53-60. doi: 10.1021/bi301475q.
66. Socha K, Karpińska E, Kochanowicz J, Soroczyńska J, Jakoniuk M, Wilkiel M, et al. Dietary habits; concentration of copper, zinc, and Cu-to-Zn ratio in serum and ability status of patients with relapsing-remitting multiple sclerosis. Nutrition. 2017;39-40:76-81. doi: 10.1016/j.nut.2017.03.009.
67. Feng D, Zhao Y, Li W, Li X, Wan J, Wang F. Copper neurotoxicity: induction of cognitive dysfunction: a review. Medicine (Baltimore). 2023;102(48):e36375. doi: 10.1097/md.0000000000036375.
68. Barnham KJ, Bush AI. Metals in Alzheimer's and Parkinson's diseases. Curr Opin Chem Biol. 2008;12(2):222-8. doi: 10.1016/j.cbpa.2008.02.019.
69. Adlard PA, Bica L, White AR, Nurjono M, Filiz G, Crouch PJ, et al. Metal ionophore treatment restores dendritic spine density and synaptic protein levels in a mouse model of Alzheimer's disease. PLoS One. 2011;6(3):e17669. doi: 10.1371/journal.pone.0017669.
70. Squitti R, Simonelli I, Ventriglia M, Siotto M, Pasqualetti P, Rembach A, et al. Meta-analysis of serum non-ceruloplasmin copper in Alzheimer's disease. J Alzheimers Dis. 2014;38(4):809-22. doi: 10.3233/jad-131247.
71. De Riccardis L, Buccolieri A, Muci M, Pitotti E, De Robertis F, Trianni G, et al. Copper and ceruloplasmin dyshomeostasis in serum and cerebrospinal fluid of multiple sclerosis subjects. Biochim Biophys Acta Mol Basis Dis. 2018;1864(5 Pt A):1828-38. doi: 10.1016/j.bbadis.2018.03.007.
72. Aaseth J, Skaug MA, Cao Y, Andersen O. Chelation in metal intoxication--principles and paradigms. J Trace Elem Med Biol. 2015;31:260-6. doi: 10.1016/j.jtemb.2014.10.001.
73. Flora SJ. Handbook of Arsenic Toxicology. Academic Press; 2014. doi: 10.1016/c2013-0-08322-3.
74. Sherif AH, Fadel A, Kasem EA, Mahfouz ME, Eldessouki EA, Fahmy HA. The nanocomposite of chitosan-vitamin C modulates the expression of immune and antioxidant-related genes in Nile tilapia stressed with lead (Pb). Aquaculture International. 2025;33(2):136. doi: 10.1007/s10499-024-01806-8.
75. Lynes MA, Kang YJ, Sensi SL, Perdrizet GA, Hightower LE. Heavy metal ions in normal physiology, toxic stress, and cytoprotection. Ann N Y Acad Sci. 2007;1113:159-72. doi: 10.1196/annals.1391.010.
76. Pal R, Rai JP. Phytochelatins: peptides involved in heavy metal detoxification. Appl Biochem Biotechnol. 2010;160(3):945-63. doi: 10.1007/s12010-009-8565-4.
77. Asagba SO. Role of diet in absorption and toxicity of oral cadmium-a review of literature. Afr J Biotechnol. 2009;8(25):7428-36.
78. Wang G, Fowler BA. Roles of biomarkers in evaluating interactions among mixtures of lead, cadmium and arsenic. Toxicol Appl Pharmacol. 2008;233(1):92-9. doi: 10.1016/j.taap.2008.01.017.
79. Flora SJ, Mittal M, Mehta A. Heavy metal induced oxidative stress & its possible reversal by chelation therapy. Indian J Med Res. 2008;128(4):501-23.
80. Aaseth J, Crisponi G, Anderson O. Chelation Therapy in the Treatment of Metal Intoxication. Academic Press; 2016. doi: 10.1016/c2014-0-01302-0.
81. Flora SJ, Pachauri V. Chelation in metal intoxication. Int J Environ Res Public Health. 2010;7(7):2745-88. doi: 10.3390/ijerph7072745.
82. Gracia RC, Snodgrass WR. Lead toxicity and chelation therapy. Am J Health Syst Pharm. 2007;64(1):45-53. doi: 10.2146/ajhp060175.
83. Miller AL. Dimercaptosuccinic acid (DMSA), a non-toxic, water-soluble treatment for heavy metal toxicity. Altern Med Rev. 1998;3(3):199-207.
84. Waller EJ. Radiological contaminants: triage, treatment and medical management of exposed persons. Disaster Management: Medical Preparedness, Response and Homeland Security. CABI; 2013. p. 337-77. doi: 10.1079/9781845939298.0337.
85. Kalia K, Flora SJ. Strategies for safe and effective therapeutic measures for chronic arsenic and lead poisoning. J Occup Health. 2005;47(1):1-21. doi: 10.1539/joh.47.1.
86. Hoet P, Haufroid V, Lison D. Heavy metal chelation tests: the misleading and hazardous promise. Arch Toxicol. 2020;94(8):2893-6. doi: 10.1007/s00204-020-02847-7.
87. George T, Brady MF. Ethylenediaminetetraacetic acid (EDTA). In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2025.
88. Dorrigiv M, Zareiyan A, Hosseinzadeh H. Garlic (*Allium sativum*) as an antidote or a protective agent against natural or chemical toxicities: a comprehensive update review. Phytother Res. 2020;34(8):1770-97. doi: 10.1002/ptr.6645.
89. Ortega R, Carmona A. Neurotoxicity of environmental metal toxicants: special issue. Toxics. 2022;10(7):382. doi: 10.3390/toxics10070382.
90. Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Front Pharmacol. 2021;12:643972. doi: 10.3389/fphar.2021.643972.
91. Soltaninejad M, Ilaghi M, Saboori Amleshi R, Shabani M. Quercetin as a complementary therapy in substance use disorder: a narrative review. J Kerman Univ Med Sci. 2025;32(1):1-8. doi: 10.34172/jkmu.3816.