Lead-induced neurotoxicity: molecular mechanisms, oxidative stress and emerging pharmacological neuroprotective strategies

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Abstract:

Lead (Pb) is a persistent environmental toxicant that poses a significant threat to human health, particularly because of its adverse effects on the central nervous system (CNS). Both acute and chronic lead exposure can interfere with normal neuronal function, while exposure during prenatal and early postnatal development may produce long-lasting neurological and cognitive abnormalities. Lead-induced neurotoxicity involves multiple interconnected molecular mechanisms, including disruption of calcium homeostasis, altered neurotransmitter signalling, mitochondrial dysfunction, oxidative stress, neuroinflammation and neuronal apoptosis. Among these mechanisms, oxidative stress plays a central role by increasing reactive oxygen species (ROS), reducing endogenous antioxidant defence, promoting lipid peroxidation and damaging cellular proteins and DNA. Lead also interferes with antioxidant enzymes, including superoxide dismutase, catalase and glutathione peroxidase, thereby weakening neuronal resistance to oxidative injury.

Conventional management of lead poisoning involves eliminating the exposure source, supportive care and chelation therapy in appropriately selected patients. However, chelation does not reliably reverse established neurological damage. Consequently, increasing attention has been directed towards pharmacological neuroprotective agents, including N-acetylcysteine, vitamins C and E, curcumin, resveratrol, melatonin, alpha-lipoic acid and mitochondria-targeted antioxidants. These compounds have demonstrated antioxidant, anti-inflammatory or anti-apoptotic properties in experimental models. Furthermore, modulation of Nrf2/ARE, NF-κB, SIRT1/AMPK and mitochondrial apoptotic pathways represents a promising direction for future drug development. This review critically discusses the molecular mechanisms of lead-induced neurotoxicity, the importance of oxidative stress and the potential of emerging pharmacological interventions. It also identifies limitations in current research and highlights the need for controlled clinical investigations to establish the safety and therapeutic efficacy of experimental neuroprotective agents.

Keywords:

Lead toxicity; neurotoxicity; oxidative stress; reactive oxygen species; mitochondrial dysfunction; neuroinflammation; neuronal apoptosis; antioxidant therapy; chelation therapy; neuroprotection.

1. Introduction

Lead (Pb) is a naturally occurring heavy metal that has been widely used in industrial manufacturing, construction materials, batteries, paints, ceramics and plumbing systems. Despite regulatory restrictions in many countries, environmental contamination remains a major public health concern. Human exposure occurs through ingestion, inhalation and, to a lesser extent, dermal absorption. Important sources include contaminated drinking water, soil, food, household dust, industrial emissions and occupational environments (World Health Organization, 2021).

The nervous system is particularly sensitive to lead toxicity. Children are more vulnerable because their nervous systems are still developing, their gastrointestinal absorption of lead is relatively high and their detoxification mechanisms are immature. Prenatal and childhood exposure may interfere with neuronal differentiation, synapse formation, myelination and neurotransmitter regulation. These alterations have been associated with impaired intelligence, attention deficits, behavioural abnormalities and learning difficulties (Lanphear et al., 2005; Bellinger, 2008).

Lead toxicity is also relevant to adults, in whom prolonged exposure may contribute to cognitive impairment, peripheral neuropathy, altered motor function and disturbances in memory. The ability of lead to accumulate in bones and subsequently re-enter circulation further complicates long-term exposure management (Flora et al., 2012).

At the molecular level, lead interferes with several essential biological processes. It can mimic calcium and other divalent metal ions, alter intracellular signalling, impair mitochondrial activity and disturb neurotransmitter release. It also increases oxidative stress and promotes inflammatory responses, ultimately contributing to neuronal dysfunction and cell death (Bressler et al., 1999; Virgolini and Aschner, 2021).

Oxidative stress is especially important in lead-induced neurotoxicity because the brain has a high metabolic demand, consumes substantial oxygen and contains abundant polyunsaturated fatty acids that are susceptible to lipid peroxidation. Lead-induced ROS generation, glutathione depletion and impaired antioxidant enzyme activity can therefore cause considerable neuronal damage (Ahamed and Siddiqui, 2007).

The development of pharmacological strategies capable of reducing oxidative injury and preserving neuronal function has consequently become an important area of research. This review examines the major mechanisms of lead-induced neurotoxicity, with particular emphasis on oxidative stress, and evaluates emerging pharmacological approaches for neuroprotection.

2. Literature review methodology:

This article presents a narrative review of published literature concerning lead-induced neurotoxicity, oxidative stress and pharmacological neuroprotection. Relevant studies were selected from biomedical literature databases, including PubMed and PubMed Central, together with authoritative reports from international health organisations.

The literature selection focused on research addressing:

1. Environmental and occupational lead exposure.
2. Molecular mechanisms of lead-induced neuronal injury.
3. Oxidative stress and antioxidant defence.
4. Mitochondrial dysfunction and neuronal apoptosis.
5. Neuroinflammation and neurotransmitter disturbances.
6. Chelation therapy and its clinical limitations.
7. Natural antioxidants and emerging pharmacological interventions.

Peer-reviewed original research, mechanistic investigations, clinical studies and relevant review articles were considered. Human evidence was distinguished from animal and in-vitro findings. The article is a narrative synthesis and does not claim to be a systematic review or meta-analysis.

3. Sources, Absorption and Distribution of Lead:

3.1. Environmental and occupational exposure:

Lead exposure commonly occurs through contaminated water, food, soil and airborne particles. Deteriorating lead-containing paints and household dust represent important exposure sources, particularly for children. Industrial activities such as battery manufacturing, mining, smelting, welding and metal recycling may expose workers to lead-containing dust and fumes.

Inadequate waste management and informal recycling of lead-acid batteries are important environmental concerns in developing countries. Occupational exposure may result in long-term accumulation and neurological complications (Flora et al., 2012).

Absorption and tissue distribution:

Following absorption, lead enters systemic circulation, where a substantial proportion becomes associated with erythrocytes. It subsequently distributes to soft tissues and bone. Bone represents the major long-term storage compartment and may release previously accumulated lead during pregnancy, ageing and increased bone turnover.

Lead can reach the developing and adult CNS through interactions with metal transport systems and pathways associated with divalent cations. Its ability to interfere with calcium-dependent transport and signalling contributes to neuronal toxicity (Virgolini and Aschner, 2021).

3.2. Blood–brain barrier penetration:

The blood–brain barrier (BBB) consists of specialised endothelial cells connected by tight junctions, together with pericytes, astrocytic end-feet and basement membranes. It regulates the movement of substances between circulation and brain tissue.

Lead can cross brain barriers through mechanisms involving essential metal transporters and calcium-permeable pathways. Once inside the CNS, it may accumulate in neuronal and glial cells and disturb cellular metabolism, neurotransmission and antioxidant defence (Virgolini and Aschner, 2021).

The hippocampus, cerebral cortex, cerebellum and other regions involved in cognition and motor control are particularly important targets in experimental investigations.

4. Molecular mechanisms of lead-induced neurotoxicity:

4.1. Disruption of calcium homeostasis:

Calcium ions (Ca^{2+}) are essential regulators of neuronal excitability, neurotransmitter release, synaptic plasticity and intracellular signalling. Lead can mimic calcium because of similarities in their ionic properties, but it cannot perform normal calcium-dependent physiological functions.

Lead interferes with voltage-gated calcium channels, calcium-binding proteins and intracellular signalling pathways. It may alter calcium concentrations and disturb the activity of calmodulin-dependent enzymes and protein kinases.

These disturbances affect synaptic vesicle release, neuronal communication and long-term potentiation. Consequently, lead-induced calcium dysregulation is considered an important contributor to learning and memory impairment (Bressler et al., 1999; Lidsky and Schneider, 2003).

4.2. Alteration of neurotransmitter systems:

Lead affects several neurotransmitter systems responsible for normal neuronal communication.

Glutamate: Glutamate is the principal excitatory neurotransmitter in the CNS. Its NMDA receptors are essential for synaptic plasticity and memory formation. Lead-induced alterations in NMDA receptor activity and calcium-dependent signalling can impair hippocampal long-term potentiation.

Dopamine: Dopamine regulates movement, motivation, reward and cognitive processes. Lead exposure may alter dopamine synthesis, metabolism and receptor signalling, contributing to behavioural and motor disturbances.

Acetylcholine: Acetylcholine plays an important role in attention, learning and memory. Alterations in cholinergic neurotransmission may contribute to cognitive impairment.

GABA: Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter. Disturbances in GABAergic signalling may affect the balance between neuronal excitation and inhibition.

Together, these alterations interfere with neuronal communication and contribute to functional impairment (Sanders et al., 2009).

4.3 Mitochondrial dysfunction:

Mitochondria regulate cellular energy production, calcium homeostasis and apoptotic signalling. Neurons are particularly dependent on mitochondrial activity because of their high ATP requirements.

Lead exposure can impair mitochondrial electron transport, disrupt oxidative phosphorylation and increase mitochondrial ROS generation. It may also reduce mitochondrial membrane potential and interfere with ATP synthesis.

Mitochondrial injury can promote cytochrome c release and activation of apoptotic pathways. Excessive ROS production subsequently damages mitochondrial proteins, membrane lipids and mitochondrial DNA, creating a cycle of progressive mitochondrial dysfunction (Virgolini and Aschner, 2021).

4.4. Neuroinflammation:

Neuroinflammation contributes to neuronal damage through activation of microglia and alterations in astrocytic function.

Activated glial cells may release inflammatory mediators, including tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). These mediators can disturb neuronal signalling and amplify oxidative injury.

Nuclear factor-kappa B (NF-κB) is an important transcriptional regulator of inflammatory responses. Its activation can increase the expression of inflammatory genes, contributing to a potentially self-amplifying relationship between oxidative stress and neuroinflammation (Jiang et al., 2021).

4.5. Neuronal apoptosis:

Apoptosis is a regulated form of programmed cell death. Lead exposure can activate apoptotic pathways through oxidative stress, mitochondrial dysfunction and intracellular calcium disturbances.

The intrinsic mitochondrial pathway involves changes in the balance between pro-apoptotic and anti-apoptotic proteins.

Important components include:

1. Bax, which promotes mitochondrial membrane permeabilisation.
2. Bcl-2, which inhibits apoptosis.
3. Cytochrome c, which contributes to apoptosome formation.
4. Caspase-9, which initiates intrinsic apoptotic signalling.
5. Caspase-3, which executes apoptosis.

An increased Bax/Bcl-2 ratio and activation of caspase signalling may contribute to neuronal cell death. The extent of apoptosis depends on exposure intensity, duration, cell type and the effectiveness of cellular defence mechanisms (Singh et al., 2018).

4.6. Impaired neuronal development and synaptic plasticity:

Normal brain development requires coordinated neuronal proliferation, migration, differentiation, synapse formation and myelination.

Lead exposure can interfere with these processes, particularly during prenatal and early postnatal development. Alterations in synaptic protein expression, neuronal connectivity and receptor-mediated signalling may result in persistent cognitive and behavioural abnormalities (Bellinger, 2008).

5. Oxidative stress: A central mechanism of lead-induced neurotoxicity:

Oxidative stress occurs when ROS production exceeds the capacity of endogenous antioxidant systems. The brain is highly susceptible to oxidative injury because of its high oxygen consumption, abundant membrane lipids and substantial mitochondrial activity.

Lead-induced oxidative stress is a central mechanism connecting mitochondrial dysfunction, neuroinflammation, membrane damage and neuronal apoptosis (Ahamed and Siddiqui, 2007; Flora et al., 2012).

5.1. Generation of reactive oxygen species:

Important ROS include superoxide anions ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals (•OH).

Lead is not a classical redox-cycling metal. Instead, it increases oxidative stress indirectly through mitochondrial dysfunction, disruption of antioxidant systems and interference with cellular metal homeostasis.

Major contributing mechanisms include:

1. Mitochondrial electron transport dysfunction.
2. Increased activity of ROS-generating enzymes.
3. Inflammatory activation of microglia.
4. Depletion of intracellular glutathione.
5. Impaired antioxidant enzyme activity.

Excessive ROS production damages neuronal membranes, proteins and nucleic acids.

5.2. Glutathione depletion:

Glutathione (GSH) is a major intracellular antioxidant that protects cells against oxidative damage.

It exists predominantly in reduced (GSH) and oxidised (GSSG) forms. GSH participates in free-radical neutralisation, maintenance of protein thiol groups and glutathione-dependent enzymatic reactions.
Lead exposure may decrease GSH availability through increased oxidative consumption, interference with synthesis and disruption of cellular redox balance. A reduced GSH/GSSG ratio is therefore an important indicator of oxidative stress.

5.3. Alteration of antioxidant enzymes:

Table. 1: The endogenous antioxidant system includes several enzymes that protect neurons from oxidative injury

Enzyme	Normal physiological function	Potential alteration during lead exposure
Superoxide dismutase (SOD)	Converts superoxide into hydrogen peroxide	Altered or reduced activity
Catalase (CAT)	Converts hydrogen peroxide into water and oxygen	Impaired peroxide removal
Glutathione peroxidase (GPx)	Reduces hydrogen peroxide and lipid peroxides	Reduced antioxidant capacity
Glutathione reductase (GR)	Regenerates reduced glutathione	Disturbed glutathione recycling
Glutathione-S-transferase (GST)	Supports detoxification of electrophilic compounds	Altered detoxification activity

The direction and magnitude of enzyme changes may differ according to exposure duration, dose, brain region and experimental conditions. Some enzymes may initially show compensatory increases before antioxidant capacity becomes impaired.

5.4. Lipid peroxidation:

Neuronal membranes contain large quantities of polyunsaturated fatty acids, which are highly susceptible to ROS-mediated oxidation.
Lipid peroxidation produces reactive secondary compounds, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE).
Increased lipid peroxidation disrupts membrane integrity, alters membrane-associated receptors and enzymes, and interferes with ion transport. These changes can impair neuronal excitability and synaptic communication (Valko et al., 2007).

5.5. Oxidative DNA and protein damage:

Excessive ROS can damage nuclear and mitochondrial DNA. One commonly investigated marker is 8-hydroxy-2′-deoxyguanosine (8-OHdG), which reflects oxidative DNA modification.
Protein oxidation may also alter enzyme activity, receptor function and intracellular signalling. When oxidative damage exceeds cellular repair capacity, neuronal survival becomes compromised.

5.6. Nrf2/ARE antioxidant signaling:

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a major regulator of cellular antioxidant defence.
Under normal conditions, Nrf2 is regulated by Kelch-like ECH-associated protein 1 (Keap1). Oxidative stress can promote Nrf2 stabilisation and its translocation into the nucleus, where it regulates antioxidant response element (ARE)-dependent genes.
Important Nrf2-regulated proteins include:

1. Heme oxygenase-1 (HO-1).
2. NAD(P)H quinone dehydrogenase 1 (NQO1).
3. Glutamate-cysteine ligase.
4. Glutathione-related enzymes.

Activation of Nrf2/ARE signalling is an attractive experimental strategy because it may improve endogenous antioxidant capacity and reduce oxidative injury (Itoh et al., 1999; Dinkova-Kostova et al., 2002).

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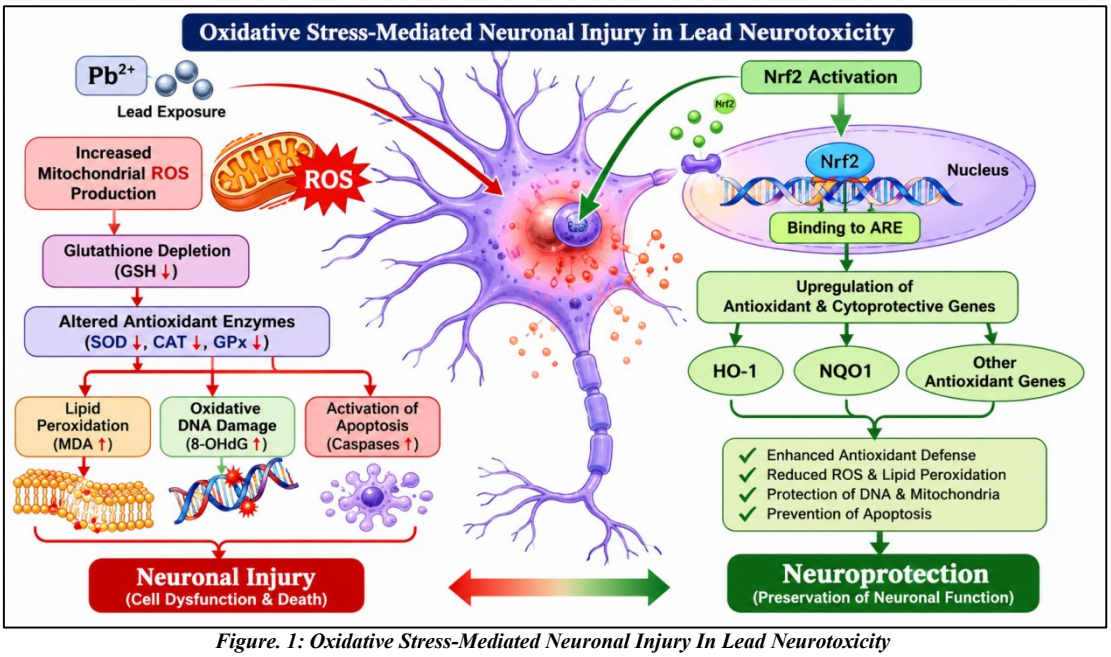


Figure. 1: Oxidative Stress-Mediated Neuronal Injury In Lead Neurotoxicity

6. Pharmacological neuroprotective strategies:

The treatment of lead-induced neurotoxicity remains challenging because exposure can produce persistent biochemical and structural alterations in the CNS. Removal of the exposure source is essential, while pharmacological interventions may reduce the toxicant burden or target specific mechanisms of neuronal injury.

Importantly, the following experimental neuroprotective agents should not be interpreted as established treatments for human lead poisoning.

Chelation therapy: Chelation therapy is an established medical intervention for selected patients with significant lead poisoning. Chelating agents bind lead ions and facilitate their elimination.

Calcium disodium EDTA ($CaNa_2EDTA$): This agent binds lead and promotes urinary elimination. It is used in selected cases under specialist supervision.

Dimercaprol (BAL): Dimercaprol is a sulfhydryl-containing chelator used in certain severe cases, generally in combination with other agents when clinically indicated.

Succimer (DMSA): Succimer is an orally administered chelating agent used in selected patients to increase lead elimination.

Chelation has limitations. It does not reliably reverse established neurological damage, can produce adverse effects and may affect essential trace-element balance. Treatment decisions must therefore be based on clinical assessment and appropriate blood lead measurements.

The Treatment of Lead-Exposed Children trial demonstrated that succimer lowered blood lead concentrations in children with moderate exposure but did not improve long-term cognitive outcomes (Rogan et al., 2001). This finding highlights the distinction between reducing circulating lead and reversing established neurodevelopmental injury.

N-acetylcysteine: N-acetylcysteine (NAC) is a cysteine-containing compound that acts as a precursor for intracellular glutathione synthesis.

Potential protective mechanisms include:

1. Increasing intracellular GSH availability.
2. Improving antioxidant defence.
3. Reducing oxidative injury.
4. Supporting mitochondrial function.
5. Modulating inflammatory responses.

Because glutathione depletion is associated with lead-induced oxidative stress, NAC is a relevant experimental neuroprotective candidate. Nevertheless, its clinical efficacy for lead-induced neurological injury has not been established through adequate controlled trials.

Vitamin C: Vitamin C (ascorbic acid) is a water-soluble antioxidant that contributes to the neutralisation of reactive oxygen species.

It may reduce oxidative damage, support endogenous antioxidant systems and influence metal-related oxidative processes. Experimental studies have investigated its potential to reduce biochemical indicators of lead toxicity.

However, findings vary according to dosage, exposure conditions and experimental model. Vitamin C supplementation cannot replace exposure removal or clinically indicated chelation therapy.

Vitamin E: Vitamin E is a lipid-soluble antioxidant that protects biological membranes against lipid peroxidation.

Its principal protective mechanism involves interruption of lipid radical chain reactions. It may therefore be particularly relevant to neuronal membrane protection during lead exposure.

Experimental investigations have examined vitamin E in relation to reduced lipid peroxidation and preservation of antioxidant enzyme activity. However, clinical efficacy in lead-induced neurotoxicity remains insufficiently established.

Curcumin: Curcumin is a polyphenolic compound derived from Curcuma longa. It has been investigated for antioxidant, anti-inflammatory and cytoprotective properties.

Potential mechanisms include modulation of Nrf2/ARE signalling, inhibition of NF-κB-associated inflammatory responses, reduction of ROS and regulation of apoptotic proteins.

Its poor aqueous solubility, limited oral bioavailability and rapid metabolism are important limitations. Nanoformulations and other delivery systems are being explored to improve its pharmacokinetic properties (Anand et al., 2007).

Resveratrol: Resveratrol is a naturally occurring polyphenolic compound found in grapes and several other plant sources.

Its potential neuroprotective effects are associated with antioxidant activity, mitochondrial regulation and modulation of inflammatory signalling.

Important pathways include SIRT1, AMP-activated protein kinase (AMPK) and Nrf2. Resveratrol may also influence mitochondrial biogenesis and cellular energy metabolism.

Despite encouraging experimental findings, low bioavailability and limited lead-specific clinical evidence remain major challenges (Baur and Sinclair, 2006).

Melatonin: Melatonin is a hormone primarily associated with circadian rhythm regulation. It also has antioxidant and anti-inflammatory properties.

Potential neuroprotective actions include reduction of mitochondrial ROS, preservation of mitochondrial membrane potential, regulation of antioxidant enzymes and modulation of apoptotic pathways.

Its ability to influence mitochondrial redox processes makes it an interesting experimental candidate. However, clinical evidence for its use in lead-induced neurotoxicity remains insufficient.

Alpha-lipoic acid and quercetin: Alpha-lipoic acid is an organosulfur compound involved in mitochondrial enzyme activity and cellular redox regulation. It may support antioxidant regeneration and glutathione homeostasis.

Quercetin is a naturally occurring flavonoid with antioxidant and anti-inflammatory properties. It may influence Nrf2 and NF-κB signalling and regulate cellular responses to oxidative injury.

Both compounds have been investigated in experimental toxicological models, but further lead-specific investigations are necessary to establish their safety, pharmacokinetics and therapeutic value.

Mitochondria-targeted antioxidants: Because mitochondria are both a source and a target of oxidative stress, mitochondria-targeted compounds represent an emerging therapeutic approach.

MitoQ is a mitochondria-targeted antioxidant designed to accumulate within mitochondria and reduce oxidative injury. SS-31 (elamipretide) is a mitochondria-targeted peptide investigated for its interaction with mitochondrial membrane components and its potential to support mitochondrial function.

These compounds are mechanistically attractive, but their efficacy specifically against lead-induced neuronal injury remains investigational (Murphy and Smith, 2007; Szeto, 2014).

Nanotechnology-based drug delivery: The BBB restricts the entry of many pharmacological compounds into the CNS. Nanotechnology-based delivery systems may improve drug stability, solubility, controlled release and brain distribution.

Potential delivery platforms include:

1. Polymeric nanoparticles.
2. Liposomes.
3. Solid lipid nanoparticles.
4. Nanoemulsions.
5. Dendrimers.
6. Targeted nanocarriers.

These systems are being explored for delivering curcumin and other antioxidant or anti-inflammatory molecules. However, long-term biocompatibility, particle accumulation, reproducibility and toxicity require careful investigation before clinical use.

7. Comparative evaluation of neuroprotective agents:

Table. 2: The principal experimental neuroprotective candidates and their molecular targets are summarised below

Agent	Major target	Proposed protective mechanism	Evidence status
N-acetylcysteine	Glutathione	Supports GSH synthesis	Preclinical
Vitamin C	ROS	Supports antioxidant defence	Experimental
Vitamin E	Membrane lipids	Reduces lipid peroxidation	Experimental
Curcumin	Nrf2, NF-κB	Antioxidant and anti-inflammatory actions	Preclinical
Resveratrol	SIRT1, AMPK	Mitochondrial and metabolic regulation	Preclinical
Melatonin	Mitochondrial redox balance	Antioxidant and anti-apoptotic actions	Experimental
Alpha-lipoic acid	Redox regulation	Supports antioxidant regeneration	Experimental
Quercetin	Nrf2, NF-κB	Antioxidant and anti-inflammatory actions	Preclinical
MitoQ	Mitochondrial ROS	Mitochondria-targeted antioxidant action	Investigational
SS-31	Mitochondrial membranes	Supports mitochondrial integrity	Investigational
Succimer	Circulating lead	Chelation and lead elimination	Established clinical use in selected patients

These evidence categories indicate the general research status of each intervention, not proof of clinical efficacy for lead-induced neurotoxicity.

8. Potential Molecular Targets for Future Drug Development:

Nrf2/ARE pathway: Enhancement of Nrf2 activity may increase the expression of antioxidant and detoxification-related proteins. Pharmacological activation could potentially improve glutathione synthesis and reduce oxidative injury.

NF-κB pathway: NF-κB regulates numerous inflammatory genes. Selective modulation of this pathway may reduce excessive neuroinflammatory responses and secondary neuronal damage.

SIRT1/AMPK signaling: SIRT1 and AMPK regulate energy metabolism, mitochondrial function and cellular stress responses. These pathways are important candidates for investigating compounds such as resveratrol.

Mitochondrial apoptotic pathway: Regulation of Bax, Bcl-2, and cytochrome c and caspase activation may help preserve neuronal viability. Future drug development could focus on mitochondrial membrane stability and apoptotic signalling.

NLRP3 inflammasome: The NLRP3 inflammasome regulates inflammatory signalling and maturation of IL-1β and IL-18. Investigating its contribution to lead-associated neuroinflammation may identify additional therapeutic targets, although its precise role requires further validation.

9. Experimental models and biomarkers:

Experimental models:

Rodent models are commonly used to investigate lead accumulation, oxidative stress, mitochondrial function, neurotransmitter changes, histopathological alterations and behavioural abnormalities.

Cell culture models provide controlled systems for examining ROS production, mitochondrial membrane potential and apoptosis. However, they cannot fully reproduce the complexity of the intact nervous system.

Zebrafish models are also useful in developmental neurotoxicity research because of their rapid development, transparent embryos and suitability for molecular and behavioural investigations.
Recent comparative work has further highlighted the value of combining rodent and zebrafish models to investigate oxidative stress, blood–brain barrier disturbances and neurodevelopmental abnormalities (Firdous et al., 2026).

Biomarkers:

Table. 3: Several biochemical indicators are used to investigate lead-induced neurotoxicity

Biomarker	Biological significance
Blood lead concentration	Recent or ongoing systemic exposure
Brain tissue lead concentration	Experimental tissue accumulation
MDA	Lipid peroxidation
4-HNE	Oxidative lipid damage
GSH/GSSG ratio	Intracellular redox balance
SOD	Antioxidant defence
CAT	Hydrogen peroxide metabolism
GPx	Peroxide detoxification
8-OHdG	Oxidative DNA damage
TNF-α	Inflammatory response
IL-1β	Neuroinflammatory signalling
Bax/Bcl-2 ratio	Apoptotic regulation
Caspase-3	Execution of apoptosis
Nrf2 and HO-1	Antioxidant response signalling

No single biomarker is sufficient to characterise the complete neurotoxic response. Combining exposure measurements, biochemical indicators and neurological assessments may provide a more comprehensive evaluation.

10. Integrated mechanism of lead-induced neurotoxicity:

The available evidence indicates that lead-induced neurotoxicity develops through a series of interconnected pathological events.
Initially, lead enters the body through environmental or occupational exposure and reaches systemic circulation. It subsequently distributes to different tissues, including the brain.
After entering the CNS, lead interferes with calcium-dependent signalling and essential metal homeostasis. These disturbances affect neuronal excitability, neurotransmitter release and synaptic plasticity.
Simultaneously, mitochondrial dysfunction increases ROS production and disrupts cellular energy metabolism. Oxidative stress damages membrane lipids, proteins and DNA while reducing antioxidant defence capacity.
Oxidative injury and mitochondrial dysfunction may activate apoptotic pathways. In parallel, microglial and astrocytic activation promotes neuroinflammatory responses that further amplify neuronal injury.
Ultimately, the combined effects of oxidative stress, impaired neurotransmission, inflammation and apoptosis can produce synaptic dysfunction, neuronal loss and cognitive impairment (Virgolini and Aschner, 2021).

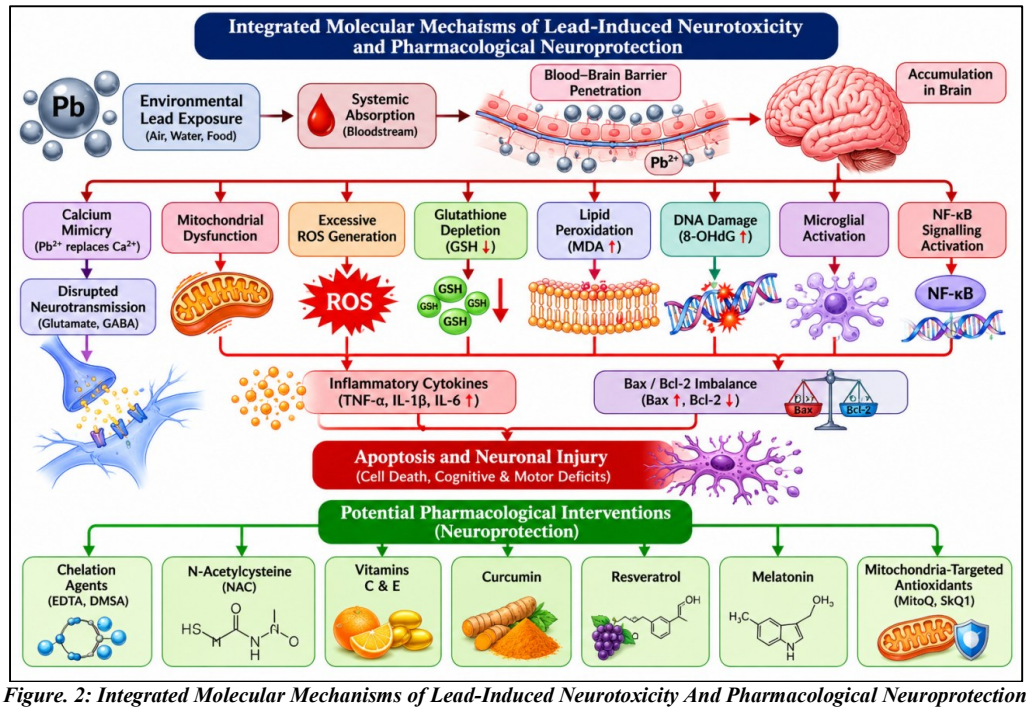


Figure. 2: Integrated Molecular Mechanisms of Lead-Induced Neurotoxicity And Pharmacological Neuroprotection

11. Research gaps and future perspectives:

Despite considerable progress in understanding lead-induced neurotoxicity, important scientific and clinical questions remain unanswered.

Limited clinical evidence: Most antioxidant interventions have been evaluated in animal models or cell culture. Adequately powered clinical studies are needed to determine their efficacy, safety and appropriate treatment duration.

Blood–brain barrier delivery: Many potential neuroprotective compounds have limited brain penetration. Targeted drug delivery may improve CNS bioavailability, but its long-term safety must be established.

Biomarker development: Reliable biomarkers may help identify individuals at increased risk of neurological complications. Future research should investigate combinations of oxidative stress markers, inflammatory mediators and mitochondrial biomarkers.

Developmental neurotoxicity: Longitudinal investigations are needed to understand whether neuronal alterations caused by prenatal and early-life exposure can be reversed and to identify critical intervention periods.

Combination therapy: Since lead toxicity involves multiple mechanisms, future studies should investigate whether combining chelation, antioxidant and anti-inflammatory approaches provides additional benefit.

New regulated cell-death pathways: Ferroptosis and pyroptosis have recently attracted attention as possible contributors to lead-associated neuronal injury. Their roles and potential therapeutic targets require further mechanistic investigation.

12. Critical discussion:

Lead-induced neurotoxicity is a multifactorial pathological process involving interconnected molecular and cellular pathways. Oxidative stress is particularly important because it connects mitochondrial dysfunction, inflammatory responses, membrane damage and apoptosis.

Glutathione depletion and alteration of antioxidant enzyme activity can further increase neuronal susceptibility to oxidative injury. In addition, the reciprocal relationship between ROS production and neuroinflammation may amplify cellular damage and contribute to persistent neurological dysfunction.

Chelation therapy remains important for selected patients with significant lead poisoning. However, the TLC trial demonstrated that reducing blood lead concentrations does not necessarily restore established cognitive impairment (Rogan et al., 2001). This distinction highlights the need to investigate interventions that may preserve neuronal function in addition to reducing the systemic toxicant burden.

NAC, curcumin, resveratrol, melatonin and mitochondria-targeted antioxidants offer possible pharmacological opportunities because they act on different components of oxidative and inflammatory signalling.

Nevertheless, their experimental benefits should not be interpreted as established clinical effectiveness. Differences in experimental doses, exposure duration, and bioavailability and treatment schedules make direct comparison difficult.

Furthermore, oxidative stress is not the only mechanism responsible for lead toxicity. Calcium dysregulation, synaptic dysfunction, neurotransmitter disturbances and glial activation may continue to contribute to neuronal injury even when oxidative stress is reduced.

Therefore, future therapeutic development should focus on multi-target strategies supported by mechanistic studies and controlled clinical investigations. These approaches must complement, rather than replace, environmental exposure prevention and appropriate medical management.

13. Conclusion:

Lead-induced neurotoxicity is a complex pathological condition resulting from the interaction of multiple molecular and cellular mechanisms. Lead disrupts calcium homeostasis, alters neurotransmitter signalling, impairs mitochondrial function and activates neuroinflammatory and apoptotic pathways. Oxidative stress represents a central mechanism of neuronal injury through increased ROS production, glutathione depletion, altered antioxidant enzyme activity, lipid peroxidation and oxidative damage to proteins and DNA. Although chelation therapy is an established intervention for selected cases of lead poisoning, it cannot reliably reverse previously established neurological damage. This limitation has encouraged investigations into emerging pharmacological neuroprotective approaches. N-acetylcysteine, vitamins C and E, curcumin, resveratrol, melatonin, alpha-lipoic acid, quercetin and mitochondria-targeted antioxidants represent potential candidates for further investigation. Nrf2/ARE, NF-κB, SIRT1/AMPK and mitochondrial apoptotic signalling pathways also provide promising molecular targets for future drug development.

However, most experimental neuroprotective strategies remain supported primarily by preclinical evidence. Their clinical efficacy, optimal dosage, safety and long-term neurological benefits must be established through rigorous research. Ultimately, an integrated strategy combining environmental prevention, early diagnosis, appropriate chelation and scientifically validated neuroprotective treatments may provide the greatest opportunity to reduce the neurological consequences of lead exposure.

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