

Oxidative Stress–Mediated Neurotoxicity Induced by Lead and Its Modulation by Curcumin and Quercetin

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Abstract

Lead (Pb) is a ubiquitous neurotoxicant in the environment, and the developing and adult brain are highly vulnerable to its adverse effects. Pb crosses the blood-brain barrier, accumulates in susceptible areas, causes an imbalance between reactive oxygen/nitrogen species and endogenous antioxidant defences, which leads to lipid peroxidation, glutathione loss, mitochondrial dysfunction, DNA damage, neuroinflammation and impairment of blood-brain barrier integrity. The result of these oxidative stress-mediated events is neuronal apoptosis, dysfunctional synaptic plasticity and chronic cognitive and behavioural impairments. Curcumin, a polyphenolic compound of *Curcuma longa*, and quercetin, a dietary flavonol, have various neuroprotective properties against free radicals, metal chelating, anti-inflammatory, and signalling-modulatory properties. The experimental research suggests that both compounds decrease the burden of Pb in brain tissue by reinstating superoxide dismutase, catalase, and 8-hydroxytryptophan dehydratase; replenishing glutathione; inhibiting lipid peroxidation; and modulating microglial activation and pro-inflammatory cytokine release. Moreover, curcumin stimulates Nrf2-dependent antioxidant pathways but inhibits NF- κ B. In contrast, quercetin stimulates protein kinase A, Akt, CaMKII, nitric oxide synthase, and CREB signalling, all of which increase neuronal survival and synaptic activity. Oxidative and inflammatory marker normalisation and neurobehavioral effects of curcumin or quercetin are generally more pronounced when co-administered than when given alone, possibly indicating mechanistic complementation and synergy. This paper aims to summarise the existing evidence on oxidative stress-mediated Pb neurotoxicity, critically appraise the modulatory actions of curcumin and quercetin, and emphasise the gaps in the research that need to be addressed in future preclinical and clinical studies.

Keywords

Neurotoxicity of Lead, Oxidative Stress, Curcumin, Quercetin, Neuroprotection, Blood-Brain Barrier, Reactive Oxygen Species, Neuroinflammation.

1. Introduction

Lead (Pb) is a toxicant in the environment and workplace, and it remains an issue because it occurs in almost everything, including air, water, soil, industrial waste, paints, batteries, and household dust. The effects of Pb on the central nervous system are one of the most alarming effects of the substance. Due to its ubiquity, it cannot be avoided, and it enhances regulatory controls in poorer nations. Pb is especially harmful to developing

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children. Any exposure can have harmful effects on a child's learning and behaviour, even in small amounts. Repeated exposure may also have grave effects on cognitive, emotional, and motor functioning in adults.

There are several different mechanisms of neurotoxicity caused by lead (Pb), and the central one is oxidative stress. Lead causes the uncontrolled generation of oxidative stress factors (ROS) and reactive nitrogen species (RNS), in addition to damaging defence mechanisms and enhancing, among others, lipid peroxidation, DNA damage, and mitochondrial dysfunction. In addition, lead neurotoxicity also leads to neuroinflammation, interference with the blood-brain barrier (BBB), and dysregulation of several intracellular signalling pathways, eventually leading to neuronal cell death.

Given the shortcomings of chelation therapy, particularly regarding neuro-cognitive and toxicity, other neuroprotective modulations have been scientifically explored. Plant-based products (Phytochemicals) that have been reported to contain both powerful antioxidant and metal-modulating activities have been considered in this line of approach. Therefore, Quercetin (a widespread dietary flavonoid found in various plant species) and curcumin (a polyphenolic compound derived from the rhizomes of *Curcuma longa*) have been the team's main targets. They also have free-radical-scavenging and anti-inflammatory effects and, to some extent, can cross the blood-brain barrier. In both combination and individual studies, Curcumin (and Quercetin) have been shown to reduce Pb-induced oxidative stress and neuronal damage.

The paper reviews current knowledge of Pb neurotoxicity mediated by oxidative stress and evaluates, specifically, the effect-modifying roles of curcumin and quercetin. It provides a summary of the mechanism, empirical evidence, parallel profiles, and translation prospects to assess their application as supplementary compounds in Pb-exposed at-risk populations.

2. Lead Exposure, Disposition, and Neurotoxicity

2.1 Toxicokinetics and sources of the environment.

There are several possible sources of lead exposure, including drinking water, some foods, industrial emissions, lead paint, batteries, electronic waste, and some traditional medicines and cosmetics. After exposure, lead (Pb) might be ingested or inhaled (more importantly). A route does not matter; Pb enters the gastrointestinal (GI) or respiratory system, is then absorbed through an epithelial layer, and finally enters the bloodstream. When in the bloodstream, some of Pb gets trapped in the erythrocytes, and the rest of Pb is carried to soft tissue (e.g. liver, kidney and most worrisome of all, the brain) where it is deposited in the bone; the bone is a long-term depositor (depot) of Pb. The biological half-life of Pb is weeks, but the half-life of Pb in bone is decades, so chronic exposure to Pb can result from bone sequestration and remodelling.

Lead (Pb) may cross the blood-brain barrier (BBB), and in the brain, Pb is accumulated in the cortex, hippocampus, cerebellum, and basal ganglia. The latter, control and regulation functions, deal with high mental capabilities, learning, memory, and fine and gross motor skills and control. Thus, it is not a secret that lead exposure may have fairly serious neurological effects.

2.2 Neurobehavioral and cognitive.

Psychological and medical doctors have shown that even minimal increases in blood lead levels can affect an individual's social and educational performance. They pay attention to children's low IQ, attention deficits, executive functioning, and academic achievements. The studies further reveal that occupational-related chronic lead exposure in adults has adverse effects on memory and processing speed, destabilises mood, and impairs fine psychomotor activities. Similar behavioural effects are also observed in animal studies based on Pb exposure. These works demonstrate that the effects of lead are adverse in behavioural disorders, and lead deficit also leads to an absence of neuromuscular performance, along with anxiety, spatial learning disability and distorted movement. The reduction in performance across various activities is also due to Pb, which influences and reduces the biases and activity of the new muscular system.

Most impact effects impair the system's psychological and physiological framework. Pb exposure has been shown to inhibit synapse formation, reduce dendritic spines, and induce vitreous changes, accompanied by changes in neural activity and the overlap of neural activity within the network. The main issue in such activities is an increase in systemic oxidation and inflammation.

3. Oxidative Stress and Role in Lead-induced Neurotoxicity.

Oxidative stress is said to take place when the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds the capability of the (antioxidant) systems within the body to neutralize the injury. The brain is particularly vulnerable to stress because the levels of oxygen and polyunsaturated lipids ingested are high, and the levels of inbuilt antioxidant resources are low.

3.1.1 The heightened synthesis of reactive oxygen and nitrogen species.

Lead compounds can generate reactive oxygen species in several ways. The production of superoxide is enhanced through the stimulation of membrane-bound NADPH oxidase, and in particular, microglial cells. Lead compounds interfere with the electron transport chain of mitochondria and thereby enhance electron abandonment and the formation of superoxide. Lead compounds are also known to inhibit nitric oxide (NO) synthesis. They can uncouple nitric oxide synthase, thereby switching nitric oxide generation to the production of reactive nitrogen species such as peroxynitrite. The resultant reactive oxygen species and reactive nitrogen species damage lipids, proteins and nucleic acids, and also participate in redox-sensitive signalling.

3.2 Indefense Deficiency of antioxidants.

The non-enzymatic systems, such as reduced glutathione (GSH), vitamins C and E, and uric acid, are endogenous antioxidant defences. Lead can interfere with the activity of many enzymes by binding to sulfhydryls and other important cofactors. A sensitive enzyme is delta-aminolevulinic acid dehydratase (delta ALAD), a sulfhydryl-containing enzyme in the heme synthesis pathway. The suppression of this enzyme not only leads to heme production but also increases the level of delta-aminolevulinic acid, a precursor of free radicals.

Many experimental models of lead (Pb) exposures exhibit decreased GSH, superoxide dismutase (SOD) and catalase (CAT) levels and increased susceptibility of neuronal membranes and organelles to attack by reactive oxygen species (ROS). These alterations are antecedent to self-perpetuating oxidative stress.

3.3 Membrane lipid peroxidation and injury.

The brain is not spared by the peroxidative degeneration of lipids due to its high volumes of polyunsaturated fatty acids. Reactive oxygen species (ROS) attack membrane lipids, causing peroxidation byproducts, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Such by-products can alter proteins (cross-link), alter the viscosity of membranes, inhibit receptor functions, and interfere with ion transport. High concentrations of MDA, along with other similar compounds, are associated with functional impairment and have been observed in brain tissue from animals exposed to Pb (lead).

3.4 Mitochondrial injury, DNA injury, and programmed cell death.

The Pb (poisoned brain) lead is likely to produce ROS (reactive oxygen species) and RNS (reactive nitrogen species) that may cause the single and double-stranded breaks of the DNA (deoxyribonucleic acid), changes in the bases, and cross-linking of the DNA. The mitochondria are the main mediators of energy production and apoptosis (programmed cell death), and thus are the most affected. Pb (lead) impairs the potential of the inner mitochondrial membrane, suppresses ATP (adenosine triphosphate) generation, and favours opening of the mitochondrial permeability transition pore, whereby released cytochrome c (an apoptosis-inducing molecule) activates the caspases (family of cysteine proteases) to trigger apoptosis. The combination of mitochondrial dysfunction and DNA (deoxyribonucleic acid) damage leads to the loss of specific neurons, decreased neurogenesis, and permanent changes in brain morphology.

3.5 Disruption of neuroinflammation and BBB.

Two closely related processes are neuroinflammation and oxidative stress. Exposure to Pb causes ROS that trigger microglia and astrocytes. These cells produce pro-inflammatory cytokines (e.g., TNF, IL-1, and IL-6), thereby further enhancing ROS production and disrupting neuronal activity and synaptic plasticity. BBB damage due to oxidative stress leads to tight junction dysfunction (e.g., occludin, claudin, zonula occludens), thereby increasing BBB permeability and allowing peripheral toxins and immune cells to gain access to the brain. This worsens local inflammatory and oxidative damage.

Table 1. Representative Oxidative and Inflammatory Changes in Lead-Exposed Brain

Parameter / Process	Typical Change in Lead Exposure
ROS/RNS production	Increased superoxide and RNS; activation of NADPH oxidase
Antioxidant enzymes (SOD, CAT, δ -ALAD)	Decreased activity; inhibition via binding to sulfhydryl sites
Glutathione (GSH)	Depletion due to direct binding and consumption by ROS
Lipid peroxidation (e.g., MDA)	Increased levels indicate membrane lipid damage
DNA integrity	Enhanced DNA strand breaks and oxidative base modifications.
Mitochondrial function	Depolarised membrane potential, reduced ATP, pore opening.
Neuroinflammatory cytokines	Elevated TNF- α , IL-1 β , IL-6 from activated glia
BBB integrity	Disruption of tight junctions; increased permeability

4. Curcumin: A Multifunctional Modulator of Lead-Induced Oxidative Neurotoxicity

4.1 Chemical nature and pharmacokinetic profile

Curcumin is a diarylheptanoid polyphenol, chemically diferuloylmethane, derived from the rhizome of *Curcuma longa* (turmeric). Its conjugated β -diketone structure, with phenolic hydroxyl groups, confers strong free-radical-scavenging and metal-binding capacities. Curcumin is lipophilic, allowing it to partition into cell membranes and cross the BBB to some extent. However, it has limited aqueous solubility and is rapidly metabolised and eliminated, reducing its oral bioavailability. Various strategies, such as adjuvants (piperine), nanoparticles, phospholipid complexes, and analogues, have been developed to overcome this limitation.

4.2 The antioxidant and chelating properties

Direct scavenging of various ROS, such as superoxide, hydroxyl radicals and peroxy radicals, is a direct scavenger of curcumin. It can also chelate metal ions through its diketone and phenolic groups, potentially lowering metal-catalysed oxidative reactions. The curcumin treatment in the Pb exposure models has been known to:

- Restore SOD and CAT activities in the brain and blood.
- Increase GSH content or prevent its depletion.
- Decrease lipid peroxidation markers such as MDA.
- Improve δ -ALAD activity, indirectly supporting heme synthesis and antioxidant capacity.

These effects collectively attenuate the oxidative burden imposed by Pb and help preserve membrane integrity and enzyme function.

4.3 Inflammatory and survival signal transduction.

In addition to such a direct antioxidant effect, curcumin regulates various signalling mechanisms involved in oxidative stress and inflammation. It has been known to affect nuclear factor κ B (NF κ B). This critical transcription factor regulates inflammatory gene expression and activates nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates antioxidant response element-driven genes. Enhancement of endogenous defences by upregulation of Nrf2-dependent enzymes (e.g. heme oxygenase 1, glutamate-cysteine ligase) and suppression of the generation of pro-inflammatory cytokines and adhesion molecules by inhibiting NF- κ B.

Curcumin also influences mitogen-activated protein kinase (MAPK) pathways and can potentially alter Bcl-2 family proteins, caspases, and other apoptotic regulators. The effects have been linked to reduced neuronal loss, maintenance of synaptic proteins, and improved performance in behavioural results in experimental neurotoxic and neurodegenerative models.

4.4 Lead neurotoxicity experimental evidence.

Co-administration of curcumin with Pb has been linked to:

- Reduced levels of Pb in blood and brain, which is consistent with the chelating effect.
- Normalise normal antioxidant enzyme activities and GSH levels.
- Less lipid peroxidation, protein carbonyl formation.
- Reduce the histopathological changes, including neuronal degeneration, vacuolation and gliosis.
- Enhance behavioural test performance in terms of learning, memory and locomotion.

These results indicate that curcumin mitigates Pb-induced oxidative injury, inflammation, and cell death, thereby maintaining neurobehavioral function.

5. Quercetin: A Flavonoid with Neuroprotective and Metal Modulatory Effects.

5.1 Chemical properties and the central nervous system.

Quercetin is a flavonol polyphenol that is produced in abundance in fruits, vegetables, tea, and wine. It possesses numerous hydroxyl groups on its flavone skeleton and exhibits high radical-scavenging and metal-chelating properties. Quercetin can penetrate the BBB but is susceptible to metabolism into various conjugates. Quercetin has antioxidant, anti-inflammatory, and anti-apoptotic effects in the central nervous system across a variety of injury models, including ischemia, trauma, and neurodegenerative diseases.

5.2 Metal modulating and antioxidant mechanisms.

Quercetin inhibits the superoxide, hydroxyl radicals, and peroxynitrite and can inhibit lipid peroxidation in neuronal membranes. It promotes endogenous antioxidant systems by maintaining or improving SOD, CAT, and glutathione-related enzymes and preserving GSH concentrations. Quercetin can bind divalent cations through its metal-binding sites, thereby decreasing redox capacity and tissue deposition.

The quercetin treatment has been linked to Pb-exposed mice:

- Lessening of Pb concentration in blood and brain.
- Lipid peroxidation and oxidative damage of proteins are reduced.
- Re-establishment of antioxidant enzyme functions and re-establishment of biomarkers of oxidative stress.

Such results mean that quercetin corrects the oxidative imbalance caused by Pb by decreasing the Pb load and enhancing cell defences.

5.3 signalling pathways and synaptic dysfunction: Modulation.

Quercetin is also an inhibitor of intracellular signalling pathways important for neuronal survival and plasticity. It has been experimentally demonstrated that quercetin is capable of:

- Stimulate the production of NO and the activity of protein kinase A (PKA).
- Enhance phosphorylation of the protein kinase B (Akt) and calcium/calmodulin-dependent protein kinase II (CaMKII).
- Improve neuronal and endothelial nitric oxide synthase (nNOS, eNOS).
- Upregulate phosphorylated cAMP activity regulator element binding protein (CREB) transcription factor, which is the key to learning, memory and neuroprotection.

Taken together, these alterations work towards enhanced synaptic transmission, neurogenesis and resistance to toxic attacks. Quercetin has also been reported to correct Pb-induced deficits in learning and memory in behavioural paradigms, which align with its molecular activity.

6. Comparison and interactive effects of Curcumin and Quercetin.

6.1 Intersecting and differentiated mechanisms.

Curcumin and quercetin share several characteristics: both are polyphenols, both can chelate metals and scavenge ROS, and both can regulate the activity of redox-reactive transcription factors and inflammatory responses. They, however, also show different preferences in signalling targets and pharmacokinetic behaviour.

Curcumin is particularly known to regulate NF- κ B, Nrf2, and downstream genes involved in inflammatory and antioxidant defence. Although it also inhibits these pathways, quercetin has been particularly highlighted for its effects on PKA, Akt, CaMKII, NOS isoforms, and CREB. Therefore, curcumin may be better positioned to inhibit inflammatory cascades and enhance overall antioxidant effects, while quercetin may be more potent in modulating synaptic signalling and plasticity.

6.2 Protection by synergy or additivity.

Research comparing the effects of curcumin and quercetin when administered together in animals exposed to Pb indicates that the combination usually yields better results than using either compound alone. There are reported benefits in the form of:

- Enhanced decreases in Pb levels in blood and brain, which indicates that they act complementarily and have distribution-modifying effects.
- Even stronger resurgence of SOD, CAT, and δ ALAD functions.

- Increased inhibition of lipid peroxidation.
- Enhanced maintenance of histology and density of neurons.
- Improved behavioural recovery in learning and memory activities.

Mechanistically, synergy is likely due to overlapping antioxidant and metal-binding activities, as well as differences in targeting signalling and gene-regulatory networks. The overall outcome is the widening of protective action against Pb-induced oxidative and inflammatory harm at multiple levels.

6.3 Translational and safety considerations.

The dietary histories of both curcumin and quercetin are extensive, and the two are considered largely safe at traditional consumption levels. Preclinical trials usually use higher doses than can be obtained by diet alone, and in such situations, they tend to be well tolerated. However, concerns about bioavailability, metabolism, and potential drug interactions (e.g., by altering cytochrome P450 or transporter activity) should be addressed before high-dose supplementation can be recommended as standard.

Translational-wise, several issues need to be considered:

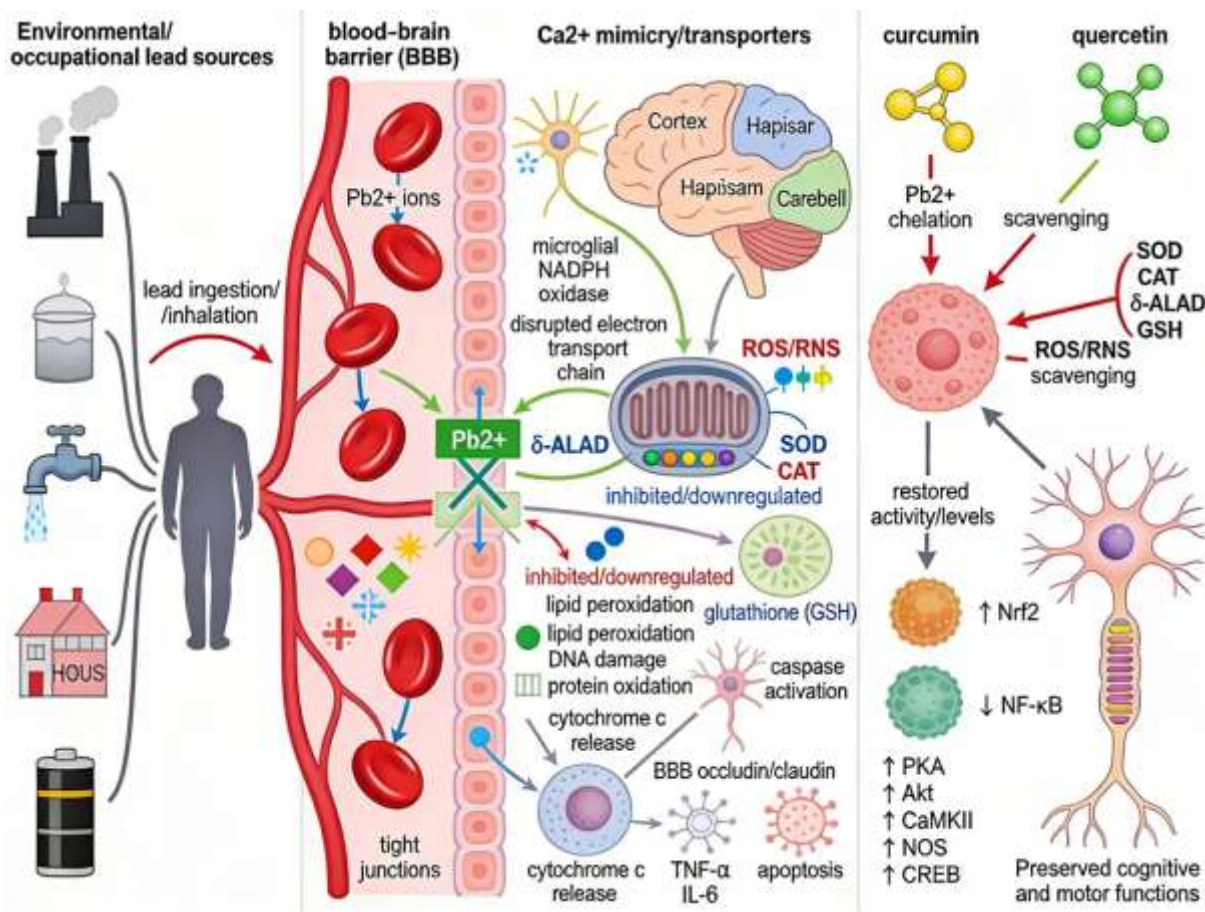
- Formulation optimisation to enhance systemic bioavailability and brain bioavailability.
- Normalisation of dosage schedules and treatment times.
- Long-term safety assessment of pharmacological doses.
- Integration into the traditional chelation therapy in clinical regimens.

Feature	Curcumin	Quercetin	Combination (Curcumin + Quercetin)
Chemical class	Polyphenolic diarylheptanoid	Polyphenolic flavonol	Phytochemical mixture
BBB penetration	Lipophilic, moderate BBB crossing	Crosses BBB as aglycone or metabolites	Both are present in brain tissue
Metal interaction	Chelates Pb and other metals via the β -diketone group	Chelates Pb and other metals via catechol groups	Greater reduction in Pb burden
Antioxidant actions	Scavenges ROS, induces Nrf2, restores SOD/CAT/GSH	Scavenges ROS/RNS, supports SOD/CAT/GSH	Stronger normalisation of redox balance
Anti-inflammatory pathways	Inhibits NF- κ B and related cytokine expression	Attenuates inflammatory mediators and enzymes	Enhanced suppression of neuroinflammation
Synaptic and survival pathways	Modulates MAPKs, the Bcl-2 family, and caspases	Activates PKA, Akt, CaMKII, NOS, CREB	Broader coverage of pro-survival signalling
Effects on behaviour	Improves Pb-induced cognitive and motor deficits	Ameliorates Pb-related learning and memory deficits	Often superior behavioural recovery

Feature	Curcumin	Quercetin	Combination (Curcumin + Quercetin)
Safety (preclinical)	Generally safe at tested doses; bioavailability limits	Generally safe; metabolism and interactions to consider	A combination is usually well tolerated in animals

7. Conceptual Model

Figure 1. Mechanistic overview of lead-induced oxidative neurotoxicity and modulation by curcumin and quercetin



Lead (Pb) enters the body as an environmental and occupational agent (contaminated water, air, paint, batteries) and circulates in the blood, as the majority is bound to erythrocytes. Once systemically distributed, Pb enters the blood-brain barrier, in part, by binding to Ca^{2+} and is deposited in brain regions, including the cerebral cortex, hippocampus, and cerebellum. In the central nervous system, Pb activates microglial NADPH oxidase and impairs mitochondrial electron transport, leading to an excess production of reactive oxygen and nitrogen species. Pb is also bound to sulfhydryl-containing enzymes and glutathione (GSH), and hence antioxidant capability is impaired, and delta-aminolevulinic acid dehydratase, superoxide dismutase and catalase are inhibited. The high level of ROS causes lipid peroxidation, DNA damage, and protein oxidation, and mitochondrial dysfunction leads to cytochrome c release, caspase activation, and neuronal apoptosis. Activated glial and astrocytes secrete pro-inflammatory cytokines (e.g., $\text{TNF-}\alpha$, $\text{IL-1}\beta$, IL-6) that further enhance the oxidative stress and lead to the breakdown of the blood-brain barrier through the destabilisation of tight junction proteins.

Curcumin and quercetin interfere with several steps of this disease pathway. Both phytochemicals chelate Pb and reduce its effective burden on the blood and brain, directly scavenge ROS and RNS, replenish superoxide dismutase, catalase, and GSH levels, and suppress lipid peroxidation. Curcumin mainly increases the Nrf2-initiated antioxidant genes and inhibits the NF κ B-initiated inflammatory signalling. Quercetin, on the contrary, increases the production of nitric oxide and promotes the activation of PKA, Akt, CaMKII, NOS, and CREB pathways and, as a result, improves the functioning of the synapses and provides neurons with the chance to survive. The overall impact of these interventions is to mitigate oxidative stress, neuroinflammation, disruption of the blood-brain barrier, and neuronal apoptosis, thereby preserving cognitive and motor functions.

8. Weaknesses of Existing Evidence.

Even though preclinical data are positive, several limitations limit direct translation to humans:

- Majority of the evidence is based on the controlled Pb exposures of animal and cellular models that do not necessarily reflect human exposure patterns, mixtures, and comorbidities.
- Experimental doses of curcumin and quercetin are usually larger than those possible by diet and may need specialised preparations to be taken by humans.
- There is a paucity of clinical studies examining these compounds in particular as an intervention in populations exposed to Pb, and making more stringent neurocognitive and biomarker outcomes.
- Inter-study variability in animal species, age, dose, and duration of Pb administration, timing of phytochemical administration and outcome measures makes it difficult to compare the results quantitatively.

The solution to these problems will involve standardised experimental designs, more pharmacokinetic characterisation and controlled human studies.

9. Future Directions

Future work should focus on:

- Serial assessment of curcumin, quercetin, and a combination of both during developmental and adult models of Pb exposure, harmonised on the dosage and endpoints.
- Nanoformulations, liposomal systems and conjugates, which improve the stability and brain delivery of the two compounds, were developed and tested.
- The combination of transcriptomic, proteomic and metabolomic methods to chart the entire range of molecular alterations reverted by these phytochemicals. Placebo-controlled clinical trials in a population with high Pb levels are carefully designed to include chelation therapy with curcumin and/or quercetin and to assess blood Pb, biomarkers of oxidative stress and inflammation, neuroimaging, and specific neuropsychological performance.

Those studies would help determine whether these agents can make a significant contribution to neurological outcomes that cannot be achieved through exposure reduction and chelation.

10. Conclusion

The primary adverse effects of lead on the brain are oxidative stress, neuroinflammation, and BBB dysfunction, which together constitute the core of lead's neurotoxicity. Two well-characterised phytochemicals, curcumin and quercetin, have been shown to reverse these processes via complementary antioxidant, anti-inflammatory, metal-chelating, and signalling-modulatory activities. Evidence-based practice: Pipera et al. (2013) consistently demonstrate that all agents can reduce the effects of Pb-induced oxidative injury and neurobehavioral impairments, and that a combination can provide better protection. Even though there are still critical barriers to translation for these compounds (particularly regarding bioavailability,

dosing, and clinical validation), they are viable as adjunct options to address the effects of oxidative stress-induced neurotoxicity in lead-exposed groups.

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