Degenerative Neurological and Neuromuscular Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Manganese-Induced Parkinsonism: A Review of Etiologies and Treatments

Nitish M Khindri*, Mary C Maj*

School of Medicine, St. George's University, Grenada, West Indies

*These authors contributed equally to this work

Correspondence: Nitish M Khindri, Department of Biochemistry, School of Medicine, St. George's University, Grenada, West Indies, Email nitish85288@gmail.com

Abstract: Parkinson's disease is a neurodegenerative disorder that leads to neuronal loss. Though a variety of genetic and environmental factors may be involved in the etiology, the presentation of the disorder is very similar. Trace minerals such as manganese are essential for brain development and function though effective concentrations are paramount. Exposure to high concentrations of manganese is known to cause neurotoxicity and has been recently associated with manganese-induced parkinsonism, which will be explored in this review. This review synthesizes findings from peer-reviewed clinical, epidemiological, and experimental studies to explore the underlying mechanisms and contributing factors of manganese-induced parkinsonism. Specifically, it examines alterations in lipidomic and oxidative profiles, enhancement of redox cycling, transporter dysfunction and deficiency, ion homeostasis, dysregulation of signaling pathways and autophagy, mRNA disruption, dopamine toxicity, manganese contamination, and neuroprotective mechanisms. Preventative and therapeutic interventions—including chelation therapy with ethylene-diamine-tetra-acetic acid ($CaNa_2EDTA$), with or without plasma exchange and para-aminosalicylic acid (PAS), as well as natural compounds such as vinpocetine (VIN), punicalagin (PUN), niacin, vitamin E, DNLA, curcumin, and sesame oil—are also reviewed. Given manganese's role as an oxidant in the synthesis of neurotoxic compounds, therapeutic strategies targeting both manganese, its associated molecular pathways, and its downstream neurotoxic effects may represent the most promising direction for future research.

Keywords: oxidative stress, manganese transporters, yin yang 1 transcription factor, protein kinase C delta, neuroprotection, chelation

Introduction

Parkinson's Disease

With the increasing prevalence of Parkinson's disease, there is an ever-growing topic of interest in the puzzle surrounding its causes. Especially since this understanding can then clue in on therapeutic strategies for parkinsonism. Environmental causes of these symptoms are also of interest such as toxic exposure to manganese.

The clinical features related to parkinsonism are very similar regardless of the etiology. Idiopathic Parkinsonism is typically referred to as Parkinson's disease. Parkinson's disease presents with motor symptoms such as resting tremors, bradykinesia, and rigidity. Nonmotor symptoms are also present such as cognition, gastrointestinal motility, and rapid eye movement sleep behavior disorder.[1]

The pathophysiology involves potentially starting in the medulla and olfactory bulb and ending in the midbrain where the substantia nigra pars compacta is located.[1] As the medulla is the origin of the vagus nerve, a theory exists that the intestine may be the origin of Parkinson's disease because α-synuclein tends to spread to the vagus nerve from the intestinal wall.[2] As the substantia nigra pars compacta is an important source of dopamine in its nigrostriatal pathway, the dopaminergic neuronal loss is followed by symptomatic treatments with dopamine agonists, carbidopa-levodopa, monoamine oxidase B inhibitors, and deep brain stimulation for the motor symptoms. On the other hand, the non-motor symptoms may be treated with serotonin reuptake inhibitors or cholinesterase inhibitors.[1] The symptoms can only be treated due to it being unknown how Parkinson's disease initiates.

Received: 21 June 2024
Accepted: 21 May 2025
Published: 6 June 2025

Another feature found in Parkinson's disease is the presence of Lewy bodies, which are abnormal aggregations of many proteins, including mainly α-synuclein. Lewy bodies are found in the nucleus basalis of Meynert, locus coeruleus, and the substantia nigra, which are also the areas of neurodegeneration in Parkinson's disease.[3] A significant part of the nonmotor diagnosis for Parkinson's disease is dementia. However, both Parkinson's disease dementia and Lewy body dementia can have similar symptoms, so it is important to differentiate between the two. If a patient begins experiencing cognitive symptoms after 12 months, then they are considered to have Parkinson's disease with dementia, and if the symptoms begin before 12 months, then they are generally considered to have Lewy body dementia.[4]

Manganese-Induced Parkinsonism

Manganese-induced parkinsonism is a condition that develops from excessive exposure to manganese and leads to neuropathology. This exposure leads to manganese levels beyond the normal range of 7 to 12 μg/L in whole blood and 0.6 to 4.3 μg/L in serum.[5] Moreover, manganese-induced parkinsonism presents with symptoms concerning one's general constitution, neurobehavior, dystonia, and motor symptoms of parkinsonism.[6] It is important to note that the dystonic and Parkinsonian symptoms, or extrapyramidal side-effects, seen in manganese-induced parkinsonism, such as oculogyric crisis, torticollis, rigidity, and bradykinesia, can also be seen when antipsychotics affect the nigrostriatal dopamine pathway.[6,7] Specifically, research has shown that the globus pallidus of the basal ganglia is implicated in the area of manganese neurotoxicity, the substantia nigra pars compacta seems to have no disturbances, and that there are no Lewy bodies.[8] This presents significant differentials when comparing manganese toxicity to Parkinson's disease; however, it is important to understand that Perl & Olanow discuss manganism and not manganese-induced parkinsonism.[8] An individual's exposure intensity, duration, and genetic susceptibility may be involved in determining which condition develops regardless of similar motor symptom presentations. For instance, in acute durations of high doses of manganese, manganism may be the most likely diagnosis because of an effect on the globus pallidus. However, in chronic durations of low doses of manganese, parkinsonism may be present because of an effect on the entire basal ganglia, which then implicates the substantia nigra pars compacta.[9] Low doses of manganese over long periods more accurately reflect environmental situations and may be implicated in why long-term occupational exposures to manganese can be diagnosed as manganese-induced parkinsonism.

Even if the general areas of neuropathology are known, we do not know exactly the reasons for neurotoxicity, so it is important to discuss the known potential causes, mechanisms, and treatments.

Methods

To explore the connection between manganese exposure and parkinsonism, I gathered and reviewed a range of peer-reviewed sources, including clinical studies, mechanistic papers, and scholarly reviews that touch on idiopathic Parkinson's disease as well as manganese-induced forms of the condition. Most of the material was found through searches in databases like PubMed, ScienceDirect, and a few university-hosted repositories. I used search terms such as "Parkinson's disease", "manganese neurotoxicity", "dopaminergic neurodegeneration", "manganese AND parkinsonism", and "glutamate dysregulation", among others, depending on what each platform returned.

The review draws from a wide timespan—starting with early research from the 1980s and continuing through to studies published as recently as 2023. I used a narrative literature review framework, which allowed for a broader synthesis of environmental, genetic, and biochemical findings relevant to the topic.

Priority was given to peer reviewed sources that offered insight into the main themes of Parkinson's disease and manganese-induced parkinsonism, such as from the mechanistic and therapeutic standpoint. Therefore, I excluded studies that focused on other neurodegenerative conditions like Alzheimer's or Huntington's disease unless there was an overlap with parkinsonism. I also excluded articles that repeated the findings from articles already mentioned and did not offer new data or perspectives.

Results

Mechanisms and Causes

The SLC30A10 is a manganese efflux transporter that is found in high concentrations in the liver and basal ganglia nuclei that reduces manganese levels in cells and protects against manganese toxicity. Deficiencies in this process are typically

inherited through an autosomal recessive fashion, as reviewed by Guilarte & Gonzales.[10] As a result, an individual with such a deficiency will have a higher susceptibility to manganese toxicity as manganese will continue to stay trapped inside cells without their efflux function. For example, Kwakye et al reviewed that deficiency of SLC30A10 activity can cause significant increases of manganese in the blood, liver, and brain.[11–15] A study by Lechpammer et al followed a patient with homozygous SLC30A10 mutations and the resulting autopsy revealed significant levels of manganese in the liver and brain.[12] A study by Quadri et al followed two families to show how the involvement of SLC30A10 mutations can result in similar neurological and hepatic symptoms. They used rodents to show that the greatest amount of SLC30A10 expression is in the liver, intestine, and central nervous system (CNS) with quantitative reverse transcription polymerase chain reaction (qRT-PCR) assays.[13] Tuschl et al discovered an autosomal recessive disorder in which there were significant extrapyramidal effects, polycythemia, and manganese levels.[14] In another study, Tuschl et al identified Parkinsonian symptoms in individuals from two consanguineous families carrying SLC30A10 mutations, alongside hyperintensities observed in the basal ganglia via T1-weighted magnetic resonance imaging (MRI), and liver damage attributed to elevated manganese deposition.[15]

SLC39A14 is a manganese influx transporter that can similarly lead to manganese toxicity in the blood and brain with a loss-of-function mutation, which can then lead to parkinsonism in patients.[16] Rodichkin et al followed SLC39A14 knockout mice and reported a 68-fold increase in blood manganese levels in males and a 55-fold increase in females.[17] In another SLC39A14 knockout study, there was a reduced amount of manganese in the liver and gallbladder when manganese was injected subcutaneously.[18] This demonstrates that SLC39A14 is active in the liver and biliary systems and that the uptake of manganese into the liver is dysfunctional with the mutation. When manganese is not available to be excreted into bile, it makes sense that it would accumulate to toxic levels in the blood and brain, as evidenced by the elevated observed levels in the study.[18] It also makes sense why patients with the SLC39A14 mutation do not have liver dysfunction, while patients with SLC39A10 do.[19] Furthermore, Mukhopadhyay reviews the fact that since patients, mice, and zebrafish without SLC39A14 have elevated brain manganese, the transporter may not be involved in neuronal cell function.[16,20]

Another transporter that may be involved in manganese-induced parkinsonism is the sodium-coupled neutral amino acid transporter 3 (SNAT3). Sidoryk-Wegrzynowicz & Aschner review that SNAT3 is involved with glutamine transport in astrocytes and that it may be the most manganese-sensitive transporter in astrocytes.[21] Moreover, protein kinase C (PKC) signaling resulting from manganese exposure may be involved in the ubiquitination of SNAT3 and its resulting proteolysis according to a prior study by Sidoryk-Wegrzynowicz et al.[22] Sidoryk-Wegrzynowicz & Aschner further review that glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1) are also affected by being downregulated by manganese exposure and that it may also be a result of PKC signaling according to prior 2009 and 2012 studies.[21–23]

The yin yang 1 (YY1) transcription factor may be involved in the downregulation of GLT-1 and GLAST in manganese exposure. For instance, Karki et al review that manganese-induced tumor necrosis factor-alpha (TNF-α) release from astrocytes may increase nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), YY1 promoter activity, and then a reduction in GLT-1 expression.[24] In addition, YY1 overexpression is associated with a significant decrease in GLAST expression in cultured Bergmann glial cells, which are specialized astrocyte cells from the cerebellar cortex.[25]

In the review by Sidoryk-Wegrzynowicz & Aschner, it was stated that increased caspase-3, protein kinase C delta (PKCδ) activity, resulting in cell apoptosis may be associated with manganese treatment.[21] Furthermore, mesencephalic dopaminergic cells with mutants of PKCδ, such as its catalytically inactive and caspase cleavage-resistant protein forms, are resistant to apoptosis after manganese treatment.[26]

In chronic liver failure, the body may not be able to clear manganese from the bloodstream; consequently, a toxic amount may accumulate and result in hyperintensities of the globi pallidi and substantia nigra in T1-weighted MRI.[27] Direct occupational exposure to manganese can also occur, such as through industrial and vehicular emissions, and these chronic emissions have been linked with earlier onsets of parkinsonism.[28] Furthermore, occupational exposures to iron, copper, lead, mercury, and manganese have possible links to neuropsychological and motor symptoms.[29] For example, Gonzalez-Guyar et al have shown through inductively coupled plasma-mass spectrometry (ICP-MS) that manganese concentrations are higher in olfactory tract and bulb tissues in exposed mineworkers in comparison to non-exposed individuals.[30] Since the olfactory tract and bulb tissues were involved, it may indicate the ability for manganese to enter the CNS through the nasal pathway. The study also showed that cumulative exposure of manganese over time was more

indicative of higher tissue concentrations than recent exposure.[30] Prolonged manganese exposure due to nearby smelters in South Africa demonstrated significantly lower cognitive performance in individuals from a high-exposure community than in a low-exposure one.[31] On the other hand, a study with 811 welders may indicate the risks for developing parkinsonism related to both short and long-term exposure, as there was a U-shaped dose–response relationship between years of exposure and parkinsonism.[32] Diffusion Basis Spectrum Imaging (DBSI), a specialized MRI technique, has revealed findings of neuroinflammation in white matter and signs of swelling in the caudate nucleus linked with increased manganese and parkinsonism.[33]

In 2007, an interesting case study demonstrated that a patient's Parkinsonian symptoms may be related to their self-prepared drug use. The patient's bradykinesia, motor deficits, and T1-MRI hyperintensities of the basal ganglia were attributed to his daily use of a methcathinone hydrochloride (ephedrone) solution formed from pseudoephedrine hydrochloride and potassium permanganate.[34] Potassium permanganate is a useful oxidant in organic chemistry, which explains its use in the formation of Ephedrone.[35,36] Since potassium permanganate's chemical formula has manganese, the patient's symptoms may be related to manganese poisoning.

Another concerning exposure to manganese may be from lithium-ion batteries containing materials like nickel manganese cobalt (NMC). In a study using C57BL/6J mice, inhalation of NMC particles led to oxidative stress, disruptions in the lung microenvironment, and evidence of liver and kidney toxicity.[37] Wang et al observed NMC deposition in lung tissue and suggested systemic distribution through the bloodstream as a mechanism for damage to other organs.[37]

In an experimental study, mice and a mouse dopaminergic neuronal cell line (MN9D cells) were used to investigate the oxidative effects of manganese overexposure. After intraperitoneal injections of manganese chloride ($MnCl_2$) for 14 days, the collected midbrains of the mice exhibited significant alterations in 12 lipid subclasses, as determined by liquid chromatography-mass spectrometry (LC-MS), with notable decreases in sphingomyelin levels. The reduction was associated with biosynthesis downregulation and upregulation of sphingomyelinase activity in the midbrains, as detected with qRT-PCR assays.[38] In addition to lipidomic disturbances, the midbrains showed reduced activity of antioxidant enzymes, including glutathione peroxidase, glutathione, and superoxide dismutase, alongside increased malondialdehyde (MDA) levels.[38] Neurobehavioral assessments on randomly selected mice after the treatments showed Parkinson-like motor deficits. Similarly, MN9D cells treated with $MnCl_2$ exhibited increased reactive oxygen species (ROS) and MDA, further supporting oxidative damage induced by manganese.[38]

Manganese may be responsible for neurotoxicity in the presence of dopamine derivatives. For example, dopamine can form cysteinyl-dopamine naturally in the brain, which can potentially react with hypochlorite to form a dopathiazine, DTZ-2.[39] In the presence of manganese, DTZ-2 undergoes redox cycling that results in the formation of ROS, but it is noteworthy that nonphysiological amounts of hypochlorite were used in the formation of DTZ-2.[39] Nachtman et al also explained that manganese is involved in the autoxidation of dopamine.[40]

The NF-κB signaling pathway has been implicated in possible manganese-induced neuroinflammation in microglia and astrocytes, and it has been demonstrated that 17-β-estradiol (E2) provides significant inflammatory resistance in the striatum of juvenile mice.[41] Mice exposed to manganese contamination have shown manganese toxicity to be higher in the male mice in comparison to the female mice in a contaminated water sediment exposure model, which indicates a possible protective factor for female mice.[42] The study by Rodichkin et al on SLC39A14 knockout mice also showed a greater increase in manganese in male mice than in female mice.[17] As such, one's biological sex can be important in considering manganese sensitivity.

Zhang et al state that the cyclic guanosine-adenosine synthase (cGAS)−stimulator of interferon genes (STING) pathway is involved in manganese neurotoxicity.[43] They hypothesize that the mechanism involves manganese increasing the susceptibility of cGAS to activation and subsequently increasing the expression of interferon using the STING protein, resulting in neurodegeneration.[43] They also note that since ROS can activate the cGAS-STING pathway both directly and indirectly—by causing mitochondrial DNA leakage—this may represent another modality of manganese neurotoxicity, given that manganese increases ROS production.[43] Recent findings suggest that the cGAS-STING pathway and ferroptosis—a type of programmed cell death—are functionally interconnected, with oxidative stress and mitochondrial dysfunction serving as shared triggers that promote both immune activation and regulated cell death, with manganese potentially exacerbating this interplay.[43] Lastly, the cGAS-STING pathway may promote NF-κB inflammation, and in turn, NF-κB enhances and prolongs STING signaling by preventing its degradation.[44]

In astrocytes, it has been observed that manganese treatment is linked with reducing cell viability, increasing ROS, triggering the JNK signaling cascade, and activating the FOXO3a transcription factor, which promotes apoptosis.[45] Simultaneously, in microglia, manganese downregulates SIRT1—a key NAD^+-dependent deacetylase—compromising its regulatory control over FOXO3a-mediated autophagy and thus may reduce clearance and increase neuroinflammation.[46] Adding another layer, manganese can interfere with SIRT1's ability to deacetylate the growth arrest and DNA damage-inducible protein 34 (GADD34) regulatory protein, resulting in a persistent integrated stress response (ISR).[46] Together, these studies show that manganese may initiate a cascade involving JNK signaling and the disruption of SIRT1.[46]

Manganese neurotoxicity may also have mechanisms related to nitrosylation, mitochondrial dysfunction, and autophagy. For example, Liu et al have proposed that manganese exposure can cause the S-nitrosylation of PINK1, which impairs translocation of Parkin to damaged mitochondria, disrupts mitophagy, and increases mitochondrial-induced apoptosis, as demonstrated in their study using primary neuronal cultures.[47] This modification can also prevent the degradation of ZNF746, a repressor of PPARGC1A, thereby impeding PPARGC1A-mediated mitochondrial biogenesis, according to another study by Liu et al.[48] Additionally, manganese has been found to increase α-synuclein expression, which subsequently aggravates mitochondrial injury by disrupting PINK1/Parkin-mediated mitophagy and increasing neurotoxicity.[49] Experimentally, manganese-induced overexpression of α-synuclein has also been seen to result in the accumulation of synaptic vesicles due to the dysregulation of Rab26-dependent autophagy.[50] Sun et al suggest that the α-synuclein accumulation may be a result of the activation of the $GABA_BR$ receptors and ATP-sensitive K(+) channels.[51] They also found that the downstream neurotoxicity may occur through the activation of calmodulin and subsequent stimulation of calmodulin-dependent protein kinase (CaMK), which in turn promotes phosphorylation of the cAMP response element–binding protein (CREB) transcription factor.

As ion homeostasis is important in preventing neurotoxicity, it is clear why the clearance of synaptic vesicles with Rab26-dependent autophagy is significant.[50] Similarly, the presence of manganese causes changes in the expression and activity of the α3 isoform of Na+, K+-ATPase in the striatum and cerebellum of mice.[52] As Na+, K+-ATPase is an active transporter responsible for maintaining the Na+ and K+ balance in cells, any disruption may be neurotoxic to cells. However, the cognitive and motor deterioration seen in the manganese-exposed mice of this study did not correlate with the changes in Na+, K+-ATPase activity.[52]

The s-nitrosylation of other signaling proteins, such as JNK, Bcl-2, and Ikkβ, in the presence of manganese has also been associated with the dysregulation of autophagy.[53] Ma et al describe that the S-nitrosylation of Bcl-2 inhibits its phosphorylation and causes it to bind more tightly to Becilin1, leading to a suppression of autophagy.[53] They also state that the S-nitrosylation of Ikkβ leads to reduced phosphorylation of AMPK, resulting in the activation of the mTOR pathway, which disrupts autophagy.[53] Both in vivo and in vitro experimentation using cultured neurons and animal models have shown that mTOR activation with excessive manganese can cause the inhibition of autophagy and neuronal apoptosis.[53,54]

According to Yang et al, manganese exposure can activate neuroprotective autophagy and anti-inflammatory microglial M2 polarization to counteract neurotoxicity from endoplasmic reticulum stress.[55] They explain that manganese may result in a decrease in the active form of GSK-3β, which can then promote autophagy via ULK1 signaling. Simultaneously, manganese exposure can cause the activation of the signal transducer and activator of transcription 3 (STAT3) signaling pathway and limit neuroinflammation by supporting M2 polarization of microglia.[55,56]

Microglial leucine-rich repeat kinase 2 (LRRK2) may have increased activation and expression with manganese.[57,58] Pajarillo et al show that LRRK2 G2019S knock-in mice and BV2 microglia transfected with the human G2019S mutation exhibited increased inflammatory markers in comparison to the wild types with manganese treatment.[58] The mice had increased levels of LRRK2 protein, TNF-α, IL-1β, and activation of the NLRP3 inflammasome in the striatum and midbrain, with a greater increase in the knock-in mice.[58] Similarly, the BV2 microglia showed increased TNF-α, IL-1β, and NLRP3 inflammasome activation, with a greater increase in G2019S-transfected BV2 microglia.[58] Furthermore, through Western blotting, there was increased RAB10 activation in its phosphorylated form seen in both BV2 cells and mice, especially with the G2019S mutation, that may lead to autophagy impairment.[58] RAB10 activation was shown by increased levels of its phosphorylated form—detected through Western blotting—in both manganese-exposed microglial cells and LRRK2 mutant knock-in mice, highlighting its role in disrupted autophagy.[58]

The dopaminergic Repressor Element Silencing Transcription factor/Neuron-restrictive Silencing Factor (REST/NRSF) may also have a role in preventing manganese neurotoxicity.[59] Pajarillo et al used REST conditional knockout mice to show increased vulnerability to manganese.[59] Additionally, upon infusion of REST-expressing adeno-associated viral vectors to restore REST in the substantia nigra of knockout mice, there was decreased neurotoxicity and motor symptoms.[59]

Another protective mechanism may involve circular RNA (circRNA) circREST, which has been found to be significantly downregulated in manganese-treated neuroblastoma cells in a study by Lu et al.[60] CircREST acts as a sponge for miR-6914-5p, a microRNA that represses Ephb3 to reduce manganese.[60] Sequestering miR-6914-5p indirectly may upregulate Ephb3 to prevent apoptosis.[60] Overexpression of circREST and Ephb3, as well as inhibition of miR-6914-5p, was shown to reduce manganese-induced apoptosis in neuroblastoma cells.[60]

Western blot and qPCR analyses suggest that the MEK5 and ERK5 kinase proteins are significantly upregulated with manganese exposure.[61] The MEK5/ERK5 pathway may have a neuroprotective role, since when inhibited, there is greater ROS production and apoptosis in MN9D dopaminergic cells.[61]

The disruption of the blood–brain barrier (BBB) may be an important mechanism of manganese neurotoxicity through the reduction of tight junction proteins, like Occludin.[62] The proposed mechanism is the activation of RhoA, a small GTPase, and Rho-associated protein kinase 2 (ROCK2), leading to the disruption of the BBB.[62] Moreover, whenever Occludin is over-expressed, BBB damage is reduced, which further supports the protective role of tight junction proteins.[62]

Mitochondrial damage is a potential component of manganese neurotoxicity. One proposed mechanism involves oxidative damage resulting from decreased histone acetyltransferase lysine acetyltransferase 2A (KAT2A), subsequent decrease in H3K36ac levels, and thus a disruption of the H3K36ac-dependent antioxidant pathway.[63] Liu et al propose the subsequent increased oxidative stress causes mitochondrial damage in the nervous system.[63]

In summary, when the liver is unable to clear manganese from the bloodstream, such as in chronic liver failure, or when there are SLC30A10 and SLC39A14 mutations in cells, manganese toxicity can occur. Other significant amino acid transporters, such as SNAT3, GLAST, and GLT-1 from the CNS, may be affected by manganese toxicity through PKC signaling and YY1 transcription upregulation. The conditions that can facilitate manganese toxicity are industrial exposure, occupational exposure, self-made ephedrone use, and NMC found in lithium-ion batteries. In addition, prolonged exposure to manganese in certain environments, such as mining and smelting regions, has been associated with earlier-onset parkinsonism, suggesting the cumulative effects of manganese are a concern. In manganese over-exposure, increased oxidative stress, sphingomyelinase activity, and lipid metabolism disorders are seen. Dopamine-derived neurotoxins, like DTZ-2, can form ROS in the presence of manganese. Moreover, manganese toxicity may activate the cGAS-STING pathway, which plays a critical role in neuroinflammation and immune activation, further contributing to neuronal damage. Dopaminergic cell death can also be caused by manganese-dependent activation of PKCδ by caspase-3 or through the NF-κB signaling pathway, with estrogen acting as a potential protective factor. Neuroprotective mechanisms involving kinase proteins, histone acetylation, and the BBB may be disrupted with manganese exposure. Additionally, disruptions in autophagy pathways, including those mediated by SIRT1/FOXO3, LRRK2, and circREST, may further exacerbate neuroinflammation and contribute to neurodegeneration in manganese exposure (See Table 1 for a summary of mechanisms and causes with categories and references).

Table 1 Summary of Mechanisms and Causes for Manganese-Induced Neurotoxicity

Category	Mechanism	Cause / Description	Key Refs
Transporter Dysfunction	SLC30A10, SLC39A14, SNAT3, GLAST, GLT-1	Genetic mutations or manganese exposure disrupt efflux/influx and amino acid transport, leading to systemic or brain Mn accumulation.	[10–23]
Transcriptional Regulation	NF-κB, YY1, FOXO3a, CREB, REST/NRSF	Manganese activates or disrupts transcription factors (NF-κB, FOXO3a, CREB) linked to inflammation, apoptosis, and stress; REST loss increases vulnerability.	[24–26,45,59]

(*Continued*)

Table 1 (Continued).

Category	Mechanism	Cause / Description	Key Refs
Liver Failure	Impaired hepatic clearance of manganese leading to systemic accumulation	Manganese build up in brain, especially in the globus pallidus and substantia nigra	[27]
Contamination	Mineworkers, smelter proximity, welding, NMC	Exposure via inhalation leading to manganese deposition in the CNS and major organ tissues	[30–33,37]
Dopamine Toxicity	DTZ-2	DTZ-2 undergoes redox cycling to form ROS in the presence of manganese.	[39,40]
Neuroimmune Pathways	cGAS–STING Pathway, Ferroptosis, NLRP3 Inflammasome	Mn increases cGAS sensitivity and ROS, triggering interferon expression via STING, promoting neurodegeneration; ferroptosis and STING-NF-κB feedback loop exacerbate inflammation. Mn also upregulates inflammasome pathways (eg, NLRP3 via LRRK2 mutation).	[43,44,57,58]
Epigenetic/miRNA Disruption	circREST–miR-6914-5p–Ephb3 Axis	Mn downregulates circREST, leading to miR-6914-5p repression of Ephb3, promoting apoptosis. Restoration of circREST reduces toxicity.	[60]
Mitochondrial Dysfunction	PINK1/Parkin Impairment, ZNF746, Oxidative Stress, KAT2A/H3K36ac Disruption	Mn impairs mitophagy by S-nitrosylating PINK1, increases α-synuclein expression, disrupts mitochondrial biogenesis via ZNF746, and decreases KAT2A–H3K36ac antioxidant pathway.	[47–49,63]
Autophagy Dysregulation	SIRT1-FOXO3a Axis, GADD34, Rab26, Bcl-2/Beclin1, AMPK-mTOR	Mn reduces SIRT1 activity, activates JNK-FOXO3a cascade, inhibits GADD34 regulation, causes α-synuclein overexpression, disrupts Rab26-mediated vesicle clearance, and impairs autophagy via mTOR or tight Bcl-2–Beclin1 binding.	[45,46,50–54,58]
Ion Homeostasis	Na^+, K^+-ATPase α3 Isoform	Mn changes expression/activity in striatum and cerebellum, but dysfunction may not correlate directly with behavioral decline.	[52]
Signaling Pathways	JNK, STAT3, ULK1, MEK5–ERK5, RhoA–ROCK2	Mn activates pro-apoptotic (JNK), anti-inflammatory (STAT3), autophagic (ULK1), and neuroprotective (MEK5–ERK5) pathways. RhoA–ROCK2 activation reduces BBB tight junctions.	[45,55,56,61,62]
Protein Modifications	S-Nitrosylation of PINK1, JNK, Bcl-2, Ikkβ	Mn-induced nitrosylation impairs mitophagy and autophagy, reduces phosphorylation (eg, of AMPK), activates mTOR, suppresses Beclin1, and promotes cell death.	[47,53]
α-Synuclein & Synaptic Toxicity	α-Synuclein Overexpression, Rab26 Vesicle Accumulation, GABABR Activation	Mn-induced α-synuclein expression disrupts vesicle turnover and mitophagy; GABABR signaling may drive downstream CaMK and CREB activation, contributing to toxicity.	[49–51]

(*Continued*)

https://doi.org/10.2147/DNND.S482018

Table 1 (Continued).

Category	Mechanism	Cause / Description	Key Refs
Neuroprotective Mechanisms	M2 Microglial Polarization, REST/NRSF, circREST, MEK5/ERK5, Occludin (BBB integrity)	Mn can trigger compensatory protective responses (autophagy, M2 polarization, REST restoration, MEK5/ERK5 signaling, tight junction maintenance). Their dysregulation or failure enhances neurotoxicity.	[55,56,59–62]

Abbreviations: NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; CREB, cAMP response element–binding protein; REST, Repressor Element Silencing; cGAS, cyclic GMP-AMP synthase; ROS, reactive oxygen species; STING, stimulator of interferon genes; LRRK2, leucine-rich repeat kinase 2; KAT2A, acetyltransferase lysine acetyltransferase 2A; GADD34, DNA damage-inducible protein 34; STAT3, signal transducer and activator of transcription 3.

Treatments

A diagnostic criterion for manganese poisoning has been the effectiveness of levodopa in which there is not supposed to be a significant response. For instance, patients with manganese or ephedrone intoxication are believed to generally not be responsive to levodopa.[64,65] Yet, if the entire basal ganglia, including the substantia nigra pars compacta, is affected by low doses of manganese overtime, then levodopa may result in a positive treatment response as reviewed by Lucchini & Tieu.[9] In this case, levodopa will only treat the motor symptoms of manganese-induced parkinsonism but not the underlying manganese toxicity and damage.

Preventive treatments are also important, such as in situations of increased manganese levels in water supplies. For example, increased manganese levels in drinking water have been associated with a decrease in performance IQ and an increased risk of attention-deficit hyperactivity disorder (ADHD).[66,67] C57/BL6 mice have been used to show that manganese-contaminated sediment exposure to drinking water may result in reduced toxicity and motor symptoms in comparison to exposures of just manganese in water.[42] This is likely because manganese bound to sediment is less bioavailable to be absorbed in the gastrointestinal tract and accumulate in the brain.[42]

Vinpocetine, punicalagin, niacin, and vitamin E have been shown to be neuroprotective in Sprague Dawley rats that were exposed to manganese-induced imbalances in monoamines, excitatory and inhibitory neurotransmitters, MDA, cytokines, and inflammatory biomarkers. Additionally, the cerebral cortex, hippocampus, and striatum had slowed degeneration. Neuroprotection was enhanced with a combination of all the factors in the presence of manganese.[68] As for why vitamin E may be neuroprotective, Song et al describe that it may upregulate cholinergic receptor muscarinic 1 (CHRM1) and potassium inwardly rectifying channel subfamily J member 4 (KCNJ4) expression in the substantia nigra of C57BL/6 mice.[69] Since CHRM1 is a muscarinic acetylcholine receptor, it may increase cholinergic signaling, and since KCNJ4 is a potassium channel, it may help maintain resting membrane potential in the CNS.[69]

$CaNa_2EDTA$ can be used in chelation therapy for patients diagnosed with manganese-induced parkinsonism even though it has been traditionally used for treating lead poisoning. The recommended short-term chelation therapy is intravenous $CaNa_2EDTA$ twice daily for 20 mg/kg for 5 days to check for the effectiveness of the treatment. Once confirmed, long-term treatment is a monthly 5-day course of intravenous $CaNa_2EDTA$ with the same dosing and schedule.[70] In one study, when chelation treatment with 2 grams of intravenous $CaNa_2EDTA$ was performed on seven workers, the majority of patients showed greatly improved clinical outcomes in the regression of parkinsonism symptoms.[71] This clinical follow-up study did not specify the schedule of the treatment, but it did state that it was carried out throughout the years 1998–2004.[71] $CaNa_2EDTA$ therapy has also been used on a Korean patient with a mutation in the SLC39A14 transporter, who first received parenteral $CaNa_2EDTA$ at 500 milligrams per day for five consecutive days every 3 weeks and then later received 1 gram twice once a week for a 5-year period.[72] There were no significant side effects from $CaNa_2EDTA$ over the period, and it resulted in a significant decrease in serum manganese levels from 222.9 μg/L to a stable range of 37.5 μg/L to 41.9 μg/L.[72] Furthermore, there were significant decreases in T1-MRI hyperintensities over a 4, 12, and 36-month treatment period.[72] Tuschl et al show that a 5-year-old patient with an SLC30A10 mutation had a major reduction in motor symptoms after receiving $CaNa_2EDTA$ at 500 milligrams per day for five consecutive days.[20] Although the discussed studies do not mention significant adverse effects in the patients

receiving $CaNa_2EDTA$, it is important to note that some possible adverse effects may include hypocalcemia, nephrotoxicity, hypoglycemia, hypotension, and trace metal and vitamin deficiencies.[73]

Para-aminosalicylic acid (PAS) has also been shown to be effective in treating chronic manganese exposure as a chelator. Treatments may reverse memory and learning issues, reduce Parkinsonian motor symptoms, and restore antioxidant enzymes.[74–76] The dosing schedule of PAS for manganese toxicity seems to be higher than EDTA in patients. For example, both Jiang et al and Shuqin et al report using 6 g/day via intravenous drip to alleviate manganese poisoning.[74,76] In rat basal ganglia neurons exposed to $MnCl_2$ for 24 hours, PAS concentrations of 50 μM, 150 μM, and 450 μM had dose-dependent protective effects, which may explain why higher concentration treatments are beneficial.[75] However, some adverse effects to be wary of are abdominal pain, nausea, diarrhea, and hypothyroidism.[77,78]

Complementary medicine has been explored to improve the outcome of traditional treatments. Natural extracts have been shown to increase available cellular antioxidants, decrease apoptosis, restore neurotransmitters, restore reproductive function, reduce oxidative stress, and chelate heavy metals.[79,80] For example, Echium amoenum (E. amoenum) extract has been shown to reduce neurotoxicity in manganese-poisoned rats because of its anti-inflammatory properties, reduce ROS, and increase catecholamines.[79,80] Alkaloid compounds extracted from the orchid plant Dendrobium nobile Lindley have also been shown to be neuroprotective.[81] Dendrobium nobile Lindl. alkaloids (DNLA) alleviated manganese in pretreated cells and restored PINK1 and Parkin levels.[81] Furthermore, without a correction of PINK1 and Parkin levels, there can be a continuous disruption of this mitophagy pathway by α-synuclein as its expression is increased with manganese.[49]

Alongside chelation therapy, Uyar et al have described that therapeutic plasma exchange (TPE) is an option for manganese toxicity.[82] In their case study, a 13-year-old girl with severe manganese toxicity was subject to TPE with EDTA chelation.[82] After 2 days of just the TPE, blood manganese levels dropped from 46 μg/dL to 22 μg/dL.[82] Chelation with EDTA was started on the 3rd hospital day alongside TPE, resulting in blood manganese levels of 9 μg/dL on the 14th hospital day, which is when all treatment was stopped.[82] T1-MRI hyperintensities indicating intracranial manganese showed significant improvement before and at 8 days of treatment.[82] Also, any motor and cognitive symptoms were resolved before the patient's discharge.[82]

SIRT1 activation may be neuroprotective in manganese toxicity.[83] Cong et al describe the use of manganese-exposed C57BL/6 mice, in which they were either exposed to EX527, a selective SIRT1 inhibitor, or resveratrol, a SIRT1 activator.[83] The researchers found a significant decrease in neuroinflammation and ROS levels with resveratrol, whereas EX527 exacerbated both.[83]

Two recent studies elucidated how curcumin may mitigate manganese-induced neurotoxicity in relation to histone acetylation. The first study found that curcumin upregulated KAT2A expression, restored H3K36ac levels, and enhanced the expression of antioxidant genes.[63] As a result, the H3K36ac-dependent antioxidant pathway was restored. The second study found that manganese treatment reduces the acetylation of H3K27 at the manganese superoxide dismutase (SOD2) gene promoter, while curcumin restores it to alleviate oxidative stress.[84]

Sesame oil has demonstrated neuroprotective effects in a rat model of manganese-induced parkinsonism.[85] In a dose-dependent manner, it reduced MDA levels, increased glutathione, mitigated neuronal degeneration in the striatum, improved motor function, and restored GABA and dopamine levels.[85]

In review, current and potential treatments for manganese-induced parkinsonism include ones that only treat symptoms, are preventative, neuroprotective, or directly remove manganese from the bloodstream. Levodopa may be used to treat symptoms resulting from damage to the substantia nigra pars compacta. Ensuring clean drinking water free of excessive manganese levels is essential so the use of sediment–manganese interactions in contaminated water can be a good preventative measure. Vinpocetine, punicalagin, niacin, vitamin E, DNLA, resveratrol, curcumin, and sesame oil may provide neuroprotection to individuals with toxic manganese exposure. Lastly, chelation with $CaNa_2$ EDTA, PAS, or other natural extracts, such as E. amoenum, can help treat manganese-induced parkinsonism, and chelation may benefit from being paired with TPE (See Table 2 for a summary of treatments with categories and references).

Table 2 Summary of Treatments for Manganese-Induced Neurotoxicity

Category	Treatment	Description	References
Symptomatic treatment	Levodopa	Typically ineffective in manganese toxicity, but may help motor symptoms if the entire basal ganglia is affected.	[9,64,65]
Preventative	Manganese-sediment exposure	Sediment-bound Manganese in water is less bioavailable and leads to reduced motor and neurotoxic effects.	[42]
Neuroprotective (combined)	Vinpocetine, punicalagin, niacin, Vitamin E	In Mn-exposed rats, combination therapy reduced neurodegeneration and biochemical markers of damage.	[68]
Neuroprotective (specific)	Vitamin E	May upregulate CHRM1 and KCNJ4 to support cholinergic signaling and membrane potential maintenance.	[69]
Chelation Therapy	$CaNa_2EDTA$	Intravenous chelation therapy for Manganese-induced parkinsonism; improves symptoms and reduces serum Mn with minimal side effects, used in both acquired and genetic transporter-related toxicity cases.	[20,70–73]
Chelation Therapy	Para-aminosalicylic acid (PAS)	Improves motor and cognitive function in Mn poisoning; effective at high doses but may cause GI and thyroid side effects.	[74–78]
Complementary Medicine	Echium amoenum extract	Reduces ROS, inflammation, and boosts catecholamines in Mn-poisoned rats.	[79,80]
Complementary Medicine	Dendrobium nobile Lindl. alkaloids (DNLA)	Restores PINK1/Parkin-mediated mitophagy and protects neurons against Mn toxicity in vitro.	[81]
Combined Therapy	Therapeutic Plasma Exchange (TPE) + EDTA	TPE rapidly reduces blood Mn; combined therapy resolved symptoms and improved MRI findings in a pediatric case.	[82]
Molecular Pathway Targeted	SIRT1 activator (resveratrol)	Resveratrol reduced Mn-induced oxidative stress and inflammation; inhibitor (EX527) worsened these effects.	[83]
Epigenetic Intervention	Curcumin	Regulates histone acetylation (H3K27, H3K36ac) via KAT2A and restores antioxidant gene expression in Mn-induced stress.	[63,84]
Nutritional Intervention	Sesame oil	Reduced MDA, increased glutathione, restored GABA/dopamine levels, and improved motor function in Mn-parkinsonism model.	[85]

Abbreviations: ROS, reactive oxygen species; PAS, Para-aminosalicylic acid; TPE, therapeutic plasma exchange; KAT2A, acetyltransferase lysine acetyltransferase 2A; MDA, Malondialdehyde.

Discussion

Manganese-induced parkinsonism is a neurodegenerative disorder thought to occur due to the dysregulation of cellular pathways leading to oxidative stress, neuroinflammation, and neuronal damage. This review discusses the impact of manganese toxicity within the cell, which may lead to alterations in gene expression and cellular signaling, and describes treatments currently being explored.

We first reviewed the involvement of transporters in manganese toxicity. Mutations in the SLC30A10 and SLC39A14 transporters can directly cause elevated manganese levels in the body and decreased SNAT3, GLAST, and GLT-1, leading to glutamine and glutamate imbalances.[11,21] As YY1 overexpression and PKC signaling in the presence of manganese may result in the suppression of the expression of the transporters GLAST and GLT-1, there can be a disruption of the neural environment of the CNS.[21,24,25] Additionally, the suppression of SNAT3 expression is also likely mediated by PKC signaling and is found in astrocytes and on the BBB.[21,86] Inhibition of these above transporters can be involved in the pathogenesis of manganese-induced parkinsonism, so exploration of YY1 transcription factor expression and the regulation of PKC activity may be important targets to explore treatment of manganese-induced parkinsonism.

The oxidative effects of manganese are critical in the pathogenesis of manganese-induced parkinsonism. Specifically, manganese treatment in mice has shown increased sphingomyelinase activity, which is implicated in the oxidative stress pathway indicated by elevated MDA, decreased antioxidant activity, motor deficits, and lipid profile disturbances in the midbrain.[38] Toxic amounts of manganese are shown to present typically with depositions in the globi pallidi and substantia nigra as shown through MRI.[27] As there are apparent neurological effects of manganese overexposure, understanding the neuroprotective treatments that are currently available is vital.

CaNa2EDTA and PAS are current chelation treatments that can be useful in removing manganese from the bloodstream and restoring cognitive, motor, and antioxidative functions.[67,74–76] Even though this is an initially recommended treatment, it is essential to note that chelating molecules have trouble crossing the blood–brain barrier and may reduce essential metals in the bloodstream.[87] Furthermore, the benefits of chelation therapy, such as with CaNa2EDTA, are less effective in patients who are treated after more extended periods of exposure.[71] For example, a Korean patient with an SLC39A14 mutation receiving $CaNa_2EDTA$ treatment had a significant reduction in T1-MRI hyperintensities and serum manganese levels, but there was little improvement in the patient's dystonia symptoms.[72] Additionally, in a study following two patients with SLC39A14 mutation, the 3-year-old patient had a significant reduction in motor symptoms with $CaNa_2EDTA$, but the 17-year-old's condition continued to worsen.[20] Therefore, the earlier treatment is much more beneficial, but other supplementary or preventative measures are important to explore if they are unavailable to a patient. One supplementary treatment to EDTA that has been effective is TPE in a case study on a patient with severe manganese toxicity. Notably, in the initial stages of therapy, if EDTA was continued without TPE, the patient's clinical symptoms became worse, indicating that TPE might be beneficial in the early stages of severe toxicity.

It may also be helpful to conduct further research on whether a natural extract, like E. amoenum, can reduce neurotoxicity and cell death in patients, as it has in manganese-treated rats through oral administration.[79,80] New research with natural extracts like E. amoenum also shows promise as a supplementary treatment pathway.[79,80] For example, another natural extract, DNLA, helps restore PINK1/Parkin-mediated mitophagy and can alleviate toxicity.[79–81]

A combination of vinpocetine, punicalagin, niacin, and vitamin E, as well as sesame oil alone, can also be used to prevent neurodegeneration, oxidative stress, and neurotransmitter imbalances.[68,85] Both the combination and sesame oil may also serve as supplementary or preventative treatments to prevent cell death in addition to chelation. Vitamin E has been described to be potentially helpful because of its upregulation of CHRM1 and KCNJ4.[69] However, the article incorrectly identifies KCNJ4 as a potassium voltage-gated channel instead of a potassium inwardly rectifying channel, so it is not clear if this misinterpretation led to any misleading results.[69]

Bioactive compounds affecting specific mechanisms of manganese toxicity may also be helpful, such as by reducing the downregulation of SIRT1 with resveratrol to restore SIRT1/FOXO3-mediated autophagy and restoring acetylation by KAT2A with curcumin.[46,63,83,84] Oxidative stress is an important part of manganese toxicity, which may be driven by the reduced KAT2A, H3K36ac levels, and antioxidant gene expression.[63,84] Curcumin may therefore be useful in mitigating the oxidative stress from manganese.[63,84] These studies, however, were tested on rats, and the effect on human patients remains to be elucidated.

Also, it was reviewed that if caspase-3 is activated in the presence of manganese and increases PKCδ activity, there is cell apoptosis of mesencephalic dopaminergic cells.[26] This may be a pathway for why there is an effect specifically on the basal ganglia in manganese toxicity; however, further research on the comparison of effects on more cell types may be needed. It is also possible that dopamine is involved in the oxidative stress and pathogenesis of manganese-induced parkinsonism. Marwah et al describe the formation of DTZ-2, which is a dopamine derivative and a possible neurotoxin that results in oxidative stress in the presence of manganese.[39] Other metals were also compared, and manganese produced the most significant redox cycling.[39] Since the formation of DTZ-2 requires cysteinyl-dopamine and hypochlorite, it is vital to understand which compound is neurotoxic. Mehta et al answered this, explaining that cysteinyl-dopamine is only significantly toxic once exposed to a hypochlorite treatment.[88] It may be beneficial for future research to target dopamine derivatives, as this can be another reason for the effect of the basal ganglia in manganese-induced parkinsonism. More importance may be placed on dopamine-derivatives as Marwah theorizes in a dissertation that manganese may stabilize a reaction that results in the formation of DTZ-1 (another dopathiazine), but further research is required as this is editorially reviewed and not peer-reviewed.[89] Since there can be neurodegeneration of dopaminergic neurons in the substantia nigra over prolonged periods with low doses of manganese and result in manganese-induced parkinsonism, levodopa can be a viable treatment.[9] Though it is well

described that levodopa provides temporary symptom relief, in the presence of manganese, dopamine and its derivatives may undergo autoxidation and cause further oxidative stress and neurodegeneration.[40,71] In addition, this may be why levodopa shows short-term relief of symptoms followed by a failure to sustain its effects, such as in the double-blind study conducted by C.S. Lu et al on four patients with chronic manganese intoxication.[64]

Neuroinflammation and toxicity may also be associated with one's susceptibility to manganese and the resulting activation of the NF-κB signaling pathway. Interestingly, the cGAS-STING pathway has been implicated in promoting NF-κB inflammation and forming a feedback loop with STING signaling.[44] This synergistic effect is further exacerbated with the interconnection between cGAS-STING and ferroptosis, leading to both increased inflammation and apoptosis.[44] Since the activation of the cGAS-STING pathway involves ROS, reducing oxidative stress may be a viable option.

Estrogen is implicated to act as a protective agent as it has been shown to suppress the NF-κB pathway and reduce manganese toxicity symptoms, but we are not sure if this then has an effect on STING signaling and ferroptosis.[41] The inhibition or induction of the NF-κB pathway may potentially treat cancer and inflammation, according to Yamamoto & Gaynor.[90] Studies have also shown greater manganese toxicity in male mice than female mice, both after exposure and in knockout models.[17,42] As such, it may be necessary to further explore the roles of estrogen and interventions in the NF-κB pathway.

Understanding the mode of toxicity is just as important as the underlying mechanisms. Studies show manganese can enter the brain through the nasal pathway, as seen in elevated levels in the olfactory bulbs of exposed workers and reduced cognitive performance.[30,31] Chronic exposure, rather than recent contact, better predicts tissue accumulation, and has been linked to cognitive decline and parkinsonism.[30] Even unusual cases, like drug use involving potassium permanganate, highlight manganese's neurotoxic potential.[34] Newer sources, such as inhaled particles from lithium-ion batteries, also show systemic toxicity in animal models, underscoring the importance of monitoring emerging exposure routes.[37]

Conclusion

The underlying mechanism of cellular and neurological dysfunction due to environmental/occupational exposure to manganese is actively being investigated. Understanding the various pathways identified as affected by manganese toxicity paves the way to discover novel therapeutic approaches. In the future, potential treatments could target PKCδ mediation of apoptotic activity in dopaminergic cells, neuroprotective kinase proteins, other autophagy pathways, α-synuclein, NF-κB and the cGAS-STING pathway in inflammation, YY1 transcription factor, BBB disruptions, histone acetylation, or transporters in the CNS. Additionally, researchers can explore using TPE, vinpocetine, punicalagin, niacin, vitamin E, DNLA, resveratrol, curcumin, and sesame oil, or other natural extracts as supplementary treatments to chelation. Further investigation into neuroprotective factors may be instrumental in developing effective treatments. However, the reliance on previously published studies means the findings are limited by the quality of existing research and are subject to potential selection bias, as this is a narrative review.

Abbreviations

CaNa2EDTA, ethylene-diamine-tetra-acetic acid; PAS, para-aminosalicylic acid; VIN, vinpocetine; PUN, punicalagin; CNS, central nervous system; SNAT3, sodium-coupled neutral amino acid transporter 3; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; YY1, yin yang 1; TNF-α, tumor necrosis factor-alpha; PKCδ, protein kinase C delta; ICP-MS, inductively coupled plasma-mass spectrometry; DBSI, Diffusion Basis Spectrum Imaging; NMC, nickel manganese cobalt; $MnCl_2$, manganese chloride; LC-MS, liquid chromatography–mass spectrometry; ROS, reactive oxygen species; cGAS, cyclic GMP-AMP synthase; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; E2, 17-β-estradiol; STING, stimulator of interferon genes; GADD34, DNA damage-inducible protein 34; ISR, integrated stress response; CaMK, calmodulin-dependent protein kinase; CREB, cAMP response element–binding protein; STAT3, signal transducer and activator of transcription 3; LRRK2, leucine-rich repeat kinase 2; REST/NRSF, Repressor Element Silencing Transcription factor/Neuron-restrictive Silencing Factor; circRNA, circular RNA; BBB, blood–brain barrier; ROCK2, Rho-associated protein kinase 2; KAT2A, acetyltransferase lysine acetyltransferase 2A; cAMP response element–binding protein; PTEN, phosphatase and tensin homolog; PINK1, PTEN-induced putative kinase 1; ADHD, attention-deficit hyperactivity disorder; E. amoenum, Echium amoenum; TPE, therapeutic plasma exchange.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA*. 2020;323(6):548–560. doi:10.1001/jama.2019.22360
2. Liddle RA. Parkinson's disease from the gut. *Brain Res*. 2018;1693:201–206. doi:10.1016/J.BRAINRES.2018.01.010
3. Wakabayashi K, Tanji K, Odagiri S, Miki Y, Mori F, Takahashi H. The Lewy body in Parkinson's disease and related neurodegenerative disorders. *Mol Neurobiol*. 2013;47(2):495–508. doi:10.1007/s12035-012-8280-y
4. Haider A, Spurling BC, Sánchez-Manso JC. Lewy Body Dementia. StatPearls; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482441/. Accessed January 1, 2024.
5. Flora SJS. Metals. In: *Biomarkers in Toxicology*. Academic Press; 2014:485–519. doi:10.1016/B978-0-12-404630-6.00029-4
6. Cersosimo MG, Koller WC. The diagnosis of manganese-induced parkinsonism. *Neurotoxicology*. 2006;27(3):340–346. doi:10.1016/j.neuro.2005.10.006
7. Siafis S, Wu H, Wang D, et al. Antipsychotic dose, dopamine D2 receptor occupancy and extrapyramidal side-effects: a systematic review and dose-response meta-analysis. *Mol Psychiatry*. 2023;28(8):3267–3277. doi:10.1038/s41380-023-02203-y
8. Perl DP, Olanow CW. The neuropathology of manganese-induced Parkinsonism. *J Neuropathol Exp Neurol*. 2007;66(8):675–682.
9. Lucchini R, Tieu K. Manganese-induced Parkinsonism: evidence from epidemiological and experimental studies. *Biomolecules*. 2023;13(8). doi:10.3390/biom13081190
10. Guilarte TR, Gonzales KK. Manganese-induced Parkinsonism Is Not idiopathic Parkinson's disease: environmental and genetic evidence. *Toxicological Sciences*. 2015;146(2):204–212. doi:10.1093/TOXSCI/KFV099
11. Kwakye GF, Paoliello MMB, Mukhopadhyay S, Bowman AB, Aschner M. Manganese-induced Parkinsonism and Parkinson's disease: shared and distinguishable features. *Int J Environ Res Public Health*. 2015;12(7):7519–7540. doi:10.3390/IJERPH120707519
12. Lechpammer M, Clegg MS, Muzar Z, Huebner PA, Jin L-W, Gospe SM. Pathology of inherited manganese transporter deficiency. *Ann Neurol*. 2014;75(4):608–612. doi:10.1002/ANA.24131
13. Quadri M, Federico A, Zhao T, et al. Mutations in SLC30A10 cause Parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. *Am J Human Genetics*. 2012;90(3):467–477. doi:10.1016/j.ajhg.2012.01.017
14. Tuschl K, Mills PB, Parsons H, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia—A new metabolic disorder. *J Inherit Metab Dis*. 2008;31(2):151–163. doi:10.1007/S10545-008-0813-1
15. Tuschl K, Clayton PT, Gospe SM, et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a Manganese transporter in man. *Am J Human Genetics*. 2012;90(3):457–466. doi:10.1016/j.ajhg.2012.01.018
16. Rodichkin AN, Guilarte TR. Hereditary disorders of Manganese metabolism: pathophysiology of childhood-onset dystonia-Parkinsonism in SLC39A14 mutation carriers and genetic animal models. *Int J Mol Sci*. 2022;23(21):12833. doi:10.3390/IJMS232112833
17. Rodichkin AN, Edler MK, McGlothan JL, Guilarte TR. Pathophysiological studies of aging Slc39a14 knockout mice to assess the progression of manganese-induced dystonia-parkinsonism. *Neurotoxicology*. 2022;93:92–102. doi:10.1016/J.NEURO.2022.09.005
18. Aydemir TB, Kim M-H, Kim J, et al. Metal transporter Zip14 (Slc39a14) deletion in mice increases Manganese deposition and produces neurotoxic signatures and diminished motor activity. *J Neurosci*. 2017;37(25):5996–6006. doi:10.1523/JNEUROSCI.0285-17.2017
19. Tuschl K, Marin-Valencia I, Gospe SM. Disorders of manganese transport. In: *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease*. Academic Press; 2025:787–800. doi:10.1016/B978-0-443-19176-3.00057-1
20. Tuschl K, Meyer E, Valdivia LE, et al. Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism–dystonia. *Nat Commun*. 2016;7(1):1–16. doi:10.1038/ncomms11601
21. Sidoryk-Wegrzynowicz M, Aschner M. Role of astrocytes in manganese mediated neurotoxicity. *BMC Pharmacol Toxicol*. 2013;14(1):23. doi:10.1186/2050-6511-14-23
22. Sidoryk-Węgrzynowicz M, Lee E, Albrecht J, Aschner M. Manganese disrupts astrocyte glutamine transporter expression and function. *J Neurochem*. 2009;110(3):822–830. doi:10.1111/J.1471-4159.2009.06172.X
23. Sidoryk-Wegrzynowicz M, Lee E, Aschner M. Mechanism of Mn(II)-mediated dysregulation of glutamine–glutamate cycle: focus on glutamate turnover. *J Neurochem*. 2012;122(4):856–867. doi:10.1111/J.1471-4159.2012.07835.X
24. Karki P, Smith K, Johnson J, Aschner M, Lee E. Role of transcription factor yin yang 1 in manganese-induced reduction of astrocytic glutamate transporters: putative mechanism for manganese-induced neurotoxicity. *Neurochem Int*. 2015;88:53. doi:10.1016/J.NEUINT.2014.08.002
25. Rosas S, Vargas MA, López-Bayghen E, Ortega A. Glutamate-dependent transcriptional regulation of GLAST/EAAT1: a role for YY1. *J Neurochem*. 2007;101(4):1134–1144. doi:10.1111/J.1471-4159.2007.04517.X
26. Latchoumycandane C, Anantharam V, Kitazawa M, Yang Y, Kanthasamy A, Kanthasamy AG. Protein kinase Cδ Is a key downstream mediator of Manganese-induced apoptosis in dopaminergic neuronal cells. *J Pharmacol Exp Therap*. 2005;313(1):46–55. doi:10.1124/JPET.104.078469
27. Hauser RA, Zesiewicz TA, Rosemurgy AS, Martinez C, Olanow CW. Manganese intoxication and chronic liver failure. *Ann Neurol*. 1994;36(6):871–875. doi:10.1002/ANA.410360611
28. Finkelstein MM, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. *Environ Res*. 2007;104(3):420–432. doi:10.1016/J.ENVRES.2007.03.002
29. Gorell JM, Rybicki BA, Johnson CC, Peterson EL. Occupational metal exposures and the risk of Parkinson's disease. *Neuroepidemiology*. 1999;18(6):303–308. doi:10.1159/000026225
30. Gonzalez-Cuyar LF, Nelson G, Nielsen SS, et al. Olfactory tract/bulb metal concentration in Manganese-exposed mineworkers. *Neurotoxicology*. 2024;102:96–105. doi:10.1016/J.NEURO.2024.04.001
31. Racette BA, Nelson G, Dlamini WW, et al. Environmental manganese exposure and cognitive control in a South African population. *Neurotoxicology*. 2022;89:31–40. doi:10.1016/J.NEURO.2022.01.004
32. Racette BA, Criswell SR, Lundin JI, et al. Increased risk of parkinsonism associated with welding exposure. *Neurotoxicology*. 2012;33(5):1356–1361. doi:10.1016/J.NEURO.2012.08.011

33. Criswell SR, Nielsen SS, Faust IM, et al. Neuroinflammation and white matter alterations in occupational manganese exposure assessed by diffusion basis spectrum imaging. *Neurotoxicology*. 2023;97:25–33. doi:10.1016/J.NEURO.2023.04.013
34. De Bie RMA, Gladstone RM, Strafella AP, Ko JH, Lang AE. Manganese-induced Parkinsonism associated with methcathinone (Ephedrone) Abuse. *Arch Neurol*. 2007;64(6):886–889. doi:10.1001/ARCHNEUR.64.6.886
35. Fatiadi AJ. The classical permanganate ion: still a novel oxidant in organic chemistry. *Synthesis*. 1987:85–127.
36. Shaabani A, Tavasoli-Rad F, Lee DG. Potassium permanganate oxidation of organic compounds. *Synth Commun*. 2005;35(4):571–580. doi:10.1081/SCC-200049792
37. Wang J, Fang X, Wu R, et al. Airway exposure to lithium nickel manganese cobalt oxide particles induces alterations in lung microenvironment and potential kidney and liver damage in mice. *Toxicology*. 2025;511:154036. doi:10.1016/J.TOX.2024.154036
38. Lu M, Deng P, Yang L, et al. Manganese overexposure induces Parkinson-like symptoms, altered lipid signature and oxidative stress in C57BL/6 J mouse. *Ecotoxicol Environ Saf*. 2023:263. doi:10.1016/J.ECOENV.2023.115238
39. Marwah PK, Paik G, Issa CJ, et al. Manganese-stimulated redox cycling of dopamine derivatives: implications for manganism. *Neurotoxicology*. 2022;90:10–18. doi:10.1016/J.NEURO.2022.02.007
40. Nachtman JP, Delor S, Brennan CE. Manganese neurotoxicity: effects of varying oxygen tension and EDTA on dopamine auto-oxidation. *Neurotoxicology*. 1987;8(2):249–253.
41. Moreno JA, Streifel KM, Sullivan KA, Hanneman WH, Tjalkens RB. Manganese-induced NF-κB activation and nitrosative stress is decreased by estrogen in juvenile mice. *Toxicological Sciences*. 2011;122(1):121–133. doi:10.1093/TOXSCI/KFR091
42. Freeman DM, O'Neal R, Zhang Q, Bouwer EJ, Wang Z. Manganese-induced Parkinsonism in mice is reduced using a novel contaminated water sediment exposure model. *Environ Toxicol Pharmacol*. 2020;78. doi:10.1016/J.ETAP.2020.103399
43. Zhang Z, Yang J, Zhou Q, et al. The cGAS−STING-mediated ROS and ferroptosis are involved in manganese neurotoxicity. *J Environ Sci*. 2025;152:71–86. doi:10.1016/J.JES.2024.05.003
44. Zhong S, Zhou Q, Yang J, et al. Relationship between the cGAS−STING and NF-κB pathways-role in neurotoxicity. *Biomed Pharmacother*. 2024;175:116698. doi:10.1016/J.BIOPHA.2024.116698
45. Li WH, Xiang ZTY, Lu AX, Wang SS, Yan CH. Manganese-induced apoptosis through the ROS-activated JNK/FOXO3a signaling pathway in CTX cells, a model of rat astrocytes. *Ecotoxicol Environ Saf*. 2023;262:115326. doi:10.1016/J.ECOENV.2023.115326
46. Yan D, Yang Y, Lang J, et al. SIRT1/FOXO3-mediated autophagy signaling involved in manganese-induced neuroinflammation in microglia. *Ecotoxicol Environ Saf*. 2023;256:114872. doi:10.1016/J.ECOENV.2023.114872
47. Liu K, Liu Z, Liu Z, et al. Manganese induces S-nitrosylation of PINK1 leading to nerve cell damage by repressing PINK1/Parkin-mediated mitophagy. *Sci Total Environ*. 2022;834:155358. doi:10.1016/J.SCITOTENV.2022.155358
48. Liu K, Liu Z, Liu Z, et al. Manganese-induced PINK1 S-nitrosylation exacerbates nerve cell damage by promoting ZNF746 repression of mitochondrial biogenesis. *Sci Total Environ*. 2023;863:160985. doi:10.1016/J.SCITOTENV.2022.160985
49. Liu ZQ, Liu K, Liu ZF, et al. Manganese-induced alpha-synuclein overexpression aggravates mitochondrial damage by repressing PINK1/Parkin-mediated mitophagy. *Food Chem Toxicol*. 2021;152:112213. doi:10.1016/J.FCT.2021.112213
50. Ma Z, Liu K, Zhang R, et al. Manganese-induced α-synuclein overexpression promotes the accumulation of dysfunctional synaptic vesicles and hippocampal synaptotoxicity by suppressing Rab26-dependent autophagy in presynaptic neurons. *Science of the Total Environment*. 2023;858:159753. doi:10.1016/J.SCITOTENV.2022.159753
51. Sun Y, He Y, Yang L, et al. Manganese induced nervous injury by α-synuclein accumulation via ATP-sensitive K(+) channels and GABA receptors. *Toxicol Lett*. 2020;332:164–170. doi:10.1016/J.TOXLET.2020.07.008
52. Smolyaninova LV, Timoshina YA, Berezhnoy DS, et al. Impact of manganese accumulation on Na,K-ATPase expression and function in the cerebellum and striatum of C57Bl/6 mice. *Neurotoxicology*. 2023;98:86–97. doi:10.1016/J.NEURO.2023.08.002
53. Ma Z, Wang C, Liu C, et al. Manganese induces autophagy dysregulation: the role of S-nitrosylation in regulating autophagy related proteins in vivo and in vitro. *Sci Total Environ*. 2020;698:134294. doi:10.1016/J.SCITOTENV.2019.134294
54. Cen Y, Yang J, Su L, et al. Manganese induces neuronal apoptosis by activating mTOR signaling pathway in vitro and in vivo. *Food Chem Toxicol*. 2024;185:114508. doi:10.1016/J.FCT.2024.114508
55. Yang Y, Gao L, Meng J, et al. Manganese activates autophagy and microglia M2 polarization against endoplasmic reticulum stress-induced neuroinflammation: involvement of GSK-3β signaling. *Biomed Pharmacother*. 2024;170:116053. doi:10.1016/J.BIOPHA.2023.116053
56. Guo S, Wang H, Yin Y. Microglia Polarization From M1 to M2 in Neurodegenerative Diseases. *Front Aging Neurosci*. 2022;14:815347. doi:10.3389/FNAGI.2022.815347/XML/NLM
57. Chen J, Su P, Luo W, Chen J. Role of LRRK2 in manganese-induced neuroinflammation and microglial autophagy. *Biochem Biophys Res Commun*. 2018;498(1):171–177. doi:10.1016/J.BBRC.2018.02.007
58. Pajarillo E, Kim S, Digman A, et al. The role of microglial LRRK2 kinase in manganese-induced inflammatory neurotoxicity via NLRP3 inflammasome and RAB10-mediated autophagy dysfunction. *J Biol Chem*. 2023;299(7):104879. doi:10.1016/J.JBC.2023.104879
59. Pajarillo E, Kim S, Digman A, et al. Dopaminergic REST/NRSF is protective against manganese-induced neurotoxicity in mice. *J Biol Chem*. 2024;300(9):107707. doi:10.1016/J.JBC.2024.107707
60. Lu W, He J, Wei S, et al. Circular RNA circRest regulates manganese induced cell apoptosis by targeting the mmu-miR-6914–5p/Ephb3 axis. *Environ Pollut*. 2024;344:123395. doi:10.1016/J.ENVPOL.2024.123395
61. Ding H, Wang F, Su L, et al. Involvement of MEK5/ERK5 signaling pathway in manganese-induced cell injury in dopaminergic MN9D cells. *J Trace Elements Med Biol*. 2020;61:126546. doi:10.1016/J.JTEMB.2020.126546
62. Ma Y, Chen H, Jiang Y, et al. RhoA/ROCK2 signaling pathway regulates Mn-induced alterations in tight junction proteins leading to cognitive dysfunction in mice. *Curr Res Toxicol*. 2025;8:100207. doi:10.1016/J.CRTOX.2024.100207
63. Liu Y, Zeng JM, Zhao H, et al. Mechanism of KAT2A regulation of H3K36ac in manganese-induced oxidative damage to mitochondria in the nervous system and intervention by curcumin. *Ecotoxicol Environ Saf*. 2024;273:116155. doi:10.1016/J.ECOENV.2024.116155
64. Lu CS, Huang CC, Chu NS, Calne DB. Levodopa failure in chronic manganism. *Neurology*. 1994;44(9):1600–1602. doi:10.1212/WNL.44.9.1600
65. Janocha-Litwin J, Marianska K, Serafinska S, Simon K. Manganese encephalopathy among ephedron abusers-case reports. *J Neuroimag*. 2015;25(5):832–835. doi:10.1111/JON.12173

66. Kullar SS, Shao K, Surette C, et al. A benchmark concentration analysis for manganese in drinking water and IQ deficits in children. *Environ Int*. 2019;130:104889. doi:10.1016/J.ENVINT.2019.05.083
67. Schullehner J, Thygesen M, Kristiansen SM, Hansen B, Pedersen CB, Dalsgaard S. Exposure to manganese in drinking water during childhood and association with attention-deficit hyperactivity disorder: a nationwide cohort study. *Environ Health Perspect*. 2020;128(9):1–10. doi:10.1289/EHP6391/SUPPL_FILE/EHP6391.S003.VIDEO.ACCO.ZIP
68. Abu-Elfotuh K, Hamdan AME, Abbas AN, et al. Evaluating the neuroprotective activities of vinpocetine, punicalagin, niacin and vitamin E against behavioural and motor disabilities of manganese-induced Parkinson's disease in Sprague Dawley rats. *Biomedicine & Pharmacotherapy*. 2022:153. doi:10.1016/J.BIOPHA.2022.113330
69. Song R, Chen H, Zhan R, Han M, Zhao L, Shen X. Vitamin E protects dopaminergic neurons against manganese-induced neurotoxicity through stimulation of CHRM1 and KCNJ4. *J Trace Elements Med Biol*. 2024;81:127326. doi:10.1016/J.JTEMB.2023.127326
70. Tuschl K, Clayton PT, Sidney M, Gospe J, Mills PB. Hypermanganesemia with Dystonia 1. *GeneReviews®*; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK100241/. Accessed April 25, 2025.
71. Herrero Hernandez E, Discalzi G, Valentini C, et al. Follow-up of patients affected by manganese-induced Parkinsonism after treatment with CaNa2EDTA. *Neurotoxicology*. 2006;27(3):333–339. doi:10.1016/J.NEURO.2005.09.003
72. Lee JH, Shin JH. Effect of chelation therapy on a Korean Patient with brain Manganese deposition resulting from a compound heterozygous mutation in the SLC39A14 gene. *J Mov Disord*. 2022;15(2):171–174. doi:10.14802/JMD.21143
73. Mukhopadhyay S. Familial manganese-induced neurotoxicity due to mutations in SLC30A10 or SLC39A14. *Neurotoxicology*. 2018;64:278–283. doi:10.1016/J.NEURO.2017.07.030
74. Jiang YM, Mo XA, Du FQ, et al. Effective treatment of Manganese-induced occupational Parkinsonism with p-Aminosalicylic Acid: a case of 17-year follow-up study. *J Occup Environ Med / Am Coll Occup Environ Med*. 2006;48(6):644. doi:10.1097/01.JOM.0000204114.01893.3E
75. Li SJ, Li Y, Chen JW, et al. Sodium para-aminosalicylic acid protected primary cultured Basal Ganglia neurons of rat from Manganese-induced oxidative impairment and changes of amino acid neurotransmitters. *Biol Trace Elem Res*. 2016;170(2):357–365. doi:10.1007/S12011-015-0472-7/FIGURES/5
76. Shuqin K, Haishang D, Peiyi X, Wanda H. A report of two cases of chronic serious manganese poisoning treated with sodium para-aminosalicylic acid. *Occup Environ Med*. 1992;49(1):66–69. doi:10.1136/OEM.49.1.66
77. Macgregor AG, Somner AR. The anti-thyroid action of para-aminosalicylic acid. *Lancet*. 1954;264(6845):931–936. doi:10.1016/S0140-6736(54)92552-0
78. Das KM, Eastwood MA, McManus JPA, Sircus W. Adverse reactions during Salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *New England J Med*. 1973;289(10):491–495. doi:10.1056/NEJM197309062891001
79. Sadeghi L, Tanwir F, Yousefi Babadi V. Physiological and biochemical effects of Echium Amoenum extract on Mn2+-imposed Parkinson like disorder in rats. *Adv Pharm Bull*. 2018;8(4):705–713. doi:10.15171/apb.2018.079
80. Safaeian L, Javanmard SH, Ghanadian M, Seifabadi S. Cytoprotective and antioxidant effects of Echium amoenum anthocyanin-rich extract in human endothelial cells (HUVECs). *Avicenna J Phytomed*. 2015;5(2):157–166.
81. Fu X, Chen S, Wang X, et al. Dendrobium nobile Lindl. alkaloids alleviate Mn-induced neurotoxicity via PINK1/Parkin-mediated mitophagy in PC12 cells. *Biochem Biophys Rep*. 2021;26:100877. doi:10.1016/J.BBREP.2020.100877
82. Uyar E, Gurkas E, Aksu AU, et al. Can therapeutic plasma exchange be life-saving in life-threatening manganese intoxication? *Transfus Apheresis Sci*. 2022;61(4):103417. doi:10.1016/J.TRANSCI.2022.103417
83. Cong L, Lei MY, Liu ZQ, et al. Resveratrol attenuates manganese-induced oxidative stress and neuroinflammation through SIRT1 signaling in mice. *Food Chem Toxicol*. 2021;153:112283. doi:10.1016/J.FCT.2021.112283
84. Yang Y, Liu Y, Zhang AL, et al. Curcumin protects against manganese-induced neurotoxicity in rat by regulating oxidative stress-related gene expression via H3K27 acetylation. *Ecotoxicol Environ Saf*. 2022;236:113469. doi:10.1016/J.ECOENV.2022.113469
85. Sarawi WS, Attia HA, Alomar HA, et al. The protective role of sesame oil against Parkinson's-like disease induced by manganese in rats. *Behav Brain Res*. 2024;465:114969. doi:10.1016/J.BBR.2024.114969
86. Ruderisch N, Virgintino D, Makrides V, Verrey F. Differential axial localization along the mouse brain vascular tree of luminal sodium-dependent glutamine transporters Snat1 and Snat3. *J Cerebral Blood Flow Metabol*. 2011;31(7):1637–1647. doi:10.1038/JCBFM.2011.21/ASSET/IMAGES/LARGE/10.1038_JCBFM.2011.21-FIG5.JPEG
87. Schlageter NL, Carson RE, Rapoport SI. Examination of blood — brain barrier permeability in Dementia of the Alzheimer Type with [68Ga]EDTA and positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism*. 1987;7(1):1–8. doi:10.1038/JCBFM.1987.1
88. Mehta NJ, Asmaro K, Hermiz DJ, et al. Hypochlorite converts cysteinyl-dopamine into a cytotoxic product: a possible factor in Parkinson's disease. *Free Radic Biol Med*. 2016;101:44–52. doi:10.1016/J.FREERADBIOMED.2016.09.023
89. Marwah PK. *Hypochlorite-Mediated Oxidation of Dopamine: Implications in Parkinson's Disease and Manganism* ProQuest Dissertations Publishing; 2021.
90. Yamamoto Y, Gaynor RB. Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. *J Clin Invest*. 2001;107(2):135–142. doi:10.1172/JCI11914