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Manganese Induced neurodegenerative diseases and possible therapeutic approaches

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Abstract

Introduction: Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and prion disease represent important public health concerns. The etiology of neurodegenerative diseases is not completely understood, but genetic factors and environmental factors clearly contribute to their development. As environmental factors, heavy metals such as manganese (Mn) an essential trace element, are

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required for several physiological processes. In addition, exposures to high levels may culminate in adverse health effects.

Areas covered: In this critical review, the authors address the role of Mn in the etiology of neurodegenerative diseases and discuss emerging treatments of Mn overload, such as chelation therapy. In addition, the authors discuss natural and synthetic compounds under development as prospective therapeutics. Moreover, bioinformatic approaches to identify new potential targets and therapeutic substances to reverse the neurodegenerative diseases are discussed.

Expert opinion: Here, the authors highlight the importance of better understanding the molecular mechanisms of toxicity associated with neurodegenerative diseases, and the role of Mn in these diseases. Additional emphasis should be directed to the discovery of new agents to treat Mn-induced diseases, since present day chelator therapies have limited bioavailability. Furthermore, the authors encourage the scientific community to develop research using libraries of compounds to screen those compounds that show efficacy in regulating brain Mn levels. In addition, bioinformatics may provide novel insight for pathways and clinical treatments associated with Mn-induced neurodegeneration, leading to a new direction in Mn toxicological research.

Keywords

Alzheimer’s disease; Huntington’s disease; Parkinson’s disease; amyotrophic lateral sclerosis; manganese; heavy metals

1. Introduction

Neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer’s disease (AD), Huntington’s disease (HD), Parkinson’s disease (PD) and prion disease are global public health concern. These diseases are characterized by progressive dysfunction and loss of neurons in certain anatomical regions with involvement of different functional systems and a variety of clinical presentations. There are several pathways that contribute to neuronal and/or glial cell damage, and a fundamental phenomenon inherent to most neurodegenerative diseases is the deposition of proteins such as alpha-synuclein, β-amyloid, tau, prion protein in the human brain. These proteins show conformational changes and biochemical modifications with altered physicochemical properties. Moreover, genetic mutations heighten susceptibility to these disorders [1].

Several studies have shown that chronic exposure to pesticides [2,3], particulate matter [4,5], and high levels of heavy metals [6-8] increase the risk of developing different neurodegenerative diseases. Epidemiological studies demonstrated an association between toxic non-essential metals, for instance mercury and AD [9,10], cadmium and AD and PD [11,12]. However, long- term exposure to high levels of essential elements, such as manganese (Mn), may also be toxic to humans and trigger neurodegenerative diseases [13,14].

The Mn is one of the most important metals in mammals and it is required for physiological processes, including brain and skeletal development, blood clotting, reproduction, neuronal function, antioxidant defense, and immune integrity [15]. Mn has also an important function as cofactor of numerous enzymes required for glial and neuronal cells, as well as enzymes

involved in synthesis and metabolism of amino acids, proteins, lipids, such as pyruvate carboxylase, glutamine synthetase and isocitrate dehydrogenase [15-17].

Several trace elements, such as iron (Fe), calcium (Ca), zinc (Zn) and cupper (Cu) may interfere with Mn homeostasis [18]. In fact, Mn and other metals may compete for the same transporters, for instance, the divalent metal transporter 1 (DMT-1), which is not specific and able to transport multiple metals and may influence the Mn uptake and tissue distribution, affecting Mn and Fe homeostasis [19]. Moreover, Mn exposure may interfere with Ca^{2+} absorption, leading to calcium signaling dysfunction that is associated with neurodegenerative diseases [20].

Mn is found in a large variety of foods, including rice, nuts, whole grains, leafy green vegetables, chocolate, seafood, fruits and seeds [15]. The major, non-occupational source of exposure to Mn is food with high levels of Mn or contaminated water (where rocks with high levels of Mn into the aquifers may increase Mn concentrations in groundwater in certain geologic regions) [21-23]. In addition, the use of total parenteral nutrition in ill infants and upon surgical resections may be an important source of Mn overload, since in parenteral nutrition, 100% of the Mn present in the preparation is bioavailable, while only 3–5% is bioavailable by enteral nutrition [24,25] and inhalation of combusted methylcyclopentadienyl manganese tricarbonyl (MMT), an Mn-containing gasoline additive, also represents an important source for Mn overload [26-28]. Exposure to Mn may also occur in several industrial activities, such as mining, welding, ferroalloy production, smelting and battery manufacturing. Mn-containing fumes and dust in industrial settings represent especially a high risk of increased exposure, where chronic inhalation of high levels of airborne particulate may result in elevated levels of Mn in the brain [29,30]. Chronic occupational exposure has been associated with development of neurotoxicity and neurodegenerative diseases [31]. For instance, in an American welding cohort study it was reported that Mn exposure generated a dose-dependent progression of manganism [32]. Similarly, a dose-dependent dopaminergic dysfunction associated with neurotoxicity in Mn occupational workers was observed as well as Mn exposure positive dose-response to occupational Mn exposure and severity of clinical symptoms of manganism[33].

Regulatory agencies have determined the limit to occupational exposure. The U.S. Federal Occupational Safety and Health Administration (OSHA) set a value of 5000 μg/m3 as an exposure limit, while according to the National Institute for Occupational Safety and Health (NIOSH) this value is 1000 μg/m3 [29]. The first course of action in the event of high Mn exposure is to remove the individual from the source of the exposure [34].

Manganism, a disease associated with exposure to high levels of Mn, has phenotypic features analogous to idiopathic PD such as tremors, cognitive deficits, bradykinesia, and rigidity, reflecting excessive Mn accumulation in the basal ganglia [31,35,36]. However, manganism is void of one of PD's hallmark, namely the presence of Lewy bodies [36,37]. This is commensurate with the clinical presentations which appear distinct for clinical idiopathic PD *vs.* manganism.

Overexposure to Mn may be associated with neurological disorders such as AD, PD, HD and ALS [38-41]. In fact, potential mechanisms underlying Mn-induced neurotoxicity and neurodegenerative diseases include changes in proteins aggregation; for instance, β-amyloid, tau, α-synuclein and huntingtin. Indeed, these proteins have been studied as possible new targets to treat Mn poisoning and neurodegenerative disorders [42-44]. Moreover, intracellular signaling pathways such as PI3K/Akt/mTOR, ERK, p53, and transcription factors such as NF-E2-related factor 2 (Nrf2) and NF-κB, may be also involved in neurotoxic effects of Mn and the understanding of how Mn induces changes in these pathways may be used as a strategy to treat or prevent neurodegenerative diseases [45-47].

Although the mechanisms associated with Mn-induced neurotoxicity are not entirely understood, there is abundance of evidence showing that Mn promotes reactive oxygen species (ROS) generation, impairs endoplasmic reticulum (ER) homeostasis, promotes mitochondrial dysfunction, and contributes to apoptosis [13,48].

A growing number of studies has detailed promising neuroprotective strategies to mitigate Mn neurotoxicity in different models (*in vitro* and *in vivo*). In this review, we address cellular and molecular mechanisms of Mn-induced neurotoxicity and neurodegenerative diseases, and highlight contemporary neurotherapeutic approaches, such as chelation, and natural and synthetic compounds in mitigating its neurotoxicity.

2. Role of Mn in neurodegenerative diseases

The most common neurodegenerative disease is AD, which is characterized by cognitive impairment with progressive dementia in the elderly [49]. Since Dr. Alois Alzheimer reported the first case in 1907, several studies have identified the pathology, risk factors for the development of the disease, as well as possible pathways involved its etiology [49,50]. The major features of AD are misfolding and aggregation of two proteins, Aβ and tau, forming Aβ plaques and neurofibrillary tangles [51,52].

A study performed by Tong et al. [38] showed an inverse correlation between Mn levels in whole blood with various cognitive and neuropsychological test scores where individuals with lower Mn levels had better score in Mini-Mental State Examination. Interestingly, they also observed that plasma Aβ peptides increase with raised Mn levels, suggesting that Mn in whole blood may be correlated with the progressive cognitive impairment of AD.

Mn homeostasis is perturbed in AD, triggering aggregation of Aβ peptides, the hallmark of AD. Rats exposed to Mn show high concentrations of this metal in several brain regions such as hippocampus and cortex, suggesting that Mn accelerates Aβ deposition and memory dysfunction [53]. Moreover, Mn exposure has been linked to alterations in the expression of amyloid precursor-like protein 1 (APLP1, a member of the amyloid precursor protein family with limited expression in the brain), resulting in diffuse Aβ plaques and degenerating cells, which can potentiate Mn neurotoxic effects [42,54]. Animals exposed to Mn show increased APLP1 protein expression in apoptotic neurons and glial cells, leading to Aβ plaques formation in the frontal cortex, and thereby resulting in cognitive and working memory deficits in these animals [42]. Chronic Mn exposure produces increases in p53 levels (a

transcription factor that regulates DNA synthesis and repair, and its activation occurs after injuries leading oxidative stress and genotoxicity) in cortical neurons associated with neurodegeneration [42,55]. Binding of Mn to monomeric Aβ peptide demonstrated weak affinity and transient interactions *in vitro* when evaluated by spectroscopy and fluorescence methods, suggesting no prolonged effects on plaque formation, even though future studies are required to elucidate the effects of Mn/Aβ peptide interaction in plaque formation [56]. Although AD is a widely studied neurodegenerative disease, how Mn contributes to neurodegenerative process and AD progression are still unclear.

The second most prevalent neurodegenerative disorder is PD, which is characterized by movement disorder, tremor, rigidity, and bradykinesia leading to loss of motility. Other neurological effects, such as dementia, are also observed in PD patients [57]. Although the etiology of PD has yet to be fully understood, both genetic and environmental factors are involved [58]. Exposure to Mn is associated with a parkinsonian-like symptoms that resembles idiopathic PD (referred to as manganism) [59]. This was first described by Couper (1837) among workers exposed to excessive airborne Mn levels. Chronic occupational exposure to high levels of Mn upon welding, smelting, mining, battery manufacturing, ferroalloy and Mn-rich agro-chemicals, is known to cause PD-like manganism [36,60].

Several epidemiological studies evaluated the correlation between Mn exposure and parkinsonism. In a cohort study with 886 American workers, exposed to Mn-containing welding fume was associated with progression of parkinsonism in a dose-dependent manner [32]. Likewise, it was reported that Mn mine workers in South Africa associated cumulative Mn exposure with parkinsonian signs and poorer quality of life [61]. Methcathinone abuse, a psychostimulant that uses potassium permanganate as an oxidant, has also been correlated with extrapyramidal syndrome [62]. However, other authors do not report cognitive deficits and there is a lack of neuropathological studies in methcathinone users to clarify the association between methcathinone users and the PD development [63,64].

Putative mechanisms associated with its neurotoxicity are shown in Figure 1. An important role has been ascribed to alpha-synuclein (αSyn) [65,66]. αSyn is a chaperon protein which is expressed and localized mainly in presynapitic terminals and regulates synaptic plasticity and dopaminergic neurotransmission [67]. The major aggregated component of Lewy body depositions (a PD's hallmark) is αSyn. Nonetheless, the role of αSyn in PD is controversial, with a complex role in both neuroprotection and neurodegeneration. Mn exposure alters αSyn expression, aggregation and cytotoxicity [68,69]. In fact, a study using neuronal PC12 cells reported that Mn induces overexpression of αSyn, leading to αSyn aggregation and misfolding, which is associated with cytotoxicity [69]. Interestingly, αSyn acts as neuroprotective chelator in acute Mn exposure by binding to C-terminal sites of this protein [70,71]. However, in chronic Mn overexposure, the natively conformed proteins undergo misfolding, then promoting αSyn aggregation, a critical factor responsible for Mn-induced autophagic degradation and neuronal damage [68]. Indeed, it was reported that Mn exposure could promote cell-to-cell transmission of αSyn, enhancing release of misfolded αSyn that evoke pro-inflammatory responses, potentially contributing to progressive neurodegeneration in dopaminergic neurons [72-74].

There are other factors associated with PD, such as genes of familial form (*parkin*, *pink1* and *dj1*) that regulate oxidative stress pathways and are implicated in the onset of PD. Using a *C. elegans* model, Bornhorst et al. [70] showed that worms lacking *pdr1* and *djr1* have increased Mn-induced oxidative stress. Interestingly, the overexpression of αsyn in these worms was able to rescue this effect, suggesting a complex interplay among αsyn, Mn and *pdr1* or *djr1* (Figure 1)

HD is an autosomal dominant neurodegenerative disorder, which neuropathological features result from the loss of projections from striatal neurons, and clinically is characterized by psychiatric and cognitive alteration, and progressive motor impairment, ultimately leading to death of patients [75]. Altered Mn homeostasis is likely involved in HD pathology, as suggested by several lines of evidence showing a gene-environment interaction between Mn and the mutant (*HTT*) gene [76,77]. Williams et al. [77] reported that transgenic mice in a HD mouse model had a selective Mn accumulation in the striatum (the most susceptible brain region in HD) compared to wild-type. In addition, another study demonstrated that the disease-metal interaction changes dendritic morphology characterized by length and branching complexity, and decreases DA levels in the striatum [76].

Building evidence supports a role for Mn deficiency to underlie HD pathology through diminished activity of Mn-dependent processes, including Mn-dependent enzymes such as arginase glutamine synthetase and pyruvate carboxylase, as well as Mn-dependent cell signaling networks and cell processes such as insulin growth factor receptor and autophagy [44,78,79]. Strong evidence in support of this includes the amelioration of arginase metabolic activity deficits by a one-week Mn supplementation in a mouse model of HD [80]. Likewise, supplementation with Mn rescues an HD defect in autophagic cargo loading [81]. The HD pathophysiology is associated with deficits in Mn accumulation in human and mouse neuroprogenitors with pathogenic alleles of Huntingtin. This deficiency induces ATM-p53 activation with enhanced p53 accumulation and phosphorylation in HD patients and mice [82]. Therefore, perturbations in Mn homeostasis can contribute to HD, and future studies to further elucidate the intracellular signaling alterations and mechanisms are warranted.

Another important neurodegenerative disease is ALS that affects more than 12,000 people in the United States, mainly occurring in younger people [44]. This fatal neurodegenerative disease is characterized by loss of motor neurons in the brain and spinal cord, resulting in motor neuron degeneration. This leads to loss of voluntary muscle control, resulting in a progressive paralysis of skeletal muscles and, in late-stages, respiratory failure [83,84]. Although the etiology of ALS is unknown, some patients have a family history of ALS, suggesting a genetic origin factor [85,86]. However, environmental factors play an important role in ALS development. Metal ion dysregulation is a relevant environmental factor, since Mn overexposure and ALS was first reported in German smelters [85,87]. In this regard, Mn has been studied to evaluate the association between Mn levels and ALS disease with conflicting results reported in the literature. The concentration of Mn in cerebrospinal fluid and plasma were higher in ALS patient than control group [88]. Kapaki et al. [89] demonstrated that Mn levels were enhanced in serum of ALS patient but no differences were observed in cerebrospinal fluid. On the other hand, in an Italian cohort of ALS patients, no

significant difference was found in serum Mn levels in ALS patients and controls [90], and similar evidence was reported by Peters et al. [91]. Thus, studies to clarify these intriguing findings and studies to develop novel treatments for this illness are necessary.

Prion diseases are progressive neurodegenerative diseases that affect animals, such as goats and sheep (scrapie), cattle (bovine spongiform encephalopathy (BSE)), as well as human s(Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease and kuru) [92]. Prion diseases are associated with neuropathological changes in normal cellular prion protein (PrP^{C}) leading to the formation of an abnormal pathogenic prion protein (PrP^{Sc}). The latter triggers a chain-reaction-like process of protein misfolding and progressive accumulation of abnormal isoforms and substantial neuronal degeneration [93]. Prion disorders are associated with metal dyshomeostasis. The prion protein PrP^{C} has a high-binding affinity for divalent metals such as Cu^{2+}, Zn^{2+}, Fe^{2+} and Mn^{2+} [18,94]. Indeed, studies have been reported that Mn could be involved in the misfolding and aggregation of the PrP^{SC} both *in vitro* and *in vivo* studies [95,96]. Brown et al. showed that Mn may be incorporated into PrP expressed by astrocytes generating proteinase resistance and loss of function [97]. Likewise, it was reported that Mn can induce stabilization of prion protein, contributing to prion protein misfolding and prion disease pathogenesis [95]. Interestingly, individuals with Creutzfeldt−Jakob Disease, the most common form of human prion disease, have increased Mn levels in the blood and brain, suggesting that Mn blood in prion disease is a highly specific characteristic of the disease [98]. However, neurodegenerative mechanisms are not completely elucidated and need further exploration to better understand the role of Mn in prion diseases.

3. Treatment of Mn induced neurotoxicity

3.1 Calcium disodium ethylene-diamine-tetra-acetic acid ($CaNa_2EDTA$)

There are few clinical treatment options for Mn-induced neurotoxicity. Putative treatment modalities are shown in Figure 1. Chelation therapy is by far the principal treatment modality. This thrapy is based on the infusion of ions or molecules that bind to the metal, removing it through complex formation and urinary excretion [99,100]. Calcium disodium Ethylene-diamine-tetra-acetic acid ($CaNa_2EDTA$) is a synthetic compound that has been used with some success as chelator. Its mode of action is based on the ability of toxic metals to replace calcium in the EDTA core [101]. Both *in vitro* and *in vivo* studies have demonstrated the efficacy of $CaNa_2EDTA$ to reduce dopaminergic autooxidation upon Mn exposure and the decrease in Mn concentration in both brain and liver of rats exposed to Mn [102,103].

The first study using $CaNa_2EDTA$ to treat Mn intoxication evaluated miners [104]. In this study, seven welder/foundry workers affected by Mn-induced Parkinsonism which had deposition of Mn in the basal ganglia received intravenous $CaNa_2EDTA$ chelating therapy. Four workers exhibited effective regression of the disease with improved muscle rigidity, while another worker showed a mild improvement of tremor. Also, increased Mn elimination in urine and reduction of Mn in blood were noted [105]. Likewise, two patients with hypermanganesemia that received $CaNa_2EDTA$ chelating therapy had decreased Mn blood levels and increased Mn urinary excretion that were associated with improvement of

symptoms [106,107]. In addition, hypermanganesemia may occur by mutations in the *SLC30A10* gene, which encodes a Mn transporter resulting in Mn accumulation in the brain [108]. In this regard, a report of the 2 year follow-up after chelation therapy in individual carrying *SLC30A10* mutations showed reduced clinical disability due to parkinsonian-like movement disorder [109]. Likewise, it was reported a new variant of SLC39A14 gene mutation that may affect Mn accumulation. The patient carrying this mutation underwent chelation therapy with intravenous $CaNa_2EDTA$[110]. Moreover, a strong correlation between chelating treatment and clinical improvement by MRI confirmed by the reduction of Mn deposition in basal ganglia was reported after treatment in workers exposed to Mn [111]. Taken together, these findings suggest that chelation therapy has a therapeutic benefit with positive results. However, some limitations of chelating therapy should be considered, once that positive results were demonstrated in small sample size [34]. For instance, increased Mn excretion in urine and decreased blood Mn levels may not be associated with significant improvement in clinical symptoms [112,113]. In addition, chelating molecules do not readily cross the blood-brain barrier, thus they exhibit low bioavailability and efficacy, which leads to controversial results regarding amelioration provided by $CaNa_2EDTA$ [114]. Moreover, other limitation is that chelator substances may not be specific to Mn, since they also decrease other essential metals, potentially increasing possible toxic metals in the body [99]. Additionally, common adverse effects in patients receiving chelation therapy consist of fever, headache, nausea, vomiting, gastrointestinal stress. In some cases, severe adverse effects were reported, such as heart and respiratory failure, breathing difficulty, low blood pressure, convulsions, and low blood calcium [99].

3.2 Para-aminosalicylic acid (PAS)

The substance para-aminosalicylic acid (also known as PAS, 4-amino-2-hydroxybenzoic acid or 4-aminosalicylic acid) is used as antibacterial drug for treatment of tuberculosis [115]. PAS consists of carboxyl, hydroxyl and amine groups, providing favorable chelating properties for metals [101]. This substance was tested for three and a half months in a patient chronically and occupationally exposed to Mn, and authors observed improvement in clinical symptoms such as tremor in hands, handwriting ability, and walking [116]. In fact, another study followed one woman who was exposed for 21 years to airborne Mn and, after treatment with PSA, all clinical symptoms and signs of manganism at the time of treatment were improved, while 17 years after treatment, clinically normal conditions were observed [114].

Yuan et al. demonstrated that Mn exposure disturbs the balance of most divalent metals (particularly in cortex), and that PAS post-treatments can repair these alterations [117]. Impaired spatial learning and memory abilities, which were observed in rats after Mn exposure, returned to levels indistinguishable from controls by PAS treatment [118]. In fact, PAS treatment efficiently reversed the Mn-induced learning and memory deficits associated to decreased Mn levels in the whole blood and brain tissue such as cortex, hippocampus and thalamus [119].

Some antioxidant enzymes and neurotransmitters may be affected by Mn exposed and are related with neurodegenerative disease. Consistent with this observation, decreased

glutathione peroxidase and catalase activity were noted in basal ganglia after Mn exposure, which were restored upon PAS treatment [120]. In addition, recent studies have investigated the efficacy of PAS treatment not only as chelating agent to mobilize whole blood Mn, but also in its efficacy to reduce inflammatory cytokines that are related with neurodegenerative diseases, suggesting that PAS may be used to ameliorate and retardate symptoms related with inflammatory responses after Mn exposure [121,122].

3.3 Natural compounds

Plants are frequently able to tolerate extreme concentrations of toxic metals. Such ability has been explored in phytoremediation strategies (e.g., Amaranth (*Amaranthus crentus*)) since Mn can be oxidized and hyperaccumulated in plants [123,124]. Here, we discuss new perspectives considering natural extracts and phytochemicals reported as prevention or therapy alternatives to Mn intoxication. We considered several outcomes from animal models since natural products are not the first choice for the clinical intervention of Mn poisoning.

Oxidative stress has been implied to mediate Mn toxicity; this is a crucial connection for plant extract usage as a therapy, especially for the ubiquitous antioxidant and chemoprotective properties of phytomedicines. Plant metabolites possess chelating activity against several metals, and generally act by improving the activity of endogenous antioxidants (e.g., superoxide dismutase (SOD), catalase (CAT), glutathione *S-transferase* (*GST*)) [125,126]. We discuss here some of the latest outcomes regarding natural compounds or isolated phytomedicines used for Mn-induced toxicity in animal models (Table 1).

Echium amoenum (*E. amoenum*) has been reported as an important source of phenolic compounds, presenting natural antioxidant compounds, such as rosmarinic acid, cyaniding, and delphinidin [127,128]. Phenolic compounds are characterized by their capacity to eliminate high levels of ROS as well as chelating activity for metals [129,130]. The extract of *E. amoenum* invoked beneficial effects by inhibiting Mn neurotoxicity in the rat hippocampus, which was likely related to decreased oxidative stress, caspase 3 and 9 induction, and apoptosis [131]. The neuroprotective mechanisms of *E. amoenum* have been attributed to the presence of cyanidin 3-glucoside, the most common anthocyanin in petals of this plant. Cyanidin 3-glucoside can inhibit inflammation by blocking the translocation of c-Jun and NF-κB factors into the nucleus [132]. Mn has been reported both to activate *c-Jun* and upregulate mRNA expression of NF-κB [133,134]. Moreover, *E. amoenum* also increased catecholamine levels and improved depression-like behavior in rats [131]. Mn overexposure has been invoked to reduce catecholamine levels, which are frequently associated with behavioral changes in different models. including rat, *Drosophila melanogaster* (*D. melanogaster*), and *Caenorhabditis elegans* (*C. elegans)* [131,135,136]. Previous data support the concept that Mn can chemically interact with dopamine, leading to autoxidation and decreased dopamine levels [137].

Açaí (*Euterpe oleracea* Mart.) extract attenuated Mn-induced oxidative stress in primary cultured astrocytes at nutritionally relevant concentrations. The authors also revealed the potential of anthocyanins obtained from açaí to mitigate Mn neurotoxicity [138]. Açaí berry

is consumed worldwide in beverages, fruit mix, ice cream and capsules. Besides the palatable taste, açaí berry provides a unique nutritional profile due the high levels of antioxidant compounds, including carotenoids, flavonoids, anthocyanins, and other polyphenols [139]. Açaí is a Mn dietary source. However, it needs to taken into account that a daily consumption of 300 ml açaí pulp exceeds by six-fold (14.6 mg on average) the reference daily intake of Mn for an adult [140], hence at high consumption açaí may have toxic effects despite it antioxidant properties.

Polyphenolic extract of *Euphorbia supina* (PPEES) has been evaluated against Mn-induced neurotoxicity in both neuroblastoma SKNMC cells and Sprague-Dawley male rat brain. PPEES treatment decreased Mn-induced oxidative stress in both models while reestablished Mn-changed parameters related to endoplasmic reticulum (ER) stress and ER stress-mediated apoptosis markers (GRP78, GADD34, XBP-1, CHOP, Bcl-2, Bax and cleaved caspase-3) [141]. The phenolic features that trigger cellular protection from oxidation have been investigated in the context of several neurodegenerative diseases, including PD and AD [142,143]. In addition to quercetin, eight biologically polyphenols were isolated from *Euphorbia supina* including gallic acid, protocatechuic acid, nodakenin, quercetin 3-O-hexoside, quercetin 3-O-pentoside, kaempferol 3-O-hexoside, kaempferol 3-O-pentoside, and kaempferol [144].

Similar to *E. supina*, *Melissa officinalis (M. officinalis*) presented a neuroprotective role in an AD model [145,146]. *M. officinalis* extract combines free radical scavenging and antioxidant polyphenolic compounds, including rosmarinic acid, trimeric compounds, and some flavonoids [147]. The neuroprotective effect of *M. officinalis* was also observed in Mn-induced neurotoxicity in mice, as well as the attenuation in oxidative stress and recoversion of SOD enzyme activity [148].

In several cases, the pharmacological properties have been assigned to their phytomedical compounds. On the other hand, many studies have compared the differences between the extract effects and the isolated phytomedical compounds (Table2). For instance, the efficacy of the alkaloid boldine, component of boldo *(Peumus boldus)* extract, in preventing/ameliorating the Mn toxic effects in *D. melanogaster* has been shown. Interestingly, while Boldo extract reduced the mortality rate of flies exposed to Mn, boldine did not show such effectiveness [135]. Boldine partially improved the Mn-induced locomotor dysfunction and decreased TBARS levels, which were fully ameliorated by boldo's crude extract [135]. The protective properties of an alkaloid extract from African Jointfir *(Gnetum africanum)* leaf against Mn toxicity was also tested in *D. melanogaster* as a model. The extract counteracted Mn-induced increase in acetylcholinesterase enzyme (AChE) activity, nitric oxide (NO), and ROS levels [149].

Flavonoids belong to a class of secondary metabolites of plants, having a polyphenolic structure and being widely found in fruits and vegetables [150]. It has been recognized that flavonoids show antioxidant and anti-inflammatory activities, as well as anti-mutagenic and anti-carcinogenic properties, and their effects on human nutrition and health are considerable [150]. Their ability to diminish oxidative stress as an antioxidant function includes the capacity of flavonoids to chelate metal ions [130].

Silymarin, an antioxidant flavonoid complex isolated from the seed of *Silybum marinum (milk thistle),* has been reported as an Aβ aggregation inhibitor, antioxidant, and neuroprotective compound [151]. Beyond affecting the CNS, Mn-induced toxicity is inherent to other organs, including the liver, lungs, and heart, as well as the reproductive system [101]. Chtourou et al. investigated the Mn-associated nephrotoxicity, as well as the beneficial effects of Silymarin, which reduced the alterations in the renal and urine markers, decreasing lipid peroxidation endpoints, increasing the antioxidant cascade, and decreasing Mn-induced damage [152].

Human exposure to Mn mainly occurs via intake of contaminated food and water, by occupational sources (inhalation of industrial applications, dust, mist, or fumes with Mn), and by environmental sources which include pesticides containing Mn [101]. Maneb (ethylenebis-dithiocarbamate) is a Mn-containing fungicide whose chronic exposure may produce symptoms and signs of central nervous system (CNS) Mn poisoning. Maneb exposure in rats caused a reduction in fertility and testosterone levels. In contrast, its co-administration with *Basella alba L.* (Basellaceae) extract minimized such changes in reproductive function [153]. *B. alba* showed efficacy in restoring the antioxidant system in the testicular tissue likely due to the presence of various antioxidant compounds, including phenolic compounds, carotenoids, ascorbic acid, saponins, coumarins and limonoids [154]. Finally, beyond the pharmacological advantages of plants usage, an extensive historical background of their consumption is available, thus reducing toxicological risks and adverse effects when compared to newly synthesized molecules.

4. New approaches to identify targets and molecules to treat Mn neurotoxicity and neurodegeneration

Currently, chelators are widely used to treat conditions of Mn overload. Nonetheless, life-long chelation treatment may induce imbalance in other essential trace element and collateral effects such as nausea, causing vomiting, gastrointestinal intolerance and abdominal discomfort [155]. Therefore, to avoid these adverse effects, searching for new targets and new substances for the treatment of Mn poisoning and its related diseases through new approaches such as bioinformatics, is increasing.

Bioinformatics methods have been used to identify key genes and pathways, predicting the possible molecular mechanisms underlying Mn-induced neurotoxicity and neurodegeneration, as well as screen potential molecules to reverse the neurotoxicity or potential therapeutic agents. For instance, to explore a possible molecular mechanism underlying Mn induced AD, a screening of differentially expressed genes showed 140 upregulated and 267 downregulated genes. Using the connectivity map (CMAP) tool, it was shown that Tyrphostin AG-825, an inhibitor of tyrosine phosphorylation, might prevent and reverse process related with Mn induced neurotoxicity and AD [156]. Thus, bioinformatics methods are important tools to investigate potential targets and new therapeutic substances to reverse neurodegenerative diseases.

Proteomic analyses are also an important tool to identify altered proteins. In this regard, a study explored changes in wild type and HD (YAC128Q) mutant mice exposed to Mn. The

results showed changes in proteins involved in the inhibition of glycolysis and energy metabolism, excitotoxicity and dysregulation in cytoskeletal dynamics in the striatal region, suggesting that altered proteins may be used as novel markers of Mn toxicity [157]. Additionally, using a metabolomic approach in HD immortalized striatal neurons of mouse to identify metabolic disruptions after Mn exposure, the authors showed lower metabolite levels of pantothenic acid and glutathione in HD striatal cells compared to control cells. Also, the authors observed impaired induction of isobutyryl carnitine in response to increasing Mn exposure, and induction of metabolites in the pentose shunt pathway, demonstrating that changes in energetic processes underlie the pathobiology of both HD and Mn neurotoxicity [158].

Recently, Fernandes et al. reported metabolomic responses to Mn in SH-SY5Y human neuroblastoma cells, showing that changes in cellular metabolism, such as amino acids, neurotransmitters, energy, and fatty acids metabolism, occur in response to Mn, resulting in subsequent cell death. This suggests that metabolomics analyses represent a valuable approach to investigate and evaluate the toxic molecular responses to Mn toxicity [159].

Kumar et al. performed a high throughput screen of 40,167 small molecules for modifiers of cellular Mn content in a mouse striatal neuron cell line using chemical informatics with stringent validation assays to identify a chemical ‘toolbox’ with 41 small molecules modifiers of neuronal transport [160]. Two of these molecules, VU0063088 and VU0026921, were tested in the *Caenorhabditis elegans* model, showed potential protective efficacy against Mn-induced DAergic neurodegeneration, consistent with partial recovery in DAergic neuronal morphology and behavior in worms exposed to Mn [161]. Another of these molecules (MESM) was found to be a Mn-selective ionophore that rapidly reduced excessive cellular manganese levels in cultured cells (lowering >90% excess Mn levels in ~15 minutes). It is noteworthy; the MESM molecule was able to decrease even the basal levels of intracellular Mn without altering levels of calcium, iron, cobalt, copper, zinc or molybdenum. This specificity suggests that future studies of MESM as a therapeutic molecule in patients with excess levels of Mn may hold promise [162].

Taken together these studies demonstrate that new technical approaches are essential to better understand the molecular mechanisms underlying Mn-induced neurodegenerative disorders, as well as the identification of new targets for its treatment.

5. Conclusions

Mn exposure is an important health issue, mainly for individuals receiving parenteral nutrition and workers in occupational settings that are exposed to high levels from air. Growing evidence suggests the involvement of Mn in neurodegenerative diseases. Chelation therapy with EDTA and PSA has been widely used in response to Mn poisoning. Several studies have advanced the efficacy of several natural compounds and isolated phytochemicals in treating Mn neurotoxicity, its reprotoxic and nephrotoxic effects, secondary to their antioxidant and chelating properties.

Although, the association between Mn overexposure and neurotoxicity has been well characterized, treatment modalities are scarce. Bioinformatics may provide novel insight for pathways and clinical treatments associated with Mn-induced neurodegeneration. Furthermore, research on new therapeutic targets and new substances that can be used in the treatment of diseases related to Mn are necessary and may recognize a new direction in Mn toxicological research.

6. Expert opinion

Mn is required for proper physiological functions in the brain and other tissues, yet at high exposures it may lead to neurological disorders. To date, a limited number of studies have investigated Mn brain levels in of patients afflicted with the neurological diseases mentioned above. Better understanding the role of Mn in these brain diseases is a timely step. In addition, it will be incumbent upon the scientific community to determine whether patients suffering from the above disorders show elevated levels of brain Mn by means of MRI. While readily feasible, it is prohibitable expensive, hence such efforts have been curtailed to date. Therefore, new modalities should be advanced to cost-effectively monitor brain Mn content. Additional emphasis should be directed at developing Mn transport regulators such as the small molecule noted above, which will be able to pharmacologically control Mn homeostasis. The challenge with those, will be also to develop the means to directly target them to those brain areas which exhibit high or low Mn levels. Thus, it is incumbent upon the scientific community to develop large libraries of compounds to screen those that show efficacy in regulating brain Mn levels. In addition, it is abundantly clear that none of the chelators available to date is even remotely efficacious for reducing bodily Mn levels. Hence, a contemporary need exists for the development of new chelators to treat these Mn-induced diseases.

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Article highlights

- Manganese (Mn) is an essential trace element that is required for several physiological process and it has an important function as cofactor of numerous enzymes required for glial and neuronal cells. However, the Mn overload may result in neurotoxicity and development of diseases.
- Neurodegenerative diseases, such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), prion diseases are global public health concern. These diseases are characterized by progressive dysfunction and loss of neurons in certain anatomical regions with a variety of clinical presentations. Environmental factors such as Mn exposure may be involved in the etiology and progression of these diseases.
- Chelation therapy using $CaNa_2EDTA$ and PAS have been utilized to treatment of symptoms related to Mn over exposure. However, several limitations, such as low bioavailability and efficacy, absence of specificity of chelating molecules, difficulty to cross the blood-brain barrier, and potential common and severe adverse effects in patients receiving chelation therapy hinder effective treatment.
- Several natural compounds and isolated phytochemicals have been studied in the treatment of Mn neurotoxicity. Phenolic compounds, such as rosmarinic acid, cyaniding, and delphinidin, and silymarin, an antioxidant flavonoid, have demonstrated promising results in mitigating Mn neurotoxicity.
- Bioinformatic analysis to identify key genes and pathways, predicting possible molecular mechanisms underlying Mn-induced neurotoxicity and neurodegeneration and new approaches such as proteomic and metabolomic analyses are essential to better understand the molecular mechanisms underlying Mn-induced neurodegenerative disorders, as well as the identification of new targets for its treatment.

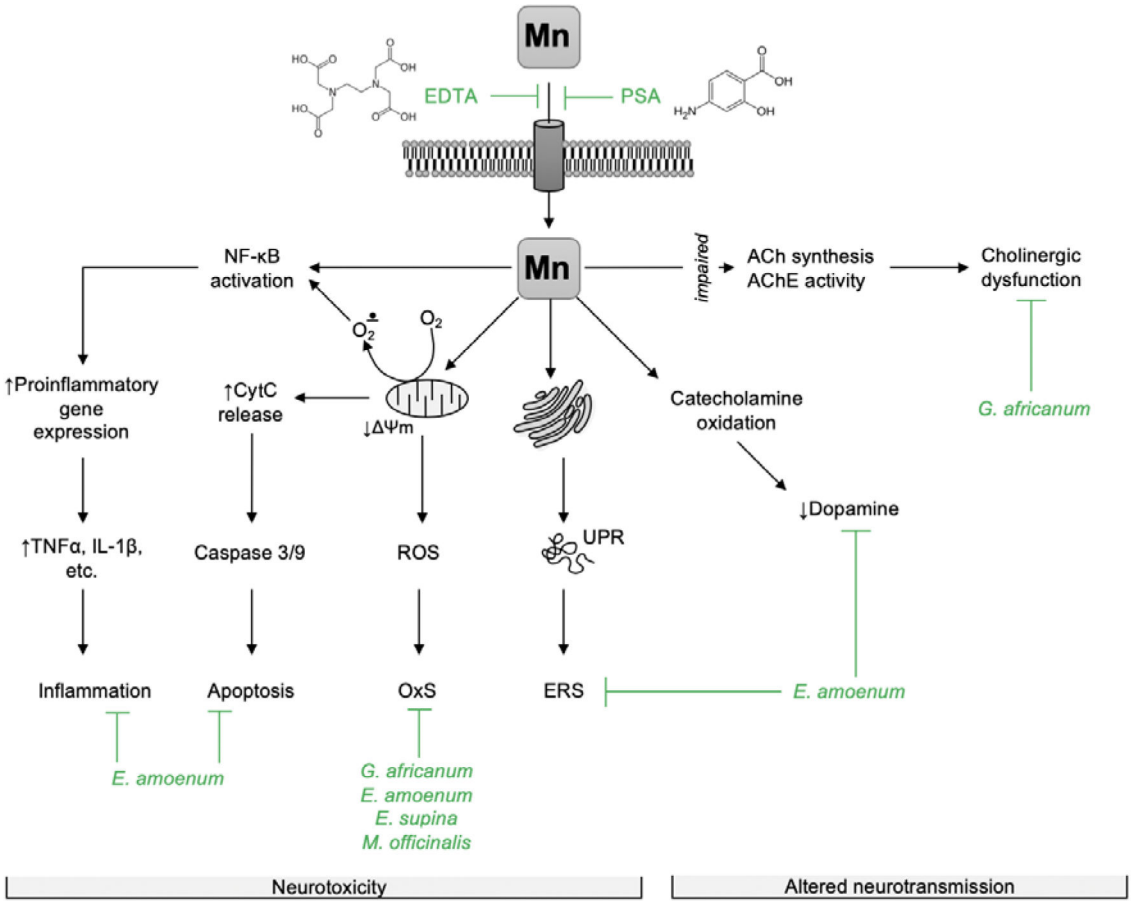


Figure 1.

Potential mechanisms of chelators and phytoextracts against Mn-induced neurotoxicity. Briefly, EDTA and PSA prevent Mn^{2+} from entering the cell, thus reducing its intracellular level and toxic effects. Phytoextracts and particular phytochemicals were shown to counteract mechanisms of Mn^{2+}-induced neurotoxicity including NF-κB activation with subsequent proinflammatory cytokine expression (*E. amoenum*); mitochondrial dysfunction resulting in ROS overaccumulation and oxidative stress (*G. africanum, E. amoenum, E. supina, M. officinalis*), as well as apoptotic signaling (*E. amoenum*); alteration of protein folding, unfolded protein response, and endoplasmic reticulum stress (*E. amoenum*). Natural extracts were also shown to prevent reduction of catecholamine levels due to autooxidation (*E. amoenum*) and counteract cholinergic dysfunction (*G. africanum*). Other plant extracts sharing similar phytochemical spectrum may also possess protective effect. It is also highly expected that these phytoextracts or other phytochemicals may modulate specific mechanisms of Mn^{2+}-induced neurodegeneration, including amyloid-β (Alzheimer's disease) and α-synuclein (Parkinson's disease) aggregation, although direct evidence for these effects have yet to be established.

EDTA - ethylenediaminetetraacetate, PSA – para-aminosalicylic acid, ACh - acetylcholin, AChE - acetylcholinesterase, ROS – reactive oxygen species, OxS – oxidative stress, UPR –

unfolded protein response, ERS – endoplasmic reticulum stress, CytC – cytochrome c, TNFα – tumor necrosis factor α, IL-1β – interleukin 1β.

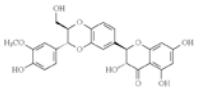
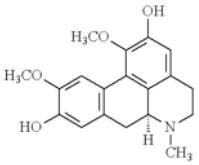
Table 1:

Natural extracts used against Mn toxicity.

Plant	Phytochemical composition	Manganese protective effects	Experimental model
Echium amoenum Fisch. & CA Mey Popular name: Red feathers Family: Boraginaceae	Rosmarinic acid, anthocyanin and delphinidin [127,128]	Anti-apoptotic Antioxidant Increased catecholamine levels Behavioral improvements [131]	Rat
Euterpe oleracea Mart. Popular name: Açaí Family: Arecaceae	Carotenoids, flavonoids, anthocyanins, and other polyphenols [138] [139].	Antioxidant [138]	Primary cultured astrocytes
Euphorbia supine Raf. Popular name: Prostrate spurge Family: Euphorbiaceae	Quercetin, gallic acid, protocatechuic acid, nodakenin, quercetin 3-*O*-hexoside, quercetin 3-*O*-pentoside, kaempferol 3-*O*-hexoside, kaempferol 3-*O*-pentoside, and kaempferol [144]	Reduced the oxidative and endoplasmic reticulum (ER) Reestablished apoptotic markers [141]	Neuroblastoma SKNMC cells and *Sprague-Dawley* male rat brain
Melissa officinalis L. Popular name: Common balm Family: Lamiaceae	Rosmarinic acid and flavonoids [147]	Neuroprotection Antioxidant Reestablished superoxide dismutase (SOD) activity [148]	Mice
Gnetum africanum Welw. Popular name: African jointfir Family: Gnetaceae	Alkaloids [149]	Reestablished acetylcholinesterase (AChE) activity Reduced nitric oxide (NO), and reactive oxygen species (ROS) levels [149]	*Drosophila melanogaster*
Basella alba L. Popular name: Malabar spinach Family: Basellaceae	Phenol compounds, carotenoids, ascorbic acid, saponins, coumarins, limonoids [153]	Improved the reproductive dysfunction induced by Mn-containing compound MANEB [153]	Rat

Table 2:

Plant extract effects on Mn intoxication in animal models

Phytomedicines	Class	Molecular structure	Manganese protective effects	Experimental model
Silymarin (*Silybum marianum*)	Flavonoid		Nephroprotection Decreased lipid peroxidation Antioxidant [152]	Rat
Boldine (*Peumus boldus*)	Alkaloid		Partially improved locomotor dysfunction and TBARS levels [135]	*Drosophila melanogaster*

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