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Biometals in Neurodegenerative Diseases: Their Beneficial and Detrimental Roles in Brain Health.

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ABSTRACT

Biometals are essential to many physiological functions, including the normal functioning and development of the brain. Notably, altered levels of these biometals in the body have been observed in patients living with neurodegenerative conditions like Alzheimer's, Huntington's, Parkinson's, and Amyotrophic Lateral Sclerosis. This review will establish how these biometals can enter and accumulate in the body and the mechanisms for exhibiting neurotoxic effects. Correlations between the level of biometals and other non-essential metals and the existence of neurodegenerative diseases make them worthy of study. Researchers have looked toward biometals and biometal homeostasis as potential sources of biomarkers, diagnostic breakthroughs, and therapeutic solutions for neurodegenerative conditions. In addition, we will explore how biometals can benefit brain health, their role in neurodegenerative conditions, and the next frontiers in biometal-based diagnostics and therapy research.

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1. INTRODUCTION

The importance of biometals to living organisms, humans especially, is evident in the fact that almost 40% of human proteins require a biometal cofactor to facilitate their activity (Gonzalez-Alcocer et al., 2023; Teh et al., 2024; Zoroddu et al., 2019). The importance of these biometals to the normal functioning of the body and brain means that the body employs cell entry mechanisms to control their intake, homeostatic regulation to maintain physiologically safe levels and cell extrusion mechanisms to remove toxic metal accumulation (Leal et al., 2023; Martinez-Finley et al., 2012; Teh et al., 2024; Zhang et al., 2023).

Biometals such as copper, zinc, iron, and manganese are important to developing CNS function, brain organisation, neurotransmission, and neuronal differentiation. Their absence or imbalance, particularly of those connected with redox activity, could lead to higher levels of oxidative stress, cognitive deficits and the consequent development of neurodegenerative diseases (Chin-Chan et al., 2022; Leal et al., 2020; Wandt et al., 2021).

These neurodegenerative diseases are more likely to occur as people age; they develop due to a loss of function in nerve cells and have no cure (Ijomone et al., 2020; National Institute of Environmental Health Sciences, 2022; Reitz et al., 2023; Vegeto et al., 2020; Younas et al., 2022). The most common of them is Alzheimer's disease, but other popular ones include Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS) (Alzheimer's Association, 2024; Davenport et al., 2024; Toader et al., 20224).

Leal et al. (2020) used the link between biometal biology and neurodegenerative diseases to justify metal-based therapy or biometal pharmacology research. Specific links between the development of neurodegenerative diseases and biometals remain elusive. Still, studies have shown that biometal dyshomeostasis and toxic metal accumulation are commonly found in patients living with neurodegenerative conditions (Li et al., 2017; Grubman et al., 2014).

Studies have shown that copper, zinc, iron, and selenium have beneficial properties. However, when in excess, they can lead to the hyperphosphorylation of tau protein and an increase in oxidative stress (Lavado et al., 2019). On the other hand, calcium and magnesium had favorable effects on the regulation of biometal uptake. The study on the relationship between biometals and iron-binding proteins demonstrates that Zinc, Magnesium, and Calcium ions have beneficial effects on amyloid β-peptide. In contrast, Iron (II) and Copper (II) ions exert harmful effects, and both Zinc and Iron (II) ions have detrimental effects on tau protein (Lavado et al., 2019). This review will examine the importance of biometals in brain health, their roles in neurodegenerative diseases, and their potential as biomarkers for diagnostic and therapeutic purposes.

2. ESSENTIAL BIOMETALS AND THEIR ROLES IN BRAIN HEALTH

Biometals have broad applications in health and have been applied in therapeutic solutions, supplementation, and diagnostic tools. However, such applications are only possible because many biometals possess inherent physiological importance (Colombo et al., 2014; Ghosh et al., 2016). These metals have both beneficial and detrimental roles in the brain as shown in Table 1 (Foulquier & Legrand, 2020; Ghosh et al., 2016; Honrath et al., 2017; Scassellati et al., 2020).

Some biometal activity directly impacts aspects of central nervous system function (Figure 1), which may impact brain development, function, and health. Some of these biometals, such as copper, zinc, iron, etc., are essential for many physiological functions. For example, copper has many physiological functions, including as a static enzyme cofactor (in energy production and maintenance, synthesis of biocompounds, etc.) and as a dynamic signalling molecule (for kinases, lipolysis, regulation of potassium channels, etc.) (Tsang et al., 2021). Regarding the brain and nervous system specifically, copper has roles in synaptogenesis, neuromodulation, neuronal differentiation, and synthesising neuropeptides and neurotransmitters (Gonzalez-Alcocer et al., 2023). The metal also plays a role in Superoxide Dismutase 1 (SOD1), which detoxifies and neutralises reactive oxygen species, thus helping to reduce oxidative stress (Chen et al., 2022; Litwack, 2018).

Like copper, zinc also offers antioxidant protection by maintaining SOD-containing zinc and protecting sulfhydryl groups in proteins to improve the antioxidant capacity of biological systems (Litwack, 2018; Oyagbemi et al., 2021). In a study conducted on Peruvian children aged 6–18 months, zinc supplementation supported normal neurodevelopment (Colombo et al., 2014). Zinc is just as popularly helpful in biological processes, and studies have shown that it is essential for neuronal signalling and helps modulate neuronal plasticity and synaptic activity in humans of all ages and stages (Kumar et al., 2021; Li et al., 2022). Along with selenium, it also plays a part in detoxification following non-essential metal poisoning, consequently preventing and suppressing their neurological and cancer-causing effects (Chasapis et al., 2020; Hudson et al., 2025).

As a biometal, iron is important in many physiological processes, including oxygen transport and

DNA synthesis (Chen et al., 2025). Iron is also a cofactor for enzymes required in lipid, cholesterol, and ATP synthesis and is directly needed for myelination in the CNS (Cheli et al., 2020; Teh et al., 2024). The synthesis of neurotransmitters such as serotonin, dopamine, and noradrenaline depend on iron, as the metal functions as a cofactor for tryptophan hydroxylase and tyrosine hydroxylase (Berthou et al., 2021). Metals like iron and copper, etc., that are redox active and participate in electron transfer reactions are important to brain health because of their links with the development of oxidative stress, and their homeostasis must be maintained (Acevedo et al., 2019; Jomova et al., 2022). In cases where they are not maintained, high levels of iron and copper have been linked with mild cognitive impairment and Alzheimer's disease (Mateo et al., 2023).

Other biometals have biological effects on brain health and development as well. Manganese and magnesium have antioxidant neuroprotective effects. Manganese also interacts with neurotransmitter systems, with its effects particularly felt in dopaminergic neurotransmission and neuromotor function (Balachandran et al., 2020; Taylor et al., 2023). Mathew & Panonnummal (2021) reported that certain brain functions are linked to the concentration of magnesium ions in the cerebrospinal fluid. The alteration of this concentration correlates with the presence of neurological disorders. In line with other effects of abnormalities in the concentration of these essential biometals, the prevalence of Parkinson's dementia correlates with increased levels of manganese, iron, and zinc (Mateo et al., 2023).

Selenium, which has one of the narrowest ranges between deficiency and toxicity levels of all biometals, supports antioxidant systems via its incorporation as selenoproteins and can cause cognitive decline when deficient and other neurological problems when in excess (Collins, 2017; Genchi et al., 2023).

Table 1: Beneficial and detrimental roles of metal ions in the brain

Biological Processes	**Neurotoxic Effects**
Enzymatic activities	Neuroinflammation
Learning and memory	Oxidative stress
Mitochondrial functions	Dysregulation of signaling and metabolic pathways
Myelination	Pathogenic peptide aggregation
Synaptogenesis and plasticity	Apoptosis induction
Neurotransmission	Loss of synaptic transmission
Inflammation	Metal imbalance

Source: Scassellati et al., 2020.

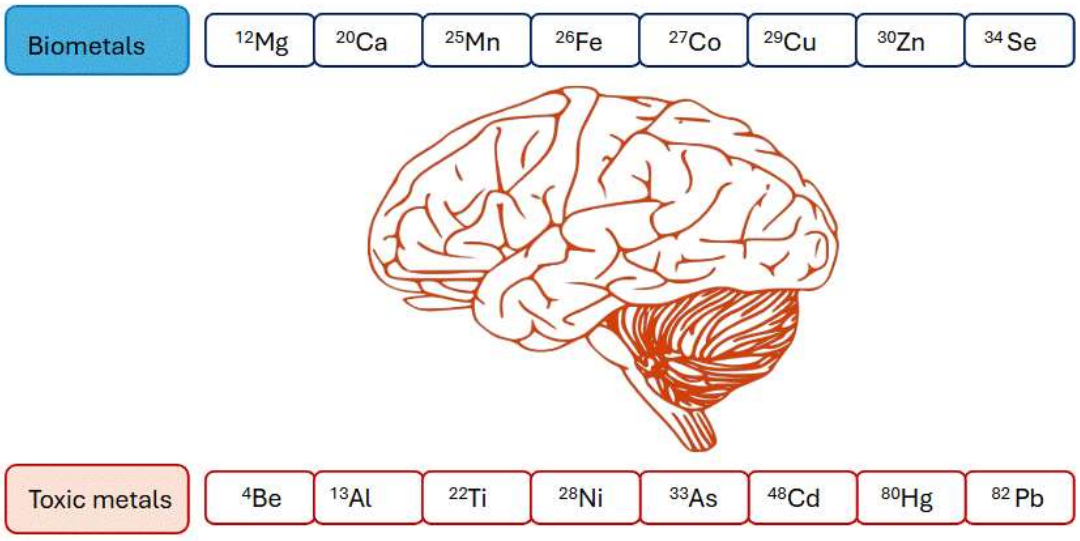

Figure 1: Essential and toxic metals in brain Health (Scassellati, et al., 2020).

Mg- Magnesium, Ca - Calcium, Mn - Manganese, Fe - Iron, Co - Cobalt, Cu - Copper, Zn - Zinc, Se - Selenium, Be – Berylium, Al – Aluminium, Ti – Titanium, Ni – Nickel, As – Arsenic, Cd – Cadmium, Hg – Mercury, Pb – Lead.

3. ROLES OF TOXIC AND NON-ESSENTIAL METALS IN NEURODEGENERATION

Despite being the third most common metal in the earth's crust, aluminium is widely seen as a neurotoxin and one that is not excreted from the brain quickly (Exley, 2014; Kawahara et al., 2021). In various studies in animal models, aluminium has been shown to compete with the iron transporter (transferrin), influence calcium homeostasis, affect the permeability of the blood-brain barrier, and negatively impact the neuronal glutamate nitric oxide-cyclic GMP pathway (Dales & Desplat-Jégo, 2020; Pérez et al., 2005; Walton, 2012).

A review of studies on the role of heavy metals in neurotoxicity showed that cadmium and arsenic led to the formation of reactive oxygen species, increased oxidative stress, caused neuroinflammation, and led to neuronal death (Branca et al., 2018; Garza-Lombó et al., 2019; Vellingiri et al., 2022).

It is not only non-essential metals that can cause neurotoxicity, the dual nature of essential metals is exemplified by manganese, which, when present in elevated levels, leads to neurological symptoms in people of all ages and sexes (Peres et al., 2016; Singirisetty et al., 2025). It is also important to recognise the relationship between essential and toxic metals. Since some metals share the same transporters, a low dietary intake of essential metals can leave more transporters unoccupied, potentially leading to increased absorption of toxic metals (Bressler et al., 2007; Leal et al., 2023).

4. MECHANISMS OF BIOMETAL-INDUCED NEUROTOXICITY

Homeostasis of the essential biometals is important, and when impaired, a resulting imbalance can initiate neurodegeneration via multiple mechanisms (Pokusa & Kráľová Trančíková, 2017; Wilson et al., 2023).

Murumulla et al. (2023) study on heavy metal-mediated neurodegeneration identified neuroinflammation, oxidative stress, dysregulation of signalling and metabolic pathways, apoptosis induction, metal imbalance, loss of synaptic transmission, and pathogenic peptide aggregation as some of the most common mechanisms for metal-induced toxicity and neurodegeneration. These findings are consistent with those of Ketlen et al. (2021), who found that lead caused oxidative stress, negatively impacted cell metabolism and signaling, modulated neurotransmission-related proteins, and impaired motor function when administered to adult Wistar rats.

Different pathomechanisms that feed off dyshomeostasis of biometals in the brain have also been suggested for Huntington’s disease, which includes mitochondrial dysfunction, impaired autophagic breakdown, alteration in essential genes such as brain-derived neurotrophic factor (BDNF), impairment of synaptic transport, and neuroglia dysfunction (Nabi & Tabassum, 2022; Research Anthology on Diagnosing and Treating Neurocognitive Disorders, 2021, pp. 59–69).

Furthermore, several studies have indicated a relationship between abnormal protein expression, accumulation of biometals, and the development of neurodegenerative diseases (Bourdenx et al., 2017; Koszła & Sołek, 2024). Abnormal protein aggregation is a hallmark of various neurodegenerative diseases (Bäuerlein et al., 2020; Vendredy et al., 2020). Metals such as copper (II) interact with tau and Amyloid-βeta proteins and thus affect their aggregation and toxicity in the brain (Di Natale et al., 2022; Martic et al., 2013; Savelieff et al., 2013). Similarly, they may interfere with Apolipoprotein E expression, the most potent genetic risk factor for late-onset AD (Lippi et al., 2021; Zhang et al., 2022).

The blood-brain barrier partly maintains the homeostasis of the brain via its control over the exchange of materials across the brain parenchyma (Knox et al., 2022). Blood-brain barrier disruption is also another mechanism of metal accumulation and can be caused by neuroinflammation, healthy ageing, trauma, genetic factors, and oxidative stress (Aragón-González et al., 2022; Yokel et al., 2006; Zheng et al., 2012). The blood-brain barrier has long been recognised to be a target for lead toxicity (Zheng et al., 2003)

However, biometal-induced cognitive decline can occur independently of neurodegenerative conditions. For instance, aluminium can lead to a gradual increase in inflammatory events within the ageing brain, thus complementing the presence of neurodegenerative diseases like Alzheimer's and aiding cognitive decline (Bondy, 2010; Bondy & Campbell, 2017; Zhu et al., 2023).

5. SOURCES AND PATHWAYS OF BIOMETAL ACCUMULATION

Biometals can enter and accumulate in the body via various routes as shown in Figure 2. Heavy metals, naturally abundant in the environment and present in pesticides, herbicides, and various industrial pollutants, can contaminate the body and cause neurotoxicity (Bradl, 2005; Micó et al., 2006). Their toxicity depends on concentration, exposure duration, and entry route (Jyothi, 2020). Additionally, heavy metals can disrupt the balance of essential biometals by interfering with gene expression and metabolic pathways, leading to either accumulation or deficiency (Rehman et al., 2021; Schauder et al., 2010). For example, heavy metals can compete with iron for transporters, affecting the cellular iron pool and binding to proteins (Schauder et al., 2010).

The body obtains its essential biometals from food sources and water (Kawahara et al., 2023; Pfaender & Grabrucker, 2014). Manganese is ingested in water and food and is readily absorbed through the intestine. However, it competes with other metals (particularly iron) for absorption via the divalent metal transporter 1 (DMT1); as such, a deficiency of iron in the diet can increase manganese (Liu et al., 2025; Mani et al., 2021). Iron dyshomeostasis is prevented through regulatory mechanisms that enhance metabolic activity in the liver while reducing absorption in the gastrointestinal tract (Darshan, 2007; Soares et al.., 2020). Furthermore, manganese can accumulate due to occupational exposure via inhalation, as it is readily absorbed by the lungs and enters circulation through the ZIP8 and ZIP14 transporters (McCabe & Zhao, 2024).

Bakulski et al. (2020) report that primary exposure to lead is via lead dust and water from lead pipes, while cadmium contaminates the body primarily through inhalation and smoking. However, the entry of metals into the body is not limited to ingestion, inhalation and absorption through the skin. For example, orthopaedic implants have been linked to chromium and cobalt exposure (Agarwal et al., 2021; Ajibo et al., 2023).

However, the potential for the accumulation of any metal and neurotoxic effects in the brain requires adequate transportation in the body and the ability to cross the blood-brain barrier (Li et al., 2021; Zheng & Monnot, 2012). For instance, mercury achieves this via its association with a methyl group to form methylmercury, and Copper can build up in the brain because of mutations to ATP7A that affect the removal of the excess intracellular metal (Agarwal et al., 2021; Martinez-Finley et al., 2012; Puty et al., 2019).

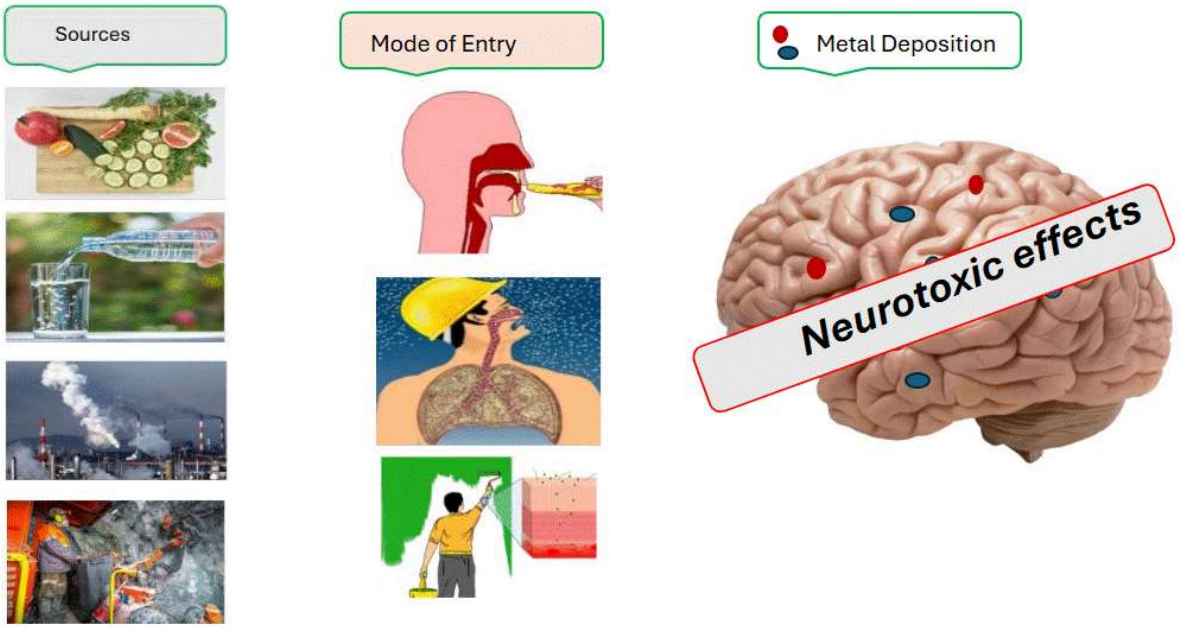

Figure 2: Sources and mode of entry of metals into the human body (Agarwal et al., 2021).

6. BIOMETALS AS MARKERS IN NEURODEGENERATIVE DISEASES

Biometals are essential metals that play biological roles and have broad applications in health, disease, drug development, and drug delivery (Ghosh et al., 2016; Prakash et al., 2017; Skalny et al., 2021). As individuals age or develop neurodegenerative diseases, the normal balance (homeostasis) of essential biometals such as zinc, copper, and iron in the brain is disrupted, leading to their accumulation in specific regions, like microscopic proteopathies. At the same time, other areas or cells may experience deficiencies (Barnham & Bush, 2014).

The absence of specific biomarkers for neurodegenerative diseases negatively affects the prospects of early detection and treatment, and identifying such biomarkers for the assessment of previous exposure to neurotoxicants holds the key to effective and timely care of these disorders (Nabi & Tabassum, 2022; Witt et al., 2020).

Several hypotheses, including oxidative stress, amyloid-β aggregation, and the accumulation of tau-forming neurofibrillary tangles, have been proposed in

the pathobiology of Alzheimer's disease, yet none have led to an approved diagnostic framework or cure (Fasae et al., 2021; Lavado et al., 2019); however, Mesa-Herrera et al. (2022) found that alterations in CSF biometal levels, antioxidant and detoxifying activities, along with signs of mild cognitive impairment, may serve as more reliable early-stage Alzheimer's disease identifiers than classical markers of proteinopathy.

Like many neurodegenerative diseases, the cause of Parkinson's is unknown. However, mitochondrial dysfunction, oxidative stress, inhibition of the ubiquitin-proteasome system (UPS), and autophagy have been shown to impact dopaminergic neuronal health negatively (Gonzalez-Alcocer et al., 2023). The aggregation of alpha-synuclein, a key player in Parkinson's disease, has been enhanced by biometals such as copper, aluminum and magnesium (Maass & Lingor, 2018). In a study by Genoud et al. (2020), copper and iron were quantitatively indicated in the development of Parkinson's disease. They found that copper and iron levels were significantly higher and lower, respectively, in the degenerating substantia Nigra. In contrast, iron levels in the serum were higher than in the control group. Also, Squadrone et al. (2019) found an increased level of iron, chromium, selenium, zinc, and arsenic in the blood of patients with Huntington's disease.

7. THERAPEUTIC STRATEGIES TARGETING BIOMETAL HOMEOSTASIS

Interaction between proteins and biometals in the nervous system is important to developing, preventing, and suppressing neurodegeneration (Singh et al., 2024). Targeting biometals by restoring metal ion homeostasis represents a promising exploratory approach for treating neurodegenerative diseases such as Alzheimer's disease (Mesa-Herrera et al., 2022; White et al., 2017). The study by Babić Leko et al. (2022) further supports the findings that biometals hold potential as new avenues for diagnostic development and therapeutic strategies in Alzheimer's disease (AD) research. Their study revealed a positive correlation between essential metals (Calcium, Cobalt, Copper, Iron, Magnesium, Manganese, and Zinc), heavy metals (Arsenic, Mercury, Nickel, and lead) and essential non-metals (such as Selenium) with CSF biomarkers of Alzheimer's disease, including phosphorylated tau isoforms, Visinin-like protein 1 (VILIP-1), S100 calcium-binding protein B (S100B), Neurofilament light chain (NFL), and Chitinase-3-like protein 1 (YKL-40).

However, despite recognising the link between biometal dyshomeostasis and Alzheimer's disease, as well as the potential of metal chelation as a therapeutic approach, the lack of relevant data, definitive conclusions, and potential complications associated with chelator use have remained significant barriers to its implementation (Gucký & Hamuľaková, 2024). Aaseth et al. (2016) proposed the use of selenium as a prophylactic in Alzheimer's disease and supplement for Europeans with mild cognitive impairment, citing its role in overcoming extracellular selenium trapping by beta-amyloid (Aβ) in the brain, its ability to cross the blood-brain barrier, and its tolerability as selenised yeast. According to Yadav et al. (2023), the accumulation of certain biometals and the suspicions surrounding their caused oxidative stress in Alzheimer's pathogenesis mean that antioxidant vitamins C, E, and B12 could play significant roles in Alzheimer's disease therapy. In addition, Benson et al. (2023) suggested molybdenum and iodine as potential new frontiers in investigating Alzheimer's therapy and diagnosis. They proposed that future research should strive to determine the expected level of iodine in the brain and establish the mechanism by which iodine and molybdenum exert their effects on brain function.

8. FUTURE RESEARCH DIRECTIONS AND CONCLUSION

Future directions in developing therapeutics for neurodegenerative diseases may focus on restoring metal homeostasis in the brain. While metal chelators have been successful in treating metal overload diseases like hemochromatosis and Wilson's disease, they are not suitable for neurodegenerative conditions due to their inability to cross the blood-brain barrier and their indiscriminate removal of essential metals from the brain (Barnham & Bush, 2014). To address this, new approaches are needed to design brain-penetrant, moderate-affinity chelators that selectively target misdistributed or accumulated metals without disrupting essential neurochemical processes. This represents a novel pharmacological challenge, as no chelating agents are currently approved for clinical use. Researchers must innovate new strategies to safely modulate metal homeostasis in the brain, opening the door to potential disease-modifying treatments for neurodegenerative disorders. Benson et al. (2023) went on to identify several potential biometal research lines for future studies into effective Alzheimer's therapy. Some of these include cobalt and its subsequent effect on vitamin B12 and PIN-1 (peptidyl-prolyl cis-trans isomerase NIMA-interacting 1), molybdenum, and iodine.

From a diagnostic perspective, further research into multimodal imaging of metal distribution within biological samples could aid the understanding of biometal homeostasis (New et al., 2017; Perry et al., 2020). In conclusion, biometals play both beneficial and detrimental roles in the body, particularly in the brain. As such, altered levels of these metals make them worthy candidates for potential biomarkers and therapeutic strategies in diagnosing and treating neurodegenerative diseases.

Competing Interests: The authors declare no competing interests.

Authors' Contributions

T. Akingbade conceptualised and drafted the review. E. Ojo and O. Adebisi conducted the literature search. T. Akingbade and E. Ojo revised the manuscript, and T. Akingbade and O. Adebisi handled table and figure preparation. T. Akingbade and E. Ojo provided supervision. All authors reviewed and approved the final manuscript.

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