Deciphering the Significance of Metal Ions in the Pathogenesis of Alzheimer’s Disease and Forging Pathways Towards Prospective Therapeutic Strategies

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Abstract

Alzheimer’s disease (AD), a neurodegenerative condition, is characterized by its progressive cognitive decline, which includes memory impairment, language alterations, visuospatial challenges, and compromised executive functions. The primary pathological features of AD involve the formation of extracellular senile plaques primarily composed of β-amyloid (Aβ) and the accumulation of hyperphosphorylated tau proteins, leading to the creation of neurofibrillary tangles. With an aging global population and a lack of effective AD treatments, there is an urgent need for comprehensive AD research. Metallic elements like iron, zinc, copper, and manganese play essential roles in human development, metabolic pathways, and brain maturation. Accumulating evidence suggests that these metal ions significantly influence the development of AD, contributing to processes such as Aβ deposition, oxidative stress, neuroinflammatory responses, and disruptions in autophagy and apoptosis, among other cascading effects. Therefore, a thorough investigation into the relationship between metals and AD is crucial, not only to identify new pre-pathogenic interventions targeting metal ions but also to support the development of tailored AD treatments. This manuscript extensively explores the connection between metallic elements, specifically copper, iron, zinc, and manganese, in physiological processes and their intricate relationship with AD. It emphasizes the importance of understanding the regulation of the metal ion signaling network throughout the AD continuum to offer new perspectives and potential approaches for developing innovative metal ion modulators to combat AD. This research holds promise for addressing the global challenge of AD.
Abstract: Alzheimer’s disease (AD), a neurodegenerative condition, is characterized by its progressive cognitive decline, which includes memory impairment, language alterations, visuospatial challenges, and compromised executive functions. The primary pathological features of AD involve the formation of extracellular senile plaques primarily composed of β-amyloid (Aβ) and the accumulation of hyperphosphorylated tau proteins, leading to the creation of neurofibrillary tangles. With an aging global population and a lack of effective AD treatments, there is an urgent need for comprehensive AD research. Metallic elements like iron, zinc, copper, and manganese play essential roles in human development, metabolic pathways, and brain maturation. Accumulating evidence suggests that these metal ions significantly influence the development of AD, contributing to processes such as Aβ deposition, oxidative stress, neuroinflammatory responses, and disruptions in autophagy and apoptosis, among other cascading effects. Therefore, a thorough investigation into the relationship between metals and AD is crucial, not only to identify new pre-pathogenic interventions targeting metal ions but also to support the development of tailored AD treatments. This manuscript extensively explores the connection between metallic elements, specifically copper, iron, zinc, and manganese, in physiological processes and their intricate relationship with AD. It emphasizes the importance of understanding the regulation of the metal ion signaling network throughout the AD continuum to offer new perspectives and potential approaches for developing innovative metal ion modulators to combat AD. This research holds promise for addressing the global challenge of AD.

Keywords: alzheimer’s disease; metal ions; beta-amyloid; hyperphosphorylated tau protein; oxidative stress; neuroinflammation

Introduction

Alzheimer’s disease (AD) represents a manifestation of dementia, characterized foremost by the inexorable descent into cognitive decline. Evident clinical manifestations encompass, albeit are not confined to, memory deficits, linguistic alterations, and disruptions in visual-spatial or executive functioning [1]. AD’s definitional pathological underpinnings revolve around escalated amyloid-β (Aβ) concentrations, culminating in extracellular senile plaque deposition, and the accrual of intracellular neural protofibrillary tangles (NFTs) comprising hyperphosphorylated tau protein (p-tau) [2, 3]. Epidemiological inquiries reveal that dementia afflicts an estimated 50 million individuals on a global scale, a predicament further exacerbated by the burgeoning aging demographic. AD, in particular, has emerged as an ominous international challenge, poised to escalate the count of its afflicted populace to an alarming 152 million by 2050. This projection portends dire ramifications, adversely impacting the quality of life among older adults and thrusting substantial strain upon both families and society at large [4, 5]. It is paramount to emphasize that prevailing therapeutic strategies offer but modest amelioration of cognitive functioning, and a remedy for AD remains an elusive quest. Consequently, a zealous and unwavering commitment to AD research is an imperious mandate in our present age.

In the quest to unravel the etiology of AD, a multitude of epidemiological investigations and comprehensive meta-analyses have underscored potential lifestyle modifications, medical antecedents, and exposure to occupational and environmental contaminants—such as pesticides, air pollutants, and heavy metals—as plausible AD risk factors [6]. Within the confines of physiological homeostasis, metallic elements, including iron, zinc, copper, and manganese, orchestrate pivotal roles in human growth, metabolic pathways, and cerebral development. Consequently, perturbations in metal ion equilibrium may precipitate diverse maladies within the human organism [7]. AD, an affliction characterized by a complex pathogenesis and a multitude of risk factors, has been the subject of meticulous scrutiny, revealing the potential involvement of metal ions across various facets of AD pathogenesis. These ions are implicated in the promotion of Aβ deposition, NFTs initiation, induction of oxidative stress, neuroinflammatory responses, autophagic dysregulation, and apoptotic cascades. Recognizing the pivotal role of metal ions in the realm of AD, a comprehensive grasp of the nexus between metals and AD not only furnishes strategic avenues to counteract metal ion-related damages antecedent to the onset of the disease but also offers targeted therapeutic objectives. This treatise canvases the physiological roles of metallic species, such as copper, iron, zinc, and manganese, in the con-
text of AD, with the intention of engendering novel insights and orientations for the formulation of chelation agents directed at metal ions, to ameliorate AD pathology by restoring the signaling framework through which metal ions modulate AD progression.

**Metal Ions in Living Systems**

Metal ions exert a panoply of vital functions within the realm of living organisms. Their multifaceted contributions encompass: (i) **Enzyme Catalysis**: Eminent among these roles is their function as essential cofactors for a myriad of enzymes. Prominent examples include zinc, copper, and iron, which act as cofactors in numerous enzymatic processes, expediting crucial biochemical reactions. For instance, zinc assumes a pivotal role in various enzymes, including DNA synthetases and degradative enzymes of enzyme inhibitors, thereby exerting a profound influence on cell division and DNA repair dynamics [8-11]. (ii) **Cellular Structural Stability**: Further underscored is the role of metal ions such as calcium, magnesium, and iron in upholding the integrity of cell membranes and the formation of the cytoskeleton. These processes constitute indispensable cornerstones for the regular form and function of neurons [12-14]. (iii) **Nerve Conduction**: Another cardinal facet of metal ion involvement resides in their contributions to electrical signaling between neurons. Ions like sodium, potassium, calcium, and magnesium occupy pivotal positions in the regulation of membrane potential in neural cells. Their orchestration is indispensable for cogitative processes, cognitive memory, and motor function [15-17]. (iv) **Antioxidant Defense**: Lastly, a subset of metal ions, including zinc, copper, and selenium, assumes a prominent role as constituents of antioxidant compounds. These agents act to neutralize free radicals and mitigate oxidative stress, thus affording a protective shield to neural cells against oxidative damage [18-20]. In summary, metal ions are integral components of the intricate machinery that sustains life. Their diverse physiological roles reverberate through the intricate tapestry of living organisms, profoundly affecting the health and function of the nervous system.

**The Role of Metal Ions in AD**

Metal ions assume a pivotal role in the intricate dynamics of the nervous system, where perturbations in their levels, either excessive or deficient, wield the potential to exert detrimental consequences upon neural function. Their influence on the pathogenesis of AD traverses multifarious pathways, including, but not confined to, the subsequent avenues: (i) Metal ions manifest a paramount regulatory influence within the nervous system, with a particular emphasis on synaptic transmission. This regulatory orchestration stands as a linchpin for erudition, memory consolidation, and its corollary, neurodevelopment and neuroprotection. (ii) Iron ions, integral constituents of hemoglobin, occupy a pivotal role in the transport of oxygen to the cerebral and neural tissues. Any insufficiency in iron availability precipitates anemia, thereby engendering adverse repercussions on cerebral functionality. (iii) The stewardship of neuronal membrane potential constitutes yet another facet of metal ions’ purview, with deviations from the norm engendering heightened neural excitability and the concomitant onset of neurological maladies.

**Metal ions and Alzheimer’s**

The amyloid cascade hypothesis stands as the prevailing paradigm in our comprehension of AD pathogenesis. This hypothesis underscores the primacy of the Aβ protein contained within the cerebral amyloid deposits characterizing the ailment. The genesis of these amyloid deposits hinges on the proteolytic generation of Aβ peptides from the amyloid precursor protein (APP), a process executed via the amyloidogenic pathway, orchestrated through enzymatic cleavage executed by β- and γ-secretase enzymes. The subsequent aggregation of these Aβ peptides into amyloid plaques has been well documented [21, 22]. Key mechanisms governing Aβ generation entail missense mutations in the APP, PSEN1, and PSEN2 genes, which have been revealed to trigger augmented release of Aβ, resulting in the formation of longer Aβ peptides. In terms of the intricacies of Aβ clearance mechanisms, both genetic factors and aberrant Aβ degradation serve to exacerbate Aβ aggregation and oligomerization in the limbic and associated cortex. These Aβ oligomers exert a detrimental influence on synaptic function, ultimately culminating in the development of NFTs, which progressively evolve into the characteristic plaque structures [23, 24]. The interplay between metal ions and Aβ entails multifaceted biochemical mechanisms that may exert a modulatory effect on AD development. This influence arises from the binding of metal ions to Aβ proteins, thereby affecting Aβ aggregation and interfering with the clearance of Aβ [25-28]. Notably,
metal ions such as copper, zinc, iron, and aluminum possess the capability to engage in ligand bonds with functional groups present within the amino acid residues of Aβ proteins. Such binding events induce conformational alterations and aggregation state changes in Aβ proteins. Consequently, they contribute to the aggregation of Aβ proteins, ultimately culminating in the formation of Aβ plaques and fibronectin, the principal pathological features observed in the AD-afflicted brain. Furthermore, excessive or anomalous binding of metal ions may perturb the Aβ clearance mechanism, leading to the abnormal accumulation of Aβ. In the realm of iron homeostasis disruption, the repercussions extend to the cerebral Aβ milieu [29]. Elevated iron concentrations or iron overload instigate structural perturbations within the iron response element region (IRE) of APP mRNA, engendering augmented APP expression and concurrent elevation of Aβ levels. Conversely, in instances of diminished intracellular iron, iron-regulated protein 1 finds affinity with the APP mRNA IRE, thereby diminishing Aβ42 synthesis [30, 31]. The culmination of Aβ42 aggregates, birthing the genesis of amyloid plaques. Intriguingly, experimental cellular inquiries unveiled the promoting influence of iron (III) on Aβ42-related neuronal deterioration [32]. Noteworthy is the affinity of copper to Aβ under a spectrum of pH conditions, particularly through histidine, aspartic acid, glutamic acid, and alanine residues, establishing a high binding affinity to Aβ42. This binding affinity, in turn, substantiates an influential sway upon Aβ aggregation and fibrillar formation [33–37]. Moreover, copper, through interactions with Aβ, forges copper and amyloid-β (Cu-Aβ) complexes wielding peroxidase activity, which may be the harbinger of AD-related oxidative insult, emerging as a novel hallmark of this pathological malaise [38]. Parallel to copper, structural zinc assumes a pivotal role, binding tenaciously to proteins and peptides, and undertaking a pivotal function in proper protein folding, catalytic/co-catalytic duties, and numerous enzymatic endeavors [39]. Zinc exhibits dichotomous comportment, manifesting cytotoxicity toward Aβ and associated cytotoxicity persists as a point of contention [40]. At diminished concentrations, zinc serves a defensive role against Aβ neurotoxicity by seemingly mitigating Aβ levels in PC12 cells, attributable to a decline in γ-secretase activity [41]. In contraposition, escalated zinc levels engender an upswing in APP levels, as well as heightened β- and γ-secretase activities, whereby elevating sAPPβ secretion vis-à-vis sAPPα in transgenic murine brains [42, 43]. Notably, zinc, at high concentrations, intertwines with Aβ, harnessing histidine residues to expedite the formation of the noxious oligomeric entity, Zn-Aβ, representing a distinctive pathway [44, 45]. This collective mélange of perturbations constitutes a significant facet of Aβ pathology. On a distinct metal note, aluminum emerges as a pathological instigator in the pathogenesis of AD, imparting neurotoxicity and substantiating influence upon Aβ genesis [46]. Preliminary investigations elucidate the propensity of aluminum ions to potentiate the aggregation of physiological Aβ concentrations in vitro [47]. In animal models, the introduction of aluminum leads to augmented levels of APP and Aβ within the neurons of treated rodents [48, 49]. Furthermore, in vivo, Al triggers a conformational metamorphosis in Aβ peptides, inducing a β-sheet configuration, thereby accelerating Aβ aggregation into senile plaques. Concomitantly, aluminum profoundly stimulates the assembly of APP, β-secretase, γ-secretase enzymes, and the production of Aβ42, all of which contribute to the conglomeration of pernicious amyloid species [50–52]. Lastly, the influence of certain metal ions, such as magnesium and manganese, upon Aβ levels and the ensuing trajectory towards AD development is a subject warranting further scrutiny. Elucidation of the underlying mechanisms necessitates additional exploration [53–56].

Metal Ions and Tau Protein

Tau proteins, pivotal constituents of the nervous system, assume a prominent role in microtubule assembly, neuronal axon fortification, and orchestration of microtubule transport via intricate regulatory mechanisms, encompassing the transformative processes of phosphorylation and dephosphorylation [57]. Notably, tau proteins traverse a multifaceted landscape of post-translational modifications, encompassing phosphorylation, acetylation, glycosylation, ubiquitination, and truncation [58]. Tau proteins are subject to the influence of numerous key players, including p38 MAPK and GSK3, whose involvement, particularly through the phosphorylation of proximate enzymes, leads to the conversion of tau into its deleterious, neurotoxic conformation from its conventional, functional state [59, 60]. It is worth emphasizing that, in stark contrast to Aβ, the pathophysiological progression of tau is inexorably intertwined with cognitive decline and the grievous onset of neurodegenerative cognitive impairments and dementia in AD [61].
tau proteins, culminating in their erroneous aggregation into NFTs, a potent etiological force in AD pathogenesis [62]. Furthermore, it is discernible that metal ions wield an influential role in shaping the destiny of tau proteins and the trajectory of AD development, wielding dominion over the intricate phosphorylation and dephosphorylation machinery. These ions intricately interact with distinct structural domains of tau proteins, orchestrating their intricate folding, aggregation, and biological functionality, thereby fomenting the maladaptive aggregation and deposition of tau proteins, along with the concomitant emergence of NFTs. Moreover, these metal ions act as catalysts for the formation of liquid-liquid phase-separated droplets or granules characterized by high concentrations, which might be the predominant drivers of tau protein amyloidosis. These structures are postulated as precursors for the eventual assembly of tau protein amyloid fibrils. Intriguingly, metal ions exert a modulatory effect on the release and propagation of tau proteins, engendering shifts in the charge distribution of tau proteins. This, in turn, prompts their interaction with neuronal membrane receptors or ion channels, thereby inducing an inward or outward flux of calcium ions. Such perturbations disrupt calcium homeostasis, consequently influencing the phosphorylation of tau proteins, the stability of the cytoskeletal architecture, and the orchestration of gene expression [63, 64].

Intricacies in copper homeostasis potentially underpin AD pathogenesis [65]. Copper ions possess the capability to interface with tau proteins, thereby fostering anomalous aggregation and facilitating the genesis of NFTs [66-68]. Investigations have expounded upon the propensity for chronic copper exposure to induce tau hyperphosphorylation within murine models of AD, concurrently engendering the untoward activation of cyclin-dependent kinase 5 (CDK5)-p25, thereby accentuating tau pathology [25, 69]. Analogous to copper ions, zinc ions substantiate a role in interacting with tau proteins, participating in their atypical phosphorylation and aggregation. In vitro experiments have demonstrated that the release of zinc in response to excitatory glutamatergic neuronal activity promotes tau protein phosphorylation and subsequent NFT formation, a phenomenon potentially associated with protein phosphatase 2A inactivation [70, 71]. Furthermore, zinc ions hold the potential to influence tau aggregation and toxicity through the activation of glycogen synthase kinase-3β (GSK-3β) or the Raf/mitogen-activated protein kinase-kinase/extracellular signal-regulated kinase pathway [34-36], as well as by accelerating the fibrillation of tau protein fragments [72-74]. This effect is attributed to zinc ions binding to specific amino acids within tau proteins, thereby fostering structures prone to accumulation. Such accumulation begets endogenous tau protein accrual and the attendant aberrant phosphorylation, thereby intensifying tau protein toxicity. In a study evaluating the impact of chronic low-level zinc supplementation on tau proteins within a murine tauopathy model, it was discerned that zinc supplementation exacerbated the behavioral and biochemical deficits induced by tau proteins [75]. Moreover, an ex vivo examination unveiled a correlation between iron deposition within the inferior temporal gyrus and an accelerated rate of cognitive decline in subjects manifesting significant Aβ and tau tangle pathology. Remarkably, augmented iron content did not spatially overlap with amyloid plaque formation but did coincide with regions of tau accumulation [76]. Likewise, the anomalous deposition of iron ions may expedite the untoward phosphorylation and aggregation of tau proteins. Iron’s association with Aβ or tau extends beyond the initiation of Aβ aggregation and hyperphosphorylation of tau into NFTs; it amplifies Aβ toxicity and influences the interplay between tau and neurons [77]. This phenomenon is likely mediated through the untoward activation of tau kinases, such as GSK-3β, CDK5, and MAPK [78, 79]. Furthermore, there are indications that the insulin signaling pathway may play a role in the anomalous iron-induced tau phosphorylation [80]. While both tau and Aβ represent pivotal pathological hallmarks of AD, a more comprehensive understanding of the precise ramifications of disrupted metal ion homeostasis on AD, mediated through their effects on tau proteins, necessitates further empirical exploration to corroborate this association.

Metal Ions and Oxidative Stress

In the intricate realm of oxidative stress (OS), a perturbation emerges from a delicate equilibrium between the surfeit of oxidative entities, including free radicals and oxidative molecules, and the fortress of antioxidant defenses ensconced within the sanctum of cells and tissues. These valiant guardians stand vigilant, guarding the sanctity of biomolecules, poised to stave off the encroaching malevolence [81, 82]. Within the cerebral enclaves of AD patients, the telltale vestiges of oxidative stress often manifest. Here, the nefar-
ious machinations involve the wanton accrual of oxygen free radicals and pernicious oxidative molecules, which conspire to orchestrate the aberrant assembly and deposition of proteins within the cerebral fiefdom. Notably, the likes of $\text{A}\beta$ and tau proteins are the pawns in this grim tableau, their aggregation serving as the pathological insignia of AD [83-85]. Furthermore, the reverberations of oxidative stress precipitate an inflammatory tumult, leading to the inevitable demise of neuronal sentinels. A direct onslaught upon the cerebral domain only exacerbaates this lamentable cascade [62]. The genetic legacy encoded within DNA is not immune to the malefic grasp of oxidative damage, casting ominous shadows upon gene expression, cellular harmony, and the genetic bequest of brain cells. Thus, the inexorable march of AD is hastened by these sinister forces [86]. Intriguingly, metal ions, those enigmatic actors in this grand theatrical of OS, take center stage, their roles manifold and significant, bearing upon the pathogenesis and progression of AD [87-90]. The likes of iron, copper, and aluminum wield catalytic scepters, inciting the insurrection of free radicals within the cellular arena. In their wake, proteins, lipids, and DNA stand as hapless victims, bearing the scars of oxidative assault, their very cellular existence imperiled [87-90]. Yet, the machinations of these metal ions extend further, entwining with the intricate redox dances within cells, further fanning the flames of OS. This orchestration ultimately induces the perilous oxidation, fragmentation, and aggregation of proteins, a dire omen for the structural and functional integrity of tau proteins [87-90]. Moreover, the sly manipulation of metal ions extends to the citadels of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPX). These steadfast guardians of cellular order, their duty to quell the insurrection of free radicals, become unwitting pawns in this OS drama. The aberrant catalytic fervor of metal ions disrupts the harmonious interplay, threatening the integrity of these noble defenders [87-90].

In the realm of metal-ion dynamics within the context of neurodegenerative diseases, the presence of elevated concentrations of free copper ions has been identified as a pivotal factor in orchestrating oxidative reactions and potentiating OS, as previously documented [91]. Complexes formed between Cu-$\text{A}\beta$ exhibit a catalytic propensity towards the generation of hydrogen peroxide (H2O2) from molecular oxygen (O2). The excessive H2O2 produced consequently engenders a profusion of free radicals through the Fenton reaction, thereby precipitating a cascade of events encompassing lipid peroxidation, protein impairment, and DNA damage [92-96]. Simultaneously, the intracellular accumulation of iron, surmounting normal thresholds, augments the proclivity towards lipid peroxidation and the prodigious production of reactive oxygen species (ROS) via the Fenton reaction. This perturbation subsequently instigates an intricate array of apoptotic signaling pathways while intensifying the aggregation of $\text{A}\beta$. This perilous amalgamation sets the stage for hippocampal neuronal degeneration, and in severe cases, their ultimate demise, thereby accentuating the progression of AD [97-99]. Moreover, iron-induced cell death, attributed to an excessive accumulation of ROS and perturbed cellular lipid oxide metabolism, is modulable via GPX4 [100, 101]. The disturbance of iron homeostasis emerges as a pivotal harbinger of oxidative cell death. Notably, discerning investigations have unearthed the profound influence of autophagy on iron-mediated apoptosis through its regulation of intracellular iron homeostasis and ROS production [102]. Concurrently, Ma and colleagues have delineated how iron-mediated ROS generation can serve as an inducer of autophagy, setting in motion a multifaceted, deleterious feedback loop perpetuating iron-induced cell death and lipoxidation, thus perpetuating cellular detriment [103].

Manganese, a crucial cofactor for various enzymes including DNA and RNA polymerases, carboxylases, SOD, and glutamine synthetase, assumes a critical role in this context [104, 105]. Exposure to elevated levels of manganese is demonstrated to foment heightened oxidative stress at the organismal level. This, in turn, precipitates an upheaval in the homeostasis of iron ions, thereby activating a repertoire of iron-mediated mechanisms contributing to neuronal damage and, in a broader context, exacerbating manganese-induced neurodegeneration [106, 107]. Furthermore, the impact of manganese does not confine itself to fostering oxidative stress; it concurrently undermines the body’s antioxidant defenses. Treatment with manganese unequivocally culminates in elevated intracellular ROS levels and malondialdehyde concentrations, while simultaneously depleting levels of reduced glutathione (GSH) and attenuating the activities of SOD and GPX4 [108]. Despite the extensive body of work corroborating the pivotal role of metal ion homeostasis in orchestrating oxidative stress within the intricate milieu of the brain, a multitude of other metal ions, including but not limited to zinc, aluminum, and magnesium, remain enigmatic in their potential to modulate OS in AD. Hence, there is an imminent need for in-depth investigations to unravel the intricate...
interplay of these metal ions in the context of OS within the AD landscape [109-112].

**Metal Ions and Neuroinflammation**

The intricate interplay between neuroinflammation and AD represents a subject of intricate and ongoing investigation, and there exists compelling evidence to suggest that neuroinflammation assumes a pivotal role in the etiology and progression of AD [113]. An intriguing nexus emerges between inflammation and cognitive decline, a phenomenon poised to potentiate the symptomatology of AD. To elucidate this intricate dynamic, two fundamental mechanisms emerge: first, the incendiary cascades may foster the pathological aggregation of Aβ within the cerebral milieu, thereby engendering the hallmark amyloid plaques characteristic of AD [114, 115]. Second, inflammation exhibits the capacity to precipitate neural degeneration and demise, thus expeditiously propelling the trajectory of the ailment. Remarkably, this intricate tableau features the microglia, acting as sentinels of the immune realm, occupying a pivotal position in orchestrating the inflammatory milieu, with their release of potent inflammatory mediators exerting adverse effects upon the neurons [116-118]. Implicated within this multifaceted paradigm, metal ions manifest themselves as influential actors, cast in the role of catalyzing the onset and progression of AD, through a myriad of pathways that foment neuroinflammation and, in the process, perturb neural circuitry [119]. Their influence extends to the orchestration of immune cells, such as macrophages and T cells, provoking an augmented release of inflammatory cytokines, typified by the likes of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in the course of inflammation; these factors, in turn, serve as the trigger for the ensuing neuroinflammatory milieu. Simultaneously, metal ions are also known to be instrumental in stimulating inflammatory pathways, most notably the nuclear factor-kappa B (NF-κB) pathway. Activation of NF-κB precipitates an escalation in the expression of inflammatory genes, thereby intensifying the spectrum of neuroinflammatory responses. Furthermore, it is noteworthy that elevated concentrations of metal ions possess the unique ability to directly instigate neuronal activation, thereby inciting abnormal neuronal excitability, and ultimately culminating in neuroinflammation and neuronal impairment [120].

In the realm of neuroinflammation, copper emerges as a pivotal player orchestrating the intricate dance of microglial activation. Intriguingly, copper’s influence extends to the augmentation of cerebral inflammation, an effect seemingly tethered to the activation of the NF-κB pathway. Moreover, copper instigates microglia to unleash a torrent of pro-inflammatory factors, including IL-1β, TNF-α, and IL-6, while concurrently stifling the expression of LRP1 [121-123]. Notably, the suppression of LRP1 ushers forth a notable surge in pro-inflammatory cytokine production, eliciting a fervor of neuroinflammation within Aβ42-BV2 microglia and primary astrocytes of murine lineage [124]. Meanwhile, the delicate equilibrium of iron within the central nervous system teeters perilously on the precipice. Within this milieu, ferritin immunoreactivity has been intimately associated with the dystrophic state of cerebral microglia in individuals grappling with AD [125]. Disruptions in iron homeostasis, catalyzed by aberrations in iron transporter proteins and their attendant counterparts, serve as the catalyst for microglial and astrocytic genesis. This perturbation, executed via the NF-κB pathway, culminates in the transcription of pro-inflammatory cytokines, thereby affording prominence to the likes of TNF-α and IL-1β [126-129]. Similarly, manganese assumes its role in the regulation of cerebral immunity and the orchestration of inflammatory overtures within the brain [130]. Intriguingly, in vitro experiments lay bare manganese’s toxic underpinnings in fostering neuroinflammation. This toxicity is attributed to the activation of glial cells and the potentiation of inflammatory vesicles, thus bolstering the production of pro-inflammatory cytokines and the amplification of chemokine expression [131-133]. Intriguingly, preliminary forays into the realms of metal ions, including aluminum and lead, uncover their latent potential to expedite AD progression through the orchestration of inflammatory responses [134, 135]. Paradoxically, some metal ions, under specific concentrations, emerge as savors, bolstering immune function and nurturing inflammatory responses. The senescent transformations afoot within the aging brain, it seems, are partly instigated by disruptions in zinc homeostasis [136]. Emanating from in vitro experiments is the revelation that zinc supplementation exerts a restraining influence on lipopolysaccharide-elicted microglial-mediated inflammatory responses, culminating in the tempering of inflammatory cytokine production [137]. Ergo, zinc stands as a prospective protagonist capable of countermanding age-induced vicissitudes by curbing inflammation [138]. Nevertheless, it is incumbent upon us to underscore the inherent enigma shrouding
the exact mechanisms underpinning AD. Inflammation, though undeniably a crucial facet, represents just a fragment of the enigmatic mosaic. As the quest for enlightenment endures, it is our enduring research that will illuminate the intricate tapestry weaving neuroinflammation and AD, bestowing invaluable insights for forthcoming therapeutic and preventative endeavors.

Targeted Therapeutic Pathways

In tandem with the concerted efforts directed at Aβ and tau protein manipulation, the focused control of metal ions has garnered an ever-escalating surge of interest. The intricate maintenance of metal ion equilibrium assumes a pivotal role in the intricate tapestry of AD pathogenesis. Hence, the unearthing of metal ion modulators, and Chinese herbal compounds demonstrating not only minimal toxicity but also the capacity to traverse the formidable blood-brain barrier while exhibiting propitious affinities and selectivities, carries profound implications for the realm of both theoretical inquiry and clinical intervention in the AD domain.

Metal Ion Chelators

The realm of metal ion chelators in the context of AD has garnered significant attention within the scientific community. Chelation therapy, fundamentally, entails the use of precise compounds, often termed chelating agents, to intricately engage and regulate metal ions affiliated with AD, such as copper, iron, zinc, and aluminum. These chelating agents have demonstrated the potential to mitigate the oxidative stress and neurotoxicity inherent to AD pathophysiology [139, 140]. Remarkably, chloroiodoxyquin, a bioavailable copper/zinc chelator, has exhibited the capacity to dissolve intracerebral Aβ deposits, leading to enhanced cognitive function in both in vitro and in vivo settings. Notably, it has progressed into phase II of a clinical trial, demonstrating preliminary efficacy. The mechanistic underpinning of this efficacy seems to be linked to chloroiodoxyquin’s efficient binding of zinc and copper ions, elevating cellular uptake to stimulate neuroprotective signaling pathways, and diminishing the presence of intracellular Aβ aggregates [141-143]. Deferiprone, a potent iron chelating agent, possesses the unique ability to chelate not only iron but also copper, aluminum, and zinc, thereby curtailing their catalytic free radical activities and ameliorating oxidative damage [144-147]. An innovative study has yielded a bifunctional molecule, XH1, which amalgamates amyloid-binding and metal-chelating elements. This compound traverses the blood-brain barrier, reducing Aβ aggregation induced by zinc ions [148]. In a similar vein, ethylenediaminetetraacetic acid (EDTA) stands as an archetype of chelating agents, lauded for its antioxidant properties and adeptness at chelating and expelling detrimental metal ions. It also exhibits protective qualities against cardiovascular events and endothelial cell activation [149, 150]. A plethora of studies underscore the capacity of EDTA chelators to ameliorate neurodegenerative conditions by reducing or eliminating the levels of pernicious metal ions, with therapeutic efficacy potentially contingent upon their aptitude to infiltrate the central nervous system [151-153]. Furthermore, the concept of combination therapy emerges as an enticing strategy to augment in vivo metal mobilization while minimizing individual dosages of chelating agents, thus tempering agent-specific adverse effects. Consequently, the amalgamation of two or more drugs may be a more efficacious and tolerable approach than monotherapy [154-157]. One noteworthy example is the combined chelation therapy involving the chelators deferoxamine and deferiprone. This synergy augments the effectiveness of iron chelation in iron overload conditions and has garnered clinical attention for its potential in reducing cerebral iron overload and mitigating the progression of iron-induced neurodegeneration [158-160]. Nevertheless, it is imperative to acknowledge that currently available chelating agents lack the precision of endogenous metal chaperones. Targeting intracellular locales remains a formidable challenge in the design of novel metal-binding pharmaceuticals. As a result, the future trajectory of research endeavors will be focused on the development of targeted drugs directed at specific molecular targets. Additionally, in the pursuit of creating metal chelators as therapeutic agents to counteract the detrimental consequences of metal dysregulation in the AD-afflicted brain, a profound comprehension of ligand chemistry becomes paramount. This understanding is vital in the selection of promising drug candidates and enhancing the likelihood of success in clinical trials.

Traditional Chinese Medicinal Extracts and Formulations
Nature’s unparalleled artistry in the realm of combinatorial chemistry offers profound potential in the quest for remedies to all human afflictions. The diverse botanical tapestry that graces our planet holds a wealth of natural pharmacological agents, each with the capacity to bestow a panoply of therapeutic virtues upon the human physiology. Among these natural compounds, we unearth the multifaceted attributes of antioxidative prowess, anti-inflammatory fortitude, calcium ion channel modulation, anti-apoptotic guardianship, and neurofunctional modulators, all wielding the potential to stave off or alleviate the scourges of various neurodegenerative maladies [161, 162]. In the intricate orchestra of human biology, metal ions emerge as both indispensable trace elements and potential malefactors. Hence, diligent scientific exploration unveils the latent capacities of select botanical specimens to mitigate the detriments inflicted by these metallic interlopers. Their intrinsic potential unfurls as a means to regulate and optimize the presence and activities of these metal ions within the human corpus. For countless millennia, the rhizome of turmeric has adorned the apothecaries of diverse cultures, most prominently gracing the annals of Asian therapeutics [163]. The hydrophobic polyphenolic jewel, curcumin, nestled within turmeric’s embrace, boasts anti-inflammatory grace, antioxidant virtue, and the remarkable capacity to uplift cognitive function and emotional well-being. Moreover, it elegantly forges alliances with various metal ions, including iron, copper, manganese, zinc, and cadmium [164-166]]. Notably, curcumin has displayed its mettle by attenuating lead toxicity in the cerebral sanctuary of rats through adept chelation and the quelling of oxidative tumult, thereby restoring cerebral integrity and abating oxidative distress [167]. In a similar botanical foray, the enigmatic false amaranth, a verdant denizen of the Amaranthaceae family, unveils its traditional pedigree as an agent of memory enhancement and anxiety abatement [168]. Enter the realm of pseudomagnesium, a guardian of cognition and neuroprotection, wielding the mantle of antioxidant sentinel and masterful metal chelator. Its elixirs bear the power to reverse the somber specter of memory and cognition’s degradation, brought about by the machinations of aluminum chloride [169-171]. Beyond the realm of individual botanical mavericks, certain Traditional Chinese Medicine (TCM) formulations emerge as allies in the quest to restore harmony to the brain’s metallic equilibrium. One such elixir, the venerable Banxia-Houpu Decoction (BHD), finds its roots within the pages of the Chinese medical tome, “The Essentials of the Golden Chamber” [172]. BHD stands as a bastion against excessive iron accumulation within neurons, achieving this through the elevation of iron transport protein 1 and transferrin receptor 1 levels. Simultaneously, it orchestrates a calming of the inflammatory tempest within the glial realm, ultimately unfurling a tapestry of neuroprotection [173]. Nevertheless, it behooves the discerning investigator to recognize the kaleidoscope of variability enveloping metal ion dynamics within botanical life. Species, habitat, and processing methods interlace to weave an intricate tapestry of diversity. Hence, those who tread the path of botanical metal modulation must tread with discernment, weaving strategies aligned with individual health requisites and medical counsel. Furthermore, the troves of TCM conceal an armament of antioxidative allies poised to combat free radicals and quell the fires of oxidative distress stoked by metal ions. Within the verdant boughs of Camellia sinensis, the beloved tea plant, which bequeaths green, black, and oolong libations to humanity, lies the prized catechin[174]. This compound, a sentinel of neurodegenerative ailment, marshals its forces through metal ion chelation, free radical scavenging, and the blockade of cytokine excess and inflammatory pathways, offering a tapestry of hope and healing[175-178].

Conclusions and Future Perspectives

The maintenance of cerebral metal ion homeostasis holds pivotal significance in preserving physiological equilibrium. Nevertheless, the pervasive occurrence of perturbed metal ion dynamics and their associated transport mechanisms has been conspicuously evident within subjects afflicted by AD or in analogous animal models. This perturbation is intrinsically intertwined with the bioaccessibility of these metal ions and their systemic distribution. In the human organism, the absorption, transit, retention, and excretion of diverse metal ions are intricately choreographed by an array of influencing factors. These factors encompass the chemical speciation of the metal ions, the coordinating ligands, transmembrane transporter proteins, and metal-binding proteins. Comprehensive comprehension of the spatial allocation of metal ions within the cerebral milieu and their traversal across the formidable blood-brain barrier is indispensable for ascertaining their implications in the orchestration of physiological processes and the incitement of toxicological responses.
Some investigations have proposed a potential implication of certain metal ions, such as copper, iron, zinc, and aluminum, in the pathogenesis of AD. Yet, the modus operandi underlying the interaction between metal ions and AD-associated proteins remains exceedingly intricate. This intricate dance entails multifaceted biological processes, encompassing oxidative stress, inflammatory cascades, protein aggregation, among others. Moreover, the molecular intricacies, kinetic kinetics, and structural underpinnings of these interactions remain, for the most part, obscured. Furthermore, metal ions can serve as either cofactors or inhibitors of enzymes, wield influence over enzymatic activity and selectivity, or partake in binding or insertion with DNA or RNA molecules. Consequently, they might take part in AD development through manifold avenues, impacting gene expression, signal transduction, energy metabolism, and ion channel functionality. However, the precise regulatory mechanisms and the interconnectedness of these pathways lack definitive substantiation, and the direct causal nexus between metal ions and AD remains the subject of ongoing scrutiny. Given that the composition and dispersion of metal ions within AD are subject to dynamic alterations, influenced simultaneously by an array of variables, it becomes imperative to employ highly sensitive, high-resolution, and specifically tailored methodologies for precise quantification and profiling of metal ion levels and statuses across various cerebral regions, cellular typologies, and subcellular configurations. Consequently, although some studies have ascertained anomalous metal ion accumulation within the AD-afflicted brain, it remains arduous to unequivocally discern whether this phenomenon is a causative agent or a resultant facet of the ailment.

The burgeoning mean age of the global populace portends an inevitable upswing in age-associated neurodegenerative maladies. In congruence with the intricate multifaceted character of this ailment, there exists a mounting and persuasive body of corroboration positing that further exploration into the perturbation of metallic elements, as associated with AD, proffers valuable therapeutic avenues. However, the governance of metal ions remains ensconced within a quagmire of unresolved complexities. Notably, perturbations within metal ion concentrations within the context of AD predominantly gravitate toward an excessive accretion and overabundance. With the growing acumen regarding AD, therapeutic modalities necessitate ever-increasing specificity. Consequently, investigators have embarked on exhaustive inquiries into the employment of metal ion chelators aimed at ameliorating the pathophysiology and cognitive functions in AD. Though a gamut of therapeutic schemes predicated on metal chelation agents or conveyance vectors have been conceived to modulate the levels and activities of metal ions, with the intent of either inhibiting or reversing the AD trajectory, these stratagems grapple with a litany of challenges, inclusive of the intricate dose-effect relationships, dearth of selectivity, impediments in traversing the blood-brain barrier, and untoward side effects. Hence, the conundrum at hand is the conception of more efficacious, safer, and precisely targeted metallo-modulators, and the appraisal of their applicability in the clinical milieu. In this vein, the amalgamation of metal ions with nanomaterials stands as an avenue replete with potential, rooted in their unique dimensional and surface attributes, thereby enhancing biocompatibility, stability, sensitivity, and functionality. It is imperative to underscore that, despite the commendable attributes intrinsic to the manipulation of metal ion homeostasis as a therapeutic paradigm, it remains predominantly ensnared within the confines of research. Although preliminary insights augur prospective merits in metal ion modulation concerning AD, a more comprehensive corpus of investigations is imperatively warranted to discern the most efficacious interventions and their protracted ramifications. These collective endeavors shall pave the trajectory toward meticulously crafted interventions predicated on metal ion modulation or the judicious utilization of specific bioactive constituents. They are poised to furnish deeper insights into the underlying mechanisms and, in turn, the cultivation of efficacious and benign approaches in the realm of AD prevention and mitigation.

Author contributions
JL and YW: writing – original draft. JL, XD, and YW: data collection and integration. BL, WC, NZ, and HZ: conceptualization. BL, XD, and NZ: supervision. BL and NZ: project administration. WC and HZ: funding acquisition. All authors contributed to the article and approved the submitted version.

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