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Integrating molecular docking and biological evaluation of metal-phytochemical complexes in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuronal loss. Its pathogenesis involves multiple interconnected mechanisms, including amyloid-β (Aβ) aggregation, τ hyperphosphorylation, oxidative stress, neuroinflammation, and metal ion dyshomeostasis. Current therapeutic strategies primarily provide symptomatic relief, underscoring the urgent need for multitargeted approaches. Natural products have emerged as promising candidates due to their structural diversity and ability to modulate several pathological pathways simultaneously. Among these, triterpenoid glycosides such as momordicoside L exhibit notable antioxidant and anti-inflammatory properties.

Recent advances highlight the potential of metal-phytochemical complexes in enhancing pharmacological efficacy. Complexation with metals such as copper may improve the stability, bioavailability, and biological activity of phytochemicals while modulating metal-induced toxicity associated with AD. Molecular docking studies provide insights into interactions with key targets, while *in vitro* and *in vivo* investigations demonstrate improved neuroprotective effects, including enhanced cell viability, reduced inflammatory responses, and cognitive improvement. This review emphasizes the integration of analytical characterization, computational modeling, and biological validation, supporting the development of metal-natural product complexes as innovative multitarget therapeutic agents for AD.

Key words: Alzheimer's disease, molecular docking, acetylcholinesterase inhibition, STZ-induced model, drug discovery.

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Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and represents a major global health challenge, particularly in aging populations. It is clinically characterized by progressive cognitive decline, memory impairment, and loss of neuronal function. Histopathologically, AD is defined by extracellular deposition of amyloid-β (Aβ) plaques and intracellular accumulation of neurofibrillary tangles composed of hyperphosphorylated τ protein, both of which contribute to synaptic dysfunction and neuronal degeneration.[1,2] While familial forms exist, the majority of cases are sporadic and associated with aging, environmental influences, and metabolic dysregulation.[2]

The etiology of AD is complex and multifactorial. Although the amyloid cascade and τ hypotheses have long dominated the field, increasing evidence highlights the critical roles of oxidative stress and neuroinflammation in disease progression.[3] Activation of microglia and astrocytes in response to Aβ accumulation leads to the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, which exacerbate neuronal damage and contribute to chronic neurodegeneration.[3,4] While initial inflammatory responses may facilitate amyloid clearance, prolonged activation becomes detrimental.

Another key factor in AD pathology is the disruption of metal ion homeostasis. Transition metals, particularly copper, are essential for neuronal function but can become neurotoxic when dysregulated. Copper interacts with Aβ peptides, promoting aggregation and generating reactive oxygen species (ROS) through redox cycling.[5] This enhances oxidative stress and accelerates neuronal damage.

Given this complexity, single-target therapeutic strategies have shown limited success. Consequently, there is a growing interest in multitarget approaches, especially those based on natural products. Phytochemicals exhibit antioxidant, anti-inflammatory, and anti-amyloidogenic properties, making them suitable candidates for AD therapy.[3] Furthermore, metal complexation has emerged as a promising strategy to enhance the pharmacological properties of natural compounds. This review focuses on the potential of natural product-metal complexes, particularly

those involving triterpenoid glycosides, as novel therapeutic agents for AD.

Methods

Search strategy and selection criteria

A comprehensive literature search was conducted to identify relevant studies on AD, metal ion dysregulation, neuroprotection, and metal-phytochemical complexes. Electronic databases, including PubMed, Scopus, and Web of Science, were systematically searched for articles published between 2000 and 2025.

The search strategy employed combinations of keywords such as "Alzheimer's disease", "metal ions" "copper", "oxidative stress", "neuroinflammation", "phytochemicals" and "metal-phytochemical complexes". Additional relevant studies were identified through manual screening of reference lists.

Inclusion criteria

Studies were included if they: i) addressed AD pathophysiology, including Aβ, τ, oxidative stress, or neuroinflammation; ii) investigated the role of metal ions in AD; iii) reported neuroprotective effects of natural products or metal-phytochemical complexes; iv) were published in peer-reviewed journals in English.

Exclusion criteria

Studies were excluded if they: i) were not directly related to AD; ii) were conference abstracts, editorials, or non-peer-reviewed articles; iii) lacked sufficient scientific or methodological detail. Relevant studies were screened based on titles and abstracts, followed by full-text evaluation. Priority was given to high-impact and recent studies to ensure scientific relevance and accuracy.

Pathophysiology of Alzheimer's disease

AD is characterized by a complex network of pathological mechanisms that collectively lead to neuronal loss and cognitive impairment. The amyloid cascade hypothesis describes the abnormal processing of the amyloid precursor protein, resulting in the formation of insoluble Aβ peptides that aggregate into plaques.[6] Soluble Aβ oligomers are particularly neurotoxic, disrupting synaptic transmission, altering calcium homeostasis, and impairing memory-related processes.

The τ pathology represents another central feature of AD. Hyperphosphorylation of the τ protein leads to its detachment from microtubules and aggregation into neurofibrillary tangles, resulting in cytoskeletal instability and impaired axonal transport.[7] This process contributes directly to neuronal death and correlates strongly with disease severity.

Neuroinflammation plays a crucial role in amplifying these pathological events. The accumulation of Aβ and τ activates microglia and astrocytes, leading to sustained production of pro-inflammatory mediators such as TNF-α and IL-6.[8] Chronic inflammation perpetuates neuronal damage and contributes to disease progression.

Oxidative stress further exacerbates neurodegeneration. The excessive production of ROS and reactive nitrogen species leads to lipid peroxidation, protein oxidation, and DNA damage.[9] Mitochondrial dysfunction worsens this condition by impairing energy metabolism and promoting apoptotic pathways.

Disruption of metal ion homeostasis, particularly involving copper, iron, and zinc, significantly contributes to AD pathology. These metals interact with Aβ peptides, promoting aggregation and oxidative stress. The convergence of these mechanisms ultimately results in synaptic loss, neuronal degeneration, and cognitive decline. The major pathological mechanisms underlying AD, highlighting their roles in neuronal damage and cognitive decline, are illustrated in Table 1.

Role of metal ions in Alzheimer's disease

Metal ions are essential for normal brain function, but their dysregulation is strongly implicated in AD pathogenesis.[10] Copper, due to its redox properties, plays a dual role. While necessary for enzymatic processes, excess copper promotes Aβ aggregation and ROS generation, leading to oxidative damage.[11] Similarly, iron contributes to oxidative stress through Fenton reactions, generating highly reactive radicals that damage neuronal components. Zinc, although not redox-active, stabilizes Aβ aggregates and disrupts synaptic signaling, contributing to cognitive impairment.

Metal dyshomeostasis also promotes neuroinflammation, as metal-induced oxidative stress activates glial cells and triggers inflammatory pathways.[12] Given this, therapeutic strategies targeting metal homeostasis have gained attention. Metal-phytochemical complexes, in particular, offer the advantage of modulating metal-induced toxicity while providing additional antioxidant and anti-inflammatory effects.[13] The role of metal ions in the pathogenesis of AD is summarized in Table 2, highlighting

Table 1. Key pathological mechanisms in Alzheimer's disease.

Pathological feature	Key mechanism	Molecular markers	Outcome
Amyloid-β accumulation	APP cleavage by β- and γ-secretase	Aβ42, plaques	Synaptic dysfunction
τ hyperphosphorylation	Kinase activation (GSK-3β, CDK5)	NFTs (τ tangles)	Neuronal death
Oxidative stress	ROS/RNS overproduction	MDA, SOD, CAT	Lipid and protein damage
Neuroinflammation	Microglial activation	TNF-α, IL-6	Chronic inflammation
Metal dyshomeostasis	Copper, iron, zinc imbalance	Metal-Aβ complexes	ROS generation
Mitochondrial dysfunction	Impaired ATP synthesis	Cytochrome c	Apoptosis

ROS, reactive oxygen species; RNS, reactive nitrogen species; ATP, adenosine triphosphate; NFTs, neurofibrillary tangles; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; TNF, tumor necrosis factor; IL, interleukin; Aβ, amyloid-β.

Table 2. Role of metal ions in Alzheimer's disease.

Metal ion	Physiological role	Pathological role in Alzheimer's disease
Copper (Cu)	Enzyme cofactor	Promotes amyloid-β aggregation
Iron (Fe)	Oxygen transport	Oxidative stress
Zinc (Zn)	Synaptic signaling	Amyloid-β stabilization

the contributions of copper, iron, and zinc to Aβ aggregation, oxidative stress, and neurotoxicity. The mechanism of action of metal-phytochemical complexes in AD is illustrated in Figure 1.

Natural products in neuroprotection

Natural products have gained significant attention in AD research due to their ability to target multiple pathological pathways simultaneously. Phytochemicals such as flavonoids, alkaloids, and terpenoids exhibit strong antioxidant activity by scavenging ROS and protecting neuronal cells from oxidative damage. Many of these compounds also inhibit acetylcholinesterase, thereby enhancing cholinergic neurotransmission and improving cognitive function.[14]

In addition to their antioxidant properties, natural products demonstrate anti-amyloidogenic and anti-τ effects. They can inhibit β-secretase activity, reduce Aβ production, and prevent aggregation into toxic oligomers. Furthermore, several compounds modulate kinase activity involved in τ hyperphosphorylation, thereby preventing neurofibrillary tangle formation.

The anti-inflammatory effects of phytochemicals are equally important. By suppressing microglial activation and reducing cytokine production, these compounds help mitigate chronic neuroinflammation.[15] Among these, triterpenoid glycosides such as momordicoside L have shown promising neuroprotective effects, including antioxidant and anti-inflammatory activity.

Despite their potential, natural products often suffer from poor bioavailability and limited pharmacokinetic profiles. Metal complexation has emerged as an effective strategy to overcome these limitations, enhancing stability, solubility, and biological activity.[16]

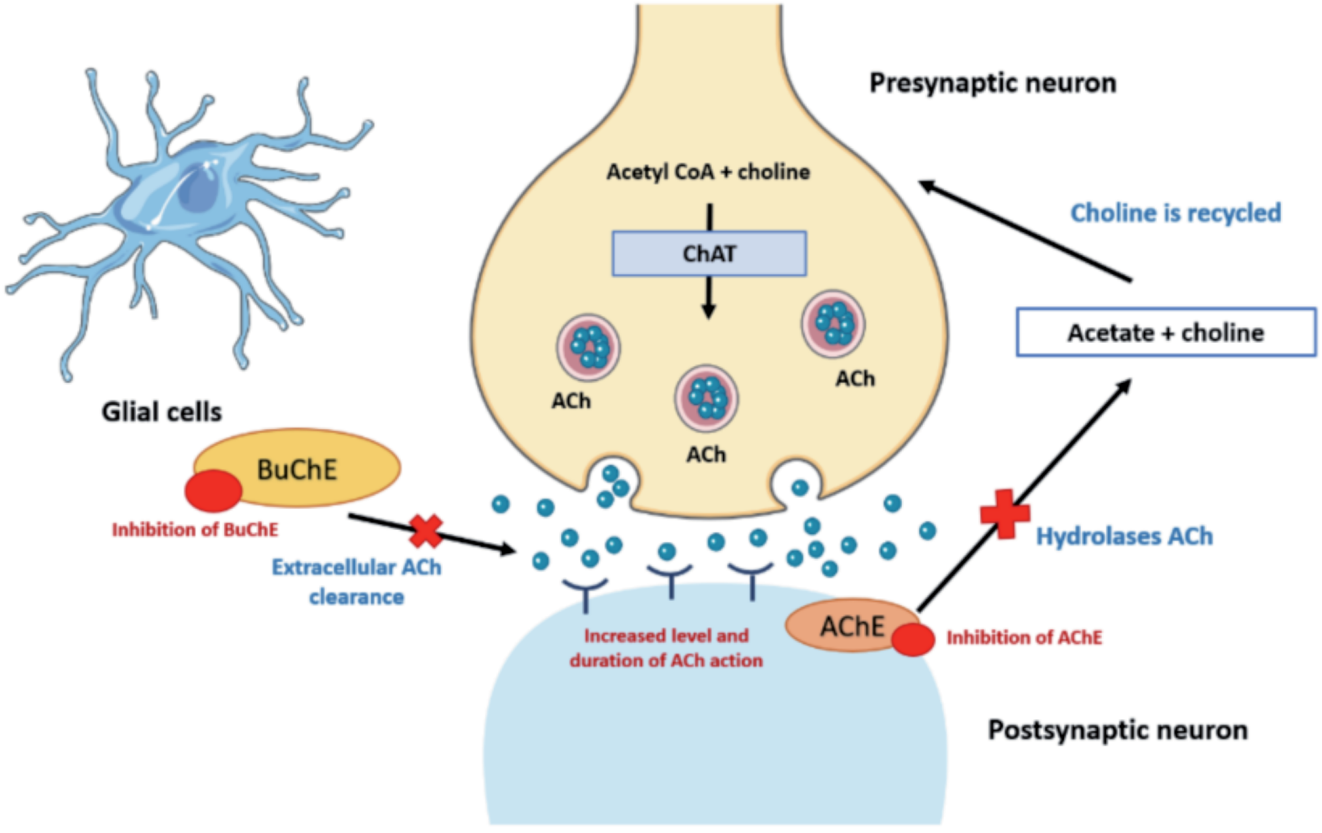

Figure 1. Mechanism of action. CoA, coenzyme A; ACh, acetylcholine; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Metal-phytochemical complexes

The development of metal-phytochemical complexes represents a novel approach in AD drug discovery. By combining the bioactivity of natural compounds with the unique properties of metal ions, these complexes exhibit enhanced therapeutic potential. Metal coordination can improve lipophilicity and facilitate cellular uptake, thereby increasing bioavailability.

These complexes exert neuroprotective effects through multiple mechanisms, including inhibition of Aβ aggregation, reduction of oxidative stress, and modulation of neuroinflammatory pathways.[17] Unlike traditional chelators, metal-phytochemical complexes can regulate metal homeostasis without causing depletion, maintaining physiological balance.

Triterpenoid glycosides are particularly suitable for complexation due to their functional groups capable of metal binding. Although research is still emerging, these complexes show enhanced antioxidant and anti-inflammatory activity compared to their free forms.[18] The multifactorial mechanism of action of metal-phytochemical complexes in AD is illustrated in Figure 2, highlighting their role in modulating amyloid aggregation, oxidative stress, and neuroinflammation.

While numerous studies report promising neuroprotective effects of metal-phytochemical complexes, the findings are not entirely consistent across different experimental models. Variability in metal ion selection, ligand structure, and experimental conditions often leads to differences in reported efficacy. Some studies demonstrate significant inhibition of amyloid aggregation and oxidative stress, whereas others report only modest or context-dependent effects. In addition, the lack of standardized protocols and limited comparative studies makes it difficult to draw definitive conclusions regarding their superiority over uncomplexed phytochemicals. Therefore, a more systematic and comparative evaluation is required to establish their true therapeutic potential.

Molecular docking plays a crucial role in identifying potential therapeutic agents for AD by predicting ligand-protein interactions. It enables the evaluation of binding affinity and interaction mechanisms with key targets such as acetylcholinesterase and β-secretase.[19] Tools like AutoDock Vina provide efficient and accurate predictions of binding energies and interaction profiles.[20]

Molecular docking studies further support the therapeutic potential of metal-phytochemical complexes in AD. Several reports indicate that these complexes exhibit enhanced binding affinity toward key targets such as acetylcholinesterase and β-secretase (BACE1) compared to their parent phytochemicals. This improved interaction is attributed to the presence of metal ions, which can facilitate additional coordination interactions and stabilize ligand-protein binding. These interactions are often supported by hydrogen bonding and hydrophobic contacts with key amino acid residues involved in enzyme activity.

Despite their usefulness in predicting ligand-protein interactions, molecular docking studies have several inherent limitations. These include reliance on simplified scoring functions, limited consideration of protein flexibility, and the absence of dynamic biological environments. As a result, docking outcomes may not always accurately reflect *in vivo* binding behavior. Therefore, computational findings should be interpreted cautiously and validated through experimental studies to ensure their biological relevance.

In addition to computational findings, *in vitro* studies have demonstrated that metal-phytochemical complexes can inhibit Aβ aggregation and reduce oxidative stress, while *in vivo* studies suggest improvements in cognitive function and neuroprotection in experimental models. However, the magnitude of these effects varies depending on the structure of the complex, the type of metal ion, and experimental conditions. Collectively, these findings highlight the potential advantage of metal complexation in enhancing the biological activity and target speci-

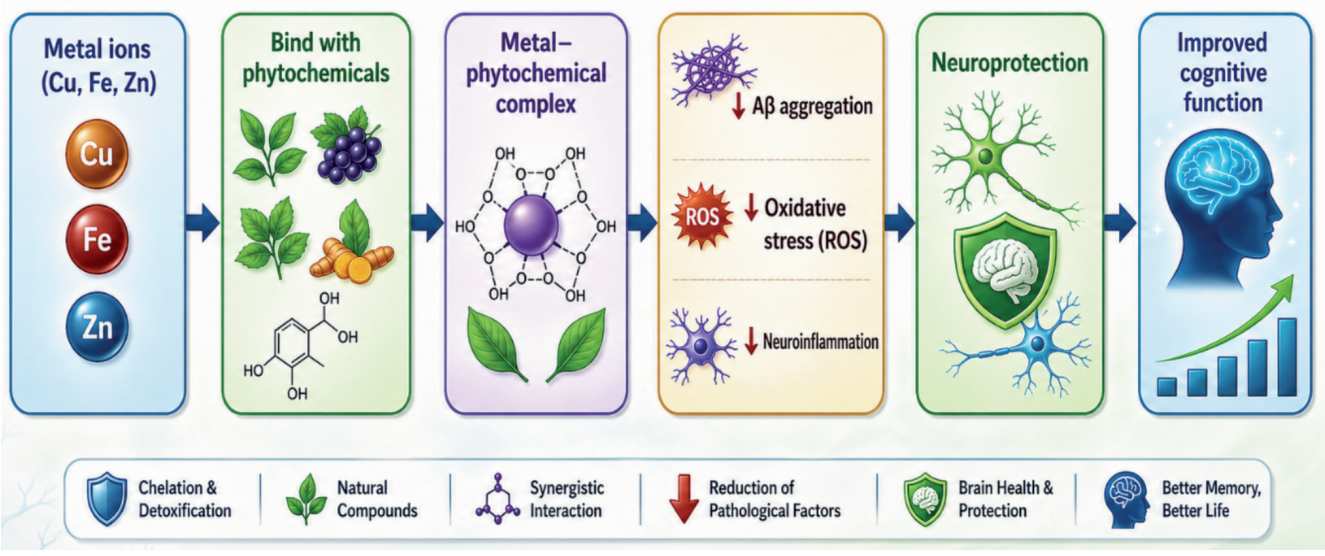

Figure 2. Mechanism of action of metal-phytochemical complexes in Alzheimer's disease. Molecular docking in drug discovery. Cu, copper; Fe, iron; Zn, zinc; Aβ, amyloid-β; ROS, reactive oxygen species.

ficity of phytochemicals, although further systematic validation is required.

Docking studies have been widely used to evaluate natural products and their metal complexes, providing insights into their multitarget potential.[21] However, limitations such as protein rigidity and simplified scoring functions necessitate experimental validation.

In vitro and *in vivo* evaluation

In vitro studies provide essential insights into the neuroprotective effects of compounds by assessing cell viability, oxidative stress, and inflammatory responses. Assays such as MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] and ROS measurement help evaluate the protective efficacy of test compounds, while cytokine analysis reveals their anti-inflammatory potential.

In vivo models offer a more comprehensive evaluation by assessing cognitive function, biochemical parameters, and histopathological changes.[22] The streptozotocin-induced model is widely used to mimic sporadic AD, demonstrating key features such as oxidative stress and cognitive impairment.[23] Behavioral tests, such as the Morris water maze, provide quantitative measures of memory and learning.

Correlation of multilevel studies

The integration of *in silico*, *in vitro*, and *in vivo* approaches enhances the reliability of drug discovery. Molecular docking provides initial predictions, which are validated through cellular and animal studies.[24] A strong correlation among these methods improves the likelihood of successful therapeutic development, particularly for metal-phytochemical complexes.[25]

Despite encouraging preclinical findings, the translation of neuroprotective agents into effective clinical therapies for AD has been largely unsuccessful. Several compounds that showed promise in *in vitro* and animal studies have failed in clinical trials due to poor bioavailability, inadequate target engagement, or unexpected adverse effects. This highlights the need for more robust translational strategies and emphasizes that preclinical efficacy does not necessarily guarantee clinical success.

Challenges and future perspectives

Despite the promising therapeutic potential of metal-phytochemical complexes, several challenges must be addressed before their clinical application. One of the major limitations is blood-brain barrier permeability, which restricts the efficient delivery of these compounds to the central nervous system. Many phytochemicals exhibit limited ability to cross the BBB, thereby reducing their therapeutic efficacy *in vivo*.[26]

Another critical concern is toxicity and safety.[27] While metal ions such as copper and iron play essential physiological roles, their redox activity may lead to unintended pro-oxidant effects under certain conditions. Therefore, careful optimization of metal concentration and complex stability is required to minimize potential cytotoxicity.

An important concern associated with metal-phytochemical complexes is their potential to exhibit pro-oxidant behavior at higher concentrations. Transition metals such as copper and iron can participate in redox cycling, leading to the generation of ROS under certain conditions. This dual role highlights the importance of dose optimization and careful selection of metal ions to minimize toxicity. Furthermore, long-term safety data remain limited, and comprehensive toxicological evaluations are necessary before clinical translation.

Bioavailability and pharmacokinetic limitations also represent significant challenges. Natural compounds often suffer from poor solubility, rapid metabolism, and low systemic availability, which hinder their clinical translation. Additionally, variability in experimental models and a lack of standardized protocols contribute to inconsistencies in reported findings.[28]

To overcome these limitations, several strategies have been explored. Nanotechnology-based delivery systems, such as nanoparticles and liposomes, have shown potential in improving BBB penetration and enhancing drug stability. Similarly, prodrug approaches and structural modifications can be employed to optimize pharmacokinetic properties and target specificity. Advances in structure-activity relationship studies further aid in the rational design of more effective metal-phytochemical complexes.

Despite encouraging preclinical results, the translation from animal models to human clinical applications remains a major hurdle. Differences in disease pathology and drug response between experimental models and humans limit the predictive value of preclinical studies. Therefore, well-designed clinical investigations are necessary to validate the safety and efficacy of these compounds.

Future research should focus on improving the selectivity, stability, and delivery of metal-phytochemical complexes, as well as integrating advanced computational and experimental approaches to accelerate drug development.[29-32]

Conclusions

AD remains a complex and challenging disorder requiring multitarget therapeutic strategies. Natural products, particularly triterpenoid glycosides, offer significant potential due to their diverse biological activities. The incorporation of metal ions into phytochemical frameworks enhances their pharmacological properties and provides a novel approach to modulating metal-induced toxicity.

Recent studies have demonstrated that nanoparticle-based delivery systems, such as polymeric nanoparticles and liposomal formulations, can enhance the brain delivery of phytochemicals by improving blood-brain barrier permeability and protecting compounds from rapid degradation. Similarly, structural modifications and prodrug strategies have been explored to increase lipophilicity and facilitate central nervous system penetration. However, despite these advances, challenges related to large-scale production, stability, and regulatory approval remain significant barriers to clinical application.

The integration of computational, *in vitro*, and *in vivo* studies provides a comprehensive framework for drug discovery. Metal-phytochemical complexes, therefore, represent a promising avenue for the development of effective therapies for AD, addressing both the complexity of the disease and the limitations of current treatments.[33,34] The mechanism of metal-phytochemical complexes in AD is illustrated in Figure 3.

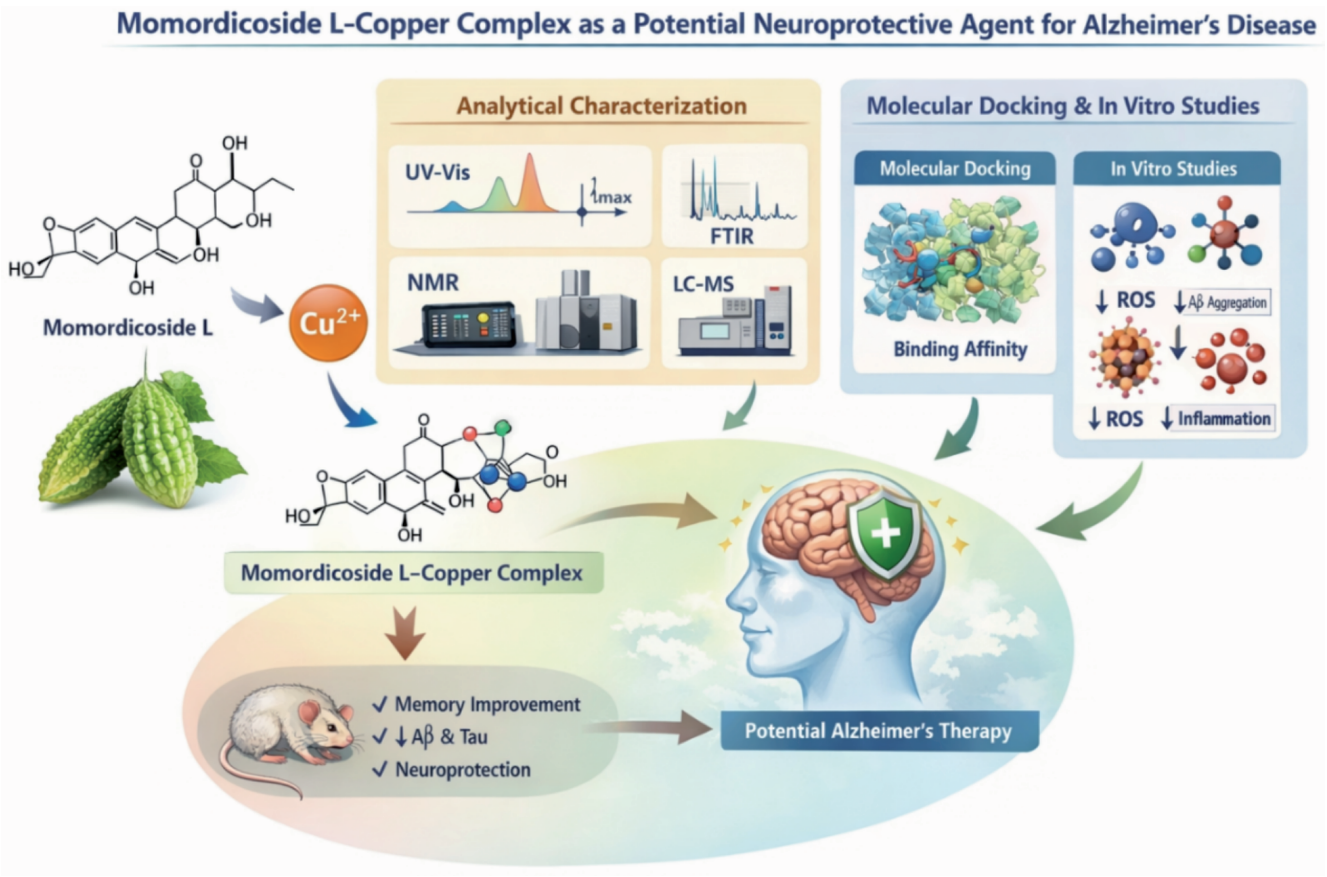

Figure 3. Mechanism of metal-phytochemical complexes in Alzheimer's disease. UV-Vis, ultraviolet-visible spectroscopy; FTIR, Fourier-transform infrared spectroscopy; NMR, nuclear magnetic resonance; LC-MS, liquid chromatography-mass spectrometry; ROS, reactive oxygen species; Aβ, amyloid-β.

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Availability of data and materials: data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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