Journal of Applied Organometallic Chemistry

2026, Volume 6, Issue 1

Review Article

Nanostructured Metal Complexes for Targeted Delivery in Alzheimer's Therapy

Ratakonda Deepak Srinivas[a] | R. V. Valli Kumari[b] | Ashutosh Pathak[c,*] | Venkata Ramana Singamaneni[d] | Voleti Vijaya Kumar[e] | Poonam Popatrao Taru[f] | M. Sandeep Kumar[g] | P. Balaji[h*]

[a]*Department of General Medicine, Vels Medical College and Hospital, Vels Institute of Science, Technology and Advanced Studies, Manjankaranai, Thiruvallur - 601 102, Tamil Nadu, India*
[b]*Department of Pharmaceutical Analysis, Malla Reddy Institute of Pharmaceutical Sciences, Maisammaguda, Dhulapally, Secunderabad 500100, Hyderabad, India*
[c]*Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, UP 244001, India*
[d]*Department of Analytical Research and Development, Cambrex, Charles City, Iowa- 50616, USA*
[e]*Department of Pharmaceutics, School of Pharmacy, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India*
[f]*Department of Pharmacognosy, School of Pharmacy, Vishwakarma University, Kondhwa, Pune, Maharashtra 411048, India*
[g]*Koneru Lakshmaiah Education Foundation, Vaddeswaram, Vijayawada, Andhra Pradesh, India*
[h]*Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai - 600 117, India*

Use your device to scan and read the article online

Citation R. Deepak Srinivas, R.V. Valli Kumari, A. Pathak, V. Ramana Singamaneni, V. Vijaya Kumar, P.Popatrao Taru, M. Sandeep Kumar, P. Balaji, **Nanostructured Metal Complexes for Targeted Delivery in Alzheimer's Therapy.** *J. Appl. Organomet. Chem.*, **2026**, *6*(1), 174-206.

https://doi.org/10.48309/JAOC.2026.549118.1339

Article info:
Submitted: 2025-09-01
Revised: 2025-10-04
Accepted: 2025-11-04
ID: JAOC-2509-1339

Keywords:
Nanostructured, Metal complexes, Targeted delivery, Neuroprotection, Alzheimer's therapy

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β (Aβ) aggregation, tau hyperphosphorylation, metal-ion dyshomeostasis, oxidative stress, and chronic neuroinflammation, all of which contribute to cognitive decline and neuronal loss. Increasing evidence highlights the critical role of aberrant transition metals, such as copper, iron, zinc, and aluminum, in accelerating protein misfolding and redox imbalance, thereby amplifying disease pathology. Conventional therapies have shown limited efficacy due to poor blood–brain barrier (BBB) penetration, lack of specificity, and inability to target multiple pathogenic pathways simultaneously. Emerging nanostructured metal complexes offer a novel multimodal approach that combines tunable physicochemical properties, versatile ligand functionalization, and incorporation into advanced nanoformulations (*e.g.*, liposomes, dendrimers, and polymeric nanoparticles). These systems enhance BBB permeability, enable targeted delivery, provide controlled drug release, and reduce systemic toxicity. Mechanistically, they inhibit Aβ aggregation, modulate tau hyperphosphorylation, chelate excess metal ions, and provide antioxidant and anti-inflammatory neuroprotective effects. Copper-, iron-, zinc-, ruthenium-, and platinum-based complexes have demonstrated promising preclinical efficacy, particularly when integrated into ligand-decorated, stimuli-responsive, or multifunctional theranostic platforms. Synergistic co-delivery with small molecules or genetic materials further expands the therapeutic versatility. The remaining challenges are BBB navigation, precision targeting, scalable manufacturing, and regulatory approval. Leveraging precision medicine, artificial intelligence, and computational modeling can accelerate rational design, optimization, and clinical translation. Overall, nanostructured metal complexes represent a cutting-edge, multitargeted, and clinically translatable strategy for AD therapy.

***Corresponding Authors: Ashutosh Pathak** (ashutosh4088@gmail.com), **P. Balaji** (pharmacology.balaji@gmail.com)*

Table of Content

1. Introduction
    1.1. Alzheimer's disease: pathophysiology and clinical burden
    1.2. Role of metal ions in alzheimer's progression (Cu, Fe, Zn, Al, etc.)
    1.3. Rationale for metal complex-based therapeutics
    1.4. Advantages of nanostructured delivery systems
2. Nanostructured Metal Complexes: Concept and Design
    2.1. Structural and physicochemical features
    2.2. Strategies for metal–ligand functionalization
    2.3. Nanoformulation approaches (liposomes, dendrimers, polymeric nanoparticles, etc.)
    2.4. Blood–brain barrier (BBB) penetration challenges and solutions
3. Mechanistic Insights into Therapeutic Action
    3.1. Inhibition of Aβ aggregation and toxicity
    3.2. Modulation of tau hyperphosphorylation
    3.3. Metal chelation and redox homeostasis
    3.4. Neuroprotection via antioxidant and anti-inflammatory pathways
4. Categories of Nanostructured Metal Complexes in Alzheimer's Therapy
    4.1. Copper-based complexes
    4.2. Iron-based complexes
    4.3. Zinc-based complexes
    4.4. Ruthenium and platinum complexes
    4.5. Other emerging metal-based nanoformulations
5. Targeted Delivery Strategies
    5.1. Ligand-decorated nanocarriers (antibodies, peptides, aptamers)
    5.2. Stimuli-responsive metal complex nanoparticles (pH, ROS, enzyme-responsive)
    5.3. Multifunctional and theranostic nanoplatforms
    5.4. Synergistic delivery with small molecules or genetic materials
6. Challenges and Future Perspectives
    6.1. Overcoming the Blood–brain barrier: Emerging approaches
    6.2. Precision medicine and personalized nanomedicine
    6.3. Regulatory and manufacturing challenges
    6.4. Integration of artificial intelligence and computational modelling
    6.5. Roadmap toward clinical translation
7. Conclusion

1. Introduction

1.1. Alzheimer's disease: Pathophysiology and clinical burden

Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for nearly 60–70% of cases globally, and is recognized as one of the greatest public health challenges of the 21st century. It is a progressive and irreversible neurodegenerative disorder clinically characterized by memory impairment, language deficits, impaired executive functioning, personality changes, and eventually a complete decline in independence [1]. From a neuropathological perspective, AD is defined by the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, synaptic dysfunction, and widespread neuronal death, particularly in the hippocampus and cerebral cortex. The progressive nature of the disease leads to substantial neuronal loss, cortical atrophy, and brain shrinkage, which

manifest as worsening cognitive and functional impairments over time [2].

The global burden of AD is rising at an alarming rate, primarily because of increasing life expectancy and aging populations. According to recent estimates, over 55 million people worldwide live with dementia, and this number is projected to triple by 2050, if no effective interventions are developed. AD not only places an enormous emotional and physical toll on patients and caregivers, but also imposes a significant socioeconomic burden. Direct healthcare costs, long-term care, and lost productivity result in hundreds of billions of dollars in expenditures annually, straining healthcare systems worldwide. Furthermore, the absence of curative treatments underscores the urgency of developing innovative therapeutic approaches that address both the symptomatic and disease-modifying aspects of AD [3]. Despite decades of research, currently approved drugs, such as acetylcholinesterase inhibitors (pezil, rivastigmine, and galantamine) and the NMDA receptor antagonist memantine, provide only symptomatic relief and do not halt disease progression. More recently, monoclonal antibodies targeting Aβ, including aducanumab and lecanemab, have gained regulatory approval; however, their clinical benefits remain controversial, and issues of safety, efficacy, and cost-effectiveness continue to limit their widespread use [4]. Thus, there is a pressing need to explore novel therapeutic paradigms that can effectively target the multifaceted pathology of AD, particularly those addressing oxidative stress, neuroinflammation, and metal ion dysregulation, which play pivotal roles in disease progression [5]. In a healthy brain (a), tau proteins stabilize microtubules, supporting normal neuronal structures and functions. In the Alzheimer's brain (b), tau proteins become hyperphosphorylated, leading to tau tangles and neurofibrillary tangles that destabilize microtubules, resulting in disintegrating microtubules and diseased neurons, as shown in **Figure 1**.

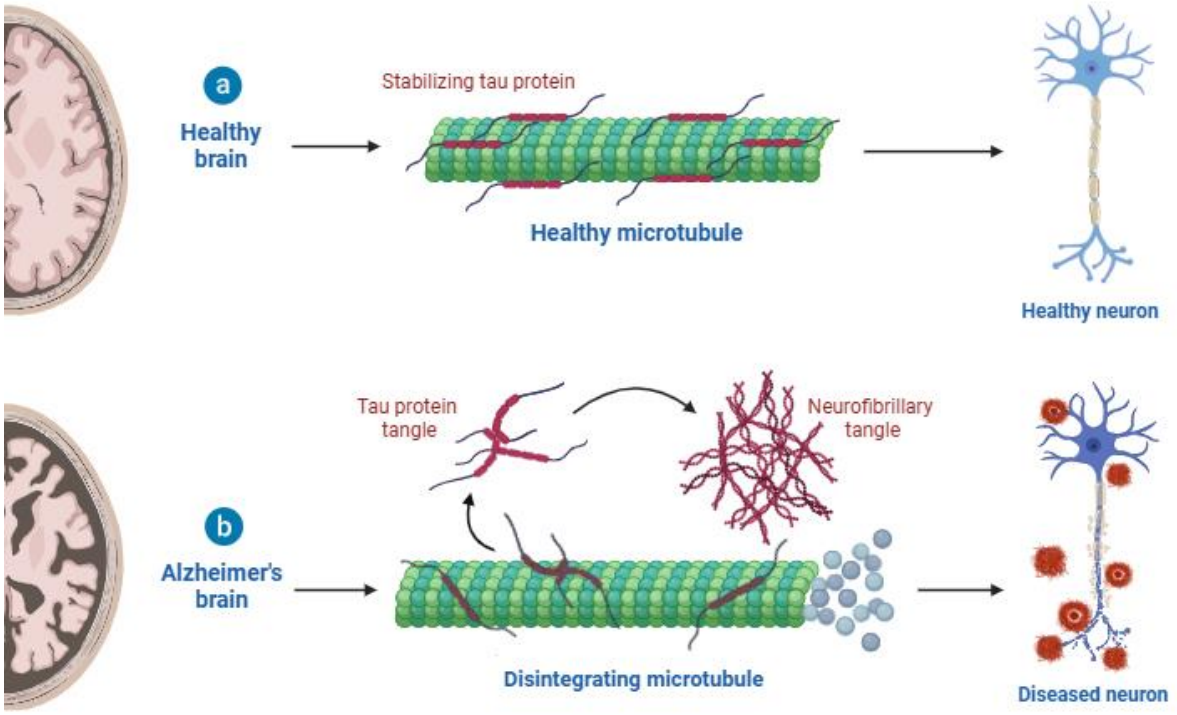

Figure 1. Schematic comparison of neuronal microtubule stability in a healthy brain versus an Alzheimer's-affected brain. In the healthy state, tau proteins stabilize microtubules, supporting normal neuronal structure and function. In Alzheimer's disease, tau proteins become abnormally hyperphosphorylated, leading to neurofibrillary tangles, destabilized microtubules, and progressive neuronal dysfunction

1.2. Role of metal ions in alzheimer's progression (Cu, Fe, Zn, Al, etc.)

Metal ions are essential for normal brain physiology, and serve as cofactors for numerous enzymes, neurotransmitter synthesis, myelination, and synaptic plasticity. However, the dysregulation of metal homeostasis has been increasingly recognized as a central contributor to Alzhimer's disease (AD) pathology. Post-mortem studies of AD brains have consistently revealed abnormal accumulation of transition metals, including copper (Cu), iron (Fe), zinc (Zn), and aluminum (Al), particularly in amyloid plaques and neurofibrillary tangles. This imbalance contributes to amyloid aggregation, tau phosphorylation, oxidative stress, and mitochondrial dysfunction, thereby exacerbating neuronal damage [6]. Copper (Cu) is vital for enzymatic processes such as cytochrome c oxidase and superoxide dismutase activity. However, in AD, excess redox-active Cu can interact with Aβ peptides, accelerating their aggregation and generating reactive oxygen species (ROS) through Fenton-like reactions. Elevated ROS levels cause oxidative damage to lipids, proteins, and nucleic acids, which leads to synaptic dysfunction and neuronal death. Conversely, Cu deficiency in specific brain regions has also been reported, suggesting a complex region-specific dysregulation that affects AD progression [7]. Iron (Fe) plays key roles in oxygen transport, electron transfer, and neurotransmitter metabolism. In AD brains, iron accumulation is observed in the hippocampus and cortex, which correlates with increased oxidative stress and cognitive decline. Iron can bind to Aβ and tau, enhancing their aggregation and toxicity, while Fe(II)/Fe(III) cycling generates hydroxyl radicals via the Fenton reaction, leading to oxidative stress and neuronal injury. Iron accumulation also disrupts mitochondrial function, further impairing neuronal energy metabolism [8]. Zinc (Zn) is critical for synaptic signaling and neuronal communication. However, excessive Zn is sequestered within amyloid plaques where it promotes Aβ aggregation and deposition. Although Zn is not redox-active, its displacement of Cu and Fe from amyloid-binding sites can indirectly enhance redox cycling and oxidative stress. Moreover, Zn deficiency has been linked to synaptic dysfunction and memory impairment, highlighting the delicate balance required to maintain Zn homeostasis [9]. Although the role of Al in AD remains controversial, evidence suggests that it can exacerbate neurotoxicity by promoting Aβ aggregation and tau hyperphosphorylation. Al exposure is associated with increased oxidative stress, mitochondrial dysfunction, and disruption of iron metabolism, collectively contributing to neuronal degeneration. Although not an essential trace element, its neurotoxic potential cannot be disregarded in the context of AD pathogenesis [10]. Collectively, these findings highlight the dual nature of metal ions in the brain, which are essential for physiological function but are deleterious when dysregulated. The interplay between metal imbalance, Aβ aggregation, tau pathology, and oxidative stress underscores the need for therapeutic interventions to restore the metal balance while minimizing neurotoxicity. This has spurred interest in metal chelation therapy and the design of metal complexes capable of regulating these processes in a controlled manner [11].

1.3. Rationale for metal complex-based therapeutics

Metal-complex-based therapeutics have emerged as a rational and promising strategy, given the critical involvement of metal imbalance in AD progression. The underlying concept is the development of small molecules or complexes that can selectively chelate excess metal ions, modulate their redox properties, and prevent their interaction with pathogenic proteins, thereby mitigating downstream neurotoxic events [12]. Unlike traditional chelators used in systemic metal overload disorders, such as deferoxamine, the design of therapeutic metal complexes for AD requires greater specificity, blood–brain barrier (BBB) penetration, and minimal systemic side effects [13].

1.3.1. Metal complexes can serve multiple roles in AD therapy

Metal Chelation and Redistribution: Properly designed ligands can sequester excess Cu, Fe, or Zn from amyloid plaques and redistribute them to restore physiological homeostasis, without depleting essential trace metals from other biological systems.

Inhibition of Amyloid and Tau Pathology: Certain complexes can bind directly to Aβ peptides or tau proteins, preventing aggregation or destabilizing existing aggregates, thereby reducing neurotoxicity.

Redox Modulation: By controlling the redox activity of Cu and Fe metal complexes can suppress ROS generation and oxidative damage, which are the key drivers of neuronal loss in AD. Neuroprotection and multifunctional metal complexes can be engineered to incorporate antioxidant, anti-inflammatory, or enzymatic mimetic functions.

Some complexes possess intrinsic imaging capabilities that enable simultaneous diagnosis and therapy (theranostics), which is highly desirable for monitoring disease progression and treatment response in AD.

Examples of such approaches include clioquinol and PBT2, which have been investigated for their ability to chelate Cu and Zn and disrupt Aβ–metal interactions. Although early clinical trials demonstrated promising results in reducing Aβ levels and improving cognitive function, later studies were less conclusive, highlighting the challenges in translating metal complex-based therapies into clinical success. Nevertheless, these studies paved the way for next-generation designs that focus on improved selectivity, reduced toxicity, and multifunctional properties tailored to the AD brain [14]. The rationale for metal complex-based therapeutics lies in their ability to simultaneously address multiple pathological hallmarks of AD, including metal imbalance, oxidative stress, amyloid aggregation, and tau pathology, through a unified molecular strategy. This multi-target approach aligns well with the complex, multifactorial nature of AD, where single-target interventions have repeatedly failed to yield significant clinical outcomes [15].

1.4. Advantages of nanostructured delivery systems

Although metal complex-based therapeutics hold promise, their clinical translation faces significant barriers, including poor solubility, instability in biological fluids, systemic toxicity, and inadequate BBB penetration. The blood–brain barrier, a highly selective endothelial interface, restricts the entry of most therapeutic agents into the central nervous system (CNS), limiting the effectiveness of conventional drugs. To overcome these challenges, nanostructured delivery systems have emerged as transformative platforms for targeted delivery of metal complexes in AD therapy [16].

Enhanced bioavailability and stability: Encapsulation of metal complexes within nanocarriers, such as liposomes, polymeric nanoparticles, dendrimers, or solid lipid nanoparticles, enhances their solubility, stability, and resistance to enzymatic degradation. This prolongs circulation time, allowing sustained release and controlled pharmacokinetics [17,18].

Targeted delivery and BBB penetration: Nanostructures can be engineered with surface modifications, such as peptides, antibodies, or aptamers, that facilitate receptor-mediated transcytosis across the BBB. Ligand-decorated nanocarriers can selectively target neurons or pathological aggregates, thereby maximizing therapeutic efficacy while minimizing off-target effects [19].

Multifunctionality and synergy: Nanocarriers can be co-loaded with metal complexes and other therapeutic agents, such as antioxidants, anti-inflammatory drugs, or genetic materials (siRNA and miRNA), to achieve synergistic effects. Additionally, stimuli-responsive nanoparticles (pH, redox, enzyme, or ROS-sensitive) allow site-specific release in the diseased microenvironment [20].

Reduced toxicity and improved safety profile: By controlling the release and biodistribution of metal complexes, nanostructured carriers

minimize systemic toxicity, which is a major limitation of conventional chelation therapy. The ability to fine-tune the nanoparticle composition, size, and surface charge further improves biocompatibility and safety [21,22].

Theranostic potential: Nanostructured systems can incorporate imaging agents (fluorescent dyes, MRI contrast agents, and radionuclides) alongside therapeutic metal complexes, enabling real-time monitoring of drug delivery, biodistribution, and therapeutic outcomes. This integration of diagnosis and therapy holds great promise for personalized treatment strategies for AD [23]. In addition to these advantages, advances in nanotechnology offer the possibility of precision medicine for AD, where treatment can be tailored to individual patients based on genetic, biochemical, and imaging biomarkers. This is particularly important, given the heterogeneity of AD pathology and patient responses to therapy. By integrating molecular design with nanoscale engineering, nanostructured metal complexes represent a paradigm shift in AD drug development, combining disease-modifying potential with targeted and safe delivery [24].

2. Nanostructured Metal Complexes: Concept and Design

Nanostructured metal complexes represent a rapidly evolving frontier in biomedical research that combines the therapeutic versatility of metal ions and ligands with the structural and functional benefits of nanotechnology. In the context of AD, these constructs are particularly appealing because they can integrate multiple functionalities within a single platform, such as metal chelation, antioxidant activity, inhibition of Aβ aggregation, and targeted delivery to the neurons [25]. Nanostructured metal complexes are engineered systems in which metal ions or organometallic frameworks are integrated into nanoscale carriers or directly self-assembled into nanostructures with tailored physicochemical properties. Their design requires careful consideration of structural stability, biocompatibility, physicochemical features, and the ability to overcome physiological barriers, most notably the blood–brain barrier (BBB) [26]. The modularity of these systems allows for the fine-tuning of size, charge, surface chemistry, and ligand architecture, ensuring optimized pharmacological performance [27]. This section provides a detailed discussion of the structural and physicochemical features of nanostructured metal complexes, strategies for metal–ligand functionalization, nanoformulation approaches, and the critical issue of BBB penetration that defines their success in AD therapy [28].

2.1. Structural and physicochemical features

The therapeutic performance of nanostructured metal complexes is determined by their structural and physicochemical characteristics. Parameters such as particle size, shape, surface charge, solubility, stability, and metal–ligand coordination strongly influence biodistribution, circulation half-life, cellular uptake, and ultimately, therapeutic efficacy [29]. Particle size is the primary determinant of pharmacokinetics and biodistribution. Nanoparticles in the range of 10–200 nm are generally considered optimal for drug delivery because they can avoid rapid renal clearance (<10 nm) and uptake by the reticuloendothelial system (>200 nm). For AD applications, sizes between 50 and 100 nm are particularly favorable, enabling prolonged circulation while facilitating passage across the BBB via receptor-mediated transport [30]. Surface charge (zeta potential) is another critical parameter. Positively charged particles exhibit strong interactions with negatively charged cell membranes, enhancing cellular uptake. However, they are also prone to nonspecific protein adsorption and rapid clearance. In contrast, negatively charged or neutral particles display longer circulation times, but reduced internalization. Thus, surface modification with hydrophilic polymers such as polyethylene glycol (PEG) is often employed to balance the stability, circulation, and targeting efficiency [31]. Shape and morphology also affect biological interactions. While spherical nanoparticles are the most common, alternative geometries, such as rods, cubes, or platelets, exhibit distinct

cellular uptake pathways and biodistribution profiles. Emerging evidence suggests that rod-shaped nanostructures may penetrate the tight junctions of endothelial cells more effectively, a feature relevant to BBB transport [32].

Metal–ligand coordination chemistry plays a central role in defining therapeutic functions. Transition metals, such as copper, iron, zinc, ruthenium, and platinum, are often employed because of their ability to engage in redox reactions or coordinate with pathological biomolecules, such as Aβ and tau. The choice of ligand determines not only the stability, but also the biological activity of the complexes. Strong chelating ligands, such as polyhydroxyquinolines, phenanthrolines, or macrocycles, can sequester redox-active metals and inhibit ROS generation, whereas biologically active ligands (antioxidants, peptides, or anti-inflammatory agents) provide synergistic therapeutic benefits [33]. Stability is a double-edged sword in design. High stability ensures that complexes remain intact during systemic circulation; however, excessive stability may hinder metal release at the target site. In contrast, labile complexes may degrade prematurely, leading to off-target toxicities. Smart designs integrate stimuli-responsive ligands or carriers that release their payload under specific conditions, such as acidic pH, high ROS levels, or enzyme activity characteristic of the AD microenvironment [34]. Finally, biocompatibility and toxicity remain as key concerns. If not carefully tuned, metal complexes may trigger cytotoxicity, immunogenicity, or unintended interactions with healthy biomolecules. Nanostructured carriers help mitigate these risks by encapsulating or shielding the metal center until it reaches the diseased site, thereby enhancing therapeutic selectivity and safety [35]. Together, these physicochemical features provide a blueprint for the rational design of nanostructured metal complexes, allowing researchers to balance stability, reactivity, targeting ability, and safety for their effective use in AD therapy [36].

2.2. Strategies for metal–ligand functionalization

Functionalization strategies lie at the heart of nanostructured metal complex design as they dictate both therapeutic and targeting capabilities. The versatility of coordination chemistry enables a wide range of ligand modifications to optimize the stability, bioactivity, and disease specificity. Several design strategies have been employed in this regard [37]. Chelation-based functionalization, strong chelating ligands such as hydroxypyridinones, 8-hydroxyquinoline derivatives, and desferrioxamine analogs have been used to capture and neutralize excess Cu, Fe, and Zn ions implicated in AD pathology. These ligands prevent metal-induced amyloid aggregation and redox cycling, while maintaining essential metal homeostasis [38]. Bioactive ligand integration: Ligands with intrinsic therapeutic effects, such as curcumin, resveratrol, or polyphenols, can be conjugated to metal centers to provide dual functionality. For example, curcumin-based ligands not only stabilize the complex, but also exert anti-inflammatory and anti-amyloid effects, amplifying therapeutic outcomes [39]. Targeting ligand modification to achieve selective delivery to the brain and neuronal cells, ligands are engineered with targeting moieties, such as transferrin, lactoferrin, apolipoproteins, peptides (*e.g.,* RGD and TGN), or antibodies against Aβ. These moieties facilitate receptor-mediated endocytosis across the BBB and their accumulation in AD-relevant regions [40]. Stimuli-responsive functionalization smart ligands have been designed to release metal payloads under specific stimuli. For example, disulfide-containing ligands respond to the reductive environment of neurons, while pH-sensitive groups enable their release in the slightly acidic microenvironment of amyloid plaques. Similarly, ROS-sensitive linkers enable targeted drug release in oxidative stress-enriched AD tissues [41]. Multifunctional hybridization, a key advantage of nanostructured complexes, is the ability to incorporate multiple ligands, combining chelation, antioxidants, targeting, and imaging

functionalities. For example, a ruthenium complex can be functionalized with both a chelating ligand for redox control and a fluorescent ligand for imaging, thus achieving theranostic potential [42]. Surface engineering of nanocarriers beyond direct metal–ligand interactions, nanocarriers encapsulating metal complexes can be surface-functionalized with hydrophilic polymers, peptides, or aptamers to enhance stability and targeting. PEGylation remains the gold standard for prolonging circulation, while specific ligands such as Angiopep-2 or transferrin, improve BBB transport [43]. Thus, functionalization strategies provide a versatile toolkit for tailoring nanostructured metal complexes to the multifactorial demands of AD therapy, enabling the precise modulation of pharmacokinetics, biodistribution, and therapeutic action [44].

2.3. Nanoformulation approaches (liposomes, dendrimers, polymeric nanoparticles, etc.)

The success of nanostructured metal complexes also depends on the choice of nanoformulation platform, which dictates the delivery efficiency, stability, and therapeutic performance. Several nanocarrier systems have been developed to incorporate or conjugate metal complexes [45]. Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate hydrophilic and hydrophobic drugs. Depending on their solubility profiles, metal complexes can be integrated within the lipid bilayer or aqueous core. Liposomes offer high biocompatibility, tunable sizes, and surface modifiability. PEGylated liposomes or immunoliposomes decorated with targeting ligands have been shown to cross the BBB effectively and deliver chelating agents to amyloid plaques [46]. Dendrimers are highly branched monodisperse macromolecules with abundant surface functional groups for ligand conjugation. They can encapsulate metal complexes within their interior cavities or bind to them via surface groups. Their well-defined architecture allows for precise control of size, charge, and drug loading. In particular, poly (amidoamine) (PAMAM) dendrimers have demonstrated potential for delivering chelating agents and antioxidants across the BBB with minimal toxicity [47]. Biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and PEG-based block copolymers, have been extensively explored for nanoformulations [48]. Metal complexes can be encapsulated or covalently conjugated to these polymers, enabling a controlled and sustained release. Polymeric nanoparticles offer superior stability, scalability, and the potential for stimuli-responsive release [49,50]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as lipid-based systems exhibit high biocompatibility and the ability to encapsulate lipophilic metal complexes. They provide controlled release, protection from degradation, and surface functionalization potential. Their lipidic nature favors interactions with biological membranes and enhances cellular uptake [51]. Materials such as mesoporous silica, gold, and magnetic nanoparticles serve as scaffolds for metal-complex delivery. Mesoporous silica nanoparticles can encapsulate complexes within their pores, whereas gold nanoparticles allow facile conjugation via thiol chemistry. Magnetic nanoparticles, typically iron oxide-based, enable both therapy and imaging (theranostics), offering unique advantages for AD diagnosis and treatment [47]. Hybrid and multifunctional systems: Researchers are increasingly exploring hybrid nanocarriers that integrate the features of multiple platforms. For instance, liposome-coated gold nanoparticles or polymer–lipid hybrids combine the stability of inorganic systems with the biocompatibility of organic carriers. Multifunctional nanoformulations can also co-deliver metal complexes along with conventional drugs, peptides, or nucleic acids, achieving synergistic effects against AD pathology [52]. Each nanoformulation approach offers distinct advantages and limitations, and the choice depends on the physicochemical properties of the metal complex, the desired pharmacokinetics, and the therapeutic goals. Importantly, scalability, reproducibility, and regulatory considerations must also guide

formulation development for clinical translation [53].

2.5. Blood–brain barrier (BBB) penetration challenges and solutions

The BBB remains the most formidable barrier for the design of nanostructured metal complexes for AD therapy. Comprised of tightly packed endothelial cells, pericytes, and astrocytic end-feet, the BBB restricts the passage of over 98% of small molecules and nearly all macromolecules, allowing only essential nutrients and specific transport substrates to enter the brain. While this protective function is critical for maintaining brain homeostasis, it significantly limits drug delivery to the central nervous system [54]. Challenges in BBB penetration of metal complexes often include unfavorable properties such as hydrophilicity, high molecular weight, and ionic charge, which hinder passive diffusion across the BBB. Furthermore, efflux transporters, such as P-glycoprotein, actively pump foreign molecules back into systemic circulation. Even nanoparticles face challenges, as large or unmodified particles are recognized and cleared by the mononuclear phagocyte system before reaching the brain [55].

Nanostructured designs offer multiple strategies to overcome BBB penetration, including receptor-mediated transport using ligands such as transferrin or insulin, adsorptive-mediated transport via cationic surface modifications, and CPPs such as TAT or Angiopep-2 for enhanced uptake. Stimuli-responsive systems enable site-specific drug release, while PEGylation imparts stealth properties to prolong circulation. Exosome-inspired carriers, with their innate BBB-crossing ability and biocompatibility, further represent a promising approach for effective brain-targeted delivery (**Figure 2**).

Figure 2. Nanostructured strategies to overcome BBB penetration challenges. The illustration highlights approach such as receptor-mediated transport (*e.g.,* transferrin and insulin), adsorptive-mediated transport via cationic modifications, cell-penetrating peptides (CPPs), stimuli-responsive release, and PEGylation. These strategies enhance nanocarrier delivery across the BBB for Alzheimer's therapy

Overcoming the BBB is critical for translating nanostructured metal complexes into effective therapies for AD. Researchers are steadily advancing toward clinically viable solutions by integrating receptor-targeted ligands, optimizing physicochemical properties, and employing biomimetic or stimuli-responsive designs [56]. The neurovascular unit (left) comprises neurons, astrocytes, microglia, oligodendrocytes, and pericytes, which interact with the cerebral blood vessels to maintain brain homeostasis. The blood–brain barrier (right, cross-section) is formed by endothelial cells connected via tight junctions, supported by pericytes, astrocyte end-feet, and the basement membrane, providing selective permeability and protecting the brain from harmful substances, as diagrammatically shown in **Figure 3**.

3. Mechanistic Insights into Therapeutic Action

The therapeutic efficacy of nanostructured metal complexes in AD arises from their ability to simultaneously target multiple pathogenic mechanisms underlying the disease simultaneously. Unlike conventional therapies that primarily address symptoms, these advanced systems offer a multipronged approach aimed at disease modification [57]. Central to AD pathogenesis are Aβ aggregation, tau hyperphosphorylation, metal imbalance, oxidative stress, and chronic neuroinflammation. By integrating metal chelation, redox control, molecular targeting, and multifunctional ligands within nanoscale platforms, nanostructured metal complexes can act on diverse pathways to restore neuronal homeostasis and prevent disease progression [58]. This section provides mechanistic insights into their therapeutic action, focusing on four major axes: inhibition of Aβ aggregation and toxicity, modulation of tau hyperphosphorylation, restoration of metal and redox homeostasis, and neuroprotection via antioxidant and anti-inflammatory pathways [59].

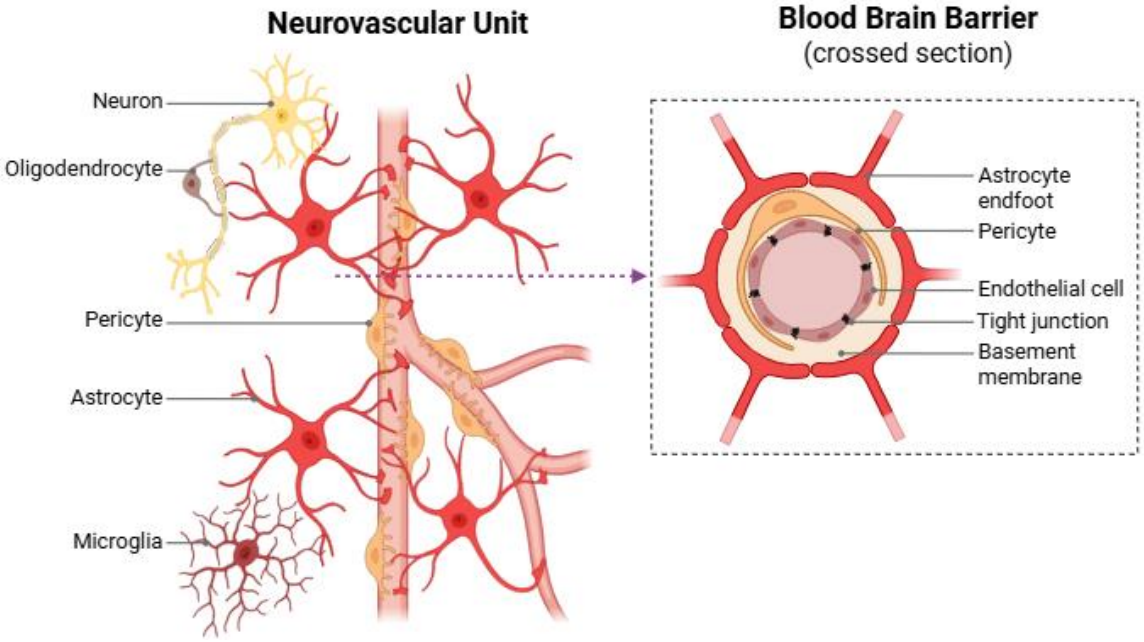

Figure 3. Diagrammatic representation of the neurovascular unit and the BBB. The neurovascular unit consists of neurons, astrocytes, microglia, oligodendrocytes, and pericytes, all interacting with cerebral blood vessels

3.1. Inhibition of Aβ aggregation and toxicity

The deposition of Aβ plaques is a pathological hallmark of AD and one of the earliest triggers of neuronal dysfunction. Aβ peptides, generated by the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases, are prone to self-aggregation into oligomers, protofibrils, and insoluble fibrils. Among these, soluble oligomers are considered as the most neurotoxic, impairing synaptic function, disrupting calcium homeostasis, and activating apoptotic pathways. Therapeutic interventions aimed at preventing or reversing Aβ aggregation are therefore of great significance [60].

Nanostructured metal complexes can contribute to this goal through several mechanisms. First, direct binding to Aβ peptides can block aggregation-prone regions, thereby stabilizing peptides in non-toxic conformations. For example, copper and ruthenium complexes functionalized with aromatic ligands exhibit π–π stacking interactions with hydrophobic Aβ sequences, thereby preventing nucleation and fibril elongation. Second, disruption of metal-Aβ interactions is critical. Excess Cu, Zn, and Fe bind Aβ with a high affinity, promoting aggregation and generating ROS through redox cycling. Chelating complexes sequester these metals from Aβ, destabilize aggregates, and reduce oxidative stress [61]. Certain nanocarriers facilitate enzymatic degradation of Aβ by enhancing the delivery of metal complexes that modulate proteolytic pathways. For instance, Zn(II)-based complexes can activate matrix metalloproteinases that are capable of degrading Aβ peptides. Other designs exploit stimuli-responsive release: nanoparticles loaded with complexes that respond to the acidic microenvironment of plaques release chelators specifically at the site of pathology, maximizing local efficacy while minimizing systemic side effects [62]. A further layer of action involves the neutralization of Aβ oligomer toxicity. Some nanostructured complexes preferentially interact with oligomeric rather than fibrillar forms of Aβ, thereby attenuating their ability to disrupt synaptic signaling. The presence of antioxidant ligands also reduces ROS produced by Aβ-metal complexes, protecting neurons from lipid peroxidation and DNA damage. Importantly, nanoscale design ensures enhanced brain accumulation and prolonged activity, which are not achievable with conventional small-molecule inhibitors [63]. Collectively, by preventing Aβ aggregation, disrupting metal–Aβ interactions, and reducing oligomeric toxicity, nanostructured metal complexes directly address a central pathological event in AD. This mechanism provides both symptomatic benefits through the preservation of synaptic function and disease-modifying potential by reducing the plaque burden [63]. In the amyloidogenic pathway, the amyloid precursor protein (APP) undergoes sequential cleavage by β-secretase and γ-secretase, producing soluble APPβ (sAPPβ), amyloid intracellular domain (AICD), and Aβ peptides. Aggregation of Aβ peptides in the extracellular space leads to the formation of amyloid plaques, a hallmark of AD pathology, as demonstrated in **Figure 4**.

3.2. Modulation of tau hyperphosphorylation

In addition to Aβ pathology, the intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles is a defining feature of AD. Under normal conditions, tau stabilizes the microtubules, thereby supporting axonal transport and neuronal integrity. However, abnormal hyperphosphorylation by kinases, such as glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and mitogen-activated protein kinases (MAPKs), disrupts tau function, leading to aggregation into paired helical filaments and tangles. These aggregates interfere with axonal transport, trigger mitochondrial dysfunction, and ultimately induce neuronal death [64]. Nanostructured metal complexes offer the unique opportunity to modulate tau pathology at multiple levels. Certain complexes act as kinase inhibitors that directly or indirectly suppress enzymes responsible for tau hyperphosphorylation. For instance, ruthenium-based complexes have been shown to modulate GSK-3β activity, thereby reducing the abnormal phosphorylation of tau.

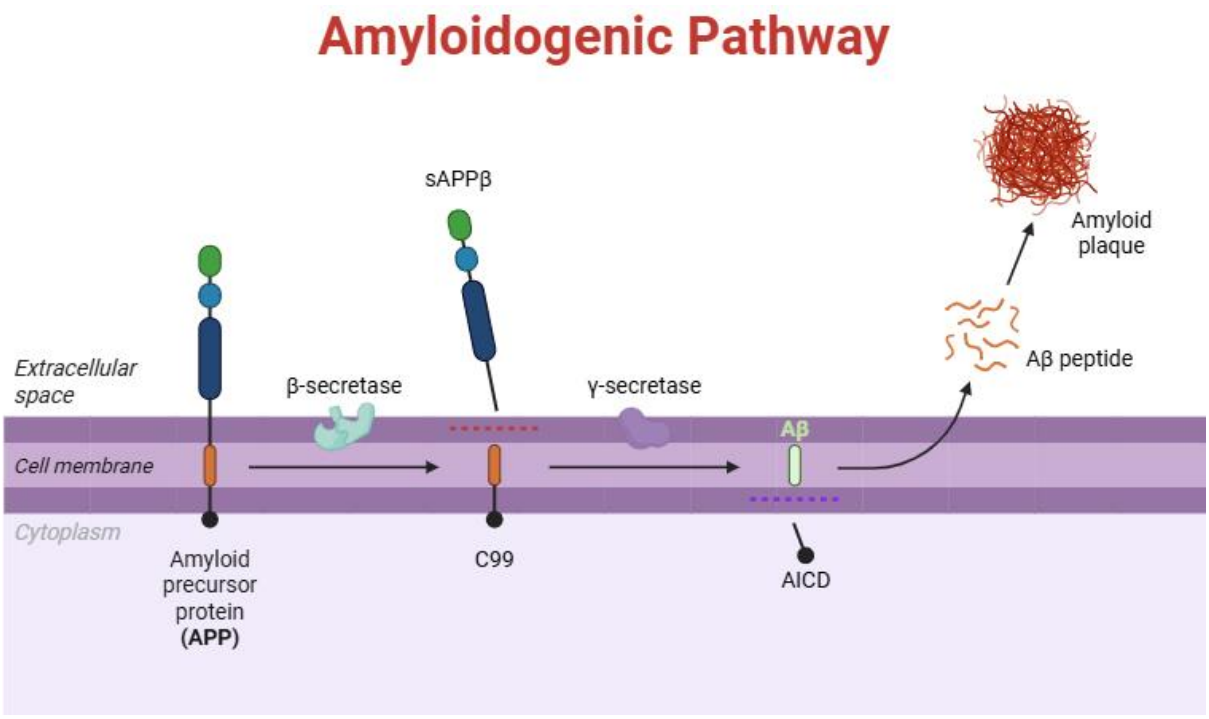

Figure 4. Amyloidogenic pathway of amyloid precursor protein (APP) processing leading to amyloid plaque formation. APP undergoes sequential cleavage by β-secretase and γ-secretase to generate amyloid-β (Aβ) peptides

Similarly, zinc complexes can regulate protein phosphatases, such as PP2A, restoring the balance between phosphorylation and dephosphorylation [65].

Another approach involves direct interaction with the tau protein. Specific ligands on metal complexes can bind to tau and prevent its aggregation into fibrils. These complexes maintain microtubule dynamics and neuronal function by stabilizing monomeric and low-order tau species. Nanocarrier-based formulations enhance this effect by improving the bioavailability of tau-targeting complexes and enabling targeted delivery to the neurons [66]. Tau pathology is closely linked to oxidative stress and metal imbalances. Excessive ROS promotes aberrant activation of kinases and tau modifications, while metals, such as Fe and Cu, exacerbate phosphorylation cascades. Metal complexes with antioxidant ligands can mitigate these secondary pathways and indirectly reduce tau pathology. For example, iron chelation reduces Fe-mediated activation of kinases, whereas antioxidant moieties scavenge ROS, which otherwise trigger hyperphosphorylation [67]. Importantly, tau pathology also contributes to neuroinflammation as tau aggregates activate microglia and astrocytes. Nanostructured complexes that reduce tau burden, therefore, have downstream effects on inflammatory pathways, further preserving neuronal viability [68]. Overall, by inhibiting tau hyperphosphorylation, preventing aggregation, and modulating kinase activity, nanostructured metal complexes provide a mechanistic advantage for addressing the second major pathological axis of AD. The ability to act simultaneously on both amyloid and tau pathologies highlights their multifunctional therapeutic potential [69].

3.3. Metal chelation and redox homeostasis

One of the most distinctive mechanisms of action of metal complexes in AD therapy is their ability to restore metal homeostasis and redox homeostasis. As discussed previously, the dysregulation of Cu, Fe, and Zn in AD brains leads

to Aβ aggregation, tau hyperphosphorylation, and oxidative damage. Redox-active metals, especially Cu and Fe, catalyze the Fenton and Haber–Weiss reactions, generating hydroxyl radicals that damage cellular macromolecules and impair neuronal viability. Effective therapy requires a delicate balance: sequestration of excess toxic metals without depriving neurons of the essential trace elements required for physiological processes [70]. Nanostructured metal complexes can achieve this through selective chelation and controlled redistribution. Chelating ligands such as hydroxypyridinones, hydroxyquinolines, and desferrioxamine analogs are designed to bind metals tightly but reversibly, allowing for controlled sequestration. Encapsulation within nanocarriers enhances their stability and ensures targeted release in the brain, thereby minimizing systemic depletion. Some complexes have been engineered to act as ionophores, redistributing metals from sites of pathological accumulation (plaques and tangles) to regions where they are needed for enzymatic activity [71]. Another critical function is the regulation of the redox activity. For instance, ruthenium and platinum complexes can mimic antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, thereby detoxifying ROS and restoring oxidative balance. By preventing metal-driven ROS generation, these complexes protect neurons from oxidative stress, mitochondrial dysfunction, and apoptosis [72]. Nanocarrier-based systems further contribute to redox homeostasis by enabling stimuli-responsive chelation. For example, nanoparticles can be designed to release chelating complexes in response to elevated ROS levels in diseased brain tissues. This ensures that chelation occurs precisely, where it is necessary to avoid systemic metal depletion. Similarly, pH-sensitive formulations release chelators in the slightly acidic microenvironment of amyloid plaques, enhancing site-specific actions [73]. In addition to direct chelation, certain complexes provide redox modulation without metal removal. By stabilizing metals in non-redox-active oxidation states, these complexes prevent harmful cycling, while maintaining physiological availability. For example, Zn-based nanostructures can stabilize Cu(II) in non-redox-active forms, reducing ROS generation without completely removing Cu from neuronal circuits [74]. Through selective chelation, controlled redistribution, and redox modulation, nanostructured metal complexes are among the most critical and underexplored dimensions of AD pathology. Their ability to restore homeostasis while avoiding systemic imbalances underscores their superiority over conventional chelation therapies [75].

3.4. Neuroprotection via antioxidant and anti-inflammatory pathways

Oxidative stress and chronic neuroinflammation are interlinked processes that accelerate the progression of AD. Elevated ROS levels damage neuronal DNA, proteins, and lipids while also activating inflammatory cascades through microglial and astrocytic responses. In parallel, neuroinflammation perpetuates oxidative stress by releasing pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and nitric oxide, creating a vicious cycle that contributes to synaptic loss and neuronal death. Therefore, effective AD therapy requires interventions that simultaneously provide antioxidant and anti-inflammatory protection [76]. Nanostructured metal complexes are uniquely positioned to fulfill this dual role. Antioxidant activity arises from both the intrinsic properties of metal complexes and the presence of antioxidant ligands. For instance, Mn, Cu, and Ru complexes can mimic superoxide dismutase (SOD) and catalase activities, catalytically decomposing superoxide and hydrogen peroxide into less harmful species. The incorporation of antioxidant ligands such as flavonoids, curcumin, or polyphenols further enhances the ROS scavenging capacity. At the nanoscale, these activities are amplified due to the increased surface area and enhanced reactivity [77]. Nanocarrier encapsulation protects the antioxidant complexes from premature degradation and ensures sustained activity in the brain. Stimuli-responsive designs enable complexes to release their antioxidant function specifically in regions of oxidative stress,

maximizing therapeutic benefits while minimizing off-target effects [78]. Anti-inflammatory effects are mediated by multiple mechanisms. By reducing amyloid-beta (Aβ) and tau pathology, nanostructured complexes indirectly decrease microglial activation and cytokine release. Certain complexes also exert direct immunomodulatory effects by inhibiting pro-inflammatory transcription factors, such as NF-κB, or activating anti-inflammatory pathways, such as Nrf2/ARE. For example, iron chelation reduces Fe-driven microglial activation, while ruthenium complexes can suppress NF-κB signaling, thereby attenuating the release of TNF-α and IL-6 [79].

Figure 5 shows that microglia maintain brain homeostasis by adopting either protective or harmful phenotypes in response to the stimuli. Under normal conditions, homeostatic microglia support neuronal health through anti-inflammatory activities, release neurotrophic factors, phagocytose debris, and promote neuroprotection. However, upon exposure to inflammatory stimuli, microglia become pro-inflammatory and release inflammatory cytokines that contribute to neuronal degeneration, tissue inflammation, and cell death. The balance between anti-inflammatory and pro-inflammatory microglial states determines whether the neurons are preserved or damaged. Furthermore, nanoparticles themselves can be functionalized with anti-inflammatory agents or designed to release therapeutic gases such as nitric oxide (NO), which exerts vasodilatory and anti-inflammatory effects at controlled levels. Co-delivery strategies in which metal complexes are combined with corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) in a single nanocarrier further amplify neuroprotective effects [80].

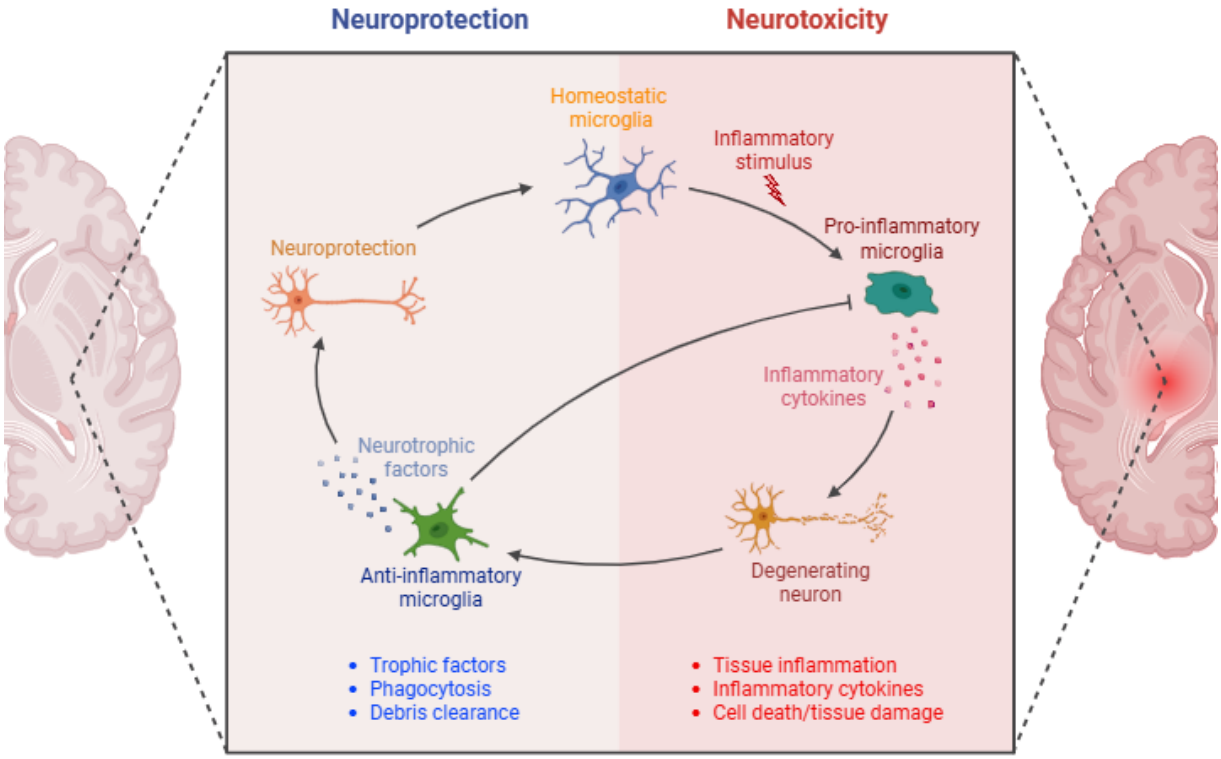

Figure 5. Role of microglia in neuroprotection and neurotoxicity. Under homeostatic conditions, microglia exert neuroprotective effects by clearing debris, releasing neurotrophic factors, and maintaining anti-inflammatory balance

The synergy between the antioxidant and anti-inflammatory pathways is critical. By reducing oxidative damage, nanostructured complexes prevent the secondary activation of inflammatory cascades. Conversely, by suppressing inflammation, they reduce ROS generation from activated immune cells. This bidirectional regulation preserves synaptic integrity, enhances neuronal survival, and slows the disease progression [81]. Thus, through their combined antioxidant and anti-inflammatory actions, nanostructured metal complexes offer a comprehensive neuroprotective strategy that addresses key downstream processes that exacerbate AD pathology and contribute to clinical decline [57].

4. Categories of Nanostructured Metal Complexes in Alzheimer's Therapy

The therapeutic potential of nanostructured metal complexes in AD has been increasingly recognized due to their ability to modulate pathological pathways, such as Aβ aggregation, tau hyperphosphorylation, oxidative stress, and neuroinflammation. Metal ions play a dual role in AD; while essential for neuronal signaling and homeostasis, their dysregulation contributes to neurotoxicity and disease progression [82]. Nanostructured metal complexes combine the biological activity of metal ions with the physicochemical versatility of nanoscale carriers, offering enhanced blood–brain barrier (BBB) penetration, improved pharmacokinetics, and targeted delivery. These complexes can be tailored for multifunctionality, enabling therapeutic and diagnostic theranostic applications. The following subsections detail the major categories of nanostructured metal complexes investigated for AD therapy, focusing on Cu, Fe, Zn, Ru, Pt, and other emerging systems [83].

4.1. Copper-based complexes

Cu is an essential trace element involved in redox reactions, neurotransmitter biosynthesis, and enzymatic processes. However, in AD, copper homeostasis is disrupted, leading to the aberrant accumulation of amyloid plaques and facilitation of reactive oxygen species (ROS) generation. Free copper ions catalyze Fenton-like reactions, causing oxidative damage to neurons. Thus, copper-based nanostructured complexes have been explored as chelating agents to sequester excess copper and as modulators of copper-dependent enzymes [84]. One prominent strategy is the design of copper-chelating nanocomplexes to reduce amyloid aggregation. Ligands, such as clioquinol, dithiocarbamates, and 8-hydroxyquinoline derivatives, have been incorporated into nanoparticle formulations to enhance BBB penetration and target copper-enriched amyloid plaques. For instance, polymeric nanoparticles decorated with copper-binding ligands have demonstrated improved solubility and sustained release, effectively lowering extracellular copper levels in preclinical models. Additionally, liposome-encapsulated copper complexes have been shown to disassemble Aβ–copper aggregates and reduce neurotoxicity [85]. Interestingly, copper complexes can serve as therapeutic agents by restoring enzymatic activity. For example, copper complexes of bis(thiosemicarbazones) have been investigated for their antioxidant properties and their ability to normalize copper-dependent enzymatic pathways. Incorporating these complexes into nanocarriers protects them from degradation and improves their selectivity for neuronal tissues. Moreover, copper-containing nanoparticles have been engineered as theranostic agents; when conjugated with imaging probes, they enable the simultaneous tracking of drug biodistribution and therapeutic response [86]. However, achieving a balance between copper chelation and supplementation is challenging. Excessive chelation may disrupt physiological processes such as cytochrome c oxidase activity, while supplementation risks enhancing oxidative stress. Nanostructured delivery allows fine-tuning of copper release kinetics and tissue distribution, making copper-based complexes an attractive, though delicate, strategy for AD therapy [87].

4.2. Iron-based complexes

Iron is another critical element in neuronal metabolism; however, its dysregulation is strongly linked to AD pathology. Abnormal accumulation of iron in the hippocampus and cortex contributes to Aβ aggregation, tau hyperphosphorylation, and oxidative stress via Fenton's chemistry. Iron also influences mitochondrial dysfunction, which is a central driver of neuronal death in AD [88]. Iron-chelating nanocomplexes represent a promising therapeutic strategy. Traditional iron chelators, such as deferoxamine (DFO) and deferiprone, suffer from poor BBB permeability and systemic toxicity. The incorporation of these chelators into nanocarriers such as liposomes, dendrimers, or polymeric nanoparticles has markedly improved their brain delivery. For example, PEGylated nanoparticles loaded with DFO demonstrated enhanced neuroprotective effects by reducing iron-induced ROS production and restoring mitochondrial function [89]. In addition to chelation, iron oxide nanoparticles (IONPs) have attracted interest as multifunctional theranostic agents. Their superparamagnetic properties make them ideal for magnetic resonance imaging (MRI), enabling noninvasive monitoring of AD pathology. When functionalized with targeting ligands, such as antibodies against Aβ or tau, IONPs can selectively accumulate in diseased regions, providing both diagnostic imaging and therapeutic intervention. Additionally, IONPs can be engineered to release iron-modulating drugs or antioxidants in response to local stimuli such as pH or ROS, creating a smart delivery system [90]. Recent studies have highlighted the potential of iron-based coordination complexes to regulate iron metabolism and oxidative stress. For instance, iron–polyphenol complexes incorporated into nanosystems exhibit potent antioxidant activity, scavenging free radicals while simultaneously modulating iron levels. Moreover, the targeted delivery of iron chelators via nanocarriers reduces systemic toxicity by avoiding the widespread depletion of essential iron [91]. However, their safety remains a major concern. Excessive iron removal may impair essential metabolic functions, while long-term accumulation of IONPs in tissues raises questions regarding biocompatibility. Thus, the precise design of Fe-based nanocomplexes, with careful consideration of dosage, release kinetics, and biodegradability, is essential for their clinical translation [92].

4.3. Zinc-based complexes

Zinc is the second most abundant trace element in the brain and plays a vital role in synaptic transmission, neurogenesis, and enzymatic function. Dysregulated zinc homeostasis is a hallmark of AD, particularly due to its interaction with Aβ peptides. Zn ions promote Aβ aggregation into insoluble plaques, and their accumulation in synaptic vesicles is linked to excitotoxicity. Conversely, zinc deficiency impairs synaptic plasticity and cognitive function, suggesting a bidirectional role of zinc in AD pathology [93]. Nanostructured zinc complexes aim to restore zinc balance while preventing pathological aggregation. One approach involves the use of zinc-chelating ligands, such as clioquinol, conjugated to nanoparticles to prevent zinc-induced Aβ aggregation. These formulations improve solubility, prolong circulation time, and enhance the targeting of amyloid plaques [44]. Interestingly, zinc-based nanocomplexes can also be neuroprotective when designed as controlled zinc-delivery systems. For example, zinc oxide nanoparticles at carefully optimized concentrations have been shown to enhance synaptic activity and protect against oxidative stress in neuronal cultures. Surface functionalization of these nanoparticles with stabilizing ligands or polymers reduces their cytotoxicity, while enabling targeted delivery to specific brain regions [94]. Zinc complexes have been incorporated into multifunctional nanocarriers that combine metal chelation with antioxidant and anti-inflammatory properties. For instance, hybrid polymer–lipid nanoparticles co-delivering zinc-binding agents and curcumin exhibited synergistic inhibition of Aβ aggregation and reactive oxygen species (ROS) production. Another emerging strategy

involves zinc–peptide conjugates, in which zinc ions stabilize therapeutic peptides that modulate tau phosphorylation pathways [56]. The therapeutic window for zinc modulation is narrow, as both deficiency and excess zinc contribute to the pathology. Thus, nanostructured systems offer the advantage of precise control over zinc release and minimize side effects. Zinc-based complexes, when combined with multifunctional nanocarriers, represent a versatile platform for addressing multiple pathological hallmarks of AD [74]. The zinc-based complexes used in Alzheimer's therapy are shown in **Table 1**.

Table 1. Mechanistic and translational insights of zinc-based complexes in Alzheimer's therapy

Representative Zinc complex / Formulation	Mechanism of action	Primary biological target	Impact on AD pathology	BBB penetration approaches	Clinical / Translational relevance	Ref.
Zn(II)-curcumin nanoparticles, Zn–clioquinol liposomes	Aβ aggregation modulation	Aβ fibrils and oligomers	Disrupts Aβ–Zn/Cu binding, prevents plaque growth	PEGylated NPs, transferrin peptide decoration	Potential disease-modifying approach, early preclinical validation	[63]
Zn(II)-quercetin nanoformulations	Tau phosphorylation control	GSK-3β, tau protein	Reduces hyperphosphorylation and neurofibrillary tangles	Peptide-decorated liposomes for neuronal uptake	Promising for tauopathy-dominant AD subtypes	[95]
Zn(II)-pyrithione NPs, ZnO nanogels	Synaptic zinc homeostasis	Synaptic clefts, Zn^{2+} ion channels	Restores Zn^{2+} signaling balance, improves neurotransmission	Nanoencapsulation to avoid systemic Zn overload	Relevant for memory and learning restoration	[96]
Zn–polyphenol complexes (Zn–curcumin, Zn–quercetin)	Antioxidant & redox balance	ROS, mitochondrial pathways	Scavenges free radicals, protects mitochondria	ROS-responsive nanocarriers	Adjunct therapy to reduce oxidative burden in AD	[97]
Zn–clioquinol, Zn–pyrithione complexes	Metal chelation & redistribution	Cu^{2+}, Fe^{3+}, and Zn^{2+} bound to Aβ	Chelates misregulated ions, lowers metal-induced ROS	Liposomal encapsulation	Bridges AD with metal imbalance disorders	[98]
Zn-based MOFs with imaging probes	Multifunctional theranostics	Aβ plaques + oxidative stress	Combines therapy with MRI/fluorescence imaging	Ligand-functionalized MOFs	Enables monitoring + therapy, useful for precision medicine	[99]
ZnO nanoparticles with surface modification	Neuroinflammation regulation	Microglia and astrocytes	Downregulates pro-inflammatory cytokines	Biocompatible coatings (PEG, chitosan)	Adds neuroprotective angle to zinc therapy	[100]
Zn(II)-loaded nanocarriers + siRNA	Gene modulation approaches	β-secretase, tau-related genes	Dual effect: metal regulation + gene silencing	Aptamer-functionalized polymeric carriers	Represents futuristic precision nanomedicine	[101]

4.4. Ruthenium and platinum complexes

Transition metals, such as ruthenium and platinum, have been extensively studied in oncology for their redox activity, ligand versatility, and DNA-binding capacity. More recently, their unique chemical properties have been harnessed for neurodegenerative disorders, including AD [102]. Ruthenium complexes are particularly attractive due to their rich redox chemistry and their ability to modulate oxidative stress. Ruthenium-based nanocomplexes have strong antioxidant properties, scavenging ROS, and restoring mitochondrial function in neuronal cells. Additionally, ruthenium complexes can interact with Aβ peptides, inhibiting fibril formation, and destabilizing preformed aggregates. Their incorporation into nanocarriers, such as polymeric nanoparticles or dendrimers, improves their stability and brain targeting. Moreover, ruthenium complexes exhibit photophysical properties, enabling their use in photoactivated therapies, where controlled light irradiation triggers localized drug release and ROS modulation within the brain [103]. Platinum complexes, best known for their role as chemotherapeutics (*e.g.,* cisplatin), have also been explored for AD therapy. The ability of platinum to form covalent bonds with biomolecules allows it to interfere with Aβ and tau aggregation. However, their systemic toxicity and poor BBB penetration limit their use [104]. Nanostructured delivery of platinum complexes addresses these issues by shielding drugs from off-target tissues and enhancing brain delivery. For example, platinum nanoparticles functionalized with Aβ-targeting ligands exhibit strong anti-aggregation effects with reduced systemic toxicity. In addition, platinum complexes have been integrated into theranostic platforms, where their optical properties enable imaging along with therapeutic action [105]. Despite these advantages, the long-term safety of Ru and Pt complexes remains uncertain. Both metals are non-essential to human physiology, raising concerns regarding their accumulation and toxicity. Nanocarriers that enable controlled release and biodegradation are critical in mitigating these risks. If carefully designed, ruthenium- and platinum-based nanocomplexes could offer a novel class of multifunctional therapeutics targeting oxidative stress, protein aggregation, and mitochondrial dysfunction in AD [106].

4.5. Other emerging metal-based nanoformulations

In addition to copper, iron, zinc, ruthenium, and platinum, several other metal-based nanostructures have emerged as promising candidates for AD therapy. Gold nanoparticles (AuNPs) are among the most studied because of their biocompatibility, ease of surface modification, and optical properties. AuNPs functionalized with peptides or antibodies against Aβ have shown strong inhibitory effects on fibril formation [107]. Additionally, their photothermal properties allow light-triggered disaggregation of amyloid plaques, offering a minimally invasive therapeutic strategy. AuNPs also serve as imaging agents due to their strong surface plasmon resonance, thus supporting theranostic applications. Silver nanoparticles (AgNPs) with potent antimicrobial and antioxidant properties have been explored for their ability to reduce oxidative stress and inflammation in neuronal models. However, concerns regarding their long-term toxicity and accumulation limit their clinical prospects, necessitating careful surface modification and dosage control [108].

Manganese-based nanoparticles are gaining attention as therapeutic and diagnostic tools. Manganese acts as a cofactor for antioxidant enzymes, such as superoxide dismutase (Mn-SOD), and its complexes can enhance antioxidant defenses in the AD brain. Additionally, Mn nanoparticles provide MRI contrast capabilities, serving as dual-function theranostic platforms [109]. Gadolinium complexes, traditionally used as MRI contrast agents, have been investigated for AD diagnosis and therapy when incorporated into nanocarriers targeting amyloid plaques. Although concerns regarding nephrogenic systemic fibrosis persist, nanostructured delivery may improve safety and specificity

[110]. Cerium oxide nanoparticles (CeO_2NPs) represent another promising avenue of research because of their catalytic antioxidant activity. These nanoparticles can scavenge ROS through redox cycling between the Ce^{3+} and Ce^{+} states, mimicking natural antioxidant enzymes. Their incorporation into targeted nanocarriers enhances neuroprotective efficacy and reduces the oxidative burden in AD models [111]. Hybrid nanostructures that combine multiple metals are being developed to harness the synergistic effects. For example, gold–iron oxide nanohybrids provide both photothermal therapy and MRI capabilities, whereas multifunctional platforms combining copper or zinc complexes with antioxidant nanoparticles enable the simultaneous modulation of multiple pathological pathways [112]. The exploration of nanostructured metal complexes in AD therapy underscores the versatility of metal ions and nanotechnology for tackling multifactorial neurodegeneration. Copper-, iron-, and zinc-based complexes directly address metal imbalances, whereas ruthenium, platinum, and emerging metals such as gold, manganese, and cerium offer multifunctional advantages. Nanostructured delivery systems not only enhance brain penetration and pharmacokinetics but also provide opportunities for theranostics and precision medicine [113]. However, challenges, such as long-term toxicity, biodegradability, and regulatory hurdles, remain. Continued interdisciplinary research integrating chemistry, nanotechnology, neuroscience, and clinical sciences will be crucial for translating these innovative systems from bench to bedside.

5. Targeted Delivery Strategies

The therapeutic application of nanostructured metal complexes in AD requires not only the design of stable, biocompatible formulations, but also precise delivery systems that can cross the blood–brain barrier (BBB) and accumulate at sites of neurodegeneration. Therefore, targeted delivery strategies have emerged as a crucial component in the development of advanced nanomedicine platforms for AD therapy. These strategies aim to maximize therapeutic efficacy while minimizing off-target effects and systemic toxicity [114]. The pathophysiological features of AD, including aberrant protein aggregation, oxidative stress, neuroinflammation, and metal ion dysregulation, can be engineered to deliver metal-based complexes directly to diseased neurons, synapses, or plaques. Unlike conventional small-molecule drugs, which often exhibit poor BBB permeability and nonspecific distribution, nanocarrier-based targeted systems can be functionalized with ligands, stimuli-responsive moieties, or multifunctional elements to ensure site-specific delivery and controlled drug release. This approach not only enhances drug accumulation at the desired site, but also prolongs circulation time, reduces premature clearance, and improves the pharmacokinetic and pharmacodynamic profiles of therapeutic agents [115]. The design of targeted delivery strategies for AD represents a paradigm shift from passive drug distribution to active precision-based nanomedicine. The functionalization of nanocarriers with biological ligands such as antibodies, peptides, and aptamers provides specificity toward neuronal receptors or amyloid aggregates, thereby promoting selective uptake by diseased cells [116]. Stimuli-responsive nanoplatforms further refine delivery by enabling controlled release in response to pathological microenvironmental triggers, such as pH fluctuations, reactive oxygen species (ROS), or enzymatic activity. Multifunctional nanoplatforms and theranostic systems integrate therapeutic and diagnostic functions, providing real-time monitoring of drug distribution and disease progression [117]. The combination of metal complexes with small molecules or genetic materials allows synergistic interventions that target multiple pathways involved in AD pathogenesis. Together, these advanced targeted delivery strategies offer a holistic approach to overcoming the limitations of traditional therapies and open new avenues for translating nanostructured metal complexes into effective clinical interventions for AD [118].

5.1. Ligand-decorated nanocarriers (antibodies, peptides, aptamers)

Ligand-decorated nanocarriers represent one of the most widely explored strategies for targeted delivery in AD therapy (**Table 2**). In this approach, nanostructured metal complexes are conjugated with biological ligands such as monoclonal antibodies, peptides, or nucleic acid aptamers that specifically recognize and bind to disease-associated targets. For example, antibodies against Aβ can be used to guide nanocarriers to amyloid plaques, thereby increasing the local drug concentration at the pathological site while sparing healthy tissues [119]. Peptide ligands that mimic natural receptor substrates, such as transferrin or insulin, can facilitate receptor-mediated transcytosis across the BBB, significantly improving brain uptake of therapeutic nanocomplexes. Aptamers, which are synthetic oligonucleotides capable of binding proteins or receptors with high specificity, also provide versatile and stable alternatives to antibodies. Their ability to be chemically synthesized and modified enables precise tuning of binding affinity, stability, and targeting efficiency. By decorating nanocarriers with such ligands, therapeutic metal complexes can achieve enhanced targeting of neuronal cells, amyloid aggregates, or tau pathology, thereby improving therapeutic outcomes [120]. The major advantage of ligand-functionalized nanocarriers is their ability to integrate active targeting with the inherent benefits of nanostructured delivery. This approach reduces off-target toxicity, enhances drug retention at the disease site, and improves the bioavailability of metal complexes, which often suffer from rapid clearance or instability in the systemic circulation. In Alzheimer's therapy, ligand-decorated nanocarriers have been shown to improve the pharmacokinetics of copper, iron, and ruthenium complexes, while simultaneously enabling precise delivery to regions of high pathological burden [107]. Challenges remain in terms of large-scale manufacturing, maintaining ligand activity during formulation, and avoiding immune recognition and degradation *in vivo*. Despite these hurdles, ligand-decorated nanocarriers hold significant promise as a cornerstone strategy in the development of targeted nanomedicine for AD, offering a means to selectively engage diseased brain regions with unprecedented precision selectively [121].

Table 2. Ligand-decorated nanocarriers for targeted delivery of metal complexes in Alzheimer's therapy

Ligand type	Ligand	Target Site / Mechanism	Nanocarrier type	Therapeutic payload (Metal complex/Drug)	Therapeutic outcome in AD models	Advantages	Limitations & Challenges	Ref.
Antibody-based	Anti-Aβ monoclonal antibody	Aβ plaques recognition and binding	Liposomes, polymeric nanoparticles	Cu(II), Ru(II) complexes, antioxidant-loaded NPs	Enhanced targeting of amyloid plaques, reduced Aβ aggregation and neurotoxicity	High specificity, strong binding affinity, promotes receptor-mediated transport	High cost, immunogenicity, stability issues in vivo	[122]

	Anti-Tau antibody	Hyperphosphorylated tau aggregates	Dendrimers, solid lipid nanoparticles	Pt(II) or Au-based complexes	Reduction in tau pathology and neurofibrillary tangles	Disease-specific targeting of tau protein	Limited penetration across intact BBB, potential immune clearance	[123]
Peptide-based	Transferrin peptide	Transferrin receptor-mediated transcytosis across BBB	Polymeric nanoparticles, PEGylated liposomes	Fe(III), Ru(II) complexes	Enhanced BBB penetration and neuronal uptake	Exploits natural receptor pathway, improves systemic stability	Receptor saturation, competition with endogenous transferrin	[120]
	Angiopep-2	Low-density lipoprotein receptor-related protein-1 (LRP1)	PEGylated nanoparticles	Cu(II) complexes, antioxidant conjugates	Increased BBB transport, higher drug accumulation in neurons	High efficiency for CNS delivery, non-immunogenic	Limited clinical data, possible enzymatic degradation	[124]
	RGD peptide	Integrin receptors overexpressed in AD-related inflammation	Polymeric micelles	Zn(II) complexes, anti-inflammatory co-drugs	Improved uptake in inflamed neuronal microenvironment	Promotes both targeting and anti-inflammatory benefits	Limited brain selectivity, risk of non-specific binding	[125]
	RVG (rabies virus glycoprotein peptide)	Nicotinic acetylcholine receptors on neurons	Lipid nanoparticles	Ruthenium complexes, neuroprotective agents	Enhanced neuronal targeting and synaptic localization	Strong neuronal affinity, efficient CNS uptake	Stability issues in circulation, potential off-target effects	[126]
Aptamer-based	Aβ-targeted DNA aptamer	Aβ oligomers/plaques	Gold nanoparticles, polymeric nanogels	Au(III), Ru(II) complexes	Reduced plaque burden, inhibition of Aβ toxicity	High specificity, chemically tunable	Nuclease degradation, shorter half-life in vivo	[127]
	Tau-targeted RNA aptamer	Tau fibrils	Polymeric nanocarriers	Metal chelators + Pt(II) complexes	Disruption of tau aggregation and stabilization of microtubules	High binding affinity, selective targeting	Difficult synthesis, limited clinical validation	[128]

	TfR aptamer	Transferrin receptor on BBB	Polymeric nanoparticles	Iron chelators, Cu(II) complexes	Enhanced BBB penetration, reduced oxidative stress	Non-immunogenic, versatile modification	Competition with endogenous ligands, risk of low yield targeting	[129]
Hybrid (Antibody +	Aptamer - antibody conjugate	Dual targeting (Aβ + Tau, or BBB receptor + plaque)	Multifunctional polymeric NPs	Co-loaded Cu(II) + antioxidant complexes	Multi-pathway targeting, improved efficacy	Synergistic activity, theranostic potential	Complexity in synthesis, regulatory hurdles	[130,131]

5.2. Stimuli-responsive metal complex nanoparticles (pH, ROS, enzyme-responsive)

Stimuli-responsive nanocarriers offer an advanced level of control over drug delivery by releasing their therapeutic payload in response to specific internal or external triggers. In the context of AD, internal stimuli, such as pH gradients, oxidative stress, and enzymatic activity, are particularly relevant. For example, the acidic microenvironment surrounding amyloid plaques or inflamed neuronal regions can be exploited by pH-sensitive nanocarriers, which release their metal complex payloads only when encountering such conditions [132,133]. The overproduction of ROS in AD brains provides a pathological trigger for ROS-responsive nanoplatforms, enabling site-specific drug release while simultaneously scavenging excess free radicals [134]. Enzyme-responsive systems also show considerable potential, as AD pathology is associated with upregulated enzymes such as matrix metalloproteinases or cholinesterases [135]. By designing nanocarriers that respond to these stimuli, researchers can ensure that therapeutic metal complexes are released precisely where needed, thereby maximizing efficacy and minimizing collateral damage [136]. The stimuli-responsive approach not only enhances spatial and temporal precision, but also improves therapeutic safety. These platforms reduce systemic toxicity and adverse effects by restricting drug release to diseased regions, which is a common challenge associated with conventional metal-based therapeutics [137]. Combining multiple stimuli-responsive mechanisms within a single nanocarrier, such as dual pH/ROS responsiveness, offers an even more refined level of control, allowing synchronized responses to complex pathological microenvironments. In Alzheimer's therapy, such platforms have been applied for the targeted delivery of copper, zinc, and ruthenium complexes, demonstrating enhanced BBB penetration and controlled drug release in preclinical models [138]. While the clinical translation of these systems requires overcoming barriers such as reproducibility and regulatory approval, stimuli-responsive nanocarriers represent a powerful strategy to address the dynamic and heterogeneous environment of the AD brain, paving the way for next-generation precision nanomedicine [139].

5.3. Multifunctional and theranostic nanoplatforms

Multifunctional and theranostic nanoplatforms represent the evolution of nanomedicine by integrating diagnostic, therapeutic, and monitoring capabilities into a single system. In the case of AD, where early detection and continuous monitoring are essential for effective treatment, theranostic nanocarriers offer several advantages. These platforms can deliver therapeutic metal complexes while simultaneously enabling imaging through

modalities, such as magnetic resonance imaging (MRI), positron emission tomography (PET), or fluorescence imaging [114]. Iron oxide-based nanocarriers can be employed as both therapeutic agents and MRI contrast enhancers, allowing clinicians to monitor drug biodistribution and plaque targeting in real time. Similarly, Ru or Pt complexes incorporated into multifunctional nanocarriers can provide therapeutic benefits while serving as imaging probes because of their inherent luminescent or catalytic properties. By combining therapy and diagnostics in a single nanoplatform, theranostic strategies enable personalized treatment regimens tailored to disease stage, patient response, and progression dynamics [140]. Multifunctional nanocarriers allow for combination therapy wherein metal complexes are co-delivered with anti-inflammatory agents, antioxidants, or amyloid aggregation inhibitors. This synergistic approach addresses the multifactorial nature of AD by simultaneously targeting multiple pathogenic pathways such as oxidative stress, tau hyperphosphorylation, and amyloid toxicity [133]. Theranostic nanoplatforms can incorporate surface modifications that facilitate BBB penetration, targeted delivery, and stimuli-responsive release, thereby integrating multiple strategies into a single, coherent system. Although the complexity of such designs poses challenges in terms of reproducibility, scalability, and regulatory approval, multifunctional and theranostic nanoplatforms are considered cutting-edge approaches in AD nanomedicine. They not only improve therapeutic efficacy but also allow clinicians to track treatment outcomes in real time, significantly advancing the field toward precision and personalized Alzheimer's therapy [141].

5.4. Synergistic delivery with small molecules or genetic materials

The synergistic delivery of nanostructured metal complexes with small molecules or genetic materials has gained significant attention as a strategy to enhance the therapeutic efficacy in AD. Small molecules, such as cholinesterase inhibitors, antioxidants, and anti-inflammatory drugs, can be co-delivered alongside metal complexes to achieve additive or synergistic effects. For instance, co-encapsulation of a copper complex with an antioxidant compound within a nanocarrier can simultaneously restore metal homeostasis and neutralize free radicals, effectively targeting the two central features of AD pathology. Similarly, combining metal complexes with amyloid aggregation inhibitors can provide a dual mechanism of action, slowing disease progression more effectively than single-agent therapy. Such synergistic strategies allow for the reduced dosing of individual drugs, thereby minimizing toxicity while maximizing therapeutic benefits [142]. Small molecules and genetic materials, such as siRNA, miRNA, or plasmid DNA, can be co-delivered with metal complexes to regulate gene expression associated with AD pathology. For example, siRNAs targeting β-secretase can be co-delivered with a ruthenium complex to simultaneously reduce amyloid production and mitigate oxidative stress. Similarly, the delivery of miRNA modulators alongside iron complexes may help restore neuronal signaling and reduce neuroinflammation [143]. The integration of genetic therapeutics with metal complexes represents a powerful approach to address both symptomatic and root causes of AD. However, this approach introduces challenges related to stability, immune recognition, and efficient intracellular delivery. Despite these obstacles, synergistic delivery systems combining nanostructured metal complexes with small molecules or genetic materials are at the forefront of AD nanomedicine research, offering a holistic and multi-targeted therapeutic paradigm that aligns with the complex and heterogeneous nature of the disease [144].

6. Challenges and Future Perspectives

Despite the remarkable progress in developing nanostructured metal complexes for AD, several critical challenges remain before their successful clinical implementation. These challenges arise from the complexity of the disease, the intricacies of brain delivery, safety and

scalability of nanomedicines, and regulatory framework governing their approval. Simultaneously, rapid advancements in emerging technologies such as precision medicine, artificial intelligence (AI), and computational modeling offer opportunities to overcome these barriers and accelerate translation. This section outlines the key hurdles and future perspectives, focusing on blood–brain barrier (BBB) penetration, personalization of nanomedicine, regulatory and manufacturing constraints, AI-driven innovation, and the roadmap toward clinical translation.

6.1. Overcoming the blood–brain barrier: Emerging approaches

One of the most formidable challenges in AD therapy is the selective delivery of therapeutics across the BBB, a highly restrictive physiological barrier that protects the brain from xenobiotics but also hinders drug penetration. Traditional small molecules often achieve limited bioavailability, whereas nanostructured metal complexes face additional clearance by the reticuloendothelial system because of their size and surface properties. Emerging strategies aim to enhance BBB permeability and ensure site-specific drug delivery. Surface functionalization of nanoparticles with ligands, such as transferrin, lactoferrin, or apolipoproteins, enables receptor-mediated transcytosis, thereby improving uptake into brain endothelial cells. Similarly, the use of peptide ligands (*e.g.,* Angiopep-2 and TAT) facilitates active transport mechanisms, while PEGylation prolongs circulation time and reduces immune clearance. Another promising approach is the exploitation of stimuli-responsive systems, in which nanoparticles release metal complexes in response to local triggers, such as pH, redox gradients, or enzymatic activity in the AD brain. Furthermore, advances in nanocarrier engineering, such as biomimetic coatings with exosomes or cell membranes, offer stealth properties and improve the BBB traversal. Although these approaches hold promise, balancing efficient brain delivery with minimal off-target accumulation remains a key challenge, requiring careful optimization of the particle size, surface charge, and ligand density.

6.2. Precision medicine and personalized nanomedicine

AD is a heterogeneous disorder that is influenced by genetic variation, environmental factors, and differential progression patterns. Consequently, a "one-size-fits-all" therapeutic approach often fails to achieve meaningful outcomes. Precision medicine combined with nanotechnology offers an avenue for tailoring therapies to individual patient profiles. Nanostructured metal complexes can be engineered with modularity, allowing specific adjustments in ligand chemistry, particle size, and surface functionalization to match patient-specific needs. For example, patients with APOE4 genetic variants may benefit from nanomedicines that more effectively target lipid metabolism pathways, while those with a high oxidative stress burden may require complexes with stronger antioxidant and redox-modulating capabilities. Advances in biomarker discovery, including circulating exosomes, imaging signatures, and cerebrospinal fluid (CSF) analytes, have provided valuable tools for stratifying patients and monitoring therapeutic responses. Moreover, the integration of patient-derived organoids and induced pluripotent stem cells (iPSCs) into preclinical testing allows for the evaluation of nanostructured metal complexes in personalized disease models. These strategies represent a paradigm shift from conventional symptomatic treatment to individualized nanomedicine, ensuring improved therapeutic efficacy and fewer adverse effects.

6.3. Regulatory and manufacturing challenges

While the therapeutic potential of nanostructured metal complexes is clear, regulatory and manufacturing hurdles represent significant obstacles to clinical translation. The current regulatory frameworks are not fully adapted to the unique physicochemical properties and multifunctional nature of

nanomedicines. Unlike small molecules, nanostructured complexes exhibit complex biodistribution, long-term retention, and dynamic interactions with biomolecules, which complicate toxicological assessments. Standardized assays for safety evaluations, including immunogenicity, genotoxicity, and long-term stability, are still evolving. On the manufacturing side, achieving scalable, reproducible, and cost-effective production remains a major challenge. Nanocarrier synthesis often involves multi-step procedures, stringent control of particle size, and incorporation of sensitive ligands, all of which must meet Good Manufacturing Practice (GMP) standards. Batch-to-batch variability further complicates the clinical-grade preparation. Additionally, regulatory agencies require extensive characterization of stability, pharmacokinetics, and quality assurance, which can prolong the approval timelines. To overcome these barriers, interdisciplinary collaboration between chemists, pharmacologists, bioengineers, and regulatory authorities is essential, alongside the development of clear guidelines tailored to nanomedicine evaluation.

6.4. Integration of artificial intelligence and computational modelling

Artificial intelligence and computational modeling are increasingly being recognized as transformative tools in drug discovery and nanomedicine optimization. For nanostructured metal complexes, AI-driven approaches can accelerate ligand design, predict BBB permeability, and optimize nanoparticle formulations for stability and therapeutic efficacy. Machine learning algorithms trained on large datasets can identify correlations between the structural features of complexes and their biological activity, enabling rational design rather than trial-and-error approaches. Similarly, computational docking and molecular dynamics simulations provide mechanistic insights into how metal complexes interact with Aβ peptides, tau proteins, or key kinases, thereby guiding the development of more selective inhibitors. On the formulation side, AI can assist in predicting nanoparticle biodistribution, clearance kinetics, and patient-specific responses, paving the way for precision nanomedicine. Furthermore, AI-powered imaging analysis can enhance the monitoring of therapeutic outcomes in preclinical and clinical settings, allowing the real-time evaluation of disease progression and treatment response. Although still in its early stages, the integration of AI and modeling represents a powerful strategy for reducing development costs, shortening timelines, and increasing the likelihood of clinical success [145-149].

6.5. Roadmap toward clinical translation

Bridging the gap between preclinical promises and clinical applications requires a carefully structured framework. Preclinical studies must provide comprehensive data on the efficacy, pharmacokinetics, long-term toxicity, and BBB penetration in physiologically relevant models, including transgenic animals and patient-derived organoids. Early phase clinical trials should prioritize safety, tolerability, and biomarker-driven endpoints rather than solely cognitive outcomes to ensure a robust assessment of target engagement. Parallel efforts in regulatory harmonization and standardized characterization methods are essential for streamlining approval processes. Strategic collaborations between academia, industry, and government funding bodies can accelerate development, while public–private partnerships may help overcome high production costs. Another critical aspect of translation involves patient and caregiver engagement, as adherence to and acceptability of nanomedicine-based therapies are crucial for success. Ultimately, a stepwise approach beginning with niche applications, such as imaging-guided diagnosis or adjunctive therapy, may facilitate entry into the clinical landscape before expanding into broad disease-modifying treatments. By integrating mechanistic insights, advanced delivery systems, regulatory innovations, and precision medicine frameworks, nanostructured metal complexes

have the potential to transform the therapeutic landscape of AD in the coming decades.

7. Conclusion

Nanostructured metal complexes represent a transformative approach in the quest for effective Alzheimer's therapy by integrating the advantages of coordination chemistry with nanoscale drug delivery. Their unique ability to modulate Aβ aggregation, tau hyperphosphorylation, metal imbalance, and oxidative stress highlights their multifaceted therapeutic potential in the complex pathology of the disease. Through rational design, these complexes not only exploit the structural and functional diversity of metal–ligand interactions, but also benefit from advanced nanoformulation strategies such as liposomes, dendrimers, and polymeric nanoparticles that enhance blood–brain barrier penetration, stability, and targeted delivery. The incorporation of ligand-functionalized nanocarriers, stimuli-responsive systems, and multifunctional theranostic platforms further extends their utility, offering precision in treatment, while enabling real-time monitoring of disease progression. Despite these advancements, several challenges remain, including safety evaluations, large-scale manufacturing, regulatory approval, and the translation of preclinical findings into clinical outcomes. Future research must emphasize personalized nanomedicine, computational modeling, and artificial intelligence-driven design to optimize therapeutic efficacy and minimize off-target effects. Collectively, nanostructured metal complexes hold immense promise as next-generation therapeutics, paving the way toward disease-modifying and potentially preventive strategies for Alzheimer's disease, where conventional drugs have largely failed.

Acknowledgments

None.

Conflict of Interest

Authors have declared that there is no conflict of interest exists.

ORCID

Ratakonda Deepak Srinivas
https://orcid.org/0009-0007-0073-5946

R. V. Valli Kumari
https://orcid.org/0009-0005-8150-2700

Ashutosh Pathak
https://orcid.org/0009-0000-9158-9356

Venkata Ramana Singamaneni
https://orcid.org/0009-0006-4328-8253

Voleti Vijaya Kumar
https://orcid.org/0000-0003-4735-3105

Poonam Popatrao Taru
https://orcid.org/0000-0002-6644-8305

M. Sandeep Kumar
https://orcid.org/0009-0006-5920-3402

P. Balaji
https://orcid.org/0000-0001-5317-1661

References

[1]. Silva, M.V.F., Loures, C.d.M.G., Alves, L.C.V., De Souza, L.C., Borges, K.B.G., Carvalho, M.d.G., Alzheimer's disease: Risk factors and potentially protective measures. *Journal of Biomedical Science*, **2019**, 26(1), 33.
[2]. Zhang, H., Wei, W., Zhao, M., Ma, L., Jiang, X., Pei, H., Cao, Y., Li, H., Interaction between aβ and tau in the pathogenesis of alzheimer's disease. *International Journal of Biological Sciences*, **2021**, 17(9), 2181.
[3]. Xiaopeng, Z., Jing, Y., Xia, L., Xingsheng, W., Juan, D., Yan, L., Baoshan, L., Global burden of alzheimer's disease and other dementias in adults aged 65 years and older, 1991–2021: Population-based study. *Frontiers in Public Health*, **2025**, 13, 1585711.
[4]. Yiannopoulou, K.G., Papageorgiou, S.G., Current and future treatments in alzheimer disease: An update. *Journal of Central Nervous System Disease*, **2020**, 12, 1179573520907397.

[5]. Singh, B., Day, C.M., Abdella, S., Garg, S., Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. *Journal of Controlled Release*, **2024**, 367, 402-424.
[6]. Duce, J.A., Bush, A.I., Biological metals and alzheimer's disease: Implications for therapeutics and diagnostics. *Progress in Neurobiology*, **2010**, 92(1), 1-18.
[7]. Cong, C., Cong, H., Yao, Y., Bai, Y., Xu, L., Copper homeostasis and cuproptosis in alzheimer's disease. *International Journal of Molecular Medicine*, **2025**, 56(5), 172.
[8]. Ward, R.J., Zucca, F.A., Duyn, J.H., Crichton, R.R., Zecca, L., The role of iron in brain ageing and neurodegenerative disorders. *The Lancet Neurology*, **2014**, 13(10), 1045-1060.
[9]. Watt, N.T., Whitehouse, I.J., Hooper, N.M., The role of zinc in alzheimer′ s disease. *International Journal of Alzheimer's Disease*, **2011**, 2011(1), 971021.
[10]. Kawahara, M., Kato, M., Kuroda, Y., Effects of aluminum on the neurotoxicity of primary cultured neurons and on the aggregation of β-amyloid protein. *Brain Research Bulletin*, **2001**, 55(2), 211-217.
[11]. Bacchella, C., Capucciati, A., Monzani, E., A focus on the link between metal dyshomeostasis, norepinephrine, and protein aggregation. *Antioxidants*, **2025**, 14(3), 347.
[12]. Yoo, J., Lee, J., Ahn, B., Han, J., Lim, M.H., Multi-target-directed therapeutic strategies for alzheimer's disease: Controlling amyloid-β aggregation, metal ion homeostasis, and enzyme inhibition. *Chemical Science*, **2025**, 16(5), 2105-2135.
[13]. Trapani, G., Satriano, C., La Mendola, D., Peptides and their metal complexes in neurodegenerative diseases: From structural studies to nanomedicine prospects. *Current Medicinal Chemistry*, **2018**, 25(6), 715-747.
[14]. Du, B., Chen, K., Wang, W., Lei, P., Targeting metals in alzheimer's disease: An update. *Journal of Alzheimer's Disease*, **2024**, 101(s1), S141-S154.
[15]. Liu, Y., Ma, J., Zhang, Q., Wang, Y., Sun, Q., Mechanism of metal complexes in alzheimer's disease. *International Journal of Molecular Sciences*, **2024**, 25(22), 11873.
[16]. Romero-Ben, E., Goswami, U., Cruz, J.S., Mansoori-Kermani, A., Mishra, D., Martin-Saldana, S., Munoz-Ugartemendia, J., Sosnik, A., Calderón, M., Beloqui, A., Polymer-based nanocarriers to transport therapeutic biomacromolecules across the blood-brain barrier. *Acta Biomaterialia*, **2025**.
[17]. Adnan Raza, M., Firdous, A., Gupta, U., Patil, U., Singh, A., Ajazuddin, Emerging trends in designing the dendrimer-based drug delivery for antineoplastic therapies. *ACS Applied Bio Materials*, **2025**.
[18]. Din, F.U., Aman, W., Ullah, I., Qureshi, O.S., Mustapha, O., Shafique, S., Zeb, A., Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *International Journal of Nanomedicine*, **2017**, 7291-7309.
[19]. Li, Y., Liu, R., Zhao, Z., Targeting brain drug delivery with macromolecules through receptor-mediated transcytosis. *Pharmaceutics*, **2025**, 17(1), 109.
[20]. Wei, X., Song, M., Li, W., Huang, J., Yang, G., Wang, Y., Multifunctional nanoplatforms co-delivering combinatorial dual-drug for eliminating cancer multidrug resistance. *Theranostics*, **2021**, 11(13), 6334.
[21]. Tiwari, P., Prajapati, S., Dixit, V., Raza, M.A., Gupta, S.K., Sharma, M., Recent advancements in nanoparticle drug delivery systems to cure neurological disorders via the nasal route. *Neurología Argentina*, **2025**.
[22]. Imani, S., Moradi, S., Faraj, T.A., Hassanpoor, P., Musapour, N., Najmaldin, S.K., Abdulhamd, A.H., Mohammadi, A.T., Taha, C.H., Aminnezhad, S., Nanoparticle technologies in precision oncology and personalized vaccine development: Challenges and advances. *International Journal of Pharmaceutics: X*, **2025**, 100353.
[23]. Kelkar, S.S., Reineke, T.M., Theranostics: Combining imaging and therapy. *Bioconjugate Chemistry*, **2011**, 22(10), 1879-1903.
[24]. Puccetti, M., Pariano, M., Schoubben, A., Giovagnoli, S., Ricci, M., Biologics, theranostics, and personalized medicine in drug delivery systems. *Pharmacological research*, **2024**, 201, 107086.
[25]. Shahalaei, M., Azad, A.K., Sulaiman, W.M.A.W., Derakhshani, A., Mofakham, E.B., Mallandrich, M., Kumarasamy, V., Subramaniyan, V., A review of metallic nanoparticles: Present issues and prospects focused on the preparation methods, characterization techniques, and their theranostic applications. *Frontiers in Chemistry*, **2024**, 12, 1398979.
[26]. Sadiq, S., Khan, S., Khan, I., Khan, A., Humayun, M., Wu, P., Usman, M., Khan, A., Alanazi, A.F., Bououdina, M., A critical review on metal-organic frameworks (mofs) based nanomaterials for biomedical applications: Designing, recent trends, challenges, and prospects. *Heliyon*, **2024**, 10(3).
[27]. Sharma, N., Khatoon, N., Raza, M.A., Saoji, S.D., Singh, D., A pioneer review on lactoferrin as versatile macromolecular ligand for targeting cancer: Recent advances. *Journal of Drug Targeting*, **2025**, 1-19.
[28]. Hossain, A., Shuvo, M.R.H., Khan, S., Sayem, A.S.M., Islam, S., Hossain, N., Functional nanoparticle

developments for 3d-printed biodegradable implants-a comprehensive review. *Results in Surfaces and Interfaces*, **2025**, 19, 100541.
[29]. Barhoum, A., García-Betancourt, M.L., Rahier, H., Van Assche, G., Physicochemical characterization of nanomaterials: Polymorph, composition, wettability, and thermal stability. *Emerging Applications Of Nanoparticles and Architecture Nanostructures*, **2018**, 255-278.
[30]. Kulkarni, S.A., Feng, S.S., Effects of particle size and surface modification on cellular uptake and biodistribution of polymeric nanoparticles for drug delivery. *Pharmaceutical Research*, **2013**, 30(10), 2512-2522.
[31]. Honary, S., Zahir, F., Effect of zeta potential on the properties of nano-drug delivery systems-a review (part 2). *Tropical Journal of Pharmaceutical Research*, **2013**, 12(2), 265-273.
[32]. Niżnik, Ł., Noga, M., Kobylarz, D., Frydrych, A., Krośniak, A., Kapka-Skrzypczak, L., Jurowski, K., Gold nanoparticles (aunps)—toxicity, safety and green synthesis: A critical review. *International Journal of Molecular Sciences*, **2024**, 25(7), 4057.
[33]. Drewry, J.A., Gunning, P.T., Recent advances in biosensory and medicinal therapeutic applications of zinc (ii) and copper (ii) coordination complexes. *Coordination Chemistry Reviews*, **2011**, 255(3-4), 459-472.
[34]. Sharma, A., Verwilst, P., Li, M., Ma, D., Singh, N., Yoo, J., Kim, Y., Yang, Y., Zhu, J.H., Huang, H., Theranostic fluorescent probes. *Chemical Reviews*, **2024**, 124(5), 2699-2804.
[35]. Al-Thani, A.N., Jan, A.G., Abbas, M., Geetha, M., Sadasivuni, K.K., Nanoparticles in cancer theragnostic and drug delivery: A comprehensive review. *Life Sciences*, **2024**, 352, 122899.
[36]. Fayek, A.A., Mansour, M., Abdelrahman, A.A., El-Sherif, M.A., Abd El-Karim, A.T., El-Sherif, A.A., Nanostructured metal-schiff base complexes: Recent advances in synthesis, characterization and biomedical applications. *Materials Today Chemistry*, **2025**, 48, 102982.
[37]. Abdelkawi, A., Slim, A., Zinoune, Z., Pathak, Y., Surface modification of metallic nanoparticles for targeting drugs. *Coatings*, **2023**, 13(9), 1660.
[38]. Santos, M.A., Marques, S.M., Chaves, S., Hydroxypyridinones as "privileged" chelating structures for the design of medicinal drugs. *Coordination Chemistry Reviews*, **2012**, 256(1-2), 240-259.
[39]. Adhikari, S., Nath, P., Das, A., Datta, A., Baildya, N., Duttaroy, A.K., Pathak, S., A review on metal complexes and its anti-cancer activities: Recent updates from in vivo studies. *Biomedicine & Pharmacotherapy*, **2024**, 171, 116211.
[40]. Pineiro-Alonso, L., Rubio-Prego, I., Lobyntseva, A., González-Freire, E., Langer, R., Alonso, M.J., Nanomedicine for targeting brain neurodegeneration: Critical barriers and circadian rhythm considerations. *Advanced Drug Delivery Reviews*, **2025**, 115606.
[41]. Gade, L., Boyd, B.J., Malmsten, M., Heinz, A., Stimuli-responsive drug delivery systems for inflammatory skin conditions. *Acta Biomaterialia*, **2024**, 187, 1-19.
[42]. Yu, M.K., Park, J., Jon, S., Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy. *Theranostics*, **2012**, 2(1), 3.
[43]. Kobayashi, K., Wei, J., Iida, R., Ijiro, K., Niikura, K., Surface engineering of nanoparticles for therapeutic applications. *Polymer Journal*, **2014**, 46(8), 460-468.
[44]. Liu, L., He, H., Du, B., He, Y., Nanoscale drug formulations for the treatment of alzheimer's disease progression. *RSC Advances*, **2025**, 15(6), 4031-4078.
[45]. Jadhav, V., Roy, A., Kaur, K., Rai, A.K., Rustagi, S., Recent advances in nanomaterial-based drug delivery systems. *Nano-Structures & Nano-Objects*, **2024**, 37, 101103.
[46]. Rahim, M.A., Zahran, H.A., Jaffar, H.M., Ambreen, S., Ramadan, M.F., Al-Asmari, F., Castro-Muñoz, R., Zongo, E., Liposomal encapsulation in food systems: A review of formulation, processing, and applications. *Food Science & Nutrition*, **2025**, 13(8), e70587.
[47]. Fateh, S.T., Aghaii, A.H., Aminzade, Z., Shahriari, E., Roohpour, N., Koosha, F., Dezfuli, A.S., Inorganic nanoparticle-cored dendrimers for biomedical applications: A review. *Heliyon*, **2024**, 10(9).
[48]. Raza, M.A., Sharma, M.K., Nagori, K., Jain, P., Ghosh, V., Gupta, U., Recent trends on polycaprolactone as sustainable polymer-based drug delivery system in the treatment of cancer: Biomedical applications and nanomedicine. *International Journal of Pharmaceutics*, **2024**, 666, 124734.
[49]. Guidi, L., Cascone, M.G., Rosellini, E., Light-responsive polymeric nanoparticles for retinal drug delivery: Design cues, challenges and future perspectives. *Heliyon*, **2024**, 10(5).
[50]. Saif, M., Raza, M.A., Patravale, V.B., Polysaccharide copolymeric conjugates and their applications in targeted cancer therapy. *International Journal of Biological Macromolecules*, **2025**, 147380.
[51]. Ghasemiyeh, P., Mohammadi-Samani, S., Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: Applications, advantages and disadvantages. *Research in Pharmaceutical Sciences*, **2018**, 13(4), 288-303.

[52]. Parveen, S., Gupta, P., Kumar, S., Banerjee, M., Lipid polymer hybrid nanoparticles as potent vehicles for drug delivery in cancer therapeutics. *Medicine in Drug Discovery*, **2023**, 20, 100165.
[53]. Islam, S., Ahmed, M.M.S., Islam, M.A., Hossain, N., Chowdhury, M.A., Advances in nanoparticles in targeted drug delivery-a review. *Results in Surfaces and Interfaces*, **2025**, 100529.
[54]. Jiménez, A., Estudillo, E., Guzmán-Ruiz, M.A., Herrera-Mundo, N., Victoria-Acosta, G., Cortés-Malagón, E.M., López-Ornelas, A., Nanotechnology to overcome blood–brain barrier permeability and damage in neurodegenerative diseases. *Pharmaceutics*, **2025**, 17(3), 281.
[55]. Zha, S., Liu, H., Li, H., Li, H., Wong, K.L., All, A.H., Functionalized nanomaterials capable of crossing the blood–brain barrier. *ACS Nano*, **2024**, 18(3), 1820-1845.
[56]. Chen, L., Guan, Y., Wang, S., Han, X., Guo, F., Wang, Y., Engineered nanoplatforms for brain-targeted co-delivery of phytochemicals in alzheimer's disease: Rational design, blood-brain barrier penetration, and multi-target therapeutic synergy. *Neurotherapeutics*, **2025**, e00722.
[57]. Chen, G., Su, Y., Chen, S., Lin, T., Lin, X., Polyphenols and alzheimer's disease: A review on molecular and therapeutic insights with in silico support. *Food Science & Nutrition*, **2025**, 13(9), e70496.
[58]. Charissopoulos, E., Pontiki, E., Targeting metal imbalance and oxidative stress in alzheimer's disease with novel multifunctional compounds. *Molecules*, **2025**, 30(17), 3512.
[59]. Fydrych, A., Moir, R., Huang, C., Shi, Y., Rogers, J., Huang, X., Amyloid-targeted metal chelation, anti-oxidative stress, and anti-inflammation as potential alzheimer's therapies. *Current Bioactive Compounds*, **2008**, 4(3), 140-149.
[60]. Fruhwürth, S., Zetterberg, H., Paludan, S.R., Microglia and amyloid plaque formation in alzheimer's disease–evidence, possible mechanisms, and future challenges. *Journal of Neuroimmunology*, **2024**, 390, 578342.
[61]. Vyas, N.A., Bhat, S.S., Kumbhar, A.S., Sonawane, U.B., Jani, V., Joshi, R.R., Ramteke, S.N., Kulkarni, P.P., Joshi, B., Ruthenium (ii) polypyridyl complex as inhibitor of acetylcholinesterase and aβ aggregation. *European Journal of Medicinal Chemistry*, **2014**, 75, 375-381.
[62]. Gao, L., Wang, J., Bi, Y., Nanotechnology for neurodegenerative diseases: Recent progress in brain-targeted delivery, stimuli-responsive platforms, and organelle-specific therapeutics. *International Journal of Nanomedicine*, **2025**, 11015-11044.
[63]. Randhawa, S., Saini, T.C., Bathla, M., Bhardwaj, R., Dhiman, R., Acharya, A., Nanomaterials in targeting amyloid-β oligomers: Current advances and future directions for alzheimer's disease diagnosis and therapy. *Beilstein Journal of Nanotechnology*, **2025**, 16(1), 561-580.
[64]. Liu, E., Zhang, Y., Wang, J.Z., Updates in alzheimer's disease: From basic research to diagnosis and therapies. *Translational Neurodegeneration*, **2024**, 13(1), 45.
[65]. Rajendran, K., Sukumar, A.J., Krishnan, U.M., Emerging paradigms in alzheimer's therapy. *European Journal of Pharmacology*, **2024**, 981, 176872.
[66]. Kuret, J., Chirita, C.N., Congdon, E.E., Kannanayakal, T., Li, G., Necula, M., Yin, H., Zhong, Q., Pathways of tau fibrillization. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, **2005**, 1739(2-3), 167-178.
[67]. Zubčić, K., Hof, P.R., Šimić, G., Jazvinšćak Jembrek, M., The role of copper in tau-related pathology in alzheimer's disease. *Frontiers in Molecular Neuroscience*, **2020**, 13, 572308.
[68]. Chen, Y., Yu, Y., Tau and neuroinflammation in alzheimer's disease: Interplay mechanisms and clinical translation. *Journal of Neuroinflammation*, **2023**, 20(1), 165.
[69]. Tang, Y., Song, X., Xiao, M., Wang, C., Zhang, X., Li, P., Sun, S., Wang, D., Wei, W., Liu, S., Inhibition of aβ aggregation and tau phosphorylation with functionalized biomimetic nanoparticles for synergic alzheimer's disease therapy. *ACS Applied Materials & Interfaces*, **2024**, 16(45), 61774-61786.
[70]. Meng, D., Luo, G., Liu, P., Copper metabolism and cuproptosis in alzheimer's disease: Mechanisms and therapeutic potential. *Biomedicine & Pharmacotherapy*, **2025**, 190, 118354.
[71]. Yokel, R.A., Aluminum chelation: Chemistry, clinical, and experimental studies and the search for alternatives to desferrioxamine. *Journal of Toxicology and Environmental Health, Part A Current Issues*, **1994**, 41(2), 131-174.
[72]. Murillo, M.I., Gaiddon, C., Le Lagadec, R., Targeting of the intracellular redox balance by metal complexes towards anticancer therapy. *Frontiers in Chemistry*, **2022**, 10, 967337.
[73]. Yang, J., des Rieux, A., Malfanti, A., Stimuli-responsive nanomedicines for the treatment of non-cancer related inflammatory diseases. *ACS Nano*, **2025**, 19(16), 15189-15219.
[74]. Mu, S., Yang, H., Wang, S., Tong, A., Ding, R., Wang, J., Wang, D., Li, J., Zinc-based nanomaterials in cancer

therapy: Mechanisms, applications, and future directions. *Theranostics*, **2025**, 15(15), 7841.
[75]. Xiong, L., Liang, B., Yu, K., Magnetic hyperthermia in oncology: Nanomaterials-driven combinatorial strategies for synergistic therapeutic gains. *Materials Today Bio*, **2025**, 102070.
[76]. Fakorede, S., Lateef, O.M., Garuba, W.A., Akosile, P.O., Okon, D.A., Aborode, A.T., Dual impact of neuroinflammation on cognitive and motor impairments in alzheimer's disease. *Journal of Alzheimer's Disease Reports*, **2025**, 9, 25424823251341870.
[77]. Zhang, Y., Zhang, Y., Liang, R., Zou, J., Pei, R., Chen, X., Targeted ROS scavenging for disease therapies using nanomaterials. *Advanced Materials*, **2025**, e04435.
[78]. Li, Z., Luo, B., Chen, Y., Wang, L., Liu, Y., Jia, J., Chen, M., Yang, S., Shi, H., Dai, L., Nanomaterial-based encapsulation of biochemicals for targeted sepsis therapy. *Materials Today Bio*, **2025**, 102054.
[79]. AmeliMojarad, M., AmeliMojarad, M., The neuroinflammatory role of microglia in alzheimer's disease and their associated therapeutic targets. *CNS Neuroscience & Therapeutics*, **2024**, 30(7), e14856.
[80]. Zhang, H., Chen, H., Hu, X., Muhammad, W., Liu, C., Liu, W., Inflammation-modulating polymeric nanoparticles: Design strategies, mechanisms, and therapeutic applications. *EBioMedicine*, **2025**, 118, 105837.
[81]. Muscolo, A., Mariateresa, O., Giulio, T., Mariateresa, R., Oxidative stress: The role of antioxidant phytochemicals in the prevention and treatment of diseases. *International Journal of Molecular Sciences*, **2024**, 25(6), 3264.
[82]. Sugandhi, V.V., Gadhave, D.G., Ugale, A.R., Kulkarni, N., Nangare, S.N., Patil, H.P., Rath, S., Saxena, R., Lavate, A., Patel, A.T., Advances in alzheimer's therapy: Exploring neuropathological mechanisms to revolutionize the future therapeutic landscape. *Ageing Research Reviews*, **2025**, 102775.
[83]. Zmejkovski, B.B., Pantelić, N.Đ., Kaluđerović, G.N., Advanced nanomaterials functionalized with metal complexes for cancer therapy: From drug loading to targeted cellular response. *Pharmaceuticals*, **2025**, 18(7), 999.
[84]. Li, Y.Q., Tan, S.S., Wu, D., Zhang, Q., Wang, T., Zheng, G., The role of intracellular and extracellular copper compartmentalization in alzheimer's disease pathology and its implications for diagnosis and therapy. *Frontiers in Neuroscience*, **2025**, 19, 1553064.
[85]. Yang, X., Cai, P., Liu, Q., Wu, J., Yin, Y., Wang, X., Kong, L., Novel 8-hydroxyquinoline derivatives targeting β-amyloid aggregation, metal chelation and oxidative stress against alzheimer's disease. *Bioorganic & Medicinal Chemistry*, **2018**, 26(12), 3191-3201.
[86]. Duncan, C., White, A.R., Copper complexes as therapeutic agents. *Metallomics*, **2012**, 4(2), 127-138.
[87]. Ren, X., Luo, X., Wang, F., Wan, L., Wang, X., Xiong, J., Ye, M., Rui, S., Liu, Z., Wang, S., Recent advances in copper homeostasis-involved tumor theranostics. *Asian Journal of Pharmaceutical Sciences*, **2024**, 19(5), 100948.
[88]. Gao, Q., Zhou, Y., Chen, Y., Hu, W., Jin, W., Zhou, C., Yuan, H., Li, J., Lin, Z., Lin, W., Role of iron in brain development, aging, and neurodegenerative diseases. *Annals of Medicine*, **2025**, 57(1), 2472871.
[89]. Galanello, R. Iron chelation: New therapies. *Seminars in Hematology*, **2001**, 38, 73-76.
[90]. Kiwumulo, H.F., Muwonge, H., Lubwama, M., Ibingira, C., Kirabira, J.B., Ssekitoleko, R.T., Evans, S., Iron oxide nanoparticles in leukemia: Design, diagnostic applications, and therapeutic strategies. *Journal of the Egyptian National Cancer Institute*, **2025**, 37(1), 44.
[91]. Ru, Q., Li, Y., Zhang, X., Chen, L., Wu, Y., Min, J., Wang, F., Iron homeostasis and ferroptosis in muscle diseases and disorders: Mechanisms and therapeutic prospects. *Bone Research*, **2025**, 13(1), 27.
[92]. Rajan, A., Laha, S.S., Sahu, N.K., Thorat, N.D., Shankar, B., Recent advancements and clinical aspects of engineered iron oxide nanoplatforms for magnetic hyperthermia-induced cancer therapy. *Materials Today Bio*, **2024**, 29, 101348.
[93]. Shippy, D.C., Oliai, S.F., Ulland, T.K., Zinc utilization by microglia in alzheimer's disease. *Journal of Biological Chemistry*, **2024**, 300(5).
[94]. Tang, K.S., See, W.Z.C., Naidu, R., Neuroprotective properties of zinc oxide nanoparticles: Therapeutic implications for parkinson's disease. *Bioscience Reports*, **2024**, 44(11), BSR20241102.
[95]. Song, L., Oseid, D.E., Wells, E.A., Robinson, A.S., The interplay between GSK3β and Tau Ser262 phosphorylation during the progression of tau pathology. *International Journal of Molecular Sciences*, **2022**, 23(19), 11610.
[96]. Benarroch, E., What are the functions of zinc in the nervous system? *Neurology*, **2023**, 101(16), 714-720.
[97]. Jomova, K., Alomar, S.Y., Valko, R., Liska, J., Nepovimova, E., Kuca, K., Valko, M., Flavonoids and their role in oxidative stress, inflammation, and human diseases. *Chemico-Biological Interactions*, **2025**, 111489.
[98]. Spinello, A., Bonsignore, R., Barone, G., K. Keppler, B., Terenzi, A., Metal ions and metal

complexes in alzheimer's disease. *Current Pharmaceutical Design*, **2016**, 22(26), 3996-4010.
[99]. Chandra, D.K., Kumar, A., Mahapatra, C., Smart nano-hybrid metal-organic frameworks: Revolutionizing advancements, applications, and challenges in biomedical therapeutics and diagnostics. *Hybrid Advances*, **2025**, 100406.
[100]. Liang, H., Chen, A., Lai, X., Liu, J., Wu, J., Kang, Y., Wang, X., Shao, L., Neuroinflammation is induced by tongue-instilled zno nanoparticles via the Ca2+-dependent NF-κB and MAPK pathways. *Particle and Fibre Toxicology*, **2018**, 15(1), 39.
[101]. Tapia-Arellano, A., Cabrera, P., Cortés-Adasme, E., Riveros, A., Hassan, N., Kogan, M.J., Tau-and α-synuclein-targeted gold nanoparticles: Applications, opportunities, and future outlooks in the diagnosis and therapy of neurodegenerative diseases. *Journal of Nanobiotechnology*, **2024**, 22(1), 248.
[102]. Tűz, B., Correia, I., Martinho, P.N., A critical analysis of the potential of iron heterobimetallic complexes in anticancer research. *Journal of Inorganic Biochemistry*, **2024**, 112813.
[103]. Li, J., Peng, C., Huang, C., Wan, L., Wang, K., Wu, P., Chen, T., Sun, G., Guo, R., Lin, H., Metal ruthenium complexes treat spinal cord injury by alleviating oxidative stress through interaction with antioxidant 1 copper chaperone protein. *Advanced Science*, **2024**, 11(45), 2407225.
[104]. Kenche, V.B., Hung, L.W., Perez, K., Volitakes, I., Ciccotosto, G., Kwok, J., Critch, N., Sherratt, N., Cortes, M., Lal, V., Development of a platinum complex as an anti-amyloid agent for the therapy of alzheimer's disease. *Angewandte Chemie*, **2013**, 125(12).
[105]. Haque, A., Khan, T., Islam, R.U., Naseem, S., Nanomedicine breakthroughs in cancer and neurodegenerative disease therapy. *Next Nanotechnology*, **2025**, 8, 100233.
[106]. Xiang, W., He, S., Kuang, T., Yin, J., Hu, B., Sun, C., He, J., Wang, J., Yu, C.-Y., Wei, H., Rhodium-based metallodrugs for biological applications: Current status and future perspectives. *Materials Today Bio*, **2025**, 101941.
[107]. Joseph, S., Chakrabarty, R., Paira, P., Advances in nano-drug delivery systems for metallic compounds in cancer therapy: Challenges and future perspectives. *Dalton Transactions*, **2025**, 54(37), 13820-13850.
[108]. Gao, F., Hou, Y., Wang, Y., Liu, L., Yi, X., Xia, N., Photothermal and photodynamic strategies for diagnosis and therapy of alzheimer's disease by modulating amyloid-β aggregation. *Biosensors*, **2025**, 15(8), 480.
[109]. Zhang, L., Roy, S., Guo, B., The role of manganese-based mri contrast agents for cancer theranostics: Where do we stand in 2025? *Theranostics*, **2025**, 15(9), 4147.
[110]. Aboushoushah, S.F., Iron oxide nanoparticles enhancing magnetic resonance imaging: A review of the latest advancements. *Journal of Science: Advanced Materials and Devices*, **2025**, 100875.
[111]. Dowding, J.M., Dosani, T., Kumar, A., Seal, S., Self, W.T., Cerium oxide nanoparticles scavenge nitric oxide radical (˙ no). *Chemical Communications*, **2012**, 48(40), 4896-4898.
[112]. Ko, M.J., Min, S., Hong, H., Yoo, W., Joo, J., Zhang, Y.S., Kang, H., Kim, D.H., Magnetic nanoparticles for ferroptosis cancer therapy with diagnostic imaging. *Bioactive Materials*, **2024**, 32, 66-97.
[113]. Singh, R., Panghal, A., Jadhav, K., Thakur, A., Verma, R.K., Singh, C., Goyal, M., Kumar, J., Namdeo, A.G., Recent advances in targeting transition metals (copper, iron, and zinc) in alzheimer's disease. *Molecular Neurobiology*, **2024**, 61(12), 10916-10940.
[114]. Anitha, K., Chenchula, S., Surendran, V., Shvetank, B., Ravula, P., Milan, R., Chikatipalli, R., Advancing cancer theranostics through biomimetics: A comprehensive review. *Heliyon*, **2024**, 10(6).
[115]. Sharma, A., Srivastava, S., Gupta, P., Sridhar, S.B., Tariq, M., Rao, G.K., Kumar, S., Malik, T., Targeting protein misfolding in alzheimer's disease: The emerging role of molecular chaperones. *Biomedicine & Pharmacotherapy*, **2025**, 191, 118531.
[116]. Driscoll, J., Gondaliya, P., Zinn, D.A., Jain, R., Yan, I.K., Dong, H., Patel, T., Using aptamers for targeted delivery of rna therapies. *Molecular Therapy*, **2025**, 33(4), 1344-1367.
[117]. Srivastava, R., Stimuli-responsive nanomaterials for the precision delivery of mrna cancer vaccines. *Nano Trends*, **2025**, 100147.
[118]. Hossain, M.S., Hussain, M.H., Multi-target drug design in alzheimer's disease treatment: Emerging technologies, advantages, challenges, and limitations. *Pharmacology Research & Perspectives*, **2025**, 13(4), e70131.
[119]. Cheng, H., Liao, J., Ma, Y., Sarwar, M.T., Yang, H., Advances in targeted therapy for tumor with nanocarriers: A review. *Materials Today Bio*, **2025**, 101583.
[120]. Baghirov, H., Mechanisms of receptor-mediated transcytosis at the blood-brain barrier. *Journal of Controlled Release*, **2025**, 381, 113595.
[121]. Sabit, H., Pawlik, T.M., Radwan, F., Abdel-Hakeem, M., Abdel-Ghany, S., Wadan, A.-H.S., Elzawahri, M., El-Hashash, A., Arneth, B., Precision nanomedicine: Navigating the tumor microenvironment for enhanced cancer immunotherapy and targeted drug delivery. *Molecular cancer*, **2025**, 24(1), 160.

[122]. Van Dyck, C.H., Anti-amyloid-β monoclonal antibodies for alzheimer's disease: Pitfalls and promise. *Biological Psychiatry*, **2018**, 83(4), 311-319.
[123]. Gallardo, G., Holtzman, D.M., Antibody therapeutics targeting aβ and tau. *Cold Spring Harbor Perspectives in Medicine*, **2017**, 7(10), a024331.
[124]. Tapia-Arellano, A., Gallardo-Toledo, E., Ortiz, C., Henríquez, J., Feijóo, C.G., Araya, E., Sierpe, R., Kogan, M.J., Functionalization with PEG/angiopep-2 peptide to improve the delivery of gold nanoprisms to central nervous system: In vitro and in vivo studies. *Materials Science and Engineering: C*, **2021**, 121, 111785.
[125]. Javid, H., Oryani, M.A., Rezagholinejad, N., Esparham, A., Tajaldini, M., Karimi-Shahri, M., Rgd peptide in cancer targeting: Benefits, challenges, solutions, and possible integrin–rgd interactions. *Cancer Medicine*, **2024**, 13(2), e6800.
[126]. Pinheiro, R., Granja, A., Loureiro, J.A., Pereira, M., Pinheiro, M., Neves, A., Reis, S., Rvg29-functionalized lipid nanoparticles for quercetin brain delivery and alzheimer's disease. *Pharmaceutical Research*, **2020**, 37(7), 139.
[127]. Zheng, Y., Zhang, L., Zhao, J., Li, L., Wang, M., Gao, P., Wang, Q., Zhang, X., Wang, W., Advances in aptamers against aβ and applications in aβ detection and regulation for alzheimer's disease. *Theranostics*, **2022**, 12(5), 2095.
[128]. Murakami, K., Izuo, N., Bitan, G., Aptamers targeting amyloidogenic proteins and their emerging role in neurodegenerative diseases. *Journal of Biological Chemistry*, **2022**, 298(1).
[129]. Su, J., Yao, Z., Chen, Z., Zhou, S., Wang, Z., Xia, H., Liu, S., Wu, Y., Tfr aptamer enhanced blood-brain barrier penetration of biomimetic nanocomplexes for intracellular transglutaminase 2 imaging and silencing in glioma. *Small*, **2022**, 18(40), 2203448.
[130]. Xu, Y., Zhao, M., Zhou, D., Zheng, T., Zhang, H., The application of multifunctional nanomaterials in alzheimer's disease: A potential theranostics strategy. *Biomedicine & Pharmacotherapy*, **2021**, 137, 111360.
[131]. Ramesh, M., Govindaraju, T., Multipronged diagnostic and therapeutic strategies for alzheimer's disease. *Chemical Science*, **2022**, 13(46), 13657-13689.
[132]. Mi, P., Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. *Theranostics*, **2020**, 10(10), 4557.
[133]. Wang, K., Yang, R., Li, J., Wang, H., Wan, L., He, J., Nanocarrier-based targeted drug delivery for alzheimer's disease: Addressing neuroinflammation and enhancing clinical translation. *Frontiers in Pharmacology*, **2025**, 16, 1591438.
[134]. Kim, S., Jung, U.J., Kim, S.R., Role of oxidative stress in blood–brain barrier disruption and neurodegenerative diseases. *Antioxidants*, **2024**, 13(12), 1462.
[135]. Sahu, K., Firdous, A., Raza, M.A., Saoji, S.D., Patravale, V.B., Enzyme-responsive natural nanocarriers for rna delivery in the tumor microenvironment: A comprehensive review. *Journal of Drug Delivery Science and Technology*, **2025**, 107455.
[136]. Dash, U.C., Bhol, N.K., Swain, S.K., Samal, R.R., Nayak, P.K., Raina, V., Panda, S.K., Kerry, R.G., Duttaroy, A.K., Jena, A.B., Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. *Acta Pharmaceutica Sinica B*, **2025**, 15(1), 15-34.
[137]. Singh, D., Sharma, Y., Dheer, D., Shankar, R., Stimuli responsiveness of recent biomacromolecular systems (concept to market): A review. *International Journal of Biological Macromolecules*, **2024**, 261, 129901.
[138]. Iqbal, I., Saqib, F., Mubarak, Z., Latif, M.F., Wahid, M., Nasir, B., Shahzad, H., Sharifi-Rad, J., Mubarak, M.S., Alzheimer's disease and drug delivery across the blood–brain barrier: Approaches and challenges. *European Journal of Medical Research*, **2024**, 29(1), 313.
[139]. Kamath, A.P., Nayak, P.G., John, J., Mutalik, S., Balaraman, A.K., Krishnadas, N., Revolutionizing neurotherapeutics: Nanocarriers unveiling the potential of phytochemicals in alzheimer's disease. *Neuropharmacology*, **2024**, 259, 110096.
[140]. Yang, Y., Teng, P., Yu, S., Meng, Y., Zuo, J., Guo, H., Liu, G., A review of combined imaging and therapeutic applications based on mnms. *Frontiers in Chemistry*, **2025**, 13, 1595376.
[141]. Hoang, C.N.M., Nguyen, S.H., Tran, M.T., Nanoparticles in cancer therapy: Strategies to penetrate and modulate the tumor microenvironment–a review. *Smart Materials in Medicine*, **2025**.
[142]. Mahadik, N., Barron, G.A., Thoo Lin, P.K., Thompson, C.J., Synthesis and evaluation of polymer-drug conjugates as potential antioxidants and cholinesterase inhibitors for neurodegenerative diseases. *Chemistry of Materials*, **2024**, 36(21), 10514-10527.
[143]. Kumari, A., Rahaman, A., Zeng, X.A., Baloch, Z., Therapeutic potential and microrna regulating properties of phytochemicals in alzheimer's disease. *Molecular Therapy Nucleic Acids*, **2025**, 36(1).
[144]. Naimi, N., Seyedmirzaei, H., Hassannejad, Z., Khaboushan, A.S., Advanced nanoparticle strategies for optimizing rna therapeutic delivery in neurodegenerative disorders. *Biomedicine & Pharmacotherapy*, **2024**, 175, 116691.

[145]. Lin, Z., Chou, W.C., Cheng, Y.H., He, C., Monteiro-Riviere, N.A., Riviere, J.E., Predicting nanoparticle delivery to tumors using machine learning and artificial intelligence approaches. *International Journal of Nanomedicine*, **2022**, 1365-1379.
[146]. Villa Nova, M., Lin, T.P., Shanehsazzadeh, S., Jain, K., Ng, S.C.Y., Wacker, R., Chichakly, K., Wacker, M.G., Nanomedicine ex machina: Between model-informed development and artificial intelligence. *Frontiers in Digital Health*, **2022**, 4, 799341.
[147]. Singh, A.V., Varma, M., Laux, P., Choudhary, S., Datusalia, A.K., Gupta, N., Luch, A., Gandhi, A., Kulkarni, P., Nath, B., Artificial intelligence and machine learning disciplines with the potential to improve the nanotoxicology and nanomedicine fields: A comprehensive review. *Archives of Toxicology*, **2023**, 97(4), 963-979.
[148]. Aman, S.S., Agbo, D.D.A., N'guessan, B.G., Kone, T., Design of a data storage and retrieval ontology for the efficient integration of information in artificial intelligence systems. *International Journal of Information Technology*, **2024**, 16(3), 1743-1761.
[149]. Shaban-Nejad, A., Michalowski, M., Buckeridge, D.L., Health intelligence: How artificial intelligence transforms population and personalized health. *NPJ Digital Medicine*, **2018**, 1(1), 53.