

NANOTECHNOLOGY-DRIVEN CONVERGENCE OF HERBAL AND SYNTHETIC THERAPEUTICS FOR ALZHEIMER'S DISEASE: FROM MECHANISTIC INSIGHTS TO CLINICAL TRANSLATION

¹ANJANA A.S, ²Dr. MATHAN. S, ³Dr. SHAIJU S DHARAN

¹M Pharm Student, ²Professor/HOD, Department of Pharmaceutics, ³Principal

¹M Pharm Student, Department of Pharmaceutics

¹EZHUTHACHAN COLLEGE OF PHARMACEUTICAL SCIENCES,
MARAYAMUTTOM, TVM, KERALA, INDIA

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory impairment, cognitive decline, extracellular amyloid- β (A β) plaque accumulation, intracellular neurofibrillary tangles, oxidative stress, neuroinflammation, and neuronal loss. Despite extensive research, currently approved pharmacological agents such as donepezil, rivastigmine, galantamine, and memantine provide only symptomatic relief and fail to halt disease progression. Herbal bioactive compounds including curcumin, resveratrol, quercetin, bacosides, and ginsenosides possess significant antioxidant, anti-inflammatory, anti-amyloidogenic, and neuroprotective activities. However, their clinical application is limited by poor aqueous solubility, low bioavailability, rapid metabolism, and inadequate blood-brain barrier (BBB) penetration. Nanotechnology-based drug delivery systems have emerged as promising platforms to overcome these limitations by enhancing brain targeting, improving drug stability, and enabling controlled drug release. Co-delivery of herbal and synthetic therapeutics using nanocarriers represents a novel multi-target therapeutic approach capable of simultaneously modulating various pathological pathways involved in AD. This review discusses the pathophysiology of Alzheimer's disease, limitations of conventional therapies, therapeutic potential of herbal and synthetic drugs, nanotechnology-based delivery systems, and recent advances in nano-enabled combination therapies for Alzheimer's disease management.

Keywords: Alzheimer's disease, nanotechnology, herbal therapeutics, synthetic drugs, blood-brain barrier, solid lipid nanoparticles.

INTRODUCTION

Alzheimer's disease (AD) has emerged as one of the most pressing public-health concerns of this century. As global life expectancy climbs, this motor neuron disease has become the leading driver of dementia among older adults. As per the World Health Organization, millions worldwide are currently navigating the realities of dementia, with Alzheimer's accounting for an overwhelming 60% to 70% of those cases^{1,2}. The clinical hallmark of the disease is a devastating, gradual erosion of memory, cognitive capacity, language skills, and daily independence.

Despite decades of intense scrutiny, the exact trigger of Alzheimer's remains elusive due to its incredibly complex, multifactorial nature. It is not driven by a single flaw, but rather a cascade of destructive cellular events. These include the deposition of amyloid-beta plaques in extracellular spaces, the formation of intracellular neurofibrillary tangles from hyperphosphorylated tau proteins, widespread oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, and the selective loss of cholinergic neurons³. As these pathological forces intersect, they dismantle neural networks across the brain, systematically stripping away memory and cognitive function. To date, a definitive cure remains frustratingly out of reach.

The modern clinical arsenal relies primarily on symptomatic management, utilizing cholinesterase inhibitors like donepezil, rivastigmine, and galantamine, alongside the NMDA receptor antagonist memantine^{4,5}. While these drugs can offer temporary relief

by tuning neurotransmitter activity and slowing immediate cognitive decline, their impact is modest. They are frequently bottlenecked by adverse side effects and, crucially, do nothing to alter, halt, or invert the underlying neurodegenerative process tearing through the brain⁶.

Faced with these constraints, researchers have increasingly turned to nature. A wealth of plant-derived bioactive compounds—such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and bacosides—have shown profound neuroprotective promise in preclinical models^{7,8}. Because these molecules boast potent antioxidant, anti-inflammatory, and anti-amyloid properties, they can attack the disease from multiple angles simultaneously. Unfortunately, translating these benefits to human patients has proven incredibly difficult. Most of these herbal compounds suffer from abysmal water solubility, low bioavailability, rapid metabolic breakdown, and an inability to permeate the blood-brain barrier (BBB) in therapeutic amounts⁹.

Nanotechnology offers a sophisticated toolkit to solve these delivery dilemmas. Advanced nanocarriers—including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and polymeric nanoparticles—can shield these delicate compounds from early degradation, optimize their release profiles, and significantly boost their bioavailability^{10,11}. Most importantly, these engineered nanosystems are uniquely equipped to ferry therapeutic payloads across the stubborn blood-brain barrier, concentrating the active ingredients exactly where they are vital.

The next logical leap in AD therapeutics is the combination of both herbal and synthetic elements into a single, cohesive nanocarrier. This dual-delivery strategy offers the best of both worlds, allowing synthetic drugs to stabilize neurotransmission and preserve immediate cognitive function while herbal compounds work in parallel to fight oxidative stress and inflammation. Among the various pairings under review, the co-delivery of curcumin and memantine has evolved as a particularly exciting frontrunner. Early nanoformulations combining the two have shown a remarkable ability to target the brain effectively, ease the amyloid burden, and improve cognitive performance, all while keeping systemic side effects to a minimum¹³.

Consequently, this review provides an exhaustive look into how nanotechnology is bridging the gap between herbal wisdom and synthetic pharmacology to redefine Alzheimer's care. Over the following sections, we will break down the complex pathophysiology of AD, dissect the failures of conventional treatments, evaluate the potential of key herbal and synthetic candidates, and observing closely the latest breakthroughs in nano-enabled combination therapies as we look toward clinical translation.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by declining cognition, memory impairment, and neuronal death. It results from the interplay of several pathological processes, including amyloid-beta ($A\beta$) plaque accumulation, hyperphosphorylation of tau protein, oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity, and disruption of the blood-brain barrier (BBB)^{1,14}.

The pathological process is believed to begin with the abnormal production and accumulation of $A\beta$ peptides, particularly $A\beta_{42}$, which aggregate to form extracellular amyloid plaques³. These plaques trigger oxidative stress and activate microglia and astrocytes, leading to chronic neuroinflammation^{4,15}. At the same time, tau protein becomes abnormally hyperphosphorylated, producing intracellular neurofibrillary tangles that disrupt neuronal transport machinery and ultimately lead to cell death⁵.

Oxidative stress and mitochondrial impairment compound neuronal injury by raising levels of reactive oxygen species (ROS) and disrupting cellular energy metabolism^{6,7}. Degeneration of cholinergic neurons leads to reduced acetylcholine levels, contributing to memory and learning deficits. In addition, excessive activation of NMDA receptors causes excitotoxicity, resulting in calcium overload and neuronal injury. Blood-brain barrier dysfunction further promotes neuroinflammation and impairs the clearance of toxic proteins from the brain.

Collectively, these interconnected mechanisms lead to synaptic dysfunction, neuronal degeneration, and progressive cognitive decline. The multifactorial nature of Alzheimer's disease underscores why multi-target therapeutic strategies, including nanotechnology-based co-delivery of herbal and synthetic drugs¹⁸.

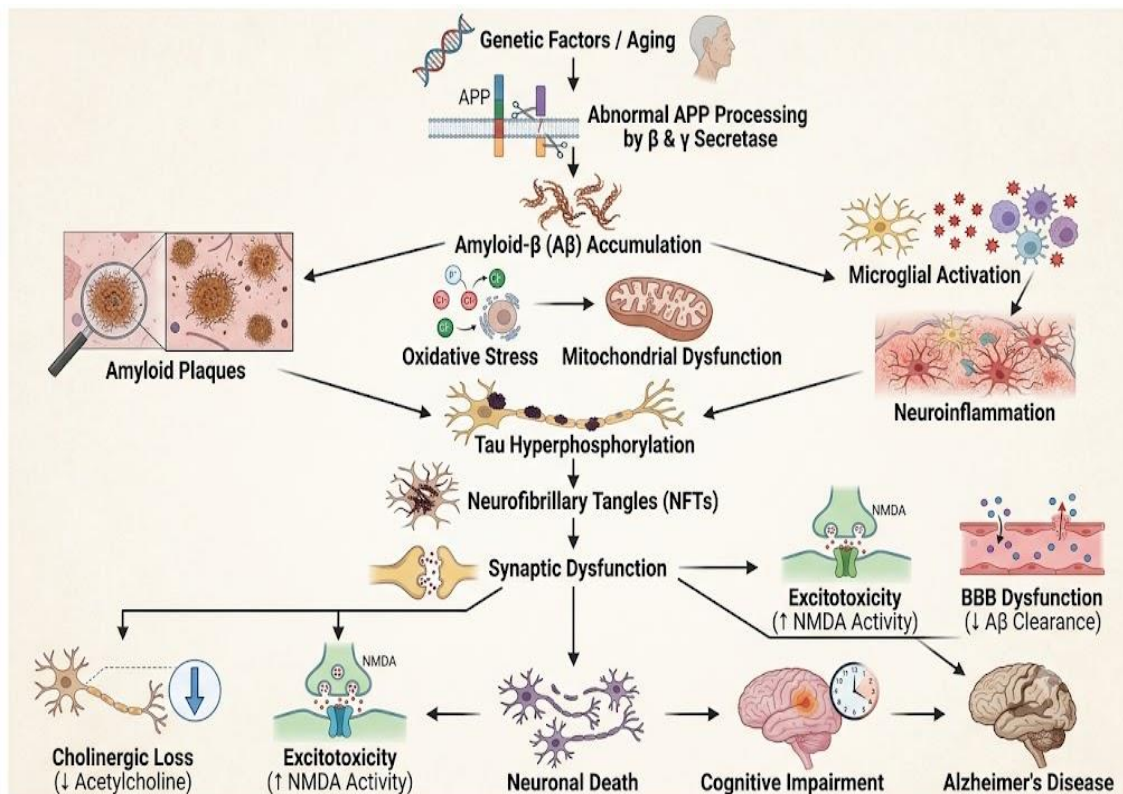


Figure 1. Schematic representation of the pathophysiology of Alzheimer's disease

LIMITATIONS OF CONVENTIONAL THERAPY

Despite significant strides in decoding the intricate biology of Alzheimer's disease (AD), modern clinical interventions remain frustratingly superficial. First-line treatments rely almost exclusively on symptomatic management using cholinesterase-inhibiting agents such as donepezil, rivastigmine, and galantamine, together with the NMDA receptor antagonist memantine^{8,17}. While these pharmaceuticals can temporarily shore up cognitive function, preserve memory, and lift the burden of daily activities, they offer only modest benefits. Crucially, they are entirely incapable of halting, reversing, or preventing the relentless, underlying neurodegenerative process that drives the disease forward^{9,18}.

A core limitation of conventional pharmacology lies in its single-target architecture, which cannot capture the intricate, multi-causal biology underlying Alzheimer's. The disease progresses through an intertwined network of cellular failures, including amyloid-beta accumulation, tau hyperphosphorylation, persistent oxidative damage, sustained neuroinflammatory activity, breakdown of mitochondrial function, and widespread neurotransmitter imbalance. Because existing drugs typically isolate and attack only one of these pathways-such as cholinergic failure or glutamatergic excitotoxicity-their overarching therapeutic efficacy is inherently capped, allowing the broader neurodegenerative cascade to continue unchecked⁹.

This therapeutic deficit is severely worsened by the blood-brain barrier (BBB). Although this selective physiological barrier plays a critical role in shielding the central nervous system from circulating toxins, it likewise limits access for beneficial medications^{10,11}. Consequently, standard anti-Alzheimer's agents suffer from poor brain bioavailability, drastically minimizing their real-world clinical impact. This challenge is further complicated by unfavourable pharmacokinetic profiles; many available compounds exhibit poor water solubility, limited absorption, rapid metabolic degradation, and exceptionally short half-lives^{12,13}. In an elderly population already managing multiple medications for other conditions, the resulting requirement to take doses several times a day often lowers treatment adherence.

Furthermore, the clinical utility of conventional treatments is frequently compromised by a heavy toll of adverse side effects. Acetylcholinesterase inhibitors routinely trigger distressing gastrointestinal complications including nausea, vomiting, loose stools, and abdominal discomfort and can occasionally provoke severe cardiovascular risks like bradycardia and syncope^{14,15}. Meanwhile, memantine therapy is regularly limited by central nervous system complaints, such as dizziness, headache, confusion, fatigue, and persistent constipation^{16,17}. These toxicities not only diminish the patient's immediate quality of life but also severely undermine long-term compliance^{18,19}.

This systemic failure to deliver true disease-modifying therapies has triggered an urgent search for alternatives. Although numerous investigational candidates have been engineered to clear amyloid-beta plaques or dismantle tau tangles, the vast majority have foundered in clinical trials due to safety concerns, delivery failures, or inadequate efficacy¹⁹. This clinical stagnation underscores the

reality that single-target approaches are fundamentally ill-equipped to combat the disease's multi-layered damage, particularly when it comes to neutralizing pervasive oxidative stress and neuroinflammation, which continue to destroy brain tissue even during active treatment^{11,20}.

Beyond the clinical toll, this lack of effective intervention imposes an escalating economic strain, driving up long-term care, monitoring, and supportive costs for families and global healthcare systems alike²⁰. Resolving this crisis demands a radical shift toward integrated, multi-functional therapeutic strategies. By merging the holistic, multi-targeted properties of herbal bioactive compounds with the specialized precision of synthetic pharmaceuticals-and encapsulating them within advanced nanocarriers designed to effortlessly bypass the blood-brain barrier-modern medicine may finally bridge these persistent gaps to achieve meaningful, disease-modifying outcomes.

HERBAL THERAPEUTICS FOR ALZHEIMER'S DISEASE

The shifting paradigm in Alzheimer's drug discovery increasingly favors plant-derived bioactives due to their inherently pleiotropic nature. Unlike conventional, single-target pharmaceuticals, these phytochemicals-most notably curcumin, *Bacopa monnieri*, *Ginkgo biloba*, resveratrol, quercetin, and epigallocatechin-3-gallate (EGCG) can simultaneously act on oxidative stress, chronic neuroinflammation, amyloid accumulation, and apoptosis¹². Despite their profound preclinical success in shielding neural architecture and preserving cognitive networks, their clinical translation faces a universal bottleneck. These botanical compounds suffer from poor water solubility, rapid systemic metabolism, and an inability to cross the blood-brain barrier (BBB) in therapeutic amounts, creating an urgent mandate for advanced nanotechnology-based delivery systems²¹.

Curcumin

Among these candidates, curcumin-the principal polyphenol from *Curcuma longa*-stands out as a highly investigated neuroprotective agent²¹. It acts through a dual mechanism, scavenging reactive oxygen species while suppressing the inflammatory cytokine pathways that sustain chronic neuroinflammation^{5,21}. At the macromolecular level, curcumin physically interferes with the assembly of amyloid-beta monomers, accelerates the clearance of existing senile plaques, and mitigates tau hyperphosphorylation. Despite this remarkable therapeutic profile, its real-world efficacy is severely hampered by low bioavailability, which has driven researchers to wrap the molecule in protective nanocarriers to optimize its journey to the brain.

Bacopa monnieri

In a similar vein, *Bacopa monnieri* (Brahmi) brings centuries of traditional Ayurvedic validation into modern neurobiology, primarily through its active saponins known as bacosides. Bacoside A in particular protects cortical neurons from oxidative damage while enhancing cholinergic transmission by increasing synaptic acetylcholine levels. Beyond merely managing neurotransmitters, *Bacopa* exhibits a capacity to reduce amyloid burdens, sharpen memory retention, and actively foster neuronal regeneration, positioning it as a cornerstone for multi-target management strategies²¹.

Ginkgo biloba

Where *Bacopa* optimizes neurotransmission, *Ginkgo biloba* excels at vascular and cellular preservation through its rich matrix of flavonoids and terpenoids. The therapeutic fingerprint of *Ginkgo* is defined by its ability to enhance cerebral microcirculation, ensuring that vulnerable brain tissues receive an adequate supply of oxygen and essential nutrients. By stabilizing mitochondrial membranes and neutralizing amyloid-beta-induced neurotoxicity, *Ginkgo* extracts have shown a measurable, albeit modest, capacity to steady cognitive decline in patients navigating mild-to-moderate stages of the disease^{21,22}.

Resveratrol

The metabolic defense of the brain is further supported by resveratrol, a potent dietary polyphenol found in red wine and berries, celebrated for its unique survival signaling mechanisms. Resveratrol primarily operates by activating sirtuin-1 (SIRT1), an enzyme that promotes mitochondrial longevity, suppresses apoptotic triggers, and drives the clearance of neurotoxic protein aggregates. However, much like curcumin, its brilliant preclinical success is frequently compromised by an incredibly short biological half-life and rapid metabolic breakdown, making nano-encapsulation essential to exploit its true disease-modifying potential²¹.

Quercetin

Operating along complementary antioxidant pathways is the ubiquitous flavonoid quercetin, a free-radical scavenger that aggressively halts lipid peroxidation within neural membranes. Quercetin plays a decisive role in suppressing neuroinflammatory signaling and steering survival pathways away from programmed cell death in AD models¹⁸. Still, the story remains the same: its clinical utility is fundamentally restricted by poor aqueous solubility and minimal BBB permeability, demanding innovative delivery architectures to unlock its benefits^{19,21}.

Epigallocatechin-3-Gallate (EGCG)

Epigallocatechin-3-gallate (EGCG), the dominant catechin in green tea, offers a fascinating biophysical intervention by directly reshaping the landscape of protein misfolding²⁰. EGCG binds to unstructured amyloid-beta peptides, redirecting them away from toxic oligomeric pathways toward benign, non-toxic aggregates, thereby arresting plaque-induced neurotoxicity at its source²¹. Combined with its ability to attenuate tau pathology and rescue failing mitochondria, EGCG represents a highly sophisticated botanical weapon against Alzheimer's-provided its structural instability and low systemic availability can be successfully corrected through modern nanotechnology²².

SYNTHETIC DRUGS USED IN ALZHEIMER'S DISEASE

Despite exhaustive insights into the molecular pathology of Alzheimer's disease (AD), the current pharmaceutical treatment remains focused primarily on symptomatic relief rather than disease modification. Conventional interventions are fundamentally palliative, engineered to temporarily optimize cognitive performance, preserve basic activities of daily living, and offer a modest extension of patient autonomy. The clinical standard of care relies almost exclusively on two mechanistic classes: acetylcholinesterase inhibitors (AChEIs)-including donepezil, rivastigmine, and galantamine-and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine^{1,23}.

While these molecules selectively fine-tune neurotransmitter dynamics to manage symptoms across mild, moderate, and severe stages of the disease, they leave the underlying neurodegenerative cascade entirely unaltered. Consequently, they represent essential yet fundamentally limited pillars of contemporary AD management.

Donepezil

As a highly selective, reversible inhibitor of acetylcholinesterase, donepezil serves as a primary, frontline intervention for mild-to-moderate AD³. Its mechanism revolves around the preservation of synaptic acetylcholine; by blocking its primary degradative enzyme within the synaptic cleft, donepezil artificially amplifies cholinergic signaling across depleted cortical networks, offering measurable improvements in executive function, memory, and language processing^{22,23}. These benefits, however, are ultimately limited by the ongoing loss of post-synaptic targets. Its cholinergic action also frequently causes gastrointestinal side effects (nausea, vomiting, and diarrhea), sleep disturbances, and critical cardiovascular liabilities such as bradycardia and syncope, which can compromise patient adherence.

Rivastigmine

Rivastigmine broadens the scope of cholinergic intervention through its pseudo-reversible, dual-target inhibition of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Because glial-derived BuChE activity paradoxically scales upward as the AD brain undergoes progressive neurodegeneration, rivastigmine's secondary target provides a sustained neurochemical advantage in advanced disease stages. Clinical deployment of this compound effectively stabilizes behavioral fluctuations and cognitive deficits. Notably, its availability as a transdermal patch circumvents first-pass hepatic metabolism, offering a steadier pharmacokinetic profile that significantly reduces systemic gastrointestinal toxicities, though localized skin irritation and dose-dependent nausea during titration remain persistent challenges²³.

Galantamine

Galantamine is a tertiary alkaloid that offers a unique, dual-action approach to cholinergic deficiency¹⁹. Beyond its primary role as a reversible acetylcholinesterase inhibitor, it functions as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs). This secondary mechanism sensitizes remaining receptors to both endogenous acetylcholine and the drug itself, amplifying synaptic transmission and neuroprotective cell-signalling pathways. While galantamine demonstrably preserves global cognitive functioning in mild-to-moderate AD cohorts, its real-world utility remains bottlenecked by typical cholinomimetic adverse effects, heavily dominated by acute gastrointestinal intolerance²³.

Memantine Hydrochloride

In contrast to the cholinergic focus of AChEIs, memantine hydrochloride targets the glutamatergic system to combat the destructive forces of chronic excitotoxicity. Under pathological conditions, sustained, low-level glutamate exposure keeps NMDA receptors open, driving an abnormal influx of intracellular calcium (Ca^{2+}) that triggers mitochondrial collapse, free-radical generation, and cell death. Memantine operates as a low-affinity, uncompetitive NMDA receptor antagonist; its rapid off-rate allows it to selectively block

pathological, tonic receptor activation without disrupting the transient, high-concentration glutamate bursts required for normal physiological learning and memory formation²³.

Indicated primarily for moderate-to-severe AD, memantine stabilizes behavioral deficits and is frequently co-administered with AChEIs to generate a complementary therapeutic baseline. Though generally well-tolerated, it is occasionally associated with central nervous system side effects, including dizziness, persistent headaches, confusion, and fatigue.

RATIONALE FOR HERBAL–SYNTHETIC DRUG COMBINATION THERAPY IN ALZHEIMER'S DISEASE

The web of interconnected pathological pathways in Alzheimer's disease (AD) presents a formidable obstacle to conventional monotherapeutic approaches. While standard synthetic drugs offer vital palliative support, they are restricted to modulating specific neurotransmitter circuits and lack the capacity to alter the underlying neurodegenerative trajectory. Conversely, plant-derived bioactives show profound preclinical neuroprotective potential but are heavily bottlenecked by poor biopharmaceutical properties and low solo efficacy². This clinical divide has sparked significant momentum toward a paradigm shift: merging herbal and synthetic pharmacology into a unified, multi-targeted regimen designed to rewrite AD management²⁴.

This therapeutic rationale rests on the fact that Alzheimer's does not progress via a isolated cellular failure, but through a synchronized cascade of neurotoxic events. Consequently, isolating a single mechanism leaves parallel destructive pathways free to advance. Botanical bioactives and synthetic agents possess deeply complementary mechanistic profiles. Phytochemicals like curcumin, resveratrol, quercetin, EGCG, and bacosides function as molecular shields—scavenging free radicals, dampening chronic microglial neuroinflammation, preventing amyloid-beta oligomerization, and preventing pro-apoptotic signaling. In contrast, synthetic clinical stalwarts like donepezil, rivastigmine, galantamine, and memantine operate downstream, correcting immediate signaling deficits by reinforcing cholinergic neurotransmission or shielding synapses from glutamate-mediated excitotoxicity^{5,23,24}.

By strategically pairing these two classes, clinicians can simultaneously mitigate acute cognitive symptoms and slow the underlying cellular decay. The primary advantage of this dual-action architecture is the exploitation of true pharmacological synergism, where the combined therapeutic impact far exceeds the sum of its individual components. For instance, co-administering curcumin alongside memantine creates a powerful metabolic shield: curcumin actively suppresses upstream neuroinflammation and clears amyloid-beta burden, while memantine selectively cushions post-synaptic NMDA receptors against excitotoxic death. This multi-layered intervention yields far superior neural protection and cognitive preservation than single-agent protocols²⁴.

Beyond magnifying efficacy, this combination model directly resolves the historical problem of drug toxicity. Synthetic acetylcholinesterase inhibitors and NMDA antagonists carry a heavy burden of dose-limiting side effects, including severe gastrointestinal distress, syncope, headaches, and confusion, which frequently compromise patient compliance. Integrating cytoprotective herbal bioactives can lower the therapeutic threshold of these synthetic agents, achieving comparable or superior clinical efficacy at significantly reduced doses, thereby preserving patient comfort and long-term treatment adherence. Furthermore, these plant molecules directly neutralize pervasive oxidative stress and chronic inflammation—two critical drivers of progressive neuronal death that conventional therapeutics largely leave unaddressed²³.

Despite this compelling rationale, translating these combinations into practical clinical successes faces severe pharmacokinetic barriers. Most high-potency herbal extracts suffer from abysmal water solubility, rapid systemic clearance, and extensive first-pass metabolism. More critically, both herbal and synthetic molecules are routinely turned away by the blood-brain barrier (BBB), severely restricting their concentration within the central nervous system. To bridge this delivery gap, researchers are leveraging advanced engineered nanotechnology^{23,24}.

Sophisticated nanocarrier architectures—such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, polymeric nanoparticles, and nanoemulsions—serve as an ideal platform for synchronized co-delivery. These biocompatible matrices encapsulate both hydrophilic and lipophilic payloads within a single vector, shielding delicate molecules from peripheral degradation, orchestrating controlled-release kinetics, and exploiting specialized transport mechanisms to cross the blood-brain barrier. Co-encapsulating synergistic pairs, such as curcumin and memantine, within a single nanovector ensures they travel through the systemic circulation together and arrive at the neurodegenerative site in exact, optimized ratios^{14,23}.

Ultimately, integrating herbal bioactives with synthetic pharmaceuticals represents a highly rational and innovative leap forward in neurodegenerative medicine. By treating Alzheimer's disease as a complex, multi-system failure rather than a single-receptor deficit, this approach delivers a holistic, multi-pronged attack on the disease. Supported by the targeted precision of modern nanotechnology, this hybrid framework overcomes old bio-delivery limitations and lays a solid foundation for the next generation of disease-modifying Alzheimer's therapies²⁵.

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR ALZHEIMER'S DISEASE

Clinical translation of otherwise effective Alzheimer's disease (AD) therapeutics is significantly hindered by the body's physiological defenses, particularly the blood-brain barrier (BBB)¹. This highly selective endothelial shield successfully insulates the central nervous system from systemic fluctuations and potential toxins, but it simultaneously intercepts and rejects the vast majority of small-molecule synthetic pharmaceuticals and neuroprotective herbal bioactives. Consequently, standard systemic administration routinely fails to achieve minimal effective concentrations within the cerebral parenchyma, leading to poor clinical performance and secondary peripheral toxicities²⁶.

To bridge this biophysical deficit, advanced engineering has turned to nanotechnology. By utilizing engineered nanocarriers (typically operating within the sub-micron scale of 1 to 1000 nm), pharmacology can now bypass classical restrictions²⁶. These nanosystems optimize the therapeutic index of fragile payloads by drastically increasing apparent aqueous solubility, shielding molecules from early enzymatic degradation, enforcing controlled-release profiles, and exploiting endogenous receptor-mediated or adsorptive transport pathways to ferry compounds across the BBB.

Crucially, this nanotechnology platform acts as a versatile vehicle capable of handling diverse physicochemical architectures. It enables the synchronized co-delivery of hydrophobic botanical extractives alongside hydrophilic synthetic agents, orchestrating a simultaneous attack on the disparate, parallel pathways that drive Alzheimer's progression^{24,26}.

Advantages of Nanotechnology in Alzheimer's Disease Therapy

The shift from conventional molecular formulations to nano-engineered delivery vehicles relies on distinct biophysical advantages. Minimizing carrier morphology to the nanoscale drastically elevates the surface-area-to-volume ratio, facilitating rapid dissolution and enhanced membrane interfacial contact. Furthermore, surface functionalization chemistry allows for the conjugation of targeting moieties, optimizing interactions with specific BBB transporters²⁵.

The primary operational advantages of these platforms include:

- Facilitated transit across the blood-brain barrier via specialized active or passive transport pathways.
- Enhanced thermodynamic stability and structural protection of encapsulated payloads against systemic degradation.
- Maximized systemic bioavailability and circulation residence times for poorly soluble molecules.
- Precise control over spatial and temporal drug release kinetics.
- Attenuation of peripheral peak plasma concentrations, leading to a marked reduction in systemic toxicities.
- Multi-payload carrying capacity, enabling synchronized, multi-target therapeutic regimens within a single vector⁶.

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) represent a foundational class of lipidic nanocarriers, constructed from a solid crystalline lipid matrix stabilized within an aqueous surfactant phase²⁷. Their entirely biocompatible and biodegradable lipidic core mimics endogenous chylomicrons, giving them an excellent safety profile and an innate affinity for biological membranes. This lipophilic character heavily promotes passive endothelial permeation and receptor-mediated endocytosis across the blood-brain barrier^{26,27}.

AD research, SLNs have been extensively deployed to encapsulate challenging compounds like curcumin, resveratrol, donepezil, and memantine. Preclinical evaluations consistently demonstrate that SLN encapsulation shifts the pharmacokinetic profile of these molecules, yielding marked increases in cerebral bio-accumulation and superior cognitive rescue compared to free-drug suspensions^{26,28}.

Nanostructured Lipid Carriers (NLCs)

Developed as a second-generation iteration of lipidic technologies, nanostructured lipid carriers (NLCs) deliberately resolve the structural limitations of classical SLNs²⁸. By blending spatially distinct solid lipids with liquid lipids (oils), NLCs form a highly distorted, less ordered crystalline lattice. This structural imperfection prevents the drug expulsion that typically occurs during SLN storage as a result of lipid crystallization.

Consequently, NLCs exhibit significantly elevated drug-loading capacities and exceptional formulation stability. These carriers ensure highly reproducible sustained-release kinetics and superior brain targeting, making them powerful tools for delivering delicate, highly hydrophobic phytochemicals like quercetin and curcumin into the deep structures of the brain^{26,27,29}.

Polymeric Nanoparticles

Polymeric nanoparticles represent highly customizable colloidal matrices synthesized from either natural or synthetic biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone. These architectures allow for extreme engineering flexibility: payloads can be physically entrapped within the core, dissolved throughout the matrix, or covalently bound to the outer corona²⁸.

These polymeric shells provide excellent protection against premature metabolic clearance while offering finely tuned, degradation-dependent drug release. Moreover, the ease with which their surface chemistry can be modified with brain-targeting ligands makes polymeric nanoparticles a preferred choice for the targeted delivery of polyphenols like EGCG and resveratrol, forcing therapeutic accumulation directly within vulnerable cortical and hippocampal pathways^{26,28}.

Liposomes

Liposomes are classic spherical vesicles composed of concentric phospholipid bilayers enclosing a central aqueous core, structurally mirroring eukaryotic cellular membranes. This unique amphiphilic architecture gives them the rare ability to simultaneously carry lipophilic agents within the lipid bilayer and hydrophilic compounds within the interior aqueous chamber.

While unmodified liposomes are susceptible to rapid clearance by the mononuclear phagocyte system, surface engineering—such as PEGylation or the integration of cell-penetrating peptides—extends circulation longevity and enhances blood-brain barrier transport¹⁷. Liposomal configurations loaded with donepezil, curcumin, or quercetin have shown significant promise in preclinical AD models, minimizing systemic toxicities while boosting immediate neuroprotective efficacy²⁸.

Nanoemulsions

Nanoemulsions are thermodynamically or kinetically stabilized, isotropic dispersions consisting of oil and water phases tightly woven together by an optimized surfactant mix, with droplet diameters restricted below 200 nm²⁹. Their small size provides a large surface area that supports rapid absorption across mucosal and endothelial membranes.

In Alzheimer's therapeutics, nanoemulsions have gained significant traction as specialized vehicles for intranasal delivery. This nose-to-brain route exploits the olfactory and trigeminal nerve pathways to bypass the blood-brain barrier entirely, offering a direct anatomical channel from the nasal cavity into the central nervous system^{20,29}. This approach has proven especially effective for delivering poorly water-soluble herbal compounds like resveratrol and quercetin, providing rapid brain targeting while avoiding first-pass hepatic metabolism²¹.

Dendrimers

Dendrimers are uniquely structured, monodisperse macromolecular architectures characterized by highly branched, three-dimensional symmetric geometries stemming from a central core. The precise control over their generation number allows for predictable size scaling, while their highly dense surface corona provides a massive layout of functional groups for drug conjugation or ligand targeting.

Molecules can be securely encapsulated within the internal hydrophobic cavities of the dendritic tree or electrostatically bound to the surface. These highly organized nanocarriers offer exceptional payload density, reproducible release kinetics, and an unmatched ability to cross complex biological membranes, making them useful for dismantling neurotoxic β oligomers directly within the parenchymal space²⁹.

Magnetic Nanoparticles

Superparamagnetic iron oxide nanoparticles (SPIONs) represent an advanced class of multifunctional inorganic nanocarriers used in neurodegenerative research²⁵. When exposed to an external magnetic gradient, these particles can be actively guided through the systemic circulation, forcing localized accumulation within targeted regions of the brain.

Beyond their utility as a highly directed drug delivery platform, SPIONs also serve as contrast agents for MRI imaging. This dual capability forms the basis of advanced "theranostic" platforms, allowing clinicians to simultaneously treat neurodegeneration and visually monitor real-time clearance of amyloid burden or disease progression within a single clinical procedure²⁹.

Nanotechnology for Co-Delivery of Herbal and Synthetic Drugs

The ultimate integration of nanotechnology into Alzheimer's medicine lies in its ability to manage multi-drug delivery. Because Alzheimer's is a complex disease driven by multiple parallel pathologies, single-target therapies are fundamentally limited. Nanocarriers resolve this by acting as unified transport hubs capable of simultaneously encapsulating distinct herbal and synthetic compounds within a single, target-specific vector²⁸.

This coordinated delivery ensures that complementary mechanisms -such as curcumin's anti-inflammatory action paired with memantine's NMDA-receptor blockade - reach the brain together in precise, synergistic ratios. By stabilizing both payloads, maximizing blood-brain barrier crossing, and concentrating the active ingredients at the degenerative site, combination nanomedicines achieve superior clinical outcomes at significantly reduced doses²⁹.

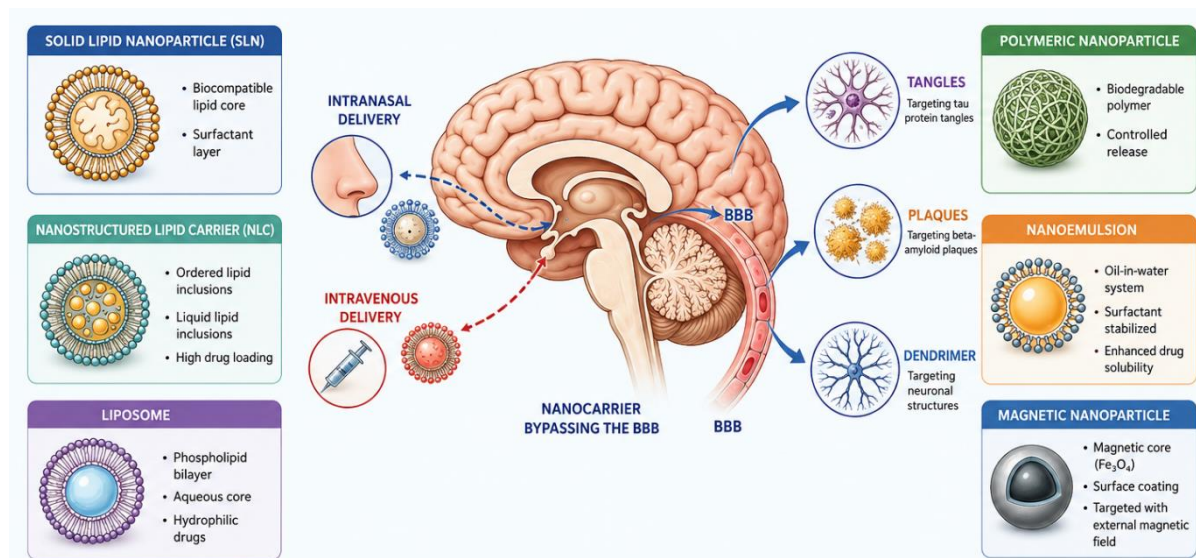


Figure 2: various nanotechnology-based drug delivery systems for AD showcase the mechanisms by which different nanocarriers can bypass physiological barriers

MECHANISMS OF SYNERGISTIC NEUROPROTECTION

Synergistic neuroprotection has gained attention as a promising therapeutic direction for Alzheimer's disease (AD), largely because it can act on several disease pathways at once rather than just one. Conventional monotherapies tend to focus on a single target, but pairing herbal bioactive compounds with synthetic drugs brings together complementary mechanisms of action, an approach that appears to improve therapeutic efficacy and offer broader protection for neurons³⁰.

Acting on Multiple Pathways at Once

Synthetic drugs such as donepezil, rivastigmine, galantamine, and memantine work mainly by improving neurotransmission and limiting excitotoxicity. Herbal compounds, by contrast, including curcumin, resveratrol, quercetin, EGCG, and bacosides, bring a different set of properties to the table: antioxidant, anti-inflammatory, anti-amyloidogenic, and neuroprotective effects. Used together, these two classes of agents allow several disease pathways to be addressed at the same time, something neither approach achieves as effectively on its own^{29,30}.

Countering Oxidative Damage

Oxidative stress is a key contributor to neuronal degeneration, causing damage to lipids, proteins, and DNA. Polyphenolic compounds such as curcumin, quercetin, resveratrol, and EGCG counteract this damage by neutralizing reactive oxygen species (ROS) and reinforcing the body's natural antioxidant defenses, thereby protecting neurons from oxidative injury^{31,32}.

Suppressing Neuroinflammation

In Alzheimer's disease, microglia and astrocytes remain in a persistently activated state, sustaining chronic neuroinflammation. Herbal bioactives can dampen this response by inhibiting inflammatory mediators such as TNF- α , IL-1 β , and IL-6, largely through their effects on signaling pathways like NF- κ B. This lead to reduced neuronal damage and better-preserved cognitive function^{32,33}.

Inhibiting Amyloid-Beta and Tau Pathology

number of phytochemicals have shown the ability to limit amyloid-beta aggregation, support plaque clearance, and reduce the hyperphosphorylation of tau. Curcumin, EGCG, and resveratrol stand out in particular for their effectiveness in modulating these hallmark pathological features, which in turn appears to slow disease progression^{5,32}.

Protecting Mitochondrial Function

Mitochondrial dysfunction is closely tied to impaired energy metabolism and neuronal apoptosis in Alzheimer's disease. Resveratrol, curcumin, and quercetin help preserve mitochondrial integrity, support ATP production, and reduce oxidative stress, collectively improving the odds of neuronal survival^{32,33}.

Supporting Neurotransmission

While synthetic drugs work to improve cholinergic and glutamatergic neurotransmission, herbal compounds such as *Bacopa monnieri* offer complementary support by enhancing cholinergic signaling and protecting synapses. Together, these effects contribute to better memory and overall cognitive performance³⁴.

Preventing Neuronal Apoptosis

Oxidative stress, inflammation, and mitochondrial dysfunction all eventually converge on the same outcome: neuronal apoptosis. Phytochemicals such as curcumin, resveratrol, and quercetin help regulate the apoptotic pathways involved, boosting cell survival proteins while suppressing pro-apoptotic mediators, and in doing so help preserve neuronal integrity³⁴.

Enhancing Delivery Through Nanotechnology

Nanotechnology-based delivery systems add another layer of benefit to this synergistic approach, improving drug stability, bioavailability, and the ability to cross the blood-brain barrier. Nanocarriers such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and polymeric nanoparticles enable co-deliver herbal and synthetic agents together, ensuring they reach the brain in a targeted way and maximizing their combined therapeutic effect³⁵.

RECENT ADVANCES

The therapeutic landscape for Alzheimer's disease (AD) is undergoing a significant shift away from purely symptomatic treatment toward genuine disease-modifying approaches. Driven by a deeper understanding of the disease's interconnected cellular pathology, modern research focuses on multi-targeted strategies. The most significant trend in this evolution is the integration of herbal bioactives and synthetic pharmaceuticals into sophisticated, nano-scale delivery systems, establishing a comprehensive and multi-layered approach to neuroprotection³⁶.

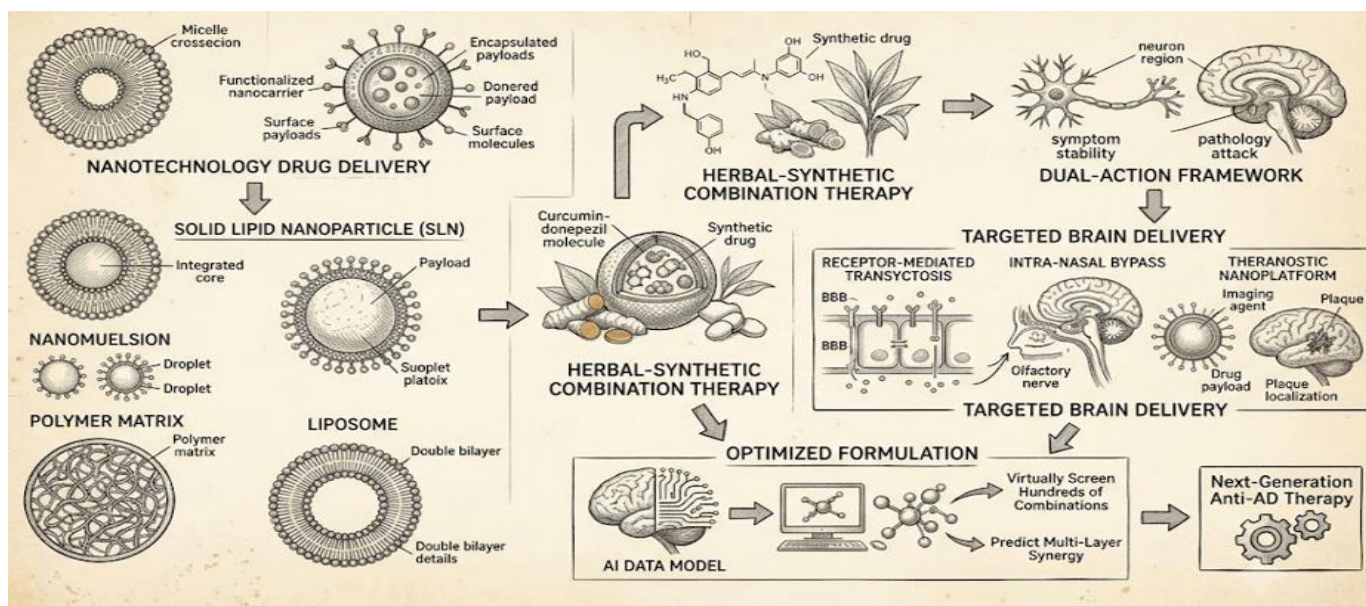


Figure 3: Recent Advances in AD Therapy

Multifunctional Nanoformulations

The development of engineered, multifunctional nanoformulations represents a breakthrough in overcoming the historical pharmacokinetic limitations of anti-Alzheimer's compounds. Advanced nanocarriers -such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, polymeric matrices, and nanoemulsions-have effectively addressed the issues of poor aqueous solubility, rapid systemic clearance, and metabolic breakdown. Beyond shielding these delicate payloads from early

degradation, these biocompatible vehicles offer precise, controlled-release kinetics and dramatically improve localization within the brain parenchyma^{36,37}.

Synchronized Co-Delivery of Phytochemicals and Synthetic Drugs

A major milestone in recent neuro-pharmacology is the synchronized encapsulation of both botanical extractives and conventional synthetic drugs within a single nanovector. This dual-action framework exploits true therapeutic synergy by simultaneously attacking parallel paths of neurodegeneration. For example, co-loading curcumin alongside memantine or donepezil creates a highly effective metabolic shield: the curcumin aggressively suppresses background neuroinflammation and oxidative stress, while the synthetic agent stabilizes synaptic neurotransmission³. Similar therapeutic success has been achieved preclinically using nano-vehicles loaded with resveratrol, quercetin, and EGCG, yielding superior cognitive rescue compared to single-drug treatments³⁷.

Surface Engineering and Targeted Nanomedicine

Advances in surface chemistry have significantly improved the targeting precision of these nano-vehicles. By decorating the outer corona of nanoparticles with specific ligands, homing peptides, monoclonal antibodies, or receptor-targeting molecules, researchers can exploit receptor-mediated endocytosis to actively ferry therapeutic payloads across the blood-brain barrier (BBB). This active targeting maximizes drug accumulation at the neurodegenerative site while keeping systemic exposure low, successfully protecting peripheral tissues from dose-limiting toxicities^{37,38}.

Intranasal Delivery: Bypassing the Blood-Brain Barrier

The development of the intranasal delivery route represents a major practical advance in neuro-therapeutics. This non-invasive, nose-to-brain channel utilizes the olfactory and trigeminal nerve pathways to deliver drugs directly into the central nervous system, bypassing the blood-brain barrier entirely. Intranasal nanoemulsions and polymeric nanoparticles carrying both botanical bioactives and synthetic drugs have demonstrated rapid cerebral uptake and high bioavailability, completely avoiding first-pass hepatic metabolism and systemic degradation³⁷.

Theranostic Nanoplatfroms

The development of smart "theranostic" nanoplatfroms marks a major step forward, merging diagnostic imaging and targeted therapeutics into a single colloidal vehicle. These highly integrated systems carry both a therapeutic payload and a contrast agent (such as superparamagnetic iron oxide nanoparticles), allowing clinicians to locate amyloid-beta plaques early, monitor real-time treatment response, and deliver targeted therapies simultaneously. This dual-action capability serves as a foundational tool for early clinical intervention and highly personalized medicine^{38,39}.

Computational Design and Artificial Intelligence

The pace of drug discovery and formulation optimization has been greatly accelerated by the integration of artificial intelligence (AI), machine learning algorithms, and computational molecular docking³⁹. These digital toolkits allow researchers to predict drug-target interactions, model how nanocarriers behave across biological membranes, and virtually screen hundreds of herbal-synthetic combinations to find the most effective synergistic ratios. This computational foresight minimizes experimental trial-and-error and fast-tracks the optimization of next-generation nanomedicines.

CHALLENGES AND LIMITATIONS

As compelling as the rationale for hybrid herbal-synthetic regimens and their nanoformulations may be, a number of translational barriers still stand between these systems and routine clinical use. Alzheimer's disease itself adds to the difficulty: it is a highly heterogeneous, multifactorial condition, and patients differ considerably in genetic background, rate of cognitive decline, and how they respond to treatment. This patient-to-patient heterogeneity makes it challenging to obtain uniform, replicable outcomes across broad patient populations^{40,41,42}.

Standardization and Pharmacokinetic Bottlenecks

A major obstacle to the clinical adoption of botanical medicine is the lack of strict molecular standardization. The concentration and composition of active phytochemical fractions can vary considerably depending on the plant species used, growing conditions, harvest timing, and extraction methods⁴². This kind of chemical inconsistency makes batch-to-batch reproducibility difficult to guarantee, which in turn complicates the quality-control standards needed for manufacturing at scale.

On top of that, raw herbal bioactives tend to have genuinely unfavorable baseline pharmacokinetics. Compounds such as curcumin, resveratrol, quercetin, and EGCG are poorly soluble in water, are broken down quickly during first-pass metabolism in the liver, achieve low systemic bioavailability, and cross the tightly regulated blood-brain barrier (BBB) only to a limited extent. In practice, this means conventional oral delivery is largely insufficient for getting these compounds where they need to go^{41,42}.

Nanoformulation Liabilities and Toxicological Profiles

Engineered nanocarriers offer an effective way to overcome many of these delivery challenges, yet they introduce their own technical and biological considerations. Questions around the long-term safety, material toxicity, biodistribution, and tissue accumulation of these structural nanocarriers remain under active investigation⁴². Repeated exposure to certain nanomaterials can provoke unwanted immune responses or localized cellular stress, and manufacturing these advanced nanomedicines at scale is itself a challenge, limited by the cost of complex synthesis, fragile long-term colloidal stability, and a demanding regulatory approval process.

Herb-Drug Interactions and Preclinical Gaps

When multiple therapeutic agents are combined, the possibility of herb–drug interactions becomes a real clinical safety concern. Botanical extracts and synthetic pharmaceuticals frequently compete for the same cytochrome P450 enzymes and efflux transporters, so thorough pharmacodynamic and pharmacokinetic profiling is necessary to rule out toxic accumulation or one agent blunting the effect of another⁴³.

It's also worth being candid about where the evidence currently stands. While preclinical laboratory and animal studies have shown promising results, relatively few rigorous, double-blind clinical trials have evaluated herbal–synthetic nanoformulations specifically in Alzheimer's disease patient populations. Solid human clinical evidence is still needed to confirm long-term safety, demonstrate real therapeutic advantages, and establish disease-modifying outcomes beyond what conventional monotherapies already provide^{44,45}.

FUTURE PERSPECTIVES

The direction of Alzheimer's therapeutics is shifting away from older, purely symptomatic treatments toward strategies that are more layered, more personalized, and more genuinely disease-modifying. Since AD pathology behaves as an interconnected network of cellular damage rather than a single faulty pathway, next-generation therapies will likely need to reflect this same complexity, acting on multiple upstream and downstream targets at once⁴⁶.

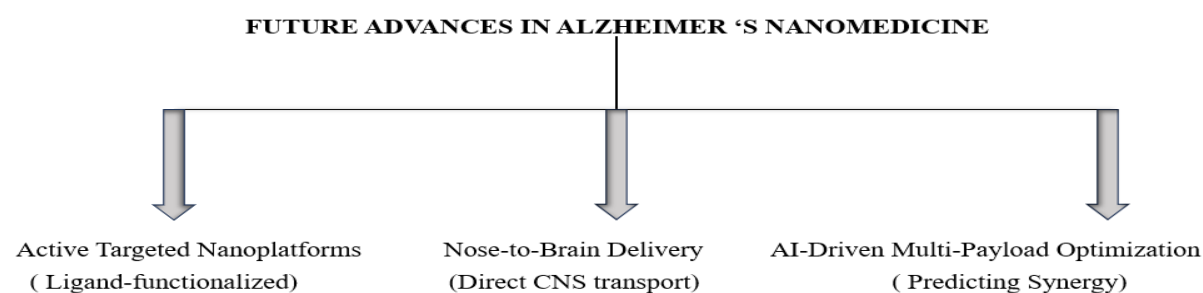


Figure 4: Future advances in Alzheimer's nanomedicine

Next-Generation Bio-Responsive and Targeted Nanocarriers

Drug delivery platforms are expected to become considerably more sophisticated in their surface design. Upcoming systems are likely to incorporate biomimetic coatings, ligand-based targeting molecules such as transferrin or lactoferrin, and structural matrices that respond to specific stimuli, releasing their payload only when triggered by local pathological signals such as oxidative stress or shifts in pH⁴⁷. This kind of precision would allow more drug to reach degenerated brain tissue while sparing peripheral organs from unnecessary, off-target exposure.

Non-Invasive Nose-to-Brain Delivery

Validating intranasal delivery in the clinic is a major translational priority. By using the olfactory and trigeminal nerve pathways, intranasal nanoformulations offer a direct, non-invasive route into the central nervous system^{47,48}. This approach bypasses the blood-brain barrier entirely and avoids hepatic clearance, which could substantially improve the absolute bioavailability of fragile herbal-synthetic compounds that would otherwise be lost through conventional administration⁴⁸.

Precision Medicine, Multi-Omics, and Artificial Intelligence

Bringing together artificial intelligence, deep learning, and multi-omics data, spanning genomics, proteomics, and metabolomics, has the potential to transform how combination therapies are designed. Machine learning models can analyse through enormous digital libraries to identify herbal-synthetic ratios likely to produce genuine synergy for a given patient's molecular profile.

None of this happens in isolation, though. Turning these laboratory advances into scalable, real-world treatment options will require large, collaborative clinical trials that bring together neuroscientists, clinical trialists, and regulatory agencies working toward the same goal^{48,49,50}.

CONCLUSION

Alzheimer's disease remains one of the most persistent public health challenges of our time, placing an enormous clinical, financial, and emotional burden on healthcare systems worldwide. Its pathology progresses along several parallel tracks - amyloid accumulation, tau hyperphosphorylation, neuroinflammation, oxidative damage, and bioenergetic collapse, which goes a long way toward explaining why conventional, single-target synthetic drugs tend to offer only modest, temporary symptomatic relief.

Pleiotropic herbal compounds bring broad, far-reaching neuroprotective and anti-inflammatory effects to the table, while conventional synthetic drugs remain essential for the more immediate work of controlling neurotransmitter kinetics and limiting excitotoxicity. Bringing these two complementary toolkits together into a single therapeutic framework creates a genuine pharmacological synergy, one capable of stabilizing acute symptoms while also protecting neuronal health over the longer term.

When delivered through advanced, surface-functionalized nanocarriers - such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and polymeric matrices- this hybrid strategy can help resolve many long- standing pharmacokinetic obstacles, particularly poor water solubility and restricted blood-brain barrier transport. Technological scale-up and regulatory hurdles still need to be worked through, but the convergence of botanical medicine, synthetic chemistry, and nanomedicine offers a genuinely promising blueprint for the next generation of disease-modifying therapies in Alzheimer's care.

REFERENCES

1. Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-821.
2. Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*. 2018;25(1):59-70.
3. Knopman DS, Amieva H, Petersen RC, Ch  telat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. *Nat Rev Dis Primers*. 2021;7(1):33.
4. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362(4):329-44.
5. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8(6):595-608.
6. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*. 2019;14(1):32.
7. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease. *Molecules*. 2020;25(24):5789.
8. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2024. *Alzheimers Dement (N Y)*. 2024;10(1):12465.
9. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid- pathway in Alzheimer's disease. *Mol Psychiatry*. 2021;26(10):5481-503.
10. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. *Cell*. 2019;179(2):312-39.
11. Saraiva C, Pra  a C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery. *J Control Release*. 2016; 235:34-47.
12. Teleanu DM, Chircov C, Grumezescu AM, Teleanu RI. Neurotoxicity of nanomaterials and nanomedicine. *Nanomaterials*. 2019;9(1):96.
13. Patel T, Zhou J, Piepmeier JM, Saltzman WM. Polymeric nanoparticles for drug delivery to the CNS. *Adv Drug Deliv Rev*. 2012;64(7):701-5.
14. Tapeinos C, Pandit A. Physical, chemical, and biological structures based on nanomaterials for Alzheimer's disease. *Adv Mater*. 2016;28(27):5553-85.
15. Karthivashan G, Park SY, Kweon MH, Kim J, Haque ME, Cho DY, et al. Ameliorative potential of nanotechnology in Alzheimer's disease. *Int J Nanomedicine*. 2018; 13:557-76.
16. Rajinikanth PS, Chellian J. Nanotechnology in Alzheimer's disease management. *Int J Nanomedicine*. 2021;16:1317-45.
17. Pardridge WM. Drug transport across the blood-brain barrier. *J Cereb Blood Flow Metab*. 2012;32(11):1959-72.
18. Savelieff MG, Nam G, Kang J, Lee HJ, Lee M, Lim MH. Development of multifunctional therapeutic agents for Alzheimer's disease. *Chem Rev*. 2019;119(2):1221-322.

19. Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Patel RJ, et al. Nose-to-brain drug delivery. *Drug Discov Today*. 2018;23(5):891-907.
20. Illum L. Nasal drug delivery—possibilities, problems and solutions. *J Control Release*. 2003;87(1-3):187-98.
21. Bhattamisra SK, Shak AT, Xi LW, Safian NH, Choudhury H, Lim WM, et al. Nose-to-brain delivery of nanoparticles. *Pharmaceutics*. 2020;12(12):1235.
22. Howes MJ, Perry NS, Houghton PJ. Plants with traditional uses and activities relevant to Alzheimer's disease. *Phytother Res*. 2003;17(1):1-18.
23. Ahmed T, Gilani AH. Therapeutic potential of turmeric in Alzheimer's disease. *Phytother Res*. 2014;28(4):517-25.
24. Mishra S, Palanivelu K. The effect of curcumin on Alzheimer's disease. *Ann Indian Acad Neurol*. 2008;11(1):13-19.
25. Cox KH, Pipingas A, Scholey AB. Investigation of curcumin for Alzheimer's disease. *J Psychopharmacol*. 2015;29(7):642-51.
26. Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, et al. Oral curcumin for Alzheimer's disease. *J Alzheimers Dis*. 2012;31(1):1-12.
27. Voulgaropoulou SD, van Amelsvoort TA, Prickaerts J, Vingerhoets C. Preventive and therapeutic effects of resveratrol in Alzheimer's disease. *Nutrients*. 2019;11(9):2169.
28. Pasinetti GM. Novel role of red wine-derived polyphenols in Alzheimer's disease. *Eur J Pharmacol*. 2012;668: S43-S48.
29. Bastianetto S, Quirion R. Natural extracts as possible treatments for Alzheimer's disease. *Mini Rev Med Chem*. 2002;2(5):485-506.
30. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and treatment. *Pharmacol Rep*. 2015;67(2):195-203.
31. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin. *Mol Pharm*. 2007;4(6):807-18.
32. Tiwari SK, Agarwal S, Seth B, Yadav A, Nair S, Bhatnagar P, et al. Curcumin-loaded nanoparticles and neuroprotection. *ACS Chem Neurosci*. 2014;5(9):890-902.
33. Mathew A, Fukuda T, Nagaoka Y, Hasumura T, Morimoto H, Yoshida Y, et al. Curcumin-loaded PLGA nanoparticles. *Biomaterials*. 2012;33(15):3842-53.
34. Maiti P, Dunbar GL. Use of curcumin and nanocurcumin in neurodegenerative diseases. *Int J Mol Sci*. 2018;19(8):2180.
35. Kakkar V, Kaur IP. Evaluating nose-to-brain delivery of curcumin. *Drug Deliv*. 2011;18(1):65-72.
36. Cummings JL. Use of cholinesterase inhibitors in Alzheimer's disease. *J Clin Psychiatry*. 2003;64(Suppl 9):3-7.
37. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2004;350(13):1333-41.
38. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348(14):1333-41.
39. Shalaby KS, Soliman ME. Memantine-loaded nanoparticles for brain targeting. *Drug Dev Ind Pharm*. 2020;46(6):947-58.
40. Agrawal M, Saraf S, Saraf S, Antimisariis SG, Chougule MB, Shoyele SA, et al. Nose-to-brain delivery of memantine. *Drug Deliv Transl Res*. 2021;11(4):1355-81.
41. Tapeinos C, Larrañaga A, Sarasua JR, Pandit A. Functionalized nanoparticles for neurodegenerative disorders. *Biomaterials*. 2017;121:172-88.
42. Gulyaev AE, Gelperina SE, Skidan IN, Antropov AS, Kivman GY, Kreuter J. Brain targeting using polysorbate-coated nanoparticles. *Pharm Res*. 1999;16(10):1564-69.
43. Wilson B, Samanta MK, Muthu MS, Vinothapooshan G, Suresh B. Chitosan nanoparticles as drug carriers for Alzheimer's disease. *Int J Biol Macromol*. 2010;46(2):258-62.
44. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain delivery. *J Control Release*. 2008;127(2):97-109.

45. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles for controlled drug delivery. *Eur J Pharm Biopharm.* 2000;50(1):161-77.
46. Beloqui A, Solinís MA, Rodríguez-Gascón A, Almeida AJ, Prést V. Nanostructured lipid carriers in drug delivery. *Nanomedicine.* 2016;12(1):143-61.
47. Youssef A, Salem HF, Hassan NH, Awad GA. Intranasal lipid nanoparticles for brain targeting. *Drug Deliv.* 2019;26(1):645-58.
48. Tiwari V, Patel AB, Tiwari M. Nanotechnology-based approaches in Alzheimer's disease therapy. *J Drug Target.* 2020;28(6):597-614.
49. Sharma S, Singh N, Kakkar V. Nanotechnology-mediated combinational therapy for Alzheimer's disease. *Drug Discov Today.* 2022;27(4):1034-48.
50. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress and Alzheimer's disease: role of natural and synthetic therapeutics. *Antioxidants.* 2019;8(12):626.

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