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NOVEL DRUG DELIVERY SYSTEM: A PANDORA BOX FOR THE MANAGE MENT OF ALZHEIMER NOVEL DRUG DELIVERY IN ALZHEIMER

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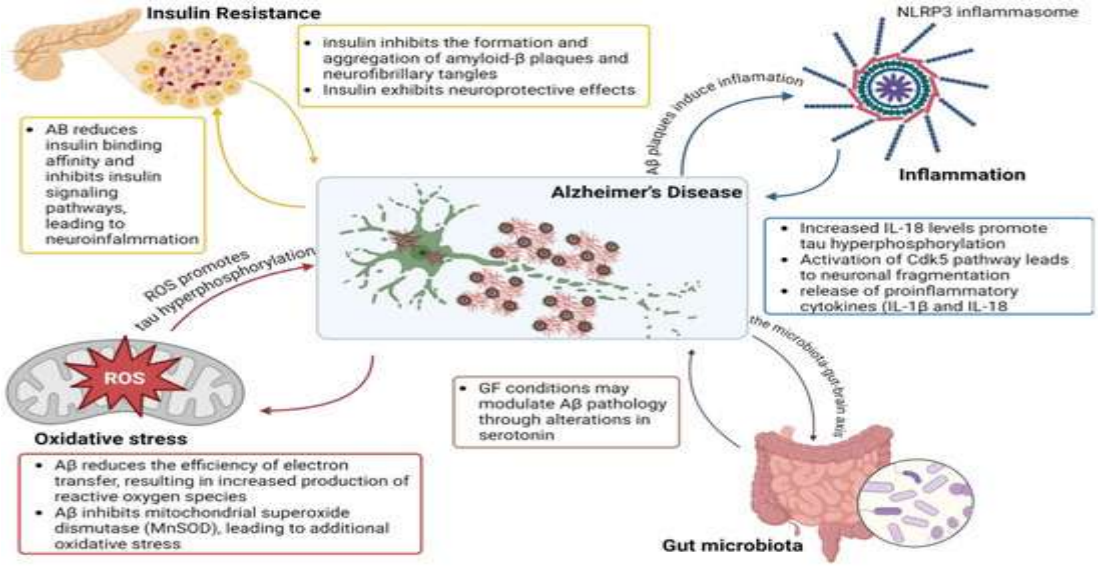
GRAPHICAL ABSTRACT



ABSTRACT

One of the biggest health issues of the twenty-first century is Alzheimer's disease (AD), which is the most prevalent cause of dementia. With an estimated 40 million affected worldwide, the number is expected to increase significantly as the population ages, resulting in significant medical, social, and financial problems. Common neuropathological alterations that contribute to cognitive decline and functional impairment include amyloid-β (Aβ) plaque accumulation, neurofibrillary tangles made of hyperphosphorylated tau protein, synaptic dysfunction, and progressive neuronal loss. The exact cause of AD is still unknown despite decades of research, involving a complex interaction of lifestyle, environmental, and genetic factors. The chance of developing the condition is greatly increased by the apolipoprotein E (APOE) ε4 allele, mutations in APP, PSEN1, and PSEN2, and modifiable variables such cardiovascular diseases, traumatic brain injury, and lifestyle choices. Memantine, an NMDA receptor antagonist, and cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are examples of current pharmaceutical treatments that provide symptomatic relief without changing the course of the disease. Disease-modifying monoclonal antibodies that target Aβ, such as aducanumab and lecanemab, have recently raised cautious optimism, despite ongoing concerns about accessibility, safety, and efficacy. The need for a better understanding of AD pathophysiology and the conversion of basic science into useful clinical interventions is underscored by the growing emphasis on novel therapeutic approaches, such as gene-based interventions, neuroprotective approaches, and lifestyle changes. This review highlights new avenues for therapy development while giving a broad overview of the genesis, pathophysiology, and current therapeutic landscape of AD.

KEYWORDS: Alzheimer's disease; Etiology; Pathophysiology and therapeutic strategies

INTRODUCTION

One of the most serious health issues of the twenty-first century is Alzheimer's disease (AD), which is the primary cause of dementia. It is predicted that 40 million people worldwide suffer from dementia, and due in major part to population aging and longer life expectancies, this figure is expected to triple by 2050.1. The prevalence and impact of AD will increase significantly as countries around the world move toward older demographic profiles, as most dementia cases involve those over 60. This has serious social, emotional, and financial ramifications for patients, families, and caregivers in addition to endangering healthcare systems. Amyloid-β (Aβ) plaques build up extracellularly, hyperphosphorylated tau aggregates in neurons to form neurofibrillary tangles (NFTs), chronic neuroinflammation, oxidative stress, synaptic dysfunction, and progressive neuronal death are some of the pathological hallmarks of AD. Alterations decrease synaptic plasticity, interfere with neuronal communication, and cause widespread brain atrophy, especially in the cortex and hippocampus. These pathological changes show up clinically as gradual memory loss, executive dysfunction, disorientation, impaired judgment, and ultimately loss of independence, which in the latter stages leads to complete dependence on caregivers. Even after decades of study, the etiology of AD is still complex and poorly understood. The APOE ε4 allele and genetic variables such mutations in the APP, PSEN1, and PSEN2 genes are closely linked to both familial and sporadic types of AD. Disease risk is also influenced by environmental and lifestyle factors, such as food, physical inactivity, diabetes, obesity, head trauma, and cardiovascular health. Since AD is becoming more widely acknowledged as a complex and diverse disorder, the interaction of various factors makes the development of treatments more difficult. The majority of the current treatments are symptomatic rather than therapeutic. Cholinesterase inhibitors, such as galantamine, rivastigmine, and donepezil, boost cholinergic neurotransmission and offer slight enhancements in everyday functioning and cognition. Memantine, an NMDA receptor antagonist, provides a limited but additional therapeutic benefit by lowering excitotoxicity linked to glutamate dysregulation. The effectiveness of these medications decreases with time, and while they may momentarily reduce symptoms, they do not stop or reverse the course of the disease.

There is cautious optimism because to recent developments in disease-modifying treatments (DMTs). Amyloid-β-targeting monoclonal antibodies, such aducanumab and lecanemab, offer a novel therapeutic approach by directly treating the pathological features of AD. Their therapeutic effectiveness is still debatable, nevertheless, due to a number of factors, including uneven trial results, safety issues (such as anomalies in imaging caused by amyloid), and high cost. In light of the anticipated rise in the frequency of AD, current research is investigating novel approaches such as gene-based treatments, neuroprotective medicines, anti-tau therapy, lifestyle modifications, and sophisticated drug delivery systems. For solutions to be successful, scalable, and long-lasting, it is essential to close the gap between fundamental molecular understanding and clinical application.2,3 In the end, advancing AD care will require combining disease-modifying therapies with patient-specific supportive and preventative strategies.

Etiology of Alzheimer's Disease

A complex interaction of biological, environmental, and genetic risk factors contributes to the etiology of Alzheimer's disease (AD), a multifactorial neurodegenerative illness. After the age of 65, the prevalence of AD increases exponentially, making aging the strongest non-modifiable risk factor. Particularly in familial early-onset AD, where mutations in the amyloid precursor protein (APP) gene as well as the presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes cause aberrant processing of amyloid-β (Aβ) and early plaque deposition, genetic impacts are significant. The apolipoprotein E (APOE) ε4 allele is the most important genetic risk factor for sporadic late-onset AD because it is linked to decreased Aβ clearance and increased Aβ aggregation.[5] In addition to genetics, genome-wide association studies (GWAS) have discovered other susceptibility genes like TREM2, PICALM, and CLU, which emphasize the part that immunological response, synaptic function, and lipid metabolism play in the etiology of disease.[8] Lifestyle and environmental factors also have a major role in disease risk. AD has been associated with metabolic and cardiovascular disorders, including as diabetes, obesity, hypertension, and hyperlipidemia, through pathways involving reduced cerebral perfusion and vascular damage.

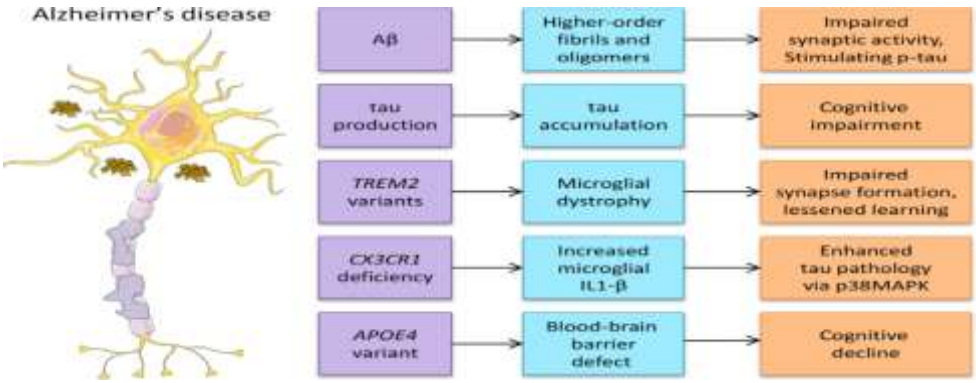


Figure .1: Genetic and Environmental factors in Alzheimer

Other factors include smoking, long-term alcohol consumption, traumatic brain damage, and exposure to environmental pollutants. Lifestyle factors that promote susceptibility include poor food, sedentary activity, and a lack of social or cognitive interaction. Women have a higher prevalence of AD, probably as a result of post-menopausal estrogen reduction.

Sex and hormonal state also affect risk. When taken as a whole, these elements imply that AD arises from a complex etiology in which genes and modifiable risk factors combine to cause neurodegeneration.[6,7]

Pathophysiology of Alzheimer's Disease

Understanding the pathogenesis of AD has long been dominated by its primary pathological characteristics, which include neurofibrillary tangles of hyperphosphorylated tau protein and amyloid-β plaques. According to the amyloid cascade hypothesis, misfolded Aβ peptides produced by abnormal cleavage of amyloid precursor protein (APP) collect extracellularly as plaques, interfering with synaptic communication and triggering inflammation. Concurrently, tau proteins experience hyperphosphorylation, which disrupts microtubules, creates intracellular tangles, hinders neuronal transport, and disperses disease over different areas.

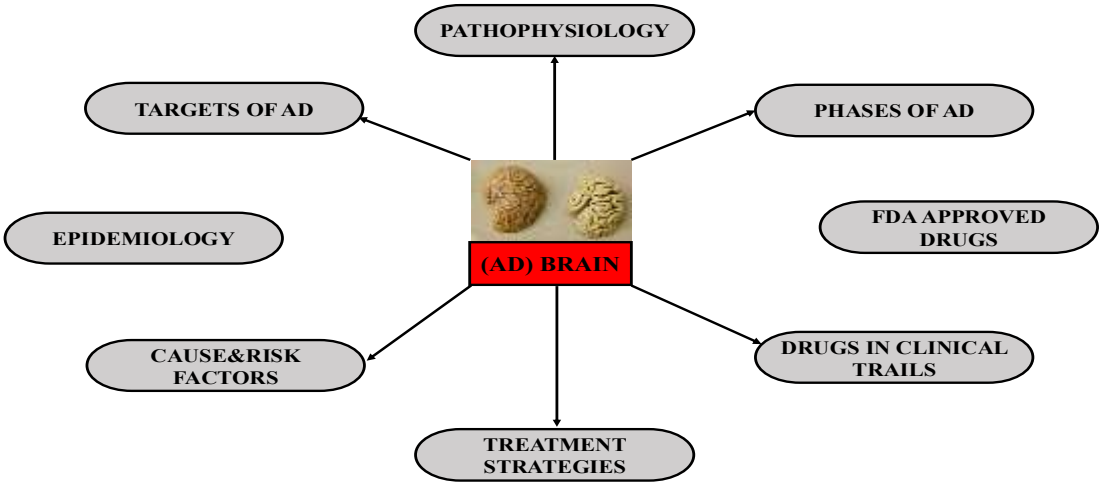


Figure 2: Pathophysiology Diagram Representation

It is becoming more well accepted that neuroinflammation is a major factor: When activated microglia and astrocytes are unable to effectively remove Aβ, they release inflammatory cytokines such IL-1β, which further compromises synaptic integrity. At the same time, oxidative stress and mitochondrial malfunction cause reactive oxygen species buildup, which damages neurons and results in energy deficiencies. Progression is further aggravated by vascular dysfunction, which includes impaired amyloid clearance and blood–brain barrier damage.[7-9] A multi-mechanistic paradigm that goes beyond amyloid and tau alone is supported by new data. According to AI-integrated evaluations, metabolic collapse, mitochondrial failure, and neuroinflammation may combine to form a single model of AD progression. Additional pathways highlighted include neuronal death and ion-channel disruptions brought on by Aβ-induced membrane disturbances, as well as epigenetic changes that interfere with synaptic plasticity and neurogenesis, such as BDNF repression and microRNA dysregulation.[10]

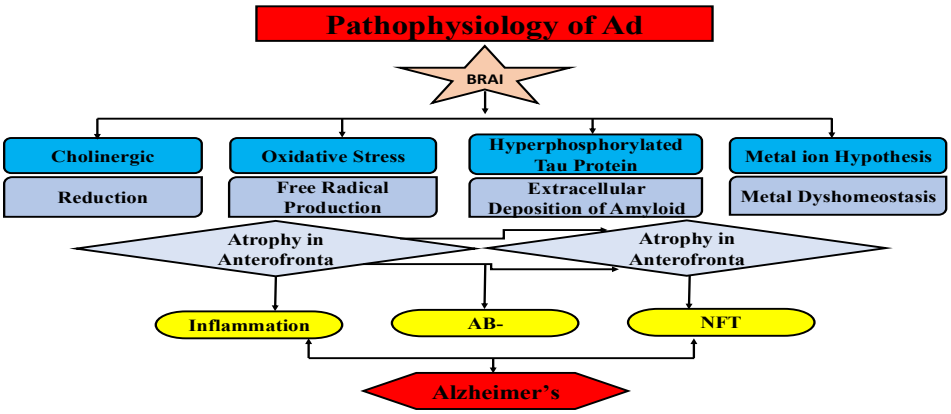


Figure 3: Diagrammatic Explanation (Pathophysiology)

Conventional Treatments available

Memory loss, cognitive decline, and behavioral abnormalities are hallmarks of Alzheimer's disease (AD), a progressive neurological illness. Most of the medicines that are now on the market are symptomatic rather than disease-modifying, despite tremendous advancements in research. These treatments do not correct or stop the underlying pathology of amyloid-beta accumulation, tau hyperphosphorylation, and neurodegeneration; instead, they aim to improve quality of

life, reduce cognitive and behavioral symptoms, and momentarily slow the progression of the disease. Cholinesterase inhibitors, which include donepezil, rivastigmine, and galantamine, are the most often utilized class of medications in the treatment of AD. Agents function by preventing the breakdown of acetylcholine, a neurotransmitter essential for memory and learning, by the enzyme acetylcholinesterase. These medications boost cholinergic neurotransmission and cognitive processes like memory and attention by raising acetylcholine levels in the synaptic cleft. They have a limited effectiveness, though, and are linked to adverse effects like bradycardia, diarrhea, vomiting, and nausea.

Memantine, an NMDA (N-methyl-D-aspartate) receptor antagonist, is another significant medication. Memantine prevents excitotoxicity, which is a contributing factor to neuronal damage in AD, by controlling glutamatergic neurotransmission. For moderate-to-severe AD, memantine is typically given. It can be used either by itself or in conjunction with cholinesterase inhibitors for further advantages. The behavioral and psychological symptoms of dementia (BPSD), such as agitation, sadness, anxiety, sleeplessness, and psychosis, are frequently managed using adjunct therapies in addition to these basic medications. Sometimes doctors will prescribe antidepressants such selective serotonin reuptake inhibitors (SSRIs), antipsychotics, and anxiolytics, but these should be used carefully because of the possible side effects, especially in older patients. Drug therapy is essential for symptom management, but so are non-pharmacological approaches such cognitive therapy, lifestyle changes, and caregiver support. These traditional therapies have a lot of drawbacks even though they provide symptomatic relief. do not alter the biological progression of the illness, and their advantages are usually fleeting, ranging from a few months to several years. Furthermore, tolerability problems frequently prevent prolonged use. Current treatments for AD, which primarily consist of memantine and cholinesterase inhibitors, concentrate on managing symptoms rather than treating the underlying causes of neurodegeneration. function to improve neurotransmission, stabilize cognitive function, and manage behavioral problems, all of which contribute to increased patient autonomy and quality of life. The dearth of truly disease-modifying drugs highlights the pressing need for innovative therapeutic approaches, which are currently being investigated in research. These include gene therapy, immunotherapy, and drug delivery systems based on nanotechnology.

Common treatments for Alzheimer's disease (AD) are included in this Table No. 1 with the proper justification.[10-16]

Table No. 1 Common treatments for AD

Drug/Class	Mechanism of Action	Clinical Use & Benefits	Limitations / Side Effects
Cholinesterase Inhibitors (Donepezil, Rivastigmine, Galantamine)	Inhibit acetylcholinesterase → increase acetylcholine levels in synaptic cleft → enhance cholinergic transmission.	First treatment for mild to moderate AD. Enhance daily functioning, memory, and cognition; some patients see a gradual decrease.	GI upset (nausea, vomiting, diarrhea), bradycardia, insomnia, dizziness.[10]
NMDA Receptor Antagonist (Memantine)	Blocks excessive glutamate activity at NMDA receptors → prevents excitotoxic neuronal damage.	For mild to severe AD, use this. enhances behavior, cognition, and global functioning. Cholinesterase inhibitors may be used in conjunction with it.[11]	Dizziness, confusion, headache, constipation; limited benefit in early AD.
C**ombination Therapy** (Donepezil + Memantine)	Targets both cholinergic deficit (ACh) and glutamate excitotoxicity (NMDA).	Helps moderate to severe AD in a synergistic or additive way. reduces the stress on caregivers and enhances daily activities.	Costly; side effects similar to individual drugs.[12,13]
Antipsychotics (Risperidone, Olanzapine, Quetiapine)	Dopamine & serotonin receptor antagonism → reduces aggression, agitation, psychosis.	For severe behavioral and psychological dementia symptoms (BPSD), off-label use is utilized.	↑ Risk of stroke, sedation, extrapyramidal symptoms, mortality in elderly.[14]
Antidepressants (SSRIs: Sertraline, Citalopram)	Inhibit serotonin reuptake → enhance serotonergic neurotransmission.	In patients with AD, treat concomitant sadness, anxiety, and irritability.	Nausea, insomnia, sexual dysfunction; QT prolongation (citalopram at high doses).[15]
Benzodiazepines & Hypnotics (Lorazepam, Zolpidem)	Enhance GABA-A receptor activity → anxiolytic, sedative effects.	Reduce agitation, anxiety, and insomnia temporarily.	Cognitive worsening, risk of falls, dependence, tolerance. Not recommended long term.[16]

Limitations of Conventional Treatment.[17-21]

The progressive neurodegenerative disease known as Alzheimer's disease (AD) is typified by behavioral abnormalities, cognitive impairment, and memory loss. Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine are the mainstays of current conventional therapy. These medications are frequently administered, but because they primarily treat symptoms rather than altering the fundamental causes of the condition, their therapeutic usefulness is still limited.

Symptomatic relief only
The main disadvantage of traditional treatment is that current medications cannot stop or reverse the course of the disease. Rather, they improve cholinergic neurotransmission or alter glutamatergic signaling to momentarily reduce symptoms. As a result, patients may experience transient improvement in memory or daily functioning, but neurodegeneration continues unabated. This means that despite treatment, patients ultimately experience cognitive and functional decline over time.

Limited efficacy[18,19]
According to clinical investigations, these drugs only produce slight and transient effects. After starting treatment, cognitive scores could go up a little, but the gains usually wear off in six to twelve months.
Similar limitations apply to everyday activities and independence, which do not significantly change the course of the disease. These medications' low effectiveness is a reflection of their incapacity to address the underlying pathogenic mechanisms of AD.Patient reaction that varies

Variable patient response
The inconsistent patient response is yet another important drawback. While some people exhibit little to no gain, others see discernible changes in their everyday lives and cognitive abilities. This variability makes therapeutic decision-making more difficult and frequently results in non-responders stopping their treatment. Treatment results may vary, which could be explained by the diversity of AD pathology, genetics, and comorbidities.

No disease-modifying effect
Amyloid-β plaques, tau protein tangles, and persistent neuroinflammation are the three main pathological features of AD that are not addressed by the medications that are currently on the market. Regardless of treatment, these processes continue to proceed and are essential to neuronal malfunction and death. Therefore, the underlying neurodegeneration continues unabated even if patients may enjoy symptomatic alleviation.

Short duration of benefit
As the disease progresses, the therapeutic effects diminish, even for those who respond at first. Eventually, the benefit of symptom relief is outweighed by progressive neuronal death, leaving patients in advanced stages with little to no response to treatment. This brief window for treatment emphasizes how urgently disease-modifying measures are needed.

High caregiver and healthcare burden
Families and healthcare institutions confront increasing issues as a result of the decrease persisting even after therapy. Caregivers are under a great deal of emotional, physical, and financial strain as a result of patients' growing needs for supervision, medical appointments, and social assistance. This burden is made worse by the lack of long-term effectiveness.

Behavioral symptom management issues
Additional medication management is frequently necessary for behavioral and psychological symptoms of dementia (BPSD), including agitation, psychosis, depression, and sleep difficulties. However, there are significant hazards associated with these treatments:
1. In older patients, antipsychotics raise the risk of stroke, drowsiness, extrapyramidal symptoms, and possibly death. They are occasionally given to treat severe agitation or psychosis.
2. Benzodiazepines, which are prescribed to treat anxiety and sleep disorders, can exacerbate cognitive impairment, raise the risk of falls, and cause dependence.
3. Antidepressants may help treat depression, but their usefulness is limited by their associations with QT prolongation, nausea, and a delayed onset of therapeutic activity.

Side effects of approved drugs
1. There are noticeable side effects even with the main AD drugs:
2. Bradycardia, sleeplessness, and gastrointestinal side effects such nausea, vomiting, and diarrhea are frequently brought on by cholinesterase inhibitors.
3. Memantine may worsen headaches, constipation, dizziness, and confusion, all of which can lower a patient's quality of life.

Traditional therapies for Alzheimer's disease are still palliative in nature, providing only short-term symptom relief without modifying the course of the illness. Their long-term utility is limited by their moderate efficacy, unpredictable patient response, brief duration of benefit, and severe side effect profile. Furthermore, using adjunct drugs to treat behavioral symptoms frequently raises risks rather than improves results. In order to slow or stop the progression of the disease, new disease-modifying medicines that can target amyloid pathology, tau aggregation, and neuroinflammation are necessary. As a result, the strain on caregivers and healthcare systems continues. [38,39]

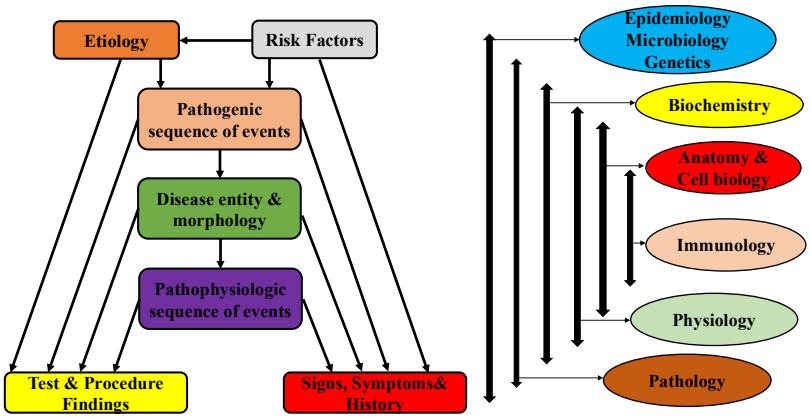


Figure 4: Diagram for Mechanistic approaches of Treatment

Novel Drug Delivery System [41-55]

The blood-brain barrier's (BBB) restrictiveness, which keeps the majority of therapeutic medicines from getting to the brain in pharmacologically meaningful concentrations, presents significant therapy hurdles for Alzheimer's disease (AD). With little effect on the course of the disease, traditional methods, such as the oral and systemic injection of medications like cholinesterase inhibitors and NMDA receptor antagonists, simply provide symptomatic relief. Additionally, these medications have a low absorption, a quick systemic clearance rate, and unfavourable side effects like cardiovascular and gastrointestinal issues. Consequently, novel approaches that improve targeted drug delivery to the central nervous system (CNS) while reducing systemic toxicity are desperately needed. Novel Drug Delivery Systems (NDDS) are being developed to get around these obstacles and enhance AD treatment results. Liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles are examples of nanoparticle-based carriers that have become useful for encapsulating medications, shielding them from enzymatic breakdown, and enabling controlled release. By functionalizing these carriers with ligands like lactoferrin, transferrin, or antibodies, receptor-mediated transcytosis across the blood-brain barrier is made possible, improving delivery to the brain.

Another interesting NDDS strategy is intranasal medication administration. Drugs, peptides, and even gene therapies can more effectively enter the brain through intranasal administration, which circumvents the blood-brain barrier by directly transporting them along the olfactory and trigeminal nerve pathways. For instance, intranasal insulin administration has been proven to improve memory and cognition in AD patients. Stimuli-responsive nanocarriers provide an extra degree of accuracy by releasing their payload in response to alterations in pH, enzyme activity, or redox conditions within sick brain regions. Similar to this, exosome-based delivery systems are becoming more popular due to their biocompatibility and innate capacity to pass the blood-brain barrier, which may make them ideal natural carriers of therapeutic proteins, siRNA, or small compounds. Additional cutting-edge technologies include continuous-release hydrogels and in situ gelling formulations, as well as targeted ultrasound and microbubbles that can safely and temporarily breach the blood-brain barrier to permit medication entry. For targeted disease-modifying therapies, especially against tau and amyloid-beta pathology, gene therapy vectors and monoclonal antibody-conjugated nanocarriers are also being investigated.[21-23]

1. Nanoparticles (NPs)

Endocytosis or receptor-mediated transport are two ways whereby lipid-based and polymeric nanoparticles (PLGA, chitosan) can pass the blood-brain barrier and encapsulate anti-Alzheimer medications. They facilitate targeted delivery, increase medication stability, and extend circulation. For instance, in preclinical settings, rivastigmine-loaded nanoparticles have demonstrated decreased neurotoxicity and enhanced memory.[25]

2. Liposomes and Noisomes

Both lipophilic and hydrophilic medications can be transported by phospholipid vesicles, or liposomes, and non-ionic surfactant vesicles, or niosomes. Using ligands to modify the surface (such as lactoferrin or transferrin) enhances brain targeting. They lower the enzymatic breakdown of medications like donepezil and offer regulated release.[26]

3. Nanostructured Lipid Carriers (NLCs) and Solid Lipid Nanoparticles (SLNs)

These lipid-based carriers offer great stability, biocompatibility, and prolonged drug release by combining the advantages of liposomes and nanoparticles. When compared to oral preparations, memantine intranasal SLNs have demonstrated improved brain absorption.[27]

4. Dendrimers

Drug conjugation is made possible by dendrimers, which are nanoscale, highly branched polymers with many functional groups. They are intriguing candidates for disease-modifying therapy in AD because of their capacity to target amyloid-β plaques and pass the blood-brain barrier.[28]

5. Intranasal Delivery Systems

The intranasal route uses the trigeminal and olfactory pathways to get across the BBB. Intranasal delivery of medications like insulin, neuropeptides, and nanoparticles improves cognitive function in both AD humans and animal models. This method offers quick brain targeting, is non-invasive, and is patient-friendly.[29]

6. Hydrogels and In Situ Gels

For long-term release at the CNS location, hydrogel systems can be supplied with growth factors or neuroprotective medicines. After injection, in situ gels that change from sol to gel improve medication retention and bioavailability.[30,31]

7. Exosomes and Biological Carriers

Natural nanovesicles called exosomes are being investigated as biocompatible siRNA, miRNA, and protein transporters. Their ability to be specifically delivered to neurons and glial cells makes them promising for use in gene and protein-based treatment for AD.[32]

Synthetic drugs in prophylaxis of Alzheimer

By addressing underlying pathogenic pathways, several synthetic medicines have been investigated for their ability to delay or prevent the onset of Alzheimer's disease (AD). Drugs like statins (atorvastatin, simvastatin) have been researched for their capacity to lower cholesterol and enhance cerebral blood flow, which may lessen amyloid deposition, since vascular dysfunction is a significant risk factor for AD. The neuroprotective effects of antihypertensive medications such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, which lessen oxidative stress and cerebrovascular damage, are also being studied. Nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen and naproxen, are part of another family of medications that try to prevent the persistent neuroinflammation that is connected to the advancement of AD. Furthermore, in the prodromal phases of AD, cholinergic medications that improve acetylcholine transmission may offer cognitive support. Even though no synthetic medication has been approved by the government for prophylaxis yet, continuing clinical research continue to point in encouraging directions. A preventive approach for AD may eventually include early management with such medicines, especially in those with high genetic or vascular risk mentioned in Table no. 2.[33-41]

Table No. 2 Preventive approaches for AD

Class / Drug	Mechanism	Prophylactic Potential	Status
Cholinesterase inhibitors (Donepezil, Rivastigmine)	↑ Acetylcholine	May delay progression from MCI to AD	Limited use, not approved for prophylaxis.[33]
NMDA antagonist (Memantine)	↓ Excitotoxicity	Some neuroprotective effects	Supportive therapy
Statins (Simvastatin, Atorvastatin) [34]	↓ Cholesterol, ↓ Aβ deposition	Mixed results; observational support	Not approved
Antihypertensives (ACE inhibitors, ARBs)	Vascular protection	Reduced cognitive decline risk	Clinical evidence growing. [35,36]
Antidiabetics (Metformin, Pioglitazone)	Insulin sensitization	Neuroprotective, ongoing trials.[37]	Investigational
NSAIDs (Ibuprofen, Naproxen) [38-40]	↓ Neuroinflammation	Preventive signal in observational studies	Not recommended
BACE/γ-secretase inhibitors	↓ Aβ formation	Theoretical prevention in high-risk	Mostly failed, some ongoing. [41]

Bioactive compounds in prophylaxis of Alzheimer [58-61]

A variety of naturally occurring bioactive substances have demonstrated promise in postponing or preventing the beginning of Alzheimer's disease (AD), in addition to synthetic treatments. These substances, which are mostly obtained from food, herbs, and medicinal plants, have neuroprotective effects via a variety of pathways, such as antioxidant activity, anti-inflammatory qualities, tau protein stabilization, inhibition of amyloid-beta (Aβ) aggregation, and stimulation of neurogenesis. The capacity of polyphenols like curcumin (found in turmeric), resveratrol (found in grapes and berries), and epigallocatechin gallate (EGCG, found in green tea) to scavenge free radicals, lower neuroinflammation, and alter amyloid pathways has been thoroughly investigated. In preclinical models, flavonoids such as quercetin and kaempferol improve synaptic plasticity and cognitive function in addition to offering antioxidant defense. Alkaloids like huperzine A work as natural acetylcholinesterase inhibitors, maintaining cholinergic function, whereas omega-3 fatty acids, especially docosahexaenoic acid (DHA), improve neuronal membrane integrity and lower inflammatory signals.

By maintaining mitochondrial activity and regulating cellular redox balance, dietary vitamins and minerals such as vitamin E, vitamin D, and selenium also enhance neuroprotection. Clinical research suggests that frequent consumption of these

substances through diet or supplementation may lessen AD risk, making them appealing preventive options, even if the majority of the evidence comes from in vitro and animal studies shown in table no. 3.[60-71]

Table No. 3 Bioactive constituents for AD

Bioactive Compound	Source	Mechanism of Action	Prophylactic Potential
Curcumin	Turmeric (*Curcuma longa*)	Antioxidant, anti-inflammatory; inhibits amyloid-β aggregation & tau phosphorylation; reduces oxidative stress	Shown to reduce amyloid deposition and improve memory in animal models; nanoformulations under human trials. [42,43]
Resveratrol	Grapes, red wine, peanuts	Activates SIRT1, enhances mitochondrial function, reduces amyloid burden and neuroinflammation	Clinical trials suggest slowed cognitive decline in mild AD; long-term dietary intake linked to reduced risk
EGCG (Epigallocatechin gallate)	Green tea	Prevents amyloid fibril formation; antioxidant; enhances synaptic plasticity	Associated with improved cognition in tea drinkers; ongoing clinical studies in MCI
Quercetin	Onions, apples, berries	Free radical scavenger; inhibits β-amyloid fibrillization; reduces neuroinflammation via NF-κB inhibition	Preclinical studies show cognitive enhancement; nanoparticle formulations improve bioavailability
Ginsenosides	Panax ginseng	Neurogenesis, antioxidant defense, regulate amyloid/tau pathology	Long-term use linked to reduced cognitive decline; clinical trials report improved memory
Omega-3 Fatty Acids (DHA, EPA)	Fish oil, flaxseed, walnuts	Anti-inflammatory, maintain membrane integrity, reduce amyloid accumulation	Epidemiological studies show reduced AD risk with high intake; supplementation improves cognition in MCI
Ashwagandha (Withanolides)	*Withania somnifera* (Indian ginseng)	Promotes synaptic regeneration, antioxidant, reduces amyloid pathology	Clinical trials suggest improved memory & executive function in MCI
Bacopa monnieri (Bacosides)	Brahmi (Ayurvedic herb)	Antioxidant, cholinergic modulation, enhances synaptic activity	Clinical evidence supports improved memory and attention in elderly and MCI patients
Huperzine A	Huperzia serrata	Natural acetylcholinesterase inhibitor; protects neurons against glutamate toxicity	Widely used in China; trials show benefits in MCI and early AD
Polyphenols (Flavonoids, Anthocyanins)	Berries, cocoa, grapes	Antioxidant, anti-inflammatory, improve cerebral blood flow, enhance synaptic plasticity	Diet rich in flavonoids associated with reduced AD risk; trials ongoing for berry extracts

Limitations of Synthetic drugs and Bioactive compounds [71-80]

1. Synthetic Drugs

1. Memantine, rivastigmine, and donepezil are the most commonly accessible medications; they mostly improve cognition temporarily and do not stop or alter the progression of the disease.
2. Reduced ability to penetrate the blood-brain barrier (BBB) restricts the amount of medication that can reach the brain.
3. Cholinesterase inhibitors can cause hepatotoxicity, nausea, vomiting, and diarrhea. Memantine might produce hallucinations, disorientation, or confusion.
4. Poor patient compliance in older populations is caused by frequent dosage and a short half-life.
5. Limited efficacy over the long term: No medication has been shown to stop the onset of AD, and benefits frequently fade over time.

2. Bioactive Compounds

1. Poor bioavailability: Curcumin, quercetin, and resveratrol are among the many phytochemicals that have poor systemic absorption, low solubility, and fast metabolism.
2. Variable efficacy: Individual metabolism, formulation, and dosage variations all contribute to uneven clinical results.
3. Absence of standardized formulations: The concentration, strength, and purity of herbal extracts differ among commercial preparations.

4. Too few extensive clinical studies Translations of the majority of the information into clinical guidelines is limited because it comes from preclinical or small clinical trials.
5. Interactions between pharmaceuticals and herbs: Possible interactions with traditional AD medications could have unanticipated consequences.[66-101]

Novel Drug Delivery Systems (NDDS) in Alzheimer's Disease

Because most therapeutic medicines cannot reach the brain in sufficient concentrations due to the protective nature of the blood–brain barrier (BBB), treatment for Alzheimer's disease (AD) is often limited. NMDA receptor antagonists and cholinesterase inhibitors are examples of traditional oral or systemic drugs that mainly relieve symptoms without changing the course of the disease. These medications also frequently have low absorption, quick clearance, and unfavourable systemic side effects, which lessens their long-term efficacy. A lot of research is being done on Novel Drug Delivery Systems (NDDS) to address these issues. Solid lipid nanoparticles, liposomes, polymeric nanoparticles, and dendrimers are examples of nanoparticle-based carriers that provide better drug stability, regulated release, and increased BBB penetration.

It is possible to create ligand-functionalized nanoparticles for receptor-mediated transport, which enables tailored delivery to the tissues of neurons. Bypassing the blood-brain barrier through the olfactory and trigeminal nerve pathways, intranasal administration is another promising NDDS technique that allows medications or biomolecules to be transported directly from the nose to the brain. Additionally, site-specific release is provided within sick brain regions using stimuli-responsive nanocarriers, such as pH- or enzyme-sensitive systems. In addition to increasing therapeutic efficacy, these cutting-edge delivery methods also seek to reduce systemic toxicity and delay neurodegeneration. The development of disease-modifying therapies for AD thus has great potential thanks to NDDS as shown in Table no. 4.[81-95]

NDDS Type	Mechanism / Targeting	Example in AD	Advantages
Nanoparticles (NPs)	Cross BBB via endocytosis or receptor-mediated transport; stabilize drugs	Rivastigmine-loaded PLGA NPs improved memory in rats	↑ Drug stability, prolonged circulation, targeted delivery
Liposomes & Niosomes	Vesicles encapsulate hydrophilic & lipophilic drugs; ligand surface modification enhances brain uptake	Donepezil liposomes with transferrin ligand	Controlled release, reduced enzymatic degradation, improved targeting [96]
Solid Lipid Nanoparticles (SLNs) & Nanostructured Lipid Carriers (NLCs)	Lipid carriers enhance drug solubility & brain absorption [97,98]	Intranasal SLNs of memantine showed ↑ brain levels	Biocompatibility, prolonged release, high stability
Dendrimers	Branched polymers enable conjugation with drugs/genes; bind amyloid-β	PAMAM dendrimer–curcumin conjugate inhibited amyloid aggregation	Targeted delivery, multifunctional surface, BBB penetration
Intranasal Delivery	Bypass BBB via olfactory & trigeminal pathways	Intranasal insulin improved cognition in MCI/AD patients	Non-invasive, rapid brain delivery, patient-friendly
Hydrogels & In Situ Gels	Long-acting gels retain drugs at CNS site; sol–gel transition prolongs release	NGF-loaded injectable hydrogel for neuroprotection	Sustained release, improved bioavailability, local action [99]
Exosomes & Biological Carriers [100]	Natural vesicles deliver proteins, miRNA, siRNA to neurons	Exosome-loaded curcumin reduced amyloid in AD mice	Biocompatible, low immunogenicity, precise targeting

CONCLUSION

The complex etiology and multifactorial pathophysiology of Alzheimer's disease (AD), which includes amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic loss, and cerebrovascular impairment, make it one of the most difficult neurodegenerative diseases to treat. With little to no effect on the underlying disease mechanisms, traditional pharmaceutical treatments—mostly cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA receptor antagonists (memantine)—have only improved cognition and behavior symptoms. Modest efficacy, eventual loss of benefit, side effects, and patient response variability limit their long-term usefulness. Natural bioactive substances like curcumin, resveratrol, ginsenosides, and omega-3 fatty acids have been studied for their multitarget neuroprotective effects in an effort to get around these restrictions. These substances may have a function in altering illness because of their anti-inflammatory, anti-amyloidogenic, antioxidant, and mitochondrial-protective effects.

Nanoparticles, liposomes, dendrimers, polymeric micelles, solid lipid nanoparticles, and intranasal carriers are examples of novel drug delivery systems (NDDS) that have shown improved BBB permeability, controlled release, improved drug stability, and decreased systemic toxicity. Precision targeting and long-term medication availability in the brain are further

promised by injectable hydrogels and exosome-based delivery. They can improve the therapeutic potential of both natural and manufactured medications, according to early preclinical and clinical research. Significant obstacles still exist, nevertheless, such as cost-effectiveness, large-scale manufacturing, long-term safety evaluations, and formulation standardization. Integrating NDDS with precision medicine techniques, biomarker-based patient classification, and multi-targeted medicines should be the main goals of future research. Ultimately, the care of AD may change from only relieving symptoms to actually altering the illness and possibly preventing it through a synergistic combination of synthetic medications, bioactive substances, and sophisticated delivery systems.

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