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LIPOSOMES AGAINST ALZHEIMER'S DISEASE: CURRENT RESEARCH AND FUTURE PROSPECTS

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ABSTRACT

Alzheimer's disease, the most common neurodegenerative disease, affects more than 60 million people worldwide. It is characterized by progressive memory loss, impaired behavior, mood changes and disturbed daily routine of the patient. There are several active molecules which have potential to slow the disease progression. The drug delivery is significantly restricted by the Blood–Brain Barrier. Therefore, targeted drug delivery are used to enhance the efficacy of drug. Liposomes are lipophilic carriers that consist of a phospholipid bilayer structure, simulating the physiological lipidic layer of the blood–brain barrier and enabling better delivery of the drug to the brain. Nanotechnology-based drug delivery systems have emerged as promising approaches to overcome these limitations. Among them, liposomes have gained considerable attention because of their biocompatibility, biodegradability, low toxicity, and ability to encapsulate both hydrophilic and hydrophobic drugs. Their phospholipid bilayer structure resembles biological membranes, enabling improved BBB penetration and targeted brain delivery. Surface-functionalized liposomes further enhance therapeutic efficacy by improving drug stability, bioavailability, and site-specific targeting while reducing peripheral toxicity. This review highlights the stages and pathophysiology of Alzheimer's disease, challenges associated with brain drug delivery, currently approved therapies, and the role of nanotechnology in AD management. Particular emphasis is placed on liposome-based drug delivery systems, including their mechanisms, functionalization strategies, therapeutic potential, and current research developments. Furthermore, the review discusses the challenges and future prospects of liposomal nanocarriers in achieving safe and effective treatment for Alzheimer's disease.

KEYWORDS: Alzheimer's ; Liposomes; Nanotechnology; Targeted therapy; Drug delivery; Neurodegeneration.

1. INTRODUCTION

Neurodegenerative diseases are characterized by the gradual and irreversible loss of neuronal cells, with each disorder exhibiting a distinct pattern of neuronal degeneration. Among these, Alzheimer's disease is one of the most severe and prevalent disorders affecting the central nervous system (CNS).[1] It is associated with progressive memory loss, cognitive decline, neuronal dysfunction, behavioral disturbances, and a significant reduction in quality of life. Although considerable progress has been made in the diagnosis and therapeutic management of Alzheimer's disease, the development of more effective treatment strategies remains a major clinical need. Currently, approximately 6.7 million individuals aged 65 years and older in the United States are living with Alzheimer's disease, and this number is projected to increase to nearly 13.8 million by 2060 if effective preventive or disease-modifying interventions are not achieved. Furthermore, the global prevalence of dementia is expected to triple by 2050, with Europe alone anticipated to experience a twofold increase.[2] One of the major challenges limiting the effectiveness of therapeutic interventions is the presence of physiological barriers, particularly the blood–brain barrier (BBB) and blood–cerebrospinal fluid (CSF) barrier, which restrict drug delivery to the brain. In addition, the incomplete understanding of the underlying pathophysiological mechanisms of neurodegeneration continues to hinder the development of successful treatments.[3,4]

In Alzheimer's disease, neuronal degeneration initially affects brain regions responsible for memory, language, and higher cognitive functions. As a result, difficulties with memory, thinking, and communication are often among the earliest clinical manifestations. Evidence suggests that pathological changes in brain function may

begin nearly two decades before the appearance of noticeable symptoms.[5] The disease progresses gradually and irreversibly, although the pattern of symptoms and rate of progression vary among individuals. In the advanced stages, Alzheimer's disease causes extensive neuronal loss in brain regions controlling essential physical functions such as walking and swallowing, eventually leaving patients bedridden and dependent on round-the-clock care. Studies indicate that individuals diagnosed with Alzheimer's dementia at 65 years of age or older generally have an average survival of 4–8 years, although some may live as long as 20 years after diagnosis.[6]

Liposome-based therapy represents a promising nanotechnological strategy for the treatment of Alzheimer's disease, as liposomes have the potential to enhance drug delivery across the blood–brain barrier (BBB), one of the primary challenges limiting the effectiveness of conventional therapeutic approaches.

2. Stages of Alzheimer's

According to the Global Deterioration Scale Alzheimer's disease have 7 stages. Stages 1-3 represent pre-dementia (mild), while 4-7 cover progressive cognitive decline (moderate to severe).

Stage 1: No Impairment
Persons appear cognitively normal, but pathological changes are happening in the brain.

Stage 2: Very Mild Decline
Prodromal stage: mild memory loss, but generally this is indistinguishable from normal forgetfulness.

Stage 3: Mild Decline (Early Stage)
Progression into mild cognitive impairment (MCI). Individuals may get lost or have difficulty in finding correct wording.

Stage 4: Moderate Decline
Moderate dementia; poor short-term memory. Individuals forget some of their personal history.

Stage 5: Moderately Severe Decline
Cognition continues to decline and at this point individuals need help in their daily lives. They suffer from confusion and forget many personal details.

Stage 6: Severe dementia
Requiring constant supervision and care. Patients fail to recognize many of their family and friends and have personality changes.

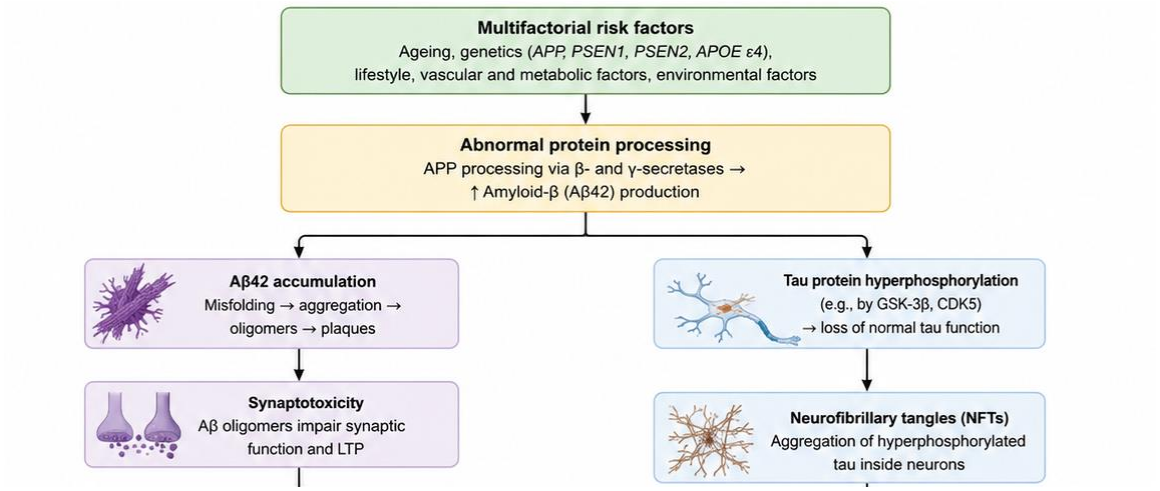
Stage 7: Very Severe Decline
Individuals are nearing death. They show motor symptoms, have difficulty communicating, are incontinent and require assistance in feeding.

3. Pathophysiology of Alzheimer's

Alzheimer's disease is characterized by the progressive accumulation of amyloid plaques and neurofibrillary tangles in the brain. Amyloid plaques are extracellular deposits primarily composed of β-amyloid peptides that accumulate in the spaces between nerve cells, disrupting normal neuronal communication. Neurofibrillary tangles are intracellular twisted fibers formed by abnormal aggregation of tau protein within neurons (**Figure 1**).

Research has shown that the formation of plaques and tangles increases with aging; however, in individuals with Alzheimer's disease, their accumulation is more extensive and follows a predictable pattern. The pathological changes typically begin in brain regions associated with memory, such as the hippocampus, and gradually spread to other areas involved in cognitive and functional processes.

The major pathological hallmarks of Alzheimer's disease include β-amyloid deposition in amyloid plaques and hyperphosphorylated tau protein accumulation in intracellular neurofibrillary tangles. The aggregation of these abnormal proteins leads to synaptic dysfunction, impaired neuronal signaling, and ultimately neuronal death. In addition, deposition of amyloid within cerebral blood vessels contributes to cerebral amyloid angiopathy, further exacerbating neurovascular damage.[7-9]



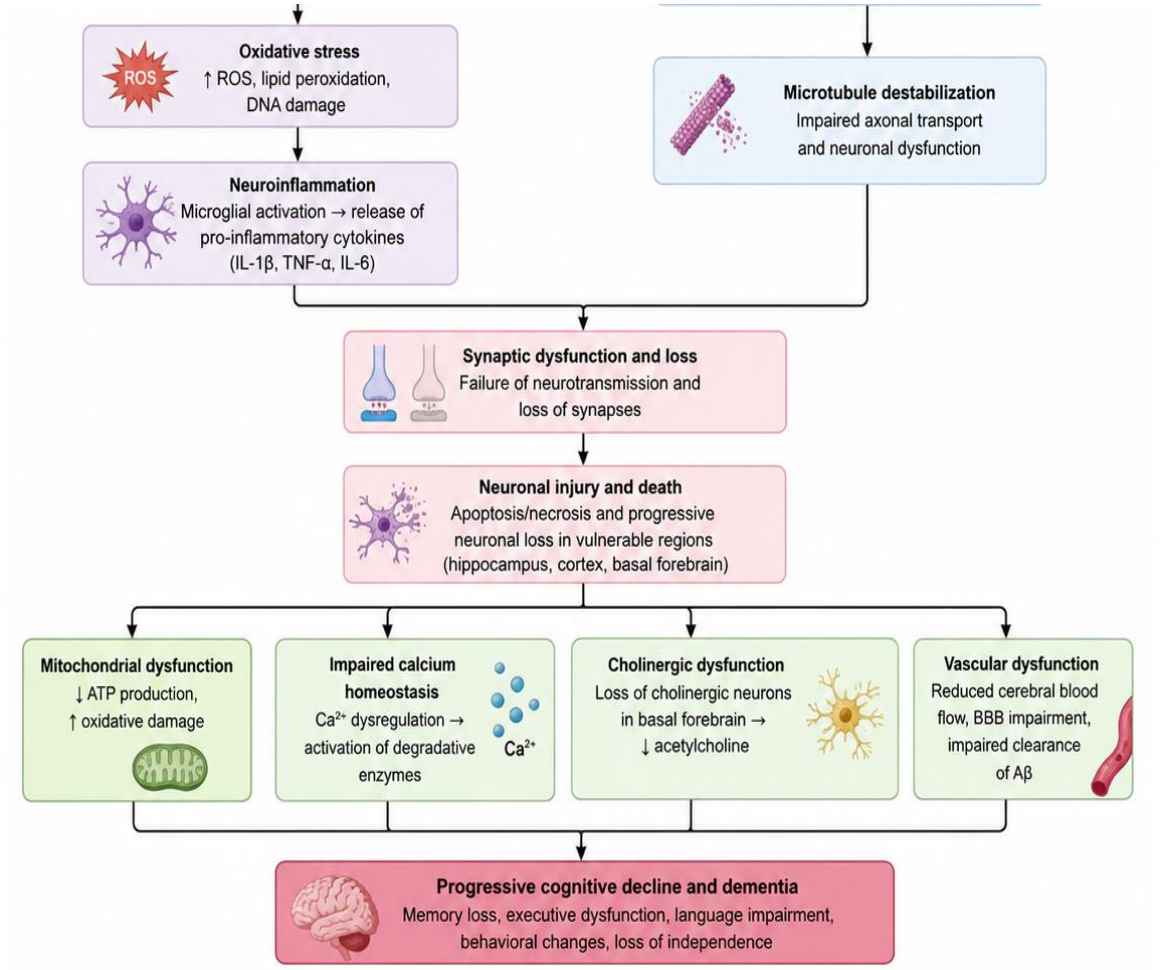


Figure 1: Pathophysiology of Alzheimer's.

4. Drug Delivery Challenges in Brain to treat Alzheimer's

Due to the structural properties of the BBB, the delivery of drugs to the brain poses a unique challenge in patients with Alzheimer. Several strategies have been investigated to delive therapeutic medicines to the treat neurodegenerative disorder. Now a day's technology and mechanistic tools are devised to assist in overcoming the BBB for more efficient and improved drug bioavailability in the treatment of neurodegenerative disease[10]).

The BBB plays a crucial role in regulating the exchange of substances between the systemic circulation and the CNS. Lipophilic substances can readily cross the BBB by passive diffusion through endothelial cell membranes. In addition, water and certain very small hydrophilic or charged molecules may pass through the BBB via paracellular transport. However, membrane barriers significantly restrict the passage of larger molecules. As a result, the BBB presents a major challenge in the pharmacological treatment of CNS disorders, as it prevents the entry of nearly all macromolecular therapeutics and more than 98% of small-molecule drugs into the brain, thereby limiting their therapeutic effectiveness. Insufficient drug delivery to the brain often leads to accumulation of these agents in peripheral organs and tissues, which can increase systemic side effects while reducing treatment efficacy.

Systemically administered drugs often distribute throughout the body, resulting in limited brain delivery and increased risk of systemic toxicity. Nanotechnology offers an effective approach to overcome these challenges by enabling targeted brain delivery, reducing off-target side effects, enhancing drug concentration at the site of action, and improving overall therapeutic efficacy.[11]

5. FDA -approved treatments for Alzheimer's disease

U.S. Food and Drug Administration (FDA) approved five medicine for the treatment of Alzheimer (**Figure 2**).[12]

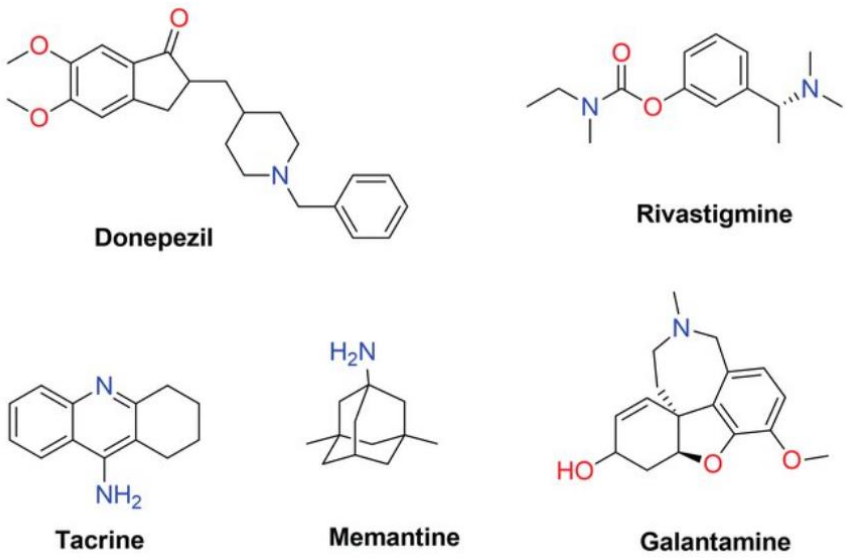


Figure 2: USFDA approved medicine for the treatment of Alzheimer.

Symptomatic treatment of Alzheimer's disease mainly includes cholinesterase inhibitors such as Donepezil, Galantamine, and Rivastigmine, which help improve cognitive functions including memory, thinking, judgment, and language.[13]

A combination of Donepezil and Memantine has been approved by the FDA for the treatment of moderate-to-severe Alzheimer's disease. This combination therapy has shown improved cognitive performance and overall mental function, while reducing side effects associated with donepezil monotherapy.

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist approved in the United States and Europe, is used for moderate-to-severe Alzheimer's disease and helps improve memory, attention, reasoning, language, and the ability to perform daily activities.

In June 2021, aducanumab, a humanized recombinant monoclonal antibody to amyloid β was the first disease-modifying therapy that received accelerated approval by the US Food and Drug Administration (FDA) to treat Alzheimer's disease and mild cognitive impairment.[14]

6. Nanotechnology in the treatment of Alzheimer's disease

Nanotechnology offers a promising strategy for Alzheimer's disease treatment by overcoming the limitations of conventional therapies, particularly poor drug penetration across the blood–brain barrier (BBB). Nanocarriers such as Liposomes, Polymeric Nanoparticles, Solid Lipid Nanoparticles, Dendrimers, Nanoemulsions, and Metallic Nanoparticles enhance targeted brain delivery, improve drug stability and bioavailability, and reduce systemic side effects (**Figure 3)** Additionally, nanotechnology supports early diagnosis and enables targeted intervention against amyloid-β, tau aggregation, oxidative stress, and neuroinflammation, making it a promising approach for Alzheimer's management.[15,16]

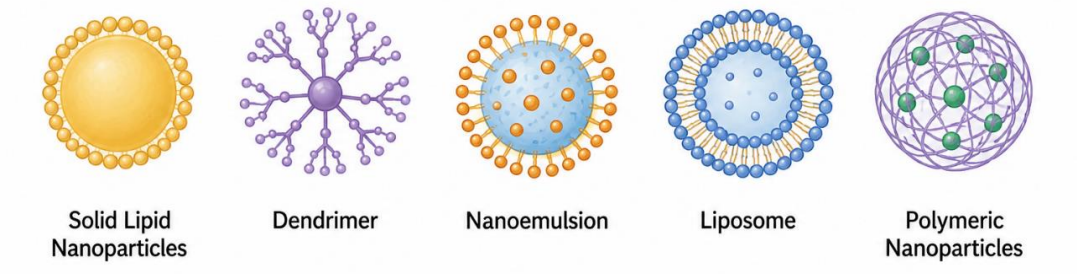


Figure 3: Different Nano-carriers for the treatment of Alzheimer's disease.

6.1. Lipid nanoparticles

Lipid Nanoparticles are colloidal drug delivery systems developed as alternatives to liposomes, nanoemulsions, and polymeric nanoparticles.[17] They offer several advantages, including low toxicity, protection of drugs from degradation, sustained drug release, site-specific targeting, and easy large-scale production. Lipid nanoparticles are classified into two generations: Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs). SLNs contain a solid lipid core, while

NLCs combine solid and liquid lipids to overcome limitations such as low drug loading and poor long-term stability. NLCs provide improved stability and enhanced drug-loading capacity; however, drug loading in both systems is influenced by drug properties, lipid composition, surfactants, and the manufacturing process.[18]

6.2. Nanostructured Lipid Carrier (NLC)

Muller in 2000 has developed nanostructured lipid carriers and launched the first two products in 2005, namely Nanorepair Q10 cream and Nanorepair Q10 serum (Manufacturer Dr. Rimpler, Wedemark, Germany). It took five years to launch these two products. Nanostructured lipid carrier is the advanced version of solid lipid nanoparticles consist of solid lipid, which is entrapped in liquid lipid.[19]

6.3. Liposomes

A.D. Bangham and his colleague R.W. Thorne were first explained the concept of liposomes after testing and investigating phospholipid dispersion (in water) under an electron microscope.[20] They observed that the phospholipids arrange themselves in a bag-like structure. Gerald Weissman proposed a structural arrangement named as "liposome" and defined as "microscopic vesicular structure contained lipid bilayers (one or more)." Now a day, liposomes are used in cosmetics as drug delivery systems.[21]

Liposomes are among the earliest and most widely studied nanocarriers for drug delivery. Composed mainly of phospholipids, cholesterol, and PEGylated lipids, they exhibit low toxicity, high biocompatibility, and good biodegradability. Their unique structure allows encapsulation of both hydrophilic and hydrophobic drugs, improving drug stability and bioavailability. In Alzheimer's disease, surface-modified liposomes have shown the ability to cross the blood–brain barrier, enhance targeted brain delivery, reduce amyloid-β plaque deposition, and improve cognitive function, making them promising carriers for AD therapy.[22]

7. CONCLUSION

Alzheimer's disease remains one of the most challenging neurodegenerative disorders worldwide due to its progressive nature, complex pathophysiology, and limited therapeutic options. The presence of the blood–brain barrier significantly restricts the effective delivery of conventional drugs to the brain, thereby reducing therapeutic efficacy and increasing systemic side effects. Although currently approved therapies such as cholinesterase inhibitors, memantine, and monoclonal antibodies provide symptomatic relief or modest disease modification, they are unable to completely halt disease progression.

Nanotechnology-based drug delivery systems have emerged as promising strategies to overcome these limitations. Among them, liposomes have gained significant attention because of their biocompatibility, biodegradability, low toxicity, and ability to encapsulate both hydrophilic and hydrophobic therapeutic agents. Their structural similarity to biological membranes enables improved penetration across the blood–brain barrier and targeted delivery to the central nervous system. Functionalized liposomes further enhance brain targeting, improve drug stability and bioavailability, reduce amyloid-β aggregation, and potentially minimize adverse effects.

Recent advances in liposomal formulations, including ligand-mediated targeting and surface modification, have demonstrated encouraging outcomes in preclinical studies for Alzheimer's disease therapy. However, several challenges still remain, including formulation stability, large-scale manufacturing, long-term safety, limited clinical translation, and optimization of targeting efficiency. Further research is therefore required to improve liposomal design, understand their interactions within the brain microenvironment, and validate their clinical effectiveness through well-designed clinical trials.

Overall, liposome-based nanocarriers represent a highly promising and innovative therapeutic platform for Alzheimer's disease management. Continued advancements in nanomedicine and targeted drug delivery may pave the way for more effective, safer, and patient-friendly therapies in the future.

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