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Cellular and Molecular Pathways of Nanoliposome Action in the Treatment of Alzheimer's Disease

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ABSTRACT: Amyloid-β (Aβ) plaques and neurofibrillary tangles play a major role in the progression of Alzheimer's disease. This condition leads to cognitive impairment and cell death. It is challenging to transport therapeutic medications over the blood-brain barrier, which is which limits the availability of effective treatments for this disease. Nanoliposomes are amphiphilic bilayer structure that can carry medicinal chemicals across the blood-brain barrier. Because of this, they are often used to deliver drugs. The objective of this study is to examine how nanoliposomes reduce the detrimental consequences of Alzheimer's disease by focusing on Aβ oligomers, diminishing neuroinflammation, and maintaining neuronal integrity. Adding ligands that target Aβ to nanoliposomes makes the treatment work better and have fewer side effects. Sphingolipids, gangliosides, curcumin, and monoclonal antibodies are all examples of ligands. Animal models of Alzheimer's disease have also shown that nanoliposomes can help with memory and congnitive functions. There have been big steps forward in using biological systems, but there are still problems with biocompatibility, scalability, and getting regulatory approval. Nonetheless, considerable data from preclinical studies indicates that nanoliposomes may serve as a crucial tool in the treatment of Alzheimer's disease. This technique would provide a new and personalized approach to treating this terrible disease.

Keywords: Alzheimer's disease, Beta-amyloid, Neurodegeneration, Neuroinflammation, Therapeutic strategies

1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that is marked by the aberrant accumulation of extracellular amyloid-β [Aβ] plaques and the production of intracellular neurofibrillary tangles. It is a complex and progressive condition that affects the nervous system. Improving the productivity of the body's waste disposal mechanisms in order to reduce the amount of A that gets absorbed by the brain is an efficient method for reducing the severity of this fatal disease. The term "sink effect" is commonly used to refer to this natural phenomenon. This method aims to stop Aβ oligomer and polymer formation, which could reduce the damage caused by their buildup. Because of their small size and lipid content, tailored nanoliposomes can be created to improve transport across the blood–brain barrier, whereas many traditional therapies generally show poor blood–brain barrier penetration. An increasing number of people are getting interested in nanoliposome derivatives because of the considerable potential they have as therapeutic agents that are able to bypass this crucial barrier [1]. By executing this intensive study, the researchers want to gain a better understanding of the intricate physiological and molecular mechanisms whereby nanoliposomes are used to demonstrate their influence on Alzheimer's disease. Because of the blood-brain barrier (BBB), it can be highly challenging to discover effective treatments for neurological conditions affecting the brain. However, nanoliposomes can transport therapeutic chemicals, such as peptides, directly to the blood-brain barrier, which is difficult to access. Researchers have successfully developed numerous innovative approaches to utilise nanoliposomes and specific Aβ ligands, like sphingolipids, gangliosides, curcumin, and monoclonal antibodies that preferentially bind to Aβ. Due to the fact that it significantly enhanced spatial learning and memory in APP/PS1 mice, the nanosystem PLGA-PEG-

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B6/Cur has shown a great deal of promise as an intervention. There is a growing body of evidence suggesting that nanoliposomes could be an effective treatment for Alzheimer's disease. In spite of this, it is crucial to remember the fact that just a few of these compositions have met the criteria for clinical testing up to this point [2] and When it comes to delaying the onset of Alzheimer's disease (AD) in those who are already recognised with the condition, one of the most effective methods is to prevent the accumulation of Aβ peptides. The results of recent studies have demonstrated that exosomes, which are minuscule nuclei that are produced by cells, have the potential to be of significant benefit when exploited in therapeutic and preventive therapy programs. It is considered by medical professionals that these exosomes contain essential signalling substances that have the potential to affect the functioning of illnesses associated with Alzheimer's disease. It has been demonstrated that three synthetic nanoliposomes are suitable for a variety of medical applications. These nanoliposomes may be created with careful attention to meet specific dimensions, and they may be further functionalised or loaded with active medicinal chemicals in order to enhance their effectiveness [3]. Liposomal formulations and PEG-PACA systems are two examples of nanoparticles that are not substantially changing the conduct of blood vessels or the way in which the body reacts to inflammation. Consequently, this indicates that these nanoparticles have the potential to be especially effective in the treatment of Alzheimer's disease. For the purpose of determining the overall effectiveness of these novel treatments, it makes sense to conduct a comprehensive analysis of the levels of nitric oxide. For the purpose of estimating therapeutic dosage ranges for in vivo applications, in vitro fabrication is essential [4].

2. DEFINITION OF NANOLIPOSOMES

Nanoliposomes are small phospholipid vesicles with two bilayers that are less than 100 nm in diameter [5]. Because they are amphiphilic, nanoliposomes can transport numerous molecules within their aqueous environment, spherical phase, or outermost layer. There are usually both unsaturated and saturated phosphatidylcholines in the lipid bilayer. These lipids possess a high phase transition temperature (Tc), resulting in them being rigid at normal body temperatures. There are actually many kinds of nanoliposomes determined by their size and how many lamellae they have. Large unilamellar vesicles (LUVs) are between 50 and 200 nm in size, small unilamellar vesicles (SUVs) are less than 50 nm, large multilamellar vesicles are over one hundred nm, and multivesicular vesicles might be as big as 1000 nm [6]. Amphiphilic vesicles are small liposome structures (20–60 nm) that may build themselves within water. They can stick to small amphiphilic molecules and modifications of their physical properties. Those characteristics are extremely crucial for molecules to go via and through biological membranes [7].

2.1 THE STRUCTURE OF NANOLIPOSOMES

Nanoliposomes possess an extremely distinctive shape consisting of numerous bilayers of fatty acids that overlap along with compartments that grasp water. These elliptical capsules are extremely complicated and typically have sizes of 20 to 100 nm. This excellent adaptability has made it possible to successfully wrap up an extensive spectrum of compounds. The water-based gaps work extremely well to prohibit hydrophilic substances from getting in, and the bilayers work very well to combine amphiphilic molecules. Organisms that are hydrophilic fit well within those alkyl chains of lipids. These cells have been proven safe for continuous use in patients since they appear like biological membranes, are incredibly environmentally friendly, and have very low toxicity [8]. You may openly adjust the methods you use for creating these stimulated vesicles to produce other kinds, such as the previous unilamellar and multilamellar ones. One of the most desirable things about nanoliposomes is that their bodies may cross across the stiff blood-brain barrier, depending on their size. Their adaptable physicochemical properties additionally provide researchers and drug developers with an unparalleled degree of control over essential variables such as solubilisation, lamellarity, particle size, drug absorption kinetics, and overall stability. Nanoliposomes are extremely flexible and can be customized to be targeted delivery systems. This demonstrates how much potential you have, particularly as it comes to developing creative methods for dealing with Alzheimer's disease. The precision of medicine delivery might significantly enhance the patient's standard of living and the efficacy of treatment options [9].

2.2 DIFFERENT KINDS OF NANOLIPOSOMES

Nanoliposomes contain very small vesicles inside, which are surrounded by a membrane. They're distinguished by an uncommon ability to hold onto active substances in their enlarged core or throughout their bilayer structure. Phospholipids, which may be created in a lab or occur in nature, are the main parts of these intriguing and new structures. The tiny vesicles inside nanoliposomes are encased in a membrane. Their capacity to hold onto active ingredients inside their expanded core or throughout their bilayer structure sets them apart. The primary constituents of these structures are phospholipids, which can be synthesised or found naturally. The tiny vesicles inside nanoliposomes are surrounded by a membrane, and cholesterol is frequently added to stabilise the membrane and preserve ideal structure. What distinguishes them is their ability to retain active substances across their bilayer structure or within their enlarged core. Phospholipids, which can be synthesised or produced naturally, are the main components of these formations.and function [10]. They can include plasmalogens, which are commonly found in brain tissues and support cellular activity and membrane integrity under a variety of physiological circumstances. One of the most prominent

kinds is the 1,2-Dimyristoyl-sn-glycero-3-phosphocholine nanoliposome, which resembles the outer layer of high-density lipoprotein (HDL) [11]. This resemblance may help biological systems handle cholesterol and provide resilience against oxidative stress [12]. The size and quantity of lipid bilayers can also be used to classify liposomes. The average size range of multilamellar vesicles (MLVs) is between 500 and 5,000 nm. Large unilamellar vesicles (LUVs], which offer benefits for drug delivery and targeting in a variety of therapeutic situations, typically range in size from 100 to 1,000 nm, whereas small unilamellar vesicles (SUVs) are typically between 15 and 100 nm [13]. Additionally, other liposome variants have been designed to perform specific therapeutic functions. Additionally, other liposome variants have been designed to perform specific therapeutic functions. Multivesicular liposomes (MVL) show better effectiveness in delivering and transporting drugs since they are made up of many vesicles. On the other hand, enormous unilamellar liposomes (GUV) are massive, having a diameter of more than 1,000 nm. This characteristic makes them ideal for uses that need a lot of cargo space. The selection of the appropriate liposome type is mostly determined by the unique properties of the encapsulated therapeutic substances and the techniques of manufacture. These factors affect how well liposomes work in treatments and how quickly they release their contents [14].

2.3 SYNTHESIS METHODS

The Way to Create Synthesis Ethanol dissolves lipids, which are then quickly added to a water-based media. Freezing lipids makes liposomes by making bilayers instantly. This process is quick and might make liposomes of different sizes, although it could be challenging to control their final properties. Reverse-phase evaporation is a method for mixing solvents that utilises an emulsion of oil and water to disperse lipids in an organic solvent. Lipids form liposomes when the pressure drops and they are properly hydrated [15]. Choosing the right procedure for making nanoliposomes is challenging but very crucial since it has a big impact on their structure and function. It is vitally important to use the right production methods for nanoliposomes since these qualities affect how safe and effective these drug delivery systems are. The advantages and disadvantages of each approach have all had an effect on the size, uniformity, lifespan, and spread of liposomes in biological systems [16]. Consider the liposomal structure's potential uses and effects before deciding where to place it. After combining it well with ethanol, quickly move the lipid solution through an aqueous phase. You can make liposomes by quickly mixing ethanol and water together (Figure 1). The approach makes things easier and offers up new options, but it could be difficult to use when it comes to encapsulating hydrophilic drugs [17]. Reverse-phase evaporation is the process of sonicating a fluid solution with a naturally occurring solvent that has dissolved phospholipids. This makes an emulsion of oil and water. Liposomes occur when the pressure is slowly lowered, which slowly removes the organic solvent. These liposomes frequently have very high encapsulation efficiencies.To avoid cytotoxicity, it is important to get rid of organic solvents in the right way. The pros and cons of each production method have an effect on the physical properties and packaging efficiency of therapeutic nanoliposomes, such as the ones used to treat Alzheimer's disease. Because thin-film hydration is easy to use and works with a variety of lipid compositions, it is still frequently used in laboratories. Nevertheless, it usually produces multilamellar vesicles with a wide size distribution and frequently needs post-processing [such as extrusion or sonication] to produce uniform nanoliposomes. Microfluidization, on the other hand, is a continuous, high-shear method that can produce more homogeneous, smaller vesicles with better batch-to-batch reproducibility, which is beneficial for translational development. In terms of stability, microfluidized nanoliposomes frequently display less polydispersity and more consistent release kinetics, while thin-film hydration may show more variability unless strictly regulated and followed by standardised size-reduction procedures. However, microfluidization may provide improved scalability and manufacturing control—two essential characteristics for AD-oriented formulations meant for BBB delivery—while thin-film hydration may be advantageous for encasing lipophilic cargo within the bilayer [18].

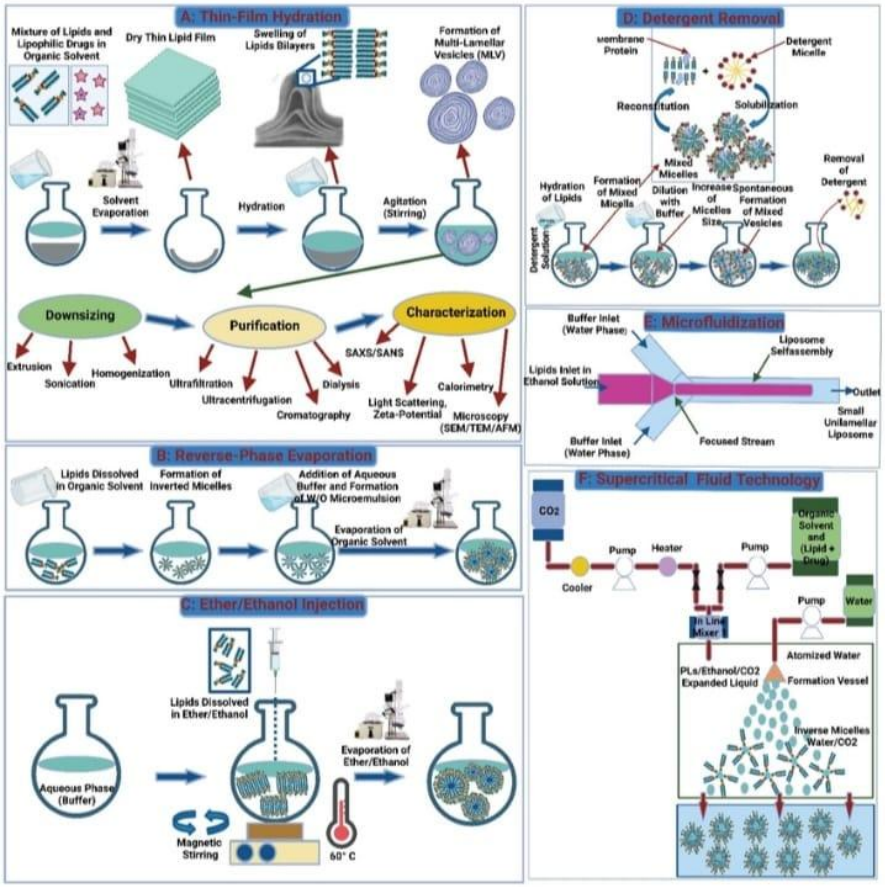

FIGURE 1. - The figure shows all of the methods that the nanoliposomes can be created with, including these [19].

• Thin-Film Hydration: The lipids are incorporated with an organic solvent to create a thin film. The film is then hydrated to create multilamellar vesicles. Once that is done, the processes of size reduction, purification, and characterisation come next.
• Return Phase Evaporation: To create liposomes, you mix an aqueous phase alongside an organic solvent featuring lipids in it, followed by slowly removing the solvent.
• Ether/Ethanol Injection: An organic alcohol has been utilised to disintegrate lipids, which are then introduced into the aqueous phase and stirred with a magnet to create liposomes.
• Eliminating Detergent: Lipids and proteins disintegrate in detergents, which are then cautiously taken away to create reconstituted vesicles.
• Microfluidization: Lipids and water undergo compression through high-pressure streams to generate tiny, identical liposomes.
• Supercritical The fluid technology: liposomes are manufactured in a place where there are no toxic solvents by expanding supercritical CO_2 with organic solvents.

2.4 CHARACTERIZATION TECHNIQUES

Nanoliposomes are like tiny capsules that are suspended in a liquid. Amphiphilic lipids, which may be found in nature or made in a lab, make up their bilayer membranes. These lipids can either self-assemble or co-assemble. An interior hydrophilic phase lets them vary the size of particles from 10 nm to a few micrometres. Sonication, injection using Alexander Hamilton syringes, grinding, high-pressure homogenisation, reverse-phase evaporation, and membrane extrusion are all ways to make things that work [20]. Because nanoliposomes have a strange form, it is harder to figure out their topographic structural aspects. There are many different ways to describe nanoliposomes, and each one has its own laws and limits. Calorimetry, electrophoresis, light scattering, and Förster resonance energy transfer are some of the methods used in physicochemical operations [21]. There are several different chemical tests, including colorimetry, chromatography, spectroscopy, and fluorimetry. Atomic force microscopy, ambient electron microscopy, scanning electron microscopy, and transmission electron microscopy are also very important. Sizing is often used to guess how proteins are linked together; however, there isn't much evidence to back this up; therefore, it should be used with other methods. While shape affects preparation stability and drug release from encapsulation, its effect on cell interactions is yet unclear. A more complex mechanism may be occurring, as a later study has

demonstrated no association between the diameters of empty nanoliposomes and the efficacy of peptide-liposome conjugation [22].

3. ALZHEIMER'S DISEASE AND RELATIONSHIP WITH NANOLIPOSOMES

Alzheimer's disease (AD) is a complex and complicated progressive neurodegenerative circumstance that significantly decreases the quality of life for afflicted people as well as placing an immense and escalating cost strain on global healthcare systems. The disorder is characterised neuropathologically by the outside-the-cell accumulation of amyloid-β [Aβ] protein, which leads to plaque formation, and by the emergence of intracellular neurofibrillary tangles that contain hyperphosphorylated tau protein [23]. Along with those hallmark attributes, additional significant features of AD encompass oxidative stress and the establishment of long-term inflammation, an elevated concentration of excitatory chemicals, the occurrence of abnormal insulin signalling within the cerebellum, and additionally the gradual yet profound loss of neurones over time. Cognitive deficiencies always arise as direct outcomes of synaptic loss, especially due to the deletion of cholinergic neurones in specific brain areas essential for retention, comprehension, and general cognitive function [24]. Liposomes, which are basically tiny bubbles made from phospholipids, have been claimed to be excellent ways for transferring drugs that make it much easier for them to pass the difficult blood-brain barrier and get to the neurones in the brain. Liposomes have the potential to be a new and better way to deliver drugs, but they still have a lot of problems that make them less useful. Some of these problems are that they don't always target the right place, drugs can be released into the bloodstream too soon, and liposomes themselves are unstable when they are in the bloodstream [25]. To tackle these major problems and find a solution, we have developed a controlled, cost-effective ultrasonic method that makes nanoliposomes [NL]. These are specially designed to only target neurone cells while greatly reducing uptake by microglia and minimising any possible haemolytic activity that might happen. The creation of NL paves the way for a novel and intriguing way to treat Alzheimer's disease. It might lead to better medication delivery methods and better outcomes for patients. [26]. Dementia is a long-term neurological illness that causes memory and cognitive deterioration over time. Throughout the world, 55 million people have it, and Alzheimer's disease (AD) is responsible for about 60–70% of these instances. Despite almost a century of extensive research, treatment alternatives for Alzheimer's Disease (AD) continue to be constrained. Nanoliposomes have recently surfaced as intriguing options due to their capacity to encapsulate diverse therapeutic chemicals, prolong circulation durations, offer substantial surface area for functionalisation, and effectively modulate immune responses. The goal of this review is to look closely at the cellular and molecular pathways that nanoliposomes use to treat Alzheimer's disease. It will also talk about their possible advantages and uses in therapy. Signs and Symptoms [27].

Alzheimer's Disease (AD) is marked by a progressive and frequently distressing decline in memory and other cognitive processes. This ongoing deterioration of cognitive functions advances from subtle, initial stages with no symptoms to severe dementia that significantly affects everyday life and overall quality of life [28]. Patients frequently display other symptoms that significantly impair their communication skills, including challenges in word retrieval, chronic confusion in familiar settings, sudden mood fluctuations, and a marked decline in enthusiasm to participate in previously loved activities. A prominent aspect of Alzheimer's Disease (AD) is the deterioration of working memory, which considerably hinders information processing and results in a markedly diminished attention span. As the disease becomes worse, these symptoms are much worse, and patients often have a big loss of episodic memory, which makes it hard to remember things that happened in the past or recognise people they care about. [29] It is not easy to diagnose Alzheimer's disease since there is no one test that can definitely prove that someone has it. To get the right diagnosis, you need a full set of tests, including a detailed medical history, a thorough physical exam, tests of mood and behaviour, and cognitive and memory tests. Recent improvements in medical imaging have been encouraging, especially the use of functional MRI technology to look at brain activity in the early stages of Alzheimer's disease. This has helped us understand how the illness impacts brain function even before obvious symptoms appear. This has opened up new ways to learn about how Alzheimer's disease becomes worse over time and may help with earlier intervention measures [30].

3.1 CURRENT TREATMENT OPTIONS

Currently, the treatment of Alzheimer’s disease (AD) pathology is one of the most disappointing examples of exploration for new drugs in biomedicine. The reasons for this can be attributed to numerous factors: lack of selectivity and specificity of anti-AD drugs; inability of most drugs to cross the blood-brain barrier; testing only one target in a multifactorial disease; and patients in advanced disease stages. The recruitment of patients in early stages was initially difficult due to a lack of good early diagnostic markers [31]. Amyloid plaques mainly contain amyloid-beta [Aβ] peptide, released by proteolytic cleavage of amyloid precursor protein [APP]. Cellular events during pathology progression include microglia and astrocyte activation, synaptic dysfunction, axonal transport failure, and neuronal death. The most accepted hypothesis suggests oligomerisation of Aβ triggers amyloid accumulation, with oligomeric forms being highly toxic. Parallel to this, neuronal dysfunctions lead to tau hyperphosphorylation and accumulation [32]. developed strategies specifically target the accumulation of amyloid and tau or their hyperphosphorylation. Immunotherapy is proposed to reduce Aβ accumulation and treat the underlying cause of AD. Another approach alters

the equilibrium of Aβ levels between the brain and peripheral blood, aiming to enhance peripheral clearance to lower brain Aβ levels. Incorporating drug candidates such as Edaravone, DHA, or antibody therapeutics into the LCM/ND lipid nanoemulsion can create a multitasking therapeutic targeting cell-surface SR-BI. This approach enables targeted drug delivery across the blood–brain barrier via receptor-mediated endocytosis/transcytosis through lipoprotein receptors like SR-BI. It allows modulation and repair of endothelial cells and may produce additive or synergistic effects across various cell types involved in Alzheimer's disease [33]. The therapeutic strategy aligns with findings of cerebrovascular pathology and brain arterial ageing related to endothelium dysfunction in Alzheimer's and its risk factors. Such a combination therapy could be effective at different disease stages, potentially delaying or preventing Alzheimer's. Additionally, the lipid-coated microbubbles in the nanoemulsion can reduce the acoustic power needed for noninvasive transcranial ultrasound treatments, enhancing options for Alzheimer's therapy [34].

3.2 THE FIELD OF EPIDEMIOLOGY AND RISK FACTORS

It is estimated that 60–80% of patients diagnosed with dementia have Alzheimer's disease (AD). Genome-wide association studies on patients with late-onset sporadic Alzheimer's syndrome have identified certain risk loci. However, it is evident that this intricate disorder is multifactorial, involving various linked pathological mechanisms that contribute to its progression. The plaque concept posits that collected amyloid-β [Aβ] oligomers commence a process resulting in the buildup of substantial fibrillar and insoluble Aβ agglomerates, usually known as plaques, within the brain [35]. Moreover, tau hyperphosphorylation and the accompanying intracellular buildup of tau proteins significantly contribute to the overall pathogenesis of Alzheimer's disease. As a result of all those processes, AD advances with neuronal loss and brain shrinkage as Aβ plaques progressively develop. Moreover, the assessment of peripheral biomarkers by modern proteomics and metabolomics approaches has successfully pinpointed an exclusive panel of eleven proteins capable of efficiently differentiating healthy controls from individuals diagnosed with Alzheimer's disease. This finding not only improves our understanding of how the illness works, but it also has the potential to lead to the creation of diagnostic systems that can recognise Alzheimer's disease earlier [36] Figure (2).

Alzheimer's disease (AD) is the most common cause of dementia, which is a set of different clinical disorders. From 1990 to 2016, the number of people with dementia throughout the world increased from 20.2 million to 43.8 million. The occurrence of Alzheimer's disease escalates with advancing age; however, it has also been documented in persons, predominantly in family situations, under the age of 65 years. Education, physical activity, work, and food have been recognised as significant protective factors against the onset of Alzheimer's disease. Conversely, traumatic brain injury, depression, psychological stress, inflammation, cerebrovascular illness, and diabetes mellitus are regarded as risk factors [37].

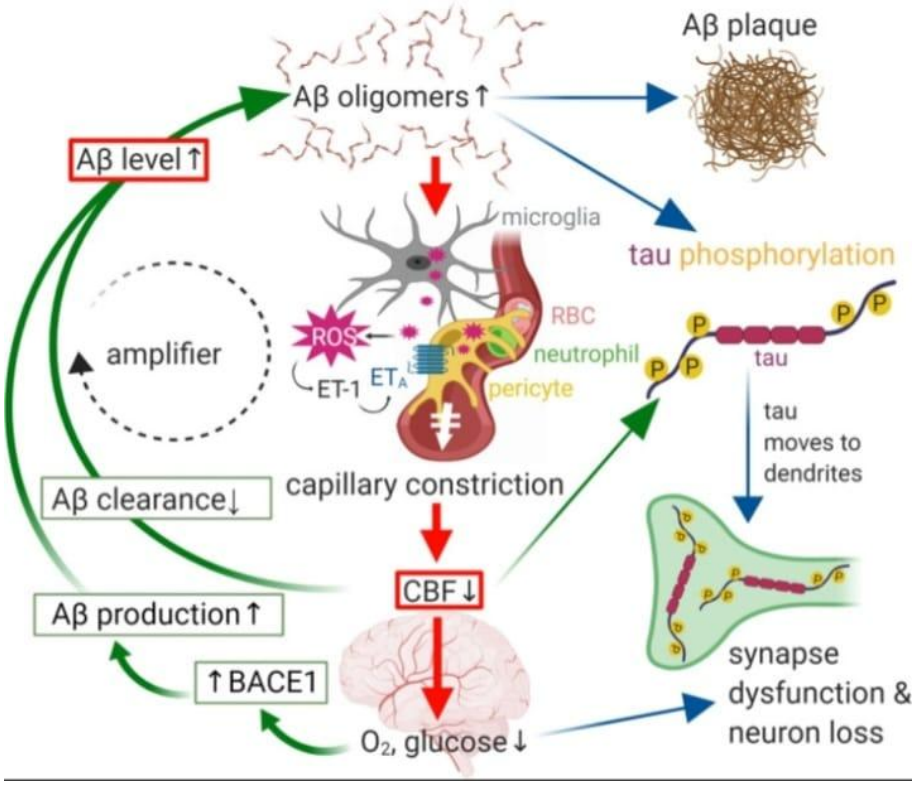

FIGURE 2. - illustrates Mechanistic Pathway Linking Amyloid-β Accumulation, Capillary Constriction, and Neurodegeneration [38].

The buildup of amyloid beta (Aβ) outside of cells and the creation of neurofibrillary tangles (NFTs) inside cells are both known to be major causes of Alzheimer's disease (AD). Because of this information, trying to halt Aβ oligomerisation or polymerisation, has evolved into a very promising strategy to lessen the accumulation of amyloid that generally happens with these severe illnesses. The A sink effect hypothesis indicates lowering the overall level of A in the brain might be an important method to improve peripheral A clearance. Most nanoparticles (NPs) have challenges passing across the blood-brain barrier, but some that originate in a specific way can use their common interactions to help fight Alzheimer's disease [39]. Researchers are now researching employing nanoliposomes that are coupled to Aβ ligands like sphingolipids, gangliosides, or the ingredient curcumin in treatment. They are also looking at employing nanoliposomes that are attached to monoclonal antibodies that just attack Aβ. Another possible plan to treat and halt AD is utilising novel nanostructures like exosomes. The fact that nanoliposomes are being examined in clinical trials for some of these captivating novel medications indicates how promising they are as an alternative for current Alzheimer's disease treatments Figure (3). As research advances, nanotechnology holds considerable promise for the future treatment of this complex neurodegenerative condition by improving the delivery and efficacy of therapies [40].

The exact physiological and molecular mechanisms via which nanoliposomes alleviate Alzheimer's disease symptoms are not yet fully understood. Nanoliposomes may enter and grow in injured cells through these specialised routes, which makes them great for delivering medications. One possible reason why nanoliposomes can help with amyloidosis is that they affect the pathway that is linked to this trait of Alzheimer's disease [41].

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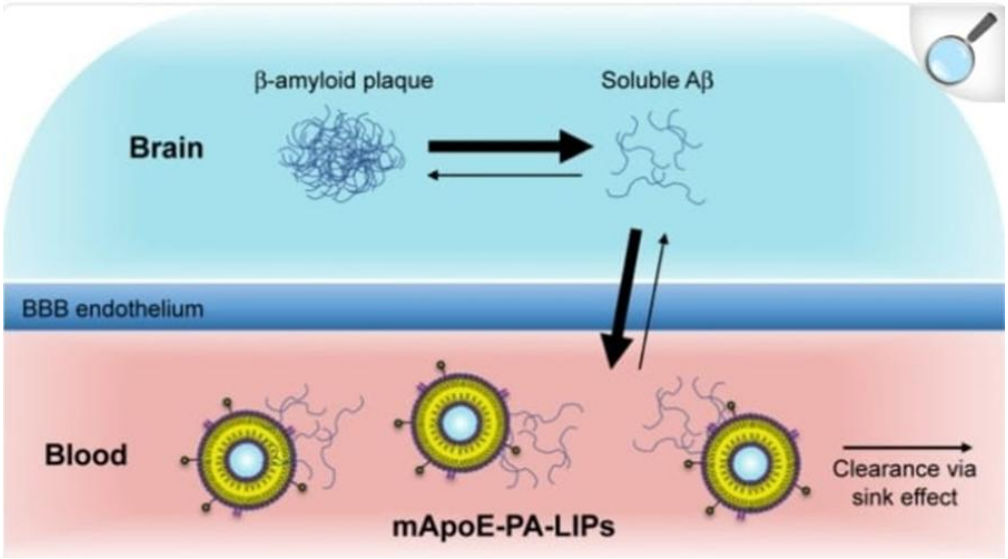

FIGURE 3. - Blood–Brain Barrier-Mediated Clearance of Amyloid-β Using mApoE-PA-Liposomes [42]

5. Targeted Drug Delivery

In the last ten years, the application of nanoscale biological drug delivery systems for localised medicine delivery has developed a lot. Medical professionals and academics are very interested in getting their hands on these new instruments. Liposomes and nanoparticles (NPs) have become the main instruments for study and use in this emerging field. One of the main reasons they are thought to be excellent transporters is because they assist in transferring important drugs to the proper sections of our bodies [43]. The surfaces of these biomaterials interact in a certain way with a certain group of cells that have too many of certain receptors, which makes drug delivery exceedingly precise. These kinds of scenarios are very unusual chances for precision medicine to happen. The major goal of the team is to create new nanoscale biomaterials that can be functionalised with different biological agents. When combined with antibodies, cell ligands, and peptides, these biomaterials work substantially better. Altered nanoscale materials might be used to target the blood-brain barrier [BBB] and plaques that cause neurodegenerative diseases. Once the right structures are found and made available, there are numerous ways to easily and quickly give the therapeutic drug. There are several ways that medicines can get into the body, such as diffusion, dissolving in fluids around them, and breaking down biomaterials. This new method lets us get a lot more of the medicine right where it needs to be[44]. This method of dissemination typically works better since it is more concentrated than others. These are some common targeted cell groupings that might benefit a lot from this new delivery technique. You could uncover glioma cells, which are helpful for treating aggressive brain tumours, and amyloid plaques, which are important for the development of Alzheimer's disease. Scientists are using these methods to try to find new ways to cure and control a lot of diseases that make people

sick. Their purpose is to make the most of nanotechnology's promise in healthcare. 4.3 Effects that protect the brain [45].

By focusing on the causes of neuronal damage in diseases like Alzheimer's, tailored nanoliposomes can offer neuroprotective benefits. Using nanoliposomes to trap β-amyloid, a peptide that is believed to cause significant neurotoxic damage in Alzheimer's disease, is one hypothetical application. To prolong neuronal survival and further reduce neurodegeneration, drug-loaded nanoliposomes can be directed to additional sites of AD pathogenesis. Many organizations have developed nanoliposomes containing curcumin, which have the ability to prevent tau hyperphosphorylation and the clumping of Aβ proteins. The amazing characteristics and chemical and physical stability of these nanoliposomes are truly astonishing [46]. Many of the molecules involved in cholesterol transport also serve to shield neurons from damage. Elevated or low cholesterol levels could potentially accelerate the onset and progression of Alzheimer's disease. It has been difficult to develop clinically useful nanoliposome formulations from statin derivatives despite their neuronal protection and effectiveness in preclinical models of Alzheimer's disease. This is because their poor physicochemical properties make it difficult to maintain low Aβ levels, reduce tau hyperphosphorylation, and prevent brain cell death. Because of its poor bioavailability and insufficient solubility, coenzyme Q10 (CoQ10) is seldom used in medicinal contexts. Nonetheless, the chemical shows strong neuroprotective and antioxidant capabilities, and liposomes have improved its bioavailability. Bypassing the blood-brain barrier, nanoliposomes loaded with Q10 effectively eliminate Aβ, decrease neurotoxicity, and enhance behavioral functions in rats suffering from Alzheimer's disease [47]. One potential application of peptide-based nanoliposomes is the targeting of BBB endothelial cells associated with Alzheimer's disease. The accumulation of Aβ in the brain is prevented by this. This process will alter the internal workings of cells. This sort of action has already been shown by nanoliposomes containing memantine or a big curcumin derivative Figure (4). Certain neuronal cells can be reached by nanoliposomes containing neuroprotective and neuroregenerative chemicals, which can penetrate the blood-brain barrier (BBB) and have a synergistic, neurorescuing effect [48]. Nanoliposomes can be internalized by target cells through endocytosis or fusion with lipid membranes. Their ability to transport nucleic acids, growth factors, and proteins allows them to directly stimulate neurogenesis. Because the drug prefers to attach to specific cells in the brain during intranasal administration, this method of drug delivery may have far better success rates. People can recover from ischemia, Alzheimer's disease, and traumatic brain injury models when nanoliposomes made from the brain are pulsed with specific CD4^+ T cell epitopes and small quantities of lipids associated with Alzheimer's disease are added [49].

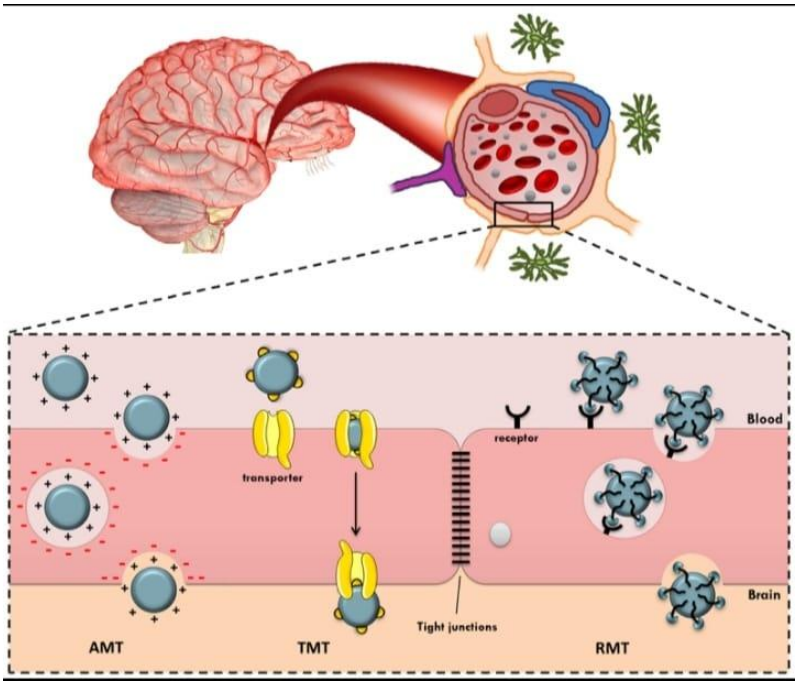

FIGURE 4. - Mechanisms of Nanoparticle Transport Across the Blood–Brain Barrier [50].

Clinical Applications of Nanoliposomes offer novel strategies for addressing Alzheimer's disease (AD), a complex neurodegenerative condition. This article talks about a lot of different ways to treat Alzheimer's disease, such as stabilizing amyloid-beta [Aβ] monomers, getting the brain to get rid of Aβ aggregates, improving peripheral clearance through the sink effect, and successfully integrating nanoliposomes with cellular therapies like macrophages in One of the most important things that nanoliposomes do is stop Aβ oligomerization. These nanoliposomes could include an

ApoE binding domain, curcumin, or sphingolipid]51[. It is very important that these nanoliposomes regulate Aβ dynamics in order to lessen the harmful effects of oligomerization. By using nanoliposomes with monoclonal antibodies that only target Aβ, it is able to inhibit these peptides from mixing and get rid of them in the brain. Preliminary data from several Alzheimer's models indicate that this medication may be beneficial. Researchers have also looked into the possibility that exosomes and other specialized nanostructures can make medicinal techniques work better. These innovative delivery technologies could drastically change how Alzheimer's disease is treated by making drugs work better and clinical studies more useful.[52].

Research on animal models of Alzheimer's disease indicates that nanoliposomes represent a promising therapeutic approach, primarily offering the advantage of reducing memory loss. Using nanoliposome-based therapy to restore or improve memory in people with Alzheimer's disease is an interesting idea. Initial experimental evidence suggests that nanoliposomes may be capable of traversing the blood-brain barrier. This is especially true when combined with peptides that target the brain, such as K16ApoE. Numerous varieties of nanoliposomes, including unilamellar liposomes and PEGylated formulations, have demonstrated low toxicity profiles in in vivo evaluations. Additional research is required to comprehensively evaluate nanotoxicity and the limited biodistribution throughout the brain [53]. Liposomes are a promising new tool in the fight against Alzheimer's disease. By changing their makeup, we may be able to make them much better at carrying tiny medicines, nucleic acids, and proteins. Long-lasting noncovalent interactions with drugs that target synaptophysin can make nanoliposomes that are more flexible. Nanoliposomes protected by the blood-brain barrier-penetrating peptide K16ApoE might be able to move things to the brain by copying ApoE's ability to cross barriers. This strategy lets you send things to numerous places in a cell at the same time, even through endothelial cells [54].

Many studies have shown that nanoliposomes, especially unilamellar and PEGylated kinds, are not extremely toxic in living things. Overall, in vivo results that are currently available show good safety profiles. Further research is necessary to fully understand the biological consequences of nanoliposomes; however, these findings support their potential as therapeutic agents for Alzheimer's disease. Table (1) To guarantee the effectiveness of nanoliposome-based therapies for Alzheimer's disease in clinical trials, comprehensive investigation into potential adverse effects and long-term biocompatibility is essential [55].

Table 1. - **Key Aspects of Nanoliposome-Based Strategies for Alzheimer's Disease Therapy**

Aspect	Details
Therapeutic Strategies	- Stabilizing amyloid-beta [Aβ] monomers - Promoting efflux of Aβ aggregates from the brain - Enhancing peripheral clearance via the sink effect - Combining nanoliposomes with cellular therapies [e.g., macrophages]
Nanoliposome Function	- Nanoliposomes loaded with Aβ ligands [e.g., sphingolipids, gangliosides, curcumin, ApoE binding domains] - Inhibiting Aβ oligomerization - Monoclonal antibodies targeting Aβ to reduce aggregation and promote clearance from the brain
Experimental Findings	- Nanoliposomes reduce Aβ aggregation in Alzheimer’s models - Early evidence indicates therapeutic benefits in Alzheimer's models - Low toxicity, especially for unilamellar and PEGylated liposomes
Blood-Brain Barrier [BBB] Crossing	- Nanoliposomes cross the blood-brain barrier [BBB] with brain-targeting peptides such as K16ApoE
Therapeutic Potential	- Potential to restore/improve cognition in AD patients - Low toxicity profiles in vivo, but further research on nanotoxicity and biodistribution is needed
Innovative Nanostructures	- Exosomes as alternative delivery systems for therapeutic agents
Targeted Delivery Systems	- Nanoliposomes mimic ApoE permeability properties for effective brain-targeted cargo transport

Toxicity & Biocompatibility	- Low toxicity observed, including for unilamellar and PEGylated variants - Long-term biocompatibility and adverse effects need thorough evaluation

6. CHALLENGES AND LIMITATIONS

There is hope that liposomes can treat Alzheimer's disease (AD); however, there are a number of issues and restrictions that make their practical application challenging. The biological link of liposome synthesis became an important consideration throughout the preclinical trials. Because they did not alter the allergic reactions of macrophages and blood vessels, liposome-PEG-PACA nanoparticles demonstrated potential as an Alzheimer's disease treatment. Determining suitable therapeutic dose ranges in vivo and finding pertinent cellular settings where nitric oxide-related pathways may be assessed are two aspects of a more thorough approach to biocompatibility evaluation [56]. Concerns about legislation are a major roadblock, particularly in light of the lack of consensus on how liposome technology ought to advance. Liposome-based drug delivery systems must undergo thorough investigation and adjustment to ensure biocompatibility, in vivo stability, biodistribution, and cellular liberation in any specific application. The large compositional difference that allows harmful AD-related components to adhere to liposomes makes it challenging to scale up and produce identical products. For mass production to be cost-effective, we must substantially improve homogeneity. The hypervariability and inadequate biocompatibility of even the most outstanding liposomes make them unsuitable for use in short- or medium-term therapeutic applications [57]. Among these features are a controlled distribution to diseased plaques, a highly controlled size and shape, and a high loading capacity.

6.1 DIFFICULTIES WITH INHERENT BIOCOMPATIBILITY

Nanoliposomes are generally biocompatible since their lipid compositions are similar to those of normal biological membranes. They are more appropriate for intravenous administration due to their interactions with the components of the circulation. The many factors that have been considered in biocompatibility studies comprise the following: size, surface charge, composition, treatment route and frequency, interaction with bodily fluids, breakdown, particular physique locations, and the presence or absence of components. When liposomes are impervious to degradation, deterioration, aggregation, cleanliness, homogeneity, and bodily interactions, their stability is ensured. It is crucial to take immunotoxicity, childhood toxicity, the condition known as cytotoxicity, and physiotoxicity into account for various liposome formulations [58].

6.2 REGULATORY HURDLES

Important regulatory challenges persist in the development of pharmaceutical medications based on nanoliposome technologies that are in the clinical stage. Nanoliposomes are complex structures that include inorganic or organic elements, proteins, and other chemicals. The process for evaluating their toxicity for these nanocarriers is laborious and expensive. The initial commercial goods made with this technology have quite a distance yet to travel before they can be sold due to these obstacles. Nanoliposomes are still in the early stages of development as a possible therapy for Alzheimer's disease, with numerous compounds receiving testing in animal and experimental models [59].

6.3 SCALABILITY OF PRODUCTION

Mastering procedures at the laboratory scale is currently the key to progress in large-scale nanoliposome synthesizing. Importantly, when scaling up, the exact structural and behavioral properties of nanoliposomes should be preserved. High drug loading efficiency, repeatable size distribution, consistency from batch to batch, and a stable nanosystem are all goals that upscale processes should strive for [60]. Despite likely process-related stability difficulties and low encapsulation effectiveness in the nanoliposomes made using the proliposome technological advances, the method is nonetheless used extensively in industrial settings for both batch and continuously operating systems. Proposed for expensive manufacturing are high-pressure-based interpreters like scRPE and DELOS-susp. These procedures offer excellent encapsulation efficiency, sterile conditions, and single-step production, all of which may be produced at the laboratory scale, allowing for the simultaneous development of nanoliposome features [61].

7. FUTURE DIRECTIONS

Conventional pharmacological treatments for Alzheimer's disease (AD) have many limits; however, liposomes show enormous promise in overcoming these limitations. Despite the need for further study of various liposomal formulations, these nanocarriers stimulate new clinical studies for improved treatment of Alzheimer's disease. Many approaches have been explored to improve therapy effectiveness, and some of these show promise. Liposomal delivery systems are an area that is undergoing research. Enhancing therapy efficacy and stability, lowering toxicity, improving cargo capacity, reducing oxidation and size variability, and enabling passive targeting are some of the aims for these systems [62]. Developing liposomes and other items to a standard would allow for their mass production at a reduced

cost by standardizing their composition and fabrication procedures. A major goal is to develop multifunctional liposomes that can attack multiple facets of brain damage at once. Further research is required for determining the most secure method of administering liposomal formulations while simultaneously minimizing their absorption by the retinal endoscopic system. Considering it can help the drugs within the liposomes pass across the blood-brain barrier and specifically target the brain regions important in the progression of Alzheimer's disease (AD), liposome-based drug delivery is an attractive method for treating AD. But there are a few issues that still require our attention [63].

7.1 INNOVATIVE FORMULATIONS

Reformulating established therapeutic compounds into new delivery systems is essential for solving biological problems such as increasing medicine bioavailability or controlling release at the target site. The development of nanocarrier systems has attracted a lot of attention from researchers over the last decade. There are a variety of them, including liposomes, dendrimers, nanoparticles, and polymeric micelles; their individual properties make them applicable to a wide range of therapeutic applications. Inhibiting premature breakdown and minimizing systemic toxicity, liposomal formulations can carry a wide variety of therapeutic molecules to targeted cells and tissues. These molecules may include medicines, gene vectors, and other bioactive compounds [64]. Small vesicles, called nanoliposomes [NLs], can encapsulate an aqueous compartment and create membranes. Their sizes range from 100 to 150 nm. Their surface is extremely hydrophobic. Transporting lipophilic or amphiphilic molecules is a key function of NLs. Their stature and dislike of water provide their primary advantage. NLs can follow the brain's ECM due to their lipid composition and these traits. You may make NLs even more effective delivery techniques by altering their surface so they are better at reaching target tissues. Because of these features, NLs are a suitable choice for brain targeting, particularly when the medicines are designed to interact with specific regions of the ECM [65].

7.2 COMBINATION THERAPIES

There is tremendous hope for overcoming the protective mechanisms that cause Alzheimer's disease (AD) pathology to persist in the brain through combination therapy, notably those that innovatively integrate nanoliposomes with magnetic resonance-guided ultrasound therapy [MRgFUS]. By utilizing MRgFUS technology, therapeutic drugs can be more precisely released and delivered to specific brain regions, yielding higher medication concentrations in the areas that require these the most. Nanoliposomes are multifunctional steric barriers that enhance safety protocols and allow for the precise delivery of medications to target tissues, cells, and receptors in the brain [66]. Integrating therapeutic medicines into ligand-targeted nanoliposomes makes possible the creation of multifunctional methods that interact with cell-surface receptors—essential for bridging the blood-brain barrier. One example of this novel method is the use of medication candidates like Edaravone and alpha-tocopherol acetate in the form of HDL-mimicking nanoliposomes. The SR-BI receptor is an excellent candidate for these potential options since it is ubiquitously expressed, mediates endocytosis, and is a key transport pathway for medications intended to reach endothelial cells in the mind [67]. In addition, the chronic arterial aging of the brain and cerebrovascular pathology that characterize Alzheimer's disease suggest that combination therapies involving ligand-targeted nanoliposomes could have positive effects at different points in the disease's progression, maybe even halting or reversing the disease's course Figure (5). Beyond these benefits, these sophisticated nanoformulations have the potential to offer a noninvasive alternative to ablation for the treatment of Alzheimer's disease in the future by utilizing constituent lipid-coated microbubbles, which significantly decrease the acoustic power required for safe transcranial MRgFUS treatments or non-ablation sonoporation procedures]68[.

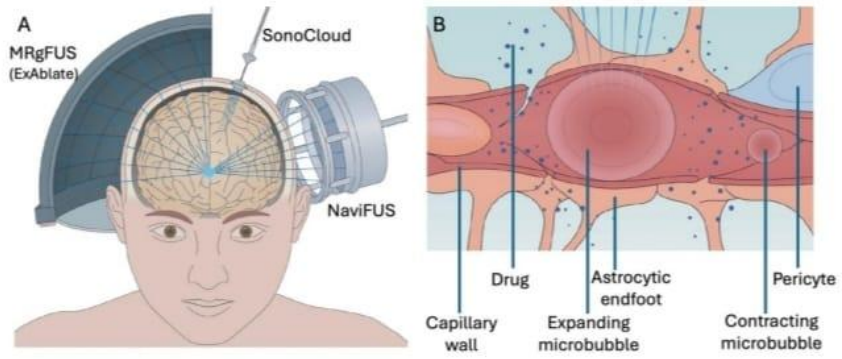

FIGURE 5. - shows MRgFUS, a very precise way to treat Alzheimer's. This graphic shows how MRgFUS technology and microbubbles that enter into the blood can momentarily break the blood-brain barrier. This technique lets you send therapeutic nanocarriers, which include ligand-functionalized [69].

7.3 PERSONALIZED MEDICINE APPROACHES

Nanoliposomes, straight to the brain. These inadequate, localized technical advances make it easier for scientists to deliver antioxidant substances like alpha-acetate to receptors with properties similar to SR-BI. This allows them to treat neurological disorders like Alzheimer's.The remarkable rise of systems biology in the last century has made biological networks more complicated while also coming up with powerful ways to figure out how they are built and how they work. Systems biology necessitates a synergistic array of techniques that elucidate the key elements of networks while simultaneously deriving broad principles of how they work and their functionality. Differential geometry techniques can be integral to the systems biology toolset, particularly since they elucidate the organizing principles of the human organism at many levels. For instance, at the molecular level, the basic concept of organization is what makes the free energy landscape change, which is what keeps proteins secure in cells [70]. Biomolecules interact at the interface, and the mathematical framework that characterizes interaction sites comprises a submanifold embedded within a high-dimensional manifold, which is a geometrical entity. Moreover, unique function is a crucial component of numerous fundamental biological molecules in nature; it can be utilized to elucidate the structured features and the underlying structure-function link of biologic molecules and biomolecular complexes. At the cellular level, feedback loops and regulatory networks are essential for controlling physiological processes and responses to the external environment; a manifold can be utilized to directly characterize the regulatory network in cell cycle and signaling transduction [71]. At the organism level, the emergence of structural complexity in biological shapes can be effectively described by high-order geometric invariants of surfaces, and geometry can be utilized to characterize various life phases of organisms. The idea of Riemann geometric invariants has been used to make Riemann geometrical molecules; however, the geometric formulation used was based on the embedding topology. Geometric invariants have not yet been used in biophysical modeling of proteins. These invariants possess successive derivatives of geometrically significant metrics, hence enabling a near-complete characterization of biomolecular structure and physical properties [72].

8. SEARCH STRATEGY AND METHODOLOGY

A narrative literature analysis was conducted to analyse the cellular and molecular routes of nanoliposome action in the treatment of Alzheimer’s illness. The literature review was conducted utilising the PubMed, Scopus, and Google Scholar databases. Combinations of "Alzheimer's disease," "nanoliposomes," "liposomes," "blood–brain barrier," "amyloid-β," "tau," "neuroinflammation," and "targeted drug delivery" were among the search terms used. Studies published mostly within the last 3–5 years [2020–2025] were prioritized to assure inclusion of recent achievements, although crucial earlier studies were kept to offer essential context. Articles were chosen for their relevance to blood-brain barrier transport, amyloid and tau pathology, neuroinflammation, and the preclinical or translational applications of nanoliposome-based treatment methods.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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