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Research Article

Advanced Drug Delivery For Alzheimer's Disease Using Targeted Nanoparticles Across The Blood-Brain Barrier

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Abstract Recent discoveries in the field of medication delivery for Alzheimer's disease (AD) have focused on the use of customised nanoparticles as a means of breaking the blood-brain barrier (BBB) and boosting the efficacy of therapeutic interventions. This is because the BBB is a barrier that prevents blood from reaching the brain. The small size of nanoparticles, their capacity to modify their surfaces, and their biocompatibility make it possible for them to transport drugs to the brain in an accurate manner. Because of these characteristics, nanoparticles are a material that is both unique and useful. Through the implementation of this focused technique, the objective is to simultaneously increase the bioavailability of the medicine in the brain while simultaneously limiting the occurrence of systemic side effects. There are a number of different types of nanoparticles that have been investigated for their potential to deliver medications that target significant pathological aspects of Alzheimer's disease (AD), such as amyloid-beta plaques and neuroinflammation. These nanoparticles include magnetic nanoparticles, solid lipid nanoparticles, polymeric nanoparticles, and liposomes. Preclinical models of Alzheimer's disease (AD) have revealed promising findings, exhibiting improved drug delivery efficiency and therapeutic outcomes. These findings have been demonstrated by investigations. This study discusses the use of targeted nanoparticles as a sophisticated drug delivery system for the treatment of Alzheimer's disease. Additionally, the paper discusses the current developments, challenges, and potential future applications of this method.

Keywords: Advanced Drug delivery, blood-brain barrier, Alzheimer's disease, targeted nanoparticles.

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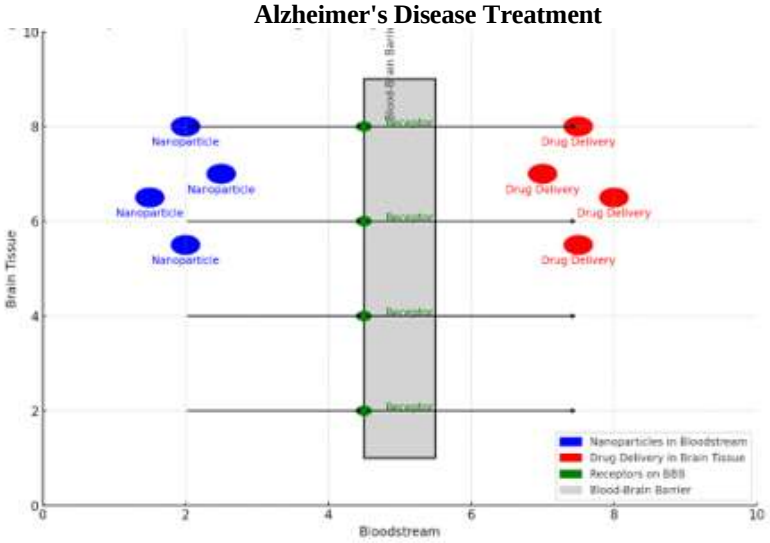
I. Introduction:

As a degenerative neurological disorder, Alzheimer's disease (AD) causes mental impairment, behavioural changes, and a gradual deterioration in cognitive abilities over time. Despite much research, the blood-brain barrier (BBB) remains a major obstacle, making it such that few viable restorative treatments are now available. An impermeable barrier that regulates the passage of essential chemicals into and out of the brain, the blood-brain barrier (BBB) uses selective porosity to keep harmful substances out.

Figure 1: Mechanism of Targeted Nanoparticle-Mediated Drug Delivery Across the Blood-Brain Barrier for Alzheimer's Disease Treatment

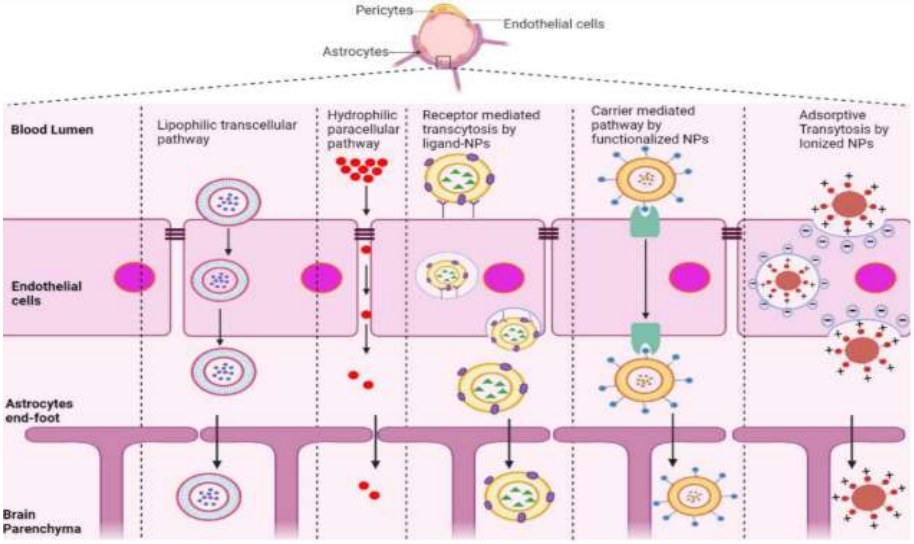


Promising approaches to overcoming these obstacles are provided by recent developments in nanotechnology. Targeted nanoparticles are a cutting-edge method of drug administration that offer improved efficacy and precision in the passage of therapeutic substances across the blood-brain barrier. Drug distribution to specific brain areas can be facilitated by engineering these nanoparticles to interact with certain receptors or transport mechanisms on the blood-brain barrier (BBB). By reducing systemic side effects and increasing the absorption of therapeutic drugs, this focused strategy paves the path for safer and more effective Alzheimer's disease treatments. In this regard, the creation of sophisticated drug delivery systems that make use of targeted nanoparticles is a noteworthy advancement in the field of Alzheimer's research. Researchers hope to improve treatment outcomes for AD patients by better delivering medications to the brain through the use of nanoparticles' special qualities.

II. Blood-Brain Barrier (BBB) Physiology and Structure:

The Blood-Brain Barrier serves as a strong guard, keeping out hurtful substances and infections. That so, it poses a significant test to the treatment of neurological conditions such as AD and Parkinson's disease (PD) because it obstructs the brain's capacity to absorb numerous possible treatments. In AD, there is an immediate connection among's tau and amyloid pathology and BBB disability. Drug-loaded nanoparticles (NPs) that append to target proteins associated with the blood-brain barrier are intensively studied as precision medications. Penetrability across the blood-brain barrier is in this manner a necessary precondition for remedial medicines to treat AD.

Figure 2: Possible routes of NP-based drug delivery systems that cross the blood-brain barrier to treat Alzheimer's disease.



Nucleotides, natural anions and cations, vitamins, and hormones are undeniably transported over the blood-brain barrier by CMT. Transmembrane fundamental proteins work with spontaneous passive transport along a fixation gradient in CMT. Because the brain requires glucose constantly, glucose transporters like Overabundance 1 and Excess 3 will ensure that glucose is transported significantly under low blood glucose conditions. The fundamental course by means of which macromolecules necessary for brain capability are transported across the blood-brain barrier is RMT. Certain medications can enter the brain all the more regularly as people age or develop clinical disorders. Through their penetration of the intercellular space and passage through the epithelium, paracellular routes empower the transmission of components. Transcellular transport, then again, makes it possible for substances to pass through a cell by spanning the basolateral and apical membranes. The BBB is penetrated by three primary types of transporters, which can be used as targets to convey medications into the brain.

III. Role of the Blood-Brain Barrier in Drug Delivery:

We presently have far more noteworthy information on the BBB's composition and operations. Additionally, a summary of a couple of BBB dysfunctions in AD has been provided. There are two types of methods for getting chemicals into the brain: invasive and painless. The direct administration of prescription into the brain is an invasive method. Using high osmolar solutions to temporarily open the tight connections, infusing medications intracerebrally, or using a catheter to direct drug infusion are different methods. Then again, invasive techniques are hazardous essentially. After prescription is administered, there is an opportunity of disease, possible brain tissue injury, and perhaps uncontrolled drug distribution. As a result, painless techniques are typically chosen. Intravenous infusion or intranasal administration are two painless therapeutic delivery methods. When the medications pass through the nasal epithelium, they can enter the brain through the nasal course. The extracellular course, which is the quickest way for molecules to enter the central nervous system, will be used to administer the medications along the olfactory and trigeminal neuronal circuits. With this strategy, transcytosis can happen without the drug binding to any receptor. Nevertheless, since each dose is just 20-30 µL, the administration needs materials that are profoundly soluble. The therapeutic plan's salinity and pH both influences how well a drug is conveyed. Outrageous weather conditions can hurt the respiratory system. Furthermore, because an ineffective injection could cause the medication to end up in the stomach or lungs, intranasal administration calls for deft manoeuvres. Intravenous delivery is therefore typically a popular option. Focused ultrasound (FUS) is another harmless strategy for brain delivery that temporarily opens the blood-brain barrier. Low-recurrence ultrasound waves can cause disruption of the blood-brain barrier when microbubbles are administered intravenously prior to sonication. This approach shows promise for conveying medicines, such as antibodies, nanoparticles, and chemotherapy, to specific areas of the brain. Besides, the BBB opening procedure is completely reversible. Five AD patients were reportedly given targeted ultrasound directed by attractive resonance. It was confirmed that the BBB had opened and been restored. The outcomes were empowering. Nevertheless, the study's sample size was restricted, and its effectiveness in treating AD was not analyzed.

Table 1: Characteristics of AD blood-brain barrier dysfunction.

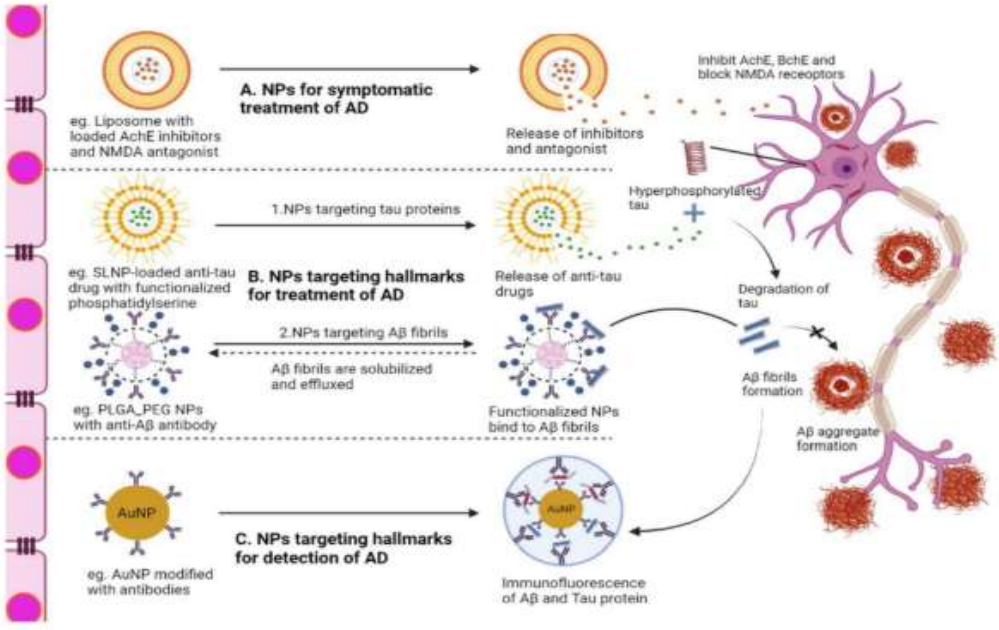
COMPONENT	FEATURES
Capillaries	Total length is shorter.
GLUT1	Downregulated, resulting in reduction of Aβ clearance.
Transferrin receptor	Number of receptors in hippocampus is less than normal.

Insulin receptor	Brain insulin receptor density decreases with aging.
Lactoferrin	Expression is upregulated.
Melanotransferrin	

Most of drugs demonstrating therapeutic advantage in AD therapy are lipophilic substances with restricted water solubility. To improve the brain's absorption of medicinal compounds, a number of approaches could be considered. Changing the structure of restorative molecules allows one to modify their physical and synthetic qualities. There are usually a number of steps in the synthesis, and sample loss increases with each one. Another approach involves combining different cell-penetrating peptides or antibodies to create the therapeutic molecules. This approach can facilitate the medication's transcytosis over the blood-brain barrier via the receptor-and adsorptive-mediated routes. The details of these routes were discussed in the preceding section. It is still necessary to tackle concerns with the drug dissociation rate from ligands and the drug/ligand and ligand/receptor ratios, even though ligand-formed drugs improve drug transport into the brain. Nanotechnology-based DDSs are a suitable substitute that should be thought about to address the previously mentioned issues.

IV. **Nanoparticle (Np)-Based Delivery System for The Treatment of Ad:** We describe the numerous kinds of nanoparticles (NPs), drug molecules they contain, parts of the carrier materials, formed ligands on the NPs surface, drug dosages, way of administration, sort of model, and results seen in various in vitro, in vivo, and ex vivo research models. NPs for symptomatic therapy, NPs focusing on AD hallmarks, and NPs focusing on hallmarks for AD diagnosis are the three primary groups into which the mechanisms of NPs fall. First, while NPs containing NMDA antagonists and Hurt inhibitors (donepezil, rivastigmine, galantamine, and memantine) show up at the objective district, they release their freight, which inhibits the enzymes that improve cholinergic transmission and stops current from flowing through NMDA channels, so lightening AD symptoms. Second, NPs loaded with medications that focus on the two fundamental characteristics of AD (tau) capability as treatments that influence the disease and may try and have the option to fix AD. The counter tau medications (TRx0237, LY3372689) block the total of tau proteins by specifically focusing on hyperphosphorylated tau proteins. Moreover, Aβ fibrils and discharge in the blood circulation are captured by NP-formed enemy of Aβ antibodies (aducanumab, pipenimab), which reduces Aβ plaques.

Figure 3: After crossing the blood-brain barrier, the action mechanism of NPs in AD-related neurons is shown



i. Liposomes:

Liposomes are tiny, spherical, double-layered vesicles with bilayer membranes made of phospholipids. While the outer lipid layers serve as a shielding layer and are appropriate for lipophilic medications, they can also transport hydrophilic pharmaceuticals such as donepezil, rivastigmine, and galantamine. They can cross the blood-brain barrier (BBB) by conjugating with targeted moieties

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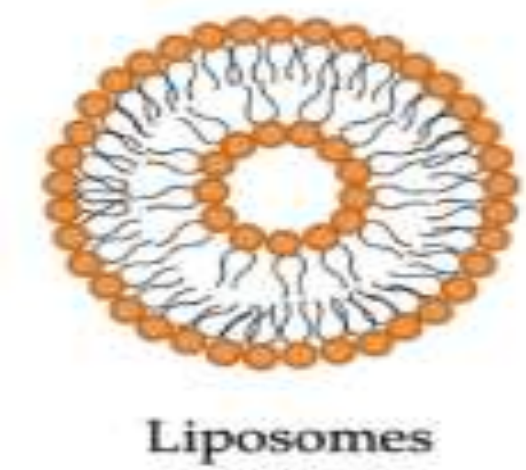
Figure 4: Liposomes

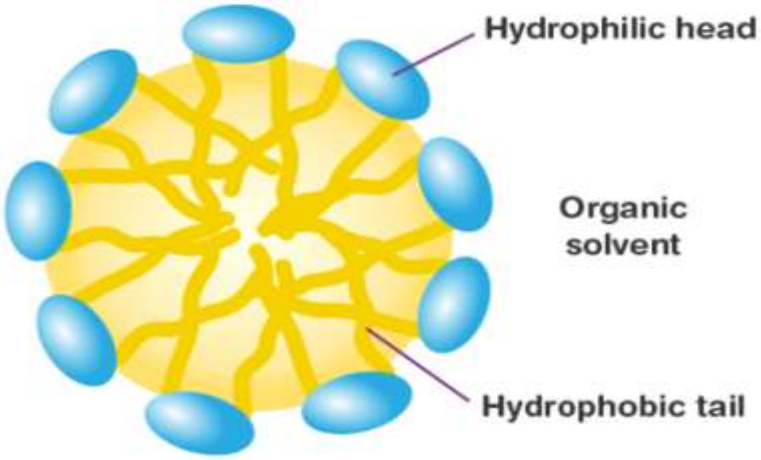


ApoE2-encoding plasmid DNA (pApoE2) can be productively conveyed to the brain using surface-altered liposomes, paving the way for successful AD treatment. The BBB-crossing delivery of amyloid-focusing on immune response fragments has been improved by PEGylated liposomes. Thousands of PEG polymer strands are joined to make Trojan horse liposomes (THLs), which are then coupled with monoclonal antibodies that are specific to peptides or receptors.

ii. Micelles:

Micelles are round, amphiphilic drug carriers that feature a hydrophilic shell and a hydrophobic centre, each with its own set of properties. Their particle size ranges from 5 to 50 nm. Micelles are able to be administered intravenously because their hydrophobic core contains the medicinal compounds and their hydrophilic coating makes them water soluble.

Figure 5: Micelles

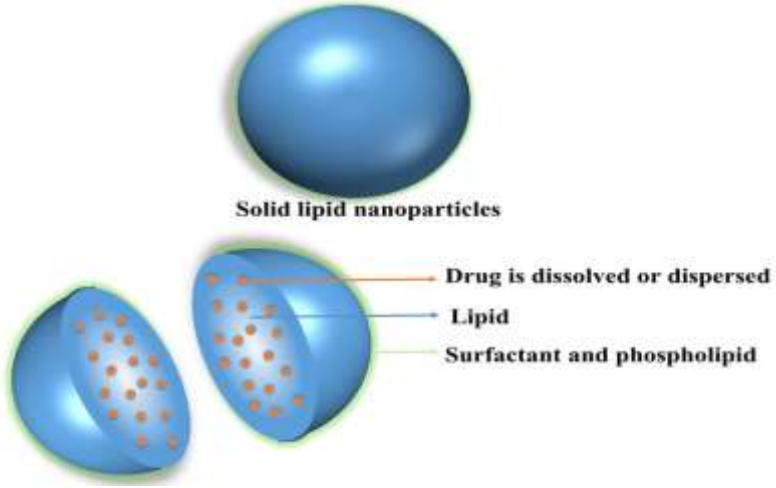


The polymeric micelle drug delivery system (ABPEG-LysB/Dog) was created using three components: an amphiphilic polymer (PEG-LysB) that is responsive to reactive oxygen species (ROS) and can remove them, a hydrophilic drug called curcumin that specifically targets the aggregation of Aβ protein, and a peptide (Stomach muscle) that specifically targets the receptor for advanced glycation end products (RAGE) derived from Aβ protein. By utilising the Aβ transportation-impersonated mechanism, this micelle gathered in the affected areas and, through microenvironmental activation, exhibited dual actions of inhibiting Aβ accumulation and scavenging ROS using polymers.

iii. Solid Lipid NPs (SLNs):

Solid-state lipid-based network systems, or SLNs, have a lipid-forming center that can develop at both physiological and room temperature. They have a width of 50-1000 nm. High trapping of hydrophobic medications with a controlled release profile is possible with these SLNs. At present, SLN is a notable drug carrier system that really moves dynamic restorative freight to precise objective locations in the brain across the BBB.

Figure 6: Solid Lipid NPs (SLNs)

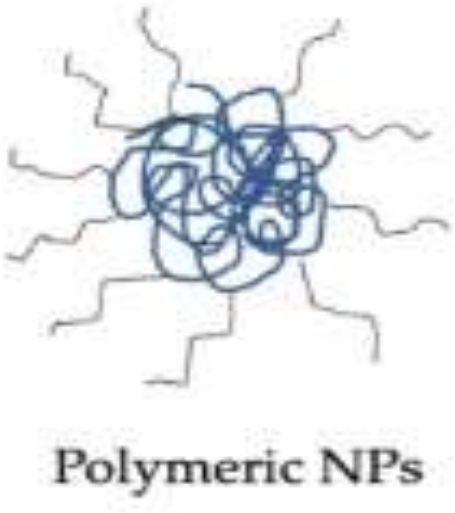


Galantamine in SLNs is comparable to liposomes in size and entrapment efficiency, measuring around 100 nm and 83%, respectively. The AUC of oral SLNs is thirty times higher than that of intranasal liposomes containing galantamine. SLNs were developed by Shah et al. to deliver hydrophilic rivastigmine intranasally with efficacy. To improve oxidative stress and mental deficits associated with vascular dementia, resveratrol, a polyphenolic particle making neuroprotective impacts, was added to SLNs. Quercetin SLNs functionalized with transferrin were made to improve cell reinforcement action and focusing on effectiveness.

iv. Polymeric NPs (PNPs):

PNPs are solid carriers of nanoscale colloidal natural chemicals derived from natural or synthetic polymetric materials. Recent years have seen extensive research into a wide variety of polymers with the hope of developing PNPs that can target certain regions of the body to deliver AD medicines. The most researched polymer is polylactic acid (PLGA) due to its biocompatibility with cells and tissues, sustained release properties, and low toxicity. According to Baysal et al., PLGA-bPEG nanoparticles loaded with donepezil can disrupt the synthesis of Aβ fibrils in laboratory settings and have a neuroprotective effect. Evidence suggests that PLGA-b-PEG exhibited a regulated release profile, with 60% of the drug loaded into the particle reaching its peak during the first two hours of release, in contrast to donepezil-laden liposomes and solid liposome nanoparticles. In addition, extended-release formulations including half-and-half PNPs delivered by poly (L-lactic acid) (PLA) and poly (L-glycoprotein A) (PLGA) can reduce dosage recurrence and adverse effects.

Figure 7: Polymeric NPs (PNPs)



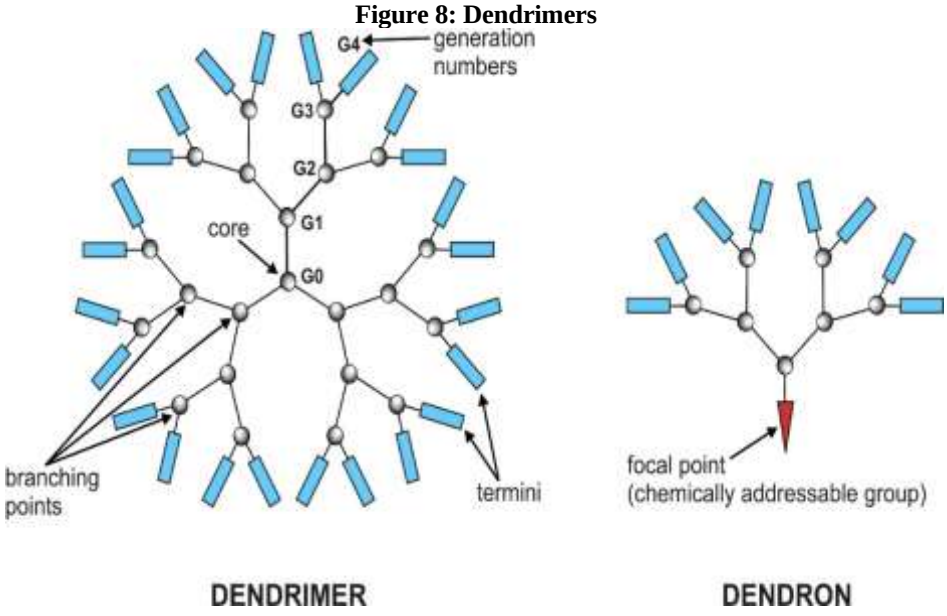
The PLA/PLGA cross breed nanoparticles that Nanaki made with galantamine demonstrated viable intranasal delivery in mouse models of Alzheimer's disease (AD). The galantamine-loaded PNP was less likely to total because of its small size of 200 nm. L-lactide-depsipeptide PNPs with rivastigmine were developed by Pager et al., and they demonstrated increased safety and adequacy. The addition of resveratrol to PNPs (RES-PNPs) improved their antioxidative capacity and relieved the effects of γ-beam radiation and overexpression of the Aβ peptide. Curcumin, a substance having calming, cell reinforcement, and hostile to amyloid qualities. Ascorbic

acid (AA) and epigallocatechin-3-gallate (EGCG) loaded in PLGA-PEG PNPs were proposed as a double pharmacological therapy by Cano et al. The neuroprotective qualities of pomiglitazone (PGZ) have made it an alluring candidate for the treatment of AD. Biodegradable PLGA NPs encapsulated with quercetin prevented zinc Aβ-incited cytotoxicity, improved mental capability and memory deficits, raised the therapeutic record, and decreased adverse effects. A potential PNP-based carrier for the transport of drugs to the brain is chitosan.

V. Dendrimers:

Consistently spreading molecules having distinct, multivalent three-dimensional shape are known as dendrimers. A dendron is the single useful unit of a dendrimer that initiates branches. The payload medications are either associated with the branches of the dendrimer or appended to its surface.

Figure 8: Dendrimers

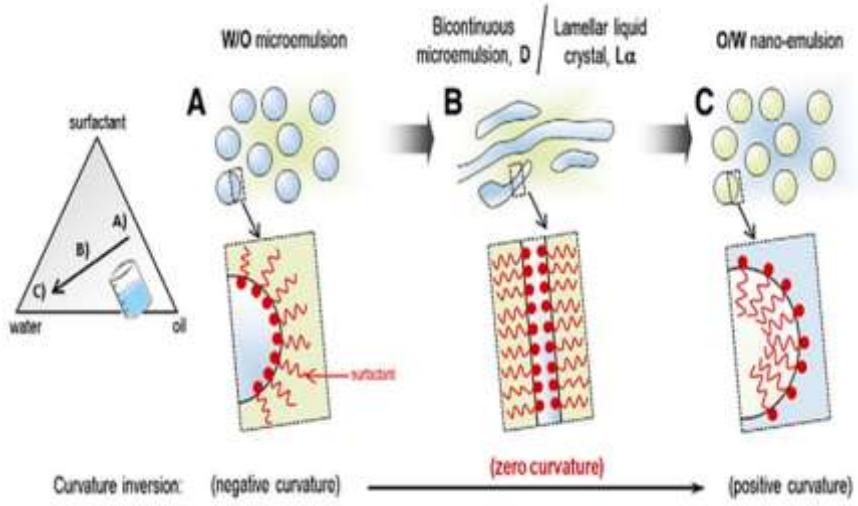


Another dendrimerPPARα/γ twofold agonist compound (D-tesaglitazar) produced a M1 to M20 phenotypic shift and upgraded macrophage Aβ phagocytosis, as per another publication.

vi. Nanoemulsions (NEs):

NEs are used to lessen side effects and hurtful reactions while improving medicine distribution to the intended locations. The sort of oil used in NEs is critical to their absorption into the central nervous system. Besides, NEs have a significant potential for conveying the freight medication to the brain by means of the blood-brain barrier due to their lipidic composition. Recently, donepezil and loaded memantine were prepared in NEs by Kaur et al. to treat AD. The Neuro 2a cell line demonstrated dose-dependent toxicity for both memantine and donepezilloaded NEs.

Figure 9: Nanoemulsions (NEs)



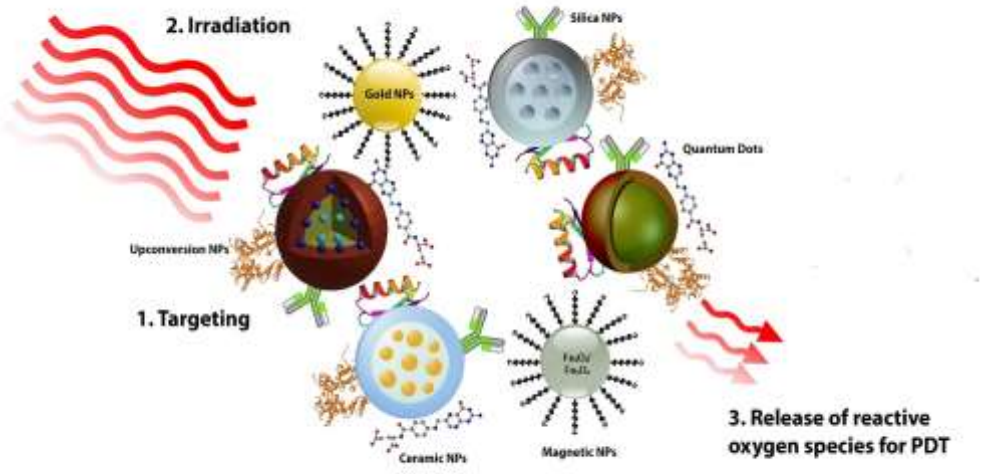
In vivo experiments using intravenous, intranasal, and oral routes to administer memantine and donepezil-loaded NEs to rats induced with AD showed that the intranasal route produced the highest brain uptake in comparison to

the other administration routes. Memantine-loaded NE demonstrated a speedier drug release pace of 80% in 6 hours, which was comparable to the memantine-loaded dendrimer's 77% rate at 6 hours.

vii. Inorganic NPs:

Gold, silver, aluminum, and silicon dioxide are examples of inorganic nanoparticles that are stable, hydrophilic, and non-poisonous. They are being explored for use in radiation, medication administration, and imaging for both therapeutic and diagnostic purposes. Among the NPs with special qualities are attractive NPs, gold NPs, and quantum dots (QDs). Ongoing research has demonstrated the potential for multi-targeted AD treatment using graphene QDs, dark phosphorous QDs, and selenium-doped carbon QDs.

Figure 10: Inorganic NPs



SeCQDs have been functionalized to restrict Alzheimer's disease (AD) neurodegeneration and lower Aβ accumulation. Cu-GQDs are extremely sensitive, stable, and selective in distinguishing the ApoE4 DNA, which causes AD. Colloidal gold particles, or AuNPs, are employed in drug administration, diagnostic assays, warm removal, and radiation therapy expansion. Stabilized L- and D-glutathione-loaded AuNPs are intended to impede Aβ42 without causing appreciable harmfulness. AuNPs have also been demonstrated to increase neuronal survival, boost spatial learning and memory, and distinguish tau, an AD characteristic. The appealing qualities of MNPs — which are composed of an attractive material and a useful compound component — stand out to them in the fields of attractive resonance imaging, biomedicine, and nanomaterial-based catalysts.

V. Conclusion:

Finally, targeted nanoparticles for blood-brain barrier (BBB) drug administration are a major achievement in Alzheimer's disease (AD) treatment. Due to the BBB's restrictions, current approaches for brain drug delivery generally fail. These nanoparticles may solve this problem. Researchers can improve BBB penetration and drug delivery to the brain parenchyma by using nanoparticles with surface changes and functionalization. In preclinical AD pathology research, liposomes, solid lipid nanoparticles, polymeric nanoparticles, and magnetic nanoparticles have showed promise. These nanoparticles can encapsulate amyloid-beta plaque, tau tangle, and neuroinflammation-targeting medicines to halt disease progression and improve cognition. Targeted nanoparticle distribution has controlled release kinetics, longer circulation time, and lower systemic toxicity than conventional drug administration. To maximise therapeutic efficacy and minimise peripheral organ damage, these traits are essential. Future studies must improve nanoparticle compositions, targeting specificity, and safety for clinical translation. These new drug delivery technologies must overcome nanoparticle stability, scalability, and long-term safety issues to go from preclinical investigations to clinical trials and AD patient applications. Overall, targeted nanoparticle-based medication delivery may improve AD treatment by overcoming biological barriers and improving results.

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