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Review Article

A Potential Notion on Alzheimer's Disease: Nanotechnology as an Alternative Solution

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Alzheimer's disease is an eventually destroying disease of the overaged people featured by the dynamic and gradual brain erosion because of construction of extracellular plaques in the hippocampus. It is an undertreated and underrecognized disease that is becoming a major public health concern. From the study, it is known that production of plaques takes place twenty years back, before the commencement of clinical syndromes. As per report, in 2019, above 50 million people got into Alzheimer's disease. Recent developments include improved clinical diagnostic guidelines and improved treatment of both cognitive disturbance and behavioral problems. Treatment majorly focus on cholinergic therapy has been clinically evaluated by different studies including randomized, double-blind, placebo-controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior. The presence of extracellular plaques of insoluble β-amyloid peptide (Aβ) and neurofibrillary tangles (NFT) containing hyperphosphorylated tau protein (P-tau) in the neuronal cytoplasm is a remarkable pathophysiological cause in patients' brains. The graph of increasing patients, suffering from Alzheimer's disease, is being ascended. The outcome of this turn into fatal, deadly situation. So, there is a possibility of breaking down world economics and human strength. There is a different kind of organic as well as inorganic nanocomponent group, those have been pursued with satisfaction. By studying and researching over pathogenesis specifically, diagnosis of this AD as per its symptoms is possibly done. Treatment of this neurodisease is under processing. The experts are playing an extremely appreciable role for displacing this disease completely. The present review summarizes the pathophysiology and role of the nanoparticle in the diagnosis and treatment of AD.

1. Introduction

Alzheimer's disease, a neurodegenerative disorder, generates memory and learning scarcity. It is not a reversible disorder. People, who are above 65, mostly suffer from this disease. Though the pathophysiology of Alzheimer's disease is very distinct to us, the procedure of treatment is not of clear perspective at all. It only gives a very less satisfaction to

minimize enhancement of symptoms of the disease and to regulate the phenomenon of disease. It stands fifth as reason of death of over 65 aged people. The approved drugs used for this treatment of Alzheimer's disease are relied on neurotransmitter or modulation of enzymes like acetylcholinesterase inhibitors. Again, it is not found as a successful treatment. It cannot pass because of less solubility, low bioavailability, and incapability of overthrowing barriers resides along with drug transportation routes as well, especially while transcending blood brain barrier. As we know, the blood–brain barrier is the most specific, made up of tightly connected endothelial cells and irregular stratum of pericytes [1]. Here, paracellular or transcellular transport is possible. Here, drugs are being enhanced and improved for targeting Aβ attestation and tau phosphorylation. There are more than 100 drugs, which are in phase II and III clinical trials and are not so effective as per depressed outcomes. In the early step of AD, AMPA dysfunction is instigated by soluble Ab as well as dendritic changes. Solanezumab is a monoclonal antibody that targets AB, basically improved to restrict cognitive deficits, and was not successful to develop cognition or sectional capability in patients with Alzheimer's disease in clinical trial. Leucomethylthioninium bis might prevent tau accumulation, but adequate trial is required to assure the potential. In these circumstances, it is highly required to have a new, innovative device for treatment of this Alzheimer's disease [2].

2. Pathogenesis of Alzheimer's Disease

Alzheimer's disease is a persistent neurodegenerative disease distinguished by the disablement of evocation and coherent obligation (Figure 1). It is one of the usual neurodegenerative diseases in the world. Mostly, people, who are aged above sixty-five, are mainly affected with this specific disease [3].

2.1. Pathophysiology. In the area of brain, deprivation of synapse widely and neuronal expiry takes place. As a result, analytical functions stop over there. Apoptosis of the neuron inside the brain comes out because of existence of accumulated amyloid plaques (amyloid beta peptide) and neurofibrillary tangles (tau protein filaments). These accumulations create diminished constraints. As per pathology, there are two types of postulations. One is based on amyloid cascade neurodegeneration and another one related to the disablement of cholinergic process (Figure 1). The initiation of Alzheimer's disease happens through the proteolytic splitting of the amyloid pioneer proteins (by disarranging of homeostatic mechanism) that effects in the excess abundance of amyloid–beta and production of amyloid plaques. There are some conditions like age, ecological, and hereditary which accelerates in shifting metabolically that can hold esteem in the system of amyloid protein pioneer. Here, two enzymes, beta-secretase and gamma-secretase (constituents of the presenilin compounds), helps to split amyloid-beta peptides (Figure 2). The outcome of mutation in the amyloid pioneer protein with a presenilin compound is enhancement of amyloid-beta accumulation in patients with Alzheimer's disease [4].

2.2. Characteristics of Nanomaterials and their Appliance in Nanomedicine. Nanomaterials play a significant role in developing drug durability and therapeutic efficiency. These possess a wide embarked surface area, which helps in lading huge amounts of drug and conserving drugs from enzymatic deterioration. These materials show specific physicochemical features because of their surface yield, quantum dimension outcomes, and macroquantum effects. Nanomedicines are very advantageous and potent as per its appliance [5]. So, choosing and designing of nanotransporters for transporting and carrying are under tough conditions. One must be very careful and responsible at the time of selection of nanomaterials. Evaluation of toxic level and safety measurement is one of the beneficial steps. For making the transport successful and increasing the efficiency of treatment, it must be focused on size, shapes, surface impose, and surface functionalization. Uptaking and transporting nanoparticles are size dependent. Size of nano-materials must be relevant because of specific route of administration, carrier procedure, fluid-chemistry. As per previous data, nanoparticles sized less than 200 nm are capable of intense brain permeation and wide space circulation as compared to bigger particle sized materials. Nanoparticles, which have diameter less than 5 nm (Figure 3), have been constructed to be impressionable to fast renal removal added to restricted dealing capacity and rapid drug deliverance dynamics that put them insufficient transport fluids. The surface charge of upgraded nanomaterials leads an important disposition regarding revival and cellular toxicity of enhanced technicality for brain transportation. Here, positively charged mediums are desired for transportation of siRNA9 (negatively charged), and earlier data revealed that nanotransporters containing positive charges produce the toxic effect to BBB (Figure 4). So, to get efficiency, transporters with a neutral to negative charge have been more generally pursued as a carrier. The surface charge of nanoporters is affected through protein adsorption. By utilizing in vitro and in vivo pattern, interrelation between nanoparticles and serum substituents are being evaluated. Apart from that surface charge also impacts over cellular intake, dispensation, and efficiency of nanodrug particles relying on route of administration, cell target, and functions [6].

2.3. Dendrimers. Dendrimers are the polymers, which are suprabranched. The structure is 3-D arranged with excess regulated mass. Size, shape, magnitude, volumes, and surface chemistry carry beneficial features for treatment and diagnosis of particular disease. These particles are framed with a basic core, surrounded by linked functional groups along the peripheral region. By affixing of subsequent strata with every generation, diameter of dendrimer maximizes by 1 nm. Dendrimers are used for transportation of drugs. These are able to maintain drug levels at therapeutic levels, maximize the circulation half-life of active components, and raise drug transport and durability. Biomolecules conjugate to the surface of dendrimers, and an excess drug

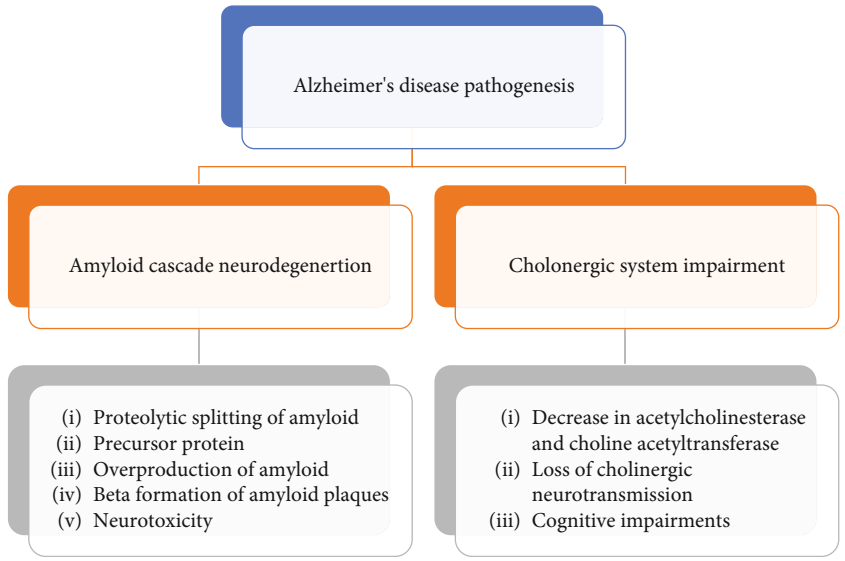

Figure 1: Chart Pathogenesis of Alzheimer's disease.

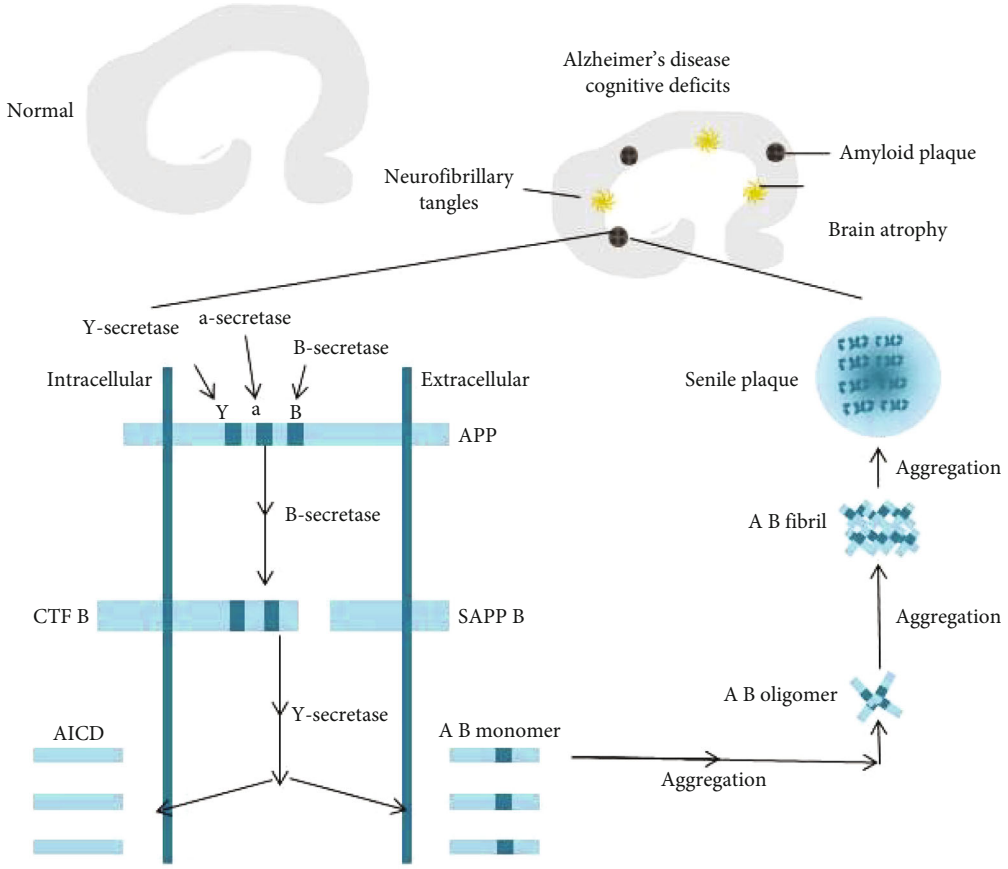

Figure 2: The major pathological characteristics of Alzheimer's disease. Accumulation of amyloid beta, neurofibrillary tangles persuaded by hyper phosphorylated tau protein and neuronal apoptosis. Amyloid beta is produced from amyloid beta precursor protein splitted by beta secretase and gamma secretase. AB monomer accumulates to produce oligomers of various molecular weight and then fibriller AB. These forms plaques in the brains of AD patients. Excessive accumulation, tau hyperphosphorylation, and neuronal apoptosis initiate series of pathological alterations including cognitive deficits and brain atrophy.

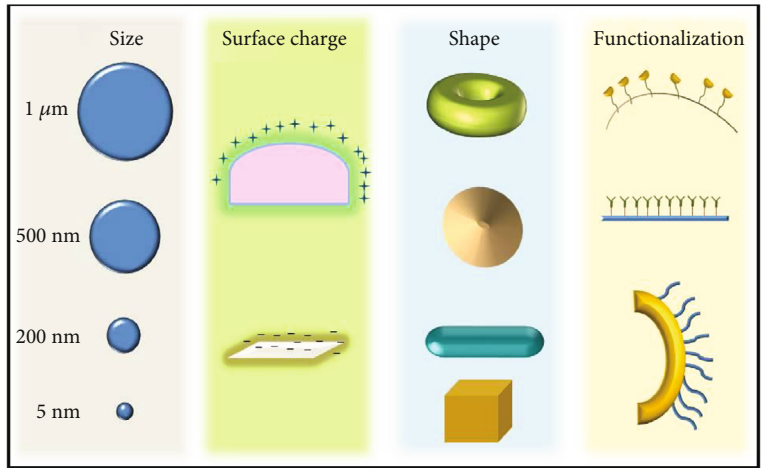

Figure 3: Key physicochemical characteristics for the development of nanomaterial technologies to cross the blood–brain barrier for Alzheimer's disease treatment. Size, shape, surface charge, and functionalization greatly influence the nanocarrier efficacy for drug delivery to the brain. Nanoparticles between 5 and 200 nm have been shown to penetrate the brain more efficiently than larger particles, in addition to being efficaciously internalized by macrophages for cell-mediated delivery across the blood–brain barrier. The surface charge of the nanotechnologies used for brain delivery must be carefully controlled to minimize the potential toxicity of each platform. Furthermore, nanoparticle shape can significantly enhance the circulation and uptake of nanomedicines. Finally, surface functionalization of the nanocarrier offers an extensive range of possibilities to improve brain penetration and target specific cell receptors with the use of small molecules, antibodies, or peptides.

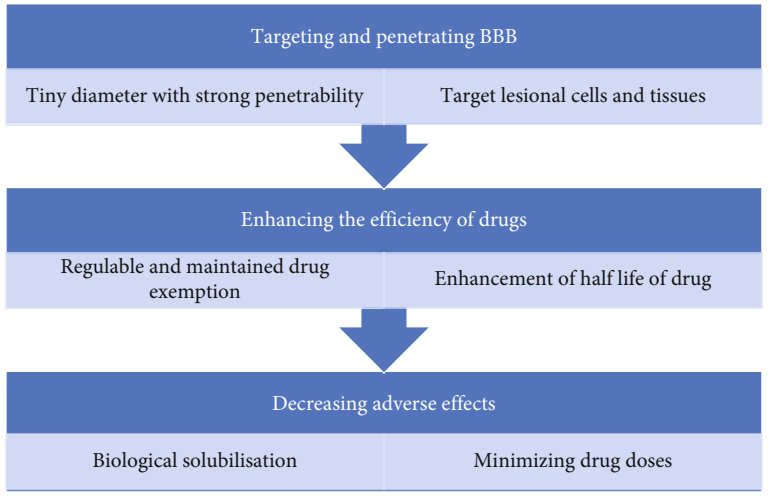

Figure 4: Characteristics of nanomaterials are shown in the chart. Modified nanomaterials can target lesional cells and tissues. Nanomaterials modified with specific molecules have small diameters with high efficient penetrability that make them focus and penetrate the blood-brain barrier with perpetuated drug release, developed bioavailability, and enhanced drug half-life, therefore minimizing drug doses, enlarging drug efficacy, and reducing adverse effects.

burdening capacity inside inner perforation is shown. These molecules are keen of proteins, peptides, lipids, ligands, and nucleic acid highly. Some dendrimers are wide in a variety like poly(aminoamine) (PAMAM), polyether hydroxylamine (PEHAM), and poly-(propyleneimine) (PPI) dendrimers. The PAMAM dendrimer has comprehensive chemical features. This polycationic PAMAM consists of te primary amine group at its surface area. Another half-generation PAMAM dendrimer is polyanionic, which contains carboxylic acid groups on surface. It helps in efficient appliance of these transporters. Dendrimers are utilized as antiamiloydogenic components. For example, fourth-generation PPI maltose (PPI-G4-Mal) and fifth-generation PPI maltose (PPI-G5-Mal) glycodendrimers have shown the efficiency of shattering the amyloid-beta peptide, especially A beta (1-40) fibrilization. Every individual process has various procedures to hinder AB fibrilization. Whereas PPI-G4-Mal produces grove fibrils at down side of dendrimers-peptide ratios as well as amorphous accumulates at elevated ratios, the fifth-generation dendrimers prevent fibril organization by producing granulated nonfibrillar amorphous assembles. From this information,

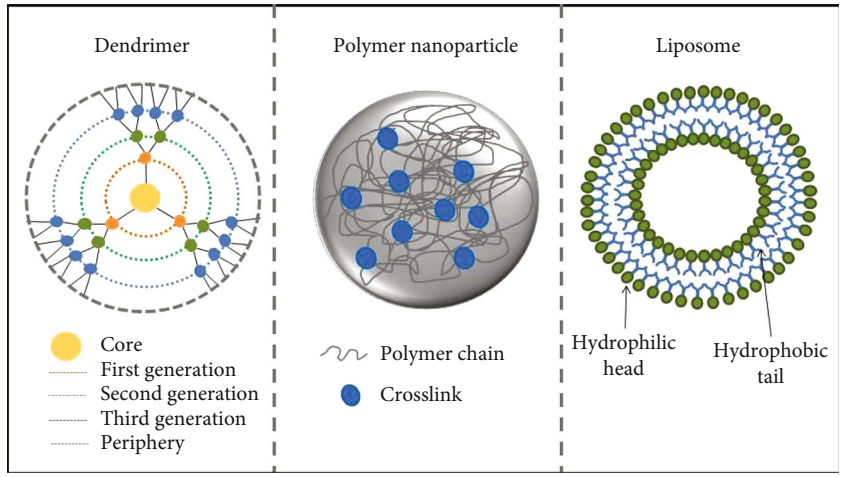

Figure 5: Anatomy of nanocarriers used for Alzheimer's disease drug delivery across the blood–brain barrier. Dendrimers, polymeric nanoparticles, and liposomes are examples of nanocarriers that have been used to deliver therapeutic agents across the blood–brain barrier for the treatment of Alzheimer's disease. To cross the blood–brain barrier, studies have shown optimal particle diameters ranging from 5 to 200 nm.

we came to know that protecting fibril clumping may be utilized as an efficient access in identifying the upgradation of Alzheimer's disease. CPDs (generation 3 and 4) have anti-inflammatory features through blocking acetylcholine hydrolysis as well as occupying antioxidant characteristics (Figure 5) [7, 8].

2.4. Polymeric Nanoparticles. The size of polymeric nanomaterials are approximately 1 to 1000 nm as well as multipurpose and harmonious process. In comparison with other materials, polymers have singular combined form of features possessing those components to be utilized for different drug transportation appliances (Figure 5) [9, 10]. Additionally, nanocomponents can be synthesized both naturally and artificially from polymers. Polysaccharides, poly(ethylenimines), poly(alkyl cyanoacrylates), poly(methylidine malonates), and polyesters are examples of polymers utilized for transportation. Polybutylcyanoacrylate (PBCA) is the earliest polymer-dependent nanocomponents used to transport therapeutic materials to the CNS. These were formed through emulsion polymerization of polyalkylcyanoacrylates. As per this information, an opoid peptide named dalargin burdened PBCA nanomolecules were wrapped with polysorbate 80 (Tween80) and transported intravenously. The ultimate object of that was to get therapeutic steps of dalargin, residing in CNS, marking drug passes through BBB. Polysorbate 80 accelerates the power of penetrating of polymeric nanomolecules through the BBB. Nanocomponents, which stream through blood, are rapidly caught by reticuloendothelial process through opsonization. Inside the process of circulation, to increase the duration time of residing, there should be minimization of particle size/absorption of surfactants (polysorbate 80) on the surface that is operative, particularly, surfactant polysorbate 80.

2.5. Liposome. Liposomes are globules, with composition of one lipid bilayer, encompassed with an inward aqueous chamber (Figure 5) [11]. Liposomes incorporate with phospholipids, and thus, unilamellar and multilamellar formations take place. There are some phenomenons, by which liposomes can be prepared like sonication, extrusion, reverse-phase evaporation, or high-pressure homogenization. The method of synthesis of liposome is simple. These have property of intense bioavailability, biocompatibility, and less poisonous. Additionally, these globules are capable of transporting such kind of drugs, which are hydrophilic, hydrophobic, and lipophilic in nature. The usage of liposome in the transportation process exhibits suitable features because of their rapid elevation by reticuloendothelial process. For increasing time of circulating, the globule size is reduced to tiny extent as well as surfaces are rectified by utilizing PEG. Liposomes trigger on $\alpha\beta$ peptides to hinder the synthesis of senile plaques. Even if, PEG-covered liposomes were active by utilizing anti $\alpha\beta$ monoclonal antibodies. Though the proper mechanism of penetrating peptide is unknown, yet, this establishment of these peptides raised penetrative power through the blood–brain barrier.

3. Diagnosis

The nanomaterial is also accepting growing focus for the treatment of AD. Nanomaterial are the nanostructural material that carries therapeutically active substance cross the BBB and have powerful target affinity and likely high effectiveness Therefore, he nanomaterial coupled to therapeutically active substance may be useful for monogenic disease like AD [12].

3.1. Nanotechnology in Diagnosis of AD. The recent focus in producing NPs for imaging and molecular tackling of biomarkers is the promise of accurate diagnosis of Alzheimer's disease. Nanotechnology allows for highly powerful signal transduction, which might aid in the early detection of Alzheimer's disease. The physical (magnetic, optical, or electrical), chemical, and/or biological quality of cleverly structured nanomolecules is the foundation for this possible application

of nanotechnology in imaging/diagnostic. Traditionally, the soluble biomarkers of Alzheimer's disease may be discovered using one of two methods. The first is relied on assessing the total amount of tau protein or Aβ concentration in CSF or plasma. Because of the overlapping of such biological markers in general and disturbed people, this technique has produced some dubious results. Only hypothesized pathogenic biomarkers, such as phosphorylated tau protein, splitter tau protein, or Aβ-derived diffusible ligands, are targeted in the second strategy (ADDL). Though this method yields more conclusive results, such pathogenic markers cannot be reliably assessed with traditional ELISA or western blotting tests because their quantities in CSF are extremely less in the previous stages of Alzheimer's disease [12, 13].

Nanodiagnostics for AD in in vitro is as follows:

(1) Nanoparticle conjugates: DNA-NP clusters may detect protein biomarkers at extremely small molar concentrations, even as low as 10–18 moles per liter. This approach has demonstrated to be effective in detecting ADDL in CSF for in vitro AD diagnosis [14]

(2) Localized surface plasmon resonance-based nanosensor (LSPR): when incoming light irradiates a solid material, the surface plasmon resonance (SPR) is a condition of resonant and collective oscillation of valence electrons. In all directions, photon absorption and emission occur with a same frequency. SPR events in several inorganic NPs make them useful for imaging and researchers can better applications in a variety of illnesses, including Alzheimer's disease. Many metallic NPs-based ultrasensitive and cost-effective approaches for detecting AD biomarkers such as ADDL have recently been developed based on the SPR effect [15]

Nanodiagnostics for AD in in vivo is as follows:

(1) Magnetic resonance imaging (MRI): in recent decades, iron oxide nanoparticles (IONPs) as well as magnetic nanoparticles (MNPs) were extensively studied as MRI contrast agents. Monocrystalline IONPs with ultrasmall SIONPs have been studied as MRI probes by two different sets of scientists. The researchers used in vivo studies of Aβ plaques in the brains of mice with Alzheimer's disease. Intravenously administered MRI enhancing agents (NPs) were deemed minimally intrusive [16]

(2) Optical imaging (OI): optical imaging (OI) with a particular near-infrared (NIR) fluorescent dye is a new method being researched with in vivo studies of molecular biomarkers in many diseases, including Alzheimer's disease. The capacity of an imaging probe to penetrate the BBB and specificity to targeting AD linked biomarkers are two of the most prevalent requirements for an AD diagnostic inquiry. NIAD-4, a fluorescent dye that works in the NIR region, was proposed for in vivo molecular detection of A. Because of its unusual structure and low molecular weight, it may quickly pass-through BBB [17]

3.2. Treatment. A nanomaterial is also accepting growing focus for the treatment of AD. The nanomaterial is a nanostructural material that carries therapeutically active substance across the BBB and has powerful target affinity and likely high effectiveness. Therefore, nanomaterial coupled to therapeutically active substance may be useful for monogenic disease like AD [18].

3.2.1. Nanomaterial as Drug Carriers in AD. The blood–brain barrier adjusts the access of polymer into the brain to ensure the CNS. These also hinder the movement of the drug inside the brain for possessing small diameter as well as elevated perceptibility; surface-modified nanostructures can be utilized as a conveyer for effectively bringing drugs to CNS. Nanodrug bringing procedures can naturalize the perception of drug molecules into the CNS and better their bioavailability in a particular brain region. This numerous nanocarries have been altering to upgrade therapeutic with delayed extrication property and better efficiency, such as by generating polymers, emulsions, lipocarries, carbon nanotubes, and metal-based carriers. Recyclable oxidized perforated silicon was used as a transporter to load. The nerve growth factor into the brain lowers cholinergic neuronal loss in AD. The liberation of NGF was delayed for over a month and its uninterrupted liberation. Inhibited AB-included cytotoxicity in differentiated PC12 cells. NGF-PSIO2 may therefore be potent carriers NGF that permit its continuity and sustain redemption while reserving bioactivity. Moreover, PSIO2 chips inserted above the dura mater for eight weeks do not show swelling or adverse effect, and biolistic bringing of PSIO2 microparticle enter the brain and reach to depth of 150 μm in the brain, purposing that recyclable PSIO2 transporters were a usable bringing process for NGF inside the brain [19, 20]. It combines with TiO_2-nanowired cerebrolysin along with neprilysin and P-tau antibodies effectively augmented neuroconservancy in rat ideal of Alzheimer's disease. This shows better significant activity than cerebrolysin, neprilysin, and P-tau antibody (administrated merely). A surface-enhanced Raman scattering- (SERS-) relied sandwich assay by utilizing a combined form of monoclonal anti-tau-functionalized hybrid magnetic NPs and polyclonal anti-tau-immobilized gold NPs was particular for tau (collection through a simple magnet). The interrelation between tau concentration (25 fM to 500 nM) found as linear. In terms of susceptibility and tackling extent for tau protein identification, Gold NPS functionalized with tau-specific monoclonal antibodies and an oligonucleotide template for immuno-polymerase chain reaction (Nano-iPCR) seemed as auspicious. A cholinesterase inhibitor, donepezil (implicated with polylactidecogycolide (PLGA)) exhibits more brain accumulation than donepezil unaccompanied.

3.2.2. Nanomaterial Targetting $\alpha\beta$ Accumulation. The paranormal congestion of $\alpha\beta$ inside brain is nothing but a significant stamp for AD, and it influences alterations of AD

neuropathologically. So, it is a very necessary condition to search out drug, which can hinder $\alpha\beta$ congestion and minimize $\alpha\beta$ toxicology. Au-NPs wrapped with PAA (Au PAA) have been expressed to impact $\alpha\beta$ fibril accumulation in mice. If it is covered by insulin, there is hapazar situation in fibril arrangements shown. The duplex action PEG-PLA-NPs toned down with TGN and QSH specially aimed amyloid plaques with less neurotoxicity. For eradicating accumulated $\alpha\beta$ through the immune process, immune therapy utilizing nanotechnical is drawing deliberation. Zinc-filled nanomolecules are used to hinder synaptic minimization and prevent neuronal inflammation.

3.2.3. Nanomaterials Targetting Tau for AD Treatment. From the present research, it is known that tau channel belongs to a very potent therapeutic trigger because it is compactly assorted with clinical upliftment of AD impediments. An $\alpha\beta$ inhibitor (LK7) coupled and PEG-stagnant black phosphorus (BP) nanoprocess exhibit nice permanency and importantly increased preventive capacity with respect to $\alpha\beta$42 fibrillogenesis.

3.3. Future Perspective. The appliance of nanotechnology in Alzheimer's disease therapy is very much worthful. Though most of the research is still in preclinical level of study, it is expected that it could turn towards upgraded therapeutics and theragnostic results. There are so many advancing modernness simultaneously with nanotechnology-dependent procedures showing prospective in drug or bioparticles or transport of any agents across the BBB deliberate for Alzheimer's disease action. There are some technical proficiencies that accelerates the enhancement of nanoparticle mediated CNS transportation smoothly [21, 22].

3.4. Ultrasound-Mediated BBB Disruption. Focused ultrasound (FUS) enhances the penetrability of drugs and drug transporters across the BBB and thus nanoparticles intended in the brain. From the past several years, as per biomedical research in that specific field, brain cancer and Alzheimer's disease are being emphasized MRI influenced FUS individually for BBB disruption. Focused ultrasound blood–brain barrier disarrangement is majorly influenced by ultrasound context including amplitude of applied pressure, prevalence, duty circle, number of cycles per pulse, dose, and magnitude of microbubble [23]. Regulation of such measurements is not so easy because of disrupting of endothelium next to sonication regarding in vivo data. Enhancement of vascular penetrability across the tissue next to sonication space takes place because of interrelation of sonication and vasculature. Application of FUS shows better result in brain cancer treatment than Alzheimer's disease treatment. Hence, damage of BBB creates complications inward streaming of circulating components into the CNS would be neuronoxious, carrier malfunction, modified protein articulation, inflammatory action, oxidative force, and neuronal disruption. Here, it is distinct evidence that disrupted BBB turns into intensified Alzheimer's disease [24].

4. Direct Convection Therapy in Alzheimer's Disease

Convection-enhanced delivery (CED) is a system to transfer the various diagnostic/therapeutic substance straightly inside the brain along with BBB. Parenteral administration of different therapeutic components into the brain has been relied on diffusion hypothesis and relies on concentration gradient to get the better of prevention because of biological obstructions. The outcome of it is restricted transportation of delivered components, and drug permeates stay enclosed to several millimeters from the location of administration. Here, CED uses a fluid pressure gradient at the infusion catheter tip and bulk stream to circulate the components within extracellular fluid place. Nowadays, CED is being evaluated clinically in the eras of neurodegenerative diseases and neurooncology due to excess drug congregation over widened regions of aimed tissues in comparison to general injection manner of administration [25].

5. Conclusion

As there is swift progression of nanotechnology, nanocomponents display extreme efficiency in biomedicine because of their extraordinary biophysical characteristics. The combined form of nanotechnology as well as biomedicines supply new eras for the diagnosis and treatment procedure. From the research and various suitable information, we came to know that nanomolecules are capable of slowing the enhancement of Alzheimer's disease through different types of systems like functioning as drug transportation vehicles, preventing $\alpha\beta$ accumulation, raising $\alpha\beta$ demote, putting down tau accumulation, minimizing tau phosphorylation, and unburdening the oxidative pressure provoked $\alpha\beta$ accumulation [26]. Overall, the toxic nature of nanomolecules varies upon several factors such as materialistic neatness, molecular size, chemical construction, dose, accumulated state, and time of exposing. To increase focus efficiency, surface modifications and other procedures can be utilized. Such that contraindications can be minimized to civilize their appliances. Again, research, concentration, development, and investigations are highly required for looking at the new horizon of success in diagnosing as well as treatment of Alzheimer's disease. To reduce, to regulate, and to eradicate advance levelled research upon nanoparticles are needed abundantly.

Data Availability

All data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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