REVIEW PAPER

A smart & precise approach with nanoparticles-based therapeutic intervention in neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases (NDs) cause cell dysfunction with a gradual loss of neurons in the central nervous system and aberrant accumulation of aggregated proteins such as synuclein, tau, and amyloid. Alzheimer's disease and Parkinson's disease are the two frequently occurring neurodegenerative disorders. Nanobiotechnology being an emerging field used in applied biotechnology holds great potential for the advancement of treatments. This review aims to give a brief but comprehensive idea about the possibilities of utilizing the advanced nanotechnological aspect to treat the Alzheimer's and Parkinson's NDs that can be explored through proper investigations. In the present study, various kinds of literature were surveyed and reviewed to appreciate the neurodegenerative disease manifestation. It is becoming challenging to treat and discuss the potentiality of effective nano-mediated treatment strategies for Alzheimer's and Parkinson's diseases. The capability of current drugs to cross the blood-brain barrier (BBB) makes NDs' treatment even more challenging. Recent therapies for such kinds of diseases are focused on symptomatic relief. Nanoparticulate drug delivery systems address all the challenges from all aspects and offer novel therapeutics for NDs. With targeted drug delivery of the required drug or protein to the site of interest, this approach is expected to turn out to be an exact and advanced therapeutic approach.

Keywords: *Administration, Classification, Dosage Nanobiotechnology, Neurodegenerative disease, Therapy, Toxicity, Therapeutic use*

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INTRODUCTION

Nanotherapeutics

In recent technological advancements, nanotechnology has proven to have great potential in designing drugs and therapeutics for diseases whose cure seemed to be impossible due to lacuna in the drug delivery strategies. Nanomedicine is an emerging nanoparticle field involving the utilization in clinical aspects against many diseases, including neurodegenerative diseases. They have proved to be one of the most capable and multifunctional drug delivery systems. These possess the ability to reach areas like the brain for the delivery of the therapeutic compound to the site of action. Nanoparticles (NPs), nanocarriers, nanotubes, microparticles (MPs), and nanomedicines (NMs) are examples of unique technological advancements that aid in the management of neurodegenerative disease and allow specialized delivery of the drug to a target location. The controlled release of drugs to the specified site of action makes nano-drug delivery systems efficient and effective in pharmaceutical drug delivery [1].

Folkman and Long's discoveries triggered human-made polymers' progress for the controlled release of therapeutic compounds. They discovered that hydrophobic dyes diffuse at a consistent rate through a silicone tube wall. Clinically, many of these materials and devices are employed. For prolonged drug delivery to specified sites in the brain, materials such as intracranial polymeric implants were investigated. The reaction of the drug delivery system with the surrounding tissue, incompatibility, non-

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uniform and restricted availability of drugs have all impeded such localized delivery systems [2]. Application of nanotechnology in the biomedical field is shown in Fig. 1.

Nano-mediated drug delivery systems

The low permeability of the Blood Brain Barrier (BBB) results in difficulty in delivering medications in neurodegenerative disease detection, targeting, and treatment. The BBB makes identifying and treating neurological ailments like Alzheimer's disease (AD) and Parkinson's disease (PD) extremely difficult.

Conventional drug delivery systems are inefficient as they fail to cross the BBB. Although advancement through research ensures the development of nano-theranostic, the possibility to incorporate it for human therapeutics is a key concern and challenge. Several nano-particles can cross the BBB (Fig. 2).

It is necessary to have a thorough grasp of how physiological systems interact with nanomaterials. Several plant-based nano-bioactive substances have been shown to demonstrate use in diagnosis and treatment of various neurodegenerative illnesses. This review article gives a quick outline of nano-theranostics applications in PD and AD. Nano-mediated drug delivery technologies including the current perspective and applications to treat various neurodegenerative illnesses are also discussed in the review [3].

Neurodegenerative diseases

Neurodegenerative diseases (Fig. 3) have become a worldwide problem as millions of people are already affected. AD and PD are the most commonly occurring neurodegenerative diseases recorded by statistical analysis. In 2016, approximately 5.4 million people had AD in the United States. In 2020, an estimated 930,000 persons in the United States have been diagnosed with PD.

A neurodegenerative illness follows the brain nerve cells' loss of their function over a while and eventually death. There are presently no methods and known therapies to delay the progression of the disease, however, treatments may alleviate some of the symptoms. Neurodegenerative

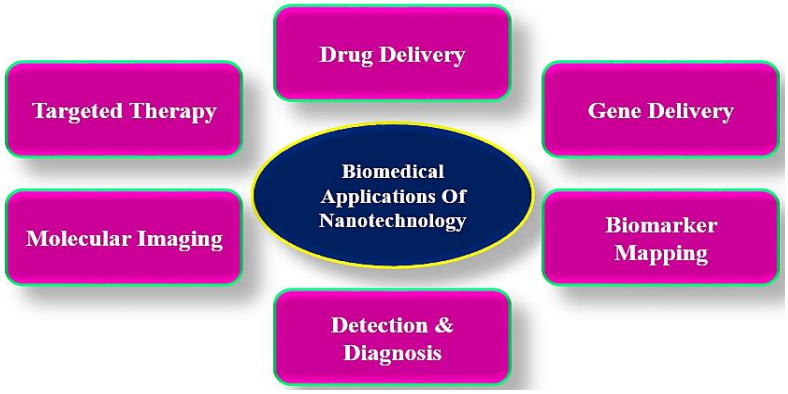

Fig. 1. Biomedical applications of nanotecnology

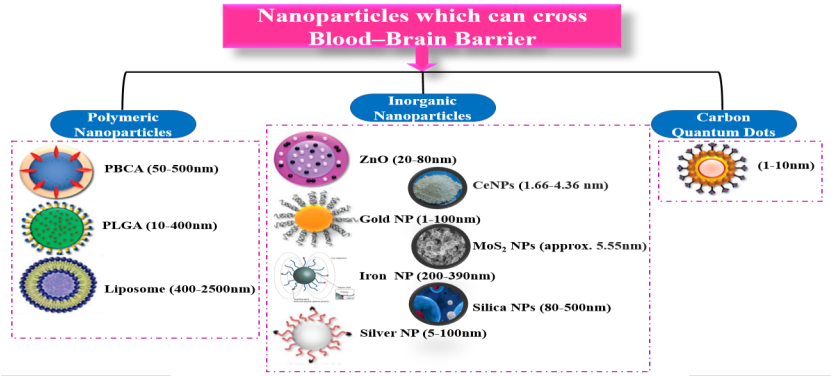

Fig. 2. Nanoparticles that can cross the BBB

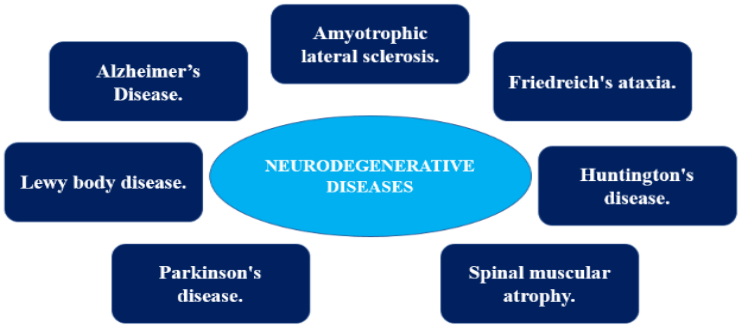

Fig. 3. Different types of neurodegenerative diseases

disorders are prone to occur with age gradually.

Neurodegenerative disease is the effect of the combination of a person's genes as well as the environment. A genotype may be present in an individual which can cause the disease at any period of life, but environmental exposures determine the impact at which the disease occurs. The research challenges are critical for detecting and evaluating potential exposures that occurred before an individual was diagnosed, as well as disentangling the effects of these exposures [4].

Common neurodegenerative disorders

Alzheimer's disease (AD)

Across the world, AD is a commonly observed neurodegenerative disorder that causes dementia in the elderly, also contributing to the mortality of large populations in affluent countries around the world.

Neurodegeneration, which appears to be begun by protein deposition or synaptic damage, ultimately leading to neuronal loss, causes memory loss, cognitive difficulties, and behavioral changes in patients, and is a critical consequence of the disorder seen in people suffering from this disease [3]. The shrinkage in the cerebral cortex and hippocampus region of the brain with enlarged vesicles are commonly observed diagnostic characteristics. The count of people diagnosed with Alzheimer's is predicted to be 152 million by the year 2050. Cognitive disabilities arise with the progression of the disease accompanied by infections, VitB12 deficiency, low saturation levels, and abnormality in pulmonary and circulatory systems [5]. An important factor in the cause of AD is aging and it progresses over time as a neurological illness at the age of 65 with a gradual decline in cognition and memory. The upsurge in the occasional memory loss is a significant characteristic of Alzheimer's. Speech, visuospatial orientation, and motor function all suffer as cognition declines and the disease develops. In an AD brain, the two basic cardinal neuropathologic lesions are neurofibrillary tangles, aberrant intracellular fibrous inclusions inside neuronal perikaryal cytoplasm, that when identified histopathologically, can lead to a conclusive diagnosis of AD. However, this is rarely done during life and is more commonly done after death. These neurofibrillary tangles are paired helical filaments produced in the cortices of AD patients' brains by clumps of the hyperphosphorylated microtubule-associated protein tau, and senile/neuritic plaque is another common AD pathology. Senile plaques (Fig. 4) are complex proteinaceous extracellular aggregates of amyloid-beta (A) protein that form in the cortices of Alzheimer's patient's brains [5, 6].

Parkinson's disease (PD)

The second most generally occurring chronic condition after Alzheimer's is PD, affecting over 6.3 million people worldwide. The loss of dopamine-releasing neurons in the substantia nigra of the brain along with the progressive degradation of motor capabilities is an indication of the disease onset [3].

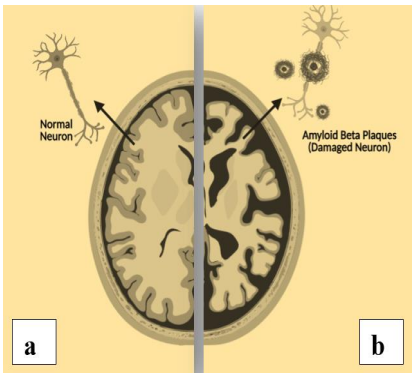

Fig. 4. Human brain, (a) healthy neuron, (b) Alzheimer's disease with amyloid plaques

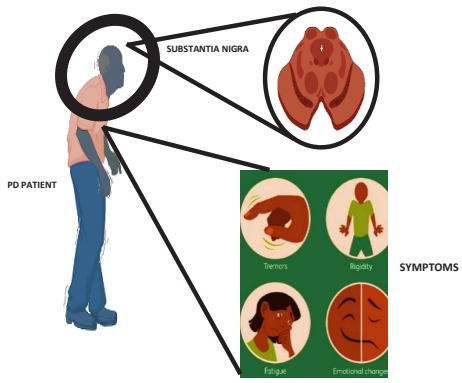

Fig. 5. Parkinson's disease – Brainstem (midbrain, superior colliculus, substantia nigra)

PD is a condition that primarily affects 1-2 people among 1000 elderly. The occurrence of the disease in people aged <50 is rare. Resting tremors, bradykinesia, stiffness, and postural instability are examples of motor and non-motor impairments in PD (Fig. 5). Cognitive inabilities, constipation, and sleep troubles are other commonly observed symptoms of PD. PD treatments are focused on relief and easing symptoms caused by the disorder. In community samples, 2–7% of the population shows the disease progression with dysfunction in motor and physical performance. Early symptoms arise within months and persist for years, the patient's prognosis is predicted based on the persistence of the symptoms from early to later stages. The advanced stage of Parkinson's implies easy confusion, memory loss, and dementia in patients [5]. In PD pathogenesis, the substantia nigra pars compacta (SNc) has selective and gradual degeneration of dopaminergic neurons that extend into the basal ganglia, resulting in the aforementioned PD symptoms. Because PD is a kind of α-synucleinopathy, it possesses a key histological feature: aberrant intraneuronal inclusions called Lewy bodies, made up of α-synuclein [5, 7].

DISCUSSION

Nanotherapeutics intervention in treating neurodegenerative diseases

In this review, we have focused on the ones that can cross the BBB and allow targeted treatment against the diseases concerned.

POLYMERIC NANOPARTICLES

PBCA [Poly(n-butyl cyanoacrylate)] nanoparticles-(50-500nm)

PBCA or (Poly(butyl cyanoacrylate) cholinesterase inhibitors (e.g., rivastigmine) are commonly carried by polymeric NPs in AD treatment. PBCA adsorbs numerous apolipoproteins in blood, allowing nanoparticles to attach to LDL receptors on endothelial cells, and thus permeating the medication into the BBB. Nanocarriers have been proposed as a novel promising way to improve the efficacy of cholinesterase inhibitors in AD treatment [8]. PBCA is involved in the carrier-mediated transport of drugs and nutrients across the brain, the mechanism involved in the transport of drugs is by the capillary endothelial luminal and abluminal membranes. The abluminal membrane and the brain extracellular fluid are connected, whereas the luminal membrane and the blood component are interconnected. Carriers such as the glucose transporter 1 in glucose, and System-L in the case of amino acids such as phenylalanine, valine, histidine, methionine, and tyrosine are the factors by which carrier-mediated transport is possible in BBB permeability. There has been no FDA approval for PBCA yet and there are several side effects observed in PBCA including depression, anxiety, insomnia, agitation, nausea, and vomiting with increased dosage [9].

PBCA coating with polysorbate 80 has shown the ability to cross the Blood Brain Barrier (BBB) and deliver drugs for the treatment of brain tumors. Drugs like doxorubicin, loperamide, tubocurarine, and hexapeptide dalargin have been shown to be effectively permeable when administered with PBCA-coated polysorbate80. Polysorbate-coated PBCA is transported via endocytosis by brain capillary endothelial cells, occurring due to the serum protein, apolipoprotein. Although several tests have reported the use of PBCA coated with polysorbate 80 has toxic and abnormal effects in some pre-clinical trials. Thus, the practical use of this therapeutic should be considered with benefit to risk ratio [9]. Another mechanism of passage by using PBCA is paracellular and transcellular. Paracellular occurs between the endothelial cells and transcellular occurs through endothelial cells, the paracellular–transcellular balance determines the degree of permeability in BBB. The permeation of the drug across the BBB is possible due to the nanoparticles that are likely to open tight junctions inducing a localized permeability of the BBB. Thioflavin T-encapsulated nanoparticles with PBCA delivery into the hippocampus region of the brain have shown the potential to induce NPs in the microglia and neurons. The study was conducted for ThTnano-capsules to detect the

synthesis of Ab peptide in biological mice model APPswe/PS1 (A246E) transgenic mice [9, 10].

PLGA [Poly (lactic-co-glycolic acid)] nanoparticles-(10–400 nm)

Galantamine (GAL) encapsulation in PLGA nanoparticles is a novel therapy that has never been documented before in PLGA as well as other polymeric nanoparticles. The production of template nanoemulsions using biocompatible and biodegradable components by PIC emulsification method sets is an advantage of nano-emulsion (NE) templating technology GAL-loaded PLGA nanoparticles preparation [11]. Non-cytotoxic GAL-loaded nanoparticles with excellent encapsulation efficiencies and continuous drug release may be generated using this method, preserving GAL pharmacological activity and allowing for long-term therapeutic benefits. For the first time, GAL-loaded nanoparticles became a promising enhanced drug delivery strategy against neurodegenerative illnesses, since they were built with the right properties [8, 12].

The delivery of the hydrophilic drug nattokinase through coating with PLGA and Tet1 peptide has been shown to promote retrograde transport and affinity towards neurons. The drug delivery by PLGA NPs improves the stability of nattokinase and successfully down-regulates amyloid aggregation promoting the drug action. This particular method of drug delivery of nattokinase with PLGA encapsulation has proved to be a potential treatment for Alzheimer's and has been approved by the FDA. One common possible toxic effect is bulk erosion in PLGAs, this particular characteristic leads to premature exposure of the therapeutic to an undesired and degradable environment. This probable characteristic feature may lead to exposure of the drug to an undesired environment and may cause toxic effects, also the efficacy of the drug will decrease [12].

Prior studies have shown that intracerebral injection of PLGA NPs can re-acidify defective lysosomes, reducing neurodegeneration. Similar results are observed with Alzheimer's with the cytosolic calcium leakage from malfunctioning lysosomes in cells with presenilin-1 mutations. PLGA-coated drugs are greatly applicable for sustained release through implants. Hydrolysis of the drug-coated PLGA results in oligomers and D, L-Lactic acid monomers. The obtained lactate from the hydrolysis gets converted to pyruvate and glycolate which further acts in Kreb's cycle forming carbon dioxide and water. The use of radioactive 14C in mice has shown that the above process can be tracked for the validation of the statement indicating the biodegradability of PLGA used as a nano-therapeutic approach [10].

Liposomes (400–2500 nm)

Liposomes, polymeric NPs, and solid-lipid NPs (SLN) have low antigenicity, biocompatibility, and high biodegradability and are considered a non-invasive method. As a result, the medication delivery system may prove to be one of the best applications in the biomedical industry (Table 1) [13].

In the CNS, macrophages, microglia, and astrocytes take up liposomes promptly. Disruption of BBB during experimental autoimmune encephalomyelitis, PEGylated liposomes aggregate more quickly in the brain (EAE). At the surface of the brain capillaries, successful conjugation of liposomes with transferrin, mannose, and insulin receptors. The transferrin receptor, in particular, is required for iron delivery across the BBB [2].

Multifunctional liposomes were also employed to treat AD, with each target being targeted sequentially. The researchers bi-functionalized liposomes from apolipoprotein-E and phosphatidic acid-derived peptide for destabilizing brain Aβ aggregates. Likewise, in Glioma multifunctional liposomes were used to achieve a dual-targeting effect. The conjugation of liposomes with folate and transferrin penetrates the BBB [14, 15]. Niosome, ethosome, transferosome, and nanosponge are significant types of colloidal drug delivery systems [16].

SLNs (Solid Lipid Nanoparticles) carry the drug in their hydrophobic core. The drug entrapment by the SLN is effective in controlled release [16]. SLNs relatively show less toxicity to cells and do not get degraded easily. Also, the use of SLNs in AD has shown to be of high affinity with beta-amyloid fibrils [17].

INORGANIC NANOPARTICLES

ZnO nanoparticles (20–80 nm)

ZnO-NP is capable of destroying hen white lysozyme amyloids with capping agent starch. A comparative analysis of the anti-amyloid activity of ZnO-NP and ZnO-NF at non-toxic dosage showed that ZnO-NF anti-amyloid activity on IA fibrils was higher compared with ZnO-NP. And hence, ZnO-NF is a potent anti-amyloid agent which may

Table 1. Present insights into possible liposomes as a means of treating neurodegenerative diseases

Surface modification	Drug model used	Disease	Mode of action	Size	Testing model	Derived Results
GSH-PEG (Glutathione targeted PEGylated)	VHH-pa2H Antibody fragment	AD	Extending the VHH's blood residence period and transport across the Blood Brain Barrier	110 nm	APPswe/PS1dE9 double transgenic mice	In comparison to wild-type controls, a considerable increase in retention in the brains of transgenic mice was observed in GSH-PEG liposomes encapsulating VHH
GSH-PEG liposomes	Carboxyfluorescein (CF)	AD	Using an autoquenched fluorescent tracer, researchers compared the pharmacokinetics and organ distribution of GSH-PEG liposomes following intraperitoneal and intravenous injections	No mention	Endothelial cells	Rat brain endothelial cells specifically took up GSH-PEG liposomes.
Curcumin-conjugated liposomes	Curcumin	AD	It shows a high affinity with Aβ peptide, but it was limited in clinical use due to its low solubility. Curcumin's affinity for Aβ was used to direct liposomes to Aβ deposits	63–200 nm	APPxPS1 mice.	Both human tissue and mice showed strong labeling of Aβ deposits, as well as in vitro amyloid peptide downregulation
Lf/NGF-liposomes	Neuron growth factor (NGF)	AD	NGF may protect cholinergic neurons in the basal forebrain from degeneration. PEG incorporation on liposomes could prevent colloidal aggregations. Lf endocytosis by receptor-mediated transcytosis (RMT) is aided by Lf receptors on HBMECs	100 nm	SK-N-MC cells	HBMECs and HAs were physically stable and biocompatible with Lf/NGF-liposomes containing cholesterol and DPPC. Surface Lf was effective at transporting Lf/NGF-liposomes across the BBB and preventing SK-N-MC cells from degenerating due to Aβ-induced neurotoxicity
(ApoE)-derived peptides-nanoliposomes	Curcumin	HD	Transcytosis could be used to transport nanoparticles that interact with LDLr via specific apolipoprotein E, circumventing lysosomal breakdown	132 ±10 nm	Rat brain endothelial cell line	By establishing a protected hydrophobic milieu, minimizing drug degradation, and thus enhancing curcumin brain bioavailability, these can be used to carry curcumin across the BBB
Transferrin (Tf) modified liposomes	α-Mangostin	AD	ineffectiveness of α-Mangostin was hampered by its inability to penetrate the BBB. To accomplish the desired penetrating effects, transferrin (Tf) was utilized as a targeted ligand to alter the liposome	196.3 ±7.09 nm	SD rats and BBB model (astrocytes and the bEnd3 cells)	Tf-liposomes were found to improve brain-targeting abilities in both qualitative and quantitative testing
mApoE–PA–LIP	Oligomers	AD	Liposomes bifunctionalized with apolipoprotein-E receptor-binding domain for BBB And phosphatidic acid for A β binding	121 ±7 nm	APP23 transgenic mice (aged 15 months)	Brain Aβ aggregates were destabilized by bifunctionalized liposomes allowing BBB permeation
TREG-Mab-ApoE-LIPs	Derivative of curcumin (TREG)	AD	Aβ peptide aggregation was inhibited by TREG, while Mab-ApoE had a strong affinity for the BBB.	<200 nm	Friend leukemia virus B mice	Shows the possibility of a specific curcumin-lipid derivative as a component of multifunctional LIPs that can effectively target the brain
Chlorotoxin-modified stealth liposomes	Levodopa	PD	Chlorotoxin (ClTx) is only found in gliomas and proliferating vascular endothelial cells in the brain. It was originally employed to develop ClTx-modified stealth liposomes (ClTx-LS) encapsulating levodopa (LD).	100 nm	MPTP-induced C57 mice PD model	The in vitro and in vivo results were well correlated, proving the notion that ClTx -LS is a potential system for BBB penetration and PD treatment

be used as a drug capable of crossing the Blood Brain Barrier for amyloidosis therapy [18]. The mechanism of action of ZnO has been predicted to be sequestration in Advanced Glycation End products (AGE), AGEs are formed in many CNS pathologies including AD and PD. The free amino acid group, as well as N-terminal amino acids, are the main targets of glycating agents. Anti-glycating drugs are thought to bind to these sites in a competitive manner. Furthermore, observations suggest that ZnONPs may reduce or prevent the development of AGE by covering amino groups or sequestering the reactive group of glycating species. Thus, prevention of AGE has significance in counteracting neurodegenerative disorders due to the inhibiting effect of the ZnO nanoparticles. ZnO shows toxicity by induction of oxidative stresses and inflammation leading to the worst disease prognosis and outcomes. ZnO nanoparticles are approved for the treatment of cancer by the US FDA, as for the treatment of neurodegenerative disorders, more insights are required.

Gold nanoparticles (1-100 nm)

Gold nanoparticles (AuNPs/ GNPs) have relatively low cytotoxicity, optical properties fit for detection/imaging, ability to penetrate the BBB while coupling with different modified ligands. Furthermore, in an AD rat model, gold nanoparticles can decrease oxidative stress, cognitive impairments, and inflammation, suggesting the use of gold NPs for AD treatment. AuNPs also contained peptide inhibitors and antioxidants, which inhibit amyloid-protein

aggregation and cytotoxicity. AuNPs treated with PEG showed potential in preventing neurodegenerative disorders compared with AuNPs alone. AuNPs are very important in imaging. In computed tomography (CT), the gold nanoparticles that target insulin can be used as contrast agents to highlight specific brain regions where they accumulate. In AD, dual-functionalized gold nano-plasmonic particles can be used to track cerebral -amyloid peptides. The biodistribution and circulation time of AuNPs are affected by their size. The size of AuNPs adjusted by L -glutathione in varied sizes (36.0 3.0 nm, 18.1 3.0 nm, and 6.0 2.0 nm) had an effect on the experimental result, which was also replicated [1, 15]. According to *in vivo* CT imaging, AuNPs tend to move to the region of high insulin receptors showing their potential in treating NDs. The findings show that using INS-GNPs as nano-vehicles to transport medications through the BBB could be helpful [1, 19].

PEGylated GNPs are commonly produced, especially in drug delivery, since PEG induces stability and reduces undesired interactions. In cell fusogen properties and membrane fusion in various types of cells caused by PEG, cell membrane integrity can be preserved by the membrane-sealing effects on both the plasma membrane and mitochondria of neuronal-damaged cells. This allows less oxidative stress along with cell apoptosis and necrosis suppression, resulting in axonal regeneration and improved function in neurodegenerative disorders. PEGylated AuNPs for drug delivery to the brain with NDs may prove as an effective treatment [20]. GNP appeared to be less toxic than other NPs, PEG administration had no side effects, and no unsatisfactory clinical responses were found. The use of peptides to functionalize AuNPs to improve BBB penetrability and NP concentration in the brain is gaining attention. As a result, active transport of AuNP can be caused by multivalent peptides binding to Aβ-amyloid fibrils [21-25].

Likewise, chiral NPs can penetrate the BBB by intravenous administration. The currently known NP systems modify P-glycoprotein function via stereotactic brain or IV injection with cyclosporine A [26].

Iron nanoparticles (200–390 nm)

Iron chelation nanoparticles prove to be effective in surpassing the BBB as they are protected by a zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) which helps in prolonging the *in vivo* lifetime by iron chelator saturation in blood circulation with HIV-1 trans-activating transcriptor (TAT). Previously, in clinical trials, iron chelators for the management of Parkinson's showed maximum chelating capability, antioxidation, and neuroprotection. Dextran-coated Fe_3O_4 MNPs loaded with osmotin under functionalized magnetic field were transported to the brains of Aβ1–42 treated mice. For the first time, a reversal was observed in Aβ-accumulation, Beta-secretase 1 expression, synapto-toxicity, tau hyper-phosphorylation, and memory impairment in an Aβ1-42 injected mouse model. Fluorophotometryis is capable of detecting DDNP-superparamagnetic iron oxide nanoparticles (SPIONs) with high affinity to Aβ (1–40) aggregates. In the brains of Tg2576 mice, amyloid plaques can be detected by curcumin-conjugated superparamagnetic iron oxides (SPIOs). In rTg4510 tau-mutant mice, fibrin 377–395 peptide-conjugated-Fe_2O_3 nanoparticles may preferentially suppress microglial cells, suggesting a potential therapeutic method for neurological diseases. Magnetic nanoparticle technology can distribute therapeutic genes or pharmaceuticals selectively and competently using external magnetic fields [27]. IONP's iron ions release causes iron buildup, oxidative stress, protein aggregation, and toxicity to brain cells. The toxicity levels of IONPs, on the other hand, are determined by their attributes, which include size, concentration, surface charge, coating type, and functional groups.

Silver nanoparticles (5–100 nm)

After being implanted *in vivo*, silver nanoparticles (SNPs) are transported to the brain via the bloodstream. Rat brain micro-vessel vascular endothelial cells (BMVECs) after 4 hr of culture in a 100 μg/ml medium of SNPs or Silver Micro Particles revealed that SNPs can penetrate the BBB and accumulate there. SNPs may cross the BBB mostly through the transcytosis of capillary endothelial cells. Amyloid precursor protein (APP) gene expression is elevated when brain cells are treated with AgNPs, according to research. Furthermore, neprilysin, a major enzyme capable of degrading the Aβ -peptide brain had its protein levels reduced in neural cells. As a result, it is critical to pay attention to AgNP distribution in the environment [27, 28]. Researchers discovered that 3–5 nm AgNPs can infiltrate mouse brain

cells stimulating pro-inflammatory cytokine release while enhancing the deposition of Aβ amyloid. Finally, it's important to consider how silver nanoparticles are used on a regular basis [28]. Nanosilver may cause mild eye irritation, skin irritations, mild skin allergens, and inhalation affects the lungs and liver. Several genotoxic effects and cell toxicity of silver nanoparticles are predicted with inflammation and production of reactive oxygen species, possibilities of sterility in animals tested with silver nanoparticles are also indicated through studies. Argyria and argyrosisis are caused by long-term usage of colloidal silver or silver salts, such as AgNO3, which deposits metallic silver beneath the skin and abdominal viscera forming an ashen-grey color skin tone. Long-term exposure to silver has harmful consequences on the central nervous system, including cerebral ataxia [28].

Cerium oxide nanoparticles (1.66–4.36 nm)

CeONPs exhibit regenerative antioxidant characteristics, which are effective for the oxidative stress caused by Alzheimer's, Parkinson's, and other neurodegenerative diseases. In accordance with the obtained result, CeONPs are currently being studied for their efficacy in a variety of neurodegenerative illnesses, with promising results. Traditional antioxidants have been used to treat the pathological problems of PD, but they have had little success due to their inability to penetrate the BBB. However, bio-distribution investigations have shown that the kidney, liver, and spleen are the predominant organs of accumulation, which could pose safety concerns in a future study. As a result, targeted methods had to be applied to CeO_2 NPs in order to increase efficacy and reduce toxicity. CeONPs are beneficial in the treatment of AD, however, there are fewer reports available for PD. The key to CeONP success is increasing the amount of CeONPs delivered via the BBB while also reducing undesired deposition in other organs. As a result, more *in vitro* and *in vivo* investigations including these disorders are needed to examine CeONPs' potential efficacy before moving forward with human clinical trials [29].

Molybdenum nanoparticles (50–100 nm)

Molybdenum disulfide (MoS_2) NPs inhibit Aβ aggregation, lower Aβ-induced oxidative stress, Aβ-mediated cell toxicity, destable Aβ fibrils, and block Ca^{2+} channel induced by Aβfibrils in the cell membrane suggesting its potential against amyloid-related diseases. This blocking mechanism of the Ca^{2+} channel induced by Aβfibrils acts by Aβ oligomers incorporation into neuronal cell membranes and formation of Ca2+ channels. This in turn induces a cascade of ROS and Ca2-mediated degenerative processes and hence, protects neurons. *In vitro* analysis does not show any toxic effects even in high concentrations.

Silica nanoparticles (80-500 nm)

Silica nanoparticles (SiO_2 -NPs) are being used in diagnosis, imaging, and medication delivery in the treatment of CNS. Recent research has found that SiO_2-NPs up-regulate α-synuclein expression and induce autophagy by the PI3K-Akt-mTOR signaling [1]. MSNs and nanosized mesoporous silica particles are excellent theranostic agents used in medication delivery systems and bioimaging. MSNs are better candidates for drug delivery systems than porous silica because of their unique properties, which include high pore volumes (0.5–2.5 cm^3/g), uniform particle sizes (80–500 nm), flexible pore diameters (1.3–30 nm), tunable particle morphology, large surface areas (1000 m^2/g). MSNs' flexible surface properties have improved medication loading capacity. When given without encapsulation, bulk medicinal chemicals such as enzymes are easily destroyed in an adverse cellular environment. These therapeutic compounds are either covalently bonded to silica nanocarriers or adsorbed onto pre-surface-modified silica nanocarriers. These strategic techniques can readily overcome challenges with medication solubility and stability, as well as provide improved control over drug release rates [1].

Carbon quantum dots (1–10 nm)

Carbon dots are novel and emerging nanomaterials sparking a lot of interest in the biomedical field because of their tiny size, high photostability, biocompatibility, excellent physicochemical qualities, chemical inertness, ease of functionalization, and customized photoluminescence capabilities. Carbon dots stand out as an exceptional possibility for bioimaging, optical sensing, and the therapy of neurodegenerative illnesses because of all of these desirable features. They are suitable nanocarriers for drug delivery via crossing the

blood-brain barrier because of their ultra-nano size. Due to their minute size, Quantum dots can easily be taken up into cells. Through an endocytotic pathway, the therapeutic potential of CdSe/ZnS QDs capped along with antibodies directed to target or non-targeted intracellular compartments has shown potential. Carbon dots are more bio-friendly since they permeate the BBB, and drug concentrations in the brain can be significantly enhanced, highlighting the potential utility of these nanocarriers in constructing an effective neuro-drug delivery system. With the ability to penetrate the BBB and the potential for treatments in CNS, therapeutic techniques based on carbon dots have opened new opportunities to disclose tight connections. The presence of green fluorescent neuron cells in the CNS of zebrafish revealed that transferrin-modified carbon dots may enter the CNS of zebrafish through BBB [30]. MTT, LDH assays, and real-time PCR analysis of cadmium-containing QDs showed the genotoxic effect when under trials with A549 showing apoptosis, cell death, and differential mRNA levels of genes along with the increased level of dosage. It also triggered lymphoblastic transformation for adaptive immunity in mice in another investigation [30].

The use of carbon nanotubes in the form of carbon nanochip has derived attention on account of its approach to tracking and maintaining dopamine level changes. This therapeutic intervention has shown potential for better prognosis of patients.

Precision nanomedicine against neurodegenerative diseases

Neurodegenerative Diseases (NDs) are some of the leading health problems in today's world. The prevalence and emergence of NDs along with the growing population are evident and the prevention of such NDs is not applicable to the current scenario and knowledge. The necessity of therapeutic applications for both treatment and better prognosis in NDs is vital [31]. Advancement in nano-medicine is on the verge of developing such therapeutics and particularly the development focuses on transporting the neuroactive proteins and peptides into the brain by crossing the BBB (Fig. 6).

Therapeutics that are protein-based such as antibody-mediated and enzyme replacement therapy have the potential for precise treatment of NDs by re-establishing the activity of neuron and glial cells. Huge attempts in the previous decades led to the discovery of strategies facilitating the delivery of protein to the brain, but all of them had their respective limitations. With the urge to develop better delivery methods, further understanding is required of the brain's physiology and pathology. The problems encountered for effective protein delivery to a localized site are tedious and require a better understanding of the nano-carriers activity when administered [32]. Moreover, it is necessary to comprehend the brain's complicated situation, including glial cell activity, neuron function, its connections, and the passage of protein to the brain. More emphasis should be placed on combining various routes of administration, particularly drug delivery and nano-carriers that take advantage of physiological pathways such as BBB receptor-mediated transport. New prospective therapeutic targets must focus and investigate experimentally, to verify them with preclinical models and then test

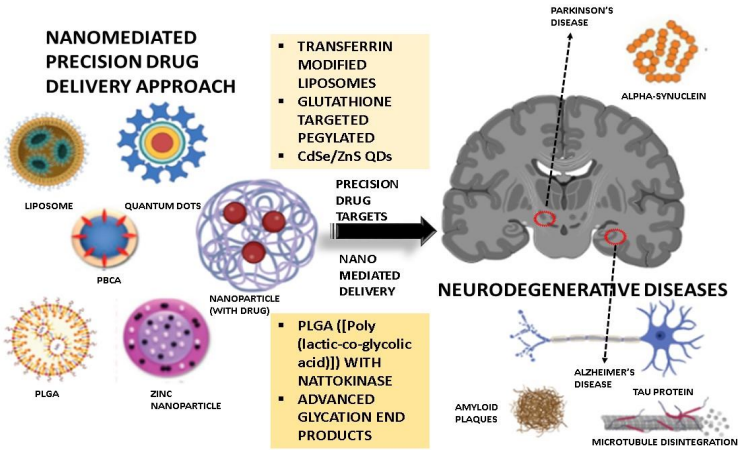

Fig. 6. Nano-mediated drug delivery precision approach for targeting aspects of neurodegenerative diseases

them clinically with the hope of providing effective treatment for NDs.

In contrast to the traditional "one-drug-fits-all" strategy, the utilization of precision medicine in the therapy and prevention of NDs has shown promising aspects. Neurodegenerative diseases can have a wide range of clinical symptoms, making a single therapy ineffective. Precision medicine allows the early diagnosis and treatment of the disease based on the patient's profile and hence, improving the quality of prognosis in patients and promoting a healthy life. Oversimplification of diseased groups to create medicines for as many people as feasible with comparable clinical features has not shown substantial results. In the era of precision medicine, the various clusters with ND patient data prove to be an approachable method having novel therapeutic potential [33-37].

In recent years, enormous attention is focused on the green synthesis method of metal NPs [38]. Green chemistry has been studied in an attempt to identify an environmentally benign method for producing well-characterized nanoparticles by the creation of metal nanoparticles utilizing organisms. Plant-based nanoparticles are more stable and show a higher rate of synthesis than microorganism-produced nanoparticles. Additionally, in comparison with those produced by other animals, the nanoparticles are more varied in shape and size. Green nanoparticles when compared with chemically generated nanoparticles, have lower toxicity. In terms of green synthesis, toxic residues and environmental risks are nil. The toxic effects of chemically generated nanoparticles make them unsuitable for use in biological systems [39]. Green synthesis nanoparticles have better stability and toxicity than chemical synthesis nanoparticles.

CONCLUSION

Nanotechnology holds great potential in the field of therapeutics; hence it is an emerging aspect of medically-oriented research. It has got various ways of delivering the drug or the compound of interest to the specific site of action along with the ability of controlled drug release [40, 41]. As NDs are diseases that require highly specific drugs and not all drugs can cross the BBB, nano-mediated drug delivery plays a major role in drug transportation to the specific site. This treatment approach is not only suitable but very precise.

ETHICAL APPROVAL

Ethical approval is not required since this is a review article.

CONSENT TO PARTICIPATE

N/A as no human subject was enrolled in this study.

CONSENT TO PUBLISH

N/A as no human subject was enrolled in this study.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

CONFLICTS OF INTERESTS

The authors declare that they have no competing interests.

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