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Review Article

HOPES AND HURDLES OF DENDRIMERS FOR THE TREATMENT OF PARKINSON'S DISEASE

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ABSTRACT

Neurodegenerative conditions include Parkinson's disease (PD), a prevalent movement disease marked by Lewy body aggregation in the midbrain and a gradual loss of dopamine neurons. It is the second most common neurological condition that progresses faster. The exact cause of this idiopathic condition is not known, while risk factors, such as aging, pesticide exposure, family history, and environmental pollutants are linked to it. Both motor and non-motor signs are displayed, such as bradykinesia, stiffness, stooping posture, and rest tremor. Additional symptoms of PD include autonomic and speech difficulties, cognitive impairment (dementia), and neurobehavioral disorders (depression). The only long-term and symptomatic treatments available for PD are inadequate. PD patients are challenging to treat medically because there are few PD medications available, and levodopa is the usual course of treatment. However, prolonged usage of levodopa results in dyskinesia. New treatments targeting pertinent targets in various diseases have been developed as a result of this challenge. Novel drug delivery systems are designed to prevent, diagnose, and treat various diseases while improving the overall efficacy of medications to overcome drawbacks, such as poor drug penetration in the brain, poor bioavailability, limited solubility, severe adverse effects, and long-term ineffectiveness. There are various novel approaches present for the treatment of different diseases, including liposomes, nanoemulsion, niosomes, dendrimers (DDs), and solid lipid nanoparticles. DDs have become viable substitutes for existing treatments. The unique polymeric structures known as DDs offer a versatile framework for creating a range of nanosystems that can be used to cure different diseases and ultimately improve the lives of millions of people worldwide. DDs have been suggested as intriguing drug delivery vehicles that can penetrate the blood–brain barrier and boost the bioavailability of traditional medications in the brain and genetic material by decreasing the synthesis of particular targets. They are also effective agents that block alpha-synuclein fibrillation and have anti-inflammatory qualities. In this review, we will talk about the novel drug delivery approach based on DD formulations and its recent advancements for the treatment of PD.

Keywords: Dendrimers, Nanotechnology, Brain, Neurodegenerative disease, Parkinson

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INTRODUCTION

Parkinson's disease (PD) is a prolonged, developing neurological disease caused by the accumulation of Lewy bodies which is made up of the intracellular protein alpha-synuclein (α-syn) and the early, noticeable deprivation of dopamine neurotransmitters in the substantia nigra [1]. James Parkinson was the first to name and describe this disease in 1817. This condition progresses gradually with time [2]. In terms of neurodegenerative diseases, it is the second most prevalent. PD manifests both non-motor and motor system functions. The early stages of the disease are marked by motor functions, such as resting tremor, gait, speech difficulties, bradykinesia, muscle dystrophy, rigidity, and postural abnormalities. The patient also shows non-voluntary symptoms such as sleep disorders, gastrointestinal or olfactory disturbances, cognitive impairment, and depression [3]. It is an age-related disease and it primarily affects older people, while some cases have been reported in considerably younger patients, particularly those under 40. It affects about 3% of persons over 65 and 5% of adults over 80. In most populations, men have twice the prevalence of PD as women [4]. By 2030, it is anticipated that the number of persons with PD will have increased by more than 50% due to longer life expectancies [5].

Degeneration of dopaminergic neurons in the extrapyramidal tract of the midbrain is one of the hallmarks of PD. This imbalance of excitatory (acetylcholine) and inhibitory (dopamine) neurotransmitters in the region results in dyskinesia, or excessive, uncontrollable movements [6]. Furthermore, the autonomic, central, and peripheral nervous systems accumulate protein α-syn, commonly referred to as Lewy bodies, as a result of genetic abnormalities that cause neuronal death, as shown in Fig. 1 [7]. Environmental conditions are also a major factor, including head injuries, rural living, pesticide exposure, physical inactivity, smoking, excessive coffee and alcohol consumption, and only 15–20% of instances that affect young people have a genetic etiology [8]. The area of the brain has lost approximately 60–80% of its neurons by the time of death, in comparison to the same area in people who are not affected by the disease [9]. The diagnosis of PD is frequently done by determining functions, such as postural instability, bradykinesia, stiffness, and rest tremor [3]. Another typical diagnostic method is the observation of a prolonged response to a trial of dopamine therapy (levodopa or dopamine agonists) [10].

Presently available treatments aim to enhance the quality of life and reduce the disease's motor symptoms [11]. The pathological causes of many diseases and their development are not altered by pharmacological or non-pharmacological method, which leads to a gradual loss of efficacy and clinical outcomes with time [12]. When a patient develops a functional disability, pharmacological treatment is initiated. This treatment consists of several medication-related therapies, including levodopa, catechol-O-methyl transferase inhibitors, ergot and non-ergot dopamine agonists, and monoamine oxidase-B inhibitors can be used at initial stages, as shown in Table 1 [13]. Levodopa drug therapy is the gold standard treatment for motor functions in PD. Levodopa is given in combination with carbidopa, an inhibitor of peripheral decarboxylase which prevents levodopa's peripheral metabolism [14]. This enables levodopa to reach the brain in therapeutic doses without causing incapacitating side effects [15]. Piribedil, Pramipexole (Mirapex), and ropinirole (Requip) are examples of dopamine agonists that directly activate dopaminergic receptors [16]. They are less effective in treating

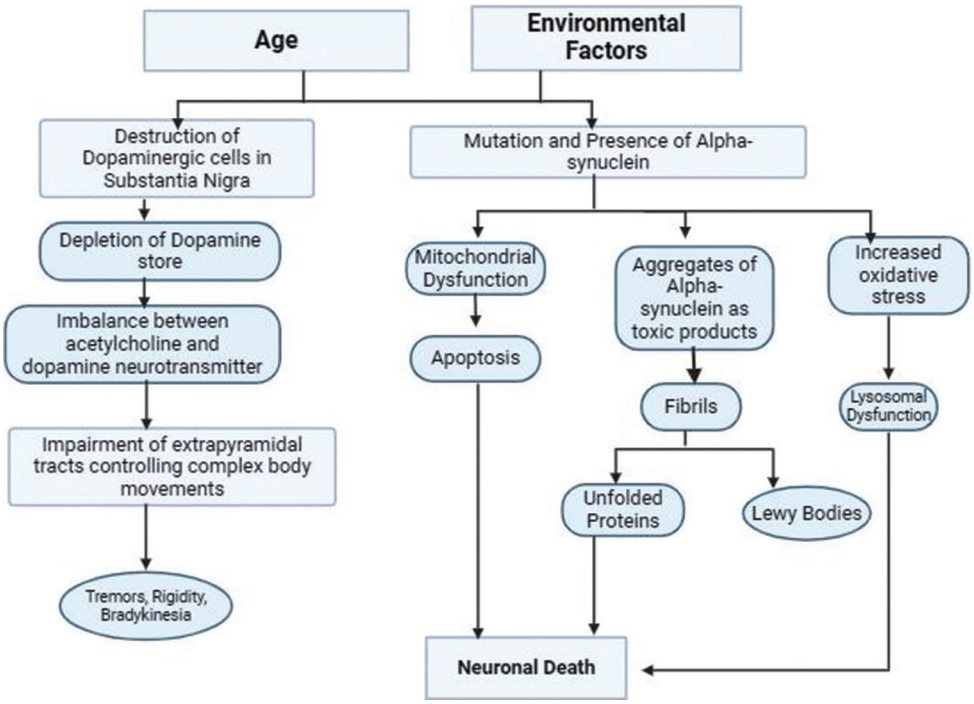

Fig. 1: Mechanism of Parkinson disease

PD's motor symptoms, although they carry a low risk of producing dyskinesias [17]. Monoamine oxidase and catechol-O-methyl transferase inhibitors extend the effects of levodopa and dopamine by delaying their breakdown, that is how they treat PD [18]. The drugs required for this disease can have a lot of negative effects. Levodopa may result in uncontrolled dyskinesia with prolonged use [19]. Hallucinations may be treated if dopaminergic medication is reduced, but motor impairment may increase [20]. Other non-pharmacological therapies that aid in the reduction of motor symptoms, such as dyskinesia, communication difficulties, and postural irregularities, include physical therapy, occupational therapy, speech therapy, and others [21]. Some drawbacks of pharmacological therapy include limited solubility, low bioavailability, poor drug penetration in the brain, severe adverse effects, and long-term ineffectiveness [22]. Novel drug delivery systems (NDDS) are designed to prevent, diagnose, and treat various diseases while improving the overall efficacy of medications to overcome these drawbacks [23]. Some examples of NDDS carriers include liposomes, solid lipid nanoparticles, nanoemulsion, dendrimers (DDs), and niosomes [24]. This review explores the design, development, and application of DD-based formulations, with a focus on their potential to enhance drug solubility, permeability, and target-specific delivery to the brain. By analyzing recent advancements, this paper aims to provide insights into the structural advantages, therapeutic implications, and challenges in utilizing DDs for PD therapy.

DDs are three-dimensional, highly branched structures made up of an active terminal group known as a functional group, branching units surrounding the core, and a core. Functional groups with a clear structure give a diverse class of DDs, whereas branching units allow DDs to grow frequently [25]. Their size, shape, and terminal group functioning can all be precisely controlled during synthesis. They are biocompatible, nanosized drug delivery carriers that allow greater BBB penetration [26].

DDs

In 1985, Donald A. Tomalia came up with the original name "dendrimers," which is a combination of the Greek words "dendron," which means tree, and "meros," which means component [34]. DDs are a nanocarrier system with a combination of 3-dimensional molecules with the central core, repeating building units, called generations and surface functional groups, as shown in Fig. 2, which are used for improved efficiency and flexibility [35]. Essentially, generations of DDs can be distinguished by their shape, size, quantity of surface functional groups, and molecular weight [25]. The amine functional core helps to develop these generations over time. The core is referred to as Generation 0 (G0). By repeatedly adding branching units results in higher generations (G1, G2 or G3, etc.) [36]. The properties of the DDs are determined by their inner portion, their viability and interactions with different molecules, cell structures and solvents are determined by the chemical composition of their end surface groups, and their morphology, especially in three dimensions, is influenced by the layers and core of the branching units [37]. All of these factors are controllable during DD synthesis. Different types of DDs can be synthesized commonly by two methods: divergent and convergent. While the divergent strategy creates DDs from the core to the shell, generation after generation, and produces a vast number of DDs, the convergent technique builds compounds from the periphery to the core [38].

DD-based drug carriers can be used to conjugate or integrate drugs that have a lower bioavailability, have trouble exerting their pharmacological effects, or do not penetrate the BBB [39]. This will increase the overall effect. High concentrations of medications, peptides, and genes can be loaded onto DDs, which then transport them to biological membranes while reducing their cytotoxicity and increasing their effectiveness [40]. To satisfy the unique needs of the target material and its therapeutic uses, the bioactive substances can be easily encapsulated within the DDs, chemically conjugated, or physically adsorbed onto the surface of the DDs [41]. DDs can have neutral, negative, or positive surface charges. Due to its potential to induce cell lysis and limited biocompatibility, the positive charge is the most harmful [42]. DDs' cytotoxicity is contingent upon the kind and configuration of surface groups. To provide DDs with more multifunctional properties, their surface structure can be readily altered. By adding various functional groups to the periphery portion, the physicochemical characteristics of medications, such as their viscosity, solubility, and stability as well as their pharmacological and pharmacokinetic profiles and target selectivity, can all be improved [43]. PD drugs have been entrapped in DD nanocarriers, which have led to a prolonged release of the drugs across the BBB and an extended duration of action. Consequently, DDs are the ideal vehicle for delivering drugs to

Table 1: Drugs used for the treatment of Parkinson's disease

Class	Drugs	Solubility	Permeability	Bioavailability (%)	Mechanism of action	References
Levodopa	Carbidopa/Levodopa (Sinemet)	3 mg/mL in water, 50 mg/mL in 0.5M HCl	0.9×10(-5)± 0.081 cm/s	30	The dopamine pre-cursor is transformed into dopamine by dopa-decarboxylase after penetration through the blood–brain barrier (BBB). It is considered as gold standard treatment. It stops the peripheral metabolism of dopamine. Long-term use of levodopa causes motor fluctuations and dyskinesias.	[27]
Non-Ergot Dopamine Agonists	Pramipexole (Mirapex), Rotigotine (Neupro), Ropinirole (Requip)	20 mg/mL in water and methanol	22.846±0.549 μg/cm^2/h	90	It activates the post-synaptic receptors D2, D3, and D4. It reduced the risk of motor complications, such as tremors and rigidity.	[28]
Ergot Dopamine Agonists	Bromocriptine (Parlodel), Cabergoline (Dostinex), Pergolide	0.8 mg/mL in water, 5 mg/mL in ethanol, 30 mg/mL in DMSO	1.98±0.12 ng/g	28	It excites the dopamine D2 receptors, 5HT1 and 5HT2 and adrenergic receptors.	[29]
Inhibitors of Monoamine Oxidase-B	Selegiline (Eldepryl), Safinamide, Rasagiline (Azilect)	0.0254 mg/mL in water	3.531±1.94μg/cm^2/h	10	It inhibits MAO-B selectively and irreversibly. It stops oxidative stress, which is caused by dopamine metabolism, and hence increases the level of dopamine in the brain. It helps to improve motor functions in advanced PD.	[30]
Anticholinergics	Benztropine Trihexyphenidyl	81 mg/mL in water and ethanol, 50 mg/mL in DMSO	1.6×10(-2)± 0.09 cm/h	29	Cholinergic transmission in striatal interneurons is possibly inhibited, which is responsible for sending signals between cells.	[31]
Injectable agonist of dopamine	Apomorphine	10 mg/mL in water	0.003±0.001 cm/h	100 (subcutaneous)	It excites the dopamine D2-D5 receptors. It opposes the action of 5HT2 and 5HT1 receptors and also alpha-2 and alpha-1 adrenergic receptors	[32]
Inhibitors of Catechol O–Methyltransferase (COMT)	Entacapone (Comtan), Opicapone (Ongentys), Tolcapone (Tasmar)	0.1 mg/mL in water, 5 mg/mL in ethanol, 30 mg/mL in DMSO	0.87×10(-4)± 0.12×10(-4) cm/s	35	It is a reversible inhibitor of COMT, responsible for the breakdown of Levodopa. It increases the half-life of dopamine and Levodopa.	[33]

Data are expressed in mean±standard deviation, such as mean 0.910(-5) with standard deviation 0.081 for Levodopa, mean 22.846 with SD 0.549 for non-ergot dopamine agonist, mean 1.98 with SD 0.12 for ergot dopamine agonist, mean 3.531 with SD 1.94 for monoamine oxidase-B inhibitors, mean 1.6×10(-2) with SD 0.09 for anticholinergics, mean 0.003 with SD 0.001 for apomorphine, mean 0.87×10(-4) with SD 0.12×10(-4) for COMT inhibitors

the brain. In addition, DDs help nucleic acids to enter cells, protect gene molecules from biodegradation, and sustain the biological function of gene molecules used in gene delivery therapy [44].

Different types of DDs, depending on their conformation, include polyamidoamine, chiral, peptide, polypropyleneimine, polyester, poly-L-lysine, phosphorus, carbosilane DDs are biocompatible and enable greater BBB penetration, have demonstrated effectiveness in halting the development of fibrillation and unstable ASN beta formation [45]. Some common DDs available for encapsulation of drugs used in the treatment of PD are:

Poly(amidoamine) (PAMAM) DDs

These DDs were composed of a core of ethylenediamine, branches comprising amide groups that create the cavity walls, and in the periphery, amine functional groups [46]. They are produced through a divergent approach, beginning with initiator core reagents such as ethylenediamine or ammonia. PAMAM DDs are available in generations G0–10, which have five distinct core types and ten functional surface groups and are commercially accessible as methanol solutions [47]. DDs of generation 5 or below are regarded as harmless. DDs may be used as nano-agents to combat viruses, bacteria, and cancers. When compared to other DDs, PAMAM has the most advantages in the field

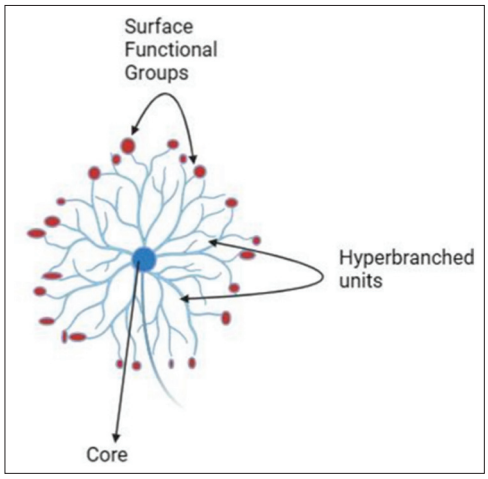

Fig. 2: Structure of dendrimer

of drug administration [42]. To treat PD, G3 to G5 PAMAM DDs have been shown by Rekas and colleagues to inhibit α-syn fibrillation and disaggregate generated fibrils.

Poly(propylene imine) (PPI) DDs

The earliest known DD to be utilized commercially for medication delivery is PPI. It is made up of repetitive units of PPI with a diaminobutane core. Amino terminal groups found in PPI DDs increase the water solubility of hydrophobic materials that are confined in the hydrophobic PPI inner cavities [48]. Nevertheless, membrane instability and cell lysis are commonly brought on by PPI's positively charged surface. PEGylation and acetylation are two surface group modifications that have been used for this. Acetylation is advised because of its strong penetrating ability and efficiency [49]. The PPI-drug conjugate is less stable than PAMAM, and PPI has a lower drug loading capacity.

Poly-L-lysine (PLL) DDs

Furthermore, referred to as dendri-grafted PLL or DGL. These DDs are made of residues of lysine. It is superior to both PAMAM and PPI because of its enhanced biocompatibility, reduced cytotoxicity, and ease of enzymatic breakdown [50]. In gene delivery, there has been extensive use of PLL DDs and their derivatives and the more advanced PLL generation works better for gene transfection [51].

Phosphorus (PPH) DDs

Phosphorus atoms, which usually have reactive terminal groups (hydroxyl or aldehyde groups), are present at each branching point of these DDs. These DDs' hydrophilic surface and hydrophobic backbone allow them to interface with cell membranes and be internalized by cells [52]. They are specifically made for DDSs. Based on the surface charges, phosphorus DD can be divided into three families: cationic, anionic, and neutral. It was discovered that positively charged DDs were more harmful than neutral or negatively charged DDs, known as viologen-phosphorous DDs. Phosphorus DDs have antiviral qualities and are effective substances for preventing the production of harmful fibrils and α-syn aggregation [53].

Carbosilane (CBS) DDs

The extremely branched nanocarriers known as CBS DDs are made up of carbon and silicon bonds at the branches, giving the compounds great flexibility, stability, and low polarity [54]. Carbosilane DDs have an internal hydrophobic core, but by adding polar moieties to their surface, they can change into hydrophilic molecules. The divergent technique has been used to synthesize many forms of CBS DDS. In PD patients, cationic carbosilane DDs at non-cytotoxic concentrations effectively prevent aberrant α-syn accumulation and aggregation in dopamine neurons [55].

NOVEL APPROACHES FOR THE TREATMENT OF PD

NDDS are now widely used for disease treatment, drug delivery, and diagnostics. To improve patient outcomes and treatment efficacy, these systems include targeted therapy, controlled-release formulations, nanotechnology, and non-invasive administration methods. A variety of hydrophilic and hydrophobic medications can be loaded onto nanoparticles, which are promising nanocarriers that can transport them to the brain [66]. Nanoparticles have several benefits, including decreased toxicity, endothelial cell clearance, enzymatic breakdown, and medication stability. They also assist in passing the BBB and enhance brain targeting and absorption [67]. Liposomes, nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, DDs, and gold nanoparticles are examples of novel treatments for PD [68]. An aqueous core and a phospholipid bilayer comprise liposomes, which are nanocarriers. In them, both hydrophilic and hydrophobic medications can be encapsulated. Liposomes have low toxicity, are biocompatible, and biodegradable. In addition, they can protect the medicine being encapsulated from degradation and improve its bioavailability [69]. Through transcytosis or attaching to a particular receptor, they can actively move across the BBB. Polymeric nanoparticles can be made from biodegradable polymers such as poly(lactide) (PLA), poly(lactide-co-glycolide) (PLGA) copolymers, poly (ε-caprolactone) (PCL), or other naturally occurring polymers, such as alginate, chitosan, gelatin, and albumin. Polymeric nanoparticles, such as other nanoparticles, provide some benefits, such as enhanced bioavailability, therapeutic efficacy, and controlled release. They can be made using a variety of techniques, such as nanoprecipitation, emulsification, and solvent evaporation [70]. Solid lipid nanoparticles are composed of lipid or modified lipids (triglycerides, waxes, or fatty acids) and range in diameter from 10 to 1000 nm. These novel nanocarriers, which may deliver drugs to the brain across the BBB, are made up of a solid hydrophobic lipid core that allows the dispersion of both hydrophilic and lipophilic pharmaceuticals [71]. By eliminating the need for organic solvents, SLNs were created to address issues with polymeric nanoparticles and lessen systemic toxicity [72]. The water and oil phases of nanoemulsions (NEs), which are colloidal dispersions, are stabilized by surfactants in particular ratios. NEs have several characteristics, including high stability as well as biocompatibility, and can be administered by different routes. Furthermore, because of their nature, they can include both hydrophilic and hydrophobic medicines [73]. One of the metal nanoparticles that has been studied the most is gold nanoparticles (AuNPs). Gold may be created using a variety of easy methods and has special qualities in its nano-scale sizes. They have been used in diagnostic assays, thermal ablation, radiation, and medication administration [74]. Numerous nanoformulations have been developed to address the treatment of PD, and some of them are mentioned in Table 2. These advancements aim to enhance therapeutic efficacy and improve patient outcomes.

ADVANCEMENT IN DD-BASED FORMULATIONS FOR THE TREATMENT OF PARKINSON

DD-based formulations are employed to treat PD because they improve the way that medications reach the brain. These tree-like nanostructures can deliver dopamine or other drugs, pass the BBB, and target the alpha-synuclein protein to reduce its harmful aggregation [95]. In addition, they enable combination therapy and regulated medication release, which enhances treatment effectiveness and reduces side effects. The P2B001 combination, which consists of the dopamine agonist pramipexole and the monoamine oxidase-B inhibitor rasagiline, has demonstrated better symptom control than either of its constituent parts and may be more effective than either drug alone. It also has a better tolerability profile than higher-dosage dopamine agonist [86]. A well-known combination in which carbidopa increases the effectiveness of levodopa by preventing its breakdown before it reaches the brain. This combination of levodopa and carbidopa was first intended for controlled or extended-release [87]. DDs can lessen neuronal damage by preventing alpha-synuclein, a protein implicated in PD pathogenesis. Non-cytotoxic DD concentrations were successful in stopping aberrant α-syn accumulation in PD [88]. DDs are being

Table 2: Nanoformulations for treatment of Parkinson disease

Drugs	Excipients	Formulation	Method	Delivery routes	Key findings	References
Selegiline	Capryol 90, Tween 80, Transcutol P, PEG 400	Nanoemulsion	Solvent evaporation	Intranasal	Rats given intranasally selegiline-loaded nanoemulsion had significantly more dopamine (16.61±3.06 ng/mL) than rats given haloperidol (8.59±1.00 ng/mL) ($p<0.05$).	[75]
Rotigotine	Tween 20, Capryol 90, ethanol	Nanoemulsion	Titration method	Intranasal	A virtually spherical nanodroplet size of less than 200 nm. A total of 85.23±0.39% of rotigotine from nanoemulsion penetrated the nasal mucosa at 4 h, while only 65.25±0.13% of the drug nanoemulsion.	[76]
Ropinirole	Capryol 90, Tween 80, Transcutol P, PEG 400	Nanoemulsion	Solvent evaporation method	Transdermal	Ropinirole nanoemulsion had AUCs ($0\rightarrow\infty$) of 928.07±206.5 ng/mL, respectively, whereas RPG and oral tablets had AUCs of 137.25±31.3 and 467.15±106.1, respectively. According to histology studies, the formulations were likewise non-toxic and non-irritating.	[77]
Tumor necrosis factor-alpha (TNFα) siRNA	Soy lecithin, propylene glycol, vitamin E tocopherol, polysorbate 80, ethanol	Cationic O\W nanoemulsion	Sonication method	Intranasal	The rat brain showed nearly five times the absorption of non-encapsulated siRNA. It provided a successful method for gene knockdown, and this strategy has great promise for preventing neuroinflammation. A nanoemulsion with particle sizes less than 400 nm was the result.	[78]
Plasmid DNA	Citrate, gold chloride, polyethylenimine (PEI), polyvinyl alcohol (PVA)	Gold nanoparticles (GNP)	Electronic adsorption	Intravenous	To prevent PC12 cells and dopaminergic neurons from dying, GNP was endocytosed into cells. GNP in the mice's brains allows them to successfully pass the blood–brain barrier, and they can cure Parkinson's disease (PD) *in vivo* by blocking α-synuclein (SNCA) expression.	[79]

(Contd...)

Table 2: ***(Continued)***

Drugs	Excipients	Formulation	Method	Delivery routes	Key findings	References
Metformin	Dopamine, polystyrene, PEG (Polyethylene Glycol)	Polydopamine nanoparticles	solution oxidation method	Oral	By reducing rotenone inhibitory effects and rescuing dopaminergic neurons, it enhanced bioavailability and a controlled release profile of the drug. Together with the neuroprotective potential of polydopamine nanoparticles and metformin nanoformulation in the treatment of Parkinson's disease.	[80]
Rasagiline	Chitosan, tripolyphosphate sodium	chitosan-coated PLGA nanoparticles	Double emulsification-solvent evaporation technique	Intranasal	The results showed that the encapsulation efficiency, polydispersity index, and mean particle size were 75.83±3.76, 0.212±0.009, and 122.38±3.64, respectively.	[81]
Rotigotine	Lactoferrin, PLGA (Polylactic-co-glycolic acid), PVA (Polyvinyl alcohol)	Lactoferrin-modified polyethylene glycol–polylactic-co-glycolic acid nanoparticles	Nanoprecipitation technique	Intranasal	The zeta potentials fell between -20 and -22 mV, more steady and effective NP transfer was made possible. The NPs had a constant spherical form and had 1.44±0.02 additional thiol groups, which was within the optimal range of 1-2. Lf conjugation has an efficiency of 18.99%±2.32%. Lf-NPs (77.8%±7.0%) and NPs (81.3%±2.1%) demonstrated a long-lasting and continuous release without burst for 48 h.	[82]
Levodopa methyl ester (LDME) and benserazide	Polylactic-co-glycolic acid, dopamine hydrochloride, homovanillic acid, dimethyl sulfoxide, 6-hydroxydopamine	Polylactic-co-glycolic acid nanoparticles	Double emulsion method	Intranasal	The nanoparticles average size of 500 nm in size. Within around 3 weeks, two medications saw sustained release, with an initial burst rate of just 18.3% and a total drug loading of 30% in the first 2 days. LDME had a lower encapsulation efficiency (60.15%±4.2%) than benserazide (62.87%±6.9%).	[83]

(Contd...)

Table 2: ***(Continued)***

Drugs	Excipients	Formulation	Method	Delivery routes	Key findings	References
Dopamine	Polylactic-co-glycolic acid, dopamine hydrochloride, homovanillic acid, dimethyl sulfoxide	Polylactic-co-glycolic acid nanoparticles	Double emulsion solvent evaporation method.	Intranasal	Nano-DOPA had a much stronger and longer-lasting effect (90±13% 24 h after delivery); additionally, it remained substantial 1 week after the treatment was stopped. The effective half-life, bioavailability, and efficacy of DOPA supplied as PLGA-based nanoparticles were all higher; intranasal delivery also effectively delivered the drug to the brain.	[84]
Ropinirole	Propylene glycol, monocaprylate, tripalmitin, Tween® 20, haloperidol, Carbopol 934, Thio barbituric acid, glutathione reductase	Solid lipid nanoparticles	Hot melt emulsification method	Oral and topical	It was demonstrated that oral treatment increased RP-SLN and RP-NLC by 2.1 and 2.7 times, while topical administration increased them by 3.0 and 3.3 times.	[85]
GDNF glial cell-derived neurotrophic factor	Stearic acid, cetyl palmitate, poloxamer 188, lecithin	Solid lipid nanoparticles	Emulsification method	Intranasal	They created GDNF nanoparticles, which had good encapsulation effectiveness and a particle size of about 130 nm. The potential of the encapsulated GDNF to shield PC-12 cells from 6-OHDA toxin was shown in the *in vitro* experiment.	[86]
Naringenin	Stearic acid, glyceryl monostearate (GMS), poloxamer 188, lecithin	Solid lipid nanoparticles	Emulsification method	Oral	The results showed an entrapment efficacy of 89.87%±0.15%, a zeta potential of−11.9 mV, a polydispersity index of 0.893, and an average particle size of 134.5±20 nm. With a regression coefficient of 0.9721, the dialysis technique's *in vitro* release profile is consistent with the Higuchi model.	[87]
Pramipexole dihydrochloride	Pramipexole dihydrochloride, Chitosan oligosaccharide, sodium tripolyphosphate	Chitosan nanoparticles	Ionic gelation method	Intranasal	Entrapment efficiency and particle size were 91.25%±0.95 and 292.5 nm±8.80, respectively. After 24 h, their diffusion across the goat nasal mucosa and artificial membrane was determined to be 93.32%±2.56 and 83.03%±3.48, respectively.	[88]

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Table 2: ***(Continued)***

Drugs	Excipients	Formulation	Method	Delivery routes	Key findings	References
Rivastigmine hydrogen tartrate	Silica, cetyltrimethylammonium bromide (CTAB), polyethylene glycol (PEG)	Silica mesoporous nanoparticle	Solvent-adsorption Equilibrium	Oral	The average diameters of the drug-loaded MSNs (MCM-41L) and the prepared blank (MCM-41B) were 145±0.4 and 114±2.0 nm, respectively, and their zeta potentials were approximately−37.6±1.4 and−43.5±1.1 mV. On average, their trapping efficiency was 88%.	[89]
Selegiline hydrochloride	Selegiline, sodium Tripolyphosphate, rotenone, Tween 80, chitosan (CHS)	Chitosan nanoparticles	Ionic gelation method	Intranasal	The resultant selegiline nanoparticles (SP18) had a size of 63.1 nm, a polydispersity index of 0.201, a zeta potential of+35.2 mV, an entrapment efficiency of 74.77%, and a cohesion of 65.4%. 52.71 ng/mL for SP18 at 2 h, 20.09 ng/mL for the commercial formulation at 1 h, and 21.69 ng/mL for the drug solution were the highest concentrations in plasma.	[90]
Apomorphine	Glyceryl monostearate (GMS) and polyethylene glycol monostearate (PMS)	Solid lipid nanoparticles	Interfacial polymerization	Oral	The bioavailability of SLNs was 12–13 times greater than that of the reference solution. The total number of rotations increased from 20 to 94 and from 20 to 115 when the medicine was administered from SLNs containing GMS and PMS, respectively.	[91]
Dopamine	cholesterol, Distearoylphosphatidylcholine	Polyethylene glycolimmunoliposomes	Evaporation method	Internal carotid artery perfusion	The absorption of this was almost eight times more than dopamine alone in the rat model. While immunoliposomes have a longer half-life of 116 and 107 min, unbound dopamine has a half-life of 45.6 min.	[92]
Bromocriptine	Stearic acid, glycerol monostearate (GMS), poloxamer 188, lecithin	Solid lipid nanoparticles	High shear homogenization or melt-emulsification	Oral	In 6-hydroxydopamine-hemilesioned rats, a model of Parkinson's disease is used. The drug's plasma level was stabilized by their 48-h sustained release. The duration and onset of the effect of encapsulated bromocriptine were both faster.	[93]

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Table 2: ***(Continued)***

Drugs	Excipients	Formulation	Method	Delivery routes	Key findings	References
Dopamine	Phosphatidylcholine, cholesterol, PEG (polyethylene glycol)	Liposomes	Thin-film hydration method	Intraperitoneal	The brain-directed liposomal technology was used to simulate Parkinson's disease (PD) in mice. It demonstrates a strong correlation between the liposomal DA dose and the behavioral effects in mice given hemiparkinsonian amphetamine, with an optimal DA dose of 60 μg/kg.	[94]

investigated as delivery vehicles for therapeutic genes to fix damaged neurons and reestablish brain function to satisfy the need for greater efficacy and reduced cytotoxicity. Comparing theangiopep-2 peptide that targets LRP1 on the BBB to unmodified nanoparticles, the former showed a significant potential for transcytosis and parenchymal accumulation *in vivo* [89]. DDs' multiple drug delivery can reduce medication resistance and enhance therapeutic benefits. These formulations improve the management of symptoms by controlled and extended release of medication. Researchers are working relentlessly to improve DD formulation. This innovative research is advancing the use and performance of DDs in a number of domains, including materials science, nanotechnology, and medicine. As part of these efforts, some researchers have successfully developed the following formulations as shown in Table 3. In this study, Rekas *et al*., [57] choose two PAMAM of generations 3.5 and 4 to investigate DDs' structure and end functional groups affect ASN aggregation and prevent fibril formation *in vitro* by looking at how they interact with the intrinsic tyrosine fluorescence of A-synuclein (ASN). Tyrosine residue fluorescence increases as a result of the PAMAM G4 DD, which also prevented AS fibrillation. Mutations, oxidative stress, post-translational modification, and abnormalities in catabolism can all encourage the aggregation of α-syn *in vivo*. Neuronal atrophy, synaptic dysfunction, and intracellular inclusions are the outcomes of ASN pathological fibrillation. It was shown that fibrillation does not suppress by PAMAM (G3.5) DDs. The surface of PAMAM G4 DDs had 64 amino groups, whereas the number of carboxyl groups at the chain ends of the PAMAM G3.5 DDs was the same. He identifies the relationship between ASN and DDs as well as how PAMAM affected ASN aggregation. ASN has no tryptophan and four tyrosine residues; fluorescence is increased when PAMAM G4 DDs are present. The exposure to PAMAM G4 DDs at doses ranging from 1 to 3 μM produced statistical significance. The inclusion of PAMAM G3.5 DDs, however, did not substantially alter the fluorescence intensity. In this study, Milowska *et al*., [56] describe how carbosilane DDs contribute to α-syn fibrillation and prevent the hippocampal cell of the mouse (mHippoE-18) from harm caused by rotenone. In addition, he looks at cell functionality, reactive oxygen species (ROS) generation, and the potential of mitochondrial membrane. Carbosilane DDs were used to pre-incubate mHippoE-18 cells before rotenone was added. Pre-incubation with DDs resulted in lower ROS levels in cells, enhanced viability, and higher mitochondrial membrane potential. According to studies, rotenone causes α-syn to accumulate. Other results reveal that deleting parkin and overexpressing α-syn increase the toxicity of rotenone and induce certain cells to undergo apoptosis. It causes the mitochondria's levels of oxidative stress to increase, which triggers caspase-dependent apoptosis and cytochrome C release. Free radical species and mitochondrial transmembrane potential were so quantified. They were tested for their capacity to prevent α-syn fibrillation using two carbosilane DDs with different functional groups and their potential to protect nerve cells from rotenone's harmful effects. The findings indicate that carbosilane DDs block ASN fibrillation and prevent cells from rotenone's harmful effects to some extent. An improvement in cell survival, a reduction in ROS generation, and the maintenance of mitochondrial function all demonstrate this. Since the rotenone amount is likely reduced due to encapsulation into DDs surface. Kecskés *et al.*, [58] produced multivalent conjugates of adenosine receptor (AR) antagonists using GPCR ligand-DD (GLiDe) combination with potent AR antagonist. GLiDe conjugates have different pharmacological properties than monomers, both in terms of quantity and quality. The natural xanthine theophylline and caffeine are classic examples of AR antagonists that have therapeutic potential for PD treatment. Triazoles were created by joining Cu(I)-catalyzed click chemistry to azide-derivatized G4 (fourth-generation) PAMAM DDs by adding an alkyne group to an extended C8 substituent of xanthine amine congener (XAC). The conjunction additionally includes triazole-linked PEG groups (8 or 22 moieties/64 terminal positions) to improve water solubility and AR binding affinity as the degree of xanthine substitution rose. In this study Dai *et al*., [59] expected that the developed DD/FN will be expanded for the treatment of different neurodegenerative diseases by leveraging the advantages of both FN and BBB-penetration hydroxyl-terminated bioactive phosphorus DDs. Investigations were conducted on AK123/FN's size, shape, and zeta potential. AK123/FN, a spherical substance with a diameter of 223 nm, is highly cytocompatible and stable in aqueous dispersion. We assessed their effects *in vitro* on M2 microglia polarization, inflammation inhibition, and reactive oxygen species (ROS) scavenging. It was also confirmed that AK123/FN might be used to treat a PD mice model *in vivo* by combining antioxidants and anti-inflammatory drugs. AK123/FN has been shown through fluorescence imaging to improve penetration into BBB and modulate the brain immune microenvironment through their anti-inflammatory and antioxidant effects. This has been shown to effectively alleviate behavioral symptoms in PD mice by gradually restoring dopamine levels, increasing dopamine synthesis, and decreasing microglia inflammation and αsyn expression in the mouse brain. Sharma *et al*., [60] discovered that the synthesis of 9-amino-minocycline DD (D-Mino) through enzyme-responsive connections can be achieved by combining microwave energy with a moderate and extremely efficient azide-alkyne click reaction (CuAAC) catalyzed by copper. The intrinsic instability of minocycline makes it difficult to perform chemical reactions with this medication. The anti-inflammatory and antioxidant properties of D-Mino were further assessed in murine microglial cells stimulated by lipopolysaccharides. Due to their quick absorption, D-Mino conjugates improved the medication's intracellular availability. They also decreased oxidative stress by inhibiting the formation of nitric oxide, decreased tumor necrosis factor α (TNF-α), a cytokine that promotes inflammation, and decreased toxicity more effectively than the free drug. According to his research, rabbit kits with cerebral palsy exhibiting a clinically relevant phenotype showed a consistent response

Table 3: Dendrimer-based formulation for treatment of Parkinson's disease

Drugs	Excipients	Method	Delivery routes	Key findings	References
Rotenonecarbosilane DDs	dimethyl sulfoxide, and trypsin	Covalent bonding	Intracerebral	Carbosilane dendrimers efficiently reduced alpha synuclein fibrillation because, unlike its ASN progression, it did not continue into the development of beta structures. It also suppresses fibril development by 91.8–96.7%.	[56]
PAMAM-Dopamine DDs	Ethylenediamine, methyl methacrylate	Divergent method	Intranasal, intracerebral	During the tyrosine fluorescence assay, PAMAMG4 enhanced the ASN's fluorescence intensity. A-synuclein aggregates that were generated changed structurally from cylindrical to dense three-dimensional ones as the PAMAM concentration rose	[57]
GPCRPAMAM DDs with xanthine	Ethylenedi amine, methyl methacrylate	Divergent synthesis	Intravenous, intranasal	It improves the AR antagonist's binding characteristics and offers high receptor selectivity and affinity for Parkinson's disease treatment.	[58]
Phosphorus dendrimers (AK123) with fibronectin (FN)	Ethylenediamine, methyl methacrylate	Electrostatic adsorption, hydrogen bonding	Intracerebral	It is 223 nm in size, spherical in shape, and has good cytocompatibility and water dispersion stability. In a PD mouse model, fluorescence imaging demonstrates that the AK123/FN NCs successfully cross the compromised blood–brain barrier.	[59]
Minocycline PAMAM Dendrimers	Ethylenediamine, methyl methacrylate	Enzyme-responsive linkages, ester bonds	Intravenous	It significantly outperformed the free medication in reducing oxidative stress by blocking the generation of nitric oxide and controlling the release of the inflammatory cytokine tumor necrosis factor α (TNF-α).	[60]
N-acetyl-L-Cysteine PAMAM Dendrimer	EthyleneAmine, methyl methacrylate	Via antioxidant effects	Post-natal	Dendrimer-based N-acetyl-l-cysteine (NAC) therapy reduces neuroinflammation and improves motor function significantly in the Cerebral Palsy kits for brain injury.	[61]
Nerve growth factor (NGF) dendrimers	Ethylenediamine, methyl methacrylate	Divergent synthesis	Intranasal, intracerebral	It causes HD sufferers' brains to produce more NGF. On the rotarod exercise, the only mice that were given mesenchymal stem cells that were genetically altered to over-express BDNF consistently showed behavioral sparing.	[62]
Poly-l-lycine-PEG-Angiopep	Ethylenediamine, methyl methacrylate	Divergent synthesis	Intravenous	NPs had 8.2±0.7 mV as zeta potential and a spherical form, measuring 119±12 nm. In brain cells, angiopep-conjugated NPs showed increased gene expression and cellular uptake.	[63]
Curcumin PAMAM dendrimers	Tetrazolium MTT salt, methanolic suspension	Ionic interactions	Intranasal, intravenous	The indirect method] s measurement of the soluble CUR concentration in the absence of the dendrimer is more than the concentration predicted by the reported solubility (1.6 μM).	[64]
Carbamazepine Polyamidoamine dendrimers	Ethylenedi amine, 5Hdibenzoaze pine-5carboxami de	Ionic or covalent interactions	Intravenous	For 90 days at 37°C, the DG4.0-CBZ and DG4.5-CBZ complexes exhibited controlled drug release, stability, and resistance to lyophilization. Enhancement of the pharmaceutical characteristics of carbamazepine and reduction in its toxicity in zebrafish, N2a, and human red blood cells.	[65]

to the intravenous administration of fluorescently labeled DD conjugate (Cy5–D-Mino) on post-natal day 1. When paired with the PAMAM DDs' innate capacity to target neuroinflammation, the increased effectiveness of D-Mino may open up new possibilities for targeted drug delivery to treat neurological conditions. Kannan *et al.,* [61] developed a DD conjugate drug to treat neurodegenerative diseases. The researchers selected the rabbit model of cerebral palsy (CP) because it reproduces both inflammation in neurons seen in human brains and the motor impairments seen in children. At almost 90% term gestation, Kannan and colleagues made this model by injecting Escherichia coli toxin into the uterus of the rabbit mother. The kits were given a saline solution, a DDNAC (D-NAC) conjugate, or a free medication called N-acetyl-L-cysteine (NAC) when they were first born. D-NAC is given post-natally on the 1st day of life, enabling them to grow properly and acquire the ability to walk and jump. The neuron counts and low levels of inflammation in the successfully treated kits were comparable to those of healthy control animals. Saline or NAC by itself had little impact. He found that conjugating NAC to the DDs enhanced astrocyte and activated microglia absorption without posing a threat to neighboring neurons. In neonatal rabbits with cerebral palsy, he demonstrates that PAMAM that are systemically delivered locate in activated microglia and astrocytes but not in healthy controls. He also demonstrates that for brain injury, DD-based NAC therapy, when administered post-natally, greatly improves motor function and lowers neuroinflammation for the treatment of various neurodegenerative diseases. Dey *et al*., [62] in his research demonstrate that slowing the rate of neuronal death can help treat neurodegenerative diseases, but in Huntington's disease (HD), a shortage of nerve growth factor (NGF) causes these cells to die. He reversed the neurodegeneration and behavioral abnormalities seen in this mouse model of HD by injecting mesenchymal stem cells (MSCs) that had been genetically modified to overproduce either BDNF or NGF into the striata of YAC 128 transgenic mice. This procedure increases the amount of NGF in the brain of HD patients. YAC128 mice, which express the full-length huntingtin protein, were used to evaluate the

long-term behavioral consequences of transplanted stem cells. This was required since behavioral problems and neurodegeneration are slow and do not become serious until the child is about 12 months old. Clasping, dyskinetic behavior and rotarod exercises were used to evaluate motor abilities. The study's main conclusions were that all transplanted YAC mice decreased clasping, regardless of whether they received MSCs genetically modified to produce BDNF, NGF, or both, and that only YAC mice that received MSCs genetically modified to over-express BDNF showed consistent behavioral sparing on the rotarod task. Huang *et al.*, [63] created a gene delivery system based on Angio pep-conjugated dendrigraft poly-Llysine (DPA) and evaluated its neuroprotective properties in a rotenone-induced model of PD. Angio pep was used as a ligand to create DGL-PEG-Angio pep (DPA), which preferred to attach to the overexpressed low-density lipoprotein receptor-related protein (LRP) at the BBB and was subsequently connected to biodegradable DGL using hydrophilic polyethyleneglycol (PEG). A characterization process was conducted *in vitro*. A sphere-like shape with a zeta potential of 8.2±0.7 mV and a diameter of 119±12 nm was observed by DPA. Rotenone developed a chronic parkinsonian model in which the neuroprotective effects were assessed through a series of intravenous dosage administrations. When compared to unconjugated PAMAM loaded with DNA, researchers have demonstrated that the administration of Angio pep-PEG-PAMAM with DNA dramatically boosted gene expression in the mice's cortex, caudate putamen, hippocampus, and substantianigra. According to the pharmacodynamic data, rats in the group that received five DPA injections demonstrated the greatest improvement in locomotor activity and apparent dopaminergic cell recovery when compared to rats in other groups. Al Igartúa *et al.,* [64] demonstrate that the bioactive molecule curcumin (CUR) is utilized to treat a number of neurological diseases, yet its limited solubility in aqueous mediums and chemical instability in physiological situations limit its usage. To get over these restrictions, he created Curcumin-PAMAM DDs of generation 4.5 (CUR-DG4.5), which internalizes CUR into the DD's pockets to improve its solubility and stability. It also demonstrated *in vitro* biocompatibility and improved CUR uptake. To treat synucleinopathies, the creation of 4.5 PAMAM DDs loaded with curcumin are employed as nanodrugs that can reduce free radical species and prevent accumulated α-syn. To treat PD, he then investigated the delivery system's ability to prevent α-syn aggregation and oxidative stress. When it comes to radical scavenging activity and H2O2-induced oxidative stress inhibition in cell culture, CUR-DG4.5 exhibits strong antioxidant activity. In addition, DG4.5 prevents α-syn from aggregating pathologically, which contributes to CUR's well-known benefits for the treatment of PD. Igartúa *et al*., [65] sought to develop and describe a novel PAMAM DD-based carbamazepine DDS for neurodegenerative diseases. Despite having erratic pharmacokinetic characteristics and being poorly soluble in water, carbamazepine (CBZ) has been demonstrated to improve autophagy and guard against neurodegeneration *in vivo*. Therefore, CBZ conjugate DD (G4.5) is intended to increase CBZ solubility and stability while lowering the dosage and frequency of administration, minimizing adverse effects, and achieving a regulated release profile. It was observed that 40% of the CBZ was maintained following a 28-h dialysis session. Furthermore, when CBZ enclosed within this DD, drug cytotoxicity was decreased. With regulated drug release, they resist lyophilization and remain stable for 90 days at 37°C. The nanotoxicity of the complexes was also assessed *in vitro* (N2a cell line), *in vivo* (zebrafish), and *ex vivo* (human red blood cells) experiments. In the *ex vivo* model, there was no erythrolysis effect. This accomplishment highlights the several benefits of employing negatively charged DDs for nanomedicine. There is various market formulations based on DDs are available in the market for different diseases as shown in Table 4.

CHALLENGES AND FUTURE PROSPECTIVE

The majority of conventional medications employed to treat PD have a short half-life, require frequent dosage, cause variations in drug levels, and are ineffective in BBB penetration. Their efficiency is diminished by their limited solubility and stability, as well as a variety of adverse effects brought on by the non-specific dispersion of medications. Dyskinesia and other motor problems can result from long-term usage of medications, such as levodopa. To overcome these drawbacks, Drug delivery based on DDs has been studied for neurodegenerative diseases, such as PD. Nanoformulations based on DDs offer several benefits, including preventing medication degradation, boosting solubility and bioavailability, enhancing the therapeutic efficacy of active ingredients, and lowering toxicity. BBB penetration is the biggest obstacle for conventional drugs. Despite DDs' potential in effective drug delivery to the brain's target location is still difficult and requires creative approaches. Long-term safety concerns are raised by the possibility that certain DD formulations will become hazardous at increasing concentrations. DD synthesis and manufacture can be costly, which could prevent accessibility and large-scale production. There is a substantial lack of clinical trial data to support the therapeutic potential of DDs for PD, despite the fact that many studies concentrate on pre-clinical data. However, cationic PPI DDs have reduced safety profile because they raise the risk of free radical damage, cell lysis, membrane instability, and cytotoxicity. Future studies can concentrate on improving DD design by adding surface coatings composed of polymers, such as polyethylene glycol to increase target specificity and BBB crossing. Nucleic acids and other ligands can also be coupled with DDs. Furthermore, developments in stimuli-responsive and biodegradable DDs may enable regulated and extended drug release while reducing toxicity issues. Advances in manufacturing processes may reduce the cost of producing DDs, encouraging broader use. Customizing DDs to meet the demands of each patient allows for individualized treatment plans that optimize effectiveness and reduce negative effects.

Table 4: Market formulations of dendrimers

Brand name	API	Company	Application	References
INNO-206	Doxorubicin	CytRx Corporation	Cancer	[96]
Dendrosome™	Paclitaxel, methotrexate	Dendritic Nanotechnologies,	Cancer	[97]
VivaGel®	Astodrimer sodium (SPL7013)	Starpharma	Prevent from HIV and AIDS	[98]
Elzonris	Tagraxofusp	Stemline Therapeutics	Blastic Plasmacytoid dendritic cell cancer	[99]
Superfect®	Epidermal growth factor receptor (EGFR) tyrosine kinase–extracellular-regulated kinase 1/2	Qiagen	Transfection agent	[100]
Priofect™	PAMAM	Starpharma	Transfection agent	[101]
DEP® oxaliplatin	Oxaliplatin	Starpharma	Colon cancer treatment	[102]
DEP® docetaxel	Docetaxel	Starpharma	Breast cancer	[103]
DEP® cabazitaxel	Cabazitaxel	Starpharma	Prostate cancer	[103]
DEP® irinotecan	Irinotecan	Starpharma	Colorectal cancer	[104]
VivaGel® BV	Astodrimer sodium (SPL7013)	Starpharma	Bacterial vaginosis	[98]
Stratus CS®	Cardiac Troponin I	Dade Behring	Cardiac-related condition diagnostic	[105]

CONCLUSION

Among the most prevalent neurodegenerative conditions affecting the elderly population, PD is linked to higher rates of morbidity and death. It is likely that both genetic and environmental factors contribute significantly to abnormal protein aggregation, which leads to cell dysfunction and eventually death. Present treatments for PD can enhance patients' quality of life and lessen clinical symptoms. In recent decades, DDs have drawn interest because of their potential as medication carriers, which are typically used to treat PD. DD-based formulations overcome important issues with traditional medications. These cutting-edge platforms for nanotechnology provide higher permeability, solubility, and targeted drug delivery, resulting in better therapeutic outcomes and fewer systemic side effects. Researchers demonstrate how PD medications can be conjugated to DDs in a novel and helpful way to stop aggregates from forming in the first place. In addition to being effective delivery systems for enhancing drug pharmacokinetics and lowering toxicity, DDs have been demonstrated to have anti-aggregation effects that either decrease or encourage protein accumulation, and some of their structures have built-in anti-inflammatory qualities. By interacting with important therapeutic targets in PD, DDs can reduce neuroinflammation, protect neurons from toxic aggregates, and decrease abnormal protein deposition. However, to guarantee their successful clinical translation, issues including toxicity, scalability, and regulatory barriers need to be settled. The results presented here highlight how DD technology has the potential to revolutionize the treatment of PD by enhancing BBB penetration, improving solubility and reducing toxicity, and advancing the field of neurodegenerative disease treatment in general.

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CONFLICT OF INTEREST

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AUTHORS CONTRIBUTION

Shalu Verma: Investigation, Conceptualization, drafting, Supervision. Tarun Parashar: Review, editing, and visualization. Khushi Aggarwal: Writing review and editing. Arjeeta Singh Rathore: writing and analysis.

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