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Review Article

Unravelling the Pathogenesis of Parkinson's Disease and Cutting-Edge Treatment Strategies Leveraging Nanotechnology

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Abstract

Background: Parkinson's disease (PD) is a complex multifactorial neurodegenerative disorder with a complex pathogenesis process. An understanding of the pathogenesis is key in understanding how to manage the condition and exploring the potential therapeutic targets, pharmacokinetic parameters. With better understanding of the pathogenesis of the new target of disease therapy is the novel nanoparticle-based approach. Therefore, the target of this review article is to review the nanotechnology approach in the treatment of PD.

Methodology: This review article was written referencing papers from: American Chemical Society, Bentham Science or Multidisciplinary, Elsevier Journals, Frontiers Media, Journals Hosted by National or Specialty Societies, New England Journal of Medicine, Springer Journals, Taylor and Francis/Informa Healthcare, The Lancet Group, Wiley Online Library, World Health Organization and various other journals and publishing.

Conclusion: Pre-clinical trials in animals have shown positive response and has been proved to be safe; showing enhanced drug bioavailability, reduced motor symptoms, and neuroprotection using nanocarriers. However further clinical studies are needed to assess the safety and efficacy in humans including toxicity, immune response, accumulation, and biodegradability of nanomaterials need extensive long-term evaluation. Additionally, there is a need for regulations and standardization for the safe manufacturing, scalability and quality control of the drug, during manufacturing, transport and administration. Therefore, although nanoparticles is a promising advancement in the field of Parkinson's disease, further studies and protocols are to be developed before it can replace traditional treatment pathways.

Keywords: *Parkinson's Disease (PD); Pathogenesis Process; Nanotechnology Approach*

Review

Parkinson's disease (PD)

Parkinson's disease (PD) is known to be the second most common neurodegenerative disorder, following Alzheimer's disease [1]. The disease primarily affects the basal ganglia of the brain, a region crucial for motor functions. As a result, the clinical symptoms of which PD is characterised by are those of neurological deficits, such as abnormal gait, bradykinesia, postural changes, and a characteristic resting tremor. However, the clinical spectrum extends to include less obvious non-motor features, such as cognitive decline and depression [2,3]. Collectively, these symptoms lead to a progressive and significant decline in the quality of life of a patient which makes daily activities increasingly difficult [2]. The disease is age-related with incidence and prevalence increasing steadily with age, though it is a misconception that it exclusively affects older people [2]. The term 'young onset Parkinson's disease' (YOPD) is defined as parkinsonism starting between the ages of 21 and 40 or even 50 [4]. In fact, the age onset for almost 5-10% of affected individuals is younger than 50 years [2].

According to the World Health organisation's (WHO) technical brief in 2022, it was reported that approximately 8.5 million individuals lived with Parkinson's disease in 2019 - a dramatic increase in prevalence since 1997, having doubled the number of cases. Additionally, PD has caused 100% more deaths since the year 2000, with 329,000 deaths recorded globally in 2019 alone [5]. This sharp increase in mortality highlights the severity and expanding burden of the disease on global health systems. This global rise in PD cases has also led to findings which suggest that it has become one of the fastest growing conditions worldwide and leading causes of neurological disability [6,7]. Parkinson's disease was first outlined in the 1817 publication, "An Essay on the Shaking Palsy" by James Parkinson, where he described the disease as a complex, progressive neurodegenerative disorder. He highlighted the long latency of the condition, noting that early symptoms may be subtle but will progress to become debilitating in later stages, therefore requiring long-term monitoring [8]. Medical research on PD spans over 200 years [9], and recent findings demonstrate that in most patients, PD is explained by genetic causes linked to mutations in known genes, specifically SNCA, LRRK2, PRKN, PINK1, and GBA. The pathophysiology of PD results from the complex combination of aberrant alpha synuclein aggregation, dysfunction of mitochondria, lysosomes or vesicle transport, synaptic transport issues, and neuroinflammation. These mechanisms collectively result in the accelerated death of dopaminergic neurons [2]. These hallmark pathological changes occur in the substantia nigra and alpha aggregation in Lewy bodies which progress to result in motor symptoms [10] and further develop into dementia [11]. However, prior to onset, patients may experience prodromal symptoms years before, which present themselves in many systems ranging from constipation, insomnia, mood disorders, and anxiety [10].

Risk factors

When it comes to the risk factors of PD, both genetic and environmental components contribute, with the male sex and advancing age being significant independent risk factors [12]. This was evident in the Oxford Parkinson's Disease Centre study in which cognitive performance was significantly worse in male PD patients of at least 3 years compared to females [13]. Modifiable risk factors such as hypertension, diabetes mellitus, obesity and dyslipidaemia have also been associated with worse cognitive performance in PD patients due to presence of white matter hyperintensities for total brain and frontal temporal regions [13]. In addition to this, a study conducted by Gorell., *et al*. 2004 found occupational factors have been associated with PD through the exposure of certain metals, copper and manganese, exposure to herbicides, insecticides and farming, and what may seem paradoxical, non-smokers [14]. The presence of family history of PD in first- or second-degree relatives may result in greater associations with PD [15]. Also, the release of oxidative stress via related genetic mutations as well as exposure to pesticides used commonly in agriculture were found to contribute to the mechanism which leads to cellular dysfunction in dopaminergic neuron metabolism and eventual cell death [16]. Other factors include traumatic brain injury and consumption of dairy products [17].

Causes/pathogenesis

Parkinson's disease (PD) is a complex neurodegenerative disease that results from multifactorial causes including a person's genetic makeup, their environment and the aging process itself. In the pathogenesis and progress of the disease three key components take the centre stage: aggregation of α-synuclein (αSyn), dysfunction of mitochondria and subsequent inflammation. As a result, there is a

pathological hallmark: the loss of dopaminergic neurons in the substantia nigra resulting in the clinical signs and symptoms of PD [18,19]. A pathological hallmark is the Lewy bodies found in these neurons that are aggregates of the αSyn protein [20].

α-synuclein is transcribed from the SNCA (synuclein) gene and is made up of 140 amino acids. The αSyn oligomers differ in their structure and weight, they can alter their monomeric sequence thus are soluble, but unstable [21]. The finding of αSyn aggregates in familial and sporadic cases of PD [22] establishes strong evidence that aggregation and misfolding of αSyn has a key role in PD, although the exact mechanism through which this happens is yet to be fully understood [23].

It is however established that through the development and progression of PD the soluble oligomers change into the insoluble amyloid fibres that result in the toxicity of αSyn. This aggregation is aided and accelerated by several environmental factors including an increase in temperature and acidic pH [20]. Other factors include prolonged exposure to polluted air [24], methamphetamine (METH) abuse [25] and heavy metal toxicity [26]. With toxic levels of heavy metals such as copper, mercury, lead, arsenic and manganese in the substantia nigra it leads to neuronal inflammation by the production of oxidative free radicals thus depleting the antioxidants this results in the disruption of the normal process of the neurons namely dysfunction of the ubiquitin-proteasome system and the electron transport chain [26]. Similarly prolonged METH abuse is correlated with an increased amount and aggregation of αSyn, possibly by activating the glial cells, inducing apoptosis of neurons or causing changes in the serotonin and dopamine transporters. Certain occupations increase the risk of developing PD, such as welders who are exposed to heavy metal fumes and agricultural workers who are in contact with pesticides. This said, there is disparity in the development of PD and exposure to the risk factors because of genetic-environmental and environmental-environmental interplays [27].

The genetic component in the pathogenesis of αSyn aggregates, is the mutation of the SNCA gene, that codes for the αSyn protein. The mutations that promote the development of PD are those that increase the expression of SNAC gene leading to increased levels of αSyn, these include alteration of the SNAC gene, its duplication or even triplication [28]. There are multiple clusters of genes that have similar outcome, the eventual aggregation of misfolded αSyn in the neurons as a result of imbalance between the production and clearance of the protein [29].

Another important method by which normal functioning of αSyn is ensured is its post translational modifications (PTMs). The PTMs include the structural alternation of αSyn by its proteolysis, phosphorylation, acetylation etc. (Figure 1) ineffective or dysfunction of PTMs influences αSyn aggregation and eventually PD [30,31].

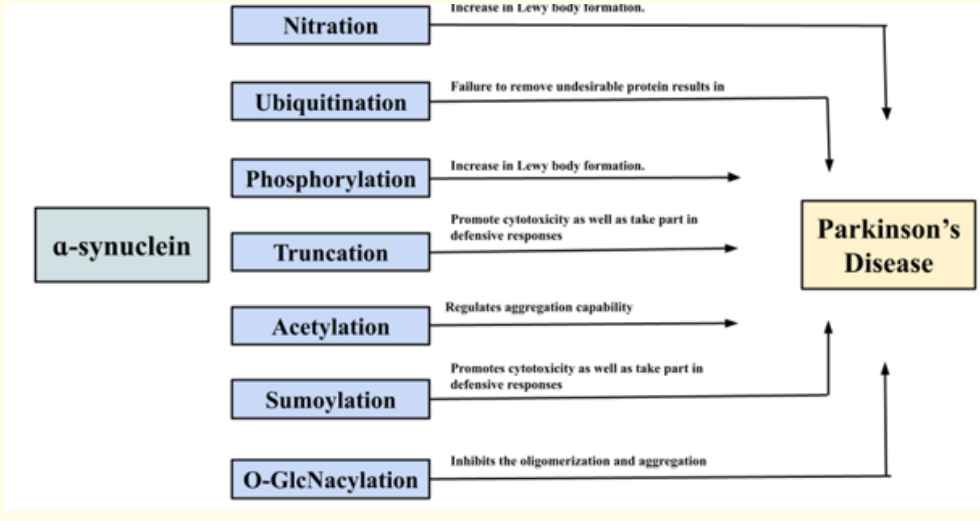

Figure 1: *The role of post-translational modification in Parkinson's disease [23].*

Inflammation in another key component of the PD pathogenesis. Post-mortem examination of brains in patients with PD showed evidence of immune cell accumulation and inflammation such as activated T cells, microglia cells and immunoglobulins. This is believed to be triggered by the misfolded αSyn [32] that trigger the immune response by binding to the toll like receptors (TLRs). In addition to αSyn, environmental toxins and oxidative free radicals can also stimulate the TLRs resulting in microglia activation [33,34] following which the downstream pathway of inflammation is triggered, and inflammatory process occur such as the formation of inflammasomes, the release of cytokines and production of oxidative species that cumulatively lead to neuronal damages and eventual death [32], when this happens to the dopaminergic neurons it results in PD. The inability of glial cells to carry out effective phagocytosis as a result of lysosomal defects is also a contributing factor of neuronal inflammation.

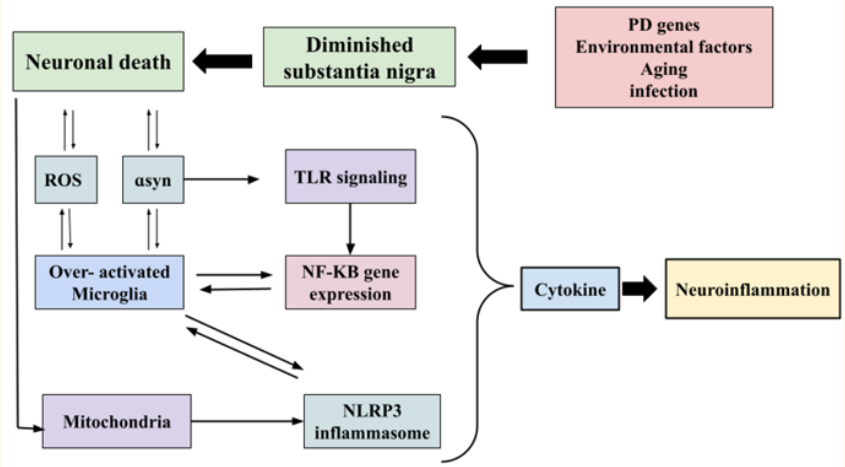

Figure 2: *The role of neuroinflammation in Parkinson's disease [19].*

The interactions between mitochondria and the Nucleotide oligomerization domain (NOD) like, leucine-rich-containing family pyrin domain containing 3 (NLRP3) inflammasomes also control and contribute to the inflammation and thus the PD itself [35]. The mitochondria react to stress by releasing danger signals and this is what regulates the NLRP3 inflammasome [36] then results in a vicious cycle that ends in neuronal death.

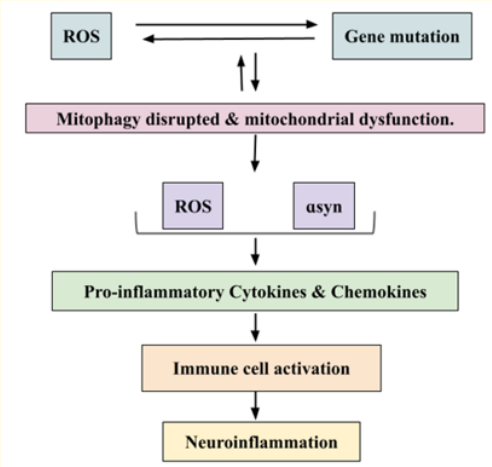

Figure 3: *Mitochondrial dysfunction and neuroinflammation in Parkinson's disease [19].*

The current accessible evidence to the pathogenesis of PD, reveals that there are several mitochondrial processes that intertwine and others that stand alone together contributing to PD. This leaves us with the need for a complex therapeutic approach while designing and developing treatments for PD, in order to stratify advancements in PD treatment and to provide great quality of life for its patients [19].

Treatment

The older approach with PD treatment is to increase the levels of dopamine available to the neurons and thereby slowing down the disease from progressing. Pharmacological therapy used for the treatment has three main mechanisms of action: 1. Replacement of dopamine with dopamine precursors that can reach the brain after crossing the blood-brain barrier such as Levodopa, L-DOPA, L-3,4 dihydroxyphenylalanine, 2. Use of dopamine agonists like amantadine, apomorphine and 3. Monoamine oxidase type B inhibitors like selegiline, rasagiline, so dopamine is not metabolised, these classes of drugs are used in monotherapy or in combination with one another [37]. L-DOPA is considered the gold standard in the treatment of PD however eventually patients develop resistance and no longer respond to the treatment [38]. It furthermore has several side effects like neurotoxicity, neuronal deterioration, wearing-off etc, the worst part being the absolute inability to predict the onset of severity of these adverse effects.

Although these approaches have been key in the treatment of PD, they have numerous side effects and limitations, including the effectiveness of the drug itself. Furthermore, the traditional treatments focus only on the management of the patients' symptoms rather than the underlying pathophysiology that eventually leads to the symptoms. The course of the therapy is life long and the cause of so many undesired effects, resulting in a lower quality of life for the patient. As a result of the behavioural changes and tiredness due to PD progression patients fail to comply with their treatment. With the discovery of the newer nanoparticle-based treatment that targets to slow down neuronal apoptosis, reduce neuroinflammation and improve the delivery of drugs directly to the brain by surpassing the blood-brain barrier. Amongst the nano-therapies being explored are nanobodies, nano-antibodies and lipid nanoparticle-based drugs [38].

Nanotechnological approach

Nanotechnology is defined as atomically precise technology that ranges from 1 to 100 nanometres in size [39]. The use of nanotechnology is promising as drug transport carriers in managing multiple neurodegenerative disorders, particularly PD. This is because they are able to overcome the pharmacological limitations of conventional drug therapy such as low solubility, rapid biodegradation, low bioavailability, adverse effects, and the most prominent drawback, low permeability through the blood brain barrier [40]. As stated previously, current treatments do not cure nor alleviate the progression but only aim to provide symptomatic relief, this is a major challenge that nanotechnology intends to tackle. These nanomaterials are smaller, faster, and lighter in size, as well as have a broad surface area which makes them highly beneficial in their effectiveness. Examples of these technologies include micelles, liposomes, polymeric nanoparticles, and solid lipid nanoparticles [41].

Drug delivery strategies using nanomaterials have shown to improve the effectiveness of PD treatments. They have unique physical and chemical properties, such as their small size which allows them to be equally distributed when administered through different routes compared to conventional ones such as intranasal administration, which is known to offer better permeability through the BBB. In addition, there can be increased complexity of the formulations, and specific changes made to the particle surface to pass through the BBB without producing toxic effects to the brain and at systemic levels [42].

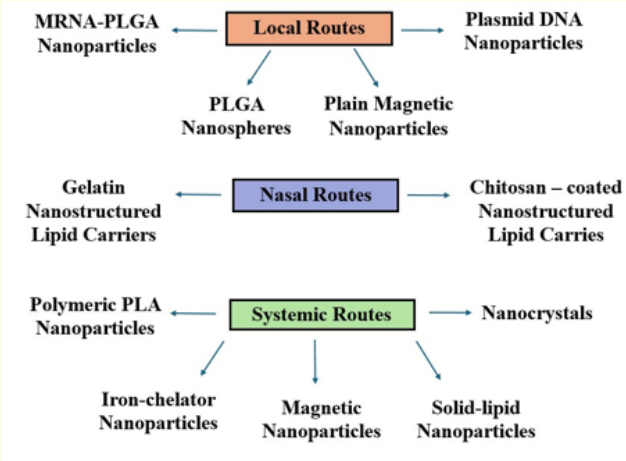

Figure 4: *Most common nanosystems used to improve PD therapy [43].*

Micelles and liposomes

Micelles are vesicles that are made of amphiphilic surfactants or amphiphilic copolymers and configure within 1-100 nm in range. Polymeric micelles in particularly have been used to explore CNS specific delivery due to their better ability to penetrate BBB, reach the brain parenchyma in the case of PD, and their property of steric stabilisation property due to PEGylation [44]. This feature provides them with an outer hydrophilic environment and an inner hydrophobic core synthesised by other molecules such as fatty acids and phospholipids which allow for the loading of hydrophobic drugs. In addition, it provides stability to the micelles structure and prolongs their circulation in the bloodstream and further facilitates their accumulation in a specific region [45]. On the other hand, liposomes used for medical purposes are typically between 50 and 450 nm and are spherical vesicles composed of phospholipids, cholesterol, or polyethylene glycol (PEG) lipids [46]. These properties provide them with a far superior biocompatibility compared to other nanostructures. They have been used for novel drug delivery systems since the 1970s, owing to their hydrophilic core, similar to that of micelles [45].

In a study by Li Y., *et al.* 2018, they developed micelles containing a substance, epigallocatechin gallate (EGCG), shown to inhibit a-syn aggregation *in vitro* but is however ineffective due to its strong binding affinities with the BBB. To fix this, the micelles have been engineered to facilitate the transport of EGCG across the BBB by utilising peptide B6 which has a high affinity for the transferrin receptor. In addition to this, ligands such as mazindol have been modified to selectively target dopaminergic neurons by facilitating the internalisation of the dopamine transporter. As a result, the findings demonstrated a significant increase in the build-up of EGCG in affected lesions of PD as well as remarkable inhibition of a-syn aggregation and increase in dopaminergic neurons [17].

In addition to this, Kuo., *et al*. conducted a study with surface modified liposomes with a formulation of laser evoked potentials (Lep), reticuloendothelial systems (RES), and EGCG. It yielded exciting findings such as the downregulation of the expression of apoptotic proteins e.g. a-syn and bcl-2-associated X protein, and the upregulation of the expression of antiapoptotic protein B-cell lymphoma 2 and dopamine transporters. These mechanisms factored together to exhibit neuroprotective effects [47].

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) have either a negative or positive charge and a high drug loading capacity. Its matrix components is either of natural or synthetic origin and they can be made of biodegradable polymers (poly (lactic-co-glycolic acid) [PLGA] or cyanoacrylate) or non-biodegradable polymers (e.g. polyurethane) [48]. They are stable, biodegradable, and can easily carry high doses of drug molecules [49].

Easy modification of PNPs surfaces to facilitate their attachments to corresponding ligands such as those specifically targeting the brain is a major advantage for PD therapy, as well as being a drug-delivery system [50]. This allows for surface modification of PNPs together with molecules that are used specifically for brain targeting, such as lipoproteins, toxins derivatives, antibodies, albumin, insulin, and cell penetrating peptides - a major advantage in CNS applications [51]. Figure 4 shows examples of ligands that are commonly used to enhance the target of PNPs to the brain [43]. Despite this, the mechanisms by which PNPs are able to cross the BBB are still unknown and may differ from its counterparts. Regardless, these unique properties of PNPs in itself define their ability to enhance the delivery and effectiveness of drugs in the brain.

An *in-vivo* study conducted by Arisoy., *et al*. 2020 delivered exogenous dopamine and L-Dopa into the central nervous system to compensate for the reduction in dopaminergic neurons and to replace the lessened amounts of endogenous dopamine. The aim was for PNP formulations to enhance the symptoms of PD via the delivery of dopamine to the brain. It involved a nanoparticulate delivery-system composed of PLGA conjugated with wheat germ agglutinin (WGA) and L-Dopa administered through the intranasal route of MPTP-induced PD mice. The route of delivery ensured an effective route to the brain and WGA to enhance adsorption and absorption of the nasal cavities to reduce elimination. The results showed significant improvement of drug delivery to the brain as little amounts were detected in the serum when compared to conventional PD drug formulations. Mice treated with the conventional formulation of L-Dopa administered orally showed 0.104 ± 0.007 and 1.868 ± 0.804 ng mL^{-1} L-Dopa in serum and brain samples, respectively. Mice treated with L-Dopa administered by the intranasal route had 0.098 ± 0.004 and 2.131 ± 0.254 ng mL^{-1} L-Dopa in their serum and brain samples, respectively. Levels of L-Dopa encapsulated in the WGA-PLGA nano system and administered *via* the intranasal route were 0.087 ± 0.004 and 4.177 ± 1.427 ng mL^{-1} in serum and brain samples, respectively. The PNP system had extended L-Dopa release of up to 9 hours [52].

Solid lipid nanoparticles

More recently, solid-lipid nanoparticles (SLNs) are becoming a major appeal as novel drug carriers and are the forefront of rapidly emerging nano-delivery system. They are a lipid matrix which possess the ability to solidify at cooler temperatures. It combines the advantages of lipid nanocarriers and polymeric nanoparticles, and avoids their limitations. The ability to solidify to form a solid matrix enables better control of drug release as well as improves stability - this is best achieved by using a biocompatible/biodegradable lipid in its formulation to also prevent cytotoxicity and increase body tolerance [52].

Testing the limitations of conventional PD therapy against SLNs, bromocriptine (BK), a potent dopamine agonist was encapsulated into SLNs using micro-emulsion technology in a study by Esposito., *et al*. The samples of SLN were obtained from different lipid mixtures and concentrations through alternative methods based on homogenisation and ultrasonication. Peak results were obtained using tristearin/tricaprin, with a stability of more than 6 months. The encapsulation yield in different formulations was similar at ~75% however, it was highest when tristearin/tricaprin was used, at 84%. This *in vivo* study demonstrated that encapsulated BK was more rapid in onset and long-lasting than that of free BK in its antiparkinsonian action. This suggests that this new system proves to be an effective strategy to prolong BK action and provide stable plasma drug levels [53].

The 'wearing off' and dyskinesia are prominent side effects of L-dopa and dopamine agonists, this is due to the peripheral conversion of L-dopa outside the BBB and inability of dopamine agonists to pass the BBB [54]. A study was carried out using SLN and micro delivery system for piribedil, a potential dopamine 2 receptor agonist, known to have a short half-life, rapid elimination, and poor water solubility. The authors used commercial lipid excipients and emulsifiers, employing both hot and cold homogenization techniques to develop the solid lipid particles [compritol (2.5%), labrasol (1.2%) with a hot homogenization size of 40.4 μm and cold homogenization size of 2 μm and an entrapment efficiency of the hot homogenization of 88:1% ± 5:3% and cold homogenization of 67:3% ± 3:7%]. In these animal models, both solid lipid suspensions demonstrated a sustained release and enhanced bioavailability when compared to the free form [55].

Limitations of levodopa in therapy

While levodopa has pioneered PD treatment since the 1960s, its pharmacological drawbacks and effects from long-term use has opened the door for exploration of other modalities, such as nanotechnology as discussed in this paper. The dopamine precursor known as L-dopa is still the most effective therapy for symptomatic treatment though is frequently associated with motor fluctuations and dyskinesias with serious impact on quality of life, as mentioned before [56]. These major side effects are largely due to the pharmacokinetic and pharmacodynamic limitations, primarily, a short half-life, poor bioavailability, and a narrow therapeutic window [57]. In 2004, a double blind study showed that dyskinesia and wearing off of levodopa occurred in 16% to 20% of patients after 9 months of treatment, and subsequently, 50% to 60% of patients after 3 to 4 years [58]. These findings suggest that motor complications eventually develop in most PD patients, as well as highlight a major disadvantage of levodopa: as PD itself causes motor disabling symptoms, the use of levodopa as a treatment paradoxically worsens the motor symptoms it aims to relieve. Furthermore, the study suggests levodopa has a rapidly developed "wearing-off" effect which causes "off" periods before the next dose is due, further highlighting its pharmacological limitations.

How nanotechnology tackles these flaws

Conventional drug therapies for PD have significant limitations, relating to side effects and pharmacological properties, which nanotechnology has the ability to overcome. Firstly, the ability to directly overcome the pharmacological challenges that limit conventional therapies like levodopa [40]. Nanocarriers such as micelles, liposomes, PNPs, and SLNs have unique and advantageous pharmacological properties, being their small size, large surface area, and modifiable surfaces, that allow them to be engineered to cross the selective BBB more efficiently than free drug molecules [41,42]. This benefit ensures that higher concentrations of therapeutic agents reach the target regions, as demonstrated in studies where micelles and liposomes successfully delivered compounds such as EGCG, which resulted in reduced α-synuclein aggregation and increased neuroprotection [47,59].

Moreover, nanoparticles have the ability to sustain a controlled drug release, which maintain stable plasma drug levels and therefore controls the 'wearing-off' effect and dyskinesia previously mentioned [53,60]. The *in vivo* study conducted by Arisoy., *et al*. demonstrated flexibility to modify surface ligands of nanoparticles, such as with PNPs to enhance targeting specificity to dopaminergic neurons and reduce systemic and peripheral side effects by preventing unwanted drug changes outside of the BBB [52].

Overall, by enhancing bioavailability, targeting precision, and sustained release, nanotechnology-based approaches effectively overcome key limitations of conventional PD treatments.

Disadvantages of nanotechnology

Alongside the many benefits of nanoparticles, there are several drawbacks that limit the widespread application of nanotechnology in PD treatment. A concern is the potential toxicity and immunogenicity of certain nanomaterials, which may cause unintended biological responses or accumulate in non-target tissues to have damaging effects [39]. Furthermore, despite positive outcomes from preclinical data, the long-term safety of many nanoparticles remains insufficiently studied, particularly for long term use over the lifetime of a patient with a chronic disease like PD. Manufacturing challenges have also posed barriers: producing nanoparticles with consistent size, drug loading, and stability can be technically complex and costly [40]. Lastly, while nanotechnology can enhance drug delivery, it does not inherently reverse neurodegeneration. Therefore, it remains primarily a tool to provide symptomatic relief rather than a definitive cure.

Conclusion

In conclusion, pre-clinical trials in animals have shown positive response and has been proved to be safe; showing enhanced drug bioavailability, reduced motor symptoms, and neuroprotection using nanocarriers. However further clinical studies are needed to assess the safety and efficacy in humans including toxicity, immune response, accumulation, and biodegradability of nanomaterials need extensive long-term evaluation. Additionally, there is a need for regulations and standardization for the safe manufacturing, scalability and quality

control of the drug, during manufacturing, transport and administration. Therefore, although nanoparticles is a promising advancement in the field of Parkinson's disease, further studies and protocols are to be developed before it can replace traditional treatment pathways.

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