Potential applications of nanomedicine in the treatment of Parkinson's disease

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease and leads to severe disability and even death in patients, causing a heavy social burden worldwide. Among the therapeutics for PD, pharmacotherapy is usually the first-line therapy and is typically the basic treatment for other therapeutics, such as surgery, exercise therapy and psychological intervention. Unfortunately, the existing PD therapeutic agents fail to cure the disease due to their low efficacy, cytotoxicity, severe side effects and poor cell targeting. With the development of nanotechnology and the emergence of nanomedicine, the application of nanomaterials has helped improve the efficacy of pharmacotherapy for PD. In the following review, the current pharmacotherapy for PD and its pros and cons are described. A summary of the nanomaterial types commonly used in nanomedicine and their applications in PD treatment is provided. Additionally, challenges related to using nanomaterials for PD pharmacotherapy are discussed.

Keywords: Parkinson's disease; pharmacotherapy; nanomedicine.

1. INTRODUCTION

Parkinson's disease (PD) has been studied for more than two centuries since its discovery in 1817 when the term "shaking palsy" was first proposed by the British doctor James Parkinson (Medical Research Council Laboratory of Molecular Biology *et al.*, 2018). Currently, PD is generally recognized as a neurodegenerative condition. It is pathologically characterized by the disorganized aggregates of intracellular α-synuclein (α-syn) inclusions and the loss of substantia nigra (SN) neurons and clinically characterized by distinctive motor disorders such as tremors, bradykinesia, muscle rigidity and postural balance disorders, moreover, nonmotor symptoms such as sleep disorders, olfactory disorders, cognitive and psychiatric disorders may also occur (Ye *et al.*, 2023). However, its pathogenesis and therapeutics remain elusive. The clinical therapeutic strategies for PD include pharmacotherapy, surgical intervention, exercise therapy, rehabilitation therapy and psychological intervention (Costa *et al.*, 2023; Rezazadeh Yazd *et al.*, 2023; Strauss *et al.*, 2014). Pharmacotherapy is usually the first-line therapy and is typically the basic treatment for other therapeutics. Unfortunately, the efficacy of drugs is limited since the blood-brain barrier (BBB) blocks their entry into the brain. Some studies have shown that nanotechnology-based drug delivery can efficiently deliver drugs across the BBB due to the small size, large surface area and high adsorption capacity of nanoparticles (Junguang *et al.*, 2021; Sisubalan *et al.*, 2023). This review discusses the application of nanomedicine in PD treatment.

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2. THE CURRENT PHARMACOTHERAPY FOR PD

PD is the second most common neurodegenerative disease after Alzheimer's disease. It is estimated that more than 8.5 million people worldwide were diagnosed with PD in 2019. Current estimates suggested that in 2019, PD resulted in 5.8 million disability-adjusted life years (DALYs), an 81% increase since 2000, and caused 329000 deaths, an increase of more than 100% since 2000 (WHO, 9 August 2023). Therefore, it is urgent to find the therapeutics to cure PD, as the current treatment can only alleviate symptoms.

The biochemical changes in PD include reduced dopamine levels in the SN and striatum, causing motor disorders. Currently, the most common clinical treatment is dopamine replacement. There are a variety of drugs available in the clinic that exert dopamine replacement effects to improve the motor symptoms of PD. (1) Levodopa (L-DOPA) is the standard treatment for PD and is the most effective symptomatic drug in PD pharmacotherapy (Poewe *et al.,* 2010). L-DOPA is a precursor substance to dopamine that can cross the BBB through L-amino acid transporters. It is taken up by dopamine neurons and converted to dopamine by aromatic L-amino acid decarboxylase enzyme. It is used to temporarily relieve the motor symptoms of PD. (2) In addition to L-DOPA, there are several dopamine receptor agonists (DAs) that bind to postsynaptic dopamine receptors to achieve therapeutic effects. There are two types of DAs: ergot DAs and non-ergot DAs, of which ergot DAs are no longer advocated in the clinic due to the serious adverse effects that may cause valvulopathy (Fox *et al.,* 2018). (3) Another therapeutic option is the monoamine oxidase type B inhibitor (MAO-BI). Monoamine oxidase B (MAO-B) converts dopamine to 3,4-dihydroxyphenylacetic acid derivatives, homovanillic acid, and hydrogen peroxide, leading to oxidative stress. Thus, MAO-BI can reduce the degradation of dopamine, increasing neuronal dopamine levels, and attenuating the motor symptoms of PD (Fox, 2013). (4) Catechol-O-methyltransferase inhibitor (COMTI) inhibits the breakdown of L-DOPA in the periphery, thereby increasing the proportion of L-DOPA entering the brain. Therefore, COMTI must be taken with L-DOPA and is not effective alone (Fabbri *et al.,* 2022). The use and concentration of the above drugs are optimized in the clinic according to the patient's actual condition.

In addition to dopamine replacement therapy drugs, there are two other drugs that target motor symptoms. (1) Anticholinergics are mainly administered to patients with tremors and are not recommended for patients without tremors (Cui *et al.,* 2023). (2) Amantadine is effective in ameliorating hyperactivity, tonus, tremors, and anisocoria (Gonzalez-Latapi *et al.,* 2020).

However, the current pharmacotherapy options for PD only treat the symptoms of PD and do not alleviate neuronal damage. As PD progresses, it might also cause side effects such as the "on-off phenomenon" and the "end-of-dose phenomenon" in patients (Fanshi *et al.,* 2023). These side effects are associated with the low bioavailability, high cytotoxicity and poor cell targeting of the current drugs. Therefore, it is vital to find more efficient targeted pharmacotherapies with few side effects.

3. THE APPLICATION OF NANOMEDICINE FOR PD PHARMACOTHERAPY

Nanotechnology was an emerging technology that first appeared in the 1990s. The rapid development of nanotechnology has given rise to a series of new disciplines, such as nanophysics and nanochemistry. With the continuous penetration of nanotechnology into medicine, the field of nanomedicine was developed (Weber, 1999). The physicochemical properties of nanomaterials, such as their size, surface charge and morphology, play essential roles in overcoming biological barriers. Size influences several biological phenomena, including circulating half-life, extravasation through leaky blood vessels and cellular uptake (Li *et al.,* 2023) whereas nanoparticles with an average diameter of 100 nm were typically found in the circulation for long periods of time (Blanco *et al.,* 2015). Nanomaterials with neutral and negative surface charges have been shown to reduce the adsorption of serum proteins, thereby prolonging the circulating half-life (Alexis *et al.,* 2008). The morphology of nanomaterials, such as ellipsoidal, cylindrical, and discoidal shapes, also affect hemorheological dynamics and cellular uptake (Blanco *et al.,* 2015). Nanomedicine has been extensively studied in the field of oncology and antimicrobials (Shen *et al.,* 2024; S. Singh *et al.,* 2024).

Nanomedicine includes the use of nanomaterials in both diagnostic and therapeutic settings (Chen *et al.,* 2016; Gawne, 2023), and we paid more attention to its therapeutic use in this review. Using

nanomaterials in the treatment of diseases has two main advantages. First, they can modulate the distribution of the payload to increase deposition at the target site and diminish systemic toxicity (Nguyen-Thi *et al.*, 2023). Second, they could create a nano environment that provides solubility, stability, and protection for payloads from degradation during transport to the destination (Mitchell *et al.*,

2021). These two attributes determined that nanomaterials have unique properties and advantages as drug delivery systems or therapeutic agents for PD pharmacotherapy. There are a variety of nanomaterials currently used in PD therapy. In this section, we briefly summarize the following four types of nanomaterials that have the potential to be employed to treat PD (Fig. 1).
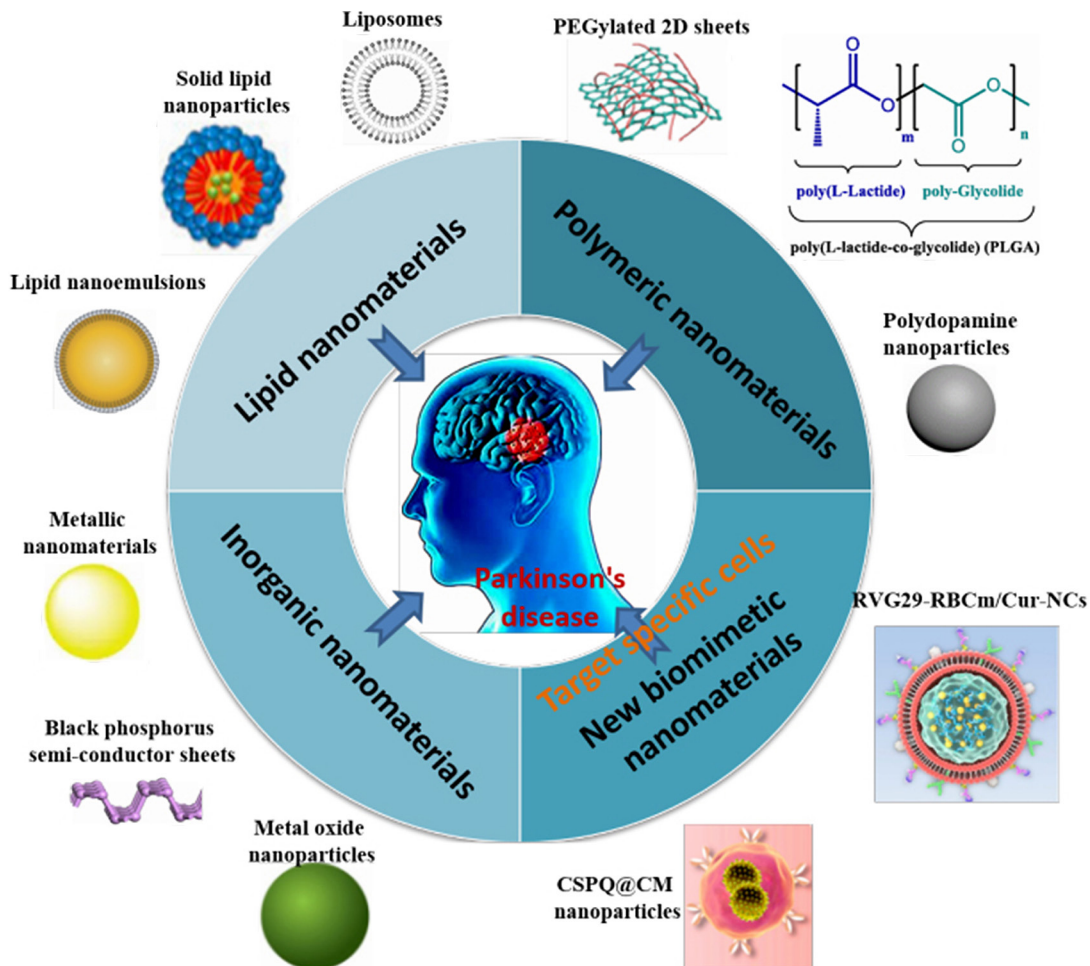

Figure 1. Summary of the potential applications of nanomaterials in the treatment of PD. This figure summarizes the different nanomaterials discussed in this current review.

(1) Lipid nanomaterials

Lipid nanomaterials are efficient nano delivery vehicles for PD pharmacotherapy due to their high bioavailability, low cytotoxicity and ability to be conjugated with drugs. Some lipid nanomaterials that have been produced include liposomes, solid lipid nanoparticles (SLNs), lipid nanoemulsions and lipid-polymer hybrid carriers (Jagaran *et al.*, 2022).

Liposomes have been widely used because they have ability to encapsulate both hydrophilic and hydrophobic molecules (Giuseppina *et al.*, 2015). Researchers have used BBB- penetrating peptides such as chlorotoxin to modify liposomes. A previous study showed that peptide-conjugated liposomes loaded with dopamine significantly increased the accumulation of dopamine in the SN and striatum and attenuated serious behavioral disorders in PD model mice (Xiang *et al.*, 2012).

Currently, nanomaterials are generally administered via the intraperitoneal or intravenous route. Furthermore, one study showed that compared with the oral administration of ropinirole (a kind of DA) alone, the oral administration of SLNs conjugated with ropinirole had a three-fold increase in potency such as increased dopamine, glutathione and catalase levels (Dudhipala *et al.*, 2020). Therefore, lipid nanomaterials could increase the pharmacokinetic and pharmacodynamic activity of drugs. The intravenous therapeutic patisiran (ONPATTRO®), which utilizes lipid nanomaterials for the delivery of a therapeutic siRNA, has been used for the clinical treatment of polyneuropathy (Urits *et al.*, 2020). Therefore, lipid nanomaterials may realize their potential in the formulation of drug delivery systems for PD soon.

(2) Polymeric nanomaterials

Polymeric nanomaterials mainly include polyesters, poly (amino esters), polyanhydrides and polyamides. Biodegradable polymeric nanomaterials such as poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) have been widely researched in the context of PD pharmacotherapy due to their biocompatibility and low cytotoxicity.

A study found that albumin/PLGA nanosystems loaded with dopamine (ALNP-DA) were effectively in crossing the BBB and replenishing dopamine in the substantia nigra pathway, significantly improving motor symptoms in the PD mouse model compared to the L-DOPA group (Monge-Fuentes *et al.*, 2021). Besides being suitable delivery carriers, polymeric nanomaterials also exert neuroprotective effects. A study found that PEGylated two-dimensional (2D) nanomaterial sheets (denoted as P-sheets) could attenuate behavioral and neuronal degeneration in PD. The mechanism was that P-sheets shielded PIP2 lipids within the membrane restrict the hydrolysis site to inhibit IP3 second messenger signaling, reducing Ca2+-related endoplasmic reticulum stress, and protecting neurons of PD model mice. These results support P-sheet nanomaterials as a novel therapeutic agent for neurodegenerative-associated membrane-lipid dysregulation and potentially for PD therapy (Liwen *et al.*, 2022).

Polydopamine nanoparticles (PDA NPs) can be assembled from dopamine through oxidation, cyclization and rearrangement (Hanmei *et al.*, 2020). These nanoparticles are utilized not only for drug delivery but also as therapeutic agents. PDA NPs were found to be able to pass through the BBB. PDA NPs could reduce the ROS level and the deposition of high-molecular-weight α-synuclein oligomers (Sardoiwala *et al.*, 2020). Moreover, PDA NPs could also be delivered to load with L-DOPA or melatonin to treat PD (Ren *et al.*, 2017; Srivastava *et al.*, 2020).

(3) Inorganic nanomaterials

In addition to organic nanomaterials, several inorganic nanoparticles have been employed as carriers or therapeutic agents for PD pharmacotherapy. These inorganic nanomaterials mainly include metallic nanomaterials, metal oxide nanoparticles, magnetic nanomaterials and carbon nanomaterials.

Metallic and nonmetallic nanomaterials can both deliver drugs efficiently. For instance, researchers used silver nanoparticles and ropinirole to synthesize the ropinirole silver nanocomposite (RPAgNC). Compared with the ropinirole group, RPAgNC exerted a greater neuroprotective effect in a *Drosophila* model of PD (Naz *et al.*, 2020). Black phosphorus (BP) semi-conductor sheets are novel nonmetallic nanomaterials. This material tends to heat up when irradiated with near-infrared rays and has been developed as a drug delivery system for PD because localized heating could increase the permeability of the BBB. A study indicated that lactoferrin-modified drug-laden BP increased the dopaminergic neuron number, and alleviated cognitive disorders in PD model mice (Xiong *et al.*, 2020).

In addition to being carriers, some inorganic nanoparticles can be used as therapeutic agents. The pathogenesis of PD might be associated with oxidative stress (Buhlman, 2017; Zuné *et al.*, 2021). Excess reactive oxygen species (ROS) cause oxidative damage to neuronal cells, resulting in neurological disorders. Because the brain has low antioxidant levels and is rich in easily oxidized lipids, it is more susceptible to ROS (Barnham *et al.*, 2004). Some studies have indicated that PtCu nanoalloys (Yu-Qing *et al.*, 2021), Cu_xO nanoparticle-clusters (Hao *et al.*, 2019), Mn_3O_4 nanozyme (N. Singh *et al.*, 2017) and vanadium carbide (V_2C) MXene nanoenzyme (Feng *et al.*, 2021) all have glutathione peroxidase (GPx)-like, catalase (CAT)-like and superoxide dismutase (SOD)-like activity to scavenge ROS in neuronal cells. Therefore, these nanomaterials with redox properties for the intracellular regulation of ROS are used to protect dopaminergic neuronal cells.

PD pathologically manifested as disorganized aggregates of intracellular α-syn. Therefore, reducing the aberrant aggregation of α-syn is considered an important therapeutic strategy for PD. A computational biology approach revealed that cerium oxide (CeO_2) NPs showed the best fitting in the active site of α-syn (Kaushik *et al.*, 2018). Further in vitro research found that CeO_2 NPs significantly reduced α-syn-induced toxicity in a dose-dependent manner using a yeast model based on the heterologous expression of human α-syn (Ruotolo *et al.*, 2020). In addition to the CeO_2 NPs, L-lysine (Lys)-coated Fe_3O_4 NPs showed strong binding to monomeric α-syn, inhibiting early aggregation events (Joshi *et al.*, 2015).

(4) New biomimetic nanomaterials

The above nanomaterials are able to cross the BBB, but their ability to target specific neuronal cells or glial cells is weak.

Researchers used red blood cell membrane (RBCm) modified with the brain-targeting peptide rabies virus polypeptide with 29 amino acids (RVG29) to carry curcumin-based drug nanocrystals (Cur-NCs), producing the new biomimetic nanomaterial RVG29-RBCm/Cur-NCs to treat PD (Y. Liu *et al.*, 2022). RVG29 binds specifically to the acetylcholine receptors (nAChR), which is expressed in both BBB and neuronal cells. The study indicated that RVG29-RBCm/Cur-NCs could ameliorate motor symptoms, decrease loss of tyrosine hydroxylase-positive neurons in the SN, and increase dopamine levels in the striatum in PD mouse models. The new biomimetic nanomaterial CSPQ@CM NPs were produced by Cu2-xSe-poly (vinylpyrrolidone) (PVP)-Quercetin (Qe) NPs with the membrane of MES23.5 neuronal cells (H. Liu *et al.*, 2020). Through the interaction between vascular cells adhering to molecule-1 (VCAM-1) expressed on the surface of MES23.5 neuronal cells and the surface α4β1 integrin of microglia, the NPs could specifically target microglia. The study showed that CSPQ@CM NPs were able to increase the dopamine level in cerebrospinal fluid and improve the movement function in PD model mice.

4. CONCLUSION AND PROSPECTS

In traditional nanomedicines, nanomaterials mostly appeared as the role of carriers for PD pharmacotherapy. However, nanomaterials are not only good carriers for delivering drugs, some nanomaterials also exhibit neuroprotective effects. The different nanomaterials types we discussed above have high efficiency, low cytotoxicity and the ability to target specific cells, but we need comprehensive therapeutic strategies that have the ability to penetrate the BBB", target specific neuronal cells or glial cells, provide neuroprotection, and destruct abnormal α-syn aggregates to restore normal motor function to treat PD. We believe that with the continuous discovery of the pathogenesis of PD and the development of nanotechnology, novel drugs that effectively treat PD will be developed.

No nanomaterials have been used for PD treatment at the clinical level because of the shortcomings or side effects of nanomedicines. Firstly, the majority of raw materials for synthesizing nanomaterials are costly. Besides, the preparation process is complicated, and important parameters such as size, morphology and zeta potential should be considered when designing nanomaterials for clinical use. Moreover, the current nanomedicine packaging process is cumbersome and not conducive to achieving mass production. And it is also lack of efficient quality control measures (Liu *et al.*, 2023). Furthermore, in the process of synthesizing nanomaterials, especially inorganic nanomaterials, the physical and chemical properties will be greatly changed, so the probability of side effects would increase (De Stefano *et al.*, 2012). It has been reported that nanomaterials may disrupt the gut microbial community (Ma *et al.*, 2023), and we need to focus more on the safety of nanomaterials while focusing on its effectiveness. Therefore, there is still a long way to go, and many issues need to be addressed before nanomaterials can be clinically used for PD pharmacotherapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ♦

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